UCL ADVANCED CENTRE FOR
BIOCHEMICAL ENGINEERING

UCL

EPSRC Life Sciences IMRC
Bioprocessing

DISCOVERING FUTURE BIOMANUFACTURE

IMRC BIOPROCESSING / ANNUAL REPORT 2010-11

Mission Statement

The Centre provides an international lead in enhancing fundamentally the way in which processes are developed for the manufacture of evolving generations of biopharmaceuticals.

The Centre's studies achieve speed to manufacture by means of microscale experimentation coupled with advanced experimental designs.

The Centre prepares the ground for bioprocess design for emerging novel macromolecular and nanomolecular biopharmaceuticals.

The Centre works closely with its industrial partners to ensure effective take up of its outputs into commercial practice.

Principal and Collaborative Investigators

IMRC for Bioprocessing Principal and Collaborative Investigators and their main research management role:

Dr Frank Baganz (fermentation and cell culture)
Dr Dan Bracewell (primary recovery and chromatography)
Dr Paul Dalby (protein engineering and formulation)
Prof. Eli Keshavarz-Moore (cell bioprocessing)
Prof Mike Hoare (whole bioprocess ultra scale-down and primary recovery)
Prof. Gary Lye (microbiochemical engineering and industrial biotechnology)
Dr Martina Micheletti (cell culture microwell engineering)
Dr Tarit Mukhopadhyay (vaccine bioprocessing)
Dr Darren Nesbeth (synthetic biology bioprocessing)
Dr Karen Smith (knowledge transfer)
Prof Nigel Titchener-Hooker (whole bioprocess analysis)
Dr Ivan Wall (regenerative medicines bioprocessing)
Prof John Ward (cell engineering)
Dr Yuhong Zhou (bioprocessing data acquisition)

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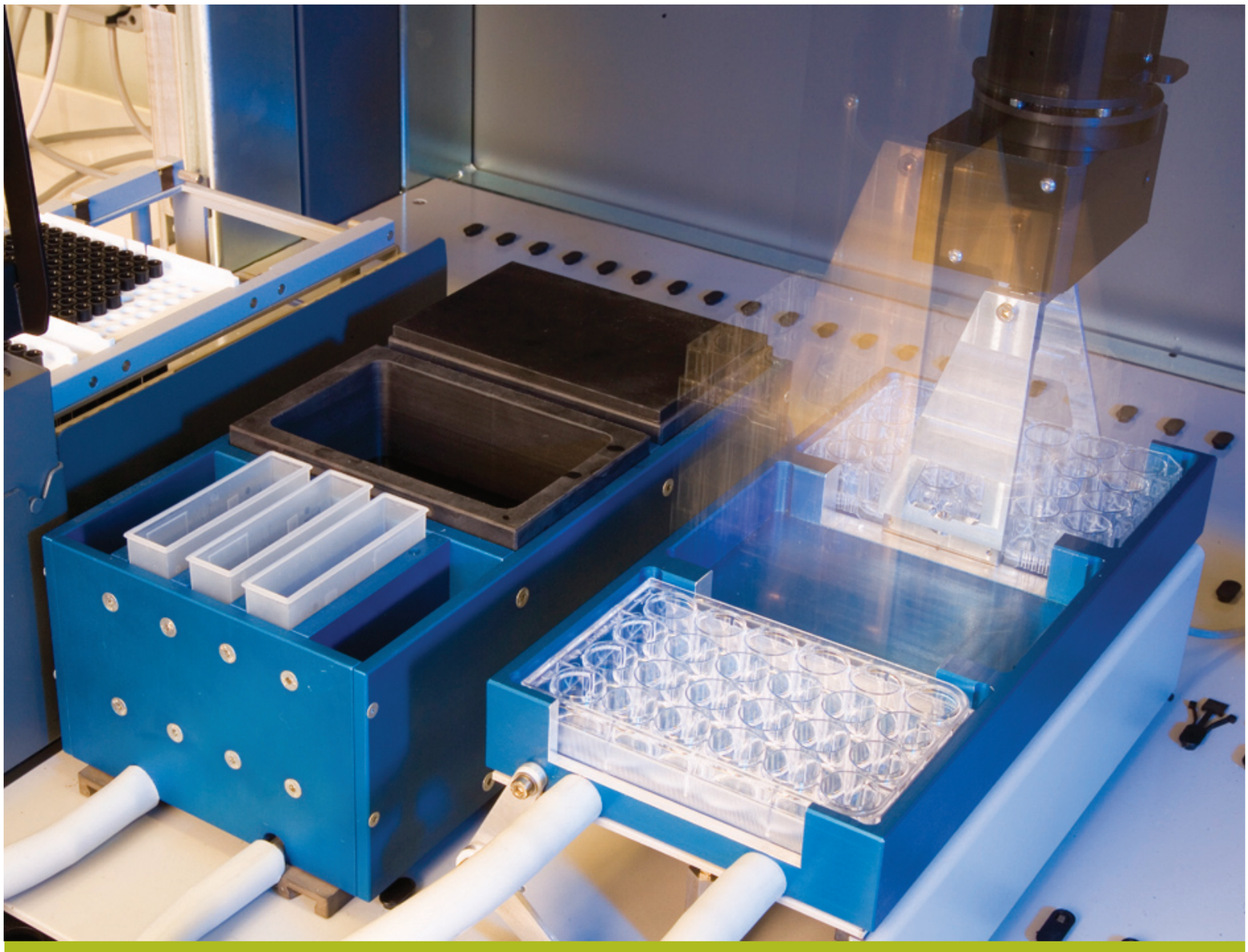


1.0 Executive Summary

“IMRC personnel have engaged with a variety of knowledge exchange and dissemination mechanisms”

1.0 Executive Summary

The IMRC for Bioprocessing at UCL has had another year with notable successes. Fundamental studies undertaken by the IMRC team of researchers and associated doctoral students have continued to advance our capacity to predict manufacturing outcomes at the early stages of a drug's development. IMRC personnel have engaged with a variety of knowledge exchange and dissemination mechanisms designed to enable industry to adopt IMRC methods in practice and for cohorts of students to become familiar with their utility. Over the past year we have made further progress in developing new relationships and endeavours which will take forward this valuable partnership with industry. Driving this is the urgent need to determine new ways which help maintain the value of this collaborative activity for the delivery of the next generations of therapeutic materials.

Particular highlights for the past year are described below.

- Post-doctoral fellowships with industry (GSK)
- 3 EPSRC-funded Knowledge Transfer Secondments (GSK, UCB, Pharma and Lonza Biologics)
- Establishment of a UCL-GSK Centre of Excellence in Bioprocessing (see Section 2.3)
- 60 IMRC-affiliated company projects underway in 2009-10
- Vaccines Bioprocessing theme created as a result of IMRC investment in academic post and geared through BBSRC pump-priming of an MBI training module. (Section 5)
- Creation of a £910k Responsive Bioprocessing Research and Training Facility. (Section 3.1)

The Centre

The Engineering and Physical Sciences Research Council (EPSRC) created its first Innovative Manufacturing Research Centres (IMRC) in 2001 from existing Innovative Manufacturing Initiative (IMI) grant activities. Each IMRC was tasked to disseminate their findings and to train personnel for crucial sectors of the UK economy. The IMRC for Bioprocessing at UCL was created in 2002 as a *de-novo* activity in collaboration with the UK biopharmaceutical industry sector.

The in depth history of operating strategic grants such as the Interdisciplinary Research Centre (IRC) for Biochemical Engineering (1990-2000) and its instincts for doctoral level training have been crucial to the success of this IMRC. A capacity to work at the interface between science and engineering has been important as has been the winning of an Engineering Doctoral Training Centre in 1999 and a successor Industrial Doctoral Training Centre (IDTC) from 2009. A masters-level post-experience mechanism for effective knowledge transfer in the form of the MBI® (Modular training for the Bioprocess Industries) programme, initiated in 1994 lies at the centre of our training ethos. It has now trained over 2000 delegates worldwide from 200 participating companies and has involved some 90 industrial experts (Section 2.2).

The achievements of the IMRC to date will prove critical to the extension and application of IMRC advances come the planned cessation of the first round of the IMRCs in 2012. The challenge will be to build upon the IMRC advances. For example to date 13 additional Knowledge Exchange activities have been established with IMRC support with a further 2 providing the basis of post IMRC continuation (Section 2.3).

The Centre works with over 30 university academics (here at UCL and beyond). Since its inception we have trained over 200 postdoctoral researchers, research assistants and doctoral students. Additionally in each year the Centre has involved some 70 undergraduates and masters students in projects which exemplify the output of the IMRC and which use IMRC advances to provide training material. Though housed in the Department of Biochemical Engineering, IMRC staff members are also drawn from other departments including Computer Science, Chemical Engineering, Immunology and Structural and Molecular Biology at UCL and others from leading institutions elsewhere. The last Research Assessment Exercise (RAE 2008) rated all collaborating departments and research groups as highly competitive internationally (Section 5).

...its instincts for doctoral level training have been crucial to the success of this IMRC.

All four of the international reviews of the IMRC have praised the research and training excellence of the IMRC and have noted the internationally leading role of the Centre in the field. The IMRC has been held up as a “benchmark” for others to emulate and each review has led to recommendations for future support in full. It is vital now that this level of support be harnessed for the future of the sector as we plan for IMRC activity post 2012. Industry has always recognised the relevance and impact of the IMRC. Since inception the Management Advisory Committee has endorsed the planned expansion of the core industrial consortium by over 30% recognising that each new partner provides a widened set of opportunities for the IMRC to influence the sector by giving access to new process challenges and targets for consideration.

Collaboration

The international industrial consortium which supports and informs the IMRC research and training vision represents one element of a wider range of collaborative opportunities which characterise the full reach of the Centre activity. Particularly crucial for direct one-to-one knowledge exchange is the close positioning of the Industrial Doctoral Training Centre (IDTC) for Bioprocess Leadership, funded by the EPSRC. This mechanism provides opportunities for collaboration with a wider range of academics, at UCL and beyond, and also with affiliated companies through which we are able to demonstrate the widest possible applications of new IMRC findings (Section 2.3).

Collaborations provide vital access to key academics involved in all three strands of the IMRC research portfolio. These include skill sets such as cellular engineering, nanotechnology and microfluidics, complex non steady-state fluid dynamics, data acquisition and knowledge-based reasoning methods. IMRC funds associated doctoral projects, frequently in collaboration with external academics. Such activities are path-finding 'discovery' projects the aims of which are to push into new areas of potential longer term benefit to the realisation of the IMRC research vision. They have proven invaluable in creating new collaborations and for bringing in new knowledge and expertise for the wider benefit of the IMRC consortium members (Section 3).

IMRC impact

The UCL IMRC for Bioprocessing creates impact through a variety of mechanisms. It produces world-leading science and engineering research and develops the most talented and capable individuals who implement our vision. It is delivering new innovations for industry adoption and is creating the capabilities to meet the challenges of the next decade. The IMRC staff collaborate with the leading industrial scientists and engineers worldwide with skills complementary to those of IMRC academics to create a unique powerhouse for change. Our links include universities, government agencies, research centres and industrial groups on an international scale. We leverage these links to ensure that the UK capabilities are maximised at all levels from the fledgling SME to the multi-national "blue-chip." This sense of a community has been central to achieving our vision and to our independently attested success (Section 2.4).

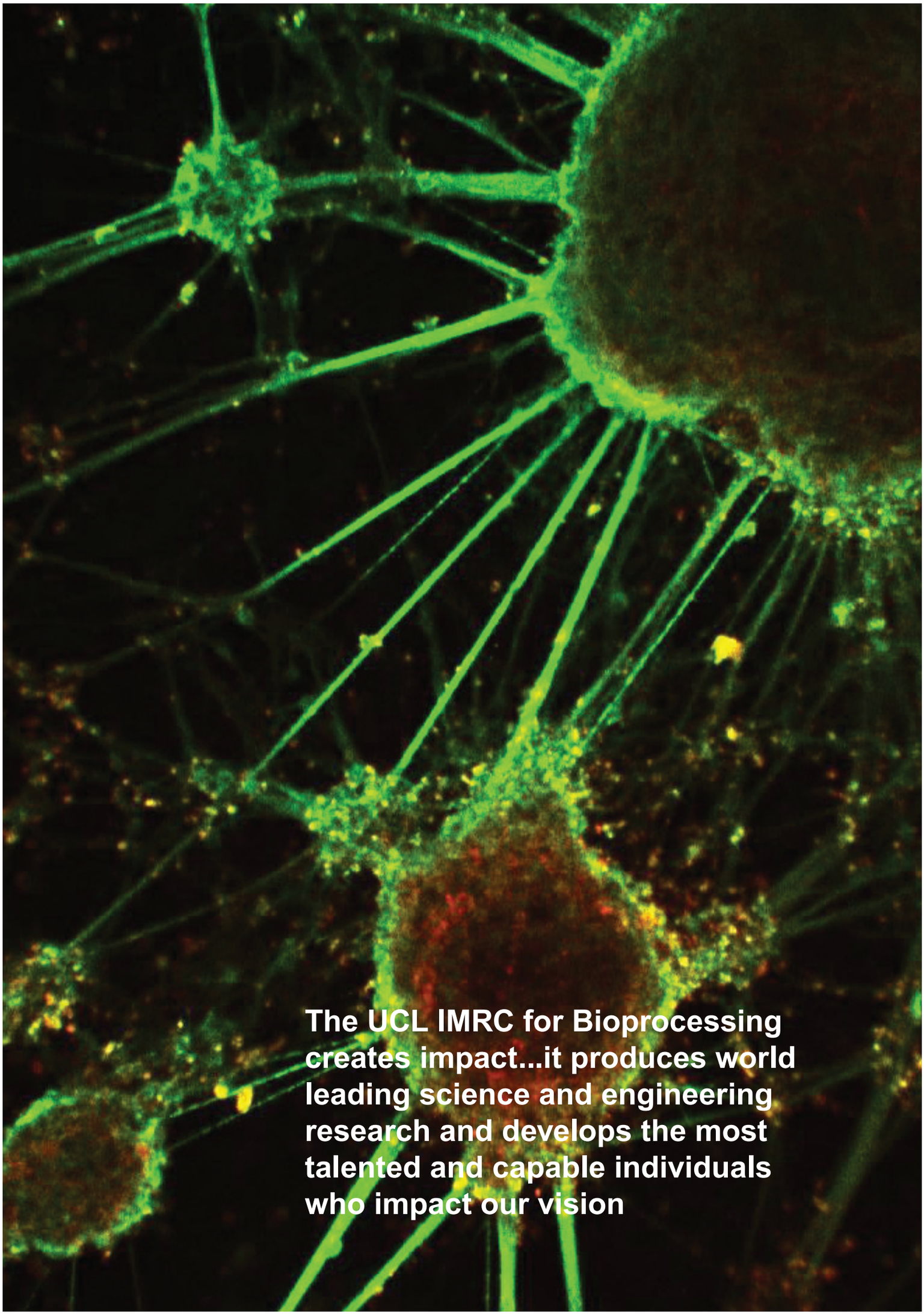
Financial pressures to restrict healthcare budgets combined with an increasing regulatory requirement for yet better process understanding creates an interesting dynamic for the IMRC to operate within. Our role is to conduct the groundbreaking research needed to provide industry with the tools and approaches necessary to succeed and to bring forward the human potential for that industry. This clearly requires a training vision. By the integration of these two elements will we achieve the success of the sector and generate a positive economic impact for the UK. Ultimate success relies on the combination of the two (Sections 2.2 and 4).

Widening the IMRC community

We recognise that to achieve the greatest overall benefit from the IMRC we have to maximise the reach of the centre activities. Here our Special Interest Groups (SIGs), designed to promulgate our findings and vision beyond the consortium and to act as a catalyst for growth, have been particularly useful. Our IMRC Bioprocess Briefings likewise, provide a window for all to learn about our work and to meet with the research team. Now in our 6th year the 2 day Annual Bioprocess Briefings are an established date in the calendar for large and small companies alike and are creating opportunities for the growth of the academic community in bioprocessing. This year we focused on the role of the IMRC part of the knowledge transfer continuum with a comprehensive set of presentations and posters (Section 7).

The future

The challenge over the next year is to build upon the mechanisms we have established whereby the industry-academic collaborations created though the EPSRC support of the IMRC can best be sustained. New issues and opportunities are emerging for the bioprocessing sector, especially vaccines and whole cell therapies which will benefit from IMRC methods developed to date. Furthermore, synthetic biology integrated with whole bioprocess ultra scale-down is developing and offering new ways to create step changes in bioprocessing. During 2011 we will need to use our industry partners' support and guidance to build for a post 2012 phase of IMRC activity. The challenge is to construct a robust model for future financing of studies and to extend still further knowledge transfer and application of our ideas. Progress with establishing a Centre of Excellence concept and in widening our remit for application of IMRC approaches beyond the biopharmaceutical domain are already in progress.



The UCL IMRC for Bioprocessing creates impact...it produces world leading science and engineering research and develops the most talented and capable individuals who impact our vision

2.0 Contributing to the Future

“The IMRC has successfully pioneered mechanisms for skills development and knowledge transfer”

2.0 Contributing to the Future

One key role for the IMRC for Bioprocessing is in skills development and knowledge transfer of its technologies. This will be in addition to further original research and the development of the technologies to help achieve speed to manufacture of next generation biopharmaceutical products for healthcare. The IMRC has successfully pioneered mechanisms for such skills development and knowledge transfer and these will form the basis for new initiatives being put in place to deliver further the value of the EPSRC investment in the IMRC and the investments of the collaborating companies and universities.

2.1 Background

The IMRC for Bioprocessing has successfully established a new way of discovering and creating processes for the manufacture of next generation biopharmaceuticals. The most significant element of these IMRC outcomes is that of ultra scale-down methodologies which comprise a series of tools and devices to determine the properties of a biological material using millilitre quantities. This is matched by the engineering skills to interpret the ultra scale-down data in terms of the design and operation of full scale manufacturing processes (Section 3.1).

These ultra scale-down methodologies have been complemented by the development of new approaches to data acquisition including use of design of experimentation and advanced search methods, robotic multiwell platforms and use of automation (Section 3.2), and approaches for whole bioprocess studies linking fermentation, recovery, purification and formulation (Section 3.3).

The future contribution of the IMRC outputs to the bioprocessing industries is centered around the continued development of ultra scale-down and complementary methodologies and their widest application.

The economic driver for the IMRC bioprocess research has been sustained by the biopharmaceutical industries, and especially the sector involved in the research and development directed towards protein-based therapies. In these industries, speed to manufacture is often an essential feature in maximizing the value of the discovery of a new therapy and the ability to recover the high product development costs within the limited period of exclusivity remaining after the long development times.

The IMRC is now increasingly addressing the challenges faced by the other sectors of the biopharmaceutical industries and in particular vaccines where the complexity of the product and the challenges of determining clinical efficacy are often greater than those posed by the protein-based therapeutic sector.

The increased complexity of the biological material is representative of the future challenges faced in demonstrating the utility of the IMRC ultra scale-down methods. In particular this is relevant to the regenerative medicines sector and the provision of human cells for therapy.

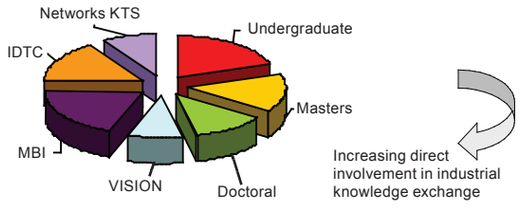
A second challenge faced in the bioprocessing sector is that of the high cost of manufacture and the pressures faced in a range of products including high dose therapies, e.g. antibodies for cancer treatment, vaccine therapies especially to meet global healthcare challenges and, outside the healthcare sectors, in the provision of biocatalysts for the food and industrial biotechnology sectors.

The strategy to deliver the future contribution of the IMRC outputs is based around a continued and increasing programme of skills development in the awareness and use of ultra scale-down methods, the establishment of research networks and centres of excellence in exploiting ultra scale-down methodologies and supply of ultra scale-down tools. The final element is the wider demonstration through collaborating partners of the impact of ultra scale-down methods on the industry's capabilities in bioprocess development. These strategic elements are detailed below.

2.2 Skills development

A series of knowledge exchange activities have been created out of the IMRC. These now routinely introduce and develop ultra scale-down skills for over 200 beneficiaries per year who go onto roles within the bioprocessing industries as those who manage and implement such capabilities.

The ability to train students in the latest IMRC techniques will mean that successive cohorts will all have first-hand knowledge of these approaches which they will use in their future careers. At undergraduate, masters and doctoral research levels, students benefit from IMRC-led whole bioprocess studies using its advanced ultra scale-down techniques. Here, the UCL ACBE's state-of-the-art whole bioprocessing facilities provide the opportunity to demonstrate the power of their ability to predict and solve full scale bioprocessing challenges faced in industry. By these means the IMRC has enabled UCL graduates to become engaged in whole bioprocess studies ranging from plasmid DNA as a basis for a flu vaccine[1] in the earlier phase of the IMRC to the most recent studies based on rec *E.coli* bioprocessing of an antibody fragment preparation (Balasundarum *et al*,2009a,b) and mammalian cell bioprocessing for antibody recovery (Tait *et al*,2009).



