Business Interaction Vouchers – Projects funded by HVCfP Network in January 2018

ID number	**BIV-HVCFP-JAN18-029**
Title	Development of a hybrid Ion-Mobility Mass Spectrometry screening approach for the detection of novel Polyketide based antibiotic compounds from plant sources.
Academic (lead) Partner	Julian Griffin, University of Cambridge
Industrial Partner	Simon Thain, TL Science Ltd
Public summary	Polyketides represent a rich source of novel antimicrobial compounds. Many existing antibiotics are based on these natural products. Because of their structural complexity de novo synthesis of polyketides has limitations. However, traditional discovery routes from nature involving extracting, testing and purifying the active components from crude extracts are hugely expensive, time-consuming and only too often end in simply rediscovering an already known compound. What is required is a way to increase the chances of success by enriching for plausible target compounds at an early stage of discovery prior to functional testing. One approach would be rapid determination of a significant level of structural confirmation of molecules from classes of compounds known to have relevant bioactivity at the primary source screening stage. This would need to be done with a reasonable level of through-put speed suitable for larger scale screenings. This project will test the feasibility of an approach using a 4-dimensional "Chemical Space" characterisation approach based on a multiple hyphenated mass spectrometry approach to define the physiochemical parameters of some important polyketide molecular classes exhibiting antibiotic properties. This will be augmented by data mining of published and in-silico predicted collisional cross-sectional area, MS/MS and structural properties of molecular candidates, to develop guided screening methods. The output will be a vital enabling technology platform supporting the longer-term intention to use plant-derived biological processes to produce useful bioactives at commercially viable yields.
Start date	1st May 2018

ID number	**BIV-HVCFP-JAN18-028**
Title	Road map for generation of "ready to fluorinate" custom terpenoids
Academic (lead) Partner	Anne Osbourn, John Innes Centre
Industrial Partner	Ted Chapman, GSK
Public summary	Plants make a huge array of natural products and are highly versatile chemical engineers that can make structurally complex molecules inaccessible to current organic chemical synthesis. The project aims to identify potential sources and routes to terpenoid drugs that do not occur abundantly in nature. The terpenoids required are ideal starting materials for existing semi-synthetic drug molecules. Better starting points for manufacturing drugs offer advantages in reduced lead times, cost, inventories of intermediate stages and a very significant environmental benefit.
Start date	1st April 2018

Business Interaction Vouchers – Projects funded by HVCfP Network in November 2017

ID number	**BIV-HVCFP-NOV17-025**
Title	Plant protection products from tomato waste
Academic (lead) Partner	Michael Roberts, Lancaster University

Industrial Partner	Stephen Price, Biotech Services Ltd
Public summary	Plants are frequently subjected to attack by pests and diseases. Consequently, they have evolved a suite of protective mechanisms based on a mix of physical and chemical defences. These mechanisms are primarily inducible (*i.e*. activated in response to attack) and include the biosynthesis of a wide array of secondary metabolites with defensive functions. Direct defences are those that act directly on the pest organism (*e.g*. antimicrobial and toxic compounds), whilst indirect defences include the production of chemicals that are used as attractants by natural enemies of the pest (*e.g*. its predators and parasites). In addition, many of these inducible metabolites, especially volatile organic compounds (VOCs) which enter the atmosphere, can also function as so-called 'priming' signals. Priming compounds can be transmitted between plant tissues, or even between plants, and enhance the defensive capacity of the receiving tissue by boosting future induced resistance responses. Some of these VOCs, such as the green leaf volatiles (GLVs) are produced within minutes of damage to plant tissues, whilst more complex VOCs, including blends of terpenoid and phenylpropanoid molecules, appear later after injury. Damaged plant tissues in which these inducible defences have been activated therefore provide a rich source of organic compounds with potential applications in plant protection. Waste from agricultural and horticultural production offers a cheap, renewable source of raw material for this purpose. In this project, we will examine the potential of waste from horticultural tomato production, currently processed by the industry partner Biotech Services Limited for anaerobic digestion, as a system for the generation of novel plant protection products.
Start date	19th February 2018

ID number	**BIV-HVCFP-NOV17-026**
Title	Synthesis and evaluation of specialty molecules and polymers from the cellulosic biomassderived platform molecule levoglucosenone
Academic (lead) Partner	Andrew Sutherland, Aston University
Industrial Partner	Fabien Deswarte, Circa Sustainable Chemicals Ltd
Public summary	Circa Sustainable Chemicals Ltd have developed methodology to enable sawdust to be converted into a small organic molecule called levoglucosenone (LGO). In addition to selling it, Circa use LGO as a starting material to make other chemicals which they also sell. Current products include Cyrene® (a solvent) and Dairy Lactone (a flavouring agent). Having conducted market research it is clear that a significant market for LGO-derived polymers (polymers are materials that are made from lots of smaller repeat units called monomers) exists and so Circa are keen to develop ways to make LGO into polymers. Whilst the company has excellent expertise in making and converting LGO into other small molecules they lack experience of making polymers and so have asked Aston to help them develop new polymers from LGO – the aim of the research proposed. Specifically, Aston will develop methodology to enable LGO to be converted into various monomers and these monomers will be used to make polymers and polymer beads. The beads will be biocompatible and will be tested for their ability to enter human cells (ultimately for drug testing, drug delivery and vaccine applications) and for their utility in making small bits of protein (peptides) which themselves are useful products for medical and other applications. The non-beaded LGO-derived polymers will be tested for their adhesive properties to enable new adhesives and cements to be developed for use in various medical scenarios

	such as dental applications. Thus in summary we propose to develop chemical and polymer methodology that will enable a waste material to be converted, via extant and new chemical steps, into bio-compatible materials with a range of applications.
Start date	1st February 2018

