## UCL Innovative Manufacturing Research Centre

| Key Data | |
|---|---|
| **Time Period** | Phase 1 (2002-2007), Phase 2 (2008-2012)<br>10 Years total duration |
| **Total Value of EPSRC Grant** | **Total: £8.9m**<br>Phase 1 - £3.1m<br>Phase 2 - £5.9m |
| **Other Funding**<br>*(Direct leverage of additional research funding specific to IMRC*) | **£10.1m total**, of which £1m cash and £9.1m contributions in kind |
| **Projects** | 60 |
| **Current Staff** | 17 total including 7 core academics, 2 admin/technical support staff and 8 PDRs |
| **PhD Students** | 89 current plus 50 completed to date<br>*(funded by IMRC grant or supervised by staff involved in IMRC)* |
| **IMRC journal publications** | 270 publications |
| **Patents granted** | 2 |
| **Key Sectors of Focus** | Biopharmaceuticals |
| **Current Research Themes / Specialisms**<br>(Phase 2) | • Theme 1: Micro-scale bioprocess engineering<br>• Theme 2: Enhanced knowledge acquisition<br>• Theme 3: Whole bioprocessing advances (disruptive technologies) |
| **Examples of key economic impacts** | • Reducing development costs for the manufacture of biopharmaceuticals – development time for CytoFab, a drug to treat sepsis, was reduced by 50% with 50% fewer resources required.<br>• Enabling biopharmaceutical manufacturers to reach market faster – CytoFab development time was reduced by a year, increasing the potential for profits before patents expire<br>• Reducing production costs for manufacture – more intelligent selection of cell lines can lead to the adoption of cells which are cheaper to produce |
| **Key value added aspects demonstrated by the IMRC** | • More strategic approach to research<br>• Understanding of industry needs<br>• Builds critical mass<br>• Longevity of funding model supports work into research themes |

# Overview

The vision of the UCL IMRC for Bioprocessing is to provide underpinning research in processing to support the bioprocessing industry – the fastest developing part of the pharmaceuticals and biotech industry.

The UCL IMRC was established in 2002 following rationalisation of the Innovative Manufacturing Initiative (IMI) grants into the IMRCs, transforming UCLs IMI bid into an IMRC for Bioprocessing. UCL had been involved in the biotechnology sector since 1990 when it was selected to host the Interdisciplinary Research Centre (IRC) for Biochemical Engineering. This wealth of knowledge meant that the newly formed IMRC was able to draw upon the experience of large scale IRC bio process studies to find ways of delivering outcomes more quickly and cost effectively. This led to a focus of the IMRC on developing 'micro-scale biochemical engineering' methods by which predictive data could be gathered at much smaller scale than conventional scale-down. This is of significant importance to the bio-processing industry, as performing initial analysis at micro-scale reduces the quantity of biological material required, which increases the speed and reduces the cost of initial analysis, and reduces the need for expensive pilot studies at larger scale. The IMRC has taken the micro biochemical studies that it pioneered and collaborated with industrial partners to demonstrate their applicability and effectiveness.

Training is supported by the IMRC via fully funded PhD's, EngD links with IMRC sponsors and affiliated companies, and from industrial secondments. The EngD links are delivered via an Industrial Doctoral Training Centre (IDTC).

**Planned Research Priorities**

Current research priorities are based upon the recommendations of the 2005 review following IMRC Steering Group discussion. There are three major demands now shaping the future of IMRC planning:

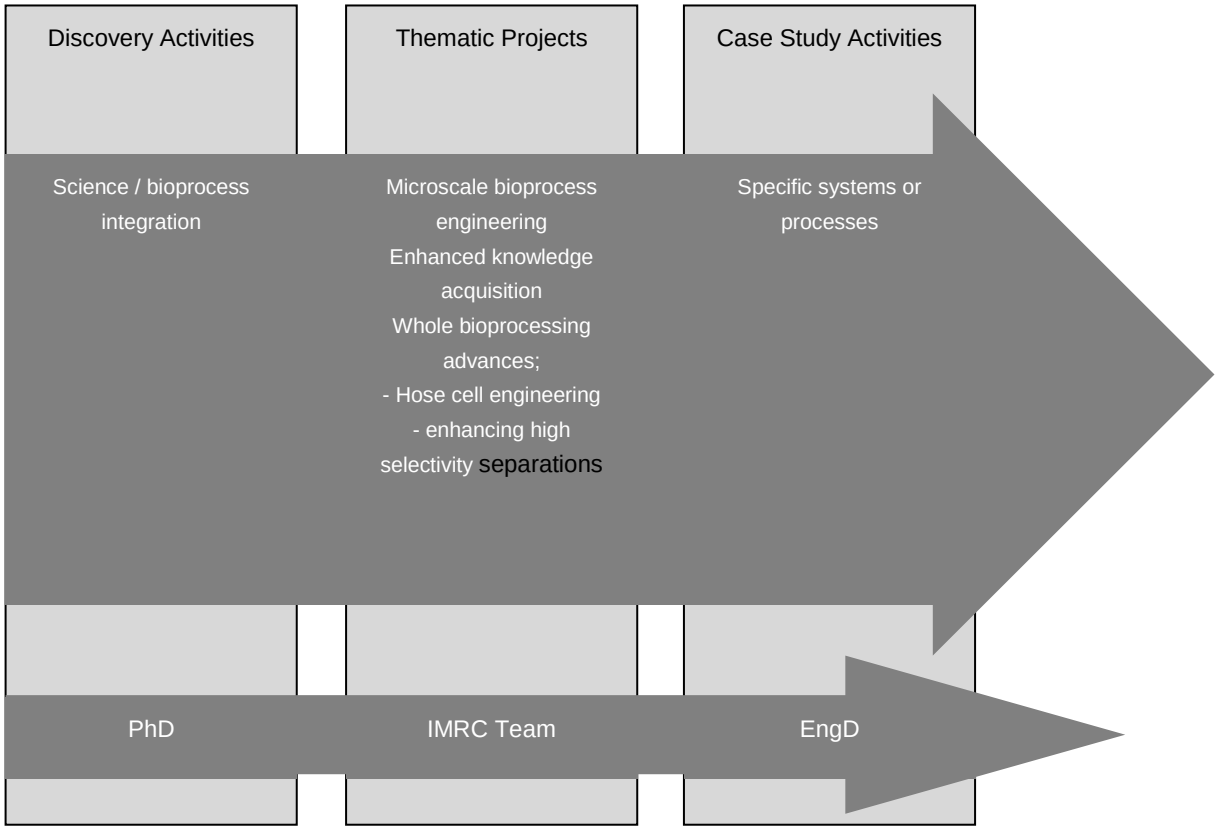
- Being able to downstream process much larger quantities of product
- Faster development of products with higher quality
- A progression towards more heavily molecularly engineered materials