Acquisition of IMRC skills. Clockwise from the top shows increasing direct involvement in industrial knowledge exchange. There are over 200 beneficiaries each year of training developed out of the IMRC research programme especially in the use of IMRC ultra scale-down tools to help speed bioprocess development. Of these, 45% were directly associated with collaborating companies during skills acquisition with a remit to transfer their skills directly to their collaborators' interests ie through MBI®[2], IDTC[3], VISION[4] programmes and Research Networks and Knowledge Transfer Schemes

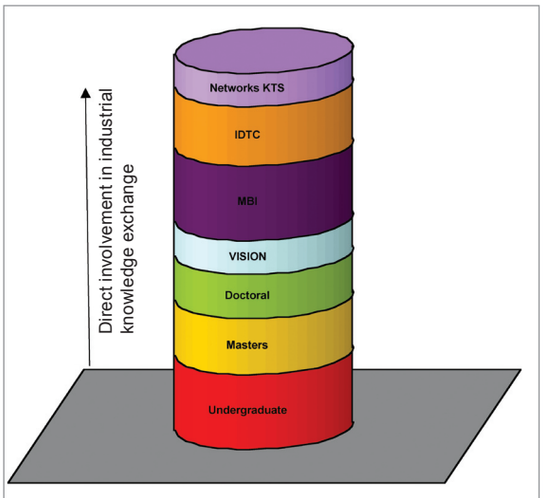
Many beneficiaries of the IMRC skills development programmes work directly with industry while at UCL. In particular both EPSRC-funded IDTC[3] researchers (EngDs) and joint EPSRC industry-funded Knowledge Transfer Scheme (KTS) research engineers are helping develop new IMRC skills and show application to biopharmaceutical candidate therapies, often while these are still in the discovery phase. The MBI® post-experience delegates are leaders from industry who are often responsible for new skills developments within their respective companies.

1 Hoare, M., Levy, M.S., Bracewell, D.G., Doig, S.D., Kong, S., Titchener-Hooker, N., Ward, J., Dunnill, P. (2005) Bioprocess engineering issues that would be faced in producing a DNA vaccine at up to 100m3 fermentation scale for an influenza pandemic. *Biotechnol. Prog.* 21, 1577-1592.
2 MBI® Modular training for Bioprocess Industries post experience programme
3 IDTC – Industrial Doctoral Training Centre – an EPSRC programmes for Engineering Doctorates in collaboration with an industrial partner
4 VISION – Life science-bioprocessing senior executive leadership programme at UCL

Most recently the IMRC has helped pioneer a leadership skills programme (VISION) for bioprocessing executives seeking to find new ways to meet future challenges of the healthcare sector e.g. more complex drugs which offer higher specificity of action and less serious side effects but are of greater cost to develop and manufacture and address smaller populations. While the IMRC methods we have developed will strongly contribute to meeting these challenges it is evident that changes in management approaches to product development are needed if the benefits are to be fully realised. For the UK such an approach will help it better realise the value of its world-leading life and biomedical science research. A new IMRC-enabled vaccine bioprocessing MBI® module complements project leadership activity in the most rapidly developing healthcare sector with demands in emergency and preventative as well as therapeutic treatments.

All of this skills development activity benefits from IP protection to allow training using advanced materials of relevance to the future bioprocessing sector, e.g. high producing cell lines or new vaccine candidates or novel engineered proteins all gained through IMRC research collaboration. All beneficiaries of IMRC skills development programmes become proficient in how collaborative research is carried out across sensitive IP boundaries, a common feature of careers in the biopharmaceutical sector.

The IMRC has helped pioneer a leadership skills programme (VISION) for bioprocessing executives seeking to find new ways to meet future challenges of the healthcare sector



Company profile of contribution to IMRC Knowledge Exchange. Diagram shows build up of industrial sectors involved with the biopharmaceutical, design, equipment and consultancy sectors providing the foundation for the introduction of the biotechnology and vaccine bioprocessing industries and more recently outreach into industrial biotechnology, regenerative medicines and innovations in environmental and sustainability issues. The collaborations are based on 79 company projects taking place with 62 different companies. These projects are carried out by postdoctoral researchers and by doctorate students . The chart shows the distribution of company projects in terms of number of researchers and the business activities of the company.

2.3 Research networking

Research networking through the IMRC with partnering and affiliated companies and university groups is enabled through the skills development activities especially of IDTC students and Postdoctoral Research Associate leaders (PDRAs). This allows the IMRC to demonstrate an increased awareness of the application of its ultra scale-down methods to the characterisation of a wide range of biopharmaceutical candidates in the early discovery phases even where IP protection is essential to the collaborator.

Over the lifetime of the IMRC there has been a five fold increase of company involvement in facilitating IMRC research and technology transfer with over 60 companies participating in 2009. Engineering Doctorate and knowledge exchange (KTS) collaborations. Here researchers work directly in both the university and company environments on IMRC activities are particularly important. This is in addition to post-experience training of company bioprocess leaders who help manage the introduction of new technologies. The breakdown of such activities shows a strong and growing emphasis in the vaccine and biotechnology discovery sectors.

An additional key mechanism for research networking has been delivered via the IMRC PDRAs where external funding has helped enhance the scope of the IMRC nearly two-fold through research linkages with a range of biotechnology and biopharmaceutical companies and university departments. Out of such research driven networking the IMRC has successfully established new ways of enhancing the value of its research outputs including: Special Interest Groups (SIGs) to share amongst leaders of research and development the new technology needs; Bioprocess Briefings by internationally leading expert commentators on the future needs of the bioprocessing sector; and annual dissemination events where the whole IMRC community is brought together (Section 7).

Research networking leading to exchange of IMRC skills and technologies

Name[a]	Associated IMRC project	Collaborators	Funding[b]
Lucy Wakeford (01/2008-09/2009)	Formulation and filling strategies	GSK	100% by GSK
Andy Tait (02/2008–01/2010)	Analysis of bioprocessing effects on human cells with vaccines	Onyvax, LGC, Bioinformatics NTU	20% by Technology Strategy Board
Ioannis Papantoniou (02/2008–03/2010)	CFD of cell vaccines flow in capillaries/vials	Onyvax, LGC, Bioinformatics NTU	50% by Technology Strategy Board
Sally Hassan (03/2008–06/2010)	Strategy for preparation of non-viral vectors	Structural and Molecular Biology, UCL	100% by BBSRC/EPSRC BRIC
Alex Berrill/Ola Olusanya (04/2009–08/2012)	Antibody formulation and USD verification	GSK	67% by GSK, 33% by EPSRC KTS
Steve Branston (06/2009–05/2012)	Exploitation of Tat machinery in *E.coli* for processing	Warwick University, RecipharmCobra	100% by BBSRC/EPSRC BRIC
Andy Tait (07/2009–06/2012)	Mammalian cell engineering for whole bioprocesses	Kent University	100% by BBSRC/EPSRC BRIC
Katherine Lawrence and Carol Chu (07/2009–12/2011)	Bioprocessing of human cells for therapy	ReNeuron, HPACC, LGC,Bioinformatics NTU, Onyvax	100% by Technology Strategy Board
Spyros Gerontas (09/2009–02/2011)	Bioprocess modelling of hepatic cells	Hepatology, RFH	30% by NHS
Sunil Chhatre (10/2009–09/2011)	Fusion virus like particle bioprocessing	IQur	50% by EPSRC Technology Strategy Board
Guijan Ma (11/2009-04/2010)	Membrane ultra scale-down verification	Pfizer	100% by Pfizer
SimYee Kong (11/2009–09/2011)	Whole bioprocess of fusion protein vaccines	ImmunoBiology, ERA	50% Technology Strategy Board/EPSRC
James Savery (03/2010–11/2010)	Bioprocessing software	BioPharm Services	100% by EPSRC KTS
Jean Aucamp (07/2010–03/2011)	Antibody fragment (Fab) bioprocessing	UCB Pharma	50% by EPSRC KTS
Ioannis Voulgaris (04/2011–03/2014)	Domain antibody bioprocessing	GSK	100% by GSK
To be appointed – two posts (04/2012–03/2014)	Design and supply of new ultra scale-down devices; training and knowledge transfer	IMRC partners	100% by IMRC partners

[a] Date ranges given are for period of collaborative funding
Tait, Papantoniou, Kong, Gerontas, Aucamp, Chhatre employed firstly as IMRC postdoctoral researchers.
Berrill, Hassan, Branston, Ma trained through IMRC doctorate scheme.
Chu, Lawrence directly appointed to collaborative programme
Savery, Wakeford – company employees seconded to IMRC
Also to note: Nesbeth (ex IMRC PDRA) and Mukhopadhay (ex IMRC doctorate with HPA) now employed at UCL as Lecturers in Synthetic Biology Bioprocessing and Vaccine Bioprocessing respectively and contributing to IMRC research, training, management and knowledge exchange activities.

[b] proportion of time funded by collaborators; for any remaining time the researchers are funded by the IMRC and carry out their separate IMRC project work and management roles.

2.4 Industrial impact studies

An ultra scale-down platform for accelerated prediction of monoclonal antibody recovery
– with Lonza Biologics

Mammalian cells are exposed to extreme levels of energy dissipation during processing in continuous flow industrial centrifuges. Microscale multiwell based methods have been created which use just a few millilitres of precious cell culture material to predict successfully the cell break up and product damage which will occur at full manufacturing scale. The insight gained allowed early prediction of manufacturing solutions e.g. the translation to centrifuges with "soft-feed" zones and use of smaller filters. Also predicted was the importance of integrating cell culture and downstream processing strategies and the predicted process savings to be made via the need for much reduced filtration trains. Also predicted was the importance of integrating cell culture and harvesting to control the resultant antibody glycosylation pattern and presence of near-neighbour antibody impurities.

The research outcome of this programme has been the ability to predict the separation performance of a production scale centrifuge obtained using ultra scale-down process mimics using millilitre and frequently microlitre quantities of process materials. Centrifuge performance at full production scale was accurately predicted using process mimics scaled down 50000-fold. A predicted 2.5-fold increase in throughput for the same clarification performance, achieved by the change to a low-shear feed zone, was verified at large-scale.

The research take up was established in a collaborative project with University of Kent, Lonza Biologics and Agilent Technologies on how mammalian cell culture and harvesting conditions affect protein structure. This demonstrated that cell fragility peaks before the end of the fermentation process and provides a direct measure of when cell harvesting should take place. The collaboration with Professor Smales at University of Kent has led to a new BRIC (EPSRC/BBSRC) grant of £820k to better understand the interaction between mammalian cell culture and recovery and purification of therapeutic proteins. The more recent work on the impact of bioprocessing on protein antibody glycosylation patterns has been supported by analysis using advanced mass spectrometry and has strengthened the collaboration with the University of Kent. There has been increased collaboration with Agilent, the supplier of mass spectrometry instrumentation, and investment at UCL of mass spec facilities (infrastructure grant of £475k). More recently applications of ultra scale-down have been demonstrated in investigation of subsequent high resolution purification stages and of process innovations eg of selective precipitation to aid mAb recovery.

All the research has been transferred to and incorporated in the teaching material for MEng/MSc/EngD degrees and also the MBI® post experience training programme, involving over 200 bioprocess engineers per annum.

The impact of the research has been to allow the prediction of the capital expenditure related to clarification to be made with much greater confidence and provides the basis to proceed to manufacture with speed whilst avoiding expensive investment errors when specifying new equipment. It has become adopted by other IMRC companies.

Further information (industrial and university collaborators are identified in bold)

Tait, A.S., Aucamp, J.P., Bugeon, A., Hoare, M. (2009). Ultra scale-down prediction using microwell technology of the industrial scale clarification characteristics by centrifugation of mammalian cell broths. *Biotechnology and Bioengineering.* 104: 321-331

Hutchinson, N., Chhatre, S., Baldascini, H., **Davies, J.**, Bracewell, D.G., Hoare, M. (2009). Ultra scale-down approach to correct for dispersive and retentive effects in small-scale columns when predicting larger-scale elution profiles – mAbs on Protein A. *Biotechnology Progress.* 25: 1103-1110

Reid, C. Q., Tait, A.S., Baldascini, H., **Mohindra, A., Racher, A., Bilsborough, S., Smales, C.M.**, Hoare, M. (2010). Rapid whole monoclonal antibody analysis by mass spectrometry: The effect of harvest time and primary recovery by centrifugation on the post-translational modification profile. *Biotechnology and Bioengineering.* 107: 85-95

Knevelman, C., **Davies, J., Allen, L**., Titchener-Hooker, N.J. (2010). High-throughput screening techniques for rapid PEG based precipitation of IgG4 mAb from clarified cell culture supernatant. *Biotechnology Progress.* 26: 697-705

Bioprocess on a deck: an automated strategy for process development
– with Merck & Co Inc.

Optimisation of fermentation conditions must consider both the quantity (e.g. the volumetric productivity) of and the quality of the product as given by the final specifications. The integrated optimisation of fermentation and downstream process steps typically requires many tens to hundreds of fermentations to be carried out and products subsequently recovered and purified at very small scale. The process train is also dependent on where the product is expressed, i.e. whether it is secreted or intracellular. Two projects working with recombinant strains of yeast (S.cerevisiae and Pichia pastoris) producing intracellular virus like particles and secreted Fc antibodies respectively created small scale and microscale techniques to allow accelerated development of a process pathway. In the first project a microscale tip chromatography format has been developed together with a small scale disruption technique that yields representative feedstocks for chromatography. In the second project methods have been created to characterise rapidly and predict the dewatering characteristics of high cell density broths for better separation of product from cells in a range of process scale centrifuges.

The research outcome of these two programmes has been a microscale chromatography process mimic using micro pipette tips which has been automated and reliably miniaturised by three orders of magnitude compared to conventional laboratory chromatography steps. This is a significant breakthrough in removing the analytical bottleneck in process development involving high throughput fermentations. A robust microscale disruption method has been developed to provide representative material for the chromatography step.

Efficient separation of secreted product from high cell density broths is a challenge because of the operational limitations of industrial scale centrifuges. The research has resulted in the creation of a robust ultra-scale down methodology to predict at 2-15mL scale the dewatering characteristics of cells in process centrifuges. The predictions were verified at pilot scale for tubular bowl and disc stack centrifuges.

The research take up of the miniaturised and automated chromatography step by Merck has led to an increase in experimental throughput by ten fold and a reduction in time and labour required to evaluate yeast fermentations by nearly 80%. The dewatering technique is currently being implemented in Merck for a range of yeast high cell density broths to speed up optimisation of centrifugation conditions by alleviating the need for costly repeated pilot scale runs as well as reducing fermentation experiments needed to identify the best harvesting time.

These methodologies have been applied by Merck and Co to the development of biopharmaceuticals, such as vaccines and therapeutic proteins including antibody fragments.

The impact of the research is that it provides a powerful toolbox of methodologies for fast evaluation of process conditions firstly in recovery of products from high cell density broths and secondly in investigating chromatographic separation and purification performance of chromatographic media using high throughput procedures in microwell format.

Further information (industrial and university collaborators are identified in bold)

Wenger, M.D., **DePhillips, P., Price, C.E.**, Bracewell, D.G. (2007) An automated microscale chromatographic purification of virus-like particles as a strategy for process development. *Biotechnology and Applied Biochemistry*. 47: 131-139.

Wenger, M.D., **DePhillips, P., Price, C.E.**, Bracewell, D.G. (2008) A microscale yeast cell disruption technique for integrated process development strategies. *Biotechnology Progress*. 24: 606-614.

Lopes, A., Hoare, M., Keshavarz-Moore, E. (2010) Ultra scale-down methodology for the rapid prediction of the impact of *P. pastoris* high cell broth quality on recovery performance of recombinant products in a pilot-scale centrifuge. *Vaccine Technology III*, 6-11 June, Mexico.

Ultra scale-down strategies from cell culture to formulation
– with MedImmune

It has been shown that high molecular weight protein aggregates in therapeutic protein products can increase immunogenicity, and such an effect is therefore an important risk factor to consider when assessing product quality. Exposure to interfaces (e.g., air–liquid and solid–liquid), light, temperature fluctuations or minor impurities can induce aggregation. Such exposure can occur during processing steps, as well as in the final product container during storage, shipment and handling.

This project, conducted in collaboration with MedImmune, investigated the processes relevant to biopharmaceutical formulation using ultra scale-down techniques and the optimisation of these processes to maintain the authenticity of the biomolecules. The effect of interfacial shear on the structural integrity of human monoclonal antibodies of an IgG4 isotype was studied using a rotating disk shear device.

A key **research outcome** has been the development of a new ultra scale-down shear device that produces quantifiable high shear strain rates at a solid liquid interface and excludes air-liquid interfaces. It has been applied successfully to understand the factors that lead to antibody degradation and to describe the relationship between shear rate and antibody aggregation.

The research uptake within the collaborating company, MedImmune, has been the incorporation of this technique into its portfolio of tools to investigate antibody stability. The technique will allow the unit operations involved in formulation and storage to be studied and the optimum conditions required during process pumping operations to protect antibody therapeutics from degradation to be identified. The researcher has been recruited by MedImmune to undertake research on formulation.

The success of this project has led to further collaborations with companies that wish to address protein aggregation. A follow-on EngD project with MedImmune has been initiated to research aggregation of antibodies in downstream processing. An EngD project and a two year sponsored Post Doc project have been initiated with GlaxoSmithKline to research the causes of aggregation of a different class of antibodies in fill-finish operations.

The impact of the research has been the improved control of the formulation processes to avoid product aggregation. This has very substantial implications for product efficacy and patient safety. According to VisionGain there are 21 FDA approved antibody therapies with an estimated market value in 2009 of over $20billion. Many of these treatments are significant as they are used to slow chronic disease progression, reduce morbidity and/or to replace essential proteins that are not produced endogenously in patients.

Details of the design and operation of the new high shear device created from this IMRC research have been published and are thus available for other researchers and process development technologists.

Further information (industrial and university collaborators are identified in bold)

Biddlecombe, J.G., Craig, A.V., **Zhang, H., Uddin, S., Mulot, S., Fish, B.C.**, Bracewell, D. G. (2007) Determining antibody stability: creation of solid-liquid interfacial effects within a high shear environment. *Biotechnology Progress*. 23: 1218-1222.

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Biddlecombe, J.G., **Smith, G., Uddin, S., Mulot, S., Spencer, D., Gee, C., Fish, B.C.**, Bracewell, D.G. (2009) Factors influencing antibody stability at solid-liquid interfaces in a high shear environment. *Biotechnology Progress*. 25: 1499-1507.

Silk, N.J., **Denby, S., Lewis, G., Kuiper, M., Hatton, D., Field, R.**, Baganz, F., Lye G.J. (2010) Fed batch operation of a GS-CHO cell culture process in shaken microwells. *Biotechnology Letters.* 32: 73-78.

Over the lifetime of the IMRC there has been a five fold increase of company involvement in facilitating IMRC research and technology transfer

Ultra scale-down chromatography - understanding our challenging separations.

Ultra scale-down shear - will our material survive mixing, pumping, vialing, centrifugation at industrial scale?

Solving the recovery to chromatography interface with ultra scale-down
– with Pfizer

The performance of high resolution chromatography is often highly dependent on the quality of the feed stream emerging from the preceding recovery stages. The challenge for the bioprocess engineer is to determine at an early stage the relationship between recovery for the concentration of the product and removal of gross contaminants and the performance of the subsequent high resolution stages. For example, the ability to define which contaminants will bind to, as opposed to simply flow through, a column provides a key route to early process optimisation.

This project involved two elements; the first to improve process insight early in development, the second to use such knowledge to achieve process gains. The use of Surface Enhanced Laser Desorption Ionisation-Time of Flight-Mass Spectrometry (SELDI-TOF-MS) technology was examined as an analytical tool for bioprocess development. This technique can be used to determine the physico-chemical properties of proteins in complex mixtures, which can then be utilized to highlight promising chromatographic conditions for purification of a target protein. The key benefits of this approach over the traditional methods are the speed and ease of sample preparation and data acquisition to generate a large amount of quality data within a few days using only microliters of the complex protein solution.Having established the SELDI method, the project then focused upon the development of a predictive ultra scale-down model that enables rapid optimisation of the operating conditions for a flocculation centrifugation sequence using only small volumes (20 mL) of a high solids (20% w/w) E. coli cell broth.

The research outcome has been the creation of a rapid microliter analytical technique based on SELDI-TOF-MS to analyse proteins and their adsorption characteristics in crude cell broths. This is suitable for application with very low volumes of process material in multi-well plate formats. It provides data to model rapidly and then to select the most appropriate chromatographic purification process conditions. This provided the necessary analytical capabilities for application in an ultra scale-down study. Here an ultra scale-down shear device and protocol have been developed that mimics the centrifugation behaviour at production scale of flocculated high density cell lysate from microbial cultures. This technique predicts the shear stability and clarification behaviour of the flocculated cell lysate and has been used to optimise the flocculant addition and the clarification performance of a large scale centrifuge process. Verification has been obtained successfully at pilot-plant scale.

The research take up has been the ultra scale-down development of a new process involving flocculation and centrifugation for the recovery and purification of a membrane associated protein, ApoA-1 Milano, from *E. coli* fermentation and its verification at pilot-plant scale. ApoA-1 is indicated as a potential therapeutic for treatment of cardiovascular disease. IMRC ultra scale-down techniques have proven critical in the creation of the purification process for this product. Pfizer is offering the ApoA 1-milano technology for licensing. Processing insights gained from the application of ultra scale-down techniques form an integral part of the licensing package now being offered by Pfizer for this product.

The impact of the research has led to the wider use of SELDI-TOF-MS for analysis in crude feeds and has been crucial in securing a £820,000 collaborative project funded by the EPSRC/BBSRC Bioprocessing Research Industry Club with the University of Kent to investigate further the application of SELDI-TOF-MS to the analysis of materials during the bioprocessing of mammalian cell broths.In a further development with Pfizer the role of membrane separations in preconditioning of broths prior to chromatography is now also being examined using new USD technologies.

Further information (industrial and university collaborators are identified in bold)

Berrill, A., **Ho, S.V.**, Bracewell, D.G. (2008) Ultra scale-down to define and improve the relationship between flocculation and disc-stack centrifugation. *Biotechnology Progress*. 24: 426-431

Berrill A., **Ho, S.V.**, Bracewell, D.G. (2010) Product and contaminant measurement in bioprocess development by SELDI-MS. *Biotechnology Progress*. 26: 881-887.

Berrill A., **Ho S.V.**, Bracewell D.G. (2011) Mass spectrometry to describe product and contaminant adsorption properties for bioprocess development, *Biotechnology and Bioengineering*. DOI: 10.1002/bit.23115.

Human cell bioprocessing using ultra scale-down to characterize impacts of process stress
- with Onyvax, ReNeuron and TAP

Human cells are forming the basis of next generation therapies including cancer vaccines which are designed to elicit an immune attack on a broad range of targets associated with types and stages of cancer through to regenerative medicines for a wide range of conditions e.g. Parkinson's, stroke. This project has examined candidate cell lines including fibroblasts, epithelial cells and neural cells to identify ways in which they respond to process stress e.g. during transport when vialling or during centrifugation when purifying the cells. The programme has provided new insights on how cells respond to stress and to factors which may determine damage such as the effect of cell-cell or cell- surface interaction.