ID number	**BIV-HVCFP-NOV17-027**
Title	Enrichment of natural UV protectants from seaweed utilising green chemistry methods and technologies
Academic (lead) Partner	James Clark, University of York
Industrial Partner	Steve Wilson, Unilever
Public summary	Seaweed is an abundant 3rd generation biomass that has been harvested for human consumption, animal feed and as a source of polysaccharides. Low levels of both hemicelluloses and lignin result in easy depolymerisation for various applications, the most attractive of which being as a fermentation feedstock. In addition to these large volume, low value applications, seaweed also contains numerous high value compounds in low concentrations such as antibacterial, antiviral and antifungal actives. An interesting group of compounds with UV-protective properties are also present at very low levels (<0.2% by dry weight) in certain seaweeds such as Dulce – common along North Atlantic coast lines. In order to access the potential value of these functional materials, they first need to be enriched to a reasonable concentration. This has proven challenging due to their high polarity and low concentration compared with other polar extractives, despite attempts to isolate them with numerous established techniques. There are two approaches that have not been trialled previously and which based on our experience in related areas may prove successful. The first is the application of mesoporous carbonaceous materials, Starbons which have tunable surface properties and have been shown to selectively adsorb and desorb a range of compounds. The second is counter current chromatography which uses two immiscible liquids to perform numerous solvent exchanges to carry out separations that have proven difficult using established techniques.
Start date	16th February 2018

<u>Business Interaction Vouchers – Projects funded by HVCfP Network in July 2017</u>

ID number	**BIV-HVCFP-JUL17-022**
Title	Biotransformation of plant-derived alkaloids
Academic (lead) Partner	Wen-Wu Li, Keele University
Industrial Partner	Matthew Hodges, Oxford Biotrans Ltd
Public summary	The nitrogen-containing natural compounds (termed alkaloids) are a large group of high value chemicals found in plant species. Numerous alkaloids (e.g. paclitaxel and quinine) are anti-cancer and anti-malarial drugs. In our laboratory, we have recently isolated a number of plant-derived alkaloids which possess interesting bioactive properties e.g. anti-microbial activity. Here, we propose to further modify these compounds using powerful biocatalysts (green chemistry) in order to provide novel and more potent molecules, which will then be tested to confirm their specific activities. Oxford Biotrans Ltd has the expertise and resources to provide such biocatalysts. Through collaboration, we aim to identify and develop safer and more effective plant-derived pharmaceuticals.
Start date	16th October 2017

ID number	BIV-HVCFP-JUL17-023
Title	Assessment and optimisation of microwave-assisted extraction of bioactive and bio-available compounds from rapeseed pomace
Academic (lead) Partner	Cherry Wainwright & Giovanna Bermano, Robert Gordon University
Industrial Partner	Stephen Roe, Advanced Microwave Technologies Ltd
Public summary	Rapeseed (*Brassica napus*; also known as canola) is a member of the family Brassicaceae (cabbage family) that is used primarily for production of animal feed and biodiesel, and the manufacture of edible oil. Rapeseed is one of the world´s major oil seeds and the third largest source for vegetable oil in human nutrition. In Scotland, rapeseed is the third biggest crop grown (amounting to 33,000 hectares of land) and is a source of cold-pressed quality virgin rapeseed oil which in nutritional terms is superior to other cold-pressed oils due to the higher levels of mono-unsaturated and polyunsaturated fatty acids vitamin E, plant sterols, phenolics, lignans, indoles and glucosinolates, all of which are believed to exhibit health promoting properties both in animals and humans. Rapeseed pomace (meal) is the waste product from rapeseed oil production and the 35 million tons produced globally every year are currently used as a supplement for animal feed. Researchers at RGU have found that chemical extraction of rapeseed meal from cold-pressed oil extraction yields an abundancy of bioactive compounds with potential human health benefits (*Food Chem* 2018, 239: 323–332;https://doi.org/10.1016/j.foodchem.2017.06.129). While little work has been done to establish what the safest and most efficient and cost-effective extraction methods are, chemical extraction may not represent the best method for scaling-up the extraction process and may render the leftover material unsuitable for use as animal feed. Advanced Microwave Technologies (AMT) has a range of capabilities that have the potential to be used as an alternative water-based extraction method and, therefore, the primary aim of this work is to assess and optimise microwave-assisted extraction as a means of isolating natural antioxidant compounds for nutraceutical, pharmaceutical or cosmetic product use. Through enhancing the efficiency of bioactive extraction prior to the pomace being used for animal feed/fuel briquette production, the addition of a high value product to the existing products will generate a sustainable and scalable production of naturally derived bioactive molecules and valorise the biomass to create a more profitable use of rapeseed meal. Although beyond the scope of the current project, there is the potential to optimise production of the key identified bioactives by using plant biotechnology approaches which use plant cells as green chemical factories for sustainable production, or alternatively to transfer production to bacterial factories as shown for production of one bioactive, indole pyruvic acid, present in rapeseed pomace (Microbial Cell Factories 2017 16:2)
Start date	23rd October 2017

ID number	BIV-HVCFP-JUL17-024
Title	Unique clostridial derived cyclodextrins: characterisation and modification
Academic (lead) Partner	Sara Kyne, University of Lincoln
Industrial Partner	Liz Jenkinson, Green Biologics Ltd
Public summary	Clostridia bacteria have been used for almost a century to produce bulk chemicals including acetone, butanol and ethanol. Recently it has been found that following modification, these bacteria can also convert starch into unique high value products, which are of potential commercial interest. The starch can be obtained from corn gluten meal, a by-product of the corn crop. Whilst this new product has been observed, it will be isolated and completely

	characterised for the first time as part of this project. The products will also be further modified through selective, and sustainable methods. An assessment will be carried out on the potential of the products for development as high value products for: functional food, biomedical and biotechnological applications.
Start date	26th October 2017

