Cooley Godward LLP

ATTORNEYS AT LAW

4401 Eastgate Mall
San Diego, CA
92121-1909
Main 858 550-6000
Fax 858 550-6420

www.cooley.com

KENT M. WALKER
(858) 550-6065
walkerkm@cooley.com

Broomfield, CO
720 566-4000
Palo Alto, CA
650 843-5000
Reston, VA
703 456-8000
San Francisco, CA
415 693-2000
Washington, DC
202 842-7800

TTAB

December 6, 2005

Commissioner for Trademarks
P.O. Box 1451
Alexandria, Virginia 22313-1451
Examing Attorney: Steven Fine
Trademark Law Office 110

Re: Response to Office Action, Declaration of James A. Schoeneck for Trademark Application, and Amendment to Allege Use
Applicant: BrainCells Inc.
Serial No. : 78/395,089
Mark: BRAINCELLS
Classes 35 & 42
Our File: Braincells, Inc./BRAINCELLS/U.S., Classes 35 & 42

Dear Commissioner:

Enclosed please find the following documents in connection with the above-identified trademark Application:

1. Notice of Appeal, and
2. Response to Office Action with exhibits
3. Declaration of James A. Schoeneck
4. Amendment to Allege Use

The USPTO is hereby authorized to withdraw the fee of $100.00 for filing the Notice of Appeal from our Deposit Account No. 03-3118. Please charge any deficiency or credit any overpayment of this fee to Deposit Account No. 03-3118. A duplicate copy of this letter as authorization is attached hereto for your convenience.

Please return the enclosed postcard acknowledging receipt of these documents.

Very truly yours,

COOLEY GODWARD LLP

Kent M. Walker
Enclosures
483534 v1/SD

12-09-2005
U.S. Patent & TMOfc/TM Mail Rcpt Dt. #64

Certificate of Mailing:

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Commissioner for Trademarks, P.O. Box 1451, Alexandria Virginia 22313-1451.

C Sager (Name)

12/6/2005 (Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

In Re the Application of:	
Applicant: BrainCells Inc.	
Mark: BRAINCELLS	Trademark Law Office: 110
Serial No.: 78/395,089	
Classes: 35 & 42	
Filed: April 1, 2004	Examining Attorney: Steven Fine
Mailing Date: June 6, 2005	

Commissioner for Trademarks
P.O. Box 1451
Alexandria, Virginia 22313-1451

12/15/2005 GTHOMAS2 00000040 033118 78395089
01 FC:6403 100.00 DA

NOTICE OF APPEAL

BrainCells Inc. ("Applicant"), hereby appeals to the Trademark Trial and Appeal Board from the decision of the Trademark Examining Attorney refusing registration of the mark BRAINCELLS.

12/15/2005 GTHOMAS2 00000041 033118 78395089
01 FC:6403 200.00 DA

Void date: 12/15/2005 GTHOMAS2
12/15/2005 GTHOMAS2 00000040 033118 78395089
01 FC:6403 100.00 CR

An appeal fee in the amount of $100 is filed concurrently herewith. 37 C.F.R. §2.6(a)(18). The USPTO is hereby authorized to withdraw this fee from our Deposit Account No. 03-3118. Please charge any deficiency or credit any overpayment of this fee to Deposit Account No. 03-3118.

Respectfully submitted,

COOLEY GODWARD LLP

Date: December 6, 2005

By: _____

Kent M. Walker
Attorneys for Applicant.
4401 Eastgate Mall
San Diego, California 92121
Telephone: (858) 550-6000
Facsimile: (858) 550-6420
Email: trademarks@cooley.com

483734 v1/SD

Certificate Mailing

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C. Soger (Name)

12/6/05 (Date)

UNITED STATES DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

In Re the Application of:	)	
	)	
Applicant: BrainCells Inc.	)	
	)	
Mark: BRAINCELLS	)	
	)	Trademark Law Office: 110
Serial No.: 78/395,089	)	
	)	
Classes: 35 & 42	)	
	)	
Filed: April 1, 2004	)	Examining Attorney: Steven Fine
	)	
Mailing Date: June 6, 2005	)	
	)	

Commissioner for Trademarks
P.O. Box 1451
Alexandria, Virginia 22313-1451

RESPONSE TO OFFICE ACTION

BrainCells Inc. ("Applicant"), by and through its counsel, responds as follows to Office Action No. 2 dated June 6, 2005 with respect to the above-captioned application for the mark BRAINCELLS ("the Mark"):

I. REQUEST FOR RECONSIDERATION

Pursuant to 37 C.F.R. § 2.64(b) and TMEP § 715.02, Applicant respectfully requests that the Examining Attorney reconsider the FINAL refusal, in light of Applicant's previous evidence and arguments, and the evidence and arguments submitted below.

A. Refusal Should be Withdrawn Because Applicant's Mark Is Not Merely Descriptive

Registration of BRAINCELLS has been refused on the basis that it is merely descriptive of Applicant's claimed services. Applicant respectfully responds that the Mark is at most suggestive of Applicant's services. Since doubts on the issue of descriptiveness are to be resolved in favor of the Applicant, *In Re Bed-Check Corporation*, 226 U.S.P.Q. 946, 948 (T.T.A.B. 1985), Applicant respectfully requests that the refusal be reconsidered and withdrawn based on the following arguments.

1. Imagination, Thought and Perception Required

Applicant previously argued that BRAINCELLS is suggestive because it "requires imagination, thought and perception to reach a conclusion as to the nature of the goods [or services]." *see Stix Products, Inc. v. United Merchants & Mfs., Inc.*, 160 U.S.P.Q. 777, 785 (S.D.N.Y. 1968). Only through an exercise of mature thought does BRAINCELLS suggest or hint at Applicant's claimed services relating to pharmaceutical research and discovery. *See Airco, Inc. v. air Products and Chemicals, Inc.*, 196 U.S.P.Q. 832, 835 (T.T.A.B. 1977) (holding that AIR-CARE was not merely descriptive, stating that "[t]he literal meaning of the mark, namely 'care of the air' may, through an exercise of mental gymnastics and extrapolation suggest

or hint at the nature of applicant's services, but it does not, in any clear or precise way, serve merely to describe applicant's preventative maintenance services.")

The evidence and arguments submitted by the Examining Attorney in support of refusal to register serve to make this point even more. The Examining Attorney correctly states that Applicant's services are business marketing and pharmaceutical research and development services. *See* Office Action No 2 at 2. The Examining Attorney next states that "the pharmaceutical products which are researched and developed by the applicant ... 'are specifically designed to effect receptors on neural stem cells in the hippocampus.'" *See id.* The Examining Attorney *then* goes on to state that "hippocampus" is defined as the "area of [the] brain associated with memory." From each of these separate points, the Examining Attorney concludes that neural stem cells in the hippocampus are "brain cells" and that, therefore, Applicant's mark is merely descriptive of its claimed services. *See id.*

As illustrated above, even the Examining Attorney's statements required several different steps of analysis before reaching the conclusion that BRAINCELLS is descriptive of business marketing and pharmaceutical research and development. It is precisely these several different steps of analysis that constitute the "mental gymnastics" required to get from Applicant's mark to Applicant's claimed services. The test of descriptiveness is not whether the consumer could figure out the relation of the mark to the services after a careful thought or study. Rather, the connection between the mark and the Applicant's services must be instantaneous for the mark to be considered merely descriptive. *See Investacorp, Inc. v. Arabian Investment Banking Corp.*, 19 U.S.P.Q.2d 1056 (11th Cir. 1991).

2. BRAINCELLS Only Hints at Claimed Services

BRAINCELLS would be considered merely descriptive only if it described an ingredient, quality, characteristic, function, feature, purpose or use of Applicant's claimed services. *See* TMEP § 1209.01(b). Applicant submits that BRAINCELLS does not meet this standard.

"Brain cells" are not an ingredient, quality, characteristic, function, feature, purpose, or use of Applicant's claimed pharmaceutical research and discovery services. Applicant does not create brain cells, nor is its research focused on brain cells. Rather, the business of the company is to develop pharmaceuticals or related services that may or may not promote the growth or differentiation of cells anywhere in the human nervous system. In this way, BRAINCELLS may hint at or suggest an ingredient, quality, characteristic, function, feature, purpose or use of Applicant's claimed services, but it does not merely describe them. The services are far removed from the mark; the mark hints at or suggests, but does not describe the goods or services.

3. Doubt Must Be Resolved In Applicant's Favor

The connection between Applicant's mark and Applicant's claimed services is not instantaneous. The fact that it takes several steps of analysis to associate BRAINCELLS with Applicant's claimed services signals that there is some doubt as to the descriptiveness of Applicant's mark. Additionally, BRAINCELLS does not merely describe an ingredient, quality, characteristic, function, feature, purpose or use of Applicant's claimed services. This aspect, too, signals doubt as to the descriptiveness of BRAINCELLS. This doubt is required to be resolved in Applicant's favor. *See In Re Bed-Check Corporation*, 226 U.S.P.Q. 946, 948 (T.T.A.B. 1985) and *In re Gourmet Bakers, Inc.*, 173 U.S.P.Q. 565, 565 (T.T.A.B. 1972) (holding that any doubt

in determining registrability of THE LONG ONE for bread was to be resolved in favor of the Applicant). Applicant therefore respectfully requests that the refusal to register be withdrawn, and the application be permitted to proceed to publication.

II. IN THE ALTERNATIVE, APPLICANT'S MARK HAS ACQUIRED DISTINCTIVENESS OF SECONDARY MEANING AND IS THEREFORE REGISTERABLE.

Although Applicant believes that "BRAINCELLS" should be registerable because it is at most suggestive of the claimed services, in the event that the refusal to register on the grounds of descriptiveness is not withdrawn, Applicant respectfully requests that the refusal to register be reconsidered and withdrawn in view of acquired distinctiveness pursuant to section 2(f) of the Trademark Act. Accordingly, via a separate document, Applicant concurrently submits an Amendment to Allege Use of the Mark in classes 35 and 42 along with supporting declaration and specimens.

Applicant respectfully submits that its Mark has come to be associated in the industry with a wide array of pharmaceutical research and development services and business marketing services in the field of licensed pharmaceutical products. Therefore, "BRAINCELLS" should proceed to registration on the Principal Register pursuant to Section 2(f) 15 U.S.C. §1052(f).

Applicant's advertising and promotion of the Mark in connection with Applicant's services is sufficient to establish that the Mark has acquired distinctiveness.

> An evidentiary showing of secondary meaning adequate to show that a mark has acquired distinctiveness indicating the origin of the goods, includes evidence of the trademark owner's method of using the mark, supplemented by evidence of the effectiveness of such use to cause the purchasing public to identify the mark with the source of the product.

In Re Owens-Corning Fiberglas Corp., 227 U.S.P.Q. 417, 422 (Fed. Cir. 1985). Under this standard, the following information is sufficient to show that Applicant's use of the Mark has caused the relevant public to identify "BRAINCELLS" with Applicant and its services.

A. Substantial and Continuous Use

No other entities appear to be using or applying to register the mark "BRAINCELLS" other than Applicant. Indeed, the Examining Attorney found no related marks that would bar registration of Applicant's mark. *See* Office Action No. 1

Applicant has used the mark substantially and continuously since July 2004. *See* Declaration of James Schoeneck, CEO of BrainCells Inc. ("Schoeneck Decl.") Applicant's business under the Mark continues to grow each year. Applicant's use of the Mark, combined with marketing and promotion of the mark over the last one and one half years, has caused consumers to recognize the "BRAINCELLS" mark and associate it with Applicant and its services. *See* Schoeneck Decl. at ¶ 3.

B. Press Releases

Applicant advertises its drug discovery and development services in different types of print and electronic media, including through press releases. Attached as Exhibit A are examples of press releases highlighting the BRAINCELLS mark.

C. Presentations at Industry Events

Applicant regularly participates in, and has a leading presence in, industry trade shows and conferences such as the Texas Life Science Conference, the C21 BioVentures Conference, "The Biotech Meeting, " CalBio, and Neuroscience, which are attended by thousands of industry professionals every year. Applicant's presence at each of these trade show events is prominent,

and Applicant promotes its services under the BRAINCELLS mark at these conferences. Attached as Exhibit B is a representative list of the industry trade shows and conferences in which Applicant has attended and participated.

Additionally, Applicant is often a featured speaker at these industry conferences, further promoting the BRAINCELLS mark in relation to its services. *See* Schoeneck Decl. at ¶ 6. Attached as Exhibit C is evidence of PowerPoint presentations and other major presentations given by Applicant at major industry conferences.

D. Examples of Recognition in the Industry

Due to its innovative pharmaceutical research and discovery services, Applicant has become well-known in the biotechnology industry. Applicant's notoriety in the industry strengthens the association between the BRAINCELLS mark and Applicant's claimed services.

Applicant is a member of BIOCOM, the largest regional life science association in the world, representing the Southern California life sciences community. Applicant has gained exposure of its BRAINCELLS mark through networking and other collaborative opportunities sponsored by BIOCOM. *See* Schoeneck Decl. at ¶ 7. Attached as Exhibit D are explanatory materials about BIOCOM, including evidence of Applicant's membership in this association.

In connection with its pharmaceutical research activities, Applicant's work is often highlighted in scientific articles relating to the biotechnology field. Attached as Exhibit E are examples of such scholarly articles, indicating participation by Applicant and its leaders.

Attached as Exhibit F are press releases and other evidence from the biotechnology industry illustrating the connection between Applicant's Mark and its pharmaceutical research and discovery services. Applicant's membership in BIOCOM, its publication of scholarly articles in the biotechnology field, and the other evidence of recognition in the biotechnology field support a conclusion that the relevant public (i.e. individuals and businesses in the biotechnology and pharmaceutical fields) have come to associate BRAINCELLS with Applicant's pharmaceutical research and discovery and business marketing services.

E. News Media Coverage

Additionally, Applicant has also garnered attention outside its industry, and in the mainstream news media. Attached as Exhibit G is evidence of unsolicited news media coverage from publications such as Corante, the San Diego Union Tribune and YAHOO! Finance, showing use of the BRAINCELLS mark in connection with Applicant's services. Each of these articles further serves to establish a connection between Applicant's mark and its claimed services.

F. Website

A significant source of publicity for Applicant's services offered under the Mark comes from the Applicant's website at www.braincellsinc.com. The comprehensive web site displays the Mark prominently on every page and receives over one thousand hits each month. *See* Schoeneck Decl. at ¶ 12. Attached as Exhibit H are excerpts from Applicant's website showing the prominent use of the Mark.

Applicant has expended substantial resources in the successful promotion of its services in connection with the BRAINCELLS mark. As a result of its use, its promotion, and industry recognition of Applicant and the Mark in association with Applicant and its services, Applicant respectfully submits that the BRAINCELLS mark has gained secondary meaning and distinctiveness in the relevant marketplace.

III. AMENDMENT TO SUPPLEMENTAL REGISTER

As more fully detailed above, Applicant believes that the Mark is suggestive, and should proceed to registration on that basis. In the alternative, Applicant argues that the Mark has acquired secondary meaning pursuant to section 2(f) of the Trademark Act, and should proceed to registration on that basis.

If and only if the Examining Attorney does not accept either one of these bases for registration, Applicant requests that the application for BRAINCELLS be transferred to the Supplemental Register and that the words "Principal Register" in its original application be changed to "Supplemental Register" pursuant to 37 C.F.R. § 2.47(c) and § 2.75(a).

CONCLUSION

For the reasons set forth above, Applicant respectfully requests that the Examining Attorney withdraw the refusal to register on the ground that the "BRAINCELLS" mark is descriptive and find that the Mark is suggestive because it only hints at or suggests the claimed services. In the alternative, Applicant has amended its application to base registration on § 2(f) and has submitted evidence showing acquired distinctiveness. Lastly, in the event the Examining

Attorney accepts neither one of those bases for registration, Applicant amends its application for transfer to the Supplemental Register.

Respectfully submitted,

COOLEY GODWARD LLP

Date: December 6, 2005

By: Kent M. Walker

Kent M. Walker
Attorney for Applicant
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6000
trademarks@cooley.com

481925 v1/SD

UNITED STATES DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

In Re the Application of:	)	
	)	
Applicant: Braincells Inc.	)	
	)	
Mark: BRAINCELLS	)	
	)	Trademark Law Office: 110
Serial No.: 78/395,089	)	
	)	
Classes: 35 & 42	)	
	)	
Filed: April 1, 2004	)	Examining Attorney: Steven Fine
	)	
Mailing Date: June 6, 2005	)	
	)	

Commissioner for Trademarks
P.O. Box 1451
Alexandria, Virginia 22313-1451

DECLARATION OF JAMES A. SCHOENECK

I, James A. Schoeneck, say and declare as follows:

1. I am the Chief Executive Officer of BrainCells Inc., the ("Applicant") in this matter ("Applicant"). I have personal knowledge of the facts set forth in this declaration. Applicant provides pharmaceutical research and development services and related business marketing services in the field of licensed pharmaceutical products. As the Chief Executive Officer, I am familiar with and have access to company records concerning the efforts to promote our services, the marketing budget and expenses for promotional events, publications, and communications to inform the press, public, and prospective customers about Applicant's services.

2. This Declaration is submitted to supplement the Response to Office Action No. 2 in the above-referenced application.

3. Applicant has used the mark substantially and continuously since July 2004. Applicant's business under the BRAINCELLS mark continues to grow each year. Applicant's use of the BRAINCELLS mark, combined with marketing and promotion of the mark since July 2004, has caused consumers to recognize the "BRAINCELLS" mark and associate it with Applicant and its services.

4. Applicant advertises its drug discovery and development services in a different types of print and electronic media, including through press releases. Attached as Exhibit A are examples of press releases highlighting the BRAINCELLS mark.

5. Applicant regularly participates in, and has a leading presence in, industry trade shows and conferences such as the Texas Life Science Conference, the C21 BioVentures Conference, and "The Biotech Meeting" which are attended by thousands of industry professionals every year. Applicant's presence at each of these trade show events is prominent, and BrainCells Inc. promotes its services under the BRAINCELLS mark at these conferences. Attached as Exhibit B is a representative list of the industry trade shows and conferences in which Applicant has participated and presented.

6. Applicant is often a featured speaker at these industry conferences, further promoting the BRAINCELLS mark in relation to its services. Attached as Exhibit C is evidence of PowerPoint presentations and other major presentations given by Applicant at major industry conferences.

7. Applicant is a member of BIOCOM, a regional life science association, representing the Southern California life sciences community. Applicant has gained exposure of its BRAINCELLS mark through networking and other collaborative opportunities sponsored

by BIOCOM. Attached as Exhibit D are explanatory materials about BIOCOM, including evidence of Applicant's membership in this association.

8. In connection with its pharmaceutical research activities, Applicant's work is often highlighted in scientific articles relating to the biotechnology field. Attached as Exhibit E are examples of such scholarly articles, indicating participation by Applicant and its leaders.

9. Attached as Exhibit F are press releases and other evidence from the biotechnology industry illustrating the connection between Applicant's Mark and its pharmaceutical research and discovery services.

10. Attached as Exhibit G is evidence of news media coverage from publications such as Corante, the San Diego Union Tribune and YAHOO! Finance, showing use of the BRAINCELLS mark in connection with Applicant's services.

11. A significant source of publicity for Applicant's services offered under the Mark comes from the Applicant's website at www.braincellsinc.com. The comprehensive web site displays the Mark prominently on every page and receives over one thousand hits each month. Attached as Exhibit H are excerpts from Applicant's website showing the prominent use of the Mark.

The undersigned, being hereby warned that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any resulting registration,

declares that the facts set forth in this application are true, all statements made of his knowledge are true, and all statements made on information and belief are true.

Dated: December 5, 2005

By: _____
James A. Schoeneck

483255 v1 SD
12/05/05 3:40 PM

Certificate of Mailing

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C Segal (Name)

12/6/05 (Date)

UNITED STATES DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

In Re the Application of:		
Applicant:	BrainCells Inc.	
Mark:	BRAINCELLS	Trademark Law Office: 110
Serial No.:	78/395,089	
Classes:	35 & 42	
Filed:	April 1, 2004	Examining Attorney: Steven Fine
Mailing Date:	June 6, 2005	

Commissioner for Trademarks
P.O. Box 1451
Alexandria, Virginia 22313-1451

AMENDMENT TO ALLEGE USE UNDER 37 C.F.R. § 2.76

Applicant hereby requests registration of the above-identified trademark in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. § 1051 et seq., as amended). One specimen showing the mark as used in commerce for each class is submitted with this Amendment.

Applicant is using the mark in commerce in connection with the following services:

"Business marketing services in the field of licensed pharmaceutical products" in International Class 35; and

"Pharmaceutical research and development services, namely assay development, compound screening, compound and chemical identification, drug target identification and characterization, performance of human clinical trials" in International Class 42.

The mark was first used in connection with the above services at least as early as July 2004. The mark was first used in connection with above services in commerce, at least as early as July 2004.

DECLARATION

The undersigned, being hereby warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any resulting registration, declares that he/she is properly authorized to execute this Amendment to Allege Use on behalf of Applicant; he/she believes Applicant to be the owner of the mark sought to be registered; the trademark is now in use in commerce; and all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

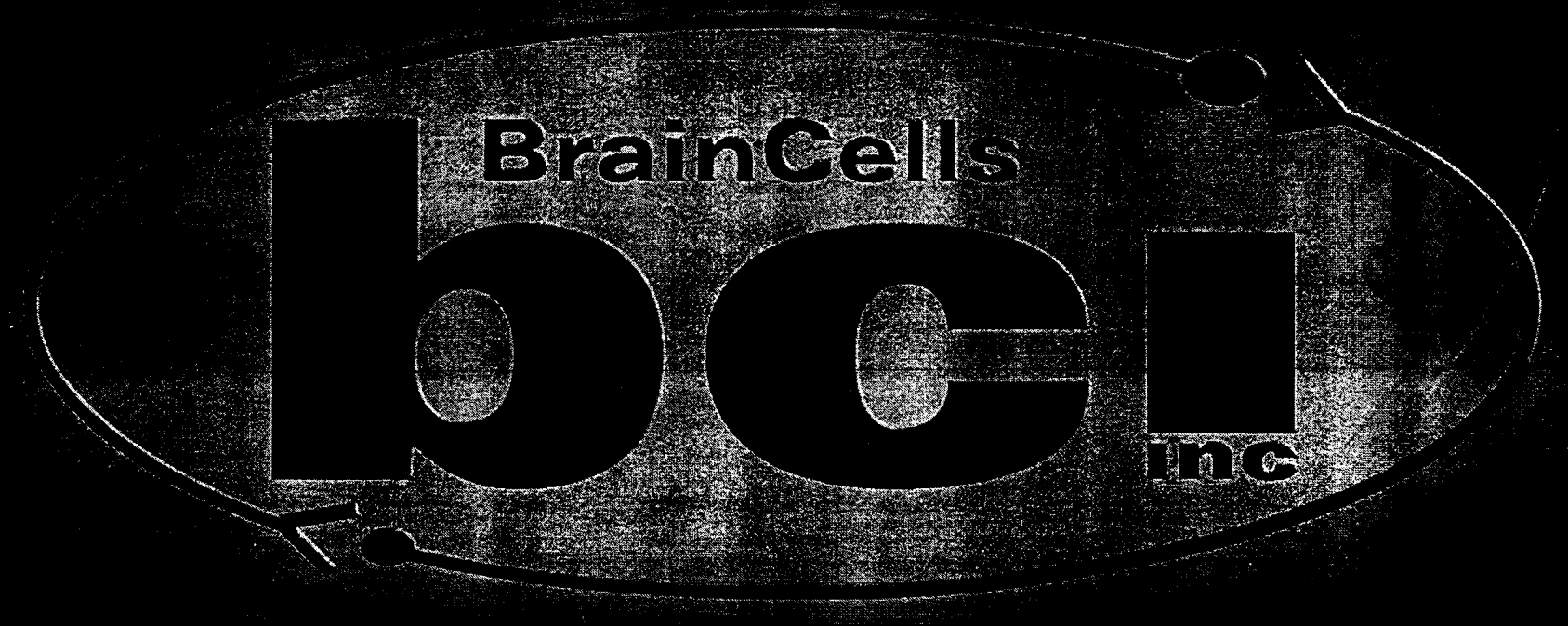
BrainCells Inc.,
a Delaware corporation

Dated: Dec 5, 2005

By: _____

Name: James Schoeneck
Title: CEO

483358 v1/SD



www.braincellsinc.com

September 20, 2005

BRAINCELLS, INC. (BCI)

BCI is the leading neurogenesis-based drug discovery and development company.

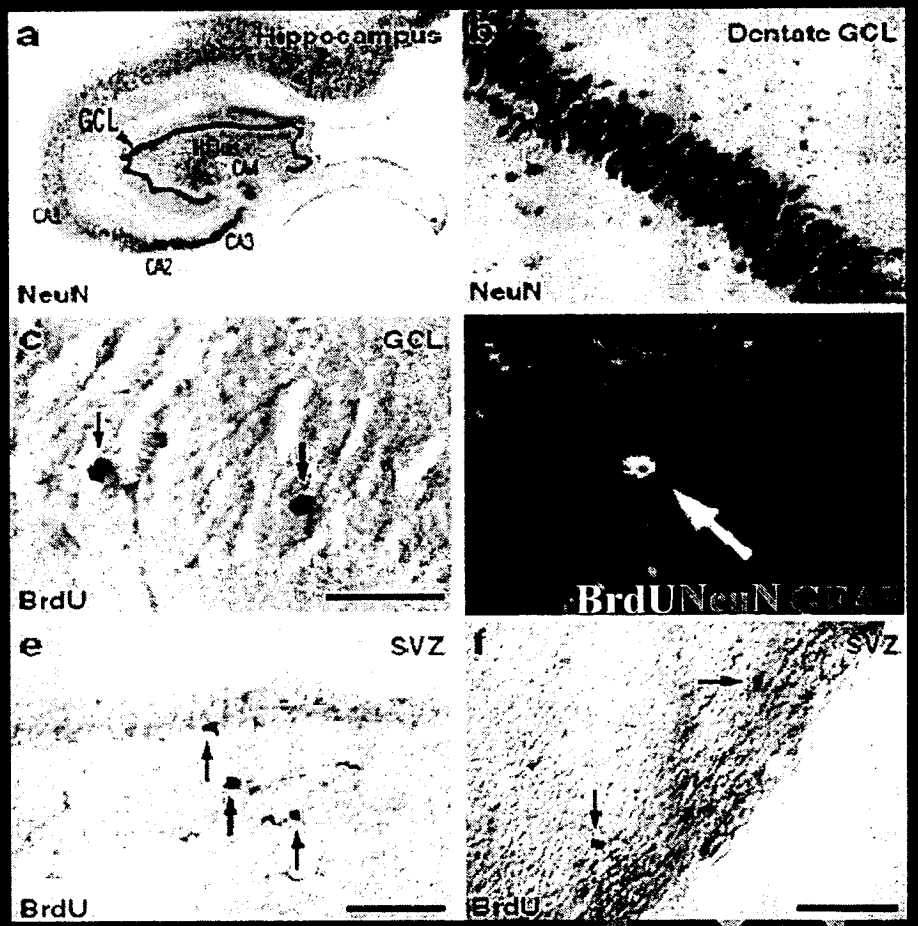
BCI is developing new therapies for depression, recovery from brain injury and other CNS diseases.

BCI Scientific Foundation

Seminal Discoveries

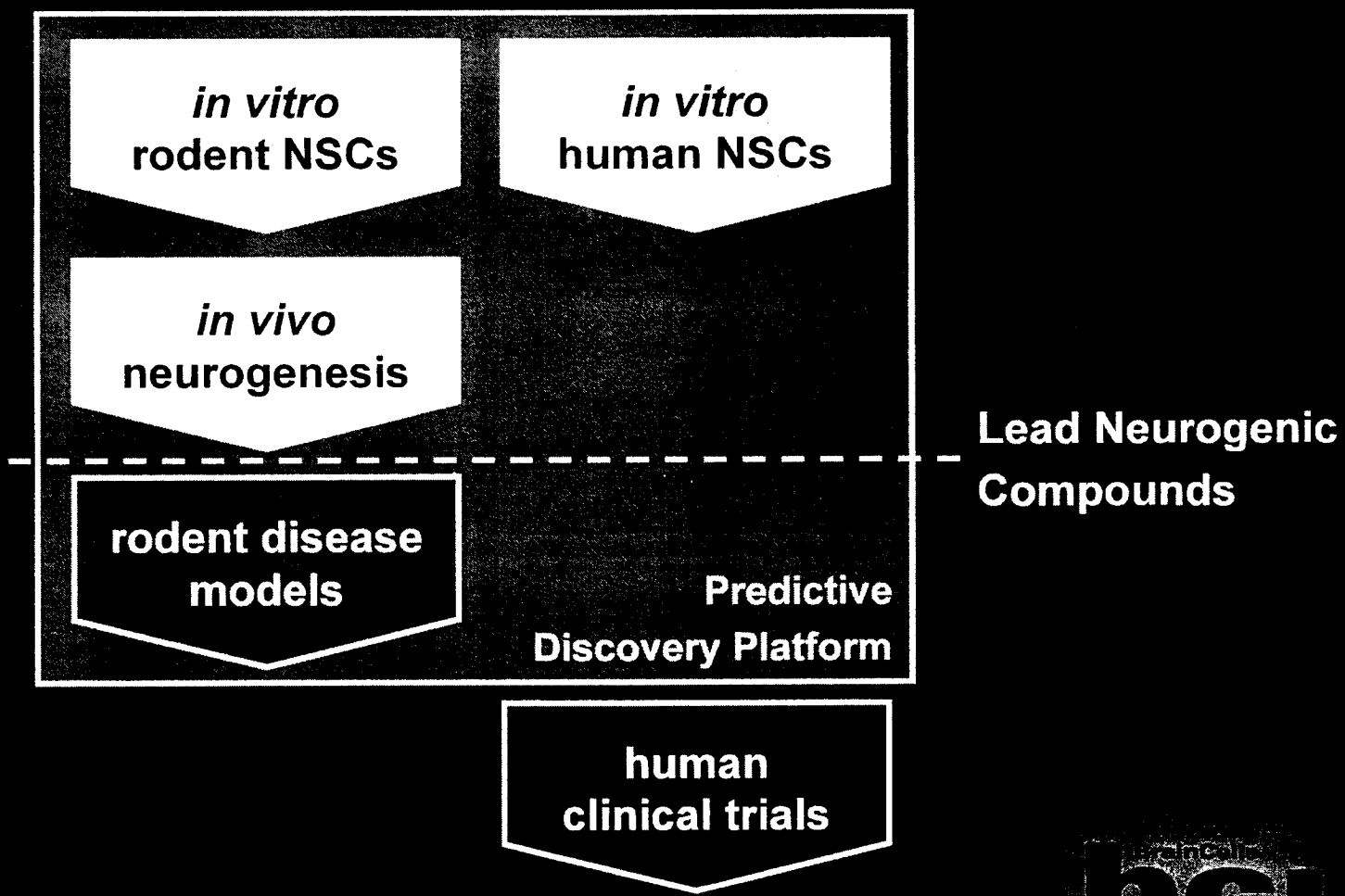
- **1998:** Gage lab discovers neurogenesis in adult human brain
- **1999:** Gage lab shows that neurogenesis can be regulated
- **2002:** Gage lab demonstrates <u>functional</u> neurogenesis in the adult hippocampus
- **2003:** Hen lab strengthens link between depression and neurogenesis

➢ **Neurogenesis has emerged as a fundamental process underlying CNS physiology and disease**



(Eriksson et al., Nat. Med 1998)

BCI Discovery Platform



Attrition by Therapeutic Area
From First-In-Man to Registration

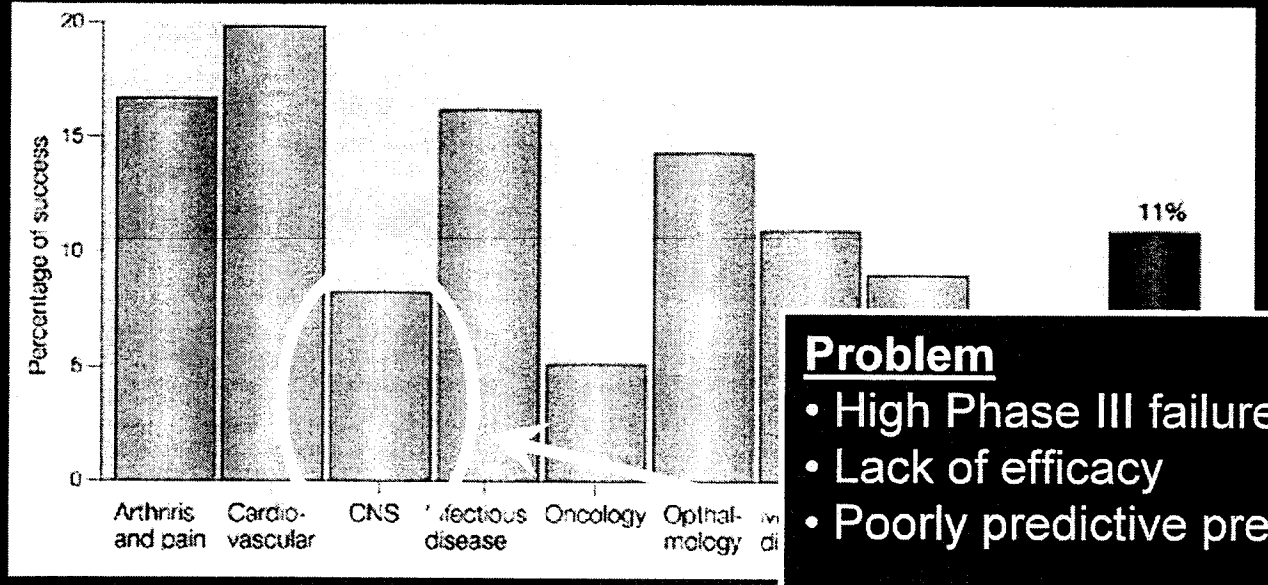
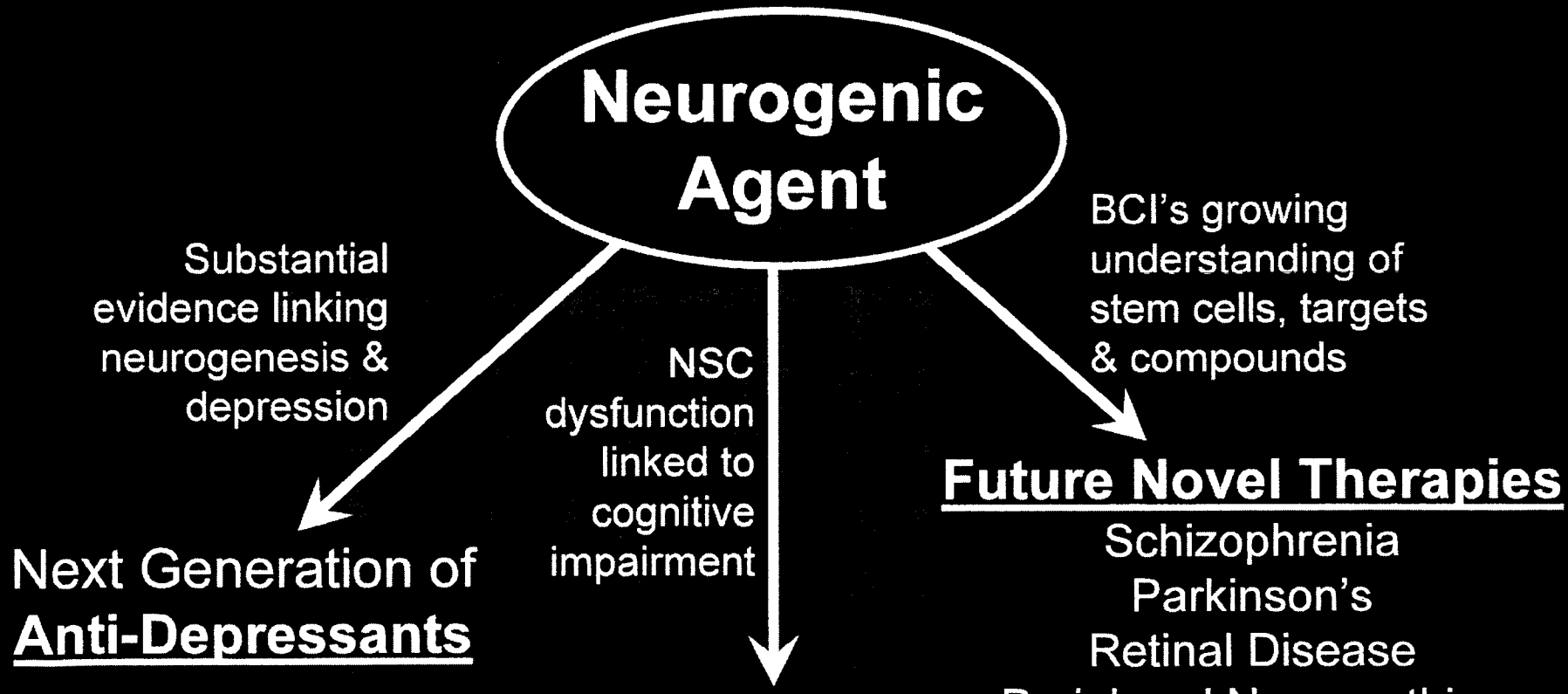


Figure: Kola & Landis, Nature Reviews: Dru
Data: DataMonitor "Pharmaceutical R&D

Problem
- High Phase III failure rate
- Lack of efficacy
- Poorly predictive pre-clinical models

BCI Solution
- Understand disease mechanism
- Physiology-relevant models
- Neurogenesis discovery platform

BCI Opportunity



BCI & Depression

- Neurogenesis enables
  - Prediction of efficacy
  - Re-positioning of in-licensed drugs
  - Optimization of dosing
  - Identification of new targets
  - Identification of active metabolites
- Market opportunity
  - Huge ($17B) market
  - Few new mechanisms
  - Partner Ph III & marketing

BCI Summary

- Founded in San Diego: Dec, 2003
- Operational: Sept, 2004
- Raised $17.7M in equity financing
- >10,000 sq. ft. lab, office & vivarium
- 14 full-time staff (17 by end-2005)
- Proprietary neurogenesis discovery platform established
- Novel neurogenic targets & compounds identified

Management Team

- James Schoeneck (ActivX, Prometheus, Centocor)
  - Chief Executive Officer
- Dr. Harry Hixson (Amgen, Neurocrine, Signal)
  - Chairman
- Dr. Edward Hodgkin (Tripos, Wyeth, British Biotech)
  - President & Chief Business Officer
- Dr. Carrolee Barlow (Merck, Salk Institute)
  - Vice President, Biology R&D

Investors & Advisors

Series A Investors

- Oxford Bioscience Partners
- Bay City Capital
- Technology Partners
- AM Pappas & Associates
- NeuroVentures

Scientific Advisors

- Fred Gage (Salk Inst.)
- Ron Evans (Salk Inst.)
- Eric Kandel (Columbia)
- René Hen (Columbia)
- Scott Small (Columbia)

Board of Directors

- Dr. Harry Hixson, Chairman
- Jim Schoeneck (CEO, BrainCells)
- Jonathan Fleming (Oxford Bioscience)
- Carl Goldfischer (Bay City Capital)
- Roger Quy (Technology Partners)
- Art Pappas (AM Pappas & Associates)
- Dr. Ellen Baron (Oxford Bioscience)
- Dr. Fred Gage (Salk Institute)
- Dr. Paul McGonigle (PsychoGenix)

Discovery Strategy

Translating Science into Products

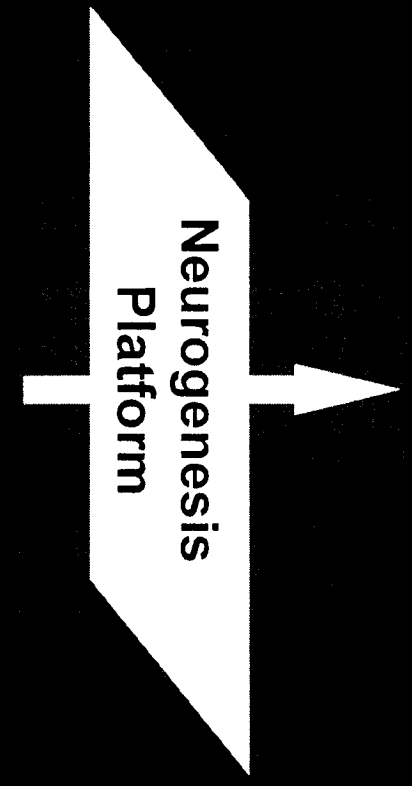
In-Licensing Candidates

Marketed Drugs

Generics

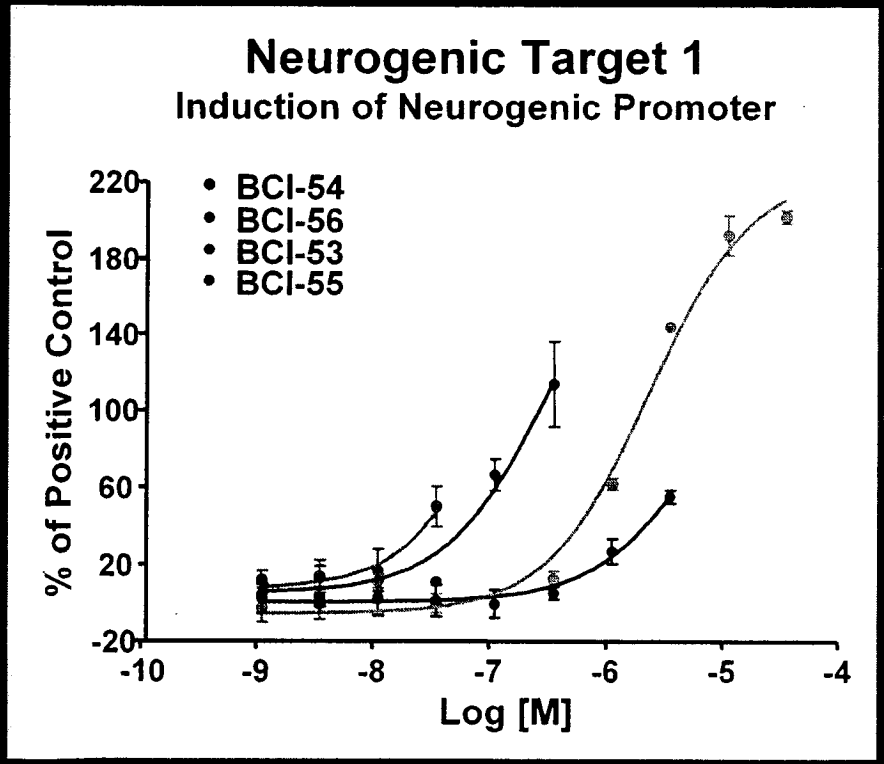
Pharmacological Standards

Discovery Project Compounds



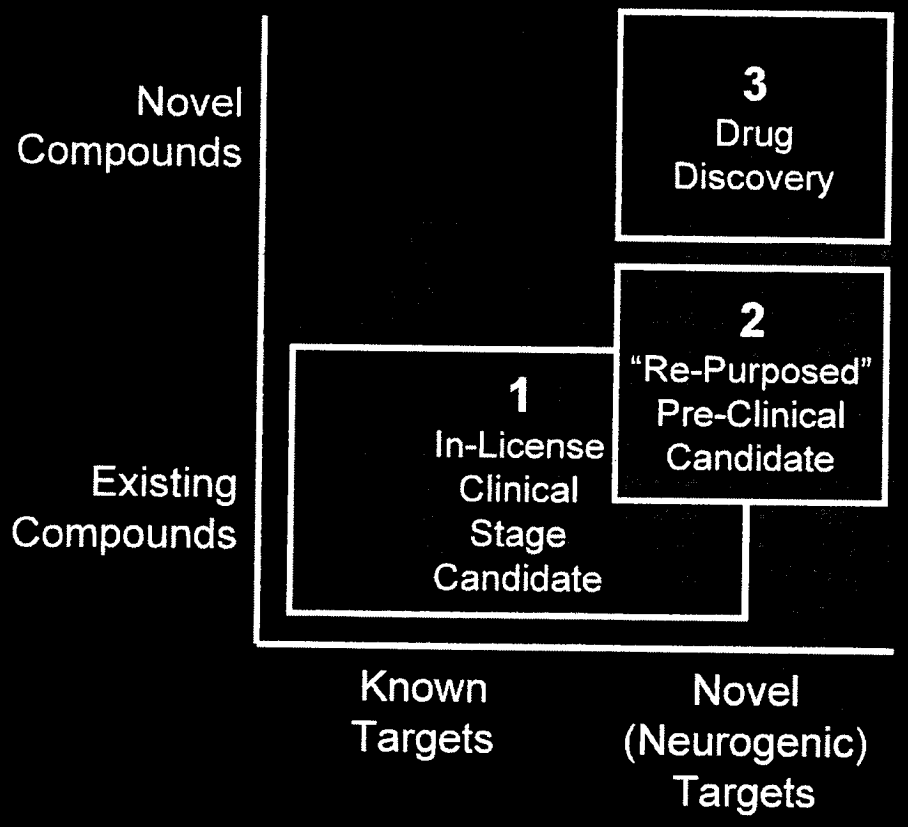
- Select in-licensing candidates
- Re-purpose existing drugs
- Understand drug mechanism
- Validate technology
- Build knowledge base
- Develop predictive models
- Establish novel patent claims
- Lead optimization & selection

Target Validation



- Proprietary list of 35 putative neurogenic targets
- Assembled toolkit of probe compounds
- Identified novel neurogenic targets
- Provide focus for in-licensing activities

Building BCI's Product Pipeline

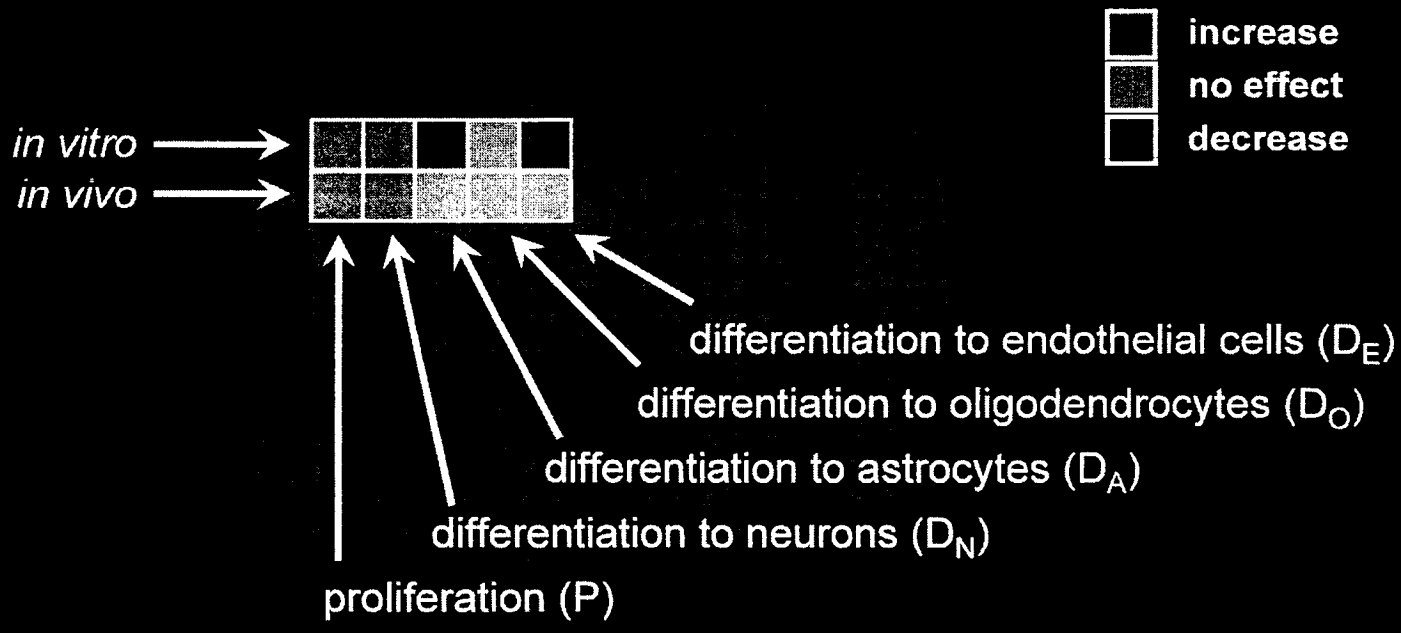


1 Clinical Stage Candidate
- Rapidly build high-value pipeline
- Use platform to select candidate
- Commence Phase II clinical trial

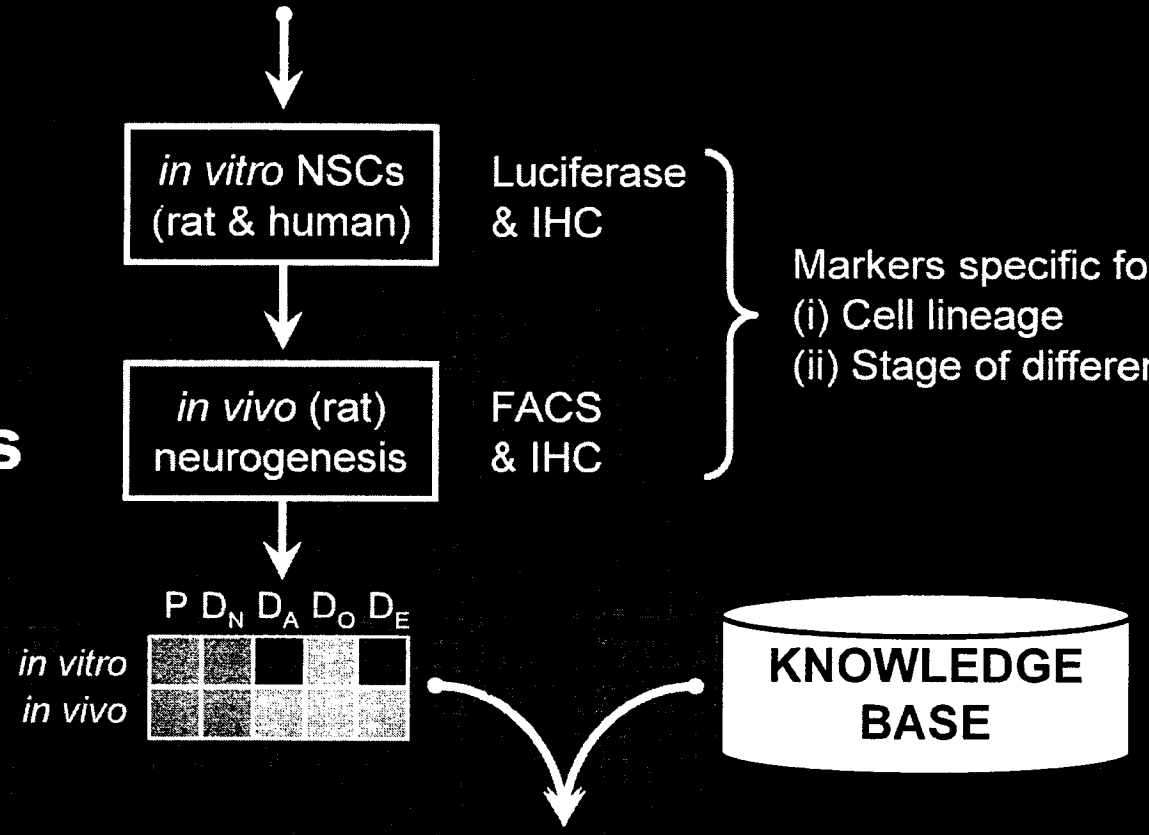
2 Pre-Clinical Candidate
- Prioritized list of 'neurogenic' targets
- In-license compound IP
- Leverage platform for selection

3 Drug Discovery Program
- Profile compound libraries
- Identify novel neurogenic targets
- Leverage platform for lead optimization
- Seek pharma collaboration

Neurogenesis Fingerprint



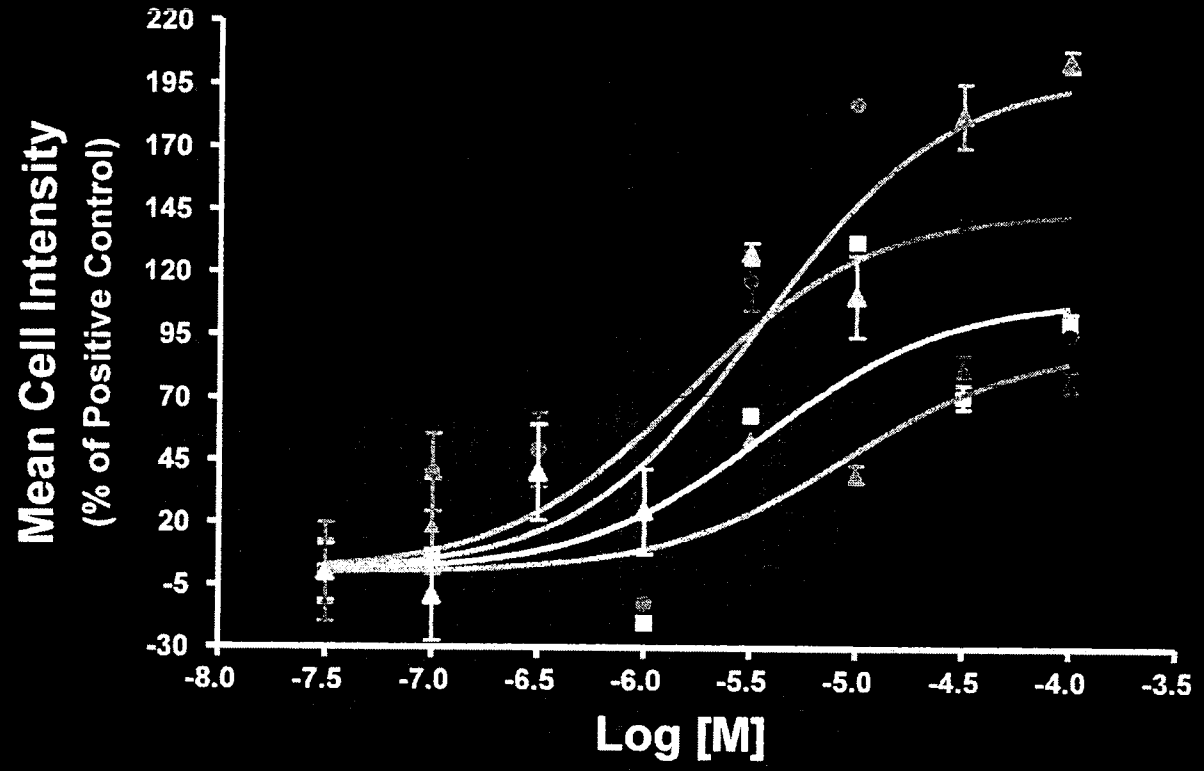
Evaluation Of Clinical Candidates



Mood Disorders	**Cognition**	**Neurology**
Standard behavioral models e.g. *Learned Helplessness* + Hen & Santarelli (Columbia U.) Chronic models of depression & anxiety	Cognition models e.g. *Morris Water Maze* + Gage (Salk Inst.) Kandel (Columbia U.)	Brain injury models (trauma & hypoxia) + Palmer (Stanford U.) Fike (UCSF) Radiation damage models

Evaluation of In-Licensing Opportunities

Demonstration of Neurogenesis in Human NSCs



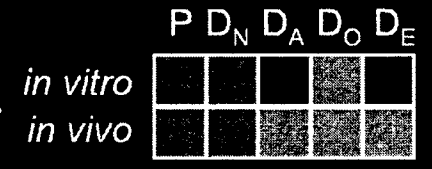
Compound	EC50 (μM)	Efficacy (%)
■ Positive Control	2.69	100
▲ Drug Comparator	5.78	77
◆ BCI-71: In-Licensing Candidate	1.81	95
▲ BCI-72: Principle Metabolite	3.54	205

Drug Discovery Collaborations

Compound Library

Known pharmacology
Prioritized by target activity
Multiple compounds per target

Neurogenesis Platform



Disease Models

Robust chemical series
Target activity tracks neurogenesis
Other known pharmacology

"Validated" Neurogenic Target + Compounds

Target-Based Drug Discovery & Intellectual Property

BrainCells Inc.

An Outstanding Investment Opportunity

- Paradigm-shifting technology
- Focus on large markets
- Fast-to-market strategy
- Experienced management team
- World-class SAB and advisors
- Top-tier investor group
- Focus on IPO criteria

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Exhibit A

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My Kept Articles +
My Suggested Articles

All Publications

All Columnists

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BrainCells Inc. Announces $17.7 Million Series A Financing
Jul 14 '05

SAN DIEGO, July 14 -- BrainCells Inc., a privately-held, neuroscience-focused, drug discovery and development company targeting novel and/or best-in-class therapies for depression, related neuropsychiatric disorders and other central nervous system diseases, announced the close of its Series A private financing. Technology Partners and seed investors Oxford Bioscience Partners, and Bay City Capital led the $17.7 million round, joined by A. M. Pappas & Associates, Neuro Ventures, Matthias Bowman, Harry Hixson, Chairman and CEO, and scientific founders Fred H. Gage of the Salk Institute and Eric Kandel of Columbia University. The participants in the financing have invested $8.0 million to date and, pursuant to the terms of the financing, will become obligated to invest an additional $9.7 million upon the achievement by the Company of certain milestones.

BrainCells (BCI) was founded by Fred H. Gage and Harry Hixson in December 2003 to capitalize on Dr. Gage's pioneering discoveries that humans generate new nerve cells throughout life and that this endogenous process -- neurogenesis -- can be manipulated using known small molecule therapeutics. In December 2004, BCI merged with NeuroGenix, a start-up founded by Drs. Eric Kandel, recipient of the 2000 Nobel Prize in Physiology or Medicine, Paul McGonigle, ...

(Continued)

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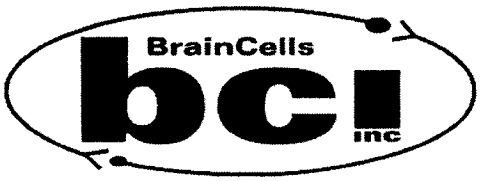

Company Contacts:
Harry F. Hixson, Jr.
Chairman and Chief Executive Officer
BrainCells, Inc.
858-812-7700

BRAINCELLS INC. ANNOUNCES $17.7 MILLION SERIES A FINANCING

San Diego, Calif., July 14, 2005 – BrainCells Inc., a privately-held, neuroscience-focused, drug discovery and development company targeting novel and/or best-in-class therapies for depression, related neuropsychiatric disorders and other central nervous system diseases, announced the close of its Series A private financing. Technology Partners and seed investors Oxford Bioscience Partners, and Bay City Capital led the $17.7 million round, joined by A. M. Pappas & Associates, Neuro Ventures, Matthias Bowman, Harry Hixson, Chairman and CEO, and scientific founders Fred H. Gage of the Salk Institute and Eric Kandel of Columbia University. The participants in the financing have invested $8.0 million to date and, pursuant to the terms of the financing, will become obligated to invest an additional $9.7 million upon the achievement by the Company of certain milestones.

BrainCells (BCI) was founded by Fred H. Gage and Harry Hixson in December 2003 to capitalize on Dr. Gage's pioneering discoveries that humans generate new nerve cells throughout life and that this endogenous process – neurogenesis – can be manipulated using known small molecule therapeutics. In December 2004, BCI merged with NeuroGenix, a start-up founded by Drs. Eric Kandel, recipient of the 2000 Nobel Prize in Physiology or Medicine, Paul McGonigle, Luca Santarelli and Rene Hen and focused on elucidating the behavioral impact of modulating neurogenesis and the relationship of neurogenesis to depression. Since then, proprietary screens have been established in BCI's laboratories to profile the neurogenic potential of various CNS active pharmaceuticals, including known antidepressants. These screens are designed to reveal the preferred activities of neurogenesis-modulating compounds to be developed for the treatment of depression and other CNS disorders. BCI believes its neurogenesis platform represents a major improvement in the predictive power of pre-clinical models for CNS disorders and will facilitate a paradigm-shift in CNS drug discovery and development.

Proceeds from the Series A financing are primarily being used to identify one or more late-stage clinical compounds currently under development for a CNS indication. Candidates include compounds being developed for indications other than depression where the compound would be repositioned - based on its profile in the proprietary neurogenesis platform – as a novel treatment for depression and/or related neuropsychiatric disorders. BCI will also evaluate and optimize new compounds, selected based on activity against previously characterized CNS molecular targets. Finally, the platform will be utilized to screen and characterize novel drug targets and to initiate drug development around these novel targets. Partnerships with larger pharmaceutical and biotech players are anticipated to play key roles in the latter two activities.

In connection with the financing, Roger Quy of Technology Partners and Arthur Pappas of A. M. Pappas & Associates joined BrainCells' Board of Directors. Other Directors include Ellen Baron and Jonathan Fleming of Oxford Bioscience Partners, Fred Gage, Carl Goldfischer of Bay City Capital, Harry Hixson, and Paul McGonigle of PsychoGenics, Inc.

FOR IMMEDIATE RELEASE

Contact:
Jim Schoeneck or Harry Hixson
BrainCells Inc.
(858) 812-7700
(858) 812-7630 fax

Holli Kolkey
Noonan Russo
(858) 546-4811
Holli.kolkey@eurorscg.com

BrainCells, Inc. Appoints James A. Schoeneck Chief Executive Officer

SAN DIEGO, California, October 18, 2005 – BrainCells, Inc. (BCI), a privately held, neuroscience-focused, drug development and discovery company targeting novel and /or best-in-class therapies for neuropsychiatric disorders and other central nervous system diseases, announced today the appointment of James A. Schoeneck as Chief Executive Officer and member of the board. Schoeneck, 48, will be responsible for continuing to develop the strategic direction and capabilities of the company.

"We are fortunate to have Jim Schoeneck join BrainCells at this important period of the company's growth," commented Dr. Harry Hixson, BrainCells' Chairman of the Board. "He is a proven leader and brings a broad skill set of hands-on experience in all operational functions, a team-oriented management style and an outstanding track record of delivering results. I look forward to working with Jim to take BrainCells to the next level."

Schoeneck joins BrainCells from ActivX Biosciences, a proteomics-based drug development company, where he served as CEO and led the strategic sale of the company to Kyorin Pharmaceuticals of Japan in December 2004. Prior to ActivX, Schoeneck was President and CEO of Prometheus Laboratories. In 2002, Prometheus was recognized by *Inc.* magazine (Inc. 500) as the 3rd fastest growing private company in America and by the San Diego Venture Group as the Venture Capital Success Story of the Year.

"I'm excited to lead BrainCells' unique approach to identifying best-in-class therapies for central nervous system disorders," commented James Schoeneck, CEO. "The scientific foundation of the company, including Dr. Rusty Gage of the Salk Institute, Nobel Prize winner Dr. Eric Kandel and Dr. Rene Hen of Columbia University along with the incredibly talented staff at BCI, has the opportunity to change the way the industry thinks about the development of products for these diseases. The company already has a strong business presence and outstanding investors. I look forward to guiding BrainCells in the further application of the company's technology to continue bringing value to our own drug development and discovery programs and, in the future, strategic collaborators."

In his years prior to Prometheus, Schoeneck was Vice President and General Manager, Immunology Business Unit at Centocor, Inc., now a division of Johnson & Johnson. He built the organization and successfully launched Remicade, a leading biologic for rheumatoid arthritis and Crohn's disease that now exceeds $3 billion in annual sales. He also negotiated and led Centocor's strategic partnership with Schering-Plough for Remicade rights outside the US and worked with Lilly and GSK on other monoclonal antibody-based partnerships. Prior to Centocor, he spent 13 years at Rhône-Poulenc Rorer, Inc. serving as Director of Healthcare Services, Director of Marketing and various other positions.

Schoeneck replaces Dr. Hixson, BCI's founding Chairman and former Chief Executive Officer. Dr. Hixson will retain the position of Chairman. In his career, Dr. Hixson has held various management positions at Amgen, including President and Chief Operating Officer during the time

more

that Amgen developed two major breakthrough products, Epogen and Neupogen. He currently serves as Chairman of Sequenom and is a Director of Discovery Partners International and Arena Pharmaceuticals.

About BrainCells Inc.
BrainCells Inc. (BCI) was founded by Drs. Gage and Hixson in December 2003 to capitalize on Dr. Gage's pioneering discoveries that humans generate new nerve cells throughout life and that this endogenous process – neurogenesis – can be manipulated using known small molecule therapeutics. In December 2004, BCI merged with NeuroGenix, a start-up founded by Drs. Eric Kandel, Paul McGonigle, Luca Santarelli and Rene Hen and focused on the behavioral impact of modulating neurogenesis and the relationship of neurogenesis to depression. BCI has established proprietary screens to profile the neurogenic potential of various CNS active pharmaceuticals, including known antidepressants. BCI believes its neurogenesis platform represents a major improvement in the predictive power of pre-clinical models for CNS disorders and will facilitate a paradigm-shift in CNS drug discovery and development. The company's investors include Oxford Bioscience Partners, Bay City Capital, Technology Partners, A.M. Pappas & Assoc. and NeuroVentures. For more information, visit www.braincellsinc.com.

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Exhibit B

Industry Conferences and Trade Shows
Braincells Inc.

JP Morgan H&Q Meeting, San Francisco:	Jan 10-12, 2005
CalBio 05 Conference, San Diego	March 22, 2005
Allicense 2005, San Francisco	May 24-25, 2005
C21 BioVentures Conference, Monterey:	May 24-26, 2005
UBS Conference, San Francisco:	Sept 26-28, 2005
Depression & Antidepressants 2005, England	Oct 3-4, 2005
Biotech Meeting, Laguna Beach:	Oct 9-11, 2005
2005 Texas Life Science Conference, Houston:	Nov 3, 2005
Neuroscience 2005, Washington	Nov 12-16, 2005

Exhibit C

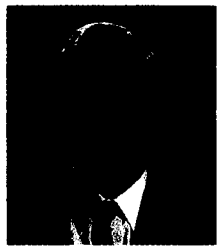
TEXAS LIFE SCIENCE CONFERENCE 2005

BREAKTHROUGH RESEARCH

COMMERCIAL SUCCESS

Underwriter:
BCM Technologies

RESEARCH OPPORTUNITY



Hello, I am **John Mendelsohn** and I have the privilege of serving as the President of The University of Texas M. D. Anderson Cancer Center. Did you know that M. D. Anderson has been ranked as the number one cancer hospital in the United States four out of the past five years? And we want you to know that in our region there are dozens of academic institutions with a combined research budget of over 1.4 billion dollars annually.

Hi, I'm **Eric Boerwinkle,** Director of the Human Genetics Center at The University of Texas Health Science Center in Houston. Can you name the medical center that is turning its 5.4 million patient visits each year into the largest patient database in history? If you said the Texas Medical Center in Houston, you're right. We're using our TexGen program to understand disease and make personalized medicine a reality.

I'm **Buz Brown,** President of BCM Technologies, an early stage venture capital group with a 20 year investment history here in Houston. In the Texas Medical Center alone, we have over a billion dollars of R&D expenditures annually and at least a half a dozen top ranked basic science and clinical departments. There's a renaissance happening here in Houston and investors are beginning to take notice.

WELCOME

As the Program Chair for the 2005 Texas Life Science Conference, I welcome you to this year's conference. We are thrilled to once again bring together life science venture investment leaders and senior management from select life science companies for stimulating discussions about emerging areas of medicine, investment strategies, and innovative technologies and products in development.

Great thought was given to this year's program, which follows a typical venture capital conference format. Leading venture capitalists will moderate our business sessions, while senior management from selected life science companies will present new product strategies and clinical results. Additional commentary will come from investment analysts and world class scientific/clinical opinion leaders. Networking opportunities have been included throughout the program to encourage discussion and interaction among conference attendees, including business leaders and researchers from the Houston area life science community.

We have created a forum for dynamic exchange between investors, executives, strategic partners, entrepreneurs, and technology managers. Our goal is to make this conference the premier national event for the life science venture industry. Not only do we want you to have an enjoyable and worthwhile experience, we'd like to see you back again next year.

In the meantime, enjoy the warm weather and take advantage of the expertise your fellow executives, investors, bankers, and entrepreneurs have assembled. Thank you for your participation in this year's conference. We are confident you will find it a unique and rewarding experience.

Buz Brown

Alfred (Buz) E. Brown, Ph.D.
Program Chair, 2005 Texas Life Science Conference
President, BCM Technologies, Inc.

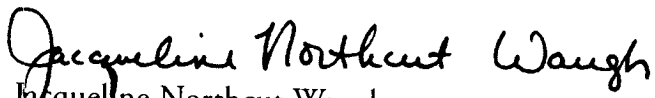
WELCOME

Welcome to the 2005 Texas Life Science Conference. We are delighted that you have joined us as we explore biotechnology's exciting road from breakthrough research to commercial success.

This year's program offers rich opportunities to learn about the latest work in some of the most promising life science areas alongside the industry's leading researchers, emerging companies and venture capitalists. You won't want to miss our presentation of the second annual BioHouston Life Science Award to Tanox, Inc. I'd like to say it was planned but it's serendipity that only last week Tanox announced Xolair's® approval for marketing in all of Europe *and* positive Phase II results for their second drug–a new class of HIV therapy. We couldn't be happier for Tanox.

Accepting the award for the company will be Tanox founder Nancy T. Chang, Ph.D., whose team first discovered a new approach to treating allergic asthma, and continues to generate commercial success as they pioneer innovative therapies for HIV, infectious disease, inflammation and cancer.

We are pleased to have this chance to introduce you to Houston's abundant investment opportunities, rooted in our world-class research infrastructure and celebrated entrepreneurial spirit. With our region's abundance of raw talent and determination, to experience Houston is to experience the frontier of biotechnology.



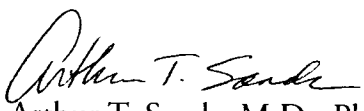
Jacqueline Northcut Waugh
President & CEO BioHouston, Inc.

MESSAGE FROM ARTHUR T. SANDS

On behalf of the Houston biotechnology community, I would like to thank you for participating in the 2005 Texas Life Science Conference.

When I co-founded Lexicon Genetics ten years ago, I realized that this region provided many advantages for a start-up biotechnology company. Now, as then, the region offers companies a unique combination of talented scientists, a premier medical center, a friendly and supportive business environment and an affordable operating environment. With more than 45 academic and research institutions and biotechnology companies, the Houston area is at the forefront of biotechnology innovation.

During last year's conference, I was honored to receive the first BioHouston Life Science Award. This year, I would like to congratulate Dr. Nancy Chang as Tanox receives the 2005 BioHouston Life Science Award. In recognition of its significant achievements, Tanox has been selected for this award from among the stellar group of healthcare and biotechnology institutions in the Houston region.



Arthur T. Sands, M.D., Ph.D.
Founder, President and CEO, Lexicon Genetics

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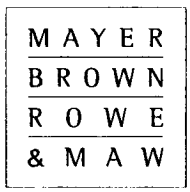


AGENDA

Wednesday, November 2, 2005

5:00 - 7:30pm — *Grand Ballroom Foyer*

Registration / Conference Check-in

5:45 - 7:30pm — *Grand Ballroom*

Welcome Reception: *Sponsored by AIG and Aon*

Thursday, November 3, 2005

7:00 - 8:15am — *Grand Ballroom Foyer*

Registration / Continental Breakfast

8:15 - 8:25am — *Grand Ballroom*

Opening Remarks: Jacqueline Northcut Waugh, President & CEO - BioHouston, and Alfred (Buz) E. Brown, Ph.D., President - BCM Technologies and Program Chair, 2005 Texas Life Science Conference

8:25 - 8:45am — *Grand Ballroom*

Opening Keynote Speaker: Commercialization of Academic Life Science Discoveries

Peter G. Traber, M.D., President & CEO - Baylor College of Medicine

8:45 - 10:15am — *Grand Ballroom*

The Great Debate: Does Preclinical Biopharm Investing Make Sense...and Dollars?

