



BRIC • BIOPROCESSING RESEARCH INDUSTRY CLUB

Workshop to promote the 3rd Call for Research Proposals

5-6 December 2007
Alexandra House, Wroughton

Workshop Report

BBSRC Executive
December 2007



MedImmune



A workshop was held at Alexandra House, Wroughton nr Swindon on 5-6 December 2007, to promote the 3rd Call for research proposals to BRIC. The aims of the workshop were to discuss the research challenges highlighted in the 3rd call and to explore how these might be addressed to ensure relevance to industry.

Presentations were given by Professor John Birch, Lonza Biologics and Chair of the BRIC Steering Group on the background of BRIC and the aims of the workshop; Dr Chris Jones, NIBSC on Analytical Methods; Dr John Woodgate, Pall Life Sciences on New Bioprocess Technologies: Requirement from a technology providers perspective and Dr Malcolm Rhodes, bioProcessUK on an Overview of the BRIC Cell Therapy Workshop. Professor Andy Lyddiatt, BRIC Programme Manager also gave an overview of the priority areas of the 3rd BRIC call. Further discussions and networking continued over dinner and into the evening.

On Day 2 the delegates participated in a collaboration exercise “the Collaboration Illuminator” which was designed to illustrate potential collaboration opportunities amongst delegates. Delegates were divided into groups and mapped their research areas exploring links to other group members. From the expertise maps the group then designed a project (real or hypothetical) that would fit the remit of the 3rd BRIC call. Industrial representatives circulated amongst the groups to provide advice and feedback on industrial relevance of the projects. The groups then reported back on their outputs from the exercise and received feedback from industrial representatives and other delegates.

During the afternoon of Day 2 the delegates were able to meet with the BRIC Steering Group and industrial representatives in surgery sessions which provided an opportunity to pitch an idea on a project proposal and receive feedback in a confidential arena. Brokering meetings were also arranged between delegates who had requested meetings prior to the event and with individuals with whom they might wish to collaborate on future projects.

The full workshop programme, the presentation slides and workshop booklet containing information on the workshop events and delegate list can be found below. Please contact Andy Lyddiatt (andy@lyddallan.co.uk) or Malcolm Rhodes (mrhodes@bioindustry.org) if you wish to discuss your outline application before submission.

Links:

[Full Programme](#)

Presentations:

- [John Birch, Lonza & Chair of BRIC Steering Group – Introduction and aims](#)
- [Chris Jones, NIBSC – Analytical Methods](#)
- [John Woodgate, Pall Life Sciences - New Bioprocess Technologies: Requirement from a technology providers perspective](#)
- [Malcolm Rhodes, bioProcessUK - Overview of the BRIC Cell Therapy Workshop](#)
- [Andy Lyddiatt , BRIC Programme Manager - Overview of the priority areas of the 3rd BRIC call](#)

[Workshop Booklet](#)



WORKSHOP PROGRAMME

Wednesday 5th December

- 4.00pm Arrival and Registration
- 4.30pm **Welcome & Introduction – John Birch, Lonza & Chair of BRIC Steering Group**
- 4.45pm Presentations from Industry
- Dr Chris Jones, NIBSC ~ *Analytical Methods*
Dr John Woodgate, Pall Life Sciences ~ *New Bioprocessing technologies: Requirements from a technology providers perspective*
Dr Malcolm Rhodes, bioProcessUK ~ *Summary of the BRIC Stem Cell Meeting April '07*
- 5.30pm 3rd Call Priority Areas Overview – Andy Lyddiatt, BRIC Programme Manager
- 6.00pm Questions and general discussion on priority areas
- 6.30pm Drinks – Bar (Ground Floor)**
- 7.15pm Dinner - Private Dining in Alexandra suite**

Thursday 6th December

- 9.00am **Introduction & Aims of the day – Andy Lyddiatt, BRIC Programme Manager**

Collaboration Exercise

- 9.15am Instructions and demonstration – Alexandra Brooks, BBSRC
- 9.30am Collaboration Exercise Part 1 – finding links and potential collaborations
- 10.00am Collaboration Exercise Part 2 – development of possible project ideas

11.00am Coffee Break

Collaboration Exercise

- 11.20am Collaboration Exercise Part 3 – reporting back of groups & feedback from industry and the Steering Group

12.45pm Lunch & Networking round posters

- 1.45pm **Surgery Session with Steering Group and Industry Club Members**
Calder and Campbell Syndicate rooms (first floor)

This session will provide a forum for project ideas to be put to the Steering Group and Club members and to get advice and feedback before submitting the application. These meetings will last for 15 minutes and will be held in strict confidence. The meetings will be based on appointments made prior to the meeting. During this session there will also be the opportunity for one-to-one meetings with other delegates who you may wish to meet.

- 3.30pm **Close of Meeting**



BRIC • BIOPROCESSING RESEARCH INDUSTRY CLUB

Workshop to discuss 3rd Call for proposals

5-6 December 2007



Prof John Birch

Chief Scientific Officer, Lonza

Chair of BRIC Steering Group



Background to BRIC

- 2003 report from Bioscience Innovation and Growth Team (BIGT) recommended increased investment in bioprocessing research.
- Working Group which identified key areas and important scientific challenges for further bioprocessing research activity.
- In 2005 Bioprocessing Research Industry Club (BRIC) was launched supported by BBSRC, EPSRC and industry



Aims of BRIC

- Strengthen and develop the research community in bioprocessing and improve academic-industry links
 - support innovative bioprocessing-related research projects
- BRIC will support industrially-relevant research projects from a joint fund in excess of £14M
 - £1M of which comes from industry
- The BRIC will operate for 5 years from 2006 to 2011, supporting research proposals through 3 rounds of funding and mechanisms to disseminate research to club members



BRIC Steering Group

The Steering Group is made up of 6 academic members and 6 industry members.

- **Professor John Birch, Lonza Biologics, Chair**
- **Industry-nominated Members:**
 - Dr Mark Carver, Avecia
 - Dr Brendan Fish, Cambridge Antibody Technology
 - Dr David Glover, UCB Celltech
 - Dr Peter Levison, Pall Life Sciences
 - Dr Carol Marshall, GlaxoSmithKline
 - Dr Simon Roe, Antisoma
- **Research Council-nominated Members:**
 - Professor Zhanfeng Cui, University of Oxford
 - Professor Kevin Brindle, University of Cambridge
 - Professor Elaine Martin, University of Newcastle
 - Dr Mark Smales, University of Kent
 - Professor Nigel Titchener-Hooker, University College London
 - Professor Phillip Wright, University of Sheffield

The role of the BRIC Steering Group is primarily to:

- to establish the scope of research to be funded in the BRIC calls
- and
- to review of applications submitted to the BRIC.



Plans for Research

- BRIC will Support industrially relevant research projects in bioprocessing
- 3 rounds of funding
 - First Call Launched October 2005
 - Announced June 2006
 - Second Call Launched October 2006
 - Announced July 2007
 - Third Call Launched October 2007



Previous Calls

First Call

Two research themes

- Bioscience underpinning bioprocessing Improved
- Tools for Bioprocessing

Strong focus on biology underlying mammalian cell culture and expression systems

Second Call

Two Research themes- identified as a result of areas funded in first call

- Tools to accelerate bioprocess development including downstream bioprocessing and formulation
- Understanding, controlling and manipulation metabolism in microbial fermentation

16 projects funded totalling £8.5M



BRIC Dissemination Events

Applicants receiving BRIC funding will benefit from participating in Club activities, increasing their interaction with industry through workshops and Club dissemination events.

BRIC provides a mechanism for dissemination of research to Club Members

- Six-monthly dissemination meetings for grant holders and club members
- Club members receive advanced notification of commercial opportunities arising from grants funded through BRIC



Industry Club Members



Academic Members



Aims of Workshop

- to promote the third call for proposals for BRIC
- to highlight the research challenges and to discuss how to address these in order to meet the needs of industry.
- to highlight the need for interdisciplinary approaches to projects
- to provide networking to identify potential collaborations for BRIC proposals and future work in the area of bioprocessing.
- to receive feedback from the Steering Group and BRIC Industry Club Members on potential project ideas in surgery sessions.

Outcome:

high quality research proposals that underpin the needs of the UK bioprocessing industry funded through the third call to BRIC.

Surgery Sessions

- The surgery sessions provide an opportunity to pitch an idea on a project proposal to the Steering Group and Industry Club members and receive feedback in a confidential arena.
- All proceedings of these meetings will remain in confidence.
- If you have not previously booked a surgery session and would like one please contact **Alexandra Brooks**, BBSRC to see if one can be made available.

Confidentiality Statement

- The workshop is a closed meeting and the proceedings should be treated as confidential
- You should not disclose any information or know-how that they may wish to subsequently patent
- A workshop report will be published, however this will focus solely on highlighting the challenges that should be addressed through proposals.
- The outcomes of the collaboration exercise will remain confidential and will not be published in the workshop report.
- The venue has plenty of space available for any confidential discussions delegates may wish to have.

Surgery Sessions are in confidence

Timetable

Wednesday 5th December Alexandra Suite – Ground Floor

4.30pm Welcome & Introduction – John Birch, Lonza & Chair of BRIC Steering Group
 4.45pm Presentations from Industry
 5.30pm 3rd Call Priority Areas Overview – Andy Lyddiatt, BRIC Programme Manager
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6.30pm Drinks – Bar (Ground Floor)
 7.30pm Dinner - Private Dining in Alexandra suite

Thursday 6th December Alexandra Suite – Ground Floor

9.00am Introduction & Aims of the day – Andy Lyddiatt, BRIC Programme Manager

9.15am Collaboration Exercise
 Part 1 – finding links (30 mins) and Part 2 – project development (60 mins)

11.00am Coffee Break

11.20am Collaboration Exercise Part 3 – reporting back

12.45pm Lunch & Networking round posters

1.45pm Surgery Session - Calder and Campbell Syndicate rooms (first floor)

3.30pm Close of Meeting



BRIC Contacts

Staff available to answer any questions you have on BRIC:

- Alexandra Brooks – BBSRC
- Andy Lyddiatt – BRIC Programme Manager
- Malcolm Rhodes – BioProcessUK

- Andy Cureton – BBSRC
- Karen Lewis – BBSRC
- Kedar Pandya - EPSRC

Analytical Methods
Horses for courses, and know the fences

Chris Jones
Laboratory for Molecular Structure,
NIBSC



Biopharmaceutical manufacturers do not sell
protein: they sell biological activity

Biological activity	100 units (\pm 10%)
Protein	1.004567835 mg

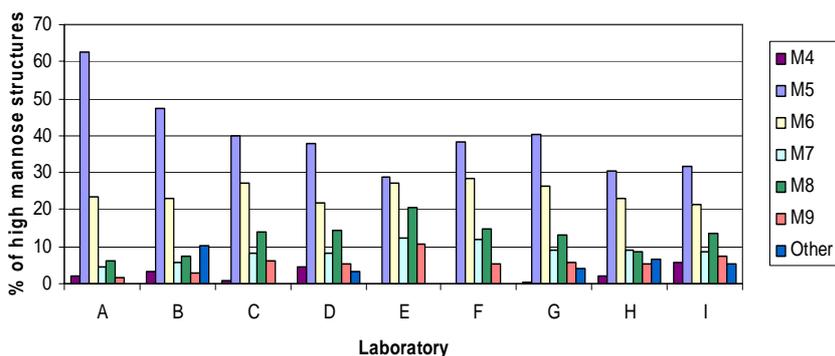
The functional assay is almost always less
precise, and much more important



Round robin studies

- NIBSC make reference standards for characterisation and potency measurement of biopharmaceuticals
 - These are characterised in round robin studies.
 - Experience shows that even very experienced labs with well validated methodologies can produce very different results
- When available, participate in such studies, and don't be surprised by the results. This is a necessary part of understanding the methodology
- The next slide shows some results from a UK study of protein glycosylation, characterising high mannose glycans

Is your right answer the same as someone else's right answer?



Glycan sample C contains mainly high mannose chains. The chart shows variability in results from different labs for the amounts of each type of chain (number of mannose residues). The proportions of Man₅ chains vary from 29 to 62%

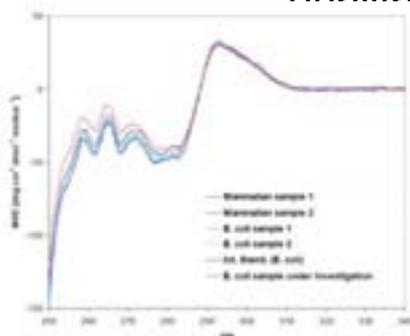
Who cares how many components?

- Analytical method → 100 variants (possibly)
- Preclinical assays → 10-20 variants (possibly)
- Clinical trial → < 3 variants (possibly)

Modern analytical methods can detect a very wide range of variants, but you will probably never know how structural variation affects clinical efficacy because pre-clinical and clinical data will be limiting.

But some minor variants may still be crucial for clinical efficacy

Differences are in the eye of the beholder: many key analytical techniques produce qualitative data



Characterisation of a novel growth hormone variant comprising a thioether link between Cys182 and Cys189

Antonio Dattoli¹, Sophie Robert², Horst Bernau³, David Agopian⁴, Anna Izzi⁵, Maria Rossi⁶, David Cregut⁷, Helene Doman⁸, Christine Schaefer⁹, Alan Van Dorsselaer¹⁰, Carlo Emanuele Giordano¹¹ and Carl Jones¹²

ChemMedChem, 2007, 2(8), 1181-1189

This example shows CD spectra, which are rarely analysed statistically to understand whether they really are different. In my opinion, the biosimilars debate will force objective analysis of complex data sets where previously expert opinion was accepted

How to do statistical analysis of very complex data sets? 2D gel electrophoresis of meningococcal OMV vaccine

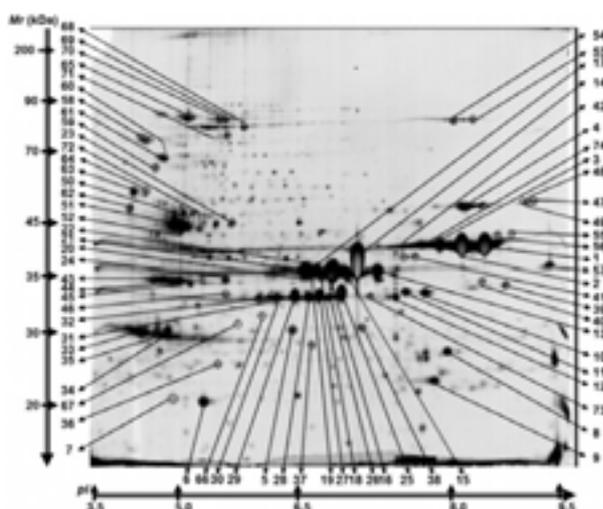


Figure courtesy of Caroline Vipond and Jun Wheeler

74 spots identified

Vipond *et al.*, *Proteomics*, 2006, **6**, 3400-3413



What is your matrix?

- Product production – in cell culture, highly impure, possibly dilute
- During purification – part purified, variable buffers, higher concentrations
- Purified bulk – relatively large amount of concentrated, purified product in simple buffers
- Final product – small amounts, excipients, adsorbed to adjuvant
- Different analytical methods often required for different steps in the manufacturing process.



Product-related impurities

- Aim to detect <1% of material (typical specification)
 - May be divided over several species
 - Several deamidated species, but specification is total
 - IEF shows 1% of deamidated protein
 - Peptide mapping shows < 0.1% of multiple deamidated forms
 - EMEA Guidelines on biosimilars highlight impurity profiles
 - May feed through into tighter regulation all round
- Analytical methods to distinguish minor product-related impurities in the presence of large amounts of product

Process-related impurities

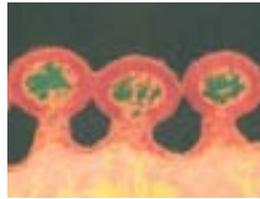
Usually present in trace amounts

- Host cell protein: < 10 ppm
 - Nucleic acid: Not much
 - Protein A: < 10 ppm
 - LOQs probably need to be 10 fold down from this
- Non-specific or specific methods?
- Non-specific methods see all impurities (good if process changes) but often fail on dynamic range
- Specific methods (eg. ELISA) often have enough dynamic range, but miss potentially important impurities

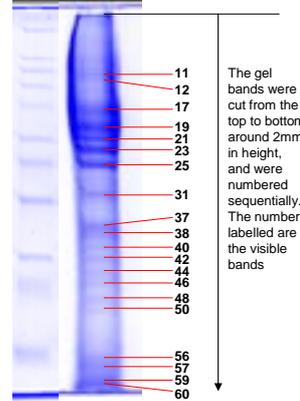
Lentiviral gene therapy vector

Specific method

Western blot
with anti-VSG



HIV-1 based
VSV-G/GFP



The gel bands were cut from the top to bottom around 2mm in height, and were numbered sequentially. The number labelled are the visible bands

Non-specific method

Proteomics analysis of cellular components in lentiviral vector production using Gel-LC-MS/MS

Jan K. Wheeler, Christopher Jones, Robin Thomas and Yoon Dhanj
Proteomics Clin. Appl. 2007, 1, 224-230

Consistency, consistency and consistency

but

Analysis which isn't linked to biological function
and/or clinical efficacy is of little long term
value

New Bioprocess Technologies: Requirement from a technology providers perspective

Dr John M Woodgate, European R&D Applications Manager

Slide 1

The R&D Applications team at Pall

- The group was started 2 years ago
- It is made up of 30 bioprocess developers who are located in:
 - UK
 - ◆ Team started in 2006
 - ◆ Recruited 4 in 2006 (including myself)
 - ◆ 2 additional in 2008
 - US
 - France
 - ...
- Recruited internally, from Academia (mainly Ph.D Biochemical Engineers) and from Industry (with Ph.D Biochemical Engineering degrees)

Slide 2

The UK outputs are/will be ...