Business Interaction Vouchers – Projects funded by HVCfP Network in April 2017

ID number	**BIV-HVCFP-APR17-020**
Title	Novel application of brown seaweed as an antibacterial coating for interdental drug delivery
Academic (lead) Partner	Birthe Nielsen, University of Greenwich
Industrial Partner	Jeremy Bishop, Mirage Health Group
Public summary	Dental caries is one of the most common chronic and multifactorial diseases affecting the human population. Plaque, a sticky film that develops naturally on teeth and gums as a result of sequential colonization and growth of bacteria, is the leading cause of tooth decay, periodontal disease (incl. gingivitis) and ultimately, tooth loss, affecting approximately 90% of the adult population. Interdental, plaque build-up is especially difficult to combat, and products have been used as delivery mechanism for fluoride, but more research is required on the delivery of antimicrobials interdentally. The action of a dental stick could deposit small amounts of antimicrobial agents directly to the areas in need of treatment. Plants have long been known for their antimicrobial properties, and with the lack of effective antibiotics rapidly becoming a global issue, the search into sourcing these from plant products is important. Carrageenan, a naturally occurring anionic sulphated linear polysaccharide extracted from certain red seaweed is used in dental products as a binder, and enzymes present in seaweed have been shown to break up plaque. Therefore, this project aims to investigate the potential use of brown seaweed extracts as coatings for a dental stick to prevent plaque build-up between teeth. **Why *Sargassum muticum*?** Brown algae are a recognised source of high value chemicals [1,2] *and* metabolites derived from *Sargassum* harbours several interesting bioactivities, ranging from immune modulators [3] to acne treatments [4], some of which have successfully been extracted and assayed in cell-based systems [3]. Although the genome of this alga has yet to be sequenced, its mitochondrial sequence has very recently become available, indicative of an existing scientific community interested in its biotechnology and bioengineering. At the same time *Sargassum muticum*, is an alien invasive species, causes acute global ecological problems, on the Kent coast and globally. The destruction of this seaweed is currently carried out at considerable financial and energy cost. We have suggested its disposal by anaerobic digestion to produce bio-methane but to make the process financially viable, high value chemical compounds need to be removed prior to processing. Previous studies has shown potential medical application of this seaweed, however this has not been confirmed and no studies have been carried out on the dental application of this species. [1] Liu L et al (2012) Towards a better understanding of medicinal uses of the brown seaweed Sargassum in Traditional Chinese Medicine: a phytochemical and pharmacological review. J Ethnopharmacol. 142:591-619 [2] Milledge, J.J., Nielsen, B.V. & Bailey, D. Rev Environ Sci Biotechnol (2016) 15: 67. [3] Chae D et al (2013) Apo-9'-fucoxanthinone, isolated from Sargassum

	muticum, inhibits CpG-induced inflammatory response by attenuating the mitogen-activated protein kinase pathway. Mar Drugs 11:3272-87 [4] Ruxton CH, Jenkins G (2013) A novel topical ingredient derived from seaweed significantly reduces symptoms of acne vulgaris: a general literature review. J Cosmet Sci. 64:219-26
Start date	25th July 2017

Business Interaction Vouchers – Projects funded by HVCfP Network in January 2017

ID number	**BIV-HVCFP-JAN17-018**
Title	Investigation of the quantity of Asparaginase present in daffodils used for galanthamine production
Academic (lead) Partner	Helen Townley, University of Oxford
Industrial Partner	Kevin Stephens, Agroceutical Products Ltd
Public summary	L-Asparaginase (L-ASP, E.C. 3.5.1.1) is used as a therapeutic agent in the treatment of acute childhood lymphoblastic leukaemia (ALL). The cancerous cells are dependent upon circulating asparagine for growth, whereas normal cells are able to synthesize their own. Therefore removal of asparagine from the circulation by the enzyme asparaginase deprives the leukaemic cells, and leads to cell death. Despite the successful role of the use of L-ASP in childhood ALL treatment, its use is limited and constantly re-evaluated due to serious side effects mainly caused by toxicity. Interestingly, most of the observed side effects arise from a second substrate specificity of asparaginase, which can also deplete the concentration of glutamine due to its structural similarity. L-asparaginases have been found in in a variety of organisms such as microbes, plants and mammals, but only the enzymes from E. coli and Erwinia chrysanthemi have been produced on an industrial scale. Due to their microbial source, drug resistance mechanisms also operate mainly due to an antibody response. Plants may therefore provide an economically viable source of the enzyme which may be better tolerated than a microbial source. In plants, L-ASP enzymes are required to catalyze the release of ammonia from asparagine (which is the main nitrogen-relocation molecule in these organisms), and are present in significant amount in a variety of plant species. For example, Withania somnifera, a traditionally Indian medicinal plant, is an alternative source of L-ASP with high specificity and potential success for future large-scale production. However, Withania is a plant native to India, and grows in hot and humid conditions. This project investigates the potential for using daffodil plants to generate L-ASP. This has the potential to provide a sustainable source, and for wealth generation in the UK. Agroceutical products currently produce the biotherapeutic Galanthamine for Alzheimers treatment, and work with experts in daffodil production. Their research has shown that inducing stress by growing daffodils at elevations greater than 1,000 ft in the Welsh mountains causes a significant increase in Galanthamine levels as well as the other alkaloids. It is also known that L-asparaginase accumulates under stress conditions, making the biomass an ideal feed stock.
Start date	3rd April 2017

