BIOGRAPHICAL SKETCH

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NAME: **Ganesh, Thota**

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POSITION TITLE: **Assistant Professor, Department of Pharmacology**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Osmania University, Hyderabad, India	B.Sc.	1992	Biology and Chemistry
Osmania University, Hyderabad, India	M.Sc.	1994	Organic Chemistry
Osmania University, Hyderabad, India	Ph.D.	1999	Organic Chemistry
Indian Institute of Technology-Bombay, India.	Post doc.	1998-2000	Organic Synthesis
University of Durham, Durham, England	Post.doc.	2000-2001	Synthesis of bioactive molecules
Virginia Polytechnic Institute and State University, Blacksburg, VA	Res. Scientist	2002-2005	Medicinal chemistry
Emory Institute for Drug Discovery, and, Chemical Biology Discovery Center, Atlanta, GA	Sr. Res. Scientist	2006-2010	Medicinal chemistry

A. Personal Statement

I have a strong background in medicinal chemistry, drug discovery and pharmacology areas. I worked on a variety of projects driven by structure activity relationships (SAR) and hit-to-lead synthesis in Emory Chemical Biology Discovery Center, subsequently Emory Institute for Drug Discovery. I designed and synthesized several preclinical lead candidates, interacted with multidisciplinary teams including bioinformatics, high-throughput screening and drug metabolism and pharmacokinetics (DMPK) to study bio-structural, biochemical and pharmacological properties of small molecules in the past. Since 2011, I have been collaborating with Dr. Ray Dingledine, a neuro-pharmacologist, to develop EP2 antagonists for acute inflammatory disease status epilepticus and chronic neurodegenerative diseases such as epilepsy and Alzheimer's disease. My research goals include development of a safe and effective therapy for chronic inflammatory disease such as arthritis and others by targeting a single prostanoid receptor EP2. I have demonstrated my research experience with over 50 peer-reviewed publications in a variety of journals with a current web of science *h*-index = 16. All of these prepared me to lead this project.

B. Positions and Honors

Positions and Employment

1994-1998	Graduate Research Student, Osmania University, Hyderabad, India
1999-2000	Research Associate, I. I. T. Bombay, Mumbai, India
2000-2001	Postdoctoral Fellow, University of Durham, Durham, UK
2002-2003	Senior Research Associate, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA
2003-2005	Research Scientist, Virginia Polytechnic Institute and State University
2006-2011	Senior Research Scientist, Chemical Biology Discovery Center and then at Emory Institute for Drug Discovery, Emory University, Atlanta, GA, USA
2011-present	Assistant Professor, Department of Pharmacology, Emory University, Atlanta, GA

Honors, and Professional Memberships

Qualified Graduate Aptitude Test in Engineering, (GATE)-1994
University Grants Commission, Junior Research Fellowship (1994-1996)
University Grants Commission, Senior Research Fellowship (1996-1998)
Council of Scientific and Industrial Research(C S I R, India), RA-Fellowship (1999-2000)
Member of the American Chemical Society (2002-present)
Alzheimer's Drug Discovery Foundation Scholar (2013-2016)
Harrington Discovery Institute Fellow (2014-2016)

C. Contribution to Science

1. My significant early contribution to the science was the determination of Taxol binding conformation on its biological target Tubulin-dimer. Taxol was approved by the FDA in 1992 for clinical use as an anti-cancer drug for a variety of cancers. It became a blockbuster drug by 2001 with sales over $ 1 billion. However, a precise binding confirmation of this drug was not known until 2004 when we first reported. It was shown that it binds to β-tubulin with a stoichiometry ratio (1 mole of Taxol to 1 mole of tubulin-dimer), and there were at least three models proposing the nature of Taxol binding on β-tubulin. However, none of these models have provided a definitive picture of binding conformation. As we detailed in my publication (Ganesh et al., PNAS, 2004), the bioactive confirmation of the Taxol was very important because Taxol is a complex molecule and it is difficult to produce in a commercial scale from the laboratory starting materials. Furthermore, it displays adverse effects on patients. The future generation of the anti-cancer drugs in the class must be simpler and retain the full activity of the patent, and they should devoid of any adverse effects resulted by the parent drug. By utilizing an electron crystallography density model, I have designed and synthesized several highly potent Bridge Taxol analogs which provided experimental evidence that Taxol binds to β-tubulin in a T-shaped conformation. Furthermore, this compound paved the way to generate very simple Taxol-like analogs with anti-proliferative activity. This work resulted in several publications, in highly impacted peer-reviewed journals. Four among them are listed below.

