Institution: Imperial College London		
Unit of Assessment: 5 – Biological Sciences		
Title of case study: A5-6 Method for producing plant extracts for the manufacture of high-value products		
Period when the underpinning research was undertaken: 2000-2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Prof Peter Nixon	**Role(s) (e.g. job title):** Prof of Biochemistry	**Period(s) employed by submitting HEI:** 1992 to present
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Research at Imperial College has led to the development of a new method for the culturing of plant cells that is cost-effective, sustainable and environmentally friendly. This technology led to the creation of Alkion BioPharma, a spin-out company that provided plant extracts to the cosmetic industry. In mid-2016 Alkion BioPharma was acquired by the giant chemical multinational Evonik for several million Euros and renamed Evonik Advanced Botanicals (EAB). Evonik has since invested over €1 million to establish a new facility for EAB in France and has increased the workforce to 15 people. The technology has expanded the business base of Evonik so that it now produces 11 different plant-derived active ingredients for companies in the cosmetic industry and a new portfolio of Evonik personal care products sold globally to consumers.

Based on the same technology, a second spin-out company, Alkion Bio-Innovations, was created in mid-2017 to target the medicinal cannabis market. This start-up has 7 full-time employees and has raised €250,000 in equity and €978,000 from National and European grants. Two exclusive licences and two contracts have been signed. The impact of the technology has been recognised by the award of 2 innovation prizes.

2. Underpinning research (indicative maximum 500 words)

Plants are a valuable source of chemicals. For example, many anti-cancer drugs are either natural products or are based on plant-derived molecules. Unfortunately, plant-based natural products can be difficult to exploit for a variety of reasons. They are chemically difficult to synthesize and are often present at low abundance in the native plant which itself can be rare and difficult to grow in greenhouses on a large scale. There is therefore a pressing need to develop new approaches to grow plant cells in a suitably differentiated state to produce target molecules of chemical, pharmaceutical and nutraceutical importance.

Plant cell cultures offer a cost-effective and environmentally friendly route for producing natural products. Much of the early work in this area has focused on the production of target molecules in undifferentiated plant cell suspension cultures. However, important target molecules are often only produced in differentiated cells, for example leaf cells. The lack of methods to control the differentiation of plant cells grown in culture has been a major bottleneck in the adoption of this technology by industry.

Initial research by the Nixon group, in collaboration with Gordon Dougan at Imperial College and Pal Maliga at Rutgers University, USA, led to the discovery that the tetanus vaccine antigen, TetC,

could be expressed at high levels in tobacco leaves through transformation of the chloroplast genome **[1]**. Such plants had the potential to produce the TetC vaccine antigen on a large scale.

Follow-up work between 2004-2007 focused on the development of robust cell culture methods for the controlled production of TetC. Although TetC could be detected in cell suspension cultures containing undifferentiated plastids, the level of expression on a fresh weight basis was 70-fold less than that found in mature tobacco plants grown in soil. To improve yield, a new method was devised to produce leafy biomass from cell suspension cultures and callus tissue. This was achieved using a temporary immersion bioreactor (TIB) and a specially formulated growth medium and culturing protocol **[2]**. The resulting leafy plant material was shown to express TetC at close to the levels found in tobacco plants on a fresh weight basis, with the added advantage that more plant biomass could be grown in a bioreactor than a greenhouse on an equal floor area basis **[2]**. This breakthrough in the production of plant leafy biomass generated a key patent published in 2011 **[3]**.

Subsequent joint research between the Nixon group and Alkion BioPharma showed that this new technology had wide impact and could be used for the production and isolation of pharmaceutically active ingredients from medicinal plants **[4]** as well as vaccine antigens from tobacco plants with severe growth defects **[5]**. Detailed studies on the hydrodynamic properties of the temporary immersion bioreactor system have identified the key parameters needed for scaling-up the growth of plant biomass **[6]**.