ID number	**BIV-HVCFP-JAN17-019**
Title	Are plant totipotent cell peptides effective in a model of chronic human skin wounds?
Academic (lead) Partner	Jelena Gavrilovic, University of East Anglia

Industrial Partner	Oscar Expósito Tarrés, Vytrus Biotech, Spain
Public summary	Skin wound healing is much less efficient in elderly people and Vytrus Biotech has developed a novel process generating products from plant stem cell cultures which may be effective in such chronic human skin wounds. Vytrus Biotech has developed the Plant Cell Biofactories Technology Platform: a new efficient and eco-sustainable way to obtain novel plant by-products with high added value, for the dermocosmetic and pharmaceutical sectors. This technology uses plant totipotent (stem) cells as biofactories to produce highly innovative multi-functional actives which have shown promise in wound-related studies of isolated human cells in cell culture. Vytrus now requires validation of these observations in a physiologically relevant human whole skin wound healing model. The objective of this project is thus to validate the potential wound healing properties of Vytrus's Phyto-Peptidic Fractions™ through an innovative human skin biopsy model, established by Academic partner, University of East Anglia (UEA) where skin wound healing can be assessed outside the body. UEA will validate the effects of Phyto-Peptidic Fractions™ and related plant cell proteins on key steps in wound healing, namely re-epithelialization, and activation of underlying dermal cells. This knowledge will direct the future development of plant stem cell culture-derived peptides and will provide evidence regarding the ongoing application of modification of plant stem cell culture processes for healing of chronic skin wounds in the future.
Start date	26th April 2017

Business Interaction Vouchers – Projects funded by HVCfP Network in July 2016

ID number	**BIV-HVCFP-JUL16-017**
Title	Discovery of a systemic bio-fungicide derived from the *Asteraceae* family
Academic (lead) Partner	Peter Rose, University of Lincoln
Industrial Partner	Apostolos Papadopoulos, Crop Intellect Ltd
Public summary	We have recently identified a wild plant of the *Asteraceae* family, indigenous to the UK that was found to be a useful companion species when grown alongside cereals. Chemicals released by this companion plant appear to suppress the growth of several common fungal species on cereal crops grown nearby and reduce fungal disease severity. Fungal diseases is a major issue for agriculture as they cause significant yield losses in crops. However, the active compounds present are currently not known. Some preliminary experiments have already been conducted which showed that extracts made from the companion plant are very effective at reducing fungal growth. In the current project we aim to identify the active compound(s) present in extracts, measure the activity on glasshouse plants and test for any unwanted toxic effects. We will also undertake a desk study to consider alternative ways to produce the active compound as commercial-scale production from the identified companion plant is unlikely to be feasible. Options may include transfer of the compound to a bacterial production system or identification of an alternative, commercially viable plant source. It is hoped that this project will further the research towards creating IP and provide evidence to determine the potential for commercialisation.
Start date	24th October 2016

Business Interaction Vouchers – Projects funded by HVCfP Network in April 2016

ID number	**BIV-HVCFP-APR16-015**

Title	Generation of novel aroma active compounds from waste plant material for use in the flavouring and fragrance industry.
Academic (lead) Partner	Ian Fisk, University of Nottingham
Industrial Partner	Arthur Kay, bio-bean Ltd
Public summary	Waste plant materials contain significant levels of chemical precursors that could be used to generate aroma active compounds. This project will facilitate a new collaboration between research and industry to quantify the precursors in a specific waste plant material and its potential to generate aroma active compounds for use in the Flavour and Fragrance Industries. This is a novel process, as the flavourings and fragrances that will be formed are currently manufactured synthetically or mechanically extracted from virgin plant material which is a highly wasteful process. Over 500kT of the target plant material is produced annually throughout the UK, the majority of which is currently landfilled or incinerated, meaning this is a scalable project with significant commercial potential.
Start date	27th July 2016

ID number	**BIV-HVCFP-APR16-016**
Title	Improving the antimalarial and anticancer properties of a natural product
Academic (lead) Partner	Colin Wright, University of Bradford
Industrial Partner	Matthew Hodges, Oxford Biotrans Ltd
Public summary	Many natural plant materials possess properties valuable to human health. The species we will investigate is endemic to Guatemala, where it is a traditional remedy for malaria. Previous scientific studies, have confirmed that compounds isolated from the species do possess moderate antimalarial activity, but this is not sufficient to provide an effective treatment for malaria. This Project will use a novel enzymatic technique to alter the complex natural products present in the Guatemalan plant to attempt to improve its reported antimalarial properties. There have also been screening results published in the literature, suggesting that extracts of the leaves may have some activity against skin cancer cell lines. We will seek to further investigate this initial observation. This Project uses the traditional knowledge of indigenous communities to direct modern research techniques; therefore any future benefits will be shared with the Government of Guatemala. If successful, this Project could lead to an effective natural treatment for serious human diseases. Furthermore, it will provide valuable information about how the enzymatic technology used in this Project can be extended to the development of other novel commercial products from plant sources.
Start date	27th July 2016

