HVCfP’s Proof of Concept (PoC) fund has been very successful. By the end of the Network (December 2018), over £1 million will have been spent on proof of concept projects: £800K from the core PoC funds, and £211K from industrial partners’ contributions.

The fund was launched in May 2014, and the final call closed in August 2017. Out of a total of 51 applications, 21 projects were funded, resulting in a success rate of 41% which indicates the demand for such funds as well as the rigour of the review process. Industrial support for the programme has been good with 13 projects having contributions from industrial partners.


This report provides highlights of the scheme and draws together common research themes for HVCfP including: discovery and characterisation of new bioactive molecules, pathway engineering for high value chemicals, extraction processes and production platforms. HVCfP’s research scope was mainly focussed on plants; however, funds were also awarded to microalgae projects targeted to high value chemicals.

New bioactives discovery and characterisation

Plants are able to synthesize a vast array of molecules, some of which are known bioactives but many are yet to be characterised. These molecules often exhibit complexity too difficult to produce by chemical synthesis alone, therefore their discovery in plants and their characterisation has been an important focus for HVCfP given the wide-ranging applications of plant-derived chemicals across many industrial sectors.

Bioactives from oats, in particular avenanthramides, were the focus of a PoC award to Luis Mur, Aberystwyth University. The project resulted in interesting data on the anti-microbial properties of both avenanthramides and a novel chemical identified as a fatty acid breakdown product.

A collaboration between Rothamsted Research (led by Mike Beale) and the University of Kent employed a systems approach to new drug discovery in willow. This enabled a much shorter timescale for bioactive discovery, allowing rapid identification of bioactives from complex mixtures. A completely novel phytochemical with anti-cancer properties was identified and isolated. Future work aims to characterise and test the compound and its analogues.

PoC funding was used to establish a new collaboration between scientists at Keele University and Phytoquest to screen for anti-microbials from a natural product library of temperate zone plants. Led by Paul Horrocks at Keele, a number of interesting compounds were identified – these discoveries were also beneficial in identifying the potential of Phytoquest’s library of compounds.

Other work on bioactives funded by HVCfP PoC awards include:

- Paul Knox (University of Leeds) collaborating with AlgaeCytess to study the functional properties of large, complex carbohydrate structures produced by microalgae in their growth media;
Peter Eastmond (Rothamsted Research) working with Unilever to investigate the use of a plant hydrolase as an industrial biocatalyst particularly applied to laundry products.

Pathway engineering

Pathway engineering in plants involves the manipulation of genetic and regulatory processes to produce metabolites of interest. A common problem with pathway engineering is the accumulation of precursors rather than the target end-products. With a PoC award from HVCfP, Paul Fraser from Royal Holloway, University of London was able to overcome this issue and demonstrate that his ‘metabolon’ – a mechanism for channelling metabolites in bacterial biosynthetic pathways also had useful applications in pathway engineering in plants for carotenoids. Carotenoids are high value plant pigments with many industrial uses such as food colourants, feed supplements and medicines. Furthermore, the technology developed is of generic interest to industry for production of other high value chemicals.

Gary Loake at the University of Edinburgh used PoC funding to investigate biosynthesis regulators of paclitaxel – a major anti-cancer drug with a global market value worth ~£3.5 billion. This project led to the discovery of new proteins that function as a molecular switch to turn off production of paclitaxel. These findings will provide new ways for enhancing production yields of paclitaxel in yew cells and will help secure the supply of this important medicine.

Work led by Anil Day (University of Manchester), in collaboration with AlgaeCytes Ltd, studied the molecular pathways responsible for synthesis of omega 3 and omega 6 polyunsaturated fatty acids (PUFAs) in algae. The library of genes obtained by their work will enable new synthetic biology approaches to improve the quality and variety of PUFAs that can be made and will expand the beneficial uses of algal oils in the personal and health care markets.

