Institution: University of Aberdeen

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Provexis plc - a University of Aberdeen Rowett Institute of Nutrition and Health spinout company marketing globally a food ingredient for vascular health through blood platelet inhibition

1. Summary of the impact

A discovery that a tomato extract could help with healthy blood flow has been translated into a functional food ingredient now marketed globally via the spin-out company Provexis plc. Fruitflow® - Provexis' lead product - is the result of findings by researchers at the Rowett Institute of Nutrition and Health, now part of the University of Aberdeen, that biologically active constituents in tomatoes inhibit blood platelet aggregation: a known cause of heart attack, stroke and venous thrombosis. In 2009 Fruitflow® was the first food ingredient to meet the requirements of the European Food Safety Agency for products with a specific health claim. Provexis – the University of Aberdeen Rowett Institute spinout – is listed on the AIM market - the London Stock Exchange's international market for smaller growing companies – has seen values of £14 - £60 million and secured co-development agreements with major international partners, including DSM, Unilever and Coca-Cola. This case study demonstrates the direct translation of research to produce a functional food ingredient of interest to global market players.

The claimed impact therefore relates to development of new product, which has received the first ever novel health claim (Article 13.5) from the European Food Safety Authority, and is being marketed as novel food ingredient globally by a multinational company.

2. Underpinning research

Underpinning research leading to the spin-out Provexis plc was carried out at the Rowett Institute of Nutrition and Health, now part of the University of Aberdeen, between 1998 and 2001 by Professor Asim Dutta-Roy's team in the Lipids and Cardiovascular Health Group. Financial support was provided by the Scottish Environment Executive Rural Affairs Department.

Dutta-Roy's research interests included the aetiology of atherosclerosis, the influence of nutrition in cardiovascular disease development, and platelet involvement in these diseases. He began a screening programme in 1998, examining the effects of a range of fruit and vegetables on platelet function. This work expanded to include aqueous extracts of herbs and botanicals [1,2] which revealed aqueous tomato has far higher anti-platelet activity than other extracts [3,4].

Further research localised the anti-platelet activity, conducted the first investigations of mode of action, tested stability under various conditions, and initiated work to identify the compounds with anti-platelet activity. This work established that the bioactives were low molecular weight, water-soluble, and heat-stable. The presence of adenosine and cytidine was confirmed in the bioactive fractions, however, these compounds alone did not account for the full bioactivity of the extract. Platelet function experiments of the biologically activation fraction revealed that more than one mode of action was likely. The presence of a range of compounds suggested that all have anti-platelet activity but act on different parts of the platelet activation/aggregation pathway. The chemical properties of the active compounds indicated their potential suitability as therapeutic agents or as functional food ingredients.

The World Health Organization (WHO) estimates that annually worldwide more than 15 million people suffer a stroke and that total mortalities from all cardiovascular disorders (CVD) exceed 17 million (the Atlas of Heart Disease and Stroke). Diet and lifestyle linked conditions such as stroke and coronary heart disease account for 5.5 million and 7.2 million deaths, respectively. Recent data has indicated that other conditions such as deep venous thrombosis (DVT) affect approximately 8 in 10,000 in the world population.

Whilst CVD is global it is more pronounced in developed countries (60% of total burden) where CVDs account for 18% of Disability Adjusted Life Years (DALYs) and estimated to equate to 82 million DALYs by the year 2020. The cost of managing this burden is significant with CVD

medication estimated by WHO to account for approximately 12% of total healthcare budgets. Therefore there are considerable commercial and public health drivers to rationalise the use of high cost medication by exploring complementary foods containing bioactive supplements and functional ingredients which could be good for health. A 2009 PricewaterhouseCoopers report estimated the US market for heart health functional foods to be worth $5 billion and to be growing at almost 7% per year.

