EPSRC

**Centre for Innovative Manufacturing**
in Continuous Manufacturing and Crystallisation

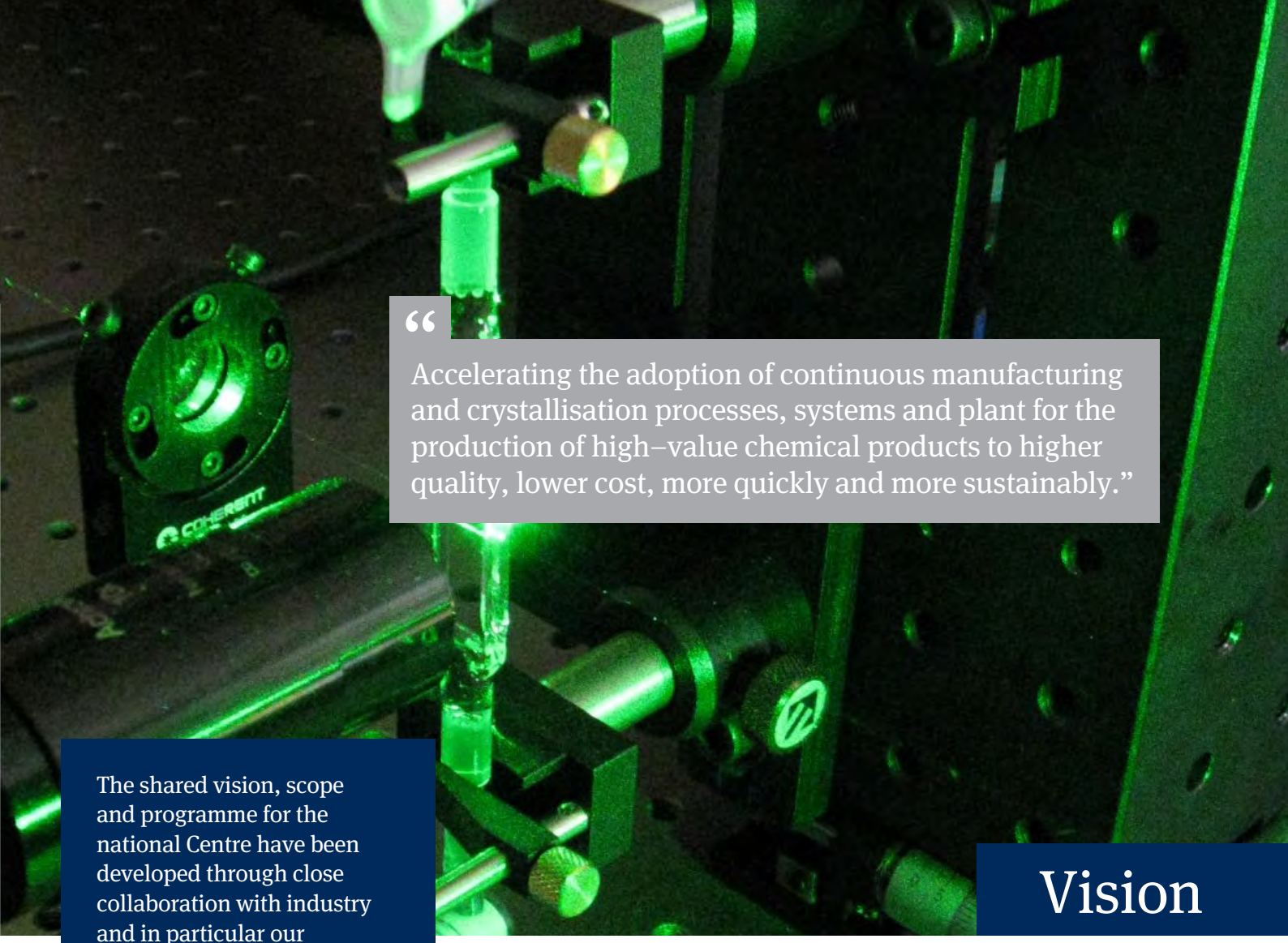
CMAC

# Annual Review

2013-2014

EPSRC
Engineering and Physical Sciences
Research Council

# Contents



> “Accelerating the adoption of continuous manufacturing and crystallisation processes, systems and plant for the production of high–value chemical products to higher quality, lower cost, more quickly and more sustainably.”

The shared vision, scope and programme for the national Centre have been developed through close collaboration with industry and in particular our founding strategic partners GSK, AstraZeneca and Novartis who continue to provide significant input and support. Together the Centre partners have a shared long-term vision: **to enable a step change from the current batch manufacturing paradigm to fully continuous manufacturing processes, systems and plants for the production of high-value chemical products to higher levels of quality, at a lower cost, more quickly and in a more sustainable manner.**

# Vision

Welcome to the 3rd Annual Report from the national EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC). Since our last report we have seen significant growth of the Centre’s programme with excellent progress in across many aspects of the Centre’s ambitious programme. This report gives an overview of the Centre’s programme in research and training as well as highlighting some of the progress CMAC academic colleagues, researchers, students and staff across all our partner universities have made and some of the new initiatives that the Centre has helped to stimulate.

It has been a pleasure to see the growth in the CMAC community across all of our partners and to build new relationships with researchers, companies and groups both in the UK as well as internationally who share common goals. This success is built on the collaborative ethos at the heart of CMAC that brings industry, the public sector and academics together to develop new engineering and physical science approaches to some of the major challenges in enabling advanced chemical and pharmaceutical manufacturing.
Looking ahead, there are several major new developments to come in the next 12 months including new intakes into both our DTC and MSc programmes as well as establishing the new state-of-the-art UK-RPIF funded national facility for pharmaceutical manufacturing research that will become CMAC’s physical hub in February 2015. These therefore continue to be very exciting times for the Centre as it continues to evolve and we look forward to continue to work with the wider community interested in accelerating the adoption of continuous manufacturing and crystallisation.

Prof Alastair Florence,
Director

# Overview of the EPSRC Centre 2013-14

## Demand-led Scope

The research scope of the EPSRC Centre has been jointly defined by the academic team together with our industrial partners. The 10 key challenge areas against the scope are summarised in Figure 1 right and provide a focus for the academic engineering and physical science research activities.

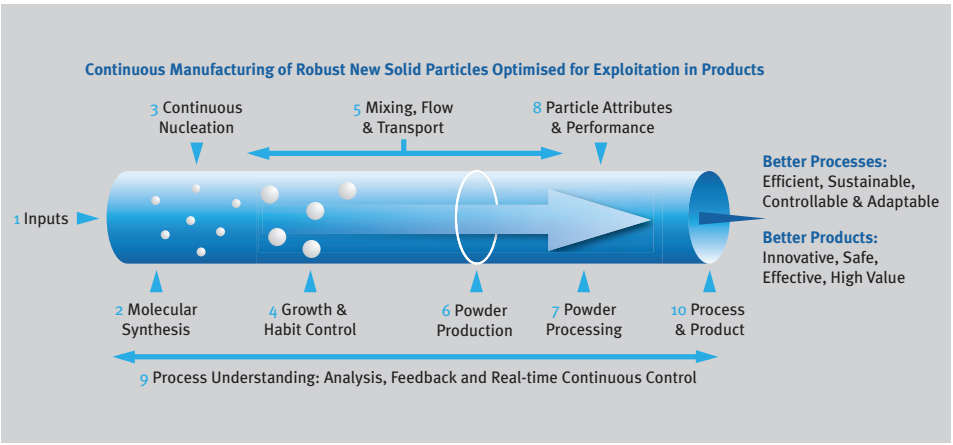



*Figure 1. EPSRC Centre research scope highlighting 10 key areas where engineering and physical science research can contribute to accelerate the adoption of continuous manufacturing.*

## Centre Mission

Through partnership and collaboration between academia, industry and public sector stakeholders we will establish a world-class Centre of Excellence in continuous manufacturing and crystallisation research. The programme will deliver continuous manufacturing research across three main thematic areas that are developing new understanding and supporting innovation across a range of products, processes and operations (Figure 2).

### Products

**Better particles through understanding particle formation and performance in continuous processes**

- Innovative, safe, effective, high-value
- Nucleation, growth, agglomeration, breakage
- 'dial-a' ...form, size, shape, purity
- Tailored bulk and surface structure and function

### Processes

**Better technologies for continuous control, formation, isolation, and processing of particles**

- Fast, efficient, sustainable, safe
- Controllable, scaleable, adaptable and agile
- Predictable, optimised
- Reconfigurable, modular, plug-play

### Operations

**Optimised high-value chemical manufacturing operations across the value chain**

- Economic, efficient, lean, world class
- Wealth creating, sustainable
- Deliver regulatory compliance
- Reduced time to market

*Figure 2. Key areas for research within the Centre to enable continuous manufacturing of high value chemical products.*

# Multidisciplinary Research

Key to the success of the Centre is the multidisciplinary academic team supporting the research programme. Our initial team involved 13 academic investigators from 7 institutions working with 9 PDRAs, 8 PhDs, technical and administrative staff, harnessing expertise in chemical and process engineering, synthetic, physical, analytical, structural and materials chemistry, crystallisation science, pharmaceutical science, manufacturing and operations management, Figure 3. In year 3 the Centre has grown to 14 investigators, 14 associate investigators, circa 50 PhD students, 12 PDRA's and a management and support team of 8. The programme will also adapt to meet the challenges of the scope in years 3-5. The academic team also contribute to the innovative training programme developed for the new EPSRC Doctoral Training Centre in Continuous Manufacturing and Crystallisation that will train 45 doctoral researchers from 2012-2016.