**How does IMRC relate to the rest of UCL?**

The IMRC is managed by the UCL Advanced Centre for Biochemical Engineering and forms the Centre's largest research activity. The Advanced Centre also manages a programme on complex small molecules (The Bioconversion-Chemistry-Engineering interface programme, BiCE) and further activity in regenerative medicine. There is some complementarity between these research programmes as they all have common areas of work with very small quantities of biological materials, however the challenges facing each research programme are quite distinct, with a requirement for different strategies.

The IMRC is managed by an executive management board with input from a steering group. The executive management board provides strategic advice on research directions and initiatives. The steering group considers operational matters and inputs at a highly specialised, technical level. The majority of academic staff are drawn from the Department of Biochemical Engineering, although collaboration with other departments is critical to the delivery of the IMRC's vision. In 2009/10 7 other UCL and 19 external academics were involved in IMRC research projects. Centre academics as investigators have won grants worth a further £2m, from sources outside of the IMRC over the same period.

The diagram below shows how the IMRC relates to other areas of activity at UCL. Discovery research is undertaken in the form of PhDs. Findings from this research phase feeds into and shapes the themes delivered by the core IMRC team. This is discussed in more detail in the IMRC research strategy section. IMRC research is transferred to industry via EngD projects and collaborations.




Source: UCL 7th year review

**Industrial Partners**

The Bioprocessing IMRC has high levels of engagement and collaboration with the bioprocessing industry – working with the vast majority of major companies in this field in the UK and overseas. This is not a large sector in terms of the number of companies involved, and UCL is highly networked in this sector – partly due to the fact that around 50% of the researchers within companies in this field previously studied at UCL.

When the IMRC was established in 2002 there was a group of 10 partnering companies with a further 2 companies added soon after. The decision of IMRC management at this point was to use this founding group of companies to prove the first tranche of IMRC research and to seek to grow the consortium only after there was clear evidence of knowledge transfer. After the 2005 review an additional three industrial partners were added bringing the overall total to 15. A further 20 companies are affiliated with the IMRC, but not classified as industrial partners. Such is the interest in the IMRC that it has been possible to be highly selective about recruitment of collaborator firms.

The industrial partners form the industrial steering group which ensures that the industrial context is always kept in mind when making scientific research decisions. They advise the director of the IMRC on research objectives and technology transfer.

A key part of the IMRC knowledge dissemination to industrial partners occurs through the EngD programme. This allows the IMRC to allocate a doctoral research student to a specific industrial

project, applying techniques developed by the IMRC to solving bioprocess manufacturing problems. This process is recognised as a key mechanism for knowledge transfer.

It also allows the IMRC to test the robustness of new concepts, such as micro-scale processing.

Evidence of the IMRC's close collaboration with industrial partners can be seen in the case studies, for example Professor Titchener-Hooker's work with Protherics (now BTG) which has helped to improve their development processes. The involvement of industrial partners helps to focus research on areas which affect the industrial community. The use of PhD and EngD students is a useful route for knowledge transfer.

# IMRC Research Strategy

### IMRC Programme Structure

IMRC phase 1 (2002-2007) comprised three research themes:

- Ultra scale down techniques
- Regime analysis and large scale verification
- Unit operation and whole bioprocess modelling

The ultra-scale down techniques developed in phase 1 were crucial to the development of themes in the second phase of the IMRC. The vision and focus of these themes were informed by the self-assessment review conducted by IMRC, the external review and an understanding of the requirements of industry.

The IMRC programme for 2007-2012 offers a holistic process view, split down into the following three themes:

- Theme 1 – Micro-scale bioprocess engineering, making micro-scale collection of bioprocess data even more effective
- Theme 2 – Enhanced knowledge acquisition, addresses ways in which we can minimise the time and effort to collect the data and convert it into useful information
- Theme 3 – Whole bio-processing advances which examines host cell engineering and enhancing high selectivity separations

Micro-scale mimics provide the means to explore the behaviour of unit operations and of process sequences with tiny quantities of material. Techniques developed under the enhanced knowledge acquisition theme are providing more efficient methods for the mapping of process behaviour. Advances in host cell engineering will help to create ways to facilitate the purification of bio-molecules. Academics have interests across these themes ensuring that there is a strong level of cross-fertilisation of ideas and knowledge. The content of the three themes has adjusted over time to meet the needs of industrial partners. Activities in Theme 1 underpin Themes 2 and 3.

