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

ELI LILLY AND COMPANY

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH

Case IPR2018-01422 (Patent No. 9,340,614)
Case IPR2018-01423 (Patent No. 9,266,951)
Case IPR2018-01424 (Patent No. 9,346,881)
Case IPR2018-01425 (Patent No. 9,890,210)
Case IPR2018-01426 (Patent No. 9,890,211)
Case IPR2018-01427 (Patent No. 8,597,649)*

ELI LILLY TRIAL DEMONSTRATIVES

November 22, 2019

Demonstrative Exhibits – Not Evidence

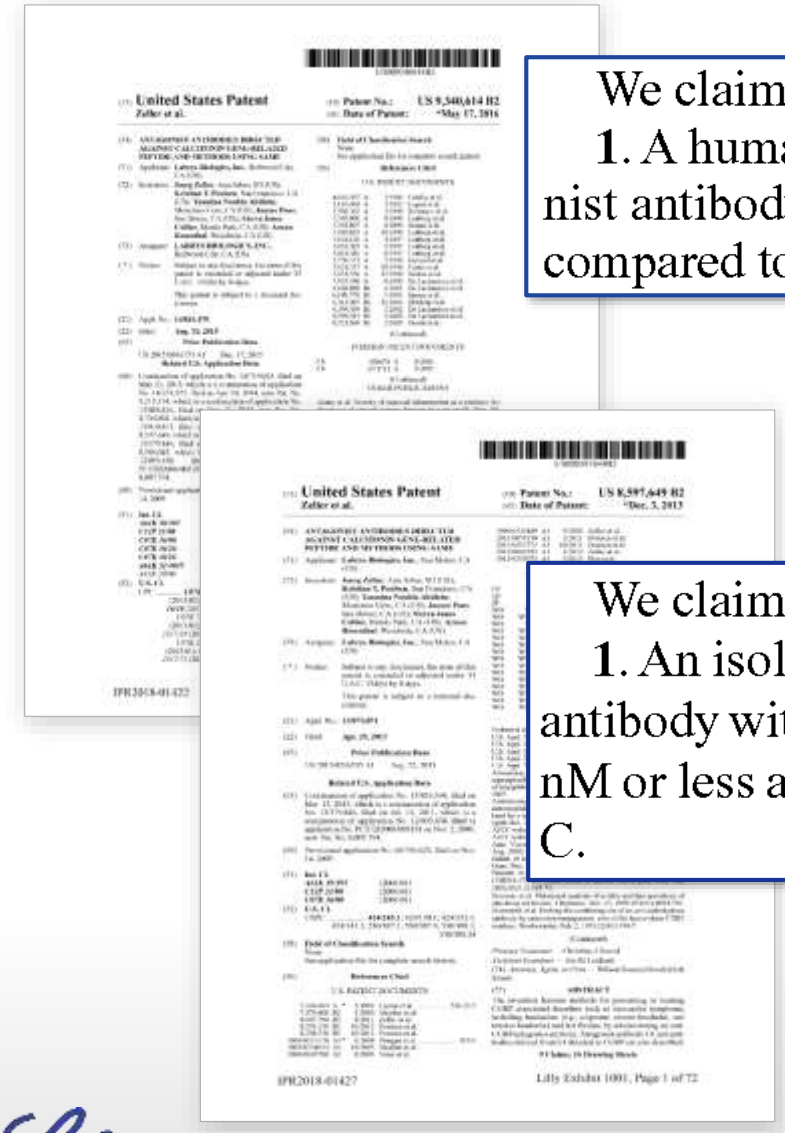
(*unless indicated otherwise, citations to papers refer to IPR2018-01422)

Eli Lilly Trial Demonstratives

Summary of Case

- Teva's patents broadly claim *any* humanized anti-CGRP antagonist antibody with known or routinely achievable features
- Tan 1995 describes an anti-CGRP antagonist antibody effective *in vivo* and provides guidance to improve immunoblockade
- Wimalawansa expressly teaches that humanized anti-CGRP antibodies "should be explored" to treat human diseases
- The prior art is replete with reports providing additional motivation to make a humanized anti-CGRP antagonist antibody
- Teva conceded it was routine to make a humanized antibody
- Neither Tan 1995 nor Teva's purported safety concerns teach away from the claimed subject matter
- Teva's purported secondary considerations lack nexus and are insufficient to overcome obviousness

The Breadth of Teva's Claims



We claim:

1. A human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α-CGRP as compared to amylin.

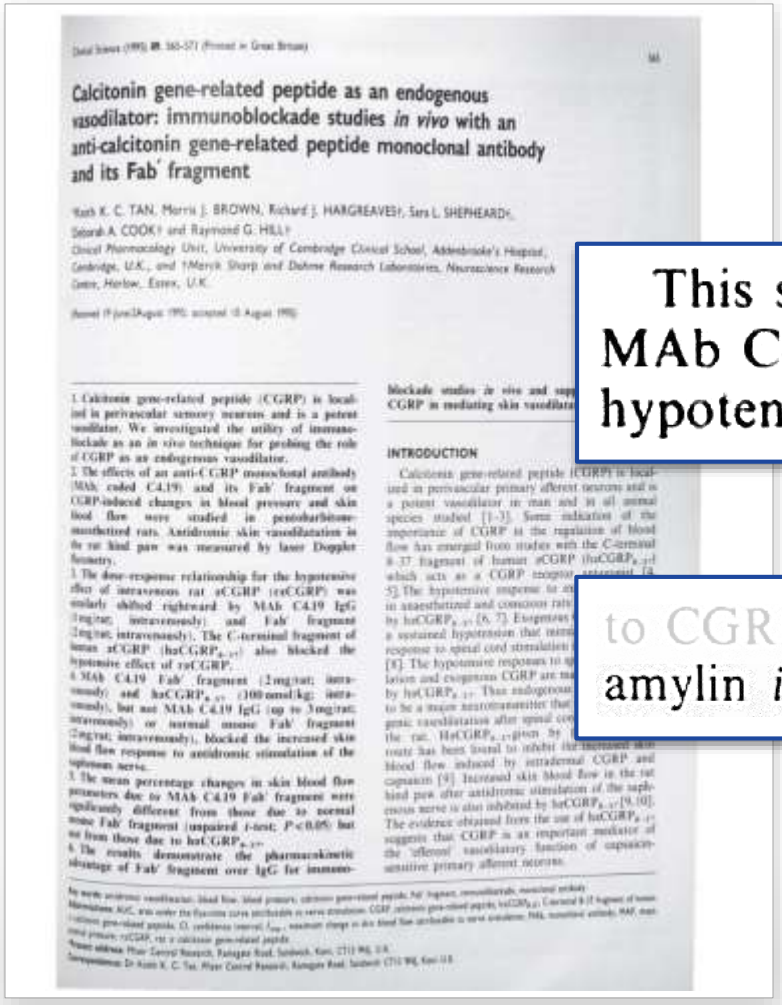
Ex. 1001 ('614 Patent), 101:31-4

We claim:

1. An isolated human or humanized anti-CGRP antagonist antibody with a binding affinity (K_D) to human α-CGRP of 50 nM or less as measured by surface plasmon resonance at 37° C.

Ex. 1001 ('649 Patent), 101:37-41

Tan 1995 (Ex. 1022) Shows MAb C4.19 Was Effective *In Vivo*



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Keith K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

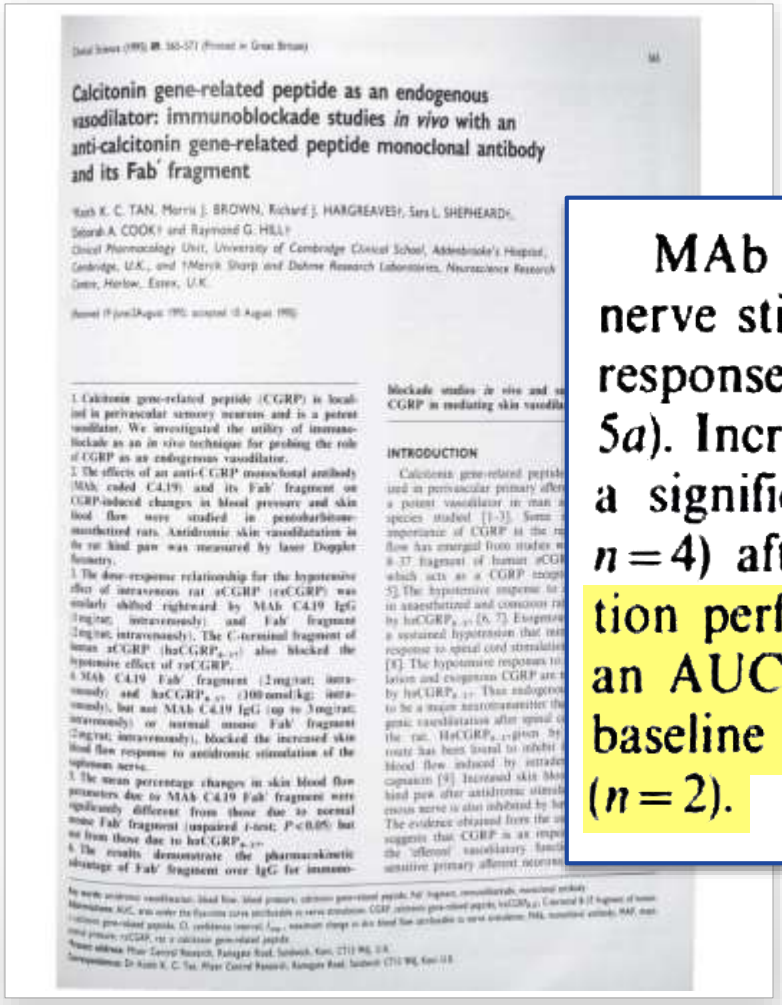
This study has clearly demonstrated the ability of MAb C4.19 IgG and its Fab′ fragment to block the hypotensive effects of exogenous rαCGRP *in vivo*.

Ex. 1022, 570; Ex. 1008, ¶71; Pet., 17

to CGRP. MAb C4.19 does not cross-react with rat amylin *in vitro* but the potential of MAb C4.19 to

Ex. 1022, 572; Ex. 1009, ¶76; Pet., 31

Tan 1995 (Ex. 1022) Shows MAb C4.19 Was Effective *In Vivo*



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Keith K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

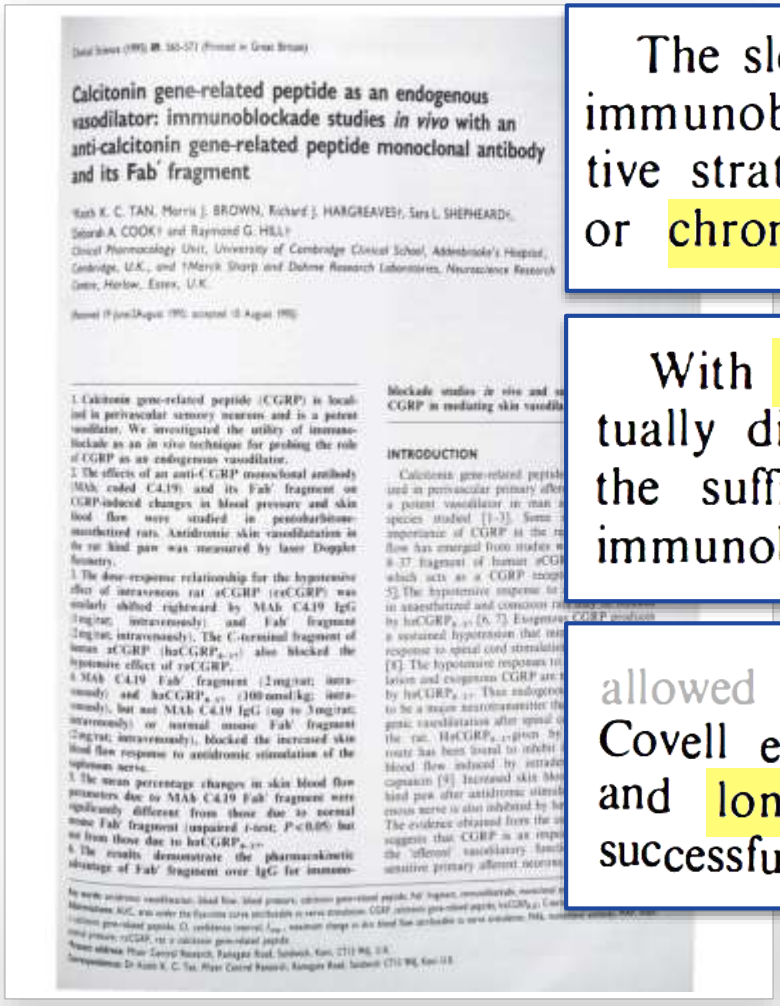
Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

MAb C4.19 IgG at 1 mg/rat given 60 min before nerve stimulation did not block the skin blood flow response to antidromic nerve stimulation ($n=2$; Fig. 5*a*). Increasing the dose to 3 mg/rat did not produce a significant difference in $F_{max.}$ or AUC ($P=0.83$; $n=4$) after 60 min (Fig. 5*a*). Further nerve stimulation performed at 2 h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% ($n=2$).

Ex. 1022, 569; Ex. 1008, ¶57; Pet., 17-18; Reply, 20

Tan 1995 (Ex. 1022) Provided Guidance to Improve Immunoblockade



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Kieth K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

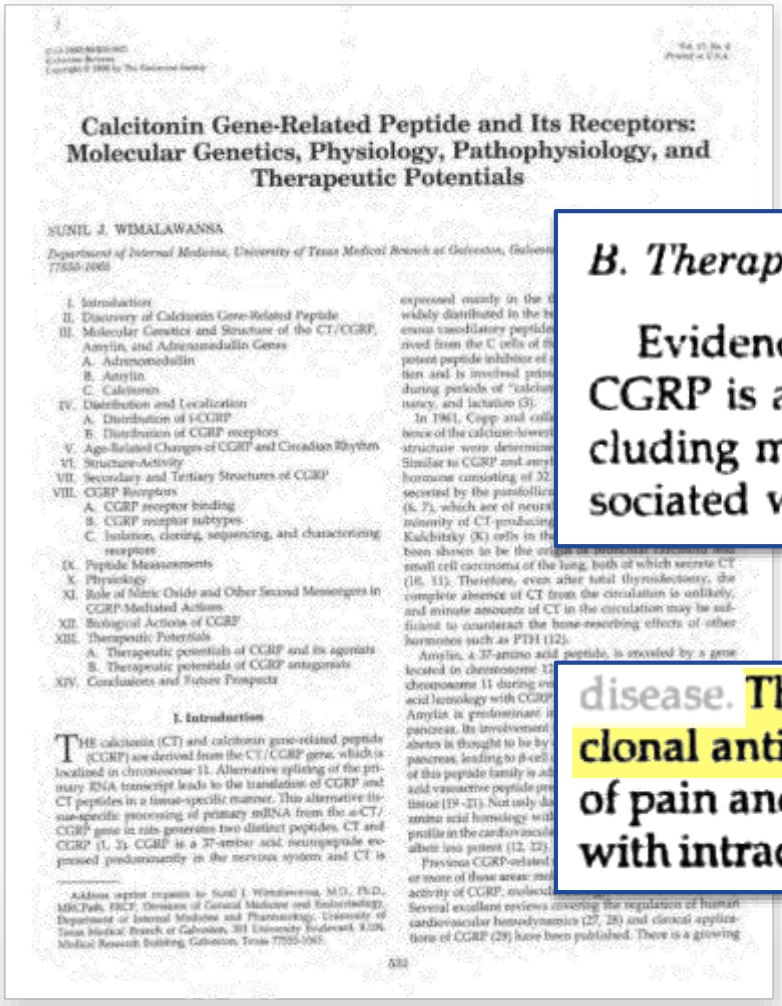
The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to

With repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade. A limited example is found in an

allowed for antibody distribution. The data of Covell et al. [14] suggest that much larger doses and longer distribution times are required for successful immunoblockade with IgG. In this

Ex. 1022, 571; Ex. 1008, ¶122; Ex. 1305, ¶¶24-29; Pet., 39-42; Reply, 20

Wimalawansa (Ex. 1096): Humanized Anti-CGRP Antagonist Antibodies "Should Be Explored"



Calcitonin Gene-Related Peptide and Its Receptors: Molecular Genetics, Physiology, Pathophysiology, and Therapeutic Potentials

SUNIL J. WIMALAWANSA

Department of Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, Texas 77555-1068

I. Introduction
II. Discovery of Calcitonin Gene-Related Peptide
III. Molecular Genetics and Structure of the CT/CGRP, Amylin, and Adrenomedullin Genes
A. Adrenomedullin
B. Amylin
C. Calcitonin
IV. Distribution and Localization
A. Distribution of I-CGRP
B. Distribution of CGRP receptors
V. Age-Related Changes of CGRP and Circadian Rhythm
VI. Structure-Activity
VII. Secondary and Tertiary Structures of CGRP
VIII. CGRP Receptors
A. CGRP receptor binding
B. CGRP receptor subtypes
C. Isolation, cloning, sequencing, and characterizing receptors
IX. Peptide Measurements
X. Physiology
XI. Role of Nitric Oxide and Other Second Messengers in CGRP-Mediated Actions
XII. Biological Actions of CGRP
XIII. Therapeutic Potentials
A. Therapeutic potentials of CGRP and its agonists
B. Therapeutic potentials of CGRP antagonists
XIV. Conclusions and Future Prospects

I. Introduction

THE calcitonin (CT) and calcitonin gene-related peptide (CGRP) are derived from the CT/CGRP gene, which is localized in chromosome 11. Alternative splicing of the primary RNA transcript leads to the translation of CGRP and CT peptides in a tissue-specific manner. This alternative tissue-specific processing of primary mRNA from the α-CT/CGRP gene in rats generates two distinct peptides, CT and CGRP (1, 2). CGRP is a 37-amino acid neuropeptide expressed predominantly in the nervous system and CT is

Address reprint requests to: Sunil J. Wimalawansa, M.D., Ph.D., MRCPath, FRCP, Division of General Medicine and Endocrinology, Department of Internal Medicine and Pharmacology, University of Texas Medical Branch at Galveston, 301 University Boulevard, 9.106, Medical Research Building, Galveston, Texas 77555-1065.

631

B. Therapeutic potentials of CGRP antagonists

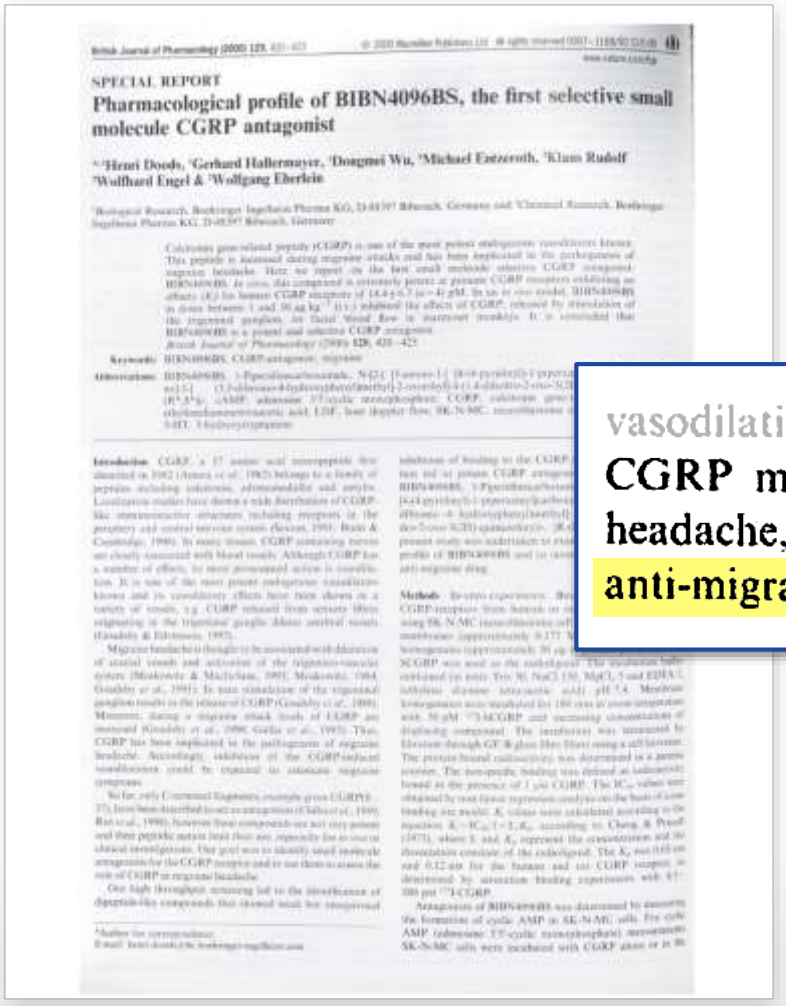
Evidence is accumulating that inappropriate release of CGRP is a potential causative factor in several diseases, including migraine, inflammation, and cardiogenic shock associated with sepsis. These postulations were derived after

Ex. 1096, 567; 1008, ¶74; Pet., 19

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 570; 1008, ¶74; Pet., 19; Reply, 2.

Doods (Ex. 1024): Motivation to Make an Anti-CGRP Antagonist Antibody



SPECIAL REPORT

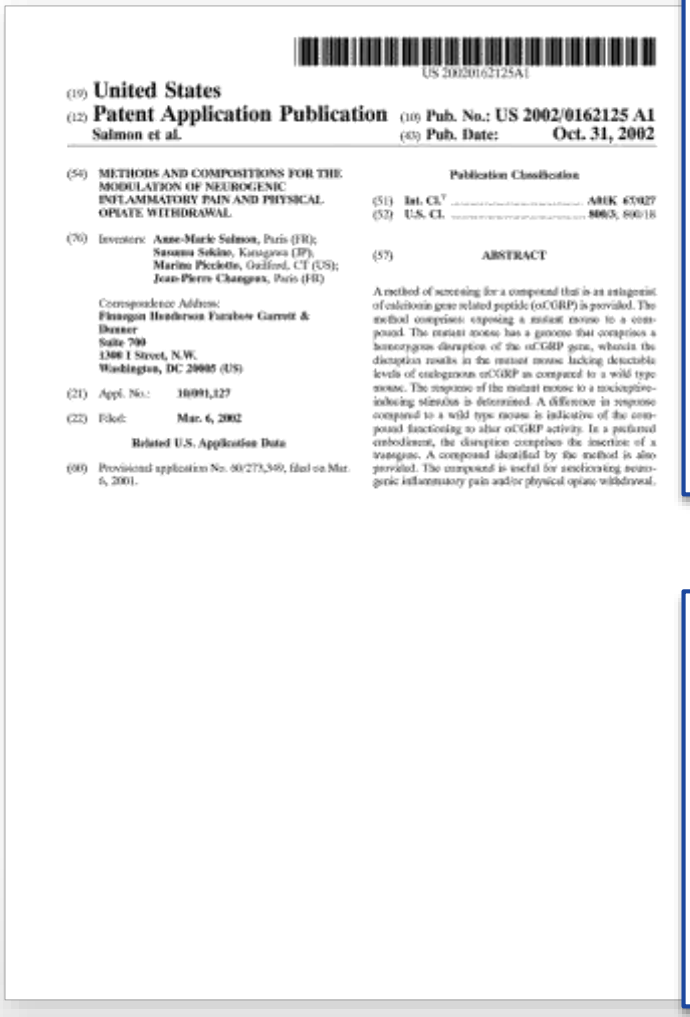
Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist

Henri Doods, Gerhard Hallermayer, Dongmei Wu, Michael Entzeroth, Klaus Rudolf, Wolfhard Engel & Wolfgang Eberlein

vasodilation. Since several lines of evidence indicate that CGRP might be a key factor in the initiation of migraine headache, we expect that CGRP antagonists will be effective anti-migraine drugs. Much remains to be investigated to

Ex. 1024, 422; Ex. 1008, ¶113; Pet., 26

Salmon (Ex. 1027) Disclosed Anti-CGRP Antagonist Antibodies for Therapeutic Use



US 20020162125A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0162125 A1**

Salmon et al. (43) **Pub. Date: Oct. 31, 2002**

(54) METHODS AND COMPOSITIONS FOR THE MODULATION OF NEUROGENIC INFLAMMATORY PAIN AND PHYSICAL OPIATE WITHDRAWAL

Publication Classification

(51) Int. Cl.[7] A01K 67/027

(52) U.S. Cl. 800/3, 800/18

(76) Inventors: **Anne-Marie Salmon**, Paris (FR); **Susumu Sekine**, Kanagawa (JP); **Marino Piccioto**, Guilford, CT (US); **Jean-Pierre Changeux**, Paris (FR)

Correspondence Address:
Finnegan Henderson Farabow Garrett & Dunner
Suite 700
1300 I Street, N.W.
Washington, DC 20005 (US)

(21) Appl. No.: **10/091,127**

(22) Filed: **Mar. 6, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/273,349, filed on Mar. 6, 2001.

(57) ABSTRACT

A method of screening for a compound that is an antagonist of calcitonin gene related peptide (αCGRP) is provided. The method comprises: exposing a mutant mouse to a compound. The mutant mouse has a genome that comprises a homozygous disruption of the αCGRP gene, wherein the disruption results in the mutant mouse lacking detectable levels of endogenous αCGRP as compared to a wild type mouse. The response of the mutant mouse to a nociceptive-inducing stimulus is determined. A difference in response compared to a wild type mouse is indicative of the compound functioning to alter αCGRP activity. In a preferred embodiment, the disruption comprises the insertion of a transgene. A compound identified by the method is also provided. The compound is useful for ameliorating neurogenic inflammatory pain and/or physical opiate withdrawal.

[0039] Described herein are compounds, including pharmaceutical compositions, which can be utilized for the amelioration of neurogenic inflammatory pain and/or physical opiate withdrawal. More specifically, said compounds are antagonists of calcitonin gene related peptide (αCGRP). Such compounds can include, but are not limited to, small peptides, small organic molecules, antisense, and triple helix molecules. Compositions can include polyclonal and/or monoclonal antibodies for the modulation of such pain and/or withdrawal symptoms.

Ex. 1027, ¶[0039]; Ex. 1008, ¶110; Pet., 25

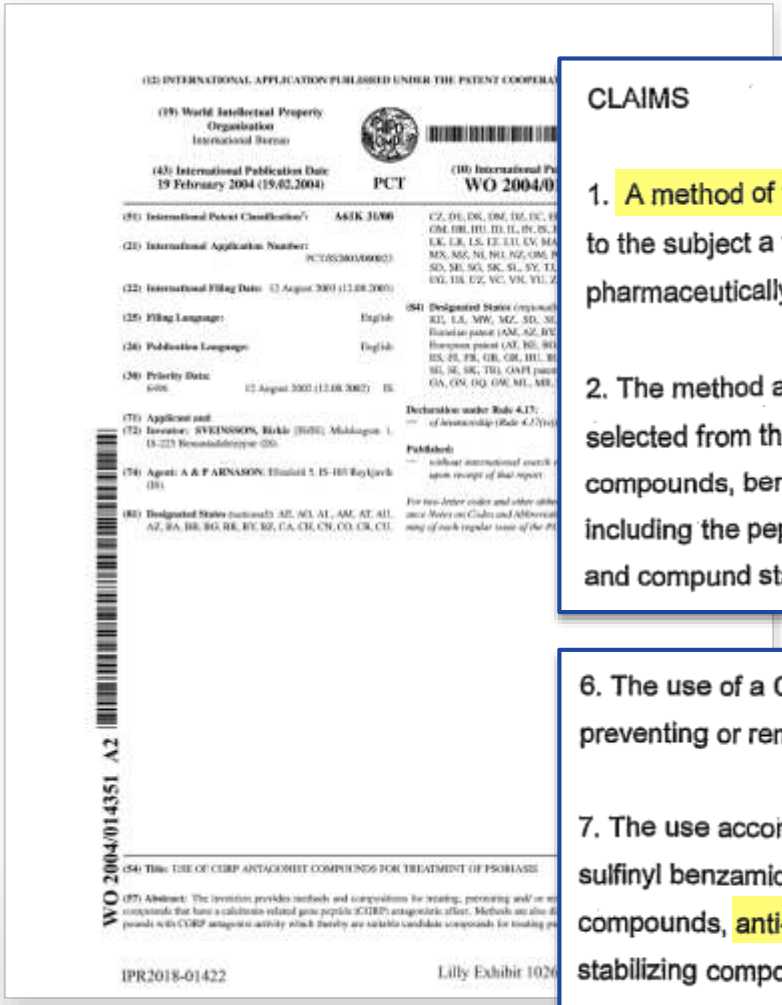
6. A compound, which is an antagonist of αCGRP, identified by the method of any one of claims 1 to 5.

7. The compound of claim 6, which is a peptide, small organic molecule, antisense molecule, or a triple helix molecule.

8. The compound of claim 6, which is a monoclonal antibody.

Ex. 1027, claim 8; Ex. 1008, ¶110; Pet., 25; Reply, 12

Sveinsson (Ex. 1026) Disclosed Anti-CGRP Antagonist Antibodies for Therapeutic Use


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERA

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date: 19 February 2004 (19.02.2004)

PCT

(10) International Pu WO 2004/0

(51) International Patent Classification⁷: A61K 31/00

(21) International Application Number:

(22) International Filing Date:

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

(71) Applicant and (72) Inventor: SVEINSSON, Ríkh

(74) Agent: A & P ARNASON;

(81) Designated States

(84) Designated States

Declaration under Rule 4.17:

Published:

(54) Title: USE OF CGRP ANTAGONIST COMPOUNDS FOR TREATMENT OF PSORIASIS

(57) Abstract:

WO 2004/014351 A2

IPR2018-01422

Lilly Exhibit 1026

CLAIMS

1. A method of treating, remedying or preventing psoriasis in a subject comprising administering to the subject a therapeutically effective dose of at least one CGRP antagonist compound in a pharmaceutically acceptable formulation.

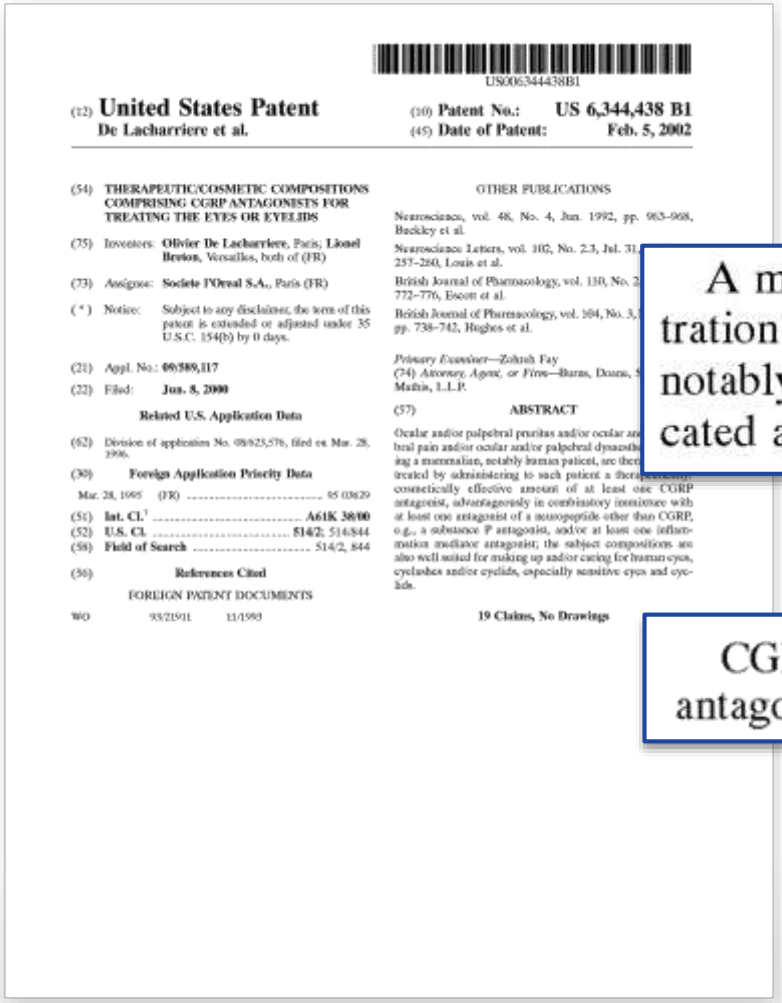
2. The method according to claim 1, wherein the at least one CGRP antagonist compound is selected from the group consisting of 4-sulfinyl benzamide compounds, 3,4-dinitrobenzamide compounds, benzamidazolinyl piperadine compounds, anti-CGRP antibodies, CGRP derivatives including the peptide CGRP 8-37, tryptase active polypeptide, and the compound BIBN4096BS, and compund stabilising tryptase, including heparin.

6. The use of a CGRP antagonist compound for the manufacture of a medicament for treating, preventing or remedying psoriasis in a subject.

7. The use according to claim 6, wherein the compound is selected from the group comprising 4-sulfinyl benzamide compounds, 3,4-dinitrobenzamide compounds, benzamidazolinyl piperadine compounds, anti-CGRP antibodies, CGRP derivatives including CGRP 8-37, tryptase, tryptase stabilizing componuds including heparin, and the compound BIBN4096BS.

Ex. 1026, claims 2 and 7; Ex. 1008, ¶109; Pet., 24-25; Reply, 12

The ’438 Patent (Ex. 1028) Disclosed Anti-CGRP Antagonist Antibodies for Therapeutic Use



US006344438B1

(12) **United States Patent**
De Lacharriere et al.

(10) **Patent No.: US 6,344,438 B1**
(45) **Date of Patent: Feb. 5, 2002**

(54) **THERAPEUTIC/COSMETIC COMPOSITIONS COMPRISING CGRP ANTAGONISTS FOR TREATING THE EYES OR EYELIDS**

(75) Inventors: **Olivier De Lacharriere**, Paris; **Lionel Breton**, Versailles, both of (FR)

(73) Assignee: **Societe l'Oreal S.A.**, Paris (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/589,117**

(22) Filed: **Jun. 8, 2000**

Related U.S. Application Data

(62) Division of application No. 08/625,576, filed on Mar. 28, 1996.

(30) **Foreign Application Priority Data**

Mar. 28, 1995 (FR) 95 03829

(51) **Int. Cl.**[7] **A61K 38/00**
(52) **U.S. Cl.** **514/2**; 514/844
(58) **Field of Search** 514/2, 844

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO 93/21931 11/1993

OTHER PUBLICATIONS

Neuroscience, vol. 48, No. 4, Jun. 1992, pp. 963–968, Buckley et al.

Neuroscience Letters, vol. 102, No. 2,3, Jul. 31, 257–260, Louis et al.

British Journal of Pharmacology, vol. 110, No. 2, 772–776, Escott et al.

British Journal of Pharmacology, vol. 104, No. 3, pp. 738–742, Hughes et al.

Primary Examiner—Zohreh Fay
(74) *Attorney, Agent, or Firm*—Burns, Doane, Swecker & Mathis, L.L.P.

(57) **ABSTRACT**

Ocular and/or palpebral pruritus and/or ocular and palpebral pain and/or ocular and/or palpebral dysaesthesia in a mammalian, notably human patient, are thereby treated by administering to such patient a therapeutically cosmetically effective amount of at least one CGRP antagonist, advantageously in combinatory intimate with at least one antagonist of a neuropeptide other than CGRP, e.g., a substance P antagonist, and/or at least one inflammation mediator antagonist; the subject compositions are also well suited for making up and/or caring for human eyes, eyelashes and/or eyelids, especially sensitive eyes and eyelids.

19 Claims, No Drawings

> A major object of the present invention is the administration of one or more CGRP antagonists to a mammalian, notably human patient, for treating the disease states indicated above.

Ex. 1028, 2:7-10; Pet., 25

> CGRP 8-37 and anti-CGRP antibodies are suitable CGRP antagonists according to the invention.

Ex. 1028, 3:21-22; Ex. 1008, ¶111; Pet., 25

Motivation to Make a Humanized Antibody

Dr. Ferrari's cross-examination:

Q: Hypothetically speaking, as an expert in the field, if a reference stated that an anti-CGRP antagonist antibody was to be administered to a human to treat a chronic human disease, would that have been understood as a reference to a humanized antibody?

A: I think that, and, again, I'm not an antibody expert, but by 2005 it was well-known that you would significantly reduce the risk of immunological side effects to an antibody by humanizing it. So developing an antibody at that time without including humanization would not mean – would not be useful to use in patients.

Ex. 1303, 49:1-20; Reply, 3

Dr. Tomlinson's cross-examination:

Q: As of 2005, by the time that an antibody in drug development reached a Phase 1 clinical study for dosing in humans, it would likely be a human or humanized antibody, correct?

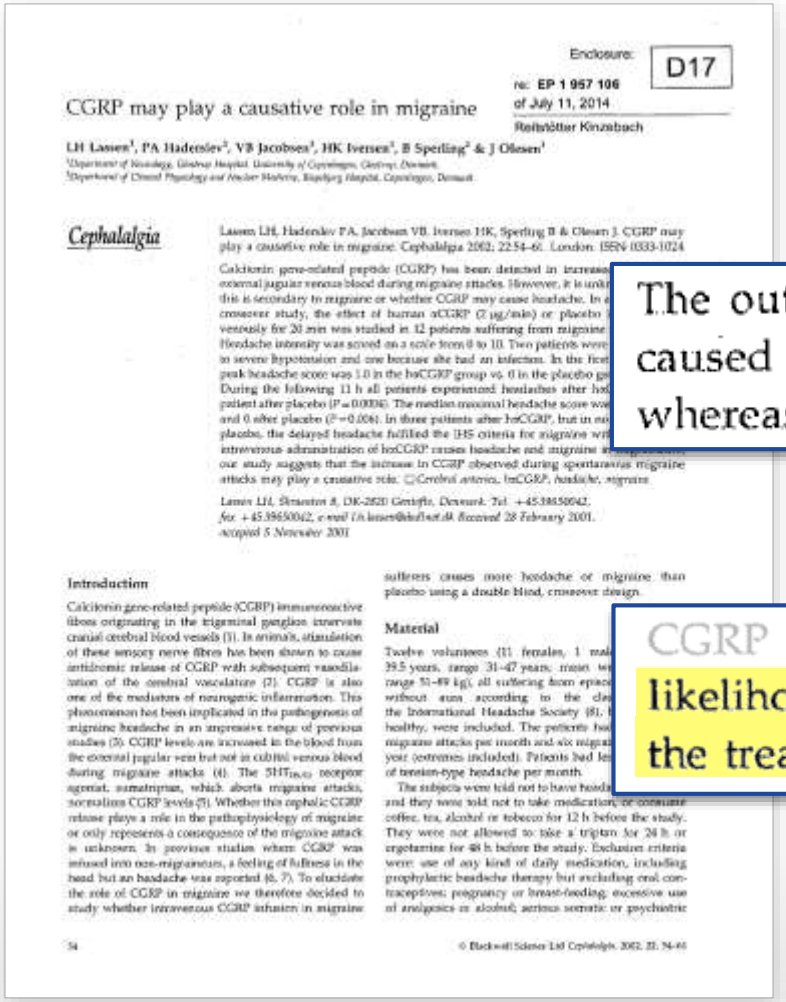
A: In 2005, yes.

