A3G can be purified and critical regions of the enzyme mapped.

Starting up the road to invention

In 2003, **Professor Harold Smith** founded his own biotech company to develop a drug-based treatment for HIV. Here, he shares his experiences and describes some of the biggest challenges he has faced in drug development

How did you become interested in the mechanisms of disease?

A professor at Purdue University, USA, named Dr Michael Forman inspired me to think about the inner structures and functions of cells. I began to take courses in chemistry and biochemistry while working on my BS degree. I conducted my Master's degree in Veterinary Physiology and Pharmacology at Purdue, which gave me a holistic understanding of how the body is regulated, but it also left me with many unanswered questions. To address the mechanisms driving health and disease one must understand the interactions between genes and molecules in the cell, so I acquired my PhD in Cell and Molecular Biology under the mentorship of Dr Ronald Berezney at the State University of New York at Buffalo and completed postdoctoral training in RNA and DNA biology working in the laboratories of Drs Harris Busch, Craig Chinault and Susan Berget at Baylor College of Medicine.

What types of activities are you involved in at your lab at the University of Rochester, USA?

I direct basic research in biochemistry and molecular biology conducted by postdoctoral fellows and students, obtain extramural grant support, publish scientific papers, file patents and present findings at scientific meetings. I also direct and teach undergraduates and serve on University committees. I have served as Director of the Pathology Graduate Program, Director of an undergraduate biochemistry methods course and Director of Medical School Biochemistry, roles in which I was responsible for three curriculum reforms including transforming the first-year medical school biochemistry course to a problem-based learning curriculum.

Are there specific highlights you can share of your scientific activities?

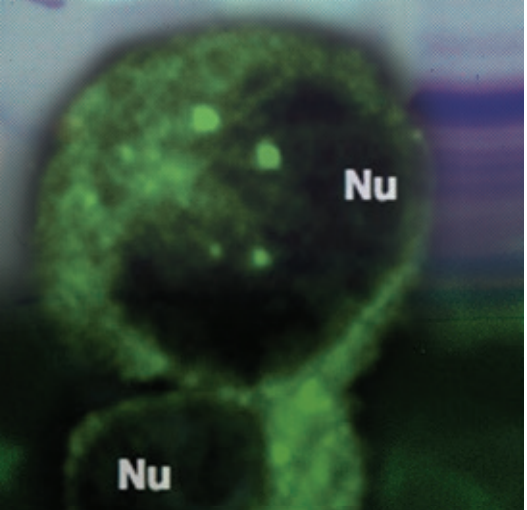
I am a molecular and cell biologist. My laboratory is a founding research group in RNA editing, having elucidated the mechanism for site-specific apolipoprotein B mRNA editing and its regulation. I played a key role in uniting the diverse research areas of RNA editing, RNA modification, nucleotide modification and DNA hypermutation by establishing the Gordon Research Conference on RNA and DNA Modification and Editing in 1997, as well as contributing papers, reviews and a book on the subject.

Can you introduce your company, OyaGen, Inc.?

In 2003, I founded OyaGen, Inc. for drug discovery and development of antiviral compounds that prevent HIV Viral infectivity factor (Vif)-dependent degradation of apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G (A3G). My current relationship with OyaGen is as Founder, President and CEO. OyaGen is based on self-generated intellectual property and licensing agreements with the University of Rochester and Thomas Jefferson University in Philadelphia, USA. The company develops unique methods that profile drug targets and applies these to robotic high throughput screening of chemical libraries of drug-like small molecules to find the preliminary scaffolds upon which the next generation of drugs can be developed.

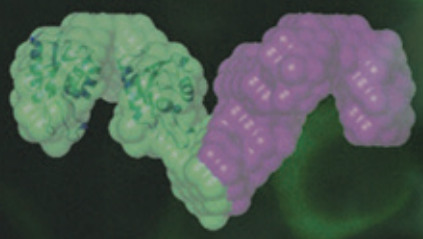
Many ideas never make it off the lab bench, and of those that do, 90 per cent of new ventures that fail to attract investors fold within the first three years. As Founder of OyaGen – which has raised US $10.7 million over 11 years from various federal, venture capital and industry sources – can you share your thoughts on while this might be the case?

This is a big issue as many discoveries are not developed to proof of concept, and industry has become risk adverse to take on this responsibility. Ten per cent may be pretty good, we don't know what to compare this to. Given that we start with knowing nothing, and then move through confusion to understanding, it seems amazing that so much has been



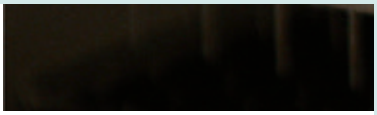
A3G is a DNA mutagenic enzyme that resides in the cytoplasm of cells, excluded from chromosomes in the nucleus (Nu).

A3G functions as a sentinal to restrict retrovirus replication. Superimposed is a low resolution X-ray image of A3G, which interfers with viral replication complexes.