Industry experts from both the venture capital and management side will contrast early-stage, preclinical investment strategies and outcomes versus later-stage investments in more mature development companies. A debate-style format promises a lively exchange of views.

Panelists:

Arthur J. Klausner, Partner - A. M. Pappas & Associates - Pro

James Schoeneck, CEO - BrainCells, Inc. - Pro

Robert J. More, Partner - Domain Associates LLC - Con
Randall E. Woods, President & CEO - NovaCardia, Inc. - Con

10:15 - 10:30am *Grand Ballroom Foyer*

Networking Break

10:30 - 12:00pm *Grand Ballroom*

Creative Financing: The Rebirth of Clinical Partnerships and Other Non-Dilutive Financing Strategies

Several recent transactions may herald a comeback for special purpose entities, a once common way of raising cash for biotech drug development. Mike Ross and his panel will discuss pros and cons of this and other non-dilutive financial alternatives for today's biotech companies.

Michael Ross, Ph.D., General Partner - SV Life Sciences

Panelists:

Andrew L. Busser, Principal - Symphony Capital LLC
Jonathan P. Gertler, M.D., Managing Director, Head of Healthcare Investment Banking - Adams Harkness, Inc.
James R. Webster, Managing Partner - Capital Royalty L.P.

12:00 - 1:30pm *Forest Ballroom*

Luncheon: Presentation of the 2005 BioHouston Life Science Award to Tanox, Inc.

Luncheon sponsored by Vinson & Elkins L.L.P.

Award Presentation:

Jacqueline Northcut Waugh, President & CEO - BioHouston
James T. Willerson, M.D., President -
The University of Texas Health Science Center at Houston
Arthur T. Sands, M.D., Ph.D., President and CEO -
Lexicon Genetics Incorporated
Nancy T. Chang, Ph.D., President and CEO - Tanox, Inc.

1:30 - 3:00pm *Grand Ballroom*

Personalized Medicine

Genomic sequencing and molecular diagnostics herald a new era for pharmaceutical companies, physicians and patients - fact or fiction? This session will explore the use of molecular diagnostics and informatics to streamline preclinical studies, better select patients for clinical studies and improve market share of marketed products. Who uses them, how they are approved by regulatory agencies, who pays for them and how confidentiality is maintained, and last of all, is the market finally here?

Seth A. Rudnick, M.D., General Partner - Canaan Partners

Presenters:

John A. Ryals, Ph.D., President & CEO - Metabolon Inc.

Charles P.R. de C. du Mée, Ph.D., Co-Founder, Vice President, Development Director - Nascent Pharmaceuticals, Inc.,

Kevin Slawin, M.D., President & CEO - Oncovance

Krishnan Nandabalan, Ph.D., President - BioXcel Corporation

Panelist:

Arthur L. Beaudet, M.D., Chairman, Molecular and Human Genetics - Baylor College of Medicine

3:00 - 3:30pm *Grand Ballroom Foyer*

Networking Break

3:30 - 5:00pm *Grand Ballroom*

New Anti-Infective Strategies

Recent high-profile M&A activity in the anti-infectives arena suggests that Big Pharma has a renewed appetite for opportunities in this sector. The immediate need for new agents to treat dangerous bugs and the emergence of robust diagnostic technologies is a strong driver of demand. Representatives from several up-and-coming biotechs will showcase their products in development for the treatment, prevention and diagnosis of infectious diseases.

John S. Swartley, Ph.D., Vice President - BCM Technologies, Inc.

Panelist:

B. J. Bormann, Ph.D., Vice President Strategic Alliances - Pfizer Global Research & Development

Presenters:

Kevin L. Eastwood, Senior VP of Business Development - Achillion Pharmaceuticals

Mimi Healy, Ph.D., CEO - Bacterial Barcodes, Inc.

William Weiss, Director of Drug Evaluation - Cumbre Inc.

5:00 - 5:10pm — *Grand Ballroom*

Closing Remarks Day 1: Jacqueline Northcut Waugh, President & CEO - BioHouston

6:00pm — *River Oaks Country Club*

Venture Networking Dinner

Sponsored by Bracewell & Giuliani LLP and Ernst & Young

Friday, November 4th

7:00 - 8:20am — *Forest Ballroom Foyer*

Continental Breakfast

8:20am — *Forest Ballroom*

Opening Remarks: Alfred (Buz) E. Brown, Ph.D., President - BCM Technologies and Program Chair, 2005 Texas Life Science Conference

8:30 - 10:00am — *Forest Ballroom*

The Climate in Biotech Investing

This investor panel will focus on recent financing trends in health care and life science venture capital. Themes include a capital market overview, updates from core and non-core markets, recent success stories, exit strategies and liquidity in the life sciences.

Christopher W. Kersey, M.D., Managing Director - Cogene Ventures

Panelists:

Charles Baltic, Managing Director, Healthcare Investment Banking - Wachovia Securities

Quynh Pham, Vice President, Equity Research - Delafield & Hambrecht

Maria P. Sendra, Partner - Baker & McKenzie

Lyle A. Hohnke, Ph.D., General Partner - Tullis Dickerson & Co., Inc.

William D. Paiva, Ph.D., Partner - Chisholm Private Capital Partners

Robert D. "Bob" Ulrich, Ph.D., General Partner - Vanguard Ventures

10:00 - 10:30am *Forest Ballroom Foyer*

Networking Break

10:30 - 12:00pm *Forest Ballroom*

Aesthetic Medicine

The growth in aesthetic procedures has grown exponentially as the growing baby boomer demographic has demanded to look younger longer. New technology has allowed these procedures to be done with minimal downtime and immediate clinical benefit. This session will review the cutting edge medicine that is offering minimally invasive and non ablative treatments to combat aging appearances.

Evan S. Melrose, M.D., Partner - PTV Sciences, L.P.

Panelist:

Spencer A. Brown, Ph.D., Director of Research of the Plastic Surgery Department - UT Southwestern Medical Center

Presenters:

Steven L. Basta, President & CEO - Bioform Medical, Inc.

Matthew A. Megaro, President & CEO - Quill Medical, Inc.

Dennis E. Condon, President & CEO - Reliant Technologies, Inc.

12:00 - 12:10pm ***Forest Ballroom***

Closing Remarks: Jacqueline Northcut Waugh, President & CEO - BioHouston, and Alfred (Buz) E. Brown, Ph.D., President - BCM Technologies and Program Chair, 2005 Texas Life Science Conference

12:10pm ***The Meadow***

Picnic Networking Lunch

*The entire Houston community was saddened by the passing of our friend and colleague **Rick Smalley** on October 28, 2005. Rick epitomized what we value: path breaking research, commitment to teaching, and contribution to the betterment of our world. His extraordinary scientific contributions, recognized with the Nobel Prize, will form the foundation of new technologies that will improve life for millions. His life's work and his brave fight against a terrible disease were an inspiration to us all. He will be greatly missed.*

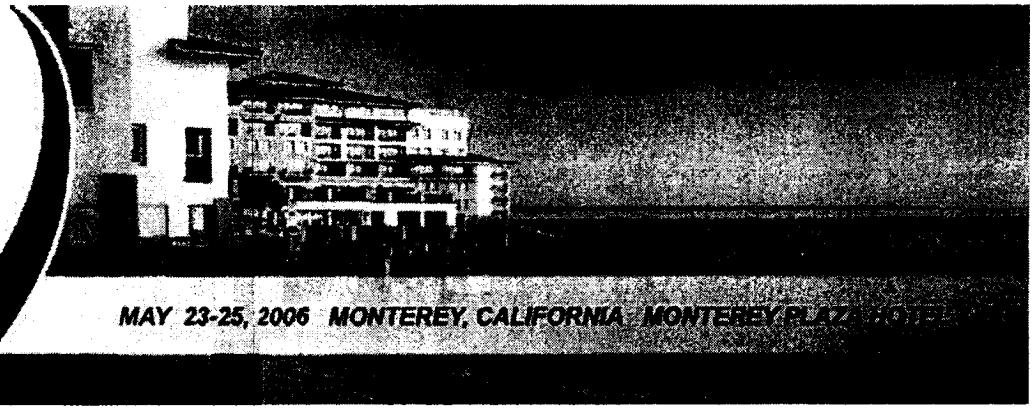
Our deepest sympathy goes out to all his loving family and friends.

with Pharmacia. Prior to joining Pharmacia, he held a research position at Somatogen, a start-up company developing a recombinant blood substitute that was subsequently purchased by Baxter. Mr. More received his B.A. from Middlebury College and his M.B.A. from the University of Virginia, Darden School of Business Administration.

Panelists

Pro–***Jim Schoeneck*** joined BrainCells, Inc. as Chief Executive Officer in September 2005. He served as Chief Executive Officer of ActivX Biosciences, a proteomics-based drug development company, until December 2004 when he sold the company to Kyorin Pharmaceuticals of Japan. Mr. Schoeneck currently serves as a strategic advisor to Kreido Laboratories. Prior to ActivX, Mr. Schoeneck was President and CEO of Prometheus Laboratories, having served previously as President and COO. While at Prometheus, he led their business strategy, research and operations during a period of exceptional growth and transformation. In 2002, Prometheus was recognized by Inc. magazine (Inc. 500) as the 3rd fastest growing private company in America. Before Prometheus, Mr. Schoeneck was Vice President and General Manager, Immunology Business Unit at Centocor, Inc., now a division of Johnson & Johnson. He built the organization and successfully launched Remicade, a leading biologic for rheumatoid arthritis and Crohn's disease that now exceeds $3 billion in annual sales. He also negotiated and led Centocor's strategic partnership with Schering-Plough for Remicade rights outside the US and worked with Lilly and GSK on other monoclonal antibody-based partnerships. Prior to Centocor, he spent 13 years at Rh_ne-Poulenc Rorer, Inc. serving as Director of Healthcare Services, Director of Marketing and various other positions. Mr. Schoeneck has served on the board of directors of BIO-COM and the Asthma and Allergy Foundation of America (AAFA), where he also served for 2 years as Chairman of the Board.

Con–***Randall E. Woods*** is the President and Chief Executive Officer of NovaCardia. Mr. Woods has more than 32 years of experience in the biotech/pharmaceutical arena. Mr. Woods served nine years as the Chief



2005 PRESENTING COMPANIES

Afecta Pharmaceuticals, California, USA
Alantos Pharmaceuticals, Massachusetts, USA
Ambit Biosciences, California, USA
Amphora Discovery Corporation, North Carolina, USA
Avera Pharmaceuticals Inc., California, USA
Avidia, California, USA
BioRexis Pharmaceutical Corporation, Pennsylvania, USA
Braincells, Inc., California, USA
Catalyst Biosciences, California, USA
Chimerix, Inc., California, USA
CyDex, Inc., Kansas, USA
Cylene Pharmaceuticals Inc., California, USA
EGeen International, California, USA
G Surge Medical Solutions, Inc., California, USA
GangaGen Inc., California, USA
GENETIX Pharmaceuticals, Inc, Massachusetts, USA
GlobeImmune, Inc., Colorado, USA
ICHOR Medical Systems, California, USA
Ilypsa, Inc., California, USA
immatics, Tüebingen, Germany
KAI Pharmaceuticals Inc., California, USA
Light Sciences Oncology, Washington, USA
LigoCyte Pharmaceuticals, Inc., Montana, USA
MaxCyte, Inc., Maryland, USA
Napa BioSciences, Inc., California, USA
Nerites Corporation, New York, USA
Novasite Pharmaceuticals, California, USA
NOXXON Pharma AG, Berlin, Germany
Nuevolution A/S, Copenhagen, Denmark
Phenomix Corporation, California, USA
PLx Pharma Inc., Texas, USA
PolyMedix Inc., Pennsylvania, USA
Proacta Inc., California, USA
Prolexys Pharmaceuticals, Inc., Utah, USA
Rejuvenon, New Jersey, USA
Rx3 Pharmaceuticals, Inc., California, USA
Sciona, Inc., Colorado, USA
Sidec Technologies AB, Stockholm, Sweden
Sirtris Pharmaceuticals, Inc., Massachusetts, USA
St. Charles Pharmaceuticals, Louisiana, USA
TargeGen, Inc., California, USA
TheraPei Pharmaceuticals, California, USA
Trellis Bioscience, Inc., California, USA

Register

Producers

Technology Vision Group LLC

Burrill & Company
A LIFE SCIENCES MERCHANT BANK

Hosts

BAYBIO

NVCA
National Venture Capital Association

Trinity Biosystems, Inc., California, USA
XDx, California, USA
Xencor, Inc., California, USA

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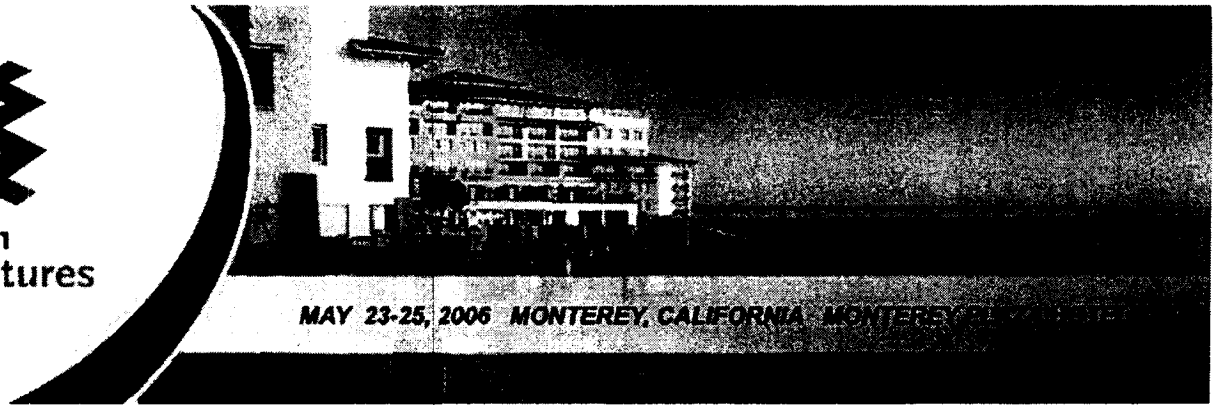

2005 CONFERENCE PROGRAM

Tuesday, May 24

4:00 **Registration**

5:30 - 7:30 **Opening Reception**

Wednesday, May 25

8:30 - 9:00 **Registration & Continental Breakfast**
Sponsored By Prism Venture Partners

9:00 - 9:15 **Welcoming Remarks**

Speaker: Robert Lee Kilpatrick, Partner, Technology Vision Group LLC
Bryant Fong, Principal, Burrill & Company
Nancy Saucier, Director, Medical Industry Group, National Venture Capital Association (NVCA)

9:15 - 10:30 **BioVenture Leadership Session 1**
What Sells in Today's Market

Chair: Barclay Kamb, Partner - Life Sciences Transactions, Cooley Godward LLP

Speakers: Stan Abel, Chief Financial Officer, Peninsula Pharmaceuticals, Inc.
Patrick Heron, General Partner, Frazier Healthcare Ventures
Wilfred Jaeger, Partner, Three Arch Partners

Scott Salka, Chief Executive Officer, Ambit Biosciences

This panel of biotech CEOs and venture capital partners will discuss the current private and public equity markets, examining the types and qualities of the companies that are successful in raising money from these sources, and will explore whether and why alternate financing and liquidity strategies, such as acquisition and spin-outs, may be on the increase.

10:30 - 10:45 **Coffee & Tea Service**

10:45 - 12:00 **BioVenture Leadership Session 2**
When To Go Public And Why?

Chair: Bryant Fong, Principal, Burrill & Company

Speakers: Daniel Janney, Managing Director, Alta Partners
Ilan Zipkin, Partner, MPM Capital
Barry Selick, CEO, Threshold Pharmaceuticals
George Milstein, Head of Investment Banking, Pacific Growth Equities

The IPO window for biotech companies now has been open for over a year and over 30 companies have completed offerings with varying degrees of success. Many companies that completed offerings raised significantly less capital than was originally hoped; more often than not less than half of what was originally sought. The decision to go public and the eventual completion of an IPO is a complex process that is ultimately determined by parties whose interests may not necessarily be aligned.

This panel will explore how this process evolves to become a reality from the perspectives of venture capitalists, senior management, investment bankers, and institutional fund managers.

12:00 - 1:00 **Networking Lunch**

1:00 - 3:15 **Company Presentations**
Moderator 1: Gert Caspritz, General Partner, Techno Venture Management
Moderator 2: Thomas Murphy, Vice President, Life Sciences, Solomon-Page Group LLC

Stream 1	Stream 2
1:00-1:14 Napa BioSciences, Inc.	1:00-1:14 Proacta Inc.
1:15-1:29 Light Sciences Oncology	1:15-1:29 KAI Pharmaceuticals Inc.
1:30-1:44 CyDex, Inc.	1:30-1:44 Trinity Biosystems, Inc.
1:45-1:59 LigoCyte Pharmaceuticals, Inc.	1:45-1:59 Cylene Pharmaceuticals Inc.
2:00-2:14 Chimerix, Inc.	2:00-2:14 Trellis Bioscience, Inc.
2:15-2:29 PolyMedix Inc.	2:15-2:29 Rejuvenon
2:30-2:44 Catalyst Biosciences	2:30-2:44 Sidec Technologies AB
2:45-2:59 Xencor, Inc.	2:45-2:59 Sciona, Inc.
3:00-3:14 Alantos Pharmaceuticals	3:00-3:14 GENETIX Pharmaceuticals, Inc

3:15 - 4:00 **Presenting Companies Tabletop Meetings**
Coffee & Tea Service

4:00 - 5:00 **Trends and Issues Session 1:**
The New War for Talent – Lessons from the Frontline

Chair: Richard Eidinger, Senior Partner & Managing Partner Global Life Sciences Practice, Heidrick & Struggles

Speakers: Frederick Baron, Chair, Employment & Labor Practice, Cooley Godward LLP
Roy Wilson, Executive Vice President Human Resources, Allergan Inc.
Richard Chin, Senior Vice President, Global Medical Affairs, Élan

The competition to identify, attract and retain the best talent has become even more intense. An aging population of workers with increasing risk aversion and longevity face employers with changing skill requirements in a global market. On both sides of the equation change and disruption have become the rule. Our panel will discuss specific cases that illustrate the impact of these issues and offer practical advice in dealing with them. Participants in the session will leave with important insights for building and preserving the human capital of their business.

4:00 - 5:00 **Trends and Issues Session 2:**
The Cost of Clinical Trials

Chair: Nicola Campbell, Partner, Sofinnova Ventures

Speakers: Albert Cha, Managing Partner, Vivo Ventures
Rodney Ferguson, Managing Director, JPMorgan Partners
James Adair, Associate Director, Genentech, Inc.
Arthur Pappas, Managing General Partner, A.M. Pappas & Associates, LLC

- What is the true cost of conducting a clinical trial? This is an age-old question that is asked by VCs and company executives alike. In this session, a panel comprised of VCs focusing on clinical products and executives running these companies will discuss the true cost per patient of clinical trials. Topics that the panel will discuss include:
- What is the true fully-burdened cost per patient? This is the actual cost to run the company for the period of time to get the clinical trial results and raise your next round of capital.
- What is the difference in cost between a virtual company (i.e. less than 20 FTEs) and a non-virtual company (i.e. 50 or 60 FTEs)? If you are starting a new clinical product company, is it better to run it one way or the other?
- What is the impact of US company geography on clinical trial costs? Are there reliable ex-US ways to get clinical trials done more cost effectively? Which other nations are excelling in clinical trials? What is the FDA response to trials done in these countries?
- What is the impact of clinical indication on company costs? Will you get clinical data "cheaper" in an oncology trial or a neurology trial? Or is it all the same? What clinical indications are the most attractive?

7:00 - 7:30 **Bus Shuttles to Dinner**

7:00 - 9:00 **Dinner at the Monterey Bay Aquarium**

Thursday, May 26

8:00 - 8:30 **Continental Breakfast**
Sponsored by Solomon-Page Group

8:30 - 9:30 **Trends and Issues Session 3:**
Filling the pipeline: who's going to pay for it?

Chair: Giovanni Ferrara, Managing Director, Burrill & Company

Speakers: Michael Ross, General Partner, SV Life Sciences
Paul Grayson, Managing Director, Sanderling Ventures
Ralph (Chris) Christoffersen, General Partner, Morgenthaler Ventures
Fran Heller, Head, Strategic Alliances, Novartis
Alfred Brown, President, BCM Technologies, Inc.

There has been a flight to investing in products since the genomic bubble burst, with the expectation that higher returns could be earned from developing drugs rather than merely assisting the pharma industry to develop them. Some of these compounds are niche products licensed from pharma, while others are the long awaited fruits from platforms that promised to deliver a pipeline of drug candidates available for licensing. This panel will explore the issues of licensing to and from pharma, retreading compounds versus innovation from drug discovery, and who will fund early stage efforts.

8:30 - 9:30 **Trends and Issues Session 4:**
The Resurgence of Medtech Investing and M&A Activity; Here To Stay or Gone Tomorrow?

Chair: William Kridel, Jr., Managing Director, Ferghana Partners Group

Speakers: Henry Tung, Corporate Vice President Global Surgical, Bausch & Lomb
John Brooks, General Partner, Prism Venture Partners
Nathan Every, Partner, Frazier Healthcare Ventures

Although it has traditionally been overshadowed by the biotech investing sector, medtech has undergone a resurgence with renewed interest from venture capitalists and corporate acquirers. The panel will examine the recent change in the climate for medtech investing, acquisitions and strategic partnerships, and will debate the reasons for this renaissance and the prospects for its sustainability.

9:30 - 9:45 **Coffee & Tea Service**

9:45 - 11:45 **Company Presentations**
Moderator 1: Stephen Richardson, Vice President, Alexandria Real Estate Equities, Inc.
Moderator 2: Victor Kleinman Executive VP, Managing Director, Solomon-Page Group LLC

Stream 1	Stream 2
9:45-9:59 Nuevolution A/S	9:45-9:59 Nerites Corporation
10:00-10:14 Sirtris Pharmaceuticals, Inc.	10:00-10:14 Ambit Biosciences

10:15-10:29 PLx Pharma Inc.	10:15-10:29 Rx3 Pharmaceuticals, Inc.
10:30-10:44 Avera Pharmaceuticals Inc.	10:30-10:44 Braincells, Inc.
10:45-10:59 EGeen International	10:45-10:59 TheraPei Pharmaceuticals
11:00-11:14 ICHOR Medical Systems	11:00-11:14 Ilypsa, Inc.
11:15-11:29 MaxCyte, Inc.	11:15-11:29 Phenomix Corporation
11:30-11:44 Amphora Discovery Corporation	11:30-11:44 Prolexys Pharmaceuticals, Inc.

11:45 - 12:30 **Presenting Company Tabletop Meeting**
Coffee & Tea Service

12:30 - 1:30 **Networking Lunch**

1:30 - 3:00 **Company Presentations**
Moderator 1: Richard Eidinger, Senior Partner & Managing Partner Global Life Sciences Practice, Heidrick & Struggles
Moderator 2: Nancy Saucier, Director, Medical Industry Group, National Venture Capital Association (NVCA)

Stream 1	Stream 2
1:30-1:44 immatics	1:30-1:44 GlobeImmune, Inc.
1:45-1:59 St. Charles Pharmaceuticals	1:45-1:59 BioRexis Pharmaceutical Corporation
2:00-2:14 Avidia	2:00-2:14 NOXXON Pharma AG
2:15-2:29 Novasite Pharmaceuticals	2:15-2:29 GangaGen Inc.
2:30-2:44 G Surge Medical Solutions, Inc.	2:30-2:44 XDx
2:45-2:59 TargeGen, Inc.	2:45-2:59 Afecta Pharmaceuticals

3:00 - 3:45 **Presenting Company Tabletop Meetings**
Coffee & Tea Service

3:45 - 5:00 **BioVenture Leadership Session 3**
Post Prop 71 - Commercializing Stem Cell Research in California - New Investment Opportunities.

Chair: Lutz Giebel, Venture Partner, SV Life Sciences

Speakers: Zach Hall, Interim President, California Institute for Regenerative Medicine
Peter McWilliams, Principal, Sanderling Ventures
Allan Robins, Vice President & Chief Technical Officer, Novocell
Charles Hsu, Venture Partner, A.M. Pappas & Associates, LLC

The passage of Proposition 71 by California voters in November 2004, creates a new framework for the expansion of stem cell research. A panel of experts will discuss the opportunities that may become available to scientists, bioscience companies, and investors in California in the coming years.

5:00 **Closing Drinks**

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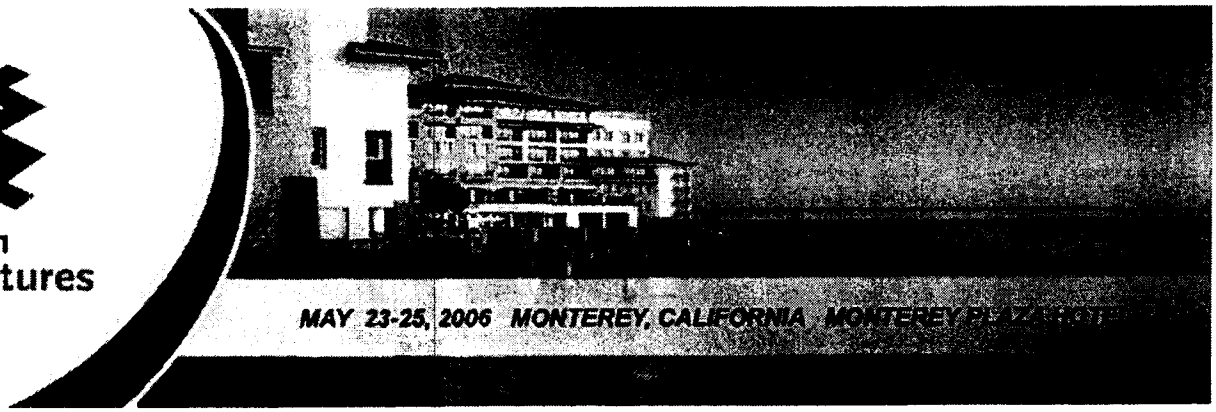

ABOUT C21 BIOVENTURES

Technology Vision Group LLC and **Burrill & Company** continue their partnership to bring together venture-stage life science companies and the investment community. The companies will co-produce the 8th Annual C21 BioVentures conference in Monterey, California May 23-25, 2006. This unique collaboration brings together two of the world's leading life science business groups.

"With the multiplicity of venues sprouting up for showcasing life science venture deals, this combined venue will clearly be the dominant venture deal meeting – a can't miss event for both companies and investors," said G. Steven Burrill, CEO of Burrill & Company a San Francisco-based life sciences merchant bank.

Dr. Robert Lee Kilpatrick, Partner at Technology Vision Group LLC says, "We are pleased to be working closely with Burrill & Company on this important strategic initiative. The synergies between our two groups are strong, and as experienced life science specialists, we offer services that are unique. There is no doubt that we have exceptional access to highly placed life science executives/companies and professional investors, and this will benefit our clients and portfolio companies around the world. We are pleased to be working closely with Steve and his team."

C21 is Shorthand for the Twenty-first Century

The mission of the 8th Annual C21 BioVentures (C21) conference is to educate all stakeholders in the bioscience industry about the trends that are driving its growth and development in the 21st century. The conference was first held in 1999 in California's Napa Valley as a meeting place to explore the future of bioventure investing. Since then, it has evolved into an annual retreat for leading technology gurus, investors and company executives to meet informally to exchange ideas and to review the business plans of innovative new companies in the fields of biotechnology, informatics, medical devices and healthcare services. In previous years, many of the presenting companies were successful IPO candidates.

Retreat for Two Days

Each year we meet in a California resort setting: Silverado Country Club, Napa (1999); Four Seasons, Santa Barbara (2000); Seascape Resort, Monterey Bay (2001); Four Seasons Aviara, San Diego (2002); Monterey Plaza Hotel and Spa (2003); Paradise Point, San Diego (2004); Monterey Plaza Hotel and Spa (2005). In 2006, C21 will take place at the Monterey Plaza Hotel and Spa in Monterey.

Register

Producers

Technology Vision Group LLC

Burrill & Company
A Life Sciences Merchant Bank

Hosts

BAYBIO

NVCA
National Venture Capital Association

"Surprised by the high quality of participants; extremely useful contacts made in the VC community."

- O. Lieberman
Proteologics

Learn About the Future of BioVentures

Education is at the heart of C21, and all delegates will participate in an issue-driven environment that facilitates a better understanding of new investment opportunities being created in bioscience through the application of novel technologies. What distinguishes C21 is that delegates are immersed in an environment which encourages discussion between scientists, venture capitalists, academics, investment bankers, bioscience company executives, and other important groups of innovative thinkers and actors. At C21 delegates will meet many of the people who are creating the 21st century's most important new industry.

Regional Host

The 8th Annual C21 BioVentures conference is hosted by BayBio, a public-private partnership and forum organized to strengthen the competitiveness of northern California as the premier global location for bioscience research, education, and industry. Leading bioscience, investment, and service firms join a regional host committee to advise on conference development issues, and stimulate greater participation from universities, entrepreneurs, institutional investors, and thought leaders in this dynamic sector. According to Matt Gardner, President of BayBio, "C21 is the type of event that goes beyond service to our members and our local community – it is an event that highlights the role Northern California plays as a gathering point in the global life science industry. C21 is an outstanding opportunity to foster greater growth and investment among life science companies."

Producers

Technology Vision Group LLC is a life sciences business development company focused on life science partnering and investing. Since 1992, we have been at the forefront of life science business innovation with clients in nearly 40 countries. We are located near Santa Cruz, California on Monterey Bay. Technology Vision Group LLC's highly respected web-enabled BioPartnering and C21 BioVentures conferences have helped bioscience companies worldwide to find partners and investors. Dates for forthcoming events are: 4th Annual BioPartnering North America (Vancouver, B.C., February 5-7, 2006), 8th C21 BioVentures (Monterey, California, May 23-25, 2006), 14th Annual BioPartnering Europe (London, UK, October 8-10, 2006). Our evolutionary internet product - biopartnering.com - showcases the companies and the people driving global bioscience business development in Europe, North America, Asia-Pacific and the rest of the world.

Burrill & Company is a San Francisco-based global leader in life sciences with principal activities in Venture Capital, Merchant Banking and Media. Founded in 1994, the company was a logical extension of G. Steven Burrill's over-37-year involvement in the growth and prosperity of the biotechnology industry. Mr. Burrill's respected reputation has positioned the firm as a prominent and preeminent venture capital firm and an industry "icon" in the life sciences arena. Burrill & Company's Life Science Media Group focuses on the organization and hosting of life sciences conferences worldwide and the publication of a wide range of industry reports and newsletters. The flagship is Burrill's annual book on the "State of the Industry", which has been an important part of the biotech industry's view of itself over the last 19 years. Biotech 2005—Life Sciences: A Move Towards Predictability is the latest in the nearly 20-year series. Burrill is also the sponsor and facilitator of leading annual industry conferences (China Partnering Forums, January; CEO Partnering Summit, February; The Stem Cell Meeting, March; India Life Sciences Partnering Meeting, April; The China Life Sciences Meeting, April; The Japan Biotech Meeting, September; The

Biotech Meeting at Laguna Niguel, October; The Personalized Medicine Meeting, October; The Midwest Life Sciences Meeting, November; The Indiana Life Sciences Forum, November; The Health & Wellness Meeting, November and the C21 BioVentures Meeting).

Program Highlights

• Presenting Companies – podium presentations will be offered by innovative lifescience companies.
• Tabletop Networking – an opportunity for all presenting companies to meet informally with delegates following their podium presentations. Refreshments are available through this session.
• "Trends and Issues" Sessions – by leading thinkers, and entrepreneurs discussing many of the most exciting trends and topical issues shaping the growth and development of the global bioscience industry.
• biopartnering.com - A unique and powerful internet tool, biopartnering.com, allows the proactive delegate to prepare for the conference long before arriving. Delegates are able to access the password protected area of the site to research investment opportunities through keyword searches of detailed profiles on all companies, contact other delegates, and stay informed of additions to the program. New features this year include a personal profile and photo for each delegate, and enhanced company profile features.

Conference Facility

The location of the Monterey Plaza Hotel and Spa, which is situated on Steinbeck's historic Cannery Row, is ideal for travel and provided easy access to the unique Monterey Bay. Within 100 miles of both the San Francisco and San Jose airports, this well appointed resort was the setting for a gathering of peers and new contacts in a relaxed "no ties allowed" atmosphere.

Audience

The audience is inclusive of all the stakeholders in the future growth and development of the global bioscience industry. Representatives from a broad spectrum include: senior executives from leading life science and IT companies, entrepreneurs, scientists, technology transfer experts, investment fund and asset managers, investment and commercial bankers, corporate finance specialists, equity analysts, venture capitalists, high net worth private investors, representatives of stock exchanges, regional bioscience associations, and government officials working in the area of technology and industrial development. In addition, a limited number of representatives from leading service providers and the media will also attend.

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BIOHOUSTON

BUILDING THE LIFE SCIENCE FUTURE

2005 Texas Life Science Conference

November 2 - 4, 2005

CONFERENCE AGENDA

The Houstonian Hotel, Club & Spa
Houston, TX

Underwritten By:

BCM TECHNOLOGIES

Wednesday

5:00 - 7:00pm: Registration / Conference Check-in

5:45 - 7:00pm: Welcome Reception / Networking Session

Thursday

7:00 - 8:15am: Registration / Continental Breakfast

8:15am: Opening Remarks

8:25 - 8:45am:
Opening Keynote Speaker: Commercialization of Academic Life Science Discoveries
• Peter G. Traber, M.D., President & CEO, Baylor College of Medicine

8:45 - 10:15am:
The Great Debate: Does Preclinical Biopharm Investing Make Sense...and Dollars?

• Arthur J. Klausner, Partner – A. M. Pappas & Associates – Pro (pictured left)
• Jim Schoeneck, CEO – BrainCells, Inc. - Pro
• Robert J. More, Partner – Domain Associates LLC – Con (pictured right)

• Randall E. Woods, President & CEO – NovaCardia, Inc. - Con

10:15 - 10:30am: Networking Break

10:30 - 12:00pm:
Creative Financing: The Rebirth of Clinical Partnerships and Other Non-Dilutive Financing Strategies
• Michael Ross, Ph.D., General Partner – SV Life Sciences
• Andrew L. Busser, Principal - Symphony Capital LLC
• Jonathan P. Gertler, M.D., Managing Director, Head of Healthcare Investment Banking – Adams Harkness, Inc.
• Jim R. Webster, Managing Partner – Capital Royalty L.P.

12:00 - 1:30pm: Lunch
Presentation of the BioHouston Life Science Award to Tanox, Inc.

1:30 - 3:00pm:
Personalized Medicine
• Seth A. Rudnick, M.D., General Partner – Canaan Partners
• John A. Ryals, Ph.D., President & CEO – Metabolon Inc.
• Charles P.R. de C. du Mée, Ph.D., Co-Founder, Vice President, Development Director – Nascent Pharmaceuticals, Inc.,
• Kevin Slawin, M.D., President & CEO, -Oncovance
• Krishnan Nandabalan, Ph.D., President – BioXcel Corporation
• Arthur L. Beaudet, M.D., Chairman, Molecular and Human Genetics – Baylor College of Medicine

3:30 - 5:00pm:
New Anti-Infective Strategies
• John S. Swartley, Ph.D., Senior Vice President – BCM Technologies, Inc.
• B. J. Bormann, Ph.D., Vice President Strategic Alliances - Pfizer Global Research & Development
• Kevin L. Eastwood, Senior VP of Business Development – Achillion Pharmaceuticals
• Mimi Healy, Ph.D., CEO – Bacterial Barcodes, Inc.
• William Weiss, Director of Drug Evaluation – Cumbre Inc.

6:00pm: ***Venture Dinner***
River Oaks Country Club
1600 River Oaks Blvd.
Houston, Texas 77019

Friday

7:00 - 8:30am: Continental Breakfast

8:20am: Welcome

8:30 - 10:00am:
The Climate in Biotech Investing
• Christopher W. Kersey, M.D., Managing Director – Cogene Ventures

• Charles Baltic, Managing Director, Healthcare Investment Banking – Wachovia Securities
• Quynh Pham, Vice President, Equity Research – Delafield & Hambrecht
• Maria P. Sendra, Partner – Baker & McKenzie
• Lyle A. Hohnke, Ph.D., General Partner – Tullis Dickerson & Co., Inc.
• William D. Paiva, Ph.D., Partner – Chisholm Private Capital Partners
• Robert D. "Bob" Ulrich, Ph.D., General Partner – Vanguard Ventures

10:00 - 10:30am: Networking Break

10:30 - 12:00pm:
Aesthetic Medicine
• Evan S. Melrose, M.D., Partner – PTV Sciences, L.P.

• Spencer A. Brown, Ph.D., Director of Research of the Plastic Surgery Department – The University of Texas Southwestern Medical Center
• Steven L. Basta, President & CEO – Bioform Medical, Inc.
• Matthew A. Megaro, President & CEO – Quill Medical, Inc.
• Dennis E. Condon, President & CEO – Reliant Technologies, Inc.

12:00pm: Lunch - Picnic in the Meadow

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BUILDING THE LIFE SCIENCE FUTURE

BIOHOUSTON

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About Us

- Management Team
  - Management Team--Staff
- Board of Directors
  - Executive Committee
  - Board of Directors
- Activities
- BioHouston Office
- Home

BioHouston, Inc., a non-profit, tax-exempt [§501(c)(3)] corporation, was founded by Houston-region academic/research institutions, and is governed by its Board of Directors. We are leading a broad effort to establish the Houston region as a vigorous global competitor in life science and biotechnology commercialization.

Our mission is to create an environment that will stimulate technology transfer and research commercialization, thereby generating economic wealth for the Houston region and making it a global competitor in life science commercialization.

BioHouston's activities provide the greatest leverage in making the Houston region a world-class competitor in the life science industry. All of our activities are designed to:

- CONVENE people and organizations that need to come together to make the life science industry in Houston ignite, including scientists, intellectual property and product development experts, venture capitalists, pharmaceutical companies, and others

- COMMUNICATE and interact so that people and organizations can learn from one another, share information and explore opportunities

- CATALYZE the discoveries and commercial development so that the true potential of the life science industry in Houston can be unlocked

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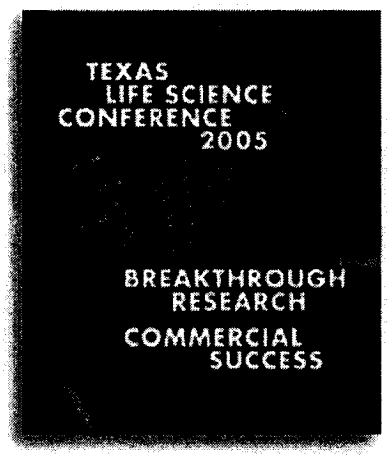
BUILDING THE LIFE SCIENCE FUTURE

BIOHOUSTON

BUILDING THE LIFE SCIENCE FUTURE

2005 Texas Life Science Conference

- Calendar
- Programs
- Events
- Home



Experience the frontier for biotechnology at the **2005 Texas Life Science Conference.** BioHouston's annual national venture capital conference, will take place on **November 2 – 4 at The Houstonian Hotel, Club and Spa.** This conference brings together the industry's leading venture capitalists, researchers and emerging companies from across the country representing some of the most revolutionary developments in the life sciences.

CONFERENCE AGENDA

BioHouston will also present its Life Science Award during the luncheon on November 3rd. If you are unable to attend the entire conference, please be sure to mark you calendar for Award luncheon. It's a terrific way to show your support of the local life science community.

REGISTER NOW

2004 Texas Life Science Conference Hits Mark in Bringing National Attention to Houston Region

The 2004 Texas Life Science Conference was held November 15-17 in Houston, drawing much praise from attendees and participants alike.

Designed in part to draw national awareness, the conference was a first step in a long-term process of building relationships between national VCs and the local life science community. The conference attracted more than 350 attendees, of which more than 100 were venture capitalists, half from non-Houston locations.

"Part of our objective for the conference is to attract the attention of the national venture capitalists," says BioHouston President & CEO, Jacqueline Northcut Waugh. "With this conference, we've made great strides in giving them a glimpse of what's happening in this region, from the caliber of VCs we have here to the promising research and viability of our life science companies. From our point of view, the conference was a great vehicle for attracting that national attention, which we'll build on in the years to come."

Citing networking opportunities, in-depth discussions focused on highly-promising investment areas, and strength of presenters, one member of the BioHouston Events Committee summarized the conference as hitting the mark related to

BioHouston's mission and the strategy defined for the conference.

"BioHouston's mission is basically to create an environment that stimulates technology transfer and research commercialization," said Daniel J. Monticello, Ph.D., President, Molecular LogiX, Inc. "This conference really was about focusing on the needs of three groups – national VCs, Houston region life science companies and conference sponsors. The feedback we've received is that all three groups hold this year's event in high regard."

Comments received from national VCs indicate that a positive impression was formed of the region, with one attendee stating "I didn't know so much was going on in Texas". Members of the Houston life science community cited outstanding networking opportunities with VCs, investment bankers and others, as proof positive that the conference was a success.

"Many attendees commented that this conference was on par with the best of the national venture capital conferences," adds Jacqueline. "We thank our conference underwriter, BCM Technologies, Inc. and its President, Alfred (Buz) E. Brown, Ph.D., who serves as the conference program chair, for their role in building the Houston life science future."

Arthur T. Sands, M.D., Ph.D. Receives First BioHouston Life Science Award

BioHouston is proud to announce Arthur T. Sands, M.D., Ph.D., as the recipient of its first annual BioHouston Life Science Award. John Mendelsohn, M.D., President of The University of Texas M.D. Anderson Cancer Center, presented the award to Dr. Sands during the recent 2004 Texas Life Science Conference held in Houston, in recognition of his role in building the life science future.

In his remarks, Dr. Mendelsohn noted that the BioHouston Life Science Award was created to recognize individuals in the Houston area who embody the aspects of vision, insight, persistence and hard work required to make that leap from breakthrough research to commercial success.

Specifically, criteria for the 2004 award were defined to recognize an individual who:
•has had a recent and significant impact on the industry
•has made a major contribution to the advancement of emerging technologies for the benefit of business and society
•has demonstrated vision, hard work and creativity; and
•whose accomplishments exemplify the value of investing in early stage technologies and companies.

In selecting Dr. Sands for the award, Dan Monticello, Ph.D., chair of the 2004 BioHouston Life Science Award cited Dr. Sands' work at Baylor College of Medicine and his contributions to the Houston life science community as founder, President and CEO of Lexicon Genetics.

"Dr. Sands recognized the scientific importance of gene knockout technology, pioneered an efficient process to industrialize the technology, and designed a business model that has revolutionized the way that new drugs are discovered today. The Houston life science community is privileged to count Dr. Sands and Lexicon Genetics among its greatest successes.

"Equally, it is our sincerest desire that through the annual BioHouston Life Science Award, we increase awareness of not only the multitude of successes in the region, but also the many opportunities that exist here."

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BUILDING THE LIFE SCIENCE FUTURE

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Conferences

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  - Agenda
  - Attending CEOs
- PERSONALIZED MEDIC
- THE MIDWEST LIFE SC MEETING
- THE INDIANA LIFE SCIE FORUM
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Save the Date

The Biotech Meeting at Laguna Niguel will be held October 9-11, 2005 at The Ritz-Carlton Hotel, Laguna Niguel

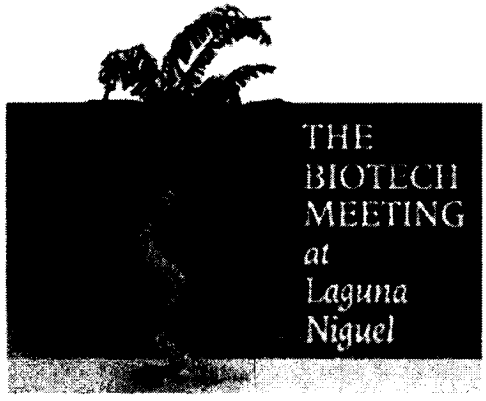
Who:
Chief Executive Officers of Biotechnology Companies

What:
The 18th Annual Biotech Meeting at Laguna Niguel

When:
October 9-11, 2005

Where:
The Ritz-Carlton Hotel
One Ritz-Carlton Drive
Dana Point, CA 92629
Phone: (949) 240-2000

Registration:
This is an invitation only event. For further information, please contact events@b-c.com.



The Biotech Meeting at Laguna Niguel is the premier industry conference exclusively for CEOs of biotechnology companies. Sponsored by Burrill & Company and Kleiner Perkins Caufield and Byers, the Biotech Meeting (now in its 18th year) is held annually at The Ritz-Carlton Hotel in Laguna Niguel (Southern California). Each October, over 200 biotech CEOs gather and share management ideas, set an agenda for the industry and network with each other. Although the program hosts a serious agenda, there is time for fun and networking. Spouses are encouraged to attend.

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Attending CEOs — In 2004

- Mark Vaeck — Ablynx NV
- Uli Hacksell — Acadia Pharmaceuticals, Inc.
- Glenn Batchelder — Acceleron Pharma, Inc.
- Thomas Klopack — ACLARA BioSciences, Inc.
- Sherri Oberg — Acusphere
- Bruce Peacock — Adolor Corporation
- Arlene Morris — Affymax, Inc.
- Stephen Fodor — Affymetrix, Inc.
- Thomas King — Alexza Molecular Delivery Corporation
- David Pyott — Allergan, Inc.
- Duane Roth — Alliance Pharmaceutical Corporation
- Michael Hart — Allos Therapeutics, Inc.
- John Maraganore — Alnylam Pharmaceuticals
- Peter Lanciano — Altus Pharmaceuticals
- Kevin Sharer — Amgen, Inc.
- Martin Haslanger — Amphora Discovery Corporation
- Kleanthis Xanthopoulos — Anadys Pharmaceuticals, Inc.
- Ei Yamada — AnGes
- V. Bryan Lawlis — Aradigm Corporation
- Jack Lief — Arena Pharmaceuticals
- John Hamer — Arete Pharmaceuticals
- Lissa Goldenstein — Argonaut Technologies, Inc.
- Harvey Berger — ARIAD Pharmaceuticals, Inc.
- Robert Williamson — Arriva Pharmaceuticals, Inc.
- Richard Glickman — Aspreva Pharmaceuticals
- Russell Medford — AtheroGenics, Inc.
- Gil Van Bokkelen — Athersys, Inc.
- Una Ryan — AVANT Immunotherapeutics, Inc.
- Peter Breining — BAS Medical, Inc.
- Mark Schwartz — Bayhill Therapeutics, Inc.
- Charles Bugg — BioCryst Pharmaceuticals, Inc.
- Jean-Pierre Sommadossi — Idenix Pharmaceuticals, Inc.
- Steven Mento — IDUN Pharmaceuticals
- Manfred Ruediger — Igeneon
- Jay Flatley — Illumina, Inc.
- Jean-Loup Romet-Lemonne — Immuno-Designed Moelcules (IDM)
- Mitchel Sayare — ImmunoGen, Inc.
- Tsvi Goldenberg — Immusol, Inc.
- William Johnston — Inhibitex, Inc.
- Jeffrey Bacha — Inimex Pharmaceuticals Inc.
- Daniel Welch — InterMune, Inc.
- Gregory Lucier — Invitrogen Corporation
- Vince Anido — ISTA Pharmaceuticals
- Jens Schneider-Mergener — Jerini AG
- Frank Striggow — keyNeurotek AG
- Steven Engle — La Jolla Pharmaceutical Company
- David Robinson — Ligand Pharmaceuticals, Inc.
- Albert Luderer — Light Sciences Corporation
- Joseph Reiser — Locus Pharmaceuticals
- Partrick Balthrop — Luminex Corporation
- Douglas Doerfler — MaxCyte Inc.
- Larry Stambaugh — Maxim Pharmaceuticals
- Russell Howard — Maxygen, Inc.
- Peter Heinrich — Medigene, Inc.
- David Mott — MedImmune, Inc.
- Frederick Dechow — Mediquest Therapeutics Inc.
- Robert Mulroy — Merrimack Pharmaceuticals
- Paul Laikind — Metabasis Therapeutics
- Harold Van Wart — Metabolex, Inc.
- Reed Prior — MicroCHIPS, Inc.
- Simon Moroney — MorphoSys AG
- Hugh Martin — Nanofluidics, Inc.
- Lisa Conte — Napo Pharmaceuticals, Inc.
- Boyd Clarke — Neose Technologies, Inc.
- Paul Freiman — Neurobiological Technologies, Inc.
- Christopher Gallen — NeuroMed

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- David Hale — CancerVax Corporation
- Lloyd Segal — Caprion Pharmaceuticals Inc.
- David Levison — Cardio Dx
- Carlton Turner — Carrington Laboratories, Inc.
- John Jackson — Celgene Corporation
- Stephen Sherwin — Cell Genesys
- K. Michael Forrest — Cellegy Pharmaceuticals, Inc.
- Bruce Cohen — Cellerant Therapeutics, Inc.
- Edward Schnipper — CellGate, Inc.
- Goran Ando — Celltech UCB Pharma
- J. Gordon Foulkes — Cengent Therapeutics, Inc.
- Frank Baldino Jr. — Cephalon, Inc.
- Paul Abrams — CEPTYR, Inc.
- Richard Hamilton — Ceres, Inc.
- Eugene Vaisberg — ChemBridge Research Laboratories, Inc.
- Thomas Schall — ChemoCentryx, Inc.
- Guy Yachin — Chisma Inc.
- David Duncan — Chlorogen, Inc.
- Mich Hein — Chromatin, Inc.
- Bob Seeman — Clera Inc.
- Thomas Wiggans — Connetics Corporation
- Roberto Crea — CreAgri, Inc.
- Karl-Peter Schlichting — CropDesign N.V.
- Louis Lange — CV Therapeutics, Inc.
- John Siebert — CyDex, Inc.
- James Sabry — Cytokinetics, Inc.
- Steve Kriegsman — CytRx Corporation
- Mitchell Gold — Dendreon Corporation
- John Fara — DepoMed, Inc.
- Riccardo Pigliucci — Discovery Partners International
- Sergio Domp, — Domp, Biotec
- Massimo Radaelli — Dompe International SA
- James Brown — DURECT Corporation
- Mark Emalfarb — Dyadic International
- Mark Braman — Efficas
- Bernd Kastler — elbion AG
- Michael Goldberg — Emisphere Technologies, Inc.
- Ron Ellis — Endocyte
- Alexander Olek — Epigenomics GmbH
- Michael Webb — EPIX Medical, Inc.
- Kathleen Mullinex — EviNu Corporation
- Don Hardison — EXACT Sciences Corporation
- George Scangos — Exelixis, Inc.
- Jonathan Thatcher — Exeter Life Sciences Technologies Inc.
- Randy Woods — NovaCardia, Inc.
- Brad Goodwin — Novacea
- Robert Towarnicki — Nucleonics Inc.
- Orn Adalsteinsson — Nucycle
- Ted Love — Nuvelo
- Marnie MacDonald — Odyssey Thera, Inc.
- Hollings Renton — Onyx Pharmaceuticals, Inc.
- Geoff MacKay — Organogenesis, Inc.
- Colin Goddard — OSI Pharmaceuticals, Inc.
- Carl Spana — Palatin Technologies, Inc.
- Michael Aldridge — Peplin Biotech
- Leslie Browne — Pharmacopeia
- Schaefer Price — Pharmasset, Inc.
- Bertold Fridlender — Phytomedics, Inc.
- Michael Kauffman — Predix Pharmaceuticals, Inc.
- Joseph Limber — Prometheus Laboratories Inc.
- Mark McDade — Protein Design Labs, Inc.
- Daniel Adams — Protein Sciences Corporation
- Andrew Heath — Protherics PLC
- Brendan Fox — Pyxis Genomics
- Paul Hastings — QLT, Inc.
- Leonard Schleifer — Regeneron Pharmaceuticals, Inc.
- Ernest Mario — Reliant Pharmaceuticals, Inc.
- Kenneth Collins — Replidyne, Inc.
- Walter Herlihy — Repligen Corporation
- Thomas Tillett — RHeoGene LLC
- James Gower — Rigel Pharmaceuticals, Inc.
- Ronald Eastman — Rinat Neuroscience Corporation
- Rodney Pearlman — Saegis Pharmaceuticals, Inc.
- Ed Lanphier — Sangamo BioSciences, Inc.
- Gerald Proehl — Santarus, Inc.
- Christopher Clement — Savient Pharmaceuticals
- Christopher Martin — Sciona Ltd.
- Yves Ribeill — Scynexis
- Clay Siegall — Seattle Genetics, Inc.
- Randall Carpenter — Sention
- Toni Schuh — Sequenom, Inc.
- Douglas Gunthardt — Siegfried Ltd.
- Christoph Westphal — Sirtris
- Michael Ashton — SkyePharma plc
- Ken Cohen — Somaxon Pharmaceuticals Inc
- John Raff — Starpharma
- Martin McGlynn — StemCells, Inc.
- Daniel Korpolinski — StressGen Biotechnologies Corporation
- Timothy Harris — Structural GenomiX, Inc.
- Dan Swisher — Sunesis Pharmaceuticals, Inc.
- Garen Bohlin — Syntonix Pharmaceuticals, Inc.
- Nancy Chang — Tanox, Inc.
- Don deBethizy — Targacept, Inc.
- H. Stewart Parker — Targeted Genetics, Inc.

- Greg Simon — Fastercures/The Center for Acclerating Medical Solutions
- John Longenecker — Favrille, Inc.
- Gail Maderis — Five Prime Therapeutics
- Anthony Giovinazzo — GB Therapeutics Ltd.
- Dan Giampuzzi — Gemin X Biotechnologies
- Henry Nordhoff — Gen-Probe, Inc.
- Kevin Rakin — Genaissance Pharmaceuticals, Inc.
- Jean-Jacques Bienaim, — Genencor International, Inc.
- Bertrand Damour — GeneProt, Inc.
- Avtar Dhillon — Genetronics Biomedical Corporation
- Randy Scott — Genomic Health, Inc.
- Mitch Eggers — GenVault Corporation
- Henri Termeer — Genzyme Corporation
- Thomas Okarma — Geron Corporation
- John Martin — Gilead Sciences, Inc.
- Geoffrey Cox — GTC Biotherapeutics
- Craig Smith — Guilford Pharmaceuticals, Inc.
- Arthur Bollon — HemoBioTech
- William Haseltine — Human Genome Sciences, Inc.
- Matthew Gantz — Hydra Biosciences
- Jim Neal — Iconix Pharmaceuticals, Inc.
- Heinrich Gugger — Icoria
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- Michael Wick — Telik, Inc.
- John Scarlett — Tercica Medica, Inc.
- Rick Winningham — Theravance
- Mark Leuchtenberger — Therion Biologics
- Lance Fors — Third Wave Technologies, Inc.
- Louis Bucalo — Titan Pharmaceuticals, Inc.
- Paul Goldenheim — TransForm Pharmaceuticals, Inc.
- Michael Astrue — Transkaryotic Therapies, Inc.
- Vipin Garg — Tranzyme Pharmaceuticals
- Steve Skolsky — Trimeris, Inc.
- Mark Skaletsky — Trine Therapeutics
- Peter Thompson — Trubion Pharmaceuticals
- Ben McGraw — Valentis, Inc.
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- Pierre Cassigneul — XDx, Inc.
- Harry Stylli — Xencor
- Markus Ewert — Xerion Pharmaceuticals AG
- Cynthia Roney — Xillix Technologies Corporation
- Martin Becker — XTL Biopharmaceuticals Ltd.
- Bruce Carter — ZymoGenetics, Inc.

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TEXAS LIFE SCIENCE CONFERENCE 2005

BREAKTHROUGH RESEARCH
COMMERCIAL SUCCESS

2005 Texas Life Science Conference
November 2-4
The Houstonian Hotel, Club & Spa

Wednesday, November 2nd

5:00 – 7:00pm	Registration / Conference Check-in
5:45 – 7:30pm	Welcome Reception / Networking Session

Thursday, November 3rd

7:00 – 8:15am	Registration / Continental Breakfast
8:15am	Opening Remarks
8:25 - 8:45am	*Opening Keynote Speaker: Commercialization of Academic Life Science Discoveries*
	Peter G. Traber, M.D., President & CEO, Baylor College of Medicine
8:45 - 10:15am	*The Great Debate: Does Preclinical Biopharm Investing Make Sense...and Dollars?*
	Industry experts from both the venture capital and management side will contrast early-stage, preclinical investment strategies and outcomes versus later-stage investments in more mature development companies. A debate-style format promises a lively exchange of views.
	Arthur J. Klausner, Partner – A. M. Pappas & Associates – Pro
	James Schoeneck, CEO – BrainCells, Inc. – Pro
	Robert J. More, Partner – Domain Associates LLC – Con
	Randall E. Woods, President & CEO – NovaCardia, Inc. – Con
10:15 – 10:30am	Networking Break
10:30 – 12:00pm	*Creative Financing: The Rebirth of Clinical Partnerships and Other Non-Dilutive Financing Strategies*
	Several recent transactions may herald a comeback for special purpose entities, a once common way of raising cash for biotech drug development. Mike Ross and his panel will discuss pros and cons of this and other non-dilutive financial alternatives for today's biotech companies.
	Michael Ross, Ph.D., General Partner – SV Life Sciences
	Andrew L. Busser, Principal – Symphony Capital LLC
	Jonathan P. Gertler, M.D., Managing Director, Head of Healthcare Investment Banking – Adams Harkness, Inc.
	James R. Webster, Managing Partner – Capital Royalty L.P.
12:00 – 1:30pm	*Presentation of the BioHouston Life Science Award to Tanox, Inc.*

1:30 – 3:00pm *Personalized Medicine*

Genomic sequencing and molecular diagnostics herald a new era for pharmaceutical companies, physicians and patients – fact or fiction? This session will explore the use of molecular diagnostics and informatics to streamline preclinical studies, better select patients for clinical studies and improve market share of marketed products. Who uses them, how they are approved by regulatory agencies, who pays for them and how confidentiality is maintained, and last of all, is the market finally here?

Seth A. Rudnick, M.D., General Partner – Canaan Partners

John A. Ryals, Ph.D., President & CEO – Metabolon Inc.

Charles P.R. de C. du Mée, Ph.D., Co-Founder, Vice President, Development Director – Nascent Pharmaceuticals, Inc.,

Kevin Slawin, M.D., President & CEO – Oncovance

Krishnan Nandabalan, Ph.D., President – BioXcel Corporation

Arthur L. Beaudet, M.D., Chairman, Molecular and Human Genetics – Baylor College of Medicine

3:00 – 3:30pm Networking Break

3:30 – 5:00pm *New Anti-Infective Strategies*

Recent high-profile M&A activity in the anti-infectives arena suggests that Big Pharma has a renewed appetite for opportunities in this sector. The immediate need for new agents to treat dangerous bugs and the emergence of robust diagnostic technologies is a strong driver of demand. Representatives from several up-and-coming biotechs will showcase their products in development for the treatment, prevention and diagnosis of infectious diseases.

John S. Swartley, Ph.D., Vice President – BCM Technologies, Inc.

B.J. Bormann, Ph.D., Vice President Strategic Alliances – Pfizer Global Research & Development

Kevin L. Eastwood, Senior VP of Business Development – Achillion Pharmaceuticals

Mimi Healy, Ph.D., CEO – Bacterial Barcodes, Inc.

William Weiss, Director of Drug Evaluation – Cumbre Inc.

6:00pm *Venture Networking Dinner & Reception* – River Oaks Country Club

Friday, November 4th

7:00 – 8:30am Continental Breakfast

8:20am Welcome

8:30 – 10:00am *The Climate in Biotech Investing*

This investor panel will focus on recent financing trends in health care and life science venture capital. Themes include geographic concentration, technology convergence, early stage vs. late stage investing and exciting new areas of investment interest.

Christopher W. Kersey, M.D., Managing Director – Cogene Ventures

Charles Baltic, Managing Director, Healthcare Investment Banking – Wachovia Securities

Quynh Pham, Vice President, Equity Research – Delafield & Hambrecht

Maria P. Sendra, Partner – Baker & McKenzie

Lyle A. Hohnke, Ph.D., General Partner – Tullis Dickerson & Co., Inc.

William D. Paiva, Ph.D., Partner – Chisholm Private Capital Partners

Robert D. "Bob" Ulrich, Ph.D., General Partner – Vanguard Ventures

10:00 – 10:30am Networking Break

10:30 – 12:00pm ***Aesthetic Medicine***

The growth in aesthetic procedures has grown exponentially as the growing baby boomer demographic has demanded to look younger longer. New technology has allowed these procedures to be done with minimal downtime and immediate clinical benefit. This session will review the cutting edge medicine that is offering minimally invasive and non ablative treatments to combat aging appearances.

Evan S. Melrose, M.D., Partner – PTV Sciences, L.P.

Spencer A. Brown, Ph.D., Director of Research of the Plastic Surgery Department – UT Southwestern Medical Center

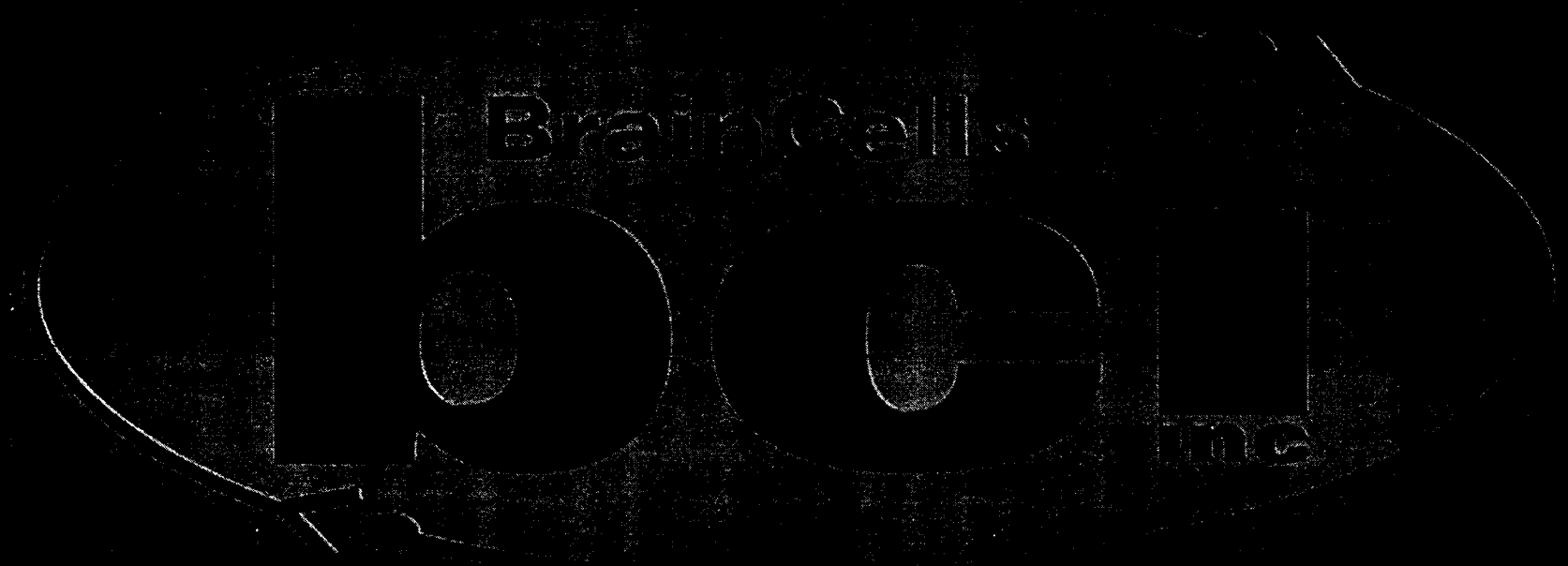
Steven L. Basta, President & CEO – Bioform Medical, Inc.

Matthew A. Megaro, President & CEO – Quill Medical, Inc.

Dennis E. Condon, President & CEO – Reliant Technologies, Inc.

12:00pm Closing Remarks dismissed for lunch

Picnic in the Meadow



www.braincellsinc.com

September 20, 2005

BRAINCELLS, INC. (BCI)

BCI is the leading neurogenesis-based drug discovery and development company.

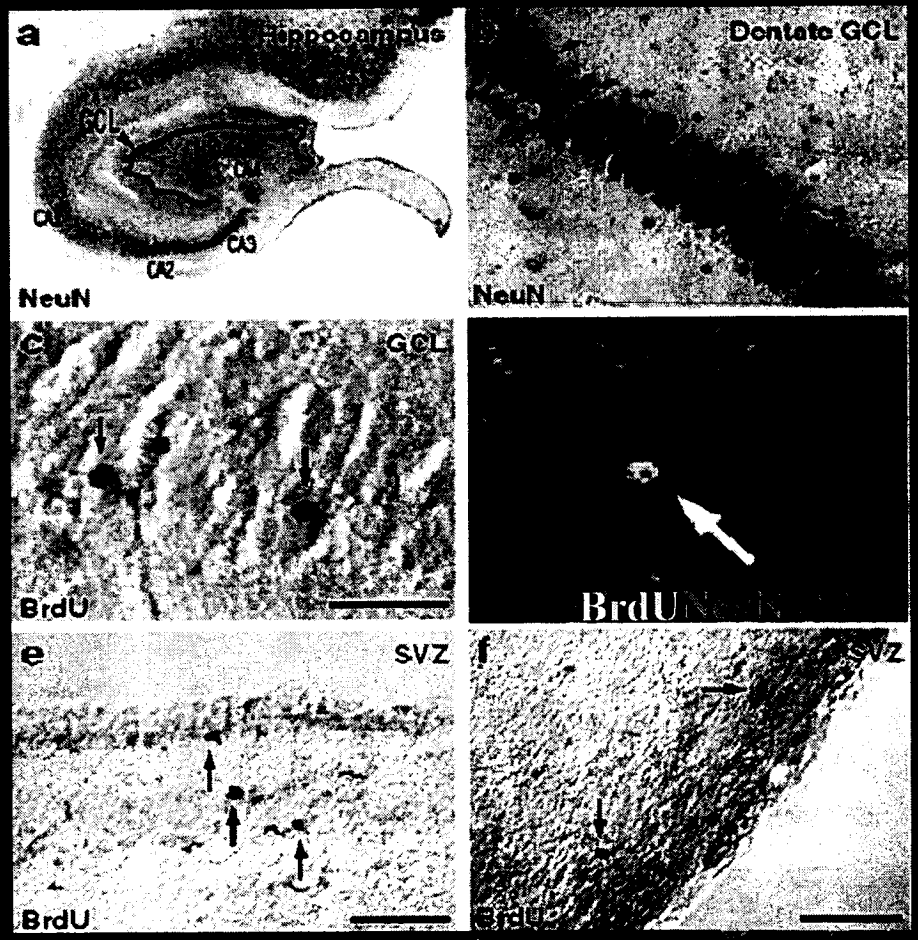
BCI is developing new therapies for depression, recovery from brain injury and other CNS diseases.