Q: And then as of 2005 in a clinical trial program, it would not have been acceptable for a person of ordinary skill to have administered a murine antibody to a human for chronic use without first humanizing it, correct?

A: I would say that was quite very unlikely.

Ex. 1301, 211:2-15; Reply, 3

Lassen 2002 (Ex. 1047): Motivation to Make an Anti-CGRP Antagonist Antibody



Enclosure: D17
re: EP 1 957 106
of July 11, 2014
Reihnötter Knoebach

CGRP may play a causative role in migraine

LH Lassen[1], PA Haderslev[2], VB Jacobsen[1], HK Iversen[1], B Sperling[2] & J Olesen[1]
[1]Department of Neurology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark.
[2]Department of Clinical Physiology and Nuclear Medicine, Bispebjerg Hospital, Copenhagen, Denmark.

Cephalalgia

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B & Olesen J. CGRP may play a causative role in migraine. Cephalalgia 2002; 22:54–61. London. ISSN 0333-1024

Calcitonin gene-related peptide (CGRP) has been detected in increased external jugular venous blood during migraine attacks. However, it is unkn this is secondary to migraine or whether CGRP may cause headache. In a crossover study, the effect of human αCGRP (2 μg/min) or placebo venously for 20 min was studied in 12 patients suffering from migraine Headache intensity was scored on a scale from 0 to 10. Two patients were to severe hypotension and one because she had an infection. In the first peak headache score was 1.0 in the hαCGRP group vs. 0 in the placebo gr During the following 11 h all patients experienced headaches after hα patient after placebo ($P = 0.0036$). The median maximal headache score wa and 0 after placebo ($P = 0.006$). In three patients after hαCGRP, but in no placebo, the delayed headache fulfilled the IHS criteria for migraine wi intravenous administration of hαCGRP causes headache and migraine in our study suggests that the increase in CGRP observed during spontaneous migraine attacks may play a causative role. ©Cerebral arteries, hαCGRP, headache, migraine.

Lassen LH, Strandvej 8, DK-2820 Gentofte, Denmark. Tel: +45.38650042, fax: +45.39650042, e-mail: l.h.lassen@dadlnet.dk Received 28 February 2001, accepted 5 November 2001

Introduction

Calcitonin gene-related peptide (CGRP) immunoreactive fibres originating in the trigeminal ganglion innervate cranial cerebral blood vessels (1). In animals, stimulation of these sensory nerve fibres has been shown to cause antidromic release of CGRP with subsequent vasodilatation of the cerebral vasculature (2). CGRP is also one of the mediators of neurogenic inflammation. This phenomenon has been implicated in the pathogenesis of migraine headache in an impressive range of previous studies (3). CGRP levels are increased in the blood from the external jugular vein but not in cubital venous blood during migraine attacks (4). The $5HT_{1B/D}$ receptor agonist, sumatriptan, which aborts migraine attacks, normalizes CGRP levels (5). Whether this cephalic CGRP release plays a role in the pathophysiology of migraine or only represents a consequence of the migraine attack is unknown. In previous studies where CGRP was infused into non-migraineurs, a feeling of fullness in the head but no headache was reported (6, 7). To elucidate the role of CGRP in migraine we therefore decided to study whether intravenous CGRP infusion in migraine sufferers causes more headache or migraine than placebo using a double blind, crossover design.

Material

Twelve volunteers (11 females, 1 male, 39.5 years, range 31–47 years; mean weight range 51–89 kg), all suffering from episodic without aura according to the classification of the International Headache Society (8), healthy, were included. The patients had migraine attacks per month and six migraine year (extremes included). Patients had less of tension-type headache per month.

The subjects were told not to have headache and they were told not to take medication, or consume coffee, tea, alcohol or tobacco for 12 h before the study. They were not allowed to take a triptan for 24 h or ergotamine for 48 h before the study. Exclusion criteria were: use of any kind of daily medication, including prophylactic headache therapy but excluding oral contraceptives; pregnancy or breast-feeding; excessive use of analgesics or alcohol; serious somatic or psychiatric

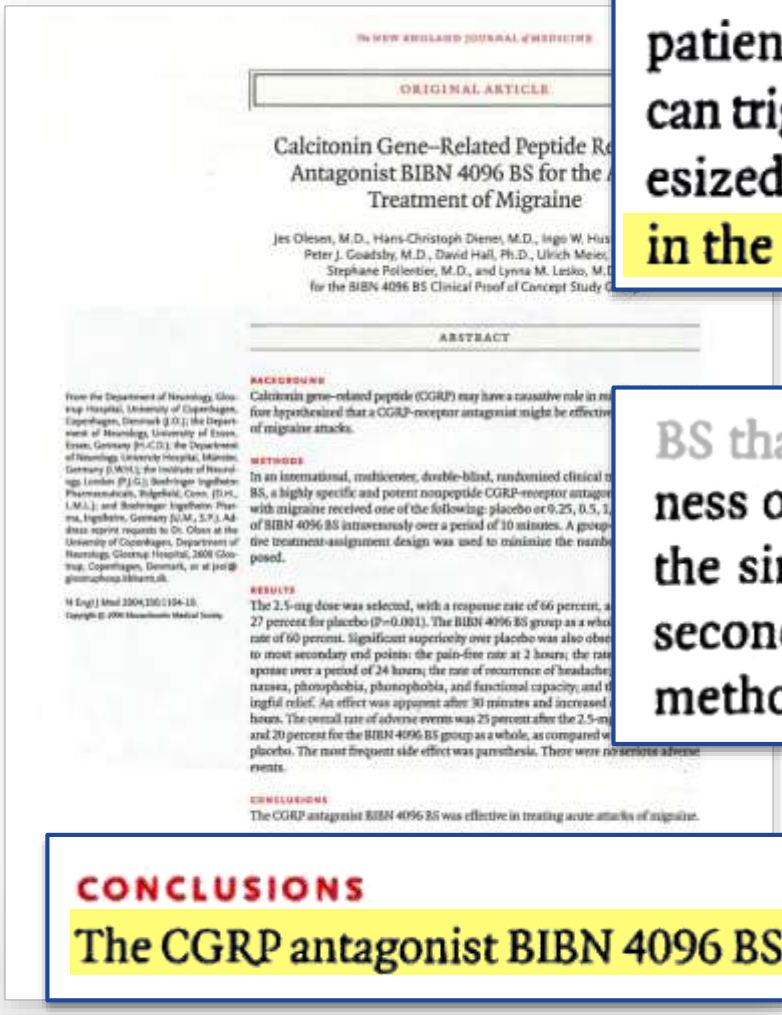
The outcome of the present study is very clear. CGRP caused headache in virtually all migraine sufferers, whereas placebo did not. The headache occurred during

Ex. 1047, 59; Ex. 1008, ¶113; Pet., 26

CGRP in migraine. This finding greatly increases the likelihood that a CGRP antagonist may be effective in the treatment of migraine attacks. Several drugs that in

Ex. 1047, 60; Ex. 1008, ¶113; Pet., 26

Olesen (Ex. 1025): Motivation to Make an Anti-CGRP Antagonist Antibody



ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Re
Antagonist BIBN 4096 BS for the
Treatment of Migraine

ABSTRACT

vasodilation.[7] Cranial CGRP levels are elevated in patients with migraine,[8] and an infusion of CGRP can trigger a migraine attack.[9] We therefore hypothesized that CGRP antagonists might be effective in the treatment of acute migraine.

Ex. 1025, 1105; Pet., 10-11

BS than after the infusion of placebo. The robustness of this primary conclusion was confirmed by the similarly positive results we found for all the secondary end points with the use of descriptive methods. Proof of concept was thus established.

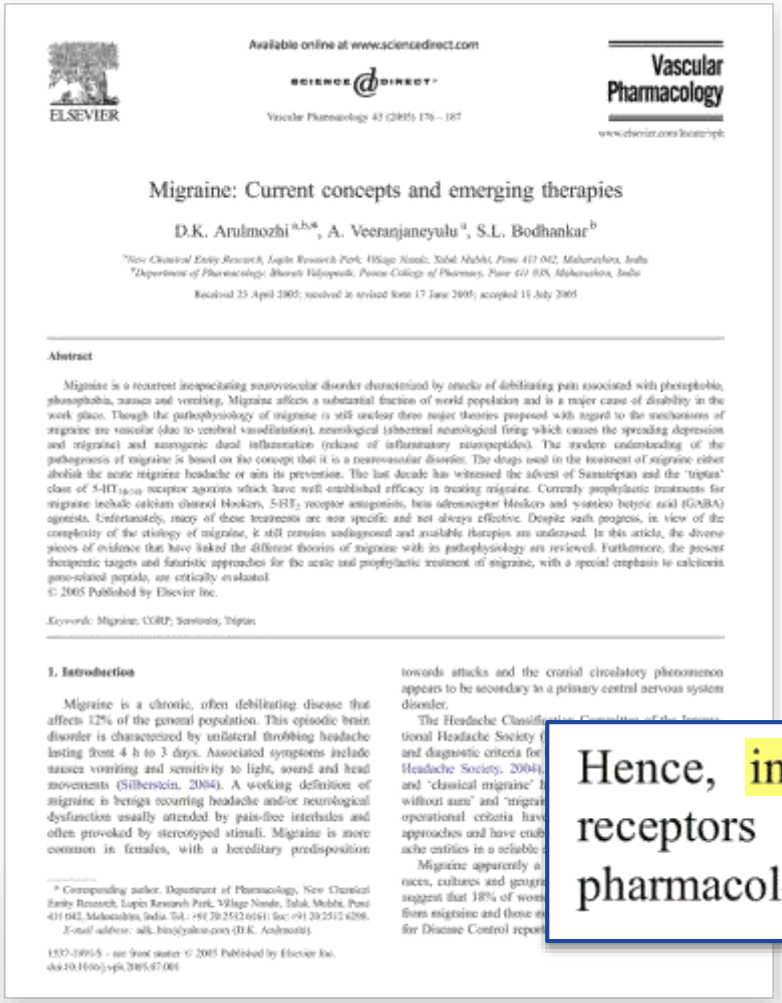
Ex. 1025, 1108-1109; Ex. 1008, ¶¶41-44, 113; Pet., 10-11, 24, 26

CONCLUSIONS

The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine.

Ex. 1025, 1104; Ex. 1008, ¶¶41-44, 113; Pet., 10-11, 24, 26

Targeting CGRP and Its Receptor Were Alternatives



Available online at www.sciencedirect.com

SCIENCE DIRECT

Vascular Pharmacology

ELSEVIER

Migraine: Current concepts and emerging therapies

D.K. Arulmozhi [a,b,*], A. Veeranjaneyulu [a], S.L. Bodhankar [b]

Abstract

1. Introduction

Dr. Rapoport's statements in 2018:

1.2 Why Block CGRP or Its Receptor?

Based on all this information, it was considered that blocking CGRP or its receptor might treat an acute migraine attack or prevent migraine from occurring. The first studies were performed on short-acting, small molecule, CGRP receptor antagonists. All the acute care

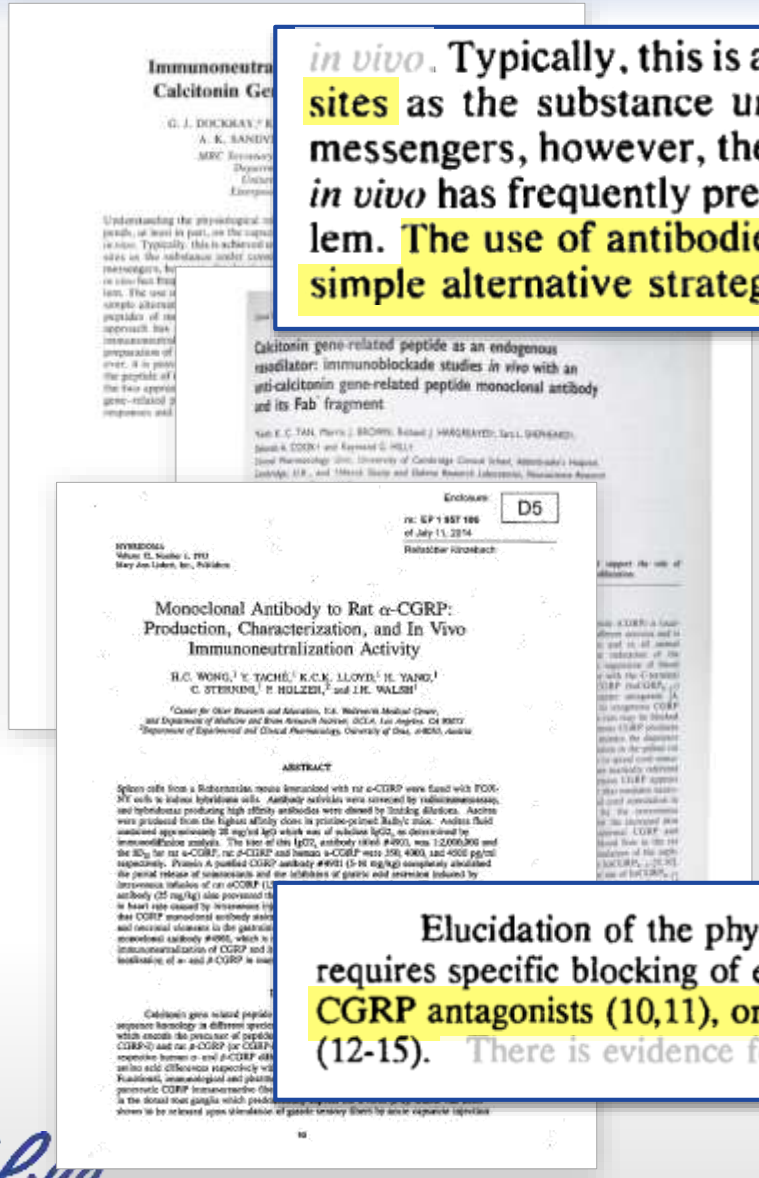
Ex. 2169, 915; Ex. 1306, ¶86; Opp. Mot. Excl., 12

Arulmozhi 2005:

Hence, inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine (Edvinsson, 2004).

Ex. 1040, 182; Ex. 1008, ¶116; Pet., 27; Reply, 9

Targeting CGRP and Its Receptor Were Alternatives



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab fragment

Enclosure D5

Monoclonal Antibody to Rat α-CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity

> *in vivo*. Typically, this is achieved using antagonists that occupy the same receptor sites as the substance under consideration. In the case of peptide and protein messengers, however, the development of antagonists of suitable affinity for work *in vivo* has frequently presented a formidable, although not insurmountable, problem. The use of antibodies to neutralize endogenous regulatory peptides offers a simple alternative strategy. It is generally straightforward to raise antibodies to

Ex. 1049, Abstract; Reply, 20

> The aim of the present study was to investigate immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator *in vivo*.

> Immunoblockade should be regarded as a technique that is complementary to the use of receptor antagonists. A comparison of the two approaches

Ex. 1022, 566, 571; Ex. 1008, ¶114; Ex. 1305, ¶37; Reply, 9

> Elucidation of the physiological relevance of the pharmacological actions of CGRP requires specific blocking of endogenous CGRP either at the receptor level using specific CGRP antagonists (10,11), or by neutralizing endogenous peptide with a specific antibody (12-15). There is evidence for the existence of various CGRP receptor subtypes (10, 16) for

Ex. 1033, 95; Ex. 1305, ¶37; Reply, 9

Teva's Patents Do Not Address Safety

Alcon Research Ltd. v. Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012)

"Although Alcon argues that Kamei would not give a skilled artisan an expectation of success because it does not teach that olopatadine is safe for the human eye, we find this contention to be without merit. While it is true that [the prior art] does not expressly disclose that olopatadine would be safe for use in human eyes, neither does the '805 patent. The patent is not based on testing in humans; instead it reports only in vitro tests."

Reply, 4-5

Dr. Ferrari's cross-examination:

Q: [Y]ou would agree that the '614 patent does not disclose any safety studies at all, correct?

A: There is no text mentioning data from safety studies.

Q: Teva's patents do not disclose any studies in humans at all, correct?

A: The patents do not disclose studies in humans.

…

Q: …And you would agree with me Teva's patents do not mention cardiovascular effects resulting from anti-CGRP antagonist antibodies, correct?

A: The same answer, yes.

Ex. 1303, 56:4-57:19; Reply, 4

Teva's Patents Do Not Address Safety

Dr. Foord's cross-examination:

Q: [W]ould a description of a successful use, whether a statistically significant efficacy was shown of an anti-CGRP antibody in a rat saphenous nerve assay, have adequately resolved the concerns you identify in your declaration about safety and efficacy?

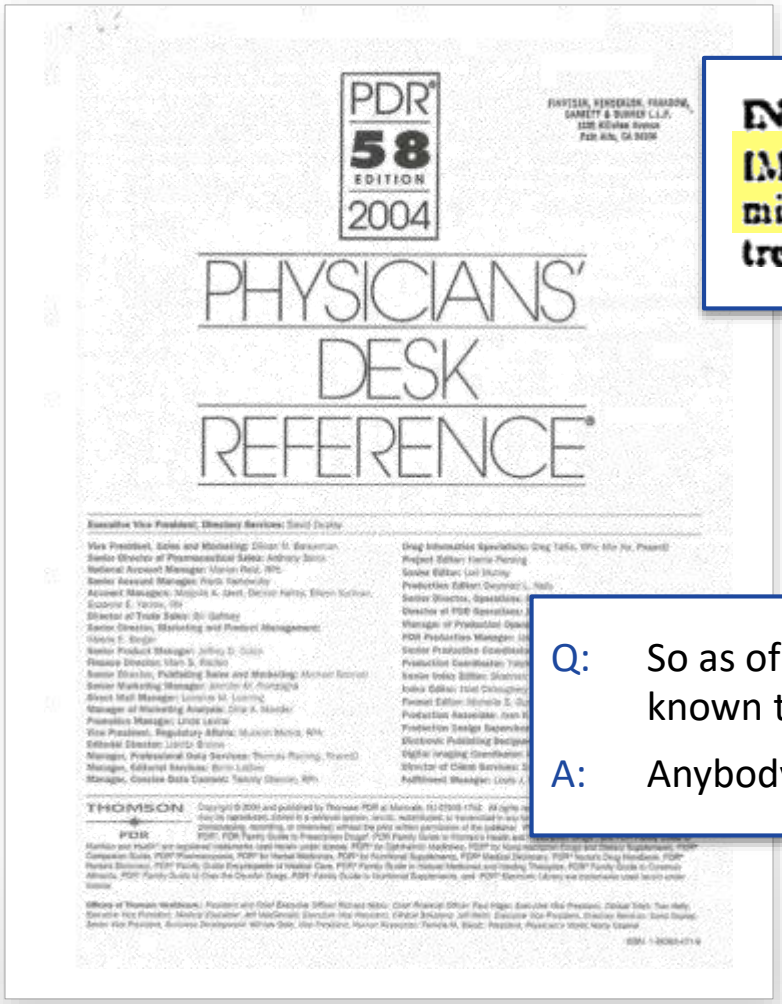
A: No.

Q: Would the description of the successful use of anti-CGRP antibodies in the rat closed cranial window assay have adequately resolved the concerns you identified about safety and efficacy?

A: No. These are preclinical animal experiments that will never satisfy concerns about safety and efficacy, until that agent goes into man.

Ex. 1300, 173:20-174:11; Reply, 4

Sumatriptan, FDA-Approved for Treating Migraine, Was Understood to Inhibit CGRP Release


PDR 58 EDITION 2004

PHYSICIANS' DESK REFERENCE

THOMSON PDR

INDICATIONS AND USAGE

IMITREX Injection is indicated for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.

Ex. 1282, 1520; Ex. 1306, ¶64; Reply, 7

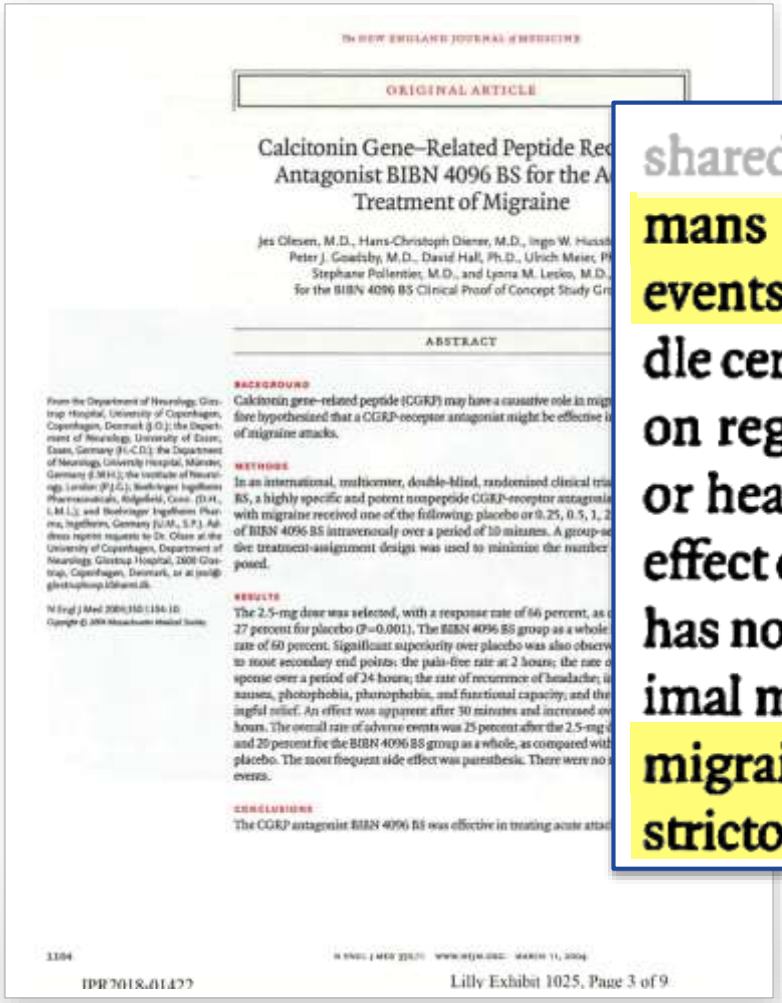
Dr. Rapoport's cross-examination:

Q: So as of 2005, a person of ordinary skill in the art would have known that triptans inhibit the release of CGRP, correct?

A: Anybody reading that article [published in 1999] would have.

Ex. 1304, 90:10-15; Reply, 7;
see also Ex. 2212, ¶21; POR, 45-46

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1025)



ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Rec
Antagonist BIBN 4096 BS for the A
Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husst
Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, P
Stephane Pollentier, M.D., and Lynna M. Lesko, M.D.
for the BIBN 4096 BS Clinical Proof of Concept Study Gr

ABSTRACT

BACKGROUND
Calcitonin gene–related peptide (CGRP) may have a causative role in migr
fore hypothesized that a CGRP-receptor antagonist might be effective i
of migraine attacks.

METHODS
In an international, multicenter, double-blind, randomized clinical tri
BS, a highly specific and potent nonpeptide CGRP-receptor antagonis
with migraine received one of the following: placebo or 0.25, 0.5, 1, 2
of BIBN 4096 BS intravenously over a period of 10 minutes. A group-s
tive treatment-assignment design was used to minimize the number
posed.

RESULTS
The 2.5-mg dose was selected, with a response rate of 66 percent, as c
27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole
rate of 60 percent. Significant superiority over placebo was also observ
to most secondary end points: the pain-free rate at 2 hours; the rate o
spense over a period of 24 hours; the rate of recurrence of headache; i
nausea, photophobia, phonophobia, and functional capacity; and the
ingful relief. An effect was apparent after 30 minutes and increased ov
hours. The overall rate of adverse events was 25 percent after the 2.5-mg
and 20 percent for the BIBN 4096 BS group as a whole, as compared wit
placebo. The most frequent side effect was paresthesia. There were no
events.

CONCLUSIONS
The CGRP antagonist BIBN 4096 BS was effective in treating acute attac

1104

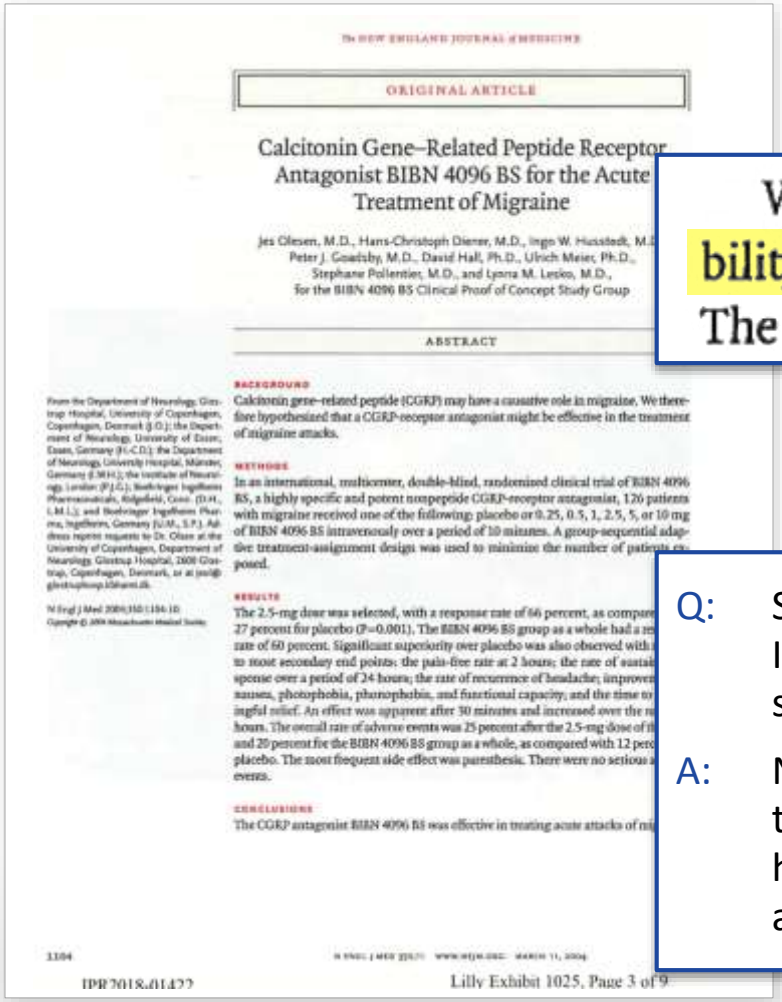
IPR2018-01422

Lilly Exhibit 1025, Page 3 of 9

shared with ergot derivatives and triptans.[31] In humans BIBN 4096 BS caused only minor adverse events[32] and had no constrictor effect on the middle cerebral, radial, or superficial temporal artery or on regional cerebral blood flow, blood pressure, or heart rate.[33,34] It antagonized the extracerebral effect of infused CGRP in humans.[33] BIBN 4096 BS has not shown vasoconstrictor activity in several animal models or in human studies, and it is the first migraine-specific medication that is not a vasoconstrictor.

Ex. 1025, 1108; Reply, 7-8

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1025)



ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynne M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

ABSTRACT

BACKGROUND

Calcitonin gene–related peptide (CGRP) may have a causative role in migraine. We therefore hypothesized that a CGRP-receptor antagonist might be effective in the treatment of migraine attacks.

METHODS

In an international, multicenter, double-blind, randomized clinical trial of BIBN 4096 BS, a highly specific and potent nonpeptide CGRP-receptor antagonist, 126 patients with migraine received one of the following: placebo or 0.25, 0.5, 1, 2.5, 5, or 10 mg of BIBN 4096 BS intravenously over a period of 10 minutes. A group-sequential adaptive treatment-assignment design was used to minimize the number of patients exposed.

RESULTS

The 2.5-mg dose was selected, with a response rate of 66 percent, as compared with 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole had a response rate of 60 percent. Significant superiority over placebo was also observed with respect to most secondary end points: the pain-free rate at 2 hours; the rate of sustained response over a period of 24 hours; the rate of recurrence of headache; improvement in nausea, photophobia, phonophobia, and functional capacity; and the time to meaningful relief. An effect was apparent after 30 minutes and increased over the next few hours. The overall rate of adverse events was 25 percent after the 2.5-mg dose of BIBN 4096 BS and 20 percent for the BIBN 4096 BS group as a whole, as compared with 12 percent for placebo. The most frequent side effect was paresthesia. There were no serious adverse events.

CONCLUSIONS

The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine

IPR2018-01422 Lilly Exhibit 1025, Page 3 of 9

We confirmed the favorable safety and tolerability results reported in a previous phase 1 study.[32] The overall rate of adverse events was low. All events

Ex. 1025, 1109; Ex. 1306, ¶33; Reply, 7

Dr. Charles's testimony:

Q: So isn't that the point that the reader would say, "Well, I don't know if this is safe or not based on the data sample that I have here in this Exhibit 1025"?

A: No. I think the reader would . . . be reassured by the fact that – that there were no demonstrable changes in – in heart rate, blood pressure, and there were no vascular adverse effects reported

Ex. 2272, 93:22-94:6

Tan 1995 Did Not Raise Safety Concerns

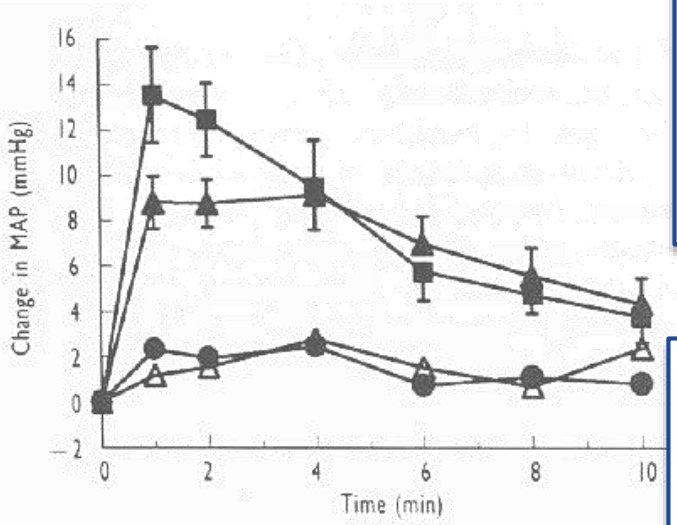


Fig. 2. Effect of 1 mg/rat (●) or 3 mg/rat (■) MAb C4.19 2 mg/rat MAb C4.19 Fab′ fragment (▲) or 2 mg/rat normal mouse Fab′ fragment (△) on baseline MAP. Mean results are plotted with standard error bars ($n = 4$–6). Some error bars have been omitted for clarity.

MAb C4.19 IgG at 1 mg/rat increased baseline MAP slightly but significantly (mean increase 2.4 mmHg; Fig. 2). Increasing the dose of MAb C4.19 IgG to 3 mg/rat raised MAP by 13.5 mmHg (95% CI 7.7 to 19.3; $P = 0.02$). A maximum response was observed at 1 min followed by gradual recovery over 10 to 15 min (Fig. 2). MAb C4.19 Fab′ frag-

Ex. 1022, 568; Ex. 1305, ¶58; Ex. 1306, ¶42; Reply, 10-11

significantly. Like the whole IgG, the MAP increase due to MAb C4.19 Fab′ fragment reached a maximum at 1 min, with recovery within 10 to 15 min (Fig. 2).

Ex. 1022, 568; Ex. 1305, ¶58; Reply, 11

Effect of hαCGRP$_{8-37}$ on blood pressure responses

HαCGRP$_{8-37}$ (100 nmol/kg) increased baseline MAP slightly but significantly (mean increase 3.3 mmHg). A mean decrease in MAP of 35.5 mmHg

Ex. 1022, 569; Ex. 1305, ¶59; Reply, 11

Tan 1995 Did Not Raise Safety Concerns

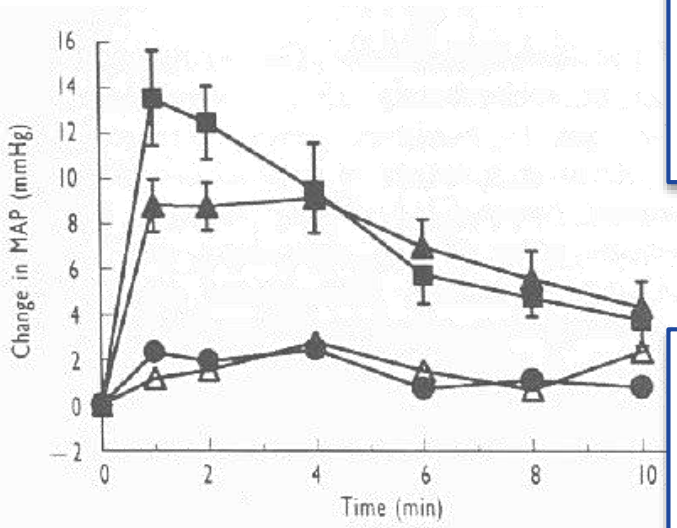


Fig. 2. Effect of 1 mg/rat (●) or 3 mg/rat (■) MAb C4.19 2 mg/rat MAb C4.19 Fab' fragment (▲) or 2 mg/rat normal m Fab' fragment (△) on baseline MAP. Mean results are plotted standard error bars ($n = 4$–6). Some error bars have been omitte clarity.

Dr. Ferrari's cross-examination:

Q: And sumatriptan was observed to cause transient increases in blood pressure in some patients; is that correct?

A: I don't think that increase in blood pressure has ever been a major concern for sumatriptan.

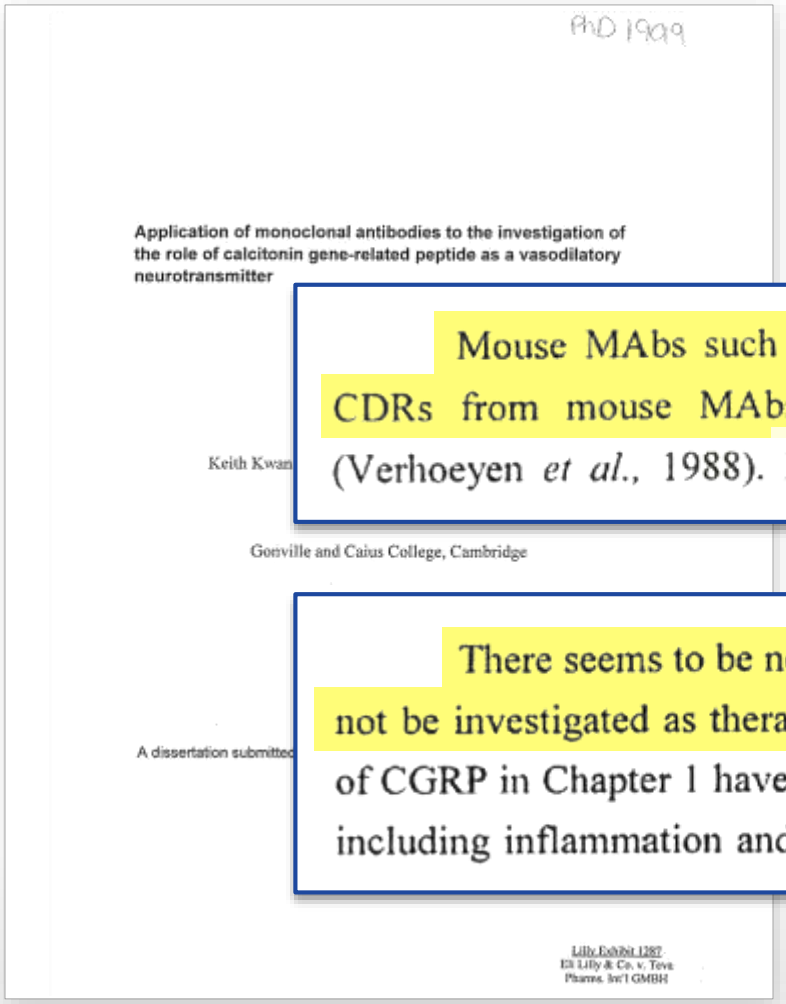
Ex. 1303, 25:11-17; Reply, 11

Dr. Charles's testimony:

44. In my opinion, the transient blood pressure change in anesthetized rats observed in Tan 1995 would not have deterred a POSA from generating a humanized anti-CGRP antagonist antibody. From over a decade of experience with triptans, a POSA would have understood that such transient changes in blood pressure in clinical settings are a manageable event. For example, sumatriptan was known to cause a transient change in blood pressure in some patients. (Ex. 1282, 1521.) Despite this, triptans were considered "very safe" as of November 2005 because clinicians were able to select appropriate migraine patients and treat them with a minimal risk of safety concerns. (*See* Ex. 1308, 1673.) Indeed,

Ex. 1306, ¶44; Reply, 11

Tan Did Not Raise Safety Concerns



PhD 1999

Application of monoclonal antibodies to the investigation of the role of calcitonin gene-related peptide as a vasodilatory neurotransmitter

Keith Kwan

Gonville and Caius College, Cambridge

A dissertation submitted

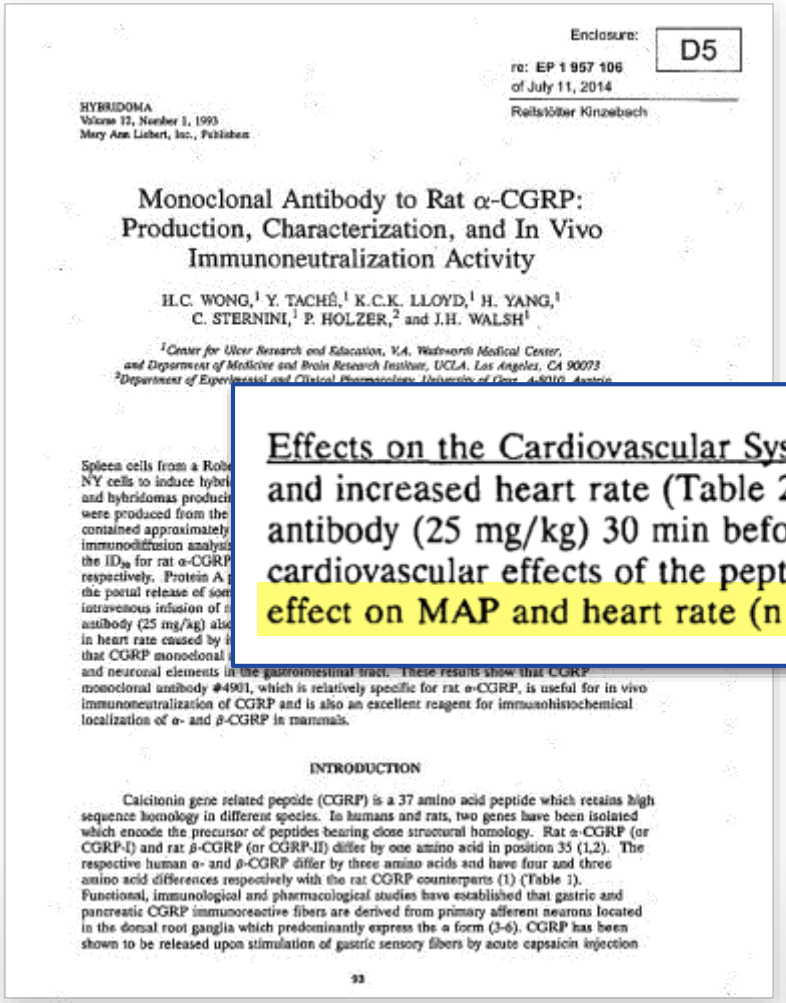
Lilly Exhibit 1287
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH

Mouse MAbs such as MAb C4.19 may be humanized by transplanting the CDRs from mouse MAbs on to human antibody variable region frameworks (Verhoeyen *et al.*, 1988). In such "classical" antibody engineering, hybridomas of

There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents. The review of the pathophysiological roles of CGRP in Chapter 1 have suggested several therapeutic targets for CGRP blockade, including inflammation and migraine. Conversely, CGRP itself may be beneficial in

Ex. 1287, 247; Reply, 3, 11-12

Anti-CGRP Antagonist Antibodies Were Reported to Be Safe



Enclosure: D5
re: EP 1 957 106
of July 11, 2014
Reitstötter Kinzebach

HYBRIDOMA
Volume 12, Number 1, 1993
Mary Ann Liebert, Inc., Publishers

Monoclonal Antibody to Rat α-CGRP: Production, Characterization, and In Vivo Immunoneutralization Activity

H.C. WONG,[1] Y. TACHÉ,[1] K.C.K. LLOYD,[1] H. YANG,[1] C. STERNINI,[1] P. HOLZER,[2] and J.H. WALSH[1]

[1]Center for Ulcer Research and Education, V.A. Wadsworth Medical Center, and Department of Medicine and Brain Research Institute, UCLA, Los Angeles, CA 90073
[2]Department of Experimental and Clinical Pharmacology, University of Graz, A-8010, Austria

Spleen cells from a Rob
NY cells to induce hybri
and hybridomas produci
were produced from the
contained approximately
immunodiffusion analysi
the ID_{50} for rat α-CGRP
respectively. Protein A
the portal release of sor
intravenous infusion of
antibody (25 mg/kg) als
in heart rate caused by
that CGRP monoclonal
and neuronal elements in the gastrointestinal tract. These results show that CGRP monoclonal antibody #4901, which is relatively specific for rat α-CGRP, is useful for in vivo immunoneutralization of CGRP and is also an excellent reagent for immunohistochemical localization of α- and β-CGRP in mammals.