The Phase 2 spending of the IMRC is shown in the table below, split by theme. The largest proportion of resources has been allocated to Theme 1 – Micro-scale bioprocess engineering (45% of the total committed expenditure so far). This underlines the fact that research undertaken in Theme 1 forms the foundation upon which Themes 2 and 3 are built.

| Phase 2 – Theme | EPSRC Funding (£) (Budget Allocation) | Design | Technology | Management |
|---|---|---|---|---|
| Micro-scale bioprocess engineering | 2.3m (45%) | 65% | 35% | 0% |
| Enhanced Knowledge Acquisition | 0.96m (19%) | 70% | 0% | 30% |
| Whole bioprocessing advances (disruptive technologies) | 1.8m (36%) | 75% | 20% | 5% |
| Total | 5.06m | | | |

Source: UCL IMRC

**Theme 1 – Micro-scale bioprocess engineering**

The vision of theme 1 is to gather data very early on in the development process for biopharmaceutical products. By reducing the scale further and applying automation, time and costs can be cut. If subsequent human trials fail, which is becoming more likely due to more stringent regulations, then the costs are less likely to be crippling. If clinical trials continue to be promising then this early data forms the basis for rapid completion of large scale trials and launch of new pharmaceuticals. This increased speed and higher chances of success are of vital importance to industrial partners, especially as governments are keen to encourage the entry of biosimilar copies at the earliest opportunity. The window of opportunity for licensed products is small.

The impact that these methods will have on the early stages of biopharmaceutical development will include:

- The ability to work with a large number of candidate macromolecules and their assemblages e.g. for vaccine, and a range of host cost options, including microwell and related bioprocess platforms.
- The identification of novel bioprocess solutions which can be scaled-up with greater confidence
- The early definition of final whole bioprocess sequence for manufacture, i.e. the bioprocess which is most likely to meet requirements for validated material supply for clinical trials as well as manufacture
- The ability to assess a greater range of bioprocess options in a cost effective manner while enhancing speed to market

**Theme 2 – Enhance knowledge acquisition**

The vision of theme 2 is to support theme 1 by increasing the efficiency by which research and data is translated into useful knowledge.

Increased automation and a reduction in the scale of data collection to the microwell level, allows a broad range of data to be collected. Laboratory methods will often not match the scale of experimentation and therefore analysis becomes a bottleneck. Methods developed under this theme aim to allow decisions on new experiments on a rolling basis, such that time spent on 'wasted' experiments is minimised as much as possible. This can dramatically enhance the speed and efficacy of bioprocess development.

Research within this theme seeks to apply algorithms to successive rounds of experimental trials to be informed by previous experience and new methods for the interpretation of data. This will help to:

- Achieve greater process understanding
- Identify the best regions for operation with robust process performance and highlight the boundaries of failure
- Identify process bottlenecks for resolution

**Theme 3 – Whole bioprocessing advances**

The vision of theme 3 is to develop new, efficient and robust processing strategies for advanced biologics such as fusion proteins and novel vaccines.
Two areas of improvement have been selected to demonstrate how micro-scale bioprocessing approaches can deliver insights leading to understanding and an effective translation into industrial practice:

- Use of novel separation strategies which can address issues in product titre from the upstream processes
- The manipulation of the cell host to create new opportunities to achieve improved yields and resolution but with fewer stages

Project proposals for IMRC funding are submitted to Management Advisory Committee (MAC) on a one side proforma, which details evidence of the likely impact and scientific quality. Particular focus is placed on the relevance of projects to strategic research priorities and an emphasis on involving collaboration beyond the IMRC. Projects selected by the MAC are then invited to complete more detailed proposals for final sanction by the Principal Investigator committee. At this point company sponsors and doctoral candidates will be recruited if required.

**Beyond IMRC Phase 2**

UCL recognise the significance of the work which has been carried out within the IMRC, and the significant application to industry. In order to further the work of the IMRC, UCL are currently working on the following:

- 'IMRC Phase 3' (post 2012) – entering a knowledge transfer phase, where UCL will work on further industrial applications of techniques developed through the IMRC Phase 1 and 2 – to embed the techniques and technologies in industry. This will require additional post-doctoral research time to demonstrate the value of the research to industrial partners. UCL are currently working on the business plan for this activity, which will be completed in March 2011. UCL have already entered into an agreement with GSK to host a Centre of Excellence in Advanced Antibody Therapies, which will provide funding of £1 million over 4 years; and an additional Centre of Excellence on Antibody Formulation (£0.4 million). These centres will build on the intellectual property held within the IMRC, and operate under the IMRC label.

# Economic Impact Analysis

**Funding and Leverage**

According to data provided by UCL:

- £10.1m of funding (cash and in-kind) has been contributed by the IMRC's industrial partners. This predominately consists of in-kind contributions (£9.1m), with another £1m in cash.
- Therefore for every £1 of funding from EPSRC a further £1.12 has been received from industrial partners. All of the partner contributions have come from the private sector demonstrating the IMRC's strong links with industry.

- Companies include GSK, Lonza Biologics, GE Healthcare, Eli Lilly and Company, Pfizer and Merck.

**Human Capital Impacts**

The IMRC grant currently funds 19 staff. This includes 7 core academics, 2 FTE admin/ technical support staff and 8 Post Doctoral Researchers (PDR). The IMRC work has allowed the department to expand the staff base by 50-60%. In addition to IMRC-funded staff, the university has also funded three staff appointments within the department (relating to vaccines, stem cell research, and chromatography respectively) in part due to the success of the IMRC.

Between April 2007 and March 2010 29 IMRC research associates (EngDs and PhDs) graduated to join a range of destinations in industry, commerce and higher education. Approximately 70% of these have moved into roles in the biopharmaceutical sector, with around 25% moving into other positions in academia (the destinations of the final 5% are not known). This demonstrates the close links that the IMRC has developed with industry.