BCI Scientific Foundation

Seminal Discoveries

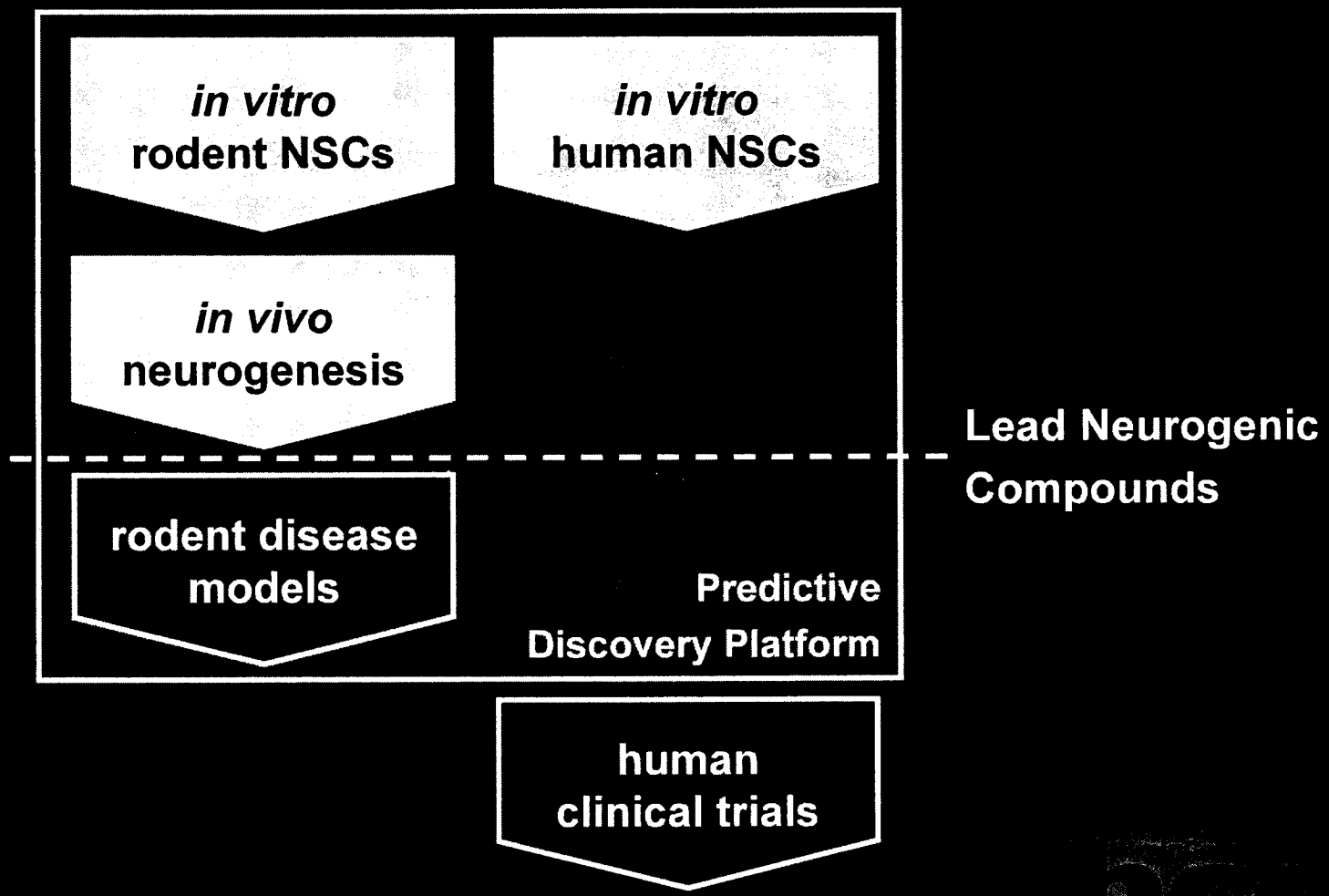
- **1998:** Gage lab discovers neurogenesis in adult human brain
- **1999:** Gage lab shows that neurogenesis can be regulated
- **2002:** Gage lab demonstrates <u>functional</u> neurogenesis in the adult hippocampus
- **2003:** Hen lab strengthens link between depression and neurogenesis

➢ **Neurogenesis has emerged as a fundamental process underlying CNS physiology and disease**



(Eriksson et al., Nat. Med 1998)

BCI Discovery Platform



Attrition by Therapeutic Area
From First-In-Man to Registration

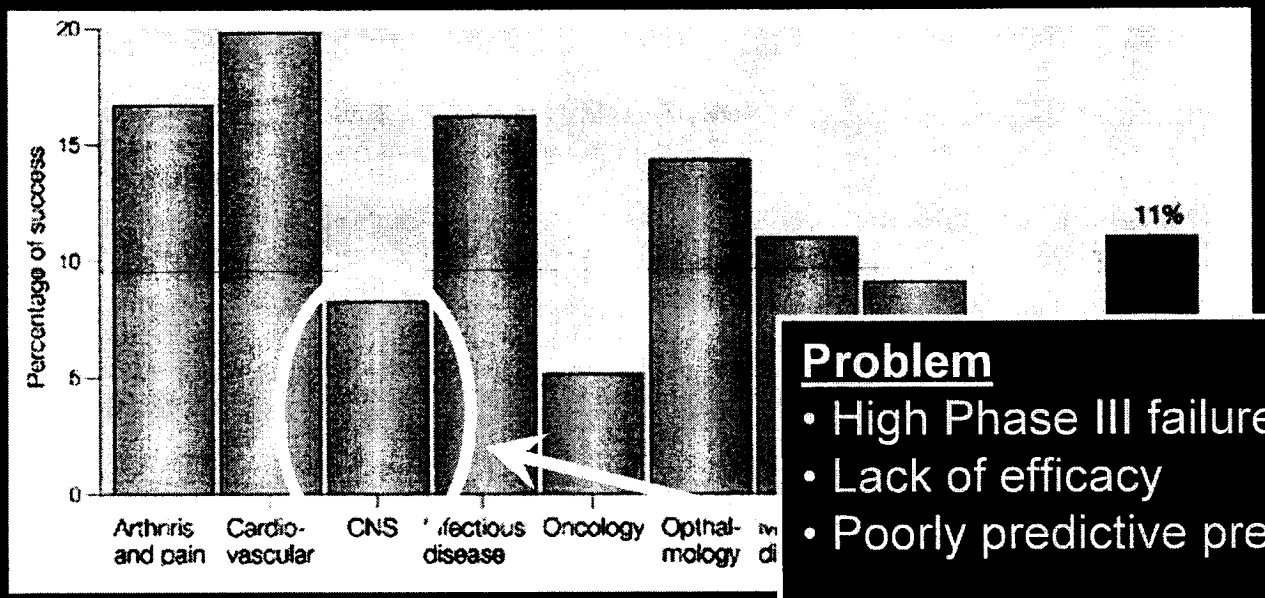
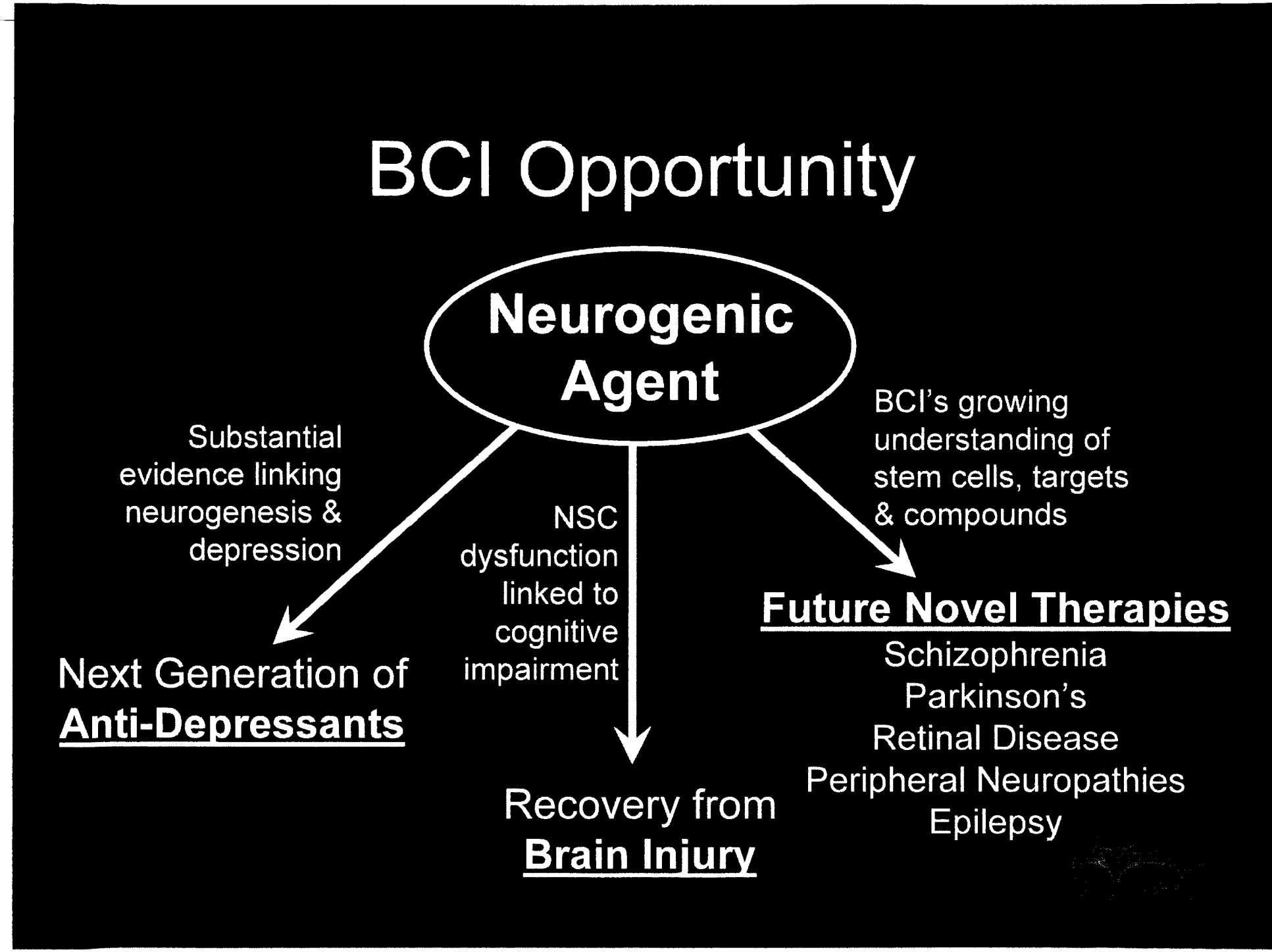


Figure: Kola & Landis, Nature Reviews: Dru
Data: DataMonitor "Pharmaceutical R&D

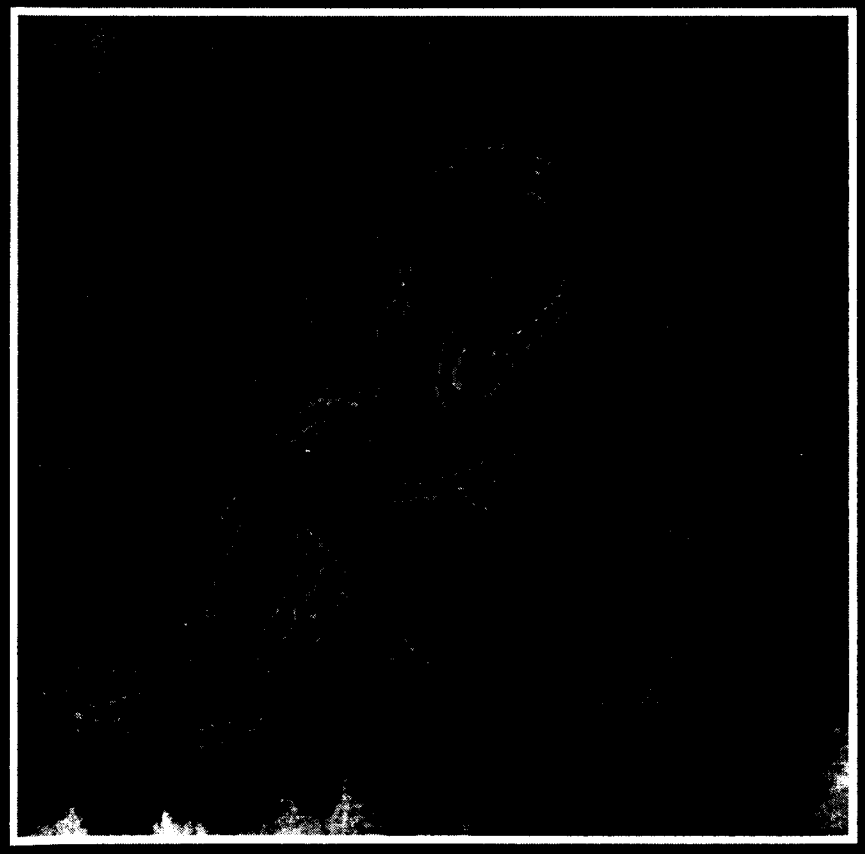
Problem
- High Phase III failure rate
- Lack of efficacy
- Poorly predictive pre-clinical models

BCI Solution
- Understand disease mechanism
- Physiology-relevant models
- Neurogenesis discovery platform

BCI Opportunity



BCI & Depression



- Neurogenesis enables
  - Prediction of efficacy
  - Re-positioning of in-licensed drugs
  - Optimization of dosing
  - Identification of new targets
  - Identification of active metabolites
- Market opportunity
  - Huge ($17B) market
  - Few new mechanisms
  - Partner Ph III & marketing

BCI Summary

- Founded in San Diego: Dec, 2003
- Operational: Sept, 2004
- Raised $17.7M in equity financing
- >10,000 sq. ft. lab, office & vivarium
- 14 full-time staff (17 by end-2005)
- Proprietary neurogenesis discovery platform established
- Novel neurogenic targets & compounds identified

Management Team

- James Schoeneck (ActivX, Prometheus, Centocor)
  - Chief Executive Officer
- Dr. Harry Hixson (Amgen, Neurocrine, Signal)
  - Chairman
- Dr. Edward Hodgkin (Tripos, Wyeth, British Biotech)
  - President & Chief Business Officer
- Dr. Carrolee Barlow (Merck, Salk Institute)
  - Vice President, Biology R&D

Investors & Advisors

Series A Investors

- Oxford Bioscience Partners
- Bay City Capital
- Technology Partners
- AM Pappas & Associates
- NeuroVentures

Scientific Advisors

- Fred Gage (Salk Inst.)
- Ron Evans (Salk Inst.)
- Eric Kandel (Columbia)
- René Hen (Columbia)
- Scott Small (Columbia)

Board of Directors

- Dr. Harry Hixson, Chairman
- Jim Schoeneck (CEO, BrainCells)
- Jonathan Fleming (Oxford Bioscience)
- Carl Goldfischer (Bay City Capital)
- Roger Quy (Technology Partners)
- Art Pappas (AM Pappas & Associates)
- Dr. Ellen Baron (Oxford Bioscience)
- Dr. Fred Gage (Salk Institute)
- Dr. Paul McGonigle (PsychoGenix)

Discovery Strategy

Translating Science into Products

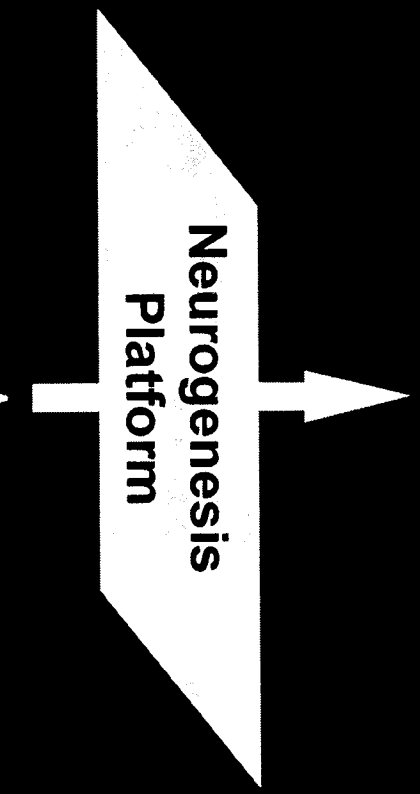
In-Licensing Candidates

Marketed Drugs

Generics

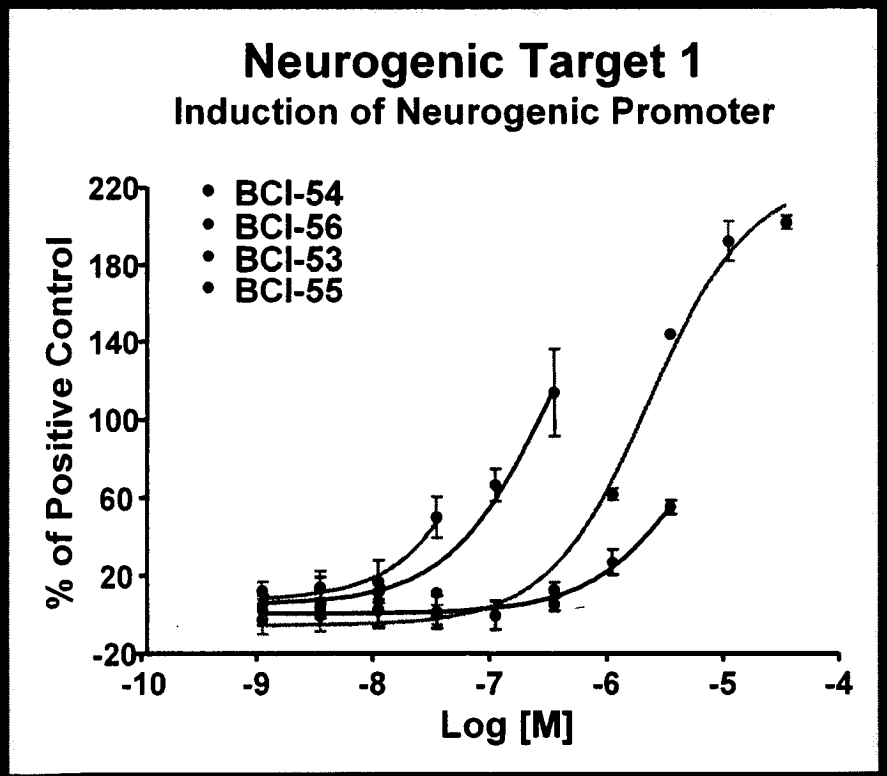
Pharmacological Standards

Discovery Project Compounds



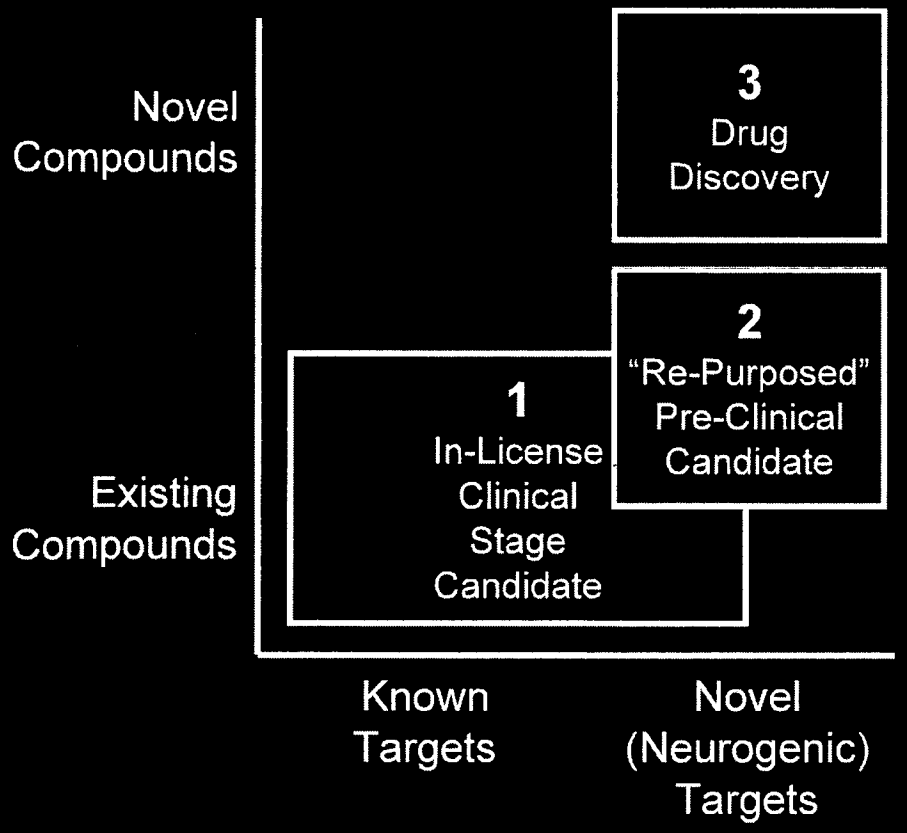
- Select in-licensing candidates
- Re-purpose existing drugs
- Understand drug mechanism
- Validate technology
- Build knowledge base
- Develop predictive models
- Establish novel patent claims
- Lead optimization & selection

Target Validation



- Proprietary list of 35 putative neurogenic targets
- Assembled toolkit of probe compounds
- Identified novel neurogenic targets
- Provide focus for in-licensing activities

Building BCI's Product Pipeline

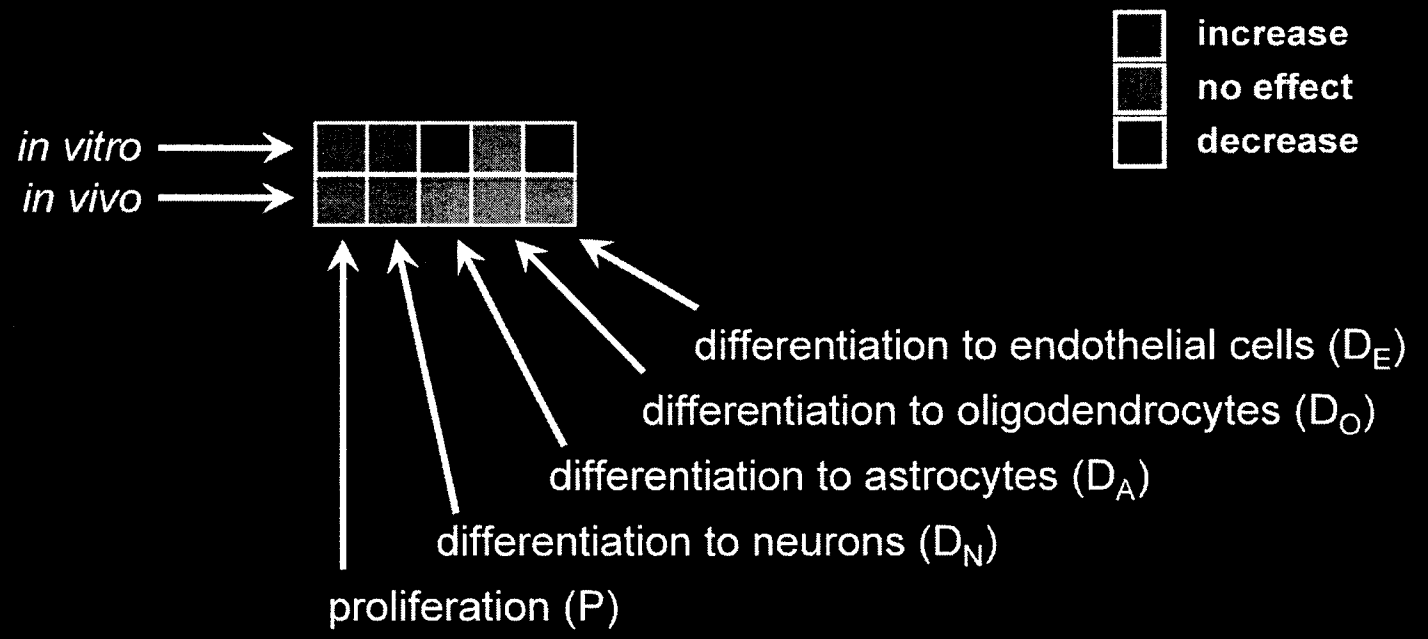


1 Clinical Stage Candidate
- Rapidly build high-value pipeline
- Use platform to select candidate
- Commence Phase II clinical trial

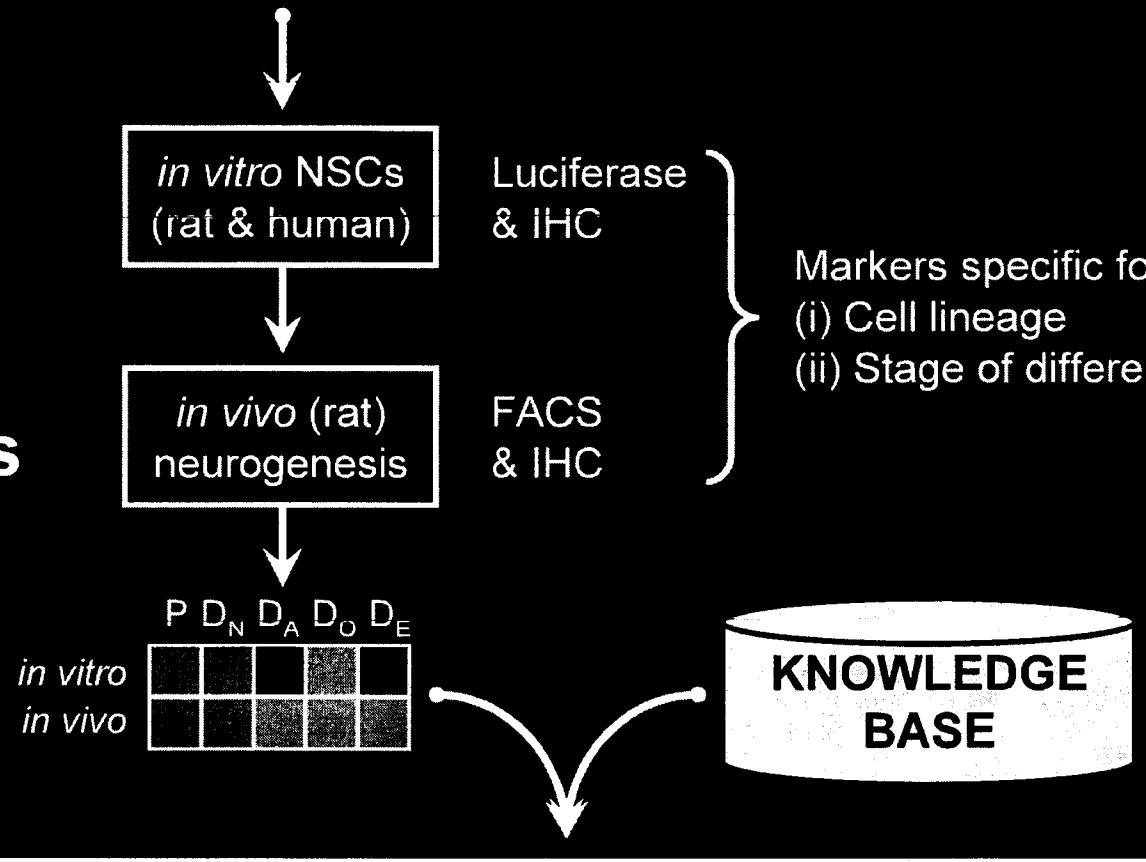
2 Pre-Clinical Candidate
- Prioritized list of 'neurogenic' targets
- In-license compound IP
- Leverage platform for selection

3 Drug Discovery Program
- Profile compound libraries
- Identify novel neurogenic targets
- Leverage platform for lead optimization
- Seek pharma collaboration

Neurogenesis Fingerprint



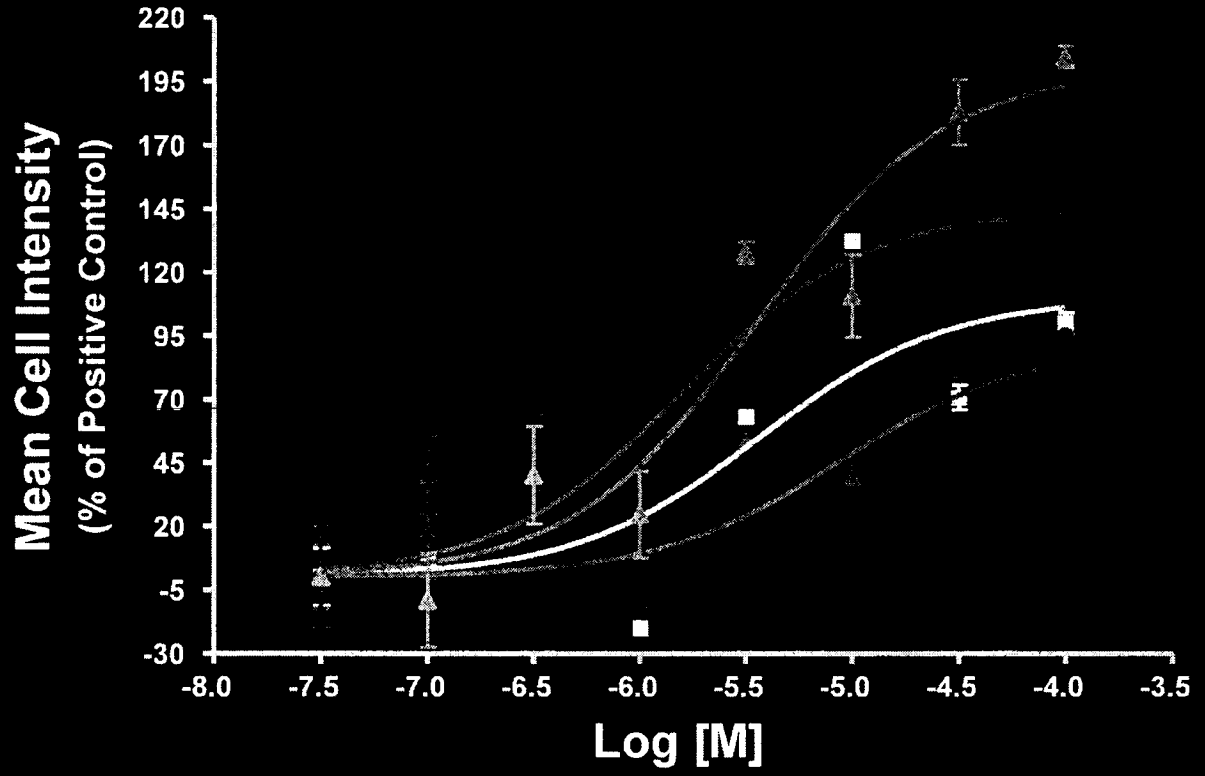
Evaluation Of Clinical Candidates



Mood Disorders	**Cognition**	**Neurology**
Standard behavioral models e.g. *Learned Helplessness* + Hen & Santarelli (Columbia U.) Chronic models of depression & anxiety	Cognition models e.g. *Morris Water Maze* + Gage (Salk Inst.) Kandel (Columbia U.)	Brain injury models (trauma & hypoxia) + Palmer (Stanford U.) Fike (UCSF) Radiation damage models

Evaluation of In-Licensing Opportunities

Demonstration of Neurogenesis in Human NSCs



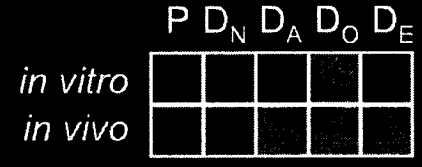
Compound	EC50 (μM)	Efficacy (%)
■ Positive Control	2.69	100
▲ Drug Comparator	5.78	77
● BCI-71: In-Licensing Candidate	1.81	95
▲ BCI-72: Principle Metabolite	3.54	205

Drug Discovery Collaborations

Compound Library

Known pharmacology
Prioritized by target activity
Multiple compounds per target

Neurogenesis Platform



Disease Models

Robust chemical series
Target activity tracks neurogenesis
Other known pharmacology

"Validated" Neurogenic Target + Compounds

Target-Based Drug Discovery & Intellectual Property

BrainCells Inc.

An Outstanding Investment Opportunity

- Paradigm-shifting technology
- Focus on large markets
- Fast-to-market strategy
- Experienced management team
- World-class SAB and advisors
- Top-tier investor group
- Focus on IPO criteria

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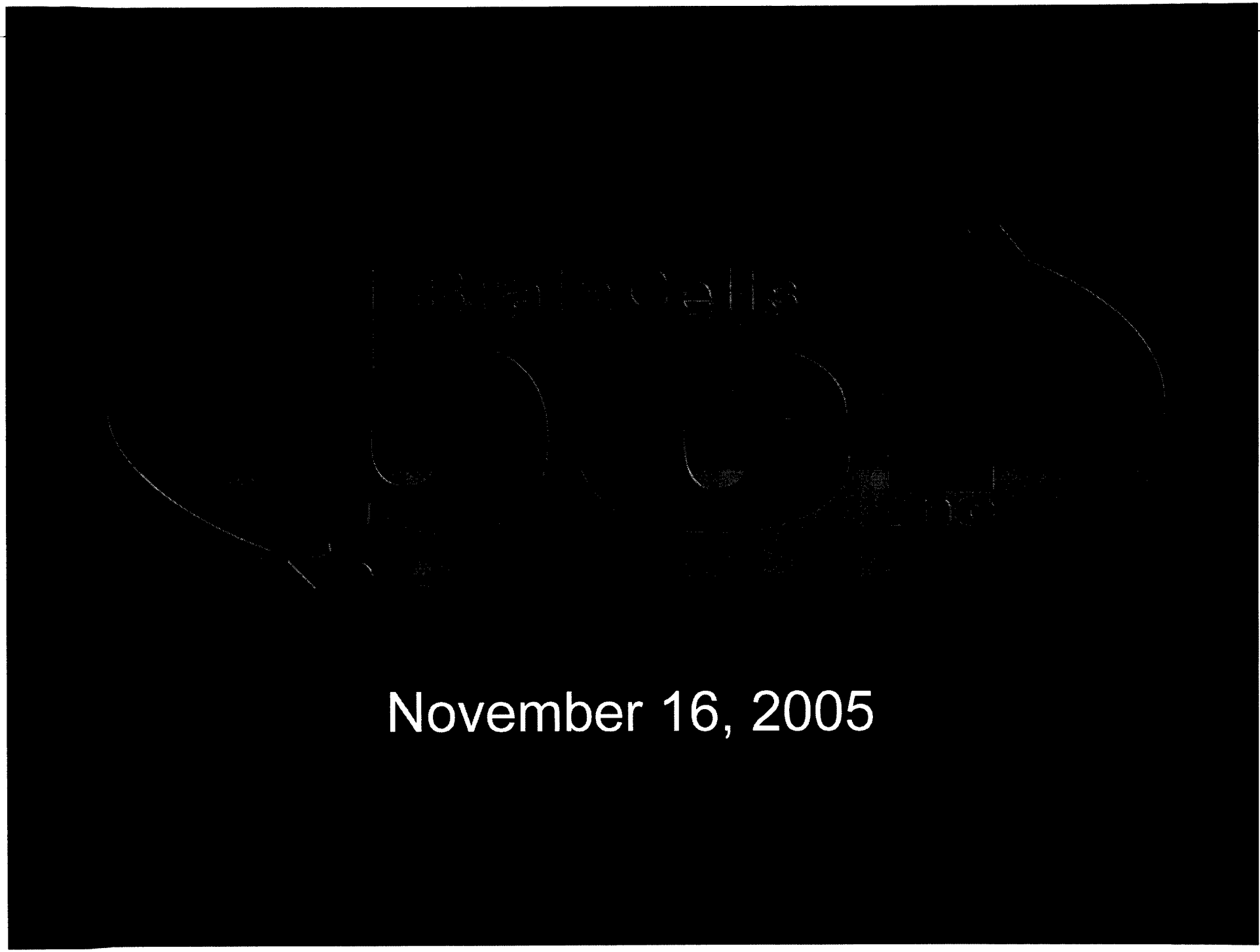
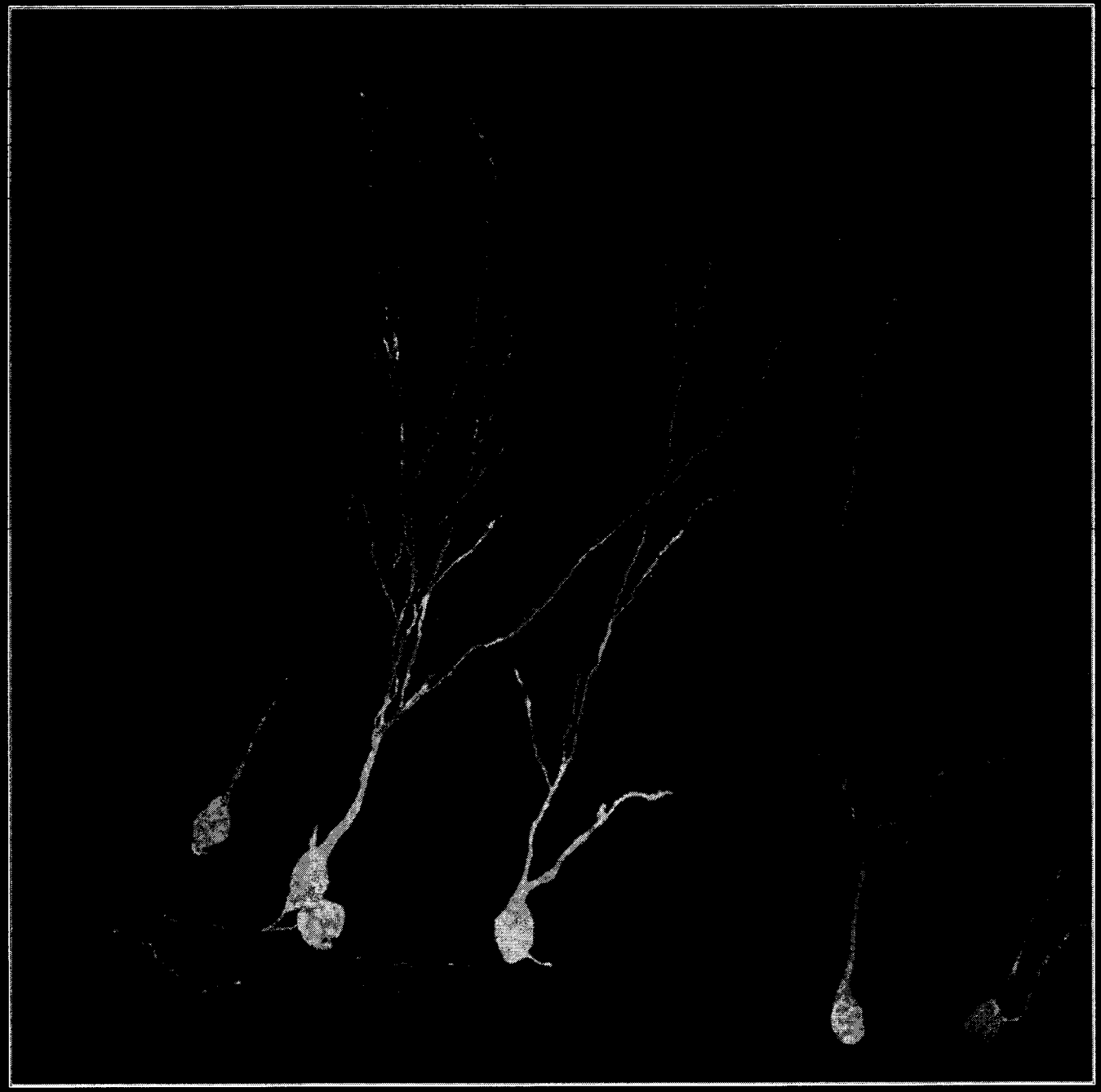

November 16, 2005



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BCI Overview

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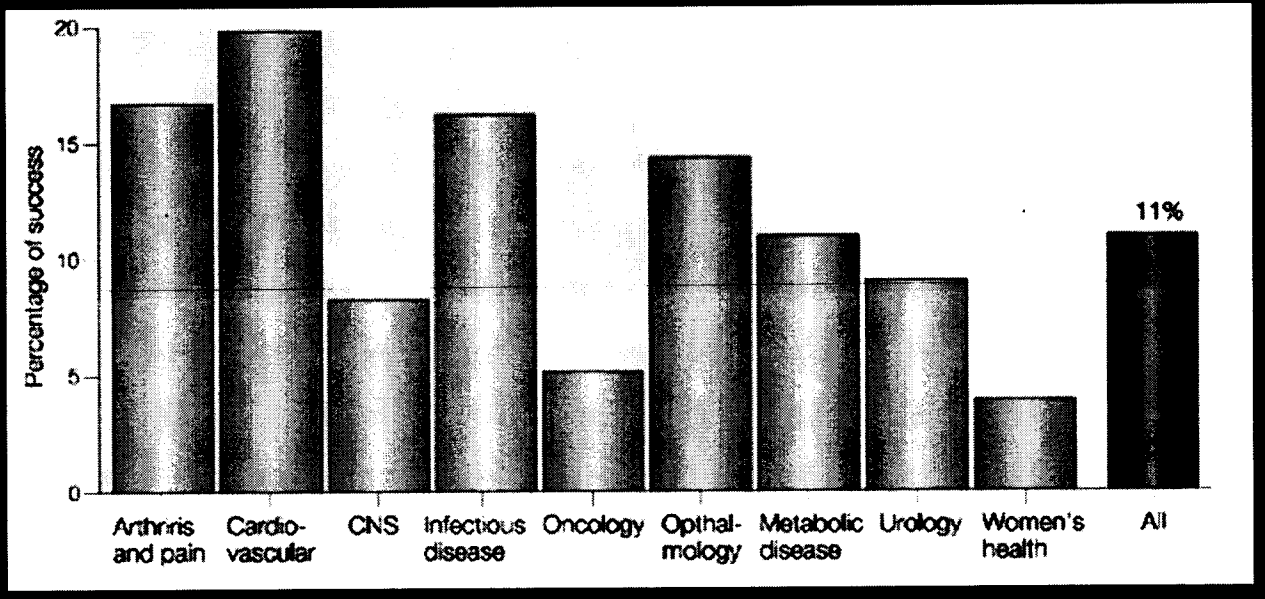

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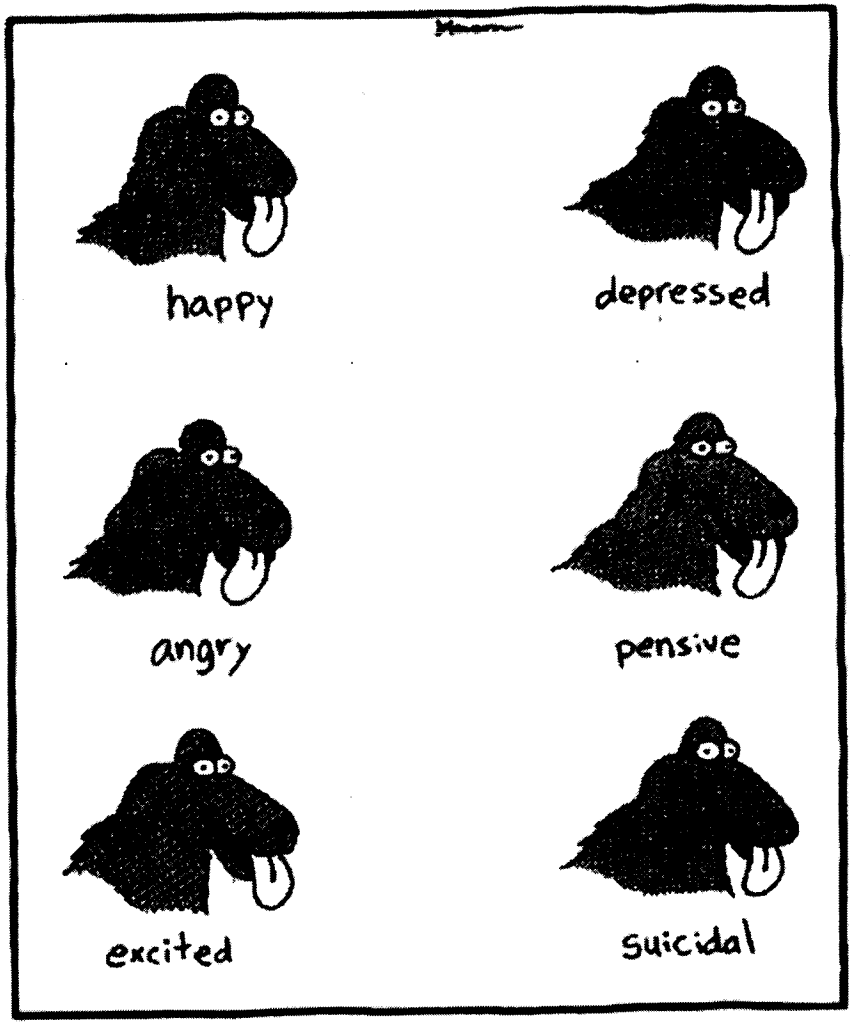

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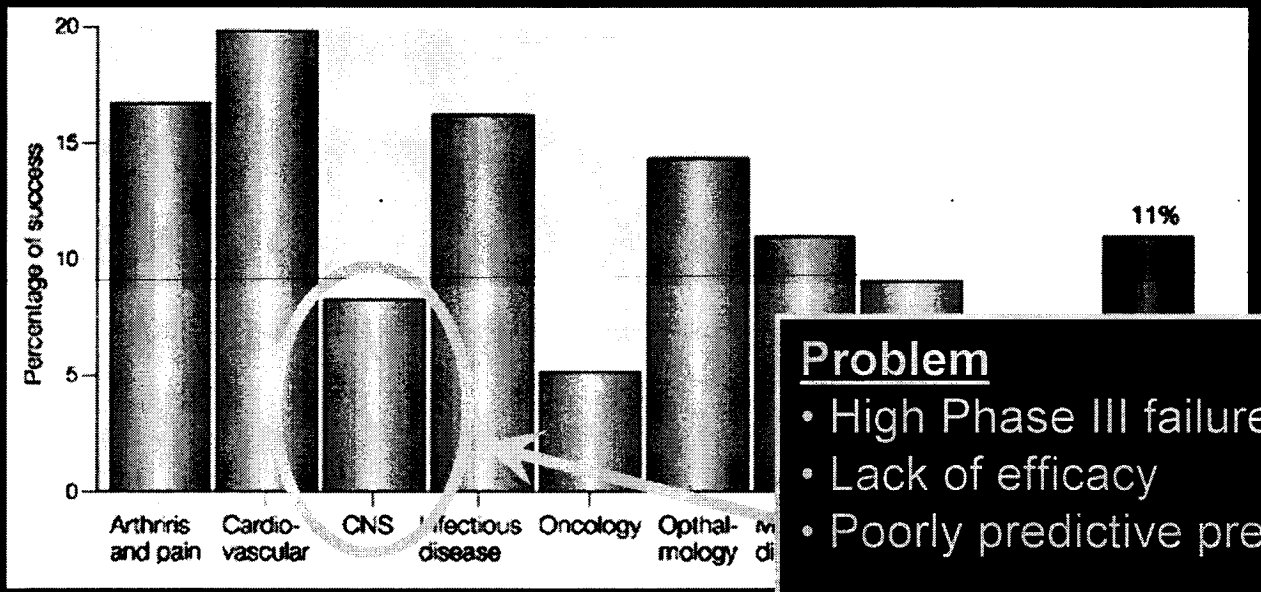

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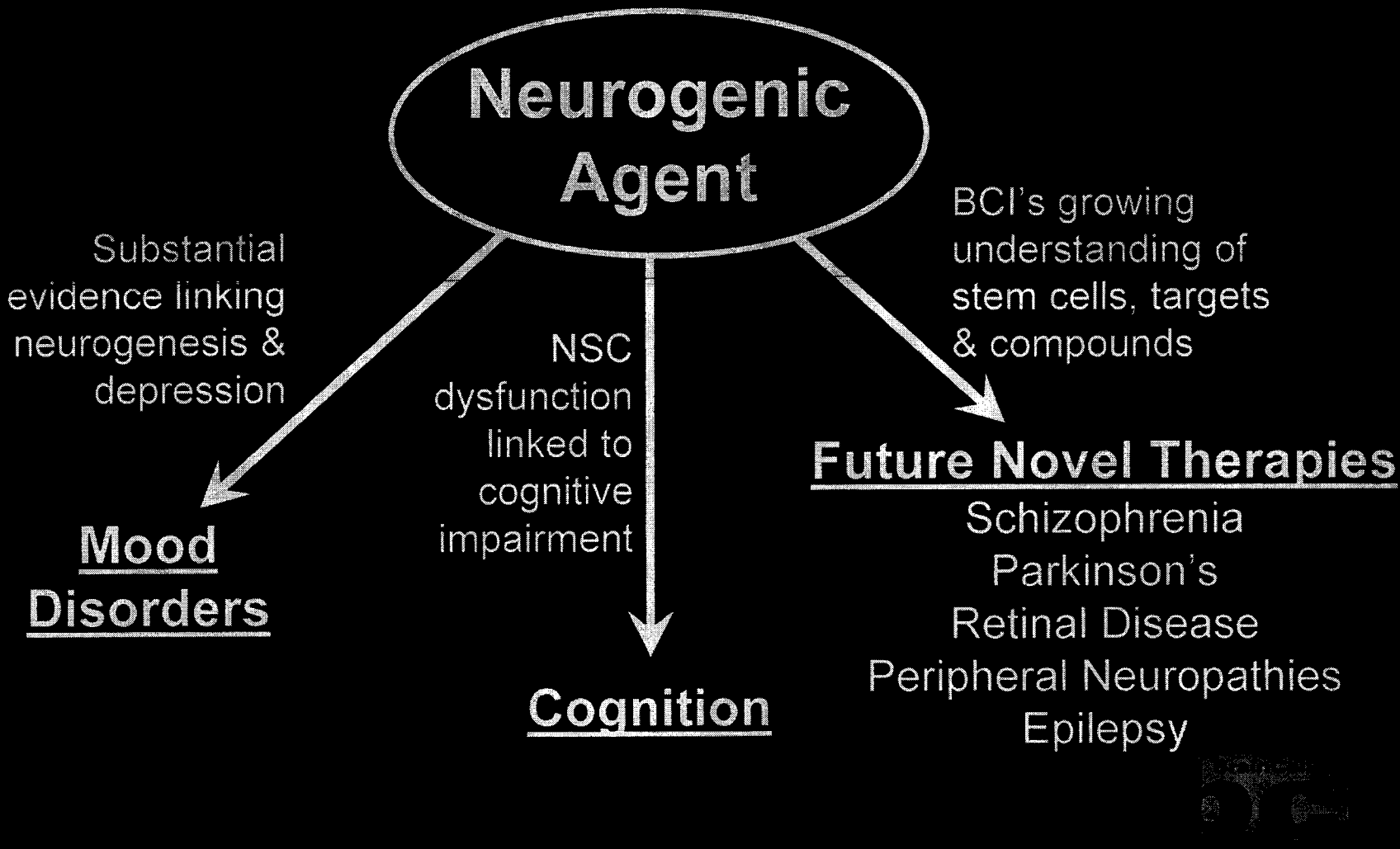

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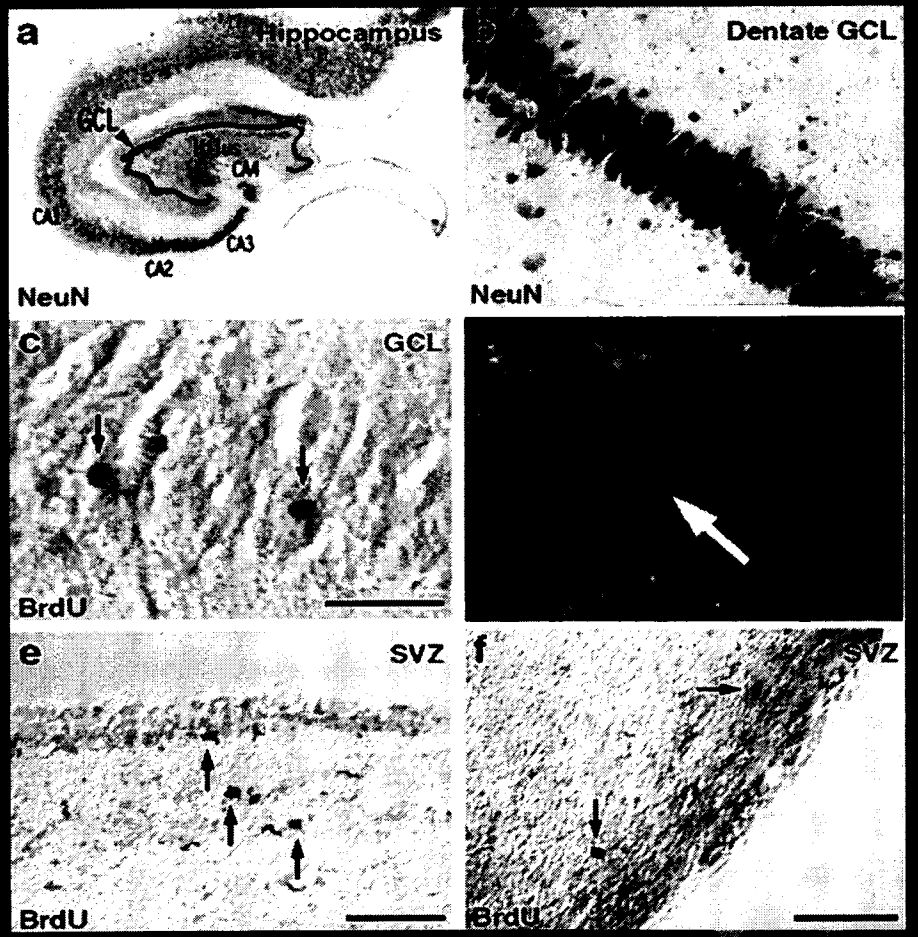

(Eriksson et al., Nat. Med 1998)

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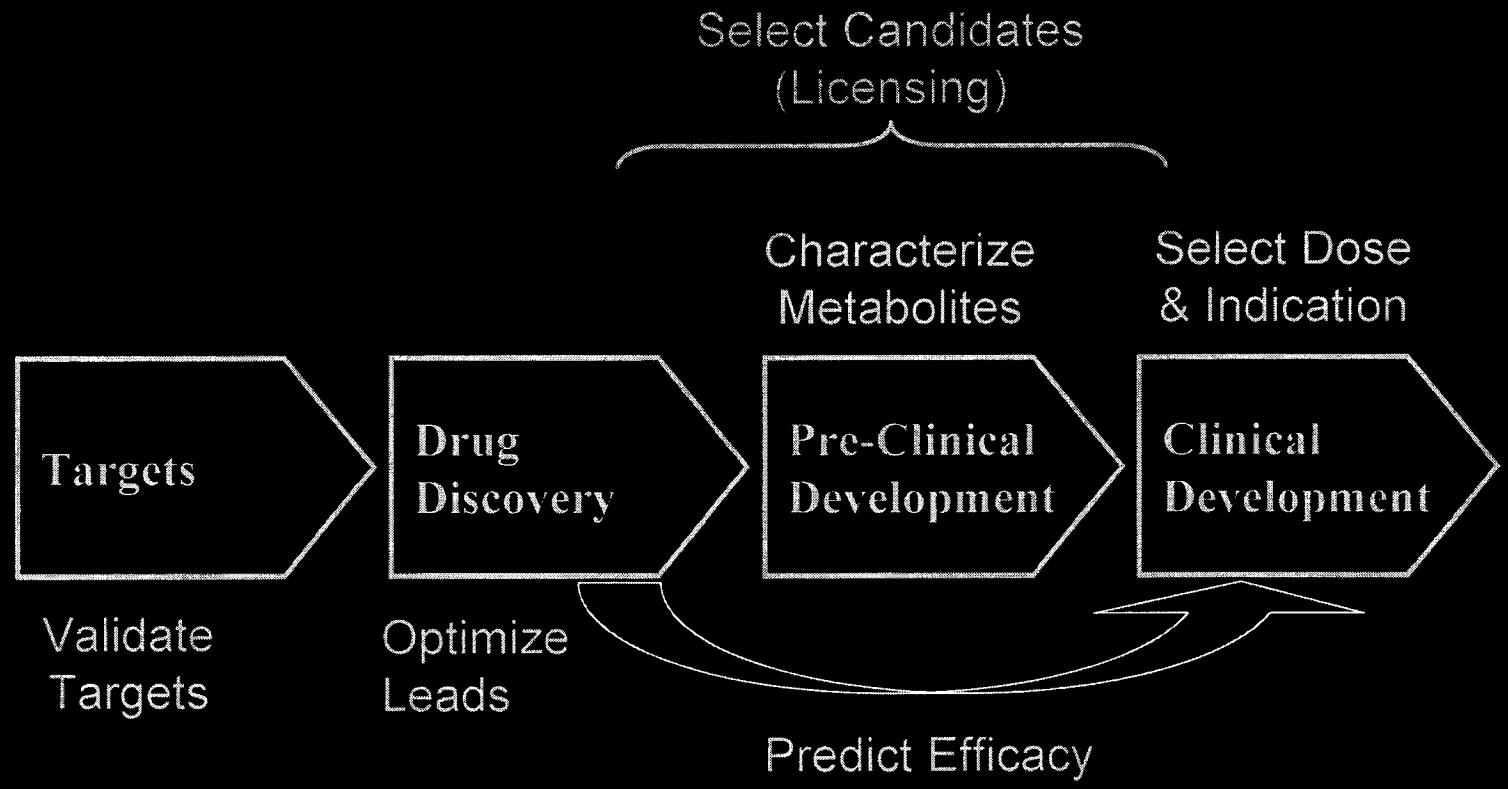

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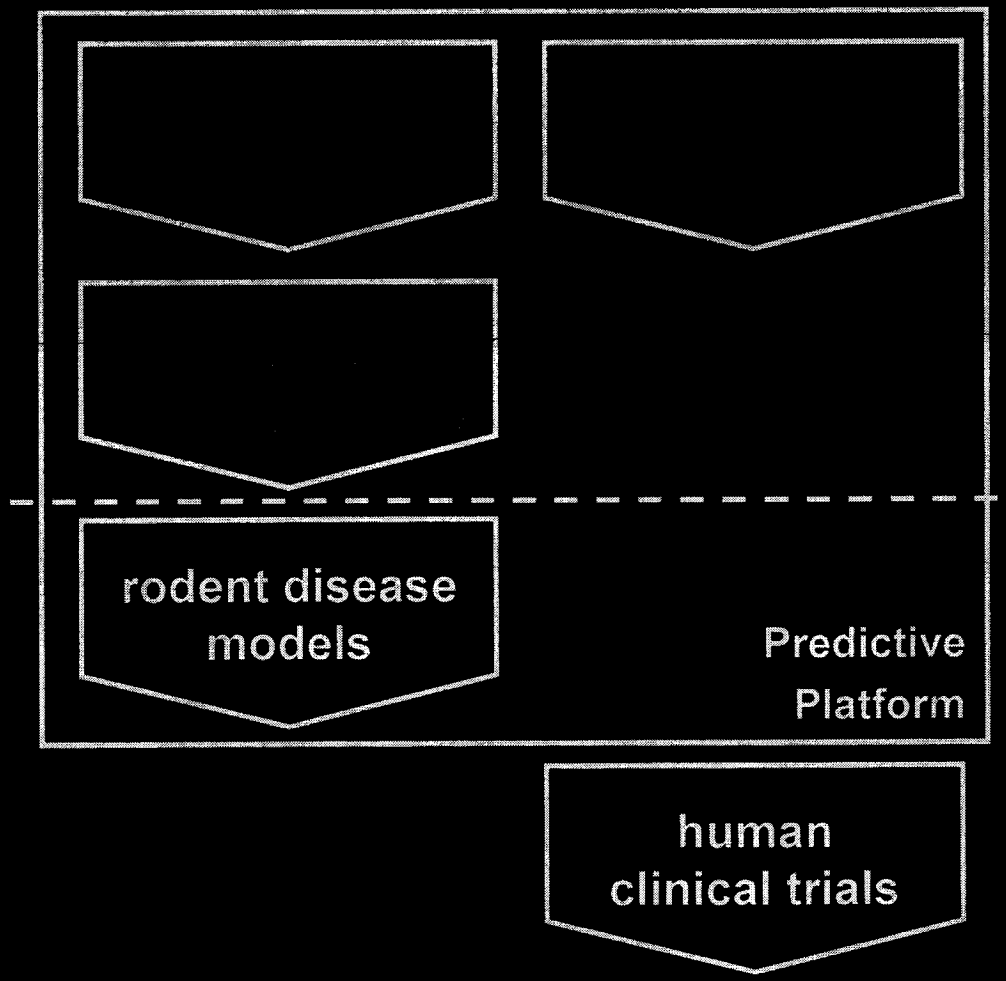
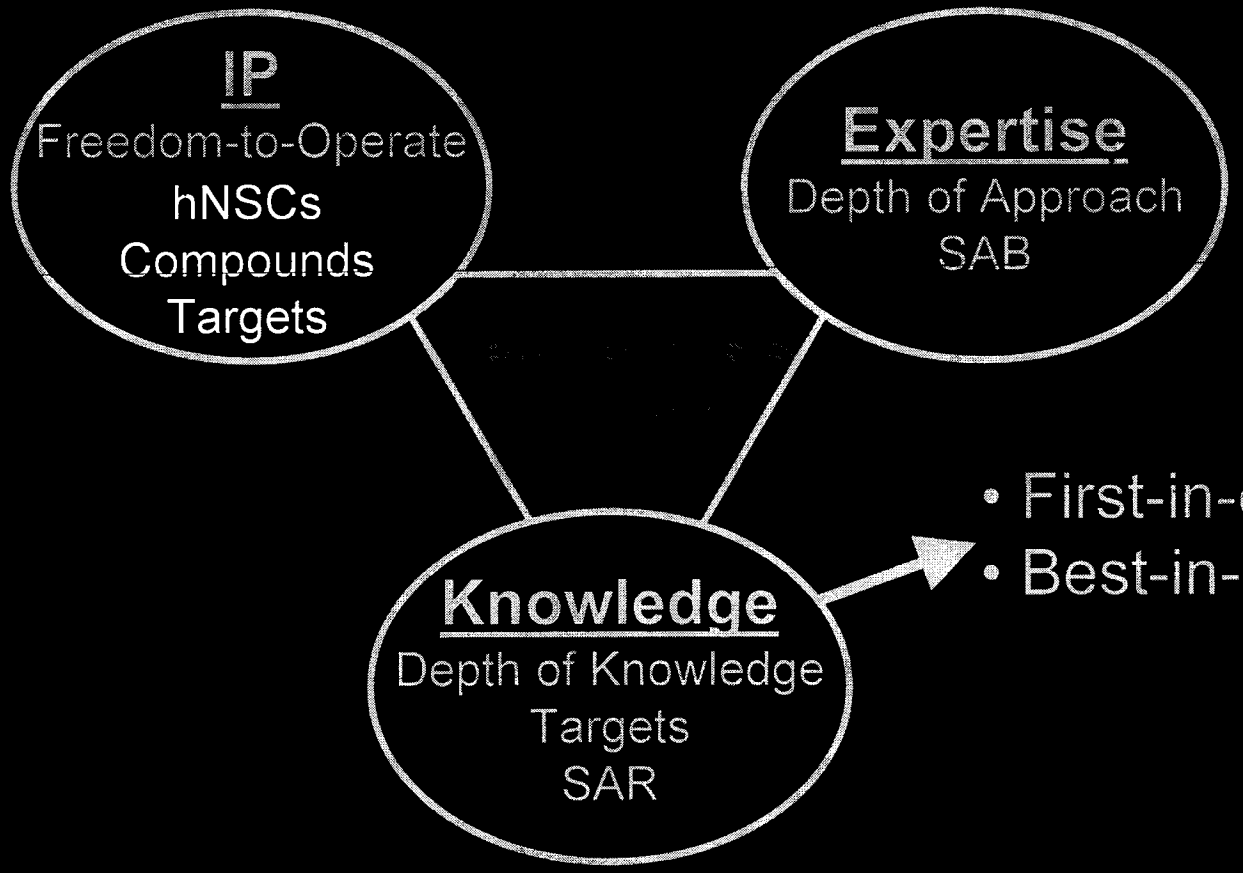


Lead Neurogenic Compounds

Business Review

First Mover Advantage
Sustainable Competitive Edge



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Marketed Drugs

Generics

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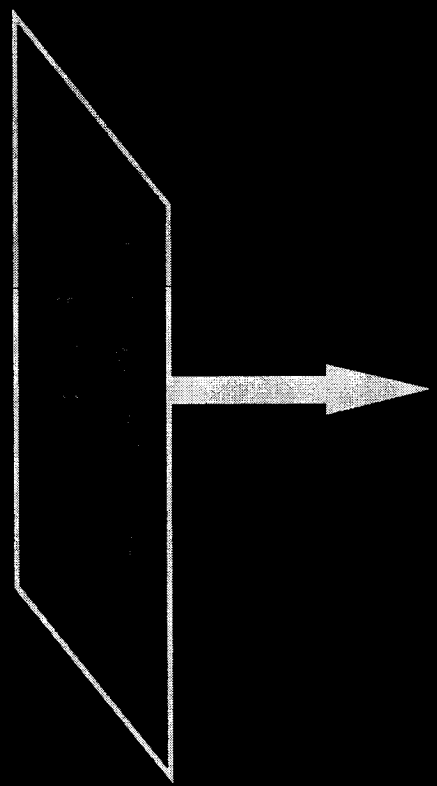

- Select in-licensing candidates
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- Understand drug mechanism
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- Establish novel patent claims
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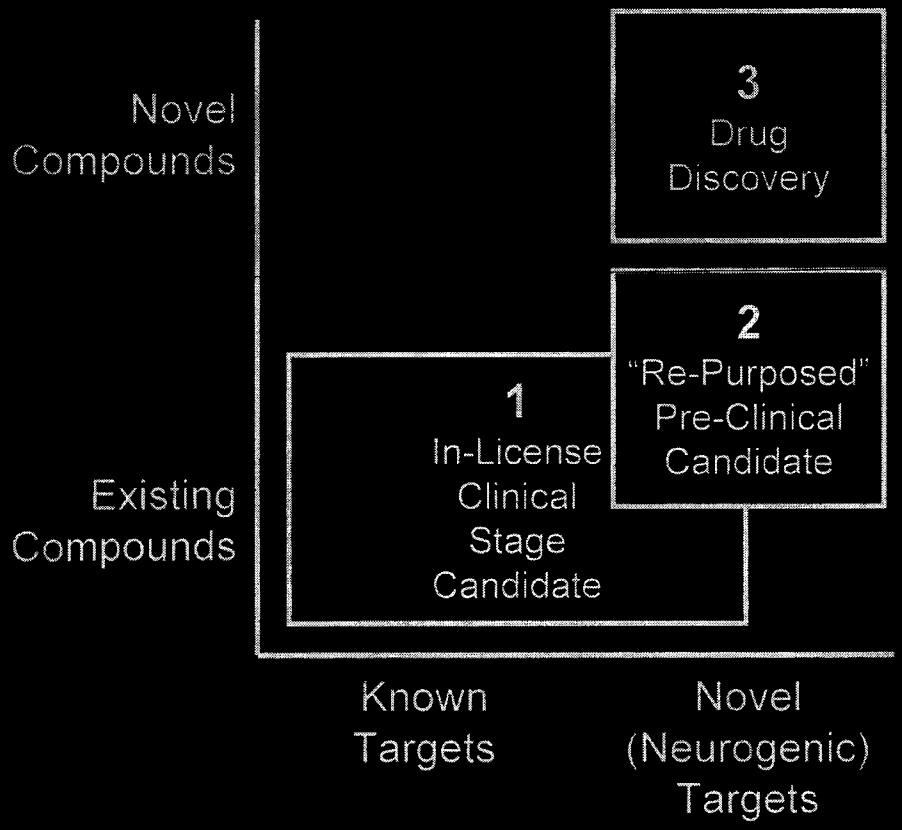
Building BCI's Product Pipeline



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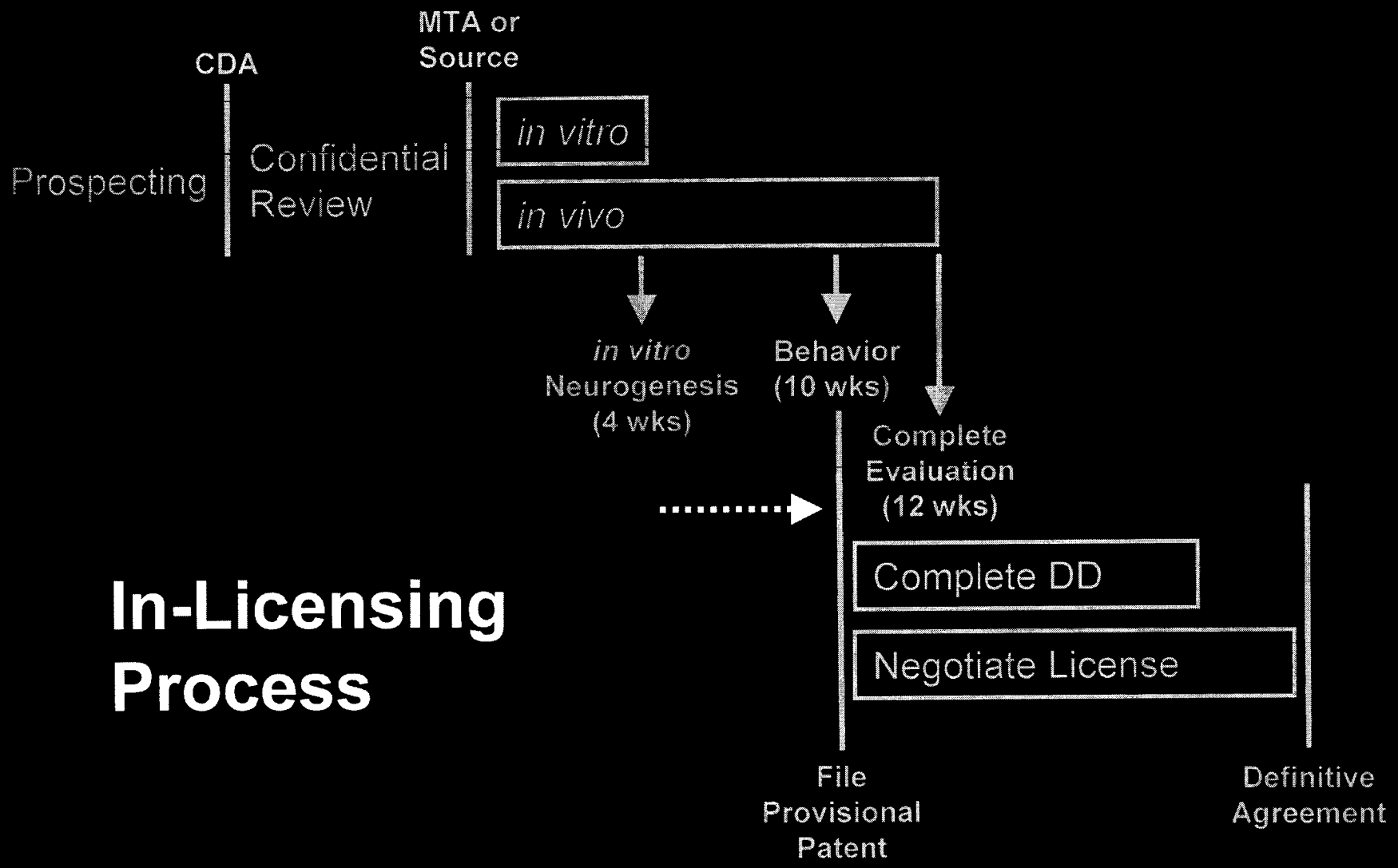

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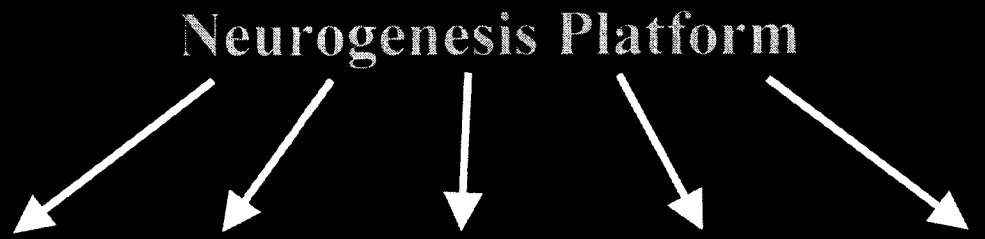

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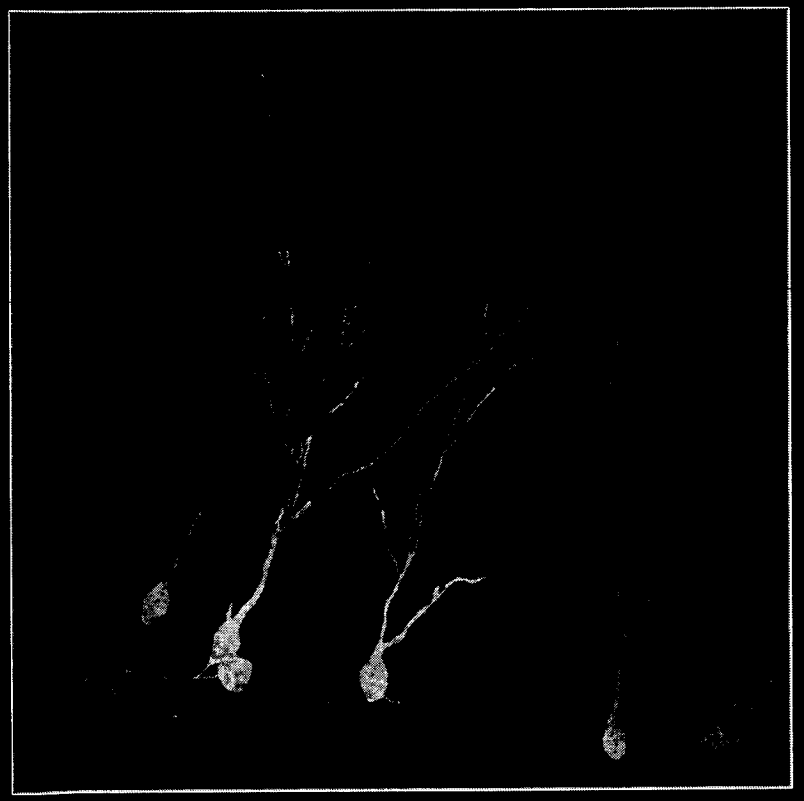

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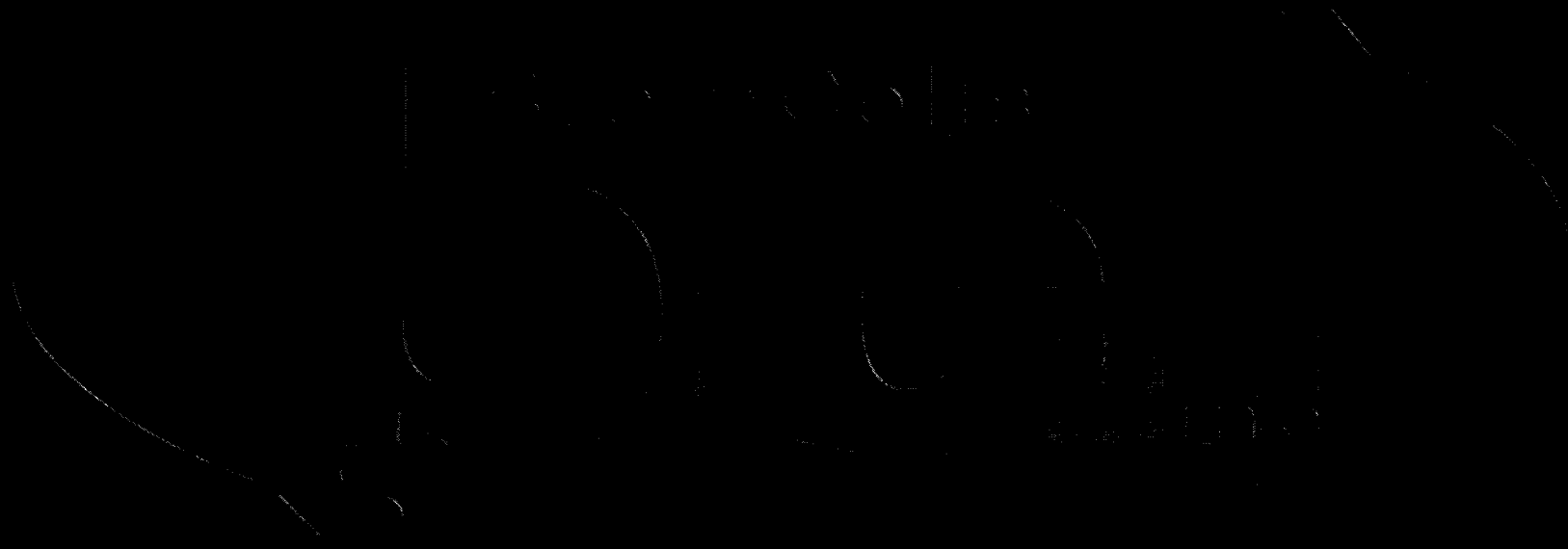