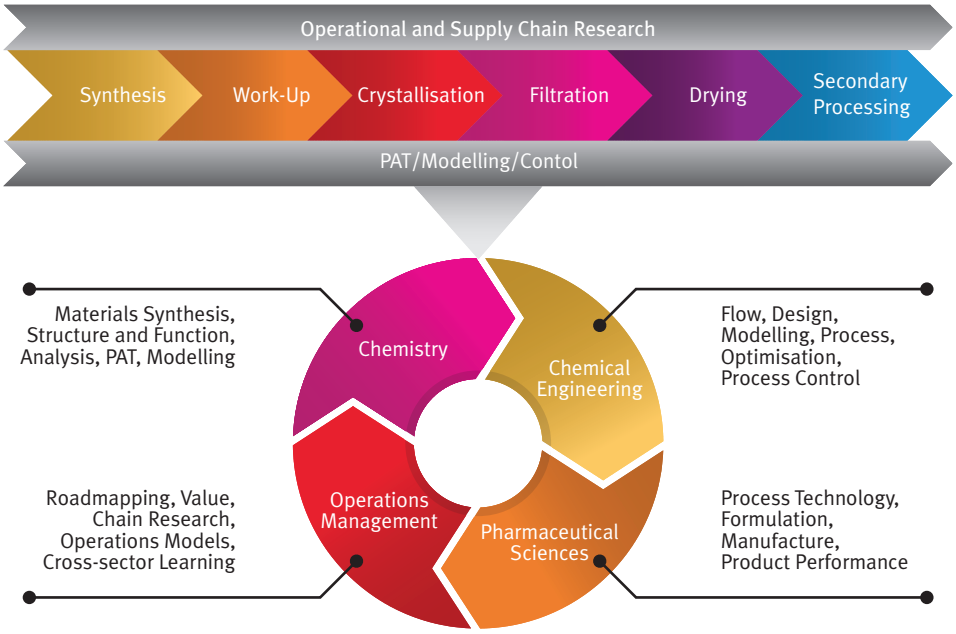



*Figure 3. Key disciplines contributing to the initial EPSRC Centre research programme and Doctoral Training Centre programme.*

# Flagship Projects – Years 1-2


*Figure 4. EPSRC Centre flagship research projects in initial programme.*

Our foundation research activity is delivered via our flagship research projects against key areas of the research scope (Figure 4). Along with the Centre's core researchers a platform RA and technician have also been appointed to carry out short-term feasibility projects and assist in evaluation of new technologies.

# Phase II Themes and Vision

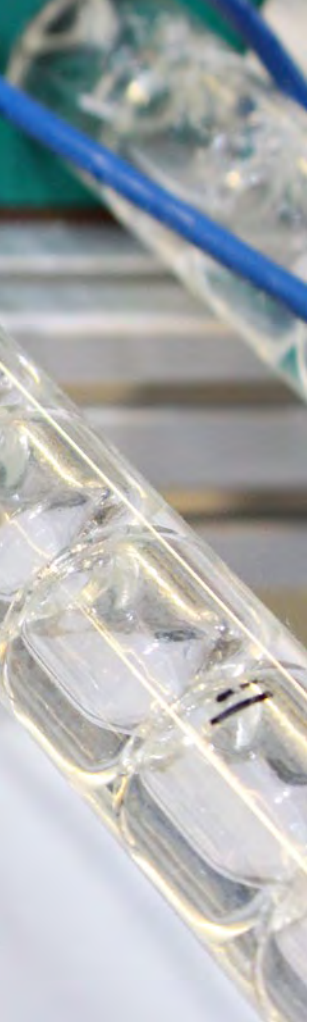
With the initial Centre flagship research programmes having come to an end, the Centre programme moves into Phase II (years 3-5). This builds on the capabilities established and progress made in the initial flagship themes and will deliver an ambitious co-ordinated programme of research that will transform capabilities for continuous manufacturing of high value chemicals and in particular, pharmaceuticals. The direction of Phase II draws on the technical targets and industry problem statements collated by the Centre's industry technical committee and by extensive discussion across the academic team. Whilst the emphasis of the programme will remain in controlled continuous crystallisation, Phase II also builds on new and emerging projects involving downstream processing including continuous filtration and drying and secondary processing of API into formulated product. This includes understanding how particle attributes impact on performance in downstream operations. Key enablers of Phase II will be new processing and analytical capabilities supported by the £34m UK RPIF award as well as new PhD and academic appointments. The Phase II research programme will be delivered through three core work packages supported by the Phase II Centre funded RAs.

### WP1 Laboratory-scale continuous process capabilities to support end-to-end manufacturing

Continuous processing at laboratory scale is an important target for CMAC offering a range of benefits including use of less material, improved process understanding, rapid process development, enabling research with a broader range of solvents and API. A suite of continuous platforms is being developed alongside the experimental infrastructure to accelerate process development. These platforms will support specific continuous synthesis, work-up, crystallisation, isolation and secondary processing operations.

### WP2 Tools and workflows for rapid product assessment and continuous process selection

We will develop rapid methodologies for assessing the physical properties of molecules, particles, formulated products and their physical transformation to inform future process and platform selection (e.g. batch vs. continuous, MSMPR vs COBR). By exploiting a comprehensive suite of automation, characterisation and measurement tools, and the developing CMAC informatics infrastructure we will deliver a robust foundation for systematic, rapid continuous crystallisation development including a crystallisation classification approach.



## A Focus on Particles
## Exploit continuous manufacturing to deliver:

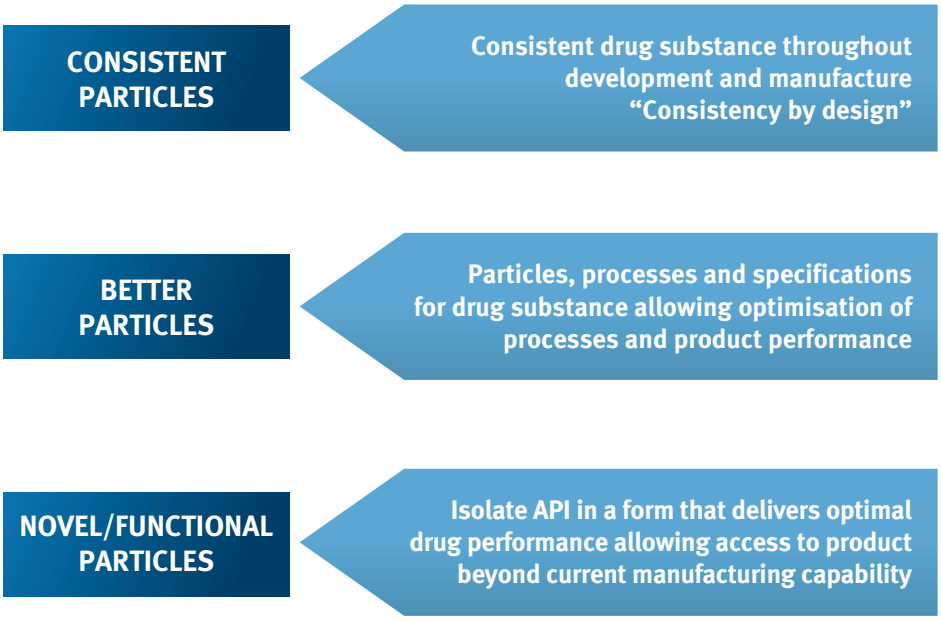



*Figure 1. Focus of Phase II deliverables.*

**WP3 Product-process archetypes that support supply chains of the future**

The widespread adoption of continuous manufacturing and crystallisation processes in pharmaceutical industrial practice is not solely dependent upon the technical requirements of each process step.
For such technologies to become more generally accepted the business case and impact on current industry supply chain configurations needs to be understood. This workpackage is focussed on addressing these issues and providing an informed view of the combinations of product and process attributes that would benefit from continuous manufacturing and the potential impact on future supply chain configurations.

Associated with these core activities, the Centre will also:

- Deliver the UK RPIF funded national facility, delivering the equipment and characterisation infrastructure to support the Centre's Manufacturing Research Programme.
- Grow our capabilities in modelling continuous processing of API and product.
- Continue to build collaborations across the Centre, leveraging outputs of current projects through coordinated integration of projects. Currently the Centre has 45 active research projects.

**Making Medicines**

As part of the Phase II programme, research in the Centre is now actively targeting specific pharmaceutical products where there is a clear opportunity to develop new manufacturing technologies that can aid access to medicines in developing countries as well as addressing the healthcare needs of western economies. Projects will target anti-malarials as well as treatments for HIV, type II diabetes and elevated cholesterol with outcomes demonstrating the ability to improve the medicines supply chain of the future.

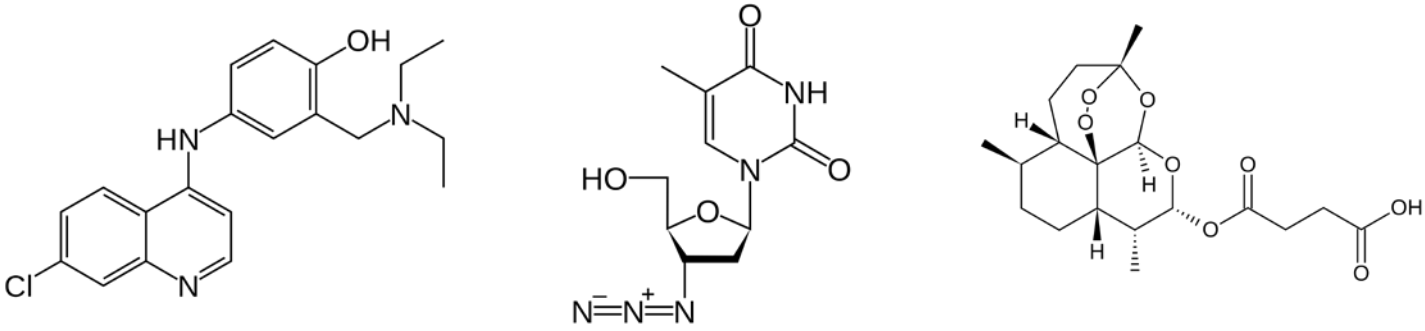



*Figure 2. Developing continuous manufacturing of model medicines.*

# Continuous Crystallisation: A 12 Month Review

The Centre's programme has seen tremendous growth of the last 12 months as we move into Phase II with new DTC and industry projects contributing to a portfolio of ca. 50 active research projects. Building on the rich activity of developing techniques and technologies for understanding and controlling continuous crystallisation processes, the programme has extended to include upstream synthesis and work-up processes, as well as downstream filtration, drying and secondary processing stages. Work from the Cambridge team in Supply Chains has gathered momentum with their activity developing to inform practical aspects of the research programme.