The research outcome of this programme has been the identification of new process engineering parameters such as the critical stress beyond which loss of cell membrane integrity can occur and the sensitivity of this design parameter to the way in which cells have been handled previously such as their generation number, any holding times or the composition of the growth media. It is also evident that the critical stress does vary with cell type making cell selection a key parameter to define ease of processing. The full characterization of the cells is a major challenge and a key feature has been the match of ultra scale-down methods with the cell quantities required for analysis. The range of methods used to date include the cell surface markers type and density, the cell growth characteristics, the cytokine levels determining the response in the patient as well as the immune response elicited when mixing the cells with cultivated T-cells. Key successes have been for example the prediction and verification of capillary designs where no cell damage is observed and new ways to recover cells by centrifugation with reduced cellular damage.

The research take up has been the application of the ultra scale-down methods in a Technology Strategy Board funded programme with: ReNeuron to examine application to preparation of human neural stem cells; with LGC to explore the discovery of new cell markers to help define the impact of process stress; with Bioinformatics Centre at Nottingham Trust University to develop Artificial Neural Networks to help define more robust whole bioprocesses for cell therapy preparation. Most recently the research has opened the way for collaborations with Pall to help develop alternatives to centrifugation for cell recovery.

The impact of the research has been to provide a platform of ultra scale-down devices for the training of life scientists and engineers seeking to translate bench scale studies of individual cell lines to their preparation for therapeutic application. Such a training base will be housed at UCL and disseminated e.g. via collaborative knowledge exchange activities with industry.

Further information (industrial and university collaborators are identified in bold)

Zoro, B.J.H., **Owen, S., Drake, R.A.L.**, Hoare, M. (2008) The impact of process stress on suspended anchorage-dependent mammalian cells as an indicator of likely challenges for regenerative medicines. *Biotechnology and Bioengineering*. 99: 468-474.

Zoro, B.J.H., **Owen, S., Drake, R.A.L.**, Mason, C., Hoare, M. (2009) Regenerative medicine bioprocessing: concentration and behaviour of adherent cell suspensions and pastes. *Biotechnology and Bioengineering*. 103: 1236-1247.

McCoy, R., **Ward, S.**, Hoare, M. (2009) Ultra scale-down studies of the effect of shear on cell quality; processing of human cell line for cancer vaccine therapy. *Biotechnology Progress*. 25: 1448-1458.

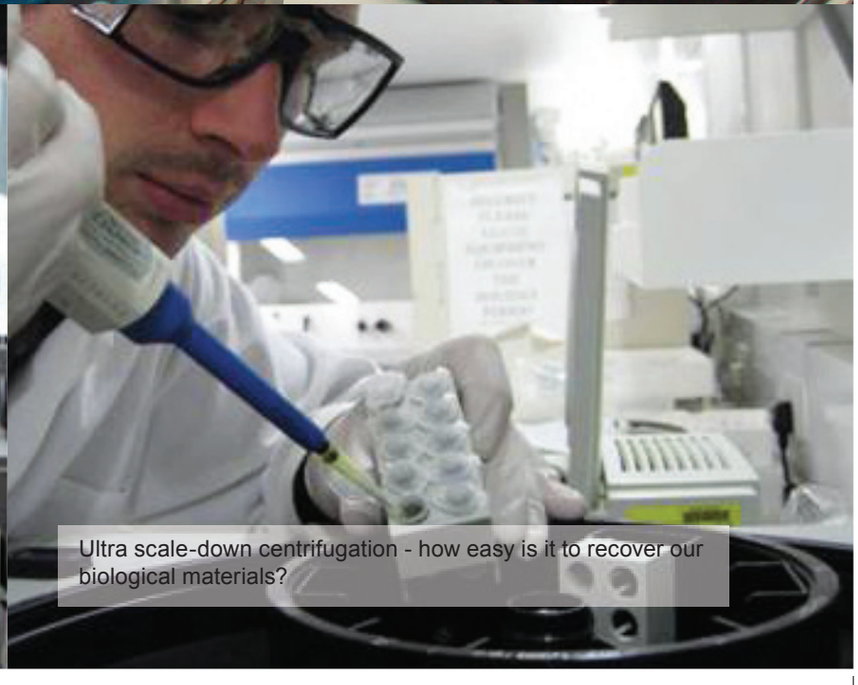
McCoy, R., **Ward, S.**, Hoare, M. (2010) Sub-population analysis of human cancer vaccine cells – ultra scale-down characterisation of response to shear. *Biotechnology and Bioengineering.* 106: 584-597.

Papantoniou, I., Hoare, M., Veraitch, F.S. (2011) The release of single cells from embryoid bodies in a capillary flow device.*Chemical Engineering Science*. 66: 570-281

Acosta-Martinez, J.P., Papantoniou, I., Lawrence, K., **Ward, S.**, Hoare, M. (2010) Ultra scale-down analysis of the bioprocessing of whole human cells as a basis for cancer vaccines. *Biotechnology and Bioengineering*. 107: 953-963.

IMRC funded researchers are trained to validate the ultra scale-down technology at laboratory and pilot scales

Ultra scale-down filtration - what size industrial filters will we need?



Ultra scale-down centrifugation - how easy is it to recover our biological materials?

Prediction and optimization of industrial-scale chromatographic sequences
– with GE Healthcare

A powerful complement to ultra scale-down technologies is the use of theoretically-based models to a) gain insight into the complex interactions which occur when processing real many-multi-component feed streams and b) to allow effective rapid and low cost prediction of the impact of imposed processing changes. This project set out to establish a robust model based on sound theoretical principles that would predict the performance of production scale chromatography. The chromatographic model developed is based on an understanding of the underlying physical mechanisms and describes the convective and dispersive flow in the column, the diffusion in the adsorbent particles, and the protein adsorption / desorption using Langmuir kinetics with mobile phase modulators. The method consists of three steps. In the first step, the model is calibrated against ultra scale-down experiments (1 mL columns). In the second step, the model is verified against a series of ultra scale-down experiments designed to seek out optimal operating windows. In the third and final step, the model is used to predict and optimise scale-up separation – in this case at 150,000 fold scale up.

The research outcome has been a new modelling method calibrated and validated against scale-down experiments. The prediction of scale-up separation has been undertaken and based on input data from ultra scale-down experimental predictions of separations at pilot and production scale have been validated.

The research take up has been via a new EngD project with Wyeth Biopharma (now Pfizer) on the scale up of chromatography operations. The methodology provides confidence to take forward the data generated from the high throughput experimentation generated in the IMRC Theme 3 activities. For GE Healthcare it will become part of the portfolio of techniques to reduce the risks in selecting new chromatographic matrices and to demonstrate their benefits at production scale. It has also led to a new EngD project to examine how best to achieve efficient searches of large experimental spaces such as those represented by chromatographic separations.

The impact of the research relates to the scale up of chromatographic steps in biopharmaceutical processes which is extremely expensive in terms of very valuable biological materials as well as the high cost of plant time and personnel. Access to good predictive models will reduce the number of scale up experiments required. This will have an economic impact across the biopharmaceutical industry as each bioprocess generally has multiple chromatographic steps. The work builds upon previous studies with GE Healthcare as a partner which examined the ways in which column cycling could improve process throughput and also assessed the role of alternative operations to provide non-chromatographic resolution in bioprocesses. The most recent studies, via an EngD, are examining how best to deploy analytics in order to avoid analysis becoming a bottleneck in high throughput process development studies.

Further information (industrial and university collaborators are identified in bold)

Tran, R., Joseph, J.R., Bracewell, D.G., Zhou, Y., Titchener-Hooker, N.J. (2007) A framework for the prediction of scale-up when using compressible chromatographic packings. *Biotechnology Progress.* 23: 413-422.

Tran, R., **Lacki, K.**, Zhou, Y., Titchener-Hooker, N.J. (2008) A methodology for the comparative evaluation of alternative bioseparation technologies. *Biotechnology Progress.* 24: 1007-1025.

Gerontas, S., **Asplund, M., Hjorth, R.**, Bracewell, D.G.(2010) Integration of scale-down experimentation and general rate modelling to predict manufacturing scale chromatographic separations. *Journal of Chromatography.* 44: 6917-6927.

3.0 Current Research Portfolio

“The research focus of the Centre is to establish an ultra scale-down platform for the whole bioprocess of existing as well as future generations of biopharmaceuticals.”

3.0 Current Research Portfolio

The research focus of the Centre is to establish an ultra scale-down platform for the whole bioprocess of existing as well as future generations of biopharmaceuticals from early steps in the development of cells through to the purification and formulation of product. The research portfolio is enriched by enhanced experimental design techniques for rapid acquisition of information about the process and by cell engineering methods designed to improve, simplify and speed the development of bioprocesses.

The Centre's research portfolio consists of three thematic elements. **Research Theme 1** seeks to examine and establish new micro biochemical engineering fundamentals in three areas of cell culture and fermentation **(Theme 1.1)**, primary recovery **(Theme 1.2)** and chromatography and formulation **(Theme 1.3)**. The integration of the sub-themes is particularly helped by collaborations with industry whose whole bioprocess studies involve research from the cell to the final product.

Research Theme 2 focuses on speeding up the acquisition of process knowledge by creating generic experimental design methodologies which can quickly and efficiently identify the most appropriate region of operation.

Research Theme 3 provides the third strand in research to help lead to faster and more efficient processing. New approaches in cell manipulation which will result in cleaner process stream and improved productivity, potentially requiring operating stages are addressed in **Theme 3.1**. New alternative technologies in downstream processing which will impact the whole process train are examined in **Theme 3.2**.

Each Research Theme is complemented with research conducted via doctoral projects. These are described as affiliated projects and support the postdoctoral research effort. Affiliated doctoral projects are supported by both IMRC and non-IMRC partners and also funded by a range of scholarships and charities. In 2010 a total of 58 such projects were under way. Each contributes to the overall thrust of the IMRC and is individually important for both widening and deepening the nature of the research undertaken in the IMRC core. Such affiliated projects are selected competitively via Management Advisory Committee endorsement (Section 5). The appraisal is on the basis of their originality and relevance to the IMRC agenda.

In some cases an affiliated project bears on more than one theme and these interactions are hence noted under each theme to which they relate.

3.1 Research Theme 1 Microscale bioprocess engineering

3.1.1 Theme 1.1 Ultra scale-down preparation of next generation macromolecular and nanomolecular materials

N,Gill, Q.Li, I. Papantoniou, M. Micheletti, G.J. Lye, F. Baganz, T. Mukhopadhyay, M. Hoare plus 19 affiliated researchers

Project value: £1.07m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.31m direct and £1.87m indirect external contribution.

Research focus

This theme seeks to establish and examine new micro biochemical engineering fundamentals related to growth of cells and microorganisms and associated macromolecular and nanomolecular product formation. These will provide the foundation of novel ultra scale-down methods for the study of fermentation and cell culture. The methods will predict and inform the design of full scale operations and the impact of their performance on the whole bioprocess.

The ability to prepare cells in controlled engineering environments at the microscale will provide the platform to understand the impact of cell engineering and synthetic biology on whole bioprocesses.

The principal aim is to create the platform and to characterise the engineering transport processes and the resultant cell and product properties. Two main expression systems forming macromolecular products will be addressed; mammalian cells with secreted monoclonal antibodies and fusions and rec *E. coli* cells with periplasmically located antibody fragments.

Next generation targets are particularly focussed on nanomolecular vaccine candidates including viral particles through to whole cells. More recently the focus has also been extended to ultra scale-down of new methods of culture using single-use facilities, and to application to new industrial sectors especially those concerned with sustainability and environmental impact.

For all of the targets and cell lines addressed a key aim is to use primary recovery ultra scale-down skills (Research Themes 1.2, 3.1 and 3.2) to characterise resultant properties of materials produced in the bioreactors and hence to determine the impact on the whole bioprocess.

Notable achievements

The necessary components have been created for a mammalian cell microscale bioprocess engineering platform as the basis for whole bioprocess studies in this key biopharmaceutical sector.

The main focus to date has been in the area of mammalian cell cultivation in particular for the ranking of high producing cell lines suitable for large scale culture and recovery (Barrett *et al*, 2010). Here mixing time has been shown to be the main large scale engineering variable to be mimicked at the microscale to give predictive growth rates (Silk *et al*, 2010).

The impact of cell preparation on centrifugal broth clarification has been demonstrated at microscale (Tait *et al*, 2009) as well as for the first time the effects on antibody product quality in terms of glycosylation patterns (Reid *et al*, 2010).

A platform has been established for the characterisation of microbial growth in microscale bioreactors using Design of Experimentation skills (Islam *et al*, 2007) and quantification of engineering parameters (Gill *et al*, 2008 a, b; Islam *et al*, 2008). This is the basis for a new phase of IMRC affiliated projects (see below) integrating the bioreactor and product recovery strategies.

The establishment of ultra scale-down skills has allowed parallel work to occur for a wide range of targets and hence create the skills to enable cross-comparisons between the processability of different materials in several classes e.g.:

- macromolecules such as antibodies ranging from polyclonals (BTG), monoclonals (Lonza Biologics, MedImmune, GSK), fragments (UCB Pharma), domains (GSK) and protein fusions (Royal Free Hospital and ImmunoBiology);

- nanomolecular complexes and assemblages including virus-like particles as a basis for hepatitis B or HPV cervical cancer vaccines (with Merck), virus-like particle fusions (with IQur), membrane vesicles as the basis of

a Herpes vaccine (with BioVex) and enveloped viruses (flavivirus for Japanese Encephalitis with Intercell) and non-enveloped viruses (lentivirus for gene therapy with Oxford BioMedica);

- whole cellular entities including advanced host cells for biomanufacture (GS-CHO, NSO, Lonza Biologics, MedImmune, GSK), rec *E. coli* (UCB Pharma, GSK, Pfizer, Lonza Biologics), rec P. pastoris, (Merck), human cells for virus formation (HEK with Oxford BioMedica) and cells for therapy or diagnostics/screening (prostate with Oxyvax Ltd and neural with ReNeuron) and most recently algae cells for sustainability studies.

Future directions

This theme will now continue through the affiliated projects (see below) transferring ultra scale-down skills to the study of growth and preparation of new materials relevant to the next generation biopharmaceutical industries. This will allow integration with Research Themes 1.2 and 1.3 to deliver on whole bioprocess platform as the final phase of this aspect of IMRC research – see Research Theme 1.2 for details. Furthermore, the establishment of a new Responsive Bioprocessing facility initiated via collaborations with Sartorius Stedim Biotech, Applikon Biotechnology, Pall Life Sciences, Infors HT, GE Healthcare and PBS Biotech is now providing the opportunity to link ultra scale-down technologies with the power of using single-use equipment to help gain speed to manufacture.

Affiliated projects – current

Project	Title	Collaborators
1.1.1	Scale-down and whole process evaluation of thermophilic bioethanol production by a metabolically engineered Geobacillus strain. (N. Conroy, G.J. Lye, I.Tebble)	TMO Renewables
1.1.2	Engineering characterisation of single-use wave-type bioreactors for improved cell culture process development and scale-up. (D. Marsh, G.J. Lye, M. Micheletti, M. Osborne)	Eli Lilly
1.1.3	Design and evaluation of an internally radiating photobioreactor for the algal-based production of biofuels, biorenewable chemicals and biopharmaceuticals. (K. Miller, F. Baganz, S. Purton)	Structural and Molecular Biology, UCL
1.1.4	Incorporation of developability into cell line selection: a high-throughput small-scale mimic for a mAb manufacturing process. (J. Betts, G.J. Lye, G. Finka)	GSK
1.1.5	Microscale process characterisation of Lentivirus vectors as targets for vaccine delivery. (H. Guy, T. Mukhopadhyay, G.J. Lye, S. Denby, K. Mitrophanous)	Oxford BioMedica
1.1.6	Microscale vaccine bioprocessing with application to an attenuated Japanese Encephalitis Virus. (M. Hughson, T. Mukhopadhyay, N.J. Titchener-Hooker, K. Queen, D. Low)	Intercell Biomedical
1.1.7	Biological and chemical characterisation of sensor surfaces and the use of scale-down techniques for bioprocess monitoring. (M. Perez Pardo, D.G. Bracewell, W.Jones)	Biopharm Enterprises
1.1.8	Design and characterisation of a miniaturised bioreactor system for parallel cell culture process development. (O. Al Ramadhani, F. Baganz, M.Appleton)	HEL (Hazard Evaluation Labs)
1.1.9	Evaluating the response of mammalian cells to environmental perturbations using a parallel microwell approach. (A. Pinto, F. Baganz, C. M. Smales)	Biosciences, University of Kent
1.1.10	Microscale process development of a Lentivirus platform for application to vaccines. (S. Tagestam, T. Mukhopadhyay, M.Collins)	Division of Infection and Immunity, UCL
1.1.11	Engineering characterisation of disposable bioprocess technology for the establishment of novel scale-up approaches in mammalian cell culture. (A. Odeleye, M. Micheletti)	IMRC supported
1.1.12	Exploring the potential for therapeutic protein production in algae. (S. Braun, F. Baganz, S. Purton)	Structural and Molecular Biology, UCL
1.1.13	Oxygen monitoring and control in a microfluidic reactor for embryonic stem cells. (A. Super, N. Szita)	IMRC supported
1.1.14	The impact of bioreactor aeration and mixing on Chinese Hamster Ovary cell physiology and structure during antibody production. (M. Velez Suberbie, D.G. Bracewell)	IMRC/CONACYT supported
1.1.15	Engineering characterisation of single-use, wave-type bioreactors and scale-up considerations for early phase cell culture process development. (N. Gill, G.J. Lye)	IMRC supported

1.1.16	Bioprocessing of antibody based fusions for vaccine preparation-control of biorector recovery interface (E. Lau, S.Y.Kong, M.Hoare, C.Entwistle, S.McNulty).	ImmunoBiology, ERA
1.1.17	Establishing high cell density fed-batch fermentation at millilitre scale and integrating with ultra-scale down recovery methods. (S. Ali, F. Baganz)	IMRC supported
1.1.18	A bioprocessing discovery tool to speed up cell-based process development and manufacturing. (C. Chu, K. Lawrence, S. Ward, G. Balls, N. Harris, M. Hoare)	ReNeuron; Onyvax; LGC; Bioinformatics, Nottingham Trent University
1.1.19	Integrating upstream host cell line selection and development with improved downstream processing. (A. Tait, D.G. Bracewell, C.M. Smales)	Biosciences, University of Kent

See also projects 3.1.6, 3.1.7 and 3.1.8

Affiliated projects – completed

Project	Title	Collaborators
1.1.20	Ultra scale-down characterisation of resistance to process stress for human cells for cancer vaccine therapies. (R.McCoy, M.Hoare, S.Ward)	Onyvax
1.1.21	A tool kit for in-process determination and control of structural and conformational authenticity of complex biopharmaceuticals. (C. Reid, M. Hoare, C.M.Smales, A. Racher, A. Tait, S. Bilsborough)	Biosciences,University of Kent; Lonza Biologics; Agilent
1.1.22	Bioprocessing properties of antibody fusions equipped with flexible linker regions. (P.Blas, M. Hoare, K. Chester)	Department of Oncology,UCL; Royal Free Hospital
1.1.23	An automated miniaturised bioreactor to test bioprocessing of new biopharmaceutical candidates. (L.Foley, M. Hoare, R. Wales, S. Owen)	TAP
1.1.24	Pharmaceutical processing of enveloped viruses for gene therapy applications. (N. Pheasey, M. Hoare, C. Love, J.M. Ward, R.A.Coffin)	BioVex; Structural and Molecular Biology,UCL; Molecular Pathology, UCL

See also projects 3.1.15, 3.1.17 and 3.1.18

Our new Responsive Bioprocessing facility is providing the opportunity to link ultra scale-down with single-use equipment to gain speed to manufacture

3.1.2 Theme 1.2 Ultra scale-down primary recovery

S.Y.Kong, A.Tait, N.J.Titchener-Hooker, D.G.Bracewell, G.J.Lye, Y.Zhou, M.Hoare plus 11 affiliated researchers

Project value: £1.23m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.33m direct and £1.41m indirect external contribution.

Research focus

This theme seeks to establish and examine new micro biochemical engineering fundamentals related to the processing of the complex broths derived from fermentation and cell culture. These fundamentals will provide the foundation of novel ultra scale-down methods for the early stage removal of contaminants and hence the crucial interface between fermentation cell culture and high resolution purification. The methods will predict and inform the design and operation of full-scale processes and the impact of process choice on whole bioprocess performance.

he recovery stages provide the crucial interface between fermentation/cell culture with all its inherent variability and sensitivity to cellular stress (Research Theme 1.1) and the very high cost chromatography and formulation stages which require well controlled feed streams for successful operation.

The ability to understand at the microscale the impact of the engineering environment on the complex materials encountered in the early recovery stages is central to successful process discovery. This combined with critical regime analysis of the full scale operations provides the innovative route to ultra scale-down as a means for speeding bioprocess manufacture.

The principal aim is to provide an ultra scale-down platform which will allow early process comparison of a range of primary recovery operations the key ones being centrifugation, filtration and membrane separation, all with the potential of integration with selective precipitation and flocculation stages.

Notable achievements

The comparative primary recovery platforms using ultra scale-down methods have now been successfully established and for centrifugation this has progressed to a multiwell approach adapted to either laboratory operation or to use on robotic platforms (Tait *et al*, 2009).This complements extensions now made to the manual/robotic multiwell approach developed for depth filtration in the earlier IMRC phase (Jackson, NB, Liddell, JM, Lye, GJ, 2006, An automated microscale technique for the quantitative and parallel analysis of microscale operations, *J Membrane Sci*, 2006: 276, 31) and the first new ultra scale-down approaches for cross flow membrane separation using low volume rotating disc devices (Ma *et al*, 2010) and robotic controlled cross-flow devices (Rayat *et al*, 2010).