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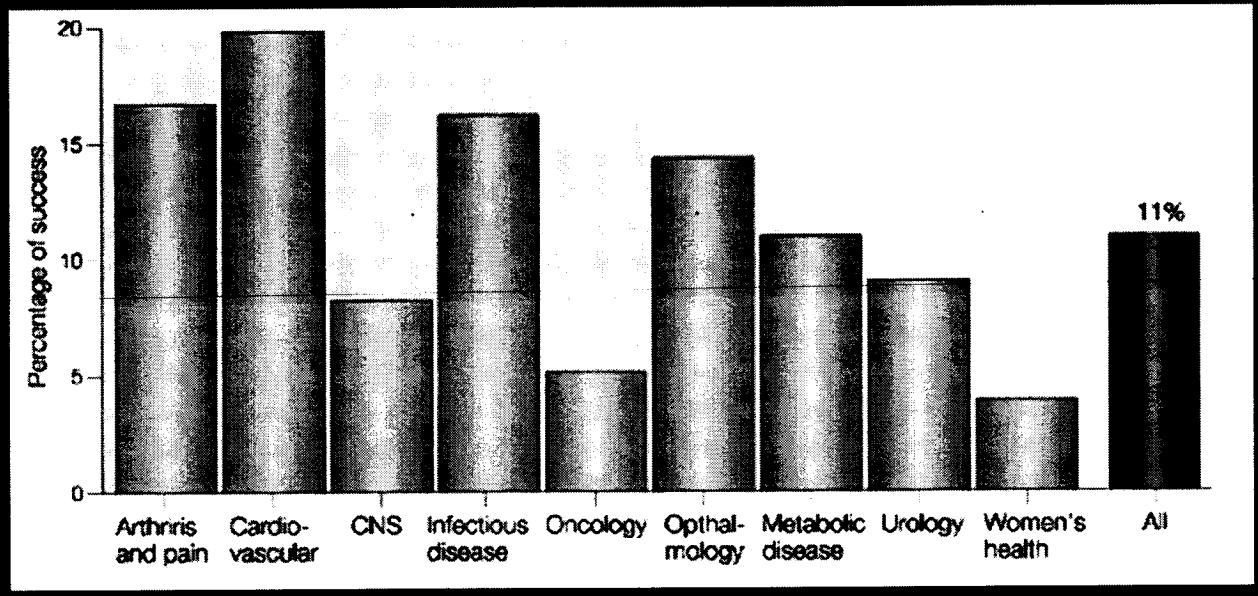

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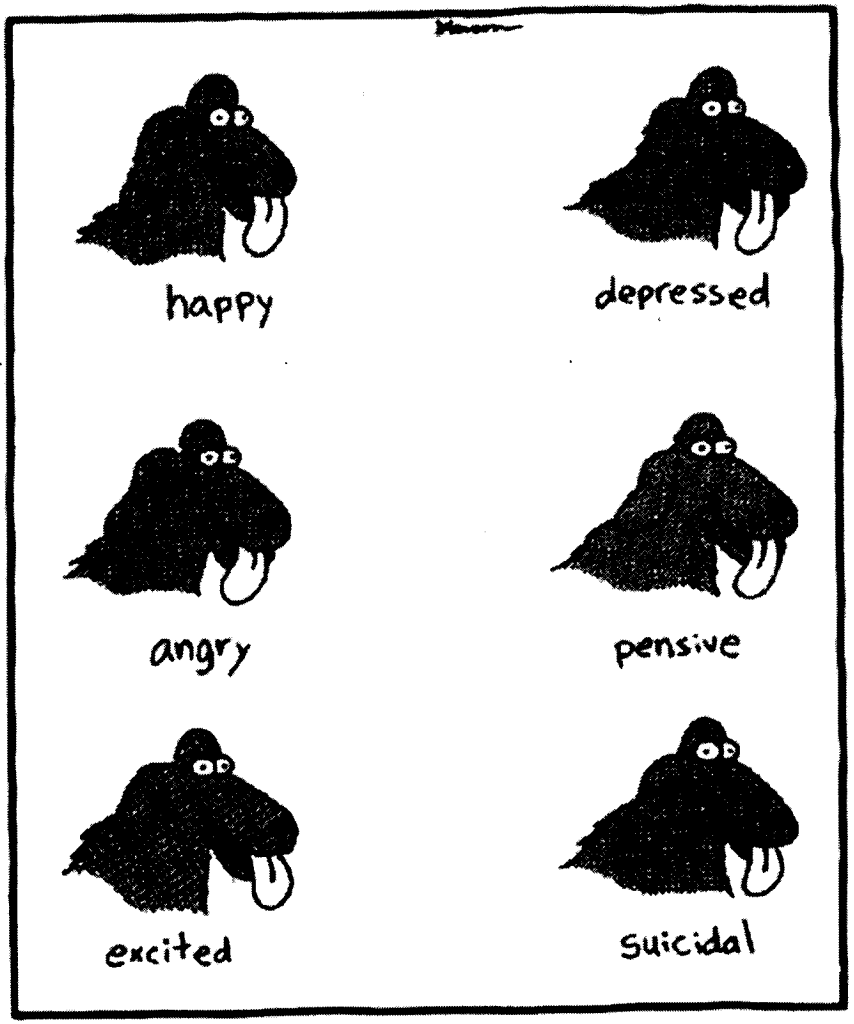

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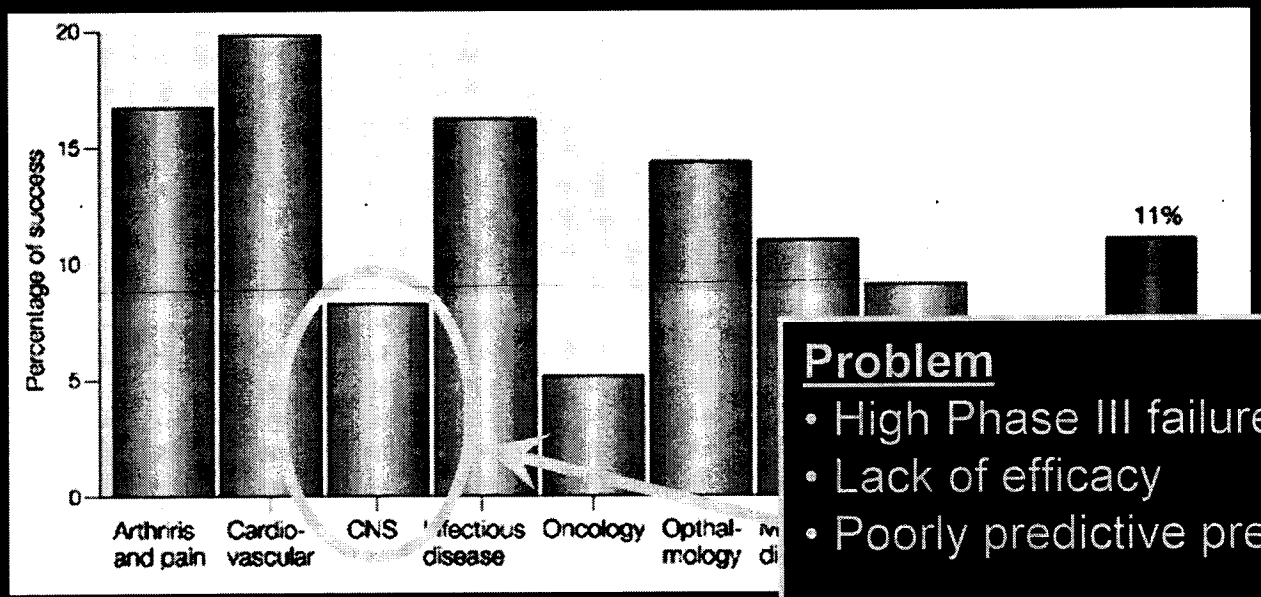

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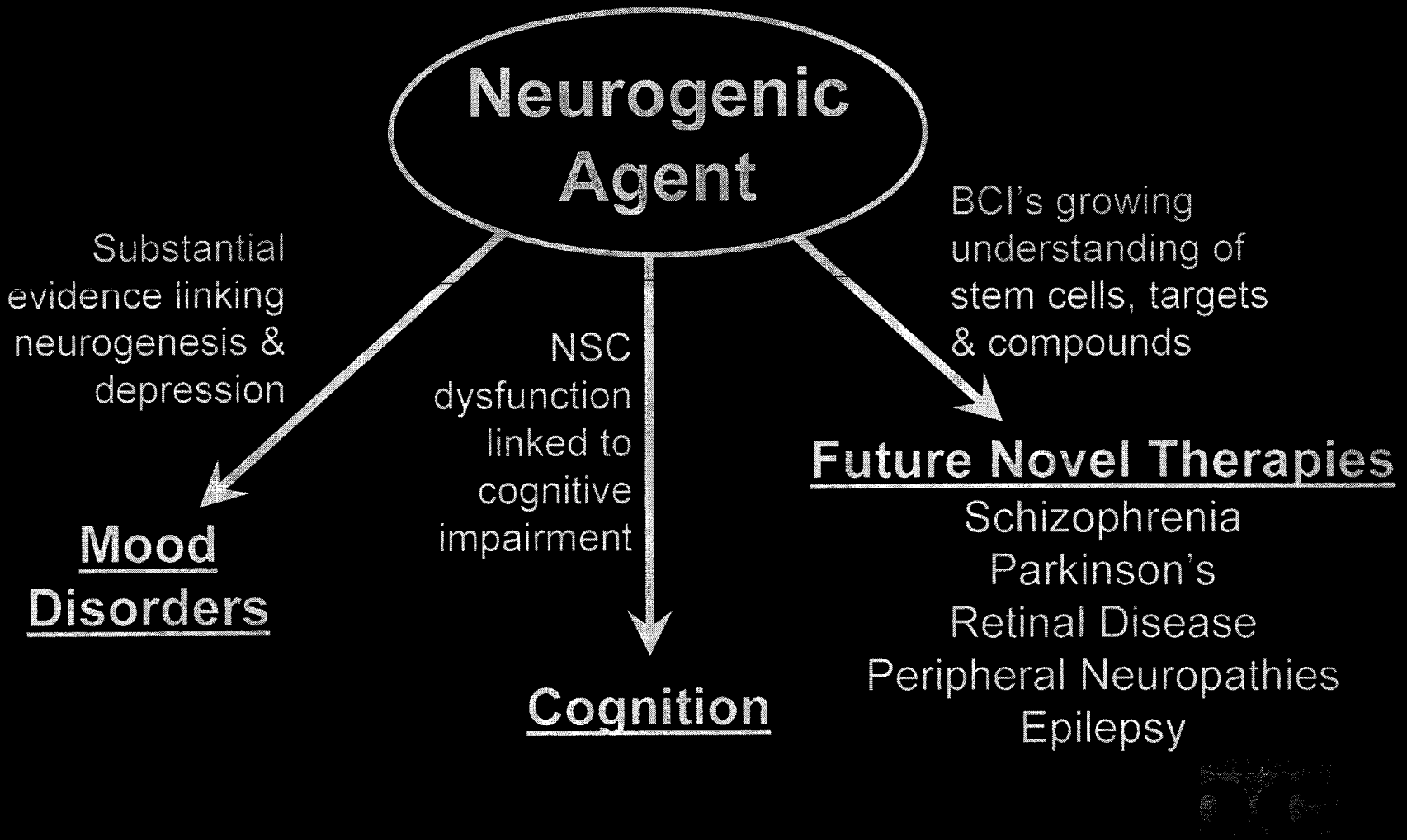

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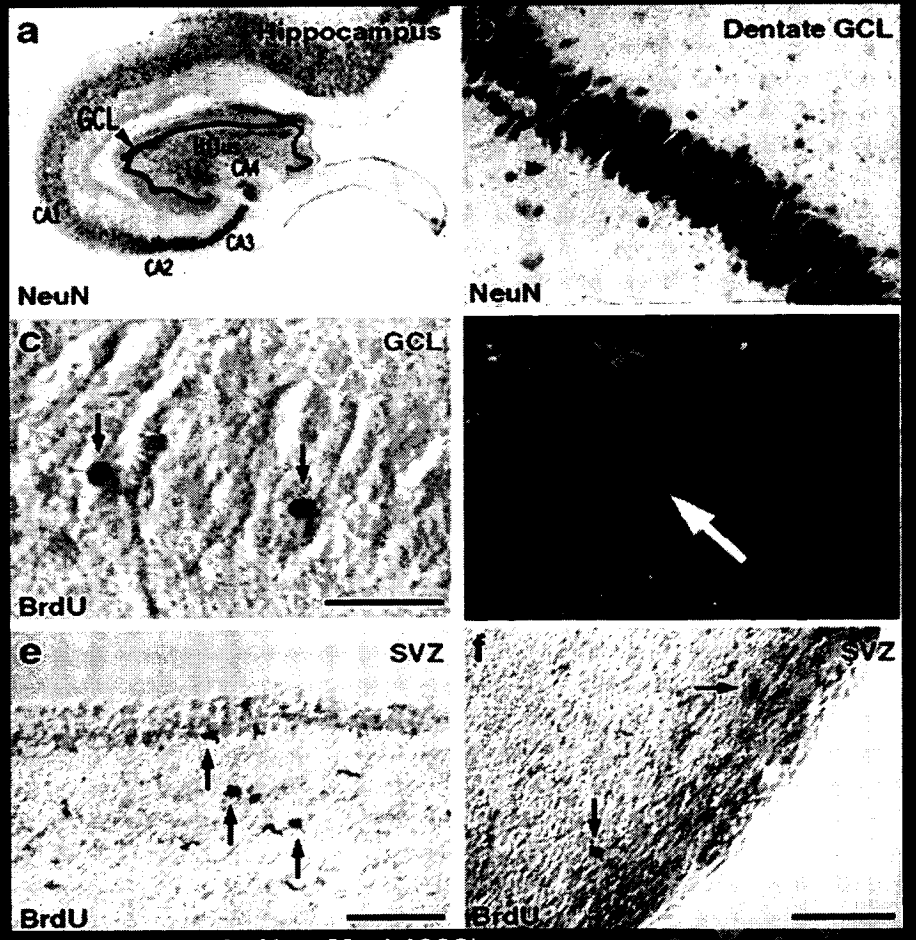

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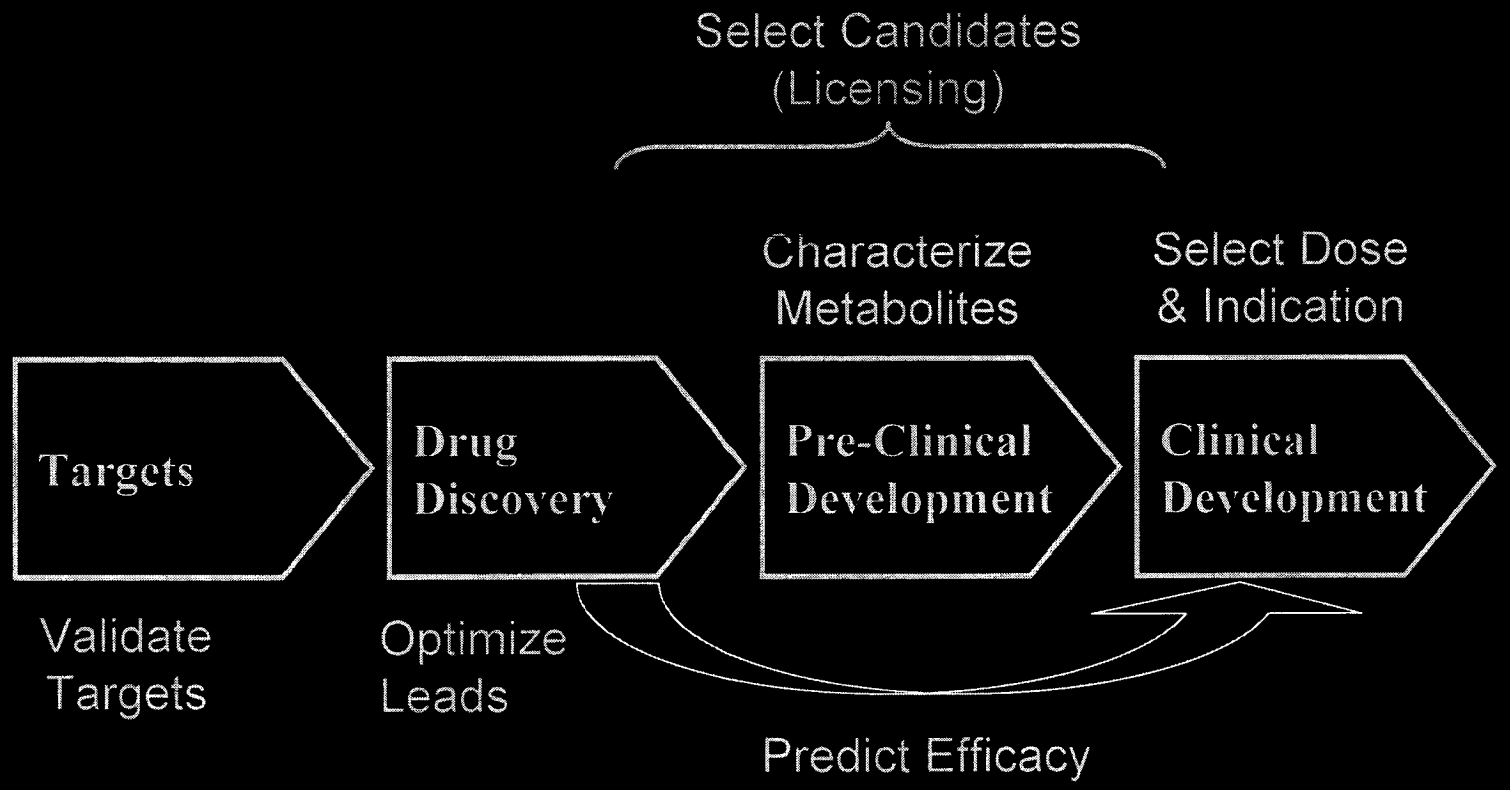

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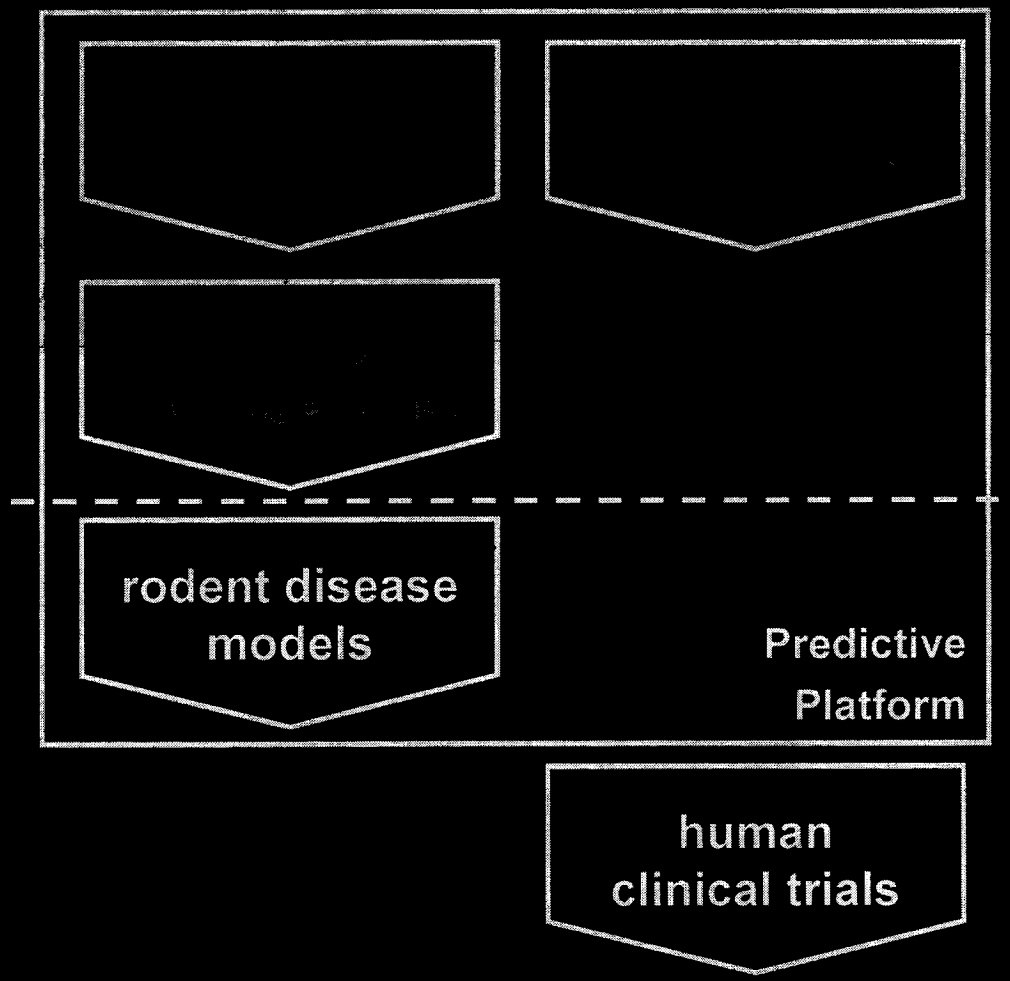

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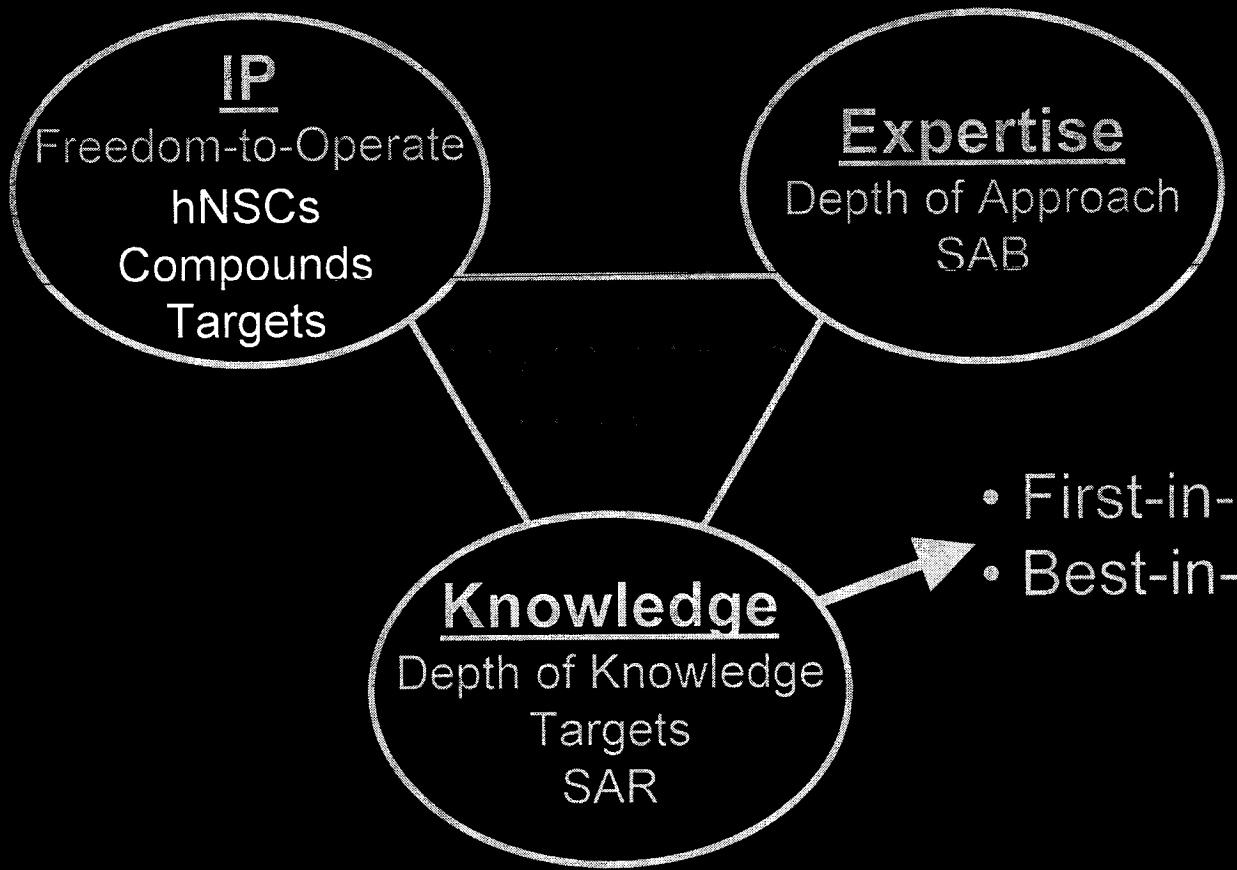

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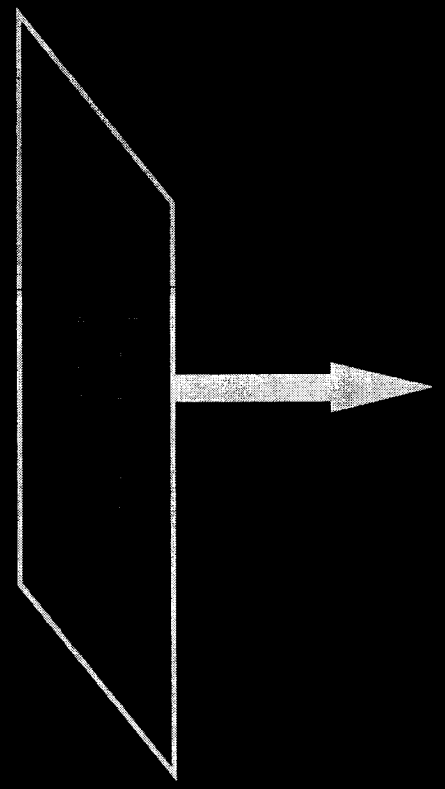

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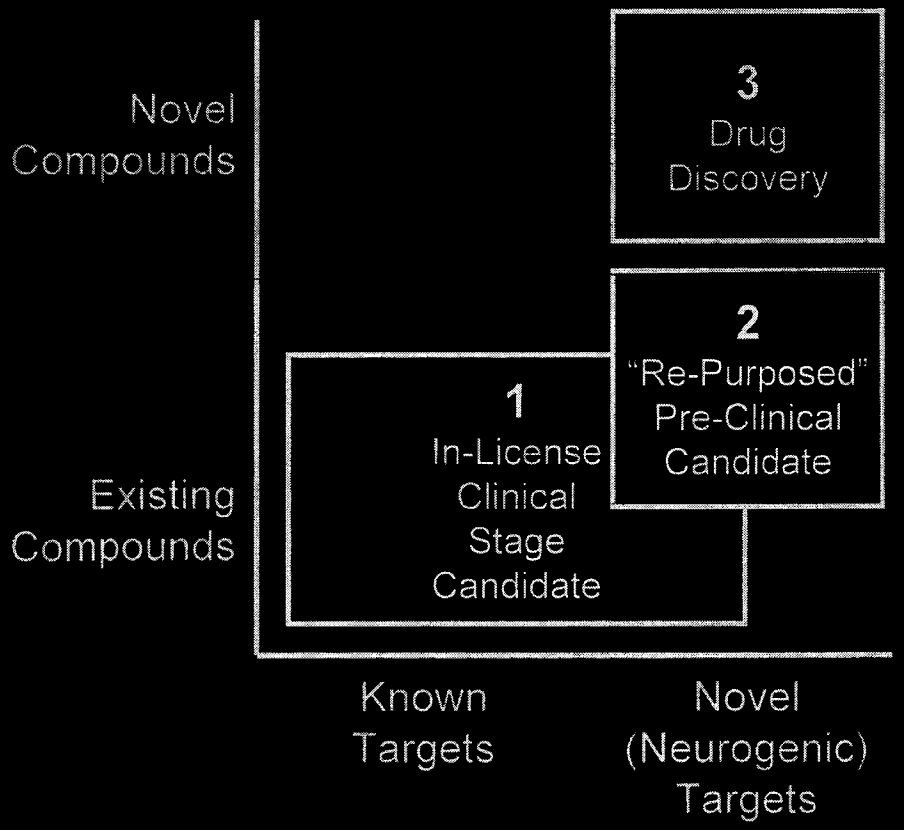

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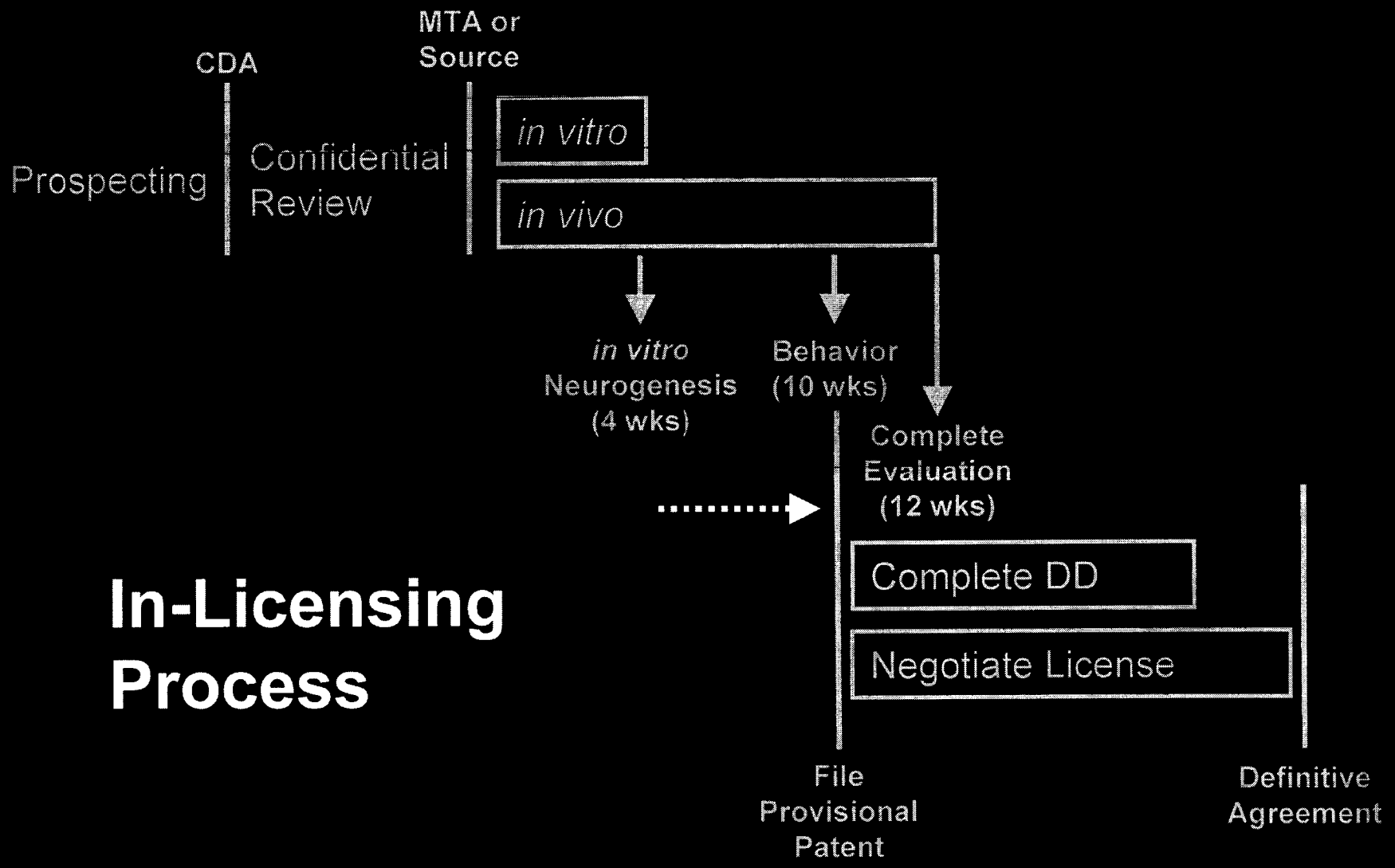

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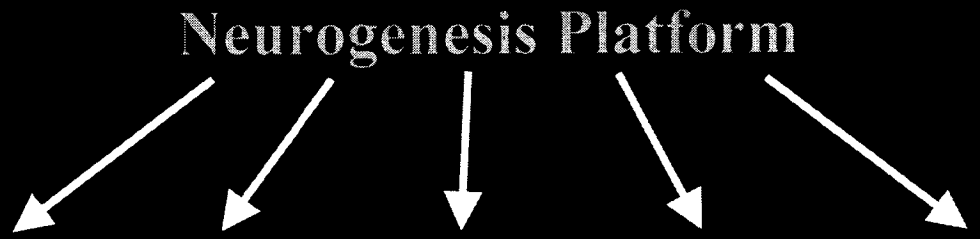

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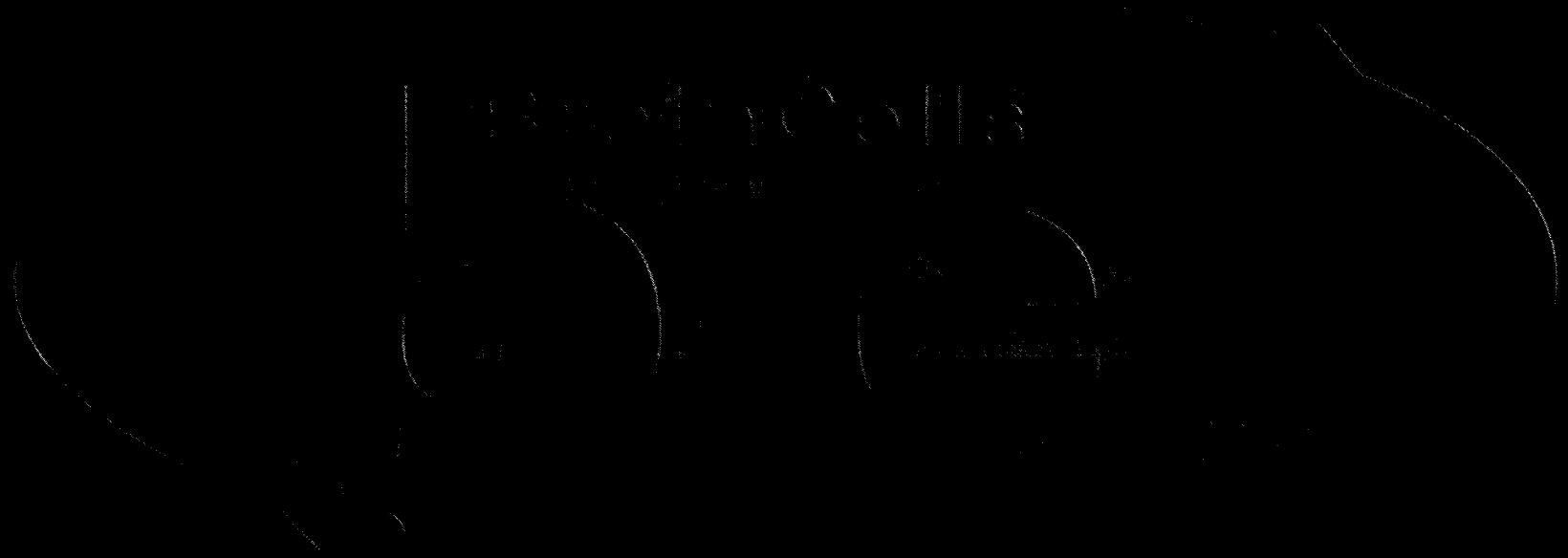

CASE STUDY in Preclinical Investing

Jim Schoeneck, CEO

Presentation Overview

What is BrainCells?

Why does BrainCells exist?

Why preclinical assets are important?

True or False:

Once you are an adult, you have all the brain cells you will ever have.

Answer: False

In 1998, Rusty Gage and coworkers from Salk Institute first reported that the adult human brain generates new cells – The process is called *neurogenesis*.

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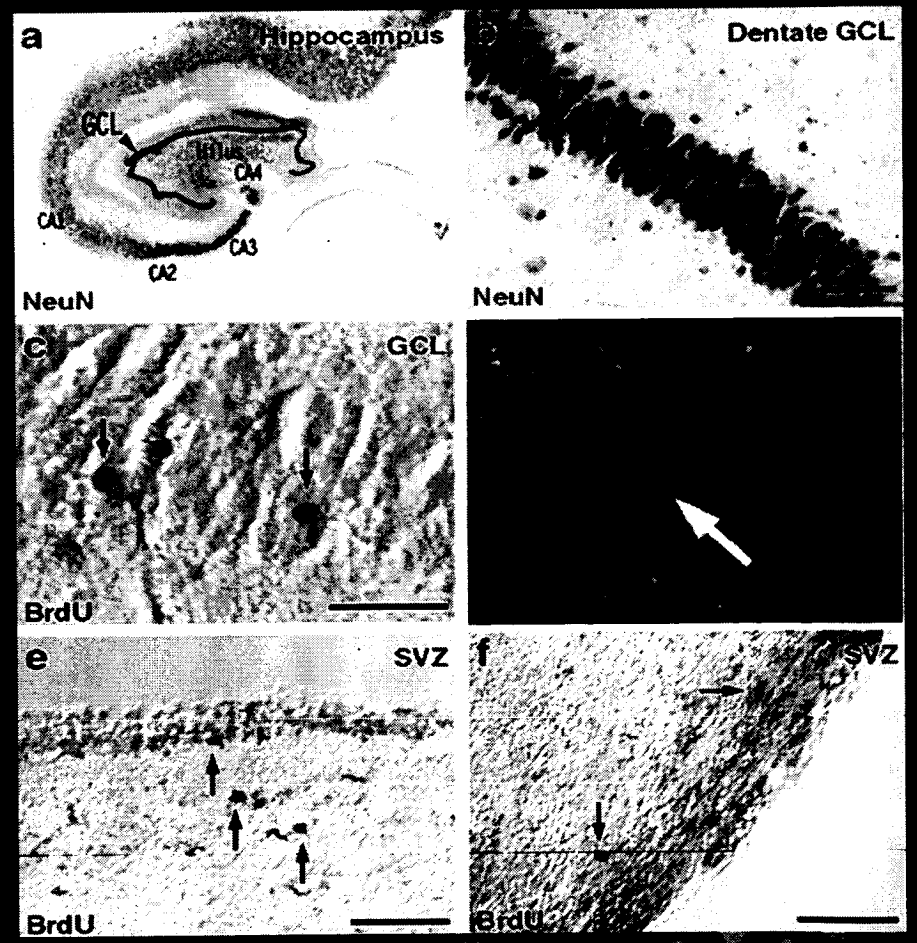

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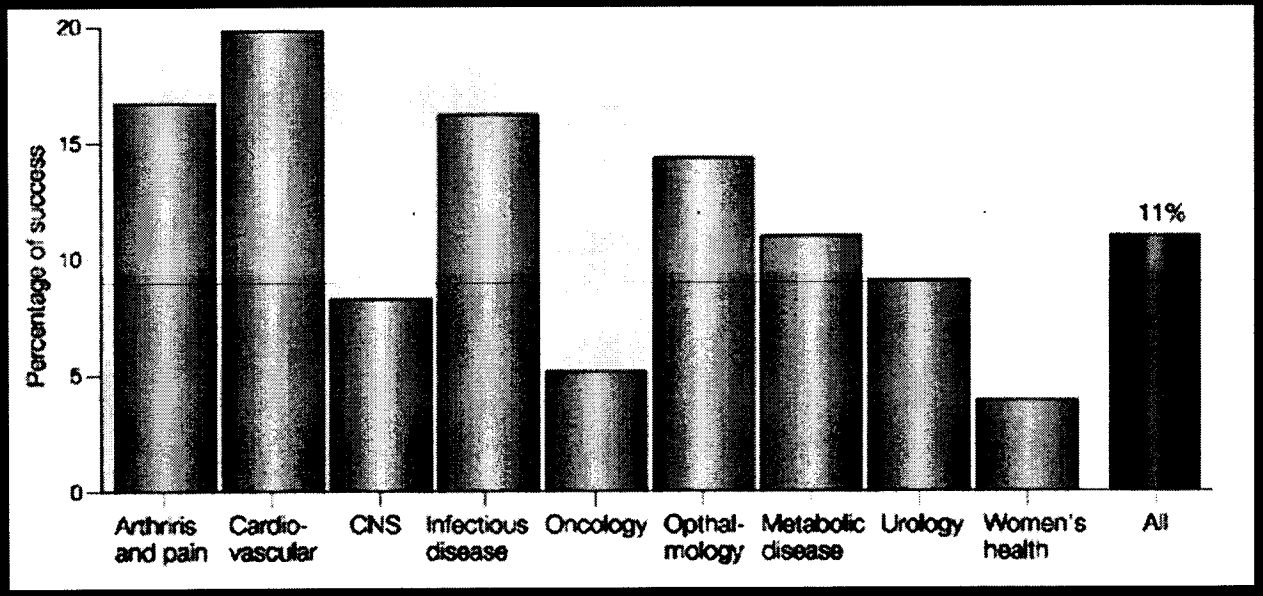


Figure: Kola & Landis, Nature Reviews: Drug Discovery **3** (2004) 711.
Data: DataMonitor "Pharmaceutical R&D Benchmarking Forum"

Why are they so different?

- Some Therapeutic Areas, like cardiovascular (20% success), have well developed science and good animal models

Others, like CNS, are much lower…
From First-In-Man to Registration

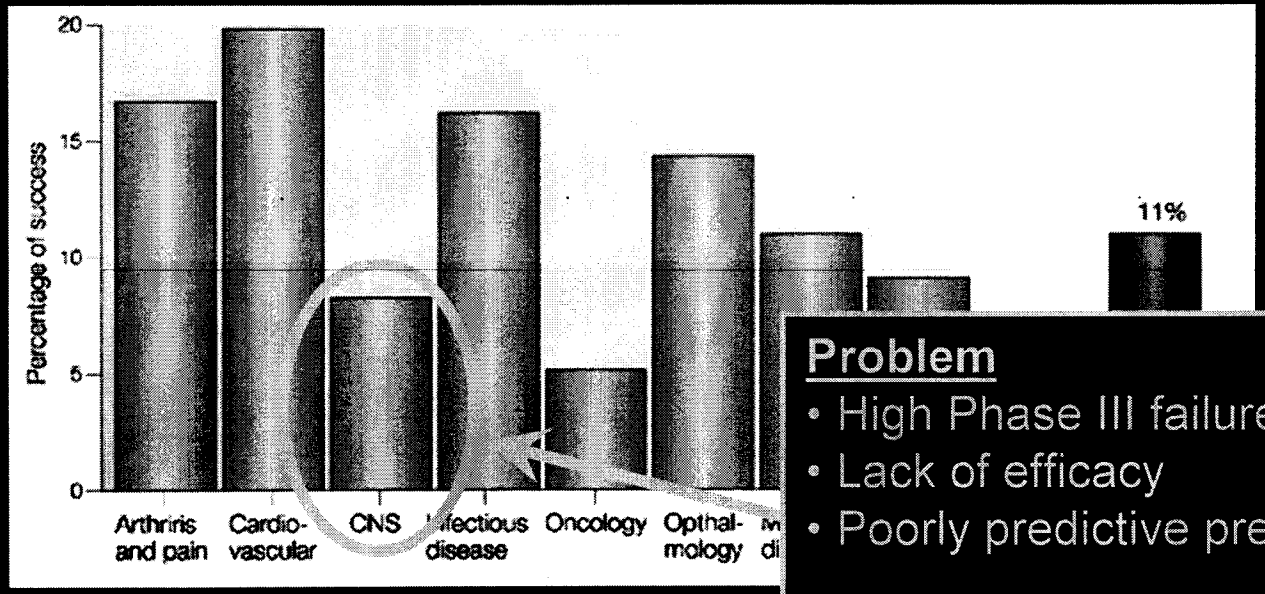
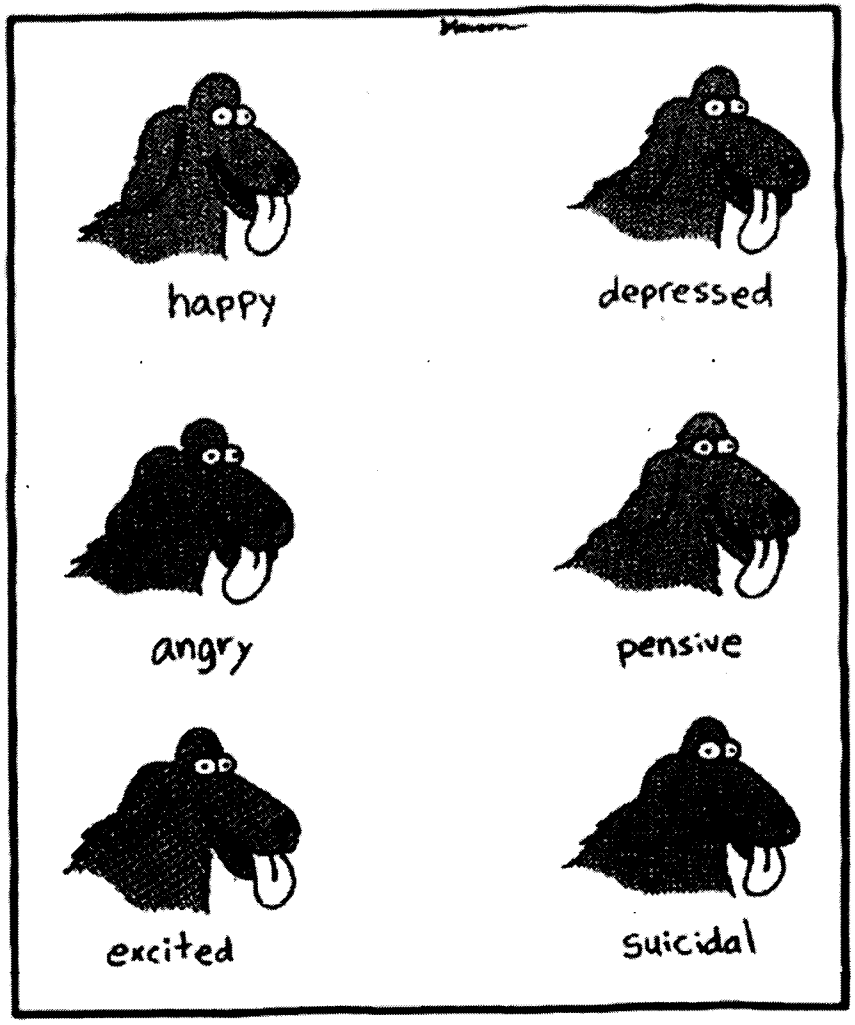


Figure: Kola & Landis, Nature Reviews: Dru
Data: DataMonitor "Pharmaceutical R&D

Problem
- High Phase III failure rate
- Lack of efficacy
- Poorly predictive pre-clinical models

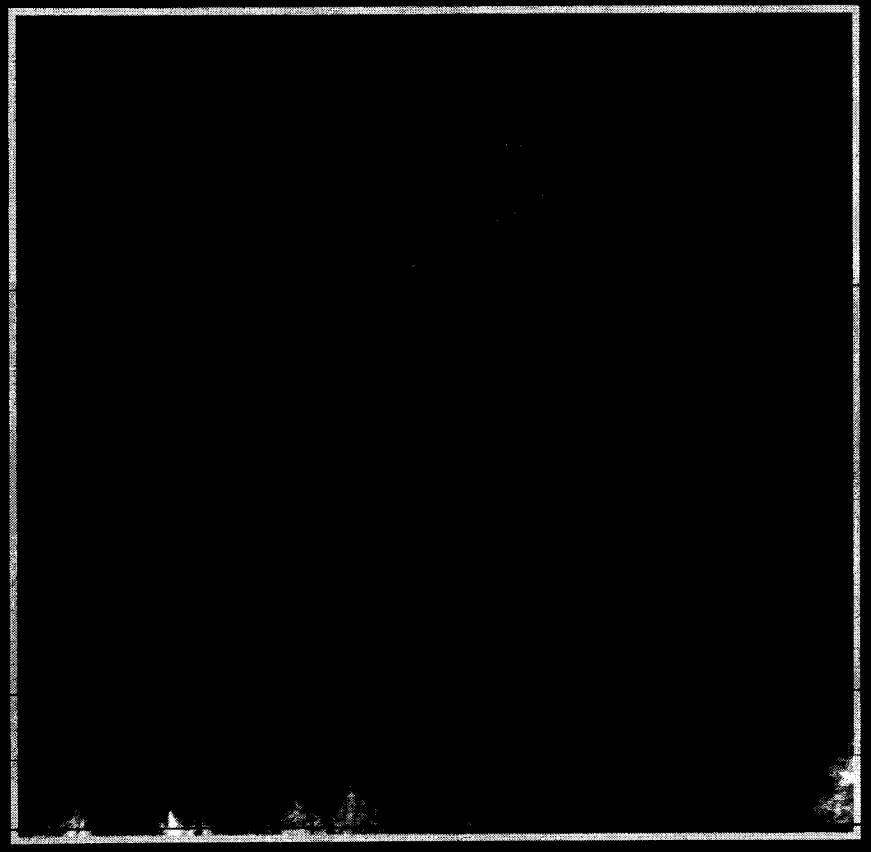
BCI Solution
- Understand disease mechanism
- Physiology-relevant models
- Neurogenesis discovery platform

The issue with CNS preclinical animal models



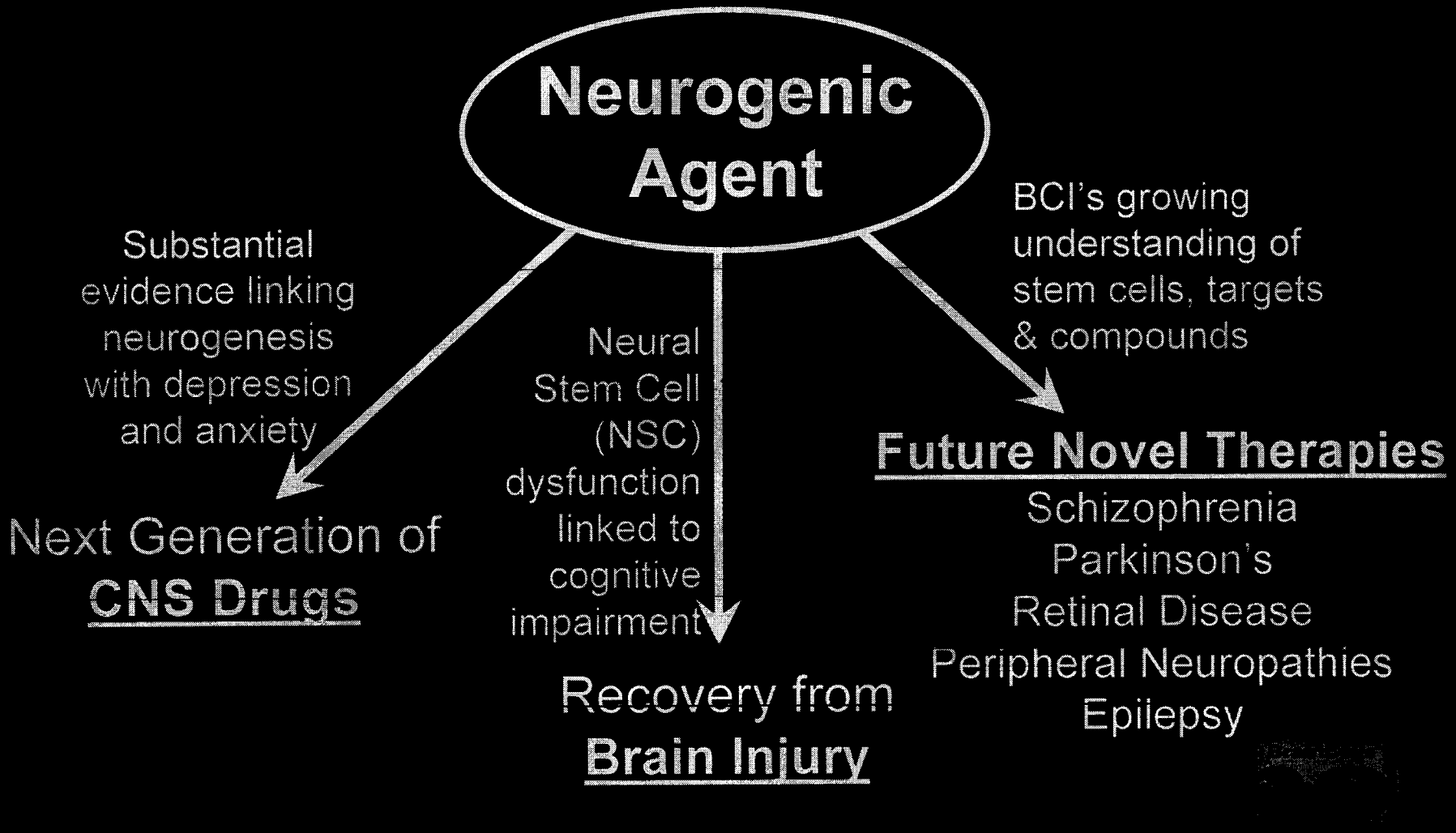
How to recognize the moods of an Irish setter

BCI & CNS Disorders

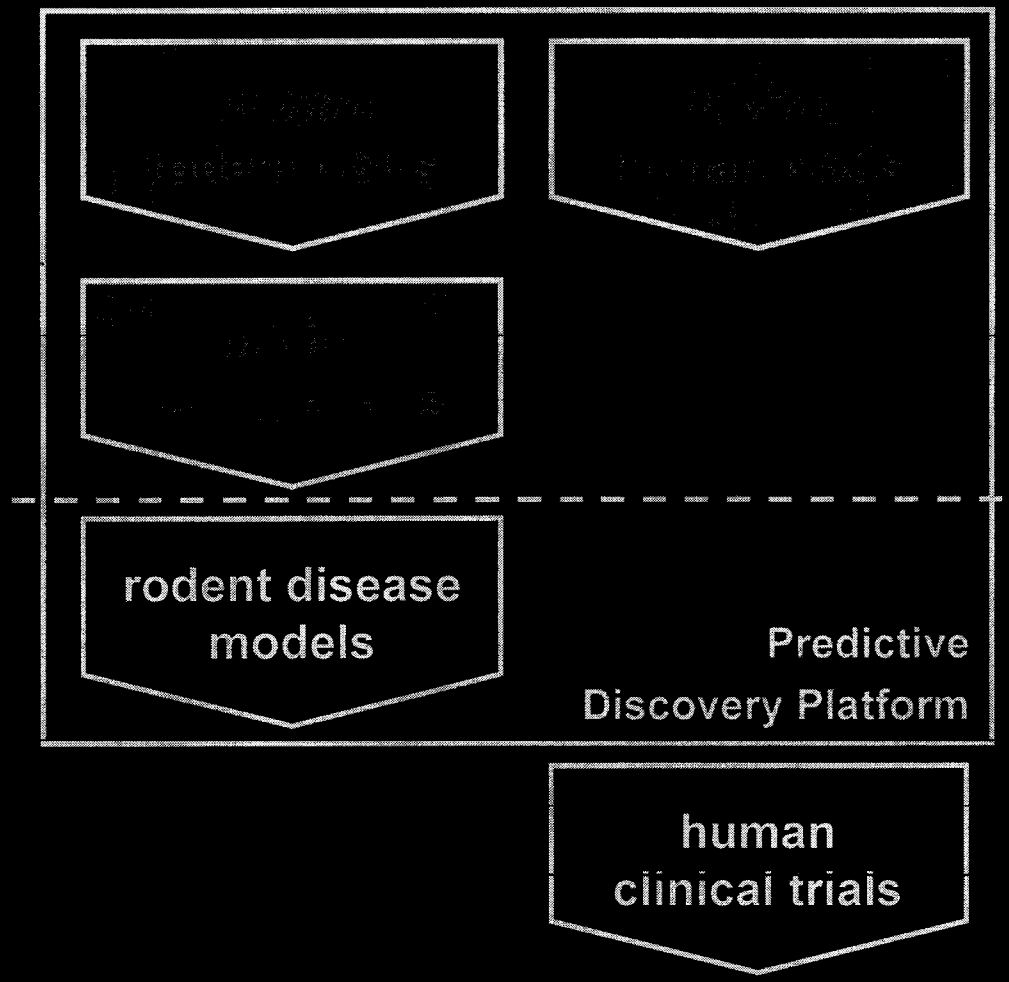


- Studying Neurogenesis enables
  - Prediction of efficacy/ toxicity
  - Optimization of dosing
  - Identification of new targets
  - Identification of active metabolites
- Market opportunity
  - Huge markets ($20+B)
  - Few new mechanisms

BCI Opportunity



BCI Neurogenesis Platform



Lead Neurogenic Compounds

Development Strategy
Translating Science into Products

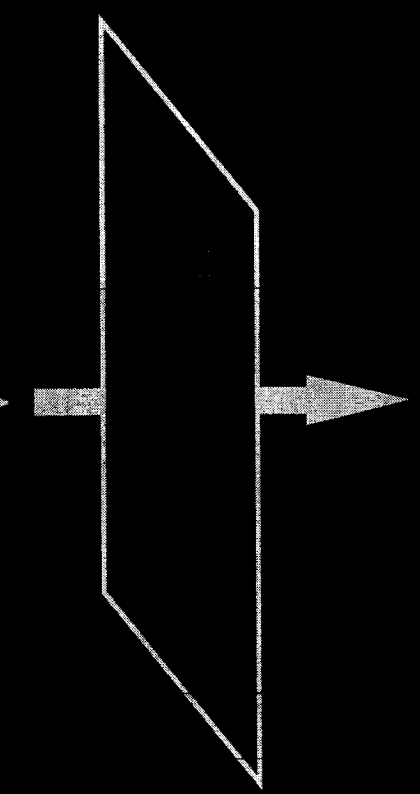
In-Licensing Candidates

Marketed Drugs

Generics

Pharmacological Standards

Discovery Project Compounds



- Select in-licensing candidates
- Re-purpose existing drugs
- Understand drug mechanism
- Develop predictive models
- Establish novel patent claims
- Lead optimization & selection

BrainCells, Inc. Summary

- Paradigm-Shifting Science directly addresses significant development hurdle in CNS
- Candidate Selection driven by high-value data, not just ideas
- Repeatable Success based on Neurogenesis Platform
- Investor groups looking for more than "incremental" improvements

Management + Investors

Management Team

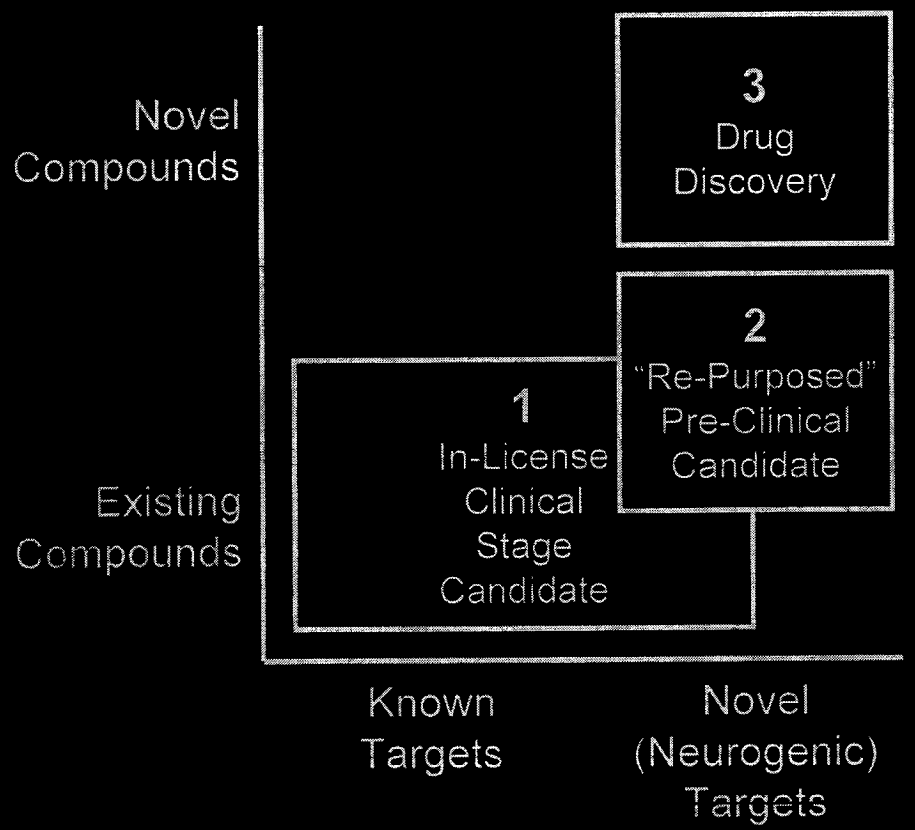
- James Schoeneck (ActivX, Prometheus, Centocor, RPR)
  - Chief Executive Officer
- Harry Hixson, Ph.D. (Amgen, Neurocrine, Signal)
  - Chairman
- Edward Hodgkin, D.Phil. (Tripos, Wyeth, British Biotech)
  - President & Chief Business Officer
- Carrolee Barlow, M.D. Ph.D. (Merck, Salk Institute)
  - Vice President, Biology R&D

Series A Investors

- Oxford Bioscience Partners
- Bay City Capital
- Technology Partners
- AM Pappas & Associates
- NeuroVentures

Back up slides

Building BCI's Product Pipeline



1 Clinical Stage Candidate
- Rapidly build high-value pipeline
- Use platform to select candidate
- Commence Phase II clinical trial

2 Pre-Clinical Candidate
- Prioritized list of 'neurogenic' targets
- In-license compound IP
- Leverage platform for selection

3 Drug Discovery Program
- Profile compound libraries
- Identify novel neurogenic targets
- Leverage platform for lead optimization

Exhibit D

BIOCOM thanks our Premium Members MERCK Paul Hastings ATTORNEYS Pfizer PILLSBURY WINTHROP

BIOCOM

Accelerating Life Science Success

BIOCOM MEMBERSHIP SEARCH

Search the BIOCOM Member Database for member companies and links to their websites. Use the search form below to search by company category or company name.

OPTION 1: Search By Category

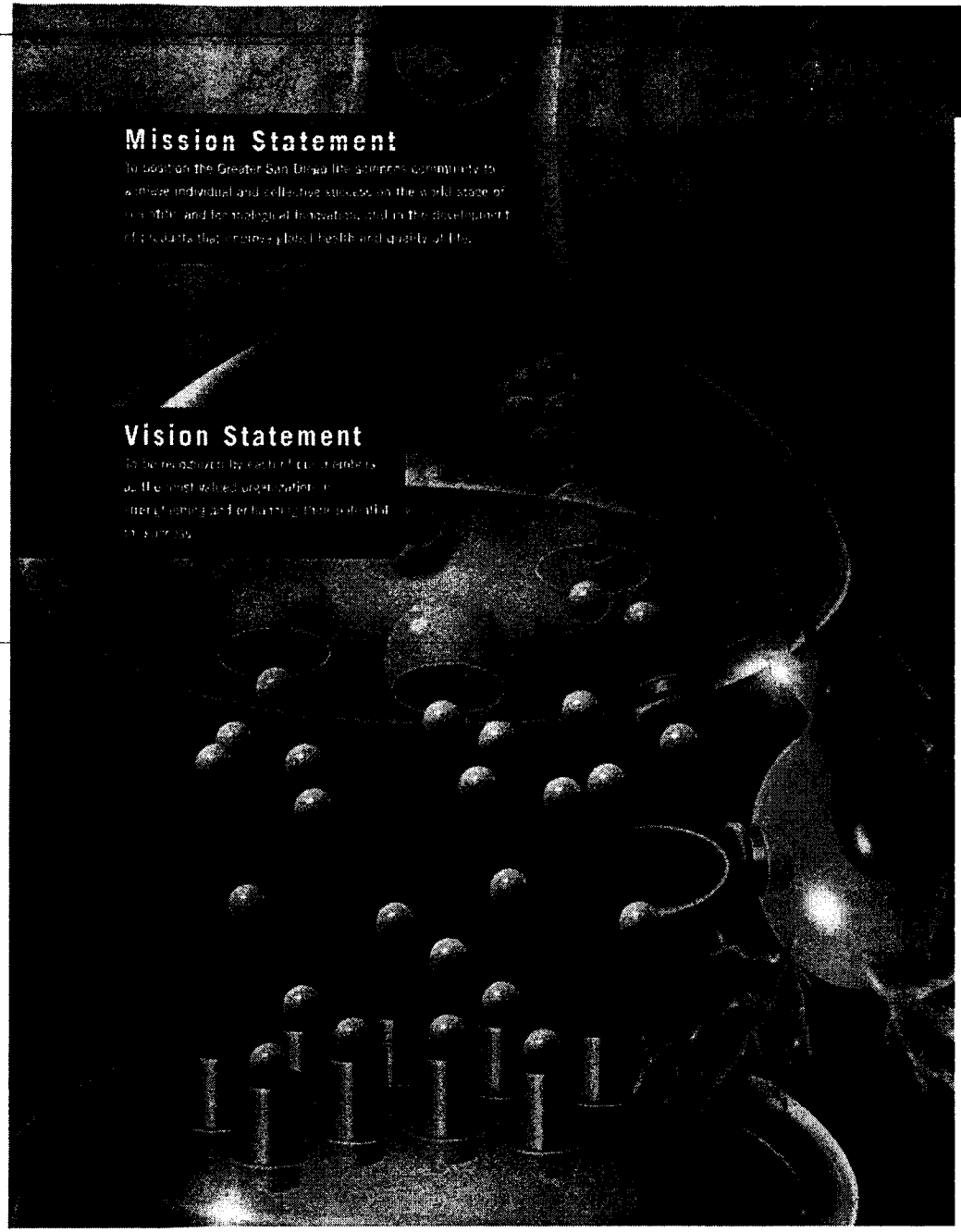
Category: Any

Company Name: braincells

Search

Company Name	Website
BrainCells, Inc	www.braincellsinc.com

4510 EXECUTIVE DRIVE, PLAZA ONE, SAN DIEGO, CA 92121 OFFICE 858-455-0300, FAX 858-455-0022



Mission Statement

To lead the Greater San Diego life sciences community to enhance individual and collective success in the worldwide pursuit of scientific and technological innovation, and in the development of products that improve global health and quality of life.

Vision Statement

To be recognized by each of our members as the most valued organization for fostering and facilitating their collective success.

Welcome to BIOCOM

Proudly representing the Greater San Diego and Southern California life sciences community, BIOCOM has become the largest regional life sciences association in the world. Highly focused on the success of its 450+ members and the San Diego life sciences community, BIOCOM consistently creates value through its programs and relevant member benefits.

BIOCOM has implemented a cutting-edge, three-year strategic plan and leadership agenda that incorporates five strategic goals to help accelerate life science success for its members. These five strategic goals are:

1. BIOCOM will work collaboratively with partner organizations and firms to implement and manage aggressive **financial capital development** programs that attract, sustain, and fuel growth of the region's biotech industry.
2. BIOCOM will work collaboratively with partner firms and organizations to create and manage image, business development, and outreach platforms that position the Greater San Diego life sciences community as a **center of innovation and scientific development** to audiences throughout the world.
3. BIOCOM will partner with its members to create and manage **legislative, regulatory, and public affairs agendas,** at the local, state, and national levels.
   - These agendas will directly support the needs of its membership.
   - BIOCOM will also pursue primary industry leadership on those issues/challenges deemed strategic to the success of its members and the BIOCOM mission.
4. BIOCOM will, through the capabilities of its members, create and manage a collaborative network that enhances the environment for and performance of **scientific/technology discovery, transfer, and development** in the Greater San Diego region.
5. BIOCOM will partner with local/state agencies, member firms, and learning institutions to establish and implement an aggressive **workforce development** agenda to support member needs and fuel growth of the region.

BIOCOM

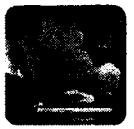
Membership
Strength. Value. Success.

The strength of BIOCOM's membership comes from the diversity of company size, range of industry sub-sectors, and goals of membership.

There is no "typical" BIOCOM member. Member companies span the spectrum of life sciences, ranging in size from Pfizer, Merck, and Amgen to smaller start-up spinoffs from U.C. San Diego, the Salk Institute or the Scripps Research Institute. A complementary segment of BIOCOM membership includes companies that provide top-of-the-line support services and products that are critical to the continued success of our community.

Diversity notwithstanding, all BIOCOM members have one thing in common: they value their membership because BIOCOM successfully ensures that Greater San Diego is the best place in the world for doing business as a life sciences company.




Membership in BIOCOM is an investment in your company, your San Diego life sciences community, and your industry as a whole.

BIOCOM committees are here to serve our diverse membership. Get involved now.

- Capital Formation
- Communications
- Education
- Environmental Health and Safety
- Executive and Strategic Oversight
- Facilities
- Finance
- FDA
- Financial Community Relations
- Infrastructure
- Intellectual Property and Patent Law
- Legislative
- Medical Device
- Member Services
- Public Policy & Regulatory Action
- Purchasing Group Board
- Science and Technology
- Workforce and Capability Development

"BIOCOM provides significant value to CancerVax and the biomedical industry in a number of important areas. They are a powerful advocate at the state and local level for the life sciences industry on important legislative initiatives. Their educational and networking events and committee structure have tremendous benefits for our staff. We have also benefited with significant savings through the activities of the Purchasing Group."

David F. Hale
President and CEO
CancerVax Corporation

"Membership in BIOCOM helps us stay abreast of the issues facing the life science industry. Our participation better positions us to service our clients and allows us to meet new companies. Marsh has found great value in the time we have dedicated in supporting the life science community through BIOCOM."

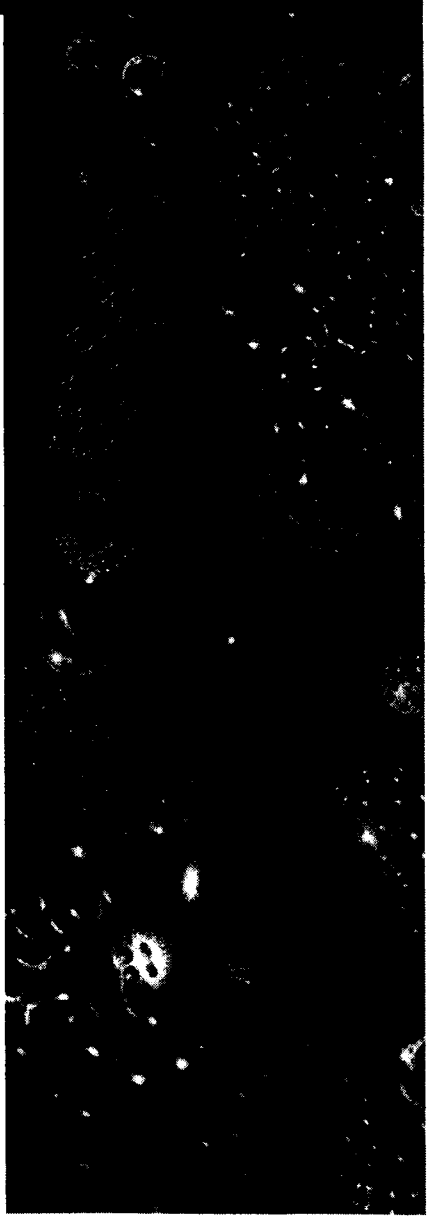
Trindl Reeves
Managing Director
Head of Office
Marsh Risk & Insurance Services

"BIOCOM has been of tremendous value to PhotoThera. BIOCOM membership has enabled our company to save thousands of dollars through the Purchasing Group and has given the company valuable information about critical public policy issues."