The Centre has also been developing automated workflows, our cross-centre ELN platform and a comprehensive data management infrastructure, building on the links with the ICT CMAC project. This will accelerate progress in the coming years exploiting the rich value in the data being collected across our projects. This is a key aspect of our strategy to deliver new tools to support process development and control through rigorous understanding.


Over the past 12 months the Centre has produced 25 research publications and has had a dedicated presence at conferences in the manufacturing, crystallisation, flow chemistry and formulation conferences with over 40 oral presentations from investigators and researchers.

## Publications


Bhardwaj, R.M.; Johnston, B.F.; Oswald, I.D.H.; Florence, A.J.: A Complementary Experimental and Computational Study of Loxapine Succinate and its Monohydrate. Acta Crystallographica Section C: Structural Chemistry, EI 1600-5759 PD NOV PY, 2013, VL 69. DOI: 10.1107/S0108270113029363.

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## Patents


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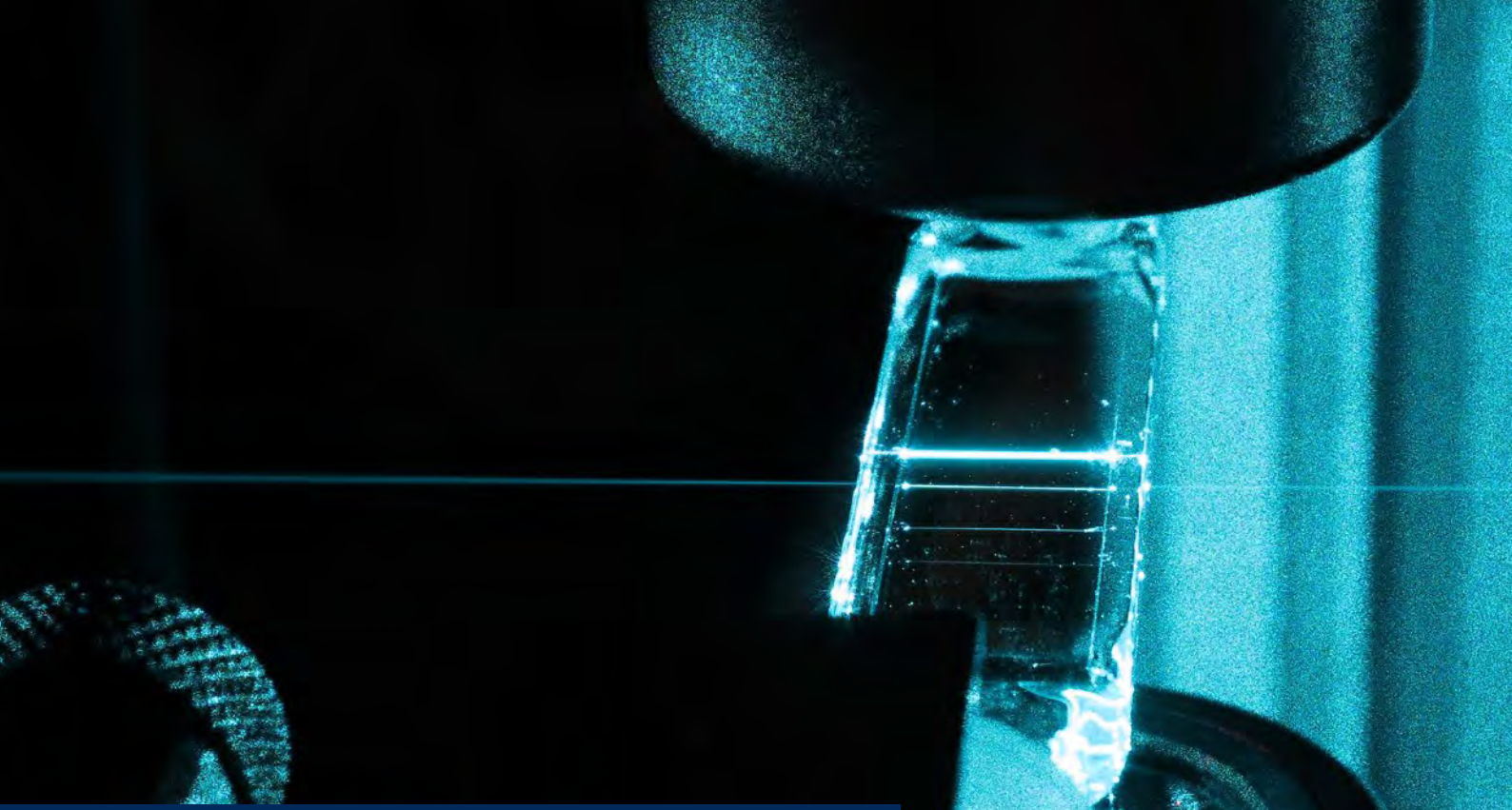


# Manufacturing with Light: Laser-induced nucleation for crystallisation of high-value materials in continuous manufacturing processes


**Principal Investigator:**
Dr Andrew Alexander
**Co-Invesitgator:**
Prof Colin Pulham
**Researcher:**
Dr Martin Ward

**Co-Investigators:**
Prof Jan Sefcik and
Dr Iain Burns
**Researcher:**
TBA


## Manufacturing with Light

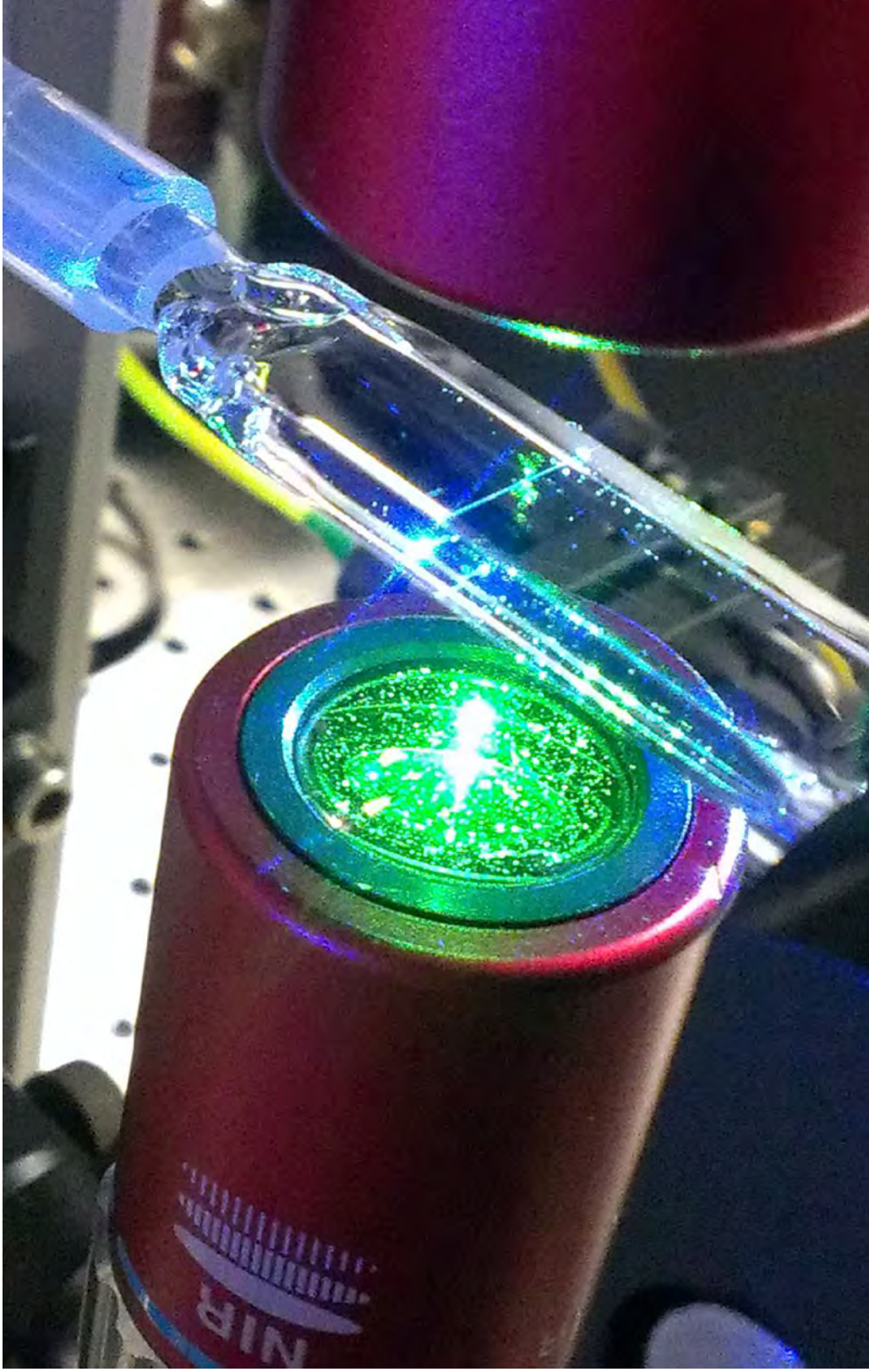
Through Manufacturing with Light we seek to revolutionise the use of light for manufacture of solid materials. Our project is exploring new techniques to induce nucleation under flow conditions, to control product particle attributes such as size, morphology and solid form (polymorph). We use short (nanoseconds) laser pulses to induce nucleation in metastable (e.g. supersaturated) fluids. Using light allows us to induce nucleation remotely—without the need for a seed—and to access fluid conditions that would be difficult to obtain by other methods. So far, laser induced nucleation of a wide range of substances has been demonstrated, from simple salts to proteins.

## Flow Field and Particle Measurement

The Strathclyde and Edinburgh groups are also employing light to study the structure of supersaturated solutions, product particle concentrations, flow fields and structure. Recent work shows that higher pulse energies give increased concentrations of primary nuclei up to a distinct saturation regime where other photophysical mechanisms operate. Control of the breeding of these nuclei to form seeds will allow us to manufacture better-defined particle distributions. We are also investigating use of polarization to select and enhance nucleation of specific polymorphs.