INTRODUCTION

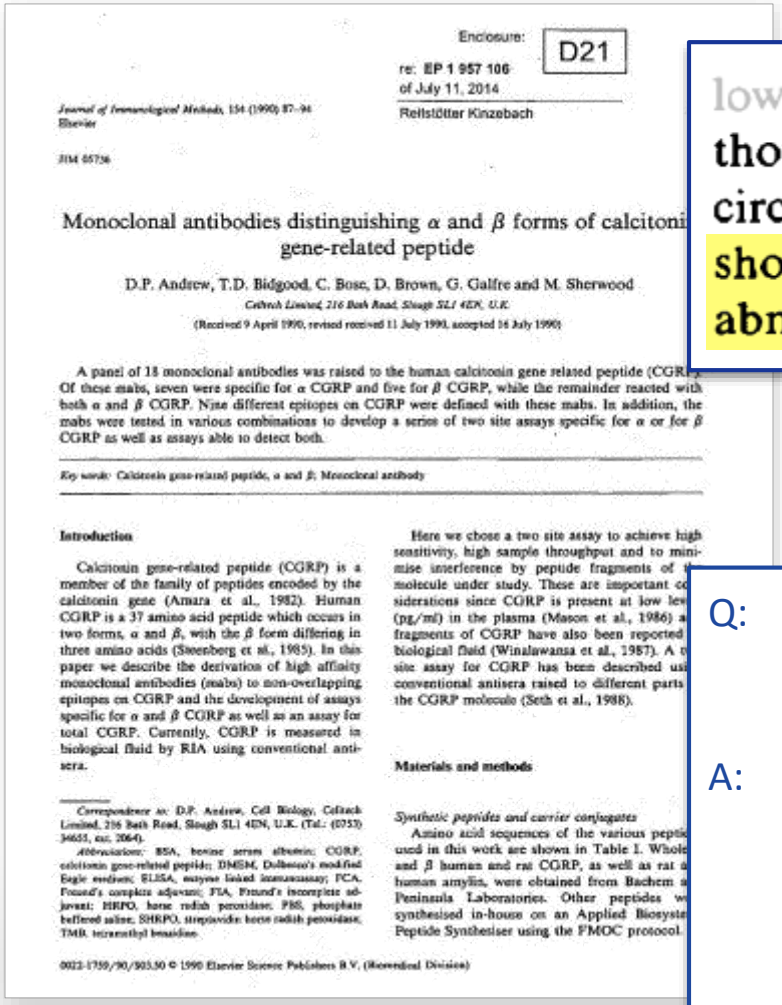
Calcitonin gene related peptide (CGRP) is a 37 amino acid peptide which retains high sequence homology in different species. In humans and rats, two genes have been isolated which encode the precursor of peptides bearing close structural homology. Rat α-CGRP (or CGRP-I) and rat β-CGRP (or CGRP-II) differ by one amino acid in position 35 (1,2). The respective human α- and β-CGRP differ by three amino acids and have four and three amino acid differences respectively with the rat CGRP counterparts (1) (Table 1). Functional, immunological and pharmacological studies have established that gastric and pancreatic CGRP immunoreactive fibers are derived from primary afferent neurons located in the dorsal root ganglia which predominantly express the α form (3-6). CGRP has been shown to be released upon stimulation of gastric sensory fibers by acute capsaicin injection

93

Effects on the Cardiovascular System. Intravenous injection of rat α-CGRP decreased MAP and increased heart rate (Table 2). Intravenous injection of non purified CGRP monoclonal antibody (25 mg/kg) 30 min before that of rat α-CGRP (0.8 μg/kg) completely inhibited the cardiovascular effects of the peptide (Table 2). The monoclonal antibody had no significant effect on MAP and heart rate (n=6).

Ex. 1033, 101; Ex. 1305, ¶62; Ex. 1306, ¶43; Reply, 12

Anti-CGRP Antagonist Antibodies Were Reported to Be Safe



Enclosure: D21
re: EP 1 957 106
of July 11, 2014
Reifstötter Kinzebach

Journal of Immunological Methods, 134 (1990) 87–94
Elsevier

JIM 05736

Monoclonal antibodies distinguishing α and β forms of calcitoni gene-related peptide

D.P. Andrew, T.D. Bidgood, C. Bose, D. Brown, G. Galfre and M. Sherwood

Celltech Limited, 216 Bath Road, Slough SL1 4EN, U.K.

(Received 9 April 1990, revised received 11 July 1990, accepted 16 July 1990)

A panel of 18 monoclonal antibodies was raised to the human calcitonin gene related peptide (CGR Of these mabs, seven were specific for α CGRP and five for β CGRP, while the remainder reacted with both α and β CGRP. Nine different epitopes on CGRP were defined with these mabs. In addition, the mabs were tested in various combinations to develop a series of two site assays specific for α or for β CGRP as well as assays able to detect both.

Key words: Calcitonin gene-related peptide, α and β; Monoclonal antibody

Introduction

Calcitonin gene-related peptide (CGRP) is a member of the family of peptides encoded by the calcitonin gene (Amara et al., 1982). Human CGRP is a 37 amino acid peptide which occurs in two forms, α and β, with the β form differing in three amino acids (Steenberg et al., 1985). In this paper we describe the derivation of high affinity monoclonal antibodies (mabs) to non-overlapping epitopes on CGRP and the development of assays specific for α and β CGRP as well as an assay for total CGRP. Currently, CGRP is measured in biological fluid by RIA using conventional antisera.

Here we chose a two site assay to achieve high sensitivity, high sample throughput and to minimise interference by peptide fragments of t molecule under study. These are important co siderations since CGRP is present at low lev (pg/ml) in the plasma (Mason et al., 1986) a fragments of CGRP have also been reported biological fluid (Winalawansa et al., 1987). A t site assay for CGRP has been described usi conventional antisera raised to different parts the CGRP molecule (Seth et al., 1988).

Materials and methods

Synthetic peptides and carrier conjugates

Amino acid sequences of the various peptid used in this work are shown in Table I. Whole and β human and rat CGRP, as well as rat a human amylin, were obtained from Bachem a Peninsula Laboratories. Other peptides w synthesised in-house on an Applied Biosyste Peptide Synthesiser using the FMOC protocol.

Correspondence to: D.P. Andrew, Cell Biology, Celltech Limited, 216 Bath Road, Slough SL1 4EN, U.K. (Tel.: (0753) 34655, ext. 2064).

Abbreviations: BSA, bovine serum albumin; CGRP, calcitonin gene-related peptide; DMEM, Dulbecco's modified Eagle medium; ELISA, enzyme linked immunoassay; FCA, Freund's complete adjuvant; FIA, Freund's incomplete adjuvant; HRPO, horse radish peroxidase; PBS, phosphate buffered saline; SHRPO, streptavidin horse radish peroxidase; TMB, tetramethyl benzidine.

0022-1759/90/$03.50 © 1990 Elsevier Science Publishers B.V. (Biomedical Division)

low levels of CGRP present in the blood. Although the immunised rats had high levels of circulating antibodies to rat CGRP, they did not show any signs of physical or behavioural abnormality.

Ex. 1055, 93; Ex. 1305, ¶65; Ex. 1306, ¶49; Reply, 12

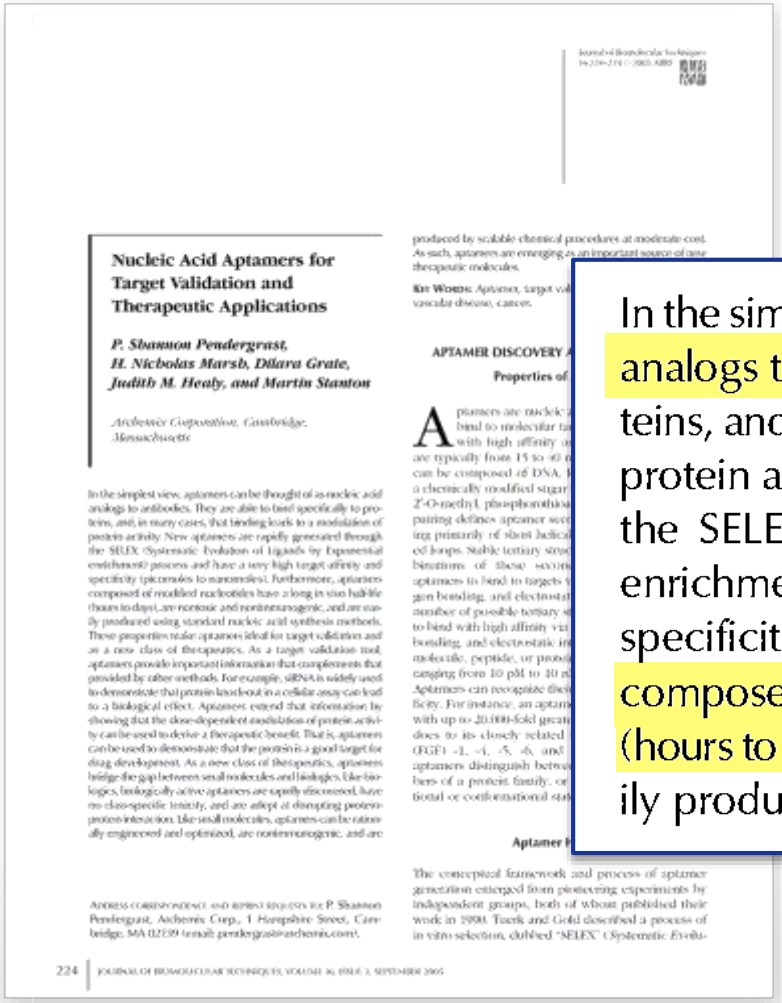
Dr. Balthasar's testimony:

Q: So when Andrews says that there were no signs of physical or behavioral abnormality, what he is referring to is the animal did not die or pass out, right?

A: Yeah, I could only speculate on what they would be looking at and measuring to be able to make that statement, but I think that most institutional animal use committees would require assessment of a wide range of parameters to evaluate safety of treatments.

Ex. 2273, 138:15-139:3

Purported Safety Concerns Did Not Deter Researchers



Nucleic Acid Aptamers for Target Validation and Therapeutic Applications

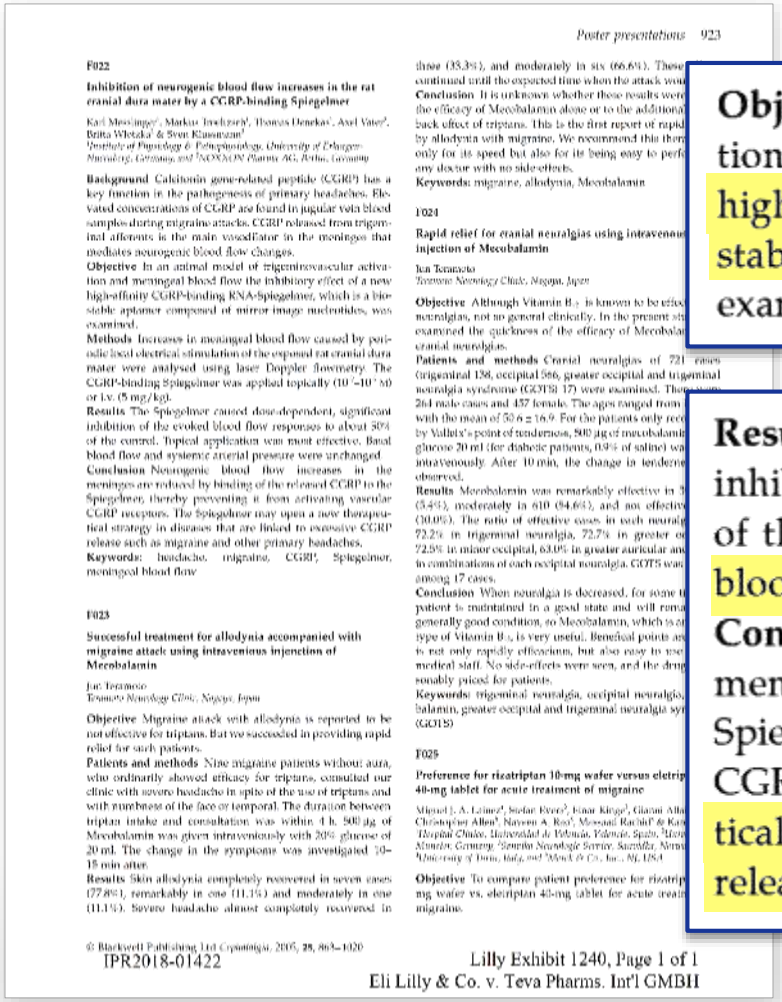
P. Shannon Pendergrast, H. Nicholas Marsh, Dilara Grate, Judith M. Healy, and Martin Stanton

Archemix Corporation, Cambridge, Massachusetts

In the simplest view, aptamers can be thought of as nucleic acid analogs to antibodies. They are able to bind specifically to proteins, and, in many cases, that binding leads to a modulation of protein activity. New aptamers are rapidly generated through the SELEX (Systematic Evolution of Ligands by Exponential enrichment) process and have a very high target affinity and specificity (picomoles to nanomoles). Furthermore, aptamers composed of modified nucleotides have a long in vivo half-life (hours to days), are nontoxic and nonimmunogenic, and are easily produced using standard nucleic acid synthesis methods.

Ex. 1309, Abstract; Ex. 1305, ¶51; Reply, 9

Purported Safety Concerns Did Not Deter Researchers



Poster presentations 923

F022

Inhibition of neurogenic blood flow increases in the rat cranial dura mater by a CGRP-binding Spiegelmer

Karl Messlinger[1], Markus Imdahl[1], Thomas Deneka[2], Axel Vater[2], Britta Wietzke[2] & Sven Klussmann[2]

[1]*Institute of Physiology & Pathophysiology, University of Erlangen-Nuremberg, Germany, and* [2]*NOXXON Pharma AG, Berlin, Germany*

Background Calcitonin gene-related peptide (CGRP) has a key function in the pathogenesis of primary headaches. Elevated concentrations of CGRP are found in jugular vein blood samples during migraine attacks. CGRP released from trigeminal afferents is the main vasodilator in the meninges that mediates neurogenic blood flow changes.

Objective In an animal model of trigeminovascular activation and meningeal blood flow the inhibitory effect of a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer composed of mirror-image nucleotides, was examined.

Methods Increases in meningeal blood flow caused by periodic local electrical stimulation of the exposed rat cranial dura mater were analysed using laser Doppler flowmetry. The CGRP-binding Spiegelmer was applied topically (10^{-7}–10^{-5} M) or i.v. (5 mg/kg).

Results The Spiegelmer caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective. Basal blood flow and systemic arterial pressure were unchanged.

Conclusion Neurogenic blood flow increases in the meninges are reduced by binding of the released CGRP to the Spiegelmer, thereby preventing it from activating vascular CGRP receptors. The Spiegelmer may open a new therapeutical strategy in diseases that are linked to excessive CGRP release such as migraine and other primary headaches.

Keywords: headache, migraine, CGRP, Spiegelmer, meningeal blood flow

F023

Successful treatment for allodynia accompanied with migraine attack using intravenious injection of Mecobalamin

Jun Teramoto

Teramoto Neurology Clinic, Nagoya, Japan

Objective Migraine attack with allodynia is reported to be not effective for triptans. But we succeeded in providing rapid relief for such patients.

Patients and methods Nine migraine patients without aura, who ordinarily showed efficacy for triptans, consulted our clinic with severe headache in spite of the use of triptans and with numbness of the face or temporal. The duration between triptan intake and consultation was within 4 h. 500 μg of Mecobalamin was given intravenously with 20% glucose of 20 ml. The change in the symptoms was investigated 10–15 min after.

Results Skin allodynia completely recovered in seven cases (77.8%), remarkably in one (11.1%) and moderately in one (11.1%). Severe headache almost completely recovered in three (33.3%), and moderately in six (66.6%). These

continued until the expected time when the attack wou

Conclusion It is unknown whether these results were the efficacy of Mecobalamin alone or to the additional back effect of triptans. This is the first report of rapid by allodynia with migraine. We recommend this ther only for its speed but also for its being easy to perf any doctor with no side-effects.

Keywords: migraine, allodynia, Mecobalamin

1024

Rapid relief for cranial neuralgias using intravenous injection of Mecobalamin

Jun Teramoto

Teramoto Neurology Clinic, Nagoya, Japan

Objective Although Vitamin B_{12} is known to be effec neuralgias, not so general clinically. In the present st examined the quickness of the efficacy of Mecobala cranial neuralgias.

Patients and methods Cranial neuralgias of 721 (trigeminal 136, occipital 566, greater occipital and trigeminal neuralgia syndrome (GOTS) 17) were examined. There 264 male cases and 457 female. The ages ranged from with the mean of 50.6 ± 16.9. For the patients only rec by Valleix's point of tenderness, 500 μg of mecobalami glucose 20 ml (for diabetic patients, 0.9% of saline) wa intravenously. After 10 min, the change in tenderne observed.

Results Mecobalamin was remarkably effective in 3 (5.4%), moderately in 610 (84.6%), and not effectiv (10.0%). The ratio of effective cases in each neuralg 72.2% in trigeminal neuralgia, 72.7% in greater o 72.5% in minor occipital, 63.0% in greater auricular an in combinations of each occipital neuralgia. GOTS was among 17 cases.

Conclusion When neuralgia is decreased, for some t patient is maintained in a good state and will retur generally good condition, so Mecobalamin, which is of type of Vitamin B_{12} is very useful. Beneficial points as is not only rapidly efficacious, but also easy to use medical staff. No side-effects were seen, and the drug reasonably priced for patients.

Keywords: trigeminal neuralgia, occipital neuralgia, balamin, greater occipital and trigeminal neuralgia syn (GOTS)

F025

Preference for rizatriptan 10-mg wafer versus eletrip 40-mg tablet for acute treatment of migraine

Miguel J. A. Láinez[1], Stefan Evers[2], Ivan Kirige[3], Gianni Allai Christopher Allen[5], Nayeen A. Rao[5], Mossaad Rachid[5] & Kat *Hospital Clínico, Universidad de Valencia, Valencia, Spain,* [2]*Mein Münster, Germany,* [3]*Semeln Neurologic Service, Sassuolo, Italy,* [4]*University of Turin, Italy, and* [5]*Merck & Co., Inc., NJ, USA*

Objective To compare patient preference for rizatrip mg wafer vs. eletriptan 40-mg tablet for acute treat migraine.

© Blackwell Publishing Ltd Cephalalgia, 2005, **25**, 863–1020

IPR2018-01422

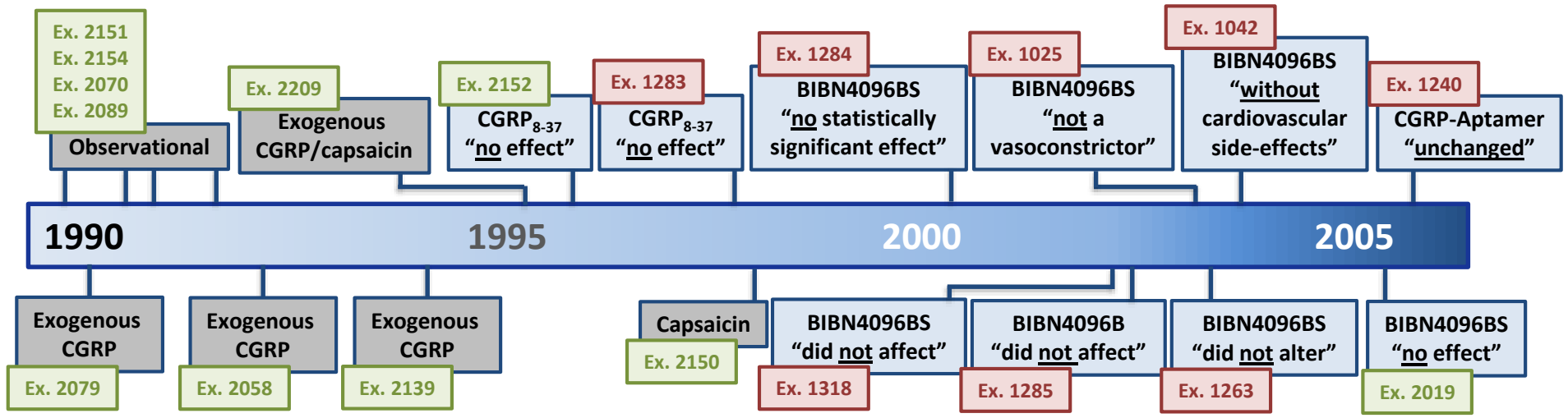
Lilly Exhibit 1240, Page 1 of 1
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH

Objective In an animal model of trigeminovascular activation and meningeal blood flow the inhibitory effect of a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer composed of mirror-image nucleotides, was examined.

Results The Spiegelmer caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective. Basal blood flow and systemic arterial pressure were unchanged. **Conclusion** Neurogenic blood flow increases in the meninges are reduced by binding of the released CGRP to the Spiegelmer, thereby preventing it from activating vascular CGRP receptors. The Spiegelmer may open a new therapeutical strategy in diseases that are linked to excessive CGRP release such as migraine and other primary headaches.

Ex. 1240, 923; Ex. 1305, ¶54; Ex. 1306, ¶¶17, 31; Reply, 9

Teva's Purported Safety Concerns Were Resolved by November 2005



Lilly Exhibit

Teva Exhibit

Ex. 1306, ¶¶20-38; Reply, 7-9, 13-14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Exs. 1025, 1042, 2019)

Dr. Charles's testimony:

Q: … You would agree that the clinical safety of targeting CGRP for therapeutic use had not been established as of 2005, correct?

A: I do not agree with that, no.

Q: And what part do you disagree with?

A: There were multiple studies in humans that indicate that, in fact, it was safe to therapeutically target CGRP, and animals also.

Ex. 2272, 40:11-20

Ex. 1306, ¶¶33-36, 38; Reply, 7-8

Researchers, Including Teva's Experts, Praised "CGRP Antagonists" Before November 2005

Review

Migraine: new treatment options from molecular biology

Anine H Stam, Joost Haan, Rune R Frants, Michel D Ferrari and Arn MJM van den Maagdenberg

Migraine is a common, disabling, multifactorial, episodic neurovascular disorder of largely unknown etiology. The disease is typically characterized by recurrent attacks of headaches and associated autonomic and neurologic symptoms. Current acute and prophylactic treatment options are far from optimal and in many cases, empirically chosen. Clearly, improved treatment is desperately needed. New drug targets may emerge from molecular research as the unravelling of the molecular basis of migraine should improve our understanding of the disease, notably why patients experience attacks so frequently. The first two migraine genes discovered in families with hemiplegic migraine encode ion transporters, emphasising that dysfunction of ion transport may be an important factor in migraine. Therefore, ion transporters can be considered as novel targets for the development of future antimigraine drugs. Molecular biologic research will increasingly become important in understanding the pathophysiology of migraine and in identifying potential molecular targets for novel treatments.

Lilly Exhibit 1290
Eli Lilly & Co. v. Teva

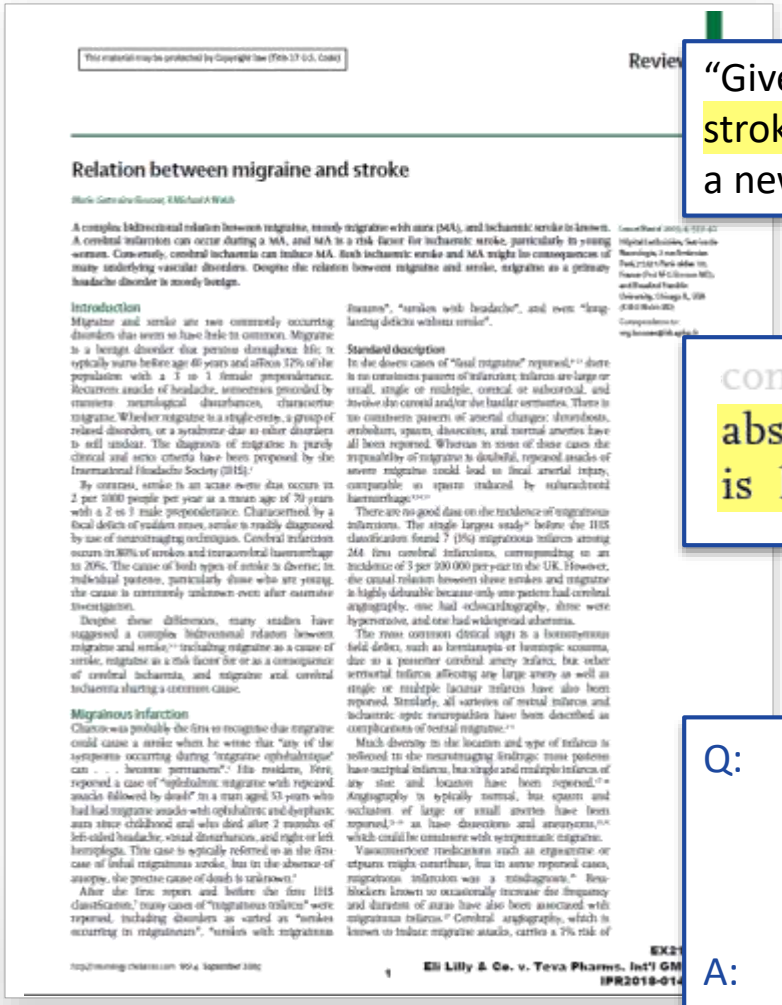
Dr. Ferrari's statements in 2005:

Calcitonin gene-related peptide antagonists

In patients with migraine, CGRP levels are elevated. CGRP infusion can trigger a migraine attack and triptans block the release of CGRP [22–24]. Therefore, CGRP antagonists may be effective in the treatment of acute migraine. Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment [56]. In a double-blind, randomized, controlled trial, patients received different doses of BIBN4096BS intravenously over 10 min. The primary end point was a response reduction of severe or moderate headache at baseline to mild or no headache at 2 h. The 2.5 mg group had a response rate, that was significantly superior to placebo. There were no serious adverse events and the most frequent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Absolute Risk of Stroke in Migraine Patients Was Very Low



Relation between migraine and stroke

Marie-Germaine Bousser, Michael A Welch

A complex bidirectional relation between migraine, mostly migraine with aura (MA), and ischaemic stroke is known. A cerebral infarction can occur during a MA, and MA is a risk factor for ischaemic stroke, particularly in young women. Conversely, cerebral ischaemia can induce MA. Both ischaemic stroke and MA might be consequences of many underlying vascular disorders. Despite the relation between migraine and stroke, migraine as a primary headache disorder is mostly benign.

Introduction

Migraine and stroke are two commonly occurring disorders that seem to have little in common. Migraine is a benign disorder that persists throughout life, is typically worse before age 40 years and affects 15% of the population with a 3 to 1 female preponderance. Recurrent attacks of headache, sometimes preceded by transient neurological disturbances, characterise migraine. Whether migraine is a single entity, a group of related disorders, or a syndrome due to other disorders is still unclear. The diagnosis of migraine is purely clinical and strict criteria have been proposed by the International Headache Society (IHS).[1]

By contrast, stroke is an acute event that occurs in 2 per 1000 people per year at a mean age of 70 years with a 2 to 3 male preponderance. Characterised by a focal deficit of sudden onset, stroke is readily diagnosed by use of neuroimaging techniques. Cerebral infarction occurs in 80% of strokes and intracerebral haemorrhage in 20%. The cause of both types of stroke is diverse; in individual patients, particularly those who are young, the cause is commonly unknown even after extensive investigation.

Despite these differences, many studies have suggested a complex bidirectional relation between migraine and stroke,[2–5] including migraine as a cause of stroke, migraine as a risk factor for or as a consequence of cerebral ischaemia, and migraine and cerebral ischaemia sharing a common cause.

Migrainous infarction

Charcot was probably the first to recognise that migraine could cause a stroke when he wrote that "any of the symptoms occurring during 'migraine ophthalmique' can . . . become permanent".[6] His residents, Hétri, reported a case of "ophthalmic migraine with repeated attacks followed by death" in a man aged 53 years who had had migraine attacks with ophthalmic and dysphasic aura since childhood and who died after 2 months of left-sided headache, visual disturbances, and right or left hemiplegia. This case is typically referred to as the first case of lethal migrainous stroke, but in the absence of autopsy, the precise cause of death is unknown.[7]

After the first reports and before the first IHS classification,[1] many cases of "migrainous infarction" were reported, including disorders as varied as "strokes occurring in migraineurs", "strokes with migrainous features", "strokes with headache", and even "long-lasting deficits without stroke".

Standard description

In the descriptive cases of "focal migraine" reported,[1,8] there is no consistent pattern of infarction; infarcts are large or small, single or multiple, cortical or subcortical, and involve the carotid and/or the basilar territories. There is no consistent pattern of arterial changes: thrombosis, embolism, spasm, dissection, and normal arteries have all been reported. Whereas in most of these cases the responsibility of migraine is doubtful, repeated attacks of severe migraine could lead to focal arterial injury, comparable to spasm induced by subarachnoid haemorrhage.[9,10]

There are no good data on the incidence of migrainous infarctions. The single largest study[8] before the IHS classification found 7 (3%) migrainous infarcts among 264 first cerebral infarctions, corresponding to an incidence of 3 per 100 000 per year in the UK. However, the causal relation between these strokes and migraine is highly debatable because only one patient had cerebral angiography, one had echocardiography, three were hypertensive, and one had widespread atheroma.

The most common clinical sign is a homonymous field defect, such as hemianopia or hemispheric scotoma, due to a posterior cerebral artery infarct, but other territorial infarcts affecting any large artery as well as single or multiple lacunar infarcts have also been reported. Similarly, all varieties of retinal infarcts and ischaemic optic neuropathies have been described as complications of retinal migraine.[11]

Much diversity in the location and type of infarcts is reflected in the neuroimaging findings: most patients have occipital infarcts, but single and multiple infarcts of any size and location have been reported.[12–14] Angiography is typically normal, but spasm and occlusion of large or small arteries have been reported,[15–18] as have dissections and aneurysms,[19,20] which could be consistent with spontaneous migraine.

Vasoconstrictor medications such as ergotamine or triptans might exacerbate, but in some reported cases, migrainous infarction was a misdiagnosis.[21] Beta-blockers known to occasionally increase the frequency and duration of auras have also been associated with migrainous infarcts.[17] Cerebral angiography, which is known to induce migraine attacks, carries a 3% risk of

Dr. Ferrari's testimony:

"Given the complex relationship between migraine and stroke, a POSA would have looked unfavorably on developing a new therapeutic that could worsen that troubling link."

Ex. 2212, ¶59

contraceptives (RR 34·4, 32·7–36·1).[70] However the absolute risk of stroke in young women with migraine is low: 18 per 100 000 per year.[67,73] A recent meta-

Ex. 2157, 535; Ex. 1306, ¶59; Reply, 15

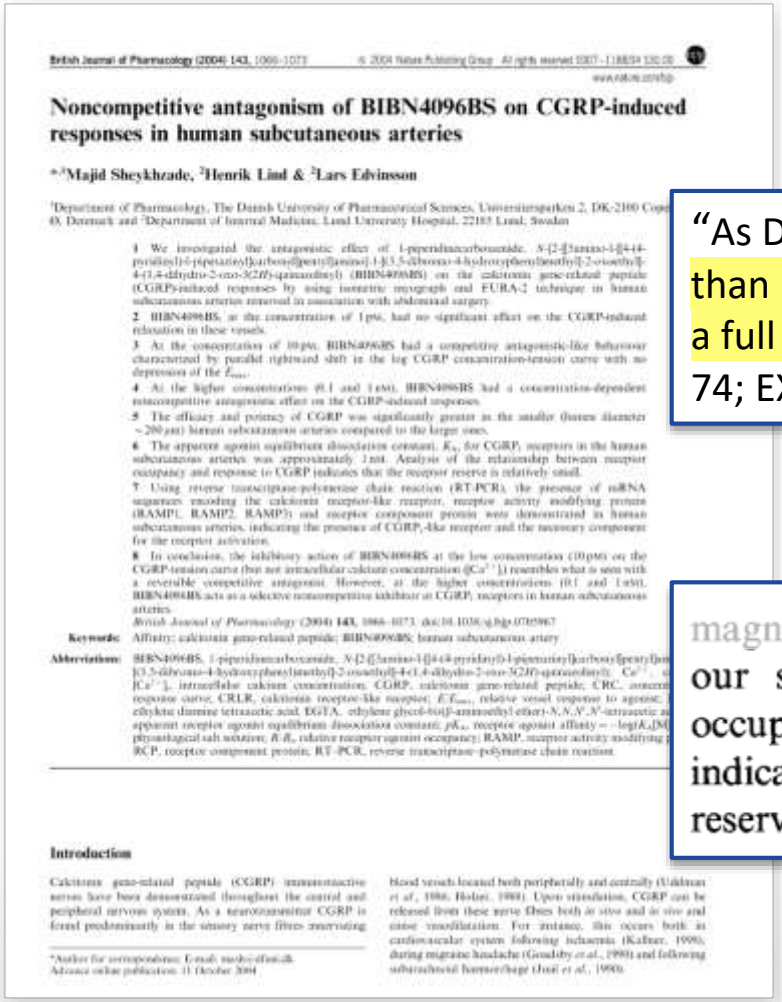
Dr. Ferrari's cross-examination:

Q: Okay. Well, for the percentage of patients that experience migraine without aura, as of 2005 there was no known association between migraine without aura and ischemic stroke, correct?

A: In 2005 there was no known association.

Ex. 1303, 193:3-10; Reply, 15; Ex. 2157, 536; Ex. 1306, ¶59

The Prior Art Contradicts Teva's Hypothetical Application of the "Spare Receptor Theory"



British Journal of Pharmacology (2004) 143, 1066–1073

Noncompetitive antagonism of BIBN4096BS on CGRP-induced responses in human subcutaneous arteries

*,1Majid Sheykhzade, 2Henrik Lind & 2Lars Edvinsson

1Department of Pharmacology, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark and 2Department of Internal Medicine, Lund University Hospital, 22185 Lund, Sweden

Keywords: Affinity; calcitonin gene-related peptide; BIBN4096BS; human subcutaneous artery

Abbreviations: BIBN4096BS, 1-piperidinecarboxamide, *N*-[2-[[3-amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2*H*)-quinazolinyl)- (BIBN4096BS); CRC, concentration–response curve; CRLR, calcitonin receptor-like receptor; E_{max}, relative vessel response to agonist; EDTA, ethylene diamine tetraacetic acid; EGTA, ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid; pK_B, apparent receptor agonist equilibrium dissociation constant; pK_A, receptor agonist affinity = $-\log K_A$[M]; PSS, physiological salt solution; *R*/*R*$_o$, relative receptor agonist occupancy; RAMP, receptor activity modifying protein; RCP, receptor component protein; RT-PCR, reverse transcription–polymerase chain reaction.

British Journal of Pharmacology (2004) 143, 1066–1073. doi:10.1038/sj.bjp.0705967

Introduction

Calcitonin gene-related peptide (CGRP) immunoreactive nerves have been demonstrated throughout the central and peripheral nervous system. As a neurotransmitter CGRP is found predominantly in the sensory nerve fibres innervating blood vessels located both peripherally and centrally (Uddman *et al*., 1986; Hoskin, 1988). Upon stimulation, CGRP can be released from these nerve fibres both *in vitro* and *in vivo* and cause vasodilatation. For instance, this occurs both in cardiovascular system following ischaemia (Kaffner, 1990), during migraine headache (Goadsby *et al*., 1990) and following subarachnoid haemorrhage (Juul *et al*., 1990).

