The reality of drug discovery in academia

Translating research findings of compounds into meaningful treatments for diseases in humans is complex and often not successfully accomplished. However, developments within the pharmaceutical industry have provided new avenues for this translation to take place. One particularly promising compound is resveratrol, originally discovered to extend lifespan. Dr Shaun Brothers, from the Miller School of Medicine at the University of Miami, is currently focused on clinically validating this compound. Together with several colleagues, Dr Brothers aims to be the first to clinically validate its usefulness in humans.

Scientists often state that their scientific breakthroughs make progress toward helping human disease. Whilst this is correct, the difficulty of the steps required to move from basic research findings toward developing drugs for humans means that this is not often achieved. Changes in the way the pharmaceutical industry, often referred to as 'Big Pharma', does business has provided new opportunities for academics to meaningfully engage in the pursuit of finding treatments. Dr Shaun Brothers and his colleagues are at the forefront of this pursuit, most recently focusing on the compound resveratrol, which has a number of potentially promising health benefits for humans.

CHANGES WITHIN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry has seen a significant change in the way it has operated over the past twenty years. A number of studies have documented the industry's declining productivity challenges, the transitioning of commercial models and the growth of emerging markets as key revenue contributors. Four key trends have been identified within the pharmaceutical industry occurring between 1995 and 2015, including: massive-to-lean, hubs-to-hotspots, primary-to-speciality and West-to-East.

Massive pharma enterprises have moved from a 'bigger is better' model towards a 'leaner and focused' model. The former model, prevalent from 1995 to 2005, resulted in large global operations including large research and development hubs, a large number of sales reps, multiple manufacturing sites and matrixed governance layers. The latter model, prevalent from 2005, was formed by divesting non-core assets and focusing on their areas of strengths.

Multiple research hubs around the world have similarly moved towards locating within more efficient bioscience hotspots. The creation of numerous research hubs was an unintended consequence of a number of acquisitions by the pharmaceutical industry, a response to the decline in research and development productivity. The hubs were used in an attempt to channel more resources into solving scientific challenges, a 'more shots on goals' strategy. In contrast, the localisation of research within hotspots, which has occurred over the last decade enables pharmaceutical industry scientists to work closely with external researchers and clinicians in progressing drug research. The hotspots way of working is thus much more open and collaborative than the hubs model.

Primary-to-speciality refers to the change in focus from primary care therapy towards speciality medicines targeted for a range of unmet needs. From 1995-2005, most of the top-selling drugs were primary care, small-molecule therapies. During this period, primary care therapy areas accounted for 80% of revenues for most of the pharmaceutical industry portfolios. The move from primary to speciality drugs was driven by several factors, including: an improved understanding of the underlying disease biology to develop targeted medicines, science and technology innovation, personalised medicines and companion diagnostics, favourable regulatory framework and development timelines for such medicines as well as pricing and reimbursement, all allowing for specialty products to be produced at a profit.

West to East refers to the change in major markets that have occurred within the pharmaceutical industry. North America and Europe were the leading major markets for the global pharmaceutical industry between 1995 and 2005 whereas the emerging markets of Asia, Latin America, Russia, Middle-East and Africa continue to spearhead revenue growth since 2005, due to strong demand and economic fundamentals. The emerging markets, particularly China, have also seen a large increase in innovation capabilities over recent years.

Resveratrol is found in red wine and chocolate, but to see any benefits, a person would have to consume massive quantities of both. Jupiter Orphan Therapeutics has developed a way to greatly increase the amount of resveratrol that reaches the bloodstream with only a pill or two.

NEW OPPORTUNITIES FOR ACADEMIC RESEARCH

These changes to the pharmaceutical industry have created new opportunities for academics. The US National Institutes of Health (NIH) has expanded its interest and funding of translational research. This has resulted in a rise in the number and sophistication of academic drug discovery centres. In 2011, the NIH Director Francis Collins initiated the National Center for Accelerating Translational Science (NCATS), established to transform the translational process so that new treatments and cures for disease can be delivered to patients faster. Early drug discovery work is now being meaningfully shifted from companies to academic institutions. In addition, an increasing number of academic-industry alliances and licensing deals have occurred in recent years. For example, one of Dr Brothers programmes recently discovered a potential use for the compound resveratrol, which has since been partnered with biotech and cleared to enter clinical trials by the US Food and Drug Administration (FDA).