Since 2002, 50 students have completed their PhD programmes under the supervision of the IMRC. There are currently another 89 PhD students whose studies are currently in progress. They are either funded by the IMRC or supervised by IMRC staff.

Skills and knowledge have been passed to industry through members of staff and students being recruited by partner companies. In particular the EngD programme delivered by the IMRC has helped to forge strong relationships between research staff and industrial partners (including IMRC partners and non-IMRC partners). Examples include:

- **Allogenic cell therapy** – IMRC worked with Onyvax to help develop a cancer vaccine for the late stage treatment of prostate cancer. This involved locating an EngD student within the company to develop cell lines using IMRC Ultra Scale Down methodologies. The success of this relationship led to a second EngD student being allocated to the company via a Technical Strategy Board grant to progress the research further.
- **Masters in Bioprocessing Industry** – the MBI training programme is run by the Department of Biochemical Engineering at UCL providing a series of short courses in bioprocessing designed specifically for people working in industry. Over 1,000 modules have been sold to more than 700 individuals from 200 companies since the start of the programme in 1994. Currently around 150 delegates attend from industry per annum.
- **Knowledge Transfer Secondments** - Recently UCL have won three Knowledge Transfer Secondments (KTS) grants. These grants will enable the direct transfer of personnel into the sponsor companies to achieve uptake of IMRC advances. The companies involved were UCB, BioPharm Services and GSK.

**Impact Case Study Selection**

3 case studies have been selected by DTZ in conjunction with the IMRC and ESPRC to demonstrate the economic impact of the research undertaken. In order to best demonstrate impact we have focused on completed research projects, meaning that many of the selected projects originated in phase 1 of the IMRC. These case studies have been selected on the basis of the shortlisting criteria, as follows:

- **Demonstrates a range of types of economic impact as defined by BIS** –The focus of this IMRC is on reducing the cost of drug development, therefore the majority of possible case studies identified relate to the improvement of existing businesses in the pharmaceutical industry. The impacts typically relate to increased productivity, reduced failure rates, and

reduced costs. Leverage of additional funding is demonstrated by the second and third case studies. The IMRC demonstrates human capital benefits which are picked up through all of the case studies identified. There are no obvious examples of public policy/public service impacts – other than the general point that reducing the cost of drug development may reduce the costs of healthcare provision. No examples of new business creation or spinouts were identified.

- **Offer convincing evidence of significant tangible impact** - All of the case studies identified offer convincing evidence of significant tangible impact. Indicative information on potential impact of these case studies has been provided in most cases.
- **Demonstrate the added value of the IMRC model** – the case studies highlight a number of added value features of the IMRC model such as high levels of collaboration with industry, critical mass of research, linkages with the DTC and IDTC, Knowledge Transfer Secondments, and the international standing of the research.
- **Coverage of the different research themes within the IMRC** – the case studies cover all three of the IMRC research themes.
- **Sector coverage** – this IMRC has a narrow focus on bioprocessing, which relates to the pharmaceutical industry

Overall, the selection of case studies is typical of the types of work which the IMRC is engaged with, whilst focusing on the examples which demonstrate significant impact and added value. In addition, the selection of case studies reflects a range of types of collaborator, from large multinationals such as Pfizer to smaller firms.

| Case study | BIS Impact Headings | Added Value aspects | IMRC research theme | Sector |
|---|---|---|---|---|
| Ultra scale down techniques (collaborative project with BTG/Protherics) | Impact on existing businesses (reduce cost of development through greater efficiency and reduced failure rate, new product development) | Links with EngD centre – secondment of industry staff to doctoral programmes | Theme 2 – Enhanced data acquisition | Pharma-ceuticals |
| Allogenic cell therapy (with Onyvax) | Leverage of funding (follow on TSB funding and new lectureship)<br>Impact on existing businesses (new product development) | Flexibility and diversity of IMRC research; Links with other institutions | Theme 1 – Micro-scale bioprocess engineering | |
| Accelerated determination of optimal conditions for biopharmaceutical recovery (with Pfizer) | Leverage of funding (follow on TSB funding)<br>Impact on existing businesses (new product development) | Flexibility and diversity of IMRC research; Links IMRC research with industrial partners | Theme 3 - Whole Bioprocessing advances | |

**Added Value of the IMRC model**

The added value of the IMRC funding model is:

- Develops a critical mass and a **portfolio of work** which becomes cross-supporting as the findings under theme 1 (micro scale processing), inform research under themes 2 and 3. Individually funded projects would most likely be more disjointed in their nature.

- **Encourages greater co-production** and sharing of research. Researchers work more closely together, making them more aware of what other work is being undertaken. The organisation of work into themes means that research effort is more focused on critical issues.
- The **involvement of industrial partners** in the steering group encourages a high level of engagement with the industrial community and focuses research on application to bio-processing manufacturing issues, i.e. the application of research to 'real-world' problems.
- It provides a **greater level of continuity**. On an individual project funding basis there is a danger that each piece of research is seen only in its own context rather than as a strategic whole. A promising piece of research may not be explored to its full extent if funding cannot be secured, as a researcher may have to move onto other positions. It is also easier to gather willing industrial collaborators if they have some security about the likelihood of a continuing partnership.
- The IMRC model allows the adoption of **best practice exit strategy** to continue to exploit the value of IMRC research once current funding has ended. 'IMRC Phase 3' will aim to work further on the industrial application of IMRC techniques. This is evidence by the agreement with GSK to host two centres of excellence.
- Provides **globally leading research** that promotes the value of UK Plc and encourages leading multinational businesses to have a presence in the UK. The IMRC's work also helps to support the manufacturing sector, which has seen an erosion of traditional industries, to countries with lower cost bases.
- The IMRC **raises the profile** of the research being undertaken. The co-location of research builds a profile of the IMRC as an important location for bio-processing research. Industry will find it easier to engage with a single centre as opposed to many individually held research projects.
- The use of EngD and PhD's is an important route for **IMRC research to reach industrial partners**. It also provides the UK research community with excellent research opportunities.
- The IMRC model **energised companies to work together on common issues**, resulting in a cross-fertilisation of ideas, and a more rapid development of the industry as a whole. IMRC findings are made available to the whole of the industry.