*Author for correspondence: E-mail: majid.s@mail.dk
Advance online publication: 11 October 2004

Teva's arguments:

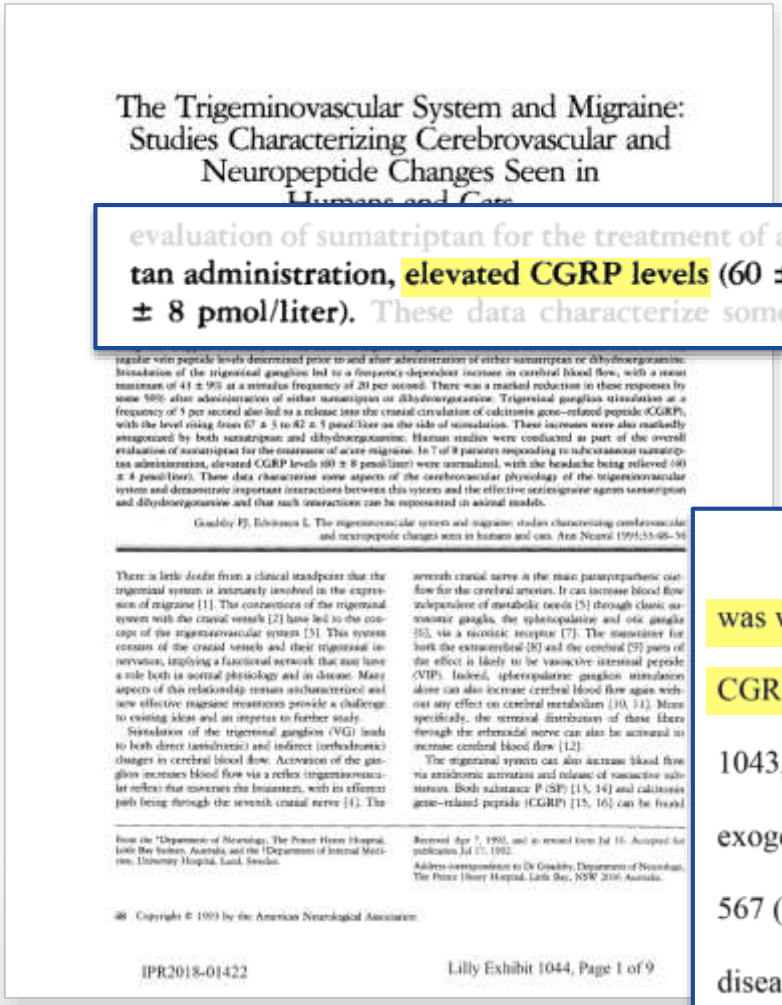
"As Dr. Foord explains, in the CGRP receptor system, less than 1% of receptors needed to be bound by ligand to elicit a full response in the cell. EX2230, ¶¶38-42, 94; EX2062, 74; EX2063, 15; EX2064, 537."

POR, 31

magnitude of response produced by an agonist (efficacy). In our study, approximately 27% of all receptors must be occupied by CGRP to elicit a half-maximal response (EC_{50}), indicating the presence of a relatively small $CGRP_1$-receptor reserve pool in the human subcutaneous arteries. The term

Ex. 2065, 1071; Ex. 1305, ¶¶41-42; Ex. 1300, 69:4-8; Reply, 17

Prior Art Clinical Evidence Undermines Teva's Hypothetical Application of the "Spare Receptor Theory"



The Trigeminovascular System and Migraine: Studies Characterizing Cerebrovascular and Neuropeptide Changes Seen in Humans and Cats

IPR2018-01422

Lilly Exhibit 1044, Page 1 of 9

evaluation of sumatriptan for the treatment of acute migraine. **In 7 of 8 patients responding to subcutaneous sumatriptan administration, elevated CGRP levels (60 ± 8 pmol/liter) were normalized, with the headache being relieved (40 ± 8 pmol/liter).** These data characterize some aspects of the cerebrovascular physiology of the trigeminovascular

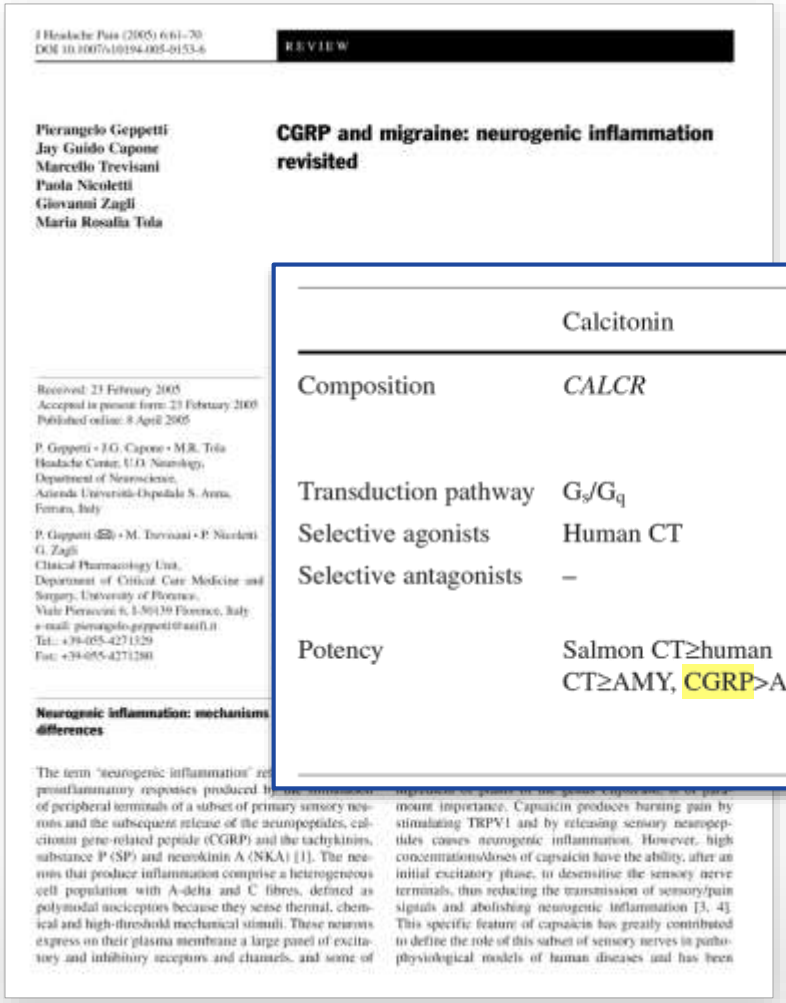
Ex. 1044, Abstract; Ex. 1306, ¶67; Reply, 17

Dr. Charles's testimony:

67. The clinical evidence contradicts Dr. Foord's assertion. As of 2005, it was widely known that migraine was linked to *elevated* or *inappropriate* levels of CGRP, and that as CGRP levels normalized migraine headache subsided. (Ex. 1043, Abstract; Ex. 1044, Abstract; *see also* Ex. 1047, 59 (administering exogenous CGRP "caused migraine in virtually all migraine sufferers"); Ex. 1096, 567 ("inappropriate release of CGRP is a potential causative factor in several diseases, including migraine"); Ex. 1008, ¶¶36-45.)

Ex. 1306, ¶67; Reply, 17

Ligand Cross-Binding Did Not Undermine Motivation



J Headache Pain (2005) 6:61–70
DOI 10.1007/s10194-005-0153-6

REVIEW

Pierangelo Geppetti
Jay Guido Capone
Marcello Trevisani
Paola Nicoletti
Giovanni Zagli
Maria Rosalia Tola

CGRP and migraine: neurogenic inflammation revisited

Received: 23 February 2005
Accepted in present form: 23 February 2005
Published online: 8 April 2005

P. Geppetti • J.G. Capone • M.R. Tola
Headache Center, U.O. Neurology,
Department of Neuroscience,
Azienda Universitá-Ospedale S. Anna,
Ferrara, Italy

P. Geppetti (✉) • M. Trevisani • P. Nicoletti
G. Zagli
Clinical Pharmacology Unit,
Department of Critical Care Medicine and
Surgery, University of Florence,
Viale Pieraccini 6, I-50139 Florence, Italy
e-mail: pierangelo.geppetti@unifi.it
Tel.: +39-055-4271329
Fax: +39-055-4271280

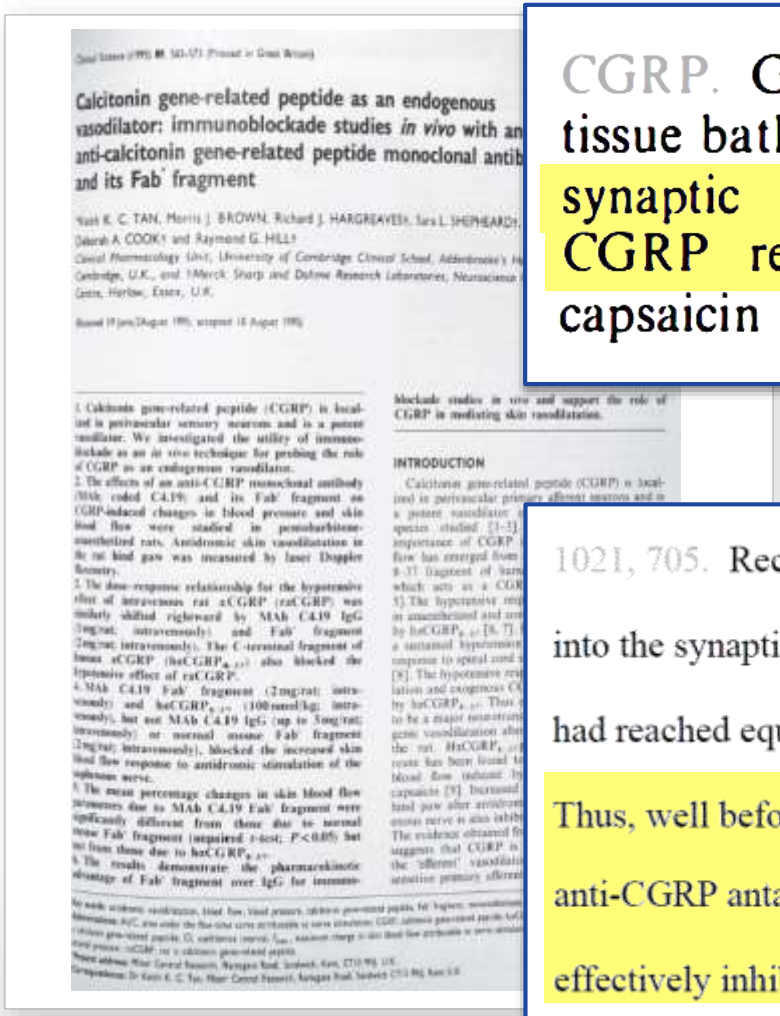
Neurogenic inflammation: mechanisms differences

The term "neurogenic inflammation" re… proinflammatory responses produced b… of peripheral terminals of a subset of primary sensory neurons and the subsequent release of the neuropeptides, calcitonin gene-related peptide (CGRP) and the tachykinins, substance P (SP) and neurokinin A (NKA) [1]. The neurons that produce inflammation comprise a heterogeneous cell population with A-delta and C fibres, defined as polymodal nociceptors because they sense thermal, chemical and high-threshold mechanical stimuli. These neurons express on their plasma membrane a large panel of excitatory and inhibitory receptors and channels, and some of… mount importance. Capsaicin produces burning pain by stimulating TRPV1 and by releasing sensory neuropeptides causes neurogenic inflammation. However, high concentrations/doses of capsaicin have the ability, after an initial excitatory phase, to desensitise the sensory nerve terminals, thus reducing the transmission of sensory/pain signals and abolishing neurogenic inflammation [3, 4]. This specific feature of capsaicin has greatly contributed to define the role of this subset of sensory nerves in pathophysiological models of human diseases and has been

	Calcitonin	Amylin (AMY)	CGRP	Adrenomedullin (AM)
Composition	*CALCR*	AMY-1: *CALCR+RAMP1* AMY-2: *CALCR+RAMP2* AMY-3: *CALCR+RAMP3*	*CALCRL+RAMP1*	AM-1: *CALCRL+RAMP2* AM-2: *CALCRL+RAMP3*
Transduction pathway	G_s/G_q	G_s	G_s/G_q	G_s
Selective agonists	Human CT	AMY	α-CGRP	AM
Selective antagonists	–	–	BIBN4096BS (+++) SB-273779 (+)	AM_{22-52}
Potency	Salmon CT≥human CT≥AMY, CGRP>AM	Salmon CT≥AMY≥ CGRP>human CT>AM	CGRP>AM≥ AMY≥salmon CT	AM-1: AM>>CGRP> AMY>salmon CT AM-2: AM≥CGRP> AMY>salmon CT

Ex. 2059, 63 (annotation added); Ex. 1306, ¶72; Reply, 18

Tan 1995 (Ex. 1022): IgG "Clearly Diffuses" to the Site of Action



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antib and its Fab' fragment

INTRODUCTION

CGRP. Given an adequate incubation period in a tissue bath, MAb C4.19 IgG clearly diffuses into the synaptic cleft since it was effective at blocking CGRP released from primary afferent nerves by capsaicin *in vitro* [11]. The most likely barrier to

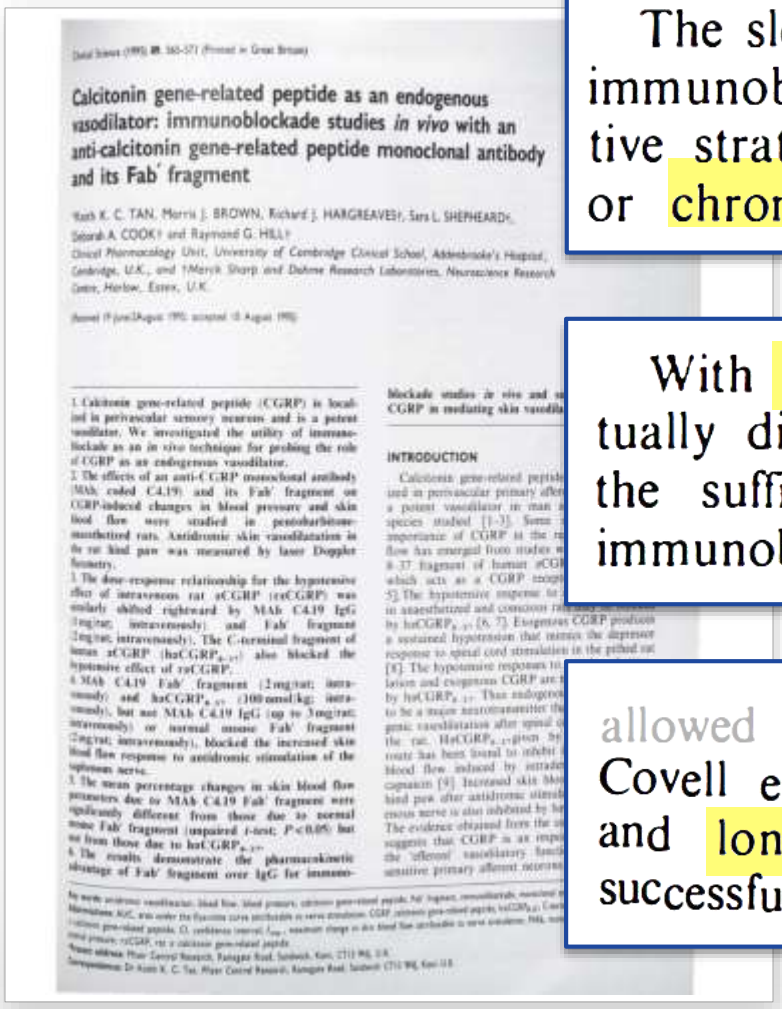
Ex. 1022, 571; Ex. 1305, ¶20; Reply, 20

Dr. Balthasar's testimony:

1021, 705. Recognizing that "time must be allowed for the MAb C4.19 to diffuse into the synaptic cleft," Tan 1994 reported that "the concentration of the antibody had reached equilibrium in the synaptic cleft after 45 min[utes]." Ex. 1021, 709. Thus, well before 2005, both Tan 1994 and Tan 1995 disclosed that full-length anti-CGRP antagonist antibodies successfully distributed to the synaptic cleft and effectively inhibited the activity of endogenous CGRP.

Ex. 1305, ¶21; Reply, 20

Tan 1995 Provided Guidance to Improve Immunoblockade



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Kieth K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to

With repeated administration, IgG should eventually distribute into interstitial space and achieve the sufficiently high concentrations required for immunoblockade. A limited example is found in an

allowed for antibody distribution. The data of Covell et al. [14] suggest that much larger doses and longer distribution times are required for successful immunoblockade with IgG. In this

Ex. 1022, 571; Ex. 1008, ¶122; Ex. 1305, ¶¶24-29; Pet., 39-42; Reply, 20

Teva Followed Tan's Express Guidance

(12) United States Patent
Zeller et al.

(54) ANTAGONIST ANTIBODIES DIRECTED AGAINST CALCITONIN GENE-RELATED PEPTIDE AND METHODS USING SAME

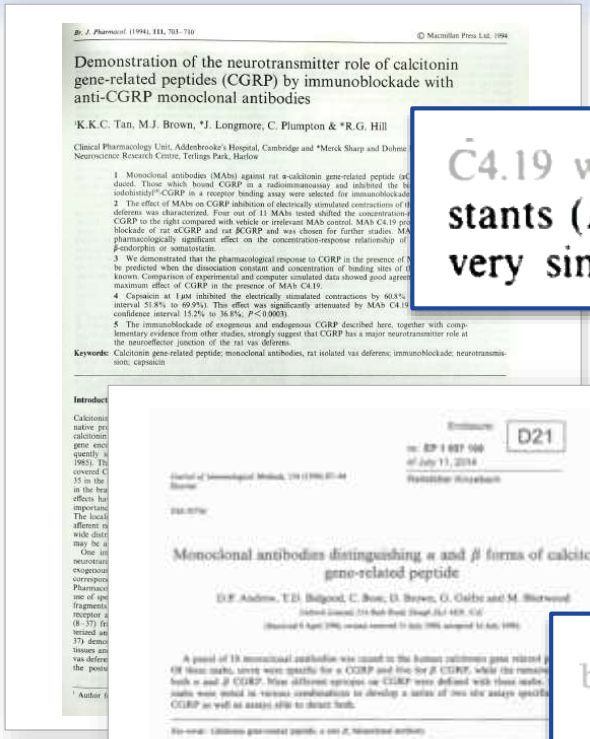
Example 3

Effect of Anti-CGRP Antagonist Antibodies on Skin Vasodilatation Induced by Stimulation of Rat Saphenous Nerve

For experiments shown in FIGS. 2A and 2B, antibody 4901 (25 mg/kg), antibody 7D11 (25 mg/kg), or vehicle control (PBS with 0.01% Tween 20) was administered intraperitoneally (IP) 72 hours before the electrical pulse stimulation.

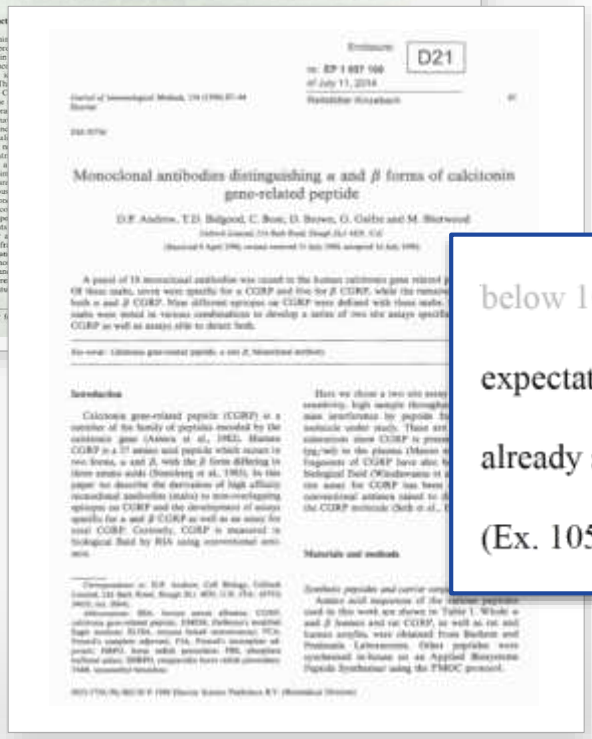
Ex. 1001, 55:7-10; Ex. 1008, ¶¶91-98; Pet., 42-43; Reply, 20

Multiple Prior Art Studies Reported Anti-CGRP Antibodies with Nanomolar Affinities



Demonstration of the neurotransmitter role of calcitonin gene-related peptides (CGRP) by immunoblockade with anti-CGRP monoclonal antibodies

K.K.C. Tan, M.J. Brown, *J. Longmore, C. Plumpton & *R.G. Hill



D21

Monoclonal antibodies distinguishing α and β forms of calcitonin gene-related peptide

C4.19 were not significantly different. The dissociation constants (K_d) of MAb C4.19 for rat αCGRP and βCGRP were very similar (1.9 and 2.5 nM respectively). Irrelevant mouse

Ex. 1021, 707; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18, 31; Reply, 18

Dr. Vasserot's testimony:

below 10 nM. Andrew would have further confirmed a similar reasonable expectation of success because its antibodies generated against human CGRP were already shown to bind to human CGRP with affinities of about 40 nM to 4 nM. (Ex. 1055, 92 (calculating K_D values from K_A).)

Ex. 1013, ¶122; Pet. (IPR2018-01426), 37

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Next-generation protein drugs

Ian M Tomlinson

Ankyrin repeats generate high-affinity protein binders with biophysical properties that may favor therapeutic applications.

Ask any major pharmaceutical company what constitutes an ideal drug and the answer would probably include the words 'specificity, affinity, solubility, stability and safety' along with the phrases 'cheap to manufacture, easy to formulate, simple to deliver and the right pharmacokinetic profile.' Ironically, many drugs on the market fail to deliver in one or more of these areas because of their sub-optimal biophysical makeup. Even blockbuster biologics, such as therapeutic antibodies[1], suffer from drawbacks, such as the requirement for an expensive mammalian cell production system and the need for intravenous, intramuscular or subcutaneous injection (with molecular weights of around 150,000, they are too large to be administered by any other route). Clearly, there is room for improvement. In this issue, Binz *et al.*[2] describe a natural scaffold, ankyrin repeat protein, that has promising biophysical properties for therapeutic application. Ankyrin repeats are one of several new types of scaffold being developed for a new generation of protein therapies.

An ideal drug would have the following qualities: it would have very high affinity and exquisite specificity for its target; it could be manufactured by the bucket-load in bacteria or yeast; it would be both incredibly soluble and remarkably stable; it could be delivered to any part of the human body by any route of administration; and, once there, it would hang around long enough to have the desired therapeutic effect. Achieving all these goals has been particularly difficult for protein drugs.

Currently, protein drugs come in all shapes and sizes: some are recombinant human proteins (for instance, insulin, growth hormone and erythropoietin), others are monoclonal antibodies (for instance, Remicade (infliximab; Johnson & Johnson, Kenilworth, NJ, USA), Rituxan (rituximab; Genentech; S. San Francisco, CA, USA) and Erbitux (cetuximab; ImClone, New York, NY, USA) and still others are viral or bacterial proteins used as vaccines to elicit a specific immune response. Nature did not evolve proteins for manufacture ex vivo. For this reason, many human proteins produced in recombinant form are difficult to manufacture and some cannot be expressed at all in microbial cell culture. Furthermore, the serum half-life and tissue distribution of endogenously expressed proteins is carefully controlled in vivo to optimize their biological activity. Most human proteins are not

Ian M. Tomlinson is Chief Scientific Officer of Domantis Limited, 315 Cambridge Science Park, Cambridge CB4 0WG, UK.
e-mail: ian.tomlinson@domantis.com

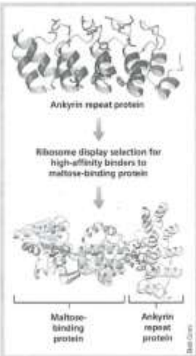


Figure 1 All in a bind. Binz *et al.* randomized 6 of the 33 amino acids (red side chains) in three ankyrin repeats (dark blue) and, using ribosome display, isolated a range of nanomolar binders to maltose-binding protein. The co-crystal structure confirms the predicted binding of the engineered ankyrin repeat protein to the maltose-binding protein target.

designed to be administered from out
body. Recombinant proteins therefor
be rapidly cleared and thus require f
injection (thus, the growing inte
extending the serum half-life by, for e
polyethylene glycol conjugation).

Antibodies have proved useful as
protein therapeutics because they e
favorable pharmacokinetic profile.
single injection, they can persist fo
time in the bloodstream, maintaini
biological activity for several weeks. H
antibodies have also evolved to be
from mammalian cells and, for a va
reasons, cannot be expressed in yeast
terial cell culture.

Given the limitations of current protein therapies, scientists are starting to develop more tailored approaches to drug design whereby you first assemble a list of the various properties you want the drug to have and then engineer a drug with precisely those properties. Over the past three years, several new biotech companies have been set up to
exploit the use of 'well-behaved' hum
teins as scaffolds to create a range of
protein drugs that have improved the
properties (see Table 1). This appro
ceeds through the following steps: fir
a human protein that is well expresse
teria and/or yeast and has good bio
properties (solubility, stability and
second, create a repertoire by intr
diversity into the loop regions of th
scaffold, preferably in a way that does
rupt the overall structure of the prote

Dr. Tomlinson's statements in 2004:

An ideal drug would have the following qualities: it would have very high affinity and exquisite specificity for its target; it could

Ex. 1266, 521; Ex. 1327, ¶78; Reply (IPR2018-01426), 18

Dr. Tomlinson's cross-examination:

Q: For therapeutic antibodies that act by binding a target antigen, is strong binding affinity to that antigen a desirable characteristic?

A: Yes.

Ex. 1301, 211:16-21; Reply (IPR2018-01426), 18

Q: And as of 2005, a person of ordinary skill could use affinity maturation techniques to improve binding affinity stronger than one nanomolar, correct?

A: Yes.

Ex. 1301, 213:21-25; Reply (IPR2018-01426), 18

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Teva's arguments:

"[A] POSA would not have concluded that Tan 1994's anti-CGRP antibodies had K_Ds of 10 nM or less, which defeats Lilly's second alleged 'reason' to make the claimed antibodies. … But, as Dr. Tomlinson explains, Tan 1994 was not designed in a manner draw conclusions regarding affinity. EX2226, ¶¶104-109."

POR (IPR2018-01426), 42-43

Dr. Balthasar's testimony:

Although these concerns are addressed below, it is important to note that the technique used to measure the affinity of antibody C4.19 has little bearing on the motivation to develop humanized anti-CGRP antagonist antibodies for treatment of migraine or other conditions. In general, Tan 1994 and Tan 1995 helped to validate CGRP as a therapeutic target and would have motivated development of at least single-digit nanomolar-range anti-CGRP antagonist antibodies for therapeutic use.

Ex. 1327, ¶71; Reply (IPR2018-01426), 18

Near-Simultaneous Disclosure

APPLICATION NUMBER: *60/753,044*
FILING DATE: *December 22, 2005*

TREATMENT OF MIGRAINE WITH ANTI-CGRP ANTIBODIES

FIELD OF THE INVENTION

The present invention is in the field of medicine. More specifically, the invention relates to antibodies to CGRP and the use of such antibodies for therapy and prophylaxis of migraines.

affinities characteristics as listed in Table 3. Neither monoclonal antibody nor Fab bound to amylin or adrenomedullin (tested at 500 nM). The anti-CGRP monoclonal antibodies and the anti-CGRP Fab tested specifically bind to rat and human α-CGRP and human β-CGRP.

Preferably an antibody of the invention to be used for therapeutic purposes would have the sequence of the framework and constant region (if a constant region is included) derived from the mammal in which it would be used as a therapeutic so as to decrease the possibility that the mammal would illicit an immune response against the therapeutic antibody. Humanized antibodies are of particular interest since they are considered to be valuable for therapeutic application and avoid the human anti-mouse antibody response frequently observed with murine antibodies. Additionally, in humanized antibodies if the

Ex. 1127, 1, 18, 32; Pet., 57


THE UNITED STATES OF AMERICA

February 01, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/753,044
FILING DATE: December 22, 2005
RELATED PCT APPLICATION NUMBER: PCT/US06/62272

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US60/753,044

Ex. 1127; Pet., 57

Nov. 14, 2005 **Dec. 22, 2005**

2005: Aug. Sep. Oct. Nov. Dec.

Teva's Secondary Considerations Are Not Commensurate with the Scope of the Challenged Claims

***In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)**

"Evidence of secondary considerations must be reasonably commensurate with the scope of the claims."

Reply, 21

Antibody Format (e.g., fragments)	Fab, Fab', F(ab')2 , Fv, single chain (ScFv), fusion proteins	Ex. 1301, 27:25-28:6; Ex. 1001, 12:40-46; Pet., 22; Reply, 23
Sequence Mutations	20^{220}	Ex. 1301, 92:8-10; Reply, 22
Antibody Class	IgA, IgD, IgE, IgG, IgM	Ex. 1301, 37:16-39:11; Reply, 23
Binding Affinity	2 pM-250 nM	Ex. 1001, 5:54-65; Reply, 22

Teva's Secondary Considerations Lack Nexus to the Claims

In re Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011)

"Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention."

Reply, 24

Dr. Rapoport's cross-examination:

Q: So let's just – I think you said you didn't consider whether it preferentially binds to CGRP as opposed to amylin, correct?

A: Right.

Q: … So it's your opinion that the antibodies that you have indicated met a long-felt need is based on their characteristic that they block the CGRP pathway, correct?

A: Correct.

Ex. 1304, 141:16-20, 142:1-8; Reply, 24

Teva's Secondary Considerations Lack Nexus to the Claims

In re Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011)

"Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention."

Teva's claims:

Reply, 24

We claim:
1. A human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α-CGRP as compared to amylin.

We claim:
1. A human or humanized monoclonal anti-CGRP antagonist antibody that (1) binds human α-CGRP and (2) inhibits cyclic adenosine monophosphate (cAMP) activation in cells.

We claim:
1. A human or humanized, monoclonal anti-CGRP antagonist antibody that (1) binds human α-CGRP and (2) inhibits human α-CGRP from binding to its receptor as measured by a radioligand binding assay in SK-N-MC cells.

We claim:
1. An isolated human or humanized anti-CGRP antagonist antibody with a binding affinity (K_D) to human α-CGRP of 50 nM or less as measured by surface plasmon resonance at 37° C.

Wimalawansa (Ex. 1096):

reached and before CGRP antagonist, humanized anti-CGRP monoclonal antibodies. or both, can be evaluated as thera-

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 567, 570; Reply, 24

Ex. 1001 ('614), claim 1;
Ex. 1001 ('951), claim 1;
Ex. 1001 ('881), claim 1;
Ex. 1001 ('649), claim 1

Teva's Secondary Considerations Lack Nexus to the Claims

Teva's claims:

We claim:

1. A humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:

two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and

two light chains, each light chain comprising three CDRs and four framework regions;

wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43.

We claim:

1. A humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising:

two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and

two light chains, each light chain comprising three CDRs and four framework regions;

wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43, and wherein the antibody binds to the CGRP with a binding affinity (K_D) of about 10 nM or less as measured by surface plasmon resonance at 37° C.

Ex. 1001 ('210), claim 1;
Ex. 1001 ('211), claim 1

Wimalawansa (Ex. 1096):

reached and before CGRP antagonist, humanized anti-CGRP monoclonal antibodies. or both, can be evaluated as thera-

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 567, 570; Reply, 24

Teva's Evidence of Industry Acclaim Is Deficient

NEWS

IN this section

Migraine drug race turns its final corner, FDA decisions in sight

First up will likely be erenumab (Aimovig).

Lilly of Indianapolis. A fourth anti-CGRP mAb, eptine-zumab from Alder Biopharmaceuticals of Bothell, Washington, could then hit the market in 2019, and at least one prophylactic CGRP-antagonizing small molecule (and several others for acute treat-ment) might not be far behind (Table 1).

Teva's arguments:

"Lilly's expert, Dr. Charles, has himself praised the claimed humanized anti-CGRP antibodies–repeatedly. Dr. Charles has touted the claimed antibodies as:

- 'very exciting and compelling, … . EX2182, 207"

POR, 49

"These are really the first therapies, ever, that have been designed based on a specific laboratory understanding of the mechanisms of migraine," says Andrew Charles, a neurologist at the University of California, Los Angeles (who consults for Alder, Amgen and Lilly). "That, to me, is very exciting and compelling."

Ex. 2182, 207; Reply, 25

Teva's Purported Evidence of Licensing Does Not Support Patentability

Dr. Stoner's cross-examination:

Q: Do you consider the settlement and license agreement to be a patent portfolio license, you, Dr. Stoner?

A: I was aware that the license related to all of these patents which are necessary to practice the Alder product.

Q: When you say "all of these patents," you mean that at least 188 patents and applications listed in schedule 1.14 in 65 countries and eight families? When you say "all these patents," is that what you meant?

A: Yes, all these related patents.

Q: … if just claims 1 through 7 and 15 through 20, which are the challenged claims of the 614 patent, if just those claims were canceled, Alder Bio would still owe the same consideration under this agreement because Alder Bio admits that it infringes the remaining claims or the 614 patent and all claims of the 187 additional licensed patents, correct?

A: That's certainly a reasonable interpretation of this paragraph.

Q: And to that same effect, if all of the challenged claims were canceled, Alder Bio would still owe the same considerations to Teva for the same reason, that they had admitted infringement of all of the 179 additional patents, correct?

A: That appears to be a reasonable interpretation of this paragraph …

Ex. 1302, 45:20-46:12, 179:14-180:19; Reply, 27

Detailed Analysis

Teaching Away Requires Criticizing, Discrediting, or Otherwise Discouraging Investigation

Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013)

"[N]or do these articles indicate in any way that the side effects would be serious enough to dissuade the development of a 0.3% adapalene product….A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions. "

Reply, 16

Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96 at 20, 21 (PTAB Feb. 14, 2019)

"We are not persuaded that the potential risk of side effects would have deterred a person of ordinary skill in the art from developing a way to block both IL-4 and IL-13 signaling. [] First, we note the literature cited by Patent Owner's expert Dr. Finkelman characterizes the side effects as theoretical."

"The problem with Patent Owner's argument is that the law does not require the prior art to explicitly suggest humanizing MAb230. … Petitioner need not show that MAb230 was the only option or even the best option for a person of ordinary skill in the art. On the contrary, Petitioner may show that MAb230 was a 'suitable option from which the prior art did not teach away."

Reply, 9-10

Lilly Need Not Identify a Specific Antibody to Humanize

Teva's argument:

"Lilly never articulated which prior art antibody a POSA would have humanized in order to arrive at the claimed antibodies."

Sur-reply, 24

Abbott GmbH & Co., KG v. Centocor Ortho Biotech, Inc.,
971 F. Supp. 2d 171, 184 (D. Mass. 2013)

A POSA would have "the motivation or attempt to combine the teachings of the prior art references to make a human, high-affinity, neutralizing antibody to IL-12" when the prior art disclosed neutralizing mouse and humanized antibodies to IL-12 and "methodology to achieve the functional result."

Pet., 31

The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation

Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96, 19-20 (PTAB Feb. 14, 2019)

"We are also persuaded that Petitioner has shown that a person of ordinary skill in the art would have had a reason to humanize Hart's MAb230 using Schering-Plough's humanization technique to create a potential therapeutic for allergic diseases with a reasonable expectation of success."

Reply, 5

Abbott GmbH & Co., KG v. Centocor Ortho Biotech, Inc., 971 F. Supp. 2d 171, 185 (D. Mass. 2013)

"Based on the jury's implicit factual findings, the Court concludes that there was clear and convincing evidence of a need to create a human, neutralizing, high-affinity antibody to IL–12. A person of ordinary skill in the art at the time knew that the overproduction of IL–12 was causing diseases, and that an antibody that neutralized IL–12 could be therapeutic."

Reply, 5

Sanofi-Aventis v. Immunex Is Highly Analogous

Sanofi v. Immunex	The instant case
Prior art antibody blocked IL-4 and IL-13 activity. (*Immunex*, IPR2017-01884, Paper 96, 18; Sur- Reply, 5)	Tan: MAb C4.19 IgG blocked "the hypotensive effects of exogenous rαCGRP *in vivo*." (Ex. 1022, 570; Pet., 17.) Wong: antibody 4901 "is extremely effective in vivo as an immunoneutralizing agent." (Ex. 1033, 104; Pet. 34.)
The prior art disclosed that anti-IL-4R antibodies "could advantageously be humanized and thus used for long term treatment of allergic disorders." (*Immunex*, Paper 96, 19.)	Wimalawansa: disclosed humanized anti-CGRP antagonist antibodies for use in treating several diseases including migraine, inflammation, and cardiogenic shock. (Ex. 1096, 567, 570 ("humanized monoclonal antibodies should be explored … ."); Pet. 19, 26.)
Potential risk of side effects not a deterring factor in the prior art. (*Immunex*, Paper 96, 20.)	Wong: Antibody 4901 "had no significant effect on MAP and heart rate." (Ex. 1033, 101; Reply, 12.) Teva's experts contemporaneously praised CGRP antagonists as "promising, new antimigraine drugs without vascular side effects." (Ex. 1290, 657; Ex. 1297, S119; Reply, 8) Doods: "we expect that CGRP antagonists will be effective anti-migraine drugs" (Ex. 1024, 422; Pet. 26.)
Claims do not require therapeutic efficacy. (*Immunex*, Paper 96, 23-24.)	Claims do not require therapeutic efficacy. (Ex. 1001; Pet., 38 n.2; Reply, 4-5.)

Phigenix Is Inapposite

Teva's argument:

"Under a similar challenge to composition of matter claims, as here, the Board held the petitioner to its 'therapeutic utility' motivation arguments. *Phigenix v. ImmunoGen*, IPR2014-00676, Paper 39, 16 (P.T.A.B. Oct. 27, 2017)"

Sur-reply, 3-4

Phigenix	The instant case
Claims recite a specific antibody conjugated to a specific toxin (Herceptin-maytansinoid)	Claims recite broad genera of humanized anti-CGRP antagonist antibodies
Key prior art human clinical study showed toxicity with a relevant immunoconjugate	Human clinical trial with relevant CGRP pathway inhibitor (BIBN) showed no toxicity
Toxicity of Herceptin was identified in later prior-art human studies	Later prior-art human studies resolved purported safety concerns
Tight nexus between objective indicia evidence and narrow claims that required a "specific antibody, linker, and toxin"	Objective indicia evidence lack nexus to extremely broad claims

Teva's REOS Arguments Are Irrelevant

Senju Pharm. Co. v. Lupin Ltd., 780 F.3d 1337, 1346-47 (Fed. Cir. 2015)

"In composition claims 12–16 of the '045 patent, there is no limitation denoting the function of the composition and we decline to import this limitation into the claims."

Pet., 38 (n. 2); Reply, 19

Sanofi-Aventis U.S. LLC v. Immunex Corp., IPR2017-01884, Paper 96 at 23 (PTAB Feb. 14, 2019)

"We agree with Petitioner that the pertinent question is not whether there is a reasonable expectation that the antibodies will actually be therapeutically effective. Rather, the question is whether a person of ordinary skill in the art would have reasonably expected to arrive at the claimed invention."

Reply, 19

Teva's Evidence of Industry Acclaim Is Deficient

***Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013)**

"[I]ndustry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration."

Reply, 24-25

Anti-CGRP Antagonist Antibodies Had Already Been Generated

***PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007)**

"Admissions in the specification regarding the prior art are binding on patentee for the purpose of a later inquiry into obviousness."

