Welcome

Industrial Biotechnology for Improving the Production of Higher Value Chemicals

Town Meeting
Introduction and Call Background

Alexandra Amey, Associate Head of Business Interaction, Capability and Innovation - BBSRC
Purpose of today

Provide potential applicants and stakeholders an opportunity to find out more about the background to the call.

Opportunity to hear from industrial representatives to get a broader understanding of the industrial research challenges in this area.

Hear about academic research being done to address industry challenges.

Insight and lessons learned from delivering a short collaborative project.

Meet with potential collaborators and discuss potential projects.
Meeting Agenda

10.30 Introduction

11.00 Session 1 – Industry Presentations
Murray Brown, GSK
Will Canon, Croda

11.50 Coffee Break

12.10 Session 2 – Academic Presentations
Ian Graham, Director of HVB NIBB
Sarah Barry, Kings College London

13.00 Lunch and Networking
Buffet - outside in foyer

14.00 Session 3 - Applying for funding
How to apply for funding - Hayley Moulding
Open Discussion – Colin Miles

15.00 Close of formal meeting

15.00 to 16.00 Networking, project discussions, etc
UK Research and Innovation

We work with the government to invest over £7 billion a year in research and innovation by partnering with academia and industry to make the impossible, possible. Through the UK’s nine leading academic and industrial funding councils, we create knowledge with impact.
As a member of UKRI, BBSRC:

- Invests in world-class bioscience research in UK Universities & Institutes
- Invests in bioscience training & skills for the next generation of bioscientists
- Drives the widest possible social & economic impact from our bioscience
- Promotes public dialogue on bioscience
BBSRC Strategic Delivery Plan

**Advancing the frontiers of bioscience discovery**
- Understanding the rules of life
- Transformative technologies

**Tackling strategic challenges**
- Bioscience for sustainable agriculture and food
- Bioscience for renewable resources and clean growth
- Bioscience for an integrated understanding of health

**Building strong foundations**
- People and talent
- Infrastructure
- Collaboration, partnerships and Knowledge Exchange

Biotechnology and Biological Sciences Research Council
Bioscience for renewable resources and clean growth

Transforming industries through bio-based processes and products in a new low-carbon bioeconomy

- Understanding and improving bio-based processes
- Improving performance at scale
- Creating value from waste
- Whole systems approaches to bio-based manufacturing
- New business models

UKRI Biotechnology and Biological Sciences Research Council
Call Background
Strategic review: Wider policy context

**Climate Change Act 2008**: amended to introduce legal target of 100% reduction of greenhouse gas emissions (compared to 1990 levels) in the UK by 2050; commonly referred to as the “Net Zero Target”. Legally-binding carbon budget targets between 2008 and 2032 require a reduction in UK emissions of 57% from 1990 to 2030 to meet the “Net Zero” target.

**UK Clean Growth Strategy 2017**: highlights the importance of Low carbon innovation, Clean energy innovation, Energy efficiency, Carbon Capture, usage and storage and zero waste by 2050

**Chemistry Council Strategy - Sustainable innovation for a better world 2018**: states that biotechnology has an increasing role to play in sustainable materials and packaging, new sustainable manufacturing routes, creating green supply chains including waste as feedstocks and clean growth through carbon efficient supply chains

**Growing the Bioeconomy 2018**: recognises the potential of bioscience and has the vision that in 2030 the UK is a global leader in developing, manufacturing, using and exporting bio-based solutions through producing innovative products, processes and services that rely on renewable biological resources instead of fossil fuels, and providing new routes to high value industrial chemicals
Strategic review: Chemicals Sector

UK Top 10 business energy consumers

- Iron, steel and metal manufacturing
- Mechanical engineering
- Agriculture
- Printing and publishing
- Mineral products manufacturing
- Food, drink and tobacco manufacturing
- Chemical manufacturing
- Manufacturing and industrial services
- Public administration
- Commercial and miscellaneous services

kilotonnes of oil equivalent (ktoe)

https://www.gazprom-energy.co.uk/blog/which-uk-businesses-use-the-most-energy/
Strategic Review: Consultation

Akzonobel     Ineos UK
Croda          Ingenza
Dr. Reddy's    Johnson Matthey
GlycoMar Ltd   Oxford Biotrans
Green Biologics PZ Cussons
GSK            Syngenta
               Unilever

MiB: Metals in Biology Network
BioCatNet: biocatalyst discovery, development and scale up
CBMNet: Crossing Biological membranes Network
FoodWasteNet
HVCfP: High Value Chemicals from Plants Network
IB Carb: Glycoscience Tools for Biotechnology and Bioenergy Network
### Key drivers for the chemistry industry to use IB

<table>
<thead>
<tr>
<th>Higher quality products</th>
<th>Reducing manufacturing costs</th>
<th>Sustainability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• high levels of stereoselectivity</td>
<td></td>
<td></td>
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<tr>
<td>• low-levels of impurities</td>
<td></td>
<td></td>
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<tr>
<td>• lowering energy costs</td>
<td></td>
<td></td>
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<tr>
<td>• reducing the number of stages required</td>
<td></td>
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<tr>
<td>• reduced downstream purification costs</td>
<td></td>
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<tr>
<td>• reducing/avoiding co-factors and/or heavy metals catalysts</td>
<td></td>
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<tr>
<td>• lowering energy consumption</td>
<td></td>
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<tr>
<td>• recycling co-factors and recover precious metals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• better utilising biobased/waste feedstocks</td>
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<tr>
<td>• avoid need for harvesting high environmental impact crops for natural products</td>
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</tbody>
</table>

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[UKRI Biotechnology and Biological Sciences Research Council](https://www.ukri.org/)

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Research Challenges highlighted in report: bioscience

- Increasing yields and concentrations
- Integrated high-throughput platforms + processes for discovery, analysis, optimisation of bioprocesses
- Plant cell culture systems as alternative production platforms
- Scale out for screening novel functionality
- Dealing with toxicity and transport of products in fermentation
Development of process engineering and process chemistry for improving biological processes

Advancing downstream processing and separation science

Specialised processes e.g. algae, or single use fermentation bio-manufacturing systems

Tools and techniques to understand and exploit complex feedstocks
Support requirements to address research challenges

**Funding activities**

- Moving research up TRLs and enabling industrial engagement
  - Supporting academic – industry – scale up consortia
  - Supporting SME engagement
  - Access to scale up facilities

**Broader support activities**

- Evidence based reports for better business planning and identifying target molecules
- Support multidisciplinary teaching and training for cross-skilling and up-skilling interdisciplinary scientists and technicians to ensure an industrially relevant research base
- Policy and legislation development and communication of opportunities

UKRI Biotechnology and Biological Sciences Research Council
September 2019 - BBSRC Executive approval of £2M

Based on the evidence provided through the consultation BBSRC Executive Leadership Team approved £2M funding to support projects for the translation of research and accelerate the de-risking of IB processes and help bridge the gap to larger-scale projects and further public or private investment.