This battery of techniques is now being brought together for the first time as a means for testing new cellular engineering approaches (e.g. in collaboration with Research Theme 3.1 to evaluate the impact of cell engineering).

The importance of these methods in determining the impact on subsequent chromatography has been demonstrated in a first study showing how the impact of lipid (a major foulant of expensive chromatographic supports) removal can be successfully predicted (Bracewell *et al*, 2008; Jin *et al*, 2010), the use of selective flocculation to remove key contaminants which impact the capacity of separation processes (Berrill *et al*, 2008), the use of detergents to enhance lipid-envelope virus-like particle recovery (Kee *et al*, 2008, 2010) and how glycosylation patterns of therapeutic proteins (a major factor in determining their stability and functionality) are affected in recovery stages (Reid *et al*, 2010).

Ultra scale-down research into the impact of process stress on biomaterials has successfully been translated to the more complex next generation materials for therapy including whole cells (Zoro *et al*, 2008, 2009; McCoy *et al*, 2009, 2010; Acosta *et al*, 2010).

A £1m GSK Centre of Excellence has been established to study the impact of the new ultra scale-down methods to speed to manufacture a next generation set of therapies based on domain antibodies. This is in addition to first whole bioprocess studies focused on the primary recovery stages for fusion proteins as a vaccine (ImmunoBiology) and enhanced antibody fragment recovery from rec *E.coli* (UCB Pharma).

In the area of preparation of cells for therapy/diagnosis/drug screening the collaborations with ReNeuron, LGC and Nottingham Trent University via Technology Strategy Board funding complement the IMRC base to help develop novel approaches to solving recovery design challenges at the totally new scale of operation facing the fledging regenerative medicines sector.

The links with cell engineering groups at Kent and Warwick Universities have been established to provide wider access to IMRC ultra scale-down methods to enhance the prospects of selection of new cell lines with the potential of delivering step changes in industrial scale bioprocessing (see Research Themes 3.1 and 3.2).

Future directions

The final phase of the IMRC will be the integration of Research Themes 1.1, 1.2 and 1.3 to establish an ultra scale-down platform for whole bioprocess discovery. This is now nearing completion for rec *E.coli* producing antibody fragments and will next be addressed for monoclonal antibodies from mammalian cells. The initial targets will be (i) the use of ultra scale-down to examine the effects on the whole bioprocess of culture methods for cells using conventional stirred tank reactors, single use reactors and microscale reactors, (ii) the effect of broth pretreatment (e.g. acid precipitation) on the recovery process especially in terms of clarification and extent of aggregation. Individual affiliated projects (see below) will help refine the use of ultra scale-down methods when investigating the full-scale processing of increasingly complex materials, eg vaccines and whole cells for therapy. Such projects will continue to contribute to the delivery of the IMRC outputs.

Affiliated projects - current

Project	Title	Collaborators
1.2.1	An engineering framework for the rapid process appraisal of protein purification by precipitation. (C. Morris, P.A. Dalby, N. Titchener-Hooker, E.Norrant)	UCB Pharma
1.2.2	Novel strategies for early downstream processing of high density mammalian cell cultures. (D. Popova, S. Farid, N. Titchener-Hooker, A Westlake)	Lonza Biologics
1.2.3	An ultra scale-down tool for the predictive design of a filtration procedure for preparation of human cell therapies. (C. Longster, M. Hoare, P. Levison)	Pall Life Sciences
1.2.4	Small scale, high-throughput bioprocess discovery for domain antibodies. (A. Chatel, M. Hoare, P. Kumpalaume)	GSK
1.2.5	Applying iDoE methods to noise-prone micro-scale studies for accelerated bioprocess design. (M. Khan, Y. Zhou, L. Allen)	Lonza Biologics
1.2.6	A bioprocess discovery tool to speed up new vaccine and cell therapy development.-ultra scale-down of bench scale centrifugation for cell recovery. (M. Delahaye, M. Hoare, S. Ward, J. Sinden, G. Balls, N. Harris)	LGC; Bioinformatics, Nottingham Trent University; Onyvax Ltd; ReNeuron
1.2.7	An integrated ultra scale-down tool set for the predictive design of a membrane separation procedure for preparation of human cell therapies. (F. Masri Rabin, M. Hoare)	IMRC supported
1.2.8	Engineering host cell protein contaminants in mammalian cell lines for improved downstream bioprocessing. (R. Tarrant, D.G. Bracewell, C.M. Smales)	Biosciences,University of Kent
1.2.9	Microscale multimodal precipitation to establish scaleable operations for contaminant removal prior to packed bed steps. (R. Hanif, D.G. Bracewell)	IMRC supported
1.2.10	Use of USD tools to facilitate strain selection in a platform based antibody fragment production process. (J. Aucamp, P.A. Dalby, A. Weiss)	UCB Pharma
1.2.11	Rapid microscale evaluation of the impact of fermentation conditions on inclusion body formation, solubilisation and protein refolding yield. (G. Ordidge, M. Micheletti, J. Liddell)	MSD Biologics

See also projects 2.1 and 3.2.10

Affiliated projects – completed

Project	Title	Collaborators
1.2.12	Development of ultra scale-down shear filtration system and modelling of large scale crossflow diafiltration. (G. Ma, Y. Zhou)	IMRC supported
1.2.13	Design of evaluation of an automated microscale system for the quantitative and parallel analysis of cross-flow filtration processes. (A. Rayat, G.J. Lye)	IMRC/ORS supported
1.2.14	An engineering study of key interactions within within the process for antibody fragment production. (A. Tustian, N. Titchener-Hooker, L. Bowering, N.Weir)	UCB Pharma
1.2.15	Accelerated determination of optimal process sequences and operating conditions for biopharmaceutical recovery and purification steps. (A. Berrill, D.G. Bracewell, S. Ho)	Pfizer
1.2.16	Automated microscale chromatography as a strategy for process development of proteins. (M. Wenger, D.G. Bracewell, P. DePhillips)	Merck
1.2.17	Ultra scale-down approaches to tangential flow ultrafiltration. (W. Domah, N.J. Titchener-Hooker, G.J. Lye, P. Levison)	Pall Life Sciences

See also projects 3.2.17 and 3.2.18

3.1.3 Theme 1.3 Ultra scale-down chromatography and formulation

J.Aucamp, P.A.Dalby, D.G.Bracewell, M.Hoare plus 7 affiliated researchers

Project value: £0.96m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.16m direct and £1.32m indirect external contribution.

Research focus

This theme seeks to establish and examine new micro biochemical engineering fundamentals related to the high resolution purification and formulation of biopharmaceuticals. These will provide the foundation of novel ultra scale-down methods for the study of operations such as chromatography, filtration, mixing and freeze drying where it is the choice of protectants and the impact of the process engineering environments which are critical. The methods will predict and inform the design of full scale operations at the stage of the whole bioprocess closest to therapeutic application.

High resolution chromatography and formulation sequences need to work in tandem to deliver biopharmaceuticals which are safe for administration. This must be achieved by careful control of the processing environment and the presence of protectants.

The process of replacement of natural but severely antigenic protectants with non-antigenic, non-toxic alternatives (e.g. surface active agents) does expose the biopharmaceutical product to the likelihood of damage in hostile environments. There is every potential of this product damage leading to the formation of new antigenic, toxic materials.

The principal aim is to devise ultra scale-down methods where small amounts of highly precious and scarce material can be used to predict full scale operation and to identify rationally the best combination of protectants to preserve the valuable material.

For chromatography the aim is to work at the micro litre scale in automated devices both to help determine the effectiveness of primary recovery stages (Research Theme 1.2) and to deliver material suited to formulation.

Notable achievements

Ultra scale-down of high resolution chromatography has been successfully achieved to provide new insights into how columns function with real protein systems (Hutchinson *et al*, 2009, Chan *et al*, 2008 a, b). Extreme scale down (a further 100 fold over previous systems) and the link with robotic platforms has now been achieved (see Research Theme 3.1 for progress to date by Shapiro *et al*, 2009.

Wenger *et al*, 2007). The basis now exists for array-based studies of the integration of processing sequences (Chhatre *et al*, 2009).

Formulation ultra scale-down has been delivered for the first time for the determination of liquid composition for freeze drying (Grant *et al*, 2009) as well as new ways for the study of product stabilization in its liquid phase (e.g. Biddlecombe *et al*, 2007, 2009; Arulmuthu *et al*, 2008; Meacle *et al*, 2007) and accompanying sterile filtration (Kong *et al*, 2010).

A Centre of Excellence activity for antibody formulation and stabilization has been established with GSK and extended by an EPSRC funded Knowledge Transfer Secondment. A similar Knowledge Transfer Secondment has now also been completed with UCB Pharma for antibody fragment stabilization studies.

The work with BTG, Lonza Biologics, UCB Pharma, GSK and ImmunoBiology is bringing together whole bioprocess studies linking primary recovery and chromatography for polyclonal, monoclonal, fragments, domain and fusion antibodies respectively. This is allowing us to demonstrate the potential of radical changes in protein configuration and the impact of bioprocessing.

Future directions

The final phase of the research in this theme will focus on ultra scale-down of chromatography this being the most challenging of the operations with respect to connecting the microscale to the full scale operation due to the complex changes which occur during the interaction of complex and ill-defined process streams with the highly sensitive separating surfaces and three dimensional bead structures. The success to date in ultra scale-down of chromatography to the microscale will provide the interface with Research Themes 1.1 and 1.2 to allow the development of platforms for whole bioprocess studies as the final phase of this part of the IMRC.

Affiliated projects - current

Project	Title	Collaborators
1.3.1	Investigation of IgG aggregate formation in biopharmaceutical processes; A study of the location and mechanism of aggregation. (R. Keshe, D.G. Bracewell, R.Turner)	MedImmune
1.3.2	Measurement of protein self-association behaviour as a determinant of aggregation in bioprocessing. (K. Kovacs-Schreiner, D.G. Bracewell, B.Fish)	GSK
1.3.3	Process modelling approaches to biological complexity in the production of therapeutic proteins. (E. Close, D.G.Bracewell, E. Sorenson , J Salm)	Pfizer
1.3.4	Non-geometric scale-up chromatographic separations. (J. Senaratne, N. Titchener-Hooker, P.Levison)	Pall Europe
1.3.5	Pre-formulation screening: High throughput tools to formulate dAbs and predict stability profiles. (U. Uye, P.A. Dalby, F.Ahmed)	GSK
1.3.6	Fundamental studies and characterization of non-viral DNA integrity in sterile filtration. (A. Affandy, E. Keshavarz-Moore, H.K. Versteeg)	Mechanical and Manufacturing Engineering/IMRC Loughborough University;
1.3.7	Characterisation of the effect of linker sequence and length on the liquid formulation properties of a therapeutic fusion protein. (J. Aucamp, P.A. Dalby, A. Weiss)	UCB Pharma

See also projects 3.2.1, 3.2.6, 3.2.9 and 3.2.11

Affiliated projects – completed

Project	Title	Collaborators
1.3.8	Design and characterisation of microlitre scale chromatography for the comparison with preparative scale chromatography. (M. Shapiro, D.G. Bracewell, S.Haswell)	Chemistry, University of Hull
1.3.9	High-throughput mutation and formulation techniques for improving the stability of proteins in solution. (M. Rose, P.A. Dalby, S. Perkins)	Structural and Molecular Biology, UCL
1.3.10	Development of microscale methods for predicting larger-scale chromatographic separations. (S. Chhatre, E. Keshavarz-Moore)	BTG plc
1.3.11	Use of novel ultra scale down methods linked to operating windows to allow rapid prediction of operating conditions for freeze drying processes. (Y. Grant, P.A. Dalby, P. Matejtschuk)	NIBSC
1.3.12	Elucidation of events leading to altered antibody quality arising from damage events occurring during processing and storage. (Y. Abe, D.G. Bracewell, S Perkins)	Structural and Molecular Biology, UCL
1.3.13	Microplate methods for determining protein hydrophobicity and propensity for aggregation. (S. Ahmad, P.A. Dalby, S. Perkins)	Structural and Molecular Biology, UCL
1.3.14	Whole bioprocessing of antibody fragments: ultra scale-down of in-process formulation stages. (P. Beard, M. Hoare, B. Smith, N. Weir)	UCB Pharma
1.3.15	Ultra scale-down methodologies development for biopharmaceutical formulations to control structural and conformational authenticity. (J. Biddlecombe, D.G. Bracewell, B. Fish, S. Mulot, S. Uddin)	MedImmune
1.3.16	Automated microscale chromatography as a strategy for process development of proteins. (M. Wenger, P. DePhillips, D.G. Bracewell)	Merck

See also projects 3.2.13, 3.2.14 and 3.2.19

The development of platforms for whole bioprocess studies will be emphasised in the final phase

3.2 Research Theme 2: Enhanced knowledge acquisition

S. Maskey, S. A. Chhatre, N. Titchener-Hooker, Y. Zhou plus 5 affiliated researchers

Project value: £0.79m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.07m direct and £0.89m indirect external contribution.

Research focus

The bioprocess industries are increasingly moving toward high throughput process development studies. Research Theme 1 is particularly key here in the provision of the engineering mimics to facilitate this high throughput approach. These advances do however, in themselves, create a set of issues not least of which is the generation of extremely large datasets and the attendant problem of acquiring robust process knowledge from these. The research in this theme focuses on creating experimental design methods that provide for the rapid acquisition of relevant bioprocessing knowledge. The capacity to achieve this goal will enhance dramatically the speed of gaining bioprocess understanding and hence of the development of more effective bioprocesses.

Specifically our research aim is to create generic experimental design methodologies that search to identify the most promising operating regions. The focus is to use search algorithms which inform successive rounds of experimental trials by applying knowledge gained from previous experiments to update the extent of process knowledge so that the search is guided toward the best operating regions. In addition we also seek to create the mathematical routines needed to interpret the wider

response surface so that we can identify not only the best operating regions but also characterise the space adjacent to these. In all of the research the ultimate objective has to be an ability to derive a sufficiently detailed and accurate process description to enable design and operating decisions to be made, whilst minimising the experimental time and resources required. A direct outcome of the research will be tools that allow industry to:

- explore large design spaces rapidly and efficiently so as to discover novel bioprocess solutions;
- achieve greater process understanding including the impact of process interactions in complex, interacting systems;
- identify the best region for operation that yields robust process performance and facilitates whole bioprocess optimisation.

Notable achievements

Our progress is best described under three headings which refer to the different kinds of approaches to enhanced knowledge acquisition that we are exploring in the IMRC.

Data-driven methods: Research projects have been focused on application to datasets arising from the processing of monoclonal antibodies from mammalian cells and antibody fragments from recombinant *E. coli* to evaluate the methods the IMRC has developed. We have created a search method that is consistent with a microtitre plate format where the matrix of available experimental conditions is set by the tolerance to which specific well compositions can be realised. This microwell-compatible method provides for a rapid characterisation of the experimental space by use of a sequence of directed searches. The creation and adaptation of efficient search routines based on the Simplex method have been completed (Chhatre *et al*, 2011). This provides the means to harness most effectively the power of microscale experimentation arising from Research Theme 1 and the resultant capacity for high throughput experimentation such formats facilitate. We have proven the effectiveness and robustness of our methods by application to several bioprocess operations including a precipitation process of an antibody fragment from a clarified lysate and a conditioning step designed to maximise the availability of the antibody fragment product ahead of high resolution processing steps. We have also shown how materials consumption can be reduced by at least 25% and the speed of the surface characterisation doubled. In tandem we have created an approach termed Strategic Assay Deployment (SAD) (Konstantinidis *et al*, 2010, conference paper). SAD ranks the available analytical methods and deploys them such that analytical resources are best used and knowledge is gained in the most effective fashion. Comparison with conventional statistical design of experiment methods provides a benchmark for the studies. A series of case studies created by working with Research Themes 1 and 3 as well as with affiliated companies have been used to demonstrate the effectiveness of the approaches.

Model-driven methods: Process modelling has played a key role in the early phase of this theme and a systematic modelling approach has been created that can accommodate realistic industrial feed materials (Chhatre *et al*, 2007a; Edwards-Parton *et al*, 2008; Chan *et al*. 2008a, 2008b; Tran *et al*, 2007). We have shown how data from microwell scale experimental mimics can be used for process model development (Chhatre *et al*, 2009; Ma *et al*, 2010). Although the developed models are material-specific, the model structure is generic. Our model-driven experimental method iteratively designs the experiments using an optimisation routine so as to extract information for parameter estimation most efficiently based on the structure of the existing model. The result of this new approach is that the accuracy of the model is increasingly improved. The method not only

identifies the potential solution rapidly but also provides process insight from the model developed. It works particularly well for processes that exhibit a high degree of nonlinearity such as when sharp changes occur in the response surface. In such cases standard statistical experimental design methods fail to predict the process output accurately because of limitations in the fitting approaches adopted (Ji *et al*, 2011, conference paper).

Knowledge-driven methods: Our research with IMRC companies shows that often large data sets and repositories of knowledge of bioprocess development have been accumulated but little has been utilised due to the diverse formats of the data and a lack of consideration as to how best to utilise the data. In an IMRC-sponsored project we have created a system that harnesses the structured data and knowledge arising from a process development environment. A reasoning-based artificial intelligence method has been used to address the process design queries and to make predictions about process performance. The knowledge-driven method of experimental design uses the suggestions generated by related experiment design queries of the system. Case studies based on centrifugation and chromatographic processes have been established and suggestions on the ranges of experimental conditions generated (Zhang, *et al*, 2010, 2011a, 2011b, conference papers). The system can also provide a platform to centralise the data and knowledge as a resource for bioprocess development.

Future directions

The final stage of Research Theme 2 will undertake evaluation studies of the developed methods by application to studies based on chromatographic processes for antibody and antibody fragment purification where the processes are complex. In addition we will explore how to apply the methods to sequences of processes under development through affiliated projects.

Affiliated projects - current

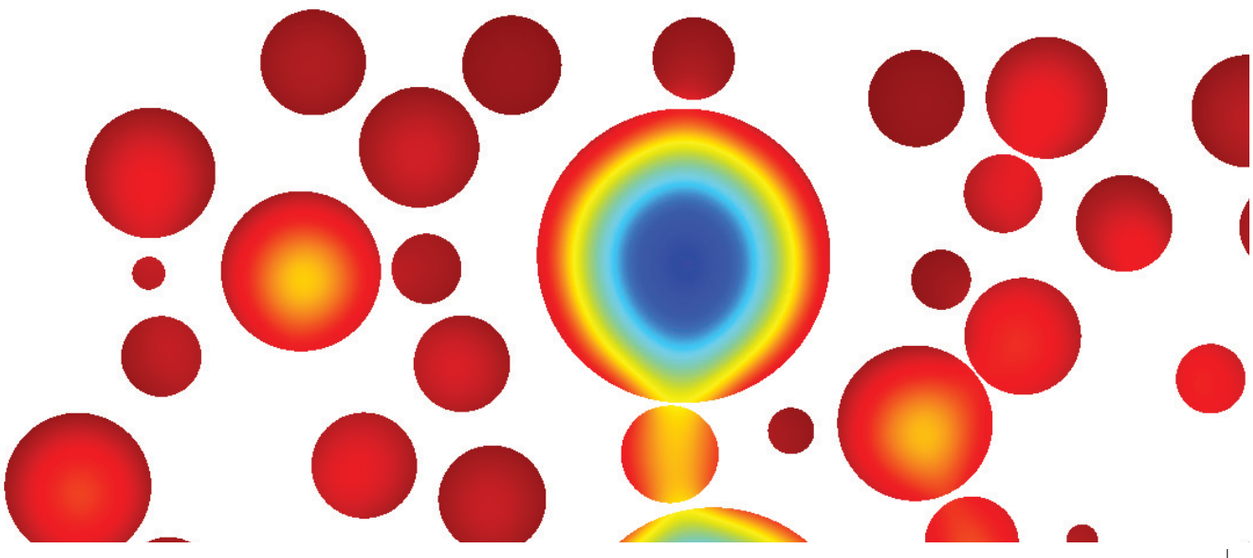
Project	Title	Collaborators
2.1.	Applying DoE methods to noise-prone microwell experimentation for accelerated process insight. (M Khan, Y Zhou, L. Allen)	Lonza Biologics
2.2	A framework to assist high throughout process developments. (S. Konstantinidis, N. Titchener-Hooker, E. Heldin)	GE Healthcare
2.3	Model based experimental design for bioprocess optimisation. (Y. Ji, Y. Zhou)	IMRC supported
2.4	Optimization in rapid bioprocess design using incomplete or conflicting information. (J. Zhang, Y. Zhou, A. Hunter)	Computer Science, UCL
2.5	Integrated intelligent microwell high throughput platform for bioprocess development. (T. Wu, Y. Zhou)	IMRC supported

See also projects 3.2.2, 3.2.8, 3.2.9

Affiliated projects - completed

Project	Title	Collaborators
2.6	Engineering tools to support the design and operation of initial capture chromatography. (J. Joseph, Y. Zhou, A. Sinclair)	BioPharm Services
2.7	Development of ultra scale-down shear filtration system and modelling of large scale diafiltration system. (G. Ma, Y. Zhou)	IMRC supported

See also projects 3.2.17, 3.2.20



3.3 Research Theme 3 – Whole bioprocessing advances

3.3.1 Theme 3.1 Host cell engineering to ease whole processing

D.Nesbeth, T.Mukhopadhyay, B.Balasundaram, J.Ward, E.Keshavarz-Moore and 12 affiliated students

Project value: £0.85m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.06m direct and £0.98m indirect external contribution.

Research focus

This research examines ways in which cells may be manipulated to help ease whole bioprocessing. We seek to alter the host cell properties and those of the expressed products and impurities to impact both upstream and downstream operations and their interactions. This approach represents a fundamental shift from traditional cell engineering which seeks improvements in product expression alone. The cell modifications we engineer address the ways to reduce the burden of contaminants without compromising the quality of the cells or of the product.

In our studies it is the whole process specification that drives the redesign of the cells. The objective is ultimately to reduce costs by developing strategies to enhance productivity, reduce contaminant levels and hence create simpler and more robust processes.

