Joint HVB and IBioIC Call

HVB Funded Projects:

Research to create new spin-outs **Royal Holloway, University of London (RHUL) Laboratory Products; creating commercial activity from knowledge transfer**	
Lead applicant's name:	**Paul Fraser**
Co-investigator's name:	**Genny Enfissi**
Research Co-investigator's name:	**Laura Perez-Fons**
University/ research institute:	**Royal Holloway, University of London**

PROJECT ABSTRACT:

Most of the bright colours observed in nature, such as the orange and red colours witnessed in flowers are due to the presence of carotenoid pigments. Carotenoids represent the largest class of natural pigments found in nature. In addition to an intrinsic ability to confer colour, most carotenoids have health promoting benefits to humans and therefore are an important/essential component of the human diet as carotenoids cannot be made in the body. Commercially, carotenoids have widespread uses in the food, feed, cosmetic, health and pharma sectors as colourants, health supplements and phytomedicines. Annual sales of carotenoids are over $1 billion and are increasing rapidly (18%/yr.), as the demand for natural carotenoids outstrips supply. Chemical synthesis has traditionally been the production method of choice for carotenoids. However, this approach has an adverse environmental impact, due to the use of petrochemical by-products, organic solvents and metal catalysts.

The laboratory at Royal Holloway, University of London has been working on carotenoids for over fifty years and routinely make their authentic reference carotenoids in-house from biobased sources. Requests are frequently received from both the academic and industry sectors for carotenoid reference compounds. In the present proposal, knowledge transfer from our research activities will be carried out to generate a range of carotenoid reference compounds, at scale, for direct entry into the market place. The approach uses biobased waste streams as the feedstock and will generate speciality chemicals of industrial value, these characteristics are synergistic to the scope of industrial biotechnology.

RESULTS REPORTED:

HVB products/ processes for industry **Chemoenzymatic upcycling of biocatalytic reaction waste: harnessing access to high value chiral building blocks**	
Lead applicant's name:	**Sebastian Cosgrove**
Co-investigator's name:	**Gavin Miller**
University/ research institute:	**Keele University**
Industrial Partner's name:	**Beatriz Dominguez**

Company:	**Johnson Matthey**

PROJECT ABSTRACT:

The mass production of waste is a pressing issue in society, with the majority of it being sent to landfill or burnt for energy. This causes many societal and environmental problems. Being able to convert waste to a high-value product can therefore offer solutions to this issue from economic and environmental perspectives. This project will use a waste material to make a chemical that can be used to produce nylon in an environmentally friendly way. Nylon is currently made from fossil-based resources in an unsustainable manner, and worldwide we produce around six million tonnes every year. It is therefore essential that we come up with new, more sustainable ways to produce the chemicals that are important in nylon production. The way this project will address the issue is by improving the way we can make a chemical called glucaric acid, which can be easily turned into one of the main components of nylon, from waste biomass resources that are made from glucose. It will use new biotechnologies to improve the way the waste glucose is converted to glucaric acid; allowing this new method to replace the old, fossil-based methods that are currently used will strengthen the UK industrial bioeconomy by making chemicals from biomass waste using bioprocesses. The benefits include a reduction in greenhouse gas emissions associated with nylon production, and the use of a free resource that would otherwise just end up in the bin, therefore reducing overall costs as well.

RESULTS REPORTED:

HVB products/ processes for industry

Commercial validation of a *Saccharomyces cerevisiae* production platform for bioactive diterpenes

Lead applicant's name:	**Ian Graham**
Co-investigator's name:	**Katherine Denby**
Research Co-investigator's name:	**Tomasz Czechowski**
University/ research institute:	**University of York**
Industrial Partner's name:	**Timothy A Miller**
Company:	**Croda Europe Ltd**

PROJECT ABSTRACT:

Diterpenoids are a chemically diverse group of natural products that have the potential to replace petrochemical derived feedstocks and deliver new functionality for various industrial applications. However, the typically low natural abundance and high structural complexity limits the development of industrial applications for these compounds. Many different classes of diterpenoids have reported bioactivity but their industrial utility has not been explored. Developing new production platforms by engineering microorganisms such as brewers yeast (*Saccharomyces cerevisiae)* is now recognised as a valid route to commercial production of these small molecule natural products.

The academic partner has already demonstrated that they can produce a relatively simple bioactive diterpene molecule, casbene, by engineering a novel strain of brewers yeast with genes taken from plants using a strategy that does not rely on existing intellectual property from other sources. The

industrial partner, Croda, will evaluate performance of this strain under conditions that relate to their production facilities and will also evaluate the commercial relevance of casbene for industrial application across their agri-tech and personal care sectors.