Funding will enable the translation of research into industrial processes, supporting the development of post-proof of concept research progressing it towards technology readiness levels (TRLs) 3, 4 and 5 address challenges in applying bioprocesses for improving the production of higher value chemicals and aims to.
BBSRC 2019 Delivery Plan

“Develop and implement new mechanisms to enable industry and academic researchers to work together to understand how industrial biotechnology can make the manufacturing of higher-value chemicals more efficient, cost-effective and sustainable.”
Thank you
Discussion: Demand Management

Total Sum: £2M
Expected grant size: £250K Max
=> Approximately 8 proposals are able to be funded with existing resources

1. Managing Demand
   • Should we anticipate a large demand from the community?
   • How might we manage demand?
   • Is there a role for the NIBB II in providing informal advice to manage demand?

2. Encouraging/ developing collaborations in support of the call
   • > 600 small grants have been supported through phase I BBSRC NIBB – many of which are relevant to this call
   • What role could phase II BBSRC NIBB play in encouraging collaborations?

Biotechnology and Biological Sciences Research Council
Feedback and questions to:

Higher Value Chemicals Call Mailbox:

ib.highervaluechemicals@bbsrc.ukri.org
Industrial Biotechnology at GSK

- Natural Product Fermentation
  - β-lactam antibiotics, mupirocin, clavulanic acid
- Whole cell processes
  - Thymidine, steroid hydroxylation, glycosylations
- Wild type enzyme biocatalysis
  - 6-APA, 7-ACA (acylases), Nelarabine (nucleoside phosphorylases), Zanamavir (NANA-aldolase)
- Engineered enzyme biocatalysis for small molecule APIs
  - KRED, Transaminase, Nitrilase, Hydrolases, Imine reductase
- Engineered enzyme biocatalysis for other biomanufacturing processes
Biocatalysis Implementation at GSK

Process

- Identify Starting Enzyme
- Engineer Enzyme
- Engineer Process

Challenges

- Limited availability and knowledge of novel enzymes for reactions outside of established enzyme classes
- Literature reports often do not correlate to even small scale industrially relevant processes
- Speed of implementation
- Availability of large quantity of enzymes needed to follow up hits
- Enzyme supply chain
Biocatalysis Implementation at GSK

Common Issues

- Low intensification
- Low activity
- Low stability

![Graph showing rate vs. [S]]

- [Low Substrate Solubility]
- Emulsions
- Slow Enzyme Filtration
- Reactor Cleaning
# Biocatalysis Implementation at GSK

## Past, Current and Desired Future status at GSK

<table>
<thead>
<tr>
<th>Process</th>
<th>Historical</th>
<th>Current</th>
<th>Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify Starting Enzyme</td>
<td>Commercially available enzymes for limited reaction classes with limited operational scope and IP restrictions</td>
<td>Licensed commercial enzymes plus in-house panels with broader reaction class coverage, somewhat broader scope and FTO</td>
<td>Broad reaction class coverage including non-natural chemistries, with broad operational scope and FTO</td>
</tr>
<tr>
<td>Engineer Enzyme</td>
<td>3\textsuperscript{rd} Party engineering of some enzymes at high cost with on-going commitments and limitations</td>
<td>In-licensed CodeEvolver technology with FTO. Internal costs and timelines ration application to projects</td>
<td>Low cost and high speed so protein engineering is an experiment rather than a commitment</td>
</tr>
<tr>
<td>Engineer Process</td>
<td>Largely Chemical Process Development with the enzyme available</td>
<td>Process Development coupled to enzyme engineering with staff familiar with biocatalysis using current infrastructure</td>
<td>Process Development with easy access to novel technologies addressing intractable biocatalysis issues (e.g. flow, membranes)</td>
</tr>
</tbody>
</table>
Case Study – Development of IREDs as new class of Industrial Biocatalysts

IREDs (Imine Reductases) catalyze the reduction of imines to amines, as depicted in the reaction:

\[ \text{imine} + \text{NADPH} \rightarrow \text{amine} \]

The IMI funded Chem21 project started, with Chem21 partners having published 50% of the global output.
Panel comprised of 85 diverse enzymes with putative imine reductase activity from 5 structural families
Predominantly 'classical IREDs'
Most (>80%) express well (>1 mg/ml in lysate)

Screened for activity as lysates at 1:1 stoichiometry

Panel activity as lysates with 1:1 stoichiometry

Chemical Route to GSK2879552

- Extra steps for classical resolution of amine
- Non-preferred solvents
- Stoichiometric sodium borohydride
- Cycle time from aldehyde 2 to intermediate 5, including resolution = ~11 days

Potential for IRED Catalysed Reductive Amination

Ideal process - using IRED for combined reductive amination and resolution

- Removal of synthetic step
- Removal of non-preferred solvents
- Cycle time reduced from 11 to 3 days

## Biocatalyst discovery

### Screening of reductive amination panel with equimolar amounts of racemic amine

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<thead>
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<th>1</th>
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<th>4</th>
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<td>-</td>
<td>55.7</td>
<td>55.7</td>
<td>43.3</td>
<td>36.4</td>
<td>42.5</td>
<td>73.1</td>
<td>-</td>
<td>17.5</td>
<td>63.9</td>
<td>-</td>
<td>-</td>
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<tr>
<td>B</td>
<td>8.6</td>
<td>34.7</td>
<td>71.3</td>
<td>41.6</td>
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<td>54.9</td>
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<td>86.4</td>
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<td>81.2</td>
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<tr>
<td>C</td>
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<td>54.8</td>
<td>-</td>
<td>67.8</td>
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<td>99.9</td>
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<td>59.3</td>
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<tr>
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<td>35.0</td>
<td>99.3</td>
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<td>43.4</td>
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<tr>
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<td>96.9</td>
<td>55.0</td>
<td>21.3</td>
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<td>-</td>
<td>4.6</td>
<td>3.5</td>
<td>-</td>
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</table>

**Legend:**
- **No conversion**
- **Conversions > 30%**
- **(1R,2S)-desired enantiomer**
- **(1S,2R)-undesired enantiomer**
- **Negative control**
Process Target Evaluation

