



# Viswanathan Natarajan: A Giant in Lipid Research and Pulmonary Disease and a True Gentleman

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## Abstract

This article is intended to recognize and the life time contribution that Dr. Viswanathan Natarajan has made to the advancement of lipid metabolism and lipid signaling. In particular, his major contributions in the last three decades have been made in understanding how lipids such as phosphatidic acid, lysophosphatidic acid, sphingosine 1-phosphate and cardiolipin contribute to healthy lung functions and to a variety of lung pathologies. We celebrate a truly remarkable career and look forward to seeing even more remarkable discoveries.

**Keywords** Endothelial barrier · Lysophosphatidic acid · Phospholipase D · Pulmonary diseases · Sepsis · Sphingosine 1-phosphate

## Introduction

I feel very privileged to be able to summarize and pay a tribute to Dr. Viswanathan Natarajan's scientific life and career. His friends know him as Nati and that is how I will refer to him.

I first met Nati in September, 1975 when I visited India for 6 weeks as a Young Visiting Scientist sponsored by the British Council. The idea was for me to interact with trainees in Indian Universities and if possible to establish research interactions and collaborations. The major part of my visit in India was to spend 4 weeks in the Department of Biochemistry at the Indian Institute of Science in Bangalore and to visit the laboratory of Dr. P. S. Sastry. It was there that I met Nati and his friend Reddy. Nati was a postdoctoral fellow at the time, having previously obtained his BSc at the University of Bombay (now University of Mumbai), an MSc at the University of Madras (Chennai) and a Ph.D. in Biochemistry at the

India Institute of Science in Bangalore. When I arrived, Nati's work with Dr. Sastry was focused on phospholipid synthesis. We discussed ideas that amphiphilic amines would likely affect the balance of phospholipid production by inhibiting phosphatidate phosphatase (now also known as lipins) and diverting synthesis through phosphatidate cytidylyltransferase to the production of acidic phospholipids. We designed experiments to test this hypothesis.

Outside of work, Nati and Reddy were really kind to me and they showed me much of Bangalore. They also advised me on where to plan my weekend visits, such as to Nandi Hills. This was very valuable since this was my first visit to India. They introduced me to Indian culture and I learned to enjoy Indian food, which I do to this day. I also learned more about Nati and realized that he was the poori eating champion of the Biochemistry Department, if not of the Institute. I seem to remember numbers such as 90–100 at one sitting being mentioned, but maybe my memory fails me and this is lost in the haze of history!

Little did I know that my interactions with Nati in Bangalore would end in a lifetime of scientific interactions, collaborations and above all, friendship with Nati and his wife, Lakshmi. This friendship was especially precious at a difficult time in my life when maintaining my research momentum was challenging. Nati reached out to offer me collaborative projects, which I will always remember.

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## Nati's Career

During his time as a graduate student and the short postdoctoral fellowship in Bangalore, Nati published seven peer reviewed papers with his supervisor, Dr. Sastry. These dealt mainly with the synthesis and metabolism of ether-linked ethanolamine phospholipids in the developing brain. This work formed an excellent basis for his career and led to a postdoctoral fellowship in 1975 with Dr. Harold Schmid at the Hormel Institute in Austin MN, which is part of the University of Minnesota. Nati progressed to become a Research Associate and then a Research Assistant Professor at the Hormel Institute. He then moved to become an Assistant Professor in the Department of Biochemistry/Molecular Cellular Biochemistry and an Associate Consultant in the Department of Neurology at the Mayo Clinic in Rochester, MN in 1985. Nati then wanted to continue his scientific career back in India and he moved to Bombay (Mumbai) as a Manager/Section Leader at Lever Brothers India Ltd., in 1986. However, he relocated back to the US in 1988 with a short appointment as a Visiting Associate Professor at the Hormel Institute, in the University of Minnesota, Austin, MN. From there, Nati was appointed as Assistant Professor, Department of Medicine/Biochemistry and Molecular Biology at the Indiana University School of Medicine, Indianapolis, IN. He rose through the ranks as Associate and Full Professor. It was during that time in Indianapolis that Nati developed an interest in the role of lipid signaling in lung pathologies through a close collaboration with Dr. Joe (Skip) Garcia.

Nati moved with Dr. Garcia to become a Professor in the Department of Medicine, Johns Hopkins School of Medicine, Baltimore and in the Department of Environmental Sciences, School of Public Health, Johns Hopkins University, Baltimore, MD from 1998–2005. After that Nati relocated to become a Professor of Medicine, in the Section of Pulmonary and Critical Care Medicine/Division of Biological Sciences at the University of Chicago, IL. In 2010, Nati became a Professor in the Departments of Pharmacology and Medicine at the University of Illinois at Chicago. He also holds the positions of Adjunct Professor in the Departments of Bioengineering and Biochemistry and Molecular Genetics, Co-Director, Institute for Personalized Respiratory Medicine, Earl M Bane Professor of Medicine, and Director of Translational Medicine.