## Nucleation in Microdroplets

Liquid microdroplets have great potential as individual containers for transport and fine control of reactions. The droplet size has a distinct influence on the size and morphology of the solid particle. Prior to laser-induced nucleation methods, nucleation in droplets could only be achieved by manipulating the surrounding bulk carrier medium to enhance spontaneous nucleation rates (e.g. by evaporation or cooling) or through contact with foreign surfaces or bodies. Figure 1 illustrates nucleation of selected droplets of aqueous ammonium chloride in a static silicone carrier. We are currently investigating the potential of microfluidic channels for nucleation of size-selected droplets under flow conditions.



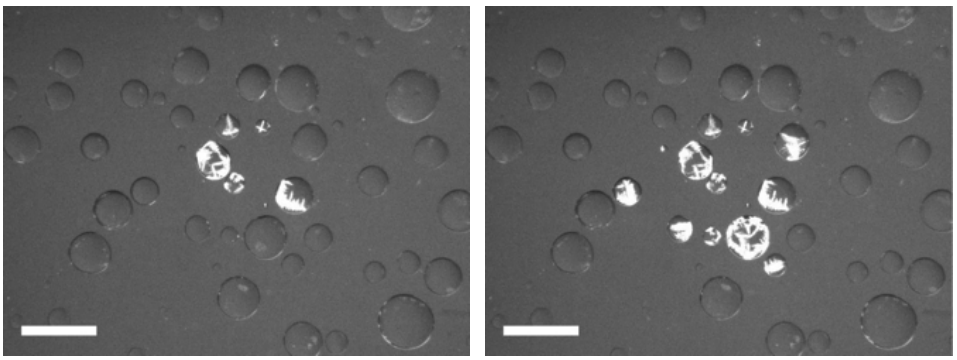


*Figure 1. Nucleation of aqueoiud ammonium chloride in a static silicone carrier (scale bar 1 mm).*

# Manufacturing Operations and Supply Chain Management Challenges in Continuous Manufacturing


UNIVERSITY OF CAMBRIDGE
IfM MANAGEMENT TECHNOLOGY POLICY

**Principle Investigators:**
Prof Sir Mike Gregory
and Dr Jag Srai
**Researcher:**
Dr Tomás Harrington


The widespread adoption of continuous manufacturing and crystallisation processes in pharmaceutical industrial practice is not solely dependent upon the technical requirements of each process step. For such technologies to become more generally accepted the business case and impact on current industry supply chain configurations needs to be understood.

Here, the overall objective is to address current issues and provide an informed view of the combinations of product and process attributes that would benefit from continuous manufacturing and the potential impact on future supply chain configurations.

## Current State and Issues

- Long, slow, expensive supply chains
- Top 25 Pharma companies are holding in the range of $100-150billion worth of inventory
- Quality 'right-first-time' manufacturing context (not quality of product) with respect to small molecules: Industry is operating at circa. 4σ, leading to $20-25billion in losses (per annum)
- R&D productivity is at a low point (numbers of molecules registered) but opportunities for continuous processing and supply chains (e.g. gains to be had in time-2-patient; quality; inventory; enhanced volume flexibility)
- Moving from current value-driven SC model to manufacturing cost base model in the future; de-centralised, smaller, agile facilities, rapid scale-up, 'multiple' supply chains and late customisation
- Previously, industry has been working in silos (between 2002-2010, $1.5billion estimated to have been spent) - move towards collaboration, integrated multi-disciplinary approach; de-risking of decisions
- Major transformational challenges

## Project Goals

- Develop models of supply chain configurations that are suitable for different product-process archetypes, optimising the benefits of continuous operations on the industry.
- Develop and apply an analytical framework/model enabling the systematic assessment of continuous manufacturing in specific product/delivery/patient contexts.

We examine how complex, multi-tiered supply chains and value networks, often managed as semi-independent sub-systems, can be better integrated end-to-end. Within many process industries, such as pharma, many sub-systems exist (e.g. clinical, commercial, API, Formulation, Pack and Distribute, Patient delivery models)

## The Analytical Framework

An analytical framework has been developed to examine future global value network configurations for the pharmaceutical industry that align with a disruptive switch in technology from batch-based manufacturing processes to continuous process manufacturing. One key aspect of this analytical framework is the integration of these critical 'sub-systems' within the total network. The analytical framework consists of a 4-step process to identify alternative value network opportunities, i.e.

**1. Identifying potential opportunities, barriers and target markets**
Our initial research identified a number of opportunities for the implementation of continuous manufacturing in the pharmaceutical industry, and potential barriers to their adoption. The barriers, however, are significant, and require a coordinated and systematic approach to redesigning the entire value network.

**2. Current state mapping and definition of critical sub-systems**
The second step involves mapping the current state of the supply network. This leads to the identification of the critical sub-systems that may be affected by the shift to continuous manufacturing. Initial analysis was conducted to identify the potential of the shift for each sub-system (for a series of candidates).

**3. Sub-systems analysis against desired benefits**
Deeper analysis of the sub-systems is then carried out to support a tailored future configuration aligned with the specific benefits identified in step 2. It also considers a range of scenarios that could emerge by adopting alternative product-process-business model innovations. These alternatives may be based on emerging process and production technologies or even technologies that are still yet to be fully developed (focus on continuous processing and crystallisation in pharmaceuticals). These scenarios may need alternative scale production footprints (dispersed, close-to-market, low-scale integrated plants, for example), or alternative supply models that might now be possible due to advances in ordering or replenishment (such as e-commerce-based last-mile supply chains). In practice, scenarios will depend on various disruptive influences that challenge the current value network model and introduce possible product or product-service models.

**Example - ACT Case study – emerging scenarios**

Based on basic data from secondary sources, analysis of unmet needs etc. a series of future scenarios are developed as part of a current-future state volume-variety analysis, e.g. there may be:

**A:** Opportunities to reformulate in order to e.g. increase bioavailability. Potential here to reduce the 'dosage', hence, volumes required for a series of new formulation(s).
**B:** Opportunities and reasons to develop more combinations; more SKUs e.g. more ACT therapies to try and control resistance.
**C:** Hybrid involving more combinations and reformulations to support e.g. new opportunities in oncology.
**D:** Projections that volumes are to increase significantly; capacity constraints; need to be more dispersed, close-to-market.

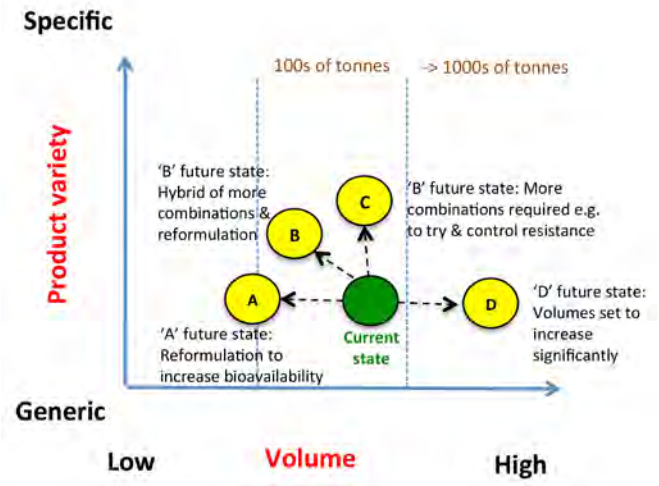



*Figure 1. Future scenarios may be developed as part of a current-future state volume-variety analysis*

**4. Integration of the critical sub-systems**
The final step of the process guides the integration of the sub-systems. This involves detailed examination of the interactions between the five areas (clinical, primary/secondary manufacturing, packaging and distribution, end-to-end supply) to identify target applications for continuous manufacturing that could work within and across the sub-systems. The target applications can then be assessed in terms of different transformation scenarios, bringing together inputs on (i) technology readiness and (ii) business viability

## Work Plan – Case Studies

Currently, we are extending the preliminary analysis conducted for selected patient populations and product-process archetypes identified as having attractive business/value propositions and promising technological feasibility in Pharma (generating dossiers on e.g. ACT, Metformin, and a series of low volume/niche oncology candidates using secondary data). This will be further tested with specific industrial candidates identified by our CMAC partners, as well as in other sector studies (e.g. continuous catalysis case study).

# Development of MSMPR Continuous Crystallisation Technology

## The Challenge

To develop a robust crystallisation strategy using a mixed suspension mixed product removal (MSMPR) crystalliser unit that avoids common problems encountered during continuous crystallisation such as fouling, encrustation and blockage of transfer lines.

## The Technology

Keddon Powell, a 3rd year Chemical Engineering PhD student at Loughborough University working under the supervision of Prof. Chris D. Rielly and Prof. Zoltan Nagy has developed a novel periodic flow crystallisation operating strategy using a modified MSMPR crystalliser unit that has been demonstrated to work effectively without fouling, encrustation or blockage issues when tested on model pharmaceutical compounds paracetamol (PCM) and glycine (GLY). The periodic flow crystallisation method involves periodic transfer of slurry (addition and withdrawal) at high flow rates between several stirred tank vessels arranged in series. This type of operation involves alternating periods of true continuous and batch operations.

The mean residence time (RT) of crystals in the case of periodic operation ($RT_{PO}$) can be extended with the duration of batch operation period ($t_{batch}$), RTPO = RTMSMPR + $t_{batch}$. The rapid transfer of slurry at high flow rates prevents sedimentation and blockage of transfer lines while operating at low supersaturation. This operating strategy further leads to the mitigation of fouling and encrustation problems often encountered during MSMPR operations. The work also introduces for the first time, the concept of “state of controlled operation” instead of “steady-state operation” to describe the periodic flow crystallisation process. It is defined as a state of the system, which maintains itself despite transitory effects caused by periodic but controlled disruptions. State of controlled operation can characterize both continuous and periodic operation in MSMPR.

## The Method

A combination of mathematical modelling approaches, experimental investigations and application of a series of process analytical technologies (PAT) have been used to design the period flow MSMPR crystalliser unit. These approaches have been evaluated for the crystallisation of PCM from isopropyl alcohol and GLY from water.