- Screening of IRED panel found revealed a wild-type with high selectivity (>99% ee)
- Low activity gave intractable workup

**Directed evolution**

<table>
<thead>
<tr>
<th>Specifications</th>
<th>WT</th>
<th>Target</th>
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<tbody>
<tr>
<td>Biocatalyst loadings</td>
<td>&gt; 450% wt/wt</td>
<td>&lt; 10% wt/wt</td>
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<tr>
<td>Aldehyde loading</td>
<td>10 g/L</td>
<td>≥ 25 g/L</td>
</tr>
<tr>
<td>Isolated yield</td>
<td>43%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Product ee</td>
<td>&gt; 99.7%</td>
<td>&gt; 99.7%</td>
</tr>
<tr>
<td>pH stability range</td>
<td>pH &gt; 6.5</td>
<td>pH &lt; 5.0</td>
</tr>
<tr>
<td>Reaction time</td>
<td>4-6 h</td>
<td>4-6 h</td>
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</table>
IRED Evolution Overview

<table>
<thead>
<tr>
<th>Rd</th>
<th>Library type</th>
<th>Positions mutated</th>
<th>TON*</th>
<th>Total FIOp</th>
<th>Mutations vs WT</th>
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<tbody>
<tr>
<td>1</td>
<td>Site Saturation</td>
<td>256</td>
<td>589</td>
<td>37</td>
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<tr>
<td>2</td>
<td>Combinatorial</td>
<td>46</td>
<td>3030</td>
<td>506</td>
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<tr>
<td>3</td>
<td>Combinatorial</td>
<td>22</td>
<td>32786</td>
<td>38719</td>
<td>13</td>
</tr>
</tbody>
</table>

* wild type turn over number (TON) = 78
## Process development

### Performance vs. target

<table>
<thead>
<tr>
<th>Specifications</th>
<th>WT</th>
<th>Target</th>
<th>Rd3 variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocatalyst loadings</td>
<td>&gt; 450% wt/wt</td>
<td>&lt; 10% wt/wt</td>
<td>1% wt/wt</td>
</tr>
<tr>
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<td>pH &lt; 5.0</td>
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<tr>
<td>Reaction time</td>
<td>4-6 h</td>
<td>4-6 h</td>
<td>4-6 h</td>
</tr>
</tbody>
</table>

All process targets met or exceeded

* Prevents pH dependent impurity formation
Scale up demonstration (20 L)

Kg amounts of product used for successful API synthesis

Reaction conditions:
- 25 g/L aldehyde
- Na acetate buffer pH 4.6
- DMSO (12.5%)
- IRED (1% wt/wt)
- GDH (1% wt/wt)
- NADP⁺ (4% wt/wt)
- Reaction time: 4h
- Aqueous work-up
- 84.4% isolated yield
- >99.9% HPLC a/a
- >99.7% ee.
Metrics comparison for chemical and biocatalytic route

### Mass intensity

- **Chemical**
- **Biocatalytic**

### Materials carbon footprint

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>MATERIALS CARBON FOOTPRINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical route</td>
<td>1,556.53 [Kg eq-CO₂]</td>
</tr>
<tr>
<td>Biocatalytic route</td>
<td>225.89 [Kg eq-CO₂]</td>
</tr>
</tbody>
</table>

**FLASC score**

- **Biocat**
- **Chem**

**Target**: Best

**Unacceptable**: Worst

---

- Mass Intensity: total mass of materials used in the process divided by total mass of product (excludes water and cleaning solvents)
- Water Mass Intensity: mass of water used in the process (as a reagent or solvent, excluding for cleaning) divided by the total mass of product.
- Process Mass Intensity: sum of Mass Intensity and Water Mass Intensity
- FLASC (Fast Life Cycle Assessment of Synthetic Chemistry) is a methodology and web based tool designed by GSK to evaluate relative sustainability of synthetic processes (http://dx.doi.org/10.1065/lca2007.03.315)
Key Learnings

– Collaboration between industrial and academic partners rapidly established proof of principle for applicability of IREDs as an industrial biocatalyst
– Diversity of enzymes in screening panels may allow identification of better starting points
– Performance can be improved by directed evolution although this process is still resource intensive and time consuming so strong business case required
– Enzyme improvements and process improvements can go hand in hand. An agile responsiveness from both parts helps develop better manufacturing

– Further improvements to manufacturing routes could be realised with more efficient (but more complex to develop) use of biocatalytic cascades…
Redox-Normal Cascade


- Remove a synthetic step
- Avoid undesirable reagents/solvents
- Avoid aldehyde isolation (poorly soluble)
KRED/IRED cascade with equimolar amine

- >400 KREDs screened in cascade direction
- Several KRED identified
  - Maximum 27% conversion in plate
- HTE for reaction optimisation
  - Equilibrium
  - Conversion increased to >80%
## KRED Evolution

### Process Performance

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Wild Type</th>
<th>Target</th>
<th>Rd2 variant</th>
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<td>Alcohol loading</td>
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<td>25 g/L</td>
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<tr>
<td>Conversion</td>
<td>&gt;80%</td>
<td>&gt;80%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Product ee</td>
<td>&gt; 99.7%</td>
<td>&gt; 99.7%</td>
<td>&gt; 99.7%</td>
</tr>
<tr>
<td>Reaction time</td>
<td>18 h</td>
<td>4-6 h</td>
<td>24 h</td>
</tr>
</tbody>
</table>

Two rounds of KRED evolution afforded 2.5X intensification and 5X reduction in enzyme loading

Successfully scaled to 5 g (48% isolated yield)
Conclusions

- A greater range of biocatalysed reactions using highly capable and broadly applicable enzymes is highly desirable
  - E.g. P450s, oxidases, halogenases, C-C bond forming (aldolases, lyases)
- Collaborations between academic and industrial groups can be highly effecting in rapidly developing a promising class of enzyme to industrial biocatalyst status
- Enzyme engineering is highly capable of improving a low level starting point to industrial applicability and is now expected to be required. However improvements in cost and timelines would be highly desirable
- More significant benefits could be realised by implementation of cascades if they could be developed without exponentially increasing resources required
Who We Are

We are the name behind the high performance ingredients and technologies in some of the biggest, most successful brands in the world: developing, making and supplying speciality chemicals that are relied on by industries and consumers everywhere.