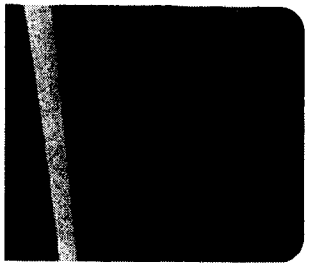
Jackson Streeter MD
Founder and CEO
PhotoThera, Inc.

"SGX is a member of BIOCOM for a number of reasons. BIOCOM is a good forum for meeting and networking with other local biotech CEOs who have similar experiences in growing their companies. The interface with the national BIO organization also helps to send political messages about our industry to Washington, and it is a way to share information with the larger life sciences community here in San Diego."

Tim Harris, Ph.D.
CEO
Structural Genomix



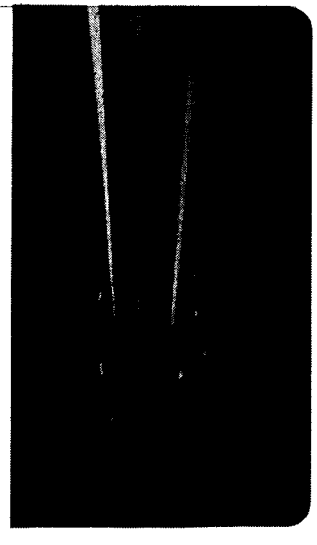
Advocacy
A United Voice



BIOCOM leads advocacy efforts for the Southern California life sciences community, representing its membership on issues critically important to the industry.

- Proactively advocates at the local, state, and federal levels on behalf of its membership.
- Works with its coalition partners to direct a united voice toward elected officials and policy makers.
- Partners with patient advocacy groups to help put a human face on its members' products by sharing life-saving success stories with legislative and regulatory bodies.
- Advocates positive policies in a variety of areas that impact the ability of companies to operate in California. The BIOCOM Legislative Committee is comprised of members with an interest in public policy who actively represent the BIOCOM membership base.
- Ensures that members have opportunities for face-to-face meetings with legislators through its legislative roundtable series, annual California Life Sciences Day, and events that focus on current concerns.

Communications
Promoting the Value in San Diego



BIOCOM reaches out nationally and internationally to position the San Diego life sciences community for success on the world stage.

BIOCOM has an aggressive communications program.

- Internal communications keep members informed about ongoing activities within the San Diego life sciences community.
- Outwardly directed communications tell the rest of the world about the strengths and successes of life science companies in the San Diego region.
- Other communications efforts include ongoing strategic media relations on a local and national basis to ensure that the press is informed about member companies and BIOCOM activities in Greater San Diego.

BIOCOM produces two publications that are widely read and circulated in the life sciences industry.

- The Biocommunique
  This free, biweekly e-mail newsletter is sent to more than 4,300 readers in the life science industry and offers informative articles, news, and event information relevant to the local biotech and medical technology industries.
- LifeLines
  This publication has a circulation of 3,500 readers and delivers an in-depth, focused look at long-term trends within BIOCOM member companies. Members receive this full-color quarterly magazine by mail and it is distributed at BIOCOM events.

Networking & Industry Promotion
Accessibility to the Life Sciences Community

BIOCOM gives members access to a unique and valuable network of individuals who represent all facets of the life sciences community.

Each year, BIOCOM hosts and sponsors more than 100 conferences, meetings, and events locally, as well as across the U.S., and worldwide. Through these dedicated efforts to promote the life science industry, BIOCOM helps members access opportunities for strategic partnerships, increased investment funding, and for educating public and opinion leaders about the life science industry.

Industry Promotion Highlights and Networking

BIOCOM builds networks for individuals throughout the entire life sciences community, from senior executives and scientists to elected officials and venture capitalists.

- The BIOCOM Annual Dinner is one of the largest life science community gatherings in California. More than 1,000 professionals attend this gathering in celebration of the industry's accomplishments for the year. The dinner features a nationally recognized keynote speaker, awards to key industry supporters, and a special video that celebrates California's life sciences achievements.
- The BIOCOM Monthly Breakfast Series, a long-standing event within the San Diego life sciences community, consistently attracts such world-class speakers as economist Arthur Laffer, FDA official David Feigal, and former U.S. Ambassador Robert Ellsworth.

Additional BIOCOM Events and Major Networking Opportunities

Life Sciences Community
Annual Dinner
CALBIOsummit
Committee Events
Facilities Workshops
Monthly Breakfast Series
Nobel Laureate Dinner
Open House

Senior Management
CEOsummit
CEO Receptions

Purchasing Group
Lunch & Learns
Quarterly Meetings
Supplier Showcase

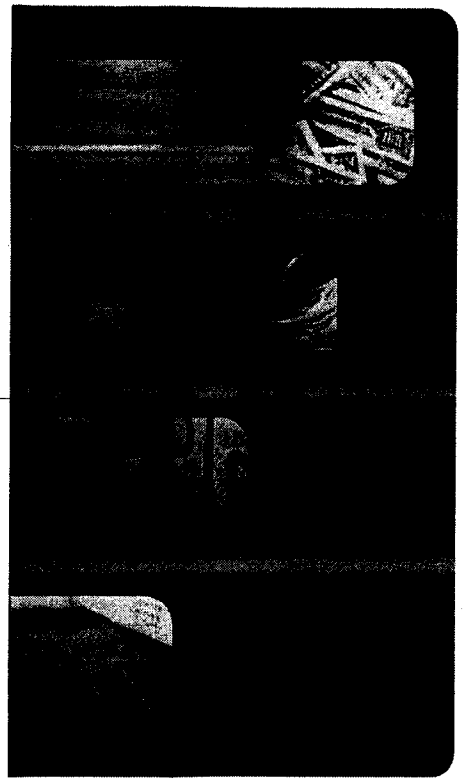
Medical Device & Diagnostics
North County Events

Elected Officials
Legislative Fly-Ins
Legislative Round Tables

Academia
Golf Tournament
Scholarship Fundraiser

Financial Community
BIO Venture Forum
CFO Receptions
Life Science Venture Forum

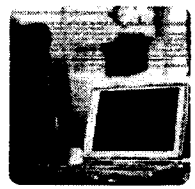
Purchasing Group
Increasing Your Buying Power



The BIOCOM Purchasing Group helps member companies achieve economies of scale that can reduce costs and translate to greater operating efficiency. The realized savings more than pay for membership dues of companies that participate in the BIOCOM Purchasing Group.

- Member participants have access to deep discounts on such commonly purchased commodities as laboratory supplies and office supplies.
- The BIOCOM Purchasing Group offers volume-based discounts to any member at no additional cost, regardless of size or industry group.
- The BIOCOM portfolio of more than 20 contracts for products and services helps members to streamline their supply chains and attain meaningful, bottom-line savings.
- The group buying process is governed by BIOCOM members, enabling member companies to obtain high quality products and services at favorable prices while they benefit from innovative supplier support.

Workforce & Education
Ensuring Continual Progress



WORKFORCE

BIOCOM works to develop a local workforce that is prepared to meet the needs of our growing life sciences industry. Our workforce goals include generating better data for the industry, securing funding to support training needs for new and incumbent employees, and creating a multiuse center to assist in the coordination of academic programs and services.

EDUCATION

Education outreach is an investment in our youth and our future employment needs. BIOCOM makes it easy for our members to make meaningful contributions to student outreach programs.

- BIOCOM Scholarship Fund
- High Tech Fair
- Speakers Bureau
- Job Shadowing
- Donation of used equipment to schools
- Internships (students and teachers)
- Nobel Laureate Dinner Essay Contest
- Company tours

PROFESSIONAL DEVELOPMENT

Developing managers and leaders

BIOCOM offers a unique series of Management and Leadership development programs designed to help managers in scientific environments to deliver more in less time. There are two programs in the series.

1. From the Laboratory to Leadership: an overview of product development in the life sciences industry, goal setting and planning, priority and meeting management, conducting performance reviews, conflict resolution, creating productive teams and more.
2. Leveraging Your Leadership: leadership skills including creating a vision, driving organizational objectives, inspiring innovation and creativity, effecting positive change, influence skills, and more.

Introduction to Biotechnology

BIOCOM offers courses designed for non-science professionals working in the life science industries. Perfect for attorneys, journalists, policy makers, marketing professionals, investors, corporate communications, human resources experts, and anyone wanting to have a better understanding of biotechnology.

Medical Technology Courses

BIOCOM offers courses for the medical technology professionals in our community. Topics include cGMP, small and large batch manufacturing, and clean room technology.

BIOCOM Member Benefits

BIOCOM membership is comprised of industry companies and service providers. Industry Members are corporate members comprised of biotechnology and medical device companies with member dues being based on number of employees and profitability. Over 65% of the life science companies in San Diego are members of BIOCOM.

INDUSTRY MEMBER

Sponsorship
- Secondary rights

Events
- Member discount
- Automatic invite to all CEO/CFO Receptions
- Automatic invite to any other event

Committees
- Any non-board standing committees with chair priority
- Event planning committees
- Board committees
- Board consideration

BIOCOM Website
- Link on BIOCOM website's membership page

Biocommunique Newsletter
- Articles: 3/year
- Event Announcements: 3/year
- Listed by name

Lifelines Magazine
- Possible profile
- Ad space: first choice
- Listed by name

Membership Directory
- Profile full page in industry member section, black and white logo
- Ad space: first choice

Purchasing Group
- Eligible for all PG discounts
- Automatic inclusion in relevant RFPs

BIOCOM Lobby Recognition
- Recognition by name in BIOCOM lobby

PREMIUM INDUSTRY MEMBER

Benefits include additional exposure and opportunities as listed on the following page under "Premium Provider."

If your company is focused on creating more contacts and building stronger relationships within the life sciences community, membership with BIOCOM is a valuable option for meeting these objectives.

PROVIDER

Sponsorship
- As available

Events
- Member discount

Committees
- Any non-board standing committees as available

BIOCOM Website
- Link on BIOCOM website's membership page

Biocommunique
- Articles: 3/year
- Event Announcements: 3/year
- Listed by name

Lifelines Magazine
- Profile: none
- Ad space: as available
- Listed by name

Membership Directory
- Profile: 1/3 page back section, no logo
- Ad space: none

Purchasing Group
- Eligible for all PG discounts
- Automatic inclusion in relevant RFPs

BIOCOM Lobby Recognition
- Recognition by name in BIOCOM lobby

KEY PROVIDER

Sponsorship
- Secondary rights

Events
- Member discount
- Free Breakfasts (up to 2 people per breakfast, $630 total value)
- Invitation to Nobel Laureate Dinner

Committees
- Any non-board standing committees
- Chair priority over Provider for standing committees
- Event planning committees

BIOCOM Website
- Recognition by name on BIOCOM homepage with link to company website
- Link on BIOCOM website's membership page

Biocommunique
- Articles: 6/year
- Event Announcements: 6/year
- Listed by name more prominently than Provider

Lifelines Magazine
- Possible profile
- Ad space: priority over Providers
- Recognition: listed by name more prominently than Providers

Membership Directory
- Profile: full page in middle section, black and white logo
- Ad space: secondary choice

Purchasing Group
- Eligible for all PG discounts
- Automatic inclusion in relevant RFPs
- Listed as Key Provider at PG events

BIOCOM Lobby Recognition
- Recognition by name in large bold type in BIOCOM lobby

PREMIUM PROVIDER

Sponsorship
- First rights

Events
- All events free, excluding: Nobel Laureate Dinner, Annual Dinner, CalBioSummit, CEOsummit (limit 4 per company for free events; member discount applies)
- Invitation for one to CEOsummit and CEO Receptions
- Invitation to Nobel Laureate Dinner
- Preferred booth space at CALBIOsummit and other events
- Recognition by logo at appropriate events

Committees
- Any non-board standing committees
- Chair priority over Key Provider for standing committees
- Event planning committees
- Board-level committees
- Board consideration

BIOCOM Website
- Recognition by logo on BIOCOM homepage with optional link to separate BIOCOM page
- Link to company website from BIOCOM homepage or separate BIOCOM page
- Link on BIOCOM website's membership page

Biocommunique Newsletter
- Articles: 12/year
- Event Announcements: no limit
- Listed by logo on separate page

Lifelines Magazine
- Automatic profile
- Ad space: first choice
- Listed by logo on distinct separate page
- Article opportunity

Membership Directory
- Profile: 2 pages with color logo, front section
- Ad space: first choice

Purchasing Group
- Eligible for all PG discounts
- Automatic inclusion in relevant RFPs
- Listed as Premium Member at PG events

BIOCOM Lobby Recognition
- Recognition by logo in BIOCOM lobby
- Collateral in BIOCOM lobby

Exhibit E

Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice

Iiris Hovatta[1], Richard S. Tennant[1], Robert Helton[1,2], Robert A. Marr[1], Oded Singer[1], Jeffrey M. Redwine[3], Julie A. Ellison[1], Eric E. Schadt[4], Inder M. Verma[1], David J. Lockhart[1] & Carrolee Barlow[1,2]

Anxiety and fear are normal emotional responses to threatening situations. In human anxiety disorders—such as panic disorder, obsessive–compulsive disorder, post-traumatic stress disorder, social phobia, specific phobias and generalized anxiety disorder—these responses are exaggerated. The molecular mechanisms involved in the regulation of normal and pathological anxiety are mostly unknown. However, the availability of different inbred strains of mice offers an excellent model system in which to study the genetics of certain behavioural phenotypes[1–3]. Here we report, using a combination of behavioural analysis of six inbred mouse strains with quantitative gene expression profiling of several brain regions, the identification of 17 genes with expression patterns that correlate with anxiety-like behavioural phenotypes. To determine if two of the genes, glyoxalase 1 and glutathione reductase 1, have a causal role in the genesis of anxiety, we performed genetic manipulation using lentivirus-mediated gene transfer. Local overexpression of these genes in the mouse brain resulted in increased anxiety-like behaviour, while local inhibition of glyoxalase 1 expression by RNA interference decreased the anxiety-like behaviour. Both of these genes are involved in oxidative stress metabolism, linking this pathway with anxiety-related behaviour.

Different inbred mouse strains have different physical and behavioural phenotypes that are heritable and stable[1–3]. We combined gene expression profiling and behavioural testing of multiple highly characterized strains in search of candidate genes for anxiety-like behaviour. We identified several strong candidates and performed follow-up functional studies to demonstrate directly that altered expression levels of the identified genes affected anxiety-like behaviour in mice (Supplementary Fig. 1).

Several methods to test levels of anxiety-like behaviour in mice have been developed and pharmacologically 'validated'; that is, shown to be specifically responsive to agents with proven anxiolytic or anxiogenic effects[4]. We used two such tests to measure anxiety-like behaviour in six inbred mouse strains—the light–dark box test and the open-field test (described in the Supplementary Methods). Strain characterization with both tests was consistent (Pearson coefficient of correlation between the 'open-field time spent in the middle of the chamber' and the 'light–dark box time spent in the light compartment' was high, $r = 0.84$), and showed that A/J, DBA/2J and 129S6/SvEvTac were the most anxious strains and FVB/NJ the least anxious strain (Fig. 1a), as reported previously[5,6]. The behaviour of C3H/HeJ and C57BL6/J animals was intermediate (Fig. 1a). In contrast, although not completely ruling out an association between locomotor activity and anxiety-like behaviour, the strain order for locomotor activity, estimated as the distance travelled in the dark compartment of the light–dark box, was different from the strain order for anxiety-like behaviour (Supplementary Information).

Several methods have been used to show that the amygdala, septohippocampal system, medial hypothalamus, central periaqueductal grey, and frontal and cingulate cortices are important brain structures involved in the regulation of anxiety and fear[7–10]. Based on this information, we selected seven brain regions (the amygdala, bed nucleus of the stria terminalis, cingulate cortex, hippocampus, hypothalamus, periaqueductal grey and pituitary gland) thought to regulate aspects of anxiety-related behaviour, and used oligonucleotide arrays (Affymetrix U74Av2) to assess the expression levels of ~10,000 genes in those regions. To ensure that our experimental methodology and data analysis methods minimized the number of false positives and maximized the reliability of the results, we carefully compared at least two independent replicate samples for each brain region from each strain[11]. Reproducibility between replicates was high (Supplementary Table 1), and the estimated false positive rate was low (0.013%; see the Supplementary Methods for details).

We identified oligonucleotide probe sets that showed statistically significant differences in expression levels between two of the most anxious (A/J and DBA/2J) and the two least anxious (FVB/NJ and C57BL/6J) mouse strains in at least one brain region (see the Supplementary Methods for details). We identified eight probe sets in the hippocampus, 12 in hypothalamus, 33 in pituitary, seven in bed nucleus of the stria terminalis, 19 in periaqueductal grey, 12 in amygdala and 12 in cingulate cortex. These probe sets cover genes that are differentially expressed between the phenotypic extremes, but may not necessarily correlate with anxiety-like phenotypes across all six inbred strains. Therefore, we performed a correlation analysis to identify a subset of genes with expression levels that correlate with anxiety-related phenotypes across all strains (see the Supplementary Methods for details). Nineteen probe sets were identified (Table 1, Fig. 1b and Supplementary Table 2), corresponding to 17 candidate genes (probe sets 93268_at and 93269_at both represented glyoxalase 1 (*Glo1*), and probe sets 96215_f_at and 98525_f_at both represented erythroid differentiation regulator 1 (*Erdr1*)). In addition to the correlation analysis described above, we analysed the data with a standard implementation of a linear mixed-effects model to assess the correlation between expression and anxiety-related behaviour (Table 1 and Supplementary Table 2). Only growth hormone (probe set 92783_at) did not show a statistically significant association using this method. Some of the identified genes showed differential expression across several brain regions, while the majority of the genes were differentially expressed between strains in only a single brain region (Table 1). To independently confirm the differences, we performed quantitative polymerase chain reaction with reverse transcription (quantitative RT–PCR; qPCR) for 11 of the 17

[1]The Salk Institute for Biological Studies, Laboratory of Genetics, 10010 North Torrey Pines Road, La Jolla, California 92037, USA. [2]BrainCells Inc., 10835 Road to the Cure, San Diego, California 92121, USA. [3]Neurome Inc., 11149 North Torrey Pines Road, La Jolla, California 92037, USA. [4]Rosetta Inpharmatics LLC, Merck & Co., 12040 115th Avenue Northeast, Seattle, Washington 98109, USA.

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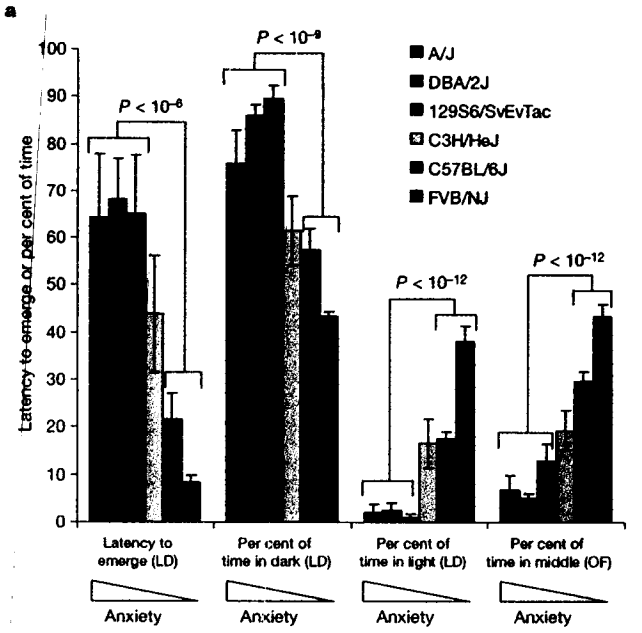
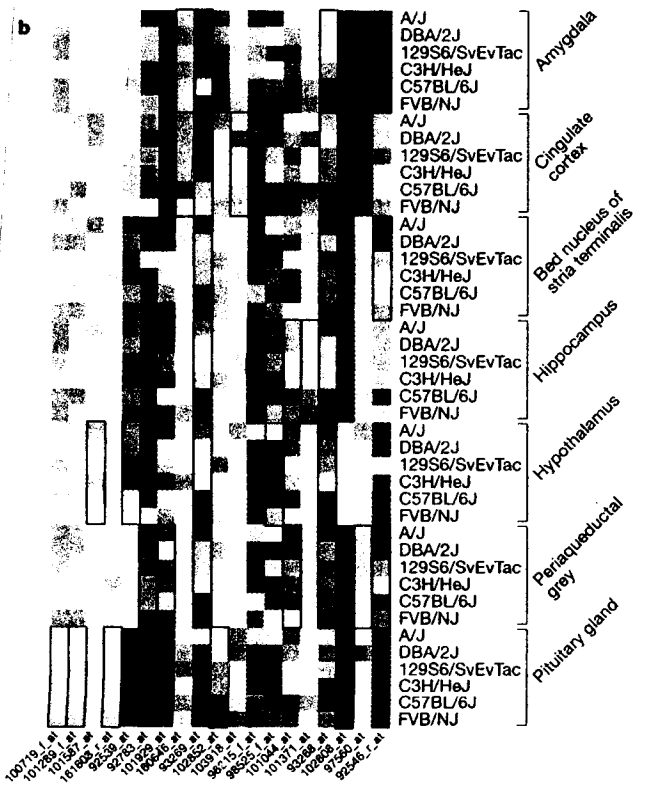
candidate genes (Supplementary Fig. 2). For most of the genes, the differences in gene expression observed by microarray analysis were confirmed by qPCR. Two genes—cadherin 2 (*Cdh2*) and epoxide hydrolase 1 (*Ephx1*)—did not show clear differential expression between the strains by qPCR. It is possible that not all of these differentially expressed genes are involved with the regulation of anxiety. For example, some of them might correlate with the phenotype by chance, so we addressed this question using functional and genetic studies.





Notably, five of the 17 candidate genes were enzymes. Enzyme activity assays were available for three of them. We measured the activities of delta-aminolevulinate dehydratase (Alad), glyoxalase 1 (Glo1) and glutathione reductase 1 (Gsr) from brain homogenates containing combined tissue of hippocampus, striatum and cortex (Supplementary Fig. 2). It seemed that *Alad* mRNA levels in FVB/NJ animals were overestimated by the microarrays, as *Alad* expression and Alad activity did not correlate with anxiety-like behaviour across the strains. In contrast, both Glo1 and Gsr enzyme activities matched the pattern found in both the microarray and qPCR analyses, with highest activities in the most anxious and lowest activities in the least anxious strains. This was particularly intriguing given that reduced glutathione (GSH), the levels of which are maintained by Gsr, is a major antioxidant in the brain. Glo1 uses GSH as a cofactor to detoxify cytotoxic methylglyoxal. Furthermore, erythrocytes from patients with anxiety disorders (such as panic disorder or obsessive–compulsive disorder) may have higher levels of antioxidant enzymes (glutathione peroxidase and superoxide dismutase)[12,13], suggesting that free radicals may have a role in the pathogenesis of anxiety disorders. Oxidative stress has also been implicated in the pathogenesis of other neuropsychiatric diseases, including schizophrenia and major depressive disorder[14,15], and Glo1 is linked to diabetes[16], Alzheimer's disease[17], autism[18] and the regulation of theta oscillations during sleep[19]. A recent study suggested Glo1 might be a biological marker for trait anxiety in bidirectionally crossed mouse lines[20]. Therefore, we sought to determine the role of these candidate genes in influencing anxiety-related behaviour in a complex genetic background.

We analysed the offspring of two different F_1 crosses of the non-anxious C57BL/6J strain and an anxious A/J strain ($AB6F_1$ and $B6AF_1$), in addition to BALB/cByJ inbred mice as this strain was shown to be very anxious. In both open-field and light–dark box tests, F_1 animals derived from the A/J and C57BL/6J crosses showed intermediate levels of anxiety-like behaviour compared to the parental strains (Fig. 2a). We hypothesized that if Glo1 and Gsr exert a strong influence on the phenotype, the activity levels of the enzymes should correlate with the anxiety-related phenotype. As expected, there was a statistically significant correlation between the open-field behaviour and the Glo1 ($P = 0.0005$) and Gsr ($P = 0.009$) enzyme activities, as measured by regression analysis over A/J, C57BL/6J, their F_1 offspring and BALB/cByJ mice (Fig. 2b and c), suggesting that these two enzymes are very strong candidates for regulating anxiety-related behaviours.

To further investigate the role of *Glo1* and *Gsr* in anxiety, we prepared lentiviral vectors to overexpress these genes *in vivo* (Supplementary Fig. 3a). The lentiviral approach was favoured over other viral vectors because lentiviral vectors efficiently transduce central nervous system cells and are not cytotoxic[21,22]. One microlitre of either *Glo1*- or *Gsr*-containing virus, or a green fluorescent protein (GFP)-containing control virus, was injected bilaterally in the region

Figure 1 | Inbred mouse strains have different levels of anxiety-related behaviours. a, Behavioural tests on inbred strains of mice. Test parameters are shown on the *x* axis. The *y* axis shows either the latency to emerge from the dark side to the light side of the light–dark (LD) chamber (zero corresponds to 0 min and 100 corresponds to 5 min), the per cent of time in the dark or light side of the light–dark chamber, or the per cent of time in the middle of the open-field (OF) chamber. See the Supplementary Methods for the test measures and analysis. Values are mean ± s.e.m. *P* values calculated using a two-tailed Student's *t*-test. **b,** A heat map based on the cluster analysis of the 19 probe sets with signals that correlated with the anxiety-related phenotype, and that were significantly different between the most and the least anxious strains (bordered by a black box). The *x* axis shows the probe set identifiers. Mouse strains are organized by tissue and level of anxiety-like behaviour on the *y* axis. Red represents high and blue represents low signal intensity, with a more intense colour showing relatively higher signal intensity.

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Table 1 | Correlation of gene expression patterns with anxiety-related phenotypes in six inbred mouse strains

Probe set	Gene title	Gene symbol	Tissue	Average fold change*	Correlation coefficient (OF behaviour)†	Association *P* value (OF-gene expression)‡
102852_at	Cadherin 2	*Cdh2*	pi	−1.72	0.95	7.7×10^{-4}
161603_r_at	Erythrocyte protein band 4.1-like 4a	*Epb4.1l4a*	pi	−3.98	0.89	2.5×10^{-2}
93268_at	Glyoxalase 1	*Glo1*	am, ci, bn, hi, **hy**, pa	−2.32	0.97	2.6×10^{-5}
93269_at	Glyoxalase 1	*Glo1*	**am**, ci, bn, hi, hy, pa	−2.53	0.94	7.8×10^{-5}
101044_at	Delta-aminolevulinate dehydratase	*Alad*	hi, **pa**	−2.17	0.84	6.0×10^{-5}
160646_at	Glutathione reductase 1	*Gsr*	am, **ci**	−2.83	0.85	2.6×10^{-3}
101371_at	Cleavage and poly-adenylation specific factor 4	*Cpsf4*	hi	−1.90	0.80	5.2×10^{-4}
97560_at	Prosaposin	*Psap*	pa	−1.73	0.80	2.4×10^{-4}
102808_at	Voltage-gated sodium channel type Iβ	*Scn1b*	pi	−2.02	0.77	1.5×10^{-3}
101929_at	Dynein light chain 2	*Dlc2*	pa	−1.85	0.76	3.2×10^{-2}
92539_at	S100 calcium binding protein A10	*S100a10*	hy	1.80	−0.76	2.0×10^{-3}
101289_f_at	Kallikrein 21	*Klk21*	pi	6.74	−0.77	3.0×10^{-2}
101587_at	Epoxide hydrolase 1	*Ephx1*	hy	2.74	−0.78	5.6×10^{-3}
92783_at	Growth hormone	*Gh*	pa	5.20	−0.80	2.9×10^{-1}
103918_at	Solute carrier family 15 member 2	*Slc15a2*	ci	4.27	−0.80	2.6×10^{-6}
92546_r_at	Prostaglandin D2 synthase	*Ptgds*	**bn**, pa	2.67	−0.82	3.1×10^{-4}
100719_f_at	Kallikrein 16	*Klk16*	pi	5.54	−0.83	1.3×10^{-3}
98525_f_at	Erythroid differentiation regulator 1	*Erdr1*	hi, **hy**	2.74	−0.87	3.5×10^{-2}
96215_f_at	cDNA clone MGC:67258	*Erdr1*	hi	3.75	−0.98	3.1×10^{-3}

* Average fold change for the C57BL/6J and FVB/NJ versus A/J and DBA/2J comparisons. Value shown is the average over all tissues showing differential expression.
† In the case of multiple tissues, the most significant value is shown (for the tissue in bold).
‡ Based on the linear mixed-effects model analysis. am, amygdala; bn, bed nucleus of the stria terminalis; ci, cingulate cortex; hi, hippocampus; hy, hypothalamus; pa, periaqueductal grey; pi, pituitary; OF, open-field test.

of the cingulate cortex of C57BL/6J and 129S6/SvEvTac mice to overexpress the corresponding genes *in vivo*. These strains were selected because they are widely used in neurobiological research, with C57BL/6J representing a non-anxious strain and 129S6/SvEvTac representing an anxious strain. Injected animals were tested in the open-field test (Fig. 2d–e and data not shown). After testing, mice were allowed to recover for a week, killed, and their brains removed for immunohistochemical and *in situ* hybridization analysis. We confirmed transgene expression associated with stereotaxic injection by *in situ* hybridization (Supplementary Fig. 3b–c).

Overexpression of *Glo1* in the cingulate cortex of the anxious 129S6/SvEvTac strain further enhanced the anxiety-related phenotype. The *Glo1*-expressing mice spent 12% more time near the walls in the open-field chamber compared to the GFP-expressing controls ($P = 0.016$; Fig. 2d). This effect was evident as early as five weeks after injection. Similarly, 129S6/SvEvTac mice overexpressing *Gsr* in the cingulate cortex were more anxious than GFP-expressing controls, although the effect was on the border of statistical significance ($P = 0.054$; Fig. 2d). The less-anxious C57BL/6J mice injected with the *Gsr* lentivirus also showed an increase in anxious behaviour, spending 16% more time near the walls in the open-field chamber compared to GFP-expressing controls ($P = 0.003$; Fig. 2e). However, overexpression of *Glo1* in the C57BL/6J background did not increase the anxiety-related behaviour compared to GFP controls ($P = 0.212$; Fig. 2e). The behaviours of the three groups (*Glo1*-, *Gsr*- and GFP-expressing animals) were significantly different at five weeks after injection in 129S6/SvEvTac mice ($P = 0.047$), and at seven weeks after injection in C57BL/6J mice ($P = 0.040$), as shown by a Kruskal–Wallis non-parametric analysis of variance (ANOVA).

To further prove that the expression level of these genes modulates anxious behaviour, we tested whether inhibition of *Glo1* gene expression led to a decrease in anxiety-like behaviour using lentiviral vectors that expressed an siRNA (small interfering RNA) against *Glo1* (siGlo1). A control vector was used that expressed an siRNA against the human *p53* gene (sihp53)[23], which has been shown not to affect the expression of mouse *p53* (Supplementary Fig. 4; O.S. and I.M.V., unpublished results). The 129S6/SvEvTac and C57BL/6J strains of mice were injected with either a virus expressing siGlo1 or sihp53. Five weeks later, animals were tested using the open-field test. The 129S6/SvEvTac mice injected with siGlo1 virus spent 49% more time in the middle of the chamber compared with control animals injected with the sihp53 virus ($P = 0.036$; Fig. 2f). Likewise, C57BL/6J mice injected with siGlo1 virus spent 38% more time in the middle of the chamber compared with control animals injected with the sihp53 virus ($P = 0.0002$; Fig. 2f), indicating that inhibition of *Glo1* expression in the cingulate cortex reduces levels of anxiety-like behaviour. We confirmed transgene expression associated with stereotaxic injection by visualizing GFP expression associated with lentiviral infection (Supplementary Fig. 3d).

The results of our lentivirus experiments show that overexpression of either *Glo1* or *Gsr* in the cingulate cortex increases, while inhibition of *Glo1* expression by siRNA decreases, the level of anxiety-like behaviour of mice. These results strongly support the hypothesis that changes in the expression levels of *Glo1* and *Gsr* in the brain lead to a significant effect on anxiety-related behaviour, and establish a causal role for these genes, which are both part of a pathway that regulates oxidative stress, in the genesis of anxiety-like behaviour.

We have shown that gene expression profiles of specific brain regions of anxious and non-anxious mice differ significantly. Our expression-based approach is expected to complement traditional QTL (quantitative trait loci) mapping: genes with expression levels that are correlated with the trait of interest and physically reside in close proximity to a QTL for the trait are good candidates for genes directly responsible for the QTL[24,25]. In fact, several of our candidate genes reside within chromosomal regions with identified QTLs for anxiety-related behaviour[26,27] (Supplementary Table 2). The newly identified genes should further our understanding of the specific genes, pathways and mechanisms that are important for the regulation of normal and pathological anxiety in mice and humans.

METHODS

Animals. Seven-week-old male mice were obtained from the Jackson Laboratory (A/J, BALB/cByJ, C3H/HeJ, C57BL/6J, DBA/2J, FVB/NJ and B6AF1/J) or from Taconic Farms (129S6/SvEvTac). $AB6F_1$ animals were bred at the Salk Institute using parental animals derived from the Jackson Laboratory. Animals were singly housed for one week before behavioural testing or dissections. All animal procedures were approved by the Salk Institute for Biological Studies institutional animal care and use committee. Different animals were used for behavioural testing and gene expression profiling in order to measure baseline gene expression differences.

Behavioural testing. Anxiety-related behaviour was measured using the light–dark box test and the open-field test (see the Supplementary Methods for details).

Tissue collection and RNA preparation. Animals were killed by cervical

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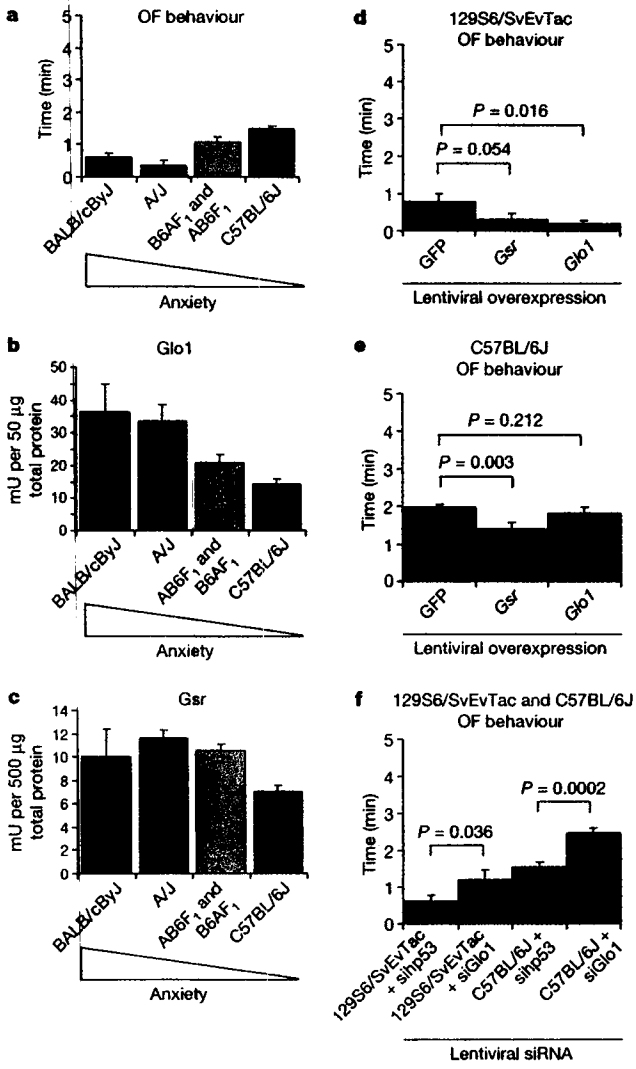

Figure 2 | Glyoxalase 1 (Glo1) and glutathione reductase 1 (Gsr) regulate anxiety-like behaviour in inbred mouse strains. a, Open-field (OF) behaviour. Mouse strains are shown on the *x* axis. Time spent in the middle of the open-field chamber is shown on the *y* axis. Values are mean ± s.e.m. **b**, Glo1 and **c**, Gsr brain enzyme activity (mean of two to four animals ± s.d.). See the Supplementary Methods for a description of the units. **d–f**, Open-field behaviour of *Glo1*-, *Gsr*- or GFP-overexpressing 129S6/SvEvTac mice five weeks after injection of the lentivirus (**d**); *Glo1*-, *Gsr*- or GFP-overexpressing C57BL/6J mice seven weeks after injection (**e**); and siGlo- or sihp53-expressing 129S6/SvEvTac and C57BL/6J mice five weeks after injection (**f**). In each case, the *x* axis shows the name of the injected lentivirus. Time spent in the middle of the open-field chamber is shown on the *y* axis. Values are mean ± s.e.m. *P* values calculated using a one-tailed Student's *t*-test.

dislocation. All dissections were performed between 11.00–17.00 h on a Petri dish filled with ice using a dissection microscope. The dissected brain regions for gene expression analysis included the amygdala, cingulate cortex, hypothalamus, hippocampus, pituitary, periaqueductal grey and bed nucleus of the stria terminalis. Hippocampus samples were directly frozen on dry ice and stored at −80 °C. The smaller brain structures were collected in RNA Later buffer (Ambion), and samples from 2–5 animals were pooled and stored at −80 °C. The extraction of total RNA from the tissues was performed using the TRIzol reagent (Invitrogen) according to the manufacturer's instructions. Only samples with an absorbance ratio at 260 nm/280 nm (A_{260}/A_{280}) greater than 2.0 in TE buffer were used for further experiments.

Microarray experiments. Gene expression levels were measured using the Murine Genome U74Av2 arrays (Affymetrix). Bed nucleus of the stria terminalis, hippocampus, hypothalamus, periaqueductal grey and pituitary gland samples were labelled using 10 µg of total RNA as the starting material. Owing to the small size of amygdala and cingulate cortex, samples from these tissues were labelled using 50 ng of total RNA as the starting material, using two rounds of complementary DNA synthesis and *in vitro* transcription (IVT). Labelling of samples, hybridization and scanning were performed as described[28]. Two-round labelling was performed using the MessageAmp kit (Ambion) according to the manufacturer's instructions, with the exception that the second IVT was done using the Enzo BioArray high yield RNA transcript labelling kit (Enzo Life Sciences).

Data analysis. See the Supplementary Methods for further details concerning the analysis of differentially expressed genes and the determination of reproducibility between measurements, as well as the regression analysis between the behavioural results and enzyme activity levels.

Quantitative RT–PCR. PCR reactions were done using the SYBR Green master mix (Applied Biosystems) in an ABI Prism SDS 7900 HT machine (Applied Biosystems) as described in the Supplementary Methods.

Enzyme activity assays. Eight-week-old mice were killed by decapitation and their cortex, hippocampus and striatum dissected under a dissection microscope, frozen on dry ice, and stored at −80 °C. The enzyme activity levels of Alad, Glo1 and Gsr were determined as described in the Supplementary Methods.

Lentivirus-mediated gene transfer. Plasmids were constructed for the production of lentiviral vectors that expressed either *Glo1* or *Gsr* with a carboxy-terminal HA-tag, or GFP, in the overexpression experiment. We sequenced the cDNA of *Glo1* and *Gsr* in order to find single nucleotide polymorphisms between the strains (see the Supplementary Methods and Supplementary Information). For the overexpression experiment, a variant of *Glo1* from the A/J strain was cloned. For the siRNA experiment, lentiviral vectors were constructed that expressed siRNA against *Glo1* (siGlo1) or human *p53* (sihp53) from the human H1-RNA promoter as described before (O.S. and I.M.V., unpublished results and ref. 23) (Supplementary Fig. 3a). Further details about virus production are given in the Supplementary Methods. A total of 50 129S6/SvEvTac and 50 C57BL/6J male mice were obtained from Taconic Farms or the Jackson Laboratory, respectively, at five weeks of age, and housed five mice per cage. After one week of acclimatization, mice were injected bilaterally with 1 µl (1.1×10^6 transducing units) of either HA–*Glo1*, HA–*Gsr*, GFP, siGlo1 or sihp53 virus (ten animals of both strains per construct) into the cingulate cortex using a stereotaxic frame. The stereotaxic coordinates were: 1.4 mm rostral to bregma, 0.5 mm lateral to midline, and 1.5 mm ventral from the dural surface. Four weeks after injection, mice were separated into individual cages. A few animals died after the injections, and the final number of animals used for further experiments are detailed in the Supplementary Methods. The open-field behavioural test was conducted five weeks and seven weeks after injection in the case of the overexpression experiment, and five weeks after injection in the case of the siRNA experiment. Mice were allowed to recover for a week, after which time they were killed and their brains were collected for the immunohistochemical or *in situ* hybridization analysis (see the Supplementary Methods for details).

Software tools. Further details on the TeraGenomics microarray analysis tool are available at http://www.teragenomics.com. The Bullfrog software can be downloaded from http://www.barlow-lockhartbrainmapnimhgrant.org/.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions D.J.L. and C.B. conceived of and initiated the project. I.H., D.J.L. and C.B. designed the research. I.H. and R.S.T. performed the microarray, enzyme activity, sequencing and real-time qPCR experiments. I.H. and R.H. performed the behavioural analyses and lentivirus injections. I.H., J.M.R., J.A.E. and C.B. designed and J.M.R. performed the *in situ* hybridization experiments. I.H., R.A.M., O.S., I.M.V. and C.B. designed the lentivirus experiment, and R.A.M., O.S. and I.M.V. contributed the lentivirus vectors. I.H., E.E.S., C.B. and D.J.L. analysed the data. I.H., E.E.S., D.J.L. and C.B. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Author Information Microarray data have been deposited in the NCBI Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) and are accessible through the GEO series accession number GSE3327. Reprints and permissions information is available at npg.nature.com/reprintsandpermissions. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to C.B. (cbarlow@braincellsinc.com).

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DNA instability in the brain: survival of the 'fittest'

Carrolee Barlow & Kai Treuner

A new mouse model suggests that genomic instability leads to neuronal cell death in Nijmegen breakage syndrome—a neurological disease associated with predisposition to cancer. Impairing ATM or p53 function in the mice holds cell death at bay, restoring normal neurological function despite persistent genetic abnormalities (pages 538–544).

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The rapid expansion of neural stem cells propels the formation of the nervous system, followed by migration and differentiation into appropriate cell types. The precise regulatory details of this program are a fertile area of investigation. In recent years, new insights into neurogenesis have come from an unexpected area—cancer biology. Mutations in genes that regulate DNA repair, genome surveillance and the cell cycle have been linked to developmental and progressive neurological diseases.

The work of Frappart *et al.*[1] in this issue further examines the interplay between DNA repair defects and neurological disease. The authors focus on the gene *NBS1*, mutated in Nijmegen breakage syndrome (NBS). NBS, a rare autosomal recessive disease, is characterized by sensitivity to radiation and predisposition to cancer in conjunction with microcephaly and mental retardation.

The authors selectively eliminated nibrin, the protein encoded by *NBS1* (called *Nbn* in mice), in the developing nervous system. They observed extensive genome damage in neural precursor cells. This damage marked the cells for destruction by apoptosis, leading to extensive cell loss and abnormal development of the cerebellum. The authors next carried out a series of *in vitro* and genetic studies designed to reduce or eliminate signaling to the DNA repair and cell cycle machinery through the tumor suppressor p53—and showed that loss of the p53 signaling pathway can rescue cells and allow for near-normal development.

One of the first genes pinned to both a cancer and neurological syndrome was ataxia telangiectasia mutated (*ATM*), the gene mutated in the disease ataxia telangiectasia. Individuals with ataxia telangiectasia resemble those with NBS with regard to radiosensitivity and cancer predisposition, but differ in the neurological manifestations of the disease, presenting with devastating progressive neurodegeneration rather than developmental defects.

ATM transmits signals through multiple proteins to repair DNA double-strand breaks and to arrest the cell cycle. The discovery of the gene and subsequent work established a clear link between a protein that repairs DNA and defects in the nervous system. Subsequent studies showed that several proteins, including nibrin, interact directly with ATM, and facilitate its activity. Understanding this complex system in the brain has been greatly facilitated by several mouse models with targeted mutations in DNA repair genes, as well as the gene encoding p53 —the key regulator of the cell cycle and apoptosis machinery and an ATM target.

One of the earliest genetic mouse models was for ataxia telangiectasia, followed quickly

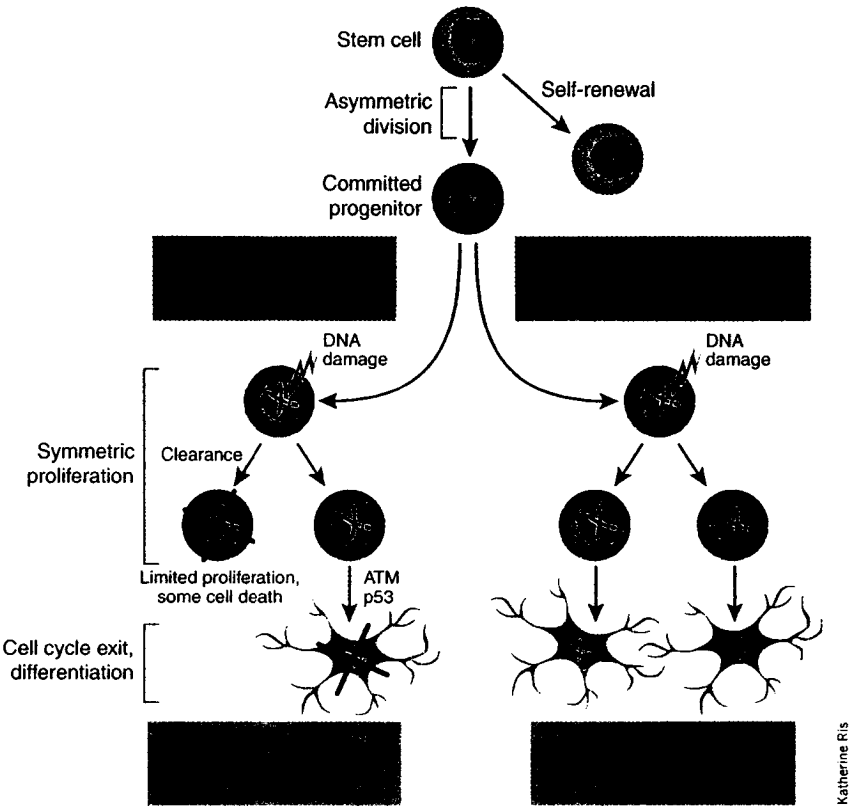

Figure 1 DNA damage in the brain during development and in the adult. During development, neural stem cells undergo asymmetric division to generate a self-renewing cell and a committed neural progenitor cell. These neural progenitors proliferate in specific areas of the fetal and adult brain. An unknown trigger then signals the cells to exit the cell cycle and initiate the process of differentiation. In the absence of DNA repair proteins (*e.g.*, Ku70, Ku80, DNA ligase IV, XRCC4 and nibrin), increased numbers of cells with chromosomal instability are generated[6,8,9]. Such cells are cleared by apoptosis through an ATM- and p53-dependent mechanism[7,10,12]—such cell clearance seems to underlie several neurological disorders. In the absence of ATM or with diminished levels of p53, cells with severe genomic instability are not cleared and differentiate into neurons. These abnormal cells then contribute to the development of the brain[1,5,7,8,10,12], as shown by Frappart *et al.* in a mouse model of NBS. The manifestions of disturbances in either pathway in the nervous system range from hypoplasia of brain structures and microcephaly associated with mental retardation to progressive neurodegeneration.

The authors are at BrainCells Inc., San Diego, California 92121, USA.
e-mail: cbarlow@braincellsinc.com

by targeted mutations in genes that interact with *ATM*. Unfortunately, the field has been plagued by two problems. Either the phenotype in the mice was more severe than in humans, leading to early embryonic lethality, or conversely, the model recapitulated all aspects of the disease except those of the nervous system; such mice had only mild brain abnormalities. This problem affected models for ataxia telangiectasia, Cockayne syndrome, xeroderma pigmentosum and other related neurological diseases[2,3].

More prosaic issues arose with the original *Nbn* null mutant[4]. Loss of function led to early embryonic lethality, which made it difficult to study the neurological manifestations of the disease.

Despite these obstacles, creative strategies eventually identified DNA repair enzymes and cell cycle regulators required for neurogenesis, and during the development and maintenance of the brain[5–9] (**Fig. 1**). Abnormal neural progenitors are usually cleared, generally through apoptosis. Blocking this clearance—either through loss of ATM or p53—rescues the cells from apoptotic clearance, leaving surviving cells with substantial chromosomal damage[6,7,10,11] (**Fig. 1**). That neurogenesis continued under such circumstances was surprising, given the detrimental nature of chromosomal instability outside of the nervous system. In these models, the developmental abnormalities in the central nervous system could be rescued, but the animals either developed progressive disease of unclear etiology or rapidly succumbed to cancer—again limiting our ability to understand the neurological manifestations of the disease.

The new study offers a clever solution to some of these problems by generating a brain-specific knockout of *Nbn* using the Cre-*lox*P system. The authors show that loss of function of *Nbn* leads to abnormal neurogenesis, mainly in the cerebellum. A decrease in the number of proliferating neural progenitors was found, in conjunction with apoptosis of cells with a committed neuronal fate. Loss of p53 function could rescue most of the defects, similar to the rescue of neurogenesis found with other models with deficiencies in DNA repair enzymes.

The authors next turned to experiments with neural stem cells isolated from embryonic brain. Using drugs that inhibit ATM they showed that, in the nervous system, ATM is an apoptotic effector acting through p53. Interruption of this pathway in cell culture led to survival of cells even in the presence of considerable DNA damage.

The conditional *Nbn* mouse is one of the first models that allows for the assessment of the specific impact of genomically compromised cells in the cerebellum. Interestingly, in ataxia telangiectasia, the cerebellum is the first area of the brain to suffer from neurodegeneration. A similar genetic approach could evaluate how combined loss of ATM function and *Nbn* might influence the brain *in vivo*. This would be a critical experiment to perform in order to determine whether ATM inhibitors might be therapeutically important for the treatment of the neurological symptons in individuals with NBS.

Another important area for future studies is to understand the differential sensitivity of neurons in various brain regions to defects in DNA repair and cell cycle regulation. Why does loss of p53 function selectively rescue the brain phenotypes yet worsen others, such as the cancer phenotype? The nervous system somehow appears to tolerate chromosomal aberrations without succumbing to a cancer phenotype or massive morphological disorganization.

The study of Frappart *et al.* is particularly relavant in light of the relatively recent findings that neurogenesis persists throughout the adult nervous system, including the retina[12]. The importance of DNA repair and genomic instability as contributing factors to progressive diseases remains an important field for investigation, not only for rare genetic diseases, but also for more common progressive neurodegenerative disorders such as Alzheimer disease. The new mouse model should aid in the effort to gauge the importance of pathways of DNA double-strand break repair in developmental and adult neurological disorders.

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Do-all receptor takes on coagulation, inflammation

Charles Esmon

How many critical functions can be jammed into one receptor? New work on thrombomodulin explores the limits. This already overtaxed protein binds HMGB1, a molecule that contributes to sepsis and other inflammatory conditions.

Blood vessels were originally envisaged as a passive barrier. They themselves did not promote blood clotting—and their only role in inflammation was to facilitate trafficking of leukocytes at sites of infection. Recent studies have identified a number of molecules on the endothelial cells lining blood vessels that actively regulate both of these complex processes. One such molecule is thrombomodulin. Found mainly on the surface of vascular endothelium, it interacts with multiple proteins to block blood clotting and inhibit inflammation.

In a recent issue of the *Journal of Clinical Investigation*, Abeyama *et al.*[1] find another partner for thrombomodulin. They report that thrombomodulin binds and inhibits high mobility group box 1 protein (HMGB1), a molecule with potent cytokine-like activity. HMGB1 appears to contribute to late-stage inflammatory disease like sepsis, so there has been intense interest in finding ways to stop it by identifying negative regulators. The new work brings one such regulator to light.

Much of the research on thrombomodulin has focused on the domains responsible for the

The author is at the Howard Hughes Medical Institute at the Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104, USA.
e-mail: Charles-Esmon@omrf.ouhsc.edu

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Aberrant recombination involving the granzyme locus occurs in *Atm*$^{-/-}$ T-cell lymphomas

Christopher J. Winrow[1], Daniel G. Pankratz[1], Cecile Rose T. Vibat[2], T.J. Bowen[3], Marie A. Callahan[2], Amy J. Warren[2], Brian S. Hilbush[2], Anthony Wynshaw-Boris[3], Karl W. Hasel[2], Zoë Weaver[4], David J. Lockhart[1,5] and Carrolee Barlow[1,6,*]

[1]The Salk Institute for Biological Studies, The Laboratory of Genetics, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA, [2]Digital Gene Technologies, Inc., 11149 North Torrey Pines Road, La Jolla, CA 92037, USA, [3]Departments of Pediatrics and Medicine, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0627, USA, [4]Avalon Pharmaceuticals, Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA, [5]Ambit Biosciences, 4215 Sorrento Valley Boulevard, San Diego, CA 92121, USA and [6]Brain Cells, Inc., 10835 Road to the Cure, San Diego, CA 92121, USA

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Ataxia telangiectasia (A-T) is an autosomal recessive disease caused by loss of function of the serine/threonine protein kinase ATM (ataxia telangiectasia mutated). A-T patients have a 250–700-fold increased risk of developing lymphomas and leukemias which are typically highly invasive and proliferative. In addition, a subset of adult acute lymphoblastic leukemias and aggressive B-cell chronic lymphocytic leukemias that occur in the general population show loss of heterozygosity for ATM. To define the specific role of ATM in lymphomagenesis, we studied T-cell lymphomas isolated from mice with mutations in ATM and/or p53 using cytogenetic analysis and mRNA transcriptional profiling. The analyses identified genes misregulated as a consequence of the amplifications, deletions and translocation events arising as a result of ATM loss. A specific recurrent disruption of the granzyme gene family locus was identified resulting in an aberrant granzyme B/C fusion product. The combined application of cytogenetic and gene expression approaches identified specific loci and genes that define the pathway of initiation and progression of lymphoreticular malignancies in the absence of ATM.

INTRODUCTION

The transformation of a normal cell to a tumor cell depends in part on mutations in genes that control the cell cycle. Cell-cycle regulation plays a major role in maintaining the integrity of the genome. Defects in checkpoint control contribute to genomic alterations such as deletions, translocations and amplifications that commonly occur during the evolution of a normal cell to a cancer cell. ATM (ataxia telangiectasia mutated) is a key protein responsible for arresting the cell cycle in response to DNA damage and has a role in genetic stability and cancer susceptibility. Nearly one-third of ataxia telangiectasia (A-T) patients develop aggressive and invasive forms of either lymphocytic leukemia or non-Hodgkin lymphomas (1,2).

A mouse model of A-T (*Atm*$^{-/-}$) closely mimics the human condition and has been useful for defining the role of ATM in cancer (3,4). All *Atm*$^{-/-}$ mice succumb to aggressive T-cell lymphoblastic lymphoma early in life, and these tumors closely resemble those found in A-T patients in several respects: (1) the tumors develop in very young *Atm*$^{-/-}$ mice, similar to the lymphoreticular cancers in A-T patients which arise in childhood (3–7); (2) the tumors are highly proliferative and invasive (1,3,8–10); (3) virtually all tumors found in *Atm*$^{-/-}$ mice and the majority of T-cell leukemias in A-T patients are CD4+/CD8+ (3,5–7,11–13); and (4) tumors from *Atm*$^{-/-}$ mice

*To whom correspondence should be addressed. Tel: +1 8588127615; Fax: +1 8588127630; Email: cbarlow@braincellsinc.com

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contain translocations of chromosomes 12 and 14 in regions homologous to translocated regions of human chromosome 14 in A-T patients (3,4,14). These regions are also frequently mutated in other human hematopoietic cancers that occur in patients that do not have A-T (15–17).

On the basis of cytogenetic data and the role of ATM in DNA repair following ionizing radiation (IR), it is likely that lymphoblastoid cancers arising in the absence of ATM are due to specific translocations at loci that undergo V(D)J recombination. In support of such an hypothesis is the finding that human chromosome 14q11.2 harbors the T-cell receptor alpha (TCRα) gene and abnormalities in this region have been detected in A-T patients (18–24) and in $Atm^{-/-}$ mice (4). Recombination of IR and V(D)J produces DNA double-strand breaks (DSBs) that are repaired by non-homologous end joining (NHEJ), and ATM is thought to activate proteins involved in NHEJ in response to IR. This has lead to the suggestion that defective V(D)J recombination due to loss of ATM function is responsible for tumor formation. However, recently we showed that V(D)J recombination is not required for lymphoma formation in the absence of *Atm*, as $Atm^{-/-}$ mice deficient in Rag1 or Rag2 (and therefore incapable of V(D)J recombination) still succumb to T-cell lymphomas (TCLs) (14,25). An alternative possibility is that following loss of ATM, the development of tumors occurs as a result of disruptions in signaling to the cell-cycle checkpoint machinery. For example, in response to IR, ATM activates p53 (26–28), and mutations that render *p53* inactive are the most frequent cause of cancers in humans (29–31). Regardless of a link between defective ATM signaling to p53 and cancer, the pattern of tumor development and chromosomal abnormalities that occur in the absence of ATM in humans and mice suggests that there is a requirement for specific chromosomal regions to undergo aberrant recombination and that these rearrangements result in molecular changes that promote tumor formation and invasion (4,24).

To identify the molecular events responsible for tumorigenesis in the absence of ATM, it is necessary to identify the loci and the genes affected by the conserved rearrangements observed in these tumors. In this paper, we show that $Atm^{-/-}$ TCLs are unique from $p53^{-/-}$ lymphomas both cytogenetically and at the level of gene expression, establishing that loss of the p53 cell-cycle checkpoint is not responsible for lymphoma formation in the absence of ATM. Further, by coupling cytogenetic analyses of $Atm^{-/-}$ TCLs with gene expression profiling we identified recurrent aberrations on chromosome 14 within the granzyme (*Gzm*) family locus at specific sites of homology between family members. The disruptions at this locus result in the rearrangement and inappropriate expression of a granzyme protein involved in cancer promotion and invasion and suggest a mechanism for tumor promotion in the absence of ATM involving aberrant homologous recombination (HR).

RESULTS

Characteristic translocations in $Atm^{-/-}$ TCLs are dependent on normal *p53* alleles

$Atm^{-/-}$ mice develop CD4+/CD8+ (immature) TCLs with characteristic cytogenetic abnormalities consisting of inter- and intra-chromosomal rearrangements of chromosomes 12 and 14 and amplification of chromosome 15 (Table 1) (3,4,14,25). Although p53 and ATM cooperate in response to DNA damage and regulating the cell cycle, tumors which arise as a result of deficiencies of p53 and ATM are markedly different (Fig. 1 and Table 1) (4,32–35). For example, $Atm^{-/-}$ mice rapidly develop TCLs, whereas $p53^{-/-}$ mice show more latent development of a variety of different tumors including TCLs. $Atm^{-/-}$ TCLs are more immature (CD4+/CD8+) than $p53^{-/-}$ TCLs (frequently CD3+) (see Table 1). $Atm^{-/-}$ TCLs have inter- and intra-chromosomal aberrations including translocations involving chromosomes 12 and 14 (4), whereas TCLs from $p53^{-/-}$ mice exhibit aneuploidy with only rare translocations (for example, see Table 1 and Fig. 1E) (30,36–39). Interestingly, both $Atm^{-/-}$ and $p53^{-/-}$ tumors have amplifications of chromosome 15 (4,30,39,40).

To identify *Atm*-specific lesions and how *p53* loss may impact the cytogenetic and molecular events underlying lymphomagenesis, mice deficient in *Atm* and lacking one or both alleles of *p53* were generated, and the TCLs that developed were isolated and studied by spectral karyotyping (SKY) and flow cytometry. SKY was done on TCLs at early passage and the karyotypes were compared with those from $Atm^{-/-}$ mice. Four of the five TCLs isolated from $Atm^{-/-}p53^{+/-}$ mice harbored translocations involving chromosomes 12 and 14 but aneuploidy was markedly increased (Table 1 and Fig. 1A–C), suggesting that haplo-insufficiency of *p53* during tumor formation results in a combined phenotype possibly due to a shared ATM pathway. Mice lacking *Atm* and both alleles of *p53* ($Atm^{-/-}p53^{-/-}$) rapidly succumb to a host of tumors including both B- and T-cell lymphomas within the first weeks of life (41) (data not shown). TCLs from $Atm^{-/-}p53^{-/-}$ mice were more mature (CD3+) and exhibited both increased aneuploidy and translocations, which no longer consistently involved chromosome 12 or 14 (Fig. 1D and Table 1). Notably, abnormalities of chromosome 12 were rarely found. Therefore, not only is the clinical pathology of $Atm^{-/-}$ TCLs different from $p53^{-/-}$ TCLs, but the two tumor types also show distinct developmental differences and unique chromosomal disruptions.

Global gene expression patterns highlight the unique nature of $Atm^{-/-}$ lymphomas

Recently, global expression profiling has proven extremely useful in identifying subtypes of leukemias and lymphomas (42–46). To test if a similar approach could be used to study ATM-specific lymphomagenesis, cDNA microarrays and Total Gene Expression Analysis (TOGA®) were used (47–50). First, cDNA microarrays were used to identify genes differentially expressed in $Atm^{-/-}$ thymus as compared to wild-type thymus prior to tumor formation (Fig. 2A). Next, samples from wild-type thymus were compared with two independent $p53^{-/-}$ TCLs and four $Atm^{-/-}$ TCLs (AT-4, AT-7, AT-12 and AT-13) using cDNA microarrays (Supplementary Material, Tables S3–S5 for gene lists and Supplemental Methods for experimental design and analysis criteria). In comparisons between the $Atm^{-/-}$ TCLs and wild-type thymus, 154 genes were identified as differentially expressed (green circle in Fig. 2B and Supplementary Material, Tables S3 and S4). A similar comparison between

Table 1. Translocations at chromosomes 12 and 14 are unique to $Atm^{-/-}$ TCLs, and this requires an intact *p53* allele[a]

Tumor	Genotype	Conserved	Unique	CD4	CD8	CD3
AT-4[b]	$Atm^{-/-}$	Del (12), +15, Del (14), T(12;14)	2n; Dp(11), T(14;X), T(X;11), T(14;15)[b]	+	+	−
AT-7[b]	$Atm^{-/-}$	Del (12), +15, Del (14), T(12;14)	2n; T(14;16), Is (14;1)	+	+	−
AT-12[b]	$Atm^{-/-}$	Del(12), +15, Del(14)	2n; T(12;9), T(9;15), +10, +13	+	+	−
AT-13[b]	$Atm^{-/-}$	Del (12), +15, Del (14), T(12;14)	2n; Ins(14;15), T(14;15)[b]	+	+	−
AT-10	$Atm^{-/-}$	Del (12), +15	2n; T(12;10), Dp14, T(X;15), Del(X), T(17;1), Dp (1), Del (16), −11	+	+	−
AT-11	$Atm^{-/-}$	Del (12), +15	2n; T(12;6), Dp(6), Dic(14;14), Dp(14), Dic(15;15), Rb(16;16), Dp(16)	+	+	−
APT-2	$Atm^{-/-}$ $p53^{+/-}$	+15, T (12;14)	2n; Rb(10.10), T(15;X), Dp(14)	+	+	+
APT-3	$Atm^{-/-}$ $p53^{+/-}$	+15, T (12;14)	2n; T(14;2), T(5;14;2), T(8;6)	−	+	+
APT-4	$Atm^{-/-}$ $p53^{+/-}$	+15, T(12;14)	2n; T(4;14), T(14;2), Dic(Del(2); T(4;14)), Dp(14)	−	+	−
APT-5	$Atm^{-/-}$ $p53^{+/-}$	+15	2n and 3n clones; Rb(9.Del(15)), +5, −13, +15	+	+	−
292-3	$Atm^{-/-}$ $p53^{-/-}$	+15	2n; T(17;6); +14	+	−	+
101-3	$Atm^{-/-}$ $p53^{-/-}$		Hyperdiploid and 4n clones, Dp(14), -8	+	+	+
p21-1	$Atm^{-/-}$ $p21^{-/-}$		T(12;9)	+	+	+
p53-1	$p53^{-/-}$	+15	+1, +4, +5, +11, +14	+	+	+

[a]Only the most frequently observed aberrations, and therefore individual karyotypes may contain additional inconsistent aberrations. Abbreviations: translocation (T), deletion (Del), duplication (Dp), insertion (Is), dicentric chromosome (Dic), Robertsonian translocation (Rb). Aberrations were defined using the nomenclature rules from the Committee on Standardized Genetic Nomenclature for Mice (www.informatics.jax.org).
[b]Tumor lines profiled by TOGA™. Bold names indicate tumor lines examined by northern analysis.

$p53^{-/-}$ TCLs and wild-type thymus identified 300 genes as differentially expressed (blue circle in Fig. 2B and Supplementary Material, Table S5). This data demonstrated that the $p53^{-/-}$ TCLs were more different from normal thymus (205 of 300 genes, or 68%) than $Atm^{-/-}$ TCLs (62 of 154, or 40%) when analyzed using similar criteria. Ninety-one genes were misexpressed in both $Atm^{-/-}$ and $p53^{-/-}$ TCLs (intersection of green and blue circles in Fig. 2B and Supplementary Material, Table S4). These 91 genes are likely lymphoma-specific genes or genes whose regulation is abnormal based on loss of cell-cycle checkpoint control, through loss of either ATM or p53. Interestingly, three of these 91 genes were not only abnormally expressed in all TCLs, but also in $Atm^{-/-}$ thymus: Igα, cystatin C and an EST (see intersection in Fig. 2B and genes colored green in Fig. 2A). The differential expression of these three genes likely reflects either the immature status of thymocytes in $Atm^{-/-}$ thymus and TCLs and/or alterations in cell-cycle regulation common to both ATM and p53 deficiency, but which are not specifically associated with cytogenetic rearrangements due to loss of ATM or lymphoma.

The conserved disruption of chromosome 14 involves the granzyme gene family

Chromosomes 12, 14 and 15 are consistently disrupted in $Atm^{-/-}$ TCLs (Table 1). Although cDNA microarrays were informative in terms of identifying gene pathways that may be involved in lymphomagenesis and survival, these experiments did not identify specific loci affected by translocations and gene fusion events. Sixty-two genes were differentially expressed exclusively in $Atm^{-/-}$ TCLs. Four of these genes were localized to chromosome 14, four to chromosome 15 and two to chromosome 12 (Fig. 2B and Supplementary Material, Table S3). Three genes on chromosome 14 were upregulated. These were cam kinase II beta, an EST (AA198542) and glia maturation factor. One gene was downregulated, TGF-beta-1-induced transcript. The two genes on chromosome 12, secreted modular calcium BP1 and Ena-vasodilator-stimulated phosphoprotein (Evl), were downregulated. *Evl* lies between the *Tcl1* and *IgH* loci on chromosome 12. The four genes that mapped to chromosome 15, ATP synthetase H+ transporting mitochondrial F1 complex subunit C, proline-rich protein, Map3k12 and cytosolic aminopeptidase P, were all upregulated consistent with the cytogenetic phenotype of chromosome 15 amplification. We combined data from cDNA microarrays with TOGA® to identify additional genes impacted by the conserved chromosome lesions affecting chromosomes 12, 14 and 15 in $Atm^{-/-}$ TCLs. Three $Atm^{-/-}$ TCLs with similar cytogenetic profiles (AT-4, AT-7 and AT-13) were compared with one TCL which had several unique chromosomal aberrations (AT-12) (Table 1).

Experiments using TOGA® identified 13 569 transcripts in AT-4, 12 999 in AT-7, 13 111 in AT-12 and 13 398 in AT-13. The expression profile of each tumor line was then compared among the four. One thousand and fifty-two transcripts were differentially expressed at ≥2-fold between any one of the four $Atm^{-/-}$ TCLs. Next, we identified genes exhibiting unique or conserved patterns of expression between the tumor cell lines (see Materials and Methods). Twenty-four genes were identified with increased expression in a single cell line (consistent with an activating translocation, Table 2), 30 genes with decreased expression in a single cell line (consistent with a deletion, Table 2) and nine genes with increased expression in two cell lines/decreased expression in two cell lines (common deletions or common activating translocations, Table 2). Two genes with equal

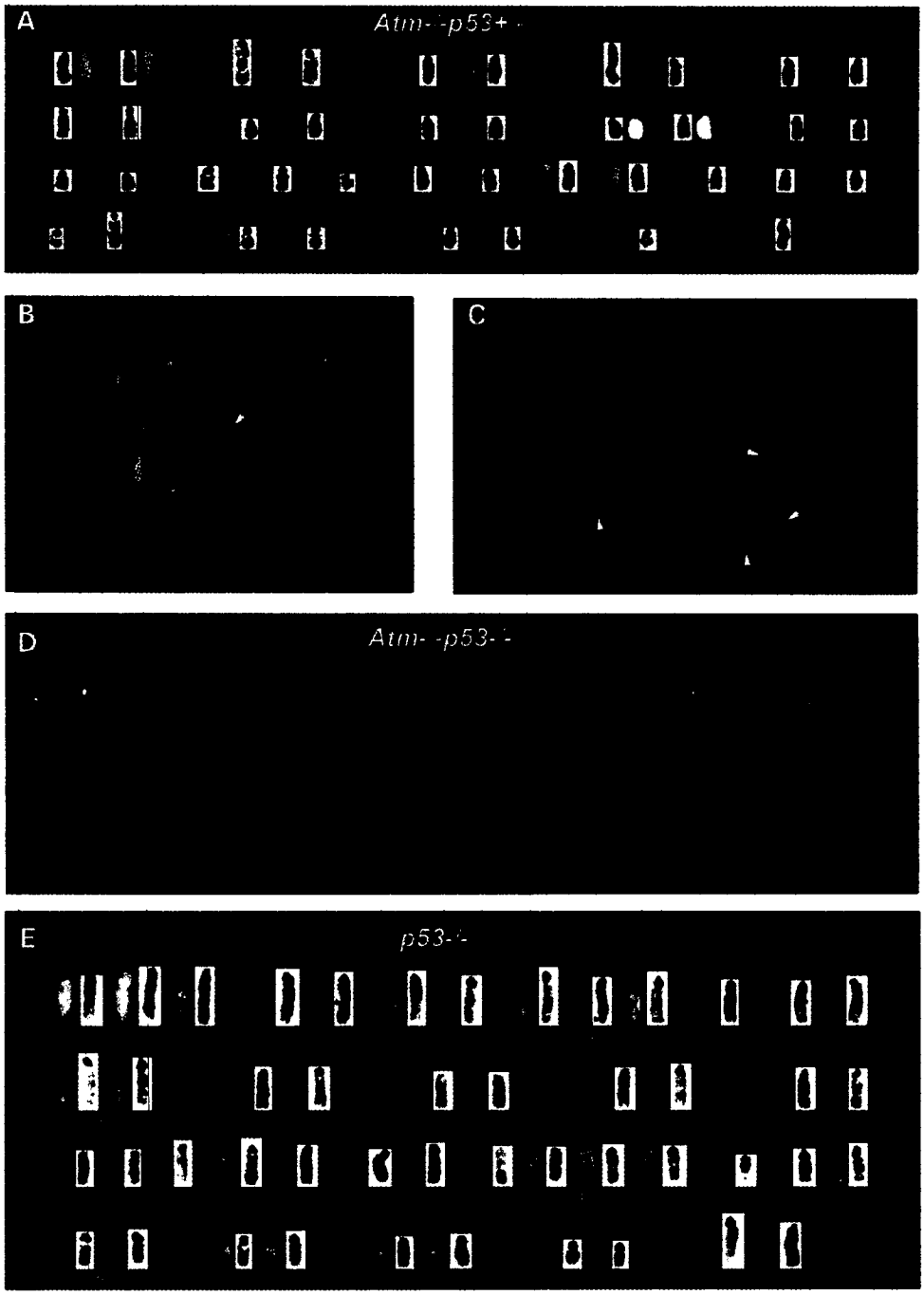

Figure 1. $Atm^{-/-}$ TCLs exhibit translocations, whereas $p53^{-/-}$ TCLs are aneuploid. (A–C) A representative $Atm^{-/-}$ $p53^{+/-}$ TCL (APT-4) that exhibits several translocations involving chromosome 14. (**A**) SKY classification of a metaphase from APT-4. The display colors are shown on the left for each chromosome, next to the inverted DAPI image and the spectra-based classification colors. The full karyotype for this metaphase is 40,X, Dic(Del(2);T(4;14)), T(4;14), Del(7), T(12;14), T(14;2), Dp(14), T(Dp(16);3), +Del(12), +15, −19, −Y. (**B**) Unclassified metaphase from (A) in hybridization display colors. Translocations are visible as 2-color chromosomes. The arrow indicates a T(4;14). (**C**) FISH analysis of APT-4 with BAC probes for the TCRα locus on chromosome 14. The chromosomes are counterstained with DAPI for visualization (blue). Hybridization with a TcrVα 3′ variable region probe (green, arrow) shows that several duplications of this region (cytogenetic band 14D1–D2) have occurred, comparable to aberrations seen in $Atm^{-/-}$ $p53^{+/+}$ TCLs. Hybridization with a TcrCα 5′ constant region probe (red, arrowheads) reveals that none of the signals colocalize with the TcrVα probe, consistent with the translocations seen by SKY. (**D**) SKY of an $Atm^{-/-}$ $p53^{-/-}$ TCL (101-3; 4n clone). Translocations involving chromosomes 1, 5 and 14 are shown in their classification colors next to the display colors. Note that the tumor is aneuploid as well. The karyotype is 85,XX, T(1;5), T(5;1), Dp(14), T(14;3), +4 × 2, −6, +10 × 2, −11 × 2, +12, +14, +15 × 5, −19, −Y × 2. (**E**) SKY analysis of a $p53^{-/-}$ TCL (p53-1). This tumor exhibits aneuploidy but has no structural aberrations. The karyotype is 47,XX, +1, +4, +5, +11, +14 × 2, +15.