3. References to the research (indicative maximum of six references)

[1] Tregoning, J. S., Nixon, P., Kuroda, H., Svab, Z., Clare, S., Bowe, F., Fairweather, N., Ytterberg, J., van Wijk, K. J., Dougan, G and Maliga, P. (2003) Expression of tetanus toxin fragment C in tobacco chloroplasts. *Nucl. Acids Res.* 4, 1174-1179. https://doi.org/10.1093/nar/gkg221

193 Scopus citations at 7th January 2021

[2] Michoux, F., Ahmad, N., McCarthy, J. and Nixon, P. J. (2011) Contained and high-level production of recombinant proteins in plant chloroplasts using a temporary immersion bioreactor. *Plant Biotechnol. J.* 9, 575-584.https://doi.org/10.1111/j.1467-7652.2010.00575.x

24 Scopus citations at 7th January 2021

[3] Patent: WO/2011/030083
International Application Number: PCT/GB2010/001537
International Filing Date: 12.08.2010
Publication Date: 17.03.2011
Title: Method for producing leafy biomass in culture
Applicants: Imperial Innovations Limited, Franck Michoux, Peter Nixon and James G. McCarthy

[4] Michoux, F. and Nixon, P. J. (2011) Towards the sustainable and continuous in-vitro production of active pharmaceutical ingredients from medicinal plants. *Planta Med* 77, PB22. https://doi.org/10.1055/s-0031-1282276

[5] Michoux, F., Ahmad, N., Hennig, A., Nixon, P. J. and Warzecha, H. (2013) Production of leafy biomass using temporary immersion bioreactors: an alternative platform to express proteins in transplastomic plants with drastic phenotypes. *Planta* 237, 903-908. https://doi.org/10.1007/s00425-012-1829-1

24 Scopus citations at 7th January 2021

[6] Barretto, S., Michoux, F., Hellgardt, K. and Nixon, P. J. (2017) Temporary immersion culture hydrodynamics affect growth, viability and transplastomic protein accumulation during in vitro shoot regeneration of *Nicotiana tabacum* callus: Implications for transplastomic plant-based bioprocess routes to biopharmaceuticals. *Biochem. Eng. J.* 117, 73-81. https://doi.org/10.1016/j.bej.2016.10.007

2 Scopus citations at 7th January 2021

4. Details of the impact (indicative maximum 750 words)

As described in section 2, research undertaken in the Nixon lab between 2004-2007 led to the development of a new method for the efficient production of green plant tissue from undifferentiated callus tissue and cell suspension cultures. The method is based on the use of a temporary immersion bioreactor (TIB) that periodically immerses plant cells in a medium containing the appropriate balance of growth hormones.

Given the potential of the technology, IP was filed in 2010, then published in 2011. The applicants were Imperial Innovations Ltd (the technology transfer company used by Imperial College) and the three inventors – Prof Peter Nixon, Franck Michoux (the PhD student who conducted experimental work), and Dr James McCarthy (Industry PhD supervisor). All the work relating to the invention was done at Imperial College London.

The technology led in January 2012 to the creation of Alkion BioPharma (CEO Franck Michoux), a spin-out company focussed on exploiting the patented Imperial technology for the cosmetics industry. Initial financial support came from Imperial Innovations and a business angel brought in by Franck Michoux. Further funding came with the award to Alkion BioPharma of an EU-FP7 grant (2013-2017) as part of a large Knowledge Based Bio-Economy (KBBE) program on commercialisation of triterpenoids **[A]**. In total, Alkion BioPharma was able to raise €240 thousand in private equity, over €1 million in EU and French grants and employed up to 8 people **[B]**.

In May 2016, Alkion Biopharma was purchased by the giant chemical multinational company Evonik and renamed Evonik Advanced Botanicals (EAB) **[C, D]**. Evonik is one of the largest manufacturers of specialty chemicals in the world with sales in 2019 of €13.1 billion and an operating profit of €2.15 billion. The acquisition price for Alkion BioPharma is confidential but is in the order of several million Euros. Evonik Advanced Botanicals was moved from Evry, close to Paris, to Tours **[B, E]** and Evonik spent over €500 thousand in renovating a building specifically for EAB activities **[B]**. In addition, Evonik has invested further in expanding the patented technology, especially scaling-up the size of the bioreactors, and recruiting 15 people in the past 4 years **[B]**.

