



International INNOVATION

Disseminating science, research and technology

ISSUE
138

BREAKING GROUND

THE FOUNDATIONS FOR MEDICAL PROGRESS

SPECIAL FOCUS

Key contributors offer their take on the greatest barriers to research excellence

EXCLUSIVES

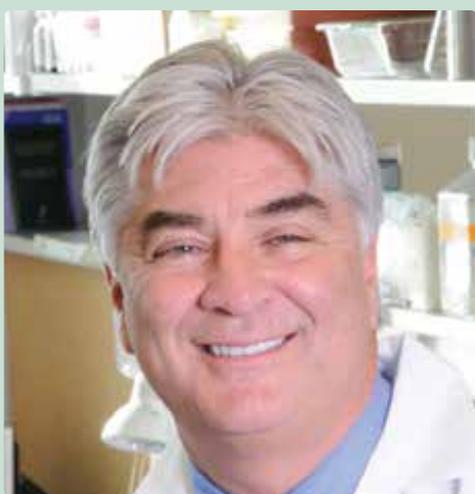
- American Society for Reproductive Medicine
- Canadian Partnership Against Cancer
- National Alliance on Mental Illness
- Canadian Lung Association

RESEARCH SPOTLIGHT

- Canadian Cardiovascular Society
- Ontario Chronic Disease Prevention Alliance

A sustainable future for lung research

Describing his collaborations with committed and expert colleagues in the field of lung research, world-class researcher **Joe G N 'Skip' Garcia, MD** discusses how his work is advancing the field of pulmonary medicine



As an internationally recognised physician-scientist, policy advisor and general polymath, how do you effectively balance your time between various commitments?

In this type of academic leadership position you are only as good as the quality of the people

around you. In my prior leadership roles I have been fortunate to be at the head of great teams. Now, at the University of Arizona (UA), I am building another high-quality and talented academic leadership group that will ensure profound synergy and success in promoting our tripartite academic mission of health education, clinical care and research.

I am passionate about biomedical research and discovery and have always believed that one leads by example. Therefore, managing my laboratory research programme that has been continuously funded by the National Institutes of Health (NIH) for the past 30 years, providing mentorship to both aspiring young investigators and seasoned department heads, and leading strategic initiatives to advance the quality and cost effectiveness of our patient care programmes are all important activities, both to me personally and to the success of the UA health sciences.

What important results emerged from your recent study investigating the relationship between blood cell gene expression and

outcomes in patients with idiopathic pulmonary fibrosis (IPF)?

IPF is a fatal lung disease characterised by scarring of the lung from an unknown aetiology that has different progression rates. No therapy is available for IPF except lung transplantation, which is highly limited by donor lung availability. Median survival rate is 3.5 years, so providing patients with an accurate prognosis is critical. We employed a genome discovery study using blood cells from IPF patients, which is less invasive than obtaining lung biopsies, and identified an expression profile that correlates with transplant-free survival. The gene profile predicts disease severity and provides clinicians with information on the priority and urgency of lung transplantation.

How does your research facilitate the development of new strategies and targets to limit the adverse effects of injured pulmonary circulation?

The pulmonary field has many unmet medical needs since many diseases have limited

Lighting the way for lung research

therapeutic options and unacceptably high mortality rates. The research strategies utilised by my lab have not only identified several novel biomarkers and targets, but also provide a blueprint for other investigators to employ genomic approaches and discover new targets. These approaches are the foundation upon which modern investigators will incorporate their research and develop the tools clinicians need to practise personalised medicine.

Can you reveal your plans for advancing the Arizona Health Sciences Center (AHSC) and expand on the areas of excellence?

We're recruiting nationally-noted physician-scientists and scholars to help lead our efforts to advance and develop AHSC by expanding research and clinical care. In December 2013, I convened advisory councils in four key research areas: Health Disparities; Precision Health; Neuroscience; and Population Health and Health Outcomes. Drawing faculty members from across both the Tucson and Phoenix campuses, and involving 11 UA colleges, the councils are charged with evaluating our internal strengths and weaknesses as well as outside threats and opportunities in their respective areas. Each council will provide recommendations to advance AHSC's distinction and national reputation. This will strategically strengthen and expand our basic, clinical and translational research programmes and improve our position in the hyper-competitive environment for federal research funding.

As a world-class researcher and the recipient of many prestigious awards, what is your proudest achievement to date?

I would say either my community service award from the State of Indiana for my work illuminating the health challenges of migrant farm workers while I was at Indiana University, or the recognition by my academic peers, nationwide chairs of Departments of Medicine, for my success in implementing novel strategies to increase diversity in an academic department of medicine.

Looking ahead, can you discuss your vision for your research over the next decade?

In the post-human genome era, identifying strategies that deliver precision health, high-quality outcomes and cost-effective therapies is a necessity given the challenges of the healthcare reform environment. I endeavour to be a leader in implementing precision medicine tactics in the critical care setting. This trend toward personalised or individualised medicine will continue to dominate healthcare over the next decade.