Research in this theme opens up a range of new process options that together with the ultra scale-down tools and new approaches developed in Research Themes 1 and 3.2 creates a powerful platform for development of more efficient bioprocesses.

Notable achievements

A major initiative has centered around the hypothesis that re-engineering of the *E.coli* host organism used to express a periplasmic Fab product could be targeted to enable the in situ degradation of contaminating DNA and to reduce the viscosity of the resultant process streams. To this end an *E.coli* strain producing a Fab fragment (UCB Pharma) has been modified to express an inducible periplasmic nuclease. The use of the new strain improved the efficiency of the recovery stage by degrading the contaminanting DNA hence also reducing the viscosity of the process fluid leading to a four-fold reduction of the settling area requirement in disc stack centrifuges (Balansundaram *et al*, 2009). The insertion of the nuclease gene did not compromise the cell growth rate, the product yield or the cell integrity and removed the need for a lengthy incubation step to yield high product levels. The results have been reported at the key conference of the discipline (Keshavarz-Moore, 2010 conference paper). Initial studies have also shown that the presence of the endogenous nuclease improves the filtration performance of dead end filters used after centrifugation.

An alternative to the periplasmic expression of the product in *E.coli* is to engineer the cells to allow the desired product to be released into the medium of the fermenter. Initial studies in collaboration with Lonza Biologics have indicated that using an anti-sense RNA approach it is possible to increase the controlled release of an industrially relevant Fab by an additional 50% even before optimisation of the secretion pathway.

We have also demonstrated that the design of the host-plasmid has major implications not only on the quantity of product formed (e.g. level of expression) but also on the quality of the product such as its topology (Yau *et al*, 2008).

Future directions

A series of affiliated projects (see below) under the supervision of the newly appointed IMRC academic member of staff (Darren Nesbeth) specialising in synthetic biology have been established.

These doctoral projects will examine how cell engineering skills can be applied to ease the manufacture of a set of next generation biopharmaceuticals. We shall examine the processing of high cell density Pichia pastoris cells. In the future we envisage these skills will be applied more broadly across a wider range of bioprocessing fields of study such as efficient biocatalysis and creation of effective bio-fuels from algae and spent plant material. A series of affiliated projects are already underway which demonstrate the outreach of the IMRC methods beyond the biopharmaceutical territory. (e.g. projects 3.1.5, 2.1.9, 3.1.10).

Affiliated projects- current

Project	Title	Collaborators
3.1.1	The characterisation of plasmid DNA complexes for application in genetic immunisation. (A. Dhanoya, E. Keshavarz-Moore)	Department of Immunology, UCL
3.1.2	A platform for inclusion body production. (A. Omotosho, E. Keshavarz-Moore, J. Klein)	Lonza Biologics
3.1.3	Exploring the potential for therapeutic protein production in algae. (S. Braun, D.G. Bracewell)	
3.1.4	Rapid microscale evaluation of the impact of fermentation conditions on inclusion body formation, solubilisation and protein refolding yields. (G. Ordidge, M. Micheletti, J. Liddell)	MSD Biologics
3.1.5	A synthetic biology approach for the diversification of simple feedstocks into higher value chemicals. (Y. Xia, F. Baganz, J. Ward)	Department of Structural and Molecular Biology, UCL
3.1.6	Cell engineering and processing of recombinant Pichia pastoris strains capable of high specific yield production. (P. Randone, D. Nesbeth, E. Keshavarz-Moore)	IMRC supported
3.1.7	Synthetic biology approaches for the production of chiral aminoalcohols in engineered *E.coli* strains. (P. Payongsri, P.A. Dalby)	IMRC supported
3.1.8	Engineering host cell protein contaminants in mammalian cell lines for improved downstream. (R. Tarrant, D.G. Bracewell, M. Smales)	Animal Cell Technology and Protein Biosciences, University of Kent
3.1.9	Synthetic biology: protein engineering of transaminase enzymes for the production of chiral aminoalcohols in engineered *E.coli* strains. (D. Deszcz, P.A. Dalby, J. Ward, H. Hales)	Departments of Chemistry, and Structural and Molecular Biology, UCL
3.1.10	Bioconversion of lignin degradation products to higher value chemicals using transaminase. (C. Du, G.J. Lye)	IMRC supported
3.1.11	Re-designing protein efflux kinetics in Pichia pastoris for improved bioprocessing. (D. Geoghegan, D. Nesbeth)	IMRC supported
3.1.12	A synthetic biology approach to re-designing host cells for improved bioprocessing. (Y. Wei, D. Nesbeth)	IMRC supported

See also projects 1.1.1, 1.1.4, 1.1.10, 1.1.19, 3.2.10

Affiliated projects- completed

Project	Title	Collaborators
3.1.13	Cell design and engineering for optimised plasmid production in *E.coli* for vaccination and human therapy. (S.Yau, E.Keshavarz-Moore, J.Ward)	Department of Structural and Molecular Biology, UCL
3.1.14	Application of novel enzymes in home care products. (R.Lilley, E.Keshavarz-Moore, N. Perry)	Unilever
3.1.15	An understanding of mammalian physiology for use in automated analysis. (T.Paoli , E. Keshavarz-Moore, J.Faulkner)	GSK
3.1.16	Molecular evolution of enterokinase for redevelopment of advanced biopharmaceutical proteins (S. Pradhan, P.A. Dalby, K. Foster, N. Allison)	Syntaxin, HPA
3.1.17	Prediction of plant processing properties by ultra scale-down and physical property measurement. (S.Hassan, E.Keshavarz-Moore, C.R. Thomas, J. Ma)	Department of Chemical Engineering, University of Birmingham; St Geroge's Hospital, University of London
3.1.18	An investigation of the properties of bacteriophase M13 and the implications for its large scale processing. (S. Branston, E .Keshavarz-Moore, J.Ward)	Department of Structural and Molecular Biology, UCL
3.1.19	Physiological characterization of *Saccharopolyspora erythraea* deletion strains: Global and pathway specific regulators. (V. Haakuria, F. Baganz, J. Ward)	Department of Structural and Molecular Biology, UCL

See also projects 1.1.22 and 1.1.24

3.3.2 Theme 3.2 Disruptive technologies in upstream and downstream processing

S. A. Chhatre, S. Gerontas, D. G. Bracewell plus 9 affiliated researchers

Project value: £0.95m EPSRC IMRC over whole project lifetime (2007-2012) with commitment to date (2007-2011) of £0.09m direct and £1.22m indirect external contribution.

Research focus

The bioprocessing industries need to be able to adopt more radical unit operations and methods of processing if the escalating demands for high yields purity all at lower cost are to be realised. Work in Research Theme 3.2 reflects these drivers and seeks to enable the development and whole process assessment of alternative downstream technologies, which may be radically different in nature to those used currently. At the heart of this aim is the need to verify the novel methods at scale and to compare and contrast with existing state-of-the-art approaches.

IMRC research builds upon advances in the sciences which underpin the formation and purification of biopharmaceuticals considered synergistically with new engineering methods to create new bioprocess solutions to produce biopharmaceuticals more effectively. Key to these advances is the deployment of the micro-scale bioprocessing approach described in Research Theme 1 to deliver the fundamental insights leading to whole bioprocess understanding and to provide the knowledge of how an effective translation into industrial practice may eventually be realised.

The objective of research in this theme is to create novel separation approaches which can accommodate the increases in product titre being achieved upstream. A key target is to able to characterise those key contaminants which impact on process performance as the targets for novel separation approaches. The alternative of seeking methods for the handling of higher cell densities, especially in the early steps of recovery, is being pursued in parallel.

In all of these targets it is critical that consideration is given to replicating the engineering environment during processing by adopting ultra scale-down methods arising from Research Theme 1.

Notable achievements

The identification of critical contaminants and the role that these play in determining process performance is key as is the analysis of process interactions (Berrill *et al*, 2010). We have shown how an understanding of how the cell and product are affected by processing conditions is critical to overall process outputs (Kee *et al*, 2010). Similarly the understanding of the impact of cell debris and contaminants that are formed during processing upon the performance of unit operations is key to making significant improvements in downstream processing (Bracewell *et al*, 2008; Jing *et al*, 2010). Advances in microscale experimentation particularly in the area of chromatography have been achieved in conjunction with Research Theme 1 (Gerontas *et al*, 2010). Linking with Research Theme 2 (Chhatre *et al*, 2009) has provided new tools with which to understand the impact of previous steps in the process enabling efficient design of precipitation or flocculation stages (Knevelman *et al*, 2010). So for example we have applied multi-variate approaches to achieve superior resolution of product and contaminants purification during chromatography (Edwards-Parton *et al*, 2008). We have also applied micro-biochemical engineering methods to demonstrate the benefits of applying novel separation approaches including biomimetics and mixed mode chemistries (Chhatre *et al*, 2009).

Future directions

The theme will now continue with two key areas through the affiliated projects listed below. Firstly the process possibilities of new adsorbent materials are being investigated – specifically nanofibres and monoliths for new product classes and for achieving process intensification. Secondly these studies of process intensification will now be extended to embrace consideration of continuous processing options. We shall examine the potential of novel precipitation and chromatographic methods via interactions with Research Themes 1.3 and 2 to enable effective understanding of the experimental space.

Affiliated projects- current

Project	Title	Collaborators
3.2.1	The economic, environmental and operational feasibility of continuous processes for glycoproteins. (J. Pollock, S. Ho, S. Farid)	Pfizer
3.2.2	Design and control of continuous separations of biomolecules. (C. Ng, E. Valery, E. Sorenson, D.G. Bracewell)	Novasep; Department of Chemical Engineering, UCL
3.2.3	The fabrication of nanofibers as adsorbents for bioprocessing. (O. Hardick, B. Stevens, D.G. Bracewell)	Rutherford Appleton Laboratory
3.2.4	In-silico development of novel ligands for affinity chromatography. (H. Mamdani, S. Burton, P.A. Dalby)	Prometic Biosciences
3.2.5	Derivitisation and characterisation of electrospun nanofibre materials for bioprocessing. (S. Dods, B. Stevens, D.G. Bracewell)	Rutherford Appleton Laboratory
3.2.6	The re-design of packed bed hydrodynamics for improved throughput. (T. Lan, N.J. Titchener-Hooker)	IMRC supported
3.2.7	Microscale methods for predicting larger-scale chromatographic separations. (S. Chhatre – IMRC PDRA)	IMRC associated companies, BTG plc
3.2.8	Development of modelling approaches for biochemical engineering unit operations. (S. Gerontas – IMRC PDRA)	IMRC associated companies
3.2.9	Process modelling approaches to biological complexity in the production of therapeutic proteins. (E. Close, E. Sorenson, D.G. Bracewell)	Pfizer; Department of Chemical Engineering, UCL
3.2.10	Microscale multimodal precipitation to establish scaleable operations for contaminant removal prior to packed bed steps. (R. Hanif, D.G. Bracewell)	IMRC supported
3.2.11	Engineering host cell protein contaminants in mammalian cell lines for improved downstream bioprocessing. (R. Tarrant, C.M. Smales, D.G. Bracewell)	Biosciences, University of Kent
3.2.12	Control of nanoplex behaviour on monolith adsorbents. (C. Burden, A. Strancar, D.G. Bracewell)	BIA Separations

See also projects 1.3.2 and 1.3.4.

Affiliated projects – completed

Project	Title	Collaborators
3.2.13	Formulation and delivery of nano-sized biomaterials. (E.R. Arulmuthu, H.K. Versteeg , M. Hoare)	Loughborough IMRC
3.2.14	The impact of fouling by cellular components on chromatography performance. (J. Jing, D.G. Bracewell)	IMRC supported
3.2.15	Pressure-flow study of chromatography: impact of pH and column inserts on column performance. (Yu-Chih Chang, N.J. Titchener-Hooker)	IMRC supported
3.2.16	Bioprocess optimisation of high resolution sequences. (J. Joseph, P.A. Sinclair, N. J. Titchener-Hooker)	BioPharm Services
3.2.17	Accelerated determination of optimal process sequences and operating conditions for biopharmaceutical recovery and purification steps. (A. Berrill, S. Ho, D.G. Bracewell)	Pfizer
3.2.18	Production and purification of Hepatitis B virus like particles (VLPs) from *S. cerevisiae* (G.S. Kee, N. Pujar, N. J. Titchener-Hooker)	Merck
3.2.19	An engineering appraisal of the utility of ultra scale-down methods in the rapid evaluation of elution chromatography. (P. Beckett, P. Levison, N. J. Titchener-Hooker)	Pall Life Sciences
3.2.20	Development of modelling approaches for biochemical engineering unit operations. (C. Knevelman, J. Davies, N. J. Titchener-Hooker)	Lonza Biologics

See also projects 1.3.15 and 1.3.16.

4.0 IMRC Training & Career Progression

“The IMRC places training of its staff and of the range of students and industrialists who are exposed to its work as a very high priority”

4.0 IMRC Training & Career Progression

The IMRC places training of its staff and of the range of students and industrialists who are exposed to its work as a very high priority. The relevance and quality of the training and experience provided by the IMRC through its various activities and collaborations is clearly evidenced through the high take up rate of personnel into relevant employment.

Employment

The IMRC impacts at all levels of employment from graduate to doctoral and post-doctoral levels. Details on the latter two are given here. All past postdoctoral research associates (PDRAs) trained by the IMRC have been employed in the sector. Since the first phase of the IMRC 70% of the IMRC PDRAs have gained employment in industry with the remainder engaged in senior research activities in higher education institutions. In the last year two PDRAs have moved onto new positions; Bala Bangaru is now a process development scientist at Plymouth Marine Laboratories Applications Ltd and Alex Berrill is now a senior scientist at Pfizer following a successful KTS programme with GSK. The depth and breadth of the training provided by the IMRC has been pivotal in their recruitment.

Doctoral employment; in the period April 2007 to February 2011 37 IMRC research associates (EngDs and PhDs) graduated to join a range of destinations in industry, commerce and higher education. Nearly 70% of the graduate doctoral cohorts were directly employed in the sector (e.g. Oxford BioMedica, GSK, Lonza, Pfizer, GE Healthcare, Accenture, Regeneron Pharmaceuticals, Merck, Unilever, BioVex, BioPharm Services, ERA Consultants, Prometic). The majority of the remainder continue to contribute to bioprocess research (Scripps Research Institiute, BRIC, Cancer Research, Leicester University, Newcastle University, Royal College of Surgeons Ireland). All of our doctoral graduates provide strong links in our continuing relationships with our existing industrial partners or creating new opportunities for collaboration with a wider range of companies and organisations.

PDRA training

The IMRC has worked hard to create a series of mechanisms that ensure frequent two-way interaction with industry. Specifically this enables PDRAs to increase their knowledge of industrial practice and for industry to become familiar with IMRC tools and methods. A programme of EPSRC Knowledge Transfer Schemes has had a particular impact in this respect. It has seen PDRAs spend time in industry e.g. Jean Aucamp at UCB Celltech and the reverse situation of industrialists spending time at UCL e.g. James Savery from BioPharm Services (further examples can be found in Sections 2.2 and 2.3 of this report).

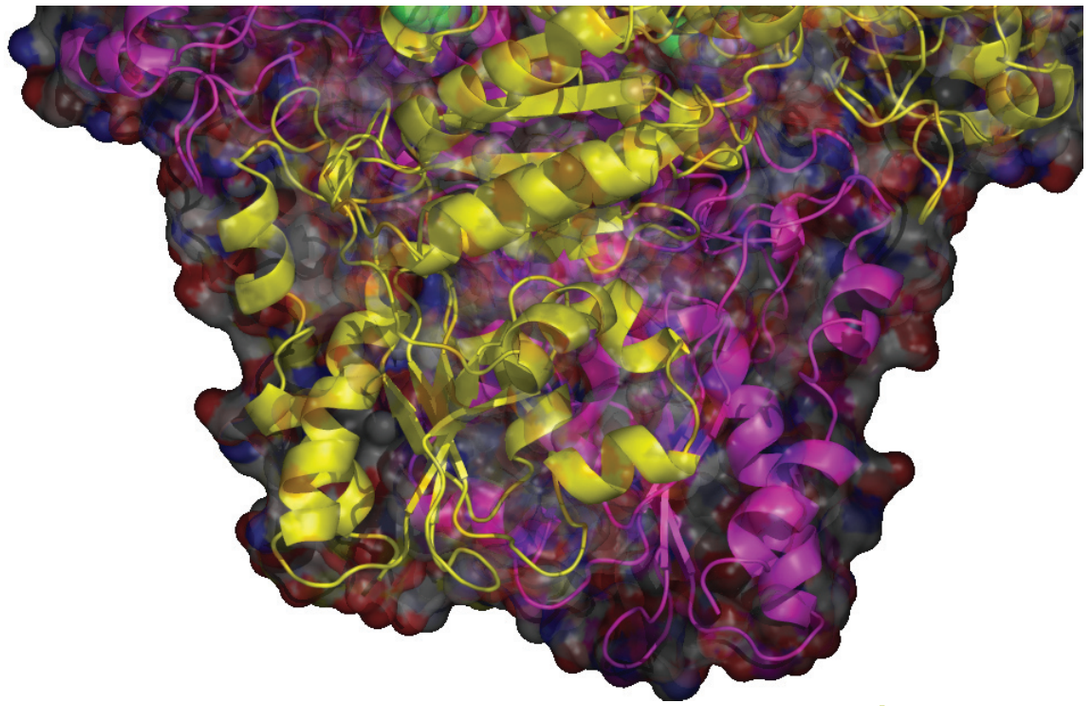
The PDRAs also develop management skills through supervisory roles with the research students at undergraduate, masters and doctoral levels. This is supported by UCL Organisational and Staff Development courses, notably “Supervising PhD students” and “Time management - effective work practices”.

Doctoral research student training

Training at a doctoral level is provided by an integration of the Department of Biochemical Engineering’s modular scheme for the bioprocessing industries (MBI®), UCL’s Centre for the Advancement of Learning and Teaching (CALT) courses, and specialist company and departmental research skills development specific to different doctoral programmes. UCL has an excellent track record; for example The Scientist has placed UCL as the No.1 Higher Education Institution within Europe for an individual to undertake their doctoral and postdoctoral training. The IMRC works closely with the EPSRC Industrial Doctorate Training Centre (IDTC) for Bioprocess Engineering Leadership where the clear synergy between the two provides a natural mechanism by which IMRC advances can be converted into training opportunities for the doctorates. This is then the prime route for dissemination of the IMRC concepts into the industry setting.

Many of the practicals used in our range of teaching and training programmes now cover both upstream and downstream and use techniques developed within the IMRC as their basis as outlined below. In total 39 doctoral researchers (PhDs and EngDs) have been active during the reporting year on research associated with the IMRC programme and have been trained in a range of skills and techniques related to the three research themes. These are a major source of opportunities to develop new science and engineering and also provide a valuable conduit for knowledge transfer.

A programme of EPSRC Knowledge transfer Schemes has had a particular impact



BioPharm Services KTS collaboration with the IMRC in process design training

The IMRC used EPSRC Knowledge Transfer Secondment funding to enable the integration of IMRC ultra scale-down technology with new software for bioprocess design. This union resulted in a novel approach which allows accurate prediction of unit operation performance and a step change improvement in the confidence of the costings results. The inward secondment was supported by beta testing of the new package at UCL. Based on this success this software-based method has been integrated into teaching of centrifugation within the relevant MBI® module and for process design teaching at both masters and undergraduate levels. This innovation in teaching was a point of great interest for the recent and highly successful IChemE accreditation exercise for our taught courses.

Taught course training

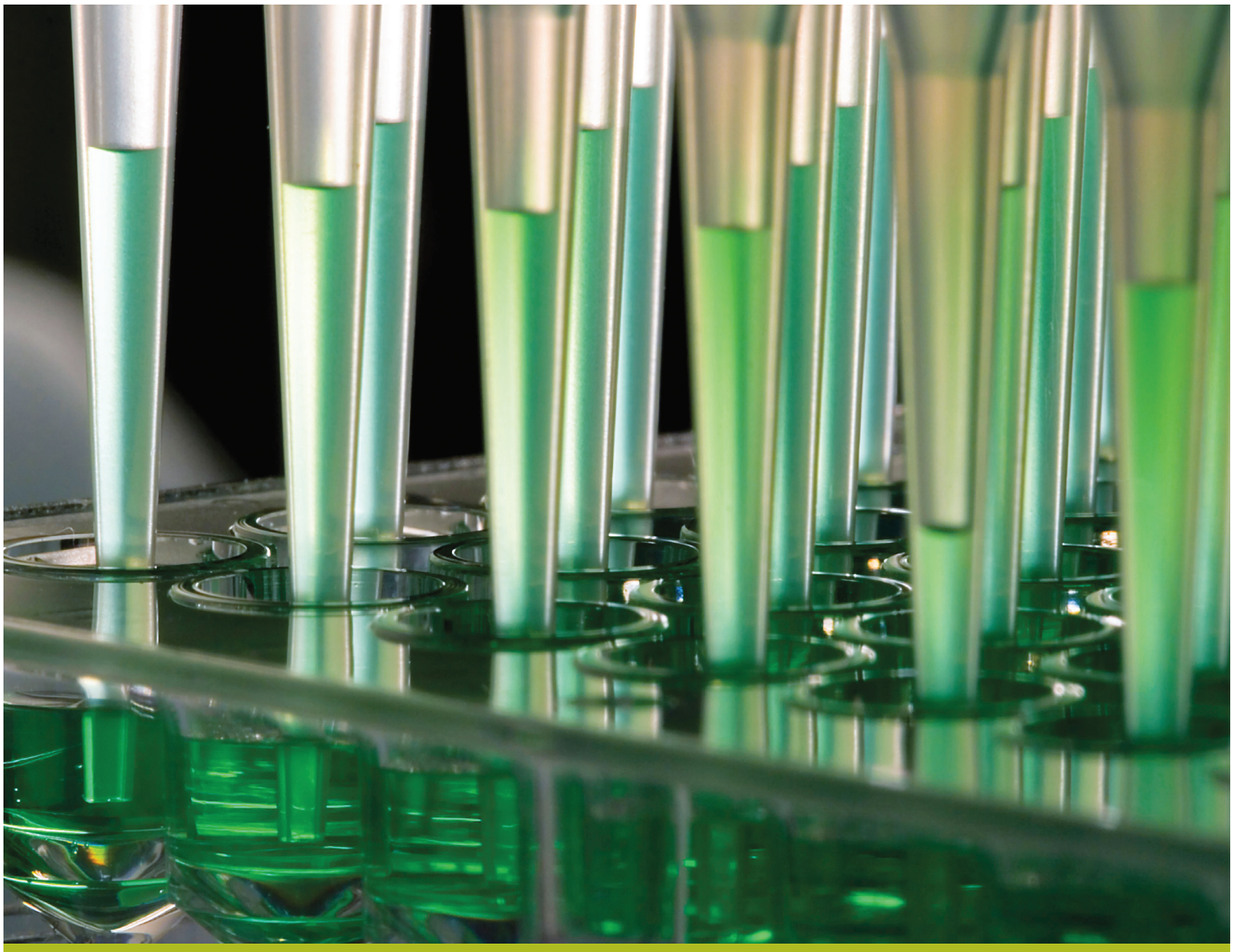
The IMRC outreach extends well beyond our research students to our undergraduate, masters and industrial short course cohorts. Here the ability to train significant numbers of students in the latest IMRC techniques means that our graduates have first-hand knowledge of these approaches to use in their future careers. To enhance this further, at an undergraduate (year 2) and MSc level and within the Primary Recovery MBI® course, practicals based on ultra scale-down methods have been introduced and are now a highly successful component of our training approach. Such training provides an additional route for dissemination with many beneficiaries going onto careers in the biotechnology and biopharmaceutical industries. A further opportunity to reinforce this exposure to IMRC technologies has been through undergraduate research projects. These include highly exploratory projects e.g. examining the impact of the engineering environment within new disposable bioreactor technologies using particle image velocimetry. These projects again involve PDRAs who gain experience in supervision roles in the projects which augment their thematic research areas.