- The R&D Applications group is tasked with:
 - Working with relevant feed material sourced internally and externally
 - Working in collaboration with Academic groups
 - Working in collaboration with Industrial groups
- The output are:
 - New product innovation
 - New process development techniques
 - Application guides
 - Conference papers
 - Peer reviewed publications (in collaboration)
- Academic collaboration:
 - Currently we support 8 Ph.D programs at 3 Universities
 - We are looking to extend that during 2008
- Investment in people:
 - We are looking to start two of the team on the UCL MSc Biochemical Engineering course in 2008

Slide 3

Where we would like to see investment ...

- Integrated upstream and downstream technologies:
 - Impact of cell line and culture development on DSP:
 - ◆ Low endotoxin fermentation strategies
 - ◆ Hydrodynamic stable of CHO
 - ◆ Automated process control
- Rapid bioprocess development tools:
 - Ultra scale down devices
 - Optimised DOE strategies
 - Active bioprocess management
- Active bioprocess management:
 - Process analytical technologies: Disposable?
 - ◆ Cell culture/fermentation contamination
 - ◆ Real time glucose, glutamine, antibody ...
 - ◆ Column loading i.e. active end point management
 - ◆ Real time virus break through i.e. active end point management
 - ◆ Real time HCP, DNA ...
- People:
 - High class of academic, project management skills with commercial awareness
 - However, creating real team players rather than individuals

Slide 4

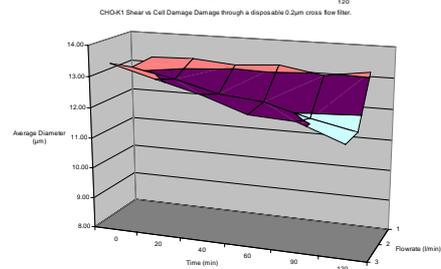
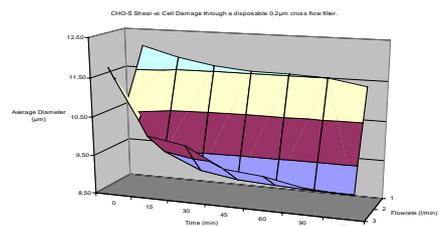
Case study: Integrated upstream and primary separation strategies ..

- Using DOE techniques to understand the impact of cell line selection:
 - CHO-S
 - CHO-K1
 - CHO-DG44
- On the primary clarification method:
 - Depth filtration
 - TFF
 - ♦ Hollow fibres
 - ♦ Cassettes
 - ♦ Disposable's
- Where operating parameters such as:
 - Harvesting viability
 - Cross flow rate
 - Permeate control
- Has on the:
 - The sustainable flux rate and throughput
 - Particle size distribution and permeate turbidity
 - HCP, DNA contamination
 - Protein A and/or MEP column efficiency and life span

Slide 5

Case study: Integrated upstream and primary separation strategies ... (continued)

- Data showing:
 - Average particle size for CHO-S (1.5×10^7 cells.ml⁻¹ top) and CHO-K1 (4.0×10^6 cells.ml⁻¹ bottom)
 - At 3.0 l.min⁻¹, a flux > 300 lmh can be sustained for both CHO-S and K1 for a 10-50 x concentration
 - However, HCP and DNA is significantly greater that at 1.0 l.min⁻¹ for CHO-S
 - Cross flow rate has little impact on HCP and DNA for CHO-K1
 - For minimal HCP and DNA:
 - ♦ CHO-S ~ 100 lmh
 - ♦ CHO-K1 > 300 lmh
 - What is the impact on Protein A and MEP?



Slide 6

Case study: Integrated upstream and primary separation strategies ... (continued)

- The outputs are:
 - A more complete understanding of how cell line selection and the cell culture locks the bioprocessor into a downstream process
 - Rapid process development tools
 - Active process management techniques
 - New ideas for automated control and active management hardware
 - ♦ Create
 - ♦ Innovate
 - Skill development within the R&D Application's team
 - Peer reviewed publication



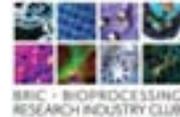
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BRIC Cell Therapy Workshop

Malcolm Rhodes

Technical Director, bioProcessUK

Background



- Challenge identified by the BBSRC working group: “Growth of stem cell and tissues in-vitro”
- No specialist cell therapy company joins BRIC initially
- One project funded in first call: “Expanded bed bioreactor systems for manufacturing stem cell therapy and tissue engineering”
Julian Chaudhuri (University of Bath) and Richard Oreffo (University of Southampton)
- Steering Group proposed theme for 3rd Call
- Workshop organised to discuss

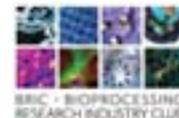
Workshop 27th April 2007



- Introduction to BRIC - John Birch
- Overview of the field - Chris Mason
- Biopharm member company viewpoint - Bo Kara,
- Cell Therapy company viewpoint – Rod Westrop
- Academic viewpoint – Zangfeng Cui
- Breakout discussion sessions

Workshop 27th April 2007

Attendees



Philip Aldridge, CELS	Kevin Shakesheff, Regentech /Nottingham
John Birch, Lonza	Mark Smales, Kent
Jeremy Bright, Glycoform	Roger Smith, Royal Veterinary College
Julian Chaudhui, Bath	Glyn Stacey, NIBSC/UK Stem Cell Bank
Zangfeng Cui, Oxford	Bill Thompson, Rotherwood
Alicia El-Haj, Keele	Hazel Thompson, Stem Cell Sciences
Chris Jones, NIBSC	Nigel Titchener-Hooker, UCL
Bo Kara, Avecia	Phil Vincent, HPA
Chris Mason, UCL	Christopher Ward, Manchester
Carol Marshall, GSK	Rod Westrop, Axordia
Greg McGarrel, Medcell	
Wesley Randle, Novathera	
Simon Roe, Antisoma	

Workshop 27th April 2007

Chris Mason UCL

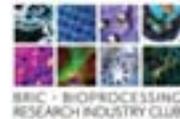


Overview of the field

- Allogeneic cells; economy of scale
- Autologous cells; automated custom production
- Supply chain options to be identified
- Platform technologies needed

Workshop 27th April 2007

Rod Westrop Axordia

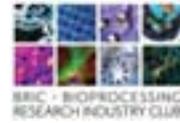


Cell Therapy company viewpoint –

- Axordia therapies: transplant rejection, degenerative blindness
- characterisation of products
- Monitor progression of cell derivation
- Serum-free chemically defined media
- Scaleable culture methods
- Tests for in-process, batch release & safety
- Cell enrichment

Workshop 27th April 2007

Zhangfeng Cui Oxford University



Academic viewpoint –

- Imaging techniques for drug and toxicology testing on stem cells
- Scale-up to make sufficient cells
- Separation and purification of cells
- Preservation & viability
- Non-invasive monitoring of quality and functionality

Workshop 27th April 2007

Bo Kara Avecia

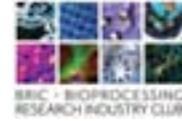


Biopharm BRIC member company viewpoint

- Case study, dermal mesenchymal stem cell project
- Why invent new bioreactors?
- Automation important; not in BRIC scope
- Product quality tests needed
- Underpinning science still needed
- ?Too early for BRIC

Breakout sessions

Main conclusions



- Cell therapy bioprocessing can learn from protein therapeutics bioprocessing
- Important to focus on generic bioprocesses
- Allogeneic products rather than autologous
- Control and measurement of product and contaminant are key issues
- Downstream processing needs more research
- BRIC would need cell therapy companies to join for a 3dr call cell therapy theme succeed

New BRIC Members

Three cell therapy companies decided to join BRIC after the workshop:





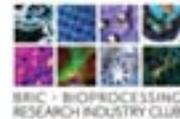
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BRIC 3rd Call

Overview of Priority Areas

Andy Lyddiatt
BRIC Programme Manager

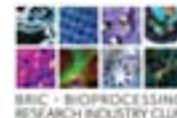
BRIC - Background



- Report from Bioscience Innovation and Growth Team (BIGT; 2003) recommended increased investment in bioprocessing research.
- BBSRC Working Group identified key areas and important scientific challenges for targeted bioprocessing research.
- ***Bioprocessing Research Industry Club (BRIC) launched (2005) supported by BBSRC, EPSRC and industrial funding.***



BRIC –Aims and Objectives

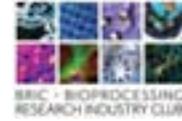


Overall: to strengthen/develop research communities in bioprocessing and improve academic-industry links

Facilitated by:

- Support of industrially relevant, innovative bioprocessing-related research projects
 - BRIC has a joint fund in excess of £14M , £1M of which comes from industrial membership subscriptions
- Mechanisms to rapidly disseminate research outputs to industry club members
- BRIC operations for 5 years from 2006 in first instance, supporting research proposals through 3 funding rounds

What is Bioprocessing?



The sphere of operation and influence of bioprocessing R&D is here defined by:

- (i) appropriate technical know-how and methodologies.*
- (ii) equipment, instrumental infrastructure, and*
- (iii) associated human skill-base*

that can be brought to bear upon:

- (i) effective and timely invention, development, clinical testing and*
- (ii) subsequent safe manufacture*

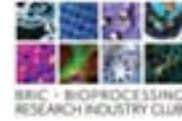
of pharmaceutically active products derived from, or facilitated by, biological systems.

Expected BRIC Outputs



- ***Novel interdisciplinary approaches***
- Greater systems-based understanding of biology to drive improved bioprocessing
- Increased predictability of biological processes in bioprocessing, including improved scale-up and reproducibility
- New tools and methodologies for bioprocessing
- Increased technical flexibility to improve product characteristics and reduce product heterogeneity
- Improved cost efficiency – both in development, manufacturing, and time to clinic/market
- ***Expanded skill-base and newly trained personnel***

Club Operation (i)



- Club managed by BBSRC, EPSRC & bioProcessUK
- Project manager facilitates networking and coordination between funded academic groups
- bioProcessUK facilitate networking and knowledge transfer between industry and academics
- ***BRIC Culture encourages grant-holders to cooperate/collaborate with other academic and industrial members***

Club Operation (ii)



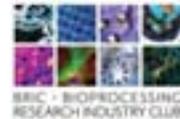
- A Club Steering Group provides strategic direction for the club by:
 - establishing (in consultation with BRIC members) the scope of research for which proposals are sought under three rounds of BRIC calls
 - reviewing outline and full proposals submitted for BRIC funding
 - monitoring progress and guiding on strategic relevance of projects

BRIC1 – Scope of Call



- Bioscience underpinning bioprocess improvement
- New tools for bioprocessing

BRIC1 funded projects (i)



The cellular requirements for efficient mRNA translation and protein folding during bioprocessing

Mark Smales (University of Kent)

Application of metabolomic profiling of recombinant mammalian cells to bioprocess design

Alan Dickson (University of Manchester)

Modelling cellular processes underpinning recombinant monoclonal antibody production by mammalian cells

David James (University of Sheffield)

Identification of novel signal transducers in mammalian unfolded protein response

Martin Schröder (University of Durham)

BRIC1 funded projects (ii)



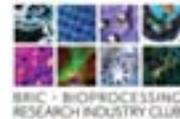
Strategy for the consistent preparation of sufficient non-viral large chromosomal vectors for biopharmaceutical applications

Eli Keshavarz-Moore (University College London)

Packaging cell lines for manufacturable viral vectors

Nigel Slater (University of Cambridge) and Farzin Farzaneh (Kings College London)

BRIC1 funded projects (iii)



Microbial physiology underpinning the production of difficult recombinant proteins

Jeff Cole (University of Birmingham)

Expanded bed bioreactor systems for manufacturing stem cell therapy and tissue engineering

Julian Chaudhuri (University of Bath) and Richard Oreffo (University of Southampton)

A new microfluidic tool for rapid analysis of protein stability and integrity in bioprocess

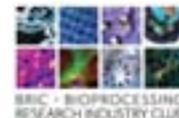
Paul Dalby (University College London)

BRIC2 – Scope of Call



- Understanding, controlling and manipulating cell metabolism in microbial fermentations
- Advances in downstream processing including formulation
- Tools to accelerate bioprocess development

BRIC2 funded projects (i)



Combined /omics approaches to understand and control library enriched microbial cell factories
Phillip Wright (University of Sheffield)

Pichia pastoris protein secretion: analysis of constraints, optimisation and methods development
David Leak (Imperial College London)

Identifying and overcoming protein secretion bottlenecks in yeast and filamentous fungal cell factories
David Archer (University of Nottingham) and Stephen Oliver (University of Manchester)

BRIC2 funded projects (ii)



New approaches to high throughput protein, isolation, purification and concentration

Barry Moore (University of Strathclyde)

Multifunctional chromatography materials for improved downstream processing

Owen Thomas (University of Birmingham)

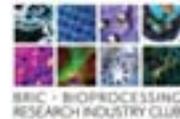
Protein nucleation and crystallisation on novel 3-D templates

Daryl Williams (Imperial College London)

Delta3D: bench top assays for the rapid detection of protein 3D structural changes

Jeremy Lakey (University of Newcastle)

BRIC scope to date (12/07)



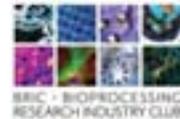
- Bioscience underpinning bioprocessing
 - Improved tools for bioprocessing
 - Understanding, controlling and manipulating metabolism in microbial fermentations
 - Improved downstream processing
- targeted at:***
- Therapeutic proteins, megamolecular complexes, cellular formulations

Background to BRIC3 Call



- Projects funded in BRIC1&2 – strong desire to fill gaps/add value
- Commercially established product groupings (therapeutic proteins) invite alternative technologies to meet new challenges – likely to be conservative change
- Newly emerging product groupings (eg megamolecular complexes) may be better serviced by radical, 'change the game' bioprocessing solutions
- Products of emerging lab cell science (eg regenerative medicine) demand test drives in *bona fide* prototype bioprocesses
- Extant bioprocessing solutions can inform the design of manufacturing processing for new product types
- All potential bioproducts (established, prototype and future categories) would benefit from early demonstration in representative downscaled bioprocesses of credible manufacturability

BRIC3 – Scope of Call (i)



- Alternative processes for the recovery and purification of all biopharmaceutical products (proteins, macromolecules, megamolecules, cells)
- Bioprocess integration and intensification for biopharmaceutical manufacture
- Quantification and characterisation of products and impurities in biopharmaceutical manufacture

Proposals sought which service nominated product groupings, and augment/unify work funded in BRIC1&2

BRIC3 – Scope of Call (ii)

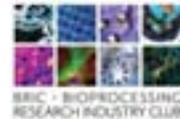


Integration with work in BRIC1&2 might:

- develop new DSP strategies to accommodate advances in expression of eukaryotic systems
- propose and evaluate credible operation sequences to accommodate alternative separation processes
- scope out robust and scalable procedures to manufacture new categories of biopharmaceutical products

Strategic relevance to bioprocess industry need and practice is essential

BRIC3 (i): Alternative product recovery and purification



Background thinking:

- Bind/elute chromatography well-established as predominant tool for protein fractionation/concentration
- Media manufacturers are hugely proactive and competitive in advancing best practice
- Similarly – broth conditioning for conventional bind/elute chromatography (centrifugation, filtration etc) well serviced by hardware and disposables suppliers
- Increasing fermentation titres must be accommodated, as might concomitant ramp-ups in host cell content

BRIC3 (i): Alternative product recovery and purification



However:

- Selective precipitation/partition of host cell & spent media contaminants may sustain bind/elute chromatography
- Customised bind/elute procedures may benefit other product groupings (megamolecules, cells etc), but flow-through chromatography could suit all product types
- Selective precipitation/crystallisation of products has many attractions – elevated product concentration good or bad?
- Liquid-liquid partition systems have inherently higher volumetric capacities than adsorptive processes, but local product concentrations may remain relatively low
- Such systems might be single-use and disposable, eliminating the cleaning needs of re-useable systems

BRIC3 (ii): Bioprocess integration/intensification



Background thinking:

Improvement/intensification of bioprocesses may be achieved by:

- (i) effective interfacing of unit existing operations
- (ii) true integration of US/DSP tasks into new unit operations
- (iii) improved scheduling of discrete US/DSP operations

All highly suited to practical and quantitative modelling studies targeted at rapid bioprocess development and demonstration of product manufacturability

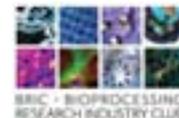
BRIC3 (ii): Bioprocess integration/intensification



Research directions?:

- Promising bioprocessing alternatives must be studied to examine/demonstrate compatibility with existing upstream/downstream operations
- Scheduling/operational effectiveness will benefit from representative down-scaled experimentation and data drawn from extant process (owned by BRIC members?)
- Scoping out and preliminary evaluation of candidate generic processes targeted at new product groupings (megamolecules, cellular therapeutics) are central to bringing these new drug substances to market

BRIC3 (iii): Measurement of bioprocess constituents



Background thinking:

- Biomolecular characterisation and analysis continues to advance – and outstrip preparative capabilities for fractionation of molecular mixtures
- Bioprocesses require robust tools for rapid, reliable system quantitation on-line or near-online
- Non-invasive methods preferred
- ***Quantitation/characterisation of process antagonists (out of spec cells, product isoforms, impurities etc) may be more important than that of target products***