Our Business Model

Engage
We work in close partnership with our customers around the world

Create
We design innovative ingredients that enhance everyday products

Make
We manufacture to consistently high standards across the world

Sell
We generate revenue by selling our ingredients directly to customers
Our Latest Financials

2018

Sales
£1,386.9m

Sales growth in constant currency
+3.8%

IFRS profit before tax
£317.8m

NPP sales as a % of Group sales
28.2%

Sales by region

Europe, Middle East & Africa: £572.4m
North America: £372.7m
Asia: £300.8m
Latin America: £141.0m

Sales by sector

Personal Care: £487.8m
Life Sciences: £324.5m
Performance Technologies: £456.4m
Industrial Chemicals: £118.2m

£1,386.9m
“Sustainability is fundamental to who we are and what we do. It touches every area of our Business: from the way we design our products and run our manufacturing sites, to the way we work with our suppliers and engage with our communities.”

**Steve Foots**, Group Chief Executive

Doing business sustainably means **doing business the right way** requiring a balanced approach that looks simultaneously at the Environment, Society and the Economy.

It’s embedded throughout our value chain and we are fully committed to:

- Using **renewable raw materials** and **environmentally sensitive processes**;
- producing **innovative ingredients** with **sustainable benefits**; and
- supporting **our people and the communities** in which we operate.
Increasing Demand for Sustainability

Customer drivers

All things environmental: reducing carbon footprint, water, waste, increased use of non-fossil fuel energy, greater efficiency of products in use and

Sustainable raw material supply: renewable vs petrochemical, the sustainability credentials of the renewable raw materials, palm being a current focus.

New product launches increasingly based on sustainability

66% of consumers are willing to pay more for sustainable brands

Source: Neilson report The Sustainability Imperative October 2015; Sustainable claims in PC launches Mintel GNPD
Industry trends in Sustainability

20th Century Feedstock

21st Century Feedstock

Growth in Product Sustainability Claims

Source: GNPD Mintel capturing Environmentally Friendly, Carbon Neutral 16-1-18
Making a positive impact - Unilever’s View

**Unilever** is a positive force for good.
Leave Nature better off after we do our business.

**Future will be Regenerative:**
- Clean and Nourish the Planet
- Positive Impact on Society
- Do no Harm

……..it’s all about **Sustainability**
- Materials should not depend on Virgin Fossil Fuels
- Renewable is the circular use of available carbon
- Regenerative is reducing free carbon level

Brand & Technical Roadmap

Less Harm ➔ No Harm ➔ Regenerative

Today’s Territory ➔ Future Territory
What is driving all of this?

Because consumers are no longer just interested in the EFFECT that products confer but also the wider environmental IMPACT they may have.

We see adoption of IB processes as a route to minimising environmental impact.
The ‘Drop-in’ Route

- Cost $200M+
- Delivery time 4 years
- No of products improved >100.

- Delivers 100% biobased products
- Lowers carbon footprint vs standard
- Potential to transform LCA when Ethanol from waste is available to purchase.
The ‘New Product’ Route

- Vegetable oil
- Yeast
- Carbon Source
- Fermentation & Bioconversion
- Separation & Purification
- Sophorolipid

History
- Started as a TSB project in 2011
- Built a plant in 2013
- Ready to launch in 2014
- REACH registration process identified sensitisation potential
- 4 Years to understand and resolve issue
- Plan to launch in 2020.

- Cost -£10 – 20M
- Delivery time 10 years
- No of Product - 1
The Biotechnology Research Process

- Isolation and screening against target assays
- Laboratory scale-up, isolation and process development
- Plant scale-up, IP and Regulatory
- Sales & Marketing Launch preparation
- Product Launch
Major Challenge – Time to market

Currently this process is measured in years, up to 10 years is not untypical.

……..We need to change the years into months
Further Challenges to adoption

- Regulatory approval of new molecules
  - Animal testing requirements vs Cosmetics directive ban

- GMO
  - Its requirement for sustainable IB vs consumer opinion

- The absence of a carbon tax
  - Fossil fuel energy sources still a fraction of electricity costs.
Opportunities

- Regulatory
  - Proposed EU legislation on microplastics

- GMO
  - Increasing acceptance of the term ‘Genetically Modified derived ingredient’ or GMDI for short across consumer businesses

- The prospect of a carbon tax
  - Potential to close the gap between cost of fossil derived carbon based processes and biogenic carbon based B ones

- Customer awareness / Action
  - Consumers are choosing products on their environmental credentials
What does it take to make it work?

- Feedstocks
- Infrastructure
- Knowledge
- Support
Because like the game of Cluedo, you can't solve the challenge with only the cards you are holding yourself.

Why am I here?
Overview of current academic work in this sector that is addressing some of the challenges outlined in the report.

Professor Ian Graham
Key drivers for the chemistry industry to use IB

**Higher quality products**
- high levels of stereoselectivity
- low levels of impurities

**Reducing manufacturing costs**
- lowering energy costs
- reducing the number of stages required
- reduced downstream purification costs
- reducing/avoiding co-factors and/or heavy metals catalysts

**Sustainability**
- lowering energy consumption
- recycling co-factors and recover precious metals
- better utilising biobased/waste feedstocks
- avoid need for harvesting high environmental impact crops for natural products

Based on consultation with industry and research community. Report will be available on the BBSRC website: https://bbsrc.ukri.org/funding/filter/2020-ib-higher-value-chemicals/
## Research Challenges highlighted in report: Bioscience

### Increasing yields and concentrations
- Genetic engineering tools for optimal and robust enzyme/microbe activity
- Identification of strains with increased commercial potential
- Diverse host/enzyme systems suited to industry process conditions
- Understanding of the bottlenecks
- Cell stability
- Predictable metalation tools and engineering catalytic metal-centres

### Integrated high-throughput platforms + processes for discovery, analysis, optimisation of bioprocesses
- Screening of functionalities of individual microbial isolates or enzymes

### Plant cell culture systems as alternative production platforms
- Further understanding plant metabolic pathways and exploitation of plant genome sequence information

### Scale out for screening novel functionality

### Dealing with toxicity and transport of products in fermentation
**Research Challenges highlighted in report: Physical Sciences**

<table>
<thead>
<tr>
<th>Development of process engineering and process chemistry for improving biological processes</th>
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<tbody>
<tr>
<td>combining both bioprocessing and chemical processing</td>
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<tr>
<td>immobilisation technologies to enable synthetic biocatalytic cascades</td>
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<td>improved bioreactor designs and developing new reactor configurations</td>
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<tr>
<th>Advancing downstream processing and separation science</th>
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<tr>
<td>working with dilute systems and product recovery require alternative downstream technologies and approaches e.g. new membrane technologies</td>
</tr>
<tr>
<td>Improved product secretion and product extraction methods</td>
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</tbody>
</table>

| Specialised processes e.g. algae, or single use fermentation bio-manufacturing systems |

| Tools and techniques to understand and exploit complex feedstocks |
Proteins for therapeutic use and commodity chemicals with multiple different applications for each chemical are out of scope.
BBSRC Networks in Industrial Biotechnology and Bioenergy Phase I 2014 - 2018