In 1999, sufficient data was available to file a patent application, and a commercialisation strategy was initiated. A human trial provided valuable proof of concept data to support this but showed that drinking 1L of fresh tomato juice did not lead to anti-platelet effects, confirming that a concentrated extract was necessary before efficacy could be observed. This was published in the journal *Platelets* [3]. By 2001, the body of evidence amassed was sufficient to secure funding for commercialisation. Provexis Ltd was formed, and a work programme commenced focusing initially on characterisation of the extract, followed by development of a prototype industrial extract.

This was followed from 2003 by extensive successive human trials to demonstrate the efficacy of the extract, mechanistic work and full industrial scale-up [6]. This work programme enabled construction of a product-specific dossier in substantiation of a health claim, submitted in 2008; which was sufficiently detailed and evidenced to allow a favourable landmark judgement from the European Food Safety Agency (EFSA) in May 2009 – the first product-specific (Article 13.5) health claim to be approved. The award set a benchmark for other companies to follow and demonstrated that the science led approach adopted by the small company could compete successfully with the intellectual inputs of major global players. This remains a definitive standard for the industry - since then very few other companies have successfully gained similar approval.

The tomato extract developed by Provexis Ltd was given the trade name Fruitflow® and is an established functional food ingredient, marketed globally after European launch in November 2010 at the Health Ingredients Europe Conference (Madrid). There the product won the 'Most Innovative Health Ingredient' award as well as best innovation in the 'Heart Health' category. Products containing Fruitflow® are already sold in a number of major global markets.

3. References to the research

All publications funded by the core research grant to the Rowett from the Scottish Government:-

[1] Dutta-Roy AK, Gordon MJ, Kelly C, Hunter K, Crosbie L, Knight-Carpentar T, Williams BC. (1999). Inhibitory effects of Ginkgo biloba extract on human platelet aggregation. *Platelets,* 10(5): 298-305. (*This paper demonstrated that this extract includes flavonoids and gingkoglides, which affect metabolism of cAMP, TxA(2) and Ca^{2+}. It is effective in the inhibition of platelet aggregation; both in PRP and whole blood, and the paper also indicated its potential use as an effective oral anti-platelet therapeutic agent*.)

[2] Pierre S, Crosbie L, and Dutta-Roy, A.K. (2005). Inhibitory effect of aqueous extracts of some herbs on human platelet aggregation *in vitro*. *Platelets,* 16(8): 469-473. (*Evaluated the effects of a range of nutriceuticals on plalelet function and the underlying mechanisms, indicating which were likely to be of most benefit for use in a clinical situation.)*

[3] Dutta-Roy AK, Crosbie, L and Gordon MJ. (2001). Effects of tomato extract on platelet aggregation *in vitro*. *Platelets* 12(4): 218-227. *(Identified that tomatoes contain anti-platelet compounds in addition to adenosine. Unlike aspirin, the tomato-derived compounds inhibit thrombin-induced platelet aggregation. Data indicated that tomato contains very potent anti-platelet components and therefore has possible benefits as a preventive and therapeutic regime for cardiovascular disease.)*

[4] Dutta-Roy, AK. (2002). Dietary components and human platelet activity. *Platelets* 13: 67-75. *(Discovery of anti-platelet factors in plants, vegetables and fruits provides a new dietary means for a long-term strategy to favourably modify human blood platelet activity; this paper summarises the effects of these dietary components on human platelet function both in vitro and in vivo indicating roles for human use.)*

[5] O' Kennedy N, Crosbie L, Lieshout MV, Webb DJ, Broom J,and Dutta-Roy AK. (2006). Effects of antiplatelet components of tomato extract on platelet function in vitro and ex vivo - a time course cannulation study in healthy humans. *American Journal of Clinical Nutrition* 84(3): 570-9. (*Study which demonstrated the time course of antiplatelet activity of specific tomato components by in vitro experimentation and established their ex vivo efficacy in healthy humans and impact on*

platelet function and coagulation in preparation for clinical trials.)
[6] O' Kennedy,N, Crosbie L, Whelan,S, Luther S, Horgan G, Webb DJ, Broom, J.,and Dutta-Roy, AK. (2006). Effects of tomato extract on platelet function - a double-blinded crossover study in healthy humans. *American Journal of Clinical Nutrition* 84: 561-569. (*Randomized, double-blinded, placebo-controlled crossover study of 90 healthy human subjects demonstrating the effects of tomato extracts on inhibition of platelet function.)*