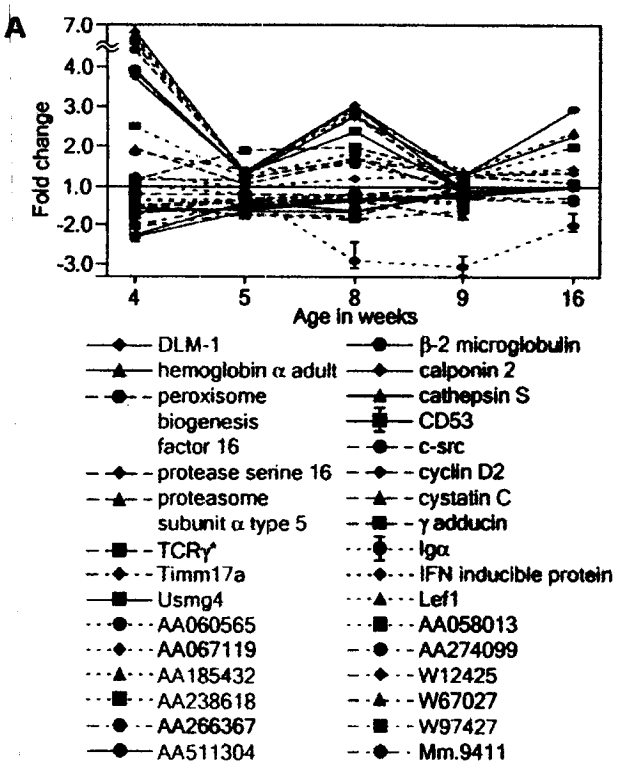

Figure 2. Gene expression patterns of $Atm^{-/-}$ TCLs are unique from pre-malignant $Atm^{-/-}$ thymocytes and $p53^{-/-}$ TCLs. (**A**) The 31 genes identified at various time points that were upregulated (red) or downregulated (green) in $Atm^{-/-}$ thymus in comparison to age-matched wild-type controls. The *X*-axis indicates age in weeks (4, 5, 8, 9 and 16) and the *Y*-axis the average FC for the replicate experiment at each time point. Both *CD53* and *Igα* are represented more than once on the arrays and the average FC ranges for those values are shown. The names of genes are listed below the panel. (**B**) Venn diagram showing the number of genes differentially expressed in $Atm^{-/-}$ TCLs (green circle), $Atm^{-/-}$ thymus (black circle) and $p53^{-/-}$ TCLs (blue circle), when compared with wild-type thymus. Those genes differentially expressed in the same direction are listed in (A) and colored as follows: $Atm^{-/-}$ thymus and $Atm^{-/-}$ TCLs (1 gene, magenta), $Atm^{-/-}$ thymus and $p53^{-/-}$ TCLs (4 genes, blue) or all three conditions (3 genes, green); genes commonly differentially expressed in both $Atm^{-/-}$ and $p53^{-/-}$ TCLs as compared to wild-type thymus (91 genes) are listed in Supplementary Material, Table S5. The number in parentheses indicates the number of genes differentially expressed in opposite directions (Fig. 3A, orange); these genes are all upregulated in $Atm^{-/-}$ thymus (Fig. 3A). Genes differentially expressed exclusively in all $Atm^{-/-}$ TCLs compared with normal thymus (62 transcripts, Supplementary Material, Table S4) and all genes different in $p53^{-/-}$ TCLs (300 transcripts, Supplementary Material, Table S6) are also shown.

expression levels in all tumor cell lines were also evaluated as controls (Table 2). These 65 candidates were sequenced and compared with the GenBank database. Of the 65 candidates isolated, 39 were known genes, 11 were uncharacterized murine homologs, 12 were ESTs and three were completely novel genes not present in GenBank (see Table 2). Follow-up validation by northern analysis was done on 25 randomly selected candidate genes. Northern analysis was consistent with TOGA® for 17 genes, five had undetectable signals, two cross-reacted with other family members precluding a definitive analysis and one showed a different pattern on northern as compared with TOGA®. One candidate that did not confirm represented a mitochondrial-encoded transcript. Therefore, the pattern of expression obtained by TOGA® for 17 of the 18 transcripts was confirmed by independent northern blot analysis.

Several genes were identified that were overexpressed and which reside on chromosome 15. But many of these genes were also differentially expressed in $p53^{-/-}$ TCLs and so were not ATM-specific or had no clear role in TCL formation (see Table 2 and Supplementary Material, Tables S3–S5 for details of fold changes and chromosomal locations). Only one gene was identified as abnormally expressed that resides on chromosome 12 near the disrupted region (*Evi*), and this gene was downregulated (Table 2, Fig. 3C and Supplementary Material, Table S4), which is unlikely to be associated with an activating translocation. In contrast, we identified the *GzmC* gene tag as upregulated by TOGA® in two of the four TCLs (Table 2). Northern analysis using an EST probe for *GzmC* showed that *GzmC* was detectable in four of the seven $Atm^{-/-}$ TCLs (Fig. 3B) but was not expressed in tumors lacking *p53*. In addition, a second abnormally large band was detected in several $Atm^{-/-}$ TCLs suggesting that not only *GzmC* was overexpressed, but also an aberrant form of the message was produced in $Atm^{-/-}$ TCLs consistent with an activating translocation event. *GzmC* belongs to a family of closely related granzymes clustered on chromosome 14 at 20.5 cM (14qC1–C2) in mice and 14q11.2 in humans (51–57). The *GzmC* locus is very close to the TCRα locus on chromosome 14 at 19.5–19.7 cM (14qC1–C2) (Fig. 3A). This is the region consistently observed to be disrupted in $Atm^{-/-}$ TCLs in both mice and humans (4,18–24). To investigate if the *Gzm* locus was involved in $Atm^{-/-}$ translocations, FISH was done using genomic probes for *GzmC* (chromosome 14), *TCRα* (chromosome 14) and *Tcl1* (chromosome 12) (Fig. 3C). TCRα was used to pinpoint the region of chromosome 14 corresponding to 19.5 cM and *Tcl1* was used to determine the region corresponding to 52.0 cM on chromosome 12 (58–61). We have previously shown that there are translocations involving chromosome 14 and regions of chromosome 12 that are near the *Tcl1* locus, although *Tcl1* is not consistently involved nor is there expression of *Tcl1* in any $Atm^{-/-}$ TCL (4). Examination of wild-type cells confirmed that the *GzmC* and *TCRα* loci are in close proximity (upper color panel in Fig. 3C, and data not shown). FISH analysis of AT-7 TCLs showed that the *GzmC* locus was duplicated and inverted on chromosome 14, and an additional copy of the gene is on the portion of chromosome 14 that was translocated to chromosome 12 (see Fig. 3C). Interestingly, although the *GzmC* locus was

Table 2. Genes exhibiting unique or conserved patterns of expression between the tumor cell lines

Gene name	Accession number	Tumor line	Mouse	Human
Genes with increased expression in a single tumor cell line				
RhoC (confirmed)[a]	X80638	AT4	3[b]	1p21–p13
Homology to human KIAA0439	AB007899	AT7	3: 41.5 cM	18q22
Mouse p162/centrosomin/EIF2	U14172	AT7	19	10q26
Mouse transglutaminase 2	M55154	AT7	2: 89.0 cM	20q12
Homology to human P53BP2	U09582	AT7	1[b]	1q42.1
EST	AW060549	AT7	n/a	14[b]
EST	AI427061	AT7	17[b]	5[b]
Gp250 precursor/sortilin-related	AF031816	AT7	9[b]	11q23.2–q24.2
Mouse four cell embryo cDNA clone	AU042200	AT7	16[b]	17[b]
Mouse TNF-receptor 2	M60469	AT7	4: 75.5 cM	1p36.3–p36.2
Mouse valosin containing protein	NM_009503	AT7	4: 23.0 cM	9p13–p12
Absent in melanoma (AIM2) Human (confirmed)[a]	AF024714	AT7	1[b]	1q22
Interleukin 4 receptor, alpha (confirmed)[a]	NM_010557	AT7	7: 62.0 cM	16p11.2–12.1
Unknown clone	Y17677	AT7	1[b]	1[b]
EST	BF118440	AT7	4[b]	1[b]
Mouse ALK-1 (confirmed)[a]	Z31664	AT12	15[b]	12q11–q14
Mouse rah g-protein	S72304	AT12	11: 44.89 cM	17[b]
EST; novel (confirmed)[a]	AB041555	AT12	4[b]	1[b]
EST: S31814 ADP, ATP carrier protein T2	AI854173	AT12	11[b]	17[b]
Annexin XI (Anx11)	U65986	AT12	14: 3.3	10q22–q23
28S ribosomal RNA	X00525	AT12	N/a	n/a
EST	BF320258	AT12	17[b]	6[b]
Rat RSTK-1 (confirmed)[a]	L36088	AT12	15[b]	12q11–q14
Soluble lectin (Mac-2) gene (confirmed)[a]	L08649	AT13	14[b]	14q21–q22
Genes with decreased expression in a single tumor cell line				
IL-4 receptor secreted form	M27960	AT4	7: 62.0 cM	16p11.2–12.1
FX-induced thymoma transcript (confirmed)[a]	U38252	AT4	5: 65.0 cM	12
Mouse p162/centrosomin/EIF3	X84651	AT7	19	10q26
EST; novel	AA259694	AT7	7[b]	19[b]
Novel	AV065690	AT7	11[b]	17[b]
Major histocompatibility complex Q region	AF111103	AT7	17[b]	n/a
CTP synthetase	U49350	AT7	4: 57.0 cM	1p34.1
ADP-ribosylation factor (confirmed)[a]	NM_007476	AT7	1[b]	1q42
Homology to human CGI-94	AF151852	AT12	4[b]	1[b]
Mouse mitochondrial DNA	AB049357	AT12	n/a	n/a
T-cell receptor rearranged gamma chain	M34970	AT12	13: 10.0 cM	7p15–p14
Rat Histone macroH2A1.2	U79139	AT12	13[b]	5q31.3–q32
Chimeric 16S ribosomal RNA (mito)	AF089815	AT12	n/a	n/a
K-ras type A mRNA, 3′ untranslated	U76425	AT12	6: 71.2 cM	12p12.1
COQ7	AF098949	AT12	7: 53.5 cM	16p13.11–p12.3
Prothymosin alpha	NM_008972	AT12	[1]	2q35-q36
Mini chromosome maintenance deficient 7	NM_008568	AT12	[16]	7q21–q22.1
EST from embryonic carcinoma	AA215215	AT12	1[b]	1[b]
EST from thymus	BE631434	AT12	1[b]	n/a
Homology to human YG81 hypothetical protein	XM_009703	AT12	16[b]	21q21.1
Inhibitor of Apoptosis 1 (confirmed)[a]	U88908	AT12	9 A2	11q22
Homology to rat Pxmp1	NM_012804	AT13	3: 56.6 cM	1p22–p21
Homology to rat glucokinase	AF217233	AT13	1[b]	1q21–q22
EST; Novel (confirmed)[a]	AA718318	AT13	11[b]	2[b]
COP9 subunit 4	NM_012001	AT13	5[b]	4q21.21–q21.23
EST	AW824167	AT13	11[b]	17[b]
Rat histone macroH2A1.2 mRNA	U79139	AT13	13[b]	5q31.3–q32
Kidney testosterone-regulated RP2	X04097	AT13	7: 15.0 cM	[19]
Replication dependent histone H2A.1	M37736	AT13	13[b]	1[b]
EST to NMLMG cDNA clone (confirmed)[a]	AI461717	AT13	11[b]	5[b]
Genes with increased or decreased expression in two of four tumor cell lines				
Mouse mo54 protein	J05261	AT4–AT12	2: 96.0 cM	20q13.1
Rat ketohexokinase promoter region	Y09339	AT4–AT12	5: 18.1 cM	2p23.2–p23.3
Unknown clone from E16 pancreas library	BG142044	AT4–AT12	3[b]	1[b]

Continued

Table 2. Continued

Gene name	Accession number	Tumor line	Mouse	Human
Nucleoside phosphorylase-1 (partial)[a]	X56548	AT4–AT13	14: 19.5 cM	14q13.1
Mouse fat specific protein 27	M61737	AT7–AT13	6[b]	3[b]
Mouse Cyp11A1	NM_019779	AT7–AT13	9: 31.0 cM	15q23–q24
Granzyme C/ccp2 (confirmed)[a]	M18459	AT7–AT13	14: 20.5 cM	14q11.2
Peripheral benzodiazepine receptor (partial)[a]	D21207	AT7–AT13	15: 43.3 cM	22q13.31
Advillin	NM_009635	AT7–AT13	11[b]	12q13.11–12q14.3
Genes with even expression in all tumor lines				
Defender against cell death (confirmed)[a]	U83628	Equal in all	14: 24.0 cM	14q11–q12
Fas-binding DAXX (confirmed)[a]	NM_007829	Equal in all	17: 17.0 cM	6p21.3

[a]Confirmed by northern analysis. Brackets indicate synteny between mouse/human chromosomes, but not direct mapping evidence.
[b]Data obtained from Celera Genomic Databases.

found at the chromosome 12/14 breakpoint in AT-7, a similar translocation of the adjacent variable region of the *TCRα* locus to chromosome 12 was not observed (Fig. 3C, upper panel).

To determine whether the rearrangement and an aberrant transcript could be detected in multiple independent $Atm^{-/-}$ TCLs or in $p53^{-/-}$ TCLs, rapid amplification of cDNA ends (RACE) was performed using RNA from the original TOGA® samples, as well as from other $Atm^{-/-}$ and $p53^{-/-}$ TCLs. Using 5′ RACE and RNA derived from AT-7 and AT-10 (not used in the TOGA® analysis), the full-length coding sequence was obtained. Sequencing of the clones showed that the aberrant message produced a transcript encoding an identical in-frame fusion between *Gzm* B and C (see Fig. 3D). Subsequent RT-PCR analysis using primers specific for *GzmB* and *GzmC* confirmed the presence of a similar abnormal fusion between *Gzm* B and C in the AT-7, AT-10 and AT-13 cell lines, and demonstrated other aberrant rearrangements in several other $Atm^{-/-}$ cell lines. In total, five of the six $Atm^{-/-}$ TCLs examined showed abnormal products derived from the granzyme locus. In contrast, no such transcript was found in RNA from normal mouse thymus or from $p53^{-/-}$ TCLs, confirming that aberrant *GzmC* products are only seen in $Atm^{-/-}$ TCLs. Interestingly, a core 20 bp sequence [TGC(T/A)(A/G)TGTGGCTGGCTGGGG] is found in all six granzymes residing on mouse chromosome 14, and is less conserved in mouse *GzmA* and *GzmK* (both on chromosome 13), and *GzmM* (chromosome 10). This core site is conserved in the *GzmB–C* fusions arising in independent $Atm^{-/-}$ TCLs (Fig. 3D). Therefore, not only was the identical *GzmB–C* fusion observed in independent $Atm^{-/-}$ TCLs, but also the site of the fusion occurs within a highly conserved region between the granzyme family members on chromosome 14.

Importantly, the aberrant in-frame fusion transcript between *GzmB* and *GzmC* in $Atm^{-/-}$ TCLs retains all functional domains (62–69). To determine whether the transcript detected in the $Atm^{-/-}$ TCLs was capable of generating an intact protein, the *GzmB–C* fusion sequence was His-tagged using the arabinose-inducible vector pBAD-HisG (Invitrogen). Induction of this construct resulted in the production of a protein of the expected size (25.8 kDa), as determined by western blot analysis with an anti-His antibody (Fig. 3E). Taken together, these results demonstrate that the rearrangements of the granzyme locus are found only in the absence of *Atm* and also that the sites of fusion involve a region of sequence homology between the family members and that the aberrant product with unique properties contains all functional domains necessary for activity.

DISCUSSION

Lymphomagenesis in the absence of ATM

The results we have obtained enabled us to develop a model for lymphomagenesis arising in the absence of functional ATM (Fig. 4). Loss of ATM results in the destruction of most CD4+/CD8+ T-cells. It is thought that this defect in T-cell maturation is due to the compromised ability of $Atm^{-/-}$ T-cells to appropriately produce a functional TCR (see Fig. 4). Those CD4+/CD8+ T-cells that do not appropriately rearrange TCRα and express a TCR undergo apoptosis (see Fig. 4) (27). Importantly, in the absence of ATM many T-cells do undergo productive TCRα/β rearrangement and mature to become functional T-cells, although we and others have demonstrated that many of these 'functional' T-cells harbor chromosomal abnormalities. These abnormalities neither appear to affect the function of the cells nor give rise to cells that eventually cause lymphoma/leukemia as indicated by the fact that the $Atm^{-/-}$ tumors are not CD3 + .

Our profiling experiments suggest that cancerous cells must arise in the less mature CD4+/CD8+ cells residing in the thymus (Fig. 4). Gene expression profiling showed that tumor-free $Atm^{-/-}$ thymus abnormally expressed several genes, consistent with the idea that a subset of abnormal cells harbors changes important for the pre-cancerous phenotype (Fig. 2A). The TCRγ locus is frequently abnormally rearranged in non-tumorigenic peripheral T-cells in A-T patients. Normally, during the process of TCRα/β maturation, expression of TCRγ is downregulated regardless of the presence of a productive TCRγ rearrangement (70). It is therefore possible that persistent expression of TCRγ in the absence of ATM is due to the lack of a productively rearranged TCRα or TCRδ allele in the setting of a productive TCRγ rearrangement in these pre-cancerous cells. These cells are able to survive when arrested at the CD4+/CD8+ stage. This type of cell must be prone to becoming cancerous, because TCRγ expression was abnormal in both the $Atm^{-/-}$ thymus and

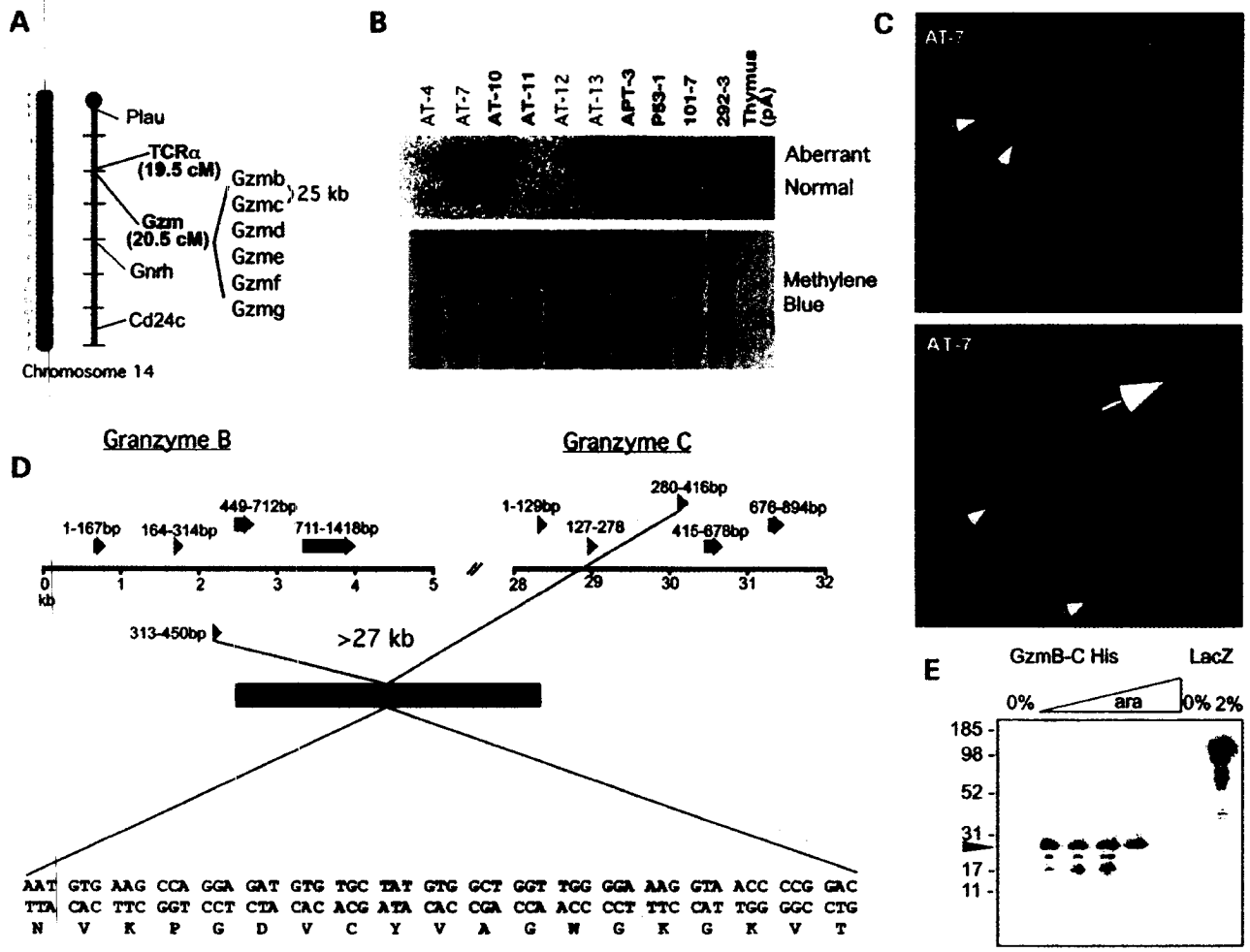

Figure 3. Chromosomal rearrangement in $Atm^{-/-}$ TCLs results in generation of an aberrant fusion within the *Gzm* gene cluster. **(A)** Ideogram and cytogenetic map of mouse chromosome 14 showing the locations of the *Gzm* gene family cluster spanning 20.5–21 cM and the *TCRα* locus at 19.5–19.7 cM. **(B)** Northern blot showing normal (*) and aberrant (**) transcripts of *GzmC*. Aberrant transcripts were observed in three of five $Atm^{-/-}$ TCLs (lanes 2, 3 and 6) and one $Atm^{-/-}$ $p53^{+/-}$ TCL (APT-3, lane 7) but not in $Atm^{-/-}$ $p53^{-/-}$ TCLs (lanes 9 and 10), $p53^{-/-}$ TCL (lane 8) or normal thymus (lane 11). Methylene blue staining in the lower panel shows equal loading of samples. **(C)** FISH of $Atm^{-/-}$ TCL (AT-7) metaphase chromosomes hybridized with probes for *GzmC* (green, chromosome 14), *TCRα* variable region (red, chromosome 14) and *Tcl1* (red, chromosome 12). Duplication and inversion of the *GzmC* locus on chromosome 14 is observed, as well as a translocation of the *GzmC* locus to chromosome 12 near the *Tcl1* locus. Translocation of the TCRα variable locus to chromosome 12 is not observed. **(D)** The sequence and structure of the aberrant *Gzm* transcript from multiple $Atm^{-/-}$ TCLs is shown. The site of the fusion corresponding to the third exon of *GzmB* with third exon of *GzmC* is indicated. This is a site of overlapping homology of 23 bp (shown in black) between the two *Gzm* genes. The lower panel indicates where the junction occurs in the fusion sequence. **(E)** Western blot using an anti-His antibody following arabinose induction of the His-tagged *GzmB–C* fusion shows that a protein of expected molecular weight (25.8 kDa indicated by an arrowhead) is produced. Lanes 1–5 show protein extracts induced with increasing arabinose concentrations (0, 0.002, 0.02, 0.2 and 2%). Expression of a control His-tagged LacZ construct (LacZ) is shown in lanes 7 (uninduced) and 8 (2% arabinose).

the $Atm^{-/-}$ TCLs. In further support of this hypothesis is the finding that in the more mature $p53^{-/-}$ TCLs, where TCRα rearrangement is not compromised, there is no similar abnormal expression of TCRγ.

Cystatin C is misregulated in pre-cancerous $Atm^{-/-}$ thymus and in both the $p53^{-/-}$ and $Atm^{-/-}$ TCLs, and others have shown that cystatin C expression is altered in other T-cell cancers (44,45,71,72). It is possible that decreased expression of cystatin C provides a survival advantage for abnormal T-cells in the $Atm^{-/-}$ thymus and later as tumors develop may increase their invasive capacity.

Common and unique gene expression changes in various T-cell-derived cancers

How then do pre-malignant $Atm^{-/-}$ thymocytes become cancerous? One possibility is that continued attempts to produce a viable TCR result in genomic instability that leads to a series of specific lesions. These disruptions (assumed to involve the *TCR* or *Ig* genes or regulatory elements) could either activate or inactivate key oncogenes or tumor suppressor genes. Although V(D)J recombination is impaired in the absence of ATM, it is not abolished, as some mature T-cells are present

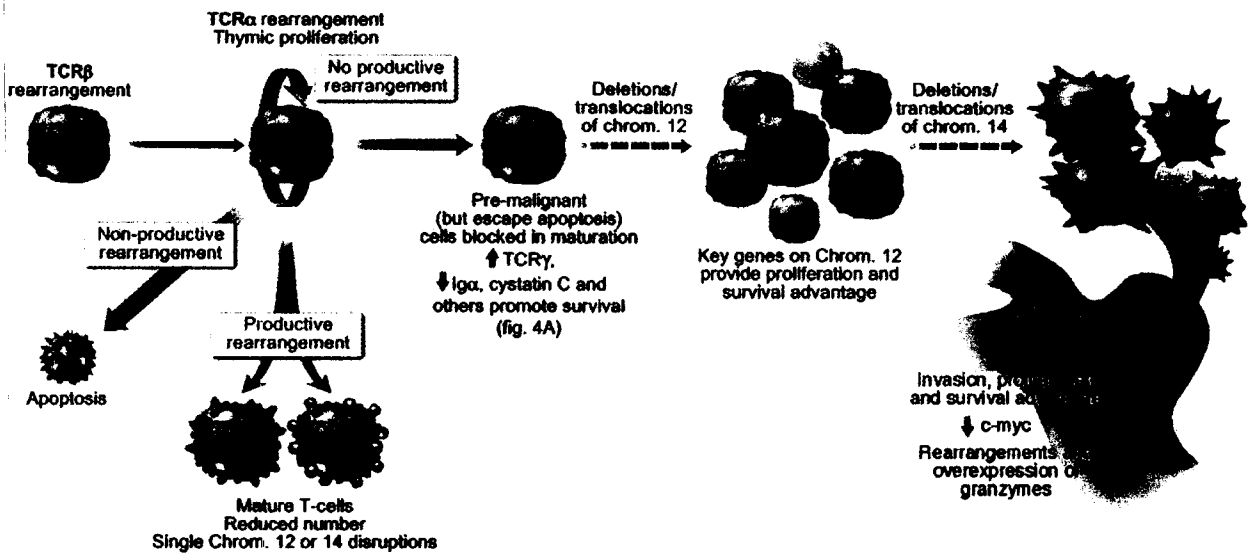

Figure 4. Mechanism of progression from thymocyte to TCL in the absence of ATM. In the absence of ATM, T-cells undergo rearrangement of TCRβ and progress to the CD4+/CD8+ stage. At this stage, the T-cell population undergoes rapid expansion and begins to rearrange the TCRα locus. Thymic selection of T-cells with non-functional TCR rearrangements occurs at this stage. In the absence of ATM, a small number of $Atm^{-/-}$ T-cells undergo proper rearrangement and migrate as functional T-cells to the periphery. These cells have single disruptions of chromosomes 12 or 14 in mice and 7 and 14 in human. However, many of these CD4+/CD8+ cells are unable to express a functional TCR. The majority of these cells undergo apoptosis, but a few escape thymic selection, and these pre-malignant cells are arrested at the CD4+/CD8+ stage of maturation. These cells likely harbor single disruptions of chromosome 12 or 14 and show misregulation of a few genes. A small number of genes show persistent misregulation in the cancer cell population, including TCRγ, Igα, cystatin C and an EST. It is possible that the misregulation of these and other genes promote the survival of the abnormal TCRγ expressing cells that should have been cleared by apoptosis, although their aberrant expression alone is not sufficient to give rise to a cancer cell. Subsequently, continued genomic instability results in the rearrangements/disruptions of loci on chromosome 12. Aberrations of the *Gzm* family may result in the expression of an aberrant product that imparts the proliferative and invasive properties of these tumors.

in the periphery of both $Atm^{-/-}$ mice and A-T patients. In addition, no clear defects have been found in V(D)J recombination involving the *TCRβ* or *Ig* loci. In fact, B-cell function and numbers are virtually normal in the majority of patients and in $Atm^{-/-}$ mice (3,6,24). Most lymphomas/leukemias found in A-T patients are of T-cell origin. Only rarely do A-T patients develop B-cell lymphomas, and B-cell lymphomas are only found in mice with combined deficiencies in ATM and other genes, such as p53 (6) (and data not shown). In addition, DNA repair kinetics are normal in A-T (73,74). However, in both Rag1/ATM- and Rag2/ATM-deficient mice, V(D)J recombination is prevented, yet mice still succumb to TCLs (even much less rapidly) and these TCLs do not harbor abnormalities at the TCRα locus. Taken together, these data suggest it is unlikely that abnormalities in V(D)J recombination alone are responsible for tumor formation and that a lesion on chromosome 14 near the TCRα locus is essential for the rapid onset of aggressive lymphomas in $Atm^{-/-}$ thymocytes.

The successful combination of immunophenotyping, clinical characterization, cytogenetic analysis and RNA profiling techniques led us to a better understanding of the genes affected by the conserved aberrations in $Atm^{-/-}$ TCLs and identified the granzyme gene cluster on chromosome 14 as consistently abnormal. This is the first demonstration of a translocation event that results in the production of an in-frame fusion between granzyme family members that yields a coding sequence for an intact protein. The distance between the fusion sites is 27 kb, and so it is unlikely that the increased expression is due to aberrant splicing events. Importantly, we show that the GzmB–C fusion observed in multiple $Atm^{-/-}$ TCLs is identical and the site of fusion maintains all the regions necessary for full activity (62,69). The three catalytic residues come from the fusion between GzmB and GzmC and the active site serine is derived from GzmC (62,75,76). Increased *GzmB* expression has already been reported in many T-cell tumors with poor clinical outcomes (64,65,68,77) where increased expression is thought to be an adoptive mechanism that enables tumors to actively destroy host immune effector cells and invade tissues (63,66,78–80). However, prior to this study, the expression of granzymes in tumors has not been associated with aberrations involving the locus. Clearly it will be interesting to test the effect of the observed granzyme fusion on normal and transformed cells in future studies to better define a role for this chromosomal aberration in tumors.

Finally, the disruption of a specific locus on chromosome 12 appears to be essential for tumor formation in the absence of ATM (see Figs 3 and 4). This locus may be of critical significance, as all $Atm^{-/-}$ and $Rag^{-/-}Atm^{-/-}$ tumor studies to date have aberrations on chromosome 12D-F. We know that the lesion involves regions near (but not affecting) the *Tcl1* locus and only rarely the *IgH* locus (4,6), although the genes and loci involved remain to be determined.

Aberrant HR as a consequence of dysfunctional NHEJ leads to tumorigenesis in $Atm^{-/-}$ TCLs

In A-T patients, no type of cell is consistently free of increased chromosomal breakage. Similar genetic instability is observed in Bloom's syndrome, which shares many of the same phenotypic characteristics of A-T including immunodeficiency, growth retardation and predisposition to cancers (81,82). Interestingly, the genetic instability in Bloom's syndrome results from increased HR and an elevated level of somatic mutations. Furthermore, the Bloom protein interacts directly with ATM and undergoes phosphorylation by ATM in response to IR (83). These observations indicate that ATM may be involved in regulating HR in response to DNA damage. Our results demonstrating specific disruption of genes in the *Gzm* cluster were particularly surprising. The observation that the granzyme gene family cluster, near the *TCRα/δ* locus on chromosome 14, is disrupted in the development of ATM-deficient lymphomas suggests a role for compensatory repair pathways to assist with the impaired V(D)J recombination. It may be that in an attempt to repair DSBs generated during V(D)J recombination, alternative repair mechanisms are employed. The alternative mechanism could involve enzymes normally responsible for HR and/or NHEJ. We have previously shown that $Atm^{-/-}$ mice have an increased frequency of intra-chromosomal HR resulting in deletions in non-hematopoietic cells (84). In $Atm^{-/-}$ T-cells, the HR machinery may be recruited to the TCRα locus during the process of V(D)J recombination, and intra-chromosomal HR would preferentially involve regions of high homology near the site of the original strand break. The adjacent granzyme cluster serves as an ideal substrate for HR because of the high sequence homology between the different granzyme family members.

In support of such a hypothesis is the finding that the site of fusion between the two different *Gzm* genes contains a conserved region of 23 bp in length (Fig. 3D). The core 20-bp sequence is conserved in all human and mouse granzymes on chromosome 14 adjacent to the *TCRα* locus. It is very likely, in fact, that additional in-frame fusion events may be occurring between other granzymes in $Atm^{-/-}$ thymocytes. However, these fusions would not have been detected because primers specific for *GzmB* and *GzmC* were used in these analyses. A more in-depth analysis in ATM-deficient mouse and human TCLs may help to identify additional granzyme fusions. Natural and synthetic mechanisms which inhibit the entry and enzymatic activity of granzymes have been described in great detail (76,85). It will be important to determine if the granzymes are overexpressed in the human cancer, as these granzyme-specific inhibitors may prove useful as therapeutic agents. Taken together, these findings help to explain many of the specific events that occur during the development of ATM-deficient TCLs, demonstrating the unique nature of these tumors and point to potential therapeutic choices for treatment.

MATERIALS AND METHODS

Cell culture

Tumor cell lines were isolated as previously described (3) and grown in RPMI medium (Life Technologies, Bethesda, MD) with 10% heat-inactivated fetal calf serum and 20 U/ml human interleukin-2 (Roche).

Flow cytometry for phenotyping of tumors

Flow cytometry and phenotyping of tumors were done as described (3).

SKY and FISH

Metaphase spreads for SKY and FISH were prepared on glass slides using standard protocols as described in Ref. (86). Cells were incubated in 0.1 mg/ml Colcemid (GIBCO/BRL) for 30–60 min and then lysed in 0.075 M KCl. Chromosomes were fixed in 3:1 methanol:acetic acid and dropped onto glass slides. SKY was performed as described (87,88). Six to ten metaphases were analyzed for each tumor. Probes for FISH were generated using bacterial artificial chromosome (BAC) clones containing the genes of interest. BAC clones were obtained by PCR screening of Down-to-the-Well pools according to the manufacturer's protocol (Genome Systems, St. Louis, MO). The clone addresses for the isolated BAC clones were as follows: 226E11 (Tcl1), 232F19 (TcrCα), 46G9 (TcrVα6), and 309K16 and 380N13 (*GzmC*). Labeled BAC probes were generated using the BioProbe nick-translation kit (Sigma). The BAC DNA clones were labeled with biotin-16-dUTP, digoxigenin-11-dUTP (Roche), or Spectrum Orange-dUTP (Vysis, Downer's Grove, IL). Hundred nanograms of nick-translated probe DNA was precipitated with 15 μg Mouse C_0t-1 DNA (Gibco) and resuspended in 50% formamide, 10% dextran sulfate, 2× SSC. The probe DNA was denatured (10 min at 75°C) and metaphase spreads were pretreated with RNase A (0.1 mg/ml, for 1 h at 37°C) and pepsin (0.1 mg/ml for 10 min at 37°C) followed by fixation in formalin (1%, for 10 min at room temperature). After 30-min preannealing of probe DNA, hybridization to metaphase spreads was carried out for 24 h, at 37°C in a humidified box as previously described (89). After hybridization, indirectly labeled probes were detected by either mouse anti-digoxigenin followed by sheep anti-mouse Cy5.5, or avidin FITC. FISH results were imaged and analyzed using QFISH software (Leica, Cambridge, UK).

Isolation of tissue and RNA

Thymus from age- and sex-matched pairs of wild-type and $Atm^{-/-}$ 129S6/SvEvTAC inbred mice were dissected between 4 and 16 weeks of age. Thymus was visually inspected for tumor foci and tumor-free samples were flash-frozen on dry ice and stored at −80°C until used for RNA isolation. RNA was isolated from TCLs and was used for TOGA® as described (47). RNA used in northern blotting and microarray analysis was isolated using TRIzol Reagent for thymus or TRIzol LS Reagent (Gibco-BRL) for cell lines. RNA quality was assessed by spectrophotometry and gel electrophoresis; RNA with A_{260}/A_{280} ratios greater than 2.0 in TE and no visible evidence of degradation by electrophoresis was used for northern blot analysis and expression profiling.

Identification of differentially expressed transcripts

TOGA® was carried out on duplicate samples of four independently isolated and characterized cells lines at passages 3 to 5. Initial candidate selections were made with the TOGA® portal using an in-house algorithm for peak detection and analysis to discriminate fold changes across samples after normalization (49). Following selection of initial candidates with the TOGA® portal, trace patterns were examined by eye, and distinct peaks with expression levels greater than 100 relative fluorescence units were selected. Sixty-five candidates were selected for follow-up analysis. The clones representing the 3′ regions of all 65 candidates identified by TOGA® were obtained, their sequences determined and compared with the GenBank database.

Northern blotting

Ten micrograms of total RNA per lane was used for northern blot analysis following the glyoxal denaturation protocol (90). Gels were transfer blotted onto Hybond™ N membrane (Amersham Pharmacia), washed and crosslinked following standard procedures (91). Blots were stained for RNA loading with 0.5 M acetic acetate (pH 5.2), 0.04% methylene blue and destained in ddH_2O. Probes corresponding to mouse *GzmC* (AA389537) were obtained (Genome Systems, Inc. and Digital Gene Technologies) and sequence verified. Fragments were gel purified using the QIAquick® Gel Extraction Kit (Qiagen) and ^{32}P random prime labeled using the Rediprime™ II labeling system (Amersham). Fragments for mouse β-actin, cyclophilin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were obtained commercially (Ambion) and labeled as described above. Labeled probes were hybridized at a specific activity of 1×10^6 cpm/ml in Church's Buffer following standard procedures (92). Blots were visualized on PhosphorImager screens overnight and signals quantified using ImageQuant software (Molecular Dynamics).

TaqMan quantitative RT-PCR analysis

Primers for TaqMan Quantitative RT-PCR analysis were designed using Primer Express 1.0 software (PE Biosystems). The cDNA used in the PCR analysis was synthesized from total RNA using Superscript II Reverse Transcriptase (Invitrogen). PCR was done using SYBR Green chemistry on an ABI Prism 7700 Sequence Detection System (PE Biosystems). The primers for TCRγ amplified an 84-bp fragment and were forward primer (5′-CACGAGGGCACTGTGATAGCT-3′) reverse primer (5′-GCCTTTTGTCAGAGGGAATTACTATG-3′). The CD53 primers amplified a 78-bp fragment and were forward primer (5′-ACCATCTTCCTGCCCATCAG-3′) and reverse primer (5′-TGCAGATGTTCAGGGTTGCTATAATAAGGCCAA-3′). Results were normalized using β-actin to amplify a 69-bp fragment using forward primer (5′-GGCGCTTTTGACTCAGGATT-3′) and reverse primer (5′-GGGATGTTTGCTCCAACCAA-3′).

5′ RACE

Analysis of *Gzm* fusions was carried out by RNA ligase-mediated rapid amplification of cDNA ends (RLM-RACE), using the GeneRacer Kit (Invitrogen). Experiments were performed according to the protocol using oligo-dT primers to generate RACE-ready cDNA. DNAseI-treated RNA samples used to generate the original TOGA® libraries (AT-4, AT-7, AT-12 and AT-13) were used as templates for RACE. In addition, RNAs from $Atm^{-/-}$ (AT-10) and $Atm^{-/-}\,p53^{+/-}$ (APT-3) TCLs and from wild-type thymus were examined.

Microarray experiments and data analysis

cDNA microarrays were prepared at the Salk Institute Functional Genomics Laboratory using 9216 sequence-confirmed mouse Unigene cluster cDNAs obtained from Genome Systems (Palo Alto, CA). Clones were spotted on aminosilane-coated, aluminized glass slides in duplicate. Total RNA for hybridization to cDNA microarrays was either labeled directly using aminoallyl labeling or was amplified using a single round *in vitro* transcription (IVT) reaction and then labeled using aminoallyl labeling. Aminoallyl labeling using 10 μg of total RNA was performed essentially as described (http:/cmgm.stanford.edu/pbrown/protocols/aadUTPCouplingProcedure.htm).

IVT amplification was performed using 2 μg of total RNA and reverse transcription (RT) with a T7-$d(T)_{24}$ primer (Genset). cDNA was extracted from the RT reaction, and purified using a Microcon C50 spin column (Millipore). Single round amplification of purified cDNA was performed using the MAXIscript™ IVT kit (Ambion), and complementary RNA (cRNA) purified using the RNeasy® Mini Kit (Qiagen). Three micrograms of IVT cRNA was labeled using the aminoallyl protocol described above. Cy5- and Cy3-labeled cDNAs were quantified by spectrophotometry. Twenty picomoles of labeled Cy5 sample and 20 pmol of Cy3 sample were lyophilized for use in the hybridization.

Pretreated slides were hybridized with 40 μl hybridization solution (20 μl formamide, 10 μl 4× Hybridization buffer v.2 (Amersham), 5 μg mouse C_0t1 DNA (Invitrogen), 5 μg polyadenylic acid (Sigma), 20 pmol of the labeled Cy5 and 20 pmol of the labeled Cy3 cDNA samples in the dark for 16 h at 42°C in humidified CMT™ Hybridization Chambers (Corning). After hybridization, slides were washed, dried with compressed air and scanned immediately (Molecular Dynamics Array Scanner GenIII). Additional information about the cDNA microarray protocols and data analysis methods are provided as supplemental data.

Database analyses

Public databases searched in these analyses were NCBI (http://www.ncbi.nlm.nih.gov) (including Locuslink, GenBank, Mouse–Human Homology Maps and Unigene) and the Mouse Genome Database (http://www.informatics.jax.org) (93). In addition, data were generated through use of the Celera Discovery System and Celera's associated databases (94).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Exhibit F

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PREVIOUS TOP STORIES

August 3, 2005
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August 1, 2005
PowderMed Manufactures a Vaccine Against HSN1 (Avian Influenza) for Clinical Development – more

July 27, 2005
AstraZeneca and Astex announce new anti-cancer drug discovery alliance – more

July 26, 2005
BioSource Signs Definitive Merger Agreement and Reports Record Second Quarter Sales – more

July 25, 2005
Exelixis Initiates Phase I Clinical Trial for Anticancer Compound XL820 – more

July 25, 2005
First Demonstration of Systemic siRNA Efficacy at Therapeutically Relevant Doses is Published by Sirna Therapeutics – more

July 14, 2005
BrainCells Inc. Announces $17.7 Million Series A Financing – more

July 12, 2005
BioProcessors' SimCell™ Platform Demonstrates Potential to Increase Amgen's Cell Culture Experiment Capacity – more

Portfolio News

July 12, 2005
Solexa Completes $24 Million Private Equity Financing – more

July 7, 2005
Sirna Therapeutics Completes Initial Closing of a $28 Million Financing – more

July 5, 2005
Elixir Pharmaceuticals: Nature Publication Reports Key Links Between Mechanisms of Aging and Metabolic Disorders – more

July 5, 2005
James B. Tananbaum, M.D. Joins Critical Therapeutics' Board of Directors – more

June 28, 2005
Cambrios Names Xina Quan as First Vice President of Research &

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NEWS

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Elixir: Want to Live Forever? – more

November 4, 2005
Memory Pharmaceuticals Commences Phase 2a Trial of MEM 1003 in Alzheimer's Disease – more

November 3, 2005
Santhera and the NIH Collaborate to Evaluate SNT-MC17 in Friedreich's Ataxia – more

November 2, 2005
Critical Therapeutics' ZYFLO(R) Reduces Need for Rescue Medication and Significantly Improves Lung Function in Severe Asthma Patients – more

November 2, 2005
AVEO Pharmaceuticals and Merck Sign Collaboration for Clinical Drug Response Prediction – more

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Cardiome Acquires Artesian Therapeutics – more

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Xanthus Initiates a Phase 2 Study Of Xanafide in Combination with ara-C for Treatment Of Secondary AML – more

October 19, 2005
Santhera Targets New Indication with its Lead Compound – more

October 18, 2005
BrainCells, Inc. Appoints James A. Schoeneck Chief Executive Officer – more

Video: IBM Promo Fe
Oxford Bioscience Pa

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October 17, 2005
Memory Pharmaceuticals Announces Collaboration to Develop PDE10 Inhibitors for Central Nervous System Disorders with Amgen – more

PREVIOUS TOP STORIES

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Dynogen Initates Phase II Trial of DDP225 for Treatment of Patients with

Diarrhea-Predominant Irritable Bowel Syndrome -- more

October 12, 2005
Cellzome and Santhera's business unit, Graffinity, awarded Euro 2.2 million grant from German Government -- more

October 10, 2005
Critical Therapeutics Announces Commercial Launch of ZYFLO(R); Studies Showed ZYFLO Reduced the Need for Rescue Medications and Improved Asthma Symptoms -- more

September 30, 2005
John P. Donoghue Honored for Cyberkinetics' Groundbreaking BrainGate (TM) Brain-Computer Interface at the 'Popular Mechanics 2005 Breakthrough Awards -- more

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Avalon Pharmaceuticals Announces the Activation of IND for AVN944 for the Treatment of Cancer -- more

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Avalon Pharmaceuticals Announces Pricing of Initial Public Offering -- more

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Xanthus Life Sciences Awarded Grant from NCI to Develop Technology for Personalized Dosing of Anticancer Drugs -- more

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Sirna Therapeutics and Allergan Enter Into Strategic Ophthalmology Alliance -- more

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Critical Therapeutics Announces FDA Approval of ZYFLO(R) for the Prevention and Chronic Treatment of Asthma; Oral Drug Blocks the Production of Mediators That Can Trigger Asthma Symptoms -- more

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Memory Pharmaceuticals Announces $31 Million Financing -- more

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Merger of Pharmagene Plc and Asterand, Inc. to Form a Leading Company in Human Tissue Supply and Human Tissue Based Research Services -- more

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Avalon Pharmaceuticals Announces Small Molecule Drug Discovery Program -- more

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ACADIA Pharmaceuticals Announces Election of Michael T. Borer to Board of Directors -- more

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Avalon Pharmaceuticals, Inc. Announces Filing of IND for AVN944 for the Treatment of Cancer -- more

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Solexa and Collaborating Scientists Illuminate the Small RNA Component of the Transcriptome; Research Published in "Science" Demonstrates the Value of High-Throughput Sequencing in Small RNA Analysis -- more

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Astex announces new drug discovery collaboration with Boehringer Ingelheim -- more

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Cardiome Announces LOI to Acquire Artesian Therapeutics -- more

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Dennis H. Langer Appointed to Sirna Therapeutics Board of Directors -- more

August 22, 2005
ALS Patients Offered Access to Cyberkinetics' BrainGate(TM) System in New Pilot Study at Massachusetts General Hospital -- more

August 22, 2005
World Renowned Geneticist David Bentley, D.Phil., Joins Solexa as Chief Scientist -- more

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X-Cell Medical Commences Randomized Clinical Trial of Estradiol Eluting Stent -- more

August 17, 2005
Biovitrum and Santhera sign an exclusive license and collaboration agreement for the development of DPP-IV inhibitors for the treatment of type 2 diabetes and other metabolic diseases -- more

Archived News Items

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OBP I	$ 5
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OBP III	$23
OBP IV	$45

Accelerated Technologies, Inc. — OBP IV
Hackensack, NJ
www.acctec.net

Accelerated Technologies creates and efficiently develops new enterprises within the medical technology arena, focusing on the cardiovascular market, by leveraging its infrastructure and the know-how of involved clinicians and researchers.

Alantos Pharmaceuticals — OBP IV
(Formerly Therascope AG)
Cambridge, MA and Heidelberg, Germany
www.alantos.com

Alantos is a drug discovery company focused on dynamic combinatorial chemistry, a process which allows the merging of the combinatorial synthesis of new compounds with their screening for target binding into a single step.

Applied Spine Technologies, Inc. — OBP IV
New Haven, CT

Applied Spine Technologies is a spine company focused on developing implantable dynamic stabilization systems for the treatment of chronic back pain.

Artesian Therapeutics, Inc. — OBP IV
Gaithersburg, MD
www.artesianrx.com

Artesian Therapeutics is developing dual pharmacophore compounds containing proven pharmacophores to treat cardiovascular disease.

Asterand, Inc. — OBP III
Detroit, MI
www.asterand.com

Asterand, Inc. specializes in providing essential tissue samples and information for use in cutting edge genomics research.

Astex Therapeutics Ltd. — OBP II, III
Cambridge, UK
www.astex-therapeutics.com

Astex is a drug discovery company applying novel protein strcture-based technologies for the discovery of small molecule therapeutics.

AVEO Pharmaceuticals, Inc. OBP IV
Cambridge, MA
www.aveopharma.com

AVEO is a cancer therapeutics discovery company using in vivo tumor models and focusing on tumor maintenance genes.

BioProcessors Corporation OBP IV
Woburn, MA
www.bioprocessors.com

BioProcessors is a start-up company that is developing an automated, parallel, miniaturized platform to enable the growth, culture, study and analysis of living cells.

BrainCells Inc. OBP IV
La Jolla, CA
www.braincellsinc.com

BrainCells Inc. is a neurogenesis-based drug discovery and development company targeting novel therapies for disorders of mood and anxiety.

Cambrios Technologies Corp. OBP IV
Mountain View, CA
www.cambrios.com

Cambrios Technologies Corp. applies peptide affinity and biological patterning technologies to commercially important materials in semiconductor and other industries. Cambrios' technologies enable rapid and low cost formation of patterned thin films of essentially any material, and are of particular use in large area electronic applications such as flat panel displays.

CardioFocus, Inc. OBP III
Norton, MA
www.cardiofocus.com

CardioFocus develops laser-based technology for the treatment of the underlying causes of atrial fibrillation.

Ceres, Inc. OBP II
Thousand Oaks, CA
www.ceresbiotech.com

Ceres is a plant genomics company identifying key genes determining seed size, quantity, and yield amounts, as well as pesticide and herbicide resistance.

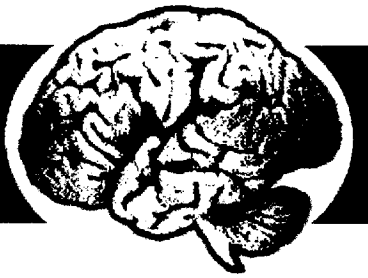
CircuLite, Inc. OBP IV
Hackensack, NJ and Aachen, Germany

CircuLite develops superficially implanted ventricular assist devices to treat congestive heart failure that align with the operating skills of the interventional cardiologist.

Cohesive Technologies Inc. OBP III
Franklin, MA
www.cohesivetech.com

Cohesive Technologies Inc. develops and markets liquid chromatography-based products for the separation, purification, and analysis of drugs from patient samples for the clinical trials and clinical diagnostics markets.

Concentric Medical, Inc. OBP IV
Mountain View, CA
www.concentric-medical.com



NeuroVentures
Partners for Emerging CNS Compa

Portfolio

NeuroVentures developing portfolio of leading CNS companies includes:

Acumen PHARMACEUTICALS

385 Oyster Point Blvd, Suite 9A
South San Francisco, CA 94080
Phone: 650-875-7700
www.acumenpharm.com

Acumen Pharmaceuticals, Inc. is an early-stage, drug discovery company committed to developing novel, disease-modifying therapeutics for Alzheimer's disease and mild cognitive impairment.

BrainCells bci inc

10835 Road To The Cure, Suite 150
San Diego, CA 92121
Phone: 858 812 7700
Fax: 858 812 7630
www.braincellsinc.com

BrainCells, Inc. is an early stage, neurogenesis-based drug discovery and development company targeting novel therapies for depression, recovery from brain injury and other CNS diseases.

Concentric Medical

2585 Leghorn Street
Mountain View, CA 94043
Phone: 650-938-2100
Fax: 650-938-2700

Concentric Medical, Inc. is pioneering new interventional approaches to treating ischemic and hemorrhagic stroke. The company's *MERCI™ Retrieval System*, a mechanical clot retrieval system, was approved by the FDA in August 2004 for use as a primary tool for intervening in acute ischemic

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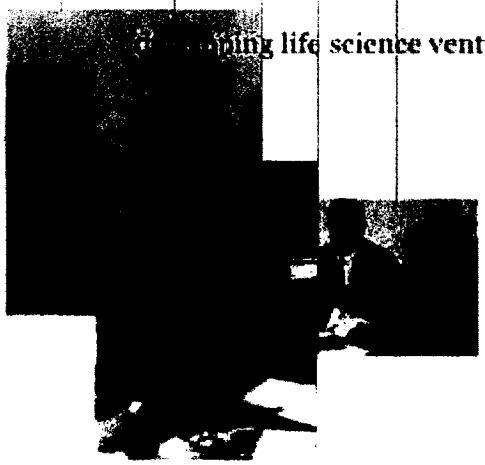
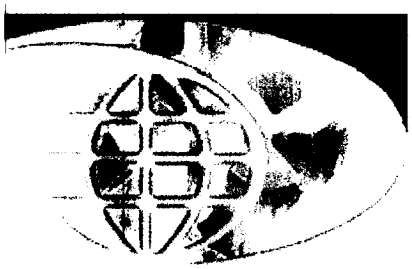


Celebrating a decade of investing in life science companies,



A. M. Pappas & Associates provides budding companies with the flexible combination of investment capital and other essential resources they need to thrive and succeed. Our investment team is made up of scientific, medical and business professionals deeply grounded in the life science industry, with the kind of expertise, experience and creativity it takes to move technologies from concept stage to commercial implementation. Everything we do is about building and strengthening relationships and working closely with our portfolio companies to help them create value.

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Portfolio News

Syntonix and Boehringer Enter Collaboration for U Million to Optimize Thera Peptide Candidates for In

BrainCells, Inc. Appoints Schoeneck Chief Executiv

Dynogen Initiates Phase DDP225 for Treatment of Diarrhea-Predominant Irr Syndrome

Dynogen Initiates Phase DDP733 for Treatment of Constipation-Predominan Bowel Syndrome

TargeGen, Inc. Closes $3 "C" Preferred Venture Fin

Cerexa, Inc. Announces C Launch and $50 Million Ir Financing

Panacos Drug Candidate Shows Potent Antiviral Ac infected Patients

TECHNOLOG
PARTNER

Life Sciences

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Roger Quy

- **Strategy**
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- **The Team**
  Biographies
- [redacted] Information Technol
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Representative Companies

BrainCells, Inc.

Calypte Biomedical
(AMEX: HIV)

Cell Pathways
Acquired by OSI Pharmaceuticals
(NASDAQ: OSIP)

Cholestech (NASDAQ: CTEC)

Cryogen
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Post a Job
Search Resumes
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Trials by Target
Investigators: Get trials with top pharma

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Bio UK™

Companies

Mini-Profile

BrainCells, Inc.

10835 Road To The Cure, Suite 150

San Diego, California 92121 U.S.A.
Phone: 858-812-7700 Fax: 858-812-7630

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- BrainCells, Inc. News from The BioSpace Beat

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Bizones

BioCrossroads™ (IN)
Bio UK™

BioSpace Beat

BrainCells, Inc. News from The BioSpace Beat

Ownership: Private

- **BrainCells, Inc.** Names **James Schoeneck** Chief Executive

  By VentureWire Staff Reporters 10/20/2005
  (See Story from BioSpace.com) *(10/20/2005)*

- **BrainCells, Inc.** Announces $17.7 Million Series A Financing

  SAN DIEGO, July 14 /PRNewswire/ -- BrainCells Inc., a privately-held, neuroscience-focuse drug discovery and development company targeting novel and/or best-in-class therapies for depression, related neuropsychiatric disorders and other central nervous system diseases, announced the close of its Series A private financing. Technology Partners and seed investors Oxford Bioscience Partners, and Bay City Capital led the $17.7 million round, joined by A. M Pappas & Associates, Neuro Ventures, Matthias Bowman, Harry Hixson, Chairman and CEO, and scientific founders Fred H. Gage of the Salk Institute and Eric Kandel of Columbia University. The participants in the financing have invested $8.0 million to date and, pursuant t the terms of the financing, will become obligated to invest an additional $9.7 million upon the achievement by the Company of certain milestones.
  (See Story from BioSpace.com) *(07/15/2005)*

MERRILL DATASITE

Make Your Next M&A Deal A GOOD DEAL

BrainCells Inc.

Industry: Life Sciences - Pharmaceuticals
San Diego, California

Develops therapies for depression, related neuropsychiatric disorders and other central nervous system diseases

Funding date	Jul 18, 2005
Amt	$8.00 mill.
Round	First

Investors (9)
A. M. Pappas & Associates LLC
Bay City Capital LLC
Eric Kandel
Fred H. Gage
Harry Hixson
Matthias Bowman, chairman
NeuroVentures Capital LLC
Oxford Bioscience Partners
Technology Partners

V-Speak: BrainCells was founded in December 2003 to capitalize on the discovery that humans generate new nerve cells throughout life and that this endogenous process (neurogenesis) can be manipulated using small molecule therapeutics. The new funding will be used to identify late-stage clinical compounds under development. The $8 million is the first tranche; an additional $9.7 million will be added once the company achieves certain milestones.

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BrainCells

Updated: 8/18/2005

BrainCells
10835 Road To The Cure
Suite 150
San Diego, CA 92121

Phone: 858 812 7700
Fax: 858 812 7630
Email:

BrainCells is a neurogenesis-based drug discovery and development company.

History:

Founded in 2003.

Employment

Email:

Fax:

Mail:
HR Director
BrainCells, INC.
10835 Road To The Cure, Suite 150
San Diego, CA 92121

General Info:

Ticker:
Employees:

Regions:
Southern California

Research Focus:
Disease Therapeutics-Research
Therapeutics-Development

Profiles:

News:

Keywords:

Venture Capital Investment in Health Industries Report*

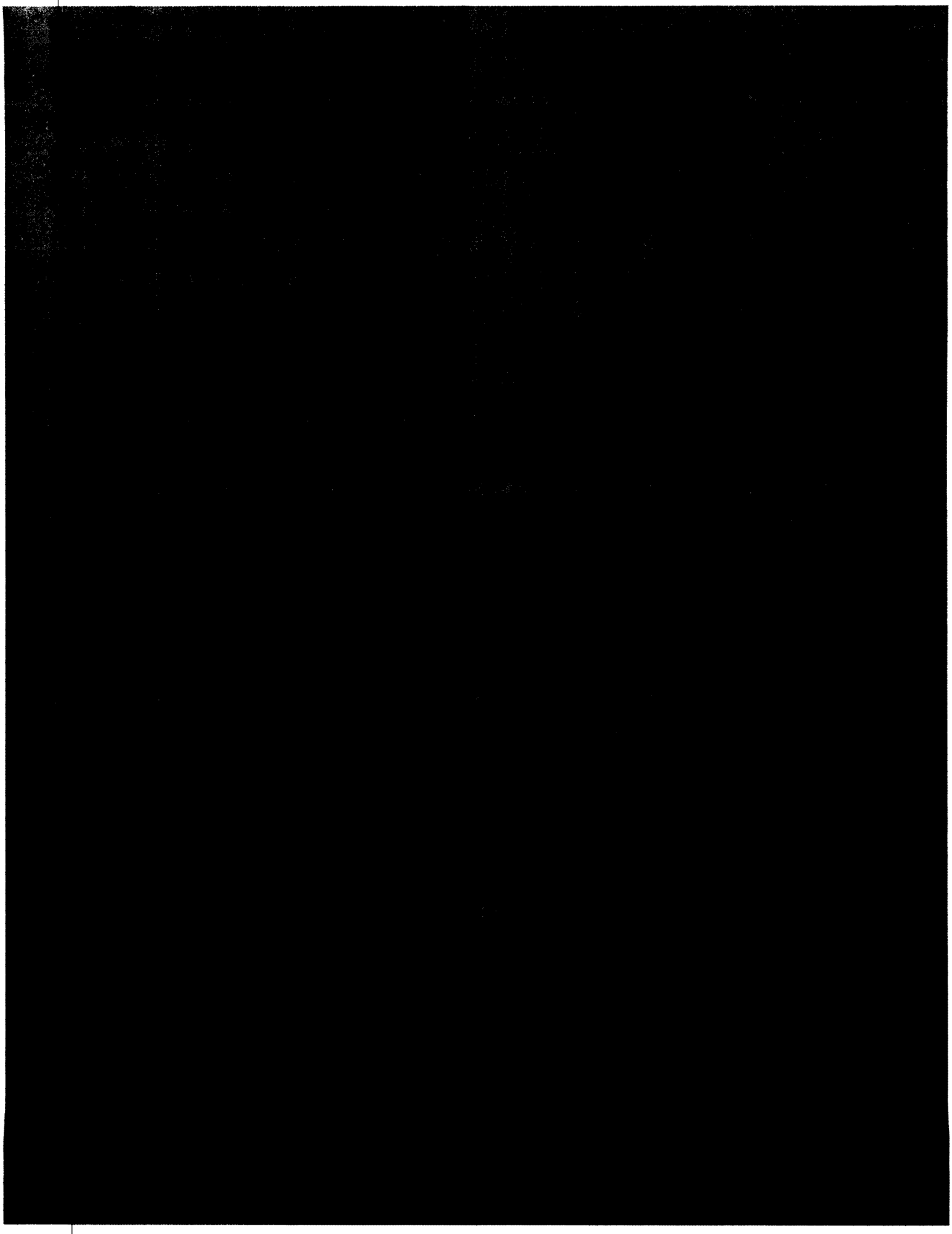
YTD Q2 2005

PricewaterhouseCoopers/Venture Economics/National Venture Capital Association MoneyTree™ Survey

Health Research Institute

*connectedthinking

PRICEWATERHOUSECOOPERS



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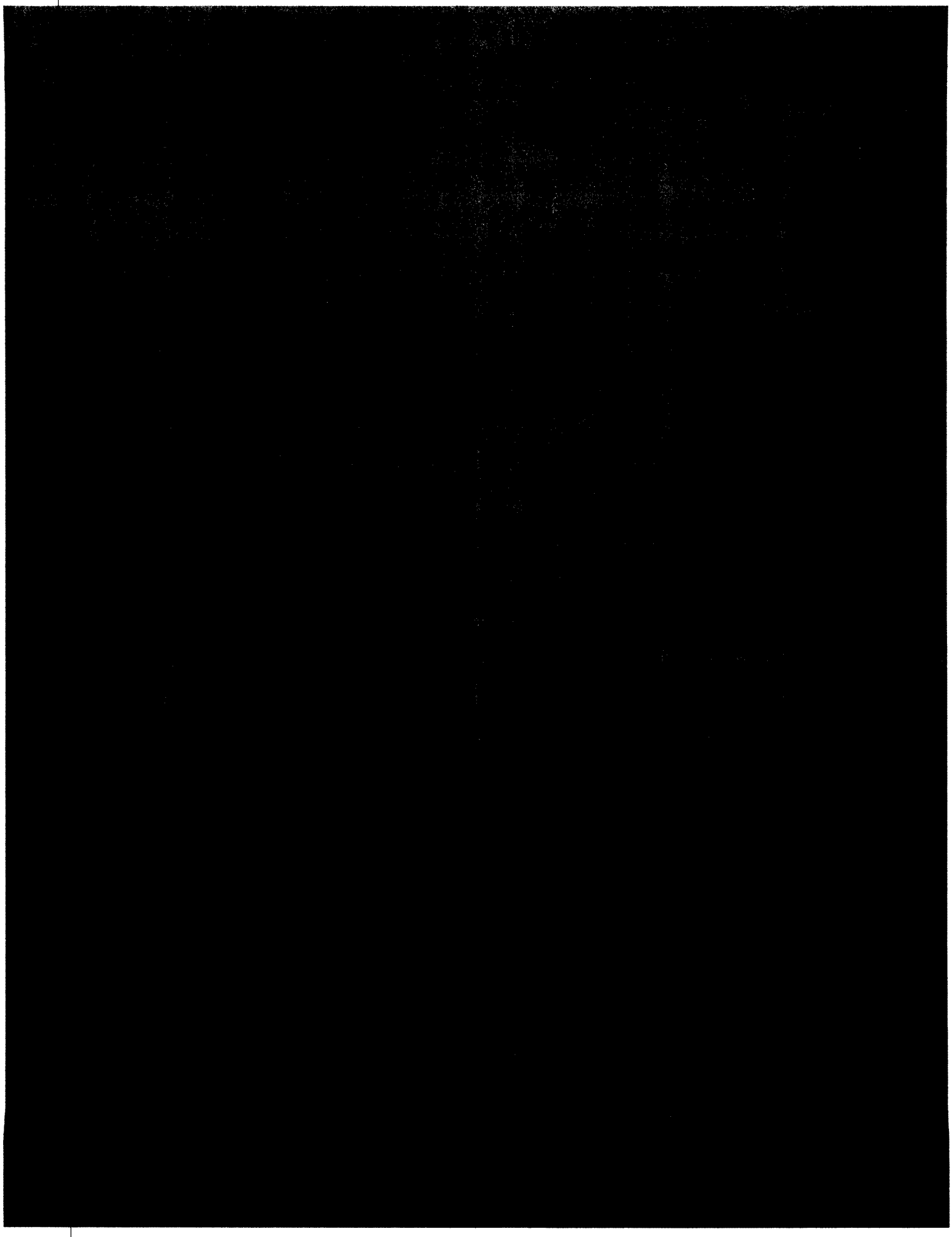


Venture Capital Investment in Health Industries Report

YTD Q2 2005 Results

Highlights of Results

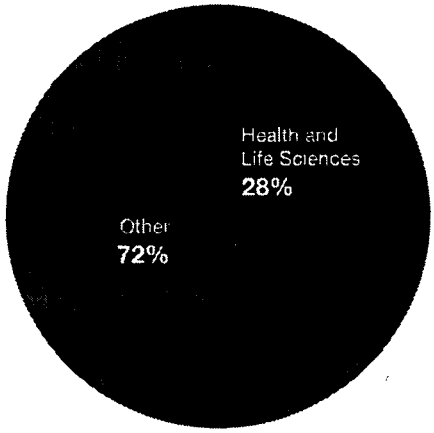
Reflecting investors' continuing enthusiasm for health-related investments, nearly a third (31%) of all venture capital dollars in Q2 2005 went to health industries, according to the MoneyTree™ Survey conducted by PricewaterhouseCoopers, Thomson Venture Economics and the National Venture Capital Association. This sector, comprised of biotechnology, pharmaceuticals, health services, health information technology and medical devices, accounted for more investment than any other industry sector. Investment in the sector has held steady at between 25 and 30% of total invested capital for ten quarters.

As a percentage of venture capital dollars, investments in health industries have generally increased in the 10-year history of the MoneyTree™ survey. Hot areas of investment include disease management, cancer drug development, genomics, molecular biology, innovative drug delivery methods, management of hospitals/clinics, and obesity/ weight-loss treatments.

Health and Life Science YTD Q2 2005 Findings

Investments by venture capital firms in health industries companies continue to outpace those of all other industries, in the first half of 2005, accounting for 28% of all venture capital dollars. Year-to-date biotechnology investments account for 16.5% of the total venture capital investments while medical devices and equipment account for 8.2% and investments in healthcare services, information and software account for 3.2% of total venture capital investments.

Distribution of Venture Capital Funds, YTD Q2 2005



In Q2 2005,

- biotechnology accounted for 19.4%
- medical devices and equipment accounted for 7.4%
- healthcare services, information and software accounted for 3.8%

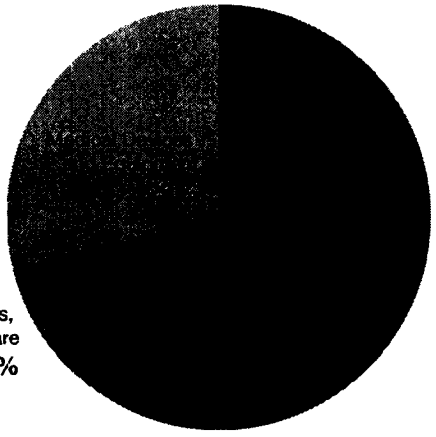
of total venture capital investments.

$ in millions

Industry	Q2 2004	YTD Q2 2004	Q2 2005	YTD Q2 2005
Biotechnology	$1,012.8	$1,902.6	$1,122.2	$1,753.8
Medical Devices	$509.7	$860.5	$425.7	$870.3
Healthcare Services	$304.8	$423.4	$219.5	$341.2
Total Health Industries VC Dollars	**$1,827.3**	**$3,186.5**	**$1,767.4**	**$2,965.2**
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Of the total $3.0 billion invested in health industries YTD Q2 2005, 59% of the investments were in the biotechnology sector. Since 2003, biotechnology, which is inclusive of pharmaceuticals, accounts for more than 50% of investments made in the health industries sector. Medical devices and equipment accounted for 29% of the total health industries investments with $870 million while investments in healthcare services, information and software amounted to $341 million or 12% of the total health industries investments.

Percent of $3.0B Invested in Health Industries by Sector, YTD Q2 2005



In Q2 2005,

- biotechnology accounted for 64%
- medical devices and equipment accounted for 24%
- healthcare services, information and software accounted for 12%

of health industries investments.

Investments in health industries companies Q1-Q2 2005 ($3.0B or 28% of the total venture capital dollars) were approximately the same as last year's Q1-Q2 2004 investments ($3.2B or 28.7%). Venture capital investments in health industries have decreased from $1.83 billion in Q2 2004 to $1.77 billion in Q2 2005 with the number of deals remaining approximately the same.

Investments in Health Industries as a Percentage of Venture Capital Dollars

Industry	% of Total Venture Capital Dollars (YTD Q2 2004)	% of Total Venture Capital Dollars (YTD 2005)
Biotechnology	17.1%	16.5%
Medical Devices and Equipment	7.7%	8.2%
Healthcare Services and Technology	3.8%	3.2%
Total Health Industries	**28.7%**	**28.0%**

Sector YTD Q2 2005 Findings

Biotechnology

Overall, there was a 7.8% decrease in investment dollars and a larger number of deals (11 more deals) in the biotechnology sector YTD Q2 2005 in comparison to the first half of 2004. The smaller amount of dollars invested may reflect the drop-off in IPO activity in the biotechnology sector that occurred in the same time period.