BBSRC NIBB Phase I Summary

The 13 Phase I BBSRC NIBB were:

1. **ADNet**: Anaerobic Digestion Network (Charles Banks, University of Southampton)
2. **Biocatnet**: Network in Biocatalyst Discovery, Development and Scale-Up. (Nicholas Turner, The University of Manchester)
3. **BioProNET**: Bioprocessing Network. (Christopher Smales, University of Kent)
4. **C1NET**: Chemicals from C1 Gas. (Nigel Minton, The University of Nottingham)
5. **CBMNNet**: Crossing biological membranes. (Jeff Green, The University of Sheffield)
6. **FoodWasteNet**: Food Processing Waste and By-Products Utilisation Network. (Dimitris Charalampopoulos, University of Reading)
7. **HVCfP**: High Value Chemicals from Plants Network. (Ian Graham, The University of York)
8. **IBCarb**: Glycoscience Tools for Biotechnology and Bioenergy. (Sabine Flitsch, The University of Manchester)
9. **LBNNet**: Lignocellulosic Biorefinery Network. (Simon McQueen Mason, The University of York)
10. **Metals in Biology**: The elements of Biotechnology and Bioenergy. (Nigel Robinson, Durham University)
11. **NPRONET**: Natural Products Discovery and Bioengineering Network. (Jason Micklefield, The University of Manchester)
12. **P2P**: A Network of Integrated Technologies: Plants to Products. (David Leak, The University of Bath)
13. **PHYCONET**: unlocking the IB potential of microalgae. (Saul Purton, University College London)
Professor Ian Graham
HVCfP Director

Professor Anne Osbourn
HVCfP Co-Director

Dr Caroline Calvert
Dr Wendy Lawley
HVCfP Network Managers

HVCfP scientific scope

FEEDSTOCK
- molecular breeding
- metabolic engineering
- bioactives discovery

PROCESSING
- extraction
- bio/chemical transformation
- production platforms

HIGH VALUE CHEMICALS
- production evaluation
- commercial translation

SOCIO-ECONOMIC / LIFE CYCLE ANALYSES

- pharmaceuticals
- personal & healthcare
- oils & fats
- nutraceuticals
- flavour & fragrance
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 - 2017

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
BBSRC Networks in Industrial Biotechnology and Bioenergy Phase II - 2019 - 2024

BBSRC, with the support of EPSRC, have committed £11 million to fund 6 unique collaborative Networks in Industrial Biotechnology and Bioenergy.

The 6 Networks are:

<table>
<thead>
<tr>
<th>Network</th>
<th>Principal investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algae-UK: Exploiting the algal treasure trove</td>
<td>Professor Saul Purton University College London</td>
</tr>
<tr>
<td>Biomass Biorefinery Network (BBNet)</td>
<td>Professor Simon McQueen Mason, University of York</td>
</tr>
<tr>
<td>Carbon Recycling: Converting waste derived GHG into chemicals, fuels and animal feed (CCNet)</td>
<td>Professor Nigel Minton, University of Nottingham</td>
</tr>
<tr>
<td>Elements of Bioremediation, Biomanufacturing &amp; Bioenergy (E3B) Metals in Biology</td>
<td>Professor Nigel Robinson, Durham University</td>
</tr>
<tr>
<td>Environmental Biotechnology Network (EBNet)</td>
<td>Professor Sonia Heaven, University of Southampton</td>
</tr>
<tr>
<td>High Value Biorenewables (HVB) Network</td>
<td>Professor Ian Graham, University of York</td>
</tr>
</tbody>
</table>

The Networks will run from 2019 to 2024, will provide flexible funding for Proof of Concept projects, and are open to new members throughout their lifetime.
BioPilotsUK - What is it?

- An alliance of four established UK open-access biorefining centres which recognise the importance of industrial collaboration to develop UK bio-based value chains.

- We will de-risk the commercialisation of bio-based products and processes by trialling new technologies to ensure our partners are investing in the right technologies for their business.

- By working as an alliance, we can provide easy access to the capabilities of all four centres to speed up the process of developing new biobased products.

BioPilotsUK Members
BioPilots UK- Capabilities

- Novel distillation
- Analytical chromatography
- 10m³ fermentation
- Cross-flow membrane filtration
- Microwave reactors
- Plant growth studies
- Fast track plant breeding
- Supercritical CO₂ extraction
- Mechanical pre-treatments
- Photo bioreactors
- Anaerobic digestion
- Freeze drying
- Dead end filtration
- C1 hydrogen feedstocks fermentation
- Microbiology
- Spinning cone distillation
- Strain development
- Genetic analysis
- Steam explosion
- Milling, shredding and cutting
- Enzymatic transformations
- Mass spectrometry
- Liquid-liquid extraction
- Pyrolysis
- Multi-scale fermentation
- Applied analysis
- Chemical transformations
- Multiscale centrifugation
National Synthetic Biology Research Centres

The SYNBOCHEM Centre is part of a nationwide network of UK Synthetic Biology Research Centres of research excellence, with each centre bringing a distinctive and complementary field of expertise. These Centres are complemented by DNA foundries and the SynBICITE Innovation and Knowledge Centre (IKC) dedicated to promoting the adoption and use of SynBio by industry.

http://synbiochem.co.uk/national-synthetic-biology-research-centres/
Graham lab research exemplars:

HIGH VALUE CHEMICALS FROM PLANTS

Industry partners and support:

- **Alkaloids** - opium poppy
  - GSK/ Sun Pharma

- **Sesquiterpenes** – *Artemisia annua*
  - Bill & Melinda Gates Foundation, East-West Seed

- **Diterpenoids** – Euphorbiaceae
  - IB Catalyst: GSK, Croda and Unilever
Bioactive casbene-derived diterpenoids from the Euphorbiaceae

- Jatropha curcas (jatroholan A)
- Euphorbia fischeriana (prostratin, anti-HIV, preclinical)
- Euphorbia lathyris (Euphorbia factor L1, MDR-reversal, preclinical)
- Euphorbia resinifera (resiniferatoxin, analgesic, phase 2 trials)
- Euphorbia peplus (ingenol mebutate, licensed for actinic keratosis)
Industrial Biotechnology Catalyst (BBSRC, Innovate UK)
Developing platforms for the production of diterpenoids
York (Ian Graham) with Cambridge (Alison Smith),
Reading (Geoff Brown), Unilever, GSK and Croda
Some production platforms need biology and chemistry.
Uptake and efflux limit many bioprocesses and can be engineered to increase yields of high value chemicals.