IMRC Annual Briefing - A training and dissemination event

The annual IMRC briefing event has evolved as the earlier IMRC technologies have gained acceptance through verification work with company partners. During this time the event has widened its scope from a purely dissemination focused event where companies were updated on the latest IMRC research via oral and poster presentations to now encompass two activities focused on training and knowledge exchange:

i) Special Interest Groups e.g. an analytical group focuses on synergies between analytical methods and ultra scale-down methods.
ii) Laboratory based introductions to the operation of ultra scale-down devices.

The briefing activities have been received with enthusiasm by the IMRC companies and have been a notable success in initiating collaborations on the introduction of ultra scale-down devices to the company environment (e.g. with Pfizer – see associated impact statement, Section 2). Further details of the 6th Annual Bioprocess Briefing can be found in Section 7.



5.0 Our Team and Collaborators

“We have assembled a unique team of researchers and collaborators who represent the cutting edge of bioprocess thinking”

5.0 Our Team and Collaborators

Academic

Professor Nigel Titchener-Hooker, Biochemical Engineering (Director)
Professor Mike Hoare, Biochemical Engineering (Chairman)
Dr Daniel Bracewell, Biochemical Engineering
Professor Eli Keshavarz-Moore, Biochemical Engineering
Dr Tarit Mukhopadhyay, Biochemical Engineering
Dr Darren Nesbeth, Biochemical Engineering
Professor John Ward, Structural and Molecular Biology
Dr Yuhong Zhou, Biochemical Engineering

Post-Doctoral researchers (2007-2011)

Dr Jean Aucamp
Dr Bangaru Balasundaram (left November 2010)
Dr Sunil Chhatre
Dr Simon Edwards-Parton (left October 2009)
Dr Spyridon Gerontas
Dr Naveraj Gill
Dr Simyee Kong
Dr Qiang Li
Dr Sabin Maskey
Dr Andy Tait (left November 2009)

IMRC collaborators

Core companies

BioPharm Services
BTG plc
Eli Lilly
GE Healthcare
GSK
HPA
Lonza Biologics
MedImmune
Merck
MSD Biologics
Novo Nordisk
Pfizer
TAP
UCB Pharma

Affiliated companies

Agilent
BIA Separations
BioPharm Enterprises
BioProducts Laboratory
BioVex
Fairfield
HEL
ImmunoBiology
Intercell Biomedical
IQur
LGC
Millipore
NPL
NIBSC
Novasep
Onyvax
Oxford BioMedica
Pall (Europe)
Prometic Bioscience
ReNeuron
Syntaxin
Talecris Therapeutics
Tecan
TMO Renewables

Steering Group membership

Dr Nigel Allison, HPA
Dr Matt Osborne, Eli Lilly
Dr Julian Relton, Lonza Biologics
Dr Mark Carver, MSD Biologics
Dr John Coffman & Dr Sa Ho, Pfizer
Dr Brendan Fish & Dr Mark Uden, GSK
Mr Richard Francis, Francis Biopharma, ex-BTG (Chair)
Dr Camilla Kornberg, Novo Nordisk
Dr Richard Tuner, MedImmune
Dr Hari Pujar, Merck
Mr Andrew Sinclair, BioPharm Services
Dr Anike Berkenstrasse, GE Healthcare
Dr Richard Wales, The Automation Partnership
Dr Amanda Weiss, UCB Pharma
Professor Mike Hoare, Biochemical Engineering
Professor Nigel Titchener-Hooker, Biochemical Engineering
Professor John Ward, Structural and Molecular Biology
Dr Daniel Bracewell, Biochemical Engineering
Professor Eli Keshavarz-Moore, Biochemical Engineering
Dr Tarit Mukhopadhyay, Biochemical Engineering
Dr Darren Nesbeth, Biochemical Engineering
Dr Yuhong Zhou, Biochemical Engineering

Management Advisory Committee

Dr Peter Foster, Consultant Scientist, SNBTS
Mr Richard Francis, Francis Biopharma ex-BTG (Steering Group Chair)
Dr Peter Hambleton (ex-HPA)
Professor Mike Hoare, Biochemical Engineering (IMRC Chairman)
Dr Tracy Hanlon, EPSRC representative
Professor Peter Lillford, Consultant, York University
Professor John Mann, Trellick Ltd (Chair)
Dr Margaret Parton, ex-CEO, NHS Technology Adoption Hub

Professor Nigel Titchener-Hooker, Biochemical Engineering (IMRC Director)
Mr Steve Vranch, Jacobs Engineering
Professor John Ward, Structural and Molecular Biology

Vision Advisory Panel

Professor Steve Arlington, PricewaterhouseCoopers
Professor John Birch, independent advisor (ex-CSO, Lonza Biologics)
Professor Barry Buckland, BiologicsB
Mr Mike Carroll, Carroll Consulting
Dr Brendan Fish, GSK
Mr Richard Francis, Francis Biopharma
Dr Tony Jones, One Nucleus
Mr Nick Medcalf, Smith and Nephew
Mr Ian Nicholson, Chroma Therapeutics
Dr Angela Osborne, eXmoor Pharma Concepts
Dr Michelle Scott, Unicorn Biologics
Dr Neil Weir, UCB Pharma (Chair)

Visiting Professors

Professor Steve Arlington, Partner, PricewaterhouseCoopers, UK
Professor John Birch, independent advisor, ex-CSO, Lonza Biologics, UK
Professor Barry Buckland, Consultant, BiologicB (Chairman) and ex-VP Vaccine Development, Merck & CO, USA

Associated academic staff (UCL except where stated otherwise) 2007-2011

Dr Frank Baganz, Biochemical Engineering
Dr Graham Balls, Bioinformatics Centre, Nottingham Trent University
Professor Benny Chain, Immunology
Dr Kerry Chester, Oncology, Royal Free Hospital
Dr Rob Coffin, Molecular Pathology
Dr Paul Dalby, Biochemical Engineering
Dr Ian Eames, Mechanical Engineering
Dr Suzanne Farid, Biochemical Engineering
Professor Robert Freedman, Biological Sciences, University of Warwick
Dr Jarka Glassey, Chemical Process Engineering, University of Newcastle
Dr Steve Hart, Institute of Child Health
Professor Steve Haswell, Chemistry, University of Hull
Professor Anthony Hunter, Computer Science
Professor Gary Lye, Biochemical Engineering
Professor Julian Ma, Molecular Immunology Unit, St Georges Hospital
Professor Elaine Martin, Chemical Process Engineering, University of Newcastle
Dr Martina Micheletti, Biochemical Engineering
Professor Gary Montague, Chemical Process Engineering, University of Newcastle
Dr Darren Nesbeth, Biochemical Engineering
Professor Quentin Pankhurst, London Centre for Nanotechnology, Royal Institution
Dr Lazarous Papageorgiou, Chemical Engineering
Professor Steve Perkins, Structural and Molecular Biology
Dr Saul Purton, Structural and Molecular Biology
Professor Colin Robinson, Biological Sciences, University of Warwick
Dr Claire Seldon, Hepatology, Royal Free Hospital
Professor Mark Smales, Animal Cell Technology and Protein Biosciences, University of Kent
Dr Eva Sorensen, Chemical Engineering
Dr Bob Stevens, Rutherton Appleton Library
Dr Nicolas Szita, Biochemical Engineering
Professor Colin Thomas, Chemical Engineering, Birmingham University
Professor Nina Thornhill, Chemical Engineering, Imperial College London
Dr Berend Tolner, Oncology, Royal Free Hospital
Dr Henk Versteeg, Mechanical and Manufacturing IMRC, University of Loughborough
Professor David Williams, Manufacturing IMRC, University of Loughborough
Dr Mark Wills, Chemical Process Engineering, University of Newcastle

Technical Staff

Dr Brian O'Sullivan, microbiochemical engineering support (100% of time)
Dr Gareth Mannall, pilot plant and biosafety support (25% of time)
Mr Mark Spurgeon, electronics and computing (25% of time)
Miss Elizabeth Eastwood, administrative support (50% of time)

Knowledge Exchange and Impact Development

(funded via IMRC company contributions and related activities)

Ms Elizabeth Barrett, Manager, MBI® post experience training
Mr Andrew Davidson, Director, Quotec
Dr Karen Smith, Director of Bioprocess Leadership

6.0 Selected Publications 2007-2011

“We provide access to our research outputs through refereed publications”

6.0 Selected Publications 2007-2011

Masking of the Fc region in human IgG4 by constrained X-ray scattering modelling: implications for antibody function and therapy.
Abe Y., Gor J., Bracewell D.G., Perkins S.J., Dalby P.A.
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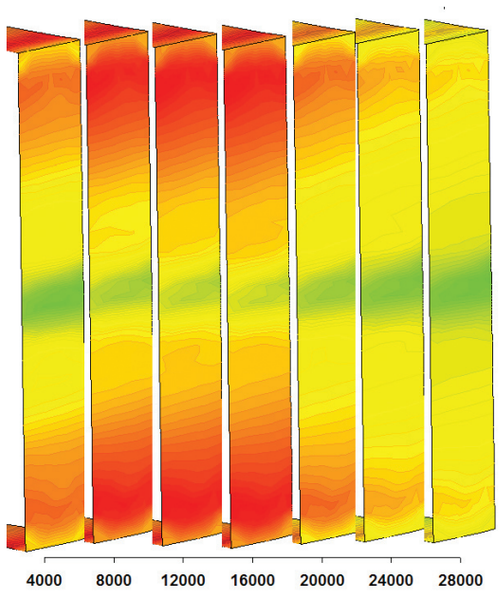



Our presentations at events provide fundamental insights for new ways forward in the sector

IMRC presentations and conference events

Date	Title	Authors	Event	Theme
29th May - 1st June 2011	Systematic data and knowledge utilization to speed up bioprocess development	Zhang, J., Hunter, A., Zhou, Y.	ESCAPE 21st, Chalkidiki, Greece	2
29th May - 1st June 2011	Designing multi-product biopharmaceutical facilities using evolutionary algorithms	Simaria, A.S., Gao, Y., Turner, R. and Farid, S.	The 21st European Symposium of Computer Aided Process Engineering Chalkidiki, Greece	2
26 -28th April 2011	Mathematical modelling for protein precipitation in multi-components feedstock	Ji, Y., Zhou, Y.	Separation for Biotechnology 2011, Advance separation technology, SCI, Manchester	2, 3.2
26 -28th April 2011	Nanofiber fabrication in a controlled environment	Hardick, O., Stevens, B., Bracewell, D.G.	Separation for Biotechnology 2011, Advance separation technology, SCI, Manchester	3.2
26 -28th April 2011	A multi-level evolutionary algorithm for the optimisation of antibody manufacturing facility configurations	Simaria, A.S., Gao, Y., Turner, R. and Farid, S.	Separation for Biotechnology 2011, Advance separation technology, SCI, Manchester	2
26 - 28th April 2011	An investigation of causes of topological changes of large plasmids in sterile filters	Affandy, A., Versteeg, H.K., Keshavarz-Moore, E.	Separation for Biotechnology 2011, Advance separation technology, SCI, Manchester	1.3, 3.2
30th March - 1st April 2011	Bioanalysis of processing effect on human cells for cell-based therapies	Chu, C., Lawrence, K., Acosta-Martinez, J., Delahaye, M., Pang, S., Faull, P., Harris, N., Sinden, J., Ward, S., Hoare, M.	UK National Stem Cell Network Fourth Annual Science Meeting, University of York	1.1
30th March - 1st April 2011	Recovery of cells and cell concentrates for therapeutic applications	Fernanda Masri, M., Longster, C., Lawrence, K., Levison, P., Ruban, L., Hoare, M.	UK National Stem Cell Network Fourth Annual Science Meeting, University of York	1.2, 3.2
30th March - 1st April 2011	Human cell bioprocessing for the production of whole cell therapies - the impact of centrifugation upon key cell quality attributes	M.Delahaye, K.Lawrence, C.Chu, R.Corteling, J.Sinden, S.Ward, M.Hoare	UK National Stem Cell Network Fourth Annual Science Meeting, University of York	1.2, 3.2
30th March - 1st April 2011	Manufacturing a whole cell therapy: what effect does the manufacturing process have on therapy biopotency?	Lawrence, K., Delahaye, M., Acosta, J.P., Chu, C., Adams, V., Dhondalay, G., Ball, G., Corteling, R., Sinden, J., Ward, S., Hoare, M.	UKNSCN Fourth Annual Science Meeting	1.1, 1.2
27-31st March 2011	Bioprocess data and knowledge framework for chromatography design	Zhang, J., Hunter, A., Zhou, Y.	241st National Meeting, Anaheim, CA, USA	2
16-19th February 2011	Exploitation of the Tat export machinery for protein production by bacteria	Matos, C. F. R. O., Branston, S., Freedman, R., Keshavarz-Moore, E., Robinson, C..	6th Recombinant Protein Production Conference, Vienna 2011	3.1
12-13th January 2011	Engineering characterisation of single-use, wave-type bioreactors and scale-up considerations for early phase cell culture process development	Gill, N.K., Micheletti, M., Lye, G.J.	ESACT-UK 21st Annual Scientific Meeting	1.1
24-25th November 2010	Systematic data and knowledge utilization to speed up bioprocess development	Zhang, J., Hunter, A., Zhou, Y.	bioProcess UK Annual Conference, Manchester	2
24-25th November 2010	Mass spectrometry to describe product and contaminant relationships for bioprocess development	Berrrill, A., Ho, S. and Bracewell, D.G.	bioProcess UK Annual Conference, Manchester	3.2
24-25th November 2010	Rapid identification of optimal facility designs using genetic algorithms	Simaria, A.S., Gao, Y., Turner, R., Farid, S.	bioProcess UK Annual Conference, Manchester	2
24-25th November 2010	Application of a novel microscale filtration device to the study the impact of DNA hydrolysis	Rayat, A., Affandy, A., Balasundaram, B., Bracewell, D.G., Keshavarz-Moore, E., Micheletti, M., Lye, G.J.	bioProcess UK Annual Conference, Manchester	1.2, 3.2

8-12th November 2010	Dual mode precipitation for the recovery of recombinant proteins from *E. coli*.	Balasundaram, B., Bracewell, D.G.	Annual AIChE meeting, Salt Lake City, Utah, USA	3.2
7-12th November 2010	Enabling T-flasks to improve bioprocess development: A novel disposable cell culture train from cell thawing to bench-scale.	Vallejos, J.R., Brorson, K.A. Moreira, A.R., Lye, G.J., Micheletti, M., Rao, G.	AIChE Annual Meeting, Salt Lake City, USA	1.1
7-12th November 2010	Rapid bioprocess development using microwell and miniature bioreactor technologies	Baganz, F.	AIChE Annual Meeting, Salt Lake City, USA	1.1
27-28th October 2010	Novel experimental and mathematical techniques for rapid characterisation of bioprocess design spaces	Chhatre, S.	BioProduction 2010 (QbD session), Barcelona, Spain	2, 3.2
20-21st October 2010	Ultra scale-down studies of human cell bioprocessing for a prostate cancer vaccine therapy - the impact of capillary shear	Chu, C., Acosta-Martinez, J., Delahaye, M., Lawrence, K., Ward, S., Hoare, M.	Planet xMAP Multiplexing Symposium 2010	1.1
4-7th October 2010	Strategic assay deployment in high throughput process development: Countering the analytical bottleneck.	Konstantinidis, S., Heldin, E., Chhatre, S., Titchener-Hooker, N.J.	HTPD10, Krakow, Poland	2
3-7th October 2010	An automated and multiplexed microfluidic bioreactor platform with time-lapse imaging for cultivation of embryonic stem cells and on-line assessment of morphology and pluripotency markers	Reichen, M., Veraitch, F., Szita, N.	mTAS 2010, Groningen, The Netherlands	1.1
21-24th September 2010	Enabling precipitation as an operation to manage critical contaminants in bioprocessing	Bracewell, D.G.	Bioprocess International 2011 Providence, Rhode Island USA	3.2
24th September 2010	Automated evaluation of microscale linked process sequences for generation of scaleable bioprocess design data	Baboo, J., Lye, G.J., Ward, J., Micheletti, M.	Miniaturisation – Micro Scale Bioprocess Development Meeting	1.2, 3.2
24th September 2010	Rapid microscale evaluation of the impact of fermentation conditions on inclusion body formation, solubilisation and protein refolding yields	Ordidge, G., Mannall, G., Liddell, J., Dalby, P., Micheletti, M.	Miniaturisation – Micro Scale Bioprocess Development Meeting	1.1, 1.2
29th August - 2nd September 2010	Towards engineering of de novo pathways for synthesis of chiral chemicals	Baganz, F., Matosevic, M., Rios-Solis, L., Lye, G.J.	5th International Congress on Biocatalysis, Hamburg, Germany	
1-6th August 2010	Host cell engineering for easier integrated bioprocessing	Keshavarz-Moore, E.	Recovery of Biological Products XIV, Lake Tahoe, USA	3.1
1-6th August 2010	Screen early - fail early: Rapid microscale screening of protein properties for bioprocessing and formulation	Dalby, P.A.	Recovery of Biological Products XIV, Lake Tahoe, USA	1.3, 3.2
1-6th August 2010	Mass spectrometry to describe product and contaminant relationships for bioprocess development	Berrill, A., Ho, S., Bracewell, D.G.	Recovery of Biological Products XIV, Lake Tahoe, USA	3.2
1-6th August 2010	Research and teaching partnership with industry to deliver future bioprocessing	Hoare, M.	Recovery of Biological Products XIV, Lake Tahoe, USA	1,2,3
1-5th August 2010	Microwell and miniature bioreactor technologies for rapid fermentation and cell culture process development	Baganz, F.	Society for Industrial Microbiology 60th Annual Meeting, San Francisco, CA, USA	1.1, 1.3
11th June 2010	Forced degradation studies of proteins formulated by high-throughput techniques	Grant, Y., Matejtschuk, P.,Dalby, P.A.	EuroSciCon, Modern Challenges in Therapeutic Protein Production, Welwyn Garden City, UK	1.1, 1.3, 3.2