### Process Monitoring with PAT and Information Systems

PCM and GLY are active pharmaceutical ingredients (APIs) with markedly different nucleation and growth kinetics. An integrated array of PAT tools, based on ATR-UV/vis, FBRM, PVM and Raman, and an in-house developed crystallisation process informatics system (CryPRINS) software tool (Figure 1 and 2) were used to monitor the periodic flow crystallisation of the two APIs in a multi-stage MSMPR (Figure 2).

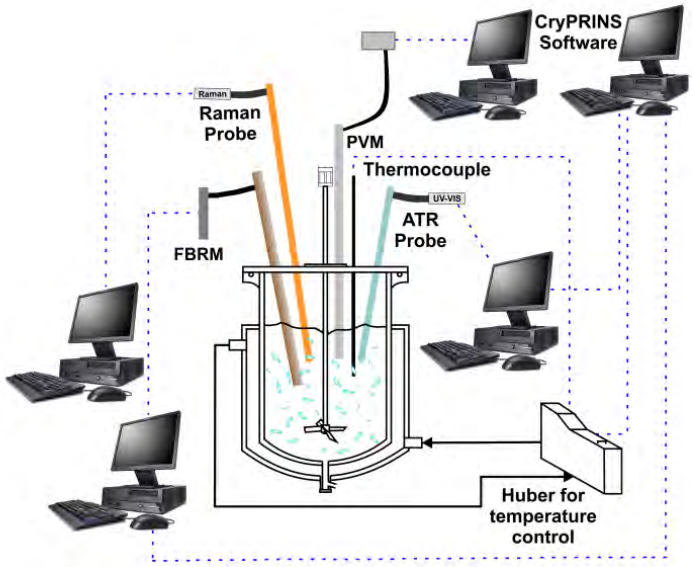
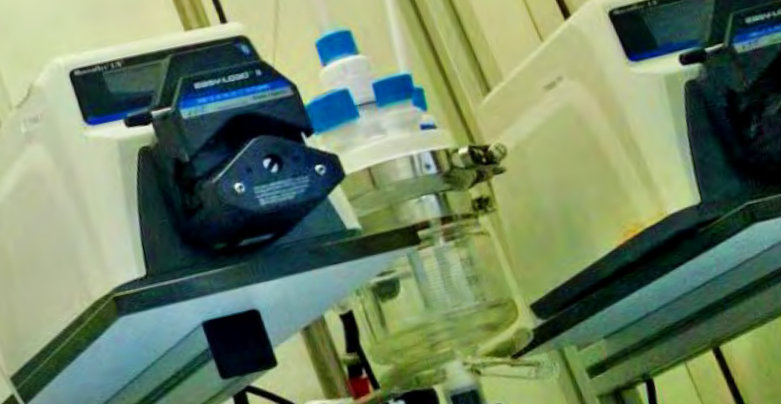



*Figure 1. PAT tools: Raman, ATR-UV/vis, FBRM and PVM used for measurements and display in CryPRINS.*



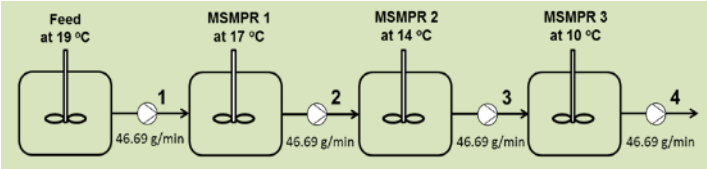



*Figure 2. MSMPR unit used for the periodic flow crystallisation of PCM and GLY.*

### Parameter Estimation and Process Modelling

Mathematical models were developed for the periodic flow crystallisation process to provide a better understanding and improve the performance of the periodic operation. The modelling framework was based on the Process System Enterprise's gCRYSTAL 4.0.0 software (Figure 3), wherein, the customized crystallisation kinetics of GLY and PCM were estimated from batch crystallisation experiments equipped with PAT tools for solute concentration and crystal size measurements. The models were in good agreement with the experimental observations from the periodic flow crystallisation process. Further investigations will consider optimisation of the periodic operation to achieve the best crystal critical quality attributes.

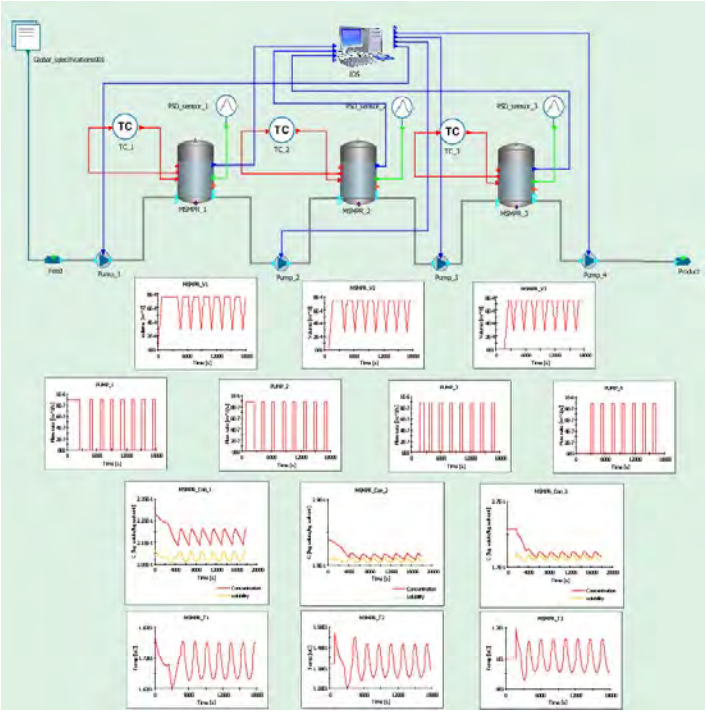


*Figure 3. Preliminary simulation results for the periodic crystallisation process in gCRYSTAL.*

## The Outcomes

This novel method of periodic flow shows promise for the mitigation of fouling, blockage and encrustation issues often encountered in continuous crystallisation systems. Furthermore, periodic operation of the modified MSMPR unit leads to extended residence times, important for controlling crystal growth. These results indicate that PCM is a slow growing system, with secondary nucleation dominating the seeded crystallisation process. On the other hand, GLY is a fast growing system, in which case secondary nucleation is suppressed and growth dominates the seeded crystallisation process (Figure 4).


*Figure 4. PVM images of product crystals obtained after 200 minutes periodic flow crystallisation experiment with GLY and PCM. NRC/F = No recycle and coarse /fine seed; and WRC/F = With recycle and coarse /fine seed.*

The robust monitoring and temperature control strategy indicated that the combined use of PAT and information systems can signify when the periodic flow process achieves a 'state of controlled operation' (Figure 5) and also provides a better understanding of the parameters and operating procedures that influence the periodic operation. While the periodic operation was demonstrated here for seeded cooling crystallisation, a similar approach can be applied for anti-solvent or combined cooling and anti-solvent systems. The periods of alternating continuous and batch operation can be tailored to accommodate crystallisation systems belonging to different classes based on their growth and nucleation kinetics.

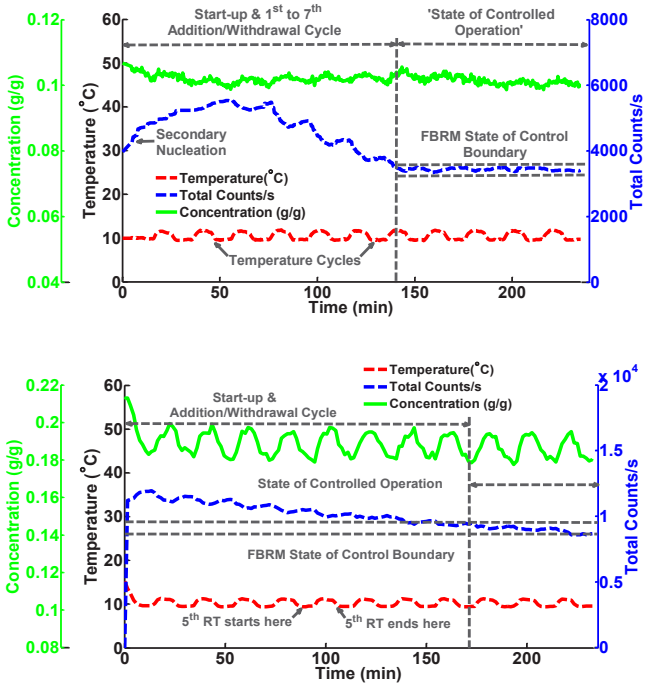



*Figure 5. Time diagrams for the seeded periodic flow crystallisation of PCM (top) and GLY (bottom), showing the temperature, particle counts/s and concentration profiles.*

# Particle Isolation and Formulation

University of Strathclyde Glasgow

**Co-Investigators:** Prof Gavin Halbert, Prof Alastair Florence and Dr Alison Nordon
**Researchers:** Rebecca Halliwell, Laura Martinez and Elanor Brammer

As the Centre research programme moves into Phase II a significant strand of research is based on building and developing downstream processing areas. New appointments are being made from academic to PhD level and this expansion of the Centre's scope will allow us to gain better understanding and control of the complete journey to the final product.