Very few, if any, small molecules, pass through biological membranes rapidly in the absence of protein mediated transport.

Through basic discovery of new efflux proteins and their direct application, efflux processes have been engineered for increased yield with many types of speciality, performance, & fine chemicals to reduce manufacturing costs through increased yields & reduced downstream processing costs.

- Amino acids and peptides
- Antibiotics
- Oligo and polysaccharides
- Organic acids
- Micronutrients – vitamins
- Natural flavour and fragrances

Still much untapped potential in transport engineering.
Adding functionality - glycosylation can influence the solubility, bioavailability, stability and efficacy of many small molecule natural products.

Functional and informatics analysis enables glycosyltransferase activity prediction

Min Yang\(^1\)\(^\ast\), Charlie Fehl\(^1\), Karen V. Lees\(^2\), Eng-Kiat Lim\(^3\), Wendy A. Offen\(^4\), Gideon J. Davies\(^4\), Dianna J. Bowles\(^3\), Matthew G. Davidson\(^5\), Stephen J. Roberts\(^2\) and Benjamin G. Davis\(^1\)\(^\ast\)

The elucidation and prediction of how changes in a protein result in altered activities and selectivities remain a major challenge in chemistry. Two hurdles have prevented accurate family-wide models: obtaining (i) diverse datasets and (ii) suitable parameter frameworks that encapsulate activities in large sets. Here, we show that a relatively small but broad activity dataset is sufficient to train algorithms for functional prediction over the entire glycosyltransferase superfamily 1 (GT1) of the plant Arabidopsis thaliana. Whereas sequence analysis alone failed for GT1 substrate utilization patterns, our chemical-bioinformatic model, GT-Predict, succeeded by coupling physicochemical features with isozyme-recognition patterns over the family. GT-Predict identified GT1 biocatalysts for novel substrates and enabled functional annotation of uncharacterized GT1s. Finally, analyses of GT-Predict decision pathways revealed structural modulators of substrate recognition, thus providing information on mechanisms. This multifaceted approach to enzyme prediction may guide the streamlined utilization (and design) of biocatalysts and the discovery of other family-wide protein functions.
Fig. 6 | GT-Predict extends functional annotation to other species, kingdoms, and GT families. a, Summary of GT-Predict prediction results for six selected individual enzymes from differing species, including accuracy and MCCs. Further details and analysis can be found in the Supplementary Note.
In conclusion:

The last decade has seen significant growth in academic research that underpins the production of high value chemicals.

The UK has established strengths in industrial biotechnology and synthetic biology.

Productive partnerships with industry are needed to identify and address the major challenges to commercial production of high value chemicals.
Lessons learned from collaboration & future directions

Sarah M. Barry
HVC Town Hall - BBSRC
18th Nov 2019
Why Biocatalysis?

**Green chemistry**
- Fewer heavy metals
- Less organic solvent
- Low Temp/pressure
- Atom economy
- Sustainable feedstocks

**Difficult chemistry**
- Regioselectivity
- Stereoselectivity
- C-H bond activation
- Chiral building blocks
- Chemical space

**Problems**
- Selectivity/substrate tolerance
- Solvent tolerance
- Stability
- Cofactor cost
- Scale/economy

**Coupling with chemocatalysis**

**Adoption by Org Chemists**

**New enzymes & Understanding**

**Developing Enzyme cascades**

**High-throughput methodology**
Natural product
Biosynthesis: New enzymes, New Chemistry
Clinically important microbial natural products

bleomycin A₂
*Streptomyces verticillus*

Aflatoxin B₁
*Aspergillus flavus*

gliotoxin
*Aspergillus fumigatus*

erythromycin A
*Saccharopolyspora erythraea*

vancomycin
*Amycolatopsis orientalis*

Mycolactone
*Mycobacterium ulcerans*

cyclosporin A
*Tolypocladium inflatum*

rapamycin
*Streptomyces hygroscopicus*
Clinically important microbial natural products

bleomycin A$_2$
*Streptomyces verticillus*

Aflatoxin B$_1$
*Aspergillus flavus*

gliotoxin
*Aspergillus fumigatus*

erythromycin A
*Saccharopolyspora erythraea*

Mylolactone
*Mycobacterium ulcerans*

rapamycin
*Streptomyces hygroscopicus*

vancomycin
*Amycolatopsis orientalis*
Genes to molecules and *vice versa*

Genome sequencing

Microbiology

Bioinformatics

Natural product isolation/characterisation/chemical synthesis

Pathway elucidation: enzymology and genetics

Projects: enzyme discovery from natural product biosynthesis
Cytochrome P450: Versatile Heme dependent enzymes

- Regio and stereoselective C-H bond functionalisation,
- Can be engineered
- NAD(P)H recycling systems and redox self-sufficient enzymes developed

Yin, ChemBioChem 2014, 15, 2443 – 2449
Biocatalysis/Chemocatalysis
Extending collaboration
Castagnolo Lab – Chemocatalysis meets biocatalysis

Photo-biocatalytic cascade with KRED

Angew. Chem., Int. Ed. 2018, 57, 5803-5807
Collaboration & Capacity at KCL

Enzymology/Biocatalysis/sustainability
Enzymes can catalyse many different industrial reactions. Industrial products/substrates typically require solvents other than water. However, enzymes are often **insoluble** and **inactive** in organic solvents.


(1) Cationization of protein surface.

(2) Nanoconjugate formation via electrostatic complexation of anionic surfactants

(3) Lyophilization and annealing to form solvent-free liquid protein.

(4) Solubilization in ionic liquids.

**Biocatalysis in Ionic Liquids**

- Cellulose: Enzyme activity significantly enhanced in ionic liquids

*Nat. Chem.* 2018
Protein chemistry to decipher biological signalling processes

Protein engineering & evolution to generate new regulation paradigms

Karola Gerecht

PIPs with Fluidic analytics
Quantify DNA binding using microfluidic diffusive sizing

iCASE Studentship
Diffusive sizing to monitor large-scale conformational changes of ‘designer’ p53
Building capacity @ KCL Chemistry

Leigh Aldous
Sustainable energy production

Andre Cobb
Enzyme inspired catalysis

Mark Wallace
Bottom up artificial cells

Ismael Diez Perez
Single molecule methods to understand enzyme catalysis

Sustainability & Catalysis

Edina Rosta
Computational methods to understand enzyme catalysis/mechanism

Maria Sanz
Structure elucidation to aid biodegradable fragrance development
Lessons...