Pet., 6, 33

Teva's specification:

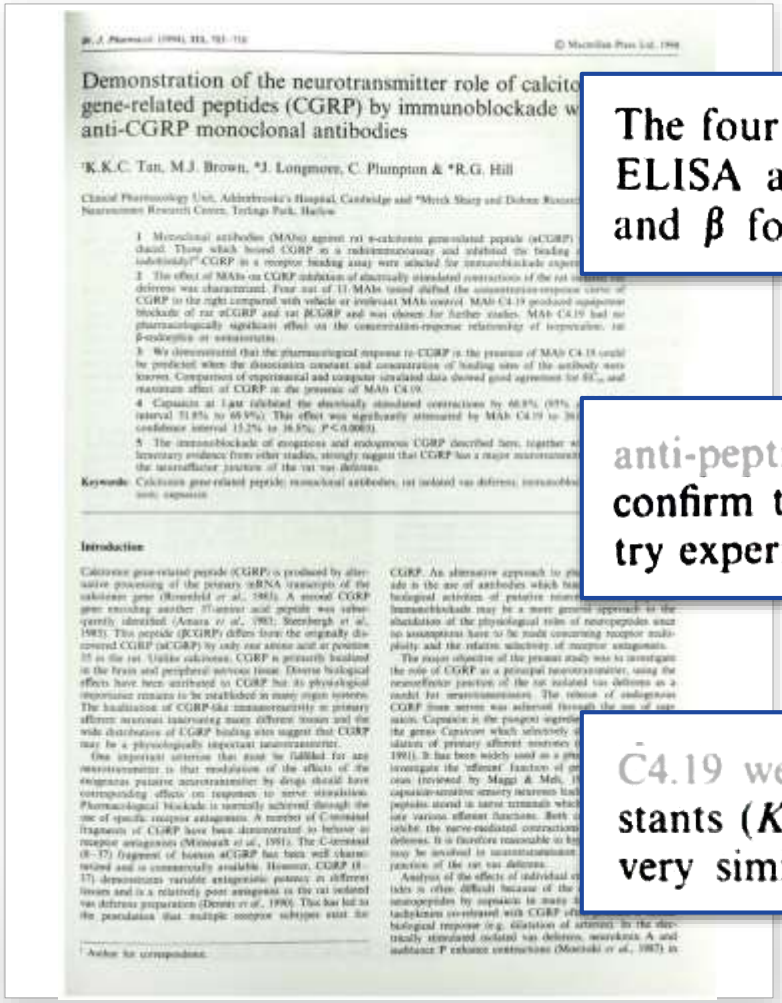
CGRP synthesis, production or release. Anti-CGRP antagonist antibodies are known in the art. See, e.g., Tan et al., Clin. Sci. (Lond). 89:565-73, 1995; Sigma (Missouri, US), product number C7113 (clone #4901); Plourde et al., Peptides 14:1225-1229, 1993.

Ex. 1001, 26:13-17; Pet., 6

The anti-CGRP antagonist antibodies may be made by any method known in the art. The route and schedule of immunization of the host animal are generally in keeping with established and conventional techniques for antibody stimulation and production, as further described herein. General techniques for production of human and mouse antibodies are known in the art and are described herein.

Ex. 1001, 27:61-67; Pet., 6-7

Tan's Anti-CGRP Antagonist MAb C4.19



Demonstration of the neurotransmitter role of calcito
gene-related peptides (CGRP) by immunoblockade w
anti-CGRP monoclonal antibodies

†K.K.C. Tan, M.J. Brown, *J. Longmore, C. Plumpton & *R.G. Hill

Introduction

The four MAbs C4.19, C4.6, R1.50, R2.73 bound CGRP by ELISA and RIA. All four MAbs cross-reacted with the α and β forms of rat and human CGRP by ELISA. CGRP

Ex. 1021, 706; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18

anti-peptide (TSH) MAb as a control. **We were also able to confirm the specificity of MAb C4.19 in immunocytochemistry experiments.** Pre-incubation of the MAb C4.19 with 1 μM

Ex. 1021, 709; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18

C4.19 were not significantly different. **The dissociation constants (K_d) of MAb C4.19 for rat αCGRP and βCGRP were very similar (1.9 and 2.5 nM respectively).** Irrelevant mouse

Ex. 1021, 707; Ex. 1012, ¶69; Pet. (IPR2018-01426), 18, 31; Reply, 18

Tan 1995 Discloses the Benefits of Anti-CGRP Antagonist Antibodies

Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Kieth K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

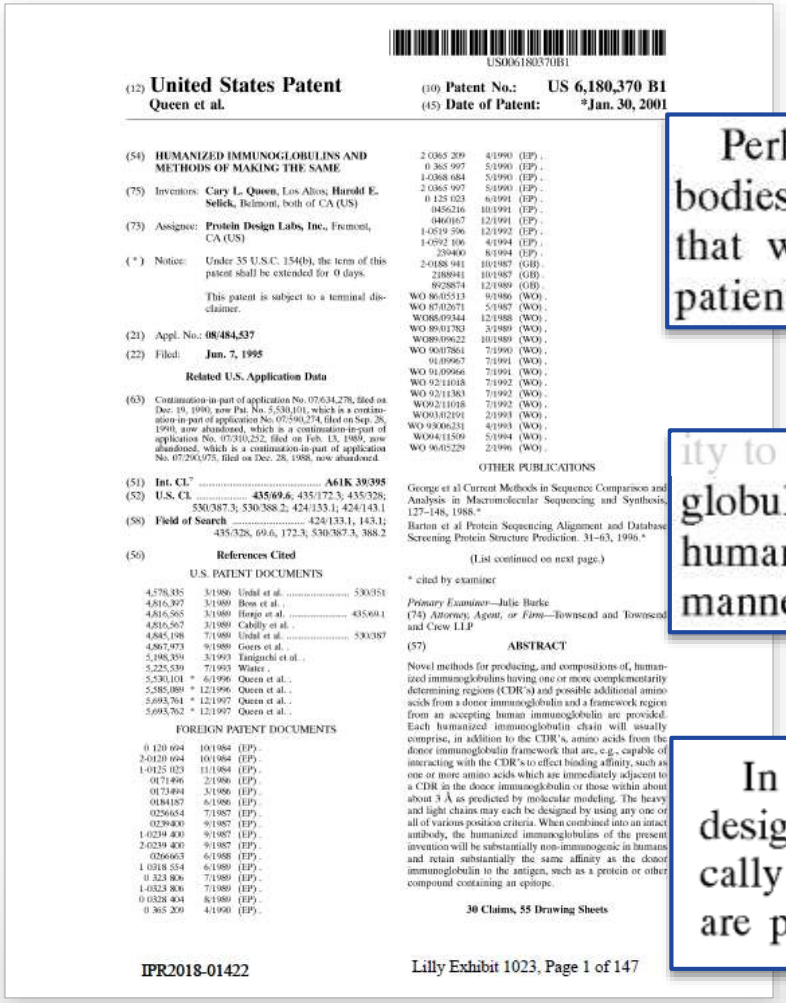
Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

and bradykinin. The present investigations have been performed with an MAb with inherent advantages of defined specificity, known affinity, reproducibility and unlimited availability. This study has

Ex. 1022, 572; Ex. 1008, ¶60; Pet., 18; Reply, 3

Queen (Ex. 1023): Humanization Techniques Were Routine



US006180370B1

(12) **United States Patent**
Queen et al.

(10) **Patent No.: US 6,180,370 B1**
(45) **Date of Patent: *Jan. 30, 2001**

(54) **HUMANIZED IMMUNOGLOBULINS AND METHODS OF MAKING THE SAME**

(75) Inventors: **Cary L. Queen**, Los Altos; **Harold E. Selick**, Belmont, both of CA (US)

(73) Assignee: **Protein Design Labs, Inc.**, Fremont, CA (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/484,537**

(22) Filed: **Jun. 7, 1995**

Related U.S. Application Data

(63) Continuation-in-part of application No. 07/634,278, filed on Dec. 19, 1990, now Pat. No. 5,530,101, which is a continuation-in-part of application No. 07/590,274, filed on Sep. 28, 1990, now abandoned, which is a continuation-in-part of application No. 07/310,252, filed on Feb. 13, 1989, now abandoned, which is a continuation-in-part of application No. 07/200,975, filed on Dec. 28, 1988, now abandoned.

(51) **Int. Cl.*** **A61K 39/395**
(52) **U.S. Cl.** **435/69.6**; 435/172.3; 435/328; 530/387.3; 530/388.2; 424/133.1; 424/143.1
(58) **Field of Search** 424/133.1, 143.1; 435/328, 69.6, 172.3; 530/387.3, 388.2

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,578,335	3/1986	Undal et al.	530/351
4,816,397	3/1989	Boss et al.	
4,816,565	3/1989	Honjo et al.	435/69.1
4,816,567	3/1989	Cabilly et al.	
4,845,198	7/1989	Undal et al.	530/387
4,867,973	9/1989	Goers et al.	
5,198,359	3/1993	Taniguchi et al.	
5,225,539	7/1993	Winter	
5,530,101	* 6/1996	Queen et al.	
5,585,089	* 12/1996	Queen et al.	
5,693,761	* 12/1997	Queen et al.	
5,693,762	* 12/1997	Queen et al.	

FOREIGN PATENT DOCUMENTS

0 120 694	10/1984	(EP)
2-0120 694	10/1984	(EP)
1-0125 023	11/1984	(EP)
0171496	2/1986	(EP)
0173494	3/1986	(EP)
0184187	6/1986	(EP)
0256654	7/1987	(EP)
0239400	9/1987	(EP)
1-0239 400	9/1987	(EP)
2-0239 400	9/1987	(EP)
0266663	6/1988	(EP)
1 0318 554	6/1989	(EP)
0 323 806	7/1989	(EP)
1-0323 806	7/1989	(EP)
0 0328 404	8/1989	(EP)
0 365 209	4/1990	(EP)
2 0365 209	4/1990	(EP)
0 365 997	5/1990	(EP)
1-0368 684	5/1990	(EP)
2 0365 997	5/1990	(EP)
0 125 023	6/1991	(EP)
0456216	10/1991	(EP)
0460167	12/1991	(EP)
1-0519 596	12/1992	(EP)
1-0592 106	4/1994	(EP)
239400	8/1994	(EP)
2-0188 981	10/1987	(GB)
2188941	10/1987	(GB)
8928874	12/1989	(GB)
WO 86/05513	9/1986	(WO)
WO 87/02671	5/1987	(WO)
WO88/09344	12/1988	(WO)
WO 89/01783	3/1989	(WO)
WO89/09622	10/1989	(WO)
WO 90/07861	7/1990	(WO)
91/09967	7/1991	(WO)
WO 91/09966	7/1991	(WO)
WO 92/11018	7/1992	(WO)
WO 92/11383	7/1992	(WO)
WO92/11018	7/1992	(WO)
WO93/02191	2/1993	(WO)
WO 93/06231	4/1993	(WO)
WO94/11509	5/1994	(WO)
WO 96/05229	2/1996	(WO)

OTHER PUBLICATIONS

George et al Current Methods in Sequence Comparison and Analysis in Macromolecular Sequencing and Synthesis, 127–148, 1988.*

Barton et al Protein Sequencing Alignment and Database Screening Protein Structure Prediction. 31–63, 1996.*

(List continued on next page.)

* cited by examiner

Primary Examiner—Julie Burke
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Each humanized immunoglobulin chain will usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the CDR's to effect binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about about 3 Å as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

30 Claims, 55 Drawing Sheets

IPR2018-01422

Lilly Exhibit 1023, Page 1 of 147

> Perhaps most importantly, non-human monoclonal antibodies contain substantial stretches of amino acid sequences that will be immunogenic when injected into a human patient. Numerous studies have shown that after injection of

Ex. 1023, 1:44-47; Ex. 1008, ¶¶128-129; Pet., 29

> ity to a predetermined antigen. These humanized immunoglobulins should remain substantially non-immunogenic in humans, yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses.

Ex. 1023, 2:30-33; Pet., 35

> In accordance with the present invention, novel means of designing humanized immunoglobulins capable of specifically binding to a predetermined antigen with strong affinity are provided. These improved methods produce immuno-

Ex. 1023, 10:57-60; 1013, ¶54; Pet. (IPR2018-01426), 21-22, 37

The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation

Dr. Vasserot's testimony:

"A POSA would have been particularly motivated to make a humanized antibody when its murine counterpart antibody had been shown to exhibit functional properties that could be useful in treating a disease. [ ] Routine humanization techniques known in the art would have provided a reasonable expectation for a POSA to obtain a humanized antibody with similar desirable properties. All of these were present for CGRP."

Ex. 1009, ¶¶70-71; Pet., 29; Reply, 5

Q: So AME is the type of company that would take Tan 1994, humanize Tan's antibody, and take it to clinic?

A: We have done worse than that.

Q: You have done worse than that. What have you done that's worse than that?

A: We have started projects with less data than that.

Ex. 2191, 99:8-100:1; Reply, 5

The Prospect of Creating a "Potential Therapeutic" Is Sufficient Motivation

Teva's sur-reply argument:

"Lilly then points to Dr. Tomlinson's acknowledgment that he "humanized antibodies all the time" as evidence of motivation in 2005. Reply, 5. But Dr. Tomlinson was discussing his humanization activities from 2007 to 2016, not prior to 2005. EX1301, 55:1-13."

Sur-reply, 7

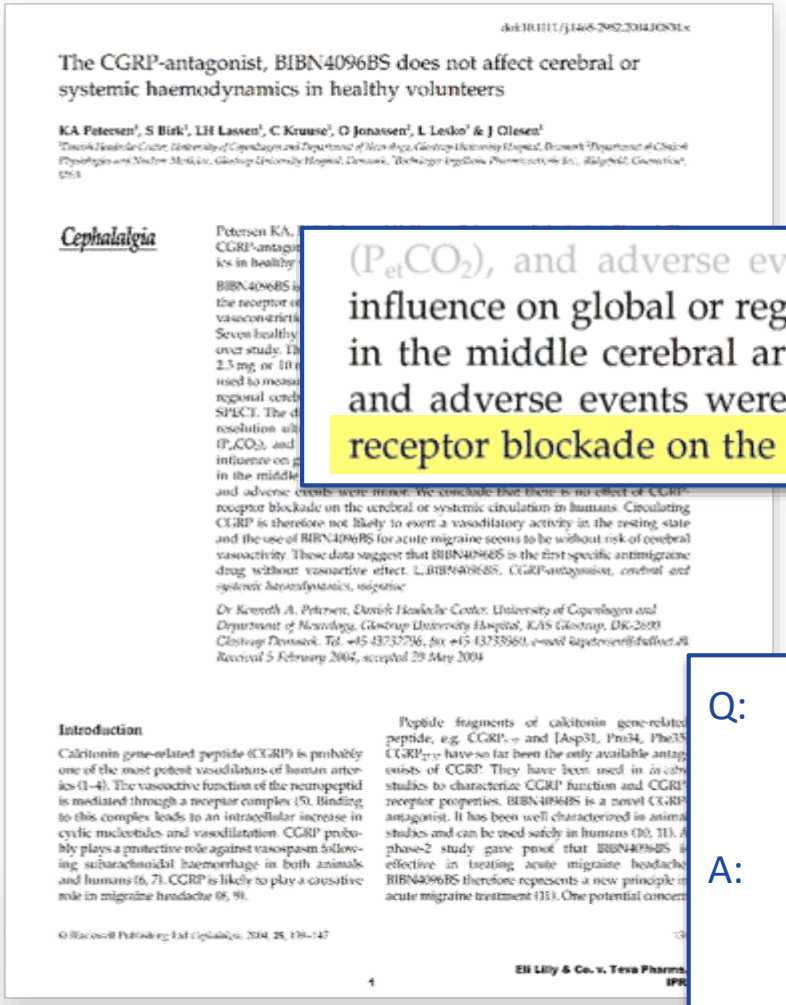
Dr. Tomlinson cross-examination:

Q: I'd like to consider the time frame before the earliest filing date of September 14, 2005. So before September 14, 2005, when was the – I guess the – the latest time before that date that you humanized a murine antibody or murine antibody fragment?

A: … during my time at the MRC I was working literally alongside the people that were doing the work on humanizing antibodies. … I spent a lot of time discussing humanization with colleagues at, for example, Genentech, and other companies that were doing a lot of humanization at the time under license from the MRC.

Ex. 1301, 55:16-56:23

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 2019)



The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers

KA Petersen[1], S Birk[2], LH Lassen[2], C Krause[2], O Jonassen[2], L Lesko[3] & J Olesen[1]

Cephalalgia

Introduction

($P_{et}CO_2$), and adverse events were monitored regularly. BIBN4096BS had no influence on global or regional cerebral blood flow, or on the blood flow velocity in the middle cerebral artery. There was no effect on systemic haemodynamics and adverse events were minor. We conclude that there is no effect of CGRP-receptor blockade on the cerebral or systemic circulation in humans. Circulating

Ex. 2019, Abstract; Ex. 1306, ¶36; Reply, 8

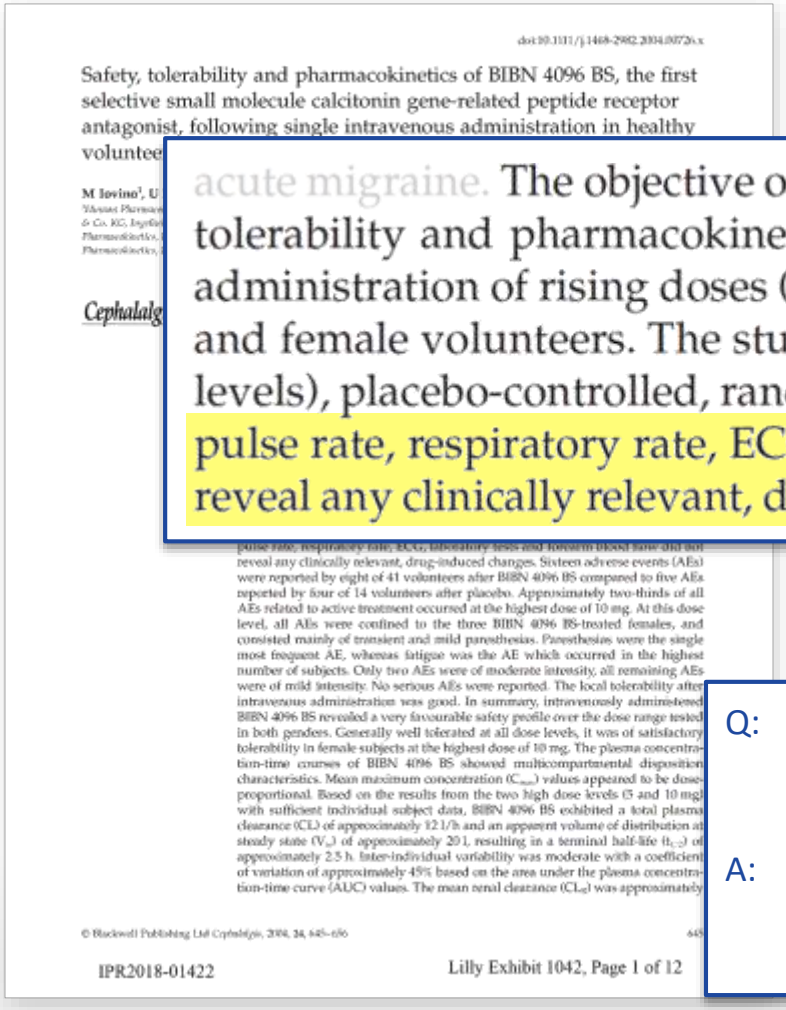
Dr. Ferrari's cross-examination:

Q: So in healthy volunteers, blocking the CGRP pathway had no clinically meaningful effect on blood pressure, correct?

A: …in healthy volunteers under physiological circumstances, there is admittedly no effect on the parameters you just mentioned.

Ex. 1303, 91:19-92:20; Reply, 8

Prior Art Clinical Studies Disclosed the Vascular Safety of CGRP Antagonism (Ex. 1042)



Safety, tolerability and pharmacokinetics of BIBN 4096 BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy volunteer

M Iovino[1], U

Cephalalg

acute migraine. The objective of this study was to obtain information on the safety, tolerability and pharmacokinetics of BIBN 4096 BS following single intravenous administration of rising doses (0.1, 0.25, 0.5, 1, 2.5, 5 and 10 mg) in 55 healthy male and female volunteers. The study was of single-centre, double-blind (within dose levels), placebo-controlled, randomized, single rising dose design. Blood pressure, pulse rate, respiratory rate, ECG, laboratory tests and forearm blood flow did not reveal any clinically relevant, drug-induced changes. Sixteen adverse events (AEs)

reveal any clinically relevant, drug-induced changes. Sixteen adverse events (AEs) were reported by eight of 41 volunteers after BIBN 4096 BS compared to five AEs reported by four of 14 volunteers after placebo. Approximately two-thirds of all AEs related to active treatment occurred at the highest dose of 10 mg. At this dose level, all AEs were confined to the three BIBN 4096 BS-treated females, and consisted mainly of transient and mild paresthesias. Paresthesias were the single most frequent AE, whereas fatigue was the AE which occurred in the highest number of subjects. Only two AEs were of moderate intensity, all remaining AEs were of mild intensity. No serious AEs were reported. The local tolerability after intravenous administration was good. In summary, intravenously administered BIBN 4096 BS revealed a very favourable safety profile over the dose range tested in both genders. Generally well tolerated at all dose levels, it was of satisfactory tolerability in female subjects at the highest dose of 10 mg. The plasma concentration-time courses of BIBN 4096 BS showed multicompartmental disposition characteristics. Mean maximum concentration (C_{max}) values appeared to be dose-proportional. Based on the results from the two high dose levels (5 and 10 mg) with sufficient individual subject data, BIBN 4096 BS exhibited a total plasma clearance (CL) of approximately 12 l/h and an apparent volume of distribution at steady state (V_{ss}) of approximately 20 l, resulting in a terminal half-life ($t_{1/2}$) of approximately 2.5 h. Inter-individual variability was moderate with a coefficient of variation of approximately 45% based on the area under the plasma concentration-time curve (AUC) values. The mean renal clearance (CL_R) was approximately

© Blackwell Publishing Ltd Cephalalgia, 2004, 24, 645–656

IPR2018-01422

Lilly Exhibit 1042, Page 1 of 12

Ex. 1042, Abstract; Ex. 1306, ¶35; Reply, 8

Dr. Charles's testimony:

Q: Any – a study showing that there were no adverse events in healthy volunteers would be reassuring for you with respect to patients who have a history of ischemia?

A: Yes . . . information about the vascular consequences of a compound in healthy volunteers is reassuring about the use of these compounds in the setting of ischemia.

Ex. 2272, 96:22-97:7

Tan 1995 Did Not Raise Safety Concerns

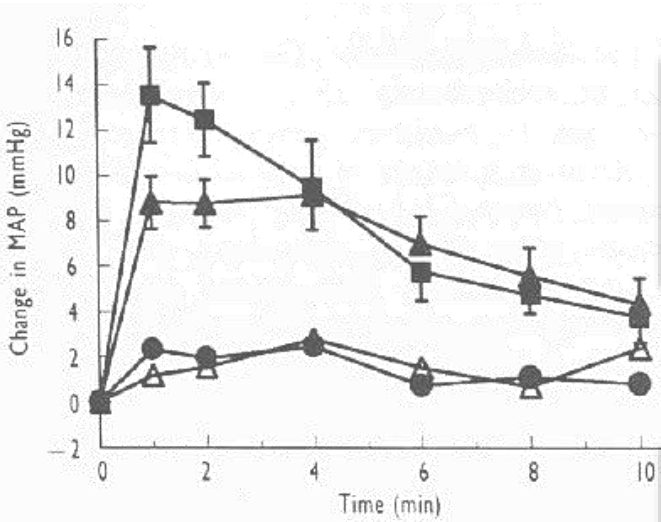


Fig. 2. Effect of 1 mg/rat (●) or 3 mg/rat (■) MAb C4.19 2 mg/rat MAb C4.19 Fab' fragment (▲) or 2 mg/rat normal m Fab' fragment (△) on baseline MAP. Mean results are plotted standard error bars ($n = 4$–6). Some error bars have been omitte clarity.

Teva's arguments:

"Moreover, at 3 mg/rat, MAb C4.19 raised [mean arterial pressure] nearly 13-fold, while having minimal, if any, effect in the saphenous nerve assay. EX1022, 568, Figure 2, 569; EX2230, ¶¶52, 78."

POR, 24

Dr. Foord's cross-examination:

Q: Is it fair to state that at the one-minute mark, the monoclonal antibodies C14, c4.19 at 3 milligrams per kilogram, raised mean arterial pressure around 1.1-fold versus baseline, as reported in Tan 1995?

A: Yes.

Ex. 1300, 129:21-130:4; Reply, 11

Tan 1995 Did Not Raise Safety Concerns

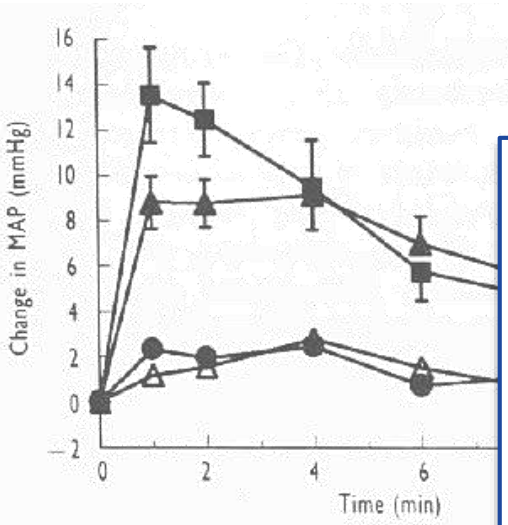


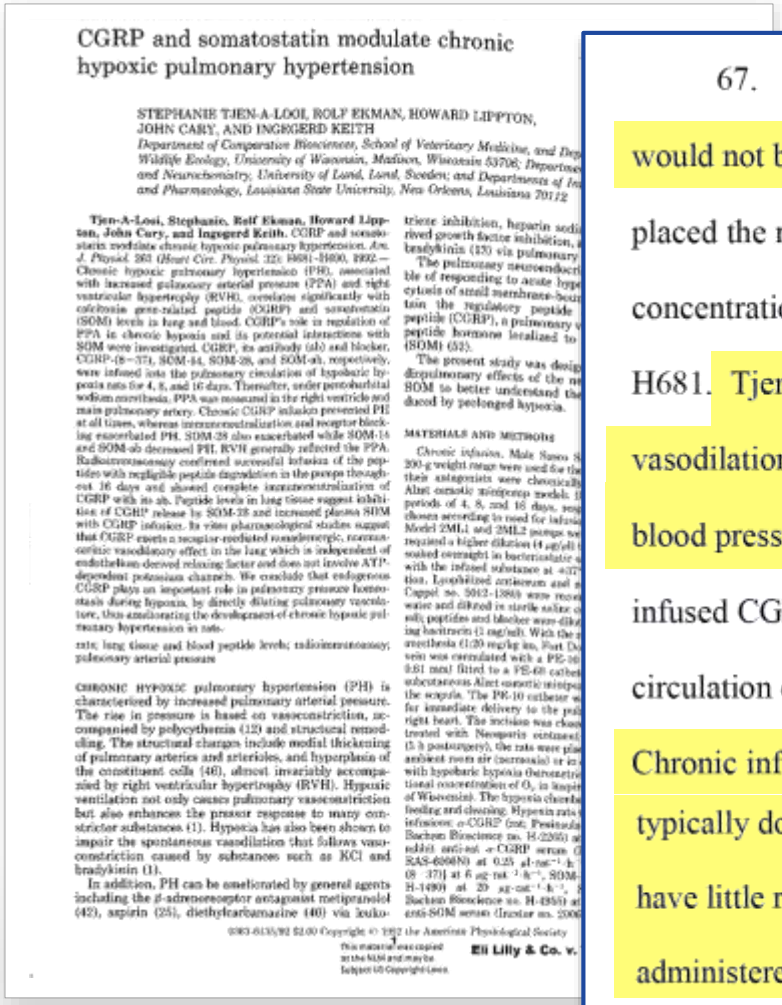
Fig. 2. Effect of 1 mg/rat (●) or 3 mg/rat (
2 mg/rat MAb C4.19 Fab' fragment (▲) or 2 m
Fab' fragment (△) on baseline MAP. Mean re
standard error bars ($n = 4$–6). Some error bars h
clarity.

Dr. Balthasar's testimony:

57. Because full-length IgG antibodies have half-lives on the order of weeks, a POSA would have understood that the minor blood pressure increase observed had no relationship to the half-life of Tan's C4.19 antibody. Ex. 1022, 568. Because the observed transient and minimal impact on blood pressure was not tied to the long half-life of MAb C4.19, Tan 1995's blood pressure study results would not have raised any concerns about long-term blood pressure increases upon anti-CGRP antagonist antibody administration.

Ex. 1305, ¶57; Reply, 11

Tjen-A-Looi (Ex. 2084) Is Not Relevant



CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension

STEPHANIE TJEN-A-LOOI, ROLF EKMAN, HOWARD LIPPTON, JOHN CARY, AND INGEGERD KEITH

Department of Comparative Biosciences, School of Veterinary Medicine, and Dep... Wildlife Ecology, University of Wisconsin, Madison, Wisconsin 53706; Departme... and Neurochemistry, University of Lund, Lund, Sweden; and Departments of In... and Pharmacology, Louisiana State University, New Orleans, Louisiana 70112

Tjen-A-Looi, Stephanie, Rolf Ekman, Howard Lippton, John Cary, and Ingegerd Keith. CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension. *Am. J. Physiol.* 263 (*Heart Circ. Physiol.* 32): H681–H690, 1992.—Chronic hypoxic pulmonary hypertension (PH), associated with increased pulmonary arterial pressure (PPA) and right ventricular hypertrophy (RVH), correlates significantly with calcitonin gene-related peptide (CGRP) and somatostatin (SOM) levels in lung and blood. CGRP's role in regulation of PPA in chronic hypoxia and its potential interactions with SOM were investigated. CGRP, its antibody (ab) and blocker, CGRP-(8–37), SOM-14, SOM-28, and SOM-ab, respectively, were infused into the pulmonary circulation of hypoxic hypoxia rats for 4, 8, and 16 days. Thereafter, under pentobarbital sodium anesthesia, PPA was measured in the right ventricle and main pulmonary artery. Chronic CGRP infusion prevented PH at all times, whereas immunoneutralization and receptor blocking exacerbated PH. SOM-28 also exacerbated while SOM-14 and SOM-ab decreased PH. RVH generally reflected the PPA. Radioimmunoassay confirmed successful infusion of the peptides with negligible peptide degradation in the pumps throughout 16 days and showed complete immunoneutralization of CGRP with its ab. Peptide levels in lung tissue suggest inhibition of CGRP release by SOM-28 and increased plasma SOM with CGRP infusion. In vitro pharmacological studies suggest that CGRP exerts a receptor-mediated noradrenergic, noncholinergic vasodilatory effect in the lung which is independent of endothelium-derived relaxing factor and does not involve ATP-dependent potassium channels. We conclude that endogenous CGRP plays an important role in pulmonary pressure homeostasis during hypoxia, by directly dilating pulmonary vasculature, thus ameliorating the development of chronic hypoxic pulmonary hypertension in rats.

rats; lung tissue and blood peptide levels; radioimmunoassay; pulmonary arterial pressure

CHRONIC HYPOXIC pulmonary hypertension (PH) is characterized by increased pulmonary arterial pressure. The rise in pressure is based on vasoconstriction, accompanied by polycythemia (12) and structural remodeling. The structural changes include medial thickening of pulmonary arteries and arterioles, and hyperplasia of the constituent cells (48), almost invariably accompanied by right ventricular hypertrophy (RVH). Hypoxic ventilation not only causes pulmonary vasoconstriction but also enhances the pressor response to many constrictor substances (1). Hypoxia has also been shown to impair the spontaneous vasodilation that follows vasoconstriction caused by substances such as KCl and bradykinin (1).

In addition, PH can be ameliorated by general agents including the β-adrenoreceptor antagonist metipranolol (42), aspirin (25), diethylcarbamazine (40) via leukotriene inhibition, heparin sodium, derived growth factor inhibition, bradykinin (13) via pulmonary

The pulmonary neuroendocrine ... ble of responding to acute hypo... cytosis of small membrane-bound ... tain the regulatory peptide ... peptide (CGRP), a pulmonary ... peptide hormone localized to ... (SOM) (52).

The present study was design... dirpulmonary effects of the ... SOM to better understand the ... duced by prolonged hypoxia.

MATERIALS AND METHODS

Chronic infusion. Male Sprague-Dawley ... 200-g weight range were used for the ... their antagonists were chronically ... Alzet osmotic minipump model ... periods of 4, 8, and 16 days, respectively ... chosen according to need for infusion ... Model 2ML1 and 2ML2 pumps were ... required a higher dilution (4 μg/ml) ... soaked overnight in bacteriostatic ... with the infused substance at 37°C ... tion. Lyophilized antiserum and ... Cappel no. 5062-1360) were reconstituted ... water and diluted in sterile saline or ... sol; peptides and blocker were diluted ... ing bacitracin (3 mg/ml). With the ... anesthesia (1:20 mg/kg im, Fort Dodge ... vein was cannulated with a PE-10 ... 0.51 mm) fitted to a PE-60 catheter ... subcutaneous Alzet osmotic minipump ... the scapula. The PE-10 catheter was ... for immediate delivery to the pulmonary ... right heart. The incision was closed ... treated with Neosporin ointment ... (5 h postsurgery), the rats were placed ... ambient room air (normoxia) or in ... with hypobaric hypoxia (barometric ... tional concentration of O_2, in Inspired ... of Wisconsin). The hypoxia chamber ... feeding and cleaning. Hypoxic rats ... infusions: α-CGRP (rat; Peninsula ... Bachem Bioscience no. H-2260) ... rabbit anti-rat α-CGRP serum ... SAS-606080) at 0.25 ml·rat^{-1}·h^{-1} ... (8–37)] at 6 μg·rat^{-1}·h^{-1}, SOM-28 ... H-1490) at 20 μg·rat^{-1}·h^{-1}, ... Bachem Bioscience no. H-4355) ... anti-SOM serum (Incstar no. 2006 ...

0363-6135/92 $2.00 Copyright © 1992 the American Physiological Society

This material was copied ... on the NLM and may be ... Subject to Copyright Laws.

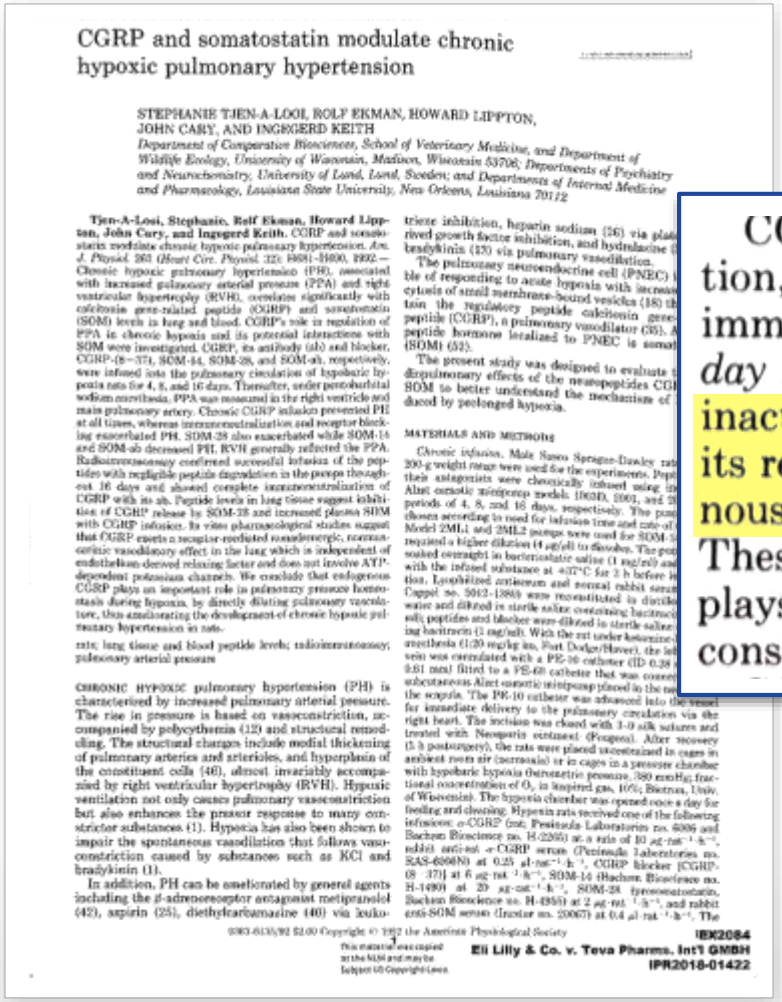
Eli Lilly & Co. v. ...

Dr. Balthasar's testimony:

67. In Tjen-A-Looi, the researchers analyzed rats under conditions that would not be encountered in any reasonable clinical setting. First, Tjen-A-Looi placed the rats under investigation in hypobaric chambers with only a 10% oxygen concentration, roughly half of the oxygen concentration of ambient air. Ex. 2084, H681. Tjen-A-Looi notes that the hypoxia conditions were designed to impair vasodilation responses in rats, and would have the effect of artificially enhancing blood pressure responses. Ex. 2084, H681. Second, Tjen-A-Looi continuously infused CGRP, rabbit anti-rat αCGRP serum, or $CGRP_{8-37}$ into the pulmonary circulation of hypoxic rats for 4, 8, or 16 days, respectively. Ex. 2084, H681. Chronic infusion over days is not a reasonable approximation of how drugs are typically dosed in practice. Thus, a POSA would have understood Tjen-A-Looi to have little relevance for assessing potential side effects of the compounds administered.