   a. Ganesh, T.; Guza, R. C.; Bane, S.; Ravindra, R.; Shanker, N.; Lakdawala, A. S; Snyder, J. P.; Kingston, D. G. The Bioactive Taxol Conformation on β-tubulin: Experimental Evidence from Highly Active Constrained Analogs. Proc. Natl. Acad. Sci. 2004, 101, 10006-10011. PMCID: PMC454156
   b. Ganesh, T.; Yang, C.; Norris, A.; Ravindra, R.; Bane, S.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. Evaluation of Tubulin-bound Bioactive Paclitaxel Conformation: Synthesis, Biology and SAR Studies of C-4 to C-3' Bridged Paclitaxel Analogs. J. Med. Chem. 2007, 50, 713-725. PMCID: PMC2585518
   c. Shanker, N.; Kingston, DG.; Ganesh, T.; Yang, C.; Alcaraz, AA.; Geballe, MT.; Banerjee, A.; McGee, D.; Snyder, JP.; Bane, S. Enhanced microtubule binding and tubulin assembly properties of conformationally constrained paclitaxel derivatives. Biochemistry. 2007, 46, 11514-27. PMID:17892304, PMCID not available
   d. Ganesh, T.; Norris, A.; Sharma, S.; Bane, S.; Alcaraz, A.; Snyder, J. P.; Kingston, D. G. I. Design, Synthesis, and Bioactivity of Simplified Paclitaxel Analogs Based on the T-Taxol Bioactive Conformation. Bioorg. Med. Chem. 2006, 14, 3447-3454. PMID: 16434198, PMCID not available.

2. My second major significant contribution to science was developing a conceptual common pharmacophore model to understand how the structurally different natural products such as epothilones, eleuthorobin, laulimalide and discodermolide display a similar mechanism of action to Taxol. In this regard, I have designed and synthesized several fluorescent and radiolabeled analogs of these natural products for studying their tubulin-interaction properties. This study resulted in several potent anti-cancer epothilone derivatives, and labeled derivatives which we reported in the following publications.

   a. Ganesh, T.; Brodie, P.; Banerjee, A.; Bane, S.; Kingston, D.G.I. Synthesis of isotopically labeled epothilones. J. Label. Compd. 2014, 57, 78-81. PMCID: PMC3979290

b. Ganesh, T.; Schilling, J. K.; Palakodety, R. K.; Ravindra, R.; Shanker, N.; Bane, S.; Kingston, D. G. I. Synthesis and Biological Evaluation of Fluorescently Labeled Epothilone Analogs for Tubulin Binding Studies. Tetrahedron 2003, 59, 9979-9984. PMCID and PMID are not available, but this article can be found at doi:10.1016/j.tet.2003.10.024
c. Chen, Q-H.; Ganesh, T.; Brodie, P.; Slebodnick, C.; Jiang, Y.; Banerjee, A.; Bane, S.; Snyder, J. P.; Kingston, D. G. I. Design, synthesis and biological evaluation of bridged epothilone D analogs. Org. Biomol. Chem. 2008, 6, 4542-4552**.** PMCID: PMC2790820
d. Chen, Q-H.; Ganesh, T.; Brodie, P.; Jiang, Y.; Bane, S.; Snyder, J. P.; Kingston, D. G. I. Novel Epothilone Lactones by an Unusual Diversion of the Grubbs' Metathesis Reaction. Chem. Commun. 2010, 46, 2019-2021. PMCID: PMC2930754

3. My recent significant contribution, which is relevant to the current project, is developing TG6-10-1 as a small molecule antagonist of the EP2 receptor. Prostanoid receptor EP2 has emerged as a major pro-inflammatory mediator in a variety of CNS disease indications, but no small molecule modulators for this receptor were available. I have created several allosteric potentiators, then selective antagonists for this key Gs-coupled receptor. This compound (TG6-10-1) displayed a number of beneficial effects in an acute brain injury model of status epilepticus, including suppression of delayed mortality, inflammation and neurodegeneration. Thus, this compound has the potential to reduce neurodegeneration in patients who may have been exposed to a nerve gas agent. Postdoctoral fellows from Dingledine laboratory (Jiang and Rojas) and I have published several articles recently in high-impact journals, shared co-first authorship in several key publications, and taken lead authorships in several other publications. Four key publications are listed below.

   a. Rojas, A.; Ganesh, T.; Lelutiu, N.; Gueorguieva, P.; Dingledine, R. Inhibition of the prostaglandin EP2 receptor is neuroprotective and accelerates functional recovery in a rat model of organophosphorus induced status epilepticus. Neuropharmacology. 2015, 93, 15-27. PMCID: PMC4387070
   b. Ganesh, T.; Jiang, J.; Yang, M-S.; Dingledine, R. Lead optimization studies of cinnamic amide EP2 antagonists J. Med. Chem., 2014, 57, 4173-4184. PMCID: PMC4032197
   c. Ganesh, T.; Jiang, J.; Dingledine, R. Development of second generation EP2 antagonists with high selectivity. Eur. J. Med. Chem. 2014, 82, 521-535. PMCID: PMC4108197
   d. Jiang, J.; Ganesh, T.; Du, Y.; Quan Y.; Serrano, G.; Qui, M.; Speigel, I.; Rojas, A.; Lelutiu, N.; Dingledine, R. Small molecule antagonist reveals seizure-induced mediation of neuronal injury by prostaglandin E2 receptor subtype EP2. Proc. Natl. Acad. Sci. 2012, 109, 3149-3154. PMCID: PMC3286971