- Complementary skills/techniques
- Industry – high throughput engineering methodology/analysis, screens, process development
- Academia – initial discovery, mechanistic investigation, method development, enabling technologies
- Short term projects / student placements: useful for setting up collaboration
- iCASE/ long term grants/follow on funding needed to cement collaboration and develop application
- Researcher training: building capacity
- Multidisciplinarity is essential to tackle these problems

Multidisciplinarity is essential to tackle these problems
Industrial Biotechnology for Improving Production of Higher Value Chemicals

How to Apply for Funding

Dr Hayley Moulding
Innovation and Skills Manager
Agenda

1 Scientific Scope
2 Project Scope
3 Timeline and Monitoring
4 Conditions and Requirements
5 Application and Assessment Process
6 Contacts
Scientific Scope
Scientific scope

• Research projects must address challenges in manufacturing a chemical using a biological process i.e. using microorganisms or enzymes
  • **The economic viability of the bioprocess should be an integral part of the proposal**

• The bioprocess can be used in the conversion of either biomass feedstocks or precursor chemicals to chemicals or biological products e.g. peptides and enzymes

• The consultation identified three ways in which biological processes used in manufacturing of HVCs can be beneficial:

  1. Manufacturing of higher quality products
  2. Reducing manufacturing costs
  3. Sustainability
Scientific Scope: Biological focused research challenges

Increasing yields and concentration of biocatalytic and microbial production of chemicals in order to increase economic viability through:

- More efficient tools including synthetic biology to engineer microbes for rapid assembly and reconfiguration of genetic structures for optimal and robust enzyme/microbe activity
- Improved understanding of the bottlenecks to increases in yield of a given product or process across a range of biocatalytic, microbial and multicellular platforms
- Improved cell stability in a productive homeostasis to allow longer lifetimes
- Development of new tools for optimizing production strains
- Improving/creating new biocatalytic processes by applying expertise in metallo-enzymes optimising and developing predictable metalation tools and engineering catalytic metal-centres
- Ensuring tools for engineering microbial systems include diverse host/enzyme systems suited to a range of industry process conditions, with well-defined comparative performance data.
Scientific Scope: Biological focused research challenges

Improved integrated high-throughput platforms and processes for discovery, analysis and optimisation of bioprocesses for higher value chemical manufacture by:

• Screening of functionalities of individual microbial isolates or enzymes will lead to the identification of strains with increased commercial potential:
  • This will reduce the time to develop new bioprocesses

• Identification of novel chemistry could speed up drug discovery and novel functionalities for the development of new materials.

Development of plant cell culture systems as an alternative production platforms for high value chemicals by:

• Further understanding plant metabolic pathways
• Exploitation of plant genome sequence information as higher plant species are sequenced e.g. Earth BioGenome Project.
Scientific Scope: Biological focused research challenges

Scale out of biochemical processes is a key challenge in the new product discovery to produce testable amounts of high number of potential products or enzyme candidates.

• Low volumes of high numbers of molecules are required for screening novel functionality.
• Scale out of fermentation systems to screen genome constructs, enzymes and microbes for industrial robustness and feasibility.
  • This was highlighted as technology development challenge and was gap in open-access facilities for SMEs.

Greater understanding of mechanisms for dealing with toxicity and transport of products in fermentation processes.
Scientific Scope: Research at the interface with Engineering

- A key part of using industrial biotechnology in manufacturing of higher value chemicals is the integration with process engineering and reducing the costs and time of process development.

- There were several research challenges that were highlighted by the respondents addressed in the following slides.

PLEASE NOTE

- The funding is provided from UKRI BBSRC.
- The significant majority of the proposed project must lie within BBSRC remit.
- The contribution of physical sciences including engineering should not be the main focus of the proposal.
Scientific Scope: Research at the interface with Engineering

Further development of process engineering and process chemistry for improving biological processes

- Improved understanding of how unit operations already employed in conventional chemical production can be better used in the biotransformation processes is necessary
  - Could transformation move from stirred tanks to flow/continuous reactors?
- Improved bioreactor designs and developing new reactor configurations and modular manufacturing processes
- Application of biochemical engineering for dealing with different substrates e.g. viscous systems, solids, dilute solutions
- Orchestration of synthetic biocatalytic cascades through immobilisation technologies
- Improving/developing inline/real-time reaction monitoring technologies appropriate for biological processes
- Detailed understanding of the operating constraints of bioprocessing and the product requirements for a feasible overall process
Scientific Scope: Research at the interface with Engineering

Advancing downstream processing and separation science and addressing the challenges of product separation for biological processes which are different to traditional chemical synthesis

- Bioprocessing is more effective at higher dilutions, chemical processes can be more concentrated leading to challenges working with dilute systems and product recovery
  - There is a need to develop/improve alternative downstream technologies and approaches including new membrane technologies, configurations and minimising costs of materials and operations;
- Purification techniques such as ion exchange columns and other resin based techniques can be difficult at larger scale
  - There is an inherent requirement of a minimal scale which has associated resource and cost implications.
  - There is a need to address the challenges of product purification and taking a purification process from lab to plant scale.
  - Improved product secretion and product extraction methods for fermentations could help make bioprocesses to be more economically viable.
Scientific Scope: Research at the interface with Engineering

Development of more specialised processes

- Applied research in cultivation and processing of algae
- Single use fermentation bio-manufacturing systems for higher value or GMP products.

Development of tools and techniques to understand and exploit complex feedstocks including low value food by-products and polysaccharide-based feedstocks:

- Extraction, purification, analysis and repurposing
- Addressing diverse/heterogenous compositions
- Overcoming technological difficulties
- Understanding regulatory issues of different feedstocks.
Examples of target products

- surfactants
- polysaccharides
- micronutrients
- natural flavour and fragrances
- silks
- next generation adhesives
- protein structures
- chelates
- butanol acetone for esters and solvents
- active pharmaceutical ingredients (APIs)
- pharmaceutical intermediates
- antibiotics

OUT OF SCOPE
- Macromolecular proteins for therapeutic use
- Commodity chemicals made in bulk with multiple different applications
- Low market value chemicals
Project Scope
Project scope

• Projects funded through this call should aim to make significant steps towards translation of research into industrial processes

• Short projects will enable translation of research into industrial processes by de-risking of IB processes in the chemicals sector
  
  • Grants up to £250K
  
  • 12 to 24 months in length
  
  • Collaborative - collaborations with industry are compulsory - help direct research toward industrially relevant challenges
Collaborative Industry Partners

It is a compulsory condition of the call that all applications include a collaborating industry partner.