Other pathway engineering projects funded by HVCfP include:

- work on steviol glycosides undertaken by Ian Graham at the University of York;
- research by Samuel Brockington at the University of Cambridge using natural genetic diversity for betalain production on an industrial scale;
- two different projects on Camelina sativa at Rothamsted Research, one led by Olga Sayanova on the biosynthesis of the non-native pharmaceutical sciadonic acid and the other by Peter Eastmond investigating diverting carbon flux away from the phenylpropanoid pathway;
- research by Cathie Martin (John Innes Centre) with Persephone Bio Ltd into engineering tomatoes for increased production of monoterpenes for industrial applications.
**Extraction and Processing**

Extraction of high value chemicals from plants can present a particular challenge for industry in ensuring cost-effective yields. Extraction processes used may involve environmentally unfriendly solvent systems and often only the freely available products can be extracted. A PoC project undertaken by Michael Hale’s group at Bangor University investigated the use of fungi as a pre-treatment prior to extraction. Results indicated that a mould fungus dramatically enhanced the amount of an alkaloid, galanthamine, which could be extracted from daffodil bulbs when compared to conventional maceration and solvent extraction alone. At laboratory scale they were able to more than double the amount of extractable high value plant metabolites.

Utilising sustainable, step-wise methods for extraction and purification techniques to isolate natural compounds from waste liquorice was the focus of a PoC award to Richard Blackburn (University of Leeds) working with industrial partners Neal’s Yard Remedies. Results indicated promising activities within the extracts including UV absorbers, skin lighteners and anti-oxidants. Work is ongoing to develop these products further towards commercialisation.

**Production systems**

Sourcing high value chemicals from plants on an industrial scale can often be impractical and unsustainable, requiring over-harvesting of rare plant species or use of arable land which could be used for food production. Plant cell cultures can offer an attractive, alternative option for high value chemicals and PoC funding has enabled several research projects in this area.

Gary Loake (University of Edinburgh) received PoC funding to work with Unilever to evaluate different aspects of plant cell cultures, aiming to develop a sustainable production system for industrial chemicals for the personal care industry. Useful chemicals have been identified in broccoli, sprout and liquorice but they are only present in low quantities so research is ongoing to develop a plant cell culture production platform. An additional award enabled work to focus on transferring the production platform to a controlled bioreactor system, allowing further culture optimisation and an important step towards scale-up for commercialisation. Peter Walley (University of Liverpool) is also working with the same group at Unilever to use mass spectrometry to model secondary metabolite pathway responses to a range of physical and chemical elicitors to increase production of target molecules of commercial interest.

A key challenge in the exploitation of plant metabolism is the tightly regulated production of plant natural products which leads to the frequent silencing of metabolic pathways in plant cell cultures. Anne Osbourn at the John Innes Centre received PoC funds to work with Croda Europe Ltd to use chemical treatments to enhance metabolite production in different plant cell cultures. Further work is planned to study a wider collection of cell cultures and metabolites of interest to establish a route through to commercial exploitation of their technique.
Combining synthetic biology with plant cell cultures was the focus of an award made to Naomi Nakayama at the University of Edinburgh whose research provides a user-friendly assembly method for multiple DNA parts for expression of genes of interest. Her laboratory is also developing ways to activate gene expression in a temporal manner. This research will enable the application of these tools to new types of plant cell cultures which have been differentiated to have physiological states tuned for production of secondary metabolites, proteins or oils.

Paul Fraser, Royal Holloway University of London was awarded funds to develop and evaluate tools to produce new, high-yielding β-carotene tomato varieties. This research was particularly timely due to recent legislation that now prevents the use of chemically synthesised carotenoids for human consumption. The project resulted in tomato hybrids rich in β-carotene content. Interestingly, these plants displayed cellular adaptations for storage of hydrophobic molecules. Whilst the traditional perception is that non-food, industrial crops should be used for the production of high value chemicals from plants; in this instance tomato fruit represents an excellent source for β-carotene production that surpasses other plant-based sources.

Impact beyond research

In addition to the research outputs, HVCfP’s PoC awards have provided multiple benefits such as: building strong, new collaborations with industry; developing new academic research consortia; providing the foundation for industrially-supported PhD studentships; enabling training opportunities for researchers to work on proof of concept research whilst gaining an appreciation of interactions with industry; enhancing the undergraduate curriculum with cutting edge research; inspiring outreach activities to the general public, school groups and policy makers; and generating new research income from external sources and internal strategic organisational funds (current total levered is £5.5 M).