**Impacts**

The case studies have identified three main ways in which working with the IMRC has impacted upon industry. Some research projects provide impacts in more than one of the impact areas.

| | Impact |
|---|---|
| Faster development process | Research helps to improve the process development of new drugs so that they can reach the market faster. This is important as drug patent expiry is timed from patent registration rather than from when the product is commercially viable. Therefore delays in product development cause reductions in product profitability. |
| Lower development costs | Research helps to reduce the resources required to develop a successful drug. This could be through using fewer human resources or identifying potential useful versions of the host material faster, reducing the effort spent on dead ends. |
| Reducing manufacturing costs | Research can be used to identify (using micro scale analysis) the most economically viable way of manufacturing an identified bio-pharmaceutical. Micro-scale analysis techniques allow researchers to mimic and predict the performance of large scale production and refining techniques – to identify those that are most economically advantageous (in terms of reduced production costs and reduced failure rates). This can assist bio-processing firms in establishing at an early stage of drug development, the likely manufacturing costs involved for commercial production. It can also assist firms in selecting the most appropriate purification process to reduce costs and failure rates. |

## Case Study 1: Instigating a Cultural Change in New Process Development - BTG (Formerly Protherics)

| Key Facts | |
|---|---|
| Time Period | Stage 1 project: 2005-2006 |
| IMRC Funding | £245k |
| Other Funding | In kind contributions including researchers time |
| Collaborator(s) | BTG (formerly Protherics Plc) |
| IMRC Research Theme | Theme 2 – Enhanced data acquisition |
| Research Output | As a result of four collaborative projects Protherics have delivered a cultural change in the way new products are developed. The IMRC projects have researched, developed and validated the use of ultra scale down (USD) methods. The development of two drug lines, CytoFab and CroFab, were assisted using this method. |
| Pathway to Economic Impact | **Via Collaborator(s) –** Protherics has used USD methodologies to achieve a reduction in development time of CytoFab and the resources it takes to deliver the development process. Drug production costs were lower in relation to CroFab. |
| Actual Economic Impact | **Impact on existing business** – The research benefitted the collaborating firm by:<br>• Reducing the time spent on CytoFab development by 50% – allowing the product to get to market quicker. To date this drug has received £36m in licensing fees.<br>• Reducing the cost of drug production by 10-20% |
| Potential Economic Impacts | An additional £160m could be generated from the licensing of CytoFab if the product is successful. Royalty fees would be applicable as well.<br>Production costs for CroFab are expected to be between 10-20% lower as a result of the USD methods adopted. |
| Sector Focus | Pharmaceuticals |

**Context**

The development of biopharmaceutical drugs is an expensive process with significant investment required in R&D for product lines, and no guarantee of financial returns. For example, research conducted by DiMasi estimates that the typical development costs for a bio-pharmaceutical product are over $1.2bn[1] (This average includes successful and unsuccessful products on a capitalised basis). Approximately two in ten of all drugs repay their investment.[2]

Biopharmaceutical companies are under pressure to develop products more quickly and to provide greater amounts of data to regulators to demonstrate the robustness of the manufacturing processes. Every day spent bringing a patented drug to market can cost the drug company millions of pounds in lost sales, as drug companies only have exclusivity for a period of 15 years (from initial patent registration), after which it is possible to legally make copycat versions of the drug for a fraction of the price. Therefore bio-pharmaceutical companies are under great pressure to fully exploit the available patented time for each successful drug.

UCL have developed the use of Ultra Scale Down (USD) techniques which allow the testing of potential mixtures of proteins in very small quantities (i.e. microlitres of material). This allows the fluid to be tested at a very early stage of development, for robustness and quality of outcomes along with a range of other variables often in multiple dimensions.

[1] The Cost of Biopharmaceutical R&D: Is Biotech Different?, DiMasi and Grabowski, Wiley InterScience, 2007.
[2] Pharmaceutical Industry Profile 2010, Pharmaceutical Research and Manufacturers of America (PhRMA)

In the immediate post-discovery stage of potential new biopharmaceuticals there are scarce amounts of bioprocess material available, which have to be used for testing and clinical trial purposes. Producing more of this material is expensive and time consuming. Therefore it is crucial to use existing materials as efficiently as possible. USD techniques use smaller quantities of the host material than traditional techniques. This allows a greater number of variations to be tested. The findings can then be scaled up to accurately predict the performance of larger quantities of the host material during the full-scale manufacturing process.

**IMRC Project**

Ultra Scale Down techniques which mimic precipitation and centrifugation processes have been developed and validated by the IMRC. Process development is based upon USD techniques which much more accurately predict process performance at a large scale. This means that processes can be accurately investigated at a small scale prior to being scaled up, and for the process to be optimised more effectively. Additionally researchers are able to work with a large number of candidates of macromolecules simultaneously.

The collaborator for this project, Protherics, used a process development programme at a small scale to map out the production parameters prior to licensing CytoFab, a new product for treating sepsis. The programme provided reliable data about the performance of the process at pilot and production stages without needing to invest in expensive plant time and materials. The data collected was inputted into process models allowing the research team to investigate various processing options offline, saving time and cost.

USD techniques developed by UCL were also used in the relation to another Protherics product CroFab, a drug used to treat snake bites. This allowed Protherics to redesign the purification process to optimise the manufacturing capability of the product.