Industry partners must also provide meaningful in-kind and/or cash contributions to support their active involvement.

Contributions can include but are not limited to:
• intellectual input to the development of a project proposal
• salaries of the personnel working directly on the project
• materials consumed in the course of the project
• access to equipment
• provision of data, software or materials.
Conditions and Requirements
Eligibility

• Fulfil the standard BBSRC eligibility criteria outlined in the BBSRC Grants Guide

• Include a collaborating industry partner to help direct research toward industrially relevant challenges and support the translation of bioprocesses into an industrial environment.
  • A signed copy of the collaboration agreement should be submitted to BBSRC within three months of the proposed start time of the project.

• Funding cannot be directly provided to an industrial company; funding allocation to eligible research organisations.
## Documentation Required at Full Stage

<table>
<thead>
<tr>
<th>Attachment</th>
<th>Maximum page length</th>
<th>Attachment type on Je-S submission</th>
<th>Notes</th>
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<td>Case for Support</td>
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<td>Collaborating Industry Partner letter of support</td>
<td>2 sides of A4 per partner</td>
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<tr>
<td>Letters of support</td>
<td>No limit</td>
<td>Letter of Support</td>
<td>Only directly relevant Letters of Support should be submitted (i.e. other potential users that may not be directly involved in the project itself but provide additional evidence of support for the proposed work.)</td>
</tr>
</tbody>
</table>
Letters of Support (LoS)

• LoS should detail:
  1. Objectives of the collaboration
  2. Key tasks, contribution and responsibilities of the different partners
  3. Agreed routes for dissemination of results and management of intellectual assets and/or intellectual property
  4. Any direct or indirect interest from the academic partner in the commercialisation of the research

• LoS need to confirm that if the grant is successful, a collaboration agreement will be put in place

• A signed LoS is required from each partner (University TTO and Industry partner(s))
Letters of Support (LoS)

1. Technology Transfer Office (TTO)
   a. A statement of support must be included from the TTO or equivalent detailing why the proposed work is needed.
   b. They should include details of any matched funding they will provide to support the activity and any additional support that might add value to the work.
   c. The Panel will be looking for a strong statement of commitment from the TTO in the host institution taking the project forward.
   d. The TTO support letter must also detail any relationships with academic, industrial or other partners relevant to the project.

2. Project Partner
   a. Each project partner named in the application must provide a LoS
   b. It must confirm their support for the proposed project, any financial or in-kind contributions to be made and outline their role in the project.
Collaboration Agreement

• The LoS from collaborative industrial partners, as well as the TTO of the funded institution will form the basis of the collaboration agreement.

• The collaboration agreement should be in place from the start of the funding and should be agreed amongst partners.

• This is vital for the distribution of the intellectual assets and property
  • With the IP and IA, the conditions that the BBSRC adhere to are outlined in the BBSRC Grants Guide
Timeline and Monitoring
Call Timeline

5 November
Launch date for Call for Proposals

19 November
Town Hall Meeting

16 January, 2020
Closing date for Call for Proposals

March 2020
Assessment of Call Proposals

By May 2020
Research grants awarded

~ October 2020
Projects start

By October 2022
Project Close Evaluation Forms Submitted
Project Monitoring Evaluation

- Grant holders should invite a BBSRC representative to attend a mid-term project management meeting if projects are between 18-24 months.

- All grant holders, regardless of length of project, are required to invite a BBSRC representative to their final project management meeting.

- At the end of the grant, grant holders are required to submit a project completion form outlining the project achievements and outcomes relevant to industry.
  - The project completion form will be provided to grant holders at the start of the project.
Application and Assessment Process
Application Process

Proposals invited from 5 November

One stage of application

Closing on 16 January 2020

Panel meeting with no external peer review

Guidance on completing the full proposal submission can be found on the Je-S Website. For any JeS related queries, please refer to the Je-S Handbook, or contact the Je-S helpdesk:

Email: JeSHelp@je-s.ukri.org
JeS Application Process

BBRSC Funding call in Je-S, select the ‘Documents’ section on the right-hand side and then under the ‘Functions’ section select ‘New Document’ and follow the options from the drop-down menus:

Applicants should select the following from the Je-S menus:

1. Log in the Joint Electronic System (Je-S)
2. Select Council: BBSRC
3. Select Document Type: Standard Proposal
4. Select Scheme: Standard
5. Select Call: 20IBHIGHERVVALUECHEMICALS
6. Select ‘Create Document’

Applications must be submitted by UK Research Organisations that are eligible to receive funding from BBSRC. Information about eligible organisations is available on the UKRI website.
Assessment Criteria

- Scientific excellence
- **Industrial and stakeholder relevance**
- Relevance to BBSRC strategy
- Economic and Social impact
- Timeliness and promise
- Value for money
- Staff training potential of the project (where resources are requested for postdoctoral or other research staff)
Other Guidance

• Read the documents and formal eligibility requirements carefully
• Address all aspects of the assessment criteria and fully address the call scope
• Ensure you communicate your proposal clearly, for both subject specialists and more general scientific audience
• Collaborative teams need to be able to demonstrate full synergy and ability to work together effectively
• Collaboration agreements need to be in place at time of award

If in doubt, please contact us for advice:
ib.highervaluechemicals@bbsrc.ukri.org
Discussion: Demand Management

Total Sum: £2M
Expected grant size: £250K Max
=> Approximately 8 proposals are able to be funded with existing resources

1. Managing Demand
   • Should we anticipate a large demand from the community?
   • How might we manage demand?
   • Is there a role for the NIBB II in providing informal advice to manage demand?

2. Encouraging/ developing collaborations in support of the call
   • > 600 small grants have been supported through phase I BBSRC NIBB – many of which are relevant to this call
   • What role could phase II BBSRC NIBB play in encouraging collaborations?
Feedback and questions to:

Higher Value Chemicals Call Mailbox:

ib.highervaluechemicals@bbsrc.ukri.org
Call status: Open for applications
Application deadline: 16 January 2020, 16:00 BST
Webpage URL: https://bbsrc.ukri.org/funding/filter/2020-ib-higher-value-chemicals/

For all questions regarding the IB HVC Call, contact:
ib.highervaluechemicals@bbsrc.ukri.org
Thank you