Focused on bringing evidence-based personalised healthcare to the fore, a team of researchers based at the **University of Arizona, USA**, is investigating the development of lung disease and exploring positive changes that could improve clinical practice

LUNGS ARE COMPLEX organs and, as such, can be affected by an array of disease pathologies. The management of lung disease is therefore challenging. Even in modern medicine the mortality associated with lung disease is extremely high and is further elevated in populations with genetic predispositions to disease initiation and progression. Increased focus is now being placed on personalised medicine in healthcare, and the pathology of lung disease is no exception. Dr Joe G N 'Skip' Garcia at the University of Arizona (UA) has spent a large portion of his career leading research teams working to elucidate lung pathology, specifically the cytoskeletal regulation of lung endothelial pathobiology such as vascular leak and permeability. Within this overarching project funded by the National Institutes of Health (NIH), Garcia and his colleagues have focused on the cytoskeletal scaffolding within cells and the key signalling molecules whose function relates to the regulation of vascular integrity. In their current research programme, the team is undertaking five distinct projects assessing a range of interlinked aspects of lung vascular pathology.

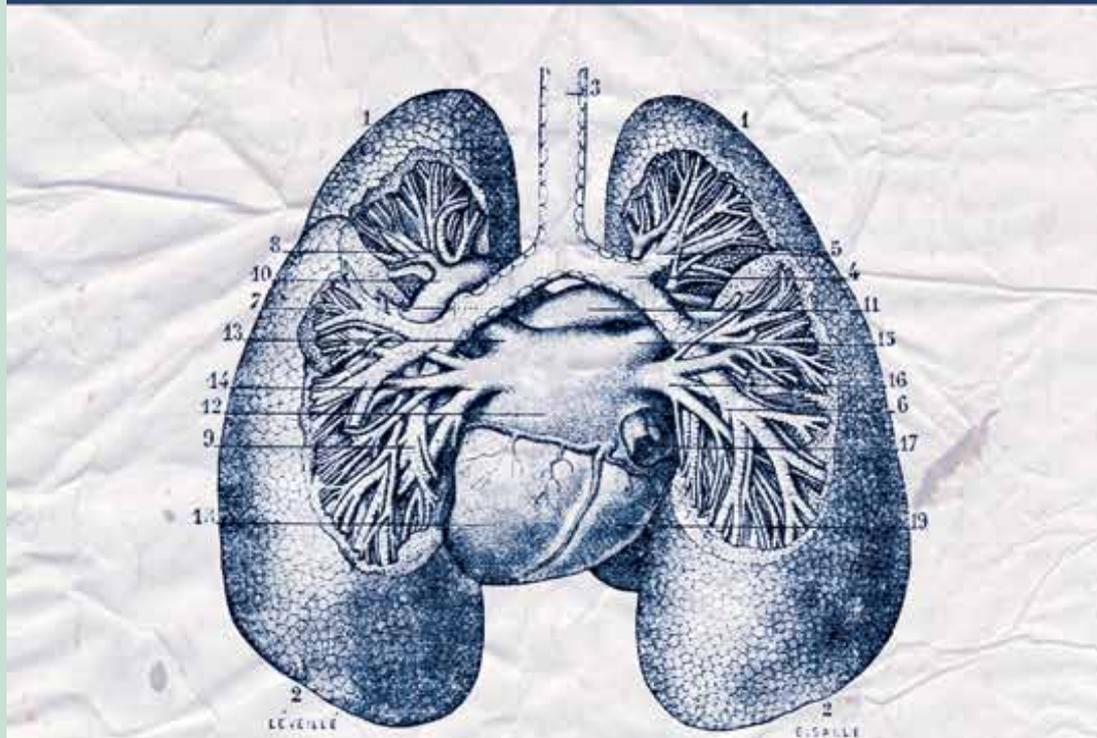
CAPABILITY TO PRODUCTIVITY

Key in-house technical abilities including biophysical imaging, tissue culturing, genome analysis techniques and the ability to produce

gene-specific animal models support the efforts within each of the five research streams. In combination, these capabilities present researchers with the tools needed to assess cytoskeletal function and define the relationships between specific genetic and morphological characteristics and disease. Garcia believes this wealth of abilities, teamed with the research expertise and experience offered by himself and his colleagues, will push the boundaries of current knowledge and provide new understanding of the lung endothelium and perhaps therapeutic options for inflammatory lung injury. This spectrum of tools allows the teams to establish both the genotype and phenotype involved in disease states, identify single nucleotide polymorphisms in these genes, and then take this understanding and test it experimentally in animal models: "We now have the capacity and technology platform to perform add-back experiments in mice to study the effects of these small genetic changes," Garcia explains.

FOSTERING A DIVERSE FUTURE

A holistic, tripartite model of practice, with an equal and consistent focus on research, clinical practice and training has been central to the success of Garcia's current work, as well as his previous efforts. In his current leadership position at the UA, and in previous roles at other institutions, Garcia has experienced



INTELLIGENCE

CYTOSKELETAL REGULATION OF LUNG ENDOTHELIAL PATHOBIOLOGY

OBJECTIVES

To develop novel therapies for critically ill patients with acute inflammatory lung disease.

KEY COLLABORATORS

Viswanathan Natarajan, PhD; **Steven M Dudek, MD**; **Jeffrey R Jacobson, MD**, University of Illinois, Chicago • **Augustine M K Choi, MD**, Cornell Medical College • **Ivan O Rosas, MD**, Harvard Medical School • **Laura L Koth, MD**, University of California, San Francisco • **Naftali Kaminski, MD**, Yale University

FUNDING

National Institutes of Health (NIH)

National Heart, Lung and Blood Institute (NHLBI)

CONTACT

Joe G N 'Skip' Garcia, MD
UA Senior Vice President
for Health Sciences

University of Arizona
Arizona Health Sciences Center
Drachman Hall
1295 N Martin Avenue
Tucson
Arizona, 85721
USA

T +1 520 626 1197

E skipgarcia@email.arizona.edu

.....
DR JOE G N 'SKIP' GARCIA is an internationally noted physician-scientist, health administrator, scholar and educator, and an elected member of the Institute of Medicine of the National Academies. He is also a leading research authority on the genetic basis of lung disease and the prevention and treatment of inflammatory lung injury.



Investigation into the pathology of lung disease demands an intelligent and sustained model of research supported by committed experts and considerable funding

the lack of minority communities in science, including African American, Latino and socially or financially disadvantaged students, first hand, and has been a key advocate of promoting diversity in research and academia: "I am very passionate about training the next generation of physician-scientists, particularly underrepresented minorities," he asserts. Throughout his career, Garcia has worked to tackle disparities by implementing a variety of measures to enable promising young men and women from underserved communities to enter medicine and academia. One example of a particularly successful programme comes from Johns Hopkins University: "I started an NIH-supported programme that granted 25-30 African American and Latino undergraduates from across the country an all-expenses-paid summer research laboratory experience," he enthuses. Garcia is particularly proud of his involvement in this effort, which culminated in almost 90 per cent of the participants entering medical or graduate school.

PRECISION MEDICINE IN CRITICAL CARE

With dramatic improvements in genomics and an increased focus on quality in healthcare associated with continued improvements in life expectancy and global economic growth, attention has now been turned to how medicine can be individualised. It is a reality of nature that all humans have a completely unique combination of genes. This is a salient point in modern medicine, as some individuals have genes that predispose them to particular forms of illness or disease and/or alter the severity of that disorder. Today, research is attempting to elucidate key genes and biomarkers that predict individual risk in disease or treatment situations to enable physicians to practise personalised medicine.

This is an area of research in which Garcia and his UA colleagues are particularly interested. One line of investigation has focused on acute respiratory distress syndrome (ARDS): "We and others have identified that black and Latino patients are at an increased risk for critical care illnesses such as ARDS and sepsis which translates to higher mortality," Garcia points out. These increased risks remain present, despite statistical correction for socioeconomic factors and other confounding variables, clearly indicating a genetic predisposition in these communities. Following this realisation, the Arizona group was able to identify genetic variants – more prevalent in black patients – that predict an increased risk of ARDS. Armed

with this understanding, the team now hopes physicians can develop different therapeutic and management strategies for treating high-risk black patients. While this research is invaluable for managing ARDS in a range of communities, it also serves to highlight the challenge of personalising healthcare. Many clinical trials fail to distinguish between sex, race and other key genetic determinants, leaving understanding of community- and gender-based differences in disease and treatment efficacy desperately lacking.

MINIMISING TREATMENT RISK

Garcia and his colleagues are also investigating the impact of treatment and management for lung disease and the assessment of risk versus benefit in these various strategies. One area of interest the researchers have focused on is the initiation of local inflammatory responses in the lung due to mechanical ventilation: "Critically ill patients with respiratory failure are placed on mechanical ventilation as a lifesaving supportive therapy," Garcia highlights. Unfortunately, this process itself can stress the lung endothelium, stimulating the release of pre-B cell colony-enhancing factor (PBEF), which acts as a chemical signal that triggers localised inflammation. This process amplifies lung inflammation and is potentially damaging. Garcia has worked to create monoclonal antibodies with the specific structure to target and inactivate PBEF, thus reducing both inflammatory responses and the risk of comorbidities in these already critically ill patients. Today, monoclonal antibodies are being developed by Aqualung Therapeutics, a company established by Garcia, for the treatment of ventilator-associated lung injury.

The work at the UA that falls under the umbrella project concerned with the cytoskeletal regulation of lung endothelial pathobiology is serving to improve understanding of disease and genetic predictors in the field, and is also highlighting the challenges of improving evidence-based personalised healthcare in modern clinical practice. Investigation into the pathology of lung disease demands an intelligent and sustained model of research supported by committed experts and considerable funding. Programmes meeting all of these criteria are few and far between and the work being conducted by Garcia and colleagues should be celebrated as a success in this context, and also emulated as a model of best practice for a holistic approach to research that simultaneously endeavours to promote ethnic and social diversity in the academic and medical professions.

AQUALUNG
THERAPEUTICS

THE UNIVERSITY
OF ARIZONA