Impact Objectives

- Exploit existing biodiversity collections in the Solanaceae and Iridaceae genera for bioactives using high-throughput bioassays
- Elucidate pathways utilising modern transcriptomic technologies and develop enabling technologies
- Generate new biosources of high-value plant-derived products
- Develop downstream processes with reduced environmental impact and demonstrate technical and economic production feasibility

The power of plants

***Professor Paul Fraser** is part of an internationally renowned research team that aims to understand plant biosynthetic pathways involved in the formation of high-value plant products. Below, he discusses some of the challenges associated with the project and some of the activities proposed for 2017*

Could you begin by talking about some of the current challenges associated with understanding the plant biosynthetic pathways involved in the formation of high-value plant products your project is attempting to address?

The biosynthetic pathways are typically secondary metabolites, so they are produced at a specific point in the development of a plant, or by specialist cells. Some of the diverse species that make the compounds are not truly amenable to large-scale production, or even cultivation in a laboratory. There is a distinct absence of authentic standards that enable the unambiguous identification of the compounds and their intermediaries. Indeed, the compartmentalisation of the pathways is extremely complex and understanding how precursors are exchanged between different parts of the cell is very challenging. Our DISCO (From DISCOvery to products: A next generation pipeline for the sustainable generation of high-value plant products) project is addressing these issues.

How will the research you are performing further our understanding of metabolic engineering and molecular breeding?

We hope that our investigations will provide a generic platform from which we can find applications for a diverse array of natural products. We also expect our metabolomics database to be extended, as well as our annotation of biosynthetic genes.

Could you discuss some of the latest technologies that the consortium will be using to develop the framework and translational pipelines?

Several of the partners involved in the project are implementing next-generation sequencing techniques that help to elucidate candidate biosynthetic components in the pathways. This has been particularly beneficial in the elucidation of saffron-derived apocarotenoids and the formation of scopolamine. Matrix-assisted laser desorption/ionisation (MALDI) imaging has also enabled the identification of metabolites and products to specific cells in the tissues.

How do you plan for this information to be transferred to different classes of natural products?

We believe that the strategies used – and the technologies employed – provide great opportunities for other secondary metabolite pathways, especially as we have built up several precursor pathways. The procedures for scaling up our findings are very important and they will have a bearing on other metabolites.

Can you talk about some of the results that you have achieved so far?

One of the most pleasing results has been the development of new varieties of valuable carotenoids which have added value to an existing pipeline and are already used in the marketplace. The technology used to facilitate inducible transplastomic expression is an excellent example of how a fundamental discovery can have application, and this approach could create a step-change in the way we produce valuable small molecules.

With the project heading into its final year, what are some of the activities proposed for 2017, and are there any planned publications or workshops coming up that might be of interest to our readers?

As it is the final year of the DISCO project, we are ensuring that work is captured through a variety of innovation workshops. We are also ensuring that the work is effectively disseminated by a number of high-profile scientific conferences, such as the Gordon Conference and Pigments in Foods (displayed on project website). Also, the Institute for Biopharmaceutical Research has had a successful product launch of a DISCO-derived output – this has helped demonstrate that the project is generating money in the resultant products, not just in our research papers.

Fuelling the move away from chemical synthesis

Focused on the sustainable generation of high-value plant products, ***DISCO*** *is a project that seeks to alleviate our reliance on chemical synthesis by utilising plant natural products. The findings will reduce environmental impact, provide new materials and stimulate economic development*

Natural products are defined as chemical compounds or substances that are produced naturally by living organisms. Plant natural products, therefore, are those derived from plants. A large number of important, chemically diverse natural products are derived from plants and plant extracts have proved useful for a wide variety of practices, including medical and cosmetic. Indeed, plant natural products have been utilised by human civilisation for thousands of years. Many contemporary pharmaceutical products are natural products or derivatives of them, but the full potential of these natural compounds is still largely unexplored because of several difficulties. First, they are often extremely complex and difficult to synthesise. Second, as they are often produced by rare plants, they are found in relatively low quantities. Third, synthesising plant natural products often relies on conditions beyond human control, such as weather conditions.

Despite the fact that there have been significant investments in deriving bioactive compounds from plant sources, new activities and new sustainable biosources are necessary to enable our move away from reliance on chemical synthesis – a refinement process that often releases a number of harmful chemicals into the atmosphere. In identifying improved means of utilising plant natural products, not only will there be a reduction in the environmental impact, new materials will also be produced that could boast an array of new and exciting properties and stimulate economic development, in terms of injecting the field with new promise and potential.

A PLETHORA OF BENEFITS FOR ALL INVOLVED

With that in mind, a four-year project was established in 2013 that sought to generate new biosources of bioactive and industrial phytochemicals. The DISCO (From DISCOvery to products: A next generation pipeline for the sustainable generation of high-value plant products) project is funded by the European Commission under the FP7 framework programme. The Project Coordinator, Professor Paul Fraser, brought together a multinational and multidisciplinary team of experts from around the world to translate their discoveries into industrial applications by determining the feasibility of their investigations.

Now in its third year, the project hopes to have significant value for both pharmaceutical and industrial sectors. 'Products with natural, phytochemical components that are not produced from synthetic chemistry have obvious benefits on the environment,' explains Fraser. 'However, the DISCO initiative will also result in cheaper products, increased availability of products, new markets for the products, better products, and more employment opportunities in the sector.'

FINDING AND FOCUSING ON PLANTS ALREADY USED

Fraser and his partners developed a project strategy that involved three interrelated but distinct modules. The first module centred on bioprospecting – the search for plant species from which commercially valuable compounds could be obtained. The specific focus was on the Solanaceae and Iridaceae genera for several reasons. These plant families tend to be of high value which immediately gives them promise in terms of translating to industrial applications; some are already produced in the petrochemical industry. In addition, both families are underexploited, as existing sources are rather poor and are not currently amenable to large-scale production.

In order to completely capture the biochemical diversity in these plant species, state-of-the-art metabolomics procedures were used to identify low-abundance secondary metabolites of interest and global metabolite composition. Furthermore, an important component of this module was in elucidating the biosynthetic pathways associated with the formation of bioactives and metabolites of interest.

The molecules and pathways targeted include carotenoids (including apocarotenoids), terpenoids and tropane alkaloids. Ketocarotenoids are natural pigments used as colourants in both the aquaculture and poultry industries; Solanesol is a terpenoid used in the production of coenzyme Q10 – used in the treatment of cardiovascular disease and atherosclerosis; and tropane alkaloids, such as scopolamine,

> *The number of industrial partners . . . helps provide an industrial perspective on what the market requires and provides a direct route to market and product development*

are used by the pharmaceutical industry for the treatment of nausea and vomiting caused by motion sickness among other things. All of these already have industrial applications, making translation of the findings easier and largely justified from the outset.

TECHNOLOGICAL PIONEERS

The second module was concerned with the application and implementation of procedures that facilitated rapid and efficient metabolic engineering and molecular breeding. This process was reliant on the DISCO partners, many of which have vast experience in the metabolic engineering of biochemical pathways. Indeed, throughout the course of the project this sometimes meant a partner had to pioneer technology from infancy to the marketplace to make use of what the team uncovered throughout their investigations.

Importantly, the second module includes considerations regarding transferring the technology to new pathways and regulatory mechanisms to create a pipeline of efficient metabolic engineering activity. Ultimately, the team's approach helps to ensure high-value products and enables improvements in the technologies to be incorporated into the overarching strategies at the earliest possible opportunity.

FROM THE LAB TO THE MARKET

The third module is concerned with the translation of the findings into feasible industrial outputs. In projects such as this, it is important to consider the ways in which innovations can be moved through to commercial practices. 'The number of industrial partners involved in the project is extremely important,' explains Fraser. 'It helps provide an industrial perspective on what the market requires and provides a direct route to market and product development.'

Accordingly, feasibilities on a production scale are performed throughout the course of the project, and the data generated will enable cost-benefit analysis, as well as identifying commercial opportunities and the potential they have in the marketplace.

In facilitating the move away from chemical synthesis, Fraser and his project partners are helping to usher in a new generation of materials that make use of what grows naturally on Earth. As well as the obvious environmental benefits from this undertaking, such materials could boast properties that lead to improved treatment of a wide range of ailments and could even help develop treatments that do not currently exist.

Importantly, the science taking place has the application of its findings in mind at every stage of the process, making the translation to industry a consideration from the outset, thereby ensuring the process is as smooth as possible. That young researchers from across Europe are involved at all stages also helps ensure that this work will continue long into the future, where environmentally responsible practices will become even more essential than they are now.

Innovation leader

The DISCO project represents a significant attempt to move away from the reliance on chemical synthesis. It seeks to achieve this through four main branches:

- Develop new sustainable biosources of plant-derived products that are of pharmaceutical and industrial interest
- Fine-tune bioactive compound extraction procedures using enabling technologies to ensure industrial relevance and commercialisation
- Eliminate future chemical refining that is detrimental to the environment through the development of 'green factories' with integrated biorefining pipelines
- Provide new plant material to benefit human activities that improve the quality of life and health of European populations, whilst stimulating the economy

Project Insights

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Professor Paul Fraser is a Professor of Biochemistry and the Head of Plant Molecular Sciences at Royal Holloway. He has over 20 years' experience working both in academia and industry within the UK and abroad. During this period Fraser has worked on the analysis, biosynthesis, regulation and metabolic engineering of carotenoids and other isoprenoids, both in plant and microbial systems. Over 100 peer-reviewed articles have been published including in high-impact journals such as *PNAS*, *Nature Biotechnology* and *Plant Cell*. He is the Coordinator of the FP7 METAPRO project, FP7 DISCO project, and the Vice-chair of Cost Action FA1006 Plant Metabolic Engineering for High Value Products (www.plantengine.eu).