## Spray Drying – Rebecca Halliwell

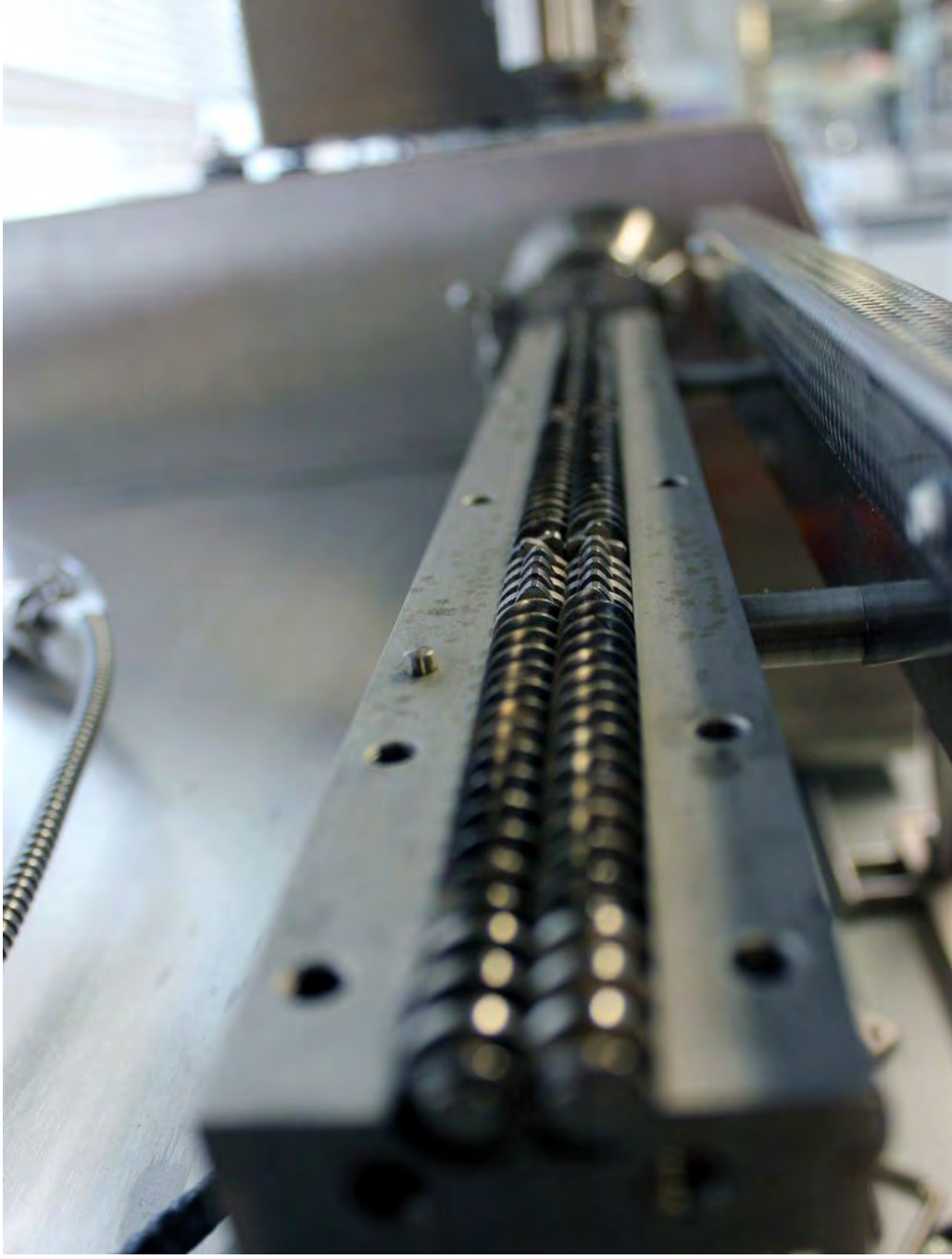
Rebecca Halliwell, a second year DTC student at the University of Strathclyde under the supervision of Professor Alastair Florence, is currently pursuing her research into the continuous spray drying of 'novel' particles for inhaled drug delivery. This research aims to engineer particles with desirable attributes to target an improvement in drug formulation and delivery. This research combines the optimisation of the Büchi B-290 Mini Spray Dryer through process automation and collaborative work to develop process control and monitoring with process analytical technology (PAT).

Currently, Rebecca has looked into simple model compounds to improve her fundamental knowledge of the technique and has found that the process parameters can influence the polymorphic form of the active pharmaceutical ingredient (API). This result is significant as it demonstrates that spray drying is an alternative technique that can produce metastable forms of an API that otherwise cannot be produced by traditional crystallisation practices.

## Hot-Melt Extrusion – Laura Martinez Marcos

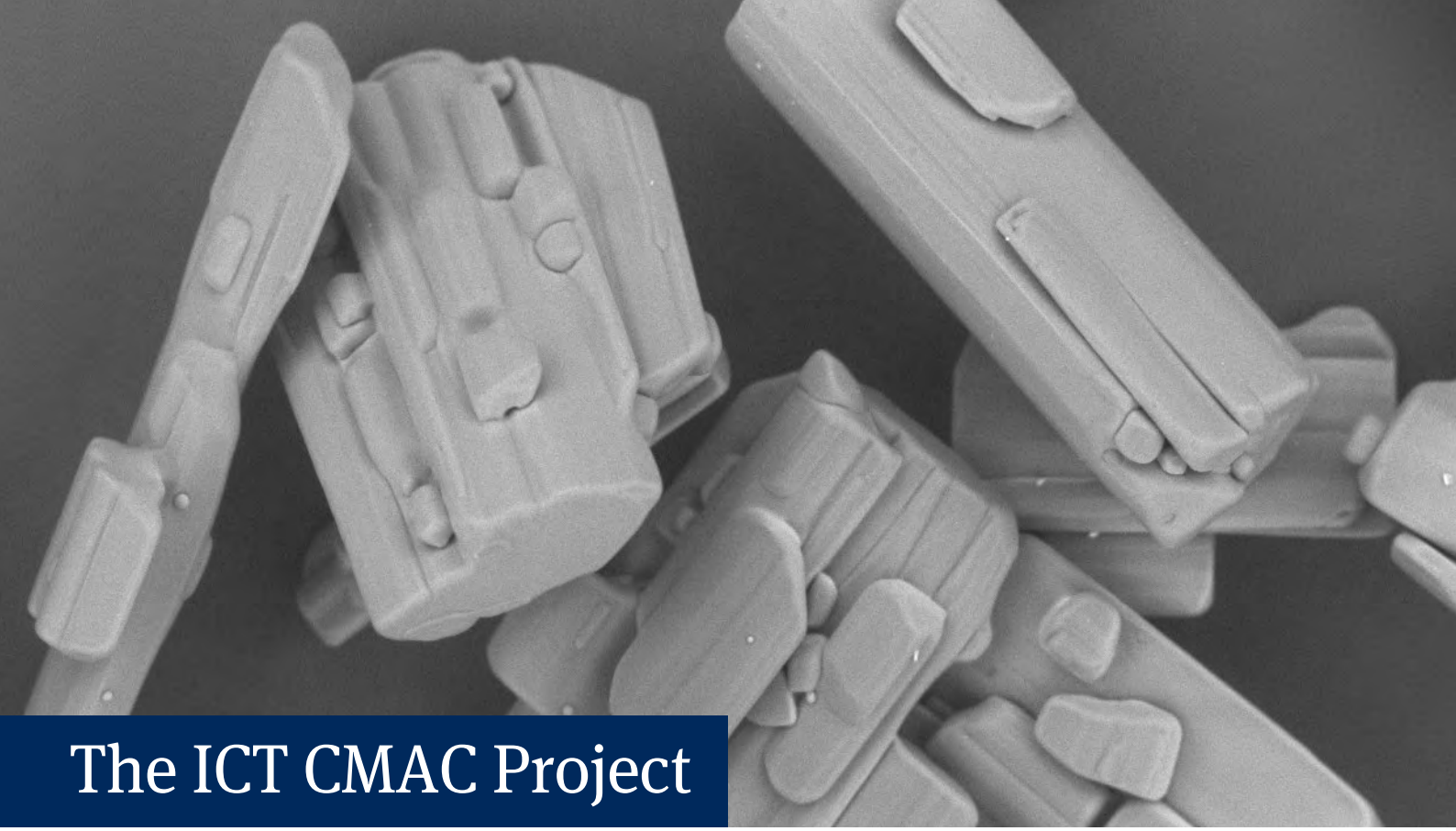
Laura Martinez Marcos, a second year DTC student under the supervision of Professor Gavin Halbert, is developing her research towards Hot-Melt Extrusion processes using a Thermo® Process 11 twin-screw extruder. A major area of development for continuous manufacturing involves the formulation and development of new medicines. Specific physico-chemical properties of drugs, such as poor solubility and therefore limited bioavailability, necessitate improvements in performance. A number of techniques are available to the pharmaceutical industry to improve the oral bioavailability of poorly soluble drugs, such as the production of amorphous solid dispersions.

From a continuous manufacturing perspective, initial stages of formulation will be covered by Laura towards Hot-Melt Extrusion (HME) and Twin-Screw Granulation (TSG). These processes offer the possibility to obtain an amorphous solid dispersion by a homogeneous mixing performance. The application of these processing techniques can dramatically reduce the manufacturing cost, in terms of equipment, space and personnel required.



## 3D Printing – Elanor Brammer

Elanor Brammer, a DTC student under the supervision of Professor Gavin Halbert, has just finished her DTC training and will now commence her research into scaleable oral dosage formulations. Also using the Thermo® Process 11 twin-screw extruder, she will begin by extruding drug loaded polymer strands that will then be fitted onto a three dimensional printer to enable formulation of the final drug product. It is hoped that, by using this technology, varying doses of tablets can be easily manufactured, laying the groundwork for future production of personalised medicines. Throughout this work, Elanor will be comparing new technologies to conventional tablet press machinery to establish and demonstrate the benefits of continuous processing. Elanor was recently featured in two articles in the UKICRS (United Kingdom and Ireland Controlled Release Society) 2014 newsletter, she was co-author in 'Continuous Manufacturing – A Paradigm Shift in the Pharmaceutical Industry' while publishing a second article entitled 'Personalised Medicine – A Manufacturing Perspective.'



# The ICT CMAC Project

The ICT CMAC (Intelligent Decision Support and Control Technologies for Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals) project is a five-year initiative funded by the EPSRC and a number of industrial co-creators (GSK, AZ, Perceptive, PSE, Mettler Toledo), with the aim of creating a comprehensive Intelligent Decision Support and Control platform using state-of-the-art data acquisition, signal processing, analysis and control mechanisms, integrated within a user-friendly Electronic Laboratory Notebook interface for the end user.

Currently there is no solution that combines real-time data from in-line and at-line sensors to extract quantitative information on particle shape, size and form during the crystallisation process. In moving from traditional batch processing to the continuous manufacture of particulate products, the multi-signal analysis approach under development in the ICT CMAC project will allow critical product quality attributes to be monitored, analysed and therefore controlled in real time.