7-8th June 2010	Attended to gain further insight into single-use technology and applications	Gill, N.	BioTech 2010, Single-use technology in biopharmaceutical manufacturing	1.2, 1.3
6-11th June 2010	Ultra-scale down methodology for rapid prediction of the impact of P. pastoris high cell density cell brothquality on recovery performance of recombinant products in a pilot-scale centrifuge	Lopes, A., Hoare, M., Keshavarz-Moore, E.	Vaccine Technology III, Nuevo Vallarta Mexico	1.1, 1.2, 3.2
6-11th June 2010	Inactivation studies on Japanese Encephalitis Virus Vaccine using Design of Experiments	Hughson, M.D., Venables, D., Queen, K., Titchener-Hooker, N. and Mukhopadhyay, T.K.	Vaccine Technology III, Nuevo Vallarta Mexico	1.1, 2
6-11th June 2010	Lipid removal strategies to enable chromatography in the purification of virus-like particles	Burden, C., Jin, J., Kovacs-Schreiner, K., Podgornik, A., Bracewell, D.G.	Vaccine Technology III, Nuevo Vallarta Mexico	1.3, 3.2
6-11th June 2010	Human cells for prostate cancer vaccine therapy - the impact of centrifugation upon key product quality attributes	Delahaye, M., Lawrence, K., Chu, C., Ward, S. and Hoare M.	Vaccine Technology III, Nuevo Vallarta, Mexico	1.1, 1.2
6-11th June 2010	Ultra scale-down studies of human cell bioprocessing for a prostate cancer vaccine therapy - the impact of capillary shear	Acosta-Martinez, J.P., Lawrence, K., Chu, C., Ward, S., Hoare, M.	Vaccine Technology III, Nuevo Vallarta, Mexico	1.1, 1.2
4th June 2010	Microscale crossflow microfiltration devices for automated evaluation of the primary recovery of biological products.	Rayat, A.C.M.E., Micheletti, M. and Lye, G.J.	IChemE Fluid Separations 'What's New in Fluid Separations?', Sunbury on Thames	1.2
3-4th June 2010	Pre-formulation of proteins by high-throughput techniques	Dalby, P.A.	VisionGain, Forced Degradation Strategies Conference, London, UK	1.3
31st May - 2nd June 2010	The impact of lipid fouling during the purification of virus-like particles using monoliths	Burden, C., Jin, J., Kovacs-Schreiner, K., Podgornik, A., Bracewell, D.G.	Monolith Summer School and Symposium, Portoroz, Slovenia	3.2
29th May - 2nd June 2010	The use of hydroxyl monoliths in the purification of virus-like particles: the characterisation of adsorption time	Burden C., Podgornik, A., Bracewell, D.G.	Monolith Summer School and Symposium, Portoroz, Slovenia	3.2
25-26th May 2010	Bioprocess tools for the realisation of a QbD future in chromatography	Chhatre, S.	IQPC PAT and Quality by Design for Biopharmaceuticals conference, London	2, 3.2
19-20th May 2010	Bioprocess tools for the realisation of a QbD future in chromatography	Chhatre, S.	6th Annual BioProcess International European Conference, Vienna, Austria	2, 3.2
25-30th April 2010	Accelerating cell culture process development: Scale-up from microwells to miniaturized and bench scale reactors	Baganz, F., Silk, N.J., Lewis, G., Al-Ramadhani, O., Appleton, M., Tait, A., Lye, G.J.	Cell Culture Engineering XII, Banff Springs, Canada	1.1
14th April 2010	Modular microfluidic bioreactor for stem cells	Reichen, M., Ruban, L., Veraitch, F., Szita, N.	4th UK Mesenchymal Stem Cell Meeting, Leeds, UK	1.1
13-14th April 2010	An automated microscale cross flow filtration device for evaluating the primary recovery of biological products	Rayat, A.C.M.E., Micheletti, M., Lye, G.J.	BESG Young Researcher Meeting, Cambridge, UK	1.2
13-14th April 2010	Impact of digestion of nucleic acids on downstream processing of biopharmaceuticals	Balasundaram, B., Bracewell, D.G.	Bioprocessing Young Researchers Meeting, Cambridge, UK	3.2
13-14th April 2010	Forced degradation studies of proteins formulated by high-throughput techniques	Dalby, P.A.	Informa, Forced Degradation for Biologics, London, UK	1.3
13-14th April 2010	Chromatography fouling during vaccine processing from yeast	Burden, C., Jin, J., Kovacs-Schreiner, K., Podgornik, A., Bracewell, D.G.	IChemE Bioprocess Young Researchers Meeting	1.3, 3.2
13-14th April 2010	A generic automated micrsocale platform for evaluating inclusion body refolding processes	Ordidge, G., Mannall, G., Liddell, J., Dalby, P., Micheletti, M.	BESG Young Researcher Meeting, Cambridge, UK	1.1, 1.2

8-9th April 2010	Investigation of hydrodynamic profiles inside sterile filtration membranes by computational fluid dynamics	Affandy, A., Versteeg, H.K., Keshavarz-Moore, E.	United Kingdom-Malaysia Engineering Conference, UCL	1.2, 1.3
16-17th March 2010	The impact of DNA topology on polyplex uptake and transfection efficiency in mammalian cells	Dhanoya, A., Chain, B., Keshavarz-Moore, E.	BRIC Meeting, Birmingham, UK	3.1
6-7th January 2010	Cell culture in miniature bioreactors: Engineering characterization, scale-up and impact on primary recovery	Lye, G.J.	ESACT UK Meeting, Loughborough	1.1
25-26th November 2009	An ultra-scale approach for predicting product yield of high cell density yeast fermentations	Lopes, A.	bioProcessUK Annual Meeting, York	1.1, 1.2
25-26th November 2009	Progress towards a generally applicable automated microscale platform for evaluating inclusion body refolding processes	Ordidge, G., Mannall, G., Liddell, J., Dalby, P., Micheletti, M.	bioProcessUK Annual Meeting, York	1.1, 1.2
25-26th November 2009	Lipid removal strategies to enable chromatography in the purification of virus-like particles	Burden, C., Jin, J., Kovacs-Schreiner, K., Podgornik, A., Bracewell, D.G.	bioProcessUK Annual Meeting, York	3.2
25-26th November 2009	Human cells for prostate cancer vaccine therapy - The impact of centrifugation upon key product quality attributes	Delahaye, M., Ward, S., Hoare, M.	bioProcessUK Annual Meeting, York	1.2
25-26th November 2009	Hydrodynamic profiles in symmetric and asymmetric sterile filters and its impact to the degradation of plasmids DNA	Affandy, A., Versteeg, H.K., Keshavarz-Moore, E.	bioProcessUK Annual Meeting, York	1.3, 3.1, 3.2
24-26th November 2009	Characterisation of plasmid DNA complexes for application in genetic immunization	Dhanoya, A., Chain, B., Keshavarz-Moore, E.	bioProcessUK Annual Meeting, York	3.1
24-26th November 2009	Recovery of high cell density yeast fermentation broths	Lopes, A., Keshavarz-Moore, E.	bioProcessUK Annual Meeting, York	1.2, 3.2
24-26th November 2009	Hydrodynamic profiles in asymmetric and symmetric sterile filter membranes and their impact on filtration of DNA and proteins	Affandi, A., Versteeg, H.K., Keshavarz-Moore, E.	bioProcessUK Annual Meeting, York	1.3, 3.2
9-12th November 2009	Viscosity reduction through co-expression of nuclease for improved clarification	Balasundaram, B., Nesbeth, D., Ward, J., Keshavarz-Moore, E., Bracewell, D.G.	Annual AIChE meeting, Nashville, TN, USA	3.2
1-5th November 2009	Oscillating jet driven microbioreactor with dissolved oxygen control for culture of eukaryotes	Kirk, T.V., Lye, G.J., Szita, N.	13th _TAS conference, Korea	1.1
29th October 2009	Academia-industry knowledge transfer initiatives in bioprocessing	Titchener-Hooker, N.J., Lye, G.J., Smith, K.S.	BioTech 2009, Westminster City Hall, London	1,2,3
27-28th October 2009	High throughput scale-down techniques to support DoE	Bracewell, D. G.	Bioproduction 2009, Barcelona, Spain	3.2
12-16th October 2009	Human cells for prostate cancer vaccine therapy - The impact of centrifugation upon key product quality attributes	Delahaye, M., Ward, S., Hoare, M.	BioProcess International, Raleigh, North Carolina, USA	1.2
12-16th October 2009	Ultra-scale down studies of human cell bioprocessing for a prostate cancer vaccine therapy	Acosta-Martinez, J.P., Ward, S., Hoare, M.	BioProcess International, Raleigh, North Carolina, USA	1.1, 1.2
13th September 2009	Micro scale-down techniques to support bioprocess development in the QbD era	Bracewell, D. G.	EFB Biochemical Engineering Science, Barcelona, Spain	1.2
8-9th September 2009	Cell engineering for manufacturability; the use of ultra scale-down experimentation	Bracewell, D. G.	EFB Downstream Processing, Mannheim, Germany	3.2
16-20th August 2009	Solid-liquid interfaces as sources of aggregation in bioprocessing	Bracewell, D. G.	238th American Chemical Society National Meeting, Washington, USA	2, 3.2

16-20th August 2009	A sensitivity analysis technique for identifying critical process parameters in biomanufacturing processes	Chhatre, S., Francis, R., Titchener-Hooker, N.J.	238th American Chemical Society National Meeting, Washington, USA	1 3.2
3-6th August 2009	Towards microwell biochemical engineering for bioprocess design: its opportunity and challenge	Zhou, Y.	4th International Symposium on Bioprocess and Biosystems Engineering, Shanghai, China	1.2, 2
3-6th August 2009	Column sizing in Protein A affinity chromatography in large scale Mab production	Joseph, J., Sinclair, A., Titchener-Hooker, N.J., Zhou, Y.	4th International Symposium on Bioprocess and Biosystems Engineering, Shanghai, China	2, 3.2
5-9th July 2009	Use of microscale bioprocessing techniques to study the influence of cell disruption conditions on Fab' fragment recovery by microfiltration	Rayat, A.C.M.E., Micheletti, M. and Lye, G.J.	ECI Biochemical Engineering XVI, Vermont, USA	1.2, 3.2
5-9th July 2009	Scaling up cell culture processes from microwells to bench scale reactors	Baganz, F.	ECI Biochemical Engineering XVI, Vermont, USA	1.1
14-19th June 2009	Prediction of large scale flux and transmission of crossflow filtration with ultra scale-down method	Ma, G., Hoare, M., Zhou, Y.	15th International Conference on Biopartitioning and Purification, Uxbridge, UK	1.2, 2, 3.2
14-19th June 2009	Measurement of product & contaminant relationships for bioprocess design and development by SELDI-MS	Berrill, A., Ho, S., Bracewell, D.G.	15th International Conference on Biopartitioning and Purification, Uxbridge, UK	3.2
14-17th June 2009	An MINLP formulation for the synthesis of chromatographic protein purification processes with product loss	Polykarpou, E., Dalby, P., Papageorgiou, L.G.	ESCAPE19, Krakow, Poland	2
2-3rd June 2009	Micro-plate methods for formulation of protein stability and freeze-drying	Dalby, P.A.	APS-Overcoming Formulation Challenges for Biopharmaceuticals, GSK House, London, UK	1.3
1-10th June 2009	Fed-batch operation of a microwell cell culture process	Silk, N.J., Denby, S., Lewis G., Hatton, D., Kuiper, M., Field, R., Baganz, F. and Lye, G.J.	21st European Society for Animal Cell Culture Technology (ESACT) conference, Dublin, Ireland	1.1
1-10th June 2009	Microwell and miniature bioreactor technologies for rapid cell culture process development	Lye, G.J.	21st European Society for Animal Cell Culture Technology (ESACT) conference, Dublin, Ireland	1.1
27-28th April 2009	Global Sensitivity Analysis as a Quality by Design technique for determining critical process parameters in bio-manufacturing operations	Chhatre, S., Zhou, Y., Keshavarz-Moore, E., Newcombe, A.R., King, J.M.P., Francis, R., Titchener-Hooker, N.J.	American Association of Pharmaceutical Scientists Utilization of Process Modeling & Advanced Process Control in QbD Based Drug Development and Manufacturing, Maryland, U.S.A.	2
26-30th April 2009	From microplate-based to microfluidic screening of protein structure and function	Dalby, P.A.	Society for Biomolecular Screening Conference, Lille, France	1.3
15th April 2009	Micro biochemical engineering techniques for the rapid selection and optimization of downstream processing operations	Lye, G.J.	Pall New Horizons Symposium, Stockholm, Sweden and Leiden, The Netherlands	1.2
9-12th March 2009	Host cell engineering directed at viscosity reduction via DNA autohydrolysis.	Balasundaram, B., Nesbeth, D., Ward, J.M., Keshavarz-Moore, E., Bracewell, D.G.	Society of Biological Engineering's 2nd International Conference on Accelerating Biopharmaceutical Development. San Diego, CA, USA	3.1, 3.2
9-12th March 2009	Modelling and segment method for flux prediction of diafiltration processes at large-scale.	Guijun, M., Titchener-Hooker, N.J., Hoare, M., Zhou, Y.	Society of Biological Engineering's 2nd International Conference on Accelerating Biopharmaceutical Development. San Diego, CA, USA	1.2, 2

9-12th March 2009	Rapid product and contaminant measurement for bioprocess development by SELDI-MS.	Ho, S.V., Berrill, A., Bracewell, D.G.	Society of Biological Engineering's 2nd International Conference on Accelerating Biopharmaceutical	3.2
25th February 2009	Micro biochemical engineering techniques for the rapid selection and optimization of downstream processing operations.	Lye, G.J.	Pall New Horizons Symposium, Cambridge, UK	1.2
13-14th February 2009	New engineering tools to speed availability of next generation biotherapeutics.	Hoare, M.	International Symposium on Recent Advances in Biotherapeutics, Navi Mumbai, India	1,2,3
4-5th February 2009	Institutional policy-embedding knowledge transfer in the institution – bioprocessing skills.	Hoare, M.	Joint HEFCE/Praxis Workshop: Pilot 'Third Stream' event for Deputy/Pro Vice Chancellors, Ware, UK	1,2,3
13th January 2009	Use of microscale bioprocessing techniques in primary recovery: Effect of heat extraction conditions on the recovery of antibody fragments	Rayat, A.C.M.E., Micheletti, M. and Lye, G.J.	BESG Young Researchers Meeting, Sheffield, UK	1.2
13th January 2009	A directed data driven experimental approach to resolving complex bioprocess designs.	Edwards-Parton, S., Titchener-Hooker, N.J., Zhou, Y.	BESG Young Researchers Meeting. Sheffield, UK	2
26th November 2008	Filamentous bacteriophage characterisations for their large-scale production.	Branston, S.D., Stanley, E.C., Ward, J. M, Keshavarz-Moore, E.	bioProcess UK Annual Conference. Brighton, UK	3.1
26th November 2008	Bioprocess challenges in the production of bacteriophage.	Stanley, E.C., Branston, S.D., Ward, J. M., Keshavarz-Moore, E.	bioProcess UK Annual Conference. Brighton, UK	3.1
8th September 2008	Stability of amino acid oxidase in reactor scale-up	Tindal, S.R., Archer, I.V.J., Carr, R., Farid, S., Hailes, H.C., Woodley, J.M.	ESBES 2008. Faro, Portugal	3
3-5th September 2008	Application of agent-based system for bioprocess description and process improvement.	Gao, Y., Kipling. K., Glassey, J., Willis, M., Montague, G., Zhou, Y., Titchener-Hooker, N.J.	KES Conference. Zagreb, Croatia	2
26-29th July 2008	Filamentous bacteriophage characterisation for their large scale production.	Branston, S. D., Stanley, E. C., Keshavarz-Moore, E., Ward, J. M.	Edinburgh International Phage Conference. Edinburgh, UK	3.1
26-29th July 2008	Pilot-scale fermentation and bioprocessing of bacteriophage.	Keshavarz-Moore, E., Ward, J.	Edinburgh International Phage Conference. Edinburgh, UK	3.1
10th July 2008	Determining antibody stability: Creation of solid-liquid interfacial effects within a high shear environment.	Biddlecombe, J.G., Craig, A.V., Zhang, H., Uddin, S., Mulot, S., Fish, B.C., Bracewell, D.G.	Controlling Aggregation in Bioprocessing, IChemE (BESG). London, UK	1.1, 3.2
29th June – 2nd July 2008	An agent based strategy for bioprocess modelling and operational improvement	Glassey, J., Martin, E., Montague, G., Zhou, Y., and Titchener-Hooker, N. J.	Foundations of computer aided process operations. Boston, USA	2
22-27th June 2008	PEG Precipitation for recovery of an igG4 monoclonal antibody from cell culture supernatant: technologies to develop high throughput methods for process scouting.	Knevelman C., Davies, J., Titchener-Hooker, N.J.	Recovery of Biological Products XIII. Quebec City, Canada	1.2
22-27th June 2008	Back to the future – the use of batch adsorption in the recovery of antibody fragments from an *E. coli* disruptates.	Ujam, S.B, Hoare, M., Titchener-Hooker, N.J. and Bracewell, D.G.	Recovery of Biological Products XIII. Quebec City, Canada	3.2
22-27th June 2008	Effect of membrane pleating upon filter membrane cartridge performance.	Brown, A.I., Lye, G.J., Titchener-Hooker, N.J., Levison, P.	Recovery of Biological Products XIII. Quebec City, Canada	1.2
11-14th June 2008	Viable cell recovery by capillary shear from mESC derived embryoid bodies.	Papantoniou, I. Hoare, M., Veraitch, F.S.	International Society for Stem Cell Research. Philadelphia, USA	1.1
1-6th June 2008	Host strain influences on supercoiled plasmid DNA production in *E.coli*; Implications for efficient design of large scale processes.	Yau, S.Y., Ward, J., Keshavarz-Moore, E.	Vaccine Technology II. Algarve, Portugal	3.1

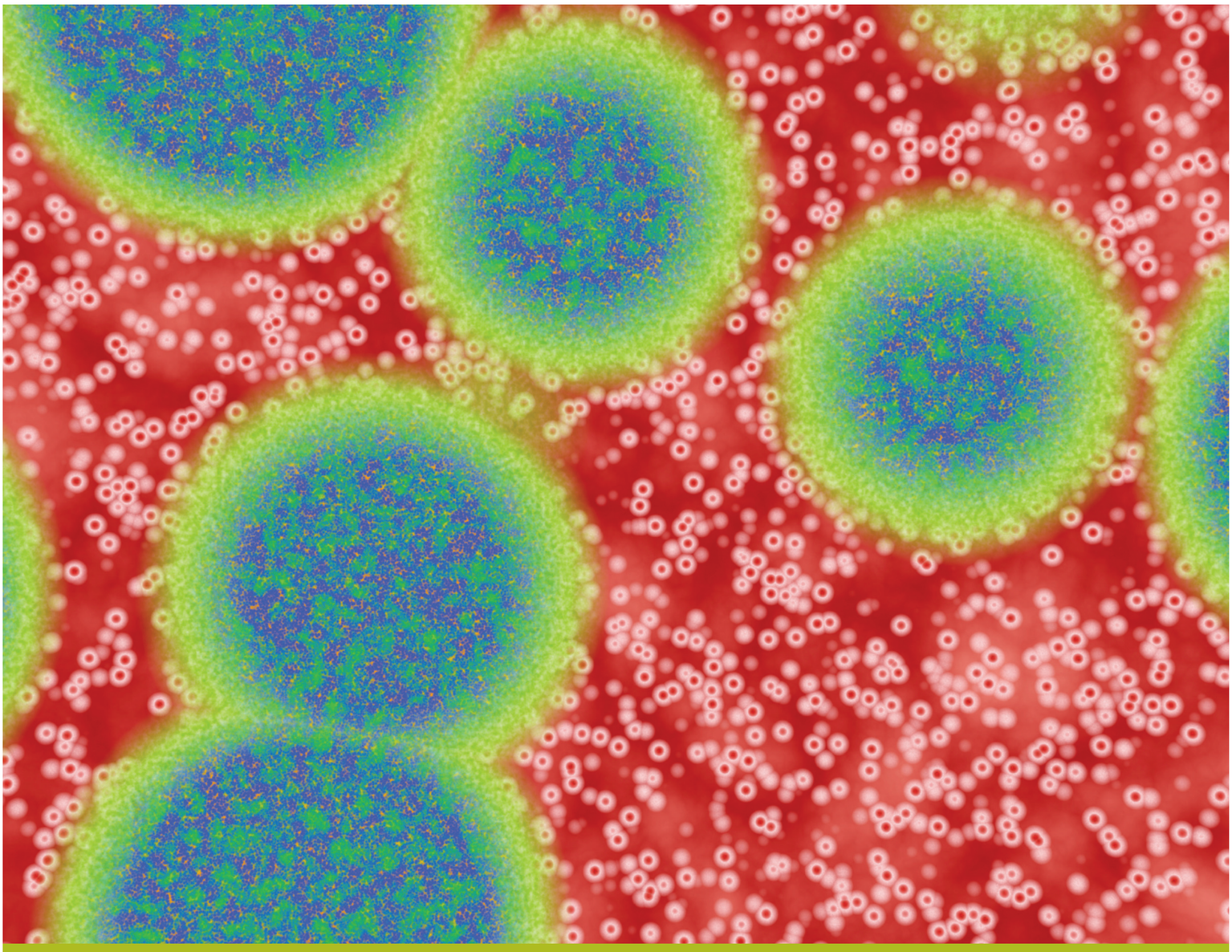
Over the lifetime of the IMRC there has been a five fold increase of company involvement in facilitating IMRC research and technology transfer

1-6th June 2008	A selective recovery methodology for the primary purification of lipid envelope virus-like particles in *S. cerevisiae*.	Kee, G.S., Pujar, N.S., Titchener-Hooker, N.J.	Vaccine Technology II. Albuferia, Portugal	3.2
8th May 2008	Filamentous bacteriophage versus plasmids: aspects of their large scale bioprocessing.	Branston, S. D., Stanley, E. C., Keshavarz-Moore, E., Ward, J. M.	Mobile Genetic Elements Workshop. Birmingham, UK	3.1
22-23rd April 2008	Microbiochemical engineering approaches to high throughput process development: the automated microscale chromatographic purification of virus-like particles.	Chhatre, S., Wenger, M., DePhillips, P., Bracewell, D.G.	BioProcess International European Conference and Exhibition. Vienna, Austria	3.2
13-18th April 2008	A microwell-based approach to predict large-scale centrifuge performance: impact of culture conditions on cell separations.	Tait, A.S., Aucamp, J.P., Baganz, F., Hoare, M.	Cell Culture Engineering XI. Queensland, Australia	1.2
13-18th April 2008	Changes in CHO culture lactate re-utilisation due to changes in scale.	Paoli, T, O'Kennedy, R., Keshavarz-Moore E.	Cell Culture Engineering XI. Queensland, Australia	3.1
6-10th April 2008	Visualisation of packed bed behaviour using 3D confocal microscopy and microfluidics.	Shapiro, M.S., Haswell, S.J., Lye, G.J., Bracewell, D.G	AIChE Spring National Meeting. New Orleans, USA	1.3
3rd March 2008	A microscale approach to study and predict large-scale transient transfection.	Tait, A.S., Wu, A., Baganz, F., Lye, G.J.	Cell Line Development and Engineering, Prague, CR	1.1
22nd February 2008	Aspects of large scale filamentous bacteriophage production: particle characterisation, contained fermentation and primary recovery.	Branston, S.D., Stanley, E.C., Keshavarz-Moore, E., Ward, J.M.	Bacteriophages: Nature and Exploitation meeting. Welwyn Garden City, UK	3.1
29th January 2008	Space is the place: using DOE and microscale techniques to define process boundaries.	Wenger, M.D., DePhillips, P., Bracewell, D.G.	12th Symposium on the Interface of Regulatory and Analytical Sciences for Biotechnology Health Products. Washington, DC, USA	3.2
26th January 2008	Pilot scale fermentation and bioprocessing of bacteriophage.	Stanley, E.C., Branston, S.D., Keshavarz-Moore, E., Ward, J. M.	Edinburgh Phage Conference: Edinburgh, UK	3.1
6-11th January 2008	Visualisation of packed bed behaviour using 3D confocal microscopy and microfluidics.	Shapiro, M.S., Haswell, S.J.,Lye, G.J., Bracewell, D.G	The role of structure in biological, chemical and environmental separations: From the molecular to the macro. Puntarenas, Costa Rica	1.3
4th January 2008	Host strain influences on supercoiled plasmid DNA production in *E.coli*; Implications for efficient design of large scale processes.	Yau, S.Y., Ward, J., Keshavarz-Moore, E.	Inaugural BESG Young Researchers Meeting (IChemE). London, UK	3.1
4th January 2008	Aspects of large scale filamentous bacteriophage production: particle characterisation and contained fermentation.	Branston, S.D., Stanley, E.C., Keshavarz-Moore, E., Ward, J.M.	Inaugural BESG Young Researchers Meeting (IChemE). London, UK	3.1
4th January 2008	Measurement of protein stability by tryptophan fluorescence in microfluidics: initial studies.	Remtulla, N., Gaudet M., Dalby P.A., Pankhurst Q. A., Bracewell D.G.	Inaugural BESG Young Researchers Meeting (IChemE). London, UK	1.3
4th January 2008	Bioreactor design for controlled formation of engineered tissues.	Gerontas, S., Farid, S., Hoare, M.	Inaugural BESG Young Researchers Meeting (IChemE). London, UK	1.1
3-4th January 2008	Microwell approaches to the high throughput process evaluation of cell lines and antibodies.	Silk, N., Barrett, T., Lye, G., Baganz, F.	ESACT-UK 18th Annual Meeting, Cambridge, UK	3.1
3-4th January 2008	Impact of cell engineering and fermentation on whole bioprocessing.	Gerontas, S., Farid, S., Hoare, M.	ESACT-UK 18th Annual Meeting, Cambridge, UK	1.1
28-29th November 2007	Factors affecting the efficient design of an *E.coli* system for plasmid DNA production.	Ward, J., Keshavarz-Moore, E.	bioProcessUK Annual Conference. Cardiff, UK	3.1