Ex. 1305, ¶67; Reply, 11

Tjen-A-Looi (Ex. 2084) Observed a Stronger Pulmonary Arterial Pressure Increase with $CGRP_{8-37}$



CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension

STEPHANIE TJEN-A-LOOI, ROLF EKMAN, HOWARD LIPPTON, JOHN CARY, AND INGEGERD KEITH

Department of Comparative Biosciences, School of Veterinary Medicine, and Department of Wildlife Ecology, University of Wisconsin, Madison, Wisconsin 53706; Departments of Psychiatry and Neurochemistry, University of Lund, Lund, Sweden; and Departments of Internal Medicine and Pharmacology, Louisiana State University, New Orleans, Louisiana 70112

Tjen-A-Looi, Stephanie, Rolf Ekman, Howard Lippton, John Cary, and Ingegerd Keith. CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension. *Am. J. Physiol.* 263 (*Heart Circ. Physiol.* 32): H681–H690, 1992.—Chronic hypoxic pulmonary hypertension (PH), associated with increased pulmonary arterial pressure (PPA) and right ventricular hypertrophy (RVH), correlates significantly with calcitonin gene-related peptide (CGRP) and somatostatin (SOM) levels in lung and blood. CGRP's role in regulation of PPA in chronic hypoxia and its potential interactions with SOM were investigated. CGRP, its antibody (ab) and blocker, CGRP-(8–37), SOM-14, SOM-28, and SOM-ab, respectively, were infused into the pulmonary circulation of hypobaric hypoxia rats for 4, 8, and 16 days. Thereafter, under pentobarbital sodium anesthesia, PPA was measured in the right ventricle and main pulmonary artery. Chronic CGRP infusion prevented PH at all times, whereas immunoneutralization and receptor blocking exacerbated PH. SOM-28 also exacerbated while SOM-14 and SOM-ab decreased PH. RVH generally reflected the PPA. Radioimmunoassay confirmed successful infusion of the peptides with negligible peptide degradation in the pumps throughout 16 days and showed complete immunoneutralization of CGRP with its ab. Peptide levels in lung tissue suggest inhibition of CGRP release by SOM-28 and increased plasma SOM with CGRP infusion. In vitro pharmacological studies suggest that CGRP exerts a receptor-mediated noradrenergic, nonvasoconstrictor vasodilatory effect in the lung which is independent of endothelium-derived relaxing factor and does not involve ATP-dependent potassium channels. We conclude that endogenous CGRP plays an important role in pulmonary pressure homeostasis during hypoxia, by directly dilating pulmonary vasculature, thus ameliorating the development of chronic hypoxic pulmonary hypertension in rats.

rats; lung tissue and blood peptide levels; radioimmunoassay; pulmonary arterial pressure

CHRONIC HYPOXIC pulmonary hypertension (PH) is characterized by increased pulmonary arterial pressure. The rise in pressure is based on vasoconstriction, accompanied by polycythemia (12) and structural remodeling. The structural changes include medial thickening of pulmonary arteries and arterioles, and hyperplasia of the constituent cells (48), almost invariably accompanied by right ventricular hypertrophy (RVH). Hypoxic ventilation not only causes pulmonary vasoconstriction but also enhances the pressor response to many constrictor substances (1). Hypoxia has also been shown to impair the spontaneous vasodilation that follows vasoconstriction caused by substances such as KCl and bradykinin (1).

In addition, PH can be ameliorated by general agents including the β-adrenoreceptor antagonist metipranolol (42), aspirin (25), diethylcarbamazine (40) via leukotriene inhibition, heparin sodium (26) via platelet-derived growth factor inhibition, and hydralazine (3) bradykinin (13) via pulmonary vasodilation.

The pulmonary neuroendocrine cell (PNEC) is capable of responding to acute hypoxia with increased exocytosis of small membrane-bound vesicles (18) that contain the regulatory peptide calcitonin gene-related peptide (CGRP), a pulmonary vasodilator (35). Another peptide hormone localized to PNEC is somatostatin (SOM) (52).

The present study was designed to evaluate the cardiopulmonary effects of the neuropeptides CGRP and SOM to better understand the mechanism of hypoxia induced by prolonged hypoxia.

MATERIALS AND METHODS

Chronic infusion. Male Sasco Sprague-Dawley rats (200-g weight range were used for the experiments. Peptides and their antagonists were chronically infused using osmotic minipumps (Alzet osmotic minipumps models 1002D, 2001, and 2ML2 for periods of 4, 8, and 16 days, respectively. The pumps were chosen according to need for infusion time and rate of infusion. Model 2ML1 and 2ML2 pumps were used for SOM-14 and SOM-28 as they required a higher dilution (4 μg/ml) to dissolve. The pumps were filled and soaked overnight in bacteriostatic saline (1 mg/ml) and primed with the infused substance at 37°C for 3 h before implantation. Lyophilized antiserum and normal rabbit serum (Calbiochem-Behring Corp. Cappel no. 5042-1360) were reconstituted in distilled water and diluted in sterile saline containing bacteriostatic (0.9%) saline; peptides and blocker were diluted in sterile saline containing bacitracin (3 mg/ml). With the rat under ketamine-xylazine anesthesia (1:20 mg/kg im, Fort Dodge/Hoechst), the left external jugular vein was cannulated with a PE-10 catheter (ID 0.28 mm, OD 0.61 mm) fitted to a PE-60 catheter that was connected to a subcutaneous Alzet osmotic minipump placed in the nape of the scapula. The PE-10 catheter was advanced into the vessel for immediate delivery to the pulmonary circulation via the right heart. The incision was closed with 3-0 silk sutures and treated with Neosporin ointment (Pfizer). After recovery (5 h postsurgery), the rats were placed unrestrained in cages in ambient room air (normoxia) or in cages in a pressure chamber with hypobaric hypoxia (barometric pressure, 380 mmHg; fractional concentration of O_2 in inspired gas, 10%; Biotron, Univ. of Wisconsin). The hypoxia chamber was opened once a day for feeding and cleaning. Hypoxia rats received one of the following infusions: α-CGRP (rat; Peninsula Laboratories no. 6006 and Bachem Bioscience no. H-2260) at a rate of 10 $\mu g \cdot rat^{-1} \cdot h^{-1}$, rabbit anti-rat α-CGRP serum (Peninsula Laboratories no. SAS-600680) at 0.25 $\mu l \cdot rat^{-1} \cdot h^{-1}$, CGRP blocker [CGRP-(8–37)] at 6 $\mu g \cdot rat^{-1} \cdot h^{-1}$, SOM-14 (Bachem Bioscience no. H-1490) at 20 $\mu g \cdot rat^{-1} \cdot h^{-1}$, SOM-28 (prosomatostatin, Bachem Bioscience no. H-4355) at 2 $\mu g \cdot rat^{-1} \cdot h^{-1}$, and rabbit anti-SOM serum (Incstar no. 20067) at 0.4 $\mu l \cdot rat^{-1} \cdot h^{-1}$. The

0363-6135/92 $2.00 Copyright © 1992 the American Physiological Society

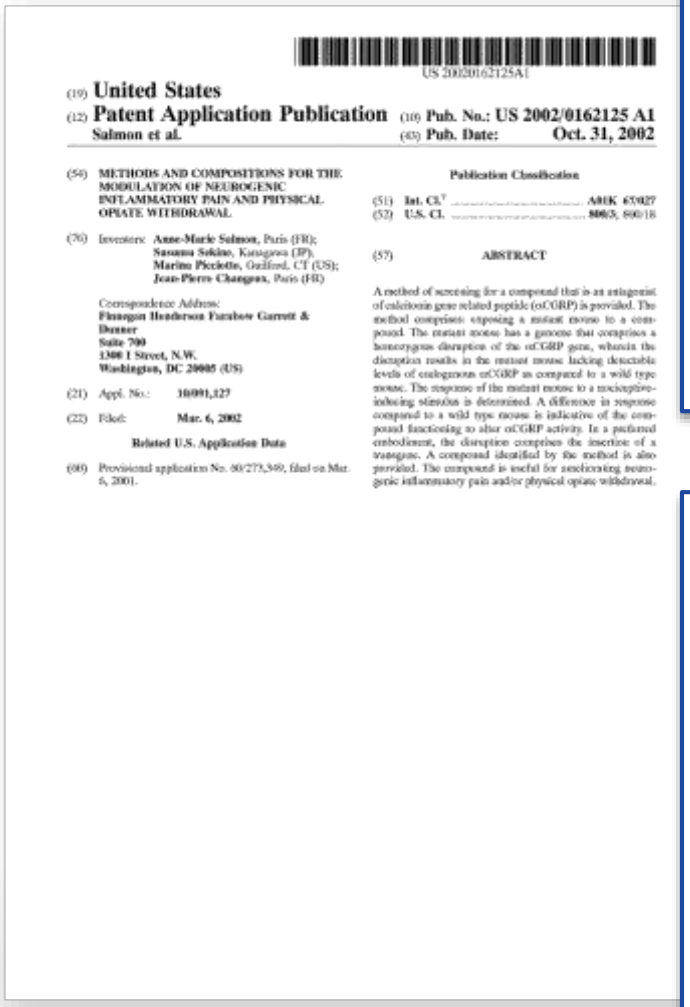
This material was copied at the NLM and may be subject to Copyright Laws.

IBX2084
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH
IPR2018-01422

CGRP antibody, infused into the pulmonary circulation, inactivated the endogenous circulating CGRP by immunoneutralization and enhanced the PPA by 22% at *day 16*. Furthermore, CGRP blocker, CGRP-(8—37), an inactive form of CGRP, prevented CGRP from binding to its receptor and eliminated the dilatory effect of endogenous CGRP, thus enhancing the PPA in hypoxia by 44%. These observations indicate that endogenous CGRP plays an important role in the homeostasis of PPA and, consequently, in PH.

Ex. 2084, H687; Ex. 1305, ¶68; Ex. 1306, ¶45; Reply, 11

CGRP Deletion Did Not Produce Safety Concerns



US 20020162125A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0162125 A1**

Salmon et al. (43) **Pub. Date: Oct. 31, 2002**

(54) METHODS AND COMPOSITIONS FOR THE MODULATION OF NEUROGENIC INFLAMMATORY PAIN AND PHYSICAL OPIATE WITHDRAWAL

Publication Classification

(51) Int. Cl.[7] A01K 67/027

(52) U.S. Cl. 800/3; 800/18

(76) Inventors: **Anne-Marie Salmon**, Paris (FR); **Susumu Sekine**, Kanagawa (JP); **Marino Picciotto**, Guilford, CT (US); **Jean-Pierre Changeux**, Paris (FR)

(57) ABSTRACT

A method of screening for a compound that is an antagonist of calcitonin gene related peptide (αCGRP) is provided. The method comprises: exposing a mutant mouse to a compound. The mutant mouse has a genome that comprises a homozygous disruption of the αCGRP gene, wherein the disruption results in the mutant mouse lacking detectable levels of endogenous αCGRP as compared to a wild type mouse. The response of the mutant mouse to a nociceptive-inducing stimulus is determined. A difference in response compared to a wild type mouse is indicative of the compound functioning to alter αCGRP activity. In a preferred embodiment, the disruption comprises the insertion of a transgene. A compound identified by the method is also provided. The compound is useful for ameliorating neurogenic inflammatory pain and/or physical opiate withdrawal.

Correspondence Address:
Finnegan Henderson Farabow Garrett & Dunner
Suite 700
1300 I Street, N.W.
Washington, DC 20005 (US)

(21) Appl. No.: **10/091,127**

(22) Filed: **Mar. 6, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/273,349, filed on Mar. 6, 2001.

[0069] The targeting construct was performed from the CT/CGRP gene (15), and the chimera mice were obtained as described (15). αCGRP −/− and +/+ mice are derived from backcrosses on the C57B16 strain after mating of heterozygous +/− mice. Homozygous mutant mice, from all generations, are healthy, fertile and do not present obvious abnormalities. The body temperature is the same in mutant and wild type mice, and no differences in the body weight of the two lines were observed during development.

Ex. 1027, ¶[0069]; Ex. 1306, ¶47; Reply, 12

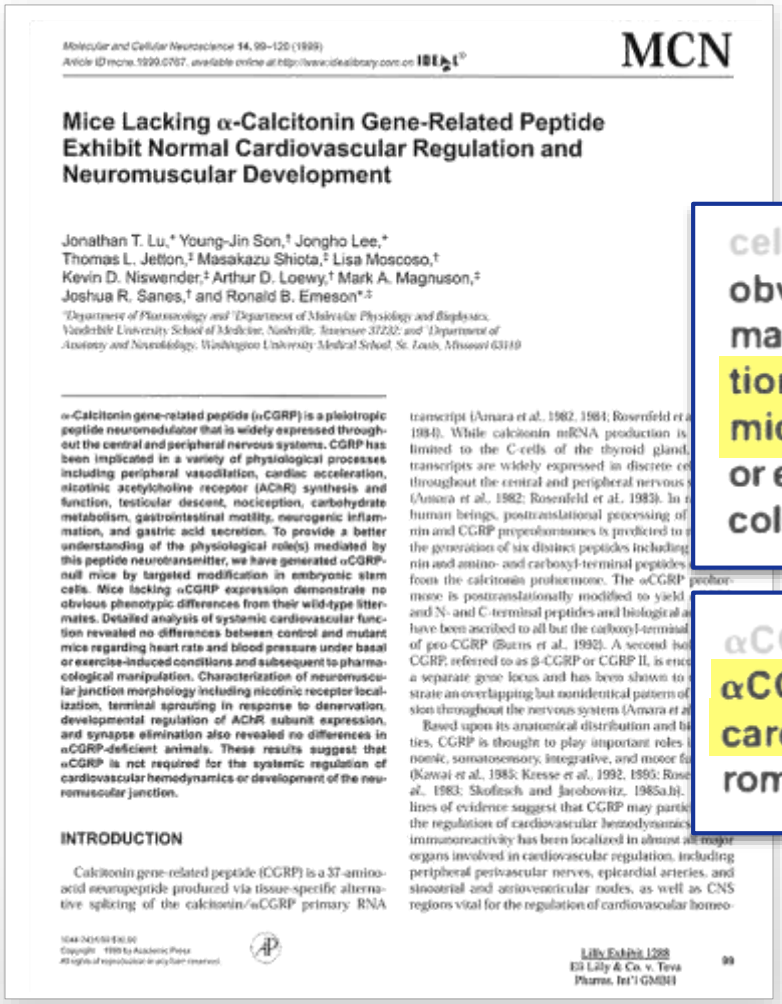
8. The compound of claim 6, which is a monoclonal antibody.

9. A method for ameliorating neurogenic inflammatory pain comprising:

administering a compound capable of specifically inhibiting αCGRP activity to an animal having neurogenic inflammatory pain symptoms in an amount sufficient to inhibit the αCGRP activity in the animal so that symptoms of neurogenic inflammatory pain are ameliorated.

Ex. 1027, claims 8 & 9; Reply, 12

CGRP Deletion Did Not Produce Safety Concerns



Molecular and Cellular Neuroscience 14, 99–120 (1999)
Article ID mcne.1999.0767, available online at http://www.idealibrary.com on IDEAL®

MCN

Mice Lacking α-Calcitonin Gene-Related Peptide Exhibit Normal Cardiovascular Regulation and Neuromuscular Development

Jonathan T. Lu,* Young-Jin Son,† Jongho Lee,*
Thomas L. Jetton,‡ Masakazu Shiota,‡ Lisa Moscoso,†
Kevin D. Niswender,‡ Arthur D. Loewy,† Mark A. Magnuson,‡
Joshua R. Sanes,† and Ronald B. Emeson*,‡

Department of Pharmacology and †Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee 37232; and ‡Department of Anatomy and Neurobiology, Washington University Medical School, St. Louis, Missouri 63110

α-Calcitonin gene-related peptide (αCGRP) is a pleiotropic peptide neuromodulator that is widely expressed throughout the central and peripheral nervous systems. CGRP has been implicated in a variety of physiological processes including peripheral vasodilation, cardiac acceleration, nicotinic acetylcholine receptor (AChR) synthesis and function, testicular descent, nociception, carbohydrate metabolism, gastrointestinal motility, neurogenic inflammation, and gastric acid secretion. To provide a better understanding of the physiological role(s) mediated by this peptide neurotransmitter, we have generated αCGRP-null mice by targeted modification in embryonic stem cells. Mice lacking αCGRP expression demonstrate no obvious phenotypic differences from their wild-type littermates. Detailed analysis of systemic cardiovascular function revealed no differences between control and mutant mice regarding heart rate and blood pressure under basal or exercise-induced conditions and subsequent to pharmacological manipulation. Characterization of neuromuscular junction morphology including nicotinic receptor localization, terminal sprouting in response to denervation, developmental regulation of AChR subunit expression, and synapse elimination also revealed no differences in αCGRP-deficient animals. These results suggest that αCGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuromuscular junction.

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is a 37-amino-acid neuropeptide produced via tissue-specific alternative splicing of the calcitonin/αCGRP primary RNA transcript (Amara et al., 1982, 1984; Rosenfeld et al., 1984). While calcitonin mRNA production is limited to the C-cells of the thyroid gland, transcripts are widely expressed in discrete cells throughout the central and peripheral nervous systems (Amara et al., 1982; Rosenfeld et al., 1983). In human beings, posttranslational processing of calcitonin and CGRP preprohormones is predicted to result in the generation of six distinct peptides including calcitonin and amino- and carboxyl-terminal peptides from the calcitonin prohormone. The αCGRP prohormone is posttranslationally modified to yield CGRP and N- and C-terminal peptides and biological activities have been ascribed to all but the carboxyl-terminal peptide of pro-CGRP (Burns et al., 1992). A second isoform, CGRP, referred to as β-CGRP or CGRP II, is encoded by a separate gene locus and has been shown to differentiate an overlapping but nonidentical pattern of expression throughout the nervous system (Amara et al., 1985). Based upon its anatomical distribution and biological activities, CGRP is thought to play important roles in autonomic, somatosensory, integrative, and motor functions (Kawai et al., 1985; Kresse et al., 1992, 1995; Rosenfeld et al., 1983; Skofitsch and Jacobowitz, 1985a,b). Several lines of evidence suggest that CGRP may participate in the regulation of cardiovascular hemodynamics. CGRP immunoreactivity has been localized in almost all major organs involved in cardiovascular regulation, including peripheral perivascular nerves, epicardial arteries, and sinoatrial and atrioventricular nodes, as well as CNS regions vital for the regulation of cardiovascular homeo-

cells. **Mice lacking αCGRP expression demonstrate no obvious phenotypic differences from their wild-type littermates. Detailed analysis of systemic cardiovascular function revealed no differences between control and mutant mice regarding heart rate and blood pressure under basal or exercise-induced conditions and subsequent to pharmacological manipulation.** Characterization of neuromuscu-

αCGRP-deficient animals. **These results suggest that αCGRP is not required for the systemic regulation of cardiovascular hemodynamics or development of the neuromuscular junction.**

Ex. 1288, Abstract; Ex. 1306, ¶48; Reply, 12

Purported Safety Concerns Did Not Deter Researchers

Nucleic Acids Research, 2003, Vol. 31, No. 21
DOI: 10.1093/nar/...

Short bioactive Spiegelmers to migraine-associate calcitonin gene-related peptide rapidly identified b novel approach: Tailored-SELEX

Axel Vater, Florian Jarosch, Klaus Buchner and Sven Klussmann*

NOXXON Pharma AG, Max-Dohrn-Strasse 8–10, D-10589 Berlin, Germany

Received August 7, 2003; Revised and Accepted September 10, 2003

ABSTRACT

We developed an integrated method to identify aptamers with only 10 fixed nucleotides through ligation and removal of primer binding sites within the systematic evolution of ligands by exponential enrichment (SELEX) process. This Tailored-SELEX approach was validated by identifying a Spiegelmer ('mirror-image aptamer') that inhibits the action of the migraine-associated target calcitonin gene-related peptide 1 (α-CGRP) with an IC_{50} of 3 nM at 37°C in cell culture. Aptamers are oligonucleotide ligands that can be generated to bind to targets with high affinity and specificity. Stabilized aptamers and Spiegelmers have shown activity *in vivo* and may be used as therapeutics. Aptamers are isolated by *in vitro* selection from combinatorial nucleic acid libraries that are composed of a central randomized region and additional fixed primer binding sites with ~30–40 nt. The identified sequences are usually not short enough for efficient chemical Spiegelmer synthesis, post-SELEX stabilization of aptamers and economical production. If the terminal primer binding sites are part of the target recognizing domain, truncation of aptamers has proven difficult and laborious. Tailored-SELEX results in short sequences that can be tested more rapidly in biological systems. Currently, our identified CGRP binding Spiegelmer serves as a lead compound for *in vivo* studies.

INTRODUCTION

Since the invention of *in vitro* selection of oligonucleotides from combinatorial nucleic acid libraries, also known as systematic evolution of ligands by exponential enrichment (SELEX), the use of these molecules termed aptamers as therapeutics, e.g. for the specific interruption of disease-related protein–protein interactions, has been predicted and argued (1–3). Aptamers usually show binding constants to their respective protein or peptide targets in the same range as most receptor–ligand interactions and exhibit a high specificity (4–6).

In order to move aptamers from the bench to the several hurdles have to be taken. The most prominent the issues of aptamer stability in biological fl production costs. Stabilization of aptamers against nucleases has been improved by the introduction of modified nucleic acid libraries (pre-SELEX modific combination with post-SELEX modifications, that be the substitution of the RNA's 2′-OH group (7–10). strategy, chiral principles were introduced into the process in order to generate nuclease resistant aptam basis of L-RNA or L-DNA, so called Spiegelmers German 'Spiegel', meaning mirror) (11). Spiegelmers are identified through *in vitro* selection of an unmodified or D-DNA library against the mirror-image conf (enantiomer) of a drug target. The selected aptamer see then synthesized in their unnatural enantiomeric ation as L-RNAs or L-DNAs. Following the rules of these Spiegelmers bind to the natural target of interes the aptamers bind to the mirror-image selection target Aptamers with pre- and post-SELEX modifications Spiegelmers have been reported to be stable for many biological fluids (11,14).

For both strategies, the ability to chemically synt lead candidates is crucial, since neither post-SELEX aptamers nor Spiegelmers can be synthesized easy due to the lack of appropriate enzymes. However, and Spiegelmers that are identified through the SELEX process usually comprise 60–90 nt, since typically selected from nucleic acid libraries with long randomized regions plus fixed primer sites of ~ on each side. Standard chemical oligoribonucleotide however, is only efficiently applicable up to 60 decreasing yields and escalating production costs incorporated base.

Therefore, the identified lead oligonucleotides nee and experimental truncation before they can be further tested in biological systems (15). Whether or not the th given lead aptamer or Spiegelmer will eventu may not be foreseen. The flanking fixed region participate in forming the scaffold that surrounds interface and may thus not simply be omitted (16

*To whom correspondence should be addressed. Tel: +49 30 726247 240; Fax: +49 30 726247 243; Email: ...

The authors wish to be known that, in their opinion, the first two authors should be regarded as joint First Authors

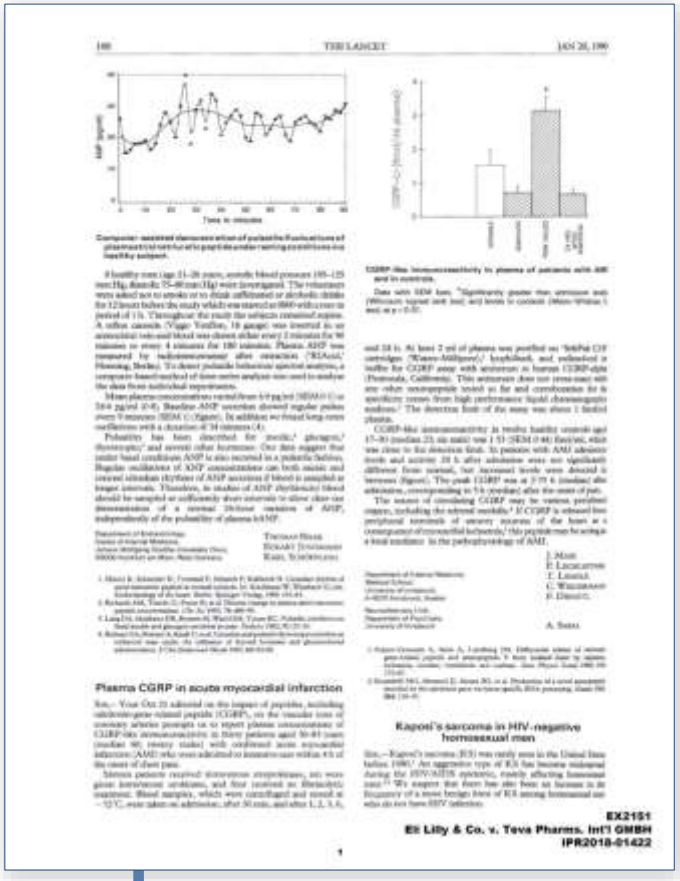
enrichment (SELEX) process. **This Tailored-SELEX approach was validated by identifying a Spiegelmer ('mirror-image aptamer') that inhibits the action of the migraine-associated target calcitonin gene-related peptide 1 (α-CGRP) with an IC_{50} of 3 nM at 37°C in cell culture. Aptamers are oligonucleotide ligands that can be generated to bind to targets with high affinity and specificity. Stabilized aptamers and Spiegelmers have shown activity *in vivo* and may be used as therapeutics.** Aptamers are isolated by

In order to prove the efficiency of Tailored-SELEX, we carried out an *in vitro* selection approach against the optical antipode of the neuropeptide calcitonin gene-related peptide 1 (α-CGRP) of rat. α-CGRP has been recognized as a potent vasodilator and has recently attracted attention as a novel target in acute migraine treatment (19–22).

19. Wimalawansa,S.J. (1996) Calcitonin gene-related peptide and its receptors: molecular genetics, physiology, pathophysiology and therapeutic potentials. *Endocr. Rev.*, **17**, 533–585.

Ex. 1082, Abstract, 2 (citing Wimalawansa as ref. 19);
Ex. 1306, ¶17; Reply, 9

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2151)



Plasma CGRP in acute myocardial infarction

Kaposi's sarcoma in HIV-negative homosexual men

EX2151
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH
IPR2018-01422

Dr. Ferrari's cross-examination:

Q: Exhibit 2151 does not study the effects of CGRP antagonism in healthy humans, correct?

A: Correct.

Q: And it doesn't study the effects of CGRP antagonism in migraine patients?

A: Correct.

Q: And, in fact, it doesn't study the effects of CGRP antagonism at all, correct?

A: Correct.

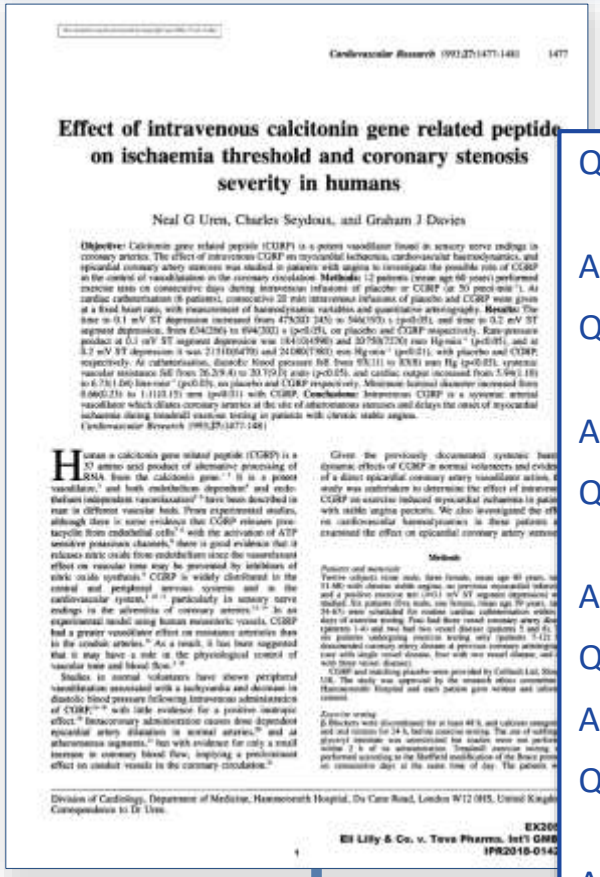
Ex. 1303, 111:11-20; Ex. 2151; Reply, 13

1990

1990 | 1995 | 2000 | 2005

Ex. 1306, ¶¶22, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2058)



Effect of intravenous calcitonin gene related peptide on ischaemia threshold and coronary stenosis severity in humans

Neal G Uren, Charles Seydoux, and Graham J Davies

Dr. Ferrari's cross-examination:

Q: Exhibit 2058 explores the administration of exogenous CGRP to patients with angina, correct?

A: Correct.

Q: Exhibit 2058 did not study the effects of CGRP in healthy humans, correct?

A: Correct.

Q: Exhibit 2058 did not study the effects of CGRP in migraine patients, correct?

A: Correct.

Q: Exhibit 2058 did not study the effects of a CGRP antagonist, correct?

A: Correct.

Q: And this study does not evaluate whether inhibiting endogenous CGRP would result in a worsening of cardiac ischemic events, correct?

A: Correct.

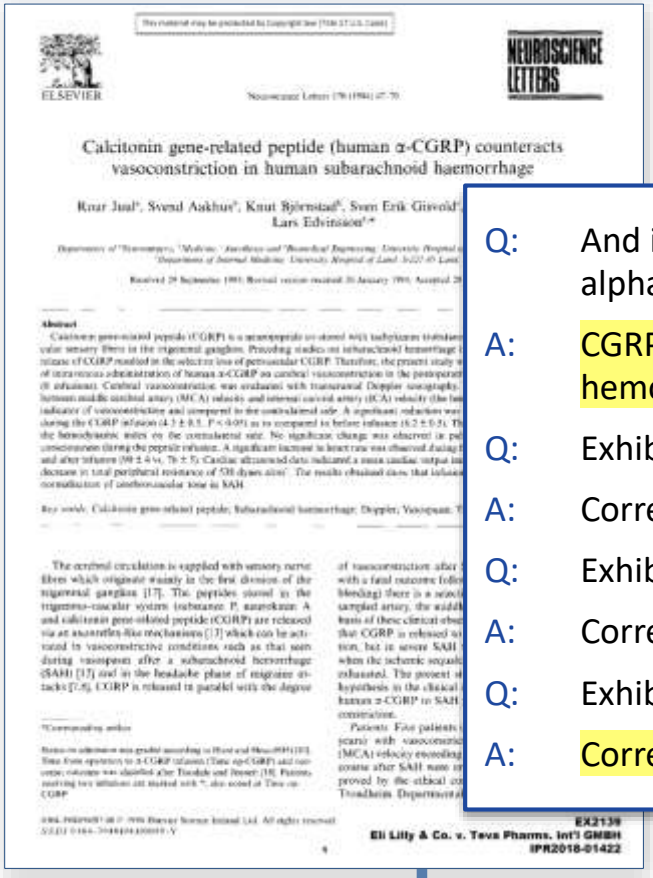
Ex. 1303, 130:7-131:2; Ex. 2058; Reply, 13

1993

1990 | 1995 | 2000 | 2005

Ex. 1306, ¶¶21, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2139)



ELSEVIER

NEUROSCIENCE LETTERS

Calcitonin gene-related peptide (human α-CGRP) counteracts vasoconstriction in human subarachnoid haemorrhage

Knut Jual*, Svend Aakhus*, Knut Bjørnstad*, Sven Erik Gisvold*, Lars Edvinsson*,*

EX2139
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH
IPR2018-01422

Dr. Ferrari's cross-examination:

Q: And in Exhibit 2139, patients were intravenously administered human alpha-CGRP after subarachnoid hemorrhage, correct?

A: CGRP was administered in a postoperative state after a subarachnoid hemorrhage.

Q: Exhibit 2139 does not study the effects of CGRP in healthy humans, correct?

A: Correct.

Q: Exhibit 2139 does not study the effects of CGRP in migraine patients?

A: Correct.

Q: Exhibit 2139 does not study the effects of a CGRP antagonist at all, correct?

A: Correct.

Ex. 1303, 126:24-127:15; Ex. 2139; Reply, 13

1994

1990 | 1995 | 2000 | 2005

Ex. 1306, ¶¶21, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2152)

ELSEVIER

ejp

Calcitonin gene-related peptide-induced preconditioning protects against ischemia-reperfusion injury in isolated rat hearts

Yuan-Jian Li *, Zhou-Sheng Xiao, Chang-Fu Peng, Han-Wu Deng

Abstract

Our previous work has suggested that the calcitonin gene-related peptide (CGRP) receptor antagonist CGRP-(8–37) can abolish the protective effect of ischemic preconditioning in the isolated rat heart. Therefore we tested the hypothesis that CGRP- or capsaicin-induced preconditioning protects against ischemia-reperfusion injury in the isolated perfused rat heart. Thirty minutes of global ischemia and 30 min of reperfusion caused a significant cardiac contractile dysfunction, ventricular arrhythmia, and an increased release of creatine phosphate kinase. Pretreatment with CGRP or capsaicin, which evokes release of CGRP from cardiac sensory nerves, for 5 min produced a significant improvement of cardiac function, a reduction in the incidence of ventricular arrhythmia, and a decrease in the release of creatine phosphate kinase. However, the cardioprotection provided by CGRP- or capsaicin-induced preconditioning was abolished by CGRP-(8–37) and ruthenium red, respectively. These findings suggest that CGRP- or capsaicin-induced preconditioning protects against ischemic myocardial injury. The present results also suggest that CGRP may be an endogenous myocardial protective substance in the rat.

Keywords: Heart; rat; Preconditioning; CGRP; Calcitonin gene-related peptide; CGRP-(8–37); Capsaicin; Ruthenium red

1. Introduction

Ischemic preconditioning was first described by Murry and his colleagues in 1986 (Murry et al., 1986), and this phenomenon has been confirmed in various animals (Schott et al., 1990; Liu et al., 1991; Liu and Downey, 1992; Yao and Gross, 1994) and in humans (Ahlsfeldt et al., 1994). The mechanism underlying preconditioning remains unknown. There is now an increasing amount of evidence which suggests the involvement of endogenous myocardial protective substances in ischemic preconditioning (Parratt, 1993, 1994). Calcitonin gene-related peptide (CGRP), a principal transmitter in capsaicin-sensitive sensory nerves, is present in the hearts of animals and humans (Wharton et al., 1986; Franco-Cereceda, 1988). It has been shown that CGRP possesses numerous physiological properties, several of which are thought to be beneficial to the ischemic myocardium (Ren et al., 1992; Li et al., 1995).

It has been shown that capsaicin, which evokes CGRP release from sensory nerves, protects against myocardial injury induced by ischemia-reperfusion in the isolated perfused rat heart (D'Alonzo et al., 1993). Recently, we showed that in the isolated rat heart, the CGRP receptor antagonist CGRP-(8–37) can abolish the cardioprotection of ischemic preconditioning (Qiao et al., 1996). These studies suggest that CGRP may play an important role in mediation of ischemic preconditioning. The present study was designed to further explore whether CGRP is an endogenous myocardial protective substance, and more specifically to answer the following questions: (1) does treatment with CGRP result in a preconditioning-like effect in the rat model of ischemia-reperfusion? and (2) does capsaicin, which evokes the release of CGRP, possess a similar beneficial effect?

2. Materials and methods

2.1. Isolated perfused heart

Male Sprague-Dawley rats weighing 200–250 g were anesthetized with ether. The hearts were rapidly excised and placed in cold Krebs-Henseleit buffer solution (4°C). Retrograde, nonrecirculating perfusion through the aorta was performed according to the modified Langendorff

* Corresponding author. Tel.: 086-731-4474411 ext. 2704; fax: 086-731-4471106.

PII S0014-2999(96)00426-4

EX2152
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH
IPR2018-01422

CGRP receptor antagonist (Tables 1–5; Fig. 1). CGRP-(8–37) itself had no effect on cardiac function and creatine phosphate kinase release in the isolated rat heart.

Ex. 2152, 165; Ex. 1306, ¶24; Reply, 13

Dr. Ferrari's cross-examination:

Q: [Y]ou'd agree that CGRP 8 to 37 had no effect on cardiac function and creatine phosphate kinase release in the isolated rat hearts?

A: Correct.

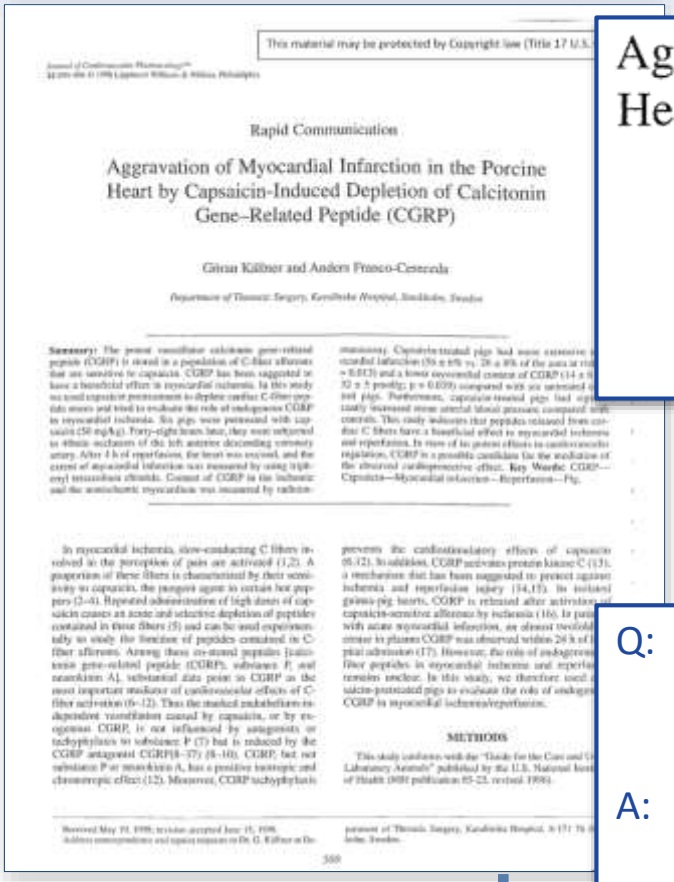
Ex. 1303, 119:9-13; Ex. 2152; Reply, 13

1996

1990 1995 2000 2005

Ex. 1306, ¶¶24, 38; Reply, 8, 13

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 2150)



Rapid Communication

Aggravation of Myocardial Infarction in the Porcine Heart by Capsaicin-Induced Depletion of Calcitonin Gene–Related Peptide (CGRP)

Göran Källner and Anders Franco-Cereceda

Aggravation of Myocardial Infarction in the Porcine Heart by Capsaicin-Induced Depletion of Calcitonin Gene–Related Peptide (CGRP)

Göran Källner and Anders Franco-Cereceda

Department of Thoracic Surgery, Karolinska Hospital, Stockholm, Sweden

Ex. 2150; Ex. 1306, ¶23; Reply, 13

Dr. Ferrari's cross-examination:

Q: Would you agree that inhibiting CGRP with a specific inhibitor would be a more specific way of testing that than as capsaicin depletion?

A: It would have been nice if they would have used, in addition, additional experiments blocking CGRP.

Ex. 1303, 134:23-135:5; Ex. 2150; Reply, 13-14

1998

1990 **1995** **2000** **2005**

Ex. 1306, ¶¶23, 38; Reply, 8, 13-14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1283)

effect on postischaemic recovery. In the present study, the CGRP-antagonist CGRP(8–37), administered either locally by retroinfusion, or systemically by intravenous infusion, did not influence the postischaemic cardiac function or infarct size, which may suggest that locally released CGRP does not function as a cardioprotective agent in this experimental model.

Ex. 1283, 498; Ex. 1306, ¶27; Reply, 14

ELSEVIER

Cardiovascular Research

Calcitonin gene-related peptide in myocardial ischaemia and reperfusion in the pig

Göran Kilbinger [*], Adrian Gomo [b], Anders Franco-Cereceda [a]

1. Introduction

1998

1990 | 1995 | 2000 | 2005

Ex. 1306, ¶¶27, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1284)

reduction of the infarct size. The cardioprotective effects of CGRP were blocked by the novel CGRP antagonist BIBN4096BS (20 nmol · kg^{-1} · h^{-1}). Although cardiac ischemia resulted in an almost 50 % increase in plasma CGRP levels in blood sampled from right cardiac ventricle, intravenous infusion of the CGRP antagonist BIBN4096BS before occlusion until the end of reperfusion had no statistically significant effect on the infarct size.