HVCfP will continue to monitor the PoC awards’ outputs and outcomes until the end of the Network grant as we anticipate continued benefits arising from these awards when results are published and new funding opportunities are realised.

July 2018
FULL LIST OF HVCfP PROOF OF CONCEPT PROJECTS

ROUND ONE – SEPTEMBER 2014

Uncovering transcriptional regulators of paclitaxel biosynthesis
Gary Loake - University of Edinburgh

Targeting the most clinically bioactive oat avenanthramides
Luis A. J. Mur, Catherine Howarth, Ifat Parveen - Aberystwyth University

Low cost extraction of galanthamine from daffodils
Michael David Hale - Bangor University

New drugs from old: a phytochemical genetics and pharmacological screen of Salix
Michael H. Beale, Jane L. Ward, Steve Hanle, Angela Karp - Rothamsted Research; Martin Michaelis, Ian Blomfield, Alessia Buscaino, Mark Shepherd, Anastasios Tsaousis - University of Kent

Screening for antiparasitic leads from a novel and diverse library of natural products from temperate zone plants
Paul Horrocks, Helen Price - Keele University; Robert Nash - Phytoquest

ROUND TWO – MARCH 2015

A synthetic metabolon for the production of high value carotenoid pigments
Paul Fraser - Royal Holloway University of London

Development of natural sweeteners from Stevia rebaudiana
Ian Graham - University of York

ROUND THREE – OCTOBER 2015

Engineering synthetic pathways for the production of pharmaceutical sciadonic acid in transgenic Camelina sativa
Olga Sayanova, Johnathan Napier - Rothamsted Research

Small molecule-mediated manipulation of specialized metabolism in plant cell cultures
Anne Osbourn - John Innes Centre; Doug Cossar - Croda Europe Ltd

Isolation/ characterisation/ activity screening of a high value bioactive complex of proteoglycans from a high exopolysaccharide (EPS) forming strain of microalgae
Paul Knox - University of Leeds; Gary Robinson - University of Kent; John Dodd - AlgaeCytes Ltd

Harnessing natural genetic diversity to drive the industrial synthesis of betalains for human health and nutrition
Samuel Brockington - University of Cambridge

Evaluation of cambial meristematic cell cultures as a source of functional phytochemicals for the personal care industry
Gary Loake - University of Edinburgh; Ravine Gungabissoon - Unilever PLC
ROUND FOUR – APRIL 2016

British liquorice – a valuable source of active ingredients for skincare applications (LIQUOREX)
Richard S. Blackburn, Christopher M. Rayner - University of Leeds; Andrea Mitarotonda - Neal’s Yard Remedies

Analysis of genes and culture conditions required for improving the yield, quality and variety of high value oils from microalgae
Anil Day - University of Manchester; John Dodd - AlgaeCytes Ltd

ROUND FIVE – NOVEMBER 2016

The development of high provitamin A (β-carotene) producing tomato lines (acronym: PROVITA)
Paul Fraser, Genny Enfissi - Royal Holloway University of London

Production of the lipid-soluble antioxidant canolol in cruciferous oilseeds
Peter Eastmond - Rothamsted Research

Differentiating plant cell factories
Naomi Nakayama - University of Edinburgh

ROUND SIX -

Utility of a plant hydrolase as an industrial biocatalyst
Peter Eastmond - Rothamsted Research; Dietmar Lang - Unilever R&D plc, Port Sunlight

Engineering enhanced content of aromatic amino acids in tomatoes for improved bioactive content
Cathie Martin, Eugenio Butelli - John Innes Centre; Jonathan Clarke - Persephone Bio Ltd

Plant cell culture for sustainable phytochemical production: natural complex flavanoids
Peter Glen Walley, Simon Charles Thain - University of Liverpool; Ravine Gungabissoon - Unilever

The optimisation and scale up of functional ingredients in plant cell cultures
Gary Loake - University of Edinburgh; Ravine Gungabissoon, Mark Berry - Unilever PLC