The changes to the pharmaceutical industry over the past twenty years have created new opportunities for academic research.

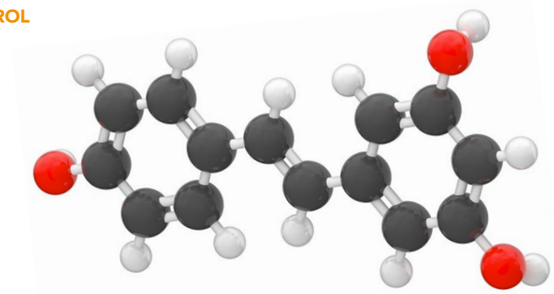
THE PROMISE OF RESVERATROL

Recent studies in mice have identified small molecules that may delay several different diseases of ageing and extend lifespan. In theory, such molecules could prevent multiple diseases in humans simultaneously, potentially extending healthy years of life. One such molecule is resveratrol, which has been implicated in helping with ageing, cancer, inflammation, cardiovascular disease, neurodegeneration as well as obesity and metabolism.

Resveratrol and related molecules have shown promising effects in several age-related disease models including cancer, types 1 and 2 diabetes, inflammation, cardiovascular disease, stroke, hepatic steatosis and others. Resveratrol supplementation prevents the development of cataracts and osteoporosis in mice during normal ageing and may also delay infertility. Resveratrol has also been found to slow the growth of numerous cancers including colon, prostate and lymphoma in animal models. Another key property of resveratrol is its anti-inflammatory activity. This has led to considerable excitement about the use of Resveratrol and similar molecules for the treatment of inflammatory and autoimmune disorders. Resveratrol also has a number of cardioprotective properties, including reducing the oxidation of low-density

RESVERATROL

$C_{14}H_{12}C$



Molecular structure of resveratrol.

Resveratrol is not only found in red wine and chocolates, it can be found in a variety of foods, including blueberries and nuts.

Recent studies in mice have identified small molecules that hold potential to delay several different diseases of ageing and extend lifespan.

lipoprotein (LDL) particles, a contributing factor to the development of coronary heart disease.

Interest in the cardioprotective effects of resveratrol was initially stimulated by observation of the "French paradox", in which mortality due to coronary heart disease was significantly reduced among people in southwestern France despite numerous risk factors such as high intake of dietary cholesterol, saturated fat and smoking. Resveratrol is a component of the red wine that is widely consumed amongst the French population. Unfortunately, the levels of resveratrol in red wine and other natural sources are extremely low. This issue along with the issue of bioavailability has long plagued the field. It has been difficult to administer resveratrol is high enough doses to achieve desired effects. Indeed, recent clinical trials have been dosing resveratrol at 5 grams daily, a dose that causes intolerable gastrointestinal issues.

While dark chocolate may have more resveratrol, it is still not enough to provide benefits.

Resveratrol is able to cross the blood-brain barrier and thus can protect against stroke and brain damage, prevent cognitive decline and promote general neuroprotection in mice. Both learning and memory are improved in aged mice given resveratrol for one week. It is also able to attenuate symptoms of age-related neurological diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Another benefit of Resveratrol and related molecules is the ability to prevent and reverse the effects of obesity and age-related metabolic decline. In mice fed a high-calorie diet, resveratrol improves metabolism, protects against obesity and insulin resistance. In addition, Resveratrol has been found to prevent the formation of fatty liver.

BENCH TO BEDSIDE

Resveratrol has shown a number of promising health benefits in animal models, however, further research is needed in humans. Translating findings from animal models to humans is complex and has traditionally not been very successful. Dr Shaun Brothers and other colleagues are currently pioneering work in this area and aim to be the first to clinically validate the usefulness of Resveratrol in humans. Dr Brothers and his colleagues first needed to address the issue of bioavailability, to solve this, additional resources were necessary, and a biotech firm, Jupiter Orphan Therapeutics provided these and more. This academic biotech partnering is also on the rise in academic circles, with Universities focusing on their intellectual property. By partnering, the additional resources can be obtained for this capital-intensive process. Dr Brothers' strategy may represent the new model for modern drug discovery programmes, initiated within academia and partnered out, or even continued in academia, efforts which used to be exclusively conducted within the pharmaceutical industry.