This sector witnessed several large investments in the second quarter of 2005, including the following which amount to more than $50 million each:

- Jazz Pharmaceuticals ($100 million): Operates as a pharmaceutical company.
- Esprit Pharma Holding Co. ($58 million): Operates as a specialty pharmaceutical company.
- Somaxon Pharmaceuticals ($55 million): Develops products to treat psychiatric and related conditions.

Total Biotech Investments by Quarter

$ in millions

	Q1	Q2	Total YTD
2004			
$ invested	$889.8	$1,012.8	$1,902.6
# deals	70	84	154
2005			
$ invested	$631.6	$1,122.2	$1,753.8
# deals	68	97	165

Medical Devices and Equipment

The medical device and equipment sector witnessed a 1.1% increase in investment dollars with 13 fewer deals in YTD Q2 2005 as compared to YTD Q2 2004. In Q2 2005, this sector attracted $426M, a 16% decrease in investment dollars from Q2 2004. Venture capitalists investing in the medical device and equipment sector invested largely in companies that develop radiation and cardiology therapies and surgical devices and materials.

The following are the largest deals in the medical device and equipment sector in Q2 2005:

- Calypso Medical Technologies ($35 million): Develops medical devices focused on radiation therapy treatments.
- AcuFocus ($27.5 million): Develops ocular implants to treat presbyopia.
- Cylene Pharmaceuticals ($26.3 million): Develops small molecule anti-cancer agents for patients.
- Cierra ($21.3 million): Operates an interventional cardiology company.

Total Medical Devices and Equipment Investments by Quarter

$ in millions

	Q1	Q2	Total YTD
2005			
$ invested	$350.8	$509.7	$860.5
# deals	60	71	131
2004			
$ invested	$444.5	$425.7	$870.3
# deals	61	57	118

Healthcare Services and Technology

There were 8 fewer deals in the healthcare services, information and software sector YTD Q2 2005 and a 19.4% decrease in the total amount invested when compared to YTD Q2 2004. These health services and technology companies attracted 28% less funding in Q2 2005 compared to the year-ago quarter. The 33 investment deals in the second quarter of 2005 amounted to $219.5 million.

The majority of investments were in companies that provide patient-specific information services and assist in the operation and management of hospitals, clinics and pharmacies. Healthcare technology firms providing software for managing clinical and financial data, developing information exchange models and providing automation systems for hospitals also received a large share of healthcare venture capital dollars.

The companies that have attracted the most funding include the following:

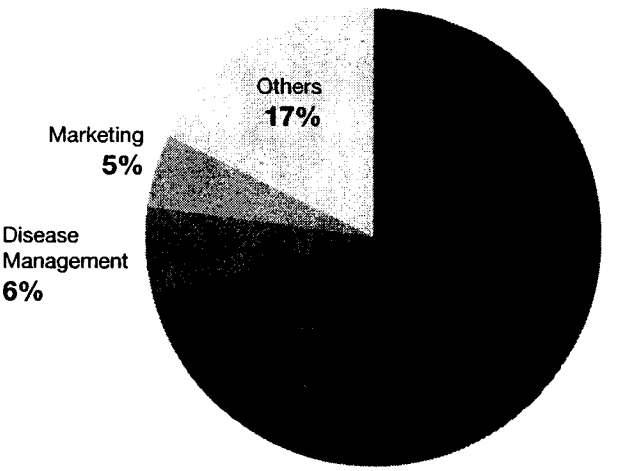
- Centerre Healthcare Corporation ($30 million): Provides inpatient rehabilitation services within acute care hospitals.
- Vantage Oncology ($22 million): Develops and operates radiation oncology treatment centers.
- OraMetrix ($18 million): Provides technology solutions for orthodontic care.
- Kelson Physician Partners ($15 million): Owns and operates a pediatric healthcare company.

Total Healthcare Services and Technology Investments by Quarter

$ in millions

	Q1	Q2	Total YTD
2005			
$ invested	$118.6	$304.8	$423.4
# deals	24	43	67
2004			
$ invested	$121.7	$219.4	$341.2
# deals	26	33	59

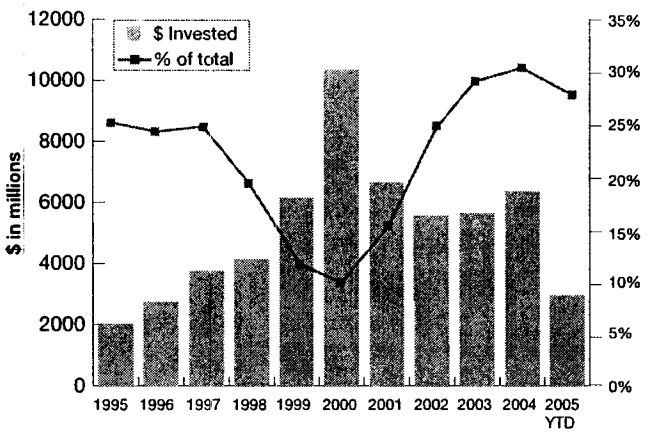
Percent of Healthcare Services and Technology Investments, Q2 2005



Health Industries Investments, 1995-YTD 2005

Health industries investments peaked in 2000 at a time when venture capital was hitting record levels, however, as a percentage of venture capital dollars, health industries investments were at the survey-high of 30.2% in 2004. YTD 2005 investments by venture capital firms in health industries companies accounts for 27.9% of all venture capital dollars.

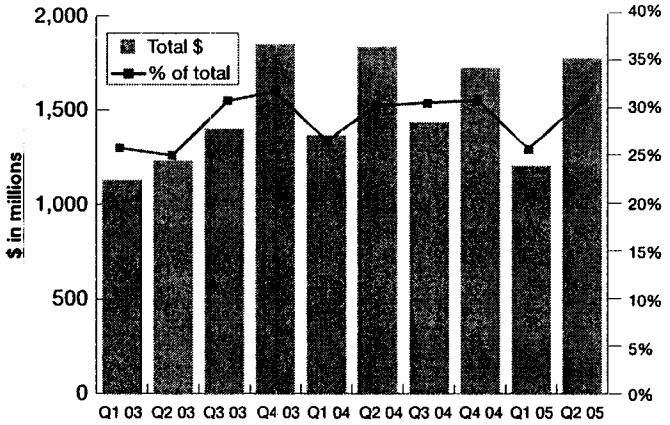
Health and Life Sciences Investments, 1995-YTD 2005



Health Industries Investments, Past Ten Quarters

Over the past ten quarters, investments in health industries companies have been stable. There was a slight decrease in investment dollars in Q2 2005 as compared to Q2 2004, however, the number of deals remained the same.

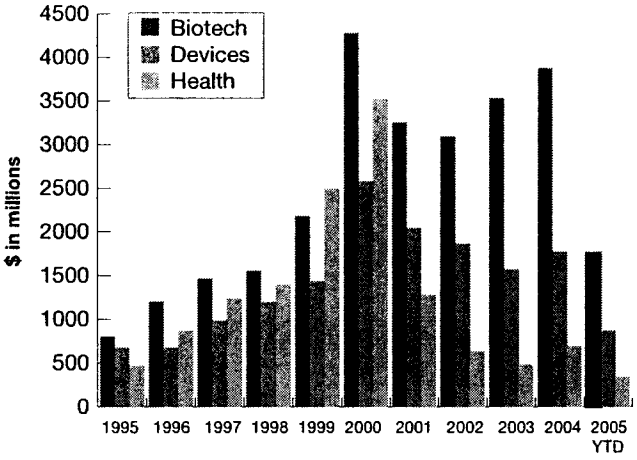
Health and Life Sciences Investments, Trailing Ten Quarters



Sector Investments, 1995-YTD 2005

While investments in all sectors were down from the 2000 peak, venture capital funding seems to have stabilized in 2004. Biotechnology remains the largest sector within health industries.

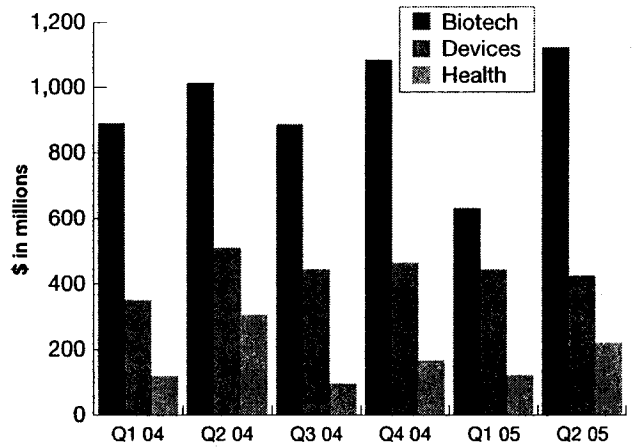
Sector Investments, 1995-YTD 2005

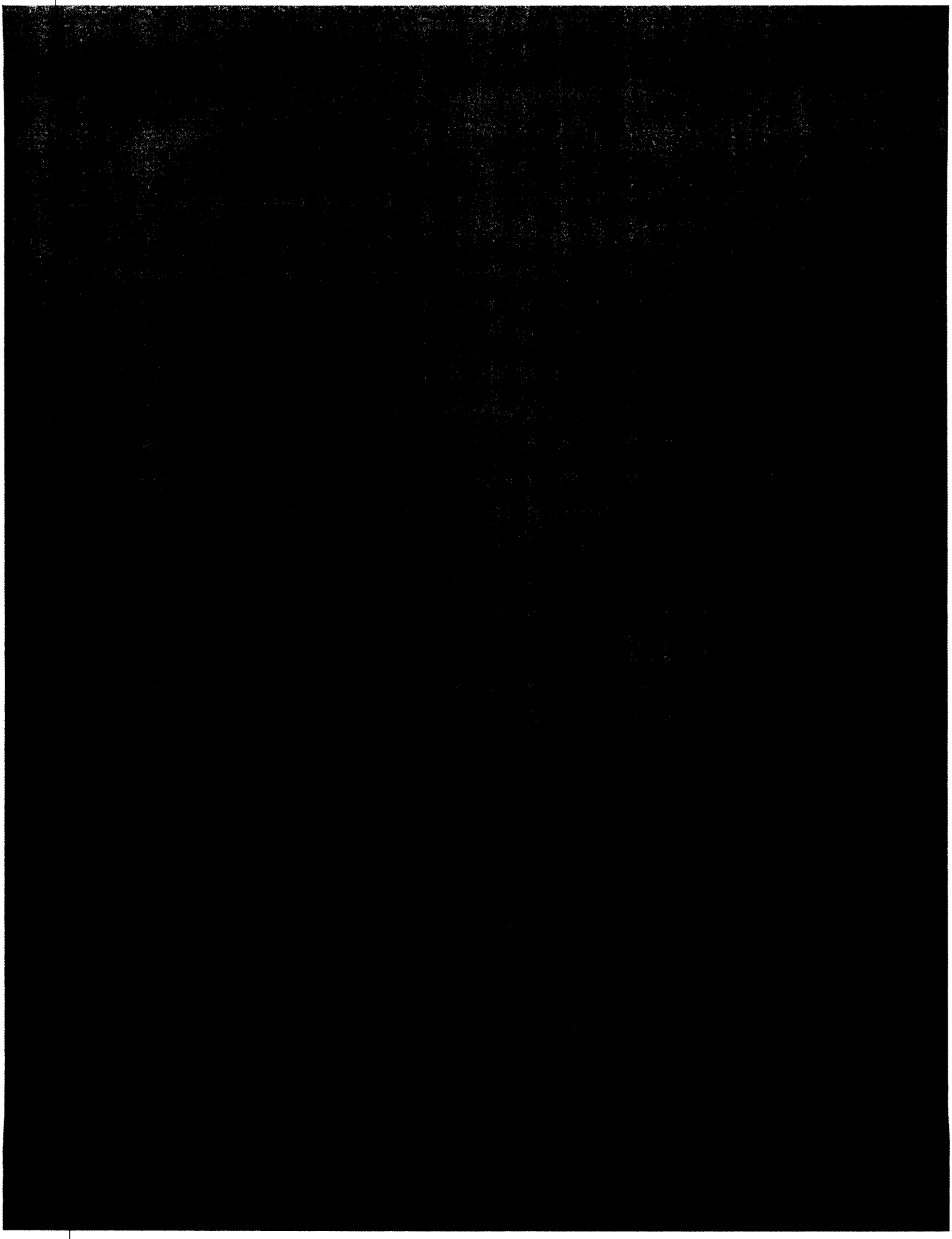


Sector Investments, by Quarter 2004-2005

Investments in medical devices and equipment companies had remained steady at $450 million from Q3 2004 through Q1 2005 and slightly decreased in Q2 2005. Biotechnology investments were higher than in the previous five quarters.

Sector Breakouts, by Quarter 2004-2005





Venture Capital Investment in Health Industries Report

Q2 2005 Results

Biotechnology and Pharma

Total Industry Investment: $ 1,122,222,800

Number of Deals: 97

Percent of Total: 19.4%

Total Investments:

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Jazz Pharmaceuticals, Inc.	Expansion	99,999,900	Operates as a pharmaceutical company.	Adams Street Partners, LLC (FKA: Brinson Private Equity), Versant Ventures
Export Pharma Holding Co. (FKA: Saturn Pharmaceuticals)	Early Stage	58,280,000	Operates as a specialty pharmaceutical company.	Apax Partners, Inc., Domain Associates, L.L.C., New Enterprise Associates
Sepracor Pharmaceuticals, Inc.	Later Stage	55,000,000	Develops products to treat psychiatric and related conditions.	BA Venture Partners (AKA: BankAmerica Ventures), CDIB BioScience Venture Management, Domain Associates, L.L.C., MPM Capital (FKA: MPM Asset Management, LLC), Montreux Equity Partners, Prospect Venture Partners (FKA: Prospect Management, LLC)
Idun Pharmaceuticals, Inc.	Later Stage	50,000,000	Provides human therapeutics focusing on controlling programmed cell death.	MPM Capital (FKA: MPM Asset Management, LLC), Pacific Firm Ventures, Prospect Venture Partners (FKA: Prospect Management, LLC), Sutter Hill Ventures, Venrock Associates, Ventana Capital Management, Inc.
Orexigen Therapeutics, Inc.	Expansion	50,000,000	Develops drug treatments for obesity and related disorders.	BA Venture Partners (AKA: BankAmerica Ventures), Domain Associates, L.L.C., Duke University, Kleiner Perkins Caufield & Byers, Montreux Equity Partners, Morgenthaler Ventures, Sofinnova Ventures, Inc.
Human Genome Sciences, Inc.	Later Stage	50,000,000	Develops monoclonal antibodies to regulate targets on the cell surface.	Integra Ventures, Pequot Capital Management, Inc., U.S. Venture Partners, Undisclosed Venture Firm
[illegible]	Later Stage	50,000,000	Develops pharmaceuticals for vaccines for cancer.	China Xin Technology Development Corp. (FKA: Fidelity VC), Prospect Venture Partners Corp., Undisclosed Venture Firm
Molecular Insight Pharmaceuticals, Inc.	Later Stage	50,000,000	Develops molecular imaging pharmaceuticals.	Cerberus Capital Management, L.P., Enlightenment Capital, Sigma-t Venture Capital Limited (AKA: SVC), Undisclosed Venture Firm

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Verus Pharmaceuticals, Inc.	Expansion	28,000,000	Develops and licenses products focused on the pediatric market.	Domain Associates, L.L.C., MPM Capital (FKA: MPM Asset Management LLC), Prospect Venture Partners (FKA: Prospect Management LLC)
Receptor Biologix, Inc.	Early Stage	26,450,200	Develops class of protein therapeutics to treat cancer and other diseases.	Domain Associates, L.L.C., Essex Woodlands Health Ventures (FKA: Woodlands Venture), MedImmune, Northwest Technology Ventures (FKA: ORTDF), Skyline Ventures, Takeda Research Investment, Inc.
Anacor Pharmaceuticals, Inc.	Later Stage	25,000,200	Develops drugs for the treatment of inflammatory and infectious diseases.	Aberdare Ventures, Care Capital, LLC, Individuals, Red Abbey Venture Partners, LLC, Rho Ventures (AKA: RHO Management), Venrock Associates
GlobeImmune, Inc.	Expansion	25,000,000	Develops vaccine platform technology for viral infections and cancers.	HealthCare Ventures LLC (FKA: Healthcare Investments), Morgenthaler Ventures, Sequel Venture Partners, Undisclosed Venture Firm
Ambrx, Inc.	Expansion	23,400,000	Develops genetically engineered protein therapeutics.	5AM Ventures (AKA: 5AM Partners), Alexandria Real Estate Equities, LLC, CMEA Ventures (FKA:Chemicals & Materials Enterprise Associa), Maverick Capital Ltd., Tavistock Life Sciences (AKA: TLS) , Twilight Venture Partners , Undisclosed Venture Firm, Venture
Orqis Medical Corporation	Later Stage	22,725,100	Develops cardiac recovery devices.	Boston Scientific Corporation (FKA EP Technologies, Inc.), Care Capital, LLC, Domain Associates, L.L.C., HealthCare Ventures LLC (FKA: Healthcare Investments), Johnson & Johnson Development Corporation, Rho Ventures (AKA: RHO Management), Undisclosed Inve
Phenomix Corporation	Expansion	20,000,300	Develops and discovers novel drugs.	Alta Partners, Bay City Capital LLC, CMEA Ventures (FKA: Chemicals & Materials Enterprise Associa), Delphi Ventures, GBS Venture Partners Ltd., Individuals, J.P. Morgan Asset Management, Novartis Corp., Sofinnova Ventures, Undisclosed Venture Firm
Ilypsa, Inc.	Early Stage	20,000,000	Develops GI based drugs for renal and metabolic diseases.	Delphi Ventures, U.S. Venture Partners
Celator Pharmaceuticals, Inc. (FKA: Celator Technologies)	Expansion	19,999,900	Develops biopharmaceutical technology for use against various cancers.	Business Development Bank of Canada(AKA:BDC Venture Capital), Domain Associates, L.L.C., Quaker BioVentures, Inc., TL Ventures (FKA: Radnor Venture Partners), Undisclosed Venture Firm, Ventures West Management, Inc.
Nephros Therapeutics, Inc.	Later Stage	19,000,000	Develops products for treatment of acute and chronic kidney failure.	Bio*One Capital, Foster & Foster, Lurie Investment Fund, North Coast Technology Investors, L.P., Portage Venture Partners (AKA: Graystone Venture Partners), Seaflower Ventures
Tandem Labs	Later Stage	18,800,000	Provides bioanalytical services.	DW Healthcare Partners
Peptimmune, Inc.	Later Stage	18,664,000	Manufactures biopharmaceuticals for treatment of autoimmune diseases.	Boston Medical Investors, Hunt Ventures, LP, Itochu Corporation, MPM Capital (FKA: MPM Asset Management LLC), New Enterprise Associates, Prism Venture Partners, Silicon Valley BancVentures (FKA: Silicon Valley Bank), Vanguard Ventures
Avidia, Inc. (AKA: Avidia Research Institute, Inc.)	Expansion	18,570,000	Develops a novel type of biotherapeutic protein.	Alloy Ventures, Amgen, Inc., Individuals, MedImmune, Morgenthaler Ventures, TPG Ventures , Undisclosed Corporate Investor
Aureon Biosciences Corporation	Later Stage	18,000,000	Provides therapeutic intervention for human tissue.	Atlas Venture, Ltd., Pfizer Inc., Sprout Group
Cellerant Therapeutics, Inc.	Expansion	16,000,000	Develops hematopoietic stem cell-based therapies for cancer treatment.	Allen & Company, Individuals, MPM Capital (FKA: MPM Asset Management LLC), Undisclosed Venture Firm
Cerexa, Inc.	Early Stage	16,000,000	Develops hospital-based anti-infective therapies.	Domain Associates, L.L.C., Undisclosed Venture Firm
SomaLogic, Inc.	Expansion	15,175,900	Develops proteomics systems and applications.	ProQuest Investments, Undisclosed Corporate Investor, Undisclosed Venture Firm
Glycomimetics, Inc.	Expansion	14,640,000	Manufactures carbohydrate based pharmaceuticals.	ProQuest Investments, SB Life Science Equity Management LLC, Undisclosed Venture Firm
AgraQuest, Inc.	Later Stage	14,400,000	Develops and markets environmentally friendly pesticides.	Calvert Funds, Otter Capital, LLC, SAM Sustainable Asset Management (AKA: SAM Equity Partners), TPG Ventures , Undisclosed Investor, Undisclosed Venture Firm, Vivo Ventures (FKA: BioAsia Investments LLC)

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Cadence Pharmaceuticals, Inc. (FKA: Strata Pharmaceuticals)	Early Stage	13,825,000	Operates as a specialty pharmaceutical drug discovery firm.	Domain Associates, L.L.C., ProQuest Investments, Undisclosed Venture Firm
BioMimetic Pharmaceuticals Inc.	Expansion	11,800,000	Develops technology products for the healing and restoration of bone.	Axiom Venture Partners, L.P., HSS Ventures, Noro-Moseley Partners, PTV Sciences (FKA: Pinto Ventures)
Conforma Therapeutics Corporation	Later Stage	11,149,900	Discovers and develops anti-cancer therapeutics.	Domain Associates, L.L.C., IngleWood Ventures, ProQuest Investments, RiverVest Venture Partners , S.R. One, Limited
Ensemble Discovery Corporation	Early Stage	11,020,000	Provides research and discovery services using the DPC platform.	ARCH Venture Partners, Flagship Ventures , Oxford Bioscience Partners, Undisclosed Venture Firm
Hamilton Pharmaceuticals, Inc.	Early Stage	11,000,100	Develops novel medical treatments for Central Nervous System Disease.	Index Ventures Management SA, Undisclosed Investor, Vivo Ventures (FKA: BioAsia Investments LLC)
Primera BioSystems (FKA: STAR Technology)	Early Stage	11,000,100	Develops transcriptional profiling technologies.	Burrill & Company, MPM Capital (FKA: MPM Asset Management LLC), Malaysian Technology Development Corp Sdn Bhd
Xenoyme, Inc.	Expansion	11,000,000	Develops small molecule therapeutics for the treatment of GI diseases.	Business Development Bank of Canada(AKA:BDC Venture Capital), Fonds de Solidarite des Travailleurs du Quebec (F.T.Q.), Greer Capital Advisors LLC, HIG Capital Management (AKA: H.I.G. Ventures), Investissement Desjardins, Pacific Rim Ventures, Quaker BioVen
Bayhill Therapeutics, Inc. (FKA: Tolerion, Inc.)	Expansion	10,400,000	Develops DNA-based pharmaceutical therapeutics.	A.M. Pappas & Associates LLC, CIDC Consultants, Inc., CMEA Ventures (FKA:Chemicals & Materials Enterprise Associa), De Novo Ventures, Latterell Venture Partners, Lilly Ventures (FKA: e.Lilly Ventures), Montreux Equity Partners, Morgenthaler Ventures, U.S.
Nanomuscular, Inc.	Early Stage	10,125,000	Develops and commercializes nanotechnology solutions.	CMEA Ventures (FKA:Chemicals & Materials Enterprise Associa), Redpoint Ventures, U.S. Venture Partners
Amgen Biosciences (Can) (FKA: Aventa Biosciences Corp.)	Expansion	10,000,200	Develops small molecule neuroprotectants.	Avalon Ventures, Canadian Medical Discoveries Fund, F. Hoffmann - La Roche, Ltd., Forward Ventures, GIMV NV, GenieChem Financial Corporation, Perseus-Soros Management Company
Predicant Biosciences (FKA: Biospect, Inc.)	Expansion	10,000,200	Provides biotechnology services and products.	Advent Venture Partners, Prospect Venture Partners (FKA: Prospect Management LLC), Venrock Associates, Versant Ventures
Kalia, Inc.	Early Stage	10,000,100	Provides biotechnology services.	5AM Ventures (AKA: 5AM Partners), ARCH Venture Partners, Venrock Associates, Venture Associates AG
Myriad Genetics (FKA: Myriad Genetic Laboratories, Inc.)	Later Stage	10,000,000	Provides genetic testing and identification services.	Alliance Technology Ventures, Enterprise Partners Venture Capital (AKA: EPVC), Tullis-Dickerson & Co., Inc., Undisclosed Venture Firm
Osiris Therapeutics, Inc.	Expansion	10,000,000	Develops biopharmaceuticals and cell therapy products.	Fredl Corporate Finance AG
Ambrx, Inc. (FKA: Ambrx Discovery Corporation)	Expansion	9,550,000	Operates a small molecule biotechnology company.	3i (US), ARCH Venture Partners, MPM Capital (FKA: MPM Asset Management LLC), Novartis Corp., Undisclosed Venture Firm, Venrock Associates, Versant Ventures
DPM Pharmaceutical Sciences Inc.	Expansion	9,000,000	Operates a topical product development company.	Essex Woodlands Health Ventures (FKA: Woodlands Ventures)
NeuroVascular Pharmaceuticals, Inc.	Early Stage	8,765,000	Develops neuroprotective medicines for central nervous system disorders.	Mohr Davidow Ventures, Undisclosed Venture Firm
Cytopia Research Pty Ltd	Early Stage	8,353,000	Develops novel cancer treatment systems.	FirstVentury AG, Scandinavian Life Science Venture (SLSV) (FKA: Medicon Valley)
Bristol-Myers Squibb Co.	Early Stage	8,000,000	Develops drugs targeting mood and anxiety disorders.	A.M. Pappas & Associates LLC, Bay City Capital LLC, NeuroVentures Capital, Oxford Bioscience Partners, Technology Partners

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Structural Genomix, Inc.	Expansion	7,499,900	Operates as a drug discovery company.	Apple Tree Partners, Atlas Venture, Ltd., BA Venture Partners (AKA: BankAmerica Ventures), Index Ventures Management SA, Sprout Group
Exagen Diagnostics, Inc.	Expansion	7,000,000	Develops molecular diagnostics products.	Tullis-Dickerson & Co., Inc., Wasatch Venture Fund, vSpring Capital
AmpliMed Corporation	Expansion	6,500,000	Develops cancer chemotherapies.	Solstice Capital, Valley Ventures (FKA: Arizona Growth Partners, L.P.), Village Ventures
Aperon Biosystems, Inc.	Expansion	6,500,000	Develops biosensor systems for diagnosis and therapeutic management.	Alliance Technology Ventures, Canaan Partners, Draper Fisher Jurvetson (FKA: Draper Associates), ONSET Ventures
BioProcessors Corporation	Expansion	6,500,000	Develops an automated, parallel platform for analysis of living cells.	Eastman Ventures, HealthCare Ventures LLC (FKA: Healthcare Investments), Oxford Bioscience Partners, Undisclosed Investor
Immune Control, Inc.	Early Stage	6,300,000	Develops drugs to stop undesirable poliferation of immune cells.	Anthem Capital Management, Domain Associates, L.L.C., NewSpring Capital, Quaker BioVentures, Inc.
TriMed Research, Inc.	Expansion	6,078,000	Develops intestinal therapeutic products .	Seroba BioVentures Limited, inventages Venture Capital GmbH
Actimis Pharmaceuticals, Inc.	Early Stage	6,000,000	Develops small molecule therapeutics for respiratory disorders.	Mitsui & Co. Venture Partners (MCVP), Sanderling Ventures
Saegis Pharmaceuticals, Inc. (FKA: David Pharmaceuticals)	Later Stage	6,000,000	Develops memory enhancement drugs.	NeuroVentures Capital, Polaris Venture Partners, Sofinnova Ventures, Versant Ventures
Solstice Neurosciences, Inc.	Early Stage	6,000,000	Develops biopharmaceutical products in the areas of neurology and pain.	Investor AB , Morgan Stanley Venture Partners (AKA: MSDW), Oxford Bioscience Partners, Thomas, McNerney & Partners LLC
Nucleonics, Inc.	Expansion	5,999,900	Develops techniques in mammalian gene silencing.	Anthem Capital Management, Burrill & Company, New Enterprise Associates, Odlander, Fredrikson & Co, Quaker BioVentures, Inc., S.R. One, Limited
Koronis Pharmaceuticals	Expansion	5,700,000	Develops technologies for the prevention and treatment of viral diseases.	Pacific Horizon Ventures LLC, Undisclosed Venture Firm
Nontigen Pharmaceuticals	Expansion	5,200,000	Operates as a drug discovery and development company.	Undisclosed Venture Firm
Esprit Pharma Holding Co. (FKA: Saturn Pharmaceuticals, Inc.)	Startup/ Seed	5,135,200	Operates as a specialty pharmaceutical company.	Apax Partners, Inc., Domain Associates, L.L.C., New Enterprise Associates
Assay Designs, Inc.	Expansion	5,000,000	Develops and manufactures reagent kits for life sciences research.	Ampersand Ventures
Cerimon Pharmaceuticals, Inc.	Early Stage	5,000,000	Provides pharmaceutical research and development services.	MPM Capital (FKA: MPM Asset Management LLC)
Centrix Corporation	Later Stage	5,000,000	Develops and commercializes proprietary clinical pharmacogenomics products.	Mitsui & Co. Venture Partners (MCVP), Research Triangle Ventures (RTV)
Surface Logix, Inc.	Later Stage	4,170,000	Develops microfabrication and surface engineering products.	ARCH Venture Partners, CW Group, Inc., HBM Partners AG (FKA: HBM BioVentures AG), Venrock Associates
ProLacta BioSciences, Inc.	Expansion	4,000,000	Develops nutritional and pharmaceutical processing of human breast milk.	Bryan & Edwards, DFJ Frontier, Draper Fisher Jurvetson (FKA: Draper Associates), Draper Richards L.P., Undisclosed Non Venture Firm
NanoString Technologies	Expansion	3,900,000	Develops a bar coding system for single molecules.	Draper Fisher Jurvetson (FKA: Draper Associates), OVP Venture Partners (FKA: Olympic Venture Partners), Undisclosed Venture Firm
VisEn Medical, Inc.	Early Stage	3,835,000	Develops molecular imaging technology platforms.	Flagship Ventures , Undisclosed Corporate Investor, Undisclosed Venture Firm

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Neotropix, Inc.	Early Stage	3,800,000	Develops virus-based therapies for the treatment of cancers.	Aurora Funds, Inc., Novartis Corp., Quaker BioVentures, Inc.
Innovative Biosensors, Inc.	Early Stage	3,500,100	Develops self-contained biosensor system technologies.	Harbert Venture Partners, Maryland DBED (AKA:Dept. of Business & Economic Development), New Markets Growth Fund
Asterand, Inc. (FKA: BioSampleX Pharmaceuticals)	Later Stage	3,500,000	Provides tissue samples to biopharmaceutical companies for research use.	ApJohn Ventures, LLC, Arboretum Ventures, Chrysalis Ventures, Fort Washington Capital Partners LLC
Collegium Pharmaceutical, Inc.	Later Stage	3,500,000	Develops proprietary, late stage pharmaceutical products.	Boston Millennia Partners
MaxCyte, Inc. (FKA: TheraMed)	Later Stage	3,428,000	Developing a technology for loading bioactive molecules into human cells.	Harbert Venture Partners, Intersouth Partners
Rib-X Pharma Inc.	Early Stage	3,300,000	Develops non-steroidal anti-inflammatory pharmaceutical agents.	Integra Ventures, Undisclosed Venture Firm
CellzDirect, Inc.	Later Stage	3,229,000	Provides cell products to the biopharmaceutical industry.	Grayhawk Venture Partners (FKA: Ironwood Capital), Solstice Capital, Technology Funding, Valley Ventures (FKA: Arizona Growth Partners, L.P.)
NAREA Pharmaceuticals, Inc.	Early Stage	3,000,000	Develops topical skin care solutions based on advanced biopolymer research.	Easton Hunt Capital Partners, L.P., Undisclosed Corporate Investor, Undisclosed Venture Firm
StemCyte, Inc.	Expansion	3,000,000	Operates a stem cell research technology company.	Sycamore Ventures, Undisclosed Venture Firm, WI Harper Group
Symphony Medical, Inc. (FKA: Biomm Therapeutics Corp.)	Early Stage	2,600,000	Develops cell therapy for developing cures for cardiovascular disease.	Domain Associates, L.L.C., Guidant Corporation, Johnson & Johnson Development Corporation, Morgenthaler Ventures
Nanoplex Technologies, Inc.	Expansion	2,550,000	Develops nanoparticle-based products.	Individuals, Undisclosed Corporate Investor
High Throughput Genomics, Inc. (AKA: HTG, Inc.)	Expansion	2,500,000	Develops products and services for genomic-based drug discovery.	Emerging Technology Partners, LLC, Individuals, Solstice Capital, Undisclosed Venture Firm, Valley Ventures (FKA: Arizona Growth Partners, L.P.), Village Ventures
HertaMed Pharmaceuticals, Inc.	Later Stage	1,999,000	Operates to acquire, license, & develop ethical and OTC pediatric products.	EssexWoodlands Health Ventures (FKA: Woodlands Venture)
Apta Therapeutics Corporation	Early Stage	1,800,000	Operates a biopharmaceutical firm focused on peptide therapeutics.	Fujisawa Research Institute of America (FRIA), Maryland DBED (AKA:Dept. of Business & Economic Development), Maryland Technology Development Corporation (TEDCO), Undisclosed Venture Firm
Elixir Pharmaceuticals, Inc.	Later Stage	1,750,000	Developing drugs for aging and age related diseases.	MPM Capital (FKA:MPM Asset Management LLC)
Crop Solution, Inc.	Expansion	1,625,000	Discovers and develops agrochemicals for crop protection.	Aurora Funds, Inc., Charlotte Angel Partners
Protedyne Corporation	Later Stage	1,035,000	Provides laboratory automation solutions for genomic-based drug discovery.	Boston Community Capital, DLJ Merchant Banking Partners, Fresh Tracks Capital, Long River Capital Partners, LLC, Meridian Venture Partners (MVP), Sprout Group, Undisclosed Investor, Worcester Capital Partners, LLC
NuKana Therapeutics, Inc.	Early Stage	1,000,000	Develops targeted medicines for the treatment of cancer.	SAM Ventures (AKA: SAM Partners), Venture Associates AG
Targa Pharmaceuticals	Expansion	1,000,000	Develops medicine to treat pain in irritable bowel syndrome.	Forward Ventures, Undisclosed Venture Firm
Cytelligent, Inc.	Startup/ Seed	900,000	Developing technologies that isolate rare cells for therapeutic purposes.	Enterprise Partners Venture Capital (AKA: EPVC), Undisclosed Venture Firm
Paratek Pharmaceuticals	Expansion	800,000	Develops new antibiotics to combat drug resistance.	Robin Hood Ventures, Undisclosed Venture Firm

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Cellumen, Inc.	Early Stage	550,000	Operates as a systems cell biology research company.	PA Early Stage (AKA: Pennsylvania Early Stage Partners)
ProNAi Therapeutics, Inc.	Early Stage	525,000	Develops Nucleic Acid inhibitor drugs.	ApJohn Ventures, LLC
Genomatix Corporation	Expansion	500,000	Provides tools for controlling gene expressions.	Third Security LLC
GeneOhm Sciences, Inc.	Expansion	200,000	Develops chip-based DNA diagnostic disease detection tools.	CB Health Ventures LLC
Thermal Gradient	Startup/ Seed	100,000	Develops biotechnology solutions for nucleic acid amplification.	Trillium Capital Partners
BioFactura, Inc.	Startup/ Seed	75,000	Offers services and support to companies foucused on biologic medicine.	Maryland Technology Development Corporation (TEDCO)
Insolin Technology, LLC	Startup/ Seed	75,000	Operates as a biotech company focused on animal feed.	Maryland Technology Development Corporation (TEDCO)
Apdex Pharmaceuticals, Inc.	Startup/ Seed	0	Develops anti-viral therapeutics focused on HIV treatments.	PA Early Stage (AKA: Pennsylvania Early Stage Partners)
Qualtica, Inc.	Expansion	0	Develops reformulations of commercially successful compounds.	Undisclosed Venture Firm

Medical Devices and Equipment

Total Industry Investment: $ 425,731,300

Number of Deals: 57

Percent of Total: 7.4%

Total Investments:

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Calypso Medical Technologies, Inc.	Later Stage	35,474,800	Develops medical devices focused on radiation therapy treatments.	Bellevue Asset Management AG, Earlybird Venture Capital, Frazier Healthcare and Technology Ventures(fka Frazier & Co), Integra Ventures, Kaiser Permanente Ventures, Merlin BioMed Group, Mitsui & Co. Venture Partners (MCVP), RiverVest Venture Partners , Ro
AcuFocus, Inc.	Later Stage	27,500,000	Develops ocular implants to treat presbyopia.	Accuitive Medical Ventures LLC (AKA: AMV Partners), Carlyle Group, The, Pequot Capital Management, Inc., SV Life Sciences Advisers (Schroder Ventures Life Sciences), Three Arch Partners, Versant Ventures
Cytrx Pharmaceuticals (FKA:Cytrx)	Expansion	26,300,400	Develops small molecule anti-cancer agents for patients.	BioVentures Investors, Coastview Capital, IngleWood Ventures, Mitsui & Co. Venture Partners (MCVP), Morningside Group, Novartis Corp., RCT BioVentures NE LLC, Sanderling Ventures, Undisclosed Venture Firm, William Harris Associates
Cierra, Inc.	Expansion	21,300,000	Operates an interventional cardiology company.	Delphi Ventures, Frazier Healthcare and Technology Ventures(fka Frazier & Co), Morgenthaler Ventures, Split Rock Partners, LLC, St. Paul Venture Capital, Inc.
SurgRx, Inc.	Expansion	21,000,000	Develops Laparoscopic Vessel Fusion tools used for surgical hemostasis.	Alta Partners, California Technology Ventures LLC, Individuals, New Enterprise Associates, Prospect Venture Partners (FKA: Prospect Management LLC), Trellis Health Ventures, LP
Interventional Rhythm Management, Inc. (AKA: IRM)	Expansion	20,000,000	Develops transvenous defibrillators.	Delphi Ventures, Frazier Healthcare and Technology Ventures(fka Frazier & Co), Guidant Corporation
Rheoptics, Inc.	Expansion	19,700,000	Develops a non-invasive blood diagnostic system.	Delphi Ventures, Frazier Healthcare and Technology Ventures(fka Frazier & Co), InterWest Partners, Versant Ventures
Elpincare	Expansion	15,000,000	Develops treatments and therapies for osteoporosis complications.	Allen & Company, New Science Ventures, LLC, Undisclosed Corporate Investor
Virtual Radiologic Corporation (VRC)	Later Stage	14,720,000	Provides hospitals and imaging facilities total radiology solutions.	Generation Capital Partners
[illegible]	Expansion	14,000,000	Operates an early stage biomedical technology company.	Angels Forum & the Halo Fund, Arboretum Ventures, Domain Partners, Fontinalis Partners, SBV Venture Partners (AKA: Sigelt, Burnette & Valleo), UV Partners (AKA: Utah Ventures), Versant Ventures
[illegible] (FKA: Accelerated Orthopedics, Inc.)	Expansion	11,600,000	Develops light therapy systems for treatment of musculoskeletal injuries.	De Novo Ventures, Delphi Ventures, Hamilton BioVentures (FKA: Hamilton Apex Technology Ventures), Solstice Capital, Vertical Group, The
[illegible]	Later Stage	10,594,500	Develops an oral drug delivery for poorly absorbed drugs.	A.M. Pappas & Associates LLC, Advent International, Brook Private Equity Management LLC, CB Health Ventures LLC, MVM, Ltd, Mitsubishi Corporation, Oakwood Medical Investors, POD Holding, Zero Stage Capital Co. Inc.
[illegible] Biologics, Inc.	Early Stage	10,200,000	Manufactures bio-implants for use in soft tissue reinforcement.	Frazier Healthcare and Technology Ventures(fka Frazier & Co), Three Arch Partners, Undisclosed Corporate Investor, Undisclosed Venture Firm
[illegible], Inc.	Later Stage	10,195,000	Develops an x-ray catheter for the prevention and treatment of restenosis.	Cutlass Capital, Frantz Medical Ventures, Frazier Healthcare and Technology Ventures(fka Frazier & Co), Guidant Corporation, MPM Capital (FKA: MPM Asset Management LLC), Maverick Capital Ltd., Mosaix Ventures, RiverVest Venture Partners, Sutter Hill Ventures
[illegible]	Later Stage	10,000,000	Develops medical devices for temperature management methods.	Cross Atlantic Partners, Inc., Kimberly-Clark Ventures, LLC, New England Partners, Partisan Management Group

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Torax Medical, Inc.	Early Stage	10,000,000	Develops technology for the treatment of digestive disorders.	Mayo Medical Ventures, Sanderling Ventures, Thomas, McNerney & Partners LLC
NovoStent Corporation	Expansion	9,650,000	Develops and manufactures implantable medical devices such as stents.	Band of Angels, Montreux Equity Partners, Peninsula Equity Partners, Sanderling Ventures, Tenex Greenhouse Ventures
Kereos, Inc.	Early Stage	9,054,200	Develops and researches methods for delivering imaging agents.	Alafi Capital Co., Charter Life Sciences, Genentech Corporation, Lux Capital, Prolog Ventures LLC, RiverVest Venture Partners, Triathlon Medical Ventures LLC
Satiety, Inc.	Later Stage	8,600,000	Develops minimally evasive treatments for moderate and morbid obesity.	Morgenthaler Ventures, Three Arch Partners
Cardiva Medical, Inc.	Expansion	8,300,000	Designs medical devices to provide vascular closure.	Harbinger Venture Management, Sycamore Ventures, Undisclosed Venture Firm, WI Harper Group
Aore Medical, Inc.	Later Stage	6,750,000	Provides Internet-based medical monitoring systems.	Flagship Ventures, S.R. One, Limited, Undisclosed Venture Firm
Mitralign, Inc.	Expansion	6,700,000	Develops a catheter-based mitral valve repair system.	ABN AMRO Capital (FKA: ABN AMRO Corporate Investments), Giza Venture Capital (FKA: Giza Investment Management), Oxford Bioscience Partners
LDK Spine Technology, Inc.	Early Stage	6,338,000	Develops medical devices.	Aberdare Ventures, Morgenthaler Ventures
Medlogics Device Corporation	Expansion	6,225,000	Develops technology that enables drugs to be coated onto the stent.	Essex Woodlands Health Ventures (FKA: Woodlands Venture), Undisclosed Venture Firm
3F Therapeutics, Inc.	Expansion	6,000,000	Develops cardio-vascular devices.	3i Bioscience Investment Trust, Boston Scientific Corporation (FKA EP Technologies, Inc.), Domain Associates, L.L.C., Undisclosed Investor
Novocell, Inc.	Expansion	6,000,000	Develops technologies for cell transplant therapies.	Pacific Horizon Ventures LLC, Undisclosed Venture Firm
Atritech, Inc.	Early Stage	5,500,000	Provides a minimally invasive treatment for treating atrial fibrillation.	Intersouth Partners, Undisclosed Venture Firm
Arux Medical, Inc. (FKA: Medinvent)	Early Stage	5,000,000	Develops innovative medical technology and solutions.	Prospect Venture Partners (FKA: Prospect Management LLC), Three Arch Partners, Venrock Associates
Homestead Clinical Corporation	Startup/ Seed	5,000,000	Develops diagnostic tools for early intervention in a variety of diseases.	ARCH Venture Partners, Alexandria Real Estate Equities, LLC, Amgen, Inc., MPM Capital (FKA: MPM Asset Management LLC), OVP Venture Partners (FKA: Olympic Venture Partners), Versant Ventures
Planmeca Oy	Expansion	5,000,000	Provides digital imaging products for the dental industry.	Richland Ventures
Exactech, Inc.	Early Stage	4,995,000	Develops axial knee realignment systems for post surgery recovery.	Skyline Ventures, Sutter Hill Ventures
Cytyc Corp.	Early Stage	4,500,000	Develops products designed for minimally invasive treatment of cellulite.	Carlyle Group, The, SV Life Sciences Advisers (Schroder Ventures Life Sciences), Undisclosed Venture Firm
Luminex Corporation (FKA: Cytognomix Inc.)	Early Stage	4,000,000	Develops medical digital imaging systems.	Morgan Keegan Merchant Banking
Ocular Medical Corporation	Startup/ Seed	3,750,000	Develops method and device used for medical eye surgery.	Kleiner Perkins Caufield & Byers
Jomed, Inc.	Early Stage	3,500,000	Operates as a medical device development company.	Advanced Technology Ventures (AKA: ATV), Frazier Healthcare and Technology Ventures (fka Frazier & Co.)
Hansen Medical, Inc.	Early Stage	3,175,200	Develops a electromechanical robot that guides catheters during surgery.	De Novo Ventures, Prospect Venture Partners (FKA: Prospect Management LLC), Skyline Ventures, Thomas Weisel Partners, LLC
Flow Remedies, Inc.	Early Stage	3,000,000	Provides medical supplies.	MedVenture Associates (AKA: MVA)

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Sensys Medical, Inc. (FKA: Instrumentation Metrics, Inc.)	Later Stage	3,000,000	Develops non-invasive clinical and industrial diagnostic instrumentation.	Adams Street Partners LLC (FKA: Brinson Private Equity), Alliance Technology Ventures, Undisclosed Non Venture Firm, Undisclosed Venture Firm
EnteroMedics, Inc.	Expansion	2,999,900	Develops medical device therapies for vagal-mediated disorders.	Aberdare Ventures, Bay City Capital LLC, Charter Life Sciences, MPM Capital (FKA: MPM Asset Management LLC)
InfraReDx, Inc.	Expansion	2,803,000	Develops technology for the early detection of heart ailments.	Sanderling Ventures
Zapaq, Inc.	Expansion	2,350,000	Discovers and develops therapeutics that target aspartic proteases.	Sanderling Ventures, Yamanouchi Venture Capital LLC
PneumRx, Inc.	Early Stage	2,199,900	Performs research and development in the medical devices industry.	Alta Partners, KBL Healthcare Ventures, Spray Venture Partners
CHF Solutions, Inc.	Expansion	2,100,000	Develops mechanical pump/filter systems to remove excess bodily fluid.	Ascension Health Ventures LLC
Talima Therapeutics, Inc.	Startup/ Seed	2,000,000	Develops localized drug delivery implant systems.	De Novo Ventures, Palo Alto Investors
Medtronal Systems, Inc. (FKA: RadioVascular Systems, Inc.)	Later Stage	1,500,000	Develops catheters that improve the success rate of angioplasty.	Boston Scientific Corporation (FKA EP Technologies, Inc.), InterWest Partners
GelonX, Inc. (FKA: Microplate Automation, Inc.)	Early Stage	1,450,000	Develops products based on patented plasma cleaning technology.	Anthem Capital Management, PA Early Stage (AKA: Pennsylvania Early Stage Partners)
TomoTherapy, Inc.	Later Stage	1,295,000	Develops precise radiation technology.	Ascension Health Ventures LLC
VivaRx (AKA: ID Wave Systems)	Early Stage	1,200,000	Develops technology for dermatological disorders of the nail and skin.	Polaris Venture Partners, Three Arch Partners
Nogen, Inc.	Expansion	1,000,000	Develops products for respiratory disease sufferers.	Accuthre Medical Ventures LLC (AKA: AMV Partners), Undisclosed Venture Firm
Senarus Medical, Inc.	Expansion	936,000	Develops surgical devices and technologies for the treatment of tumors.	Alta Partners, Capital Valley Ventures LLC, Channel Medical Partners, Forward Ventures, Kaufmann Fund, Inc., The U.S. Venture Partners
Emergent Respiratory Products, Inc.	Early Stage	750,000	Develops, manufactures, and markets proprietary medical devices.	Grayhawk Venture Partners (FKA: Ironwood Capital), POSCO BioVentures, Shepherd Ventures
Seattle Medical Technologies	Early Stage	600,000	Develops inventions in the medical/health industry.	Three Arch Partners
Sword Diagnostics, Inc.	Early Stage	500,000	Develops diagnostic systems for the identification of organisms.	New Jersey Technology Council (AKA: NJTC), Undisclosed Investor
Xsten Corporation	Startup/ Seed	325,000	Develops and markets medical devices.	Aweida Capital Management LLP, DFJ Mercury Venture Partners
[illegible]	Expansion	191,000	Develops clampless occlusion devices.	Borealis Ventures, Fresh Tracks Capital, Tenex Greenhouse Venture, Undisclosed Venture Firm, Village Ventures
[illegible]	Early Stage	[illegible]	Develops therapeutics for the treatment of autoimmune diseases.	Edmond de Rothschild Venture Capital Management, Individuals, Meltonian Investissement et Gestion
Vivant Medical Inc.	Later Stage	[illegible]	Develops surgical instruments to treat breast cancer.	Three Arch Partners

Healthcare Services, Information and Software

Total Industry Investment: $ 219,450,500

Number of Deals: 33

Percent of Total: 3.8%

Total Investments:

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
Centerre Healthcare Corporation	Expansion	30,000,200	Provides inpatient rehabilitation services within acute care hospitals.	Pacific Venture Group, River Cities Capital Funds, RiverVest Venture Partners, SightLine Partners, Three Arch Partners
Vantage Oncology, Inc.	Later Stage	22,000,000	Develops and operates radiation oncology treatment centers.	Corning Capital Partners, New Enterprise Associates, Salix Ventures, Versant Ventures
OraMetrix, Inc. (AKA: Orthotrol)	Later Stage	18,000,000	Provides technology solutions for orthodontic care.	Brentwood Venture Capital, Rho Ventures (AKA: RHO Management), STARTech, Versant Ventures
Nelson Physician Partners, Inc. (FKA: Prime Health Services)	Later Stage	15,000,000	Owns and operates a pediatric healthcare company.	FBR Venture Capital Managers, Inc., LINC Capital Partners, Inc., Undisclosed Venture Firm
AngelFix, Inc.	Expansion	15,000,000	Provides an Internet information exchange between physicians.	Acacia Venture Partners, Domain Associates, L.L.C., Montagu Newhall Associates, New Enterprise Associates, Quaker BioVentures, Inc., Wasatch Venture Fund
Posit Science Corp. (FKA: Neuroscience Solutions Corp.)	Expansion	14,520,000	Develops software-based technology for age-related cognitive decline.	Aberdare Ventures, Draper Fisher Jurvetson (FKA: Draper Associates), State Street Bank, VSP Capital (FKA: Venture Strategy Partners)
AccentCare, Inc.	Expansion	13,900,000	Provides at-home assisted living and care coordination services for seniors	Highland Capital Partners, Salix Ventures, SightLine Partners, Three Arch Partners
GTESS Corporation	Later Stage	12,000,000	Provides business process outsourcing to managed care organizations.	Alt Ventures (AKA: Adams Harkness & Hill Technology Ventures), General Catalyst Partners (FKA: General Catalyst Group LLC), HLM Venture Partners, Kodiak Venture Partners
MedVantx, Inc. (FKA: QualiRx)	Expansion	10,500,000	Provides solutions for generic drugs dispensing at the point-of-care.	ARCH Venture Partners, Advent International, Bessemer (FKA: GMA Capital LLC) (AKA: ProVen Private Equity), Brooke Private Equity Management LLC, Oakwood Medical Investors, Polaris Venture Partners, Rock Maple Ventures, L.P., Undisclosed Non Venture Firm
TheraDoc, Inc.	Expansion	7,400,000	Designs expert systems for clinical decision support.	Undisclosed Venture Firm
[illegible] Integrated	Expansion	7,368,000	Provides healthcare management services.	River Cities Capital Funds, Undisclosed Investor
[illegible] Health Corporation (FKA: [illegible] Inc.)	Expansion	7,000,000	Provides secure online healthcare communication services.	Corning Capital Partners, Lilly Ventures (FKA: Cell Genesys Ventures), SI Ventures, U.S. Venture Partners, Ventech Associates
[illegible] Inc.	Startup/ Seed	6,300,000	Provides data management products for the medical industry.	Ignition Partners (FKA: Ignition Corporation)
[illegible] Corporation	Early Stage	6,000,000	Provides solutions to managed care pharmacy.	Claritas Capital LLC (FKA: Vertical Investments), HLM Venture Partners, Undisclosed Venture Firm
[illegible] Med, Inc.	Later Stage	5,000,000	Provides reprocessing services to hospitals and healthcare facilities.	Ascension Health Ventures LLC, First Analysis Corporation, Prism Capital, Sterling Partners
[illegible] Systems, Inc. (FKA: [illegible] Corporation)	Later Stage	3,999,900	Operates as a provider of Internet-based solutions for hospitals.	CE Health Ventures LLC, UV Partners (AKA: Utah Ventures), Versant Ventures
Blue Chip Surgical Center Partners, LLC	Startup/ Seed	3,500,000	Operates as a management company for ambulatory surgery centers.	Blue Chip Venture Company, Claritas Capital LLC (FKA: Vertical Investments)

Investee Company	Financing	Amount Raised ($)	Nature of Business	Investors
RxStrategies Inc.	Expansion	3,469,200	Owns a pharmaceutical service company that serves community health centers.	Lovett Miller & Co. Incorporated, Undisclosed Corporate Investor, Undisclosed Investor
RMD Networks, Inc.	Early Stage	3,000,000	Provides system communications solutions to the healthcare community.	Sevin Rosen Funds (AKA: Sevin Rosen Management Co.)
CompassCare, Inc.	Expansion	2,750,000	Develops applications software and provides other consulting services.	Draper Fisher Jurvetson (FKA: Draper Associates), Hopewell Ventures, Portage Venture Partners (AKA: Graystone Venture Partners)
Carefx Corporation	Early Stage	2,000,200	Provides CCOW-enabled context management software to healthcare providers.	CB Health Ventures LLC, Grayhawk Venture Partners (FKA: Ironwood Capital), Highway 12 Ventures, Solstice Capital, Undisclosed Venture Firm, Village Ventures
CONFIDENTIAL	Expansion	2,000,000	**CONFIDENTIAL**	Highland Capital Partners, Undisclosed Venture Firm
CHN-Online, Inc.	Later Stage	2,000,000	Provides electronic claims transaction solutions.	Ballast Point Venture Partners
VetCentric, Inc.	Expansion	2,000,000	Operates as a veterinary pharmacy in the United States.	Asset Management Company Venture Capital, Sherbrooke Capital Partners, Three Arch Partners
Broadlane, Inc.	Expansion	1,500,000	Provides integrated expense management solutions to healthcare industry.	Falcon Investment Advisors LLC, Undisclosed Investor, Undisclosed Non Venture Firm
Ezurg, Inc. (AKA: Group Source Solutions, Inc.)	Expansion	1,043,000	Provides medical, surgical, pharmaceutical supplies, and information.	BA Venture Partners (AKA: BankAmerica Ventures), UPS Strategic Enterprise Fund
Connecture, Inc. (FKA: Simply Health, Inc.)	Expansion	1,000,000	Develops sales automation solutions for health insurance providers.	Chrysalis Ventures, LiveOak Equity Partners, SSM Partners (fka: SSM Ventures), Total Technology Ventures LLC (AKA: TTV)
[illegible] (FKA: Medical Business Applications (MBA), Inc.)	Later Stage	750,000	Provides financial management systems for clinical labs.	Boulder Ventures, Ltd., Enterprise Partners Venture Capital (AKA: EPVC), Undisclosed Venture Firm
[illegible] Technologies Corporation	Expansion	700,000	Produces voice recognition documentation software for healthcare providers.	ECentury Capital Partners L.P., Mid-Atlantic Venture Funds (FKA: NEPA Management Corp.), Undisclosed Venture Firm
Russell County Community Hospital, LLC	Early Stage	500,000	Operates a community hospital in Tennessee.	Red River Ventures
Landmark Healthcare, Inc.	Expansion	200,000	Offers physical medicine management benefit services.	Capitol Health Partners, L.P.
Healthwise for Report Systems	Startup/ Seed	50,000	Develops a clinical trial recruiting and management software application.	Maryland DBED (AKA: Dept. of Business & Economic Development)
Ascend Health Corporation	Early Stage	[illegible]	Operates as a company focused on providing psychiatric services.	Three Arch Partners

About the MoneyTree™ Survey

PricewaterhouseCoopers collaborates with Thomson Financial Venture Economics and the National Venture Capital Association to produce the MoneyTree™ Survey. The intent of the survey, which is in its 10th year, is to measure equity investments in venture-backed companies in the United States and track companies that have received at least one round of financing involving a professional venture capital (VC) firm or equivalent

Results include tranches, not term sheets, foreign VCs, qualified private placement and excludes debt, bridge loans, recaps, roll-ups, IPOs, PIPEs and leasing.

About PricewaterhouseCoopers Health Research Institute

PricewaterhouseCoopers Health Research Institute provides new intelligence, perspective and analysis on trends affecting all health-related industries, including healthcare providers, pharmaceuticals, health and life sciences and payers. The Institute helps executive decision-makers and stakeholders navigate change through a process of fact-based research and collaborative exchange that draws on a network of more than 4,000 professionals with day-to-day experience in the health industries. The Institute is part of PricewaterhouseCoopers larger initiative for the health-related industries that brings together expertise and allows collaboration across all sectors in the health continuum.

Additional Information

Health Research Institute

Jim Henry
Partner, Health Industries Leader
jim.henry@us.pwc.com
(678) 419-2328

Kelly Barnes
Partner, Health Research Institute Leader
kelly.a.barnes@us.pwc.com
(214) 754-5172

Sandy Lutz
Director
sandy.lutz@us.pwc.com
(214) 754-5434

Hindy Shaman
Director
hindy.shaman@us.pwc.com
(703) 453-6161

Benjamin Isgur
Assistant Director
benjamin.isgur@us.pwc.com
(214) 754-5091

Sheela Ramaswamy
Research Analyst
sheela.ramaswamy@us.pwc.com
(214) 754-5459

Health Research Institute Advisory Team

Steven Elek
Partner, Transaction Services
steven.elek@us.pwc.com
(267) 330-2240

Tracy Lefteroff
Partner, Life Sciences
tracy.t.lefteroff@us.pwc.com
(408) 817-4176

Kirk Walden
MoneyTree Survey
kirk.walden@us.pwc.com
(512) 867-8818

Cassie Arnold
Marketing Director, Life Sciences
kathleen.m.arnold@us.pwc.com
(408) 817-7926

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MARKET INTELLIGENCE ON HEALTH CARE VENTURE CAPITAL, M&A AND IPOS

IN THIS ISSUE

Private Equity Market

Publicly traded health care companies increasingly turned to institutional investors for capital, announcing 21% of this year's health care private equity deals in the past 30 days. **See page 1**

Venture Capital Market

The third quarter is off to a slow start, but during the first six months of 2005, more health care venture capital funding was committed and more deals got done than in the year-ago period. **See page 1**

Public Equity Market

Several initial public offerings and secondaries were priced, and some foreign-based health care companies are looking to raise capital in the United States. **See page 3**

Merger & Acquisition Market

One $7 billion deal and some unusual deals spice up the steady flow of health care mergers and acquisitions announced in the past 30 days, plus, a brief look back at the first half of 2005. **See page 6**

Departments

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PRIVATE EQUITY INVESTORS PROVIDING LIFE SUPPORT TO DEVELOPMENT-STAGE HEALTH CARE COMPANIES

Apparently the public is becoming less inclined to buy stock in technology platforms, product candidates and pipeline compounds, but institutional investors are keeping the development dream alive at many health care companies. Publicly traded health care companies raised more private equity during the past 30 days than during the two prior 30-day periods put together. From June 16 to July 15, 2005, a total of $466 million was committed to fund 29 private placements in the health care sectors, representing 21% of all private equity funding raised by public health care companies so far this year. In the past four weeks, total spending on health care private placements increased by 77%, compared with the preceding four weeks, and by 29%, compared with the year-ago period.

Fewer than half of the public companies that announced private equity deals in the past four weeks are currently marketing a product or service. In the same four weeks, 16 development-stage health care companies secured equity financing to fund research, clinical testing, FDA applications and in some cases, commercialization. The three largest deals of the month include a REIT, a biotech based in Europe and a pharmaceutical company. **Impax Laboratories** (NASDAQ: IPXLE) announced the largest deal of the month, for $75 million, but under unusual circumstances.

...continued on page 2

VENTURE CAPITALISTS HIT THE BRAKES, START SLOWLY IN THIRD QUARTER, AFTER SIX MONTHS OF STEADY FUNDING

In the past 30 days, health care companies raised just $330 million in venture capital, less than we have reported for any other 30-day period this year. Comparatively, during the period January 16 to February 15, 2005, now the second-slowest stretch of this year in terms of total venture funding, more than $450 million was raised by 35 companies. And the number of deals recorded has not been this low since our January issue, when nearly twice as much total funding was raised by nearly the same number of companies.

From June 16 through July 15, just 25 health care venture financings were confirmed, and only three of those deals were for more than $20 million. Only one large deal was announced, by **Triax Holdings, LLC**, a newly formed entity that will use the proceeds of a $77 million venture round to finance its acquisition of **Spear Pharmaceuticals, Inc.** and **Spear Dermatology Products, Inc.** In the other two venture rounds greater than $20 million, **CoreValve** raised $24 million and **Therion Biologics** raised $30 million.

...continued on page 7

continued from page 1...

Due to a technical default, specifically, IPXLE's failure to file form 10-K on time with the SEC, a holder of debentures previously issued by Impax declared the $95 million principal, plus accrued interest, due and payable immediately. The proceeds of this placement will be used to repay that debt.

Impax currently provides drugs and drug delivery technologies to the health care industry, and is also developing brand-name drugs. The company was formed in 1999 as a result of the merger between **Global Pharmaceutical Corporation** and **IMPAX Pharmaceuticals**. The technology-based specialty pharma is focused on creating novel reformulations of existing products, including controlled-release generic versions of brand-name drugs and its own brand-name drugs that are modified, differentiated or controlled-release versions of substances that are currently on the market.

Zeltia SA (PK: ZLIXF) secured $54 million in private equity financing, the second-largest health care private equity deal announced in the past 30 days. Zeltia is a biotechnology company, headquartered in Madrid, Spain, with five subsidiaries including **PharmaMar**, which was founded in 1986. The proceeds of the financing will be used to continue the research, development and commercialization efforts surrounding PharmaMar's pipeline of cancer products. **HSBC** acted as the sole book-running manager for the transaction.

PharmaMar, a biopharma that is focused on deriving therapeutic anti-cancer compounds from marine organisms, does not yet have products on the market. However, PharmaMar does have a compound that it co-developed with **Johnson & Johnson** (NYSE: JNJ), called Yondelis, in Phase II/III trials for solid tumors. Other compounds in PharmaMar's pipeline target other types of tumors, cancers and severe psoriasis.

Windrose Medical Properties Trust (NYSE: WRS), with $52.5 million, closed the third-largest health care private placement in the past 30 days. Windrose Medical Properties, a REIT based in Indianapolis, Indiana, has a portfolio of properties located primarily in the Southeastern, Southwestern and Western United States. Windrose is focused on acquiring medical office buildings, specialty hospitals, outpatient and diagnostic facilities, ambulatory surgery centers and other health care facilities.

Not long after securing $9 million in private equity, **Adherex Technologies Inc.** (AMEX: ADH; TSX: AHX), a North Carolina-based biopharma, announced it has entered into a licensing and development agreement with **GlaxoSmithKline** (NYSE: GSK) valued at $15 million. Plus, GSK invested an additional $3 million in ADH's existing private placement. ADH is in-licensing an oncology product from GSK and GSK has the option to license ADH's lead biotechnology compound.

In an update, **Solexa, Inc.** (NASDAQ: SLXA) reported the completion of the $32.5 million financing it announced three months ago, securing the final $24 million upon stockholder approval. **SG Cowen** served as the exclusive placement agent for the transaction. Solexa, a biotech headquartered in the United Kingdom, merged with **Lynx Therapeutics** earlier this year. Currently SLXA is developing DNA sequencing systems to comprehensively and economically analyze whole genomes.

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Public Equity Market

Date	Company	Symbol	Sector	Number of Shares	Price Per Share	Comments
6/16	Gentium SpA	GNT	Biopharm	2,760,000	$9.00	IPO of ADSs, bottom of range, led by Maxim Grp.
6/16	ev3	EVVV	MedDev	13,529,750	$14.00	IPO, below range, led by P. Jaffray and Banc of Am.
6/16	Micrus Endovascular	MEND	MedDev	3,737,5000	$11.00	IPO, priced mid-range, led by A.G. Edwards.
6/20	Implant Sciences	IMX	MedDev	1,394,206	TBA	Secondary filed, all by selling shareholders.
6/20	PhotoMedex	PHMD	MedDev	248,395	TBA	Secondary filed, all by selling shareholders.
6/22	Spectrum Pharm.	SPPI	Pharma	1,454,751	TBA	Secondary filed, all by selling shareholders.
6/22	CV Therapeutics	CVTX	Pharma	6,900,000	TBA	Secondary filed, to be led by Lehman Brothers.
6/22	BioMed Realty	BMR	REIT	15,122,500	$22.50	Secondary, increased size, led by Raym. James.
6/22	Allion Healthcare	ALLI	Pharma	4,600,000	$13.00	IPO, priced at top of range, led by Thos. Weisel.
6/23	Avalon Pharmac.	AVRX	Pharma	5,175,000	$10-$12	Secondary filed, to be led by Legg Mason.
6/24	Critical Therapeut.	CRTX	Biopharm	13,426,103	TBA	Secondary filed, all by selling shareholders.
6/27	Symmetry Medical	SMA	MedDev	10,00,000	TBA	Secondary filed, all by selling shareholders.
6/27	Delcath Systems	DCTH	MedDev	3,397,909	TBA	Secondary filed, all by selling shareholders.
6/28	Advanced Life Scien.	ADLS	Biopharm	5,175,000	$11-$13	IPO range filed, to be led by C.E. Unter., Towbin.
6/28	HemoSense	HEM	MedDev	4,025,000	$5.50	IPO, below range, led by Lazard and WR Hambr.
6/29	Ventas, Inc.	VTR	REIT	3,247,000	TBA	Secondary filed, to be led by Merrill Lynch.
6/29	Triad Hospitals	TRI	Hospitals	4,289,443	$53.62	Secondary, led by Merrill Lynch and others.
6/30	WellCare Plans	WCG	ManCare	7,475,000	$35.50	Secondary, all by selling shareholders.
7/8	Medical Prptys. Trust	MPW	REIT	12,066,823	$10.50	IPO, some selling shareholders, led by FBR & Co.
7/14	BioMarin Pharmaceu.	BMRN	Biopharm	8,500,000	$7.05	Secondary, led by Merrill Lynch.
7/14	CryoCor, Inc.	CRYO	MedTech	4,265,453	$11.00	IPO, bottom of range, led by WR Hambrecht.
7/14	QLT Inc.	QLTI	Biopharm	1,000,000	TBA	Secondary filed, all by selling shareholders.
7/15	Genomic Health	GHDX	Biotech	TBA	TBA	IPO filed, to be led by JPMorgan and Lehman.
7/15	Electro-Optical Sci.	MELA	MedDev	3,450,000	$10-$12	IPO filed, to be led by Ladenburg Thalmann.
7/15	Ithaka Acquisition	TBA	HealthCare	8,500,000	$6.00	IPO of units filed, to be led by EarlyBird Capital.
7/15	China Medical Tech.	CMED	MedDev	50,000,000	TBA	IPO filed, to be sold in ADSs, led by UBS.
7/15	Keryx Pharmaceutic.	KERX	Biopharm	5,780,000	$14.05	Secondary, led by JPMorgan.
7/15	Rigel Pharmaceutic.	RIGL	Pharma	4,197,500	$20.75	Secondary, led by CSFB and Lehman Bros.

Public Equity Market

We all know what happens when a window gets opened in the summertime, even if only a crack... things get hot, just like the public equity market has been for health care companies during the past four weeks. From June 16 to July 15, a total of seven initial public offerings were priced in the health care sectors and a total of six secondaries were priced. Only two IPOs were priced below range.

Once again, secondary offerings accounted for much of the public equity activity in the health care sectors during the past four weeks. In addition to those that were priced, nine secondaries were filed with the SEC, most including stock being registered for selling shareholders.

WR Hambrecht participated in the underwriting for two of the initial public offerings, including that of **CryoCor, Inc.** (NASDAQ: CRYO) and of **HemoSense** (NYSE: HEM), which was led by **Lazard Freres**. Two other offerings that got priced were led by **Merrill Lynch**, the secondary offerings of **BioMarin Pharmaceuticals** (NASDAQ: BMRN) and **Triad Hospitals** (NYSE: TRI). Merrill is also slated to underwrite a secondary offering filed by **Ventas, Inc.** (NYSE: VTR). Speaking of REITs, **BioMed Realty Trust** (NYSE: BMR) increased the size of its secondary before pricing the offering at $22.50 per share, and **Medical Properties Trust** (NYSE: MPW) priced its initial public offering.

As of this publication, MPW's shares were trading above the IPO price of $10.50 per share. The offering of 12,066,823 shares, including the over-allotment option and some selling shareholders, was led by **Friedman, Billings, Ramsey & Co., Inc.** serving as the sole book-running manager, with **J.P. Morgan Securities Inc.** as the co-lead manager. **Wachovia Capital Markets Trust** and **Stifel, Nicolaus & Company** served as co-managers.

Headquartered in Birmingham, Alabama, Medical Properties Trust is focused on acquiring and developing net-leased health care facilities. The REIT is particularly interested in hospitals for rehabilitation, long-term acute care, skilled nursing and other specialty care and surgical needs facilities, such as women's and children's hospitals and orthopedic centers.

Of the other six companies that priced IPOs during the past four weeks, **Allion Healthcare** (NASDAQ: ALLI) posted the most impressive gains, and three others were also trading above their IPO price as we were going to print: **ev3** (NASDAQ: EVVV), **Micrus Endovascular** (NASDAQ: MEND) and HemoSense. Two others were trading below their IPO prices when we were going to print.

The IPO of 4,265,453 shares of CryoCor, Inc., underwritten by WR Hambrecht & Co., **First Albany Capital** and **Roth Capital Partners**, was priced at $11.00 per share, but CRYO's stock slipped slightly into the $9 to $10 range. The offering was completed by way of an IPO auction process; the minimum bid in the auction was 100 shares.

With underwriting services provided by **Maxim Group LLC** and **I-Bankers Securities Incorporated**, **Gentium SpA** (AMEX: GNT), an Italy-based biopharma, priced the initial public offering of its American Depository Shares at $9.00 per ADS. GNT's stock was trading in the range of $8 to $9 per ADS in the days following the offering. Gentium is researching, discovering and developing drugs to treat a variety of vascular diseases and conditions related to cancer and cancer treatments.

Incidentally, Gentium is not the only European health care company tapping the United States markets for capital. **China Medical Technologies, Inc.**, a Beijing-based medical device company applying its ultrasound technologies to the treatment of tumors, filed for an IPO of ADSs just recently, with **UBS Investment Bank** serving as the underwriter. Other health care companies that have recently filed with the SEC to establish ADR or ADS programs include **Trinity Biotech plc** (NASDAQ: TRIB) of Ireland, and **ChemGenex Pharmaceuticals Limited** (NASDAQ: CSXP) and **Metabolic Pharmaceuticals Ltd.** (OTCBB: MBPLY), both based in Australia.

Allion Healthcare, a Melville, New York-based company that does business under the trade name **MOMS Pharmacy**, priced its initial public offering of 4,600,000 shares at $13.00 per share. For several days following the IPO, ALLI's closing stock price was in the neighborhood of $16 to more than $17 per share. The offering was led by **Thomas Weisel Partners LLC**, with additional underwriting provided by **William Blair & Company** and First Albany Capital.

MOMS Pharmacy is focused on serving the needs of patients with HIV/AIDS through specialty pharmacy and disease management services. MOMS sells HIV/AIDS medications, ancillary drugs and nutritional supplies to a patient population that primarily relies on Medicaid and other assistance programs to pay for their prescriptions.