The project consists of six integrated Work Packages to enable multi-disciplinary teams to create appropriate solutions to a range of challenges. The Work Packages are:

1. Data Capture and Conditioning
2. Sensor and Measurement Modelling
3. Intelligent Support Platform
4. Robust Plant-wide Control
5. People and Processes
6. System Integration and Communication Interfaces (commences in Year 3)

## ICT CMAC Work Package 1: Data Capture and Conditioning

**Objectives**
WP1 will create an integrated, multi-input data acquisition system that will bring together all measured data to a single point for subsequent processing and analysis. Existing measurement techniques such as infrared, UV and Raman spectroscopy will be combined with newer instrumentation based on acoustics and hyperspectral imaging. Data traffic will be optimised through the acquisition system, in preparation for further real-time data analysis and control.

**Researcher:** Jerzy (Jurek) Dziewierz
**Academics**: Anthony Gachagan, Alison Nordon, Stephen Marshall

## ICT CMAC Work Package 2: Sensor and Measurement Modelling

**Objectives**
WP2 will extract quantitative attributes for crystalline particles across the manufacturing process. Measured data will be used as input to data analysis and inversion techniques which will allow best estimates of particle attributes to be made at a particular process point.

**Researcher:** Okpeafoh Stephen Agimelen
**Academics**: Tony Mulholland, Jan Sefcik, Massimilano Vasile

## ICT CMAC Work Package 3: Intelligent Support Platform

**Objectives**
The aim of WP3 is to deliver an intelligent support environment for the crystallisation process using machine learning and statistical modelling. By combining data captured by WP1 coupled with expert process knowledge, the analysis performed in WP3 will inform the control decisions made by WP4.

**Researcher:** Christos Tachtatzis
**Academics**: Craig Michie, Ivan Andonovic, Robert Atkinson

## ICT CMAC Work Package 4: Robust Plant-Wide Control

**Objectives**
The aim of WP4 is to deliver a tailored, agile, self-adaptive and robust plant-wide control strategy using a model-based predictive-adaptive control framework. A hybrid approach will combine rule-based and data driven systems, including intelligent support information from WP3.

**Researcher:** Qinglin Su
**Academics**: Chris Rielly, Zoltan Nagy

## ICT CMAC Work Package 5: People and Processes

**Objectives**
After evaluation of the available options for an ICT-enabled lab environment, WP5 will implement the optimum solution, which will be deployed and trialled within the CMAC community. Electronic Laboratory Notebooks (ELNs) will be used to bring together user experiment details, data captured and analysis carried out into a single, coherent and searchable platform.

**Researcher:** Murray Robertson
**Academics**: Blair Johnston, Alastair Florence, Umit Bititci

## Case Study: Work Package 2

**The Challenge**
Work Package 2 researchers have been developing a method to estimate particle aspect ratios from Focussed Beam Reflectance Measurement (FBRM) data. Starting from the measured chord length distributions, a model relating particle size distribution to chord length distribution was formulated, and then an inverse method was used to work backwards from the chord length distributions to the probable distribution of aspect ratios in the original sample.

The goal is to provide a reliable method of taking data from a number of measurements made in-situ and without the need for any sample preparation or dilution, to estimate the particle morphology from the information available. The inverse problem is an ill-posed problem in that there are multiple possible particle size and shape distributions that could be derived from the same chord length distribution.

The solution can however be constrained in this case by setting the minimum and maximum particle diameters expected, which are calculated automatically by the algorithm. Figure 1 shows an example of measured FBRM chord length distributions, whilst Figure 2 shows the calculated volume-based particle size distributions from the inversion algorithm, where Dc is particle diameter, from samples of cellobiose octaacetate (COA).

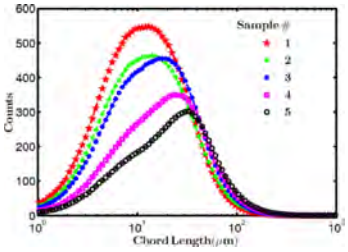



*Figure 1. Measured chord length distributions on COA.*

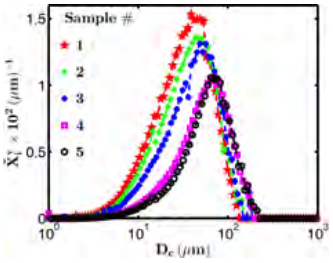
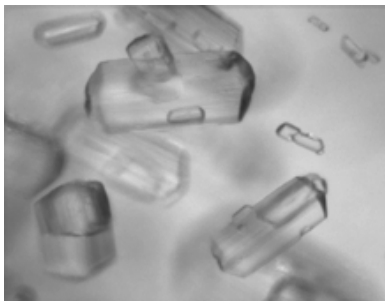



*Figure 2. Reconstructed particle size distributions from the inversion algorithm.*

## The Inversion Algorithm

The algorithm requires no a priori knowledge of the particle aspect ratios; however the search space can be narrowed by adding knowledge from complementary sensor information. Here, data from Particle Vision and Measurement (PVM) images was added to the model to narrow the search space and improve the estimation. The outline of the particles was traced using image processing techniques to provide information on the distance from the centre point to the outer edge of each particle at all perimeter points, yielding information on the aspect ratio of the particles.



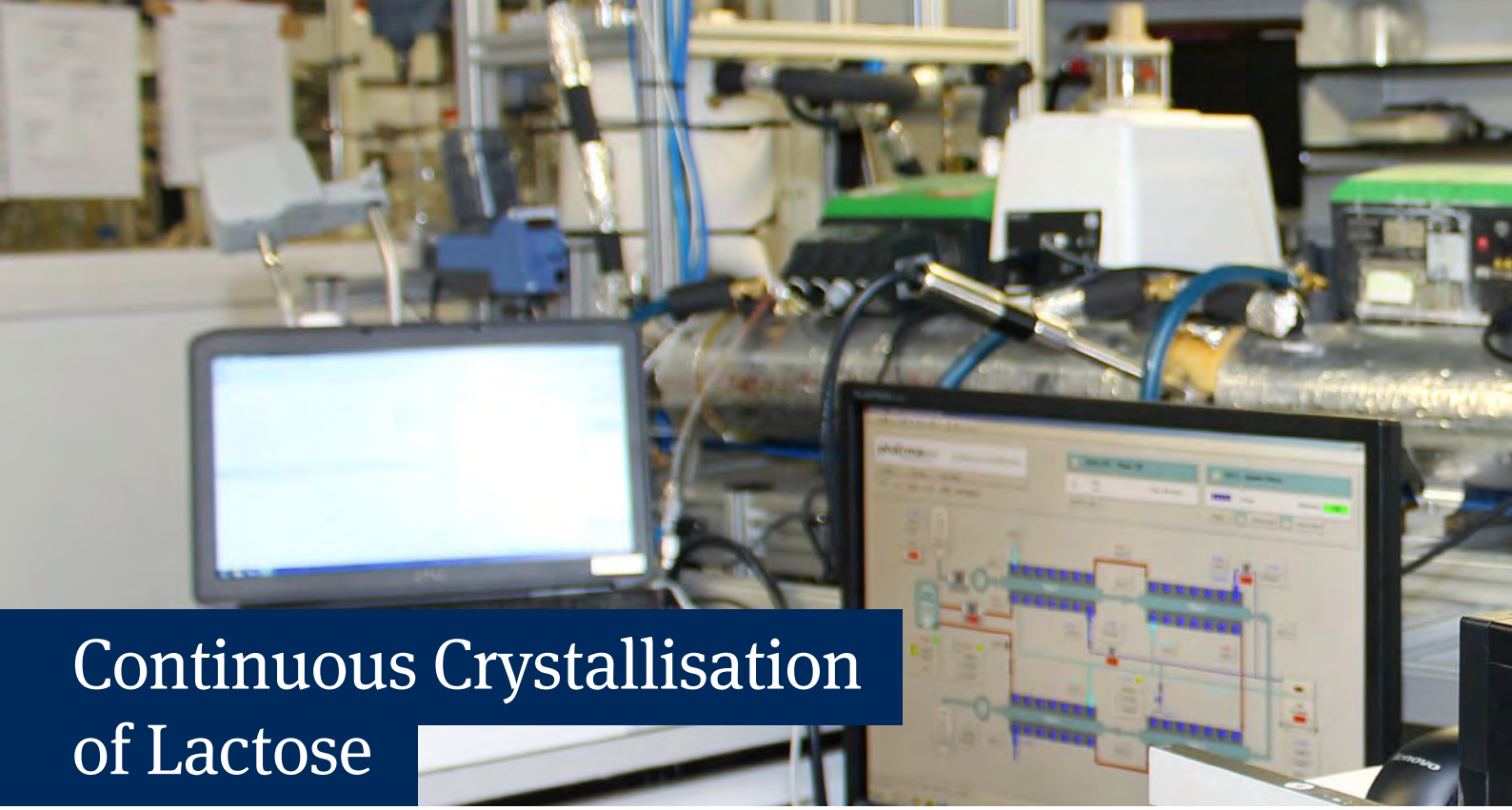
Future work will incorporate additional measurements. Full details of the developed algorithm have been submitted for publication and are currently under review. Figure 3 shows an example of particle images obtained using PVM.

*Figure 3. Example image of the particles used as input to the inversion algorithm.*

## Additional Highlights

The Loughborough team (Work Package 4) has developed a rigorous mathematical modelling framework for Mixed-Suspension, Mixed-Product Removal (MSMPR) crystallisers, the results of which have been submitted for publication.

Other highlights include the development of a non-invasive fouling early warning system using images (Work Package 3), allowing simultaneous detection of fouling and crystallisation induction time. Work Package 1 researchers have developed a modular data acquisition system which will integrate all experimental data streams, and the Work Package 5 team have introduced an ELN system which will incorporate data and analysis from all other Work Packages, allowing experimental Workflows to be established.



# Continuous Crystallisation of Lactose

University of Strathclyde Glasgow

**Lead Investigator:**
Prof Alastair Florence
**Researcher:**
Dr Humera Siddique

## The Research Challenge

This work sets out to develop a rational approach based on crystallisation fundamentals of a continuously seeded crystallisation process for alpha lactose monohydrate in a continuous multi-orifice oscillatory baffled crystalliser (Rattlesnake from Cambridge Reactor Design). The initial focus is on control of particle size (moving to other product attributes in due course) with no fouling or blockage and demonstration of continuous crystallisation at an industrially relevant throughput and scale.