Business Interaction Vouchers – Projects funded by HVCfP Network in January 2016

ID number	**BIV-HVCFP-JAN16-014**
Title	Novel tomato compounds with anti-ageing effects in a human skin bioassay using MALDI-IMS
Academic (lead) Partner	Jelena Gavrilovic, University of East Anglia
Industrial Partner	Jonathon Clarke, Persephone Bio
Public summary	The cosmetics and skincare industry exploits plant natural products (Naturals) within a wide range of skin tonics, lotions and topical skin applications. Persephone Bio has developed a tomato based production system where, through metabolic engineering, bioactive compounds can be made in high concentrations. Compounds produced in this way require validation of their biological activity. These bioassays have previously been undertaken using

	animal models, human cell cultures or using qualitative tests in human trials. In all methods, the true biological activity has been difficult to discern. The University of East Anglia has recently established a human skin bioassay platform which has the potential to overcome these limitations. In preliminary tests we have recently found that aqueous extracts of tomatoes change the activity of 86 genes (1.5-fold or above) in the human skin biopsy bio-assay. Many of these genes are thought to play important roles in skin ageing, but the picture is complex. It is likely that the effects observed depend on which of the several different cell types in skin react to the compounds. Whilst several components of the tomato extracts have shown effects in mouse skin a comprehensive approach in human skin is required. In this project we propose to use a new technique, MALDI-IMS which provides detailed information on all proteins expressed and their location within skin regions (epidermis, dermis, vasculature). Extracts of tomatoes generated by Persephone Bio will be compared with those of a control tomato using the human skin bio-assay platform and MALDI-IMS. This will provide data which will allow Persephone Bio to identify which compounds have an anti-ageing activity and which human skin cells are affected. This knowledge will direct the future development of new treatments/cosmetics from tomato.
Start date	25th April 2016

Business Interaction Vouchers – Projects funded by HVCfP Network in October 2015

ID number	**BIV-HVCFP-OCT15-013**
Title	Bio-derived compounds from levoglucosenone – 3 steps from sawdust to solvents
Academic (lead) Partner	James Clark, University of York
Industrial Partner	Tony Duncan, Circa Sustainable Chemicals Ltd
Public summary	Cellulose is the most abundant renewable feedstock on the planet. The most easily accessed high volume source of cellulose is from the lumber industry, with sawdust an underutilised by-product. Sawdust is the ideal feedstock currently employed in Circa's pilot plant for the simple and inexpensive one step production of levoglucosenone, a reduced sugar with interesting functionality. The current petroleum route to this molecule is complex and expensive and it has received little attention other than in niche applications. The new bio-based version has the potential to open up a new field of chemistry. We have already shown that bio-levoglucosenone can be easily converted to a new molecule "cyrene" which is currently generating much interest within the pharmaceutical industry as a replacement polar solvent for traditional, toxic fossil-derived alternatives. The intention of this project is to produce a range of other potential solvents or otherwise valuable molecules in two (or less) steps from levoglucosenone or in one step from Cyrene utilising bio-derived reactants and applying the principles of green chemistry. We are particularly interested in the generation of novel bio-based solvents for enzyme-catalysed reactions especially of water-insoluble substrates building on our recent publication demonstrating the effectiveness of green solvents in some important chemical transformations (Paggiola, G., Hunt, A.J., McElroy, C.R., Sherwood, J., & Clark, J.H. (2014).Biocatalysis in bio-derived solvents: an improved approach for medium optimisation. *Green Chemistry.* 16 (4), 2107-2110).
Start date	13th January 2016

Business Interaction Vouchers – Projects funded by HVCfP Network in July 2015

ID number	BIV-HVCFP-JUL15-012
Title	Natural UV-absorbing compounds from Living stones – evaluation of bioactivity and commercialisation for the cosmetic market
Academic (lead) Partner	Alison Smith, University of Cambridge
Industrial Partner	Franck Michoux, Alkion Biopharma SAS
Public summary	"Living stones" (Lithops spp.) are unique southern African plants that live partly underground in extremely hot and dry conditions. This underground life makes it difficult to get enough sunlight to photosynthesise while still conserving as much water as possible. Lithops has many adaptations to help it do just this, including a top surface with "windows" that allows light to penetrate to photosynthetic tissues deep within the subterranean leaf. The mottled window of the plant's modified leaf look solid but are actually translucent if you cut off the tops and hold them up to the light. Cleverly, these translucent windows have sunscreen properties to block out harmful UV light that these desert plants would be exposed to. The bio-cosmetic industry are interested in discovering new natural ingredients for products such as sun-screens. The UV-blocking chemicals in these Lithops have the potential to act as a natural sun screen ingredient. This exciting new collaboration between the University of Cambridge and Alkion BioCosmetics will assess whether these chemicals have the correct properties, novelty and the ability to be mass produced to meet the demands of the cosmetic industry.
Start date	22nd October 2015

Business Interaction Vouchers – Projects funded by HVCfP Network in April 2015

ID number	BIV-HVCFP-APR15-008
Title	Purification of high value molecules using vibrational membrane filtration
Academic (lead) Partner	Ray Marriott, Bangor University
Industrial Partner	Carolyn Carver, Blue Sky Botanics Ltd
Public summary	Extraction of high value labile molecules from plants using water or aqueous solvents presents unique difficulties for individual molecule separation. Recent innovations in membrane filtration in which a high frequency vibration is applied across the membrane has the potential to provide a solution to this problem and allow the separation of labile molecules without the application of heat or the use of high cost chromatographic methods. The use of water or aqueous solvent mixtures is encouraged from a green chemistry perspective and would have much wider application if a process platform can be developed to fractionate the extracts.
Start date	8th June 2015

ID number	BIV-HVCFP-APR15-009
Title	Extraction of a novel chelate from native UK plant species
Academic (lead) Partner	Vesna Najdanovic, Lancaster University
Industrial Partner	David Marks, Levity Crop Science Ltd
Public summary	Iron chelates are used extensively in agricultural production, particularly on crops grown on high pH soils, where iron becomes 'locked up' and unavailable to crops. The industry is dominated by the use of synthetic chemical chelates including Fe EDDHA, Fe EDDHSA, and Fe EDTA. The use of synthetic chelates in agriculture can free up heavy metals in soils, and contribute to environmental pollution. Levity has identified a chemical capable of chelating iron to a higher level than