There are several ongoing and future challenges for academia and the pharmaceutical industry partnerships, such as continued patent expiration, regulatory hurdles, access, pricing and reimbursement as well as R&D productivity. These challenges mean that pharmaceutical companies must innovate their strategies to remain competitive in this new business environment. In addition to the challenges, there are promising trends, such as the convergence of IT and healthcare over the coming years which will add depth and feasibility to such projects. The demand for new therapies is also expected to grow, a key benefit for long-term industry dynamics.

The answer to such challenges may reside in the marriage of unhindered academic creativity with the resources found in big pharma, these being highly synergistic with unmistakable potential for companies to gain long term competitive advantage, though possibly difficult to justify to shareholders in the short term. There is a precedent for industry-academia partnerships, but such partnerships are often impeded by misaligned expectations for success. It will be interesting to see how the industry acclimates to this different model for drug discovery being spearheaded by Dr Brothers and his colleagues.

Behind the Research

Dr Shaun Brothers

E: sbrothers@med.miami.edu **T:** +1 305 243 6113 **W:** http://uhealthsystem.com/
W: https://umiamihealth.org/sylvester-comprehensive-cancer-center/research/faculty/shaun-brothers-phd

Research Objectives

Dr Shaun Brothers' research is focused on identifying molecules that bridge the gap between research findings and treatments for diseases.

Detail

Dr Shaun Brothers
University of Miami, Florida
Miller School of Medicine,
1501 NW 10th Ave BRB415 (M860), Miami, FL 33136,
USA

Bio

Shaun Brothers, PhD MBA is an Associate Professor in the Department of Psychiatry and Behavioural Sciences at the University of Miami Miller School of Medicine and Director of the Molecular Therapeutics Shared Resource for the Sylvester Comprehensive Cancer Center. He is trained as a pharmacologist with backgrounds in GPCR molecular signalling systems and preclinical drug discovery.

Funding

- The Ryan Foundation
- National Institute of Neurological Disease and Stroke
- National Institute of Mental Health
- Jay Weiss Institute for Health Equity
- Sylvester Comprehensive Cancer Center

Collaborators

Jupiter Orphan Therapeutics

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

References

Akinwumi, B. C., Bordun, K. A. M., & Anderson, H. D. (2018). 'Biological Activities of Stilbenoids'. *International journal of molecular sciences*, *19*(3), 792.

Gautam, A., & Pan, X. (2016). 'The changing model of big pharma: impact of key trends'. *Drug discovery today*, *21*(3), 379-384.

Hubbard, B. P., & Sinclair, D. A. (2014). 'Small molecule SIRT1 activators for the treatment of aging and age-related diseases'. *Trends in pharmacological sciences*, *35*(3), 146-154.

Slusher, B. S., Conn, P. J., Frye, S., Glicksman, M., & Arkin, M. (2013). 'Bringing together the academic drug discovery community'. *Nature Reviews Drug Discovery*, *12*(11), 811.

Volmar, C. H., Wahlestedt, C., & Brothers, S. P. (2017). 'Orphan diseases: state of the drug discovery artSeltene Krankheiten: Aktueller Stand der Pharmaforschung'. *Wiener Medizinische Wochenschrift*, *167*(9-10), 197-204.

Personal Response

How do academics differently approach the problem of drug discovery?

"Academics face a different set of challenges than big pharma. Drug discovery projects are extremely expensive and each advancement along the drug discovery pipeline greatly increases cost. Academics do not have access to vast resources and funding often must be secured through relatively slow granting mechanisms. The unintended benefit is that since the projects take place over the course of years, enormous thought is put into them. Similarly, the flexibility that academics are afforded leads to the idea of cross-fertilisation and achievement of new knowledge. Such creative ideas are less likely to arise in environments solely motivated by rapid drug commercialisation."

What are your future plans for research in this area?

"We are eager to validate the utility of resveratrol in humans. So much work has been done, and so many scientists have provided evidence that resveratrol holds the potential to help people, yet it has not yet been clinically demonstrated sufficiently to be used as a drug because of problems with dosing. We have permission from the FDA to begin phase I clinical trials which should pave the way for proof of concept trials in patients. The ultimate goal is to prove that taking high dose resveratrol can result in something clinically meaningful. If we can achieve such an effect, it has the potential to help a lot of people, which is quite an encouraging thought!"