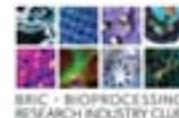
BRIC3 (iii): Measurement of bioprocess constituents



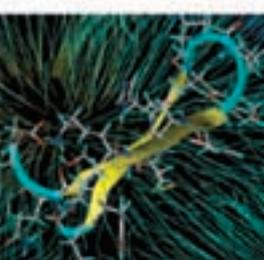
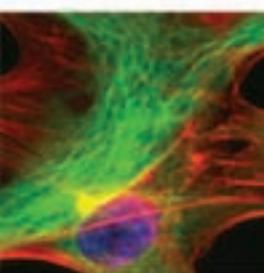
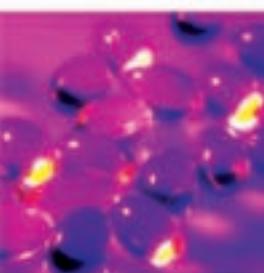
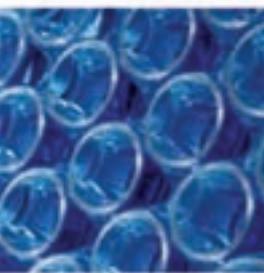
Research directions?:

- Widest possible scouting of fields of biophysics, chemistry and biology for analytical leads
- Adaptive evolution of laboratory analyses into robust, non-invasive, near process techniques
- Non-invasive assessment of cells in culture would benefit all product groupings – but particularly cells targeted at regenerative medicine
- Establish tools to reliably select all product types on the basis of demonstrable manufacturability at the earliest possible stages of product and process development

Summary guidance on applications



- ***Fit to the scope of BRIC3 and a clear, strategic relevance to BRIC Objectives and the needs of the wider bioprocess industries is paramount***
- Complementarity with work funded in BRIC1&2 Calls is encouraged – but not mandatory
- BBSRC Standards of Scientific Excellence, Contribution to Prosperity and Quality of Life, and Timeliness and Promise remain as established benchmarks of assessment



Bioprocessing Research Industry Club (BRIC)

Workshop to promote 3rd call
for research proposals

5-6 December 2007

Alexandra House
Wroughton

bbsrc
biotechnology and biological
sciences research council

EPSRC
Engineering and Physical Sciences
Research Council

bioProcessUK
Technology Transfer Network



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WORKSHOP PROGRAMME

Wednesday 5th December

Alexandra Suite – Ground Floor

- 4.00pm Arrival and Registration
- 4.30pm **Welcome & Introduction – John Birch, Lonza & Chair of BRIC Steering Group**
- 4.45pm Presentations from Industry
- Dr Chris Jones, NIBSC ~ *Analytical Methods*
- Dr John Woodgate, Pall Life Sciences ~ *New Bioprocessing technologies: Requirements from a technology providers perspective*
- Dr Malcolm Rhodes, bioProcessUK ~ *Summary of the BRIC Stem Cell Meeting April '07*
- 5.30pm 3rd Call Priority Areas Overview – Andy Lyddiatt, BRIC Programme Manager
- 6.00pm Questions and general discussion on priority areas

6.30pm Drinks – Bar (Ground Floor)

7.15pm Dinner - Private Dining in Alexandra suite

Each table will be hosted by an industrialist and during dinner delegates should take the opportunity to discuss further the challenges faced by industry in bioprocessing.

Tables for Dinner

Table 1

Roslyn Bill
Daniel Bracewell
Jeremy Bright
Hugh Guan
Chris Jones
Sue Kimber
Ian Moore
Pawel Plucinski
Leonard Seymour
Wenmiao Shu

Table 2

John Birch
Howard Chase
Robert Forbes
Ian Henderson
Ian Jones
Ioan Notingher
Tim Overton
Kedar Pandya
Mark Smales

Table 3

Simon Briggs
Chris Hewitt
Bo Kara
Naresh Magan
Judit Nagy
Malcolm Rhodes
David Stuckey
Helen Townley
Xue Wang
Paul Watts

Table 4

David Armitage
Andy Lyddiatt
Justin Perry
Robert Stevens
Robert Thomas
Martin Welch
Daryl Williams
Nik Willoughby
John Woodgate

Table 5

Simon Baker
Gary Black
Alexandra Brooks
Eugenia Dahm-Vicker
Gerard Fernando
David Humphreys
Michelle Scott
Owen Thomas
Christopher Ward

Thursday 6th December

Alexandra Suite – Ground Floor

9.00am **Introduction & Aims of the day – Andy Lyddiatt, BRIC Programme Manager**

Collaboration Exercise

9.15am Instructions and demonstration – Alexandra Brooks, BBSRC

9.30am Collaboration Exercise Part 1 – finding links and potential collaborations

10.00am Collaboration Exercise Part 2 – development of possible project ideas

11.00am Coffee Break

Collaboration Exercise

11.20am Collaboration Exercise Part 3 – reporting back of groups & feedback from industry and the Steering Group

12.45pm Lunch & Networking round posters

1.45pm **Surgery Session with Steering Group and Industry Club Members
Calder and Campbell Syndicate rooms (first floor)**

This session will provide a forum for project ideas to be put to the Steering Group and Club members and to get advice and feedback before submitting the application. These meetings will last for 15 minutes and will be held in strict confidence. The meetings will be based on appointments made prior to the meeting. During this session there will also be the opportunity for one-to-one meetings with other delegates who you may wish to meet.

3.30pm **Close of Meeting**

AIMS

The aims of this workshop are to promote the third call for proposals for BRIC, highlighting the research challenges and to discuss how to address these in order to meet the needs of industry. Presentations from the BRIC Programme Manager and Club Member representatives will focus on the priority areas of the call:

1. Alternative Processes for the Recovery and Purification of Biopharmaceutical Products
2. Bioprocess Integration and Intensification for Biopharmaceutical Manufacture
3. Quantification and Characterisation of Products and Impurities in Biopharmaceutical Manufacture

and will cover products which fall into the broad groupings of therapeutic proteins (antibodies, cytokines etc), megamolecular complexes (viruses, plasmids, multi-component assemblies) and cellular formulations (stem cells, differentiated cells, tissues etc).

The workshop will also highlight the need for interdisciplinary approaches to projects and provide networking to identify potential collaborations for BRIC proposals and future work in the area of bioprocessing. The workshop will also provide an opportunity to receive feedback from the Steering Group and BRIC Industry Club Members on ideas for potential project outlines in private meetings during the surgery sessions.

There are several opportunities for networking throughout the day and you should take the opportunity to make new contacts and exchange ideas with the potential of forming new collaborations. BBSRC, bioProcessUK and the BRIC Programme Manager will be available throughout the day for any questions you may have regarding BRIC.

The outcome of the workshop will be to have high quality research proposals that underpin the needs of the UK bioprocessing industry funded through the third call to BRIC.

Surgery Sessions

The surgery sessions provide an opportunity to pitch an idea on a project proposal to the Steering Group and Industry Club members and receive feedback in a confidential arena. All proceedings of these meetings will remain in confidence. If you have not previously booked a surgery session and would like one please contact Alexandra Brooks, BBSRC to see if one can be made available.

CONFIDENTIALITY STATEMENT

Delegates should note that the workshop is a closed meeting and that the proceedings should be treated as confidential, however, delegates should not disclose any ideas or know-how that they may wish to subsequently patent. A workshop report will be published , however this will focus solely on highlighting the challenges that should be addressed through proposals. The outcomes of the collaboration exercise will remain confidential and will not be published in the workshop report. The venue has plenty of space available for any confidential discussions delegates may wish to have.

COLLABORATION EXERCISE

Collaboration Illuminator

Collaboration illuminator is a collaboration exercise that has been designed to illustrate potential collaboration opportunities amongst delegates. Delegates, in groups of four or five, are encouraged to map the areas they work in, the techniques they routinely use and problems they are trying to solve, identifying those they have in common with others and those where they have a unique expertise. The idea is to illustrate possible areas in which they could work together. From the maps the group are asked to come up with an idea (real or hypothetical) for a project that could be submitted to the BRIC call. These expertise maps and project ideas will then be presented to all delegates to encourage the identification of potential research collaborators.

Delegates should note that the workshop is a closed meeting and that the proceedings should be treated in strict confidence. Any ideas arising from the exercise will not be published in the workshop report.

- 9.30am**
- Delegates are randomly split into groups of approximately four or five people (see table). Each group is colour-coded – the coloured dots on delegates' name badges correspond to the groups. Delegates should find their group by locating the table number as indicated in the table opposite. The colour-coding also allows for easy identification of a delegate after the network session as the colours will also be represented on the flip-charts.
 - Each group is to produce a spider chart, as per the example [to be demonstrated by BBSRC staff]. They should identify their own areas and techniques of research, and find links to other members of their group.
 - Resources to be provided per group:
 - Flip chart paper
 - Pens in 5 different colours – one colour per team member to illustrate links
- 10.00am**
- Groups should develop an idea of a potential project (real or hypothetical) and summarise this on a separate sheet of paper. You should also consider any additional collaborators, academic or industrial, you may need for your project.
 - Industry Club and Steering Group Members will move between the groups to provide advice and feedback on project ideas and will also highlight potential collaborations with industry.
 - After the spider charts have been produced, each group should appoint a spokesperson to present their chart to the rest of the groups. Rather than talking through the whole poster, each group should choose 2-3 important bullet-style points that arose from the exercise e.g. a surprising common interest, something they never knew before. The group should then briefly summarise their project idea.
 - There will then be an opportunity for the Steering Group and Club Members to comment on your idea and for you to question them on your ideas. Questions should only focus on the particular challenges being addressed and skills sets needed not feasibility of the science.
 - Delegates are asked to affix their business cards to the poster near their name so that other delegates will be able to get in contact if they identify areas of common interest from the exercise. Spider-charts will be displayed in the poster room for the duration of the workshop and delegates are encouraged to look at them to identify possible areas of shared interest and to note potential collaborators.

COLLABORATION EXERCISE

Groups

Group 1 – White Dots	Group 2 – Black Dots
David Armitage Simon Baker Ian Moore Justin Perry	Gary Black Daniel Bracewell Simon Briggs Robert Stevens
Group 3 – Red Dots	Group 4 – Green Dots
Howard Chase Hugh Guan Sue Kimber Robert Thomas	Ian Henderson Ian Jones Pawel Plucinski Wenmiao Shu
Group 5 – Blue Dots	Group 6 – Yellow Dots
Gerard Fernando Robert Forbes Chris Hewitt David Stuckey	Eugenie Dahm-Vicker Naresh Magan Judit Nagy Ioan Notingher Tim Overton
Group 7 – Orange Dots	Group 8 – Purple Dots
Owen Thomas Helen Townley Xue Wang Martin Welch	Christopher Ward Paul Watts Daryl Williams Nik Willoughby

BACKGROUND & PROGRESS FOR THE BRIC INITIATIVE

Over one third of all drugs now under development by pharmaceutical and biotechnology companies are biopharmaceuticals. The number of licensed biopharmaceuticals is forecast to grow at a rate of around 20% per annum. However biological products are large and complex molecules which require sophisticated manufacturing methods. The development phase is currently slow, expensive and complicated and, since speed to market is vital, there is a need for new tools and methods, which will contribute to accelerating development. In order to address these challenges, the Bioprocessing Research Industry Club (BRIC) was established by BBSRC, EPSRC and industry following the identification of the key industrially relevant bioprocessing research areas by a BBSRC Working Group set up in 2004, in response to the Bioscience Innovation Growth Team report.

The Club will support innovative bioprocessing-related research projects to help strengthen and develop the research community in this area and improve academic-industry links. This activity will be managed through a series of calls for research proposals. Management support for BRIC is provided by bioProcessUK, the DTI-funded Knowledge Transfer Network, enabling a mechanism for the dissemination of research outputs and networking with industrial Club members.

The overall outputs from the research funded through BRIC will be:

- a greater systems-based understanding of biology for improved bioprocessing;
- increased predictability of biological processes for bioprocessing, including improved scale-up and reproducibility;
- improved cost efficiency – both in manufacturing and development;
- increased flexibility to improve product characteristics and reduce product heterogeneity;
- increased speed to clinic and market;
- tools and methodologies for bioprocessing which may have potential for application in related fields.

The research will have an impact on bioprocesses at all scales of operation, from the small amounts required for preclinical studies through to post-license bulk manufacture. The priority areas identified are potentially IP-rich and create opportunities for value creation. The advances delivered by the research will help to eliminate the bottleneck in the development of biotherapeutics and contribute to the development of a vibrant bioprocessing community, creating wealth for UK plc.

RESEARCH CURRENTLY SUPPORTED THROUGH BRIC

The first call for research proposals under BRIC provided support for 9 research projects totalling £5M, and the second call funded 7 projects totalling £3.5M and were announced in July. Summaries of all the projects supported through the first two calls can be found on pages 17-25.

BRIC held a workshop in April to look into the area of stem cell bioprocessing and to understand the research challenges in this area. The Steering Group met in July and September to discuss the remit of the third and final BRIC call to compliment the first two rounds of funding. The scope was finalised at a meeting in September and the third call was launched in the October. Outlines will be submitted in January 2008 with full applications invited in March. Awards will be made in September 2008.

THIRD CALL FOR APPLICATIONS – PRIORITY AREAS

The focus for the third call is research targeted at the development or invention of bioprocessing technologies and strategies which will advance the effective manufacture of extant or putative biopharmaceutical products.

This will be designed to complement and build upon the 2 earlier calls which emphasised:

1. Bioscience Underpinning Bioprocessing
2. Improved Tools for Bioprocessing
3. Understanding, Controlling and Manipulating Physiology in Microbial Fermentations
4. Improved Downstream Processing.

The bioprocesses of interest to BRIC member companies yield products which fall into the broad groupings of therapeutic proteins (antibodies, cytokines etc), megamolecular complexes (viruses, plasmids, multi-component assemblies) and cellular formulations (stem cells, differentiated cells, tissues etc).

Some product types are commercially established (e.g. therapeutic proteins) but demanding of alternative bioprocessing technologies to accommodate the technical challenges of improved host cell expression, increased fermentation titres, elimination of host cell and spent media components, and recovery (or elimination) of specific product isoforms.

Other product types are newly emerging in the marketplace (e.g. viruses, plasmids, virus-like particles) but require the development of more effective and efficient procedures of manufacture for related products current in early development.

A third category (especially putative cell therapy products or prototypes) are currently produced by laboratory scale methodologies which have serviced their discovery and development as promising biopharmaceutical agents. These highly complex therapeutic products require the early scoping and evaluation of alternative practical procedures which will enable the robust manufacture at appropriate scales. In particular a BRIC-sponsored workshop in April 2007 concluded that academics might usefully contribute to the development of allogeneic stem cell products by improving understanding and reliability of cell expansion and up-scaled production empowered by non-invasive, non-destructive tools to monitor and characterise cell cultures.

Concomitant consideration of bioprocessing solutions tailored for all new product types, in tandem with the procedures of their discovery and early development, will facilitate early assessment of their relative ease of manufacture, inform the selection or introduction of useful 'handling' characteristics into new products, and reduce costly process *cul de sacs* which might yield prototypes having insurmountable issues of process-scale manufacturability.

However, it is clear that all candidate procedures for new product types (particularly megamolecular complexes and therapeutic cells) can usefully be informed by the operating philosophies and practical characteristics of bioprocesses established for current commercial biopharmaceuticals.

Priority research areas

1. Alternative Processes for the Recovery and Purification of Biopharmaceutical Products

Bind/elute chromatography is well established as the predominant downstream processing tool of choice for the concentration and highly selective purification of biopharmaceutical proteins. The BRIC Steering Group has concluded that further refinement of this technology in respect of solid-phase and/or immobilised ligand development is best left to the leading media manufacturers who can be expected to continue to develop and launch products to meet customer needs identified by comprehensive market intelligence. A similar conclusion applies to the deployment of commercial solid-liquid separation hardware (filtration, centrifugation) which pre-condition feed-streams for conventional fixed-bed chromatography. However, material and operating costs, unpredictable operational longevities and relatively limited product capacities in the face of increased product titres achievable in the contemporary culture of producer cells are likely to challenge conventional approaches to chromatographic fractionation characterised by similar or better purification potencies. In addition, new generations of products (conjugated macromolecules, megamolecular complexes and cell preparations) are likely less suited to conventional bind/elute chromatography by virtue of their size and surface complexities or heterogeneities. In order to address these practical challenges, alternatives to current chromatographic practice might embrace flow-through processes where contaminants are captured from product rich feed-streams, or more radically achieve useful fractionation of products and impurities by harnessing aqueous solvent systems, selective precipitation or crystallisation. Such partition systems might usefully exploit 'smart' components whose behaviour can be physically or chemically controlled to benefit separation or achieve component elimination and/or recovery at the end of an operational cycle.

Proposals are sought which will work toward the characterisation and demonstration of the practical worth of alternative procedures to bind/elute chromatography. Proposals should augment work already planned in the 2nd call of BRIC projects and potentially service host cell systems of the type under development in the 1st call BRIC projects. The BRIC Steering Group invites novel ideas and demonstrations of principles relevant to, and compatible with, current and future bioprocessing practice in industrial environments which requires ease of use, robustness in cleaning processes where re-use is envisaged, or economic and environmentally sound approaches to disposal. It is strongly recommended that applicants seek advice from one of the industry club members for strategic relevance on their proposal.