Ex. 1284, Abstract; Ex. 1306, ¶28; Reply, 14

Original Research

Effects of calcitonin gene-related peptide and BIBN4096BS on myocardial ischemia in anesthetized rats

2001

1990 1995 2000 2005

Ex. 1306, ¶¶28, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1285)

90 minutes followed by reperfusion after 2 weeks of pacing. After 6 weeks of pacing, LV pressure (−11 ± 6%), LV dP/dt (−53 ± 5%), and mean arterial pressure (−15 ± 4%) decreased ($P < 0.01$), while left atrial pressure (+19 ± 3 mm Hg from 7 ± 1 mm Hg) and heart rate (+53 ± 16%) increased ($P < 0.01$). Infusion of the α-CGRP receptor antagonist α-CGRP[8-37] (30 μg/kg/min, iv), which blocked the exogenous α-CGRP challenge, did not affect any of these indices. Regional blood flow, as measured by the microsphere technique, in the nonischemic myocardium, as well as cerebral and renal vasculatures were unaltered during the infusion of α-CGRP[8-37]. Plasma concen-

unchanged after 6 weeks of pacing as compared with control. Thus, we conclude that endogenous α-CGRP does not appear to play a major role in the regulation of cardiac and peripheral vascular dynamics in the late stage of heart failure.

Ex. 1285, Abstract; Ex. 1306, ¶29; Reply, 14

ORIGINAL ARTICLE

Effects of Inhibition of α-CGRP Receptors on Cardiac and Peripheral Vascular Dynamics in Conscious Dogs with Chronic Heart Failure

Yow-Tang Shen, MD, John J. Mullin, MS, Lawrence K. Hunsh, DVM, David B. Gilberto, DVM, Joseph J. Lynch Jr., PhD, Richard J. Hargreaves, PhD, Kenneth S. Kublan, PhD, Robert J. Gould, PhD, and Stefanie A. Kane, PhD

METHODS

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

2003

1990 1995 2000 2005

Ex. 1306, ¶¶29, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1318)

In conclusion, our study clearly demonstrates that BIBN4096BS is an effective antagonist at vascular CGRP receptors in anaesthetised pigs, but has little haemodynamic effects of its own, a finding that negates a major physiological role for CGRP in cardiovascular regulation. The potent blockade of the carotid haemodynamic effects of CGRP does suggest that BIBN4096BS may be effective in migraine treatment.

Ex. 1318, 76; Ex. 1306, ¶30; Reply, 14

Effects of BIBN4096BS on cardiac output distribution and on CGRP-induced carotid haemodynamic responses in the pig

Kapil Kapoor[a], Udayasankar Arulmani[b], Jan P.C. Heiligers[a], Edwin W. Willems[a], Henri Doods[b], Carlos M. Villalón[c], Pramod R. Saxena[a,*]

2003

1990 1995 2000 2005

Ex. 1306, ¶¶30, 38; Reply, 8, 14

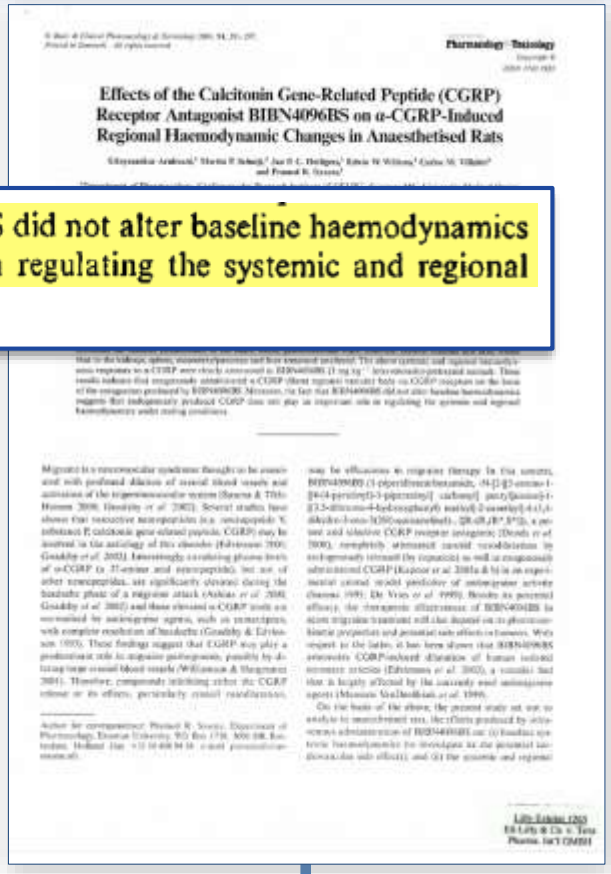
Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1263)

of the antagonism produced by BIBN4096BS. Moreover, the fact that BIBN4096BS did not alter baseline haemodynamics suggests that endogenously produced CGRP does not play an important role in regulating the systemic and regional haemodynamics under resting conditions.

Ex. 1263, Abstract; Ex. 1306, ¶30; Reply, 14

In conclusion, the present investigation demonstrates that: (i) exogenously administered α-CGRP dilates several regional vascular beds in a dose-dependent manner; and (ii) endogenous CGRP does not play an important role in regulating systemic and regional haemodynamics.

Ex. 1263, 296; Ex. 1306, ¶30; Reply, 14


Effects of the Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist BIBN4096BS on α-CGRP-Induced Regional Haemodynamic Changes in Anaesthetised Rats

2004

1990 1995 2000 2005

Ex. 1306, ¶¶30, 38; Reply, 8, 14

Teva's Purported Safety Concerns Were Resolved by November 2005 (Ex. 1240)

Objective In an animal model of trigeminovascular activation and meningeal blood flow the inhibitory effect of a new high-affinity CGRP-binding RNA-Spiegelmer, which is a biostable aptamer composed of mirror-image nucleotides, was examined.

Results The Spiegelmer caused dose-dependent, significant inhibition of the evoked blood flow responses to about 50% of the control. Topical application was most effective. Basal blood flow and systemic arterial pressure were unchanged.

Ex. 1240, 923; Ex. 1306, ¶31; Reply, 9


Poster presentations 923

IPR2018-01422

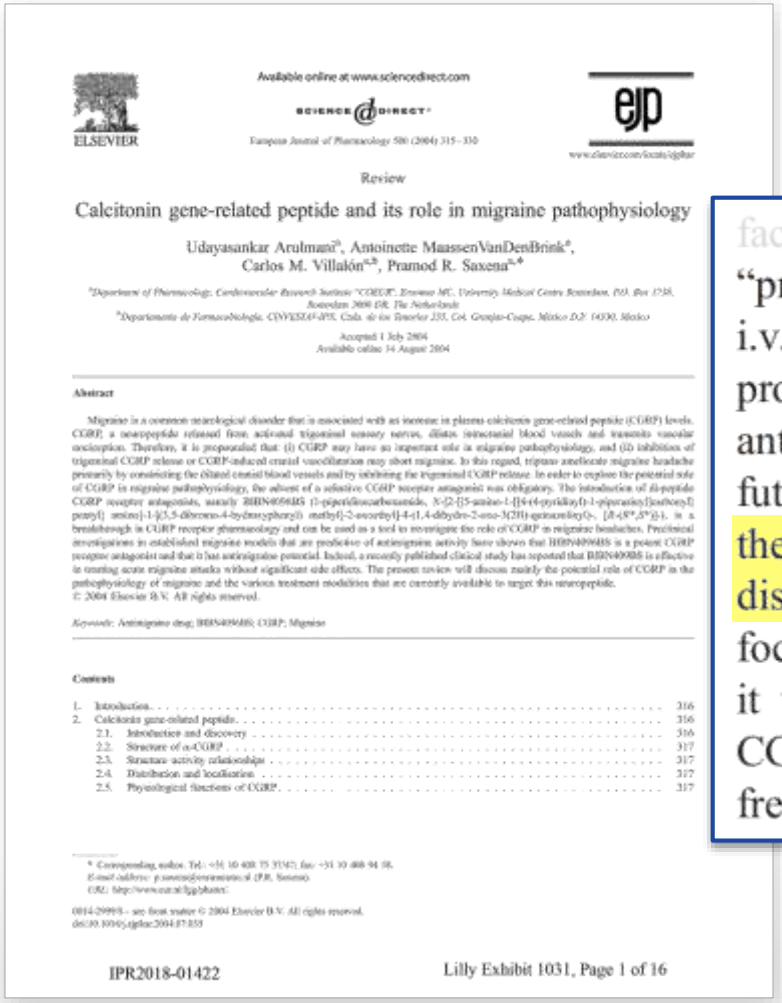
Lilly Exhibit 1240, Page 1 of 1
Eli Lilly & Co. v. Teva Pharms. Int'l GMBH

2005

1990 1995 2000 2005

Ex. 1306, ¶¶31, 38; Reply, 8, 9

Researchers Praised "CGRP Antagonists" Before November 2005



Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 500 (2004) 315–330

ejp

www.elsevier.com/locate/ejphar

Review

Calcitonin gene-related peptide and its role in migraine pathophysiology

Udayasankar Arulmani[a], Antoinette MaassenVanDenBrink[a], Carlos M. Villalón[a,b], Pramod R. Saxena[a,*]

[a]Department of Pharmacology, Cardiovascular Research Institute "COEUR", Erasmus MC, University Medical Centre Rotterdam, P.O. Box 1738, Rotterdam 3000 DR, The Netherlands

[b]Departamento de Farmacobiología, CINVESTAV-IPN, Calz. de los Tenorios 235, Col. Granjas-Coapa, México D.F. 14330, México

Accepted 1 July 2004

Available online 14 August 2004

Abstract

Migraine is a common neurological disorder that is associated with an increase in plasma calcitonin gene-related peptide (CGRP) levels. CGRP, a neuropeptide released from activated trigeminal sensory nerves, dilates intracranial blood vessels and transmits vascular nociception. Therefore, it is proposed that: (i) CGRP may have an important role in migraine pathophysiology, and (ii) inhibition of trigeminal CGRP release or CGRP-induced cranial vasodilatation may abort migraine. In this regard, triptans ameliorate migraine headache presumably by constricting the dilated cranial blood vessels and by inhibiting the trigeminal CGRP release. In order to explore the potential role of CGRP in migraine pathophysiology, the advent of a selective CGRP receptor antagonist was obligatory. The introduction of di-peptide CGRP receptor antagonists, namely BIBN4096BS (1-piperidinecarboxamide, *N*-[2-[[5-amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2H)-quinazolinyl)-, [*R*-(*R**,*S**)]-), in a breakthrough in CGRP receptor pharmacology and can be used as a tool to investigate the role of CGRP in migraine headaches. Preclinical investigations in established migraine models that are predictive of antimigraine activity have shown that BIBN4096BS is a potent CGRP receptor antagonist and that it has antimigraine potential. Indeed, a recently published clinical study has reported that BIBN4096BS is effective in treating acute migraine attacks without significant side effects. The present review will discuss mainly the potential role of CGRP in the pathophysiology of migraine and the various treatment modalities that are currently available to target this neuropeptide.

Keywords: Antimigraine drug; BIBN4096BS; CGRP; Migraine

Contents

* Corresponding author. Tel.: +31 10 408 75 37/47; fax: +31 10 408 94 58.
E-mail address: p.saxena@erasmusmc.nl (P.R. Saxena).
URL: http://www.eur.nl/fgg/pharm/

0014-2999/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.07.030

Dr. Saxena's statements in 2004:

faceted disorder. The encouraging results obtained in a "proof of concept" study with BIBN4096BS, administered i.v., in the acute treatment of migraine holds significant promise to suggest that orally effective CGRP receptor antagonists will become available in the not too distant future. An important advantage of CGRP antagonists over the triptans can be their use in patients with coronary artery disease. Moreover, migraine research is beginning to be focussed on the development of preventive medications and it would be worthwhile to explore whether inhibition of CGRP synthesis, release or its effects may reduce the frequency of migraine attacks. It is evident that further

Ex. 1031, 326; Ex. 1306, ¶39; Reply, 14-15

Absolute Risk of TIAs in Migraine Patients Was Low

Teva's arguments in Sur-reply:

"[A] patient need not have a stroke or myocardial infarction for the concern over CGRP inhibition to be pertinent. A POSA would have been concerned with 'common' ischemic episodes, such as transient ischemic attacks (TIAs) and angina, expecting that long-term loss of CGRP's protective effect would lead to the development of more serious events, e.g., stroke or myocardial infarction."

Sur-reply, 20-21

Dr. Charles's testimony:

Q: Now, would you agree that 300,000 TIAs per year is a common incidence?

A: Again, it depends on your definition of – of 'common.' You know, if you compare that, for example, with the number of migraine attacks per year, it's relatively uncommon.

Ex. 2272, 67:3-9

Q: Okay. In your experience, do ischemic episodes occur frequently in healthy individuals?

A: Again, I would have to say that it depends on the definition of ischemia, but . . . in this particular context, I would say no, that ischemic is not something that routinely occurs in healthy individuals.

Ex. 2272, 56:17-23

Angina May Not Be Caused By Ischemia

Dr. Charles's testimony:

Q: Would you review angina as an ischemic episode?

A: No.

Q: Why not?

A: Because you can have angina that . . . isn't necessarily ischemic.

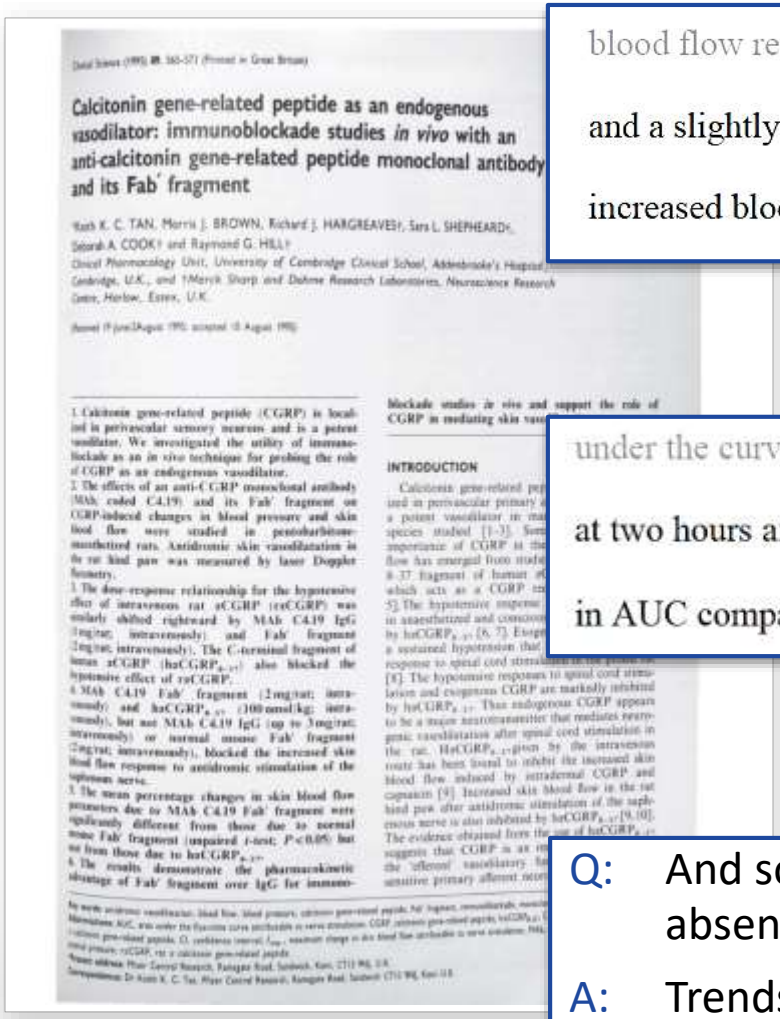
Ex. 2272, 55:9-16

Q: Okay. And I think I asked you earlier, but I'm going to ask you again. Is it your opinion that angina is a type of ischemic episode?

A: I think that angina is a clinical syndrome that can be caused by ischemia but may also occur as a consequence of other mechanisms.

Ex. 2272, 74:21-75:2

Tan 1995 (Ex. 1022) Shows MAb C4.19 Effective *In Vivo*



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab′ fragment

Kieth K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES†, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

Dr. Charles's testimony:

blood flow response. (Ex. 1022, 569.) But with a higher 3 mg dose of MAb C4.19 and a slightly longer (two-hour) duration before stimulation, a 16% block in increased blood flow was observed. (Ex. 1022, 569.) In the third study condition,

Ex. 1008, ¶57; Pet.,18; Reply, 20

Dr. Balthasar's testimony:

under the curve). Ex. 1022, 569. When further nerve stimulation was performed at two hours after a 3 mg/rat antibody dose was administered, a 16% improvement in AUC compared with baseline was observed. Ex. 1022, 569. A POSA would

Ex. 1305, ¶25; Pet.,18; Reply, 20

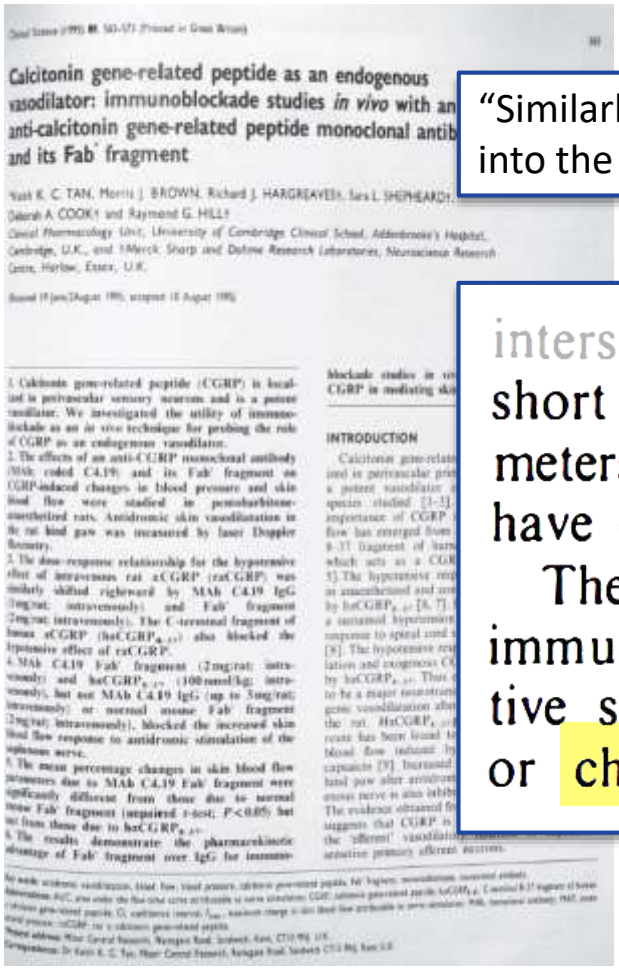
Dr. Tomlinson's testimony:

Q: And so you would agree that trends can be seen in the absence of statistical significance, correct?

A: Trends are trends.

Ex. 1301, 165:6-9; Reply, 20

Tan 1995 Offers Express Guidance to Improve Immunoblockade



Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies *in vivo* with an anti-calcitonin gene-related peptide monoclonal antib and its Fab' fragment

Kevin K. C. TAN, Morris J. BROWN, Richard J. HARGREAVES‡, Sara L. SHEPHEARD†, Deborah A. COOK† and Raymond G. HILL†

Clinical Pharmacology Unit, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, U.K., and †Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, U.K.

INTRODUCTION

Teva's arguments:

"Similarly, in the Louis/Dockray experiments, the antibodies 'leaked' into the interstitial space due to "plasma extravasation."

Sur-reply, 9

interstitial space by plasma extravasation [13]. The short stimulation period and mild stimulation parameters used in the present investigation would not have caused plasma extravasation [9].

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to

Ex. 1022, 571; Ex. 1305, ¶¶32-33; Reply, 20

Tan 1995: MAb C4.19 "Clearly Diffuses" to the Site of Action

Teva's assertion:

"But the art shows that in a carcass (a crude mix of leftover body parts), 'assignment of a site, or sites, of antibody localization was not possible.' Thus, Lilly fails to show that a full-length antibody would distribute into interstitial spaces with additional time."

Sur-reply, 8

Dr. Balthasar's testimony:

carcass. Ex. 1247, 3969, 3972. A POSA would have understood that the rat carcass evaluated in Covell includes the muscular tissues remaining after the other organs have been removed, and thus would have included hind leg muscles and tissues where the rat saphenous nerve is located. Ex. 1022, 567 (describing the saphenous nerve as located in the "right hind limb"), 571 (noting that the carcass "includ[es] muscle and skin"). Accordingly, the carcass tissue data of Covell approximates what a POSA would have expected for antibody distribution times in Tan's rat saphenous nerve assay.

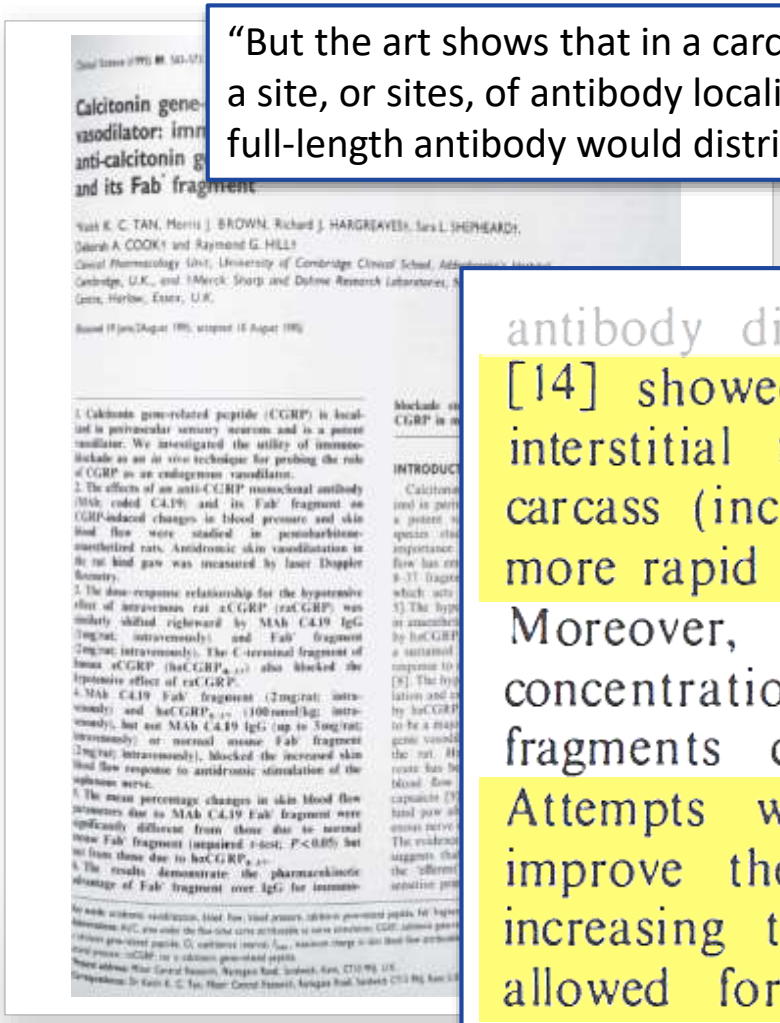
Ex. 1305, ¶27; Reply, 20

Tan's Guidance to Improve Immunoblockade Is Consistent with Well-Known Pharmacokinetic Principles

Teva's arguments:

"But the art shows that in a carcass (a crude mix of leftover body parts), 'assignment of a site, or sites, of antibody localization was not possible.' Thus, Lilly fails to show that a full-length antibody would distribute into interstitial spaces with additional time."

Sur-reply, 8



antibody distribution characteristics. Covell et al. [14] showed that the time to reach steady-state interstitial to plasma concentration ratio in the carcass (including muscle and skin) was 14 times more rapid for Fab' fragments than for whole IgG. Moreover, the steady-state interstitial to plasma concentration ratio in the carcass was 0.86 for Fab' fragments compared with 0.18 for whole IgG. Attempts were made in the present study to improve the likelihood of success with IgG by increasing the dose 3-fold and doubling the time allowed for antibody distribution. The data of

Ex. 1022, 571; Ex. 1305, ¶¶26-29; Reply, 20

Tan 1995: MAb C4.19 "Clearly Diffuses" to the Site of Action

Dr. Balthasar's testimony:

A: …what Covell did, which at the time was a major advance, is develop a physiologically based model of antibody disposition. And that's why this paper is so well-known in the field. And as part of the work that was done, they considered sites of antibody disposition, so tissues for antibody distribution to that were represented. And these tissues, then, were broken down into subspaces that were physiologically relevant for those tissues, including capillary plasma, interstitial spaces, and cell associated spaces. And they used this theoretical mathematical framework, which is called a physiologically based model, to describe antibody disposition with time in these different regions within the tissues. So it's a combination of use of experimental and theoretical work to be able to predict and understand disposition in different spaces. And it really, again, is the basis for an entire field of physiologically based modeling in antibody pharmacokinetics.

Ex. 2273, 94:5-95:6

Tan 1994 Would Inform Potential Effects of Anti-CGRP Antagonist Antibodies *In Vivo*

Dr. Balthasar's testimony:

Q: For example, the tissue bath experiment with the vas deferens, it didn't have a vascular endothelial layer, correct?

A: I don't know that that's correct. I think that probably the tissue section would include, you know, sections of vascular endothelial. The way I would picture it is it's a chunk of tissue.

Ex. 2273, 78:14-21

Q: And that 1994, the Tan 1994 tissue bath study doesn't represent a synapse?

A: Are you saying that there is not synapses within the tissue preparation?

Q: I think that's what I'm saying.

A: My expectation would be that there would be neuromuscular junctions and synapses present within the tissue preparation.

Ex. 2273, 79:11-20

Q: Now, it's fair to say that you wouldn't consider the in vitro experiment or tissue bath experiment of Tan 1994 to be representative of what would occur when administering an antibody to a whole animal?

A: Yeah, I think it's a demonstration of activity that – where the findings would be helpful in informing or understanding or predicting potential effects of in vivo, but as the in vitro system, it's not exactly equivalent to an in vivo system.

Ex. 2273, 77:14-78:3

Other Anti-CGRP Antagonist Antibody Studies Had Established *In Vivo* Effectiveness (Exs. 1048-1050)

Dr. Charles's testimony:

> own anti-CGRP antagonist antibodies). For example, Louis and colleagues used active immunization and demonstrated that anti-CGRP antagonist antibodies can effectively inhibit CGRP-induced inflammation *in vivo*. (Ex. 1048, 257.) Louis

> 1048, 259.) Later, Dockray and colleagues used the same technique and further confirmed that the amount of anti-CGRP antagonist antibodies in antisera correlated with protection against extravasation. (Ex. 1049, 258-59, 261-62.)

> 51. Another publication by Louis confirmed the antagonistic effects of passive immunization using a rabbit polyclonal antiserum to CGRP. (Ex. 1050, 582.) The administration of the antiserum significantly blocked CGRP-induced

Ex. 1008, ¶¶50, 51; Pet. 11

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Dr. Balthasar's testimony:

αCGRP. Ex. 2226, ¶¶104-107. I disagree. RIA assays were often designed to allow appropriate assessment of the affinity of an unlabeled ligand with the use of a radiolabeled tracer that is structurally different from the ligand of interest.

Ex. 1327, ¶73; Reply (IPR2018-01426), 18-19

TABLE 2. pK_i/pK_d values for BIBN4096BS

Source	pK_i/pK_d	Comments	References
Human			
CL/RAMP1 (293 EBNA cells)	10.74	pK_i	30
CL/RAMP1 (Cos 7 cells)	10.05	pK_d	10
SK-N-MC (CL/RAMP1)	10.35	pK_d	41
	10.8	pK_i	13
	11.4	pK_i	14
Rat			
CL/RAMP1 (293 EBNA cells)	8.8	pK_i	30
Brain	8.8	pK_i	
Spleen	8.5	pK_i	13
Marmoset			
Cortex	10.2	pK_d	41
	10.2	pK_i	
Total brain	9.9	pK_d	
	10.4	pK_i	
Dura mater	10.3	pK_d	
Spleen	9.7	pK_d	
	10.0	pK_i	

pK_d values obtained with [^{3}H]BIBN4096BS. pK_i values obtained by competition experiments against [^{125}I]iodohistidyl-hαCGRP.

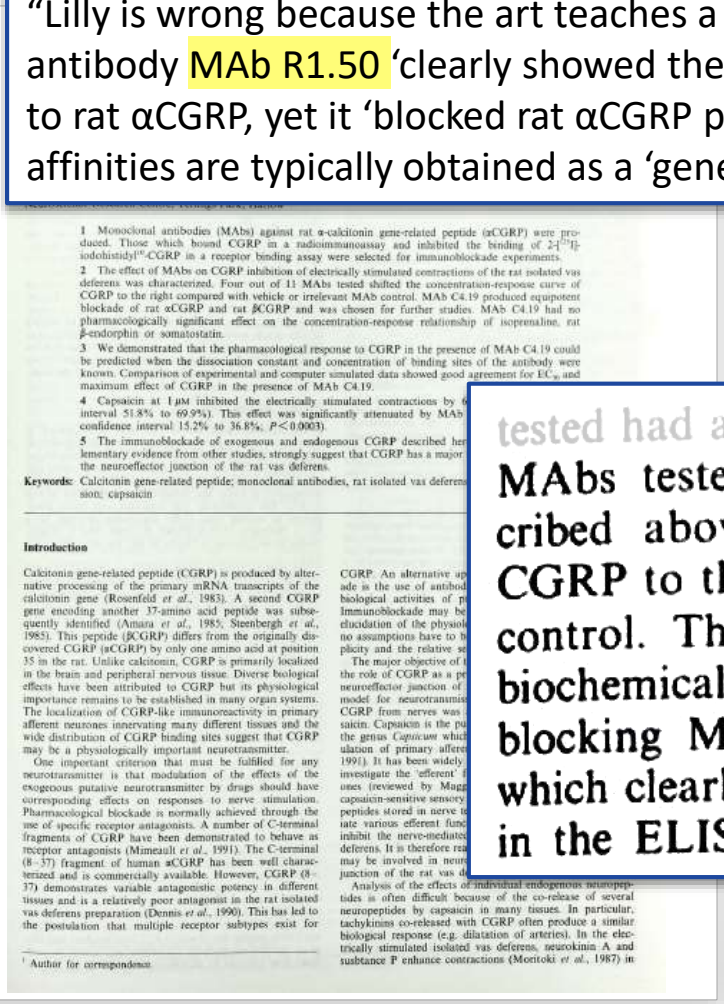
Ex. 2068, 35-37; Ex. 1327, ¶74; Reply (IPR2018-01426), 18-19

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Teva's arguments:

"Lilly is wrong because the art teaches a disconnect between binding and activity: the anti-CGRP antibody MAb R1.50 'clearly showed the greatest [binding] activity' among the tested antibodies to rat αCGRP, yet it 'blocked rat αCGRP poorly. Thus, Lilly's argument that 'single-digit nM affinities are typically obtained as a 'general rule'' is amiss with regard to anti-CGRP antibodies."

Sur-reply (IPR2018-01426), 24



1 Monoclonal antibodies (MAbs) against rat α-calcitonin gene-related peptide (αCGRP) were produced. Those which bound CGRP in a radioimmunoassay and inhibited the binding of 2-[^{125}I]-iodohistidyl^{10}-CGRP in a receptor binding assay were selected for immunoblockade experiments.

2 The effect of MAbs on CGRP inhibition of electrically stimulated contractions of the rat isolated vas deferens was characterized. Four out of 11 MAbs tested shifted the concentration-response curve of CGRP to the right compared with vehicle or irrelevant MAb control. MAb C4.19 produced equipotent blockade of rat αCGRP and rat βCGRP and was chosen for further studies. MAb C4.19 had no pharmacologically significant effect on the concentration-response relationship of isoprenaline, rat β-endorphin or somatostatin.

3 We demonstrated that the pharmacological response to CGRP in the presence of MAb C4.19 could be predicted when the dissociation constant and concentration of binding sites of the antibody were known. Comparison of experimental and computer simulated data showed good agreement for EC_{50} and maximum effect of CGRP in the presence of MAb C4.19.

4 Capsaicin at 1 μM inhibited the electrically stimulated contractions by 6[illegible] interval 51.8% to 69.9%). This effect was significantly attenuated by MAb [illegible] confidence interval 15.2% to 36.8%; $P<0.0003$).

5 The immunoblockade of exogenous and endogenous CGRP described her[illegible] lementary evidence from other studies, strongly suggest that CGRP has a major [illegible] the neuroeffector junction of the rat vas deferens.

Keywords: Calcitonin gene-related peptide; monoclonal antibodies, rat isolated vas deferens[illegible] sion; capsaicin

Introduction

Calcitonin gene-related peptide (CGRP) is produced by alternative processing of the primary mRNA transcripts of the calcitonin gene (Rosenfeld *et al.*, 1983). A second CGRP gene encoding another 37-amino acid peptide was subsequently identified (Amara *et al.*, 1985; Steenbergh *et al.*, 1985). This peptide (βCGRP) differs from the originally discovered CGRP (αCGRP) by only one amino acid at position 35 in the rat. Unlike calcitonin, CGRP is primarily localized in the brain and peripheral nervous tissue. Diverse biological effects have been attributed to CGRP but its physiological importance remains to be established in many organ systems. The localization of CGRP-like immunoreactivity in primary afferent neurones innervating many different tissues and the wide distribution of CGRP binding sites suggest that CGRP may be a physiologically important neurotransmitter.

One important criterion that must be fulfilled for any neurotransmitter is that modulation of the effects of the exogenous putative neurotransmitter by drugs should have corresponding effects on responses to nerve stimulation. Pharmacological blockade is normally achieved through the use of specific receptor antagonists. A number of C-terminal fragments of CGRP have been demonstrated to behave as receptor antagonists (Mimeault *et al.*, 1991). The C-terminal (8–37) fragment of human αCGRP has been well characterized and is commercially available. However, CGRP (8–37) demonstrates variable antagonistic potency in different tissues and is a relatively poor antagonist in the rat isolated vas deferens preparation (Dennis *et al.*, 1990). This has led to the postulation that multiple receptor subtypes exist for CGRP. An alternative ap[illegible] ade is the use of antibod[illegible] biological activities of p[illegible] Immunoblockade may be[illegible] elucidation of the physiol[illegible] no assumptions have to b[illegible] plicity and the relative se[illegible]

The major objective of t[illegible] the role of CGRP as a pe[illegible] neuroeffector junction of [illegible] model for neurotransmis[illegible] CGRP from nerves was [illegible] saicin. Capsaicin is the pu[illegible] the genus *Capsicum* which[illegible] ulation of primary afferen[illegible] 1991). It has been widely [illegible] investigate the 'efferent' f[illegible] ones (reviewed by Magg[illegible] capsaicin-sensitive sensory[illegible] peptides stored in nerve te[illegible] iate various efferent func[illegible] inhibit the nerve-mediated[illegible] deferens. It is therefore rea[illegible] may be involved in neur[illegible] junction of the rat vas de[illegible]

Analysis of the effects of individual endogenous neuropeptides is often difficult because of the co-release of several neuropeptides by capsaicin in many tissues. In particular, tachykinins co-released with CGRP often produce a similar biological response (e.g. dilatation of arteries). In the electrically stimulated isolated vas deferens, neurokinin A and substance P enhance contractions (Moritoki *et al.*, 1987) in

[illegible] Author for correspondence.

tested had any effect on baseline contractions. **Four out of 11 MAbs tested, including MAb C4.19, C4.6 and R2.73 described above, shifted the concentration-response curve of CGRP to the right compared with vehicle or irrelevant MAb control. The use of RIA and a receptor binding assay as biochemical screens was generally successful in predicting blocking MAbs. An interesting exception was MAb R1.50 which clearly showed the greatest activity in these assays and in the ELISA.** Although raised in mice immunized with rat

Ex. 1021, 707; Ex. 1327, ¶72; Reply (IPR2018-01426), 18

A POSA Would Have Been Motivated to Make Anti-CGRP Antibodies with the Claimed Affinities

Dr. Balthasar testimony:

> For example, Tan 1994, Tan 1995, and Wong performed *in vitro* and *in vivo* testing with their anti-CGRP antagonist antibodies at 37°C and successfully confirmed their biological activity at that temperature. Ex. 1021, 705 (conducting tissue bath experiment at 37°C); Ex. 1022, 567 (conducting blood pressure experiment in animals at a body temperature of 37°C); Ex. 1033, 98 (disclosing that antibody 4901 was selected based on its ability to bind at 37°C); Ex. 1033, 97 (conducting blood pressure experiment in animals at a body temperature of 36-37°C).
>
> Therefore, a POSA would have understood that using a temperature of 37°C did not adversely affect the beneficial properties of these prior art anti-CGRP antagonist antibodies.

Ex. 1327, ¶77; Reply (IPR2018-01426), 18;
see also Ex. 1013, ¶124 (Pet. (IPR2018-01426), 38-39)

Teva's Secondary Considerations Are Not Commensurate with the Scope of the Challenged Claims

Dr. Tomlinson's cross-examination:

Q: And so can you identify for me the half-life value that would be suitable or unsuitable for antibody fragments within the scope of Claim 1?

A: I think it's – you know, having worked at Domantis for, whatever, six, seven years, I think it's pretty clear that an unformatted antibody fragment is not going to be effective as a human therapeutic against that target. I think that's obvious to anyone who works in the field or worked in that field at the time.

Ex. 1301, 134:14-25; Reply, 23

Teva's Secondary Considerations Are Not Commensurate with the Scope of the Challenged Claims

Dr. Tomlinson's cross-examination:

Q: You would agree that there's about a five[-]thousand[ ]fold difference between fremanezumab's binding affinity of 2.2 picomolar and the upper end of claimed range 10 nanomolar?

A: Ten divided by 0.0022, yeah, 5,000.

Q: And you would agree that Claim 1 of the '211 patent also covers humanized anti-CGRP antagonist antibodies having femtomolar binding affinities [below] the 2.2 picomolar affinity of fremanezumab?

A: Yes.

Q: Well, you cite two antibodies, correct?

A: Yes.

Q: And one has an affinity of 2.2 picomolar and the other has an affinity of 31 picomolar, correct?