4. I have made additional significant contributions to the science at Emory University Chemical Biology Discovery Center, where I have worked on a number of drug discovery projects under NIH-MLSCN program and developed small molecule preclinical leads for a variety of biological targets, including heat shock protein 90 (HSP90), histone lysine methyltransferases (G9a and EZH_2) and NADPH oxidase-2 (NOX-2). These targets are implicated in a number of diseases such as cancer and neurodegenerative diseases. My work at this center resulted in a number of publications. Examples are shown below.

   a. Ganesh, T.; Min, J.; Thepchatri, P.; Du, Y.; Li, L.; Lewis, L.; Wilson, L.; Fu, H.; Chiosis, G.; Dingledine, R.; Liotta, D.; Snyder, J. P.; Sun, A. Discovery of Aminoquinolines as a New Class of Potent Inhibitors of Heat Shock Protein 90 (Hsp90): Synthesis, Biology and Molecular Modeling. Bioorg. Med. Chem. 2008, 16, 6903-6910. PMCID: PMC2653417
   b. Chang, Y.; Ganesh, T.; Horton, J. R.; Spannhoff, S.; Liu, J.; Sun, A.; Zhang, X.; Bedford, M.; Shinkai, Y.; Snyder, J. P.; Cheng, X. Adding lysine mimic in the design of potent inhibitors of histone lysine methyltransfersases. J. Mol. Biol. 2010, 400, 1-7. PMCID: PMC2895764
   c. Smith, S.; Min, J.; Ganesh, T.; Diebold, B.; Kawahara, T.; Zhu, Y.; McCoy, J.; Sun, A.; Snyder, J.; Fu, H.; Du, Y.; Lewis, I.; Lambeth, D. Ebselen and congeners inhibit NADPH oxidase 2-dependent superoxide generation by interrupting the binding of regulatory subunits. Chem. Biol. 2012, 19, 752-763. PMCID: PMC3383625

d. Zielonka, J.; Cheng, G.; Zielonka, M.; Ganesh, T.; Sun, A.; Joseph, J.; Michalski, R.; O'Brien, M. J.; Lambeth, D.; Kalyanaraman, B. High-throughput Assays for Superoxide and Hydrogen Peroxide: Design of a Screening Workflow to Identify Inhibitors of NADPH Oxidases J. Biol. Chem 2014, 289, 16176-16189. PMCID: PMC4047388

A complete list of published work can be found in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Ganesh%2C+Thota

D. Research Support

Ongoing

R21NS101167 (NIH/NINDS) (Ganesh, PI) 12/01/2017-11/30/2020
EP2 antagonists as novel anti-epileptogenic agents.
The purpose of this R21 grant is to derive a proof of concept that EP2 antagonism is antiepileptogenic in rat model of posttraumatic epilepsy.

U01, (NIH/NIA) AG052460 (Ganesh, PI) 09/15/2016 – 8/31/2021
Development of EP2 antagonists for suppression of Alzheimer's neuropathology
The purpose of this milestone driven project is to demonstrate whether targeting EP2 receptor is a therapeutic strategy for treating Alzheimer's disease.

R01 NS097776 (Dingledine, PI) 05/15/2016 – 04/30/21
NIH/NINDS
Inflammatory control of blood-brain barrier and epileptogenesis after seizures
The goal of this project is to test the hypothesis that neuronal COX2 induction, subsequent activation by neuron-derived PGE2 of EP2 receptors on activated microglia, and enhanced release of cytokines that act directly on capillary endothelial cells, are critical for the breakdown of the blood-brain barrier after seizures.
(Role: Investigator)

Recently Completed Support

University Research Committee award (Ganesh, PI) 04/01/2016 – 04/01/2017
EP2 antagonist proof of concept study in Alzheimer's animal model.
Emory University (Internal)
The purpose of this *internal seed funding* is to conduct POC concept studies in AD model.

U01 (NIH/NINDS) NS058158-06 (Dingledine, PI, NCE) 09/30/2011 – 08/31/2017
NIH
Prostanoid modulators that reduce the brain injury after seizures
The purpose of this milestone driven project is to develop TG6-10-1 for acute treatment of status epilepticus in animal models after exposure to an organophosphorus nerve gas agent.
(Role: Investigator)

Alzheimer's Drug Discovery Foundation grant, 20141201 (Ganesh, PI) 10/15/2013-10/31/2016
EP2 antagonist for the suppression of inflammation and neuropathology in Alzheimer's model.
The purpose of this funding is to begin the studies to demonstrate whether pharmacological inhibition of EP2 receptor is therapeutically beneficial for Alzheimer's disease.

Harrington Discovery Foundation (Ganesh, PI) 04/01/2014-03/31/2016
Supplement to the above grant.

Overlap: None