## Honors, Awards, and Named or Honorary Lectures

Nati has been honored by numerous awards including the following: National Merit Scholarship, Government of India, 1968–1970; Fellow—Indian Council of Medical

Research, 1970–1975; National Science Foundation (USA) —Fellow—Visiting Scientist to India, 1983; Sigma Xi Research Honor Society, Indiana Chapter, 1990; Mentor for 1992 National AFCR Trainee Award Recipient (Dr. Tony Su); American Lung Association (National) Career Investigator Award 1991–1996; NIH/HLBI Research Career Development Award 1993–1998; American Lung Association (Illinois) 1993–1998—Elwin “Jack” Holten Lung Cancer Research Award; MERIT Award, NIH/HLBI 2010 and the Earl M Bane Professor of Medicine 2013–Present.

## Nati's Contribution to Community Service and Editorial Boards

Nati has served on the Editorial Board of Chemistry and Physics of Lipids 1996–2005; Biochemical Journal 2001–Present; American Journal Physiology-Lung, Molecular and Cellular Physiology 2004–Present; Antioxidants and Redox Signaling, 2007–Present and Pulmonary Circulation, 2010–2015.

## Nati's Mentoring Activities

Nati has passed on his knowledge extensively through mentorship of many trainees and colleagues. He has taught generations of medical and science students throughout his career. Nati has served as a mentor for 16 Pulmonary Fellows; 24 postdoctoral fellows; two faculty members; three MSc students and three doctoral students since 2011. More than 50 high school and undergraduate students have been trained in the laboratory for 8–12 weeks as summer interns.

## Nati's Research Interests

Nati's career spanning five decades has focussed on lipid metabolism and especially the roles of lipid signaling. This work has significantly increased our understanding of the pathogenesis of various diseases that is leading to novel considerations for treatments. The main focuses of Nati's interests are as follows:

1. *Cytoskeleton and regulation of vascular endothelial barrier function:* Nati's research has advanced our knowledge of signaling in endothelial cells and in particular how this controls the regulation of barrier function. He has studied the influence of the cytoskeleton and actin binding proteins on the dysfunction of the endothelial barrier that occurs in response to oxidative stress. This includes the activation of endothelial NADPH oxidase by

cytoskeletal proteins including cortactin and coronin; the oxidant-induced activation of protein kinase Cs and non-receptor tyrosine kinases belonging to the Src family. Of particular importance are Nati's studies on the role of sphingosine-1-phosphate (S1P) and signaling in vascular endothelial cells and his studies on how activation of phospholipase D is regulated by oxidants in the endothelium [1].