28-29th November 2007	Design and characterisation of a microfluidic packed bed system for protein breakthrough determination.	Shapiro, M.S., Haswell, S.J., Lye, G.J., Bracewell, D.G	bioProcessUK Annual Conference. Cardiff, UK	3.2
28-29th November 2007	Measurement of protein stability by tryptophan fluorescence in microfluidics: Initial Studies.	Remtulla, N., Gaudet M., Dalby P.A., Pankhurst Q. A., Bracewell D.G.	bioProcessUK Annual Conference. Cardiff, UK	1.3
28-29th November 2007	Characterising process interactions for the development of 2nd generation processes for VLP vaccine candidates.	Kee, G.S., Pujar, N., Titchener-Hooker, N.J.	bioProcessUK Annual Conference. Cardiff, UK	3.2
28-29th November 2007	Process economic trade-offs in antibody manufacture.	Farid, S.S.	Animal Cell Technology Industrial Platform Meeting. Ivrea, Italy	2
12-14th November 2007	Crossflow separation of a Fab' fragment from *E. coli* lysate using an ultra scale-down rotating disc filter.	Ma, G., Craig, A., Hoare, M., Zhou, Y.	Filtration of Biological Products: Maximizing Throughput While Minimizing Cost. Seattle, Washington, USA	1.2
4-9th November 2007	Ultra scale-down to improve the flocculation disc-stack centrifuge	Berrill, A., Ho, S., Bracewell, D.G.	AIChE Annual Meeting, Salt Lake City, USA	3.2
4-9th November 2007	Accelerated physicochemical characterization of protein mixtures to aid purification sequence selection	Berrill, A., Ho, S., Titchener-Hooker, N.J., Bracewell, D.G.	AIChE Annual Meeting, Salt Lake City, USA	3.2
31st October 2007	A modelling technique for identifying critical process parameters in bio-manufacturing operations.	Chhatre, S., Francis, R., Newcombe, A., Titchener-Hooker, N.J., Keshavarz-Moore, E.	Technology Transfer for Biopharmaceuticals. Berlin, Germany	2
16-19th September 2007	Vaccine therapy: the impact of the engineering environment on cells during processing.	McCoy, R., Levy, S, Ward, J.M., Hoare, M.	13th European Congress on Biotechnology. Barcelona, Spain	1.1
16-19th September 2007	A framework for the rapid optimization and scale-up of protein expression combining microscale experiments and statistical experimental design.	Islam, R.S., Mukhopadhyay, T., Levy, M.S., Micheletti, M., Ward, J.M., Lye, G.J.	13th European Congress on Biotechnology. Barcelona, Spain	2, 3.1
26-30th August 2007	Physiological characterization of *Saccharopolyspora erythraea* deletion strains: Global and pathway specific regulators.	Akinrinsola, I., Krabben, P., Baganz. F., Sheridan, R., Ward, J.	14th International Symposium on the Biology of Actinomycetes. The Sage Gateshead, Newcastle upon Tyne and Gateshead, UK	3.1
19-24th August 2007	Considerations for large scale extraction of monoclonal antibodies targeted to different subcellular compartments in transgenic tobacco plants.	Hassan, S., Ma J-K.C., van Dollerweerd C., Keshavarz-Moore E.	ACS Fall National Meeting. Boston, USA	3.1
19-24th August 2007	A robust microscale method for yeast cell disruption in the purification of intracellular proteins.	Wenger, M., DePhillips, P., Bracewell, D.G.	ACS Fall National Meeting. Boston, USA	1.2, 3.2
19-24th August 2007	Detergent-mediated liberation of intracellular recombinant virus-like particles (VLPs) from *S. cerevisiae* homogenate.	Kee, G.S., Pujar, N., Titchener-Hooker, N.J.	ACS Fall National Meeting. Boston, USA	3.2
19-24th August 2007	Gauging the technical, regulatory and financial implications of process changes: a decision-support tool.	Hassan, I., Bulmer, M., More, J., Titchener-Hooker, N.J., Farid, S.	ACS Fall National Meeting. Boston, USA	2
19-24th August 2007	Biopharmaceutical portfolio management: A stochastic multiobjective optimization approach.	George, E.D., Farid, S.S.	ACS Fall National Meeting. Boston, USA	2
19-24th August 2007	Determining antibody stability: creation of solid-liquid interfacial effects within a high shear environment.	Biddlecombe, J.G., Craig, A.V., Zhang, H., Uddin, S., Mulot, S., Fish, B.C., Bracewell. D.G.	ACS Fall National Meeting. Boston, USA	1.1, 3.2

19-24th August 2007	Prototype software methodology for the rapid evaluation of biomanufacturing process options.	Chhatre, S., Francis, R., Newcombe, A., Titchener-Hooker N.J., Keshavarz-Moore, E.	ACS Fall National Meeting. Boston, USA	2
19-23rd August 2007	Physiological characterization of *Saccharopolyspora erythraea* deletion strains: Global and pathway specific regulators.	Akinrinsola, I., Krabben, P., Baganz, F., Sheridan, R., Ward, J.	234th American Chemical Society National Meeting and Exposition.Boston, MA, USA	3.1
15-19th July 2007	Strategy for preparation of non-viral vectors for therapy and vaccination.	Yau, S.Y., Kay, A., O'Kennedy, R., Cooke, J., Cooke, G.D., Ward, J., Keshavarz-Moore, E.	Biochemical Engineering XV: Engineering Biology from Biomolecules to Complex Systems. Quebec City, Canada	3.1
15-19th July 2007	Reconciling multiple trade-offs and decisions in biopharmaceutical development.	Farid, S.S.	Biochemical Engineering XV: Engineering Biology from Biomolecules to Complex Systems. Quebec City, Canada	2
3rd July 2007	Microscale process development technology in downstream processing.	Bracewell, D.G.	Bioprocessing: New Methods and Applications. Cambridge, UK	3.2
27th June 2007	Separation of fab fragments from realistic feedstocks using mixed mode chromatography.	Beckett, PJ, Levison, PR, Bracewell, D.G., Titchener-Hooker, NJ.	Mixed Mode Chromatography Conference, SCi, London	1
19th June 2007	Bioprocess on a deck: automated microscale chromatography to accelerate process development. oral presentation.	Wenger, M., DePhillips, P., Bracewell, D.G.	FDA (CBER) informational seminar. National Institutes of Health, Bethesda, USA	3.2
18-20th June 2007	Considerations for large scale extraction of monoclonal antibodies targeted to different subcellular compartments in transgenic tobacco plants.	Hassan, S, Ma J-KC, van Dollerweerd C, Thomas C, Liu W, Keshavarz-Moore E.	PBVA 2nd International Conference Plant-Based Vaccines and Antibodies, Verona, Italy	3.1
17-20th June 2007	Effect of harvest time and means on the glycosylation pattern of a monoclonal antibody.	Qvist, C., Baldascini, H., Smales, C.M., Mohindra, A., Racher, A., Bilsborough, S., Hoare, M.	ESACT 20th Meeting of the European Society for Animal Cell Technology. Dresden, Germany	1.1
31st May – 3rd June 2007	Capturing the business-process interface in biopharmaceutical manufacture.	Farid, S.S.	ISPE 2nd Nordic meeting on Process Analytical Technologies for Young Academics. Stockholm, Sweden	2
21-25th May 2007	The effect of shear forces on filamentous bacteriophage and the implications for their large-scale production.	Branston, S.D., Stanley, E.C., Keshavarz-Moore, E., Ward, J.M.	107th ASM General Meeting. Toronto, Canada	3.1
17th May 2007	The large-scale fermentation and bioprocessing of genetically engineered bacteriophage.	Stanley, E. C., Branston, S. D., Keshavarz-Moore, E., Ward, J.	UK Mobile Genetic Element workshop. Birmingham, UK	3.1
10-11th May 2007	Downstream processing: chicken or egg?	Bracewell, D.G.	International Workshop on Downstream Processing. Delft, Netherlands	1,2,3
24-25th April 2007	High-throughput formulation of proteins in microtiter plates.	Dalby, P. A.	Bioprocess International Conference, Paris, France	1.3
22-23rd April 2007	Microbiochemical engineering approaches to high throughput process development: the automated microscale chromatographic purification of virus-like particles.	Chhatre, S., Wenger, M., DePhillips, P., Bracewell, D.G.	BioProcess International European Conference and Exhibition, Vienna, Austria	3.2
11-14th April 2007	Measurement of protein stability by tryptophan fluorescence in microfluidics: A Feasibility Study.	Remtulla, N., Dalby P.A., Pankhurst Q. A., Bracewell D. G.	'ProStab 2007' Exeter, UK	1.3
28-30th March 2007	An engineering study of key interactions within the process for antibody fragment production.	Tustian, A.D., Bowering, L.C., Hoare M., Baganz, F., Titchener-Hooker, N.J.	2nd Singapore biologics manufacturing conference. Singapore	1.2

26-29th March 2007	The large-scale fermentation and bioprocessing of genetically engineered bacteriophage for pharmaceutical applications.	Stanley, E. C., Branston, S. D., Keshavarz-Moore, E., Ward, J.	106th SGM Meeting, Manchester, UK	3.1
26-29th March 2007	The large scale fermentation and bioprocessing of genetically engineered filamentous phage to underpin new therapeutic and industrial applications.	Branston, S.D., Stanley, E.C., Keshavarz-Moore, E., Ward, J.M.	106th SGM Meeting, Manchester, UK	3.1
19-22nd March 2007	Development of ultra scale-down mimics for high cell density recovery operations.	Tustian, A.D., Bowering, L.C., Baganz, F., Hoare, M., Titchener-Hooker, N.J	Society of Biological Engineering's First conference on Accelerating Biopharmaceutical Development. Coronado Island, California, USA	1.2
19-22nd March 2007	The use of ultra-scale-down approaches to enable rapid investigation and characterization of the initial downstream process for antibody fragment production in *E.Coli*.	Titchener-Hooker, N.J.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	1.1, 1.2, 1.3
19-22nd March 2007	Stochastic multi-objective optimization for the design of drug portfolio strategies.	George, E.D., Titchener-Hooker, N.J., Farid, S.S.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	2
19-22nd March 2007	Application of partial least squares to sparse data sets for early stage design of chromatographic separations.	Edwards-Parton, S., Bracewell, D.G., Thornhill, N.F., Liddell, J., Titchener-Hooker, N.J.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	2
19-22nd March 2007	A prototype software methodology for the rapid evaluation of bio-manufacturing process options.	Chhatre, S., Francis, R., Titchener-Hooker, N. J., Newcombe, A. R, Keshavarz-Moore, E.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	2
19-22nd March 2007	Accelerated physicochemical characterization of complex protein mixtures for optimized chromatographic separation	Berrill, A., Ho, S., Titchener-Hooker, N.J., Bracewell, D.G.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	3.2
19-22nd March 2007	Critical process economic drivers in industrial antibody manufacture.	Farid, S.S.	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	2
19-22nd March 2007	Evaluation of new manufacturing paradigms for downstream processing.	Titchener-Hooker, N.J	SBE Accelerating Biopharmaceutical Development. Coronado Island, California, USA	2
5th January 2007	Application on Global Sensitivity Analysis to the determination of parameter importance in Protein A chromatography.	Chhatre, S., Francis, R., O'Donovan, K., Titchener-Hooker, N., Newcombe, A. R.,Keshavarz-Moore, E	4th Annual Biochemical Engineering Research Network (BERN) meeting. Birmingham, UK	2
5th January 2007	Recovery of inclusion bodies from *E. coli* cell lysate using vibrating membrane filtration.	Davies, R.B., Collins, M., Leach, G.C., Woodgate, J., Lye, G.J.	4th Annual Biochemical Engineering Research Network (BERN) meeting. Birmingham, UK	1.2
5th January 2007	Extraction of monoclonal antibodies targeted to different subcellular compartments in transgenic tobacco plants with a view to large-scale processing.	Hassan S., van Dolleweerd C., Ma J., Thomas C., Liu W., Zhang Z., Keshavarz-Moore E	4th Annual Biochemical Engineering Research Network (BERN) meeting. Birmingham, UK	3.1
5th January 2007	Assessing the impact of process changes in the biotechnology sector: A survey.	Hassan, I., Bulmer, M., More, J., Titchener-Hooker, N.J., Farid, S.	4th Annual Biochemical Engineering Research Network (BERN) meeting. Birmingham, UK	2
4-5th January 2007	Microscale and automation approaches for rapid cell culture process development.	Lye, G.J.	ESACT-UK 17th Annual Meeting. Cambridge, UK	1.1
4-5th January 2007	Effect of harvest time and means on the structural profile of a monoclonal antibody.	Qvist, C., Baldascini, H., Smales, C.M., Mohihdra, A., Racher, A., Bilsborough, S., Hoare, M.	ESACT-UK 17th Annual Meeting. Cambridge, UK	1.1



7.0 Events

“IMRC events are a crucial mechanism for training the next generation of research and industry leaders”

7.0 Events

IMRC 6th Annual Bioprocess Briefing, 16th September 2010

The UCL Biochemical Engineering Knowledge Transfer Consortium

A series of oral presentations was given to demonstrate the reach of the UCL Biochemical Engineering Knowledge Transfer agenda. Topics were selected to show the breadth of our activities and included bioprocessing for cellular therapies, advances in formulation engineering and the use of modelling approaches for whole bioprocess sequence performance prediction. The event also held a poster session with 36 poster presentations whose titles were listed below.

IMRC Demonstrations run with small groups of delegates have provided an opportunity for all IMRC company sponsors to see first hand how the techniques and methods created by the IMRC team are applied and the data interpreted in the full bioprocess sequence from fermentation to high resolution chromatography.

Oral presentations:

- An EPSRC EngD with NIBSC, “Engineering high-throughput formulation development”, Yitzchak Grant, Paul Dalby (UCL), Paul Matejtschuk (NIBSC)
- An EPSRC KTS project, “Interfacial effects during the manufacturing and supply of biologics: A knowledge transfer secondment”, Alex Berrill (UCL), Gaik Sui Kee (GSK) and Dan Bracewell (UCL)
- An overview of an emerging area with strong KT potential, “Embryonic stem cell bioprocessing”, Farlan Veraitch (UCL)
- A Technology Strategy Board collaboration, “Evaluating mAb downstream processing options at the bioprocess-business interface”, Sofia Simaria, Suzanne Farid (UCL), Ying Gao (MedImmune) and Richard Turner (MedImmune)
- An EPSRC KTS project, “Integration of a bioprocess modelling tool into teaching and research at UCL”, James Savery, (formerly BioPharm Services Ltd), Andrew Sinclair (BioPharm Services Ltd) and Mike Hoare (UCL)

Poster Presentations

The following presentations represent UCL activities in bioprocessing both from the IMRC and from related areas which benefit from the IMRC, especially in regenerative medicines and industrial biotechnology. The presentations are all collaborative with industrial and academic partners. Only the researcher associated with the project is given in this instance.

Presenter	Title
Razwan Hanif	Methods to establish scaleable operations for contaminant removal prior to packed bed steps
Candy Ng	High performance affinity chromatography to optimise purification via protein A capture
Qiang Li	Ultra scale-down of large scale homogenistation of *E. coli* cells expressing a fragment antibody
Mike Delahaye	Human cells for prostate cancer vaccine therapy - the impact of centrifugation upon key product quality attributes
Juan Pablo Acosta	Ultra scale-down studies of human cell bioprocessing for a prostate cancer vaccine therapy - the impact of capillary shear
Jun Zhang	Data & knowledge engineering for intelligent bioprocess design
Yu Ji	Modelling and model-based experimental design
Ana Sofia Simaria	Process intensification of antibody purification processes: A comparison of milp versus evolutionary algorithms
Affaro Affandy	Hydrodynamic profiles inside sterile filtration membranes and it impact to supercoiled plasmid DNA.
Mike Hughson	Inactivation studies on Japanese Encephalitis Virus vaccine using Design of Experiments
Alex Chatel	An ultra scale-down approach to discovery of new opportunities when processing protein domains
Edward Close	Process modelling approaches to biological complexity in the production of therapeutic proteins
Kristina Kovacs-Schreiner	Measurement of protein self association behaviour as a determinant of aggregation in bioprocessing
John Betts	Incorporation of developability into cell line selection
Maria Velez Suberbie	The impact of bioreactor aeration and mixing on Chinese hamster ovary cell physiology and structure during antibody production
Richard Tarrant	Development and implementation of downstream processing methods to investigate host cell protein contaminants
Andrea Rayat	Application of a novel microscale crossflow filtration device to study the impact of DNA hydrolysis in the recovery of antibody fragments from an industrial *E. coli* strain
Heather Guy	Microscale characterisation of a manufacturing route for lentiviral vectors

We run numerous events throughout the year that enable IMRC company sponsors to see first hand how new techniques and methods created by the IMRC are applied

Balasundaram Bangaru	Evaluation of the effect of dual-salt precipitation as a primary recovery step on the chromatographic purification of Fab' antibody fragments
Roumteen Tavakoli-Keshe	Investigation of antibody aggregate formation in bioprocess; a study of the location and mechanism of aggregation
Shaukat Ali	Design, characterisation and feasibility of a miniaturised bioreactor to perform high cell density fermentations
Sally Hassan	Strategy for the consistent preparation of sufficient non-viral large vectors for biopharmaceutical applications
Gemma Ordidge	A generic automated microscale platform for evaluating inclusion body refolding
Jasmin Baboo	Automated evaluation of microscale linked process sequences for generation of scaleable bioprocess design data
Chuanjie Du	Bioconversion of lignin degradation products to higher value chemicals using transaminase
Leonardo Rios	A high throughput toolbox for the transketolase-transaminase synthesis of chiral amino-alcohols
Raha Jahromi	Evolutionary and mutagenesis analyses of Transketolase to guide further protein engineering
Nihal Bayir	De-novo pathway engineering for pharmaceutical synthesis: understanding and optimization of pathway interactions with host cell metabolism
Yvonne Pang	Functional isolation of dental stem cells
Tristan Pritchard-Meaker	A scalable technology to produce stem cells for clinical use
Jennifer Badger	The effect of hypoxia on the culture of stem cells for the treatment of Parkinson's disease
Sion Lewis	Activation of intracellular signalling pathways during mouse embryonic stem cell division
Nathalie Moens	Controlled studies of stem cell culture and differentiation in parallel microwell cultures
Iwan Roberts	Potential separation solutions in a hESC bioprocess to treat blindness
Owen Bain	Improving autologous bone marrow stem cell therapy for cardiac repair
Patrick Radone	Cell engineering and processing of recombinant Pichia pastoris strains capable of high specific yield production

IMRC Bioprocess Briefings for April 2010 – March 2011

Prof. M. Nazmul Karim, Department of Chemical Engineering, Texas Tech University, USA, Cellulosic biofuels: One step process for bioethanol and biobutanol production, 6th July 2010

Dr. Nuno Reis, Department of Chemical Engineering and Biotechnology, University of Cambridge, UK, Bioprocessing and healthcare in plastic microcapillary film systems, 8th July 2010

Dr. Christopher J. Roberts, Department of Chemical Engineering, University of Delaware, USA, Nonnative protein assembly and stability: kinetics, thermodynamics, and alternative aggregation pathways, 26th July 2010

Dr. Thomas Daszkowski, BTS Process Technology Healthcare, Bayer Technology Services Americas, USA, One approach at Bayer to address cost of goods in the biotech industry, 20th August 2010

Prof. Conan J. Fee, Department of Chemical and Process Engineering, University of Canterbury, New Zealand, Poly(ethylene glycol)-grafted proteins: conformation, separation and analysis, 31st August 2010

Dr. Brian Lee, PBS Biotech, Camarillo, USA, Development of novel single-use bioreactors using pneumatic mixing, 26th November 2010

Dr. Mark Seymour, Syngenta, UK, Agriculture, bioanalytical chemistry and the food we eat, 20th January 2011

Miss Mairead Looby, Pfizer Biotech Campus, Ireland, Application of Quality by Design (QbD) principles to the development and technology transfer of a major process improvement for the manufacture of a recombinant protein, 3rd March 2011


The IMRC is investing in the next generation to meet the challenges of tomorrow
Agilent Technologies

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