

Curriculum Vitae RAMAIAH MUTHYALA

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I. EDUCATION

Ph.D., Heterocyclic Chemistry - University of East Anglia, UK (1975)
Ph.D., Natural Products - Sagar University, India (1970)
M.B.A., International Management (MIM) - St. Thomas University, MN (1999)
M.P.H., Public Health Practice – University of Minnesota, MN (2017 expected)

II. ACADEMIC EXPERIENCE

UNIVERSITY OF MINNESOTA

Associate Professor, Department of Experimental Clinical Pharmacology
(August 2006-)

Adjunct Associate Professor, Department of Medicine (March, 2005 -)

Associate Professor, Department of Medicinal Chemistry (August, 2000 - 2007)

Associate Director (pre-clinical drug development), Center for Orphan Drug Research (July 2005 - 2009)

Senior Associate Director, Center for Drug Design (Aug. 2000 - June 2005)

Research activities: Anti-HIV drugs (integrase, protease and reverse transcriptase inhibitors); Antibiotics for multi-drug resistant strains; Vancomycin mimics (VanX inhibitors, efflux inhibitors); Alzheimer's Disease (□secretase inhibitors, prodrugs to cross blood-brain barrier); Rare cancers (Hemangioblastoma, biliary tract carcinoma); Rare neurological diseases (Spinocerebellar ataxia type-1, Rett syndrome); Rare hemoglobinopathies (Sickle cell anemia, thalassemia); Rare antibiotic

resistant bacterial infections; Synthetic methods development leading to bioactive natural products; Combinatorial chemistry (heterocyclic compound libraries for HTS); Molecular modeling; Assay development; high throughput screening of NIH compound libraries; Pharmacokinetic concepts, discovery of quality clinical candidates, repositioning of FDA approved drugs for orphan diseases.

Teaching: Foundations of Critical Thinking (FCT) , Medical School, University of Minnesota; Fundamentals of Medicinal Chemistry; Heterocyclic Chemistry; Synthetic Organic Chemistry; Orphan Drug Development – one day course for pharma industry, Short course (Orphan Drug Development through Repositioning) at American Association of Pharmaceutical Sciences.

Administrative responsibilities: Primary advisor to the CDD director regarding overall research, management and operation of the Center. Responsibilities included program development, supervision, policymaking, and budget preparation, hiring personnel, organizing national and international conferences, procurement of lab instrumentation and equipment, renovation and maintenance of labs, and advising the director on budgetary and related issues; Preclinical studies, phase 1 clinical trials coordinator (NDA approved projects).

NATIONAL INSTITUTE OF PHARMACEUTICAL EDUCATION & RESEARCH, Hyderabad, AP India, Adjunct Professor, 2016-

ALZHEIMER'S RESEARCH CENTER, Regions Hospital, St. Paul, MN, Research Associate (1999-2000):

Isolation and characterization of endogenous inhibitor for mAChR from brains of Alzheimer's patients; Mechanism of free radical inactivation of mAChR; SAR of Anandamide Analogues; Combinatorial Chemistry; Molecular modeling of mAChR; Substrate specific β -Secretase inhibitors; Synthesis of naturally occurring antioxidants.

UNIVERSITY OF DELHI, INDIA

Visiting Professor, Ambedkar Biomedical Research Institute (Jan 2003 -)
Adjunct Professor, Andhra University, Vishakapatnam, AP, India (Sept 2015)

EASTERN MICHIGAN UNIVERSITY, Ypsilanti, MI

Adjunct Professor (1984-1989): Graduate Research Advisor; taught advanced organic chemistry course: asymmetric synthesis, synthetic strategies for total synthesis of complex natural products, synthetic methodologies.

POSTDOCTORAL EXPERIENCE

Wayne State University, Detroit, MI (1974-1976)
Total synthesis of natural products and novel synthetic methodology.

University of North Wales, Bangor, U.K (1971-1972)
Enzymatic degradation and structure elucidation of sea weed constituent, Alginic acid

Osmania University, Hyderabad, India (1970-1971)
Synthesis of new sulfur and nitrogen heterocyclic compounds for Human Anti-parasitic diseases; anti-malarial, anti-tuberculosis

National Chemical Laboratory, Poona, India (1969-1970)
Isolation and characterization of biologically actives coumarins, isocoumarines, poly phenolic compounds (Gossypol type) from medicinal plants

III. INDUSTRIAL EXPERIENCE

3M/IMATION CORPORATION, St. Paul, MN

Senior Research Specialist, Medical Imaging Technology Center (1989-1999)

Project and program management: Responsible for development of medical imaging diagnostic materials (synthesis and structure, activity relationships of infrared dyes); photo dynamic therapy, using tumor specific dyes; combinatorial chemistry (dyes); SAR; computational chemistry and molecular modeling using semi-empirical quantum mechanical and *ab initio* methods; Mopac, Gaussian and other computational software. Taught the use and application of CAChe software (Computer-Aided Chemistry) to bench chemists, 2D NMR quantitative structure analysis;

DOW CHEMICAL COMPANY, Midland, MI

Project Leader, Pharmaceuticals Research & Development (1979-1989)

Project coordinator/manager - Design and synthesis of enzyme inhibitors (suicide-enzyme inactivators, pyridoxal-5'-phosphate dependent enzyme inhibitors, transamination of amino acids, decarboxylation of amino acids, amine oxidations, and racimization of *L*- and *D*-amino acids); new and alternate synthesis for anti-allergy and cardiotoxic drugs; practical synthesis of (+) vinylGABA (anti-epileptic) and difluoromethyl ornithine, DFMO (sleeping sickness) without resolution; kilo synthesis of fluoro amino acids for FDA approval; identification and synthesis of metabolites. Biotechnology - chemical modification of proteins, radioactive metal complexes and monoclonal antibodies for cancer diagnosis and therapy; develop GMP guidelines and work with government regulators; analytical support, enhanced training in 2D NMR; Technical project management and supervision of MS. PhD and other technical employees