Editing the approach to HIV

Developing a cure for HIV is widely considered an insurmountable challenge by the academic community. However, **OyaGen, Inc** is taking a novel approach by targeting a protein that protects the virus against newly discovered natural defences



accomplished by the scientific community in my lifetime. Some failures are due to the fact that exploring the unknown is fraught with best guess scenarios, even if the experiment is well planned and the hypothesis is well justified. Another side of this involves finances; many companies have good ideas but run out of money. Most biotechs fail in what is called the 'valley of death' – the time between sponsored research in universities and strategic partnering with industry for clinical trails and commercialisation. Failure is largely due to lack of financial resources but is also due to start-up company founders not realising the emotional and intellectual stamina that ownership demands. Academic research, while comparatively well-funded in the US, is underfunded for the ambitious endeavour of seeking to understand how life works or improving our lives through understanding of disease processes and treatments.

Do you have any advice for other scientists who are looking to traverse the valley of death?

I have many pieces of advice. Do not do it alone (at least in biotech). Do not stay within the secure hallways of a university. Recruit help from people with industrial and government experience. Be willing to sacrifice some ownership for progress. Seek non-dilutive funding and equity financing from any and all sources. Focus on accumulating as much data as possible with the goal of getting to an approval for clinical trials.

Do not conduct business as if acquisition or strategic partnering are the short-term goal or inevitable; this will take several years with or without a strategic partner. Your relationship with the company cannot be at arm's length; you must show good leadership as you would to your academic lab.

RARELY SINCE THE Black Death has a disease caused such an international frenzy as HIV/AIDS. The anxiety surrounding HIV is justified; it is highly infectious and those who go untested may not know they are infected for years because symptoms can remain hidden while the virus attacks vital immune system cells. Over time, the body's ability to respond to infection deteriorates, eventually leading to AIDS.

The World Health Organization (WHO) estimates that in 2014, 35 million people worldwide were infected with HIV. The disease reduces life expectancy and affects ability to work, resulting in devastating effects on economic development, particularly in sub-Saharan Africa where 70 per cent of HIV infection cases are found and transmission is rampant in the heterosexual community. Even in high-income countries, HIV affects the most vulnerable and stigmatised members of society, including sex workers, drug users and gay men.

Thanks to the advent of antiretroviral treatments – of which there are more than 20 – that can prolong survival, HIV is now considered a manageable chronic condition, rather than a death sentence. However, shortly following the distribution of HIV treatments to communities with AIDS, multidrug resistance rapidly emerged. New drugs are constantly required to combat this emergence, evidenced by the fact that as few as one in four people receiving antiviral therapy worldwide are able to maintain durable suppression of viral replication.

Despite urgent need, after more than 30 years of research by universities and industry, a cure remains as elusive as ever. In fact, until recently the terms 'cure' and 'cure research' were suppressed from publications and grant applications as unrealistic in expectation. However, emerging discussions and recent publications reflects a new openness to a cure being possible, but they also reveal the reality that humanity has not found a cure for AIDS yet. "Many have argued that a cure has not been discovered because our understanding of the virus, technological approaches, science policy and industrial risk taking have been inadequate to the challenge," notes Professor Harold Smith of the University of Rochester, USA. The 'challenge' Smith is referring to is humanity's ability to broadly explore and rapidly triage new ideas that are radically different than those of the past 30 years. "We have to be prepared to be flexible about the set of rules and criteria that industry uses to drive new therapeutics to the market, as 'the cure' may demand new standards," he continues.

ACCEPTING AN IMPOSSIBLE CHALLENGE

During his research in molecular biology at the University of Rochester, Smith observed that while discoveries were made regarding disease mechanisms, drugs and other products for patients rarely followed. "It then struck me that for all the things I would accomplish academically, only few people would appreciate the impact," Smith recounts. He came to acknowledge the distinction between a discovery – an explanation for a natural phenomenon – and an invention – a creation based on a discovery. In 2003, with growing appreciation for the role that industry could play in bringing the impacts of his research to the public, Smith founded OyaGen, Inc.

Smith skillfully juggles his full-time professorship at the University with his roles as President, CEO and Founder of OyaGen; overseeing research, fundraising, communications, and federal and state relationships, as well as managing its objectives. OyaGen's chief aim is to develop drug-based treatments for HIV that address the complications of viral resistance.

Traditional approaches in HIV research have targeted the components of viral entry into white blood cells, viral replication and viral particle formation. However, researchers have avoided targeting the cellular pathways that viral replication relies on due to potentially harmful side effects. "The truth is that no matter how hard the community has tried, nothing has yielded a cure," Smith explains. "Therefore exploring the same targets as we did in the past, or a combination of these targets, is unlikely to yield a different outcome."

Smith's motivation for starting OyaGen to pursue HIV research was based on very recent discoveries, primarily the discovery of Dr Ann Sheehy in Dr Michael Malim's lab at

OYAGEN INC.