Typically diterpene molecules become more bio-active and useful when the 20-carbon backbone is decorated with additional chemical groups. Oxidation is the main type of modification. Using gene tools already at hand the academic partner will engineer bioactive diterpenes reported to protect plants from fungal pathogens, perform laboratory bioassays using two fungal pathogens that cause disease in UK crops and transfer the resulting yeast strains to the industrial partner to validate the production platform and commercial relevance.

RESULTS REPORTED:

HVB products/ processes for industry

Application of high-throughput enzyme evolution using artificial selection pressure to real pharmaceutical biocatalysis challenges

Lead applicant's name:	**John Heap**
Co-investigator's name:	
Research Co-investigator's name:	
University/ research institute:	**University of Nottingham**
Industrial Partner's name:	**Francesco Falcioni**
Company:	**AstraZeneca**

PROJECT ABSTRACT:

Catalysts are essential to increase chemical reaction rates in a wide range of industries, and biocatalysts (enzymes) have various advantages. The non-natural needs of industrial applications often require enzymes with new or improved properties, but these are very difficult to design rationally. Instead, approaches mimicking evolution generate huge numbers of variants of existing enzymes. Improvements are very rare, but usually variants must be tested individually, a process like searching for a needle in a haystack. We have recently developed a new artificial selection pressure (evolution's 'survival of the fittest' principle) technology, involving genetically modified cells and special incubation conditions. It is broadly applicable, unlike other such systems. The system has been successfully used in our laboratory to evolve multiple types of new enzyme variants, and metabolic pathway variants, with desired improvements. This system is industrially relevant, and several companies are interested.

The project industrial partner is the pharmaceutical company AstraZeneca. This project will apply the new enzyme evolution technology to biocatalysis challenges of direct relevance to pharmaceutical research and manufacturing, by seeking new enzymes or variants (1) as 'greener', sustainable replacements for an existing step in the production of a candidate drug, and (2) to overcome difficulties in production of a class of chemicals which show promise as possible future medicines. Significantly, success of either aim would achieve 'Proof of Concept' for industrial application and increased

'technology readiness level', warranting further public and private investment, and opening the way towards new medicines and environmental and economic benefits.

RESULTS REPORTED:

IBioIC Funded Projects

2020 HVB products/ processes for industry (IBioIC funded)
Title: Bioactivity of Compounds Derived from *Amaryllidaceae* (Daffodil)

Lead applicant's name:	**Cherry Wainwright**
Co-investigator's name:	**Sarah Walsh, Giovanna Bermano**
Research Co-investigator's name:	
University/ research institute:	**Robert Gordon University**
Industrial Partner's name:	**Kevin Stephens**
Company:	**Agroceutical Products Ltd**

PROJECT ABSTRACT:

Heart Failure (HF) is a long-term complication of cardiovascular (high blood pressure and heart attack) and cardiovascular-related (obesity and metabolic syndrome) disorders and of drug-induced cardiotoxicity. HF is characterised by thickening (hypertrophy) and stiffening (fibrosis) of the walls of the heart, leading to reduced cardiac function and increased morbidity. Agroceutical Products Ltd (APL) produces sustainable quantities of the naturally derived alkaloid galanthamine from daffodils, which is a key active pharmaceutical used for the treatment of Alzheimer's disease. Daffodils contain an abundance of other alkaloid compounds, some of which (e.g. narciclasine and haemanthamine) APL can extract alongside galanthamine. There is emerging evidence that some of these alkaloids may target cellular events in the heart cell (cardiomyocyte) to interrupt the HF-associated structural changes, and thus have the potential for development as novel therapeutics in the prevention of HF. This project will involve testing three alkaloids extracted from daffodils in cell-based cardiomyocyte models that mimic the different stimuli for cardiac hypertrophy (high glucose, oxidative stress and doxorubicin), to determine their potential as anti-hypertrophic/anti-fibrotic molecules, and by measuring multiple cellular signalling pathways we will gain insight into cellular mechanism of action. This will provide essential "proof of concept" data that will identify the most efficacious compounds, inform the refinement of extraction methods to isolate different alkaloids, and potentially identify what structure-activity relationships may exist between alkaloids. This will inform APL as to which alkaloids have the potential to bring added value to their current production stream which will, in turn maximise the commercial potential for their products.

RESULTS REPORTED: