FUTURE TARGETED HEALTHCARE MANUFACTURING HUB

ANNUAL REPORT

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Engineering and Physical Sciences Research Council

UCL

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Loughborough University

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WARWICK THE UNIVERSITY OF WARWICK

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FOREWORD

These past two years have been hugely exciting for the Hub. While the coronavirus situation presented many challenges across all aspects of the Hub's activities, it also led to many new opportunities for those able to make significant contributions to the Covid vaccine manufacturing efforts, while also leading to an exploration of new ways of working that may even have longer term benefits. The Hub's PDRA team has been able to continue working, although largely from home, and with reduced access to laboratories for on-site experimental work. In this, the Hub researchers have shown great resilience in working in this new and very different way, showing great agility in prioritizing their experimental work and bringing forward many of the modelling and simulation aspects. The EPSRC mid-term review was postponed until early 2021, and while the two-day online event meant the panel could not take lab tours, meet people face-to-face, or benefit from our infamous hospitality, it was nevertheless a resounding success. The panel and EPSRC went away suitably impressed by the strong international presence of the Hub, its extensive user engagement, strategically important research progress, as well as the overall buzz, vitality and diversity of our researcher community.

Covid lockdown led to a seismic shift towards online events, and the Hub team rose to the challenge by not only bringing the User Steering Committee and Advisory Board online, but also the Specialist Working Groups, and a new series of webinars and workshops, which overall have been very well attended, keeping the community together. Thus, these new ways of working have really helped to ensure the Hub continues to deliver on its promise.

Hopefully most things will get back to normal in 2021. The extensive planning undertaken for the next phase of research and engagement is now bearing its own fruit, and so overall all looks very positive for the remainder of the programme, laying a powerful foundation for the National future.

Dr Stuart West.
Chair, Hub
Advisory Board

FOREWORD: MEETING THE CHALLENGE

What a year! We live in a world challenged by the emergence of the Covid-19 pandemic and changed by our response to it.

The last year has emphatically demonstrated the importance of having world class medical, bioscience and bio-processing capability in the UK to respond to such a challenge.

The UK academic and industrial science base has risen well to it as shown by its collective response in novel vaccine development, in exploration of repurposing of established medicines, in development of new diagnostic capability and in preparation of routes to large scale protective antibody production.

In all of this the Hub and its network of Spokes and industry partners, the Department of Biochemical Engineering at UCL, and individuals from both, have played their part e.g. by contributing £200K for scale up manufacturing of Oxford's ChAdOx vaccine, working on optimisation of the freeze-dried formulation of the ChAdOx vector, contributing qPCR instruments and Tecan robots to the Milton Keynes testing centre, donating PPE to UCLH, and in many other individual expert contributions. It is a statement of the obvious perhaps but this contribution has been possible because of the deep relevant bio-processing expertise held here and because it is here, now, to respond to the challenge. It is vital that this capability is maintained, nurtured and grown so that it is there when other challenges come.

In the wake of all the disruption resulting from the pandemic it would be easy to forget that the past year has been critically important for the Hub as it approached the halfway point of its funding and faced a major mid-term review by EPSRC originally planned for June 2020 and rescheduled to February 2021. The exceptional outcome of the mid-term review reflects the excellent work of the hub, the excellence of preparation for the review and response to it while it was being held, the strength of the PDRA group and the high level of active engagement with the user community. Aside from the critical work in response to the pandemic, the Hub also continued in its "day job" leading to significant advances in personalised healthcare manufacturing, while also beginning to plan the future.

In May 2019 the Hub leadership team embarked on an ambitious, wide ranging and intensive review and planning process which looked critically at what had gone well, what lessons were to be learned from the first phase of Hub activity, to plan its second phase and shape itself for the future. It ran through 2019 and into March 2020. It was a highly interactive and creative process involving detailed consultation with the Specialist Working Groups, the User Community, external

experts and critical friends, representatives from the research councils and key staff from the Hub and its Spokes and the university. It looked at achievements in Grand Challenge 1 and 2, at the work in the Hub and Spokes on Decisional Tools, Regulation and Reimbursement, Cell Free Synthesis, Formulation and CAR T-cell manufacture, driving the policy agenda and Outreach activities.

It then refined ambitious proposals for Phase II of the Hub with particular focus on alignment of Grand Challenge research to evolving user need, new modalities such as viral vectors and complex engineered proteins, a greater focus on analytics, meeting digital challenges in bio-processing, the establishment of new spokes and developing new ways of cross disciplinary working, influencing the national policy agenda and increasing links to other centres e.g. CMAC, Vax-Hub and Future Vaccine Manufacturing Hub (FVMH) and a framework to support wider research and training activity. The Phase II plans were endorsed by the Hub User Steering Committee and Advisory Board. Then UKRI-EPSRC gave permission to use the original grant income in full and Phase II began in July 2020.

Whilst recent events have shown us that we must be ready to meet new healthcare challenges they will not all be from emerging infectious disease. Revolutionary and transformational new approaches to the treatment, management and cure of disease are being invented. Many utilise Advanced Biological Medicines (ABMs) including cellular and gene therapies, complex biologics, novel vaccines and nanomedicines. These are often extremely difficult to make, and require challenging supply chains to deliver product to patient and complex supporting analytical and diagnostic methodologies. Consequently, they are expensive to develop and deploy.

So far, most ABMs have been targeted at indications with small patient populations (e.g. for spinal muscular atrophy, retinal dystrophy, acute lymphoblastic lymphoma) but the approaches offer great potential for treatment of conditions affecting much larger numbers of people including many cancers, Alzheimer's, neurological, auto-immune and infectious diseases, and even chronic pain. One of the great challenges for the future is how might these medicines be made available to large patient populations affordably?

With the right national strategic vision to coordinate, fund and support world class academic, industrial and collaborative research (TRL level ~1-4) this challenge can be met. Institutions such as UCL and centres such as the FTHM hub can play a key part in transforming the development and manufacture of Advanced Biological Medicines (ABMs) in the UK and help ensure they can be brought to large patient populations affordably, whilst maintaining fair economic return to innovators.

We have seen how important it is to have established and leading bioscience capability in the UK to meet the challenge of the now. Wise investment in research and training can ensure we will be able to meet the challenges of the future. The FTHM Hub has the skills in multiple disciplines, the bio-processing insights and is developing the technologies and training the people to help meet these future challenges.

Dr Mark Carver.
Chair, Hub
User Steering
Committee

EXECUTIVE SUMMARY

The past two years have been packed with Hub progress and events. The past year saw the Hub transition from Phase I of the Hub into planning and starting Phase II in July 2020 following endorsements from the Hub User Steering Committee, Hub Advisory Board and UKRI-EPSRC. In addition, the major mid-term review of the Hub took place in February 2021 after being postponed from summer 2020. The 2-day showcase to the mid-term review panel showed the Hub and Spokes at their very best with all members utterly committed to the vision and the collegiate nature of both the user community and the academic team clearly demonstrated. The panel acknowledged several areas of good practice and highlighted the “world-leading research undertaken in the Hub”, “high level of industry engagement”, “enthusiasm and understanding that the PDRAs demonstrated”, “positive research culture”, “Specialist Working Groups (SWGs) demonstrate very good practice” and that “the Hub successfully demonstrated that it acts as a national focus for targeted healthcare research”. As a result, the Hub funding will continue as planned for Phase II of the Hub. This Annual Report summarises the key achievements of Phase I of the Hub.

The Hub research programme has been co-developed with input from all key stakeholders including industry users, regulatory bodies and academics, through a series of structured engagement processes. This means that the work we do, the insights we gain and the training we provide are timely, appropriate and strategically relevant. Our focus remains to develop and examine technological solutions for the rapid realisation of targeted healthcare, aiding the transition from academic studies, through to practical implementation. We have conducted: pioneering studies in the utility of cell-free synthesis for just-in-time manufacture of valuable therapeutics; engineering characterization of novel bioreactor geometries for effective process development and delivery of cell and gene therapy products; as well as advanced software tools to help in decision-making for the industry.

The benefits of the Hub are being felt by many groups, well-beyond the consortium who have been actively advising and working with us to develop a strategic agenda with global reach. Our innovations are all designed to progress significantly, the reality of targeted healthcare. The vision we are pursuing is that targeted interventions will provide a step change for many patients in terms of widened access to new treatments. We have started to think about an expanded range of targets, including treatments for cancers and the re-programming of degenerative disorders such as dementia. The

processing challenges these represent are huge but the products offer radical new opportunities for the industry, and of course formidable challenges too. Our work and the consistent integrated approach we adopt in the Hub offers the very real possibility of rapid and effective development for new clinical medicines and promises a new horizon for the sector. The Hub represents a radical departure from existing research activities and a powerful mechanism for effecting change in a fast-moving industry. The past two years have demonstrated the power of the Hub and Spoke approach and the ways in which this can deliver impact and advancement.

Over the past two years, significant progress has been made in our scientific understanding and in our technology innovations. The metrics paint a picture of strong development of the Hub and the constituent Spokes with multiple modes of interaction and impact measured by joint publications, meetings and new alliances. By working closely with our user community to deliver user feasibility studies, designed to test our methods, and to gauge the utility of new approaches in an industrial setting, we have been able to amplify the insights gained in the academic setting. Over 20 feasibility studies are now complete or in progress with a strong pipeline under consideration for the next period. The enthusiasm for this mode of work is testament to the relevance of the studies and to the way in which they engage the researchers with a sponsor problem. Results arising have actively informed new research directions and contributed to furthering our understanding of the evolving manufacturing and regulatory landscape. This close integration with industry means that our progress makes a defined impact on manufacturing practice. Since launch, we have grown the user base by approximately a third and also brought in charities such as Cancer Research UK, and engaged with the newly formed Medicines Manufacturing Innovation Centre (MMIC).

In the Grand Challenge 1 area of techno-economic optimization and drug development business modelling, we now have a suite of software tools built that integrate cost of goods (COG), cost of development, uncertainty and optimization algorithms for new modalities and processes. These have been applied widely and include advanced cost of goods analysis which has highlighted the performance targets for cell-free synthesis to achieve equivalent COG/g compared to traditional CHO processes for ADCs. Detailed supply chain economics analysis has also enabled us to identify the key COG drivers for CAR T-cell therapies and the risk-reward trade-offs between centralised and bedside manufacture. In a move that heralds the next phase of the Hub research programme we have started to investigate the consequences of switching to scalable processes for viral vectors on both overall cost of development and lifecycle profitability. Working with healthcare specialists and with relevant regulatory agencies has been a particular hallmark of the past year where we have, for example, analysed how CARTs and

other high-cost therapies affect NHS England's ability to resource other health services. Such insights are informing broader studies designed for example to quantify the intended and unintended consequences to key stakeholders: manufacturers, clinicians, patients and regulators.

Engagement with clinicians has provided us the opportunity to explore the potential of data mining to help clinicians make personalised decisions on aspects such as follow-up timelines based on genomic, clinical and demographic data. A significant amount of Hub work has been devoted to aspects of clinical trials decision making where we have developed a stochastic optimisation model that generates solutions consistently better than heuristics used in industry and other state-of-the-art algorithms. Confidence in our capacity to understand the trade-offs in manufacture has enabled us to conduct a series of UK case-studies to explore particular and pertinent questions, including the bottlenecks, challenges and opportunities of the current supply-chain network, with respect to limited capacity and sensitive product nature.

Research under the second Grand Challenge, focused on sustainable manufacturing for future targeted medicines, has established new technologies with the potential for radical re-design of manufacture. Novel bioprocesses, analytics and control algorithms have been created that enable robust, safe and cost-effective manufacturing and formulation of stratified protein and personalised cell therapies. Together these provide the flexibility and speed to produce medicines for small patient populations or individuals in response to clinical diagnostic data. We have been able to demonstrate scalable cell-free synthesis with model proteins using in-house protocols and, crucially that the formation of product-related impurities can be mitigated by altering the synthesis conditions. Our pioneering studies of protein behaviours in complex co-formulations have advanced to the point where we can analyse co-formulations kinetically and this has allowed us to characterise the key mechanisms at play. In tandem new biophysical analysis methods have been developed that are able to monitor proteins, and their degradation, in complex co-formulations, leading to improved stability of proteins to aggregation and fragmentation. Parallel studies have employed Neural Networks to predict formulation stability. A particularly exciting discovery has been the ability of micro-glassification methods for longer-term storage and stability of biologics.

In research studies focused on the manufacture and analytics for autologous cell therapies we have been able to demonstrate that growth of T-cell and CAR-T production in stirred-tank bioreactors is consistently better than that in static culture, with equivalent cell quality. We have gone on to show that a CAR-T can be cultured in both the ambr15 and ambr250 platforms, with specific power input as an effective parameter for scaling between both systems. This

work has been combined with a series of inter-related studies to develop effective control strategies, and the application of statistical cluster analysis, to provide an objective assessment of the cell quality response to process developments. Most recently, analysis using industrial and experimental measurements have demonstrated that the results obtained using simulated data are transferrable to real processes.

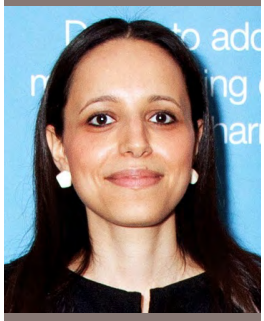
A particular feature of the Hub's work in Phase I has been the benefits of collaborative studies with a range of roundtable discussions organised at the User Steering Committee events and Specialist Working Group meetings (Decisional Tools, Regulation and Reimbursement, Cell-free synthesis, Formulation, T-cell manufacture) to help with this work. Specific user engagement has been instrumental in fostering valuable and significant collaborations including with the BioIndustry Association Manufacturing Advisory Committee (BIA MAC), where a joint feasibility study resulted in a pan-UK business case from the MMIP on "A UK Strategy for the Manufacture of GMP Viral Vectors" presented to BIA, UKRI and government. In a similar vein by working with the MHRA Innovation team we have been able to identify key regulatory challenges associated with stratified protein co-formulation approaches.

The range of industry studies has grown in each year of the Hub and we now are engaged with a comprehensive set of users where inputs range from critical insights on the cell-free synthesis process for biopharmaceuticals (mAbs and ADCs), through to helping develop design correlations to feed into the process economics models, and joint case studies examining the efficiency of current and novel supply chain structures for CAR T-cell therapies. Proof-of-concept studies to assess new manufacturing technologies and control algorithms have been conducted as an integral part of our drive to assess the relevance, and ease of adoption, of radically new process strategies. Integral to many of our studies has been the use of industrial materials, especially valuable so that we are working at relevant product/impurity concentrations and compositions. Staff secondment has enabled us to secure the technical, in-depth knowledge needed to broaden the scope of method for manufacture.

Over the past months we have been approached to broadcast our work through a range of fora including World Congresses, company-specific user events and technology showcases. Our close working with the regulatory agencies has enabled us to understand better new regulatory pathways to help innovation both in general and in the targeted/advanced therapies areas. We have noted significant differences between Europe and the United States (e.g. data needed for accessing facilitating pathways and marketing applications reviewing times), which will inform manufacturing models going forward.

Such close co-operation with our varied user base has given us unparalleled access, and ensures that our studies remain focused and industrially relevant. Scientific success has been matched by impressive progress, both in the development of the Hub as a national focus, and in the training and experience we are providing for our PDRAs and the associated doctoral students. The growth of the Hub, and the continuing breadth of that, demonstrates the relevance and the quality of what we deliver for the sector. The success of our researchers in publicity, conference and career advancement all point to the effectiveness of the EPSRC Hub mechanism, based around a focused and managed cohort, to deliver for the UK.

Professor Nigel Titchener-Hooker
Director of Strategy



Professor Suzanne Farid
Hub Co-Director

Professor Paul Dalby
Hub Co-Director

THE HUB IN NUMBERS

December 2020

28
Academic Researchers
Across 6 Leading Universities

44
Partnering Companies
& Organisations

114
Aligned PhDs
/EngDs

57
Meetings, Workshops &
Networking Events

73
Conference
Presentations

128
Publications

28
User Feasibility Studies

£18.5m
Leveraged Funding

THE HUB VISION

Mission

By 2025 targeted biological medicines will transform the precision of healthcare prescription, improve patient care and quality of life. The current “one-size-fits-all” approach to drug development is being challenged by the growing ability to create stratified and personalised medicines targeted to specific sub-populations and even individuals. Without significant manufacturing and supply innovations, the promise of targeted healthcare will remain inaccessible for many. The impact on health and well-being is profound. The Hub mission is to act as a **National Hub and Spoke collaboration to take the UK forward to a world-leading position for manufacture in the targeted healthcare sector** (Figure 1).

Vision

Our vision is 3-fold:

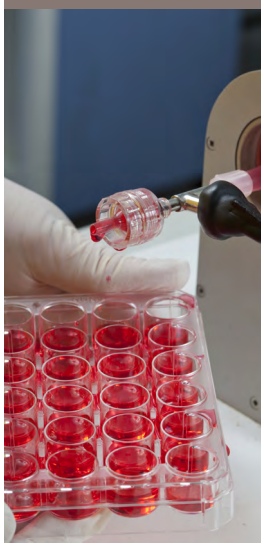
i. **To be the first globally recognized consortium** for the creation, delivery and dissemination of innovative manufacturing research, underpinning cost-effective, robust manufacture, supply and delivery of targeted biotherapeutics;

ii. **To provide the manufacturing infrastructure and capabilities** needed to enable UK manufacturers to exploit advances in precision medicine, through new technologies, skilled personnel, IP and spin-outs;

iii. **To enhance UK competitiveness** in this new era with a programme of Grand Challenges that create and combine decisional tools and manufacturing innovations.

Capacity to Deliver Vision

We have assembled a **Hub and Spoke team** with an unrivalled track record of delivery to drive forward the vision. The **Hub** is hosted in UCL Biochemical Engineering with leading academics with expertise in protein and cell therapy biomanufacturing, decisional tools, data mining, analytics, microfluidics. Wider host institution partners bring in expertise across UCL in health economics, regulation and public policy as well as extensive links with hospitals and patients. The **Research Spokes** are experts from the leading UK university groups that provide complementary expertise in formulation for drug delivery (Nottingham), cell therapy modelling (Loughborough), operational

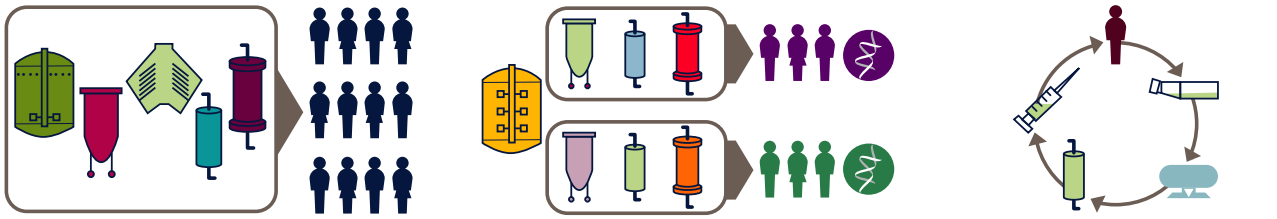


research (Warwick), supply chain optimization (Imperial), and process control (Manchester). Thus, the Hub and Spoke team have the capacity to deliver the timely vision by linking biomanufacturing strategies to the broader consequences on all these fronts. **We have a platform of activities** to network academics, industrial users, regulators and clinicians to deliver outreach and impact broadly. Consequently, the Hub is driving forward the national research and innovation agenda in this sector and engaging with the entire value chain, including the relevant Catapult Translational Spokes (CPI, CGTC) and industry, to ensure acceleration of impact and benefit to society and to the UK economy. The vision fits closely the ambitions of the Hub and Spoke **institutional strategies** related to improving "Global Health" by creating tools to enable targeted healthcare.

Vision Review and Refresh

The Hub Management Group set up **a regular cycle of consultations** with industry users, national agencies, regulatory authorities, health technology assessors, and independent external experts. More specifically, the vision was reviewed and refreshed in response to the changing landscape via the User Steering Committee (2 per year), Advisory Board (2 per year), five Specialist Working Groups (each running twice a year) and a special Hub Phase II Planning workshop with senior executives from the user community.

Figure 1: Hub vision for targeted medicines (stratified and personalised) with Hub partners



Moving from "one-size-fits-all" to "targeted" medicines… How can stratified biologics and personalised cell therapies achieve success in manufacturing and business?

Director Prof Nigel Titchner-Hooker **Grant** £10m, 2017 – 2023

Co-Directors Profs Suzy Farid and Paul Dalby

Hub UCL

Spokes Imperial College London; Loughborough University; The University of Manchester; University of Nottingham; WARWICK THE UNIVERSITY OF WARWICK; Engineering and Physical Sciences Research Council

User Steering Committee

Companies

3M; Adaptimmune; aglaris Ltd; Albumedix; applikon Part of Getinge; AstraZeneca; Autolus; BIA separations; BioLogicBLLC; biopharm; deltaDOT; FUJIFILM Diosynth biotechnologies; gsk; IPSEN Innovation for patient care; KCT Kuopio Center for Gene and Cell Therapy; kymab A SANOFI COMPANY; Lilly; Lonza; Orchard therapeutics; Oxford Biomedica; PALL; PERCEPTIVE ENGINEERING LTD; 康龙化成 PHARMARON; PURIDIFY; Purolite Life Sciences; ReNeuron; SARTORIUS; SSCBIO LTD; SUTRO BIOPHARMA; tillingbourne consulting; TrakCel; UNIVERCELLS; West; WYATT TECHNOLOGY

Industry/Govt Associations, Charities

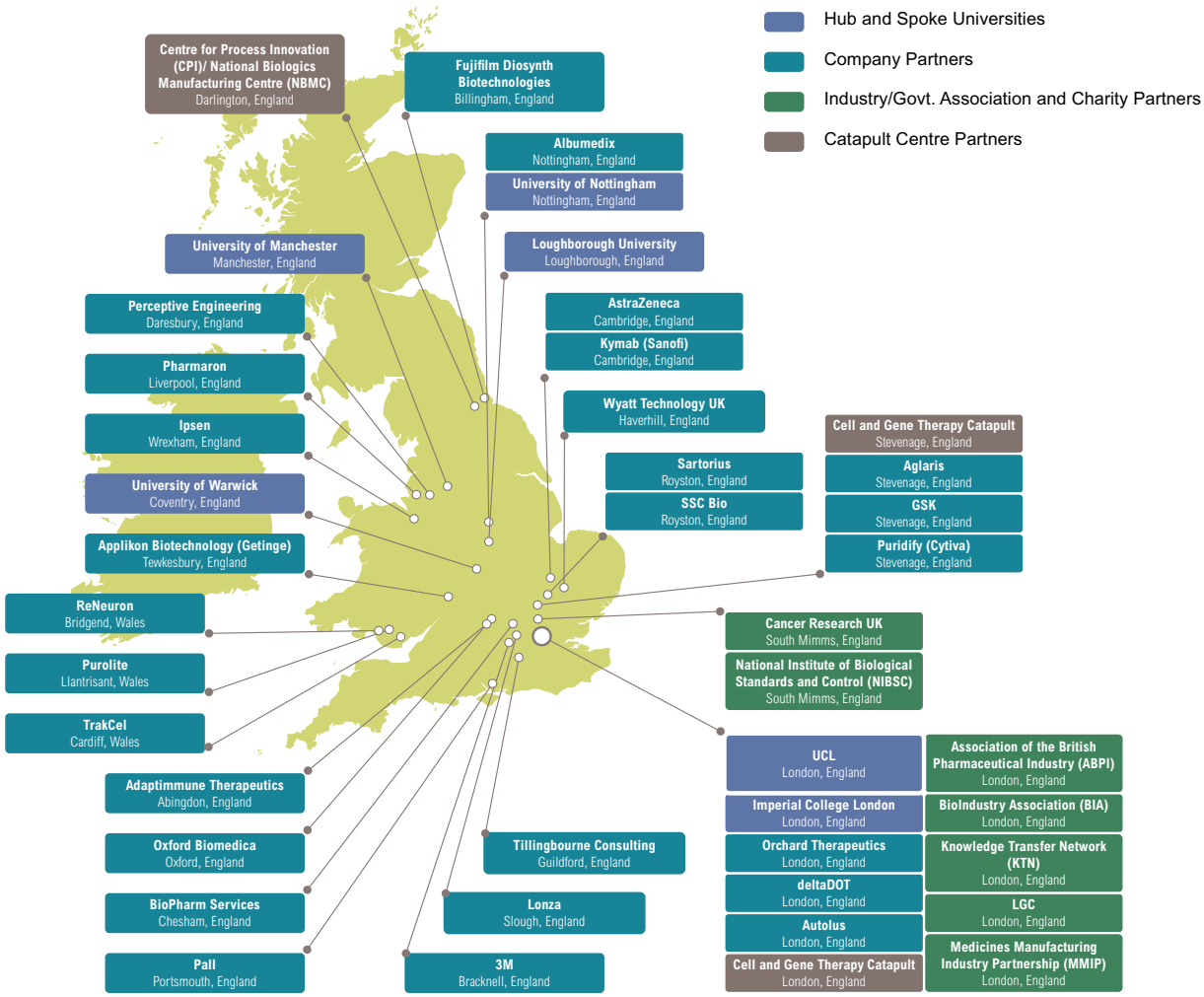
abpi; BIA; CANCER RESEARCH UK; ktn; LGC; MMIP; NIBSC

Translational Spokes

CATAPULT Cell and Gene Therapy; cpi

THE HUB LOCATIONS

FTHM Hub locations within UK



FTHM Hub global locations

HUB RESEARCH PROGRAMME

User-Driven Research Enabled by Hub & Spoke Interactions

The Hub's manufacturing research in Phase I has met the key deliverables within the two Grand Challenges (GCs):

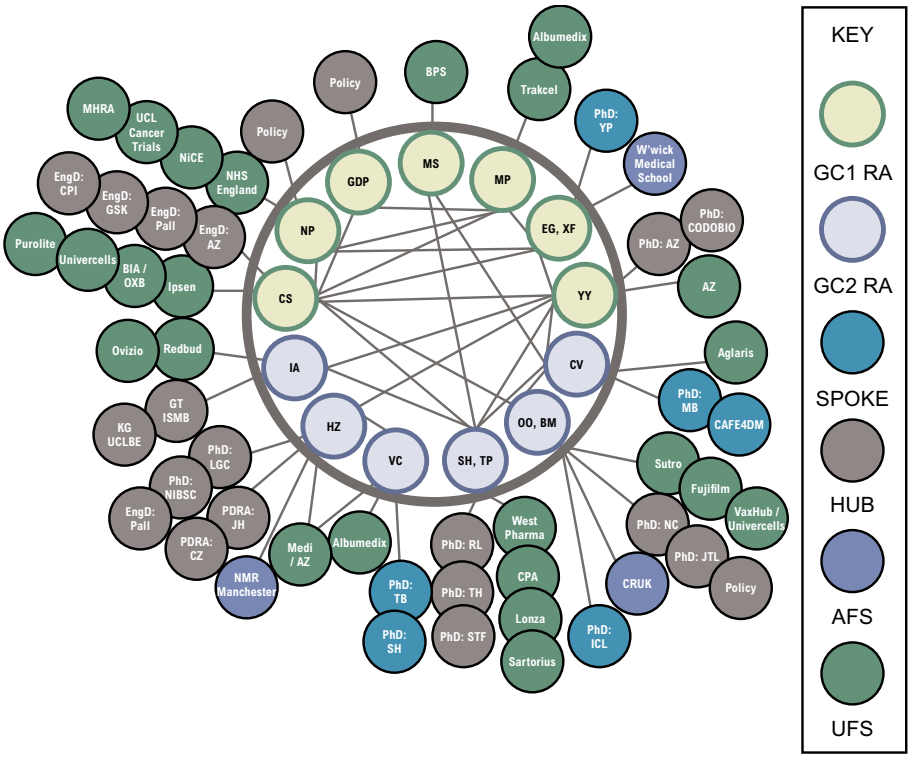
- **Grand Challenge 1 (GC1): Transforming supply chain management and economics for targeted medicines** investigated the business potential of game-changing technologies for commercial feasibility, regulatory consequences and affordability for healthcare systems;
- **Grand Challenge 2 (GC2): Sustainable manufacturing for future targeted medicines** established new technologies with the potential for radical re-design of manufacture.

The Hub Grand Challenges, with their research themes and interactions, are summarised in Figure 2.

Figure 2: Grand Challenge research themes and interactions (Hub Phase I: Jan 2017 – July 2020)

Grand Challenge Research: 65% of effort has been directed towards these two user-driven Grand Challenges at TRL2-4 and significant leverage has been exerted through interactions between the Grand Challenges. For example, GC1 has highlighted cost drivers and performance targets for novel manufacturing technologies that have helped prioritise experimentation in GC2 on cell-free synthesis and CAR-T cells and led to establishing novel technologies capable of achieving these quantified targets. Insights from such Hub interactions have helped to ascertain the most promising manufacturing innovations and provided the capacity to "future-proof" supply chains for targeted medicines. The Hub has enabled an integration of disciplines to a level that could not be delivered by separate projects, as further highlighted by the RA-centric connectivity diagram (Figure 3).

Figure 3: RA-centric view of project connectivity with the associated feasibility studies and aligned doctoral projects across the Hub and Spoke universities. RA = Research Associate, AFS = Academic Feasibility Study, UFS = User Feasibility Study



Platform Research and Impact: 35% of the Hub effort has been directed to Platform, Operational, and Pathways to Impact activities, with feasibility studies, at a network of academic (TRL2), industry and Catapult collaborators (TRL3-6), and the introduction of Policy briefings through the new appointment of a Policy researcher.

Integration of these approaches has provided an integrated enterprise, manufacturing and policy-setting perspective where the opportunity is to achieve radical innovation that greatly exceeds the sum of the isolated research areas and where the linkage of research and knowledge transfer enables a step change in the industry. This has ensured that we maximise the impact of EPSRC investment over the Hub lifetime and create sustainability, and has helped the sector to respond effectively to the shifting innovation landscape, particularly around Advanced Therapy Medicinal Products, and recombinant protein-based vaccines for COVID-19.

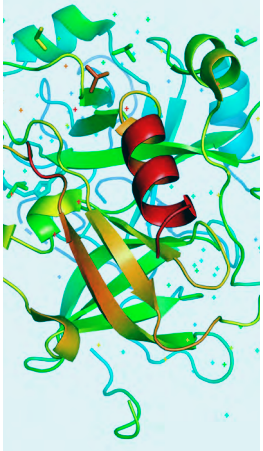
Grand Challenges: Phase I Notable Achievements

Exceptional progress in these Grand Challenges has delivered notable achievements facilitated by significant stakeholder engagement, summarized below. Appendix 1 provides details of the eight themes within the GCs.

GC1: Transforming Supply Chain Management and Economics for Targeted Medicines

Novel manufacturing- and enterprise-level computational tools have been created to determine the technical, regulatory and supply chain innovation required for commercial feasibility of targeted medicines, whilst ensuring affordability. The tools span decision-making across process development, clinical manufacturing and market supply for stratified protein and personalised cell/gene therapy medicines. Achievements in the GC1 research themes include:

- **Cell-free synthesis (CFS) economics:** Case studies highlighted cost of goods differences and innovation required for CFS compared to traditional processes for antibody-drug conjugates (Stamatis & Farid, 2020, Biotechnology Journal).
- **CAR T-cell process and supply chain economics:** Decisional tools identified the key cost of goods (COG) drivers and the risk-reward trade-offs between centralised versus bedside manufacture (Pereira Chilima *et al.,submitted*).
- **Drug development cost benchmarks:** Established process development and manufacturing cost benchmarks for different attrition rates and their contribution to R&D costs for proteins and cell therapies (Farid, Stamatis, *et al.*, 2020, mAbs).
- **CAR T-cell supply chain optimisation:** Existing supply chains have been characterized and likely future supply chain workflows



have been proposed (Papathanasiou *et al.*, 2020, Nature Cancer Gene Therapy).

- **Clinical trial scheduling under uncertainty**: Developed a stochastic optimisation model that generates solutions consistently better than industry heuristics and other algorithms (Gökalp & Branke, 2020, Computers & Chemical Engineering).
- **Regulation:** Accelerated pathways for ATMPs in EU and US mapped out including post-marketing requirements and the unintended consequences on key stakeholders (De Grandis *et al*, 2018, Risk and Regulation; De Grandis et al., submitted).
- **Reimbursement:** NICE's approach to appraising CAR T-cell therapies (Yescarta® and Kymriah®) mapped out and analysed for its longer-term feasibility and budget impact (Patel *et al*., 2020, Health Policy and Technology).
- **Data analytics:** Data mining tools have been developed for biomarker stratification to help clinicians make personalised decisions (Yang e*t al., submitted*) and for protein aggregation prediction (Zhang *et al., submitted)*.

GC2: Sustainable Manufacturing for Future Targeted Medicines:

New technologies have been established with the potential for radical re-design of manufacture. Novel bioprocesses, analytics and control algorithms have been created that enable robust, safe and cost-effective manufacturing and formulation of stratified protein and personalised cell therapies. Together these provide the flexibility and speed to produce medicines for small patient populations or individuals in response to clinical diagnostic data. Achievements in the GC2 research themes:

- **Co-formulation:** Multiple case studies have established the impacts of protein co-formulation. Established core techniques as a basis for future digital formulation capability (Zhang & Dalby, 2020, Scientific Reports).
- **Nanoencapsulation:** Scalable nanoparticle manufacturing to encapsulate co-formulated proteins and fluorophores, then deliver to cells (Al-Natour *et al.*, 2020, ACS Macro Letters; Martins et al., 2020, Reaction Chemistry & Engineering).
- **Analytics:** New instrument developed to monitor the degradation of proteins in mixtures. A second highly sensitive viral lasing technique also developed (Hales *et al.*, 2019, Nature Communications).
- **Cell-free synthesis:** Scalable in-house processes for protein and virus-like particle synthesis. Hub SWG consultation defined

objectives for Phase II, and roadmap for CFS strategy (Melinek *et al*., 2020, BioProcess International).

- **CAR T-cell manufacturing and process intensification:** 1st successful demonstration of CAR-T cell manufacturing in stirred-tank reactors. Intensified to reduce process time through a novel process control strategy. Demonstrated equivalent CAR-T yield with 45% reduction in process time (Costariol *et al*., 2020, Biotechnology Journal).
- **CAR T-cell predictive models:** Optimal supply of primary nutrient and medium volume exchange for cell culture can be predicted by model (Thomas *et al*., 2020, Cytotherapy).
- **T-cell analytics:** Digital Holography Microscopy provides rapid analytics to discern activated from non-activated T-cells. Microfluidic devices for personalised health manufacturing (Marques *et al*., 2020, Journal of Chemical Technology & Biotechnology).
- **Adaptive control algorithms developed:** Benchmark simulator designed to test new control techniques (Duran-Villalobos *et al*., 2020, Computers & Chemical Engineering).

Stakeholder Engagement Highlights

Several roundtable discussions were organized to steer Hub research at the User Steering Committee and Specialist Working Group meetings. Highlights of specific user engagement leading to significant collaboration include:

- **Sutro Biopharma:** Provided on-site cell-free synthesis (CFS) training of Hub Researcher in their San Francisco facility and CFS materials to UCL. Offered critical insights on the CFS process that fed into the process economics models at UCL and data mining at Manchester.
- **Autolus:** Interviews helped to enhance our understanding on the manufacture, supply chain and regulation of autologous therapies and fed into GC1 and GC2 at UCL and Imperial.
- **BioIndustry Association Manufacturing Advisory Committee (BIA MAC):** Joint feasibility study outputs from UCL and BIA MAC on the economic risks of not considering scalable processes early on in development fed into a pan-UK business case from the MMIP on “A UK Strategy for the Manufacture of GMP Viral Vectors”.
- **AstraZeneca:** Supplied mAbs and bispecifics for co-formulation studies at UCL. Evaluated pH sensing nanoparticles to screen for pH shock during viral inactivation in mAb production with Nottingham.

- Further examples of completed User Feasibility Studies include: **Albumedix** and Nottingham, **Ipsen** and UCL, **West Pharma** and UCL, **Aglaris** and Manchester, **Fujifilm Diosynth Biotechnologies** and UCL, **TrakCel** and Imperial.
- **Future plans** include further annual calls for User Feasibility Studies to apply Hub technologies to user challenges.

Theme Relationships

The Hub is uniquely positioned and structured to deliver its ambitious and innovative research programme. An example of the specific theme interactions across GC1 and GC2, along with input from the Specialist Working Groups (SWGs), to deliver innovative decisional tools for personalised cell therapies is summarized in Figure 4.

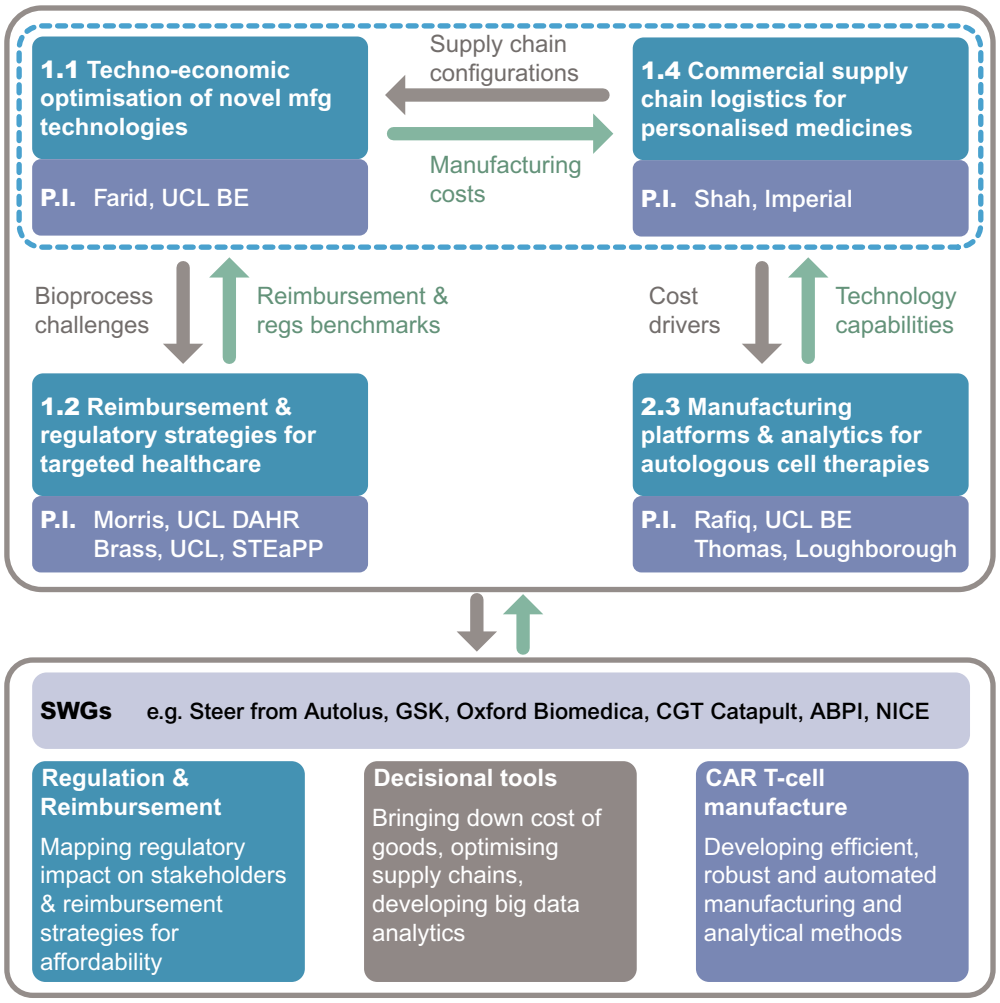
This highlights how four research themes worked together across disciplines of techno-economic optimization, supply chain logistics, reimbursement, regulation, and experimental work on manufacturing platforms. More specifically:

- **GC1.2 (UCL DAHR, UCL STEaPP) with GC1.1 (UCL BE) and GC1.4 (Imperial)**- Reimbursement benchmarks and regulatory pathways for ATMPs from GC 1.2 integrate into decisional tools in GC1.1 and supply chain models in GC1.4. Knowledge of bioprocess challenges for ATMPs guide research in GC1.2.
- **GC1.1 (UCL BE) with GC1.4 (Imperial)** - Typical cost and time for manufacturing and development activities from GC1.1 feed into GC1.4 for supply chain models. Current and future supply chain configurations from GC1.4 feed into GC1.1 techno-economic optimisation.
- **GC1.1 (UCL BE) and GC1.4 (Imperial) with GC2.3 (UCL BE, Loughborough)** - GC1.1 and GC1.4 highlight cost and supply chain drivers for novel manufacturing technologies that help prioritise experimentation in GC2.3. Experimental outputs from GC2.3 indicate current technology capabilities that feed into GC1.1 and GC1.4 tools.

The integration across the themes has been complemented further by input and steer from our SWG members from the three SWGs related to personalised cell therapy research in Phase I (Regulation & Reimbursement, Decisional Tools, CAR T-cell Manufacture), providing input from industry users (e.g. Autolus, GSK, Oxford Biomedica), CGT Catapult through to NICE, as well as clinical partners.

This set of relationships ensured that the research outcomes maximise impact and utility.

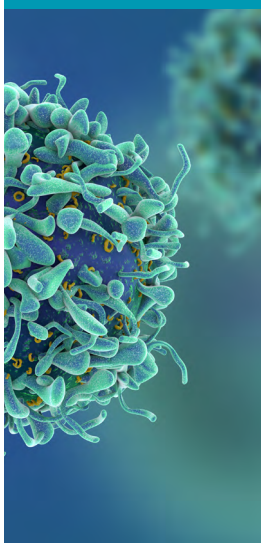
Figure 4: Hub research theme integration to deliver innovative decisional tools for personalised cell therapies. SWGs = Specialist Working Groups.



Academic Engagement Beyond the Hub

Academic feasibility studies

These establish collaborations with the wider academic community, and enable a strategic evaluation of emerging technologies that have the potential to address the key manufacturing research challenges of the Hub. The call for the first round of Academic Feasibility Studies went out in June 2019, and was open to any academics within the Hub and Spoke Institutes. Proposals were requested to test or demonstrate the potential of new approaches, tools, technologies, analytics, or data analysis, or that broadened the impact of current work into new areas. They could be used to bridge PhD students who had just submitted, to capitalise on their recent work, or to provide an extension / buy-out time of existing



PDRAs. This would enable secondments of PDRAs into/out of the Hub, to bring/learn new techniques. Studies were required to fit the remit and vision of the Hub, with some additional strategic areas also identified through round-table discussions with the User Steering Committee. Four academic feasibility studies at Manchester, UCL and Warwick, supported an existing RA, two new PDRAs and one recent PhD student, to carry out feasibility studies in the areas of NMR for bioprocess analysis, complex data analysis for personalised therapeutic target identification, cost-effectiveness analysis for targeted healthcare and cancer trials data evaluation (Table 1). A second call is planned for Autumn 2021.

Table 1: Academic Feasibility Studies supported in Phase I of the Hub

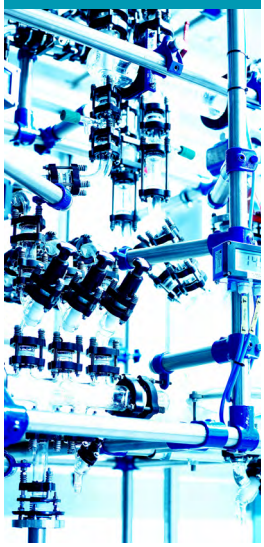
Partner University & Department	Topic
University of Manchester Department of Chemistry	Site-specific F-19 labelling of amino acids in proteins during cell-free synthesis, for NMR analysis of protein folding, assembly and aggregation
University of Warwick Warwick Medical School	Development of case-studies to demonstrate the impact of NICE cost-effectiveness assessment on fair pricing for targeted medicines
UCL Biosciences Cell & Developmental Biology	Identification of novel universal therapeutic targets for treating multiple types of breast cancer
UCL Cancer Trials Centre University College London	Cancer trials data evaluation

International collaborations

The Hub has continued to grow its international exposure and visibility through a range of collaborative and dissemination activities. In addition to presentations at international conferences (>70), and the publication of >120 papers in leading journals (see Publications), international collaborations have been integral to the Hub:

a) Collaborations / secondments on Hub GC research

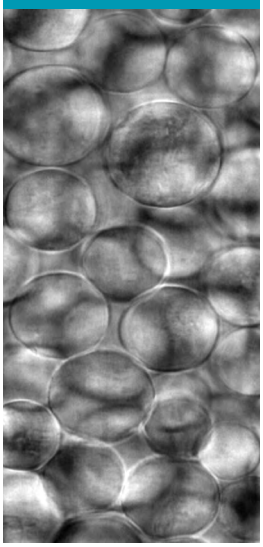
- Collaboration with Delaware (USA), NIST (USA) and ISIS (UK): Led to joint publication on neutron scattering measurement of monoclonal antibody structure during chromatography (Bracewell, UCL).



- Collaboration with National University of Singapore: Tested Hub MILP formulations under stochastic optimisation scenarios (Shah, Imperial)
- Collaboration with Instituto Butantan Brazil, and Oxford Jenner Institute: Focusing on developing Zika and COVID vaccine formulations (Dalby, UCL).
- Collaboration with Shanghai Pulmonary Hospital, Tongji University (China): Led to joint paper on machine learning for personalised lung cancer recurrence and survivability prediction (Farid, UCL)
- Secondment with the National Biomanufacturing Centre at CPI (Bracewell, UCL).

b) Collaborative grant proposals

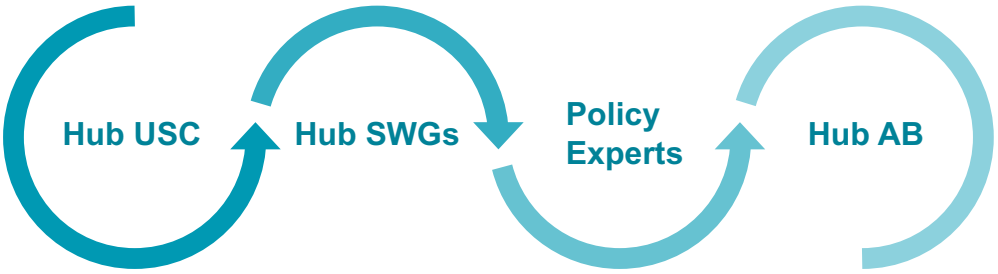
- Global Challenges Research Fund (GCRF) to establish antibody therapeutic and vaccine manufacturing in Thailand at their National Biopharmaceutical Facility, and BIOTEC Virology and Cell Technology Laboratory (Bracewell, UCL).
- Collaboration with Instituto de Engenharia Biomédica (INEB) and Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto, via an EU MSCA RISE programme in Future Formulations (Aylott, Nottingham).
- Collaborative EU IMI grant (EUR3.1M) with RiSE in Sweden and CPI (UK) to track drug stability during patient handling (Dalby, UCL).
- Horizon 2020 Marie Sklodowska-Curie Innovative Training Network Grant on Continuous Downstream Processing of Bioproducts (CODOBIO) with 20 European universities and companies (EUR3.9M) (Farid, UCL).



Developing the Research Programme for Phase II of the Hub (July 2020-December 2023)

Hub Phase II Planning Timeline

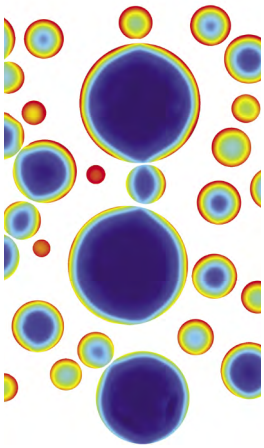
A regular cycle of consultations was held throughout 2019-20 to review and evolve the research programme, capturing perspectives from industry partners, national agencies, regulatory authorities, health technology assessors and independent external experts. In March 2020, a special Hub Phase II Planning workshop was arranged with senior executives from the Hub's User Steering Committee. The Phase II Grand Challenges and workstreams were revised and defined (Figure 5) along with associated categories of biological components and therapeutic modalities. The Phase II plans were reviewed and endorsed by the Hub's Advisory Board by the end of Q1, 2020 and the new workplans began in Q3, 2020.



Timeline:

2019

- May 2019: User Steering Committee broad consultation
- Spring and Autumm 2019: Key Theme Specialist Working Groups input ideas
- October 2019: Consultation with policy and regulatory stakeholders e.g. MHRA, HM Treasury
- October 2019: Grand Challenge leads and Co-Investigator team provided input
- November 2019: User Steering Committee briefing and feedback



2020

- Spring 2020: Key Theme Specialist Working Groups reviewed final ideas
- Spring 2020: Consultation with MHRA regulatory stakeholders
- Early March 2020: Phase II planning Specialist Working Group
- Late March 2020: Presentation to Advisory Board for approval
- Early Summer 2020: Shared plans with wider user members
- Early Summer 2020: UKRI-EPSRC permission to use original grant income in full
- July 2020: Phase II research programme begins

2021

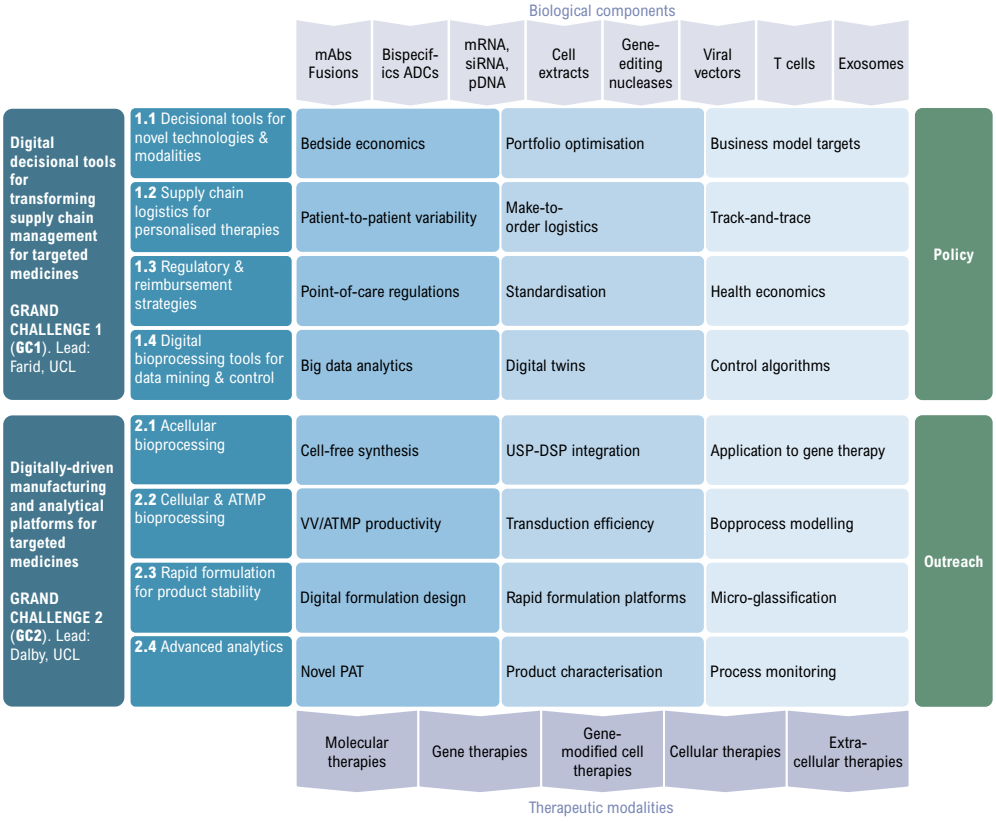
- Feb 2021: EPSRC Mid-Term Review (delayed)

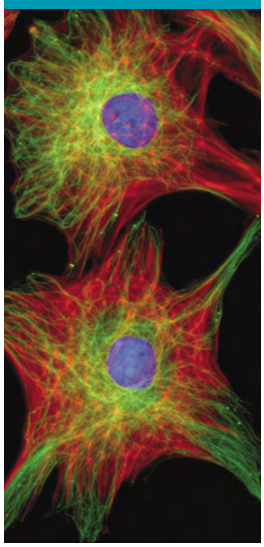
Photo of phase II Planning Specialist Working Group, March 2020, London

Phase II Grand Challenges Aligned to Changing Landscape

The flexibility of funding has enabled the Hub to adapt to the continually evolving biologics manufacturing landscape. Whilst Phase I of the Hub focused on stratified proteins (e.g. ADCs) and personalised cell therapies (e.g. CAR T-cell therapies), Phase II is addressing a broader set of modalities that include viral vectors for gene therapies and nucleic-acid based products therapies (pDNA, mRNA). In addition, new themes have been added to bridge the gaps in digitalisation and analytics. Furthermore, the success of the policy work in Phase I has led to continued support for these activities so as to drive the policy agenda in this sector.

Figure 5: Schematic of the Hub Research Programme and Grand Challenges in Phase II (July 2020-Dec 2023)





Phase II Key Research Questions

Grand Challenge 1: Digital Decisional Tools for Transforming Supply Chain Management for Targeted Medicines

GC 1.1 Cost of Goods and Portfolio Lifecycle Decisional Tools (UCL)

a) Can personalised bedside manufacture of protein and ATMP therapies be made cost-effective?

b) What is the value proposition of new modalities to manufacturers and the impact on portfolio design?

GC 1.2 Supply Chain Logistics for Personalised Therapies (Imperial, Warwick)

a) Personalised therapies: how best to configure a network of assets under uncertainty?

b) Real time optimisation of the supply chain: how best to use and existing network of assets in real time?

GC 1.3 Regulatory and Reimbursement Strategies (UCL STeAPP, UCL DAHR)

a) What challenges exist with additional post-marketing requirements?

b) What are the regulatory challenges for point-of-care manufacture?

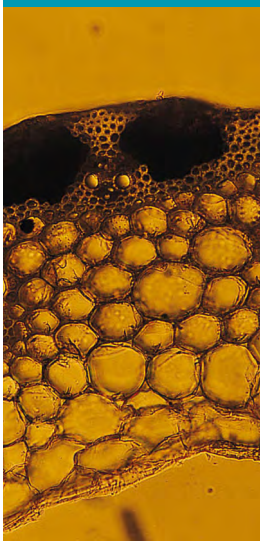
c) What are the factors affecting the cost-effectiveness of CAR Ts to the health service?

d) What is the value of ATMPs to the health service and to patients?

GC 1.4 Digital Bioprocessing Tools for Data Mining and Control (UCL, Manchester)

a) Can we leverage data from novel analytical technologies to enhance prediction e.g. CAR T heterogeneity?

b) Can we create a digital twin for new modalities to support the developing control strategies with limited datasets?



Grand Challenge 2: Digitally-driven Manufacturing and Analytical Platforms for Targeted Medicines

GC 2.1 Acellular Bioprocessing (UCL)

a) Can reactor engineering enable the manufacture of complex biological product using cell-free protein synthesis?

b) Can cell free be use for plasmid and mRNA manufacture for cell and gene therapy?

GC 2.2 Cellular and ATMP bioprocessing (UCL, Loughborough)

a) What CPPs will improve Lentiviral/AAV productivity?

b) Can non-viral transfection achieve efficiency of viral vector transduction?

c) Can the process intensification control strateties developed be applicable to adaptive, patient-specific manufacture?

d) What degree of intensification can be achieved with model-driven delivery of multiple components?

e) Can objective clustering of phenotypes improve understanding of process control?

GC 2.3 Rapid Formulation for Product Stability (UCL, Nottingham)

a) Can we achieve digital formulation design?

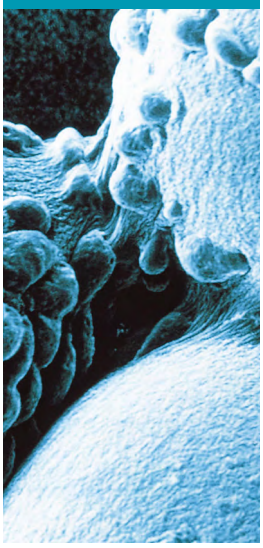
b) Can in-vitro screening and micro-glassification deliver enhanced viral vector formulations?

GC 2.4 Advanced Analytics (UCL, Nottingham)

a) What analytical approaches best assess viral vector quality and stability?

b) Can we describe, quantify and classify the heterogeneity of CAR T cells using novel optical technologies?

Finally, the Hub has been able to adapt quickly to the COVID pandemic, switching much of the PDRA-led research to modelling activities carried out from home, while others diverted onto COVID-19 vaccine formulation and analytics development to align with National interests, as well as leveraging Hub tools and industry contacts to supply materials.



HUB USER ENGAGEMENT

Evolution of Collaborator Engagement

Developing relationships with our users has been central to the continued vibrancy of the Hub. Our users span the entire value chain to ensure acceleration of impact and include the leading multinationals (e.g. GSK), SMEs (e.g. Autolus), contract manufacturers and vendors in the UK and internationally, as well as industry associations and the translational Catapults (Cell and Gene Therapy Catapult, Centre for Process Intensification). Since launch in 2017, we have extended our reach into the biopharmaceutical manufacturing sector, increasing from 34 to 44 users (Figure 6) with more currently in negotiation. Whether through conference contacts, industrial associations or word of mouth, users have continued to approach the Hub, enthusiastic to join the project.

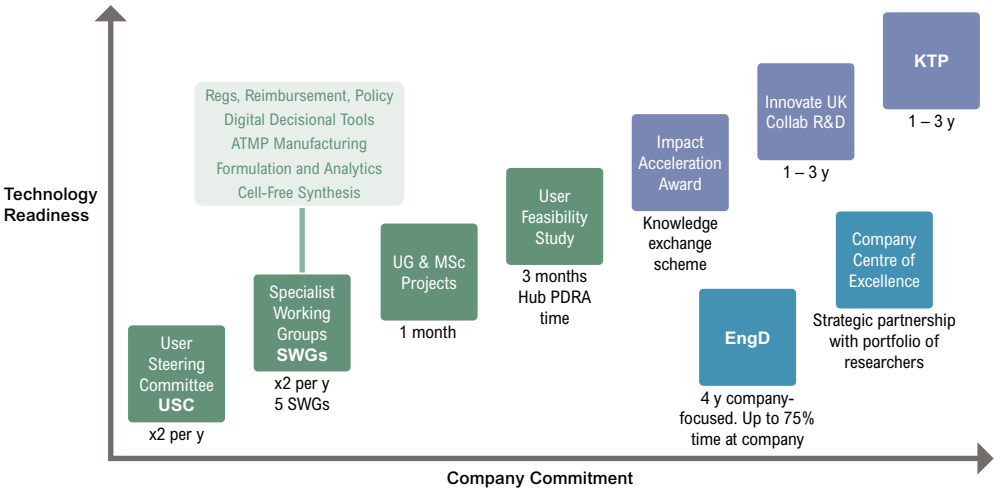
Figure 6: Growth of the Hub's User Partners since launch, in the period January 2017 to April 2021

Mechanisms of engagement with collaborators (Figure 7) include:

- **User Steering Committees (USCs)** are bi-annual opportunities to present Hub research to stakeholders, and to hear about industry trends and sector news from invited keynote speakers. The USCs have themed workshops, led by Hub Researchers or Principal Investigators designed to capture inputs and strategic directions from industrial collaborators. We have explored several new methods of obtaining different opinions, successfully using live online polls to elicit feedback, especially from those who may not have the confidence to speak out.

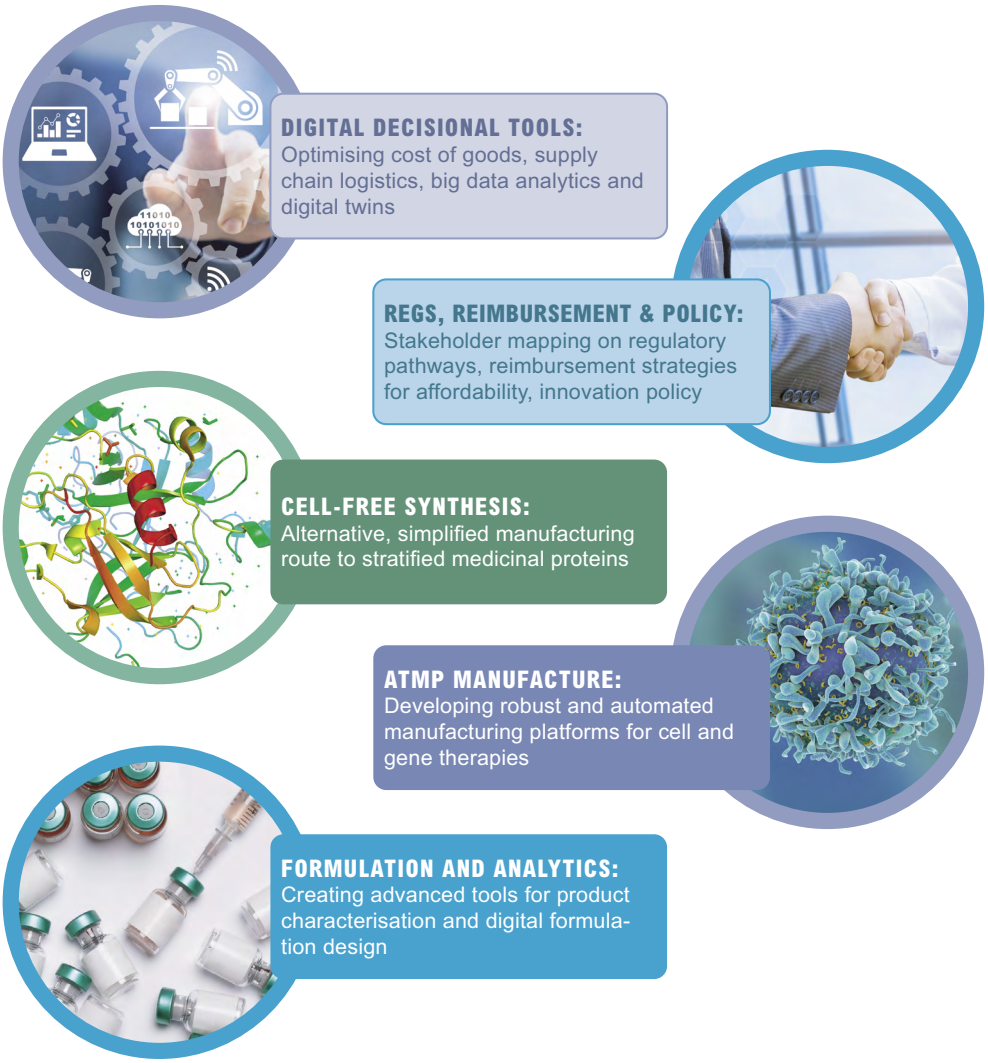
- **Specialist Working Groups (SWGs)** provide anchor events for dialogue on five specific research themes within the Grand Challenges. Each SWG meets bi-annually to present research updates, and foster discussion and strategic planning between academia and industry. The SWGs evolved in 2020, with a renaming of some to reflect the new directions in Phase II of the Hub. The SWGs moved online as a consequence of the pandemic, and numbers of user representatives attending increased from 40 in 2017 to the mid-60s in 2020.

Figure 7: Mechanisms through which Users can engage with the Hub.



- A major evolutionary inflection was the Phase II planning phase. Recognising that the targeted healthcare field changed significantly since the Hub launch, extensive consultation with industrial users at USCs and SWGs was instrumental in identifying new priorities and honing them for maximum use of Hub capabilities. This culminated in a special Phase II planning SWG with significant direction and support from senior leaders in user organisations. The output, endorsed by the Advisory Board, saw a redefining of the SWG remit (Figure 8) towards:
  - **ATMP Manufacture** – CAR T-cell remit expanded to include other cell therapies and viral vector modalities
  - **Regulation, Reimbursement and Policy** - broadened stakeholder network for policy impact
  - **Formulation and Analytics** – remit expanded to include advanced analytics for PAT of different modalities
  - **Digital Decisional Tools** – expanded to include big data analytics, leveraging PAT, digital twins and control
  - **Cell-free synthesis** – remit expanded to include newly emerged modalities.

Figure 8: Specialist Working Groups (SWGs) of the Hub adapted to align with Phase II of the Hub with greater emphasis on digitalisation, policy, viral vectors and analytics



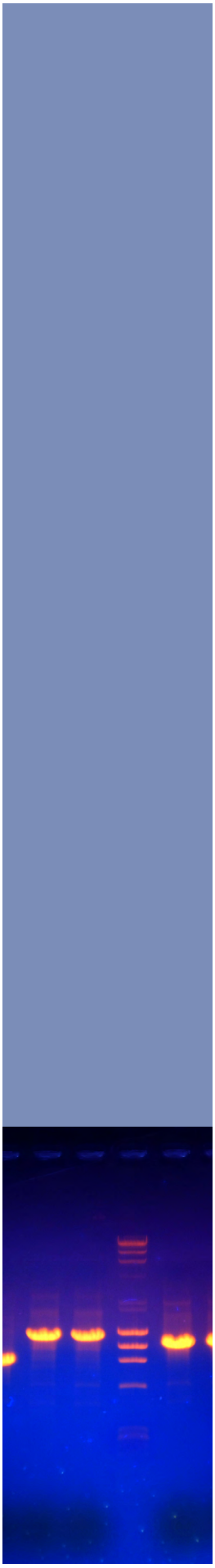
User Feasibility Studies: Enhancing Knowledge Exchange

The **Translation and Impact Committee** was formed in Y2, and has met annually to review and prioritise resourcing and identify appropriate activities to accelerate translation of research to adoption and exploitation. This group first met in January 2019 and then January 2020, chaired by one of our Catapult partners and comprises 3 additional Hub users and the Hub Management. A key role of the Translation and Impact Committee has been to assess the user feasibility study (UFS) proposals for alignment to the Hub and impact.

The **user feasibility studies** have been instrumental for promoting further engagement between Hub academics and users, beyond the Specialist Working Groups and User Steering Committees mentioned above. With 10 originally planned for the whole 7 year programme, a total of 23 (Table 2) have been initiated already as discrete mini collaborative research projects via competitive bids prioritised by the Translation and Impact Committee, and via PDRA networking and SWGs. The user feasibility studies in Phase I of the Hub spanned aspects of process control, formulation, cell-free synthesis, supply chain optimisation, economic evaluation, T-cell manufacturing process modelling, and DNA manufacturing across the Hub and Spoke universties and involved 23 users, including the Cell and Gene Therapy Catapult and the charity Cancer Research UK. Enabling users to dip into new techniques, generate decisional models or even provide data to support government business cases, the annual call generates strong interest from the users. Selection of the studies is carried out by our Translation and Impact Committee chaired by a Catapult partner and including industrial members. Outputs from the studies are relayed to the wider Hub community at SWG events, with many generating papers. User in-kind contributions (valued at £5M over 4 years) have spanned access to industrially-relevant biological materials (e.g. AstraZeneca, Sutro), loan of state-of-the-art kit and consumables (e.g. Sartorius) through to industrial datasets (e.g. Ipsen). A recent innovation has been to follow up participants post-project, obtaining feedback on the application process, project execution and outcomes in one-to-one interviews by our Outreach Consultant. The output has been used to update the application process and apply stronger project management principles. As an unexpected bonus, it was found that the general feedback often gave an insight into company direction and potential new openings. The plan is to extend and modify this interview technique further to a wider cross-section of the Hub, to capture the impact of the Hub on company operations.

The Hub has supported **secondments** of Hub Reserachers into industry settings, to enable more efficient knowledge transfer. For example, Dr Olotu Ogonah spent 2 weeks at **Sutro** learning

methodologies already established in industry, and then defining key challenges in cell-free synthesis of biopharmaceuticals. Dr Beatrice Melinek visited **Cancer Research UK** on secondment, part time across a period of 9 months, developing and transferring Hub research on novel DNA manufacturing platforms under User Feasibiliy Study. In addition, one of our Hub CoIs, Dan Bracewell, is currently undertaking a secondment at the **CPI National Centre for Biologics Manufacture (NBMC)**.



User Feedback on Hub Impact

As the Hub transitioned from Phase 1, we gave users the opportunity to express their perspectives on their experiences to date.

What did you find most useful or beneficial in Phase I of the Hub?

Users especially valued the SWGs for the networking, establishment of communities, and as a mechanism to engage with the technical activities of the Hub:

> **"Great start to help showcase the expertise in the UK to the rest of the world."**

> **"Cell-free SWG was particularly timely for CPI who were actively building in the area."**

> **"Connecting Hub to company experts also raises profile of bioprocessing within the company."**
> D Ellison, Allergan

> **"Policy brings a broader context to bring attention to government decision-makers."**
> M Kuiper, KTN

Feedback on switch to virtual meetings during COVID-19:

> **"Great organisation for all online SWGs, keeping the conversation going virtually and the scientific community informed of the work completed." "This was fabulous and very well done"**
> A Radwick, West Pharma

What aspects of the Hub's Phase II plans are you most looking forward to?

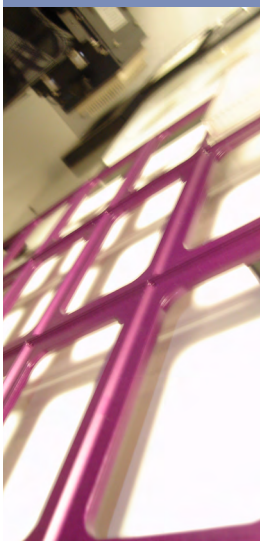
All voters at the Phase II Planning meeting endorsed the Phase II Plans.

Users were excited by greater focus on digitalisation, incorporation of viral (and non-viral) vectors into the FTHM Hub workstreams, the possibility of new SWG topics, for example viral vectors or analytics:

> **"Being able to help shape UK policy in Advanced Medicine development and enabling availability of affordable, cost-effective new therapies to patients."**

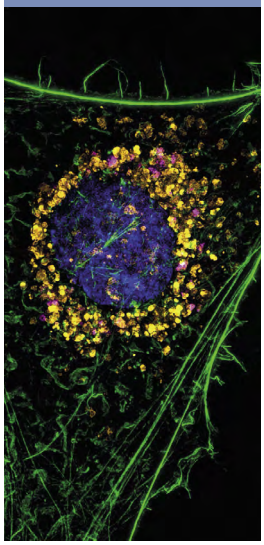
Table 2: List of User Feasibility Studies within the Hub

User-Led Feasibility Studies (FTHM Hub) funded from strategic calls	
Company Lead(s) & HEI partner	**Topic**
Aglaris University of Manchester	Historical batch analysis and trajectory optimisation for T-cell expansion process control
Albumedix University of Nottingham	Formulating recombinant human albumin as nanoparticle scaffolds and assessing the potential for drug delivery
Albumedix Imperial College London	Cell therapy supply chain optimisation: an investigation of the impact of product stability
AstraZeneca University College London	Real-time process analysis and control of continuous chromatography
BioIndustry Association **Oxford Biomedica** University College London	Economic analysis to investigate the consequences of switching to scalable GMP processes for viral vectors on drug development lifecycle costs
Cancer Research UK University College London	Novel DNA manufacturing platforms for use in targeted therapies
Cell & Gene Therapy Catapult Loughborough University	Mechanistic modelling for immunotherapy manufacture
FujiFilm Diosynth Biotechnologies University College London	Cell-free protein synthesis (CFPS) demonstration and production of industrial relevant products



User-Led Feasibility Studies (FTHM Hub) funded from strategic calls	
Company Lead(s) & HEI partner	**Topic**
Ipsen University College London	Techno-economic evaluation of a cell-free synthesis (CFS) system for the expression of a recombinant toxin
Purolite University College London	Bringing down cost of goods in monoclonal antibody downstream processing
TrakCel Imperial College London	Development of supply chain optimization models for autologous CAR T cells
Univercells University College London	Economic evaluation of Cell-Free Synthesis in personalised medicine
West Pharmaceutical Services University College London	Comparing freeze-thaw performance of vials vs bags for the containment and delivery of T-cells

User-Led Feasibility Studies (FTHM Hub) arising through PDRA networking & SWGs	
Company Lead(s) & HEI partner	**Topic**
AstraZeneca University College London	Coformulation of MAb combinations and product stability
BioPharm Services Loughborough	Application of a Simple Unstructured Kinetic Model to Support T-Cell Therapy Manufacture
LGC University College London	Characterisation of co-formulated product with mass spectrometry
Lonza University College London	Evaluation of the Cocoon bioreactor
Ovizio Imaging Systems University College London	Holographic imaging and image-based cell profiling for manufacturing of CAR-T cell therapies.
Redbud labs University College London	Mixing of immune cells in microfluidic devices
Sartorius University College London	Rocking motion perfusion bioreactor evaluation for CAR-T production



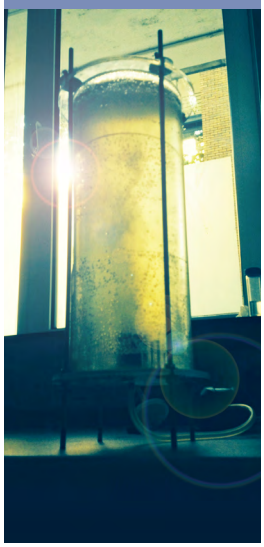
User-Led Feasibility Studies (FTHM Hub) arising through PDRA networking & SWGs	
Company Lead(s) & HEI partner	**Topic**
Sutro Biopharma University College London	Cell-free protein synthesis experimentation
Univercells / VaxHub / Leeds Univ University College London	Cell-free synthesis of Polio vaccines

Wider Engagement and Benefits

Dissemination of the benefits of our research is a key objective of the Hub. The output from the Hub includes over 120 publications, and over 70 conference presentations so far, including outputs from the User Feasibility Studies. A more recent innovation has been the creation of the Hub Webinar series, one hour sessions on emergent themes in the Hub's Phase II research programme. This popular mechanism will be continued, maintaining interaction between the SWG seasons.

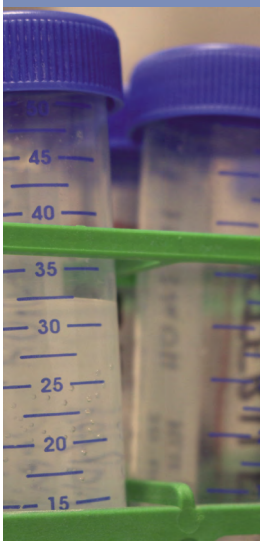
Benefits of the Hub research to collaborators can be seen beyond traditional dissemination methods, including:

- **Academics transitioning to industry** - e.g. PDRAs moving on to Oxford BioMedica and Achilles Therapeutics
- **PhDs and EngDs** aligned to the Hub mission and building on Hub outputs (52 graduated to date)
- **MBI® CPD modular courses** (425 industrialists on the relevant courses to date) disseminate Hub methods and innovations to an audience of industrialists and researchers beyond the Hub and equip them with skills to adapt to the challenges of targeted healthcare. The Hub has driven the creation of 2 new MBI® modules to disseminate Hub research: "Antibody Targeted Therapies" and "Cell and Gene Therapy Bioprocessing and Manufacture".
- **New taught MSc** in Manufacture & Commercialisation of Stem Cell and Gene Therapies (with Industry Steering Committee featuring many Hub members) to address the skills gap in this emerging sector
- **Knowledge Transfer Partnerships (KTP)** - Hub activities have led to several KTP projects to ensure advances in methods are translated effectively into the user setting. These include KTPs with Sartorius Stedim UK to develop a new bioreactor vessel for



adherent and suspension cell culture, with Biovault Technical to develop a scalable and consistent bioprocess for umbilical cord tissue (UCT) human stem cell production, with Perspectum Diagnostics Ltd to develop health economics analyss for a clinical diagnostic pathway for liver disease and with Aber Instruments to develop a biocapacitance analytical approach for cell therapies.

- **Patents:** IP has been filed by UCL Business for a novel analytical technique to monitor protein co-formulations.
- **Spin-outs:** The Hub's first spin-out, Roxijen, was established in 2020, commercialising analytical instrumentation for biologics (Dalby, UCL.
- **Company-sponsored Centres of Excellence** - two have been established with Pall and AstraZeneca.
- **Technology showcases** – e.g. "Autologous Cell Therapy Technology Showcase" with CRUK and Lonza (2019)
- **UCL's Connected Curriculum** – directing Hub research into undergraduate teaching.



DEVELOPING THE HUB TEAM

Continuous Development and Training for Leadership

Hub Researcher training is seen as a key benefit of operating as a Hub. Our key drivers are to ensure that Hub Researchers: i) work collaboratively towards cutting-edge interdisciplinary advances, while avoiding working in silos, and ii) are trained to their full potential, ready for careers in leadership roles within industry or academia. To achieve this, we have created an environment that includes new ways of working, that give Hub Researchers a voice for leadership, opportunities for teaching, training and learning from each other, and career networking with relevant industries and academics. This ensures their personal career development, while synergising their inputs across Hub research.

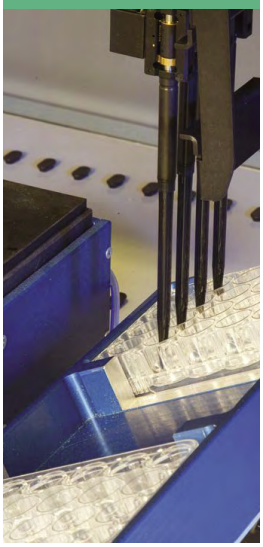
Hub Researchers are promoted actively towards progression beyond the Hub, by providing avenues into industry, academia, and policy. Engagement with industry is endemic through participation in User Feasibility Studies, User Steering Committees, co-supervision of PhD/EngD projects, Specialist Working Groups, and one-to-one conversations relating to industry materials and data. Engagement with policy is promoted through the Policy Events attended by Hub Researchers. Hub Researchers are frequently made aware of jobs and fellowship opportunities, and receive mentorship and assistance with applications at Departmental and Faculty levels. Hub Researchers also access our MBI modules as Continuing Professional Development training for industry.

Innovative Working Practices

Innovative working practices were developed in response to feedback from Hub Researchers, Users and the Advisory Board, to provide the best possible working environment for Hub and Spoke PDRA researchers, and to accelerate their progression towards leadership roles. They been trained to have the skills and experience in new ways of working required by industry to transfer and implement our new technologies in practice.

Flexible working

Flexible working is encouraged in line with UCL's HR and ED&I policies. The COVID-19 pandemic brought many of the flexible working needs to light, particularly the need to enable those with caring duties. Working from home is encouraged where possible, and a flexible working shift pattern has been introduced in the laboratories

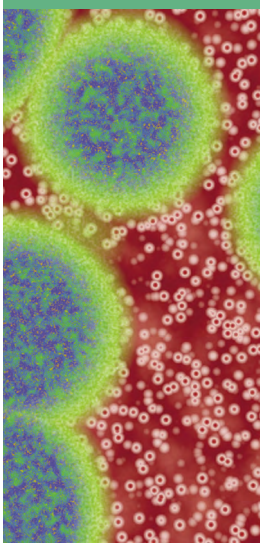


to maximise time available while meeting reduced occupancy requirements. Every care was taken to be sensitive to ED&I, health, and well-being issues when planning new ways of working, for which the Hub Researcher online forum was instrumental.

Collaborative working

The Hub Specialist Working Groups (SWGs), and Hub Researcher-led interactive technical workshops at User Steering Committees act as a forum for Hub Researchers to engage with industry, and wider stakeholders, to gain critical feedback on their research direction and impact, and also to work on team-oriented challenges.

The Hub Researcher Group, timed immediately before the monthly Grand Challenges Research Management Group (GCRMG), continues to serve a valuable role in Hub and Spoke PDRA training. Hub Researchers set their own agenda to share research needs, conferences, fellowship, and travel grant opportunities, as well as to plan collaborative work, networking, careers and social / team-building events, before reporting these back to Hub & Spoke Co-Is in the GCRMG. The very broad range of disciplines that the Hub and Spoke Hub Researchers represent has also enabled them to organise training activities for each other, across their diverse range of skillsets, so that for example, modellers can understand policy, clinical practice issues and laboratory data sources, while experimentalists can pre-design their data collection to better fit the needs of modellers. Hub Researcher -arranged bespoke activities have included: training in the UCL Bioprocessing Pilot Plant; organising a Pilot Plant Week for UCL Biochemical Engineering undergraduates; “Ideas to Impact” training with UCL Enterprise; an introduction to Healthcare Economics with UCL Applied Health Research; “Commercialisation of Technology” with UCL Business; and Policy Engagement Training with the UCL Policy Impact Unit. Feedback from this forum to the Hub Management team has been instrumental in driving the continual development of Hub Researchers according to their needs. Finally, and critically, the Hub Researcher Group, re-established as a MS Teams Group, served as a vehicle to raise and mitigate any concerns arising due to COVID-19, and the initial lab closures.



Career progression

Eight Hub PDRA Researchers have now progressed into higher roles in academia or industry. Olotu Ogonah moved to a senior role at Oxford Biomedica, while Theano Panagopoulou started in a new role as a Senior Scientist at Achilles Therapeutics. Giovanni De Grandis moved to the Norwegian University of Science and Technology as a Centre co-ordinator. Elvan Gökalp (Warwick) started a Teaching Fellowship position at the University of Warwick, while Veeren

Chauhan was accepted as a new Research Fellow in Bioinspired Therapeutics at the University of Nottingham. Xin Fei (Warwick) started as a new lecturer at the University of Bristol, and Xiaonan Wang (Imperial) started as a new lecturer at the National University of Singapore (NUS) in Chemical and Biomolecular Engineering. Most recently, Maria Papathanasiou started as a new lecturer at Imperial College London, and will continue to contribute as a Spoke PI in the Hub.

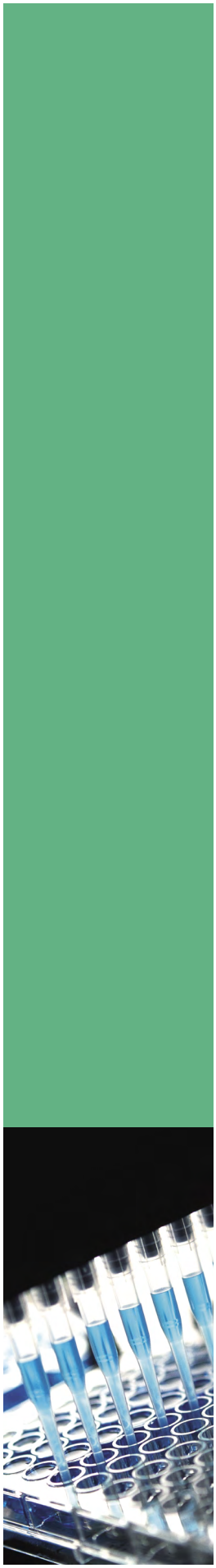
These high-achieving roles reflect the industry and academic demand for researchers trained in the sector, and also the high-regard that potential employers have for the Hub. A key feature in driving this, has been the training opportunities that the Hub Researchers have had for widening their skillbase. Not only are they exposed to regular research updates from each other, but they have also been actively engaged in collaborations with each other, facilitated by training workshops to forge multi-disciplinary learning, such as in the use of the Pilot Plant, and also in Policy.

Graduate student training within the Hub

Alongside the Hub Researchers, a total of 114 manufacturing and process specialist students have benefitted from training to PhD/EngD level in the Hub's new ways of working required for targeted medicines, and most will seek jobs in the sector. Many of these have been co-supervised by the Hub Reseracher team, providing them with further skills in leadership through research supervision and project management. The students were funded as 46 EPSRC CDT in Emergent Macromolecular Therapies (EMT) PhDs, 52 EPSRC in Bioprocess Leadership EngDs, and the remainder from DTP, UCL-scholarships and overseas scholarships. Of these, 52 PhD/EngD students have graduated so far, fully trained in Hub methods and innovations, and 48% have gone into Bioindustry roles, while 24% have taken up PostDoctoral Research posts, 8% became Teaching Fellows, and the remaining 20% went into other sector-related industries. Over 70% of the EPSRC CDT in EMT PhD students were based at external institutions, bringing these collaborating universities into the Hub's extended research community. All Y1 and Y3 students have presented posters and selected final year students have presented orally at the bi-annual Hub User Steering Committee meetings.

CPD training in Hub innovations for industry

Hub methods and innovations are regularly disseminated via our MBI training modules attended by industry, PDRAs and graduate students, for their continuing professional development. For example, the 'Antibody Targeted Therapies' MBI addresses the emerging Antibody-



drug conjugate (ADC) class of therapies, while the Cell and Gene Therapy Bioprocessing and Manufacture MBI has adopted aspects of regulation and distributed manufacturing concepts.

Equality, Diversity and Inclusion (ED&I) Goals

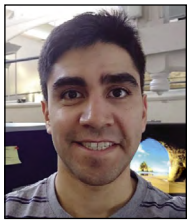
The Hub follows UCL's policy on ED&I via HR policy, and guidelines from the Faculty of Engineering ED&I committee, for which one of our Department of Biochemical Engineering staff is the Deputy Director. The Department of Biochemical Engineering that hosts the Hub, is highly pro-active in realising the goals of ED&I, and has taken the lead at UCL on achievements within the Athena Swan scheme. Crucially, all PIs across the Hub and Spoke have been required to undertake unconscious bias training prior to the advertisement and recruitment of any new Hub Researchers. The Hub Management Board manages and tracks ED&I goals and performance, with data from HR (compliant with GDPR). For Hub-aligned PhD/EngD students this is managed via respective CDT management committees, as well as the Dept of Biochemical Engineering Doctoral Committee, and reported to the Hub Management Board. The Hub ED&I action plan is reviewed and updated annually, with feedback from the Advisory Board. Goals to put in place monitoring, unconscious bias training, and ensure diversity at committees, panels and events, have already been met, and updated in line with the UCL and Faculty of Engineering ED&I strategies. Key future goals include:

- Solicit a direct review of Hub ED&I strategy and goals by the UCL ED&I committee.
- Guaranteed interviews for applicants from under-represented groups.
- Update of web-based materials and communications to ensure that images and messages are inclusive of the diversity of research staff, students and industrial sponsors.
- Foster linkages with established UCL ED&I communities: RaceMatters@UCL, LGBT+Allies, Out@UCL, Enable@UCL and the network of UCL AthenaSWAN departmental committees.

Hub Researcher Perspectives

“The Hub has given me more visibility for my career. With my research it has provided opportunities for both academic and industry collaborations. Being part of the team has helped me gain a better understanding of other research activities across the Hub, get input, ideas and useful suggestions for my research. I feel more supported as a part of a bigger research group. In engaging with the User base, the Hub has given me more visibility to our industrial partners and provided more opportunities for closer collaboration compared to a conventional postdoc. It has been a good networking opportunity too.”

Dr Maryam Shariatzadeh, Bioengineering Scientist & Pharmacist, Loughborough University

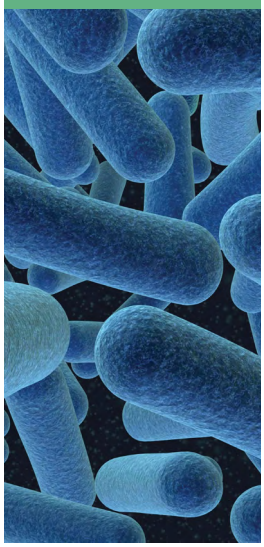


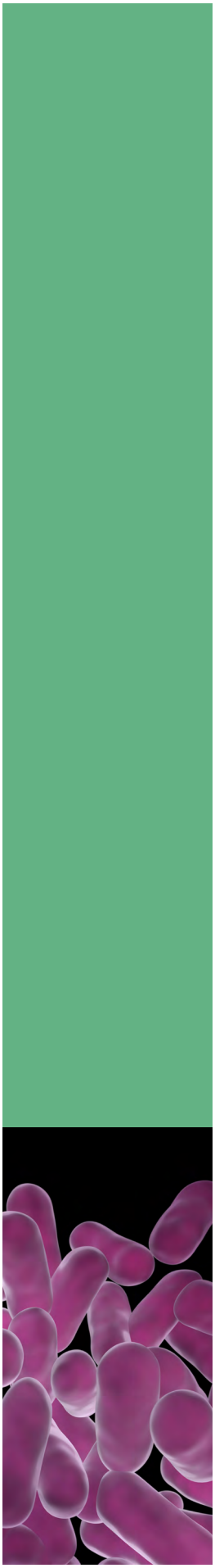
“The Hub has helped me to build a platform where I can gain new skills as well as polish existing ones and it has granted me exposure to industry. Being part of the Hub has allowed me to collaborate with a multidisciplinary team of academic researchers and experts. This has helped me to expand my knowledge of different fields and use my expertise to co-develop state-of-the-art research. I am passionate about how academic research can improve people’s quality of life. Consequently, by joining the Hub, I have an immense satisfaction knowing that my work could be part of technologies that could save lives.”

Dr Carlos-A. Duran-Villalobos, Process Control Engineer, University of Manchester

“The Hub has served as a catalyst for engaging with a cross-sector stakeholder network, that includes the the NHS, policy makers, researchers and industry. This has been vital for my research, providing valuable insights and professional growth. As well as having the freedom to explore our own research ideas, personal development has been encouraged. I have been able to pursue opportunities in leadership, teamwork, communication and future planning - marketable skills. This aligns with my aspirations to develop expertise in the field of highly specialised technologies (HST) and policy.”

Miss Nishma Patel, Health Economist, University College London



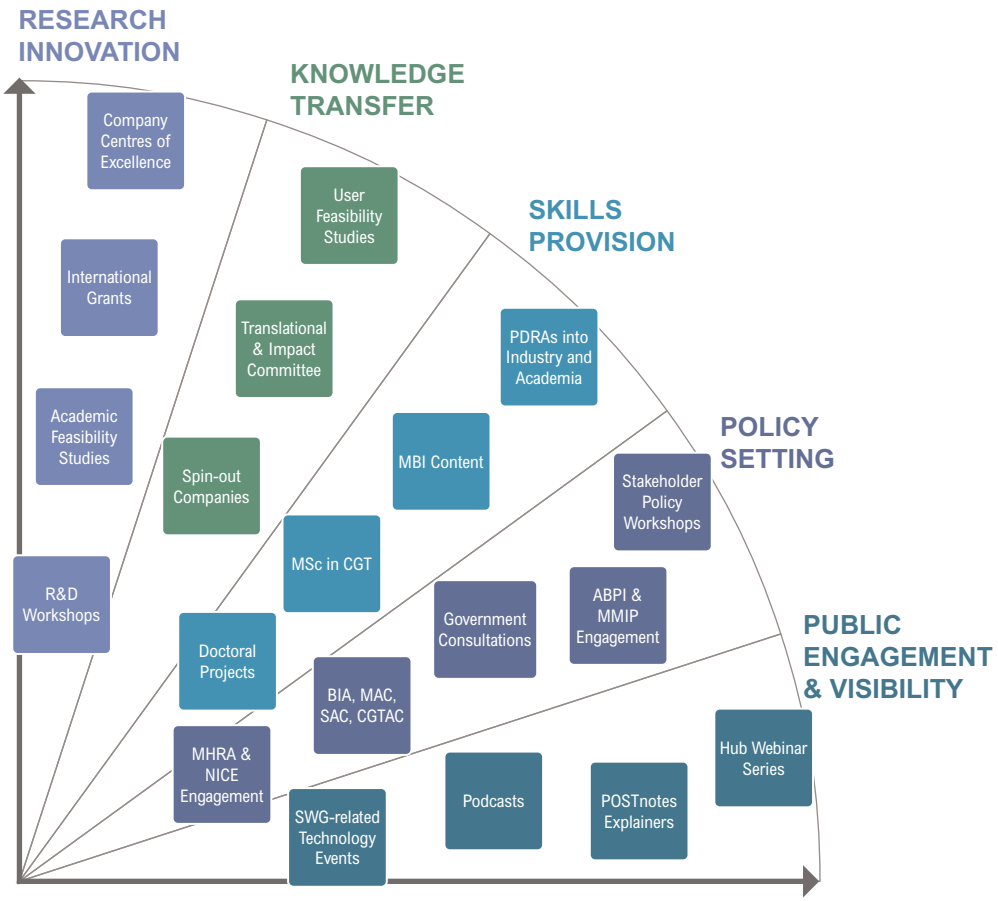


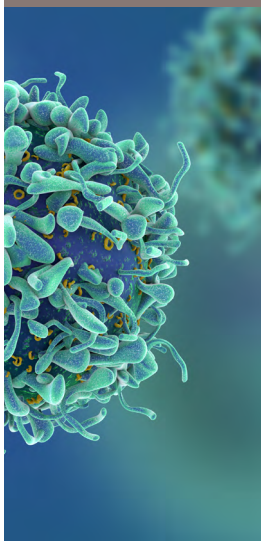
ACTING AS A NATIONAL HUB

National Hub Strategy and Outreach

The framework for Hub outreach and impact to leverage the achievements of the Hub and realise the mission to act as a world-leading National Hub and Spoke collaboration are outlined in Figure 9, and discussed in more detail below. The framework addresses deliverables The Hub has created and leads the national research and innovation landscape in this sector by engaging with the entire value chain including translational stakeholders (Innovate UK and Catapults) through to industry to ensure acceleration of impact.

Figure 9: Framework for Hub outreach activities to develop a National Hub strategy





The key deliverables relate to:

Research Innovation (see The Hub Research Programme section):

- Decision-support tools to transform supply chain economics for targeted healthcare
- Novel manufacturing, formulation and control technologies for stratified and personalised medicines.

Knowledge Transfer (see Hub Engagement with Users section):

- Network of academics, industrial users, translational spokes, regulators and clinicians to drive forward the national research and innovation agenda
- Providing the engineering infrastructure needed for sustainable healthcare and enhanced UK competitiveness.

Skills Provision (see Developing the Team section):

- Technologies, skill-sets and trained personnel needed to enable UK manufacturers to embrace fully the opportunities offered by advances in medical precision and patient screening.

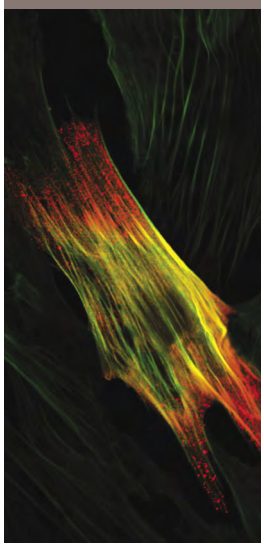
Policy Setting & Public Engagement (see sub-sections below):

- Hub expertise leveraged to contribute to matters of national importance and to influence policy.
- National resource raising the profile of high value manufacturing research in the UK.

Influencing the National Agenda & Innovation Landscape

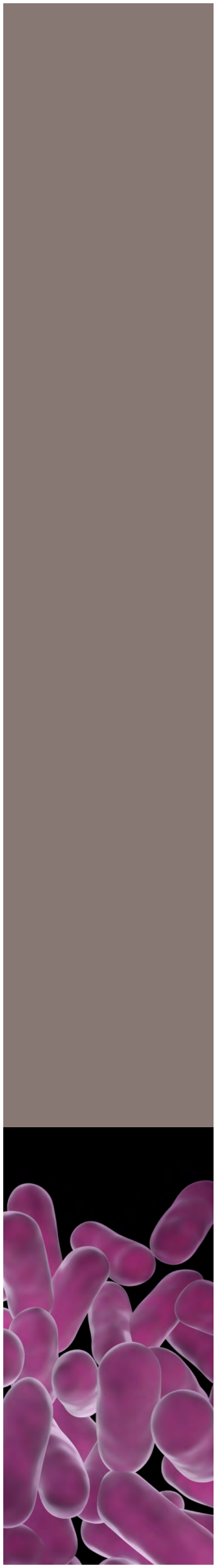
In recognition of the Hub's strategic role in enabling the life science manufacturing industry to respond to future opportunities and contribute to a prosperous UK, a policy advisor was appointed to the Hub in April 2019. The role aims to strengthen relationships with the policy community and leverage Hub expertise to contribute to matters of national importance. The policy advisor also acts as a conduit to developments in life science and manufacturing policy to ensure that the Hub is responding to the latest challenges on the minds of decision makers. The Hub has engaged with key sector policy influencing and roadmapping bodies, to influence the national research agenda:

- **BioIndustry Association (BIA)**: Our USC Chair, Mark Carver, chairs the BioIndustry Association's Science and Innovation Advisory Committee (SIAC), and provides a link to the sector roadmapping exercise that he is coordinating to define the current UK capabilities, challenges and gaps in sector funding. Farid and



Rafiq (UCL) sit on the BIA Manufacturing (MAC) and Cell & Gene Therapy (CGTAC) Advisory Committees. Dalby (UCL) attended the BIA Shaping the Future workshop (May 2018).

- **Association of British Pharmaceutical Industries (ABPI)** – Hub Advisory Board member Bryan Deane represents ABPI and is providing two-way communication on sector needs.
- **Medicines Manufacturing Industry Partnership (MMIP)** - The MMIP provides a single UK industry voice and point of engagement with government to facilitate the growth in medicines manufacture in the UK. We have engaged in a number of meetings with MMIP, the associated and newly commissioned MMIC, and their partners CMAC, to build future links in areas of mutual interest. Gill (UCL) sits on the MMIP Skills Workstream.
- **BioProNet.** Dalby (UCL) is a committee member of this >500-member Network from across the UK academic and industrial community. It plays a key role in roadmapping the capabilities and challenges of the bioprocessing sector from the life sciences perspective. It is closely linked into the BIA roadmapping exercise led by Mark Carver.
- **EPSRC Manufacturing the Future Strategic Advisory Team (SAT) and Early Career (EC) Forum** - Dalby (UCL) is a committee member of this SAT within EPSRC, which advises on the health and future strategic direction of the Research and Training Portfolio within the Manufacturing the Future Theme. Rafiq (UCL) served as a committee member of the EC forum in Manufacturing Research to shape the Manufacturing the Future research agenda.
- **Catapult secondment**. Bracewell (UCL) was seconded in 2017/8 to CPI's National Biologics Manufacturing Centre in Darlington. This strengthened connection enabled the cell free synthesis roadmapping exercise.
- **UKRI and ISCF workshops**. Several Hub PIs (Dalby, Rafiq, Titchener-Hooker) have had an active role at funding policy workshops including the EPSRC Targeted Therapeutics Delivery workshop (May 2017), Industrial Strategy Challenge Fund workshop (April 2017), EPSRC Inaugural Healthcare Technologies Hive Event (November 2017), EPSRC Manufacturing the Future Regional Workshop (March 2019).



Engaging with Wider Stakeholder Groups & Policy Makers

The Hub has engaged with a wider stakeholder network including Central Government and Government bodies:

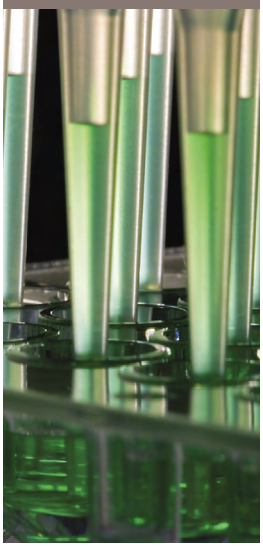
a) **NHS England and Improvement** - In 2019 significant strides were made to form meaningful and ongoing relationships with several NHS E&I teams, including the Commecial Medicines Directorate, the Medicines Analysis, Strategy and Policy team and the Accelerated Access Collaborative. These meetings provided an opportunity to gain valuable perspectives on the challenges faced by the NHS in implementing high cost therapies and to raise awareness of the Hub's research to address the manufacturing challenges for ATMPs via dialogue with Patel and Farid (UCL). Engagement with the NHS Accelerated Access Collaborative ATMP workstream led to the appointment of Hub reimbursement researcher, Patel (UCL), to their Data Infrastructure Working Group.

b) **The Medicines and Healthcare products Regulatory Agency (MHRA)** - In 2018, the Hub established a dialogue with the MHRA Innovation Office on the regulatory implications of emerging bioprocessing technologies. In 2019, opportunities for future engagement were mapped out, including input to the MHRA's Point of Care Manufacturing framework, due for completion in March 2021, by the Hub's regulatory lead, Brass (UCL).

c) **Her Majesty's Treasury (HMT)** - This year the Hub hosted a visit from HMT's Health and Social Care spending team. We provided a tour of the world-leading facilities at UCL's Advanced Centre for Biochemical Engineering, and an overview of Hub research. The HMT team were particularly interested to understand the contributing factors to the cost of goods for ATMP manufacture from Farid (UCL) and how the sector might grow and develop in coming years, an issue then also addressed in a policy-facing workshop run by the Hub in February 2020.

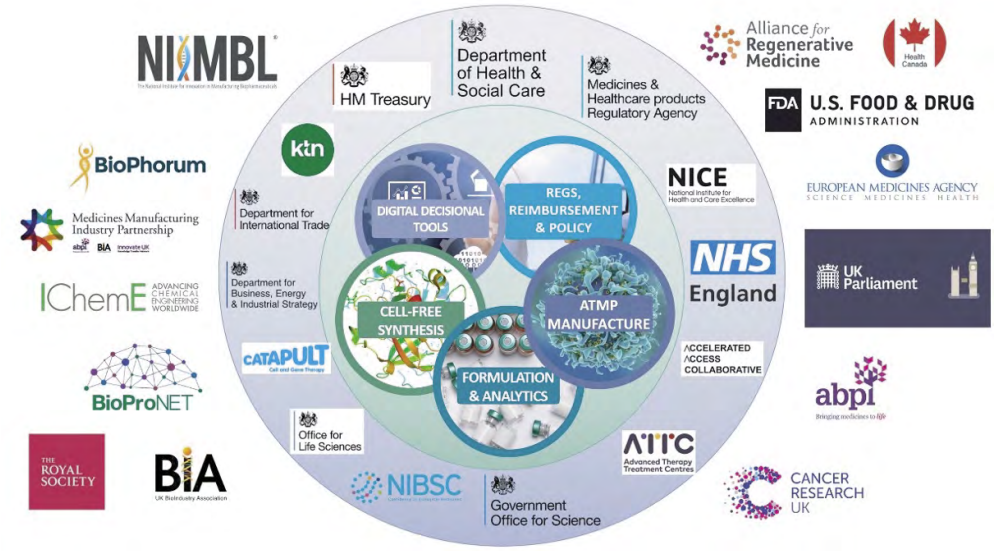
d) **Policy Dialogue** event on "Manufacturing personalised medicines: overcoming the affordability barrier" February 2020 involving stakeholders from central government and its bodies (Office for Life Sciences, Her Majesty's Treasury, NHS England), the third sector (Cancer Research UK, Bloodwise) and industry.

- **Policy briefs and POSTnotes disseminated to government and its funded policy bodies** e.g. Manufacturing Biological Medicines, Developing New Vaccines for Pandemics, Manufacturing New Vaccines for Pandemics.



- **Joint KTN/Hub events for the bioprocessing community** - "Manufacturing ATMPs - moving from approvable to commercial success (2018)", "Manufacturing of viral vectors for vaccines and cell and gene therapies (2019)".
- Other public policy stakeholders we engaged with this year include the Office for Life Sciences, The Department for International Trade's Life Sciences Organisation, the European Medicines Agency, the Better Regulation Executive (BEIS) and the All-Party Parliamentary Group for Rare Diseases.

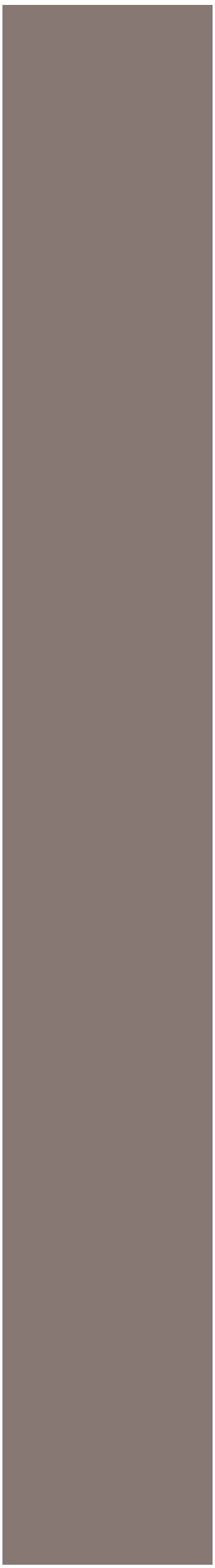
Figure 10: Engagement with key stakeholders across the sector, nationally and internationally



Public Engagement Activities

As a unique national resource in manufacturing research for the biopharmaceutical sector, we have sought to build the profile of high value manufacturing research in the UK via the following routes:

- **"Afternoon of Innovation" series run by UCL's Post-Doctoral Researcher Society** - these events involve high profile national speakers and generate a platform for knowledge exchange around innovation and enterprise in science and engineering across UCL. E.g. "*Equality Diversity and Inclusion in STEM*" (Oct 2019), "*Responsible Innovation*" (Nov 2019), "*Rare Disease, Philanthropy and Patient Groups*" (Dec 2019), "*Stratified and Personalised Therapies*" (Feb 2020).
- **Podcasts and Webinars** - e.g. UCL Minds podcast on "*Coronavirus The Whole Story: How close are we to finding a cure*" run jointly with Cheltenham Science Festival (Farid, UCL), Imperial College Never Lick the Spoon podcast on "*Getting rid of COVID*" (Papathanasiou, Imperial), BSI Education Podcast "*Why teach about standards*" (Brass, UCL)
- **Articles** - e.g. in The Engineer on "*The engineering challenges of scaling up UK vaccine manufacture*" (Shah, Imperial); in The Conversation on "Coronavirus - how the pharma industry is changing to produce a vaccine on time" (Joint FTHM Hub (Melinek, UCL) and Vax-Hub) and "Coronavirus vaccine - how we're preparing to make enough for the whole world" (Joint FTHM Hub (Rafiq, UCL) and Vax-Hub); interview in Politico on "Europe's challenge of a lifetime: Manufacturing enough coronavirus vaccines" (Farid, UCL)
- **Newsletters** - The Hub sends out biannual newsletters to its User and academic network, as a key mechanism for updating on Hub progress, and raising awareness of key dates and calls for the User Feasibility Studies.



HUB & SPOKE ACADEMIC TEAMS AND PARTNERS

THE HUB & SPOKE ACADEMIC TEAM

An overview of the current team, based across six leading universities and eight university schools and departments

THE HUB @ UCL

UCL DEPARTMENT OF BIOCHEMICAL ENGINEERING

Professor Nigel Titchener-Hooker

POSITION: Principal Investigator, Hub Director of Strategy, Professor of Biochemical Engineering, Dean of Faculty of Engineering Sciences

EXPERTISE: Creation of whole bioprocess models and the use of these to gain process insights and understanding

WEBPAGE: http://iris.ucl.ac.uk/iris/browse/profile?upi=NJTIT16

DECISIONAL TOOLS RESEARCH

Professor Suzanne Farid

POSITION: Hub Co-Director, Professor of Bioprocess Systems Engineering

EXPERTISE: Bioprocess Decisional Tools, Bioprocess Economics, Drug Development Cost Modelling, Capacity planning, Portfolio Management, Risk Analysis, Multi-Criteria Decision-Making, Multi-Objective Simulation & Optimisation, Chemometrics

WEBPAGE: http://iris.ucl.ac.uk/iris/browse/profile?upi=SFARI53

Dr Stephen Goldrick

POSITION: Hub Co-Investigator (2020-), Lecturer in Digital Bioprocess Engineering

EXPERTISE: Advanced Data Analytics, Mathematical Modelling, Machine learning, Process Analytical Technology, Digital Twin

WEBPAGE: https://iris.ucl.ac.uk/iris/browse/profile?upi=SGOLD17

Dr Christos Stamatis

POSITION: Hub Researcher

TRAINING: Chemical Engineering (MEng), Biochemical Engineering (MSc, EngD)

EXPERTISE: Decisional tools, Process economics for mAbs and bispecifics, Chromatography process development

Dr Yang Yang

POSITION: Hub Researcher

TRAINING: Computer Science (BSc, MSc), Chemical Engineering (PhD)

EXPERTISE: Bioprocess modelling and simulation, multivariate data analysis for DSP, decisional tool development

CELL-FREE SYNTHESIS EXPERIMENTAL RESEARCH

Professor Daniel Bracewell

POSITION: Hub Co-Investigator, Professor of Bioprocess Analysis

EXPERTISE: Bioprocess analysis; Speed and capabilities of the analytical techniques used

WEBPAGE: https://iris.ucl.ac.uk/iris/browse/profile?upi=DGBRA75

Dr Beatrice Melinek

POSITION: Hub Researcher

TRAINING: MEng in Chemical Engineering, EngD in Biochemical Engineering

EXPERTISE: Cell-free synthesis of biomolecules. Additionally, viral vaccine/vector purification and process simulation

FORMULATION EXPERIMENTAL RESEARCH

Professor Paul Dalby

POSITION: Hub Co-Director, Professor of Biochemical Engineering and Biotechnology

EXPERTISE: Routes to improve the stability and activity of biocatalytic enzymes and therapeutic proteins, for ease of manufacture, formulation and delivery to patients

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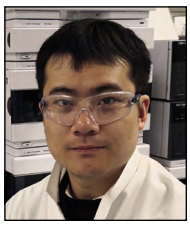


Dr Hongyu Zhang

POSITION: Hub Researcher

TRAINING: Protein aggregation specialist

EXPERTISE: Chromatography, time-resolved fluorescence spectroscopy, single-molecule spectroscopy

CELL THERAPY EXPERIMENTAL RESEARCH

Dr Qasim Rafiq

POSITION: Hub Co-Investigator, Associate Professor in Bioprocessing of Regenerative, Cellular and Gene Therapy

EXPERTISE: Bioprocessing and translation of advanced cell and gene therapies from the lab-scale to clinical and commercial scales

WEBPAGE: https://iris.ucl.ac.uk/iris/browse/profile?upi=QARAF73

Dr Nourredine Himoudi

POSITION: Hub Researcher

TRAINING: MSc Biotechnology; PhD Immunology, immunotherapy, GMP and ATIMPs manufacture management for cancer patients

EXPERTISE: Scale up, validation, manufacture and GMP production management of gene modified T cells (TCR and Chimeric Antigen Receptors) for cancer immunotherapy.

Professor Nicolas Szita

POSITION: Professor of Bioprocess Microfluidics

EXPERTISE: Translation of bioprocessing concepts into microfluidic systems (or Lab-on-a-chip systems); Use of advanced microfabrication techniques for polymers (rapid prototyping), glass and silicon

WEBPAGE: https://iris.ucl.ac.uk/iris/browse/profile?upi=NSZIT68

Dr Igor Andreyev

POSITION: Hub Researcher

TRAINING: MSc Physics, PhD Physical and Mathematical Sciences, postgraduate MSc Laser Technologies and in Biotechnology

EXPERTISE: Biophysics, laser and optical instrumentation, AFM, Raman, advanced statistics, microsystem engineering and microfluidics, nanotechnology

UCL DEPARTMENT OF APPLIED HEALTH RESEARCH (DAHR)

HEALTH ECONOMICS RESEARCH

Professor Paula Lorgelly

POSITION: Hub Co-Investigator, Professor of Health Economics

EXPERTISE: Economic evaluation particularly in the areas of oncology, genomics and precision medicine; Outcome measurement including comparing different Health Related Quality of Life instruments, eliciting patient preferences and outcome-based payment or incentive schemes

WEBPAGE: https://iris.ucl.ac.uk/iris/browse/profile?upi=PLORG17

Ms Nishma Patel

POSITION: Hub Researcher

TRAINING: Health Economist

EXPERTISE: Economic evaluation alongside clinical trials, effects of specialist cancer services, health technology adoption

UCL DEPARTMENT OF SCIENCE, TECHNOLOGY, ENGINEERING & PUBLIC POLICY (STEaPP)

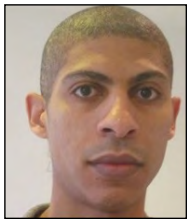
REGULATORY STRATEGIES RESEARCH

Dr Irina Brass

POSITION: Hub Co-Investigator, Associate Professor in Regulation, Innovation and Public Policy

EXPERTISE: Regulation of emerging technologies; managing emerging risks and uncertainty of disruptive innovation; public policy and governance

WEBPAGE: http://www.ucl.ac.uk/steapp/people/brass



Dr Edison Bicudo

POSITION: Hub Researcher

TRAINING: PhD, International Politics, Master's in Geography, Bachelor's Degree in Social Sciences

EXPERTISE: Social and geographical implications of biomedical technologies, e.g. bioinformatics, neuroimaging software, bioprinting

SPOKES

Imperial College London

IMPERIAL COLLEGE LONDON DEPARTMENT OF CHEMICAL ENGINEERING

SUPPLY CHAIN OPTIMISATION RESEARCH

Professor Nilay Shah

POSITION: Hub Co-Investigator, Head of Department of Chemical Engineering, Professor of Process Systems Engineering

EXPERTISE: Supply chain design and optimisation; Process synthesis and development for fine chemicals, pharmaceutical and biochemical processes; Mathematical techniques to assess and improve process safety

WEBPAGE: http://www.imperial.ac.uk/people/n.shah

Dr Maria Papathanasiou

POSITION: Hub Co-Investigator (2020-), Lecturer in Chemical Engineering

EXPERTISE: Decisional and computational tools, Process modelling, simulation and optimisation, Bioprocess modelling (bioreactors & separation processes)

WEBPAGE: https://www.imperial.ac.uk/people/maria.papathanasiou11

Dr Andrea Bernardi

POSITION: Hub Researcher

TRAINING: Chemical Engineer, PhD

EXPERTISE: Computational tools, Model-identification and parameter estimation, Process design and optimization, Supply chain optimization, Life cycle assessment

LOUGHBOROUGH UNIVERSITY SCHOOL OF MECH, ELEC & MANUFACTURING ENGINEERING

Loughborough University

CELL THERAPY FIRST-PRINCIPLES MODELLING RESEARCH

Professor Robert Thomas

POSITION: Hub Co-Investigator, Professor of Manufacturing for Cell and Gene Therapies

EXPERTISE: Production systems and processes for cell based products; Translation to commercial manufacture and clinical use; Automated and scaled production; Measurement systems for process control and quality release; defining indicators of cell product quality.

WEBPAGE: http://www.lboro.ac.uk/departments/meme/staff/robert-thomas/

Dr Maryam Shariatzadeh

POSITION: Hub Researcher

TRAINING: PharmD, Chemical Engineering, PhD

EXPERTISE: T cell manufacturing; Automated and scaled production; Cell therapies; Stem cell manufacturing; Regenerative medicine and tissue engineering

UNIVERSITY OF MANCHESTER DEPARTMENT OF ELECTRONIC & ELECTRICAL ENGINEERING

MANCHESTER 1824
The University of Manchester

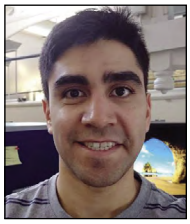
MONITORING AND CONTROL RESEARCH

Professor Barry Lennox

POSITION: Hub Co-Investigator, Professor of Applied Control

EXPERTISE: Robotics for use in Nuclear Engineering Decommissioning, Leakage and blockage detection in pipelines; Multivariate statistical process control; Model predictive control; Control loop monitoring; Monitoring and control of batch processes.

WEBPAGE: https://www.research.manchester.ac.uk/portal/barry.lennox.html



Dr Carlos Alberto Duran Villalobos

POSITION: Hub Researcher

TRAINING: Electronics Engineer/ MSc Digital Signal Processing/ PhD Process Control

EXPERTISE: Process Control, Multivariate Analysis, Adaptive Control, Data-based Models

UNIVERSITY OF NOTTINGHAM SCHOOL OF PHARMACY

NANOENCAPSULATION FORMULATION RESEARCH

Professor Jonathan Aylott

POSITION: Hub Co-Investigator, Professor in Analytical Bioscience

EXPERTISE: Design, development and implementation of miniaturized analytical devices

WEBPAGE: https://www.nottingham.ac.uk/Pharmacy/People/jon.aylott

Dr Raquel Fernandez-Garcia

POSITION: Hub Researcher

TRAINING: MPharm, PhD

EXPERTISE: Engineering and characterisation of novel formulations

UNIVERSITY OF WARWICK, WARWICK BUSINESS SCHOOL

PRODUCTION PLANNING RESEARCH

Professor Juergen Branke

POSITION: Hub Co-Investigator, Professor of Operational Research & Systems

EXPERTISE: Optimisation under Uncertainty, Multi-Objective Optimisation, Simulation-based Optimisation

WEBPAGE: http://www.wbs.ac.uk/about/person/juergen-branke/

Dr Siamak Naderi

POSITION: Hub Researcher

TRAINING: Industrial Engineering (BSc, MSc, PhD)

EXPERTISE: Operations and Supply Chain Management, Large-Scale Optimisation, Operations Research, Business Analytics

OPERATIONS & OUTREACH TEAM

Dr Eleanor Bonnist
Project Manager
UCL Biochemical Engineering

Miss Laura Pascual Buffone
Research Finance Officer
UCL Biochemical Engineering

Dr Penny Carmichael
Biomanufacturing Policy Adviser
UCL Science, Technology, Engineering and Public Policy (STEaPP), Policy Impact Unit

Dr Vaughan Thomas
Hub Outreach Consultant
Tillingbourne Consulting

FORMER TEAM MEMBERS

And next destinations after the Hub

Hub Researchers

Dr Shimaz Hashimdeen

POSITION: Researcher in Cell Therapy Experimental Research at UCL 2017-19)

DESTINATION: Senior Analytical Scientist, LGC

Dr Giovanni De Grandis

POSITION: Researcher in Regulatory Strategies Research at UCL (2017-20)

DESTINATION: AFINO Centre Coordinator, Norwegian University of Science and Technology (NTNU)

Dr Olotu Ogonah

POSITION: Researcher in Cell-Free Protein Synthesis at UCL (2017-19)

DESTINATION: Group Leader, Oxford Biomedica

Dr Veeren Chauhan

POSITION: Researcher in Nanoencapsulation Formulation at Nottingham (2017-19)

DESTINATION: Research Fellow, University of Nottingham

Dr Theano Panagopoulou

POSITION: Researcher in Cell Therapy Experimental Research at UCL (2019-20)

DESTINATION: Senior Scientist, Achilles Therapeutics

DR MARIA PAPATHANASIOU

POSITION: Researcher in Supply-Chain Modelling (2018-20)

DESTINATION: Lecturer, Imperial College

Dr Adam Collins

POSITION: Researcher in Cell Therapy First-Principles Modelling Research at Loughborough (2017-18)

DESTINATION: LabX Software Specialist, Mettler-Toledo International

Dr Xiaonan Wang

POSITION: Researcher in Supply Chain Optimization Research at Imperial College (2017)

DESTINATION: Assistant Professor, Department of Chemical and Biomolecular Engineering, National University of Singapore

Dr Elvan Gökalp

POSITION: Researcher in Production Planning Research at Warwick (2017-18)

DESTINATION: Teaching Fellow, Warwick Manufacturing Group, University of Warwick, Current: Lecturer, University of Bath

Dr Xin Fei

POSITION: Researcher in Production Planning Research at Warwick (2018-2020)

DESTINATION: Lecturer, School of Management and Bristol Digital Futures Institute, University of Bristol

Hub Co-Investigators

Prof Steve Morris

POSITION: Co-Investigator on Health Economics Research at UCL (2017-19)

DESTINATION: RAND Professor of Health Services Research, University of Cambridge

Dr Farlan Veraitch

POSITION: Co-Investigator on Manufacture and Analytics for Autologous Cell Therapies at UCL (2017-19)

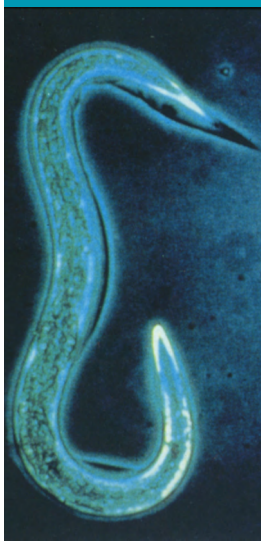
DESTINATION: Co-founder, Oribiotech

THE HUB USER PARTNERS

Partnering companies and organisations, April 2021

Companies:

- 3M
- Adaptimmune Therapeutics
- Aglaris
- Albumedix
- Applikon Biotechnology (Getinge)
- AstraZeneca
- Autolus
- BIA Separations (Sartorius)
- Biologic B
- BioPharm Services
- deltaDOT
- Eli Lilly
- Fujifilm Diosynth Biotechnologies
- GSK
- Ipsen
- Kymab (Sanofi)
- Kuopio Centre for Cell and Gene Therapy



Lonza, Orchard Therapeutics

Orchard Therapeutics

Oxford BioMedica

Pall

Perceptive

Pharmaron (Allergan)

Puridify (Cytiva)

Purolite

ReNeuron

Sartorius

SSC Bio

Sutro BioPharma

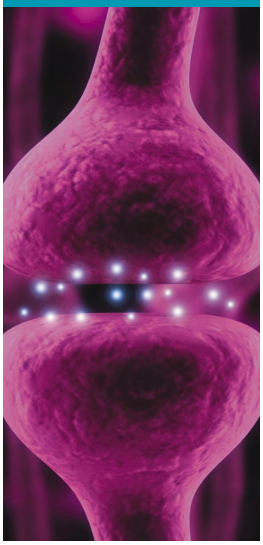
Tillingbourne Consulting

TrakCel

Univercells

West Pharmaceutical Services

Wyatt Technology



Industry/Govt Associations and Charities:

Association of the British Pharmaceutical Industry

BioIndustry Association

Cancer Research UK

Knowledge Transfer Network

LGC

Medicines Manufacturing Industry Partnership

National Institute for Biological Standards and Control

Translational Spokes:

Cell and Gene Therapy Catapult

Centre for Process Innovation/National Biologics Manufacturing Centre

EVENTS AND PUBLICATIONS

HUB EVENTS 2019-20

The Hub events are listed below. These invite members of the Hub's partnering companies and organisations to hear updates on the progress of the research and to input and interact with the project.

2019

6 February	Translation and Impact Committee
19 March	Formulation Specialist Working Group
4 April	T-Cell Processing Specialist Working Group
5 April	Cell-Free Synthesis Specialist Working Group
7 May	Decisional Tools Specialist Working Group
10 May	Healthcare Regulation and Reimbursement Specialist Working Group
21 May	User Steering Committee Meeting
22 May	Advisory Board Meeting
9 July	Autologous Cell Therapy Technology Showcase, with Cancer Research UK & Lonza
9 September	Manufacturing of Viral Vectors Event, with KTN and the Vax-Hub
19 September	T-Cell Processing Specialist Working Group
24 September	Formulation Specialist Working Group
8 October	Cell-Free Synthesis Specialist Working Group
11 October	Healthcare Regulation and Reimbursement Specialist Working Group
18 October	Decisional Tools Specialist Working Group
5 November	User Steering Committee Meeting
6 November	Advisory Board Meeting

2020

29 January	Translation and Impact Committee
5 February	Manufacturing Personalised Medicines: Overcoming the Affordability Barrier
25 February	Formulation Specialist Working Group
4 March	Phase II Planning Specialist Working Group
30 March	Advisory Board Meeting
19 May	Webinar: Looking to the Future: Phase II of the Hub
16 June	Webinar: Application of Digital Twins and Advanced Process Control
15 September	Webinar: Trends in Viral Vector Processing
30 September	Webinar: Role of Patients in Drug Dev't, Regulatory Approval, Reimbursement Decisions
6 October	Cell-Free Synthesis Specialist Working Group (online)
8 October	Formulation Specialist Working Group (online)
15 October	ATMP Manufacturing Specialist Working Group (online)
16 October	Regulation, Reimbursement and Policy Specialist Working Group (online)
20 October	Digital Decisional Tools Specialist Working Group (online)
11 November	User Steering Committee Meeting (online)
13 November	Advisory Board Meeting (online)
27 November	Webinar: Developing Therapeutic Monoclonal Antibodies for COVID-19 at Pandemic Speed

SELECTED HUB PUBLICATIONS

Journal Articles

Underlining denotes members of the dedicated Hub Research Associate team

2021

Design and development of a new ambr250® bioreactor vessel for improved cell and gene therapy applications
Rotondi M, Grace N, Betts J, Bargh N, Costariol E, Zoro B, Hewitt CJ, Nienow AW, Rafiq QA
Biotechnology Letters, 2021, *in press*, doi: 10.1007/s10529-021-03076-3

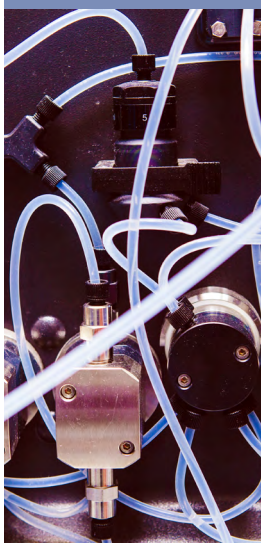
Escherichia Coli-Based Cell-Free Protein Synthesis for Iterative Design of Tandem-Core Virus-Like Particles
Colant N, Melinek B, Frank S, Rosenberg W, Bracewell DG
Vaccines, 2021, 9(3), 193, doi: 10.3390/vaccines9030193

High-Throughput Process Development for the Chromatographic Purification of Viral Antigens
Jacob SI, Konstantinidis S, Bracewell DG
In: Vaccine Delivery Technology, Pfeifer BA, Hill A (eds), Methods in Molecular Biology, 2183 Humana, New York, NY, doi: 10.1007/978-1-0716-0795-4_9

Proof-of-concept analytical instrument for label-free optical de-convolution of protein species in a mixture
Hales JE, Aoudjane S, Aeppli G, Dalby PA
Journal of Chromatography A, 2021, **1641**, 461968, doi: 10.1016/j.chroma.2021.461968

Solution structure of deglycosylated human IgG1 shows the role of CH2 glycans in its conformation
Spiteri VA, Doutch J, Rambo RP, Gor J, Dalby PA, Perkins SJ
BioPhysical Journal, 2021, *in press*, doi: 10.1016/j.bpj.2021.02.038

A Common Framework for integrated and continuous biomanufacturing
Coffman J, Brower M, Connell-Crowley L, Deldari S, Farid SS, Horowski B, Patil U, Pollard D, Qadan M, Rose S, Schaefer E, Shultz J
Biotechnology and Bioengineering, 2021,**118** (4), 1735-1749, doi: 10.1002/bit.27690



Advanced control strategies for bioprocess chromatography: Challenges and opportunities for intensified processes and next generation products
Armstrong A, Horry K, Cui T, Hulley M, Turner R, Farid SS, Goldrick S, Bracewell DG
Journal of Chromatography A, 2021, **1639**, 461914, doi: 10.1016/j.chroma.2021.461914

Lentiviral vector bioprocess economics for cell and gene therapy commercialization
Comisel RM, Kara B, Fiesser FH, Farid SS
Biochemical Engineering Journal, 2021, **167**, 107868, doi:10.1016/j.bej.2020.107868

Multivariate statistical data analysis of cell-free protein synthesis toward monitoring and control
Duran-Villalobos CA, Ogonah O, Melinek B, Bracewell DG, Hallam T, Lennox B
AIChe Journal, 2021, early view, doi: 10.1002/aic.17257

Understanding cell culture dynamics: a tool for defining protocol parameters for improved processes and efficient manufacturing using human embryonic stem cells
Kusena J, Shariatzadeh M, Thomas R, Wilson S
Bioengineered, 2021, **12** (1), 979-996, doi: 10.1080/21655979.2021.1902696

Current trends in flow cytometry automated data analysis software
Cheung M, Campbell J, Whitby L, Thomas R, Braybrook J, Petzing J
Cytometry Part A, 2021, Early View, doi: 10.1002/cyto.a.24320

The importance of cell culture parameter standardization: an assessment of the robustness of the 2102Ep reference cell line
Kusena J, Shariatzadeh M, Studd A, James JR, Thomas R, Wilson S
Bioengineered, 2021, **12**(1), 341-357, doi: 10.1080/21655979.2020.1870074

Emerging Challenges and Opportunities in Pharmaceutical Manufacturing and Distribution
Miriam Sarkis M, Bernardi A, Shah N, Papathanasiou MM
Processes, 2021, **9**(3), 457, doi: 10.3390/pr9030457

2020

PPM6 Cost-Effectiveness and Reimbursement of CELL and GENE Therapies: A Review
Patel N, Morris S
Value in Health, 2020, **23**(2), S688, doi: 10.1016/j.jval.2020.08.1723

Functional and computational identification of a rescue mutation near the active site of an mRNA methyltransferase
Colin PY, Dalby PA
*Scientific Reports,*2020; accepted

Stability enhancement in a mAB:Fab protein coformulation
Zhang H, Dalby PA
Scientific Reports 2020, **10**, 21129, 1-11, doi:10.1038/s41598-020-77989-w

Process economics evaluation of cell-free synthesis for the commercial manufacture of antibody drug conjugates
Stamatis C, Farid SS
Biotechnology Journal, 2020, doi:10.1002/biot.202000238

Rapid scale-up and production of active-loaded PEGylated liposomes. Author links open overlay panel
Rocesa CB, Emily Charlotte Port EC, Daskalakis NN, Watts JA, Aylott JW, Halbert GW, Perrie Y
International Journal of Pharmaceutics, 2020:119566, doi: 10.1016/j.ijpharm.2020.119566

Fluorescent Nanosensors Reveal Dynamic pH Gradients During Biofilm Formation
Blunk B, Perkins M, Chauhan VM, Aylott JW, Hardie KR
BioRxiv 2020.07.31.230474, doi: 10.1101/2020.07.31.230474

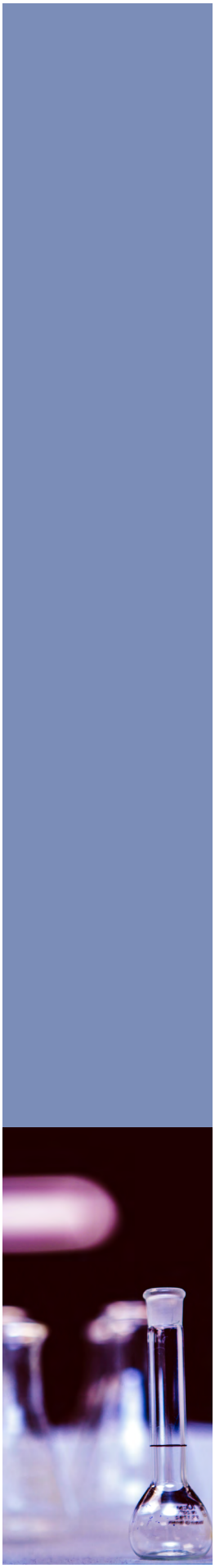
Advanced Polymeric Nanotechnology to Augment Therapeutic Delivery and Disease Diagnosis
Martins C, Chauhan VM, Araújo M, Abouselo A, Barrias CC, Aylott JW, Sarmento B
Nanomedicine, 2020; **15**(23) doi: 10.2217/nnm-2020-0145

Fluorescent Nanosensors: Real-Time Biochemical Measurement for Cell and Gene Therapies
Chauhan VM
BioProcess International, 2020

A beginner's guide to molecular dynamics simulations and the identification of cross-correlation networks for enzyme engineering
Yu H, Dalby PA
Methods in Enzymology, 2020; **643**,15-49, doi:10.1016/bs.mie.2020.04.020

Advancements in the co-formulation of biologic therapeutics
Chauhan VM, Zhang H, Dalby PA, Aylott JW
Journal of Controlled Release, 2020: 327, 397-405. doi:10.1016/j.jconrel.2020.08.013

Fine-tuning the activity and stability of an evolved enzyme active-site through noncanonical amino-acids
Wilkinson HC, Dalby PA
The FEBS Journal, 2020: early view, doi:10.1111/febs.15560



HDX and In Silico Docking Reveal that Excipients Stabilize G-CSF via a Combination of Preferential Exclusion and Specific Hotspot Interactions
Wood VE, Groves K, Cryar A, Quaglia M, Matejtschuk P, Dalby PA
Molecular Pharmaceutics, 2020; *early view*, doi:10.1021/acs.molpharmaceut.0c00877

Benchmarking biopharmaceutical process development and manufacturing cost contributions to R&D
Farid SS, Baron M, Stamatis C, Nie W, Coffman J
mAbs, 2020: **12** (1),1754999, doi:10.1080/19420862.2020.1754999

High-Throughput Raman Spectroscopy Combined with Innovate Data Analysis Workflow to Enhance Biopharmaceutical Process Development
Goldrick S, Umprecht A, Tang A, Zakrzewski R, Cheeks M, Turner R, Charles A, Les K, Hulley M, Spencer, C, Farid SS,
Processes, 2020; **8** (9), 1179, doi:10.3390/pr8091179

A rational approach to improving titer in E. coli-based cell-free protein synthesis reactions
Colant N, Melinek B, Teneb J, Goldrick S, Rosenberg W, Frank S, Bracewell DG
Biotechnology Progress, 2020; e3062, doi:10.1002/btpr.3062

Holistic process development to mitigate proteolysis of a subunit rotavirus vaccine candidate produced in Pichia pastoris by means of an acid pH pulse during fed-batch fermentation
Velez-Suberbie ML, Morris SA, Kaur K, Hickey JM, Joshi SB, Volkin DB, Bracewell DG, Mukhopadhyay TK
*Biotechnology Progress,*2020; e2966. doi:10.1002/btpr.2966

Improving the reaction mix of a Pichia pastoris cell-free system using a design of experiments approach to minimise experimental effort
Spice AJ, Aw R, Bracewell DG, Polizzi KM
*Synthetic and Systems Biotechnology,*2020; **5** (3), 137-144, doi:10.1016/j.synbio.2020.06.003

In situ neutron scattering of antibody adsorption during protein A chromatography
Papachristodoulou M, Doutch J, Leung HSB, Church A, Charleston T, Clifton LA, Butler PD, Roberts CJ, Bracewell DG
Journal of Chromatography A, 2020; **1617**, 460842, doi:10.1016/j.chroma.2019.460842

Demonstrating the Manufacture of Human CAR-T Cells in an Automated Stirred-Tank Bioreactor
Costariol E, Rotondi MC, Amini A, Hewitt CJ, Nienow AW, Heathman TRJ, Rafiq QA
Biotechnology Journal, 2020: **15**(9), 200177, doi:10.1002/biot.202000177

Expansion of human mesenchymal stem/stromal cells (hMSCs) in bioreactors using microcarriers: lessons learnt and what the future holds
Silva Couto P, Rotondi MC, Bersenev A, Hewitt CJ, Nienow AW, Verter F, Rafiq QA
Biotechnology Advances, 2020; **45**, 107636, doi:10.1016/j.biotechadv.2020.107636

Toward a Roadmap for Cell-Free Synthesis in Bioprocessing
Melinek B, Colant N, Stamatis C, Lennon C, Farid SS, Polizzi K, Carver C, Bracewell DG
BioProcess International, 2020

The two-species model of transkeletose explains donor substrate-binding inhibition and heat-activation
Wilkinson H, Dalby PA
Scientific Reports, 2020; **10**, 4148, doi: 10.1038/s41598-020-61175-z

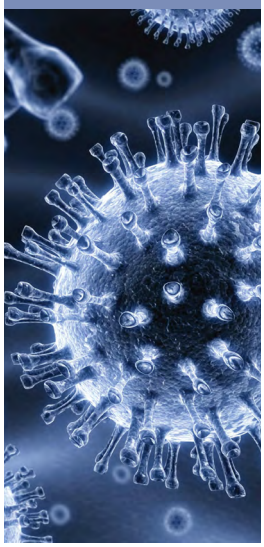
Synthesis and Assembly of Hepatitis B Virus-Like Particles in a Pichia pastoris Cell-Free System
Spice A J, Aw R, Bracewell DG, Polizzi KM
Frontiers in Bioengineering and Biotechnology, 2020; **8**, 72, doi:10.3389/fbioe.2020.00072stab

Pharmaceutical R & D pipeline management under trial duration uncertainty
Gökalp E, Branke J
Computers and Chemical Engineering, 2020; **136**,106782, doi:10.1016/j.compchemeng.2020.106782

How should we evaluate the cost-effectiveness of CAR T-cell therapies?
Patel N, Farid S.S, Morris S
*Health Policy and Technology,*2020; published online, doi: 10.1016/j.hlpt.2020.03.002

Distributed automated manufacturing of pluripotent stem cell products
Shariatzadeh M, Chandra A, Wilson SL, McCall MJ, Morizur L, Lesueur L, Chose O, Gepp MM, Schulz A, Neubauer JC, Zimmermann H, Abranches E, Man J, O'Shea O, Stacey G, Hewitt Z, Williams DJ
*The International Journal of Advanced Manufacturing Technology,*2020;**106**,1085-1103, doi:10.1007/s00170-019-04516-1

Autologous CAR T-cell therapies supply chain: challenges and opportunities?
Papathanasiou MM, Stamatis C, Lakelin M, Farid S, Titchener-Hooker N, Shah N
Cancer Gene Therapy Nature (2020) doi: 10.1038/s41417-019-0157-z



Engineering challenges in therapeutic protein product and process design
Papathanasiou MM, Kontoravdi C
Current Opinion in Chemical Engineering, 2020; **27**, 81-88 doi: 10.1016/j.coche.2019.11.010

Investment Planning in Personalised Medicine
Moschou D, Papathanasiou MM, Lakelin M. Shah N
Computer Aided Chemical Engineering, 2020, **48**, 49-54, doi: 10.1016/B978-0-12-823377-1.50009-4

Estimating Capital Investment and Facility Footprint in Cell Therapy Facilities
Pereira Chilima TD, Moncaubeig F, Farid SS
Biochemical Engineering Journal, 2020; **155**, 107439, doi:10.1016/j.bej.2019.107439

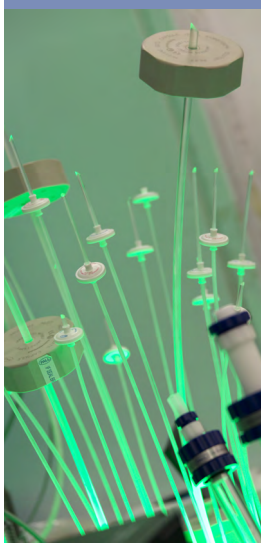
Multivariate Data Analysis Methodology to Solve Data Challenges Related to Scale-up Model Validation and Missing Data on a Micro-Bioreactor System
Goldrick S, Sandner V, Cheeks M, Turner R, Farid SS, McCreath G, Glassey J
Biotechnology Journal, 2020; **15**(3), 1800684, doi:10.1002/biot.201800684

Multivariate statistical process control of an industrial-scale fed-batch simulator
Duran-Villalobos C, Goldrick S, Lennox B
Computers & Chemical Engineering, 2020; **132**, 106620, doi: 10.1016/j.compchemeng.2019.106620

Modelling protein therapeutic co-formulation and co-delivery with PLGA nanoparticles continuously manufactured by microfluidics
Martins C, Chauhan V, Selo A, Al-Natour M, Aylott J, Sarmento B
Reaction Chemistry & Engineering, 2020; **5**, 308-319, doi: 10.1039/C9RE00395A

Facile Dye-Initiated Polymerization of Lactide–Glycolide Generates Highly Fluorescent Poly(lactic-co-glycolic Acid) for Enhanced Characterization of Cellular Delivery
Al-Natour MA, Yousif MD, Cavanagh R, Abouselo A, Apebende EA, Ghaemmaghami A, Kim D-H, Aylott JW, Taresco V, Chauhan VM, Alexander C
ACS Macro Letters, 2020; **9**(3), 431-437, doi: 10.1021/acsmacrolett.9b01014

Using microfluidics for scalable manufacturing of nanomedicines from bench to GMP: A case study using protein-loaded liposomes
Webb C, Forbes N, Roces CB, Anderluzzi G, Lou G, Abraham S, Ingalls L, Marshall K, Leaver TJ, Watts JA, Aylott JW, Perrie Y
International Journal of Pharmaceutics, 2020; **582**, 119266, doi: 10.1016/j.ijpharm.2020.119266



Prediction of the enhanced insulin absorption across a triple co-cultured intestinal model using mucus penetrating PLGA nanoparticles
Jaradat A, Macedo MH, Sousa F, Arkill K, Alexander C, Aylott J, Sarmento B
International Journal of Pharmaceutics, 2020; in press, doi: 10.1016/j.ijpharm.2020.119516

A Monte Carlo framework for managing biological variability in manufacture of autologous cell therapy from mesenchymal stromal cells therapies
Picken A, Harriman J, Iftimia-mander A, Johnson L, Prosser A, Quirk R, Thomas R
Cytotherapy, 2020; **22**, 227-238, doi: 10.1016/j.jcyt.2020.01.006

2019

Assisting continuous biomanufacturing through advanced control in downstream purification
Papathanasiou MM, Burnak B, Katz J, Shah N. Pistikopoulos EN
Computers & Chemical Engineering, 2019, **125**, 232-248, doi: 10.1016/j.compchemeng.2019.03.013

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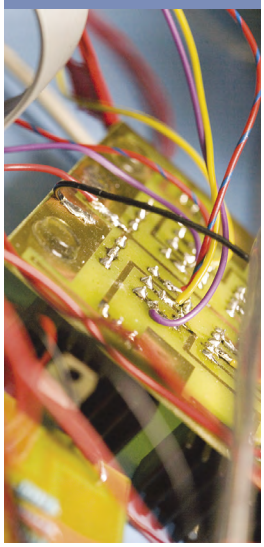

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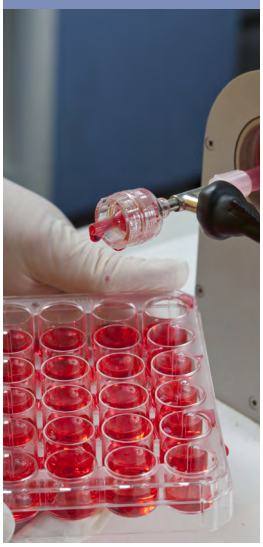

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Conference Presentations

2020

Nishma Patel
Cost-Effectiveness and Reimbursement of CELL and GENE Therapies: A Review
International Society for Pharmacoeconomics and Outcomes Research Europe
16-19 November 2020, Online

Qasim Rafiq
Bioprocessing and biomanufacturing approaches for ATMPs
European Society of Biochemical Engineering Sciences (ESBES)
15-18 September 2020, Online

Suzanne Farid
Manufacture of gene modified cell therapies workshop: COG and supply chain perspectives for CAR T
Advanced Therapies Congress and Expo
8-11 September 2020, Online

Suzanne Farid
Panel discussion: Towards affordable and sustainable ATMP costs
Advanced Therapies Congress and Expo
8-11 September 2020, Online

Qasim Rafiq
Manufacture of gene modified cell therapies workshop
Advanced Therapies Congress and Expo
8-11 September 2020, Online

Maria Papathanasiou
Enabling precision healthcare through patient-centric, model-based supply chain optimisation
Advanced Therapies Congress and Expo
8-11 September 2020, Online

Maryam Shariatzadeh
An ODE model for optimal operation of T-cell culture in suspension systems
Advanced Therapies Congress and Expo
8-11 September 2020, Online

Qasim Rafiq
Bioprocess Development of Viral Vectors and Gene Therapies
Annual Saudi Hematology Congress
27-29 February 2020, Muscat, Oman

Qasim Rafiq
Process intensification and technology development for CAR-T therapies
CAR-TCR Summit
24-27 February 2020, London, UK

Maria Papathanasiou
Enabling precision healthcare through patient-centric, model-based supply chain optimisation
Cell and Gene Therapy Innovation 2020 Summit
5-6 February 2020, Berlin, Germany

Igor Andreyev
Could key cell attributes be defined and monitored label-free for a Quality Control of manufacturing a safe and potent immunotherapeutic cell product
Cell and Gene Therapy Innovation 2020 Summit
5-6 February 2020, Berlin, Germany

Hongyu Zhang
Stability enhancement from coformulation of therapeutic proteins
Bioprocessing International Asia
26-28 February 2020, Kyoto, Japan

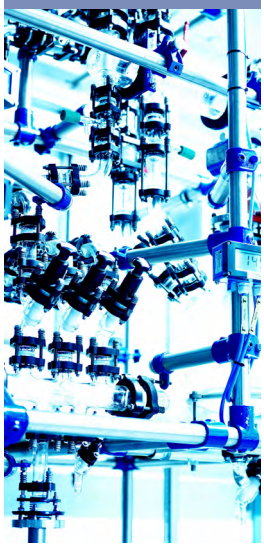
Hongyu Zhang
Coformulation of therapeutic proteins
UCLAN event: Your product in their hands
14 January 2020, Preston, UK

2019

Qasim Rafiq
End-to-end process development and manufacture of cell and gene therapies
Cell Therapy Manufacturing and Gene Therapy Congress
1-4 December 2019, Amsterdam, The Netherlands

Suzanne Farid
FTHM Hub: Next-generation biomanufacturing solutions to enable precision medicine
16th Annual BioProcessUK Conference
26-28 November 2019, Liverpool, UK

Qasim Rafiq
Automated and Scalable Manufacturing Strategies for CAR-T and Advanced Therapies
Phacilitate Leaders: Asia
15-16 October 2019, Shanghai, China



Xin Fei
A race against time: optimal schedule compression in the drug pipeline under uncertainty
30th European Conference on Operational Research (EURO)
23-26 June 2019, Dublin, Ireland

Igor Andreyev
Label-free recognition of non-activated and activated human T cells by Quantative Phase Imaging
2019 BioMAN Summit
11-12 December, 2019, Boston MA, USA

Hongyu Zhang
Coformulation of therapeutic proteins
Festival of Biologics
15-17 October 2019, Basel, Switzerland

Daniel Bracewell
Viral Vector Recovery: Design of Adsorption based Separations to Maintain Infectivity
Bioprocess International
9-12 September 2019, Boston MA, USA

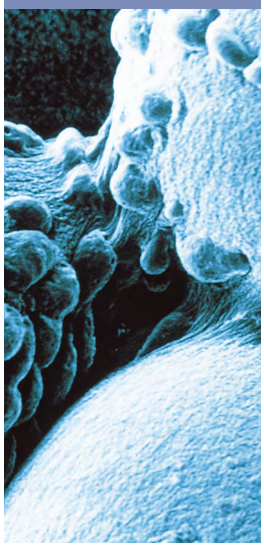
Yang Yang
Machine learning in personalised prognosis prediction of lung cancer
27th Conference on Intelligent Systems for Molecular Biology
21-25 July 2019, Basel, Switzerland

Maryam Shariatzadeh
Mechanistic Modelling for T Cell Therapy Manufacture,
BSCGT Annual Conference 2019
19-21 June 2019, Sheffield, UK

Giovanni De Grandis
Tools for Navigating the European Regulatory Framework for ATMPs
2019 PDA Europe Conference on Advanced Therapy Medicinal Products (ATMPs)
4-5 June 2019, Vilnius, Lithuania

Suzanne Farid
Creating a roadmap for CAR T-cell therapies to achieve commercial success
World Advanced Therapies & Regenerative Medicines Congress
15-17 May 2019, London, UK

Suzanne Farid
Panel discussion: Moving towards full automation and closed systems
World Advanced Therapies & Regenerative Medicines Congress
15-17 May 2019, London, UK



Paul Dalby
Analysis, control and engineering of protein dynamics, stability and aggregation
CASSS 8th International Symposium on Higher Order Structure of Protein Therapeutics
8-10 April 2019, San Francisco CA, USA

Suzanne Farid
Decisional tools for predictive data-mining & cost-effective design for biopharma facilities of the future (keynote) 257th American Chemical Society (ACS) Meeting,
March 31-April 4 2019, Orlando, FL, USA

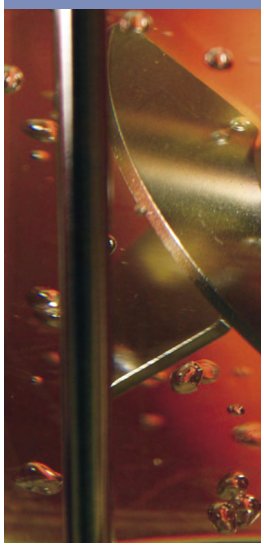
Jonathan Aylott
Sensing inside the cell with miniaturised analytical devices
MediLink East Midlands Sensing and Imaging for diagnostics, detection and monitoring
28 February 2019, Nottingham, UK

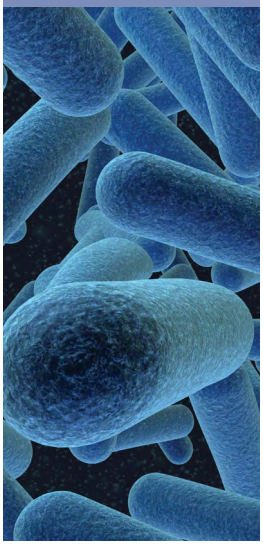
Qasim Rafiq
Process Development and Manufacturing Strategies
CART-TCR Summit Europe Meeting
25-27 February 2019, London, UK

Robert Thomas
Efficient model driven design of cell-based product manufacturing
ECI Advancing Manufacture of Cell and Gene Therapies VI
27-31 January 2019, Coronado CA, USA

Veeren Chauhan
Augmenting automated analytics using fluorescent nanosensors
Phacilitate Leaders World and the World Stem Cell Summit
22-25 January 2019, Miami, Florida, USA

Jonathan Aylott
Nanosensors and measurement of biological material in situ and in real time
ESACT-UK Annual Scientific Meeting
9-10 January 2019, Tamworth, UK



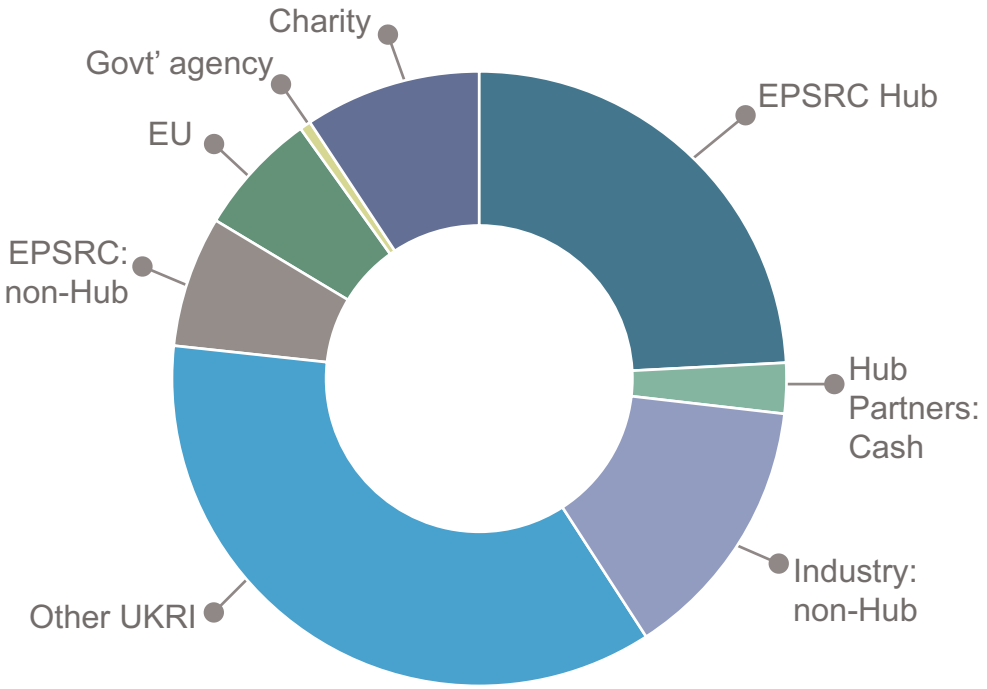


FINANCES

FINANCES

Leveraged Funding

Figure 11: Cumulative value of the Hub grant & leveraged funds awarded by Year 4 (Dec 2020)



Growth of the grant portfolio associated with the Hub is an important metric of success. We have pursued a number of different avenues, including companies, government agencies and UKRI. The Hub has secured approximately £18M from external sources, which complements the £5.8M EPSRC core funding for the first four years of the Hub. In addition to this, Users have pledged in-kind contributions to the value of £5M to date.

APPENDICIES

APPENDIX 1: RESEARCH THEME TEMPLATES

GC1.1 Techno-Economic Optimisation of Novel Manufacturing Technologies

UCL Biochemical Engineering

Team (January 2017-June-2020):

Prof Suzanne Farid (Co-Investigator, UCL), Dr Christos Stamatis (Researcher, UCL), Dr Yang Yang (Researcher, UCL)

Aim:

Create integrated biomanufacturing optimisation tools to identify the extent of technical innovation required to offer cost-effective and robust manufacturing routes for the successful commercialisation of a spectrum of proteins and cell therapies with increasing stratification through to patient-specific medicines. Establish an integrated drug development and manufacturing business model to identify routes that enable feasible business models for successful commercialisation of targeted protein and cell therapy medicines.

Key Research Challenges:

As the sector moves towards portfolios of more targeted medicines, production batch sizes will be smaller and not benefit from economies of scale to the same extent as traditional one-size-fits-all medicines. As a result, the manufacturing cost of goods will rise and may lead to infeasible business models. Determining the technical innovation required for successful commercialisation will require new disruptive and integrated manufacturing technologies for process flowsheets that start with patient source material or diagnostic information through to manufacture of the drug substance and formulation of the drug product and delivery back to the patient. Estimating the commercial feasibility of new manufacturing technologies will require the development of novel predictive process economics correlations as well as new measures of technology attractiveness to balance the financial performance with operational criteria such as complexity, ease of moving out of a controlled cleanroom environment to bedside manufacture, and agility to respond to source variability.

Research and Impact Highlights:

- **Decisional tools created:** Integrated tool comprises a manufacturing economics engine and a drug development economics engine, with uncertainty and optimisation algorithms, for stratified proteins and personalised cell therapies.
- **Database established:** Captured default process and business parameters for manufacturing, drug development and supply chain activities.
- **Cell-free synthesis economics:** Case studies highlighted cost of goods differences and technical innovation required for cell-free synthesis compared to traditional processes for antibody-drug conjugates (Stamatis & Farid, Biotechnology Journal, 2020)
- **CAR T-cell process and supply chain economics:** Decisional tools identified which manufacturing platforms are most cost-effective, the key cost of goods (COG) drivers, technical innovation required and the risk-reward trade-offs between centralised versus bedside manufacture (Pereira Chilima et al., submitted)
- **Drug development cost benchmarks:** Established process development and manufacturing cost benchmarks for different attrition rates and their contribution to R&D costs for proteins and cell therapies (Farid, Stamatis et al. MAbs, 2020)

Stakeholder Engagement Highlights:

- **BioIndustry Association Manufacturing Advisory Committee (BIA MAC) & Oxford Biomedica:** User feasibility study on "Economic analysis to investigate the consequences of switching to scalable GMP processes for viral vectors on drug development lifecycle costs". Joint user feasibility study outputs fed into a pan-UK business case from the MMIP (Medicines Manufacturing Industry Partnership) on "A UK Strategy for the Manufacture of GMP Viral Vectors" that led to funding to establish Gene Therapy Innovation Hubs.
- **Sutro Biopharma:** offered critical insights on the cell-free synthesis process for biopharmaceuticals (mAbs and ADCs) and helped develop the appropriate design correlations.
- **Ipsen:** User feasibility study on "Techno-economic evaluation of a cell-free synthesis (CFS) system for the expression of a recombinant toxin".
- **UCL CAR-T Clinicians, UCL Cancer Institute/UCLH:** helped to sanity check patient starting material characteristics for CAR-T manufacturing.

GC1.2 Reimbursement Models & Regulatory Strategies for Targeted Healthcare

UCL Biochemical Engineering (BE), UCL Department of Applied Health Research (DAHR), UCL Department of Science Technology, Engineering and Public Policy (STEaPP)

Team (January 2017-June-2020):

Prof Steve Morris (Co-Investigator, DAHR, 2017-19), Prof Paula Lorgelly (Co-Investigator, DAHR), Prof Arthur Petersen (Co-Investigator, STEaPP, 2017-18), Dr Irina Brass (Co-Investigator, STEaPP), Prof Suzanne Farid (UCL BE), Dr Giovanni De Grandis (Researcher, STEaPP, 2017-2020), Nishma Patel (Researcher, DAHR)

Aim:

Identify the main opportunities and challenges pertaining to emerging reimbursement and regulatory models to help identify feasible business models for stratified protein and personalised cell therapy medicines.

Key Research Challenges:

Biopharmaceutical (protein and cell therapy) economics are dictated by time, cost and risk. Stratified protein medicines have the potential to increase the clinical success rate. Personalised cell therapies that cure disease present a potential game changer. Yet there is significant uncertainty regarding the regulatory and reimbursement strategies for these therapies, especially under adaptive clinical trial and regulatory scenarios piloted by e.g. the European Medicines Agency (EMA). Understanding the role that regulatory and market factors play on development and manufacturing costs will thus determine the payoffs of different technological innovations, thereby helping the prioritisation of R&D investment.

Research and Impact Highlights:

- **Scoping analysis on pricing strategies for targeted healthcare:** A series of meetings conducted with key stakeholders (manufacturers, NHS) to map out reimbursement landscape for targeted therapies and identify challenges demonstrating cost-effectiveness in the NHS.
- **Affordability of CAR Ts and implications for other high-cost therapies:** NICE's approach to appraising CAR T-cell therapies, Yescarta® and Kymriah®, has been mapped out and analysed for its impact on NHS England's ability to resource other health services (Patel et al., Health Policy and Technology, 2020)

- **Systematic review on reimbursement models for ATMPs:** Comparative analysis of cost-effectiveness evidence, reimbursement models and market authorisation for personalised ATMPs (Patel et al., in prep)
- **Impact of personalised healthcare regulatory pathways on patients:** Perspective on the promises and perils of regulatory pathways for personalised healthcare for patients (De Grandis et al., Risk and Regulation, 2018)
- **Mapping out accelerated regulatory pathways for ATMPs in EU and US:** Included timelines to approval, post-marketing requirements and the unintended consequences on key stakeholders (manufacturers, clinicians, patients and regulators), (De Grandis et al. article submitted).
- **Implications of accelerated pathways for CMC Strategies:** Investigated the main consequences on Chemistry and Manufacturing Controls (CMC) development and identified frontloaded activities.

Stakeholder Engagement Highlights:

- **Healthcare Regulation and Reimbursement Specialist Working Group:** Regular engagement with the stakeholders to gather & validate primary research findings: regulatory consultants (ERA Consulting, Lex Regulatory); public bodies (Cell & Gene Therapy Catapult, Innovate UK, NICE); drug developers (Orchard Therapeutics, GSK, Autolus, Allergan); trade associations (ABPI)
- **Regulatory Science Workshop with industry and regulators:** Organised for Hub users, MHRA, regulatory consultants and Hub academic team to explore regulatory scenarios for novel Hub technologies (02/18)
- **Engagement with NHS E&I:** NHSE&I Accelerated Access Collaborative (AAC) and NHSE&I Medicines Analysis Strategy and Policy Team, discussed challenges assessing cost-effectiveness of highly specialised ‘curative’ therapies. Participated in AAC Data Infrastructure Working Group.
- **Engagement with clinical groups:** UCL CAR T Programme (ALLCART19) interaction led to a joint academic feasibility study to incorporate health economics indicators in clinical trial design.
- **British Standards Institution (BSI):** Meeting standardisation gaps in high value manufacturing (e.g. digital innovation in high quality medicines supply chains; beyond PAS 83, 93).
- **Response to Public Consultations:** Led Hub responses on EMA’s Regulatory Science Strategy to 2025 and NICE’s methods for health tech evaluation with a focus on ATMP viewpoints.

GC1.3 Clinical Production Planning & Portfolio MGT for Stratified Medicines

Warwick Business School (WBS), Imperial College Chemical Engineering, UCL Biochemical Engineering

Team (January 2017-June-2020):

Prof Juergen Branke (Co-Investigator, WBS), Prof Nilay Shah, (Co-Investigator, Imperial), Prof Suzanne Farid (Co-Investigator, UCL BE), Dr Elvan Gökalp (Researcher, WBS, 2017-2018), Dr Xin Fei (Researcher, WBS, 2019-2020)

Aim:

Develop heuristic optimisation algorithms to support integrated R&D portfolio management and clinical trial scheduling for companion-diagnostic-driven stratified protein medicines.

Key Research Challenges:

With stratified protein medicine, the development pipeline will feature more drugs or drug variants, companion diagnostics have to be developed and tested alongside drugs, and the number of patients and their timing in clinical trials will feature much larger variation. This is compounded by new adaptive clinical trial designs that put increased time pressures on clinical manufacturing. This necessitates a more integrated decision process, modelling portfolio selection, clinical production and clinical trials as one multi-stage decision problem under uncertainty.

Research and Impact Highlights:

- **Clinical trial scheduling with uncertain trial outcomes and lengths:** Developed a stochastic optimisation model using principles of reinforcement learning and statistical simulation in order to identify better decisions related to clinical trial scheduling and resource allocation across biopharma projects; the model generates solutions consistently better than heuristics used in industry and other state-of-the-art algorithms. (Gökalp & Branke, Computers and Chemical Engineering, 2020)
- **Extension 1: Resource optimisation for clinical trials with speed-up option:** The framework has been further extended to include project crashing, i.e., the allocation of additional resources to speed up certain phases of a project. Results demonstrate that project crashing can improve strategic flexibility and further increase the total projected profit. (Fei et al., article submitted)

- **Extension 2: Drug pipeline with stratified medicine:** When the drug pipeline involves stratified medicine, this extension captures the use of companion diagnostics into the portfolio planning and scheduling model. This model is currently in development to inform decision-makers whether it is worth trying to rescue a failed drug by developing a companion diagnostic.
- **Companion diagnostic incentivisation model:** A model has been created to investigate the critical combination of conditions required to incentivise drug companies to develop companion diagnostics.

Stakeholder Engagement Highlights:

- **Allergan, Polpharma, Diaceutics:** Met with Allergan to better understand their current portfolio planning approaches and needs, and with Diaceutics and Polpharma Biologics (non-Hub partners) to better understand the role of companion diagnostics in drug development.
- **University of Warwick Medical School:** joint academic feasibility study with Prof Stallard (Prof of Medical Statistics) to develop some realistic case studies to better understand what incentivizes companies to develop companion diagnostics and better align their incentives with the aims of healthcare providers.
- **Icosystem:** provided a complimentary license to their software that allows to simulate a drug development pipeline.

GC1.4 Commercial Supply Chain Logistics for Personalised Medicines

Imperial College Chemical Engineering, Warwick Business School (WBS), UCL Biochemical Engineering

Team (January 2017-June-2020):

Prof Nilay Shah, (Co-Investigator, Imperial), Prof Juergen Branke (Co-Investigator, WBS), Prof Suzanne Farid (Co-Investigator, UCL BE), Dr Xiaonan Wang (Researcher, Imperial, 2017), Dr Maria Papathanasiou (Researcher, Imperial, 2018-2020).

Aim:

Develop personalised cell therapy supply chain design and optimisation models to identify new supply chain concepts that streamline and de-risk manufacturing and delivery to patient activities.

Key Research Challenges:

The development of viable future supply chain concepts in the nascent field of personalised medicines is fraught with uncertainties in relation to markets, production technologies and product form. The challenges are therefore to a) develop high level scenarios capturing likely developments on the technology, product and patient care side (including mapping end-to-end workflows) and b) use these scenarios to develop supply chain design and operation approaches that can then deal internally with the remaining systemic uncertainties. This will require a holistic systems level understanding of the elements; fortunately the Hub team draws from experts in all these domains. A further complexity anticipated relates to the large and complex nature of the “data value chains” which should be constantly analysed and mined with feedback.

Research and Impact Highlights:

- **CAR T-cell supply chain mapping:** Existing supply chains have been characterized and likely future supply chain workflows have been proposed (Papathanasiou et al., Cancer Gene Therapy, 2020)
- **Supply chain optimisation model created:** A Mixed Integer Linear Programming (MILP) core model, based on real-world data, has been designed and serves as basis for further investigation of case studies.
- **CAR T-cell UK case studies undertaken:** Optimal supply chain concepts and their KPIs identified with MILP model to de-risk manufacturing and delivery of personalised therapies. Case studies

on cost of manufacturing/delivery versus response time trade off, in-house quality control testing versus outsourced, decentralised versus centralised manufacturing using facilities of variable capacities, opportunities in investment planning of the current supply chain model.

Stakeholder Engagement Highlights:

- **Trakcel:** User feasibility study on "Development of supply chain optimization models for autologous CAR T cells". Industrial validation and joint case study on the cost-benefit and optimisation analyses for the CAR T cell supply chain, encompassing total cost of manufacturing and transportation, therapy delivery time, demand on the supply chain network structure, cell orchestration platforms and facility optimisation.
- **Albumedix:** exploring opportunities for supply chain improvements based on the use of novel agents that will improve viability of the final formulation.
- **National University of Singapore:** tested our MILP formulation under stochastic optimisation scenarios.

GC2.1 Manufacturing Proteins for Targeted Populations

UCL Biochemical Engineering

Team (January 2017-June-2020):

Prof Daniel Bracewell (Co-Investigator, UCL), Dr Beatrice Melinek (Researcher, UCL), Dr Olotu Ogonah (Researcher, UCL, 2017-19)

Aim:

Stratified protein medicines will require small process batches, using flexible and distributed manufacture, at low cost. We will evaluate innovations that achieve this while also reducing the time and cost of development.

Key Research Challenges:

Meeting these aims requires process automation with robust process monitoring and control. Innovation is required to gain economies of scale where possible, and to rationalise traditional upstream (USP) and downstream (DSP) process operations, to reduce cost of goods. Cell-free synthesis technology promises faster process development, rapid protein supply for formulation design, and process-ready supply of clinical materials. Cell extract manufacture provides an economy of scale, prior to lower-volume stratified protein synthesis. Cell-free systems incorporating non-natural amino acids allow tighter control of drug conjugation to proteins for stratified populations.

Research and Impact Highlights:

- **Established *E. coli* based cell-free synthesis platform in-house:** An IP free system developed at UCL for process development of universal flu VLPs and synthetic viral particle processes, and for collaboration with Hub members. Developed with Hub-aligned PhD students. Applied to the synthesis of novel universal flu vaccine virus-like particles from SME/UCL Spin-out iQur. Used as the basis for a collaborative Hub project with Fujifilm Diosynth to evaluate in mAb fragment synthesis. (Colant, Melinek et al., Biotechnology Progress, 2020)
- **Established *E. coli* based cell-free synthesis platform and collaboration with Sutro:** Established a collaboration with Sutro (Material Transfer Agreement, keynote speaker at Hub USC, PDRA secondment to Sutro) to advise Hub on cell-free synthesis processes and industry challenges. Platform based on Sutro Biopharma technology used at UCL to study control of the system for mAb synthesis in collaboration with GC2.4 (Manchester). (Duran-Villalobos, Ogonah, Melinek et al., AIChe Journal, 2021)

- **Scalable cell-free synthesis:** Scalable processes for protein and virus-like particle synthesis established using in-house protocols. (Colant, Melinek, Bracewell et al., Vaccines, 2021)
- **Cell-free synthesis roadmap:** Roadmap developed with Hub SWG consultation to elucidate drivers and barriers to use of cell-free synthesis for stratified medicines manufacture and to map out desirable future states of the technology. (Melinek et al. BioProcess International, 2020)

Stakeholder Engagement Highlights:

- **CFS Specialist Working Group (SWG):** an active group of core users established and driving the agenda. Produced a review on challenges and opportunities for CFS in an era of personalised medicine. Collaborating with GC1.1 to evaluate the compare the costs of CFS-based manufacturing to conventional cell-based routes. Development of a roadmap for CFS-based manufacturing.
- **Sutro Biopharma:** Collaboration with Sutro Biopharma led to a 1 month internship for the Hub Researcher at Sutro's HQ in San Francisco. Involved training and initial research, unique access to their CFPS reagents for academic research on process control (UCL & Manchester). Input from Chief Scientific Officer into Working Group and as a keynote speaker at Hub User meetings.
- **FujiFilm:** Collaboration with FujiFilm on CFS demonstration and production of industrially relevant products. The UCL CFS system was transferred to FujiFilm manufacturing site and showed successful synthesis of superfolder Green Fluorescent Protein (sfGFP) from a plasmid. The study revealed that plasmid preparation method is a critical factor in success of this method and an important area for further development. The study opened up discussions internationally, with FujiFilm's colleagues at their HQ in Japan.

GC2.2 Formulation of Stratified Proten Medicines

UCL Biochemical Engineering, University of Nottingham School of Pharmacy

Team (January 2017 – June 2020):

Prof Paul Dalby (Co-Investigator, UCL), Prof Jonathan Aylott (Co-Investigator, Nottingham), Dr Veeren Chauhan (Researcher, Nottingham, 2017-19), Dr Hongyu Zhang (Researcher, UCL)

Aim:

Further patient stratification will arise from diagnosis of multiple biomarkers produced as stratified batch co-formulations, but potentially also personalised by co-formulations at the bedside. We will explore novel formulation strategies to enable rapid design of stable combination therapies, including co-formulated, conjugated and fused-protein options.

Key Research Challenges:

Independent administration of multiple therapies leads to complex dosage regimens, with associated patient non-compliance, and significant risk of mis-dosing. Co-formulating complex mixtures, chemical- protein conjugates, or protein fusions into a single dosage form will simplify delivery to patients yet increase the challenge to rapidly design formulations that stabilise each protein component. Innovation is required to analyse, predict and control via formulation, the stability and efficacy of multiple proteins within complex interacting mixtures.

Research and Impact Highlights:

- **Co-formulation:** Multiple case studies have established the impacts of protein co-formulation. E.g. discovered co-formulated antibody formats can stabilise each other. (Zhang & Dalby, Scientific Reports, 2020)
- **Co-formulation:** Analysis of clinical trials data identified the rapid growth of trials involving multiple biologics. Nottingham and UCL reviewed co-formulation advances and challenges in the medicines manufacturing sector. (Chauhan, Zhang et al., Journal of Controlled Release, 2020)
- **Nanoencapsulation:** Established scalable nanoparticle manufacturing to encapsulate co-formulated proteins and fluorophores, then deliver to cells. Process control ensured the correct particle size distribution and morphology, critical for regulatory acceptance. (Al-Natour et al. ACS Macro Letters, 2020; Martins, Chauhan et al., Reaction Chemistry and Engineering, 2020).

- **Analytics:** New instrument developed to monitor the degradation of proteins in mixtures, e.g. co-formulations. Formed basis of an EngD project partnership with Pall Europe, Royal Society of Edinburgh and UKRI Future Leaders Fellowships, and the business case for spin out Roxijen.
- **Analytics:** A novel viral lasing technique was co-developed for antibody detection through. (Hales et al. Nature Communication, 2019)
- **Analytics:** Established core techniques as a basis for future digital formulation capability. Neural Network predicts protein formulation stability from fluorescence spectra.

Stakeholder Engagement Highlights:

- **AstraZeneca (MedImmune):** Supplied mAb and bispecifics – critical for co-formulation studies.
- **Albumedix:** Supply of recombinant human serum albumin to investigate its use as a delivery adjunct for poorly soluble drugs, and to develop nanoencapsulation strategies for co-formulation using albumin as a carrier matrix.
- **Ipsen:** Aligned PhD project to investigate BoNT therapeutic formulations by SAXS at the Diamond Light Source.
- **Pall Europe:** EngD project to develop a portable version of the TRF analytic instrument for inline monitoring.
- **MHRA:** Met with the MHRA Innovation team to identify key regulatory challenges associated with stratified protein co-formulation approaches.
- **Albumedix:** Supply of recombinant human serum albumin for formulation studies. Feasibility study to investigate co-formulation of poorly-soluble small molecule drug in albumin microparticle scaffold.
- **AstraZeneca (MedImmune):** Use of pH sensing nanoparticles as a screen for pH shock during viral inactivation in mAb production process.

GC2.3 Manufacture & Analytics for Autologous Cell Therapies

UCL Biochemical Engineering, Loughborough University School of Mechanical, Electrical and Manufacturing Engineering

Team (January 2017-June 2020):

Dr Qasim Rafiq (Co-Investigator, UCL), Prof Nicolas Szita (Co-Investigator, UCL, Prof Rob Thomas (Co-Investigator, Loughborough), Dr Farlan Veraitch (Co-Investigator, UCL, 2017-19), Dr Igor Andreyev (Researcher, UCL), Dr Adam Collins (Researcher, Loughborough, 2017-18), Dr Shimaz Hashimdeen (Researcher, UCL, 2017-19), Dr Theano Panagopoulou (Researcher, UCL, 2019-20), Dr Maryam Shariatzadeh (Researcher, Loughborough)

Aim:

Create a robust manufacturing process for personalized cellular immunotherapies, underpinned by sound understanding of product attributes.

Key Research Challenges:

Modified autologous (personalised) T-cells, where cells are harvested from a patient, manipulated and then delivered back to the patient, are potential cures for cancers. Current production of clinical material is carried out manually with poor process control and low-yielding processes. Novel engineering solutions, providing optimal conditions throughout, are required for their robust and consistent manufacture, and reduce risk of failure. Moreover, the development of new bioprocess technologies may enable a shift from centralised to distributed manufacturing at point of care. Patient cell samples used to manufacture autologous T-cell therapies are variable in composition. Cell composition, process parameters and supplemented factors must be defined and controlled to develop processes optimised for cell quality and low risk of failure.

Research and Impact Highlights:

- **CAR T-cell manufacturing and process intensification:** First successful demonstration of functional CAR-T cells manufactured in stirred tank bioreactor. Intensified CAR-T production through a novel process control strategy with 45% reduction in process time. (Costariol et al., Biotechnology Journal, 2020)

- **CAR T-cell predictive models:** Optimal medium volume exchange can be predicted with an associated process variability. Maintained growth via prediction of primary nutrient supply. (Picken, Thomas et al., Cytotherapy 2020)
- **T-cell analytics:** Digital Holography Microscopy provides rapid analytics to discern activated from non-activated T-cells. Translated onto microfluidic platform. (Andreyev, Conference proceedings Europtrode 2020)
- **T-cell production and characterization:** Enhanced product and process characterisation for T-cell cultures has been established which has enabled improved productivity and process consistency. (Costariol et al., Biotechnology and Bioengineering, 2019).
- **T-cell microfluidics:** Microfluidic devices for personalised health manufacturing.
- **Established basis for scale from 15mL – 1L stirred-tank bioreactor:** Demonstration that CAR-T can be cultured in both the ambr15 and ambr250 platforms, with specific power input as an effective parameter for scaling between both systems. (Rotondi, Costariol, Rafiq, et al., Biotechnology Letters, 2021)
- **Development of a dynamic ordinary differential equation-based model of T-cell growth:** Applied in a suspension culture system to define the rate of medium delivery required to maintain T-Cell growth and viability. (Shariatzadeh, et al., Cytotherapy, 2020)
- **T-cell analytics:** Digital Holography Microscopy demonstrated to provide a rapid analytical tool to discern activated from non-activated T-cells.

Stakeholder Engagement Highlights:

- **UCL and West Pharmaceutical Services:** User feasibility study evaluated freeze-thaw performance of vials vs bags for the containment and delivery of T-cells.
- **UCL and Sartorius:** Evaluated stirred tank and rocking motion perfusion bioreactors for CAR-T production
- **UCL and Ovizio Imaging Systems:** Demonstrated Holographic imaging and image-based cell profiling for manufacturing of CAR-T cell therapies.
- **Loughborough and Biopharm Services:** Applied an unstructured kinetic model to support T-cell manufacture
- **Loughborough and Cell & Gene Therapy Catapult:** Developed mechanistic modelling for immunotherapy manufacture.

GC2.4 Process Control Using Advanced Data Mining & First Principles Models

University of Manchester Department of Electronic and Electrical Engineering, UCL Biochemical Engineering

Team (January 2017-June 2020):

Prof Barry Lennox (Co-Investigator, Manchester), Prof Suzanne Farid (Co-Investigator), Dr Carlos-Alberto Duran-Villalobos (Researcher, Manchester), Dr Yang Yang (Researcher, UCL)

Aim:

Increase process understanding by using multivariate statistical tools to extract information from experimental data of cell therapies and stratified protein therapies manufacture. Data mining to inform targeted healthcare patient stratification. Establish adaptive control technologies for manufacture of cell therapies and stratified protein therapies.

Key Research Challenges:

A Quality by Design (QbD) approach to process control will allow each process to adapt and meet the final outcome, rather than operating with pre-defined setpoints (e.g. culture or cell-free synthesis duration). To succeed it is necessary to build an understanding of the complex interactions of operating conditions and the performance of the unit operation. Robustness and appropriateness of different process analytics must also be evaluated. For autologous cell therapies, variability in patient-specific source material represents a major challenge to the development of robust and reproducible processes. Rapid deconvolution of complex analytical signals (e.g. Raman) is crucial to achieve real-time process control.

Research and Impact Highlights:

- **Multivariate data analysis of T cell expansion:** A series of MVDA models have been developed to enable adaptive control by linking critical process parameters and T-cell characteristics to productivity and product quality.
- **Optimisation of cell-free synthesis process:** Ideal operating conditions (e.g. pH profile) have been identified from DoE that are able to improve the productivity of cell-free synthesis processes.

- **Benchmark simulator developed to test adaptive control algorithms:** Simulator designed that provides an accurate model of a generic, industrial cell culture process and used to test new control techniques. (Duran-Villalobos et al., Computers and Chemical Engineering, 2020)
- **Industrial validation of models:** demonstrated that the results obtained using simulated data are transferrable to real processes.
- **Data analytics for biomarker stratification:** Datamining tools have been developed to help clinicians make personalised decisions on aspects such as follow-up timelines (Yang *et al.*, submitted).
- **Data analytics for protein aggregation prediction:** Novel predictive models have rapidly detected early aggregation signals and predicted the potential aggregation level and the impact of key attributes. (Zhang, Yang et al., submitted).
- **Continuous chromatography monitoring:** A tool for real-time analysis and monitoring of continuous bioprocesses with adaptive control methods has been developed and tested with user data.

Stakeholder Engagement Highlights:

- **Perceptive Engineering:** Collaborated with Manchester and UCL to develop a simulator that enables control systems to be designed, tested and benchmarked. This was transferred to PE's PharmaMV software product for testing their batch control systems and is being applied to both laboratory and industrial systems.
- **Aglaris:** User feasibility study with Manchester on 'Historical batch analysis and trajectory optimisation for T-cell expansion process control'. Identified statistical parameters that can be used to identify quality-related drifts within the first few hours of T-cell expansion and predict T-cell growth from glucose consumption and lactate production.
- **UCL Clinicians in Personalised Medicine:** helped to sanity check biomarker stratification results from UCL BE and their clinical significance.
- **Shanghai Pulmonary Hospital, Tongji University (China):** joint paper with UCL on ML for personalised lung cancer recurrence and survivability prediction.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