2. Bioprocess Integration and Intensification for Biopharmaceutical Manufacture

The improvement and intensification of bioprocesses may be achieved by the effective interfacing of existing unit operations of manufacture, the integration of upstream and downstream tasks into new unit operations, or improved scheduling of discrete upstream and downstream operations. These varied approaches are highly suited to design-led scoping, quantitative modelling and practical studies in down-scaled, high-throughput procedures appropriate for rapid process development in conventional bio-manufacture (e.g. fed-batch fermentation serviced by solid-liquid separation, chromatographic sequences and product formulation). However, there is an urgent need to target such studies at alternative bioprocessing operations in order to demonstrate their compatibility with total manufacturing sequences (fermentation to formulation) and at whole processes proposed for the effective manufacture of newer product types (e.g. megamolecular complexes and cells). Efficient scheduling and operational effectiveness will benefit from appropriate modelling studies based upon down-scaled experimentation and data from existing processes operated at representative scales. This could be sourced from BRIC industrial members, whilst

demonstration vehicles for the advanced process integration of bio-manufacture might usefully be drawn from systems and operations in studies supported by the first 2 rounds of BRIC funding.

Under this heading, there is a particular opportunity to scope out and evaluate candidate generic processes that might be broadly adopted for cellular therapeutics. Such work could be most usefully undertaken with companies active in the development of these new products where emphases might currently be on discovery and early trials rather than the practical means of commercialised, up-scaled manufacture.

3. Quantification and Characterisation of Products and Impurities in Biopharmaceutical Manufacture

The quantitative measurement and characterisation of products (macromolecules, megamolecular complexes and cell preparations), system impurities (media and host cell components, unwanted product isoforms) is critical to the monitoring and definition of all current and future bioprocesses. The third BRIC call is open to inventive proposals which will extend the current selection of practical tools that can be applied to off-line, on-line and non-invasive characterisation, definition and subsequent control of all bioprocesses harnessed for the manufacture of all types of biopharmaceutical products. There may be many opportunities to harness techniques developed for the definition of biomolecules and components in pure science fields of biophysics, chemistry and biology, but proposals should strongly feature inherent practicality, instrumental simplicity and robustness of operation that can be adopted in rapid process development and/or in the manufacturing plant. Non-invasive characterisation of cells in culture would benefit bioprocesses targeted at manufacturing macro- and megamolecular products, but is particularly needed in regenerative medicine where the quality, differentiated state and homogeneity of cell cultures demands constant assessment.

There is also an urgent need for measurement-driven, predictive tools which will confirm at an early stage of product development the inherent manufacturability of new bioproducts, whether in conventional unit operations or in alternative procedures under consideration because of particular operational advantages. This is currently a pressing problem in the manufacture of protein therapeutics where issues of aggregation, stability and molecular integrity may arise in intensified bioprocesses. Analogous issues are also likely in intensified processes applied to the manufacture of megamolecular complexes and cell therapeutics.

It is recognised that there is considerable overlap between these headings, and proposals which fall under more than one heading will be welcomed. However, all proposals should offer alternative technologies, advanced solutions or new tools to facilitate the effective manufacture of at least one of the nominated product types (biopharmaceutical proteins, megamolecular complexes, cell therapeutics).

Proposals are encouraged which are clearly configured to service, augment or integrate with the outcomes of projects funded by the 1st and 2nd funding calls. (Details of these projects can be found in the booklet and in the downloads section of the BRIC web pages.) These might feature (i) downstream strategies or practices designed to accommodate the advances expected from improved expression of macromolecular and megamolecular products in animal and microbial systems, (ii) consideration of new operational sequences to enable efficient integration of alternative separation processes (e.g. crystallisation, selective precipitation) into biopharmaceutical manufacture, or (iii) the scoping of robust and scaleable procedures to manufacture new categories of biopharmaceutical products (e.g. megamolecular complexes and cells or tissues). Collaborative links with programmes and networks already in receipt of BRIC funds or BRIC industrial affiliates are especially encouraged.

Additional guidelines

- The objectives of the research proposed must fit with the scientific challenges detailed in the 'Priority Research Areas' and the science proposed must fall within the remit of BBSRC and/ or EPSRC. Proposals may address more than one of the challenge areas; novel approaches to addressing the challenge(s) are particularly encouraged.
- Collaborative applications which bring together academic groups with relevant expertise in biosciences and engineering for the first time are encouraged. In addition the BRIC Steering Group will at the outline stage, where appropriate, identify research projects with potential for collaboration.
- The BRIC Steering Group will at the outline stage, where appropriate, identify research projects with potential for collaboration. If applicants are particularly looking for collaborators on a project they should indicate this on their form.
- It should be noted that an intended outcome of the BRIC initiative is the development of critical mass in the bioprocessing research base in key areas. This will not necessarily be delivered through support for centres at specific geographical locations, but could involve research groups with complementary expertise networking through 'virtual centres'. Whilst such groupings may be proposed at the outline stage, it is also appropriate for proposals from individual laboratories to be submitted (these may subsequently be invited to network with others).
- Outline proposals must be submitted in the first instance (see Application Procedure).
- Research proposals are sought for funding for up to five years.

BIOPROCESSING RESEARCH INDUSTRY CLUB (BRIC)

OUTLINE APPLICATION

For Office Use Only

ID:

Evaluation:

(1)	Date: / /	
(2)	Principal Investigator (co-investigators to be listed in 11)	
	Full Name:	Title:
	Position:	
	Institution:	
	Department:	
	Full Address:	
	Tel No.:	E-mail:
(3)	Title of research proposal (not to exceed 100 characters including spaces):	
(4)	Research area(s) (please refer to Research Challenges document):	
(5)	Summary of research proposal (not to exceed 500 characters including spaces)	
(6)	Amount requested: £	
(7)	Proposed starting date:	Proposed duration (in months):
(8)	Number of hours a week principal investigator proposes to spend on the research project:	
(9)	Number of co-investigators:	

(10)	Names, titles, positions and institutions of co-investigators:
(11)	Please explain how your research proposal fits the remit of the BRIC (not to exceed 500 characters including spaces):
(12)	Description of proposed research (not to exceed 12000 characters including spaces):
(13)	Outline how the expertise of your research team will add and complement the portfolio of projects currently funded through BRIC to enable it to achieve the Clubs aims and objectives.
(14)	Are you looking for collaborators? Please specify which areas you are looking for expertise.

Deadline for submission of outline proposals: 5.00pm Wednesday 23rd January by e-mail to: bric@bbsrc.ac.uk

Please leave as word document.

APPLICATIONS FUNDED THROUGH BRIC 1ST CALL JUNE 2006

A new microfluidic tool for rapid analysis of protein stability and integrity in bioprocesses

Dr Paul Dalby	University College London	£424203
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Analysis of protein stability is currently too slow and requires too much of an exceedingly valuable biopharmaceutical to be useful in guiding bioprocess development or control. Introducing the first microfluidic method for protein stability testing will reduce sample use and cost of analysis by up to 108-fold over microwell-based analysis. Combined expertise from biochemical engineering and the London Centre for Nanotechnology will enable this analysis with parallelism for up to 1000 samples per day. The new generation of protein-based medicines has rapidly become a \$30billion-a-year industry addressing previously untreatable diseases. They have the potential for much further growth but a principal constraint is the high cost of the manufacturing methods required to preserve the structural integrity of proteins with limited stability. The ability to perform rapid and parallel protein stability characterisation experiments, at the microfluidic scale, is essential to enable: a) the rapid optimisation of therapeutic protein formulations; and b) the real-time monitoring of protein product quality in process-, microwell- and microfluidic scale bioprocess development experiments. Our preliminary research has demonstrated protein stability determination using fluorescence measurements at the microwell scale (Aucamp et al., 2005). The aims of this proposal are to a) explore the fundamentals that impact on measurement accuracy and sensitivity at the microfluidic scale, so as to significantly decrease the sample volumes required for protein stability measurement; b) establish a microfluidic denaturation technique; c) overcome the challenges that will enable broad application to bioprocessing and formulation of biopharmaceutical protein products.

Application of metabolomics profiling of recombinant mammalian cells to bioprocess design

Professor Alan Dickson	The University of Manchester	£768109
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The diagnosis and treatment of many clinical conditions is dependent on developments of new therapeutic drugs / complex protein molecules that require production by mammalian cells in culture. Advances in genetic engineering and understanding in gene expression has made it possible to turn mammalian cells in defined culture conditions into "factories" to permit harvest of the valuable therapeutic protein drugs. Hence it is possible to introduce into mammalian cells in culture a gene that will direct synthesise the desired drug and allow the mammalian cells to perform all the necessary reactions required to generate the therapeutic protein. Some of the drugs generated by these approaches are household names (eg insulin and clot-buster drugs) and others are not (eg antibodies), however all are critical and essential components in treatments for many life-threatening clinical conditions. A key problem is that the development and generation of sufficient amounts of therapeutic protein drugs is limited by the capacity to generate sufficient production from the cell cultures. Consequently, the investment of development and process time to harvest sufficient amounts of therapeutic proteins makes the process costly and these are expensive drugs. Despite significant effort by industrial and academic researchers we still do not fully understand the factors that limit production by the cell culture system and such information will be essential if we are to devise means to increase production. The unit cost for certain of these therapeutic protein drugs has implications for availability for treatment and for certain "difficult-to-make" drugs financial implications may prevent the drug being developed for the market. This proposal addresses this problem and seeks to use novel approaches to ask how we can improve the process of therapeutic protein formation by mammalian cells in culture. Our approach is to take a wide vision of the events within cells that limit formation of the desired drug. Too frequently experimental approaches to study the functions of cells focus on one specific aspect or examine functions in the cell for which there is no direct certainty of involvement in the processes under study. We are building complex models that will determine how the many factors in the cell interact to define how production of the therapeutic protein is controlled. We will then test the model in response to conditions that we impose in cells and, from this, determine if there is a means to identify those cells in a population with desirable characteristics that will give excellent production or if we can engineer these functions into cells. The research team in this programme have come together from distinctive areas of research, allowing a fusion of technologies to emerge from the interactions. The fusion of analytical scientists, cell biologists, chemical engineers and mathematical modellers generates a novel team-based approach to an industrially- (and, ultimately) clinically-relevant issue. The team will be part of a wider network of scientists (in academic and industrial groups) who are part of the Bioprocessing Research for Industry Club, the government/industrial initiative to maintain the UK research strength in this area.

BRIC: Packaging cell lines for inherently manufacturable viral vectors

Professor Nigel Slater	University of Cambridge	£230652
Professor Farzin Farzaneh	Kings College London	£251318

Viruses dominate overwhelmingly the types of vectors currently being tested in clinical gene therapy trials and of these retro- and lentiviruses are the most numerous. Until recently two technological problems have hampered progress in gene therapy; production of high titre clinical grade virus and efficient tissue specific targeting. Research at Cambridge and King's College London has addressed the former and led to the development of a novel lentiviral vector packaging cell line in which manufacturability is built into the genome of the packaging cell and co-expressed on the surface of the viruses produced thereafter. We initially used simple retroviral vectors, and latterly the more complex lentiviral vectors based on a core of HIV-1, and have developed strategies for increasing the titre by several orders of magnitude. This is an active area of research amongst which our preliminary work with novel chromatographic techniques and paramagnetic particles set the foundation for a practical and efficient alternative technique to cumbersome ultracentrifugal concentration. For lentiviral vectors we engineered a new producer cell type that provides a biotin tag amenable to various lentiviral vectors produced from these cells using either VSV-G or MLV amphotropic envelopes. We have shown that these bio-lentiviral vectors are produced in the normal manner and only require the presence of biotin in the culture medium to manifest their affinity for streptavidin. Vectors can thus be retained on streptavidin Paramagnetic Magnespheres for infection, or eluted from streptavidin adsorbents. This cell line allows the capture of multiple envelope pseudotypes of lentiviral or MLV derived vectors, enabling production and concentration to titres that are several orders of magnitude higher. Using this scalable protocol we have concentrated lentivirus in excess of 4500-fold in only 3 h and have provided titers for both VSV-G and MLV amphotropic envelope pseudotypes of 1010 IU/ml. However, these viruses could not be easily eluted from adsorbents and required the addition of biotin to the growth medium of the packaging cells. This proposal aims to express the alternative desthiobiotin ligand on the surface of lentiviruses in such a way that elution from adsorbents may be more readily preformed to give higher process yields and the addition of an affinity ligand binding precursor to growth medium is avoided.

Characterization of post-transcriptional constraints that determine rP yield during bioprocessing in mammalian cells

Dr Mark Smales	University of Kent	£987761
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We all have an in-built defence mechanism to respond to infection when our body recognises a foreign 'invader'. A type of cell known as a B cell responds to infection by changing into an antibody-producing cell. Antibodies are proteins that work by attacking the foreign invader and destroying it, clearing infection by removing the foreign agent. Because antibodies are our body's natural defence against disease, many new antibody type drugs are being developed to help treat a number of human diseases such as cancer. These antibodies are usually produced by cells kept in a culturing solution under defined conditions. The problem is that these antibodies must be in a special shape; otherwise they do not work. The cells used to produce such antibodies have a very complex set of machinery to make the antibodies and put their components together into the right shape. This works very well when the cell is not expected to make much of the antibody in question. However, the cells we use to make antibodies are much less efficient at producing these drugs when we try and produce more of the product. As a result, we are not able to produce enough of these drugs and the cost and demand for them is therefore high e.g. the breast cancer drug Herceptin. The root of the problem is that when cells are asked to produce much more protein to meet our needs the machinery can no longer cope / the cells sometimes die or else don't produce antibodies of the right shape, of no clinical use whatsoever. It is largely agreed that this problem will become even serious as further antibody-based drugs are developed. The research proposed here will investigate how the cell machinery for making proteins works and examine whether, and in what ways, it can be manipulated to produce more antibody. We want to determine the different parts of this machinery that are limiting in terms of making the antibody, and then investigate how these parts work together to ultimately produce the antibody of interest. At present it is unknown if this is possible, and the process is poorly understood in the mammalian cells presently used to produce antibodies. We will employ a combination of new state-of-the-art technologies and approaches to take apart the antibody assembly line in mammalian cells in a step-wise manner, and then using the information gathered will determine the relationship between each step of the assembly process. Ultimately this should enable the manipulation of cells to change the balance of each step in the assembly line to produce more of the target antibody drug at reduced cost and higher quality. As stated above, this is extremely important as it is expected that with an increasing number of protein 'drugs' being developed we will lack the capability of producing large enough amounts to meet the required demand for these new drugs for the majority, as opposed to for those who can afford what must currently remain prohibitively expensive, but very effective, medicines.

A Novel Bioreactor System for Manufacturing in Stem Cell Therapy and Tissue Engineering

Professor Julian Chaudhuri	University of Bath	£186350
Professor Richard Oreffo	University of Southampton	£185475

The emergence of regenerative medicine offers the potential for new therapies and procedures for diseases and injuries that cannot currently be effectively treated. Regenerative medicine involves the use of living cells and other biological molecules to restore damaged structure and function in human organs and tissues. In addition, the recent excitement arising from the discovery and potential uses of stem cells makes it timely to investigate how stem cell research can be used to treat patients. One of the key issues is how to produce enough living cells (including the very rare stem cells) that have the correct function for these new therapies. The current laboratory cell culture procedures are not efficient, nor are they standardised and cannot meet the current clinical needs. This project aims to address this acute issue by the development of a new method of efficiently culturing stem cells and other human cells to give enough cells required to treat patients.

This system will be based on the idea of growing cells using a biomaterial derived from seaweed (alginate) that allows the cells to grow and develop normally. In this work, we will decide what effects the key features of the culture system will have on the growth and function of both human stem cells, and also specific human cell types (eg bone cells). As part of our experiments we will measure how the cells grow and behave in the different culture environments, and compare this to conventional methods.

Identification of novel signal transducers in the mammalian unfolded protein response

Dr Martin Schröder	Durham University	£677697
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Human proteins produced in other organisms, i.e. bacteria or mammalian cell cultures are called recombinant or heterologous proteins. These proteins have many applications in industry and medicine. They are safer to administer in the clinic than their native counterparts purified from i.e. animals. Single point mutations in a protein, i.e. isolated from pigs, that deviate from the human sequence, can have serious side effects when the protein is administered to humans. Further, their posttranslational modifications, i.e. their glycosylation pattern, are similar to those found in humans. Again, minor deviations in the glycosylation pattern between an animal and a human protein can seriously affected the performance of the protein in the human body. Finally, the risk of contamination of the protein with infectious agents is much easier controlled in production processes for recombinant proteins compared to isolation of the protein from animals. Production processes for recombinant proteins for use in the clinic rely on mammalian cell lines. Growth conditions and sterility requirements for these production processes make them expensive. Further, the number of recombinant proteins for which there is a demand on a multikilogram per year scale is rapidly growing, requiring the development of large scale (several cubic metres) production processes. The cost efficiency of a production process often determines if a recombinant protein makes it to the market and to the clinic. Several strategies have been devised to improve product yield and in turn the cost effectiveness of these production processes. To date, the rate-limiting step for production of recombinant proteins is folding into their native, active, and non-immunogenic conformation. Protein folding is assisted by helper proteins that shield a folding protein from its environment, called chaperones, and that catalyse a subset of protein folding reactions, called foldases. Recent basic research has identified signal transduction pathways that sense the folding status of a protein, and that activate expression of these helper proteins to increase the efficiency of protein folding in response to this stress situation. Genetic engineering of these signalling pathways promises to alleviate the protein folding bottleneck in recombinant protein production. However, our current understanding of these signal transduction pathways is still limited. Based on our current knowledge the outcome of engineering of these pathways on recombinant protein production is unpredictable. To address this problem we propose to characterize these pathways on a genomic scale to define their complete substrate spectra by using recently developed genomic technologies to monitor the complete mRNA and protein population of a cell. In addition, we will exploit unique biochemical characteristics of these signalling pathways to focus our study on the pathways in question. In this way we will target three unique signal transduction mechanisms, non-spliceosomal splicing of mRNAs, preferentially translated mRNAs when translation of the majority of mRNAs is inhibited, and proteolytic activation of ER membrane proteins. We anticipate to identify new proteins involved in this response to protein unfolding. We will characterise the role of new genes involved in these signalling pathways identified in our study by characterising their role in chaperone and foldase expression, and survival of ER stress. Furthermore, through defining the complete substrate spectra of these pathways we will enable the engineering of these pathways with predictable outcomes on cell specific protein production and cell viability.