4. Details of the impact

The original research and novel IP provided the springboard for the establishment of a spinout company, founded jointly with the research partner in 2001. Initial funding was provided by Angle plc, Rising Stars Growth Fund and North West Equity Fund. In 2005 the company floated on the LSE AIM market and its workforce increased in size to 13. Further funding rounds in 2008 and 2010 enabled new projects to be initiated.

Over the development timeline of this product (2001-2010), Provexis has had exclusive collaboration agreements with Unilever (12-month exclusivity agreement 2006, long term development agreement 2007-2009); The Coca-Cola Company (2007-2009), and non-exclusive development programmes with Nestlé and Cargill. Provexis plc's share price doubled between January and April 2012. The company now employs over 20 specialist staff at its business operations site in Windsor, its manufacturing plant in Nelson, Lancashire and until recently (April 2013) maintained research laboratories at the Rowett Institute in Aberdeen.

An alliance agreement was announced with DSM Nutritional Products in June 2010, to commercialise the Fruitflow® heart-health technology. The Alliance gave DSM exclusive global rights to Fruitflow® - a basis for collaboration between the partners and the development of Fruitflow® in all major global markets. The Alliance partners have now worked to develop a powder concentrate of the Fruitflow ® technology, which is being readied for tablet and capsule use. Under the terms of the alliance, DSM is responsible for manufacturing, marketing, and selling via its global sales force, while Provexis remains responsible for contributing the scientific expertise necessary for successful commercialisation. In 2010 it was given awards for the "Most Innovative Health Ingredient" and the "Best Innovation in the Heart Health" category at the Health Ingredients European Conference (Madrid). In 2011 it was awarded the Nutraward for "Best New Ingredient" at the USA trade launch at the Nutracon conference (Anaheim, California).

Fruitflow® is currently incorporated into eight marketed products worldwide including Europe, North America and Asia. In the UK it is available in Sirco®, a fruit juice drink, which is sold through a series of outlets and supermarkets including, Sainsbury's, Waitrose, Ocado, Amazon, Holland & Barrett and EH Booth Supermarkets. In the USA it is available, for example, in products produced by Swanson Health Products USA and Relaxzen, USA, and in China by Bankom Ltd as Fruitflow®.

Provexis had moved to increase its footprint in the functional food sector by taking over a company specialising in functional ingredients for sports nutrition, Science in Sport (SIS) (www.scienceinsport.com). It has signed a new 5-year deal to continue as Official Supplier of Sports Drinks and Sports Nutrition of the GB Rowing Team for Senior, Adaptive and Top Development rowers providing a range of nutritional products for hydration, energy and recovery.

In January 2013 SIS launched REGO+ Fruitflow ®, the first product of its kind designed to help endurance athletes improve recovery time after intense exercise (http://www.scienceinsport.com/sis-products/sis-rego-range/sis-rego-plus-fruitflow-gels/). The companies have since demerged into two separate entities, with continuing marketing of the Fruitflow based products.

Building on the original work by Professor Dutta-Roy's team, new research has generated novel intellectual property covering different therapeutic areas, as well as different compositions, with several further patents obtained. Several applications have now gone to grant in territories worldwide, underlining the novel and innovative qualities of both the original and subsequent research in particular in the cardiovascular and inflammation areas.