Allion made two acquisitions during the first half of this year, **North American Home Health Supply, Inc.** and **Specialty Pharmacies, Inc.** The company has incurred losses for the past several years, but actually turned a meager profit for the quarter ended March 31, 2005. The initial public offering resulted in net proceeds of approximately $53.6 million to Allion.

WebMD Corporation (NASDAQ: HLTH), with underwriters **Morgan Stanley**, **Citigroup** and **Goldman Sachs & Co.**, disclosed further details associated with the proposed initial public offering of its subsidiary, **WebMD Health Holdings**. No size or price range has yet been suggested, but it was revealed that the parent company will have a new name that does not include "WebMD" and the spin-off company will have a new name that includes "WebMD" by the time the offering is complete.

During the past four years, WebMD Corporation has acquired nine e-health and health care IT companies including seven that were privately held, plus the physicians' professional internet portal subsidiary of **Andrx Corp.** (NASDAQ: ADRX) and the portal assets, including the professional and consumer Web sites, of **MedicaLogic** (NASDAQ: MDLI). WebMD Health Holdings will continue to provide health information services to consumers, physicians and health care professionals through its public and private online portals, while the remaining consolidated business services offered by WebMD Corporation will be branded separately.

EarlyBirdCapital is providing underwriting assistance to yet another special purpose acquisition company (SPAC) that has been formed for the purpose of entering the health care arena. **Ithaka Acquisition** filed for an IPO of 8,500,000 units priced at $6.00 per unit, but has yet to target a particular health care sector. EarlyBirdCapital, with offices in New York City, specializes in SPACs.

MERGER & ACQUISITION ANNOUNCEMENTS

DATE	BUYER	SELLER	SECTOR	PRICE	TERMS/COMMENTS
6/21	Clinical Data, Inc.	Genaissance Pharmaceuticals	Biotech	$56,000,000	All stock deal. Price to rev. multiple is 2.43.
6/21	SR Pharma Plc	Atugen AG	Biotech	$11,337,000	Reverse take-over.
6/24	Celtic Pharmac. Mgmt.	Xenova Group plc	Biotech	$47,800,000	Three buyout structures offered. Pr. to rev. is 5.49.
6/30	QIAGEN, NV	Nextal Technologies	Biotech	$9,700,000	Cash for stock deal. Price to rev. mult. is 3.23.
6/30	Procyon Biopharma	Bioxalis Medica, Inc.	Biotech	$2,790,000	Stock deal; concurrent with private placement.
6/30	Genmab A/S	Intrnatl. Rights: HuMax-CD4	Biotech	$14,500,000	Upfront plus milestone & license payments.
7/6	Techne Corporation	Fortron Bio Sci./BiosPacific	Biotech	$20,000,000	Cash deal. Price to revenue mult. is 2.30.
6/20	McKesson Corporation	Medcon, Ltd.	e-Health	$105,000,000	Merger; $3.05 per share. Price to rev. is 6.18x.
7/6	Royal Philips Electronics	Stentor, Inc.	e-Health	$280,000,000	Cash deal. Price to revenue mult. is 5.60.
7/1	Amedisys, Inc.	Housecall Medical Resources	HomeHealth	$106,000,000	Cash and credit. Price to revenue mult. is 1.03.
6/27	Hospital board	St. Rose Hospital	Hospital	$22,000,000	For $125,714 per bed. Price to rev. is 0.26x.
6/30	Community Health Sys.	Bedford Medical Center	Hospital	$20,000,000	For $192,308 per bed. Price to rev. is 0.70x.
6/30	Community Health Sys.	Bradley Memorial Hospital	Hospital	$76,500,000	For $439,655 per bed. Price to rev. is 1.05x.
7/14	LifePoint Hospitals	Five rural hospitals	Hospital	$330,000,000	For $295,434 per bed.
6/7	STHC, LLC	Rivers Edge	LongTermCare	$28,000,000	185 units, for $151,351 per unit.
6/21	Real estate fund	Nine assisted living facilities	LongTermCare	$151,000,000	672 units, for $225,000 per unit.
6/21	Fortress Investment Gp.	Nine retirement communities	LongTermCare	$282,000,000	1,261 units, for $223,632 per unit.
6/30	Regional operator	Medicos Health Care Center	LongTermCare	$2,610,000	138 beds, for $18,913 per bed.
6/30	Regional operator	The Clairemont	LongTermCare	$4,050,000	161 beds, for $25,155 per bed.
6/30	Summerville Senior Lvg.	The Regency Residence	LongTermCare	$13,877,000	215 units, for $64,544 per unit.
7/1	Summerville Senior Lvg.	Beckett Lake Lodge	LongTermCare	$16,200,000	116 units, for $139,655 per unit.
7/7	American Retirement	Phoenix senior livg. cmmty.	LongTermCare	$23,400,000	172 units, for $136,047 per unit.
7/7	Vibra Healthcare, LLC	Northern CA Rehabil. Hosp.	LongTermCare	$15,250,000	88 beds, for $173,295 per bed.
7/11	United Rehab, LLC	EPI Corporation	LongTermCare	$180,000,000	2,400 beds, for $75,000 per bed.
7/6	Advocat, Inc.	Briarcliff Health Care Ctr.	LongTermCare	$6,700,000	120 beds, for $55,833 per bed.
6/24	Aetna, Inc.	HMS Healthcare	ManagedCare	$390,000,000	Cash deal.
6/20	Danaher Corp.	Pelton & Crane	MedDevices	$85,000,000	Cash deal. Price to revenue multiple is 1.06.
6/20	Roper Industries	CIVCO Medical Instruments	MedDevices	$120,000,000	Cash deal. Price to revenue multiple is 3.00.
6/22	Hologic, Inc.	Mammography intellect. ppty.	MedDevices	$32,000,000	Cash deal. Fischer Imaging is seller.
6/28	Synergy Healthcare PLC	Shiloh PLC	MedDevices	$22,800,000	Cash for stock. Price to revenue mult. is 0.94.
6/29	Medtronic, Inc.	Transneuronix, Inc.	MedDevices	$260,000,000	Plus possible revenue-based milestone payments.
6/30	Huntleigh Technology plc	Obstetrics & cardiovas. lines	MedDevices	$7,200,000	Price to rev. mult. is 0.47. Viasys is seller.
7/5	Tyco International	Vivant Medical	MedDevices	$101,000,000	For $65 million in cash, plus milestone payments.
7/5	West Pharmaceutical	Medimop Medical Projects	MedDevices	$41,800,000	For 90% stake. Price to revenue mult. is 2.61.
6/16	ML Laboratories	Quadrant Technologies Ltd.	Pharma	$85,000,000	Cash and stock deal. Price to rev. mult. is 8.19.
6/20	Matrix Laboratories	Docupharm	Pharma	$263,000,000	For majority interest. Price to rev. mult. is 1.87.
6/23	Salix Pharmaceuticals	InKine Pharmaceutical	Pharma	$190,000,000	Stock for stock deal. Price to rev. mult. is 8.60.
6/24	Cephalon, Inc.	Rights to Vivitrex	Pharma	$490,000,000	Cash plus regulatory and sales milestones.
6/27	Blairex Laboratories	Zilactin products	Pharma	$10,300,000	For cash plus working capital adjustments.
7/1	Jubilant Organosys Ltd.	Trinity Laboratories, Inc.	Pharma	$24,720,000	Two-part deal. Cash for 64% stake.

Merger & Acquisition Announcements (continued)

Date	Buyer	Seller	Sector	Price	Terms/Comments
7/5	Bausch and Lomb, Inc.	Shandong Chia Tai Freda	Pharma	$200,000,000	Cash deal for 55% stake. Price to rev. is 3.23x.
7/7	Triax Holdings, LLC	Spear Pharmaceuticals, Inc.	Pharma	$133,000,000	Acquirer is a newly formed entity.
7/11	Leiner Health Products	Pharmaceutical Formulations	Pharma	$23,000,000	For OTC assets. In bankruptcy proceedings.
7/12	Xanodyne Pharmaceut.	aaiPharma pharmaceu. division	Pharma	$209,250,000	In bankruptcy proceedings.
7/13	Takeda Pharmaceutical	Rights to DPP4 inhibitors	Pharma	$15,000,000	For upfront and milestone payments.
7/13	Hi-Tech Pharmaceuticals	U.S. rights: Zostrix brand	Pharma	$4,400,000	Primarily cash deal. Price to rev. mult. is 1.52.
7/5	Omnicare, Inc.	RxCrossroads, LLC	Other	$235,000,000	Cash deal. Price to revenue multiple is 5.11.
7/11	Omnicare, Inc.	excelleRx, Inc.	Other	$268,750,000	Cash deal. Price to revenue multiple is 2.07.
7/11	TLC Vision Corporation	Kremer Laser Eye	Other	$24,300,000	For 82% stake. Price to revenue is 1.28x.
7/11	McKesson Corp.	D&K Healthcare Resources	Other	$474,000,000	Cash plus assumption of debt. Pr. to rev. is 0.15x.
7/11	VNU, NA	IMS Health, Inc.	Other	$7,000,000,000	Price to revenue multiple is 4.32.
7/12	Intelident Solutions	Coast Dental Services	Other	$14,400,000	Price to revenue multiple is 0.26.

Mergers and Acquisitions

Based on revealed prices, during the past four weeks a total of $24.4 billion was committed to finance 77 health care mergers and acquisitions. Compared with the previous four weeks, deal volume increased by 20%. Three deals, one each in the Biotechnology, Managed Care, and "Other" sectors, account for 74% of all dollars committed to health care M&A in the past 30 days.

Pfizer, Inc. (NYSE: PFE) is paying $1.9 billion to replenish its pipeline by acquiring the King of Prussia, Pennsylvania-based biotech, **Vicuron Pharmaceuticals**. Vicuron, focused on the discovery, development and marketing of pharmaceutical products that treat infections, broadens Pfizer's anti-infective portfolio. Two of Vicuron's pipeline drugs show promise for replacing others: Pfizer's Diflucan, an infection treatment for which PFE lost exclusivity last year, and the antibiotic Zithromax, for which American patent protection expires later this year.

UnitedHealth Group, Inc., the Minnesota-based health care services provider, is acquiring **PacifiCare Health Systems, Inc.** (NYSE: PHS), the California-based provider of managed health care services, for $9.2 billion in cash, stock and assumed debt. PacifiCare currently covers 13,700,000 enrollees.

Fairfield, Connecticut-based **IMS Health, Inc.** (NYSE: RX) is being acquired for $7 billion by **VNU, NA** of Haarlem, The Netherlands, in a deal that includes cash, stock and assumption of debt. IMS Health provides market research services to the pharmaceutical and health care industries, such as disease management and the tracking of pharmaceutical sales.

McKesson Corp. (NYSE: MCK) announced two health care acquisitions in the past 30 days, of an Israel-based e-Health company, **Medcon Ltd.**, and of Missouri-based **D&K Healthcare Resources** (NASDAQ: DKHR), a regional distributor of brand-name and generic pharmaceuticals as well as OTC products. McKesson provides supply, information and care management products to the health care industry.

In the Medcon deal, valued at $105 million, shareholders received $3.05 per share and the price to revenue multiple was 6.18x. Medcon provides Web-based cardiac image and information management services internationally. The company generated revenue of $17 million for the year ended December 31, 2004.

D&K Healthcare is being acquired by McKesson for $14.50 in cash for each share of DKHR stock, plus $267 million in assumed debt, totaling $474 million. The price per share reflects a 71% premium to DKHR's stock's prior-day closing price. On a trailing 12-month basis, DKHR generated revenue of $3.2 billion, EBITDA of $29 million and net income of $4 million. The target has an existing customer base of 3,300 independent and regional pharmacies primarily located in the Midwestern, Upper Midwestern and Southern United States.

Looking back, for the second quarter ended June 30, 2005, deal volume was dominated by the Medical Device sector with 38 deals, Biotechnology with 26, Long-Term Care with 25 and Pharmaceuticals, also with 25 deals. These four sectors also had the most deals during the previous and year-ago quarters.

Merger and acquisition activity in all the health care sectors during the second quarter amounted to a total of $18.4 billion committed to fund 211 transactions. Deal volume decreased by 16% compared with the first quarter of 2005, and by 9% compared with the second quarter of 2004. Total health care M&A funding decreased by 48% compared with the previous quarter, and by 29% compared with the year-ago quarter. Deals were concentrated in the health care services sectors, while the health care technology sectors captured the greater share of total funding.

Revised half-year results for health care mergers and acquisitions indicate that a total of 463 deals were made during the period January 1 to June 30, 2005, for a total of more than $53 billion committed to fund the deals. Ten of the deals done in the first six months of the year were multi-billion-dollar transactions.

The biopharmaceutical and biotechnology sectors are attracting more attention than ever. These two sectors have accumulated more health care M&A dollars during the first six months of this year than they did in all of 2004.

Venture Capital Market

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Mid-year deal statistics indicate that health care companies secured a total of $3.9 billion in 235 venture capital transactions during the six months ended June 30, 2005. The overall number of health care venture capital financings announced during the first half of the year increased in 2005 by approximately 26%, compared with 2004, and total venture funding for health care is up slightly.

In the past 30 days, health care companies secured only about half as much venture funding as they had in the prior 30 days, but this could be the calm in the eye of the storm of venture funding that has been swirling around health care companies for months. But then again, as more development-stage health care companies become publicly traded and require continued support in the form of private equity, will investors direct more funding towards existing portfolio companies and less towards new interests?

In the largest health care venture capital transaction of the past four weeks, Triax Holdings, LLC secured funding from one investor, **Allied Capital Corporation** (NYSE: ALD), the Washington, D.C.-based business development corporation. Triax Holdings, formed for the purpose of acquiring and developing a platform of specialty pharmaceuticals, is specifically focused on dermatology.

The venture financing enables Triax Holdings to acquire substantially all of Spear's assets, including the only complete line of Tretinoin products currently being marketed and distributed. The Tretinoin line, which contains the generic equivalent of the active ingredient in the topical acne medication known as Retin-A, also includes five abbreviated new drug applications.

Allied's private finance portfolio currently includes investments in over 100 companies that generate aggregate revenues of more than $10 billion. Other health care holdings in Allied's portfolio (which spans several industries) include **Air Evac Lifeteam**, **Benchmark Medical, Inc.**, **Soteria Imaging Services** and **Haven Eldercare of New England**. Until just recently, Allied also held a majority interest in **Housecall Medical Resources**, which **Amedisys** (NASDAQ: AMED) acquired in July.

The founding leadership team of Triax includes Joe Krivulka, a founder and former president of **Reliant Pharmaceuticals**, and Leonard Mazur, formerly CEO of **Genesis Pharmaceutical**. Genesis, a dermatology products company, was acquired by a subsidiary of the **Pierre Fabre Group**. Reliant, a New Jersey-based pharma that markets cardiovascular products, filed for its initial public offering in May 2005 but has not yet priced the IPO.

Therion Biologics received $30 million, the second-largest venture capital financing announced by a health care company in the past 30 days. Headquartered in Cambridge, Massachusetts, Therion has two lead product candidates, both vaccines. One is in a Phase III trial for the treatment of pancreatic cancer, and the other is in Phase II trials for the treatment of prostate cancer; clinical data from both trials are expected to become available during 2006.

Therion's portfolio also includes potential treatments for colorectal, ovarian, breast and lung cancers, which are in various stages of planning and development. The proceeds of the financing will enable Therion to expand its infrastructure so that ongoing clinical trials can be completed. In connection with the financing, Therion appointed

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Private Placement Market

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS
6/17	**iVOW**	$2.2 million	iVOW, Inc. (NASDAQ: IVOW) is a California-based company focused exclusively on the disease state management of chronic and morbid obesity. IVOW sold 7,300,000 units, each unit comprised of one share of common stock and one five-year purchase warrant for one share of common stock. Dawson James Securities acted as the exclusive financial advisor to, and sole placement agent, to IVOW in this transaction.
6/20	**Grant Life Sciences**	$2.0 million	Grant Life Sciences (OTCBB: GLIF), headquartered in Murray, Utah, will use the proceeds of this private placement to fund the development of its proprietary blood test that detects cervical and other HPV-associated cancers, and to accelerate marketing and sales plans for its AccuDx product line, for which GLIF licensed exclusive rights from AccuDx Corp., a biotech based in La Jolla, California. Grant Life Sciences sold 10% callable secured convertible notes in connection with an investment agreement. Initially GLIF received $700,000 and will receive the balance once registration of the notes is effective.
6/23	**Peregrine Pharmaceuti.**	$6.7 million	The proceeds of this investment will be used by Peregrine Pharmaceuticals (NASDAQ: PPHM) to advance its three clinical trials and to support other pre-clinical studies related to Tarvacin, its biopharmaceutical candidate for the treatment of cancer, viruses and other diseases. Tustin, California-based PPHM sold 8,000,000 shares of its common stock to one institutional investor. The placement agent was not identified.
6/23	**Adherex Technologies**	$12.0 million	Pending the completion of a license agreement and customary approvals, Adherex Technologies (AMEX: ADH; TSX: AHX) will secure this private placement from investors in the United States, Canada and Europe by issuing approximately 32,000,000 units at a price of $0.28 per unit. Each unit consists of one common share and 0.30 of one common share purchase warrant; one whole warrant will be, for three years, exercisable at a price of $0.35 per share. Additionally, GlaxoSmith Kline contributed an equity investment of $3 million to the financing after it was announced. No placement agent was disclosed.
6/23	**Zeltia SA**	$78.0 million	Zeltia S.A. (PK: ZLIXF), headquartered in Madrid, Spain, is a biotechnology company with a biopharmaceutical subsidiary, PharmaMar, which is discovering and developing anticancer drugs derived from marine organisms. Zeltia privately placed with 30 investors 10,750,000 new ordinary shares at a price of EUR6.05 per share; the proceeds will be used to further the continued research, development and commercialization of PharmaMar's products. HSBC acted as the sole bookrunner for the transaction.
6/23	**RegeneRx Biopharmaceu.**	$5.0 million	Maryland-based RegeneRx Biopharmaceuticals (AMEX: RGN) privately placed 1,538,000 shares of its common stock at a price of $3.25 per share with one investor, Defiante Farmaceutica, which is a wholly-owned subsidiary of Sigma-Tau Group. Following a five-year lock-up period, RegeneRx, at its option, may buy back for $5.00 per share the number of shares required to maintain the equity ownership held by Sigma-Tau and its affiliates at the same percentage level (30.1%) it held prior to the transaction. RGN is a biopharma that is developing a peptide-based platform technology for the treatment of acute and chronic wounds and for a variety of human diseases involving tissue and organ repair. No placement agent was used.
6/26	**Bionomics Limited**	$6.0 million	Australia-based Bionomics Limited (ASX: BNO; OTCBB: BMICY), which is discovering and developing therapeutics for the treatment of epilepsy and other CNS disorders as well as using its discovery platform to target drugs for cancer, announced this financing concurrently with its acquisition of Iliad Chemicals. The proceeds will be used to fund the continuation of its development programs. No placement agent was named.
6/27	**Valentis, Inc.**	$4.2 million	Burlingame, California-based Valentis, Inc. (NASDAQ: VLTS) is a developer of cardiovascular therapeutics, and also collaborates with other developers that are applying VLTS's technology in the areas of infectious diseases and cancer. Valentis closed this private placement by selling units, consisting of approximately 1,860,000 shares of its common stock and warrants for the purchase of 840,000 additional shares, at a price of $2.50 per unit. The warrants are exercisable for five years at a price of $3.51 per share. The purchasers included new and existing investors, and accredited individuals. No placement agent was named.
6/27	**IMPAX Laboratories**	$75.0 million	IMPAX Laboratories, Inc. (NASDAQ: IPXLE) received notice from a holder of more than 25% aggregate principal of certain of its debentures due 2024 that as a result of technical default, the principal and premium are immediately due to the holder by IMPAX. The proceeds of this private placement will be used towards repayment of the notes. IMPAX sold $75 million aggregate principal amount of 3.5% senior subordinated convertible debentures due 2012. IMPAX, based in Hayward, California, is a specialty pharma that also has a generic products division. No placement agent was named.

Private Placement Market

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS

6/28 **Corautus Genetics Inc.** $18.0 million Corautus Genetics, Inc. (NASDAQ: VEGF), a clinical-stage biopharmaceutical company based in Atlanta, Georgia, is developing gene transfer therapy products for the treatment of cardiovascular and peripheral vascular disease. In separate transactions, Boston Scientific (NYSE: BSX) and a group of other investors purchased a combined total of 4,700,000 shares of VEGF's stock at a price of $3.80 per share. Additionally, BSX amended a loan agreement, making $5 million in loan proceeds immediately available, for total debt and equity proceeds of $23 million. With its participation in these transactions, BSX becomes the largest voting shareholder in VEGF, with holdings of approximately 17%. The proceeds are expected to fund the company's operations through 2006. VEGF did not pay any placement fees or issue any warrants.

6/28 **Windrose Medical Pptys.** $52.5 million The self-managed specialty medical properties REIT, Windrose Medical Properties Trust (NYSE: WRS), agreed to sell 2,100,000 shares of its 7.5% Series A cumulative preferred shares at a price of $25.00 per share. The preferred shares have no stated maturity but offer a conversion price of $15.75, which is equivalent to a conversion rate of 1.5873 common shares per Series A preferred share. Cohen & Steers Capital Advisors acted as the placement agent for this transaction.

6/29 **Taylor Madison Corp.** $3.2 million Taylor Madison Corp., dba Telzuit Medical Technologies, Inc. (PK: TMDN), announced this private placement of Series A preferred stock and Class B warrants. Of the total financing, $1.75 million was closed on June 23, 2005. The proceeds will be used by Florida-based TMDN to execute its business plan. Telzuit expects its FDA-approved wireless heart monitor, Bio-Patch, will become available to patients and physicians this year. The sole placement agent for this transaction was Midtown Partners & Co., LLC.

6/29 **Auxilium Pharmaceut.** $40.4 million The developer and marketer of specialty pharmaceutical products for urology and sexual health, Auxilium Pharmaceuticals (NASDAQ: AUXL), privately placed 8,200,000 shares of its common stock and warrants to purchase approximately 2,060,000 additional shares. The common shares were sold at a price of approximately $4.90 per share, and the warrants are exercisable at a price of $5.84 per share. Auxilium will use the proceeds of the financing to pursue commercialization, research and development initiatives. Deutsche Banc Securities Inc. acted as the lead placement agent for the transaction.

6/29 **Immunicon Corporation** $19.7 million Immunicon Corporation (NASDAQ: IMMC) sold 4,137,902 shares of its common stock to institutional investors at a price of $4.75 per share. The proceeds of this placement will be used to further the development and commercialization of IMMC's cancer diagnostic products and for the selective development of other new products for other therapeutic areas. Immunicon developed platform technologies for the selection and analysis of rare cells in blood, such as circulating tumor cells. Legg Mason Wood Walker served as the lead placement agent, with First Albany Capital Inc. serving as the co-placement agent.

6/30 **Procyon Biopharma** $2.9 million Concurrent with its acquisition of Bioxalis Medica Inc., Quebec, Canada-based Procyon Biopharma Inc. (TSX: PBP) completed a private placement of debentures. In this financing, Procyon issued convertible debentures with a face value of C$1,000 and a coupon of 7%, and are convertible in whole or in part into PBP's common shares at a price of C$0.45 per common share. The debentures pay interest semi-annually, in cash or common shares at Procyon's discretion. Purchasers of the debentures also received five-year warrants for 50% of the number of common shares that would be issued if the debentures were fully converted; each full warrant is exercisable at a price of C$0.50 per share. Dundee Securities Corporation received a finder's fee for a portion of the financing payable in cash and common share purchase warrants. Investors included Desjardins Venture Capital, Fonds Bio-Innovation and Societe Innovatech Quebec et Chaudieres-Appalaches.

7/5 **Novavax, Inc.** $4.0 million Malvern, Pennsylvania-based Novavax, Inc. (NASDAQ: NVAX) is a specialty biopharma that currently markets and distributes a line of prescription pharmaceutical products and prenatal vitamins, and is also researching and developing products using its proprietary drug delivery and biological technologies. NVAX expects to file New Drug Applications for two of the seven new product candidates for which it has recently completed preclinical testing using its proprietary micellular nanoparticle technology, which is also used for certain of its hormone products. In this financing Novavax issued 4,000,000 shares of its common stock at a price of $1.00 per share. The proceeds of this financing will allow NVAX to strengthen its cash position and accelerate research programs.

Private Placement Market

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS

7/7 **Sirna Therapeutics** $28.0 million The initial tranche of this private placement has been closed by Sirna Therapeutics, Inc. (NASDAQ: RNAI), through the issuance of 8,319,564 shares of its common stock, at a price of $1.60 per share, and warrants to purchase 2,999,043 shares of common stock, with an exercise price of $1.92 per share. The remainder of common shares and warrants will be issued following stockholder approval. In both closings combined, a total of 17,506,250 common shares and 6,302,246 warrant shares are issuable. The proceeds of the financing will be used for ongoing development and clinical and preclinical trials, for product candidates including therapies for age-related macular degeneration, hepatitis B and C, dermatology, asthma and other indications. Existing venture capital insiders, including Sprout Group, Oxford Bioscience Partners and Venrock Associates contributed a combined total of approximately $9 million to the financing, for which Thomas Weisel Partners served as the placement agent and Leerink Swann and Brean Murray served as co-advisors.

7/8 **Endologix, Inc.** $16.6 million Irvine, California-based Endologix, Inc. (NASDAQ: ELGX) is a developer and manufacturer of minimally invasive treatments for vascular diseases, including abdominal aortic aneurysms. ELGX completed this private placement of 4,150,000 shares of its common stock, sold at a price of $4.00 per share, for net proceeds of approximately $15.5 million, after expenses. Adams Harkness, Inc. and Montgomery & Co., LLC acted as co-placement agents on this transaction.

7/8 **Biophan Technologies** $5.0 million Biophan Technologies, Inc. (OTCBB: BIPH), is a Rochester, New York-based developer of technologies designed to improve the safety and compatibility of biomedical devices in the magnetic resonance imaging (MRI) environment, so pacemakers, catheters, stents and other implants can be imaged effectively. Concurrent with an agreement whereby Boston Scientific Corporation (NYSE: BSX) is licensing commercial rights to certain of Biophan's products and technologies, BSX is acquiring $5 million of Biophan's stock, to be priced at a 10% premium to the average of the closing price for the 30 days preceding the closing.

7/8 **Medical Services Intl.** $1.0 million Canada-based Medical Services International Inc. (PK: MSITF) signed a financing agreement with United States-based The Nutmeg Group, LLC, for a minimum of $450,000 and a maximum of $1 million. The proceeds will be used by MSITF for sales, marketing and distribution activities in China and Southeast Asia, including an aggressive strategy to increase orders and production at the company's Shanghai, China facility. MSITF sells the Vscan rapid test kit, for the screening of HIV 1&2, Hepatitis B&C, Tuberculosis, Dengue Fever, West Nile Virus, Syphilis, Malaria and prostate cancer; the test cannot be sold in Canada.

7/11 **Transgene** $42.1 million France-based Transgene (Eurolist Paris: FR0005175080; NASDAQ: TRGNY) completed an offering of 4,657,500 ABSAs (shares with warrants) sold at EUR7.50 per ABSA. The 4,657,000 warrants issued entitle the holders to purchase 2,328,750 new shares at a price of EUR8.05 per share. The proceeds of the placement will be used to fund the continued development of Transgene's therapeutic vaccines for cancers and infectious diseases, currently in Phase II trials. The company has a portfolio of clinical-stage immunotherapy drugs. No placement agent was named.

7/11 **HepaLife Technologies** $15.0 million British Columbia, Canada-based HepaLife Technologies, Inc. (OTCBB: HPLF) entered into an investment agreement to raise equity financing from Chicago, Illinois-based Fusion Capital Fund. Fusion Capital agreed to purchase, at market price, up to $15 million in shares of newly issued HepaLife common stock, in monthly amounts of $500,000, over a period of up to 30 months. HPLF may, subject to certain conditions, require Fusion Capital to purchase lesser or greater amounts of stock each month. The proceeds of the transaction will be used for the expansion and acceleration of research activities, including the development of in-vitro toxicology and preclinical drug testing platforms, and the creation of a first-of-its-kind artificial liver device.

7/11 **PhytoMedical Technol.** $10.0 million British Columbia, Canada-based PhytoMedical Technologies, Inc. (OTCBB: PYTO) also entered into an investment agreement to raise equity financing from Chicago, Illinois-based Fusion Capital Fund. PYTO is an early-stage research-based biopharma focused on the identification, development and eventual commercialization of plant-derived pharmaceutical and nutraceutical compounds. Fusion Capital agreed to purchase, at market price, up to $10 million in shares of newly issued PhytoMedical common stock, in monthly amounts of $400,000, over a period of up to 25 months. PYTO may require Fusion Capital to purchase fewer, or subject to certain conditions, greater amounts of stock each month. The proceeds of the financing will be used for the expansion and acceleration of scientific activities aimed at developing products that will address diabetes and cachexia.

Private Placement Market

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS
7/12	**LTC Properties, Inc.**	$32.6 million	This amount represents the net proceeds of a registered direct placement of 1,500,000 shares of common shares of LTC Properties, Inc. (NYSE: LTC), a self-administered REIT that invests primarily in long-term care and other health care related facilities. LTC will use the proceeds for investments in and acquisitions of health care properties, the funding of mortgage loans secured by health care properties and other general corporate purposes. No placement agent was named.
7/12	**AspenBio, Inc.**	$3.6 million	This amount represents the second and final tranche of a private placement AspenBio Inc. (OTCBB: APNB) completed to raise funds for working capital, new product development and general corporate purposes. In this tranche APNB sold a total of 4,066,162 shares and 4,066,162 warrants by issuing to investors, for each $1 million or portion thereof invested, 1,142,857 common shares and 1,142,857 five-year warrants, exercisable at a price of $1.35 per share, to purchase the same number of shares. Headquartered in Castle Rock, Colorado, AspenBio is a biotechnology company currently offering human and animal hormone and protein products and seeking to partner with big pharma to penetrate its market. Westminster Securities Corporation served as the placement agent for this transaction.
7/13	**Synthetic Blood Intl.**	$1.9 million	Synthetic Blood International (OTCBB: SYBD), which is developing a blood substitute, a liquid ventilation product and an implantable glucose monitor, sold original issue, discount, unsecured and convertible debentures in the aggregate amount of $1.85 million along with warrants for the purchase of up 8,409,083 shares of common stock. The debentures will be amortized over a three-year period with stock or cash; the warrants are exercisable at price of $0.242 per share for a period of three years. The proceeds of this financing will fund an ongoing Phase II trial of SYBD's proprietary perfluorocarbon blood substitute and therapeutic oxygen carrier as well as for working capital purposes. Palisades Master Fund led the participating investors. HPC Capital Management LLC, of Atlanta and New York, arranged the transaction.

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Kathryn Davis, formerly of the clinical operations team at **Wyeth** (NYSE: WYE), to the newly created position of Vice President, Clinical Affairs.

Oddly, one of the largest health care venture capital deals we are reporting this month was led by an individual, Hans-Werner Hector, one of the founders of the enterprise software company **SAP AG** (NYSE: SAP). Other investors participating in the financing of Therion include **Loeb Investors**, **SRK Management Company** and **Cheng Xin Venture Capital Group.**

CoreValve announced the third-largest health care venture capital deal in the past four weeks, with a $24 million Series B round. **Apax Partners** led the round, which included participation from **HealthCap**. Combined with the funding CoreValve previously raised from angel investors and **Sofinnova Partners**, the device maker has now raised $30 million in venture capital.

Founded in 2001, CoreValve is based in Paris, France and has its research and development facilities in Irvine, California. CoreValve is focused on developing its ReValving system for percutaneous aortic valve replacement, which could eventually offer patients an alternative to open heart surgery. The company has achieved clinical proof-of-concept for the device, which is expected to be in greater demand as the population ages and the incidence of degenerative aortic diseases increases.

Nanosphere, Inc. expects to close its latest financing by the end of the summer, having already raised $5 million from an existing shareholder, **Lurie Investments**. The venture round is targeted at $15 million, according to a recent conversation with Bill Moffitt, CEO of Nanosphere. The Illinois-based company makes gold nanoparticles, which are under development as a tool for the very early detection and highly specific identification of organisms, or mutations in DNA. Nanosphere also is developing a probe that tests for proteins, which it expects to have commercialized late next year. The proceeds of this round will be used to continue developing and commercializing Nanosphere's products for use in hospitals.

Unlike current methods, which require sample material to be amplified for analysis, the nanoparticles allow for the direct genomic detection of mutations and pathogens. Nanosphere attaches oligonucleotides (short-strand segments of DNA) to the gold nanoparticles, resulting in a product that is an extremely selective, ultra-sensitive diagnostic tool. Mr. Moffitt said the nanoparticles allow for between 100,000 and a million times greater sensitivity than currently available genetic testing methods. Nanosphere has the attention of the United States government, with $4 to $5 million in grant income on the way to work on an application related to the detection of biowarfare agents. No further financial figures were disclosed.

Venture Capital Fund News

Celtic Pharmaceutical Holdings announced the launch of a $300 million pharmaceutical investment fund, and has already secured commitments totaling approximately $125 million from an international syndicate of investors. The fund will primarily seek to finance acquisitions of late-stage compounds being developed by small biotechnology companies and occasionally geographic rights. Celtic Pharma, based in Bermuda, also has offices in New York City and London.

Westwood, Massachusetts-based **Prism Venture Partners** closed its **Prism Venture Partners V, L.P.** fund at $250 million, bringing the total capital under the firm's management to approximately $1.25 billion. Prism has diversified investment interests in the technology and life sciences markets; Prism V will target medical device, specialty pharmaceutical and breakthrough diagnostic opportunities as well as non-health care investments. Currently, Prism's portfolio includes **Peptimmune, Inc.**, **Axya Medical**, **Acusphere Inc.** and other medical technology and drug delivery and discovery companies.

Flywheel Ventures, founded in 1999, closed **Flywheel I, L.P.** with $31 million committed, primarily for investment in seed- and early-stage information technology and physical sciences ventures based in New Mexico, Colorado and Arizona. The **Kauffman Foundation, Hunt Holdings**, the **New Mexico State Investment Council** and other investors have contributed to the fund; its strategic advisory board includes partners from **New Enterprise Associates** and **Mohr Davidow Ventures.**

Summit Partners, the Boston, Massachusetts-based investment firm, closed two new private funds, a private equity fund and a venture capital fund, totaling $3.3 billion. **Summit Partners Venture Capital Fund II**, with $300 million committed, will invest $5 million to $25 million per company. Founded in 1984, Summit Partners has raised a combined total of nearly $9 billion in its private equity, venture capital and subordinated debt funds.

VENTURE CAPITAL MARKET

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS
6/17	**Therion Biologics Corp.**	$30.0 million	The proceeds of this financing will be used by Therion Biologics Corporation for the clinical advancement of its two lead products, one for pancreatic cancer, currently in a Phase III trials, and the other for prostate cancer, currently in Phase II trials. **Investors:** Hans-Werner Hector (lead); plus other investors, including, Loeb Investors, SRK Management Company, Cheng Xin Venture Capital Group
6/20	**Orqis Medical Corp.**	$22.7 million	California-based Orqis Medical Corporation, the developer of a catheter-based cardiac recovery system and other devices, will use the proceeds of this D round for completion of a clinical trial and to advance its pipeline. **Investors:** New investors, Boston Scientific Corporation, Lighthouse Capital Partners; plus all existing investors
6/20	**TriMed Research, Inc.**	$6.1 million	Nebraska-based TriMed Research, Inc. will use the proceeds of this Series A financing to complete laboratory work and enter the clinical stages of development. TriMed intends to commercialize proprietary therapeutic products for intestinal infections. **Investors:** inventages venture capital investments, Inc., Seroba Bioventures
6/21	**AmpliMed**	$14.3 million	This amount represents the combined proceeds of the A and B rounds for AmpliMed, the developer of drug candidates for pancreatic and other cancers, which will be used for a variety of clinical development activities. **Investors:** Valley Ventures III LP (lead, A round), Biotech Insight Ventures (lead, B round); plus other investors, including, InvestBio, Solstice Capital, Village Ventures
6/22	**Tandem Labs**	$18.8 million	Utah-based Tandem Labs, a contract research organization providing bioanalytical services to the pharmaceutical and biotechnology industries, will use the proceeds of this investment to make acquisitions and for growth initiatives. **Investor:** DW Healthcare Partners
6/23	**Cardiva Medical, Inc.**	$8.3 million	Cardiva Medical, Inc. is focused on developing and commercializing vascular closure devices that are safer and easier to use than those currently on the market. The proceeds of this round will be used to introduce new products and for continued sales growth in the United States. **Investors:** Stockton Partners (lead); plus existing investors, Sycamore Ventures, Harbinger VC Corp., W.I. Harper Group
6/28	**U.S. Spine**	$4.1 million	The Florida-based developer of spinal implant technology, U.S. Spine, announced its total venture funding to date. U.S. Spine is developing a disc replacement device and a fixation system, and one of its first generation products is being marketed by Johnson & Johnson. **Investors:** Not disclosed
6/28	**dbMotion**	$10.2 million	Israel-based dbMotion, a developer and marketer of virtual patient record technology, will use the proceeds of this financing primarily to penetrate overseas markets including the United States. **Investors:** Gemini Israel Funds (lead); plus existing investors, Vertex Venture Capital, Pitango Venture Capital
6/28	**Exagen Diagnostics**	$7.0 million	Exagen Diagnostics, the New Mexico-based developer and commercializer of genomics-based prognostic and predictive testing, closed its B round. Exagen expects to have its first two products on the market next year. **Investors:** Tullis Dickerson & Co. (lead), vSpring Capital, Wasatch Venture Fund
6/28	**Torax Medical**	$2.0 million	Torax Medical, Inc., based in Minnesota, is a clinical-stage medical device company focused on developing implantable therapies for digestive diseases. The proceeds of this Series B financing will be used to complete preclinical testing of an implant to treat gastroesophageal reflux disease. **Investors:** Thomas, McNerney & Partners (lead), Sanderling Ventures, Mayo Medical Ventures
6/29	**SoLapharm, Inc.**	$5.9 million	In this investment, Florida-based SoLapharm sold about 1,070,000 shares of its common stock at $5.50 per share. The development-stage pharma has raised nearly $12 million to date by selling common shares. **Investors:** Not disclosed
6/29	**Santaris Pharma**	$5.3 million	Denmark-based Santaris Pharma, a biopharma developing gene-targeting drugs for the treatment of cancer, reported this first close of its second round of financing, the proceeds of which will be used to fund the further development of its drug pipeline. **Investors:** BankInvest, Novo, LD Pension, InnovationsKapital, Dansk Kapitalanlaeg, Dansk Erhervsinvestering
6/29	**INNOVIVE Pharmaceut.**	$2.3 million	The New York City-based biopharma, INNOVIVE Pharmaceuticals, Inc., has licensed rights to an oncology compound that could address various types of cancer. This was a convertible note financing. **Investors:** Not disclosed; with placement assistance provided by Paramount BioCapital Inc.

Venture Capital Market

DATE	COMPANY	AMOUNT	FUNDING SOURCES/COMMENTS
7/5	**Spryance Inc.**	$6.1 million	Headquartered in Waltham, Massachusetts, Spryance Inc. is a provider of medical transcription services and technologies. Spryance will use the proceeds of this C round in the United States to enhance sales efforts and make acquisitions and globally to expand quality assurance and production operations. **Investors:** Beecken, Petty, O'Keefe & Company (lead); plus existing investors
7/6	**CompassCare**	$2.0 million	Primarily from one investor, this B-round financing is expected to enable CompassCare, a provider of medical information management software to the outpatient health care industry, to capture a share of the health care information technology market. **Investors:** Hopewell Venture (lead), others
7/6	**GANYMED Pharmaceut.**	$15.1 million	Germany-based GANYMED Pharmaceuticals AG is focused on deriving antibody-based treatments for solid tumors. The proceeds of this B round, which brings to $30.6 million in venture capital raised to date, will be used to advance its lead monoclonal antibodies into Phase II/III development. **Investors:** returning investors, including, Venture Incubator, Future Capital, Landensbank Baden-Wurttemberg, VRP Rheinland-Pfalz; plus new investors, KfW Mittelstandsbank, others
7/7	**Napo Pharmaceuticals**	$1.0 million	Napo Pharmaceuticals, based in San Francisco, California, announced an agreement with and equity investment from an India-based pharma to develop and commercialize Napo's anti-diarrhea compound. **Investor:** Glenmark Pharmaceuticals, Inc.
7/7	**Triax Holdings, LLC**	$77.0 million	One investor is financing the acquisition of Spear Pharmaceuticals and Spear Dermatology Products by newly formed Triax Holdings, LLC. The assets include the only complete line of Tretinoin, the generic equivalent of a leading prescription drug for acne. **Investor:** Allied Capital Corporation
7/8	**Pepscan Systems BV**	$6.0 million	Pepscan Systems BV, based in The Netherlands, is a drug discovery and development company serving pharmaceutical and biotechnology companies and building a pipeline of its own product candidates, including oncology vaccines. This was its first round. **Investors:** PPM Oost NV (lead), Lupus Ventures BV, Wageningen Business Generator BV, Technofund Flevoland BV; plus other existing and private investors
7/8	**Panacea Pharmaceuticals**	$7.0 million	Panacea Pharmaceuticals, Inc. is a biopharma developing genomics- and proteomics-based therapeutics and diagnostics for cancer. This was its C round. **Investors:** Mitsubishi Corporation Life Sciences Venture, Olympus, JSR, Shin-Etsu Chemical, Fuji Photo Film, Dai Nippon Printing, Tokio Marine & Nichido Fire Insurance, others; with placement assistance provided by Cosmos Alliance
7/11	**Primera Biosystems**	$11.0 million	Rhode Island-based Primera Biosystems is developing a poprietary gene expression analysis system for use in clinical development and diagnostics. The proceeds of this Series A financing will be used to develop instrument systems and disease-specific reagent kits for commercialization. **Investors:** MPM Capital, Burrill & Company, Malaysian Technology Development Corporation, others
7/11	**CoreValve**	$24.0 million	CoreValve, with headquarters in Paris, France and research and development facilities in Irvine, California, is the developer of a proprietary delivery system for percutaneous heart valve replacement that is designed to offer patients an alternative to open heart surgery. Previously, CoreValve raised $6 million. **Investors:** Apax Partners (lead), HealthCap
7/13	**Vitae Pharmaceuticals**	$15.0 million	Pennsylvania-based Vitae Pharmaceuticals secured this venture round as part of the formal completion of a licensing and development agreement with GlaxoSmithKline. The proceeds of this financing will be used by Vitae to help advance its product candidates into human clinical trials. **Investors:** GlaxoSmithKline (lead); plus existing investors
7/14	**ImmuneControl**	$11.3 million	The Conshohocken, Pennsylvania-based pharma developing compounds to treat multiple myeloma and other immunological diseases, Immune Control Inc., a spin-out of Drexel University, closed its A round to finance testing related to serotonin antagonists and anticipates starting two clinical trials this year. **Investors:** BioAdvance Ventures, NewSpring Capital, Anthem Capital
7/14	**BrainCells Inc.**	$17.7 million	Founded in 2003, San Diego, California-based BrainCells Inc. is focused on developing novel or best-in-class therapies for depression and other neuropsychiatric disorders and for central nervous system diseases. The proceeds of this A round will be used to identify one or more late-stage clinical compounds within that scope. **Investors:** Technology Partners and seed investors, Oxford Bioscience Partners, Bay City Capital (co-leads); plus other investors, including, A.M. Pappas & Associates, Neuro Ventures, individuals

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SEE YOU IN COURT: The health benefits company, **Wellpoint, Inc.** (NYSE: WLP), is close to resolving two class action lawsuits filed against it, having reached a settlement agreement with the representatives of 700,000 doctors in the United States. As part of the agreement, Wellpoint is establishing a settlement fund in the amount of $135 million from which physicians can seek compensation, and is contributing $5 million to a not-for-profit foundation that exists to enhance the quality and delivery of care to the disadvantaged and underserved. Wellpoint will also pay legal fees of up to $58 million. The company has agreed to make key changes to its business practices, which are expected to cost Wellpoint $250 million, but intended to relieve physicians of some overhead costs and time spent contesting claims.

Notes and Briefs

Six years ago a lawsuit arose from the sale of three health plan subsidiaries of **Health Net, Inc.** (NYSE: HNT), and this month a Baton Rouge, Louisiana state court issued a verdict in the case, but HNT is filing an appeal. The subsidiaries were in Oklahoma, Louisiana and Texas, where a separate case is in process. The Louisiana jury awarded approximately $117 million to the plaintiffs, including more than $52 million in compensatory and $65 million in punitive damages. HNT expects the amount of the settlement to be reduced because 15% of the compensatory damages were allocated to other parties. HealthNet, a provider of managed care services covering approximately 6.5 million people in 27 states, continues to believe the claims against it have no merit.

On a favorable note, Kentucky-based **Kindred Healthcare** (NYSE: KND) will receive approximately $55 million in cash, according to the terms of an agreement KND reached with its financial intermediary, **Mutual of Omaha**. The settlement resolves a hospital Medicare cost report issue, related to Medicare reimbursement for rents paid to Ventas, Inc. during the years 2001 through 2003.

GREY MATTER: In California, **Stanford University Medical Center** scheduled a symposium on deep brain stimulation (DBS), a neurostimulation therapy designed to provide relief from symptoms of Parkinson's disease by activating areas of the brain that control movement and block nerve impulses. Separately, **The American Society of Anesthesiologists** recently released a draft practice advisory statement in a report pertaining to intraoperative awareness and the role of brain function monitoring. The report indicates that brain function monitoring may be helpful in reducing the risk of patient awareness during a surgical procedure, especially for high-risk cases. The ASA's practice advisory on brain monitoring is good news for Newton, Massachusetts-based **Aspect Medical Systems** (NASDAQ: ASPM), the company whose BIS technology is used internationally to monitor the awareness level of patients in operating rooms. A final report, which may or may not contain stronger advisory language to support more widespread use of Aspect's BIS technology, will be submitted to the house of delegates at the ASA's annual meeting in October.

GREYER MATTER: Also on the West coast, a business school professor at the **University of California at Irvine** received a three-year, $480,000 grant to research the potential effectiveness of incorporating anti-smoking messages into the plots or dialogues of major television shows. If positive results are achieved, the goal of the research is to identify the most effective ways for television writers for teen programs to work anti-smoking messages into the scripts, and influence them to use the messages.

GREY MATTER & THE BLUES: The **United States Food and Drug Administration** approved the Vagus Nerve Stimulation (VNS) device for the adjunctive long-term treatment of chronic or recurrent depression in patients 18 and older who show an inadequate response to at least four other antidepressant treaments and are also experiencing a major depressive episode. **Cyberonics, Inc.** (NASDAQ: CYBX) manufactures the VNS device, which was already approved for refractory epilepsy.

DIALING FOR DOLLARS: Alabama-based **TeleVox Software, Inc.** might be calling you next, but put away that take-me-off-your-list spiel. TeleVox provides patient communication and messaging software applications to health care practices, clinics and hospitals, and its call center is capable of handling 5 million inbound or outbound calls per month. HouseCalls, the company's flagship product for building efficiency, makes appointment reminder phone calls so fewer appointments are missed and health care staff members do not spend valuable patient time on administrative tasks. Near the end of the second quarter of 2005, TeleVox announced that its revenues, which have been climbing since its inception in 1993, have grown by nearly 64% in the last year. For the year ended December 31, 2004, TeleVox had revenues of $18.6 million, compared to revenues of $11.4 million for 2003.

IPOs

The following table includes the medical devices, biotechnology, pharmaceuticals, and healthcare IPO pricings, filings and withdrawals announced over the previous week. Dollars ($) are expressed in millions.

	Date	Company	Ticker	Description	Size	Lead Manager
Priced	11-Jul-05	Accentia BioPharmaceutical		Tampa, FL based drug company focused on respiratory diseases and oncology	Reduced their offering to $56 million from $75 million	Jefferies & Co.
Filed						

Follow-On Offerings

The following table includes the medical devices, biotechnology, pharmaceuticals, and healthcare public follow-on pricings, filings and withdrawals announced over the previous week. Dollars ($) are expressed in millions.

	Date	Company	Ticker	Description	Size	Lead Manager
Priced						
Filed						
W/drawn						

Private Equity Placements

The following table includes institutionally placed private equity financings for private and public medical devices, biotechnology, pharmaceuticals, and healthcare companies announced over the previous week. Dollars ($) are expressed in millions.

Date	Company	Description	Size	Lead Investors
12-Jul-05	AspenBio, Inc	Castle Rock, CO based manufacturer of purified proteins and hormones	$3.557 million	Placement agent was Westminster Securities
13-Jul-05	Solexa, Inc	Hayward, CA based genetic analysis company	$24 million (2nd close to a $32.5 million deal)	Abingworth Management, Amadeus Capital Partners, Oxford Bioscience Partners, and SV Lifesciences.

Venture Capital Rounds

The following table includes venture capital fund raising for private medical devices, biotechnology, pharmaceuticals, and healthcare companies announced over the previous week. Dollars ($) are expressed in millions.

Date	Company	Round	Description	Amt. Raised	Lead Investors
11-Jul-05	CoreValve	B	Paris, France based maker of delivery systems for percutaneous heart valve replacement	$24	Apax Partners
11-Jul-05	Posit Science Corp.	B	San Francisco based neurology company	$14.52	Aberdare Ventures
11-Jul-05	ECI Biotech		Worcester, MA based protein biochemistry company focused on sensor technology	$2.50	Not disclosed.
12-Jul-05	Primera Biosystems Inc	A	Providence, RI based developer of gene-expression analysis systems	$11	MPM Capital, Burrill & Co., the Malaysian Technology Development Corp
13-Jul-05	CaseNET	A	Waltham, MA based Healthcare IT company	$3	Sigma Partners
14-Jul-05	Vitae Pharmaceuticals	C	Ft. Washington, NJ based small molecule drug discovery company (also finalized a strategic alliance with GSK)	$15	Atlas Venture, New Enterprise Associates, Prospect Venture Partners, Venrock Associates and Wellcome Trust
14-Jul-05	Immune Control, Inc.	A	Conshocken, PA based drug company focused on serotonin antagonists technology.	$11.30	Domain Associates, BioAdvance Ventures, New Spring Capital and Anthem Capital
14-Jul-05	Homestead Clinical Corp	A	Seattle based biotech formed by the local incubator, Accelerator Corp	Not disclosed	MPM Capital, Amgen Ventures, OVP Ventures, ARCH Venture Partners, Versant Ventures and Alexandria Real Estate Equities
15-Jul-05	BrainCells Inc	A	San Diego based drug company focused on therapies that modulate neurogenesis	$17.7 million (has received $8 million, add'l $9.7 will be allocated based on milestone achievement)	Technology Ventures, Oxford Bioscience Partners and Bay City Capital co-led

Mergers and Acquisitions

The following table includes mergers and acquisitions for private and public medical devices, biotechnology, pharmaceuticals, and healthcare companies announced over the previous week. Dollars ($) are expressed in millions.

Source: www.Biospace.com, www.venturewire.com,

Acquisitions

Date	Acquiror	Target	Description of Target	Transaction Value
12-Jul-05	Omnicare	excelleRx	Philadelphia based provider of pharmaceutical care services for	$269 million cash
11-Jul-05	McKesson Corporation	D&K Healthcare	St. Louis based pharmaceutical, health and beauty product distributor to independent and regional pharmacies	~$206.8 million
11-Jul-05	VNU	IMS Health Inc	Fairfield, CT based healthcare data provider.	$6.9 billion
12-Jul-05	Assay Designs Inc.	Stressgen Bioreagents Corp	British Columbia based developer of antibody and protein kits for researchers	

Mergers

Date	Company 1	Ticker	Company 2	Ticker	Terms of agreement

Compiled by : Jennifer J. Taylor

Sources: Venture Wire, Private Equity Week, Wall Street Journal, Venture Source, SEC Filings, Company press releases, and www.biospace.com

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GOVERNMENT FUNDING

NIH, Biotech Firms Oppose Grant Rules
Biotechnology firms lobbying for access to Small Business Administration funding now ha support from the National Institutes of Health, the *Washington Post* reported this week. N director Elias Zerhouni asked SBA chief Hector Barreto to waive restrictions on awarding research grants to firms that are owned 51% or more by venture capital companies.
Full Article

University Receives $10M Grant for Alzheimer's Research
The National Institute on Aging, part of the National Institutes of Health, awarded a five-y $10 million grant to the University of Michigan Alzheimer's Disease Research Center. Th money will go to the center's Memory and Aging Project as well as studies that test new treatments and ideas on how to prevent or delay the onset of the disease.
Full Article

Thromgen Awarded $1.49M Grant to Prepare for Human Trials
Thromgen, Inc., Ann Arbor, Mich., was awarded a $1.49 million grant to take its new drug candidate, Thrombostatin, to clinical trials. The award, termed a Small Business Technol Transfer Competing Continuation grant, is from the National Heart, Lung, and Blood Insti of the National Institutes of Health.
More Information

PRIVATE FUNDING

Immune Control Raises $11.3 M towards Clinical Trials
BioAdvance Ventures, Philadelphia, an early stage venture fund announced the closing c $11.3 million investment in Immune Control Inc., Conshohocken, Pa., a pharmaceutical company developing serotonin antagonists for treatment of multiple myeloma and other immunological diseases.
More Information

BrainCells Announces $17.7M in Financing
BrainCells Inc., San Diego, a drug discovery and development company targeting therap for depression, related neuropsychiatric disorders, and other central nervous system diseases, will receive $17.7 million in Series A private financing. More Information

Vitae Pharmaceuticals Announces $15M in Financing
As part of the formal completion of a licensing and development agreement with GlaxoSmithKline, Vitae Pharmaceuticals, Fort Washington, Pa., secured $15 million in ec financing from investors, which the company will apply to accelerating its multiple prograı into the clinic.
More Information

ACADEMIC FUNDING

Texas Institute for Genomic Medicine Created with $50M
The Texas Enterprise Fund has awarded $50 million for the creation of the Texas Institut Genomic Medicine, a non-profit organization founded by The Texas A&M University Syst The institute will house what is expected to be the world's largest collection of mouse embryonic stem cells.
Full Article

San Diego Startup Company to Commercialize UCSD Technology
The University of California, San Diego, signed an agreement with a startup company, InflammaGen, San Diego, to license technologies that hold promise for the treatment of s and acute inflammatory diseases.
Full Article

Gene Network Sciences Awarded Grant for Cardiac Modeling
Gene Network Sciences, Ithica, N.Y., won a Phase One Small Business Innovation Rese Grant (SBIR) from the National Heart, Lung, and Blood Institute of the National Institutes Health. The $137,800 grant will be used to further the company's cardiac modeling effort
Full Article

GRANTS AVAILABLE

Ruth L. Kirschstein NRSA Fellowships in Cancer Nanotechnology Research
Agency: The National Cancer Institute
Estimated Funding: $15.5M
Due Date for Applications: Sep 16, 2005
Description: This RFA supports the training of individuals from the basic, biomedical, clin and information sciences and engineering who are pursuing research that applies nanotechnology development and application for the prevention, detection, diagnosis, or treatment of cancer.
Full Announcement

Etiology, Prevention, and Treatment of Hepatocellular Carcinoma (R01 and R21)
Agency: The National Cancer Institute, the National Institute of Diabetes and Digestive a Kidney Diseases, the National Institute of Biomedical Imaging and Biotechnology, and th National Institute on Alcohol Abuse and Alcoholism
Estimated program funding: Not available
Due date for applications: Multiple receipt dates - See link to full announcement for detail
Description: Grant applications that address the etiology and etiologic mechanisms of hepatocellular carcinoma and development of animal models, novel approaches to preve this malignancy, and therapeutic or diagnostic studies aimed at establishing reliable prognostic indicators for disease progression and/or minimizing morbidity and mortality associated with this malignancy.
Full Announcement

Etiology, Prevention, and Treatment of Hepatocellular Carcinoma (P01)
Agency: The National Cancer Institute
Estimated program funding: Not available
Due date for applications: Multiple receipt dates - See link to full announcement for detail
Description: Program project grant applications that address the etiology and etiologic mechanisms of hepatocellular carcinoma (HCC) and development of animal models, nov approaches to prevent this malignancy, and therapeutic or diagnostic studies aimed at establishing reliable prognostic indicators for disease progression and/or minimizing morl and mortality associated with this malignancy.
Full Announcement

Testing Stem Cell Therapy in Mouse Models of Premature Aging
Agency: National Institute on Aging
Estimated program funding: Not available
Due date for applications: Multiple receipt dates - See link to full announcement for detail

Description: This PA is for applications to test stem cell therapies in mouse models of accelerated aging.
Full Announcement

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Exhibit G

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Don't miss: The Symposium on Social Architecture, Nov 14-15, Cambridge, MA. Participants include David Weinberger, Lisa Stone, John Hagel, Mary Hodder, and Liz Lawley. More info here

ABOUT THIS AUTHOR

Zack Lynch, managing director of NeuroInsights, is an economic and social forecaster advising global organizations on the impact of neurotechnology on business, government and society. He serves on the advisory boards of the Center for Cognitive Liberty & Ethics, Global Neuroscience Initiative, and SocialText, a social software company. He is currently finishing his book on Neurosociety: How Brain Science Will Shape the Future of Business, Politics and Culture. Please send newsworthy items or feedback - to Zack Lynch.

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July 18, 2005

BrainCells Taps Leading Neurotech Venture Capital

Posted by **Zack**

By Casey Lynch

Neuropharmaceutical drug discovery company BrainCells Inc of San Diego announced that it has closed a $17.7 million Series A financing from leading neurotech venture funds including Technology Partners, Oxford Bioscience Partners and NeuroVentures Capital.

Recent research from scientific founder Fred Gage and others has shown that treatment with antidepressants correlates with the appearance of new neurons in animal models. Many factors, including chronic stress, can lead to neuronal atrophy in an area of the brain called the hippocampus and it has been shown that hippocampal volume is reduced in depressed patients. **Contrary to long held dogma, certain areas of the brain, including the hippocampus, can be stimulated to generate** new neurons from resident neuronal stem cells and some believe that this neurogenesis may be the mechanism of action of drugs like Prozac.

While there is still some debate as to the causative link between neurogenesis and depression, BrainCells hopes that neurogenesis can be used as a marker to identify new antidepressants and mood disorder

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Zack Lynch, managing director of NeuroInsights, is an economic and social forecaster advising global organizations on the impact of neurotechnology on business, government and society. He serves on the advisory boards of the McGovern Institute for Brain Research at MIT,Center for Cognitive Liberty & Ethics, Global Neuroscience Initiative, the Center for Neuroeconomic Studies and SocialText, a social software company. He is currently finishing his book on Neurosociety: How Brain Science Is Shaping the Future of Business, Politics and Culture. Please send newsworthy items or feedback - to Zack Lynch.

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While there is still some debate as to the causative link between neurogenesis and depression, BrainCells hopes that neurogenesis can be used as a marker to identify new antidepressants and mood disorder treatments. This would be a big step forward considering the current difficulty in preclinical drug discovery for these large market opportunities.

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Also of note today, neurodevice company Cyberonics received FDA approval to use it's Vagus Nerve Stimulator on depression resistant patients.

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COMMENTS

1. ex nihilo nihil on July 18, 2005 05:53 PM writes...

Summary points

Recent meta-analyses show selective serotonin reuptake inhibitors have no clinically meaningful advantage over placebo

Claims that antidepressants are more effective in more severe conditions have little evidence to support them

Methodological artefacts may account for the small degree of superiority shown over placebo

Antidepressants have not been convincingly shown to affect the long term outcome of depression or suicide rates

Given doubt about their benefits and concern about their risks, current recommendations for prescribing antidepressants should be

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2. zeroin on July 18, 2005 05:57 PM writes...

Summary points

Recent meta-analyses show selective serotonin reuptake inhibitors have no clinically meaningful advantage over placebo

Claims that antidepressants are more effective in more severe conditions have little evidence to support them

Methodological artefacts may account for the small

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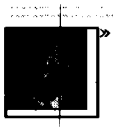
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Source: NeuroInvestment

Neurogenesis Programs Reviewed by NeuroInvestment

Tuesday October 4, 11:19 am ET

CARDIFF, CA--(MARKET WIRE)--Oct 4, 2005 -- NI Research today announced the release of the October issue of NeuroInvestment, which reviews and evaluates programs devoted to the induction of neurogenesis: accelerating the proliferation and differentiation of the neural stem cells now known to exist in the adult brain. In the field of neuroregeneration, this is the tactical counterpoint to the higher-profile area of stem cell therapy, wherein cells are implanted. In inducing neurogenesis, the goal is to utilize a patient's own cellular resources, thereby sidestepping the myriad problems associated with the selection, culturing, and surgical implantation of stem cells. However, there is still much to be learned about the location and responsivity of adult neural stem cells, the indications wherein they may prove useful, and how to avoid the risk of uncontrolled proliferation and tumor formation. The widest application of neurogenesis to this point was unplanned: antidepressants are increasingly believed to exert much of their therapeutic benefit via the stimulation of neurogenesis. The three companies whose raison d'étre has been most entwined with the pursuit of neurogenesis are: San Diego's BrainCells Inc., whose scientific founders are Fred Gage and Eric Kandel; Sweden's NeuroNova, and the hedgehog protein specialist Curis, although Curis is putting much of its energy into oncology, the restraint of neurogenic forces. Other companies with noteworthy programs involving neurogenesis include Lilly, Corcept (NasdaqNM:CORT - News), Cortex (AMEX:COR - News), and Axaron. The current status and future prospects of these and other neurogenesis-relevant programs is reviewed. Beyond this primary topic, the October issue of NeuroInvestment also reviews recent events in the neurotherapeutic field. One event receiving particular attention is the general misperception of the recent milnacipran Phase III data from Forest and Cypress (NasdaqNM:CYPB - News). Milnacipran was reported to have failed in its fibromyalgia trial due to the finding that its clinical benefit was supported at p=.058. Clinical benefit and regulatory criteria are not congruent in this case, given that the drug was 94.2% likely to have produced clinical benefit. The anachronistic embrace of .05 as a binary 'gold standard' for biostatistics is discussed in this issue.

Recent issues of NI have reviewed insomnia, ADHD, and schizophrenia. Forthcoming issues will assess programs in Mild Cognitive Impairment and Alzheimer's.

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Information about NeuroInvestment's Institutional Edition is available on request.

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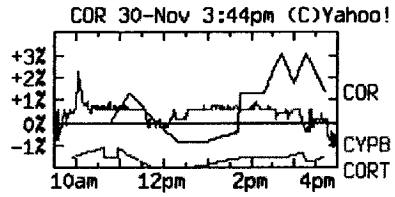

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- Judge Rules Against BlackBerry Settlement - AP (3:28 pm)
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- Oil Prices Climb on Drop in Inventories - AP (4:05 pm)

More...

NI Research is the leading publisher of independent research regarding the CNS therapeutics area. NI has just marked its tenth year, having published NeuroInvestment since 1995. NI Research also publishes the annual Private CNS Company Review, whose 2005 edition has recently been released; and provides product licensing consultation and custom research for large and small pharmaceutical firms.

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Contact:

Contact:
NI Research
P.O. Box 1028
Cardiff, CA 92024
603-379-8800
fax: 760.753.6481
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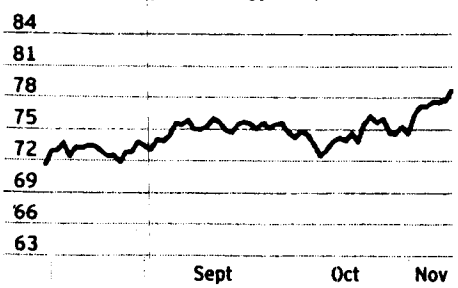
TECHNOLOGY INC.

San Diego Technology

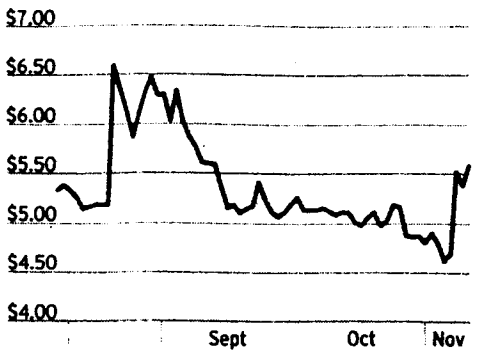
An index of the stock performances of 25 major San Diego County technology companies.



SOURCE: Bloomberg

Tech Stock of the Week | AMERICAN TECHNOLOGY CORP.

Shares of American Technology were up 21 percent this week after a cruise ship used the company's device to repel pirates off the coast of Africa. American Technology developed a "long-range acoustic device" that emits an ear-splitting warning noise.



Headquarters: Sabre Spring
Chairman: Elwood G. Norris
Employees: 53
Revenue (Fiscal 2004): $5.8 million
Net loss (Fiscal 2004): $6 million
Market capitalization: $135 million
Year-to-date stock performance: down 49.6 percent
Exchange: Nasdaq

People to watch

A conversation with key players in San Diego's technology and life sciences industries.

JIM SCHOENECK

Position: Chief executive officer

Company: BrainCells

Age: 48

San Diego biotechnology industry veteran Jim Schoeneck was hired as chief executive of BrainCells in Septmber. Schoeneck moved to California in late 1999 to work at Prometheus Laboratories, where he became chief executive. In 2003, he accepted the CEO position at ActivX Biosciences, which was sold to Kyorin Pharmaceuticals of Japan in late 2004.

Schoeneck, who broke into the life sciences industry through sales, spent the first 13 years of his career at Rhone-Poulenc Rorer, where he was director of health care services and director of marketing. He then joined Centocor, which became a division of Johnson & Johnson. He led the team that launched Remicade and negotiated the company's strategic partnership with Schering-Plough.

Why does your company exist?

BrainCells aims to find new drugs for people suffering from diseases and conditions that affect the brain. The company was founded on groundbreaking work in the area of neurogenesis, the body's ability to generate new brain cells. Until 10 years ago, it was believed that brain cells could not be generated in adulthood. Based on the discoveries of our founders, we now know that the adult brain has the ability to generate new brain cells. Our company is dedicated to finding new drugs that help the body in that process.

What about your job keeps you up at night?

Working in a startup company at the cutting edge of biotech has both great rewards and great challenges. One of the challenges is the workload. If I'm up at night, there wasn't enough time at the office to get everything done that the job demands in such a rapidly advancing field of medicine.

What about your job do you brag about?

I brag about the quality of the people that I get to work with. Our founders and advisers include a Nobel Prize winner and several members of the National Academy of Science. We also have great investors who understand the potential for this breakthrough science and outstanding people working directly for the company.

How does your profiling platform work?

One of the biggest issues in the development of drugs for diseases of the brain is that there haven't been scientific models that can really predict what will happen when a drug is given to people. This means that many of the drugs tested in diseases such as depression and Alzheimer's disease often fail when they are used in clinical trials. Our profiling platform allows us to do laboratory experiments with drugs directly in the cells that are key to the growth of new brain cells. Hopefully, we can improve the odds that a new drug will work when it is ready to be used in people.

Tell us something interesting about yourself.

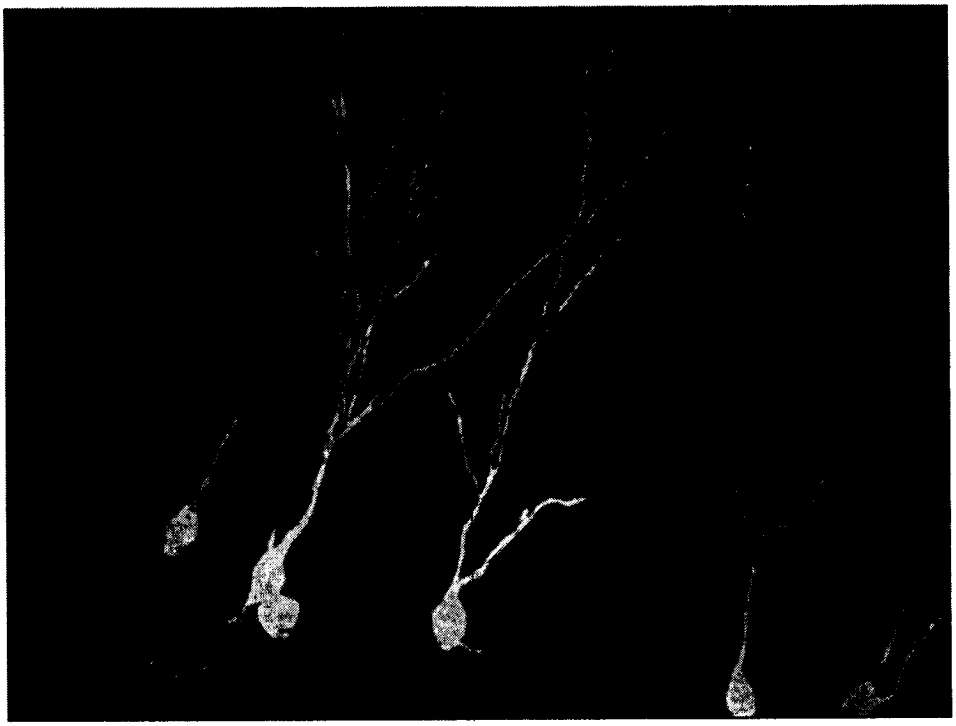
I have a very eclectic undergrad major for my industry. Most biotech CEOs have an educational background in either science or business. I haven't found any other biotech CEOs with a degree in music! My favorite types of music are classical, jazz and contemporary Christian.

—TERRI SOMERS

BrainCells, INC (BCI) is a leading-edge neurogenesis-based drug discovery and development company targeting novel therapies for depression, mood disorders and other CNS diseases.

Neurogenesis is emerging as a fundamental mechanism underlying CNS physiology and provides an opportunity for a paradigm-shifting approach to the treatment of CNS disease. BCI believes that, by targeting neurogenesis mechanisms with small molecule therapeutics, we will be able to develop and take to market first-in-class therapies for depression, mood disorders and other major CNS diseases.

Furthermore, BCI believes that the neurogenesis platform will provide a predictive pre-clinical model which will enhance the productivity of CNS drug research and reduce late-stage clinical attrition in the product pipeline.



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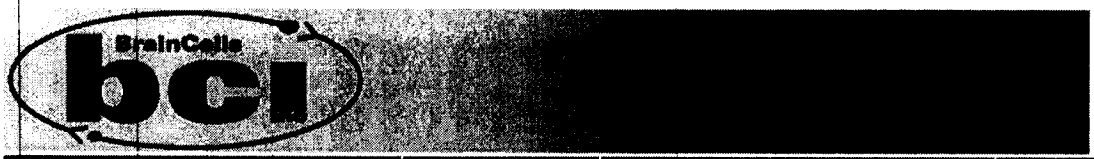

CONTACT

BrainCells, INC.

10835 Road To The Cure, Suite 150
San Diego, CA 92121
Phone: +1 858 812 7700
Fax: +1 858 812 7630

Directions

Directions from the South, including San Diego airport:
Take I-5 NORTH

Take the GENESEE AVE exit. Turn LEFT onto GENESEE AVE. (WEST)
Turn a slight RIGHT at Traffic Lights onto N TORREY PINES RD.
Turn RIGHT onto SCIENCE PARK RD.
Turn LEFT onto TORREYANA RD.
Turn RIGHT onto ROAD TO THE CURE

Directions from the North, including Los Angeles:
Take I-5 SOUTH

Take the GENESEE AVE exit. Turn RIGHT onto GENESEE AVE. (WEST)
Turn a slight RIGHT at Traffic Lights onto N TORREY PINES RD.
Turn RIGHT onto SCIENCE PARK RD.
Turn LEFT onto TORREYANA RD.
Turn RIGHT onto ROAD TO THE CURE