**Analysis of Economic Impact**

This series of projects resulted in the following economic impacts:

- Reduction in development time and cost for CytoFab, which assisted Protherics in speeding up the development process, resulting in a significant licensing fee.
- Reduction in the production cost for CroFab
- Adoption of USD techniques within wider Protherics business – leading to application within the development of other drugs

**CytoFab**

The development of CytoFab was completed in 50% of the time that it would usually take using an alternative approach (development within one year rather than two year period). The development cost was also reduced significantly – the use of USD techniques resulted in a 50% reduction in the required man years required during the development stage (4-5 man years as opposed to 10 man years). Given that sales for a drug can be millions of dollars a year, shortening the development time means that the company could potential realise greater levels of sales and profits.

Protherics subsequently licensed CytoFab to AstraZeneca in a deal worth £195 million to Protherics (Source Datamonitor). So far Protherics have received £36m with the remainder available upon meeting key milestones. Protherics will also receive royalty payments worth 20 per cent of net sales. The severe sepsis market represents an unmet clinical need and a commercial opportunity that could be worth over $1bn annually.[3]

[3] PharmaDeals Research, Deal Insight. Retrived 17th February 2011.
http://files.pharmaventures.com/deal_insight_sample_protherics_and_azstrazeneca.pdf

CytoFab is currently undergoing Phase 2 clinical trials. Research estimates that the average cost for an investigational biopharmaceutical compound during the preclinical phase is $60m.[4] On average the preclinical phase lasts 52 months, meaning that the monthly expenditure during this period is approximately $1.15m. Applying this to the development process of CytoFab could suggest impact savings of $13.8m (12 months x $1.15m) from delivering the drug development process faster.

**CroFab**

The use of USD techniques in the purification of CroFab is estimated to have led to a 10-20% reduction in the production costs for this product. An additional benefit is the more robust procedure will deliver a lower failure rate from 5% to an anticipated 1%. This will drive overall development costs down even further as smaller quantities of bio-material will be required. Marketed product revenues from CroFab were £24.2m in 2009/10.[5]

**Wider Adoption of Techniques**

Protherics were so impressed with the results of the USD techniques that they have adopted the techniques in other parts of the business, to be used on the development of other drugs. This could potentially result in wider benefits to the company, as it will improve the chances of any further investment in drug development resulting in viable products, and therefore the profitability of the firm. The use of USD techniques helps Protherics demonstrate to regulators that they understand the production process. On a separate study Merck cited IMRC work during the regulatory approval process.

It is worth noting that Protherics was bought by BTG in 2008 in a share deal worth £218 million, and Protherics' annual R&D spend at that time was estimated at around £20 million (http://www.drugdiscoverynews.com/index.php?newsarticle=2428).

Also as a result of the studies Protherics have established a series of related EngD links which are proving crucial for the transfer of knowledge from IMRC research into the company. In return Protherics staff have been seconded to the IMRC, allowing the centre to improve skills of individual staff in several key areas.

**Wider Application to other Companies**

The findings of this study could be generalised and applied to many other drug development processes. This could mean that savings at least equivalent to those seen on this project could be realised on many other projects. For example the Pharmaceutical Research and Manufacturers of America (PhRMA) spent $47bn on R&D in 2008. This includes biotechnology and non-biotechnology R&D expenditure. 27% of this is spent on the prehuman / preclinical phase of drug development. Estimates suggest that PhRMA members spent $13.7bn on biotechnology R&D[6]. Assuming that a similar proportion of expenditure is spent on the prehuman / preclinical phase as with total pharmaceutical expenditure, around $3.7bn will be spent on biotechnological preclinical R&D. Applying UCL findings to even a small proportion of this expenditure could result in significant savings. For example if USD techniques were applied to 10% of preclinical expenditure and resulted in 10% savings, this would be equivalent to $37m of R&D expenditure.

**Consultations**

The following people were consulted and reviewed a draft of the case study:

- Professor Nigel Titchener- Hooker - UCL

[4] The Cost of Biopharmaceutical R&D: Is Biotech Different?, DiMasi and Grabowski, Wiley InterScience, 2007
[5] BTG Annual Report 2010.
[6] Biotechnology includes: biotechnology-derived therapeutic proteins, vaccines, cell or gene therapy and other biologics

## Case Study 2: Allogenic Cell Therapy - Onyvax Ltd

| Key Facts | |
|---|---|
| Time Period | 2004-2009 |
| IMRC Funding | £85k |
| Other Funding | In kind contributions of researchers time and cell lines |
| Collaborator(s) | Onyvax |
| IMRC Research Theme | Theme 1 – Micro-scale bioprocessing |
| Research Output | Successful correlation between the expression of cell integrity and cell surface markers with shear related engineering environment. A USD device was developed that predicted the process conditions which allow the processing of human cell lines without affecting their therapeutic properties. |
| Pathway to Economic Impact | **Via Intermediate Agency and Via Collaborators** The findings of the project were explored further in a £1.8m Technology Strategy Board project which set up a bioprocessing discovery platform for cells for therapy. |
| Actual Economic Impact | The project sped up the development process making it clear that a potential drug was not going to be successful. The realised economic impacts were minimal but wasted resources were minimised. |
| Potential Economic Impacts | **Impact on existing business** by improving the chances of developing a successful product |
| Sector Focus | Pharmaceuticals |

**Context**

Cancer vaccines are designed to stimulate or restore the body's immune system's ability to fight infections and diseases. There are two broad areas of cancer vaccine:

- **Preventive (or prophylactic) vaccines** which are designed to prevent cancer from developing in healthy people; and
- **Treatment (or therapeutic) vaccines** which are designed to treat an existing cancer by strengthening the body's natural defences against the cancer.