SCHERING PLOUGH, Bloomfield, NJ

Research Associate, Infectious diseases department (1976-1979)

Synthesis of antibiotics and antifungal agents; Aminoglycosides: modification of gentamicin type antibiotics to reduce toxicity (muscular dystrophy); HMGA-CoA reductase inhibitors: Cerulenin and its

carbocerulein analogues as fatty acid synthase inhibitors (breast cancer), diphenylethers, (β-lactam antibiotics. Structure activity relationships using CODESSA; New synthetic methods - allyloxycarbonyl functionality for the protection of amines and carboxylic acids and deprotection with Pd; One pot multi-step reactions for gram to kilogram quantity reactions

INDIAN DRUGS & PHARMACEUTICALS LTD, Hyderabad, India
Senior Chemist, Process Control & Process Development
laboratory (1969-1971)

Laboratory head for quality control, process and pilot plant
laboratories - Manufacture of analgesics, sulfa-drugs and
vitamins.

COMMERCIAL SUCCESS

(s) Vinyl-GABA (Vigabatrin A gaba transaminase inhibitor). Antiepileptic (used for refractory complex partial seizures); under development in U.S. as an orphan drug (approved), it is available in many countries around the world for the treatment of epilepsy and infantile spasms. Prevents the biochemical and behavioral effects of alcohol, nicotine and cocaine in much the same way it prevents an epileptic seizure: by altering the way brain cells communicate to one another (Marion-Merrill-Dow).

α-Difluoromethyl Ornithine (DFMO, Diflore) Suicide inhibitors technology was originated at Merrill Research Center, Strasburg, France. DFMO, an enzyme-activated, irreversible inhibitor of ornithine decarboxylase, blocks polyamine biosynthesis and has anti-tumor effects in animal tumor models as well as in athymic mice implanted with human small cell carcinoma; reduces in vitro invasiveness and metastatic capacity of some breast cancer cells. Eventually this product was sold to the World Health Organization to treat one of the neglected diseases, African sleeping sickness (Trypanosomiasis) (Marion-Merrill-Dow).

Radiolabeled biopharmaceuticals: Tumor targeting with monoclonal antibody (MAb) with cancer-killing radioisotope technology. Radioisotope I-131 for rare thyroid cancer treatment; yttrium-90 for ovarian cancer are a few among the short lived radioisotopes investigated. Complementary to monoclonal antibody as target identifiers, stable complexes of radioisotopes with organic small molecule complexing agents (MeO-DOTA) which link with target protein to deliver the cancer-killing payload precisely where it is most needed were also developed. Dow set up a new business, ChelaMed Radiopharmaceutical Services, based on this technology (Dow Chemicals).

Allyloxy carbonyl protecting group for amines and alcohols and their applications to amino glycoside and beta lactam antibiotics were developed (only one author). This idea was further extended for other functional groups e.g., carboxylic acids by academic and industrial scientists (Schering-Plough).

Medical imaging technology: novel functional dyes (diagnostic and treatment) which were developed using predictive power of computational methods. The resulting business, Dry Silver, was sold to Imation and eventually to Kodak-Asai (3M Company).

Highlights from the University of Minnesota website:

http://www1.umn.edu/umnnews/Feature_Stories/Propolis_an_ancient_remedy_may_fight_AIDS.html

http://www1.umn.edu/umnnews/Feature_Stories/The_emerging_uses_of_biocatalysis.html

http://www1.umn.edu/umnnews/Feature_Stories/Beauty_in_the_hive_of_the_beholder.html

IV. LEADERSHIP

- Member of the Executive Board of Directors, Vorin Laboratories, India;
 - Consultant to Ranbaxy, New Delhi, India (1994-1998)
 - Member of the Executive Board of Directors, Suven LifeSciences, India, (1996 –2005)
 - Member of the Editorial Board of ARKAT Foundation, Gainesville, FL (1999 - present)
 - Co-chair, Working Group on Chemically-derived products including repurposing; Therapies Scientific Committee, International Rare Diseases Research Consortium 2014-
 - NIH Drug Discovery for the Nervous System program review panel (2012-present)
 - NIH Molecular Libraries and Imaging Roadmap initiative: Molecular Libraries Probe Production Centers (MLPCN) Evaluator, 2010-present
- Founding Member of the Board of Directors, In Need of Diagnosis Inc. Orlando, FL (2006 -2008)
- Founder, President, Indian Organization for Rare Diseases, 2005-

V. PROFESSIONAL INVOLVEMENT (selected)

- Organizer for “raising the awareness of rare diseases” A national conference at Hyderabad, Telangana, India (March 20, 2015)
- Organizer for “Therapeutics for Rare and Neglected Diseases” at Central Drug Research Institute, Lucknow, India (World Rare Diseases Day, Feb 26-8, 2013)
- Guest of Honor to Innova Children’s Heart Hospital, Hyderabad, India, to address graduating students of nursing and other hospital technologies.(Nov 26, 2011)
- Planning committee member of the iDDi workshop on Neglected and Orphan diseases, Siena, Italy, May29-June1, 2010
- Organizer, symposium – Medicinal Chemistry in Rare, Orphan and neglected Diseases; 239th ACS National Meeting, San Francisco, CA, March 21-25, 2010

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