Evonik Advanced Botanicals offers two services to the cosmetic industry. First, and foremost, cosmetic customers are offered exclusive active ingredients produced from plant cells grown using the patented technology invented by Imperial College. To date 11 tailor-made projects have been agreed, which have provided revenue of €1 million in R&D services and which are highly profitable, with the Net Present Value (NPV) for each project worth over €1 million in terms of sales over the coming 5 years **[B]**. The first product launched by a multinational company using this technology was 'Apple of Sodom' by Ahava **[F]**, a skin-care cream that contains extracts from the plant *Caloptropis procera*, naturally found in the Dead Sea region **[G]**, which reached consumers in September 2018.

The second income stream is related to the catalogue of globally available products sold through Evonik's network. The first product, released at the end of 2018, is called Neoplanta® withania (also known as Indian ginseng) which is so far sold in the USA, Japan and Europe **[H]**.

Overall, the acquisition by Evonik of Alkion BioPharma and use of the patented Imperial technology has been strategically important for Evonik as it has enabled Evonik Care Solutions (previously Evonik Personal Care) to expand into new global markets that are expected to be highly lucrative **[B, I]**. The Imperial technology also provides Evonik with a strong sustainability and technological footprint. Evonik's customers highly value the purity, traceability, limited environmental impact that the Imperial technology brings to its products.

Based on the same patented Imperial College technology, a second start-up company, Alkion Bio-Innovations, was established in March 2017 by the original founders of Alkion BioPharma **[J]**. The

focus of Alkion Bio-Innovations is on the production of natural sweet proteins from plants and medical cannabis products. In November 2018, Alkion Bio-Innovations was the first company in France to be given authorisation to work on *Cannabis sativa* **[J]**. The revolutionary approach of the Imperial College technology has been recognized by the award of 2 innovation prizes **[K]**. Currently, Alkion Bio-Innovations employs 7 full-time employees, has raised €250,000 in equity, has been awarded 5 National and European grants to a total value of €978,000, has signed 2 exclusive licences and 2 contracts with large industrial players and plans to produce medical cannabis on a large scale in the next 24 months **[J]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] Award of EU-FP7 funding to Alkion BioPharma as part of TriForC consortium working on the commercialization of terpenoids https://cordis.europa.eu/project/id/613692 (Archived here)

[B] Letter of support from Head of Evonik Advanced Botanicals, Evonik

[C] Industry press release on sale of Alkion Biopharma to Evonik https://www.cosmeticsbusiness.com/news/article_page/Evonik_acquires_French_start-up_Alkion_Biopharma/117310 (Archived here)

[D] Evonik press release on the acquisition of Alkion BioPharma https://personal-care.evonik.com/product/personal-care/en/inside/press-releases/pages/article.aspx?articleId=101744 (Archived here)

[E] Evonik press release on relocation of EAB to Tours https://corporate.evonik.com/en/Pages/article.aspx?articleId=106271 (Archived here)

[F] 'Apple of Sodom' sold by Ahava https://global.ahava.com/skincare/by-collection/apple-of-sodom (Archived here)

[G] Portugal-Cohen, M., Ish-Shalom, E., Mallon, R., Corral, P., Michoux, F. and Ma'Or, Z. (2018) Apple of Sodom (*Calatropis procera*) callus extract, a novel skincare active and its biological activity in skin models when combined with Dead Sea water. *J. Cosmetics, Dermatological Sciences and Applications* 8, 73-91. https://www.scirp.org/pdf/JCDSA_2018062817003986.pdf (Archived here)

[H] Neoplanta® withania brochure from Evonik https://personal-care.evonik.com/product/personal-care/downloads/downloads/epc_neoplanta-withania_web.pdf (Archived here)

[I] Evonik press release on strategic importance of Alkion BioPharma to its business https://corporate.evonik.com/en/quantum-leap-in-tours-125600.html (Archived here)

[J] Letter from CEO of Alkion BioInnovations

[K] Alkion BioInnovations and its awards http://alkinnov.com/about-us/ (Archived here)