2. *Lysophosphatidic acid (LPA) signaling in airway inflammation and asthma*: One of Nati's major contributions has been in studying the levels of LPA and S1P in bronchoalveolar lavage from controls and allergen-challenged asthmatics. This work also involved studying the expression of LPA and S1P receptors in normal and asthmatic lungs; mechanisms of LPA- and S1P-induced cytokine secretion and airway inflammation; the cross-talk between LPA/S1P G protein-coupled receptors and growth factor receptors in human primary epithelial cells; the role of LPA and S1P in airway remodeling; lipid phosphate phosphatases and related proteins in airway inflammation and remodeling; the development of knockout mice for LPA/S1P receptors to assess airway functions; the involvement of LPA and S1P in lung cancer and metastasis [2].
3. *Protective role of intracellular S1P in sepsis-induced lung injury*: Nati's research team established that S1P is a major barrier-protective agent that is responsible for maintaining vascular barrier integrity and endothelial/lung intergrity against injury caused by lipopolysaccharide (LPS). This involves both extracellular signaling through S1P receptors and intracellular S1P signaling involving  $Ca^{2+}$  release and the proliferation of mouse embryonic fibroblasts. The steady state concentrations of intracellular S1P are regulated by its synthesis through two sphingosine kinases (SphKs) versus degradation by two S1P phosphatases (SPPs) and S1P lyase (S1PL). Nati proposes that modulation of intracellular S1P by SphKs and changes in this balance regulate LPS-induced lung inflammation and endothelial barrier dysfunction [3]. His work is designed to investigate: (1) how S1PL and SphKs regulate intracellular S1P levels during LPS-induced inflammation and lung injury; (2) The molecular mechanisms by which intracellular S1P, S1PL and SphKs regulate LPS-induced inflammatory responses; (3) Characterize the influence of ALI-associated single nucleotide polymorphisms on SphKs and S1PL expression and activities, and (4) Evaluate S1PL and SphKs as potential therapeutic targets to attenuate LPS-induced lung injury.
4. *Sphingosine kinase 1 as a novel target in pulmonary fibrosis, pulmonary hypertension, and bronchopulmonary dysplasia*: SphK1 expression and high S1P levels occur in lung tissues from patients with idiopathic pulmonary fibrosis, pulmonary hypertension and bronchopulmonary dysplasia. Genetic deletion or inhibition of SphK1 ameliorates bleomycin-induced pulmonary fibrosis, hypoxia-induced pulmonary hypertension and hyperoxia-mediated bronchopulmonary dysplasia in murine models [4]. Nati's group demonstrated that blocking SphK1 activity with a specific inhibitor, PF-543, effectively ameliorated these lung pathologies. A patent application has been filed for PF-543 in the US and Europe and Nati continues to study the mechanisms involved in the development of these lung pathologies and the roles of SphK1/S1P signaling in these processes.
5. *Lysocardiolipin acyltransferase (LYCAT), a mitochondrial cardiolipin remodeling enzyme, in non-small cell lung cancer*: Lung cancer is the leading cause of death in the US and non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancers with a 5-year survival of only ~16%. Thus, there is an urgent need to identify biomarkers to detect NSCLC and to design new technologies for developing therapeutic targets. Mitochondrial dysfunction is involved in the development and progression of lung cancer and cardiolipin is a major component of mitochondrial membranes. Cardiolipin plays an important role in the structural organization of mitochondria and ATP production. Lysocardiolipin acyltransferase (LYCAT) is a key enzyme in the remodeling of mitochondrial cardiolipin and for establishing its content of linoleic acid. The role of LYCAT-mediated cardiolipin remodeling in lung cancer is largely unknown. Nati's group has used unique molecular tools to modulate LYCAT expression and establish how LYCAT can be used as a specific target for therapeutic intervention in lung cancer [5].
6. *Nuclear sphingolipids are epigenetic co-regulators of bacterial lung inflammation and injury*: *Pseudomonas aeruginosa* (PA) is a gram negative and opportunistic pathogen, which causes severe respiratory tract and systemic infections. This occurs especially in people with cystic fibrosis, in immunocompromised patients, and in patients with advanced chronic obstructive pulmonary disease and ventilator-associated pneumonia in intensive care units. Mortality from PA-mediated pulmonary infections has not been decreased significantly by aggressive intensive care support or by the use of potent antibiotics. Consequently, there is an urgent need to understand how patients can defend against PA infections. Understanding the signaling mechanisms that are activated by PA infections is crucial in identify new therapeutic targets. Nati's work focused on the signaling

roles of sphingolipids, particularly ceramides, sphingosine and S1P. These lipids play an important role in host-pathogen interactions and initial responses to bacterial infections. Nati's group obtained exciting evidence that genetic deletion of sphingosine kinase-2 (SphK2), but not SphK1, protected mice from PA-induced lung inflammation. Knocking down SphK2 in alveolar or bronchial epithelial cells decreased PA-mediated H3 and H4 histone acetylation and the consequent secretion of pro-inflammatory cytokines including IL-6 and TNF- $\alpha$ . SphK2 becomes phosphorylated and its translocation to the nucleus promotes inflammation. Production of S1P in the nucleus acts as an epigenetic co-regulator of histone deacetylases through NADPH oxidase (Nox) 4 protein [6]. It is significant that lungs from patients with cystic fibrosis, who are prone to PA infections, exhibit increased nuclear phospho-SphK2 immunostaining when compared to control lungs. Nati's work in this area is to understand the key role of nuclear SphK2/S1P signaling in epigenetic co-regulation during lung injury caused by bacterial infection.

## Research Funding

Nati has successfully supported his research interests, his group and all of his numerous successful trainees throughout his independent career as a PI by competitive awards from National Agencies including numerous awards from NIH. He presently holds eight grants to support his work on sphingolipid signaling and lung pathologies. This includes two as the project leader, with the rest as a co-PI or Co-Investigator.

## Publications and Presentations

Nati's publication record is remarkable with more than 262 peer-reviewed publications and an H index of 74 (Google scholar). He has also received numerous national and international invitations to present his work. Nati was also recognized by his peers by being appointed Co-Chair of the FASEB SRC on "Lysophospholipid and Related Mediators Conference: From Bench to Clinic, 2019." This was a major honor because this is the main international conference directly in the area of Nati's work on lipid mediators in health and disease.

## Conclusion

This is an appropriate time to honor and recognize an amazing colleague who has made, and is continuing to make, enormous contributions to both understanding basic scientific mechanisms and the applications of this information to health and disease. A fuller and much more authentic description of Nati's career can be obtained through his own reminiscences [7]. However, I am proud to reiterate that Nati's work has added significantly to our understanding of how lipid mediators, such as LPA and S1P, play crucial roles in normal and pathological conditions and particularly in lung pathologies. We salute Nati as a great scientist, but also as a compassionate mentor and dear friend.

## Compliance with ethical standards

**Conflict of Interest** The author declares no competing interests.

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