Onyvax were in the process of developing a therapeutic vaccine for the treatment of prostate cancer. There are an estimated 467,000 new cases of prostate cancer in each year in the US, Europe and the Pacific Rim.[7] In 2000, total medical expenditure for prostate cancer treatment in the US was $1.3bn[8]. During the development process Onyvax had found some technical problems that they did not have the required knowledge to solve. Contact was made with the IMRC to use the USD techniques and biomanufacturing expertise developed in the centre.

**IMRC Project**

After the initial meeting between the IMRC and Onyvax it was agreed that an EngD student would work with Onyvax to test the processes they had developed. The research would explore and quantify the level of stresses and strains that could be applied to the source biological material during the manufacturing process. The techniques also allowed the researchers to test different grades of materials and the potency of the products. By testing these dynamics, Onyvax and the IMRC research team were able to improve the manufacturing process of the drug's development.

[7] American Cancer Society (2003) and International Agency for Research on Cancer (WHO), GLOBOCAN 2000
[8] Prostate Cancer, Chan and Penson, Journal of Urology, Volume 177, Issue 6, Pages 2020-2029, June 2007

The techniques developed by the research permeated through many areas of the business. They were deployed by the business analytical group, which developed the regulatory affairs strategy, which in turn informed how the business took forward products to the pre-clinical stage. The improvements made in this procedure were vital because of the costs associated with the development process, with delays having significant cost implications.

The EngD student was working across many areas of the business developing different parts of the overall procedure with each. Due to the amount of work involved, a second EngD student from the IMRC was brought in to progress the collaborative work further. They focused on the filtration process during the manufacturing stage which aimed to reduce contamination during the manufacturing process. This work helped to make the product safer, improving the likelihood of a successful clinical trial.

The portfolio of work that the IMRC was developing would be engaged in between the second and third phases of the clinical trials process as manufacture of materials for Phase 3 of the trials began. Major benefits would also be realised after the clinical trials process was completed and the commercial manufacturing process was undertaken.

A £1.8m three year Technology Strategy Board (TSB) funded project was established in January 2008 as a result of the work undertaken by Onyvax. The award comprises £1.1m from the TSB with additional funding coming from consortia members including UCL, Nottingham Trent University and LGC (a science based service company). The project combined micro-scale process engineering technology with analytical and informatics techniques to predict and optimise cell line performance in large scale manufacturing processes.

**Failure of Funding**

In 2009, the cancer vaccine had reached Phase 2 clinical trials and was being tested in the form of a surrogate trial, as this was less expensive to run than a full scale clinical trial. The results of this trial were not deemed promising enough so the funding from investment groups was discontinued. As a result Onyvax became insolvent. Because of the investment from the TSB, Onyvax were encouraged to find industrial partners who might want to take on the remainder of the research programme. This led to ReNeuron being brought in as a rescue partner for some of the research. ReNeuron applied the outcomes of the research work with Onyvax to their own research relating to the use of stem cells in treatment for stroke victims.

**ReNeuron**

When ReNeuron came in as a rescue partner for Onyvax they were able to use the same techniques which had been applied to Onyvax cell lines to their own research.

ReNeuron are a company who specialise in stem cell research. They aim to develop novel stem cell therapies for areas of significant unmet or poorly met medical need. One such line of treatment related to patients left disabled by the effects of a stroke.

A stroke occurs when blood flow to, or in, the brain is blocked (ischaemic stroke) or a blood vessel in the brain ruptures (haemorrhagic stroke). This can cause damage to nerve cells in the brain and lead to a loss of bodily functions. Stroke is the largest cause of adult disability in the developed world. Over 150,000 people suffer a stroke each year in the UK. Around 80% of these strokes are ischaemic in nature.

ReNueron’s stem cell therapy (ReN001) seeks to treat patients who have suffered an ischaematic stroke and have been left disabled by it. This represents approximately 50% of stroke survivors.

The estimated annual health costs of caring for disabled stroke patients is thought to be in excess of £5 billion in the UK, with stroke victims occupying at least 25% of long term hospital beds. There are three treatment stages of stroke:

- Prevention – treatments to prevent a first or repeat strokes
- Treatment – immediately after the stroke, acute-phase treatments seek to dissolve the blood clot which has caused the infarct
- Post Stroke – Rehabilitation – the aim of the post stroke rehabilitation is to improve functional and cognitive recovery in the weeks and months after the event

There are a number of treatments which are available to treat patients in the acute phase. However, currently there are no treatments which focus on the providing therapy for patients who have a stable and fixed neurological deficit following a stroke. ReN001 focuses on this stage of treatment. ReN001 is a cell therapy product capable of treating all eligible patients.

**IMRC Project with ReNeuron**

ReNeuron work with IMRC began in 2009. ReNeuron had developed a potential cell line for the rehabilitation of stroke victims. The IMRC team were able to take the cell lines and using the Ultra Scale Down techniques they have developed, test them against a series of different parameters, such as centrifugation and shear levels. By being able to increase the amount of testing they could test for a range of parameters concurrently.

The USD process led to a much greater level of data being generated about ReNeuron cell lines, the conditions it worked under, tweaks made to improve it and boundaries beyond which it failed. By testing and refining these conditions the IMRC team were able to highlight the most promising cell lines and variations. This meant that a much broader range of cells could be considered than would have otherwise been possible.

Without the intervention of the USD techniques ReNeuron would test their cell lines for viability but would look to choose a cell line which allows them to maximise manufacturing output without considering cost implications unduly. The production of living cell lines is expensive so they know they need to have a compound that they can manufacture on a large enough scale to sell commercially.

ReNeuron's work on this particular cell line began around 10 years ago. In Dec 2010 the cell lines were submitted for the first phase of clinical trials. The clinical trials process could take another 4-5 years before the first commercial sales, if the product is deemed safe.