Microbial physiology underpinning the production of difficult recombinant proteins

Professor Jeffrey Cole

University of Birmingham

£386309

Most people appreciate the need for pharmaceutical companies to develop new vaccines to prevent disease, or drugs to combat illness, not only for humans, but also for our domestic animals. In this context, biotechnology and genetic engineering are clearly tools to be used for the benefit of society. The development of new vaccines and drugs often depends upon the ability of bioprocessing companies to harness a cell factory to produce one or more target proteins. In many cases this will mean using simple but safe bacteria to generate the required product. Bacteria can be taught to synthesise almost any protein, once they have inherited the correct DNA coding sequence. However, under the conditions they are grown in the laboratory, they are often unable to assemble the protein correctly, so the product is useless. Sometimes it is better to make less product more slowly so that it is not toxic to the cell. In other cases, extra copies of helpful genes need to be transferred to the cell factory so it can assemble and modify the target protein after it has been generated from the genetic information provided. In this project, we will discover why some proteins are so difficult to make, and how to help bacteria make them more efficiently. We will start by making a protein that is located on the outer surface of the bacterium that causes the sexually transmitted disease, gonorrhoea. It is also found in bacteria that cause teenage meningitis (the so-called "kissing disease"). Vaccines are required for both gonorrhoea and type B meningitis. We will discover how to prevent the accumulation of useless product, and how to make authentic protein. The UK bioprocessing companies who have formed a club to support this type of research will then be invited to challenge us with one of their unsolved problems. This will allow us to test whether there are general rules that must be followed if other difficult proteins are to be generated for the benefit of human health.

Strategy for the consistent preparation of sufficient non-viral large chromosomal vectors for biopharmaceutical applications

Dr Eli Keshavarz-Moore

University College London

£377945

Modern medicines and therapies are becoming increasingly complex and specific for a particular disease or group of patients. One very specific type of therapy is Gene Therapy. Gene therapy is the use of genes as medicines. These genes can be delivered to patients either by the use of genetically modified viruses to carry the genes or by using non-viral methods which employ circular DNA molecules called plasmids isolated from bacteria. Both techniques are still in their infancy but are already promising huge medical advances in vaccination, cancer therapy and the correction of genetic disorders. However, viruses suffer from several drawbacks including safety considerations and limited to carry large genetic information. On the other hand large plasmid DNA molecules called BACs (Bacterial Artificial Chromosomes) can be modified to incorporate a wide range of important control regions which allow expression of the gene in the correct tissue and at the correct time. This larger size poses a scientific and industrial challenge because the size limits the amount that can be made in a single bacterium, in addition, the size also calls for special processing considerations because BACs are fragile. The challenge is to be able to prepare the BAC molecules in the amounts needed to treat the numbers of people who could benefit from these medicines. We need to investigate then develop methods of making the DNA molecules at large scales in the biomanufacturing industry. The quality of the DNA molecules is also paramount. They need to be in the form that is most appropriate for delivering to humans (and animals) and free of contaminating material. The research we propose will enable industry to make DNA molecules that can be made at the large scales. The proposed research outcomes will allow others involved in gene therapy to prepare large DNA molecules for the treatment of cancers, for vaccines and to correct genetic disorders The science proposed will also allow other researchers in related disciplines to benefit from being able to make and manipulate large DNA constructs .We will also explore ways of making the DNA in the correct three dimensional form needed for efficient uptake into cells so that the DNA is an effective medicine.

Modelling cellular processes underpinning recombinant monoclonal antibody production by mammalian cells

Professor David James

University of Sheffield

£524266

This proposal is concerned with "bioprocessing". Bioprocessing collectively describes the range of manufacturing processes that enable the production of new biological medicines. You may be familiar with the one of the first biological medicines produced by recombinant DNA technology - a small protein called insulin. Insulin is now used very successfully to treat an increasingly common metabolic disease, diabetes. Before insulin, diabetics suffered a short life fraught with serious medical complications. This project is targeted at the production of other high-value therapeutic proteins by genetically engineered mammalian cells in culture, specifically monoclonal antibodies. In the body, natural antibodies present in the blood play an important role in our immune system: They target disease-causing microbes and foreign substances for removal. Recombinant monoclonal antibodies, being almost identical to natural antibodies, are specifically designed to target diseased cells. Unlike traditional small-molecule medicines such as penicillin and paracetamol, monoclonal antibody biopharmaceuticals are large, complex and relatively fragile proteins which have to be produced by living mammalian cells in culture, genetically engineered to produce the recombinant protein product. They are proving to be highly successful treatments for serious diseases such as rheumatoid arthritis and a range of cancers. It is anticipated that within the next five to ten years up to fifty percent of all drugs in development will be biopharmaceuticals; a very substantial proportion recombinant proteins produced by mammalian cells in culture. Since the first recombinant protein medicines produced by genetically engineered mammalian cells in culture were licensed as therapeutics over 25 years ago, we have learnt to substantially increase the productivity of biopharmaceutical manufacturing processes (bioprocesses). However, they are still complicated and expensive, and industry has to undertake time-consuming screening processes to find engineered cells making adequate amounts of recombinant protein. To date, the output of industrial bioprocesses has predominantly been increased by gradually improving the growth of producer cells in culture, and not by engineering each cell to make the product more efficiently. This is important, because if we knew how to instruct or programme the cell factory appropriately, we could substantially improve the productivity of manufacturing processes and decrease the time it takes to generate a productive cell culture. However this is not a simple problem. The cell utilises and coordinates a diverse range of its complex machinery to turn, for example, recombinant monoclonal antibody genes in its nucleus into a fully folded protein which can be secreted out of the cell. How can we understand this cellular "production line" well enough so that we can rationally implement strategies to improve flux from recombinant genes to protein product? In this project we will implement a novel, multidisciplinary combination of technical approaches to answer this question; mathematical modelling, gene expression, molecular cell biology, protein analysis and cell culture. We believe this is crucial - an integrated mathematical bioscience approach can massively increase the information content and utility of biological measurements and enable us to understand cellular processes from a systems control perspective. This project will, for the first time, provide a quantitative understanding of the cell factory on which to rationally build strategies to increase the productivity of therapeutic monoclonal antibody production systems. Without this knowledge, cell culture engineering will largely remain based on trial and error.

Total £5,068,335

APPLICATIONS FUNDED THROUGH BRIC 2nd CALL JULY 2007

Identifying and overcoming protein secretion bottlenecks in yeast and filamentous fungal cell factories		
Professor David Archer	University of Nottingham	£362590
Professor Stephen Oliver	The University of Manchester	£422247
<p>The yeasts <i>Saccharomyces cerevisiae</i> and <i>Pichia pastoris</i> are the main experimental organisms in this study. Both species are used as cell factories (in the laboratory and commercially) for secreted protein production. <i>S. cerevisiae</i> is also an excellent model organism for investigations into the basic events involved in protein secretion and stress responses. <i>P. pastoris</i> is less amenable to basic studies but is an outstanding cell factory. This project will create some tools for basic studies in <i>P. pastoris</i> as well as using both organisms for comparative studies with each other and with the principal filamentous fungal cell factory, <i>Aspergillus niger</i>. We will examine the secreted expression of lysozyme and derived variant molecules, as well as scFv antibody proteins. Many of the necessary strains are already available although some will be constructed within the project. Controlled and reproducible cell culture is a necessary part of the studies proposed. The main technical objectives and main methods to be used in the study are: 1. Use transcriptomics and proteomics to examine the stress responses due to expression of variant lysozymes in <i>S. cerevisiae</i> and <i>P. pastoris</i>. 2. Examine the fates of selected lysozyme variants, including the folded states, using imaging, conformational antibody approaches and protein turnover studies. 3. Express and examine resulting secreted protein yields and stress responses from scFv proteins, measure thermal stability of purified scFvs, and compare with lysozymes. 4. Use comparative genomics methods to compare stress responses from <i>S. cerevisiae</i>, <i>P. pastoris</i> and <i>Aspergillus niger</i> to find commonality and differences. 5. Define and test a strategy for rational strain improvement for optimized secretion of scFvs based on stress response and protein fate studies.</p>		

Combined /omics approaches to understand and control library enriched microbial cell factories		
Professor Phillip Wright	University of Sheffield	£297941
<p>This project aims to apply a genome-wide, multiscale approach for functional genomics to improve the production of recombinant proteins in <i>Escherichia coli</i>, and to take this approach further to begin to understand how to improve the production of glycosylated proteins. We will integrate data obtained from DNA microarray inverse metabolic engineering tools such as SCALEs (multi-Scale Analysis of Library Enrichment), with that obtained from high throughput quantitative shotgun proteomics (building on 8-plex isobaric mass tag technology - iTRAQ) methods as an addition, as proteomics is a level closer to the functional understanding of a phenotype. We will analysis the data using a multivariate approach. We then will seek to move beyond simple statement of whether the transcriptomic and proteomic data are concordant or discordant, but rather how these then can be interpreted in the context of biological pathways. In particular those related to recombinant protein synthesis of the model glycoprotein. Implementation of /omic based tools and the resulting data is necessary to provide a systems level understanding of an organism so that a deeper functional understanding results in bioprocess engineers being able to take advantage of findings in the biosciences, and translate these to valuable processes and products for UK bioprocessing businesses. We seek to ultimately improve the production of glycosylated recombinant proteins such as the N-glycoprotein AcrA, in <i>E. coli</i> here as an exemplar project. This protein has been demonstrated as being possible to produce in <i>E. coli</i>, following the transfer of the N-glycosylation system from <i>Campylobacter jejuni</i> into <i>E.coli</i> cells.</p>		

Pichia pastoris protein secretion: analysis of constraints, optimisation and methods development

Dr David Leak

Imperial College London

£724360

The methylotrophic yeast *Pichia pastoris* is an established expression platform for secreted and membrane proteins and is being modified to "humanise" its glycosylation pathway. However, a number of secreted proteins do not express well in this host, partly because of inefficient trafficking through the ER, which leads to the induction of the unfolded protein response (UPR). Although the initial UPR expression of chaperones may be beneficial, it can ultimately result in reduced secretion, proteolysis and increased product heterogeneity. In this project we will undertake a global transcriptome and metabolic profile analysis of the UPR in *P. pastoris*, (initially on chemostat cultures then validated in a typical fed batch regime) and use the information gained to evaluate different potential reporters for the UPR including GFP, and metabolic fingerprinting. The optimum reporter system, based on factors such as responsiveness (correlated with the protein induction profile) and sensitivity (this may depend on the scale and type of culture) will be used to explore the potential for development of an on-line UPR monitoring and control system as well as for screening of constructs on a small scale. Applications of the reporter linked to moderate/ high throughput screening will also be investigated, with the aim of devising a strategy to screen large numbers of variants to select for those with improved secretion. Even when there is no evidence of induction of UPR, the specific productivity of secreted protein production is moderate, and nothing is known about what limits productivity. Therefore, we intend to explore the physiological status of highly secreting cells using combined transcriptomic, metabolomic and flux analysis of a construct with good secretion. This should indicate whether productivity limits are due to the secretion apparatus or biosynthetic capacity. In principle, a similar surrogate reporter approach may be used to indicate secretion saturation.

Multifunctional Chromatography materials for improved downstream processing

Professor Owen Thomas

University of Birmingham

£595931

The manufacture of many of today's biopharmaceuticals already stretches technical/economic acceptability to breaking point, and the move towards ever more sophisticated biologics and therapies is expected to compound these issues yet further. The explosion in new high-level expression systems for the production of recombinant proteins has reduced upstream processing costs to the point where concentration and purification operations, i.e. downstream processing (DSP), now dominates the overall manufacturing cost for many protein therapeutics. The success of future medicines, especially those characterized by very large physical size and referred to as nanoplexes, will to a great extent hang on our ability to introduce radical and prompt changes to current biomanufacturing thinking and practice. In light of the above, and given the dominant role that chromatography has played over the past forty years and is no doubt expected to play long into the future, shouldn't we now expect much more from 'next generation' chromatography matrices? The objective of this project proposal, which targets 'Improved Downstream Processing' of the BRIC initiative is to advance new 'multifunctional' chromatography materials that enable efficient separation of future nanoplex bioproducts from smaller, but chemically very similar 'problem' contaminants in a 'one column-one bead' process that combines size exclusion with ion exchange principles. The above responds expressly to the identified challenges of improved downstream processing, as well as to areas the BIG-T report considers vitally important, i.e. novel manufacturing and bioseparation technologies.

Protein nucleation and crystallisation on novel 3-D templates		
Dr Daryl Williams	Imperial College London	£384817
<p>The direct crystallisation of proteins from fermentation broths is an industrially attractive route for protein manufacture. This proposal describes an integrated and innovative research programme for the improved understanding of the effects of both surface chemistry and topography on heterogeneous protein nucleation and crystallisation via the use of novel templates. The main objectives of this study include: 1. The use of specific surface chemistry in combination with precise surface topographical features to allow novel surface templates to be created. 2. Use of these novel templates for protein crystallisation studies 3. An improved understanding of protein nucleation via novel detection methods. 4. Improved protein crystallisation fundamentals to enable the control and optimisation of bioprocessing. The methodologies to be employed include: 1. Sub 100 nm surface topographies will be templated onto surfaces by a PDMS stamping technique and via colloidal particle arrays. Other features will be fabricated via an anodisation approach. 2. A wide range of controllable surface chemistry's to be controlled via an established method; the self-assembled monolayers (SAMS). Surface characterisation of the templates will include wettability, FTIR, zeta potential, SEM, AFM, TEM. 3. A Quartz Crystal Microbalance capable of detecting depositions of nanogram levels protein onto the surfaces will monitor crystal nucleation, as well as measuring the viscoelastic properties of the protein layer. 4. The protein structure, morphology, habit and purity will be characterised for the crystals obtained. Our hypothesis is that these novel protein crystallisation templates will be superior to current nucleation media and methodologies. Coupled with an improved understanding of the fundamentals of protein nucleation and crystallization, these templates could directly, or indirectly, facilitate direct crystallisation in the reactor broth.</p>		

Delta3D; Bench top assays for the rapid detection of protein 3D structural changes		
Professor Jeremy Lakey	Newcastle University	£363525
<p>Proteins and complex biologicals (such as viral particles) are a significant growth area in pharmaceuticals and now account for 30% of the drug pipeline and 10% of sales. Biologics present an important extra variable compared to the small molecule therapeutics that once dominated the market and that is a complex non-covalent 3D structure. Changes to this are not revealed by normal analytical processes but can adversely affect solubility, stability and function. In recent years industry has adopted a series of biophysical techniques to measure the 3D structural integrity of proteins. These include fluorescence, circular dichroism spectroscopy, analytical ultracentrifugation, NMR, X-ray crystallography, light scattering and gel permeation chromatography. Whilst powerful, these methods are expensive, require specialist analytical knowledge and often require large amounts of protein. We are avid users of biophysical methods but also wish that non-specialists may be able to detect changes to the soft 3D structure of a known protein. The methods need not define the exact alteration as this can be done with the existing methods once the problem has been identified. Thus we hope to improve the early detection of structural changes or structural heterogeneity in samples. Furthermore, we hope to extend the analysis from the pure protein stage towards the fermentation and formulation stages. The methods which include spectroscopy of protein probe complexes, small scale hydrophobic interaction chromatography, cross-linking and limited proteolysis are not new but their design for robust generic analysis of protein structure by non-specialists has not been realised. We hope to develop the foundations for some commercialisable kits which will become commonly used in industry and academia.</p>		

New approaches to high throughput protein, isolation, purification and concentration		
Dr Barry Moore	University of Strathclyde	£392967
<p>This project will investigate non-chromatographic methods for purifying proteins based on selective coprecipitation of the target in the form of protein coated microcrystals (PCMC). The resultant precipitated PCMC particles consist of protein immobilised on the surface of a crystalline excipient carrier and are stable for long-term storage. The technique is expected to be particularly useful for isolation of complex protein assemblies not well suited to chromatography. We will investigate how coprecipitation compositions can be tuned to maximise selectivity and stability via changes to parameters such as excipient, solvent, pH and ionic strength. The scale-up potential of the process will be evaluated.</p>		

Total £3,544,382

STEERING GROUP MEMBERS

Chair

Professor John Birch, Lonza Biologics

Industrial Members

Dr Mark Carver, Avecia Biotechnology

Dr Brendan Fish, Cambridge Antibody Technology

Dr David Glover, UCB Celltech

Dr Peter Levison, Pall Life Sciences

Dr Carol Marshall, GlaxoSmithKline

Dr Simon Roe, Antisoma

Academic Members

Professor Kevin Brindle, Cambridge

Professor Zhanfeng Cui, Oxford

Professor Elaine Martin, Newcastle upon Tyne

Dr Mark Smales, Kent

Professor Nigel Titchener-Hooker, UCL

Professor Phillip Wright, Sheffield

BRIC CLUB MEMBERS & COMPANY INFORMATION

Below is some information provided by some of the BRIC Club members giving information about the company and its research interests in BRIC.