OBJECTIVES

- To create orally deliverable antiviral compounds for HIV based on a novel viral drug target and methodology that displays OyaGen Inc.'s novel approach to all others in the pharmaceutical space
- To recognise that an HIV cure will require novel thinking and that the past 30 years of therapeutic research has in fact been cure research that has achieved therapeutic successes
- To overcome the cultural obstacles of getting academic institutions to truly embrace the call to drug development, even in this time when industry is providing increasing less R&D support

KEY COLLABORATORS

Dr Anthony Pinkerton; Dr Thomas Chung, Sanford-Burnham Medical Research Institute, USA • **Dr Roger Ptak,** Southern Research Institute, USA • **Dr Guillermo A Morales,** Cogent Professional, USA

FUNDING

Private investors • The State of New York • National Institutes of Health (NIH)

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http://bit.ly/HaroldSmith_RG

DR HAROLD C SMITH is a tenured professor of biochemistry and biophysics at the University of Rochester, School of Medicine and Dentistry. He is also Founder, CEO and President of OyaGen, Inc. His primary interest is understanding the composition, regulation and structure of macromolecular complexes involved in regulating gene expression at the level of messenger RNA expression and processing. He has applied this interest in HIV and Ebola drug discovery and drug development endeavours. He also mentors the next generation of biochemistry and molecular biology scientists. He has been recognised for mentorship by the University's Women in Science and Medicine Organization and received the Dean's Academic Scholars award.

the University of Pennsylvania of a cellular 'editing' enzyme residing in white blood cells that made these cells resistant to certain strains of HIV. This enzyme, known as apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G (A3G) alters the chemical structure of DNA, and hence their genetic codes. Researchers established under controlled laboratory conditions that A3G can halt the infectivity of HIV. OyaGen is taking advantage of A3G's editing capabilities in its quest to develop original therapies for HIV-infected patients.

SUPPORTING NATURAL DEFENCES

A3G's ability to edit DNA is associated with helping a robust immune system protect against infection; the editing enzyme is the body's natural defence against retroviral infection, including HIV. It induces mutations in the HIV DNA genome during its replication, resulting in the expression of mutated viral RNA genomes that code for defective viral proteins and halt the infectivity of the virus. However, HIV has evolved a protein that protects itself against A3G: the Viral infectivity factor (Vif). Vif interacts with A3G and causes ubiquitination, which adds a tag to A3G and targets it for cellular degradation, thus leaving the HIV infection to spread unimpeded.

Led by Smith, OyaGen developed a compound that inhibits the function of Vif, preventing it from causing the degradation of A3G; it suppressed the infectivity of the live HIV virus in human cells 1,000 times more effectively than in untreated cells. "While other approaches to HIV therapies have struggled to address the virus' tendency for rapid mutation, our approach of targeting HIV Vif to enable host defence is novel," Smith enthuses. "Compared with other elements of the HIV genome, the Vif regions required to bind to A3G and destroy it are more stable, and when these regions are mutated, Vif fails to protect HIV from our natural defences and I predict that it will not result in progression to AIDS."

A NEW RESEARCH CULTURE

Straddling academia and business, Smith has a unique perspective on research. His career developed with the academic view that patents are barriers to sharing, as is the business mind-set that prioritises maximisation of potential profit above all else. Smith argues that the future of the biotech industry requires federal grant funding review committees (who are largely academics) to embrace the potential for product development as a requirement for significance and for universities and colleges to appreciate that translational research needs to include entrepreneurship that has as its primary outcome public access through commercialisation. "It does not have to subvert traditional academic principles," he states. "Young scientists seeking careers in the biological and biomedical sciences – either in industry or academia – and their mentors, need to understand that a successful career in science is about passion, critical thinking, hypothesis testing and dedication to technological excellence."

For a university researcher, founding a company is a daring move. For Smith, the decision was a success. Leading OyaGen has allowed him to delve into an area dismissed by many as futile, in order to pursue his ideas freely and see them become innovations. Already, OyaGen holds licenses from the University of Rochester and Thomas Jefferson University, USA. Under Smith's direction, the company has identified three potential HIV drug leads, all in the preclinical development stage.

Using editing enzymes, OyaGen is expanding beyond HIV treatment, and has identified several new applications for its technology for other diseases. Currently, the company is seeking funding to develop drugs to slow the rapid progression of Ebola. If successful, this would decelerate the infection enough for immunisation to develop before the disease becomes fatal. For Smith, the greatest satisfaction comes from seeing his research bringing practical benefits for all: "Applying my skills in critical thinking and technology to inventions enables me to bring things to humanity in ways that underscore my science," Smith concludes. "And with any luck will allow me to make a lasting contribution to humanity."

OYAGEN ON YOUTUBE

In engaging and enlightening videos, OyaGen, Inc. describes the barriers to a cure for HIV and its novel, rational and near term approach to eliminate viral reservoirs based on drugs in development

HIV/AIDS OyaGen, Inc. Seeks a Path to a Cure

www.youtube.com/watch?v=P1ODXikMmHk

OyaGen HIV eradication and cure innovation

www.youtube.com/watch?v=6uyRyhzaoNQ