Furthermore, in April 2011, EFSA issued a set of draft guidelines (http://www.efsa.europa.eu/en/consultations/call/nda110426a.pdf) to inform applicants of

acceptable categories of health claim, as well as biomarkers/methods of analysis which would be accepted in dossiers. Health claims related to platelet function are included as an accepted category in these draft guidelines, currently open for public consultation. The approval of the Provexis health claim submission (the only submission of this type) was key to the inclusion of this category in the draft guidelines. This will be of benefit to the food industry for future submissions http://ec.europa.eu/food/food/labellingnutrition/claims/community_register/authorised_health_claims_en.htm#art135).

Claimed impact as defined by REF: This work has therefore had impact on commerce through creation of a new spin-out business with leverage of significant external commercial investment, successful creation and manufacture of a new product and creation of other commercial activity, contracts, and business performance.

5. Sources to corroborate the impact

Patents

[a] WO199955350 Antithrombotic Agents. Dutta-Roy A. *Established potential platelet aggregation effect of extracts from a number of families of fruit and the potential use prophylactic treatment.*
[b] WO2006085115 Therapeutic uses of tomato extracts. Crosbie L, O'Kennedy N. *Established use of a water soluble tomato extract or an active fraction for manufacturing a substance to lower plasma triglyceride levels, with the water soluble tomato extract or active fraction being substantially free of lycopene and from water-insoluble particulate material. It also established a method of lowering triglyceride levels in the blood of a patient through the administration of the water soluble tomato extracts.*
[c] WO2007141495 Therapeutic uses of tomato extracts. O'Kennedy N, Song, H. *Relates to tomato extracts or an active fraction thereof for use in preventing or inhibiting the initiation of venous thrombosis and fibrin clot formation in a vein.*
[d] WO2010049707 Fruit Extracts. O'Kennedy N. *Methods of making an extract of fruit of the Solanaceae family where the fruit is processed to optimise the platelet aggregation inhibiting activity of the extract together with the use of the extract in maintaining heart health by reducing platelet aggregation; benefiting the circulation; and normalizing or otherwise benefiting blood flow.*
[e] WO2010049709 Therapeutic Compositions. O'Kennedy N. *Provided compositions with a therapeutic or prophylactic effective amount of plant flavonoid or derivatives for treating or preventing development of medical conditions characterised by inappropriate platelet aggregation.*

Company Homepage

[f] http://provexis.com/, http://www.provexis.org/fruitflow/, http://www.dsm.com/content/markets/foodandbeverages/en_US/products/nutraceuticals/fruitflow.html, www.sircoheart.com, www.scienceinsport.com

Further References

[g] Press Release: Could tomato pips prevent heart attacks?
http://www.dailymail.co.uk/health/article-1226462/Could-tomato-pips-protect-heart-attack.html
[h] Press Release: Development Agreement with DSM Nutritional Products
http://online.hemscottir.com/ir/pxs/ir.jsp?page=news-item&item=612047872074339
[i] Press Release: Extension of Exclusive Fruitflow® technology assessment agreement with the Coca-Cola Company
http://online.hemscottir.com/ir/pxs/ir.jsp?page=news-item&item=74249247278908
[j] Press Release: Provexis and Unilever renew Fruitflow® Exclusivity Agreement
http://online.hemscottir.com/ir/pxs/ir.jsp?page=news-item&item=53878217379264
[k] Press Coverage : Most Innovative Health Ingredient award, 2010
http://www.bloomberg.com/apps/news?pid=conewsstory&tkr=PXS:LN&sid=aqyUQYxwXGcI
[l] Press Release :Best Partnership Award, March 2012, Provexis and DSM
http://www.provexis.org/provexis-and-dsm-collaboration-bears-fruit-at-engredea-2012/
[m] Press Release: Provexis 2011-2012 financial results and look to future revenues, Aug 2012
http://www.provexis.org/the-next-few-years-are-all-set-to-be-about-sales-and-profits/ media red
[n] Press release: Launch of SIS REGO=Fruitflow. January 2013. Provexis
http://www.provexis.org/sis-launch-new-innovative-rego-fruitflow-gel/