Antisoma
Avecia Biologics
Axordia Ltd
Centre of Excellence for Life Sciences
Cobra Biomanufacturing
Eden Biopharm
GlaxoSmithKline
GlycoForm
HPA
Ipsen Limited

Lonza Biologics plc
MedCell BioScience
MedImmune
Millipore BioProcessing Ltd
NIBSC
Novozymes Delta Ltd
Pall Life Sciences
Stem Cell Sciences UK Ltd
UCB Celltech

Antisoma

Antisoma is a London-based biotechnology company specialising in the development of novel anti-cancer drugs. Antisoma has a diverse portfolio of products in development which include three products which are being evaluated in clinical trials and three in preclinical development. Antisoma's products target tumours by several different mechanisms and are intended for the treatment of a range of cancers. Antisoma fills its development pipeline by acquiring promising new product candidates from internationally recognised academic or cancer research institutions. Its core activity is the preclinical and clinical development of these drug candidates. Our research interests in BRIC include all research topics related to the development and manufacture of recombinant proteins and in particular improvements to upstream and downstream processing.

Please visit www.antisoma.com for further information.

Contact: Dr Simon Roe, Manufacturing Manager
Tel +44 (0)20 8799 7952, email simon.roe@antisoma.com

Avecia

Avecia's Biologics business is a leading provider of development and manufacturing services in microbial and mammalian-based therapeutics and a natural partner for customers from process creation through to licensed product manufacture.

Their track record of meeting customer expectations is founded upon technical and functional excellence, a dedicated project team focus and a commitment to quality and cGMP compliance.

The Biologics Business has more than 30 years experience in developing novel biotechnology processes and has been focused exclusively on human therapeutic proteins since 1996. This experience has recently been extended to process creation and development for mammalian cell culture-derived therapeutics.

Website: www.avecia.com

Contact name: Mark Carver mark.carver@avecia.com

Axordia Ltd

Axordia is one of the UK's leading human embryonic stem cell (hESC) companies. It has a unique portfolio of patent protected technologies and proprietary materials - GMP derived hESC lines; the capacity to produce key cell line derivatives, including a patent protected endovascular line with powerful potential; RNA interference (RNAi); Wnt and Notch signalling; a suite of hESC biomarkers.

Based in Sheffield and with strong links to the University of Sheffield, the UK's leading university in the generation of stem cell related IP, Axordia is focussed on the delivery of a range of novel cells and kits that will enable drug discovery and the production of quality-assured cells for transplantation to patients suffering degenerative disease and injury.

Axordia is developing and commercialising products in three areas

- **Drug discovery** tools that will support traditional and new generation drug discovery using hESC and key cell lines derived from hESC.
- **Therapeutic** treatments derived from hESC covering transplantation, cardio-vascular disease, diabetes and Parkinson's
- **Technologies** and materials that will support the rapid and successful development effective products by the hESC industry

Website: www.axordia.com

Contact name: Rod Westrop westrop@axordia.com

Centre of Excellence for Life Sciences

CELS exists to drive growth of the healthcare & life science economies of North East England.

It does this by:

- supporting the region's existing companies
- helping to launch and support new companies
- attracting investment and new healthcare organisations to the region
- helps companies diversify into healthcare markets
- sits at the hub of a global network of healthcare and bio-clusters
- manages regional networks for healthcare R&D and inter-company collaboration
- develops and runs business incubator and bio-park facilities
- Provides a wide range of commercial, fore-sighting and business support services

CELS is working to develop distinct strengths in research, science and technology within a selected number of specific Life Sciences fields to create an engine for growth that stimulates a vibrant, fast-growing and cohesive regional healthcare economy where local and global companies will want to invest and develop and where world class talent will want to live and work.

CELS will be the strategic architect and co-ordinator of the healthcare economy of North East England by acting as a catalyst delivering economic growth by conditioning technology and innovation which it identifies and develops, combining knowledge transfer, entrepreneurship, infrastructure and networks to create a compelling environment for further investment.

Website: www.celsatlife.com

Contact name: Philip Aldridge Philip.aldridge@celsatlife.com

Cobra Biomanufacturing plc

Cobra Biomanufacturing plc is a leading manufacturer of biopharmaceuticals to the life science industry. Founded in 1992 in Keele, Staffordshire, and with a second manufacturing site in Oxford, Cobra provides innovative manufacturing solutions to overcome the hurdles in producing therapeutic proteins, viruses, DNA, and cell products to GMP. Production systems include *E. coli*, *Bacillus subtilis* and CHO cells for protein expression, packaging cell lines for virus manufacture and an antibiotic-free plasmid maintenance system for DNA vaccine/gene therapy production in *E. coli* (ORT). Additionally, Cobra has developed an effective oral vaccine delivery system, ORT-VAC, using attenuated *Salmonella*. Cobra also has considerable experience in the optimisation of microbial and mammalian cell fermentation, downstream purification and the development of QC assays. A range of unique, patented technologies underpins this revenue generating biotechnology company.

Contact: Dr Rocky Cranenburgh, Section Head of Research. rocky.cranenburgh@cobrabio.com
www.cobrabio.com

EDEN

Eden Biodesign is an integrated biopharmaceutical development organisation that evolved out of Eden Biopharm, a successful international development and manufacturing consultancy. Eden Biodesign is the operator of the UK National Biomanufacturing Centre that provides world-class process development, clinical trial cGMP manufacturing and analytical development for every significant biopharmaceutical product technology.

As product developers, Eden understands exactly how process development studies and clinical trial manufacture fit into the broader picture of clinical development.

Website: www.edenbiodesign.com

Contact name: Crawford Brown Crawford.brown@edenbiodesign.com

GlaxoSmithKline

GSK have a challenging and inspiring mission: to improve the quality of human life by enabling people to do more, feel better and live longer. They are the only pharmaceutical company to tackle the World Health Organization's three 'priority' diseases – HIV/AIDS, tuberculosis and malaria.

Headquartered in the UK and with operations based in the US, GSK are one of the industry leaders, with an estimated seven per cent of the world's pharmaceutical market.

GSK produce medicines that treat six major disease areas – asthma, virus control, infections, mental health, diabetes and digestive conditions. In addition, we are a leader in the important area of vaccines and are developing new treatments for cancer.

Website: www.gsk.com

Contact name: Carol Marshall carol.t.marshall@gsk.com

GlycoForm Limited

GlycoForm Limited is a biopharmaceutical company designing Novel Synthetic Glycoproteins. GlycoForm's competitive advantage comes from breakthrough glycochemistry and conjugation which enables the generation of synthetic glycoproteins which deliver enhanced pharmacodynamics, extended pharmacokinetics and targeted delivery. GlycoForm is building an outstanding team to translate these improvements through into patient care.

Website: www.glycoform.co.uk

Contact name: Michael Short michael.short@glycoform.co.uk

Health Protection Agency

The Health Protection Agency is a national organisation which is dedicated to protecting people's health and reducing the impact of infectious diseases, chemical hazards, poisons and radiation hazards.

Core business areas include research and development of vaccines against infectious diseases, process development and GMP manufacture of biologics derived from microbial fermentation - particularly those requiring containment or focused on the bio-defence market. In addition, a wide range of support services are offered from biosafety, through GLP immunoassay testing to *in-vivo* studies and the supply of cell cultures.

We have a proven track record in bioprocess development and optimisation for both in-house and customer derived products, including enzymes, therapeutic proteins and vaccines. Development expertise includes media & yield optimization, fermentation scale-up and purification regimes. Following development in non-GMP laboratories, processes can be transferred to our extensive GMP compliant facilities for biopharmaceutical manufacture.

Contact name for BRIC Philip Vincent, Process Scientist (Phil.VINCENT@hpa.org.uk)

IPSEN

The Company's development strategy is based on a combination of products in targeted therapeutic areas (oncology, endocrinology and neuromuscular disorders), which are growth drivers and primary care products which contribute significantly to its research financing. This strategy is also supported by an active policy of partnerships. The location of its four R&D centres (Paris, Boston, Barcelona, London) gives the Group a competitive edge in gaining access to leading university research teams and highly qualified personnel. In 2005, Research and Development expenditure reached €169 million, i.e. 20.9% of consolidated sales, which amounted to €807.1 million in the Group's pro forma accounts set up according to the IFRS. Nearly 700 people in R&D are dedicated to the discovery and development of innovative drugs for patient care.

Website: www.ipsen.com

Contact name: Andy Pickett andy.pickett@ipsen.com

Lonza Biologics plc

Lonza is a chemical and biotechnology company headquartered in Switzerland with sales of CHF 2.52 billion in 2005. It has 6300 employees in 22 production and R and D sites around the world and is one of the leading manufacturers of chemical intermediates, active ingredients and biopharmaceuticals for the pharmaceutical and agrochemical industries.

It is one of the leading companies in the field of process development and contract manufacture of biopharmaceutical proteins from both mammalian cell and microbial systems. The Company's research interests extend from gene expression technology to development and scale up of fermentation and purification processes.

Further information can be found on the Company's website www.lonza.com

MedCell BioScience

MedCell BioScience is an innovative healthcare company dedicated to developing new regenerative medicine technologies for the treatment of tendon and ligament injuries. The Company is focused on improving health and welfare by providing the medical profession with revolutionary cellular therapeutics for tendon and ligament injuries. MedCell's primary technologies utilise adult mesenchymal stem cells in the treatment of tendinitis, tendinosis and desmitis in conditions such as rotator cuff injuries (RCIs) and Achilles tendinopathies. MedCell's core technologies harness the plasticity of adult mesenchymal stem cells to promote regeneration of tendon or ligament in place of a scar tissue repair.

Having developed technologies within the veterinary market and secured the leading position in this branch of the healthcare sector, MedCell will now establish a prime position in the human market through a combination of R&D, acquisitions and strategic alliances.

MedCell initially developed and commercialised its technology in the veterinary healthcare market where clinical outcomes in racehorses have shown a 50% improvement in prognosis. We are currently translating the Company's knowledge and expertise to provide cellular therapies for man. The Company changed its name from VetCell BioScience Ltd to MedCell Bioscience Ltd in 2007 to reflect the development of the technology for the human market.

Website: <http://www.medcell.eu/default.htm>

Contact name: Greg McGarrell gmcgarrell@medcell.eu

MedImmune

MedImmune, which incorporates the former Cambridge Antibody Technology (CAT) as of October 2007, is committed to advancing science to develop better medicines that help people live healthier, longer and more satisfying lives. In June 2006, AstraZeneca (AZ) acquired CAT, and then acquired MedImmune, Inc. in June 2007. These acquisitions by AstraZeneca represent a major long-term strategic investment in novel biological therapeutics, expanding and diversifying AZ's R&D science base to address drug targets through three

technological approaches: small molecules, biologics and vaccines. CAT's leading discovery platform and early development experience is fully complementary to MedImmune's discovery and more mature development and state-of-the-art manufacturing facilities. CAT is a biopharmaceutical company committed to developing human monoclonal antibody therapeutics to bring improvements to seriously ill patients' lives.

CAT and AstraZeneca have a track record of working together: CAT commenced a major strategic alliance with AstraZeneca in late 2004 to discover and develop human antibody therapeutics, principally in inflammatory disorders. The excellent progress of the alliance demonstrated the power of combining the capabilities of both organisations and the acquisition of CAT by AstraZeneca represents the next logical step in the successful development of CAT. CAT will become central to AstraZeneca's plans to establish a major international presence in the research and development of biological therapeutics.

Website: www.cambridgeantibody.com

Contact name: Brendan Fish Brendan.fish@cambridgeantibody.com

Millipore Bioprocessing

Millipore Bioprocessing is located in Consett Co Durham and has responsibility for the manufacture of Millipore chromatography media - principally the ProSep range of Protein A adsorbents applied in the industrial scale manufacture of therapeutic antibodies. Millipore Consett also houses an R&D Team that has responsibilities for the development of new chromatography media together with a wider brief to investigate New Technologies and Pre-development of prototype services and products applicable to fully Integrated Bioprocessing. The latter depends upon a mix of 'in house' invention and outside alliances, and thus membership of BRIC is viewed as a valuable asset in respect of staying abreast of and potentially influencing the portfolio of Bioprocessing Research undertaken in UK institutions.

Further information can be found on the Company's website <http://www.millipore.com/>

National Institute for Biological Standards and Control (NIBSC)

The National Institute for Biological Standards and Control (NIBSC) is responsible to the UK Departments of Health, providing the laboratory scientific expertise for the regulation and quality control of biological medicines used in the UK. This involves characterisation of current and potential products, understanding their modes of action and those factors which impact on safety, potency and efficacy, as well as independent "batch release" of vaccines and products from human blood. In addition, NIBSC produces, calibrates and distributes the vast majority of primary biological reference materials for measuring product potency, on behalf of WHO. This involves Institute staff in drafting WHO Recommendations on the production and quality control of biopharmaceuticals. In addition to these core functions, NIBSC hosts the UK Stem Cell Bank and various other reagent repositories.

Website: <http://www.nibsc.ac.uk>

Contact name: Chris Jones (cjones@nibsc.ac.uk)

Novozymes Delta

Novozymes has acquired Delta Biotechnology Ltd from the sanofi-aventis group. Established in 1984, Delta is, from 6th July, a wholly-owned subsidiary of Novozymes A/S operating as a self-contained business unit with both its R&D and manufacturing facilities based in Nottingham, UK.

The new company will operate under the name Novozymes Delta Ltd.

Novozymes Delta develops and manufactures recombinant protein products using highly engineered, proprietary *Saccharomyces cerevisiae* yeast strains. The Company also undertakes flexible licensing of its yeast based expression system to offer its pharmaceutical, healthcare and biotech partners customised solutions to their recombinant protein needs. Recombum(r), the Company's lead product, is the world's first and only animal-free, commercially available recombinant human albumin; it is used in the manufacture of human therapeutics that have been approved by both the FDA and the EMEA.

Novozymes is the world leader in the production of enzymes in a range of microorganisms and has acquired Delta as part of its strategy to extend its portfolio of products that are used as key ingredients in biopharmaceutical products.

Website: <http://biopharmaceuticals.novozymes.com/>

Contact name: Steve Berezenko, spbe@novozymes.com

PALL

Pall's biopharmaceutical filtration and separations products are used worldwide for production of biotech products and biopharmaceutical products. Pall technology is found in Contract and OEM applications, Formulation and Filling operations, Quality Control laboratories and R&D process development labs. Our products are supported by extensive protocols and technical reports, an industry-leading scientific and technical staff, and worldwide offices and distributors for easy ordering.

Website: www.pall.com

Contact name: Peter Levison peter_levison@europe.pall.com

Stem Cell Sciences

Stem Cell Sciences (SCS) is an international research and development company specialising in the provision of stem cells and stem cell technologies for research and the clinic. SCS takes pride in its long-standing relationships with leading academic centres of excellence in the stem cell field, which help maintain the Company's position at the cutting edge of the stem cell industry. SCS has an established track record of commercialisation with international biotechnology and pharmaceutical companies including Pfizer, Sanofi-Aventis, GSK, Chemicon, Deltagen and Lexicon. The company has business and scientific operations in Edinburgh and Cambridge (UK), Melbourne (Australia) and Kobe (Japan). In 2007 SCS will open new offices in California (USA).

Stem Cell Sciences' core objective is to develop safe and effective stem cell-based therapies for currently incurable diseases. SCS' technologies provide convenient, validated solutions to problem issues with stem cells:

- isolation of stably growing human stem cell lines.
- development of a range of cell culture media products to enable the standardized, reproducible propagation of clinically acceptable cells.
- cell purification technology valuable for generating stem cells or their progeny for use in screens for functional genomic, pharmacological or predictive toxicology or appropriate cell types for transplantation.
- cell production automation enabling the generation of a consistent supply of high quality cell lines in sufficient quantities for the clinic.

Website: www.stemcellsciences.com

Contact name: Tim Allsopp tim.allsopp@stemcellsciences.com

UCB CELLTECH

UCB is a leading global biopharmaceutical company dedicated to the research, development and commercialisation of innovative pharmaceutical and biotechnology products in the fields of central nervous system disorders, allergy/respiratory diseases, immune and inflammatory disorders and oncology - UCB focuses on securing a leading position in severe disease categories.

Website: www.ucb-group.com

Contact name: David Glover David.Glover@UCB-Group.com

DELEGATE LIST

Dr David Armitage

Engineering, University of Leicester
daa9@le.ac.uk

Current Role and Expertise

I am currently Lecturer in Mechanics of Materials at the University of Leicester. My research interests include development of novel instrumentation techniques for characterisation of receptor ligand interactions and application of these techniques in the pharmaceutical sector. I am also active in the development of novel surface modified implant materials for improved osseointegration and reduced infection rates.

I have considerable expertise in optical biosensor development. This is an important area in characterising drug activity and has advantages of portability and versatility enabling easy integration into existing structures. I have worked both on the development of instrumentation for analysis of biosensor signals and on the design of suitable measurement strategies. The majority of processes I am interested in require no labelling, hence offer very high throughput. Both Surface Enhanced Raman Spectroscopy and Surface Plasmon Resonance are strong contenders for applications in the biopharmaceutical field.