**Impacts - Onyvax**

As the funding for Onyvax was discontinued before the product had completed clinical trials, the collaboration failed to feed through to an increase in sales for Onyvax. However, the application of IMRC research had the effect of reducing the development time and cost for the early stage clinical trials as Onyvax were able to calculate with more certainty which variation of their cell line would be most efficacious. By improving the accuracy of the predictions Onyvax were able to reduce the quantity of biological material that was wasted along with reducing other development costs.

Steve Ward who worked for Onyvax during this project stated *'I can't stress how important UCL were in driving the development process'.*

**Impacts - ReNeuron**

The impact of IMRC's work with ReNeuron was to focus their work on the most promising cell lines. This allowed them to focus effort on the key areas sooner, reducing the chances of working on a cell line that later on proved to be unviable.

Without the assistance of the IMRC team ReNeuron would not be able to test so many variables at once. It was not only important that the process developed a large quantity of data about each of these variations but also that the IMRC team where able to interpret the data in a meaningful way.

If USD techniques enable ReNeuron to have a better chance of passing clinical trials then this could save the company many millions in wasted development costs. Although it is difficult to estimate the possible change in success rate (especially as the clinical trials have not yet been completed) there are obvious benefits of higher success rate.

If the clinical trials were deemed to be unsuccessful it is unlikely that the cell line would be resubmitted with a slight variation. The cost implications are likely to be too great.

**Consultations**

The following people were consulted and reviewed a draft of the case study:

- Professor Mike Hoare – UCL
- Dr Steve Ward – Formerly of Onyvax
- Randolph Corteling – ReNeuron

## Accelerated Determination of Optimal Process Sequences - Pfizer

| Key Facts | |
|---|---|
| Time Period | 2004 – 2008 |
| IMRC Funding | £205k |
| Other Funding | In kind contributions of cell lines and researchers time |
| Collaborator(s) | Pfizer |
| IMRC Research Theme | Theme 3 – Whole bioprocessing advances |
| Research Output | The project applied a new technique for analysing bioprocess development to identify the best conditions purification of a particular drug. IMRC ultra scale down modelling techniques then rapidly analysed this data to suggest optimised conditions. |
| Pathway to Economic Impact | **Via collaborators –** Analytical techniques gathered large quantities of data about which variations of proteins could be the most promising. |
| Actual Economic Impact | **Impact upon existing business** – the techniques used improved the purification process for this product<br>**Via collaborators** – License payments to date are $10m with a further $400m dependant on reaching key milestones |
| Potential Economic Impacts | Reduced manufacturing costs could lead to the cheaper launch of the drug and increased profits (or reduce losses if the product is not a success).<br>Licensing fees could reach up to $400m if the product is successfully developed |
| Sector Focus | Pharmaceuticals |

**Context**

Pfizer owned the development rights to ApoA-1 Milano, a variant on a naturally occurring protein which had potential to be used as a treatment for cardiovascular disease. ApoA-1 was found in approximately 45 individuals in a small village in northern Italy. Carriers of this variant appear to have reduced risk of cardiovascular disease. In multiple non-clinical trials ApoA-1 removed excess cholesterol from artery walls, stabilising and regressing atherosclerotic plaque. A phase I-II study in 36 patients demonstrated statistically significant reductions in coronary plaque volume by 4.2% in 6 weeks.[9]

**Project**

The project had two parts; the first to improve the process insight early in development, the second to use knowledge developed to achieve process gains. This project investigated the use of Surface Enhanced Laser Desorption Ionisation – Time of Flight – Mass Spectrometry (SELDI-TOF-MS), technology, as a tool for analytical bioprocess development. The technique can be used to determine the properties of proteins in complex mixtures, which can then be used to highlight promising conditions for the purification of a target protein. This approach improves upon traditional methods because of the ease of preparation and data collection to generate a large amount of quality data within a short timeframe.

Once the SELDI method was established the project focused on a USD method which enabled rapid optimisation of testing conditions using small volumes (20mL) of materials – drawing on the IMRC's prior research into USD technologies. This meant that Pfizer were able to identify an optimal solution faster than they would have been able to without the influence of USD techniques.

The outcome from this project was to verify that the research ideas developed by UCL (in particular USD techniques) could be successfully adapted to specific industrial problems.

[9] http://ir.themedicinescompany.com/phoenix.zhtml?c=122204&p=irol-newsArticle&ID=1369038&highlight

**Impact**

ApoA-1 has potential as a therapeutic treatment for cardiovascular disease. USD techniques developed by the IMRC were critical in the creation of the purification process for this product. The USD techniques meant that Pfizer were able to run fewer cell line tests with their pilot plant partners. Typically they might have to run 4 or 5 cell lines in a pilot plant test. The confidence they had in this process meant that they only needed to run a single process aimed at testing the safety of the optimal solution they developed with USD techniques. This helped to lower development costs.

Pfizer entered a worldwide licensing agreement for the drug with the Medicines Company in Dec 2009, who will be responsible for the continuing process development and clinical manufacturing. Clinical studies are expected to commence during 2011. Pfizer have received an upfront payment of $10m and will receive additional payments of up to $410m dependant on meeting clinical, regulatory and sales milestones. Pfizer will also receive single digit royalty payments on worldwide net sales of ApoA-1. Processing insights gained from USD techniques form an important part of the licensing package offered by Pfizer.

A wider impact of this project upon Pfizer was promoting the usage of USD techniques within Pfizer. The techniques have broad applicability which could be used on other candidate cell lines once they reach an appropriate stage of development.

**Consultations**

The following people were consulted and reviewed a draft of the case study:

- Dr Dan Bracewell – UCL
- Dr Sa Ho, Pfizer