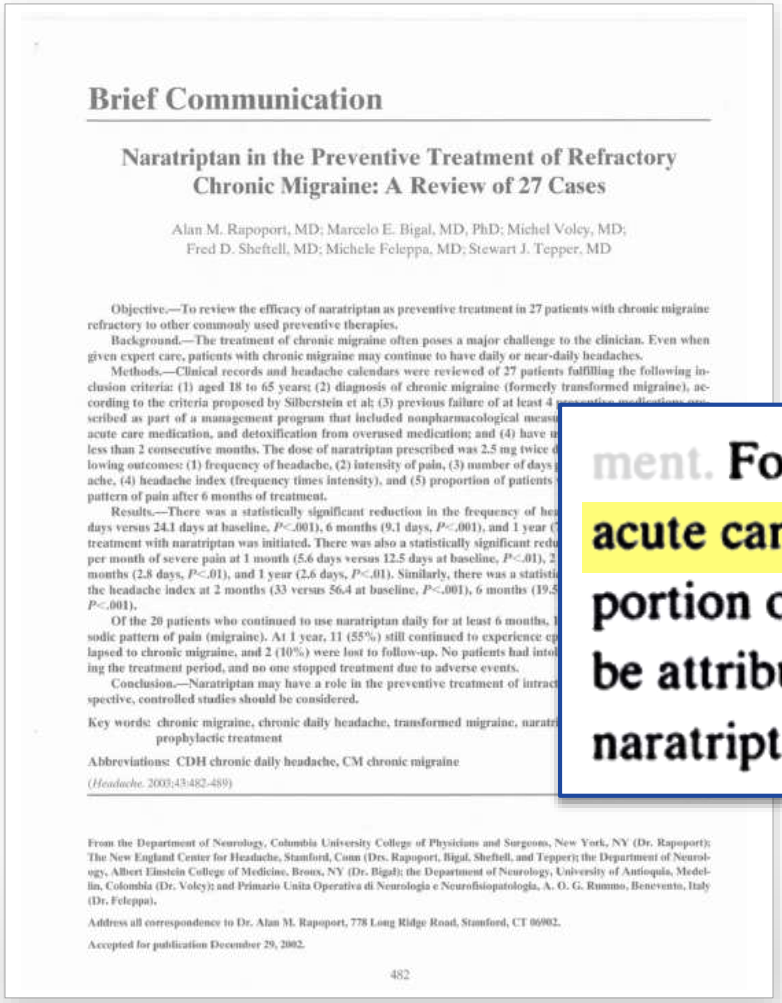
A: Yes.

Q: And those do not cover or represent the full range of affinities covered by the 211 patent's claimed range extending up to 10 nanomolar, correct?

A: No. They're just two antibodies within that range.

Ex. 1301, 102:10-22, 104:7-19; Reply, 22-23

Teva Failed to Establish Unexpected Results



Brief Communication

Naratriptan in the Preventive Treatment of Refractory Chronic Migraine: A Review of 27 Cases

Alan M. Rapoport, MD; Marcelo E. Bigal, MD, PhD; Michel Voley, MD; Fred D. Sheftell, MD; Michele Feleppa, MD; Stewart J. Tepper, MD

Objective.—To review the efficacy of naratriptan as preventive treatment in 27 patients with chronic migraine refractory to other commonly used preventive therapies.

Background.—The treatment of chronic migraine often poses a major challenge to the clinician. Even when given expert care, patients with chronic migraine may continue to have daily or near-daily headaches.

Methods.—Clinical records and headache calendars were reviewed of 27 patients fulfilling the following inclusion criteria: (1) aged 18 to 65 years; (2) diagnosis of chronic migraine (formerly transformed migraine), according to the criteria proposed by Silberstein et al; (3) previous failure of at least 4 preventive medications prescribed as part of a management program that included nonpharmacological measures, acute care medication, and detoxification from overused medication; and (4) have had less than 2 consecutive months. The dose of naratriptan prescribed was 2.5 mg twice daily. Following outcomes: (1) frequency of headache, (2) intensity of pain, (3) number of days with headache, (4) headache index (frequency times intensity), and (5) proportion of patients with pattern of pain after 6 months of treatment.

Results.—There was a statistically significant reduction in the frequency of headache days versus 24.1 days at baseline, $P<.001$), 6 months (9.1 days, $P<.001$), and 1 year (treatment with naratriptan was initiated. There was also a statistically significant reduction per month of severe pain at 1 month (5.6 days versus 12.5 days at baseline, $P<.01$), 2 months (2.8 days, $P<.01$), and 1 year (2.6 days, $P<.01$). Similarly, there was a statistical the headache index at 2 months (33 versus 56.4 at baseline, $P<.001$), 6 months (19.5 $P<.001$).

Of the 20 patients who continued to use naratriptan daily for at least 6 months, sodic pattern of pain (migraine). At 1 year, 11 (55%) still continued to experience episodic lapsed to chronic migraine, and 2 (10%) were lost to follow-up. No patients had intolerable ing the treatment period, and no one stopped treatment due to adverse events.

Conclusion.—Naratriptan may have a role in the preventive treatment of intractable spective, controlled studies should be considered.

Key words: chronic migraine, chronic daily headache, transformed migraine, naratriptan, prophylactic treatment

Abbreviations: CDH chronic daily headache, CM chronic migraine

(*Headache*. 2003;43:482-489)

From the Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY (Dr. Rapoport); The New England Center for Headache, Stamford, Conn (Drs. Rapoport, Bigal, Sheftell, and Tepper); the Department of Neurology, Albert Einstein College of Medicine, Bronx, NY (Dr. Bigal); the Department of Neurology, University of Antioquia, Medellin, Colombia (Dr. Voley); and Primario Unita Operativa di Neurologia e Neurofisiopatologia, A. O. G. Rummo, Benevento, Italy (Dr. Feleppa).

Address all correspondence to Dr. Alan M. Rapoport, 778 Long Ridge Road, Stamford, CT 06902.

Accepted for publication December 29, 2002.

482

Teva's arguments:

"Studies have confirmed that Ajovy® reduces incidences of MOH, a phenomenon nothing in the prior art suggested."

POR, 54

Dr. Rapoport's statements in 2003:

ment. Fourth, some of the patients stopped overusing acute care medication during the study, and at least a portion of the benefit they received reasonably could be attributed to analgesic discontinuation rather than naratriptan alone. Finally, since some patients were

Ex. 1294, 487; Ex. 1306, ¶¶88-89; Reply, 26

Teva's Purported Evidence of Commercial Success Does Not Support Patentability

***Pain Point Med. Sys., Inc. v. Blephex, LLC*, IPR2016-01670, Paper 44 at 19-21 (PTAB Feb. 28, 2018)**

"Although these exhibits indicate some circumstantial evidence of sales, and a potential market for the BlephEx device, what Patent Owner has not produced is any substantial evidence of market share."

Reply, 26-27

Teva's arguments:

"Third-party investment analysts, Leerink Transformation Partners, have forecasted that the migraine antibody market will break the blockbuster barrier by 2025 and that the entire class of drugs will be worth $4.5 billion by 2022, and a staggering $6.9 billion by 2025. EX2085, 2-3."

POR, 55-56; Reply, 26-27

Dr. Charles (Tan 1995)

Teva's assertion:

the unreliability of Tan's results. EX2191, 118:12-119:1; POR, 3. Dr. Charles—a clear outlier among the experts—testified that C4.19 "showed a 16% reduction in skin blood flow" in a saphenous nerve assay. EX1008, ¶122; POR, 15. But given Dr. Charles' gross mischaracterization of prior art in these proceedings (EX2192, 182:21-183:12; 154:18-20), his opinion must be given little weight. POR, 3-4.

Sur-reply, 6-7

Tan 1995 (Ex. 1022):

$n = 4$) after 60 min (Fig. 5*a*). Further nerve stimulation performed at 2 h after 3 mg/rat MAb produced an AUC which was slightly smaller compared with baseline stimulation, but not by more than 16% ($n = 2$).

Ex. 1022, 569; Ex. 1008, ¶57; Pet., 17-18

Dr. Vasserot's testimony:

may be "14 times more rapid for Fab' fragments than for whole IgG.")). But with a longer period between treatment and nerve stimulation and a higher dose, a 16% block in increased blood flow was observed. (*Id.*) In view of these results, Tan

Ex. 1009, ¶77; Reply, 20

Dr. Balthasar's testimony:

Fab' fragment significantly blocked the effects of CGRP. Ex. 1022, 569, 570. The full-length antibody significantly blocked the hypotensive effects of exogenous CGRP in rats and showed 16% reduction in skin blood flow in the rat saphenous nerve assay under the experimental conditions used. Ex. 1022, 569, 570. Tan's *in*

Ex. 1305, ¶22; Reply, 20

Dr. Charles (Wimalawansa)

Teva's assertion:

¶¶10-11, 66, 86-88; EX2212, ¶¶60-61. Similarly, Dr. Charles proclaims that "Wimalawansa states that humanized anti-CGRP antibodies 'should' be developed and used." EX1008, ¶62. But Wimalawansa says nothing of the sort, instead

POR, 4

Wimalawansa (Ex. 1096):

disease. The role of CGRP antagonists and humanized monoclonal antibodies should be explored with respect to control of pain and inflammation, type II diabetes, and in conditions with intractable hypotension, such as septic shock syndrome.

Ex. 1096, 570; Ex. 1008, ¶74; Pet., 19; Reply, 2

Dr. Charles's testimony:

for diseases associated with CGRP. (Ex. 1096, 567.) Wimalawansa concludes that humanized anti-CGRP antagonist antibodies "should be explored" for a variety of clinical conditions. (Ex. 1096, 570.)

Ex. 1008, ¶74; Pet., 19

Dr. Charles (Olesen)

Teva's assertion:

222; EX2157, 533; EX1025, 1108; EX1042, 647; EX2272, 83:22-84:13. What is more, Olesen specifically warned against relying on its study for cardiovascular safety: "our data base was too small for us to assess cardiovascular safety." EX1025, 1109; POR, 27; EX2212, ¶22. Dr. Charles blatantly ignored this warning (EX1306, ¶34), but Dr. Balthasar confirmed that Olesen's statement is consistent

Sur-reply, 16

Dr. Charles's testimony:

34. Despite Olesen's express recognition of BIBN4096BS's favorable safety profile, Dr. Ferrari asserts that little can be gleaned from it because Olesen's data base was purportedly too small. (Ex. 2212, ¶22.) A POSA, however, would have considered this study as part of the growing body of work (e.g., additional animal and clinical studies), establishing that the CGRP-pathway could be antagonized without the vasoconstrictive properties of triptans. As a result, a POSA would have viewed Olesen's study—and his comments about BIBN4096BS's lack of vasoconstrictive effects—as a further indication that blocking the CGRP pathway was expected to be both safe and effective in humans.

Ex. 1306, ¶34; Reply, 7

Dr. Ferrari's statements in 2005:

release of CGRP [22–24]. Therefore, CGRP antagonists may be effective in the treatment of acute migraine. Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment [56]. In a double-

cebo. There were no serious adverse events and the most frequent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Dr. Charles (Triptans)

Teva's assertion:

EX1306, ¶44. But triptans' mechanism of action and pharmacokinetics differ from that of antibodies and Dr. Charles has not explained the basis for equating the two classes of molecules. Moreover, because triptans were used as a treatment for *acute* migraine, physicians would not have been concerned with triptans' long-term effects. EX2212, ¶21; EX1031, 322; EX1040, 176. Even then, the

Sur-reply, 17-18

Dr. Charles's testimony:

researchers developed additional, triptans with longer half-lives. For example, frovatriptan had a relatively longer half-life of about 26 hours. (Ex. 1293, S125-26.) These longer-acting triptans were intended to reduce recurrence of migraine, but were also considered as potential preventive therapies. (*Id.*) For instance, frovatriptan and naratriptan were considered as short-term preventive therapies (daily dosing for about a week) for menstrual migraine. (*Id.*, S127.) Naratriptan was also administered daily up to 1 year as a preventative treatment for chronic migraine with no serious adverse events. (*See* Ex. 1294, Abstract; Ex. 1295, Abstract.)

Ex. 1306, ¶12; Reply, 7

Dr. Charles (CGRP-Binding Aptamer)

Teva's assertion:

anti-CGRP antibodies. First, as with BIBN4096BS and triptans, aptamers have a short half-life—"hours to days," not "weeks"—and would not have been informative on the safety of long-acting antibodies. EX1309, Abstract; EX2272, 114:6-115:5. Second, aptamers are not "analogs to antibodies," as Lilly simplistically argues. Reply, 9. Aptamers "bridge the gap between small molecules

Sur-reply, 18

Pendergrast (Ex. 1309):

In the simplest view, aptamers can be thought of as nucleic acid analogs to antibodies. They are able to bind specifically to proteins, and, in many cases, that binding leads to a modulation of protein activity. New aptamers are rapidly generated through

Ex. 1309, Abstract; Reply, 9

Dr. Charles's testimony:

they were known as "nucleic analogs to antibodies" due to their specificity, biological activity, favorable safety profile, and potential long *in vivo* half-lives ranging from hours to days. (Ex. 1309, Abstract.)

Ex. 1306, ¶17; Reply, 9

Dr. Balthasar's testimony:

requiring only weekly or biweekly dosing. Ex. 1309, 231. Indeed, aptamers were recognized as having the benefit of "a long in vivo half life" and had been analogized to antibodies. Ex. 1309, 224 ("aptamers can be thought of as nucleic analogs to antibodies").

Ex. 1305, ¶51; Reply, 9

Dr. Charles (Purported Safety Concerns)

Teva's assertion:

2901. Any increase in the incidence or severity of, e.g., TIAs, would have been a very serious concern. Dr. Charles ignores such concerns, and he has offered no rebuttal to Dr. Ferrari's testimony about the likelihood that CGRP inhibition would worsen common ischemic episodes in migraineurs.

Sur-reply, 21

Dr. Charles's testimony:

detail below, Dr. Ferrari primarily relies on outdated studies that did not reflect the consequences of antagonizing naturally-present CGRP, i.e., endogenous CGRP. By 2005, these older studies had been superseded by numerous animal and clinical studies demonstrating that blocking the endogenous CGRP pathway does *not* increase blood pressure and does *not* worsen ischemic episodes. (*E.g.*, Exs. 1283, 1284, 1285, 1318, 1263, 1240, 1025, 1042, 2019.) Based on these subsequent

Ex. 1306, ¶19; Reply, 13

Dr. Charles (Purported Safety Concerns)

Teva's assertion:

Even Lilly's EX1284 demonstrates CGRP's cardioprotective role: CGRP reduced infarct size in an ischemia rat model by up to 89%, while BIBN4096BS blocked "[t]he cardioprotective effect of CGRP." EX1284, 591-592, Figure 3. Notably, Lilly omitted this unfavorable information, and its expert refused to even acknowledge it as "germane" during cross-examination. EX2272, 20:1-21:3.

Sur-reply, 11

Dr. Charles's testimony:

significant effect on the infarct size").) Moreover, consistent with studies administering exogenous CGRP that Dr. Ferrari relies upon (*see, e.g.*, Exs. 2058, 2079, 2139), CGRP's cardioprotective effect was observed only when exogenous CGRP (about 10-fold excess over endogenous CGRP) was administered, suggesting that "[o]nly high plasma levels [of] CGRP may cause cardioprotection." (Ex. 1284, 593.)

Ex. 1306, ¶28; Reply, 13-14

Dr. Charles (Purported Safety Concerns)

Teva's assertion:

Even Lilly's EX1284 demonstrates CGRP's cardioprotective role: CGRP reduced infarct size in an ischemia rat model by up to 89%, while BIBN4096BS blocked "[t]he cardioprotective effect of CGRP." EX1284, 591-592, Figure 3. Notably, Lilly omitted this unfavorable information, and its expert refused to even acknowledge it as "germane" during cross-examination. EX2272, 20:1-21:3.

Sur-reply, 11

Dr. Charles's testimony:

Q: Now, you didn't mention that outcome in your declaration, correct?

A: I did not because it was not germane to the point that I was actually making.

Q: And the point that you were making was that in 2001, Wu and colleagues showed that endogenous CGRP did not affect myocardial infarcts?

A: Yes.

Ex. 2272, 20:16-23

Dr. Charles (Risk of Stroke/MI in Migraine Patients)

Teva's assertion:

[8] Revealing his bias, Dr. Charles even refused to acknowledge that "angina" is an ischemic event. EX2272, 55:9-11. The art says otherwise. EX2212, ¶32.

Sur-reply, 20 n.8

Dr. Charles's testimony:

Q: Would you review angina as an ischemic episode?

A: No.

Q: Why not?

A: Because you can have angina . . . that isn't necessarily ischemic.

Ex. 2272, 55:9-16

Q: Okay. And I think I asked you earlier, but I'm going to ask you again. Is it your opinion that angina is a type of ischemic episode?

A: I think that angina is a clinical syndrome that can be caused by ischemia but may also occur as a consequence of other mechanisms.

Ex. 2272, 74:21-75:2

Dr. Charles (Spare Receptor Theory)

Teva's assertion:

remains sound and effectively unrebutted. EX2230, ¶¶88-95. And to the extent that Lilly and Dr. Charles ignore the relevance of receptor reserve and argue that one would need to antagonize "only *elevated* or *inappropriate* levels of CGRP" to effectively treat migraine, there is no evidence in the record that supports this conclusion. Reply, 17 (emphasis in the original); EX1306, ¶67.

Sur-reply, 22

Dr. Charles's testimony:

67. The clinical evidence contradicts Dr. Foord's assertion. As of 2005, it was widely known that migraine was linked to *elevated* or *inappropriate* levels of CGRP, and that as CGRP levels normalized migraine headache subsided. (Ex. 1043, Abstract; Ex. 1044, Abstract; *see also* Ex. 1047, 59 (administering exogenous CGRP "caused migraine in virtually all migraine sufferers"); Ex. 1096, 567 ("inappropriate release of CGRP is a potential causative factor in several diseases, including migraine"); Ex. 1008, ¶¶36-45.)

Ex. 1306, ¶67; Reply, 17

attacks. (Ex. 1043, 185; Ex. 1044, 48, 52-53.) Researchers also reported that following effective treatment of migraine attacks (i.e., with sumatriptan), the elevated CGRP levels returned to normal. (Ex. 1044, 48, 52-53.) Meanwhile,

Ex. 1008, ¶38; Pet., 10

Dr. Charles (Cross-Reactivity)

Teva's assertion:

As for Dr. Charles' belated testimony on cross-reactivity, all he now does is state—without explanation or support— that "hypothetical and unsupported concerns about ligand-receptor cross-binding would not have deterred development of a humanized anti-CGRP antagonist antibody." EX1306, ¶71; Reply, 18. Dr. Charles misses the point: one cannot equate receptor and ligand antagonism without considering the differences between the two. EX2230, ¶83.

Sur-reply, 23

Dr. Charles's testimony:

72. Moreover, cross-binding of CGRP to these other receptors was understood to be poor before November 2005. Dr. Foord includes in his declaration a table from the Geppetti reference that illustrates that CGRP is a secondary or worse binding ligand to each of the calcitonin, amylin, and adrenomedullin receptors:

	Calcitonin	Amylin (AMY)	CGRP	Adrenomedullin (AM)
Composition	*CALCR*	AMY-1: *CALCR+RAMP1* AMY-2: *CALCR+RAMP2* AMY-3: *CALCR+RAMP3*	*CALCRL+RAMP1*	AM-1: *CALCRL+RAMP2* AM-2: *CALCRL+RAMP3*
Transduction pathway	G_s/G_q	G_s	G_s/G_q	G_s
Selective agonists	Human CT	AMY	α-CGRP	AM
Selective antagonists	–	–	BIBN4096BS (+++) SB-273779 (+)	AM_{22-52}
Potency	Salmon CT≥human CT≥AMY, CGRP>AM	Salmon CT≥AMY≥CGRP>human CT>AM	CGRP>AM≥AMY≥salmon CT	AM-1: AM>>CGRP>AMY>salmon CT AM-2: AM≥CGRP>AMY>salmon CT

(Ex. 2059, Table 1 (highlighting added); Ex. 2230, ¶34.) In addition, Geppetti

1026-1028, 1096.) Likewise, aptamers were designed to bind to the CGRP ligand "for the specific interruption of disease-related protein-protein interactions." (Ex. 1082, 1.) The anti-CGRP ligand aptamers had been shown to inhibit neurogenic blood flow increases in the rat cranial dura (Ex. 1240, 923) just as BIBN4096BS did in Doods (Ex. 1024, 422).

Ex. 1306, ¶¶72, 74; Reply, 18

Dr. Vasserot (Motivation)

Teva's assertion:

unravel. As Lilly's expert Dr. Vasserot admitted, a POSA would have needed to see much more in the way of safety and efficacy beyond what Tan disclosed before having any meaningful reason to embark on the costly and burdensome endeavor to humanize a murine anti-CGRP antibody. EX2191 65:2-71:19, 75:4-13; 97:15-106:19. This is *exactly* what Wimalawansa, Lilly's second primary reference, says:

POR, 7

Dr. Vasserot's testimony:

Q: So AME is the type of company that would take Tan 1994, humanize Tan's antibody, and take it to clinic?

A: We have done worse than that.

Q: You have done worse than that. What have you done that's worse than that?

A: We have started projects with less data than that.

Ex. 2191:99:8-100:1; Reply, 5

Teva's Experts – Dr. Ferrari

Dr. Ferrari's testimony:

of my research. I am an author on over 450 peer reviewed publications. My research efforts have included investigation of the possibility of therapeutically targeting the CGRP signaling pathway, including developing and conducting clinical trials of therapeutics targeting the CGRP pathway. These efforts began in the early 2000's.

Ex. 2212, ¶6

below), including practical experience in conducting clinical trials. In particular, I played an instrumental role inthe clinical design and testing of BIBN4096BS for its efficacy and safety in treating acute migraine. Earlier, I also played an instrumental role in the clinical design and testing of the class of drugs known as triptans for their use in treating acute migraine starting in the late 1980's.

Ex. 2212, ¶11

Teva's arguments:

not prior to 2005. EX1301, 55:1-13. Similarly disingenuous is Lilly's allegation that "Teva's experts conceded that a POSA would have found it appropriate to use humanized antibodies throughout drug development, including binding assays, *in vitro* testing, and animal studies." Reply, 5-6. The transcripts illuminate the truth:

- Dr. Tomlinson stated that a POSA would have humanized an antibody to be tested *only* when "[g]iven sufficient motivation to do so …. which at the time wasn't the case," for CGRP. EX1301, 204:4-15;
- Dr. Ferrari admitted that he is "not an expert in [the drug development] field." EX1303, 54:25-55:6;

Sur-reply, 7

Teva's Experts – Dr. Ferrari

Dr. Ferrari's testimony:

CGRP is one of the most potent microvascular vasodilator substances identified to date, and a POSA would have expected that sequestering CGRP risked causing deleterious side effects on the vascular system via prevention of CGRP-mediated vasodilation to rescue viable penumbra tissue in cardiac and cerebral ischemic events. This concern would have been particularly problematic for anti-CGRP

Ex. 2212, ¶12

Dr. Ferrari's statements in 2005:

quent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Teva's Experts – Dr. Ferrari (Olesen)

Dr. Ferrari's testimony:

events" were observed. EX2015, 1104. However, Olesen also cautioned that their study did not assess whether BIBN4096BS has any "vasoconstrictor properties" because "[its] data base was too small," and therefore Olesen could not conclude whether BIBN4096BS was different from the triptans in that regard. EX1025, 1109. Further, Olesen infused BIBN4096BS once for only 10 minutes, which is

Ex. 2212, ¶22

Dr. Ferrari's statements in 2005:

effective in the treatment of acute migraine. Olesen and colleagues evaluated the effectiveness of the CGRP-antagonist BIBN4096BS for acute migraine treatment [56]. In a double-blind, randomized, controlled trial, patients received different doses of BIBN4096BS intravenously over 10 min. The primary end point was a response reduction of severe or moderate headache at baseline to mild or no headache at 2 h. The 2.5 mg group had a response rate, that was significantly superior to placebo. There were no serious adverse events and the most frequent side effect was paresthesia. Although further trials are necessary in order to confirm this result and to compare the effectiveness of CGRP antagonists with the triptans, they seem promising, new antimigraine drugs without vascular side effects.

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Teva's Experts – Dr. Ferrari (Lassen)

Dr. Ferrari's testimony:

65. Dr. Charles also asserts that the Lassen publication's results "led to the conclusion that 'CGRP antagonism' was a therapeutic principle for treating migraine." EX1022, ¶62. I disagree with this characterization of Lassen because, as with Tan 1995, the Lassen publication would not have provided a clinician with an expectation that an anti-CGRP antibody could be of clinical use. Lassen observed that administering CGRP causes "migraine-like" symptoms in migraineurs. EX1047, 59. But a POSA would have understood that this data does not prove that CGRP has a physiological role in migraine, and a study of how CGRP functions (such as Lassen) does not provide an understanding of what would happen if CGRP activity were blocked. This distinction is important

Ex. 2212, ¶65

Dr. Ferrari's statements in 2005:

Calcitonin gene-related peptide antagonists

In patients with migraine, CGRP levels are elevated. CGRP infusion can trigger a migraine attack and triptans block the release of CGRP [22-24]. Therefore, CGRP antagonists may be effective in the treatment of acute migraine. Olesen and col-

22 Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia* 22, 54–61 (2002)

Ex. 1290, 657; Ex. 1306, ¶40; Reply, 8

Teva's Experts – Dr. Ferrari (Tan)

Dr. Ferrari's testimony:

CGRP *receptor* antagonism. I am not aware of any discussion of pursuing anti-CGRP antibodies as a therapeutic in that time frame, either in the literature or in my personal conversations with experts in the field. For example, I was in frequent contact with researchers at Merck (including authors of Tan 1995) during the pre-2005 time frame while they pursued small molecule therapeutics that targeted the CGRP receptor, and I do not recall them ever discussing the possibility of targeting CGRP, much less targeting CGRP with an antibody for clinical use in human patients—despite the direct involvement of Merck researchers in the Tan 1995 study. Therapeutic antibodies were a new

Ex. 2212, ¶70

Dr. Tan's statements:

Mouse MAbs such as MAb C4.19 may be humanized by transplanting the CDRs from mouse MAbs on to human antibody variable region frameworks (Verhoeyen *et al.*, 1988). In such "classical" antibody engineering, hybridomas of

There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents. The review of the pathophysiological roles of CGRP in Chapter 1 have suggested several therapeutic targets for CGRP blockade, including inflammation and migraine. Conversely, CGRP itself may be beneficial in

Ex. 1287, 247; Reply, 3, 11-12

Teva's Experts – Dr. Ferrari (Wong)

Dr. Ferrari's testimony:

51. A number of publications also disclosed their findings, in studies of CGRP function in rats, that administering an anti-CGRP antibody leads to an increase in blood pressure:

- Wong 1993: in testing a new anti-CGRP antibody, Wong 1993 noted that administering that antibody to rats "completely blocked the intravenous rat α-CGRP-induced decrease in blood pressure and increase in heart rate in rats." EX1033, 102.

Ex. 2212, ¶51

Wong (Ex. 1033):

Effects on the Cardiovascular System. Intravenous injection of rat α-CGRP decreased MAP and increased heart rate (Table 2). Intravenous injection of non purified CGRP monoclonal antibody (25 mg/kg) 30 min before that of rat α-CGRP (0.8 μg/kg) completely inhibited the cardiovascular effects of the peptide (Table 2). The monoclonal antibody had no significant effect on MAP and heart rate (n=6).

Treatment[1]	MAP (Δ mm Hg)	HR (Δ beats/min)
α-CGRP	-17 ± 3	25 ± 5
Saline + α-CGRP	-22 ± 3	24 ± 7
α-CGRP	-20 ± 6	18 ± 4
CGRP Ab + α-CGRP	0**	2 ± 2**

Ex. 1033, 101; Ex. 1306, ¶43; Reply, 12

Teva's Experts – Dr. Rapoport (Olesen)

Dr. Charles's testimony:

recurrence. (Ex. 1025, 1108.) In view of these clinical results on the migraine-recurrence endpoint, Olesen established that blocking the CGRP pathway was an equally viable therapeutic target for both preventative migraine applications and acute migraine treatment.

Ex. 1008, ¶43; Pet., 10

Dr. Rapoport's statements in 2005:

CGRP is one of several neuropeptides found within the sensory terminals of the trigeminal nerve. Recent data suggests that antagonising the effect of CGRP may provide acute relief of migraine headache [47]. Preventive drugs might be developed on the same principle.

47. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM; BIBN 4096 BS Clinical Proof of Concept Study Group (2004) Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine [see comment]. N Engl J Med 350:1104–1110

Ex. 1297, S119; Ex. 1306, ¶40; Reply, 8

Teva's Experts – Dr. Rapoport (MOH)

Dr. Rapoport's testimony:

69. Before 2005, nothing in the art would have suggested that prescribing an additional preventive migraine treatment to a patient who suffers from chronic migraine and MOH would have reduced medication overuse. Nor were there any studies showing that CGRP was linked to MOH. This effect is especially surprising

Ex. 2235, ¶69

Dr. Rapoport's statements in 2003:

Naratriptan in the Preventive Treatment of Refractory Chronic Migraine: A Review of 27 Cases

Alan M. Rapoport, MD; Marcelo E. Bigal, MD, PhD; Michel Volcy, MD; Fred D. Sheftell, MD; Michele Feleppa, MD; Stewart J. Tepper, MD

Ex. 1294; Ex. 1306, ¶¶88-89; Reply, 26

ment. **Fourth, some of the patients stopped overusing acute care medication during the study,** and at least a

Ex. 1294, 487; Ex. 1306, ¶¶88-89; Reply, 26

Dr. Rapoport's cross-examination:

Q: So as of 2005, a person of ordinary skill in the art would have known that triptans inhibit the release of CGRP, correct?

A: Anybody reading that article [published in 1999] would have.

Ex. 1304, 90:10-15; Reply, 7

Motion to Strike

Exhibit 1287 and Related Sections of Lilly's Reply

Teva's arguments in POR:

And even if Tan 1995's antibody is the antibody that Lilly argues a POSA would have had a reason to humanize—to be sure, a POSA would not—there is no evidence of record explaining why a POSA would have (1) begun with Tan 1995, which is a basic research paper studying vasodilation in rats, particularly where Lilly's articulated motivation is *therapeutic* (not scientific) and (2) looked to modify a CGRP antibody by humanization, rather than one of the solutions posed by the other references Lilly cites. EX2224, ¶¶79-101; EX2230, ¶50. Indeed, the question remains: why would a POSA have started with Tan 1995, a reference that was published 10 years prior to the earliest priority date of the '614 patent? Scientists from Merck were authors on Tan 1995, yet neither they nor Merck as a company were investigating anti-CGRP antibodies during this 10-year period. EX2212, ¶¶24, 70, 76. The time-gap speaks volumes, but Lilly has chosen not to

POR, 45 (citing Ferrari's declaration Ex. 2212, ¶¶24, 70, 76)

Lilly's reply:

Teva incorrectly attempts to undermine Tan's disclosures by characterizing it as a "basic research paper" and citing purported personal knowledge of its authors. Ex. 2212 ¶70; POR, 45. But in describing his own work, Dr. Tan wrote in 1994 that there was "no reason" why *humanized* anti-CGRP monoclonal antibodies should not be investigated and used as "therapeutic agents" for migraine and other diseases. Ex. 1287, 247 (similarly discussing *human* anti-CGRP MAbs as an "exciting possibility" for administration "in man"). Dr. Tan's contemporaneous statements were written with first-hand knowledge of the blood pressure results focused on by Teva and directly contradict Teva's litigation-driven position.

Reply, 11-12; Opposition to Motion to Strike, 2

Exhibit 1287 and Related Sections of Lilly's Reply

Dr. Ferrari's testimony:

70. Moreover, the testing of BIBN4096BS is reflective of the fact that, to the extent that a POSA would have been interested in targeting CGRP-related activity before November 2005, that interest would have directed that POSA to CGRP *receptor* antagonism. I am not aware of any discussion of pursuing anti-CGRP antibodies as a therapeutic in that time frame, either in the literature or in my personal conversations with experts in the field. For example, I was in frequent contact with researchers at Merck (including authors of Tan 1995) during the pre-2005 time frame while they pursued small molecule therapeutics that targeted the CGRP receptor, and I do not recall them ever discussing the possibility of targeting CGRP, much less targeting CGRP with an antibody for clinical use in human patients—despite the direct involvement of Merck researchers in the Tan 1995 study. Therapeutic antibodies were a new phenomenon, and were not yet in the general consciousness of those of us pursuing clinical neurology research.

Ex. 2212, ¶70; POR, 45

Ex. 1287:

Mouse MAbs such as MAb C4.19 may be humanized by transplanting the CDRs from mouse MAbs on to human antibody variable region frameworks (Verhoeyen *et al.*, 1988). In such "classical" antibody engineering, hybridomas of

There seems to be no reason why anti-peptide MAbs or their fragments should not be investigated as therapeutic agents. The review of the pathophysiological roles of CGRP in Chapter 1 have suggested several therapeutic targets for CGRP blockade, including inflammation and migraine. Conversely, CGRP itself may be beneficial in

Ex. 1287, 247; Reply, 3, 11-12; Opposition to Motion to Strike, 2

Exhibit 1287 and Related Sections of Lilly's Reply

Dr. Foord's testimony:

77. As stated above, the purpose of Tan 1995 was simply "to investigate immunoblockade as an alternative strategy for probing the role of CGRP as a vasodilator *in vivo*." EX1022, 566. Because Tan 1995 is only studying the role CGRP plays in vasodilation in an experimental animal, a POSA would have understood that Tan 1995 was not studying whether a CGRP antibody could be safely used for human clinical purposes. As such, and as would be expected in this type of study, Tan 1995 does not consider adverse events or side effects caused by the anti-CGRP antibody. This includes the effect of the antibody on the animal over a longer period of administration. Side effects were unimportant to Tan 1995 as the rats were likely sacrificed after the experiment, and the side effects were not relevant to confirming their basic science hypothesis—that CGRP mediates vasodilation in a whole animal.

79. The almost instant increase in mean arterial pressure after administration of Fab' or full-length antibody suggests that both are exerting an effect by binding CGRP in the systemic circulation (since the saphenous nerve assay was ineffective for a full-length antibody). A POSA would have understood that an anti-CGRP antibody would have a ***systemic*** vascular effect, leading to adverse consequences, well before it might have any ***local*** anti-CGRP effect (as in the saphenous nerve assay) for any therapeutic benefit, *e.g.*, treating migraine.

Ex. 2230, ¶¶77, 79; POR, 24

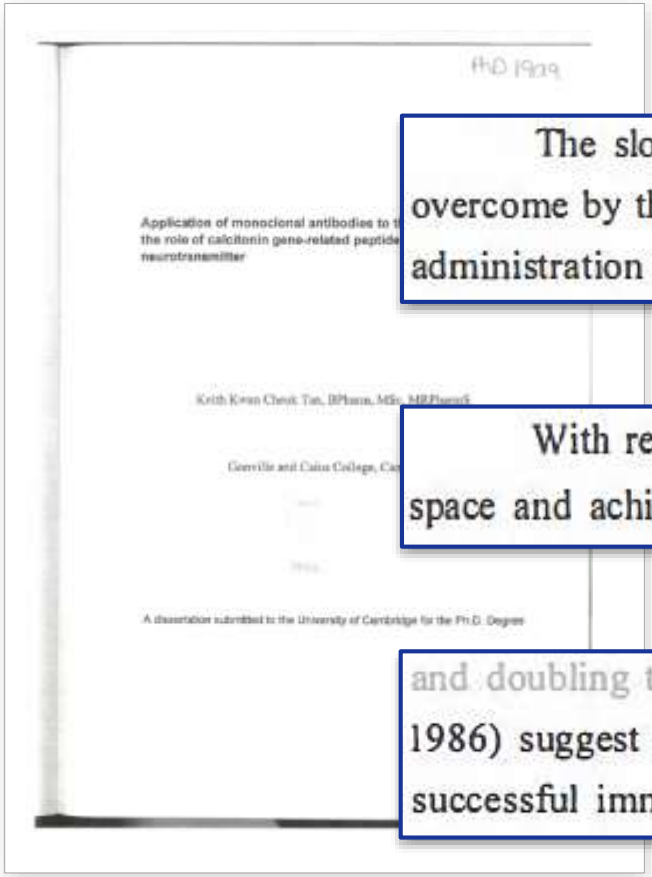
Lilly's reply:

Ex. 2212 ¶70; POR, 45. But in describing his own work, Dr. Tan wrote in 1994 that there was "no reason" why *humanized* anti-CGRP monoclonal antibodies should not be investigated and used as "therapeutic agents" for migraine and other diseases. Ex. 1287, 247 (similarly discussing *human* anti-CGRP MAbs as an "exciting possibility" for administration "in man"). Dr. Tan's contemporaneous statements were written with first-hand knowledge of the blood pressure results focused on by Teva and directly contradict Teva's litigation-driven position.

Reply, 11-12; Opposition to Motion to Strike, 3

Motion to Exclude

Exhibit 1287 Is Admissible


PhD 1989

Application of monoclonal antibodies to t
the role of calcitonin gene-related peptide
neurotransmitter

Keith Kwan Cheok Tan, BPharm, MSc, MRPharmS

Girton College, Ca

A dissertation submitted to the University of Cambridge for the Ph.D. Degree

The slow distribution of whole IgG to the site of immunoblockade could be overcome by the alternative strategies of active immunization with CGRP or chronic administration of IgG. Responses to stimuli that potentially release endogenous CGRP

With repeated administration, IgG should eventually distribute into interstitial space and achieve sufficiently high concentrations required for immunoblockade. A

and doubling the time allowed for antibody distribution. The data of Covell *et al.*(1986) suggest that much larger doses and longer distribution time are required for successful immunoblockade with IgG. In this respect, it is interesting to note that

Ex. 1287, 222-23; Opp. Mot. Excl., 2-3

Exhibit 1287 Is Admissible

Carney's declaration:

14. The title page of the Tan Thesis includes the following University of Cambridge Library stamp.

As discussed above, upon receiving a published book or report, it is standard library practice to stamp a book with the library name and then shelve the book or report within a matter of a few days or weeks.

15. Attached as Exhibit C is a true and correct copy of the current Cambridge University Library ("CUL") catalogue entry for the Tan Thesis, which I accessed at http://idiscover.lib.cam.ac.uk/permalink/f/t9gok8/44CAM_ALMA21429648480003606 on August 27, 2019. As indicated in the CUL catalogue, the entry was created in 1994 and the Tan Thesis was approved on July 29, 1994.

16. Attached as Exhibit D to this declaration is a true and correct copy of the MARC record from the Cambridge University Library Catalog for its copy of Tan Thesis, which I downloaded from http://idiscover.lib.cam.ac.uk/primo-explore/sourceRecord?vid=44CAM_PROD&docId=44CAM_ALMA21429648480003606 on August 27, 2019.

17. The MARC record for the Tan Thesis, includes a number of fields. The date field 008 lists the first six characters "020506" in "YYMMDD" format, indicating that the MARC record for the Tan Thesis was created on May 6, 2002. This means, at the latest, the Tan Thesis was catalogued by the Cambridge University Library on May 6, 2002. The first six characters are also followed by the code "s" in character position 06 and "1994" in character positions 07-10. As discussed above, this indicates that the Tan Thesis was produced in 1994.

Ex. 1307, ¶¶14-17; Opposition to Motion to Exclude, 3