Dr Simon Baker

Senior Research Fellow at Oxford Brookes University/Consultant Research Manager at ThermoFisher Scientific Life Sciences, Oxford Brookes University
simon.baker@brookes.ac.uk

Current Role and Expertise

EPSRC grant EP/D073227/1 (A Novel Process for the Continuous Production of Surfactin with Dr PJ Martin, Chem Eng Manchester) BBSRC grant E17078 (Novel Approaches to Nitrile Hydrolysis and Related Reactions, with Dr D Kelly, Org Chem Cardiff); Postgraduate studentship funded by the Taiwanese RC (Foam fractionation of surfactin, with Prof R Darton, Chem Eng Oxford and Prof R Thomas Phys & Theoretical Chem Oxford).

I am working on multidisciplinary projects with chemical engineers, organic and physical chemists. We are focusing on a model biosurfactant (surfactin) to develop new purification processes based on foam fractionation. Surfactin has many properties in common with peptide antibiotics e.g. daptomycin, and also has some interesting chiral phase transfer properties which may prove useful in the single step purification of chiral synthons. In addition I have been a consultant for ThermoFisher Scientific for the last seven years, including a 9 month period leading their R&D effort at their labs in Epsom.

Dr Roslyn Bill

Life and Health Sciences, Aston University
r.m.bill@aston.ac.uk

Current Role and Expertise

Our research activities focus on yeast – a flexible, cost-effective eukaryote – as it is the ideal host for optimisation of biotherapeutic production. We apply transcriptome analysis and parallel optimization methods to engineer new strains. Our aim is to gain an understanding of the molecular processes underpinning improved yields; facilitating new host development and streamlining bioprocessing. We are currently writing up two manuscripts: one on the development of a strain that improves yields by 50-fold (recently featured on BBC Midlands Today) and one examining fast and effective process optimization in parallel micro-bioreactors.

Our expertise is in the area of the following research challenges: 'bioscience underpinning bioprocessing – improved biological understanding to enhance bioprocessing'. In particular: 'understanding, controlling and manipulating metabolism in microbial fermentation'.

Professor John Birch

Lonza Biologics
john.birch@lonza.com

Professor Gary Black

Chair in Protein Biochemistry
School of Applied Sciences, Northumbria University
gary.black@northumbria.ac.uk

Current Role and Expertise

Personal Chair in Protein Biochemistry with research activity in the expression of recombinant enzymes in *Escherichia coli* and their biochemical and structural characterisation; proteome analysis of *Streptococcus* and *Bacteroides*; and the analysis of recombinant protein heterogeneity.

The analysis of recombinant protein heterogeneity

Dr Daniel Bracewell

Biochemical Engineering, UCL
d.bracewell@ucl.ac.uk

Current Role and Expertise

Current Role: Lecturer in Bioprocess Analysis. One of the PIs at the Innovative Manufacturing Research Centre (IMRC) in Bioprocessing, based within the Department of Biochemical Engineering at UCL. Involving supervision of doctoral student research projects (often associated with industrial collaborators) in the area outlined above.

Expertise from a range of projects associated with the processing of bio-therapeutics, common themes being the application of analytical technology, scale-down tools and models, mostly in the areas of downstream processing and formulation. I am also a co-PI on a first round BRIC project with Paul Dalby.

Dr Jeremy Bright

GlycoForm Ltd
jeremy.bright@glycoform.co.uk

Professor Howard Chase

Chemical Engineering, University of Cambridge
hac1000@cam.ac.uk

Current Role and Expertise

I am the University's Professor of Biochemical Engineering. We research into improving the separation and recovery of biological entities (therapeutic proteins, DNA sequences, virus particles, and therapeutic cells).

Novel methods for the separation of different types of human cell. Novel bioreactors for the growth and expansion of stem cells. Highly selective separation processes for biological entities. Optimisation, integration, intensification and simplification of bioprocesses.

Dr Eugenia Dahm-Vicker

Chemistry, Imperial College London
e.dahm-vicker@imperial.ac.uk

Current Role and Expertise

Project Manger of the Single Cell Proteomics (SCP) and Lipidomics Project (www.singlecellanalysis.ac.uk) which is a £5 million multidisciplinary initiative funded by the EPSRC and BBSRC to create an advanced suite of technologies for the study of single cells using proteomic approaches.

The SCP is developing both high throughput label-free methods based on 2DIR and various separation methods and microfluidic based chip approaches using fluorescence labelling for readout of the protein levels extracted in situ. The proposed instrumentation draws together a number of individual technologies from across Imperial College: 2DIR is a key component of this suite.

A suite of platform technologies for cellular analysis is being developed under the auspices of The Chemical Biology Centre at Imperial College via a £5 million grant from EPSRC and BBSRC (www.singlecellanalysis.ac.uk). Using these technologies we bring the following expertise, which we believe are relevant to the BRIC workshop; i) Cell Culture on microcarriers: We are currently culturing cancer cell lines on beads and extending this to primary and stem cell lines for the purposes of developing novel toxicological assays. The aim is to analyse and characterise differentiated stem cells, in particular hepatocytes, cultured by our collaborators at the Hammersmith Hospital (Prof Nagy Habib and Dr Natasa Levicar). Our focus on stem cells links in well with existing stem cell projects, e.g. projects from Prof Chaudhuri and Prof Oreffo. ii) Label-free Detection and Analysis: The group has established a novel laser-based infra-red analogue to NMR, known as 2DIR. It has been used successfully for protein and peptide fingerprinting trials identifying proteins by their amino acid content (paper in press: Fournier et al., Analytical Biochemistry). It currently has picomol sensitivity and can be used to disentangle the composition of highly complex mixtures of metabolites. Rapid analysis of metabolites by 2DIR would link in well with proposed work on analysis of cell interactions to define how protein production is controlled. 2DIR is a non-invasive technique which will allow us to characterise metabolites from a number of different cell cultures and tissues.iii) Microfluidics: Extensive use of microfluidic devices for cellular manipulation allows us to target specific areas of the cell membrane for subsequent analysis with 2DIR. Using microfluidic environments and 2DIR analysis of metabolites to test the differentiation state of stem cells will enable rapid evaluation and reduce sample number and cost. This would allow rapid prototype testing amenable to scale up.iv) Future plans: We would now like to put these areas of expertise together and culture differentiated stem cells, hepatocytes to begin with, in either in microfluidic devices or large scale environment, to test the efficacy of various stem cell differentiation protocols, e.g. p450 profiling or albumin production using 2DIR. This will subsequently lead to a uniquely detailed toxicological screening and analysis. The toxicological screening using 2DIR can be extended to any cell or tissue type subsequent to batch growth or rapid processing in microfluidic carriers.

Professor Gerard Fernando

Metallurgy and Materials, University of Birmingham
g.fernando@bham.ac.uk

Current Role and Expertise

I currently lead the Sensors and Composites research group that has a compliment of 4 post-doctoral fellows, 4 PhD and 3 MRes researchers. I am the PI on 3 EPSRC projects. (i) Clean filament winding - a new technique to produce filament wound composites. I want to use bio-derived polymers and materials to make composites via filament winding. (ii) Self-sensing composites – here conventional E-glass fibres are being used to enable evanescent wave spectroscopy and in-situ damage detection. I wish to deploy study the surface reactions of synthetic

and bio-derived materials using optical fibre sensors. (iii) Advanced composites life and integrity management – I am developing a range of sensors to enable the cross-linking reaction and diffusion of moisture to be detected using optical fibre sensors. These sensors can be used to study the chemical and mechanical integrity of raw materials during the extraction, refining, compounding and packaging procedures. I have also developed a novel optical fibre-based acoustic emission sensor. This sensor was developed for the electrical industry for the detection of partial discharge. In the current industrial sector, it can be adapted for detection tool-wear monitoring and fracture processes in materials.

I have recently filed a patent application for a multi-functional sensor that can monitor in real-time (i) near-infrared spectra of organic species, (ii) temperature, (iii) refractive index and (iv) strain. This sensor can be used to monitor chemical integrity or consistency of the raw material, changes in chemistry during extraction, purification and storage. The above-mentioned parameters are monitored using a single (conventional) fibre optic spectrometer. The sensor can be secured within reaction vessels or embedded in the end product (for example bio-materials). I have also developed (via an EPSRC equipment grant) a technique to enable simultaneous thermal, spectral and physical analyses of polymers. In this technique, thermal characterisation is carried out using a differential scanning calorimeter (DSC) where a custom-designed fibre optic probe is inserted into the DSC to enable the acquisition of non-contact infrared spectra whilst at the same time extracting information on the thermal expansion/contraction of the material. Areas that I would like to further develop include: (i) An optical dynamic mechanical thermal analyser to characterise polymers; (ii) adding sensing functionality to bio-derived polymers; (iii) investigating new and environmentally friendly manufacturing processes (after I understand better current techniques for extraction, refining and post-processing); (iv) developing new techniques to characterise chirality, isomers, grain structure, oxidative stability, etc using optical fibre technology; and (v) modifying a rheometer to study simultaneously the rheology and FTIR spectra and evolution of refractive index in real-time. A unique feature of the optical fibres is that they are immune from electromagnetic interference and the sensors can be interrogated remotely. They also provide an ideal platform to study surface interactions on light guides such as silica and PMMA.

Professor Robert Forbes

Professor in biophysical pharmaceuticals
IPI/ Pharmacy, University of Bradford
r.t.forbes@brad.ac.uk

Current Role and Expertise

Research interests include protein stabilisation, protein isolation, protein formulation, biopharmaceutical product development

Protein stabilisation, Protein isolation, Protein formulation, Biopharmaceutical product development.

Dr Hugh Guan

Bioengineering, Brunel University
Hugh.Guan@Brunel.ac.uk

Current Role and Expertise

I have been working with mechanical engineers and biologists to design improved and adapted counter-current chromatographic columns, and to develop competitive and commercially viable solid media-free chromatographic processes for biologically active macromolecules. These new processes are an alternative to conventional solid media-based column chromatography and would reduce the separation and purification steps and make the product recovery processes more robust and suitable for large scale industrial uses.

I can bring expertise in a broad range of bioseparation and purification technologies and their potential integration towards manufacturing biopharmaceutical products to suit today's R&D needs of industry and to reflect the government science & technology strategies. Specifically, I can bring an expert view on the large scale use of ultrafiltration, extraction using aqueous polymer two-phase systems, column chromatography, counter-current chromatography, centrifuges, and nano-technologies. Reference examples are: Guan et al., *Biotechnol. Bioeng.* 40, 517, 1992; Guan et al., *Bioseparation*, 4, 89, 1994; Guan et al. *Biotechnol. Bioeng.* 58, 464, 1998; Guan & Kemp, J. *Biotechnol.* 69, 95, 1999; Guan et al. *Enzyme & Microb. Technol.*, 28, 218, 2001; Guan et al. *J. Appl. Microb.* 94, 456, 2003; Guan et al. *J. Chromatog. A*, 1151, 115, 2007.

Dr Ian Henderson

Division of Immunity and Infection, University of Birmingham
i.r.henderson@bham.ac.uk

Current Role and Expertise

Role: Senior Lecturer Activities: Protein secretion in E. coli. Interaction of bacterial products with the immune system. Bacterial genomics. Infectious processes of bacteria

I have a degree in industrial microbiology. My group is particularly interested in developing protein secretion pathways in bacteria for commercial purification of proteins; in this respect we are currently developing a system for the purification of single chain antibodies. We have significant expertise in protein purification and biophysical analyses. I have a strong interest in the interaction of bacterial products with the immune system. We are currently investigating immune stimulants with a particular focus on cytokine stimulating factors.

Professor Chris Hewitt

Chem Eng, Loughborough University
c.j.Hewitt@lboro.ac.uk

Current Role and Expertise

I have been working in the field of Pharmaceutical Engineering for over 15 years and I am now developing the Cell Technology research group within the Interdisciplinary Centre for Biological Engineering at Loughborough University (ICBE - of which I am co-founder) which seeks to study the interaction of the organism with the process environment using such non-invasive techniques as flow cytometry, image analysis and NIR spectroscopy.

MY work seeks to improve our understanding of how cells behave within the process engineering environment covering such diverse areas as cell culture/tissue engineering, fermentation, brewing, bio-remediation, bio-transformation and food processing. This work has been carried out mostly with industrial collaborators, our motivation being process improvement and optimisation for informed scale-up/out.

Dr Chris Jones

NIBSC
cjones@nibsc.ac.uk

Professor Ian Jones

Biological Sciences, University of Reading
i.m.jones@rdg.ac.uk

Current Role and Expertise

Professor of Virology. Currently funded work includes new influenza vaccines; rapid and sensitive influenza diagnostics; structure and function of viral glycoproteins; generation and characterisation of novel monoclonal antibodies.

Expertise in the expression of recombinant proteins using viral systems. Current collaborations in the application of nanotechnology to diagnostics.

Dr Sue Kimber

Co-director NW Embryonic Stem Cell Centre Manchester
Life Sciences, University of Manchester
sue.kimber@manchester.ac.uk

Current Role and Expertise

Co-director NW Embryonic Stem Cell Centre Manchester. Human ES cell derivation, maintenance. Regulation of pluripotency and early commitment. Targeted differentiation of hES cells to Endoderm. Targeted differentiation of hES cells to chondrogenic cells. Niche biology of hES cells. Development of GMP grade hES lines.

My background is in developmental cell and reproductive biology. Current research includes the remit to develop clinical and commercial products from human embryonic stem (hES) cell biology. We have a breadth of experience in hES cells, their growth and maintenance. We are developing of GMP conditions for hES cells including xeno and feeder free in our clean rooms in Manchester.

Prof Naresh Magan

Applied Mycology Group, Cranfield Health, Cranfield University
n.magan@cranfield.ac.uk

Current Role and Expertise

I head an Applied Mycology group which is involved in both liquid, immobilised and solid substrate fermentation systems using ecophysiological stress approaches to enhance titres of useful enzymes/secondary metabolites by filamentous fungi and yeasts.

I have worked on examining multifactorial approaches to enhance production of both heterologous protein production and secondary metabolites by filamentous fungi. Thus stress physiology and enhanced production of useful products is an area of interest. Previously attempted to obtain funding to look at micro-reactors for filamentous organisms. I would be interested in integrating stress physiology with novel extraction and separation systems based on synthetic polymers which can be used for high value product extraction. Thus Area 1 and 3 would be of interest

Dr Carol Marshall

GSK
carol.t.marshall@gsk.com

Current Role and Expertise

Bioprocess Engineer with particular expertise in cell culture development and experience with cell line, purification, formulation and analytical development as well as GMP manufacturing and regulatory submissions. Process/product development for therapeutic monoclonal antibodies, DNA vaccines, proteins, viral vaccines, viral and non-viral gene therapy. Current role within the new Biopharm Center of Excellence at GSK integrates process/product development with preclinical, clinical, regulatory, manufacturing and commercial activities (from identification to commercial supply).

Dr Ian Moore

Senior Research Fellow
Plant Sciences, University of Oxford
ian.moore@plants.ox.ac.uk

Current Role and Expertise

Senior Research Fellow with academic interests in the above. I believe that we have devised a means to generate a new and artificial membrane-bound compartment in transgenic plants. This could perhaps be used to concentrate and sequester a novel protein product to protect it from other cellular activities and to protect the cell from it. Looking to develop this technology, improve its rational design, and to find a practical problem for which this may be the solution. Hoping to meet people with expertise in purification methods that could be coupled with our compartmentalisation approach.

Transgene expression technology for model and crop plants
Plant cell biology
Manipulation of intracellular compartments in plant cells
Interactions with protein biochemists

Dr David Mountford

MedCell
dmountford@medcell.eu

Dr Judit Nagy

Director of Proteomics Facility
Institute of Biomedical Engineering, Imperial College London
j.nagy@imperial.ac.uk

Current Role and Expertise

Role: Director of Proteomics Facility Research Activities: Stem cell proteomics, Investigation of conditioned media for stem cell cultures, Proteomic characterization of cellular changes after culturing on 2D and 3D scaffolds

Proteomics, protein separation and identification

Dr Ioan Notingher

Lecturer in School of Physics and Astronomy.
Physics and Astronomy, University of Nottingham
ioan.notingher@nottingham.ac.uk

Current Role and Expertise

Lecturer in School of Physics and Astronomy. My research is in optical spectroscopy (Raman spectroscopy in particular) and biophotonics. Interested in develop new optical techniques for non-invasive monitoring of cells and engineered tissues.

Optical spectroscopy, biophotonics, Raman spectroscopy, lasers

Dr Tim Overton

Lecturer in Biochemical Engineering; Director of MSc in Biochemical Engineering
Biochemical Engineering, University of Birmingham
t.w.overton@bham.ac.uk

Current Role and Expertise

Research into microbial fermentation utilising post-genomic and molecular microbiological technologies to investigate the links between physiology and gene regulation in bioprocesses, particularly responses to recombinant protein production and basic fermentation parameters. Development of flow cytometric methods for measuring heterogeneities in gene expression.

Background in molecular microbiology and microbial physiology. Extensive experience of transcriptomics and proteomics, work in gene regulation and bacterial responses to a range of stresses. Developing interests in fermentation and application of modern bioscience tools to the analysis of bacterial growth and physiology in bioreactors.

Dr Justin Perry

Senior Lecturer in Organic Chemistry
School of Applied Sciences, Northumbria University
justin.perry@northumbria.ac.uk

Current Role and Expertise

Senior Lecturer in Organic Chemistry with research activity in Biocatalysis, Developments in Marine Paint Technology, Supramolecular Chemistry and Analysis of Paints and Pigments.