	EDDHA, which is found in some plant species. Levity is developing uses for this (and related chemicals) in the agrochemical industry. A suitable feedstock that can be produced in the UK for economic extraction of the target high value chemical is required. Levity has identified a plant species which contains high levels of the chemical. This project aims to develop ways of extracting and concentrate it. Extraction methods to be explored include supercritical CO2 and solvent extraction.
Start date	1st July 2015

ID number	**BIV-HVCFP-APR15-010**
Title	Establishing genome resources for improving the production of high value chemicals from simple plant systems
Academic (lead) Partner	Anil Day, University of Manchester
Industrial Partner	John Dodd, AlgaeCytes Ltd
Public summary	Simple plant systems such as microalgae provide renewable sources of high value chemicals such as pigments, nutraceuticals and algal biomass proteins/carbohydrates. The inputs of light, water and inorganic molecules are relatively cheap and plentiful. These simple plants can be grown in purpose built bioreactors to convert cheap inorganic compounds into high value chemicals. The pathways that convert simple molecules into more complex ones involve steps that require enzymes that are encoded by genes. By identifying the genes involved in these pathways and monitoring their activities we will gain a better understanding of the steps needed to improve the productivity of these pathways. Moreover, it may allow new pathways to be assembled in these simple cells to produce a wider variety of high value chemicals. AlgaeCytes' Omega 3 algal oils are produced primarily as high value ingredients for the personal cosmetic and health care markets and have a genuine clinical use to improve cardiovascular and cognitive health. The aging population in developing countries and dwindling oily fish supplies will mean a growing market for alternative sources of Omega 3 (EPA – Eicosapentaenoic acid) in the next 25 years.(1) There is need from both research and commercial prospectives for the development of synthetic biology methods that can lead to improved algal strains. (1) Frost & Sullivan (2014). Global Omega-3 and Omega-6 Polyunsaturated Fatty Acid Ingredients Market Focus on the Impact of Microalgae Feedstock on the Supply and Demand for Omega-3 and Omega-6 Ingredients.
Start date	27th July 2015

ID number	**BIV-HVCFP-APR15-011**
Title	Screening microalgae species for waste water phosphate removal/recovery and high value chemicals production
Academic (lead) Partner	Christopher Ennis, Teeside University
Industrial Partner	Pattanathu Rahman, TeeGene Biotech Ltd.
Public summary	Microalgae are a promising source of biofuel and high value chemicals and nutraceuticals. However, there are major technological challenges limiting the extent to which microalgae can be used in this way. This project will explore suitable algal feedstock for input to a novel integrated biorefinery capable of overcoming these challenges and of cleaning waste water, recovering essential nutrients, and providing high value algal-derived chemicals and materials.

	The "enabling technology" of this biorefinery has the potential to play a central role in an integrated microalgae-based waste water treatment system capable of: • removing phosphate contamination from waste water to improve the quality of natural waters; • producing viable quantities of high value lipids (as, for example, feedstock for biodiesel production); • producing biochar for soil amendment and carbon sequestration; • recycling fertilizer phosphate. This project will investigate the value potential of algae grown in the context of waste water treatment in the UK.
Start date	1st July 2015

Business Interaction Vouchers – Projects funded by HVCfP Network in January 2015

ID number	**BIV-HVCFP-JAN15-007**
Title	Characterisation of the bioactives from Mugwort roots active against the oomycete pathogen of carrot and parsnips, *Pithium* spp.
Academic (lead) Partner	Cathie Martin, John Innes Centre
Industrial Partner	Howard Hinds, Root Crop Consultancy Ltd.
Public summary	Oomycete pathogens such as *Pithium violae* and *Pythium sulcatum* (causal agents of cavity spot) and *Phytophthera infestans* (late blight) cause major damage to root or tuber vegetable crops, often re-emerging, postharvest to cause significant losses. Treatment with metalaxyl fungicides reduces losses but leaves residues and metalaxyl fungicides are prone to evolution of resistance by these highly variable pathogens (especially *P.infestens*). Mugwort (*Artemesia vulgaris*) is an invasive weed in the UK, but high density infestation with a particular Mugwort accession in fields of parsnip and carrot, results in significantly lower levels (five-fold less infection) of cavity spot caused by *Pithium* spp. Trials by the commercial partner have shown that co-planting Mugwort with carrots reduced *Pithium* infection to the same extent as treatment with metalaxylM fungicide. The biocontrol offered by Mugwort seems to work through the roots/rhizomes of this invasive weed, because mulch formed from the aerial parts of the plant had no effect on the levels of disease in carrots. Mugwort, is a member of the Asteraceae family, and is rich in terpenes such as thujone. However, this terpenoid is produced in the leaves, so it is unlikely to be the lead bioactive in the fungicidal effect of Mugwort roots. The objectives of this application are to set up a bioassay for the root produced/exuded bioactives from Mugwort that inhibit *Pithium* growth or infection of carrots. Following identification of the active compounds produced by this specific isolate of Mugwort, by metabolic profiling, the bioactivity of exudates, and of purified compounds will be tested against *Pithium violae* and *Pythium sulcatum* and their close relative *Phytophthera infestans*. This will provide the scientific basis for development of a natural extract of Mugwort that can be used to dramatically reduce infection by *Pithium* spp. It will also show whether this extract has similar fungicidal activity against the more economically important oomycete pathogen, *Phytophthera infestans*. Whereas cultivation of an invasive weed would be impractical in controlling cavity spot on root vegetables, identification and characterisation of the bioactivity of a natural product from Mugwort could add significant value to this plant as a source of biocontrol formulations.
Start date	1st May 2015