The analysis of recombinant protein heterogeneity

Dr Pawel Plucinski

Chemical Engineering, University of Bath
p.plucinski@bath.ac.uk

Current Role and Expertise

Reader in Chemical Engineering PI in EPSRC Project "Engineering Functional Materials for Catalytic Smart Microreactors", PI in EC Project "Compact Reactor and Carbon Supported Catalyst System for Multiphase Air Oxidation" and industrially sponsored project on "Development of membrane assisted techniques for the production/separation/segregation of nano sized emulsions and particles".

My main area of the research is the kinetics of reactions in heterogeneous (liquid/liquid, gas/liquid and gas/liquid/solid) systems. This includes both: catalysis and separation, application of compartmentalised structures (micelles, microemulsions, and soft interfaces) for reactions and separations, and catalytic processes using multifunctional reactors. The last activity bases on the coupling of reactor function with other functions including e.g. heat, mass transfer and separation processes (process intensification), within one unit of the equipment. Additionally I am involved in research activities on the preparation of nanomaterials (i) for synthesis and application of magnetic nanoparticles as vehicles for easily recoverable catalysts in external magnetic field, (ii) for synthesis of nanotubes for hydrogen storage, and (iii) in membrane assisted preparation of nanoemulsions in the food industry. Work on magnetic fluids includes the preparation of various core-and-shell and/or composite nanoparticles with superparamagnetic core and organometallic or metallic shells for catalytic applications. Such functional magnetic nanoparticles could be also use for downstream processing (separation of proteins, peptides, plasmids, amino acids etc.) as well as carriers for whole cells or enzymatic bioconjugates for biochemical transformations. Our last activities are directed towards design of reactors/bioreactors with the possibility of manipulation of catalysts/biocatalysts applying external magnetic field.

Professor Colin Robinson

Biological Sciences, University of Warwick
colin.robinson@warwick.ac.uk

Current Role and Expertise

My group studies the structure and mechanism of the Tat pathway in bacteria and chloroplasts. We are using structural approaches to understand the structure of the two known Tat complexes in Gram-negative and Gram-positive organisms. We are also using a variety of biochemical/biophysical techniques to understand how the system transports folded proteins without compromising membrane integrity

Our group has been heavily involved in the study of a bacterial protein export system, termed the twin-arginine translocation (Tat) pathway. The key feature of this system is its ability to transport large, fully folded proteins into the periplasm or medium. It is able to transport foreign proteins and thus has considerable potential as a platform for the export of heterologous proteins on an industrial scale. Many processes currently use the Sec pathway to export proteins prior to purification, but this system is unable to export tightly folded proteins. Some years ago, we purified Tat complexes from *Escherichia coli* and more recently we have carried out the first in-depth analysis of a Gram-positive Tat system. We also showed that both forms of Tat system are able to efficiently transport heterologous proteins.

Dr Michelle Scott

GSK

Professor Leonard Seymour

Clin Pharmacology, University of Oxford
Len.Seymour@clinpharm.ox.ac.uk

Current Role and Expertise

Developing virotherapy for treatment of cancer, strategies for systemic delivery, and developing improved methods for scalable GMP virus purification and sterilisation

Virology, pharmaceuticals, cGMP manufacture strategies, clinical translation

Dr Wenmiao Shu

Lecturer

Mechanical Engineering, Heriot-Watt University, Edinburgh
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Current Role and Expertise

Role: Lecturer Research areas: Microsystems, Nanomechanics, Nanomedicine, Label-free Biosensors

My research expertise is focused on developing label-free, high throughput and real-time biosensing techniques for measuring molecular interactions in biological systems. In particular, we have developed microsensors integrated with novel receptor molecules for disease diagnosis, drug discovery and security applications. A recent success has been in applying one biosensor platform to probe the development and inhibition of the diseased proteins which are responsible for Parkinson's and Alzheimer's diseases (PNAS 2007 104(24):10016), and we aim to extend the approach to study other types of diseases and their development under influence of drugs to enable high-throughput analysis for drug screening.

Dr Mark Smales

Reader in Mammalian Cell Biotechnology
Dept of Biosciences, University of Kent
c.m.smales@kent.ac.uk

Current Role and Expertise

Our current understanding of the mechanisms and processes that ultimately govern recombinant protein yields from various expression systems remains somewhat limited. Our laboratory is interested in utilizing state-of-the-art technologies and approaches to improve our understanding of the limitations on such systems and combine this with a prior knowledge to generate new, informed approaches for the manipulation and control of these systems to achieve enhanced recombinant protein production.

Dr Robert Stevens

Principal Scientist and Process Technology Group Leader at the Central Microstructure Facility, Rutherford Appleton Laboratory
Technology, STFC
r.stevens@stfc.ac.uk

Current Role and Expertise

Current Position: Principal Scientist and Process Technology Group Leader at the Central Microstructure Facility, Rutherford Appleton Laboratory

Expertise: 17 years experience of Micro and Nano Technology and Vacuum Engineering. These skills have been developed whilst delivering processes to UK academics and UK industry. An example of some of the broad range of inter disciplinary projects is described below. Development of equipment, IP and Know How which enables scale-up of electrospinning and co-electrospinning complex nanofibre and nanoparticle material to large production volumes (Core Multishell nanofibres, nanotubes and nanoparticles). Such technology would be useful for implantable and transdermal drug delivery, tissue engineering, cell culture and stem cell differentiation and sterile wound care products, in addition to other engineering, energy and medical areas. Thin Film Micro Display Technology for head mounted displays and sunlight readable applications. Based on thin film phosphors, high quality dielectrics deposited by Atomic Layer deposition and wafer scale surface micro-engineering. Space and Aerospace Engineering of colloidal nanothrusters. A wafer scale process capable of delivering a compact thruster technology for space craft which can be configured as a source for charged deposition or spraying of nanoparticles and biomolecules. Medical Devices Engineering such as prototype tactile Urology Probes and Miniature fibre optic pressure sensors for in-vivo measurements. Wafer Processing and Assembly of Detectors for large scale Science Instruments. Development of processes for highly parallel Nano Electrospray sources which can be used to deposit nanoparticles and single biomolecules. Can be configured to deposit arrays of different biomolecules. Flip Chip Technology for electrical interconnect of area array based devices such as pixellated detectors and biosensors. Fabrication of micro-channelled glass templates by powder blasting for hepatocyte culture and bioprocess studies in the area of drug screening and testing. Synthesis of random mat and aligned fibre membranes for controlled differentiation of adult stem cells for retinal repair and for the repair of lesions in the Central Nervous System. BioSensor microchip fabrication and interconnect technology. Fibre Optic Pressure Sensor development for Harsh Environments which has led to a Spin Out Company (www.oxsensis.com).

Professor David Stuckey

Chemical Engineering, Imperial College London
d.stuckey@ic.ac.uk

Current Role and Expertise

Research on the areas stated

Downstream Separation and Process Intensification

Professor Owen Thomas

Chairman of the EFB's Working Group on Downstream Processing and Director of Biochemical Engineering at the University of Birmingham
Chemical Engineering, University of Birmingham
o.r.t.thomas@bham.ac.uk

Current Role and Expertise

My main research interest is in the development of innovative bioseparation technology designed for improved process integration/intensification

Downstream Processing - Bioprocess separation technology and engineering

Dr Robert Thomas

Lecturer (RCUK Academic Fellow) in the healthcare engineering group led by Professor David J Williams.

Mechanical and Manufacturing Engineering, Loughborough University
R.J.Thomas@Lboro.ac.uk

Current Role and Expertise

Lecturer (RCUK Academic Fellow) in the healthcare engineering group led by Professor David J Williams. Current research is focussed on the EPSRC funded regenerative medicine Grand Challenge, Remedi. This project addresses translational barriers to cell based therapies including manufacturing and economic barriers and involves active collaborations with multiple academic and industrial partners.

The healthcare engineering group has expertise in tissue engineering and regenerative medicine. Current research has developed scalable automated production processes for human somatic stem cells, human foetal stem cells and human embryonic stem cells. This has involved process transfer of high value potentially therapeutic laboratory scale manual stem cell culture systems to an automated cell culture platform (the Compact SelecT) in order to evaluate the potential and capability of industrial scale manufacture of cell based therapeutics. The research has also involved the application of data driven process improvement methodology and statistically designed experiments to the analysis and improvement of automated processes, and the investigation of appropriate quality metrics for characterisation of cell based products. The group also has a second major experimental platform - a novel physiologically informed programmable perfusion bioreactor system combining both uniaxial and hydrostatic mechanical actuation. The group has further broad background experience in liver tissue engineering, bio-mimetic scaffolds, quality engineering and mathematical modelling.

Dr Helen Townley

SEEDA Professorial Research Fellow
Engineering, Oxford University
Helen.Townley@eng.ox.ac.uk

Current Role and Expertise

SEEDA Professorial Research Fellow Research activities: Micro-fluid dynamics, nano-particle flows and Continuous SPLITT fractionation.

Our laboratory is involved in projects to model, design, fabricate and utilize microfluidic systems to separate biological particles whilst retaining their functionality and also the separation of other particles based upon their physical properties.

Professor Xue Wang

Chair in Intelligent Measurement and Control
Institute of Particle Science and Engineering, University of Leeds
x.z.wang@leeds.ac.uk

Current Role and Expertise

Professor Xue Z. Wang (XZW) holds a personal Chair in Intelligent Measurement and Control at the Institute of Particle Science & Engineering, University of Leeds. Prior to this he was the industry funded Malver Reader in Intelligent Measurement and Control. He is leading the strategic alliance IntelliSense (www.intellisense.org.uk). XZW's key areas of expertise are in (i) sensor data mining and knowledge discovery (wavelets, neural networks, principal and independent component analysis, multivariate statistical process control, automatic decision tree generation, link analysis, multidimensional visualisation); and (ii) on-line process analytical technology and quality control for particulate processes (NIR, ATR FTIR, zeta-potential, acoustic spectroscopy, laser diffraction). In these areas, he has published over 100 papers and one research monograph. He now leads a group of five postdoctoral research fellows and five PhD students. He is PI of several on-going projects funded by EPSRC, DTI and NERC, including DTI funded ZAPT for development of on-line photon correlation spectroscopy for size characterisation in high concentration nanoparticle slurries funded by DTI (TP/2/SC/6/1/10097), EPSRC funded SAHPE and Stereo Vision Probe for crystal morphology modelling, measurement and control (EP/C009541, EP/E045707), EPSRC funded CHFS for scaling-up a continuous hydrothermal synthesis of materials process using PAT (EP/E040624) and application of NIR to crystallisation (EP/C001788). He is also PI of a proof of concept study project funded by NERC investigating the use of QSAR for predicting nanoparticle toxicity. His PhD student Jorge Calderon De Anda (now working for GSK Res & Dev) was awarded the 1st BNFL Peter Wilson Award and Medal in 2005. He organised and co-chaired the international conference Control of Particulate Processes VII held in Nov 2006 in British Columbia Canada.

(1) on-line process analytical technology, including near infrared spectroscopy, ultrasound spectroscopy, zeta-potential, laser diffraction and attenuated total reflectance Fourier Transform infrared spectroscopy, and on-line imaging and image analysis,

(2) process data mining and knowledge discovery, QSAR and automatic model induction including research on wavelets, neural networks, principal and independent component analysis, multivariate statistical process control, automatic decision tree generation, link analysis and multidimensional information visualisation;

3) multi-scale modelling, in particular population balance modelling and process modelling

(4) combination of the above two with multi-scale modelling to develop technologies for process scale-up and control.

I have ideas and expertise that can be applied to develop generic strategies for process scale-up and control manufacture, which has not been included in previous funded projects.

Dr Christopher Ward

Centre for Molecular Medicine, Manchester University
Christopher.ward@manchester.ac.uk

Current Role and Expertise

Lecturer and BBSRC/RSE Enterprise Fellow. I have a team of 5 people studying various aspects of ES cell culture and differentiation.

My research is focused on the bioreactor culture of embryonic stem (ES) cells to provide a cost-effective method for the derivation of sufficient numbers of pluripotent or differentiated cells for industrial and research purposes. A patent has been filed for this technology and I was recently awarded a Royal Society of Edinburgh/BBSRC Enterprise Fellowship to commercialise the technology.

Dr Paul Watts

Senior Lecturer University of Hull
Chemistry, University of Hull
P.Watts@hull.ac.uk

Current Role and Expertise

Senior Lecturer University of Hull: Interested in new reactor technology (micro reactors, flow reactors and spinning disk reactors) to improve the efficiency of chemical processes.

Enzyme immobilisation in flow reactors. Use of the flow reactors for screening enzymes. Use of thermophilic enzymes (via collaboration with Jenny Littlechild, Exeter). Scale out for fast flexible product of fine chemicals. In situ monitoring for fast reaction optimisation.

Dr Martin Welch

Research Group Head and University Lecturer in Microbiology. Fellow in Molecular Medicine at New Hall (Cambridge).
Biochemistry, Cambridge University
mw240@mole.bio.cam.ac.uk

Current Role and Expertise

Current Role: Research Group Head and University Lecturer in Microbiology. Fellow in Molecular Medicine at New Hall (Cambridge). Research Activities: BBSRC-funded research: This is aimed at (i) using quantitative proteomic analysis to understand how the opportunistic human pathogen, *Pseudomonas aeruginosa*, responds to antibiotic challenge, and (ii) using quantitative metabolomic analysis to study how quorum sensing and biofilms formation affects the global profile of low molecular weight virulence factors produced by *P. aeruginosa*. EPSRC-funded research (in collaboration with Drs Spring and Huck, Cambridge University Chemistry Dept): Development of small molecule microarrays and antibacterial surfaces. We are refining novel proteomic technologies such as QconCAT (in collaboration with KS. Lilley, CCP) for the analysis of antibiotic resistance determinants in *P. aeruginosa*. MRC-funded research: Development of novel antibacterial compounds.

We are a group that works on bacterial microbiology. We are applying quantitative proteomic analysis (building on a previous BBSRC investment, The Cambridge Centre for Proteomics (CCP), as well as on our own extensive experience in the application of these technologies to problems in microbial bioscience) to the investigation of a key issue in bioprocessing; inclusion body formation / aggregation by high value proteins. The aim of our work is to develop rational approaches for the design of new strains for protein over-expression, and to generate improved in silico and experimental predictors that guide the selection of host strains resulting in improved yields of soluble protein. We also bring with us a high level of expertise in the interrogation of multivariate

datasets – this is an absolute pre-requisite for the proper analysis of proteomic data. Pilot data supporting our intended proposal looks very promising and we have initiated contacts at this stage with one of the BRIC industrial members with the intention of developing/refining these ideas further.

Dr Daryl Williams

Senior Lecturer in Chemical Engineering
Chem. Eng., Imperial College London
d.r.williams@imperial.ac.uk

Current Role and Expertise

Senior Lecturer in Chemical Engineering. Currently lead a number of projects, including some fully industrial funded. Funded on BRIC2 on Protein Crystallisation.

Materials Characterisation, especially amorphous and crystalline solids. Drying of Solids, including hydrates and other moisture sensitive materials. Colloid and Surface Science, including particle surface properties, surface heterogeneity. Physical chemistry of gas phase and liquids phase chromatography. Crystallisation and milling, especially of small organic molecule based solids. Physical and mechanical behaviour of solids including effects of humidity and temperature. Granulation of powders. Advanced scientific instrumentation for all of above.

Dr Nik Willoughby

Lecturer in Chemical Engineering
School of Engineering and Physical Sciences, Heriot-Watt University
N.A.Willoughby@hw.ac.uk

Current Role and Expertise

Currently I am working as a Lecturer in Chemical Engineering. My current research areas of interest include: Tailoring of downstream processes to increase productivity and capacity. Effects of high cell density process cultures on downstream processing performance. Novel techniques for purification of high-titre therapeutic products. Purification and separation of stem cells.

As part of the Innovative Manufacturing Research Centre for Bioprocessing at University College London I worked for 4 years in rapid bioprocess development of downstream processing operations and whole bioprocesses. I have carried out significant amounts of novel research into unit operation scale-down and optimisation in the areas of expanded bed adsorption (EBA) and centrifugation

Dr John Woodgate

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Updates to Delegate List

Additional Attendees:

Dr Simon Briggs

Clinical Pharmacology, University of Oxford
simon.briggs@clinpharm.ox.ac.uk

Current Role and Expertise

Gene therapy, chemistry, polymer chemistry, purification of biomacromolecules, bionanoparticulates.

With a background in organic chemistry and synthesis of macromolecules for gene therapy, I work on the interface of cell biology and synthetic polymer chemistry. I have significant expertise in purification and characterisation of small organic compounds, macromolecules and nanoparticles.

Dr David Humphreys - UCB Celltech

Dr Bo Kara - Avecia Biologics

Bo.Kara@avecia.com

No longer attending:

Dr Keith Firman - School of Biological Sciences, University of Portsmouth

Professor David Klug - Chemistry, Imperial College London (replaced by Eugenie Dahm-Vicker)

Professor Phil Ligrani - Engineering, Oxford University

Dr David Mountford - MedCell

Professor Colin Robinson – Biological Sciences, University of Warwick



Images courtesy of Aveeda Biologics Ltd, Lonza Biologics plc, John Innes Centre and Matt Dalby, Glasgow University

New BBSRC Website launched 30 November 2007

BRIC webpages can be found at:

www.bbsrc.ac.uk/business/collaborative_research/industry_clubs/bric/