Business Interaction Vouchers – Projects funded by HVCfP Network in October 2014

ID number	**BIV-HVCFP-OCT14-004**
Title	Identifying high value bioactive complex carbohydrates/polysaccharides from a high exopolysaccharide (EPS) forming strain of microalgae.
Academic (lead) Partner	Paul Knox, University of Leeds
Industrial Partner	John Dodd, AlgaeCytes Ltd
Public summary	AlgaeCytes is focused on developing and commercialising bioactive ingredients from microalgae including Omega 3 oils (EPA - Eicosapentaenoic acid) and Exopolysaccharides (EPS) for the healthcare, nutraceutical and personal care markets. As an early stage company, AlgaeCytes has to develop its product pipeline and as such it has natural freshwater microalgal strains producing high levels of exopolysaccharides which have shown potential as a source of unique bioactive chemicals. Products such as sunscreens, gelling agents and potentially novel anti-microbials have been produced from extracellular polysaccharides from other organisms. The laboratory at the Centre for Plant Sciences, University of Leeds has world-leading panels of monoclonal antibodies (MABs) that are highly sensitive molecular tools for the analysis and isolation of bioactives from cell wall polysaccharide complexes in plants. This project is an initial study aimed at identifying the major carbohydrate structures and potential bioactive compounds present in the EPS of AlgaeCytes' freshwater algal EPS strains as a prelude to commercial exploitation. The two entities together will potentiate and catalyse the search for new and alternative natural high value chemicals for the growing healthcare, nutraceutical and personal care markets.
Start date	14th January 2015

ID number	**BIV-HVCFP-OCT14-005**
Title	PinS - Pinitol Isolation from Senna Seeds
Academic (lead) Partner	Ana Winters, Aberystwyth University
Industrial Partner	Roger Jones, Phytovation Ltd
Public summary	Phytovation is a natural product extraction and processing company based in North Wales. Currently their principal product is standardised natural Senna powder for use in making high quality laxatives. Due to quality specifications of the product only the pods are processed leaving the seeds as a process waste stream. The seeds and leaves of leguminous trees, such as Senna, can be rich sources of d-Pinitol. D-Pinitol is known as an insulin mimicker and as a result there is a growing interest in the use of it as a food supplement because of its reported efficacy in lowering blood glucose levels with no side effects and nil toxicity. Pinitol was first isolated from pine tree (hence its name). Phytovation have a significant stock of Senna seed in dry storage and are particularly interested in innovative means for the valorisation of this waste. The PinS project seeks to evaluate state of the art technology held by IBERS in Aberystwyth for the extraction and purification of the high value component d-Pinitol from the process waste stream (seeds) of the Senna manufacturing process. The bulk of naturally sourced Pinitol is currently extracted from soybean, carob or pine, then purified employing physical separation processes such as chromatography and crystallization. This project will examine both (variable energy) ultrasonic assisted primary extraction together with high performance counter current chromatography

	for downstream isolation of Pinitol.
Start date	1st February 2015

ID number	**BIV-HVCFP-OCT14-006**
Title	PylEx – Pyrethrum liquid extraction (liquid-liquid fractionation of components of a naturally occurring insecticide)
Academic (lead) Partner	Ana Winters, Aberystwyth University
Industrial Partner	Bryan Shand, Agropharm Ltd
Public summary	Crushed and powdered *Chrysanthemum (Pyrethrum cinerariaefolium)* plants were used as an insecticide by the Chinese as early as 1000 BC. Pyrethrum extract is a long established, naturally occurring insecticide with low toxicity to man and warm-blooded animals and unique active properties that are the basis for a wide range of insecticidal products currently on the market effective against a host of harmful agricultural and household pests. Pyrethrum extract comprises 6 active esters resulting from the combination of chrysanthemic acid or pyrethric acid with one of three alcohols. The general mode of action of pyrethrum extract is to attack the insect's nervous system generating instant muscular paralysis (knock-down) and death. However, of the six pyrethrin components some have insecticidal properties while others act as insect repellents. Isolation of these components by economically viable and scalable extraction systems would facilitate the development of new products specifically addressing different target markets. This project aims to separate the different pyrethrin components through the application of state of the art hydrodynamic liquid-liquid extraction technology (High Performance Counter Current Chromatography - HPCCC).
Start date	1st February 2015

Business Interaction Vouchers – Projects funded by HVCfP Network in July 2014

ID number	**BIV-HVCFP-JUL14-001**
Title	Assessment and optimisation of microwave-assisted extraction of galanthamine and other alkaloids from daffodils for the UK pharmaceutical industry
Academic (lead) Partner	Xianmin Chang, Royal Agricultural University
Industrial Partner	Kevin Stephens, Agroceutical Products Ltd
Public summary	The UK is the world's largest producer of daffodils and narcissi cut flowers, worth c. £23 million annually to the economy. More importantly, these plants also contain over 300 alkaloids, one of which is galanthamine which has been approved since 2001 for the treatment of early stage and moderate Alzheimer's disease, an age related dementia with an estimated 800,000 cases in the UK, rising to over one million in 2021. Galanthamine is often prescribed rather late in the progress of the disease due to its expense and shortage of supplies, adding to the burden on family carers and the NHS. Chemical synthesis is possible, but difficult and expensive. Therefore, isolation from daffodil biomass gives a new industrial biotechnology use for a non-food crop. Daffodils also contain other alkaloids which have potential pharmacological activities, such as, narciclasine and haemanthamine, with demonstrated anti-cancer, anti-leukemia or anti-inflammatory properties. Although there are over 25,000 varieties of daffodils only a few have identified which contain a significant level of galanthamine. The search for new varieties that can be used for galanthamine production is important both commercially and to

	Alzheimer's sufferers across the world. However, it is vital if we can significantly enhance the alkaloids extraction efficiency. The aim of this project is to assess and optimize Microwave Assisted Extraction (MAE) of Alkaloids from Daffodils to enhance the efficiency of alkaloids extraction, and ultimately to secure the sustainable and scalable production of galanthamine and other alkaloids for the UK Pharmaceutical Industry.
Start date	1st October 2014

ID number	**BIV-HVCFP-JUL14-002**
Title	Discovery of Novel Plant-Derived Agrochemicals
Academic (lead) Partner	Ray Marriott, Bangor University
Industrial Partner	Apostolos Papadopoulos, Crop Intellect Ltd
Public summary	Advances in several industry sectors including agriculture have come from observations of nature. Plants have always been a source or new chemical discovery and such chemistry has been vital to humanity. In this project the plant investigated was selected for its ability to adjust to varying growth conditions. This achievement is attributed to the plant's evolutionary chemical composition. Crop Intellect in collaboration with Bangor University aims to understand and identify the chemistry responsible for the benefits observed in efficacy tests. Identification of the molecules responsible would allow using these in combination with crop nutrition to improve use efficiency, increase yield and produce quality.
Start date	1st October 2014

ID number	**BIV-HVCFP-JUL14-003**
Title	Road Map for the use of the Seaweed *Sargassum muticum* in high value Bioactive Compound Discovery
Academic (lead) Partner	Birthe Nielsen, University of Greenwich
Industrial Partner	David Bailey, IOTA Pharamaceuticals Ltd
Public summary	Plants naturally produce a vast array of high value chemicals, often with complex structures, and with diverse applications as pharmaceuticals, speciality chemicals and flavour and fragrance ingredients. Algae are aquatic plants, occurring as unicellular or multi-cellular organisms, generally possessing chlorophyll, but without true stems and roots. Algae can be divided by size into two groups; macroalgae, commonly known as "seaweed", and microalgae, microscopic single-cell organisms ranging in size from a few to a few hundred micrometres (μm) [1]. The use of algae for therapeutic purposes has a long history, with the search for specific, biologically active substances accelerating recently [2]. Brown algae in particular are a recognised source of high value chemicals [3], but the translation of these compounds into clinically useful drugs has proven difficult, despite some encouraging preclinical results in oncology [4]. Japanese wireweed, *Sargassum muticum*, is an alien invasive brown algal species, causing acute global ecological problems, on the Kent coast and even in California. The destruction of this seaweed is currently carried out at considerable financial and energy cost [5]. However, *Sargassum muticum* is a source of traditional Chinese medicines [3]. Could *Sargassum muticum* yield useful biologically active compounds that would transform a disposal problem into a commercial opportunity? Our project will develop a Road Map for the use of marine macroalgae in the identification and production of sustainable, renewable high value chemicals,

	using *Sargassum muticum* as a production system to evaluate methods for high value bioactive compound discovery. The project is a collaboration between the University of Greenwich, a prominent player in the algal biorefinery area [6], and IOTA Pharmaceuticals, an early-stage Anglo-Dutch SME that has pioneered the area of fragment-based drug discovery [7,8] and is currently developing new screening systems for phenotypic drug discovery in cancer research [9]. The short-term aim of the mini-project is to identify and compare methods for the production and screening of macroalgal extracts and purified natural products. The longer-term aim is to establish a robust pipeline of natural products from algae and other micro-organisms, with the intention of using them as chemical starting points in the production of drugs to cure human disease. References [1] Milledge JJ (2011) A review of the harvesting of micro-algae for biofuel production. Rev Environ Sci Biotechnol. 10, 31-41. [2] Borowitzka MA (1995) Microalgae as sources of pharmaceuticals and other biologically active compounds. J Appl Phycol. 7, 3-15. [3] Liu L, Heinrich M, Myers S, Dworjanyn SA (2012) Towards a better understanding of medicinal uses of the brown seaweed Sargassum in Traditional Chinese Medicine: a phytochemical and pharmacological review. J Ethnopharmacol. 142, 591-619. [4] Murphy C, Hotchkiss S, Worthington J, McKeown S (2014) The potential of seaweed as a source of drugs for use in cancer chemotherapy. J Appl Phycol. doi: 10.1007/s10811-014-0245-2 [5] Milledge JJ, Staple A, Harvey P (2014) Pyrolysis of invasive seaweed species. Br Phycol Soc. Annual Meeting, Galway. [6] Harvey P et al (2014) The CO2 microalgae biorefinery: high value products from low value wastes using halophylic microalgae in the D-factory. Part 1: tackling cell harvesting. 22nd European Biomass Conference and Exhibition, Hamburg, Germany. [7] de Kloe GE, Bailey D, Leurs R, de Esch IJ (2009) Transforming fragments into candidates: small becomes big in medicinal chemistry. Drug Discov Today 14, 630-46. [8] de Graaf C, Vischer HF, de Kloe GE, Kooistra AJ, Nijmeijer S, Kuijer M, Verheij MH, England PJ, van Muijlwijk-Koezen JE, Leurs R, de Esch IJ (2013) Small and colorful stones make beautiful mosaics: fragment-based chemogenomics. Drug Discov Today 18, 323-30. [9] Moffat J, Rudolph J & Bailey D (2014) Phenotypic screening in cancer drug discovery - past, present and future. Nat Rev Drug Discov. 13, 588-602.
Start date	1st October 2014