This work is part of the TSB/EPSRC funded Made to Order Process Plant project (MOPPs, Project No 101334) with Perceptive Engineering Ltd., the Centre for Process Innovation and AstraZeneca. More on this project on page 32.

## Approach

A systematic approach has been established to develop a crystallisation process from an existing batch to a novel continuous process using process analytical tools. Kinetic and thermodynamic parameters have been investigated for lactose crystallisation using FBRM (Mettler Toledo) and mid-IR (ABB) in a multi-orifice batch oscillatory baffled crystalliser (MB-OBC) to better mimic mixing, hydrodynamics and operating conditions of the rattlesnake (vs stirred tank reactors). The batch system was used to optimise the seed loading and the desired cooling profile. Seeds are generated using IKA Magic Lab wet mill system directly coupled to a Malvern Mastersizer with a mean particle size of 8-10 µm.
Full characterisation of the hydrodymanics of the Rattlesnake was carried out to identify conditions that delivered plug-flow behaviour with residence times of 1–5 hours being achievable. Perceptive Engineering has collaborated with CMAC on the installation of Model Predictive Control onto the system delivering the ability to control the cooling profile to +/- 1°C (0.5°C achieved at steady state). Primary nucleation is avoided by seeding as shown in the schematic below (Figure 1)

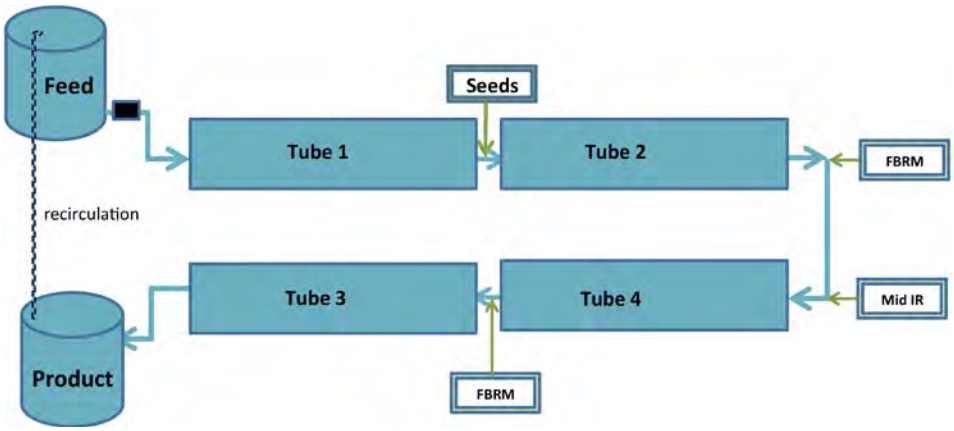
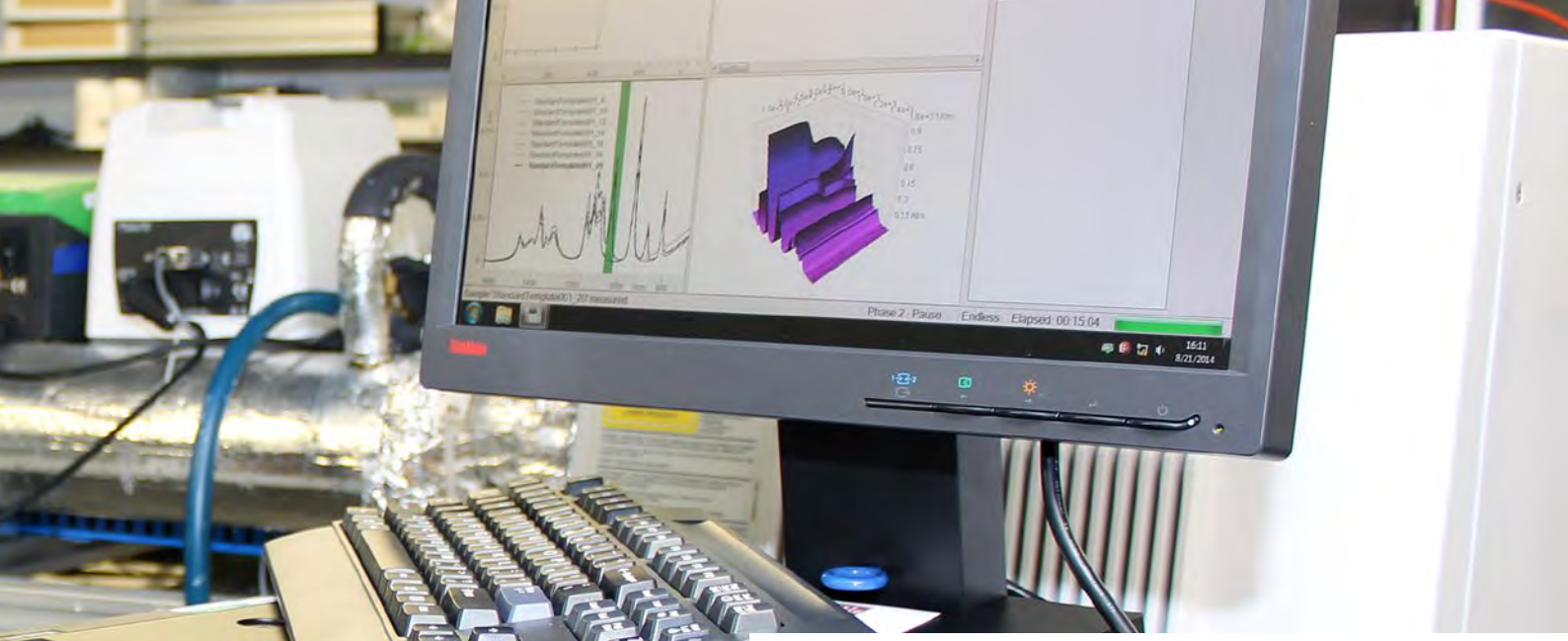



*Figure 1. Schematic of Rattlesnake.*



## Research Highlights

- Continuous crystallisation was successfully performed in Rattlesnake at a throughput of 300-500 g/hr of desired α-lactose for 96 hours without any fouling or blockage.
- 26% higher yield was obtained in continuous process as compared to batch.
- The system reached steady state after one and half residence times (Figure 2).
- Mean particle size can be easily tuned by varying the operating conditions.
- The XRPD analysis (Figure 3) confirmed the product purity with no unwanted primary nucleation and consistent crystal habit was obtained throughout the process (Figure 4).

With no issues in continuous operation over the timescales and conditions examined, this crystallisation setup has demonstrated true “Dial a particle” characteristics at industrially relevant scale. Future work will focus on control of other particle attributes as well as impurity rejection during the crystallisation.

Acknowledgements: We would like to thank Perceptive Engineering and the Strathclyde PhD and PDRAs who helped with the shift system for the 4 day continuous run.

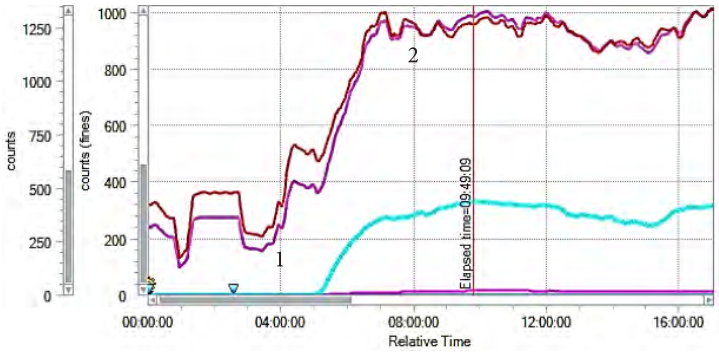



*Figure 2. FBRM data showing controlled steady state after one and half residence times with total particle count (purple), count <10μm (red), counts<50μm (blue). 1=End of first residence time, 2=End of second residence time.*

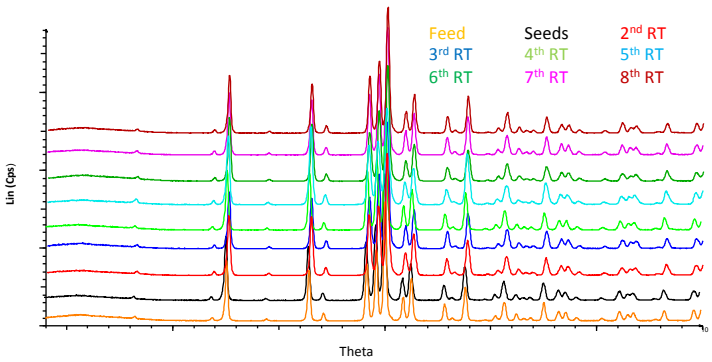



*Figure 3. X-ray powder diffraction for alpha lactose monohydrate, seed suspension and product from different residence times demonstrating polymorph control.*

*Figure 4. Product crystals from different residence times showing consistent habit.*


# Modelling and Control of Continuous Crystallisation

Loughborough University

**Co-Investigators:**
Prof Chris Reilly and
Prof Zoltan Nagy
**Associate investigator:**
Dr Brahim Benyahia

The research at Loughborough University focuses on the monitoring, modelling and control of various continuous crystallisation platforms. Keddon Powell (2nd year CMAC PhD student) has developed a novel way to operate multi-stage MSMPR continuous crystallisers in a "state of controlled" operation. In conventional "steady-state" operations, low transfer flow rates between stages are often required to provide long mean residence times for crystal growth. This leads to problems with transfer line blockage and encrustation within vessels. The "state of controlled operation" uses periodic short duration, high flow rate transfers to avoid these problems, but adds a longer duration hold period of batch operation to increase mean residence times. Promising results from slow and fast growing API systems have been demonstrated and current work is focussing on the development of population balance models to optimise the transfer and hold periods of this hybrid system. The model will also allow optimisation of the supersaturation levels to be used in each MSMPR stage of the cascade, to produce crystals with tailored size distributions.

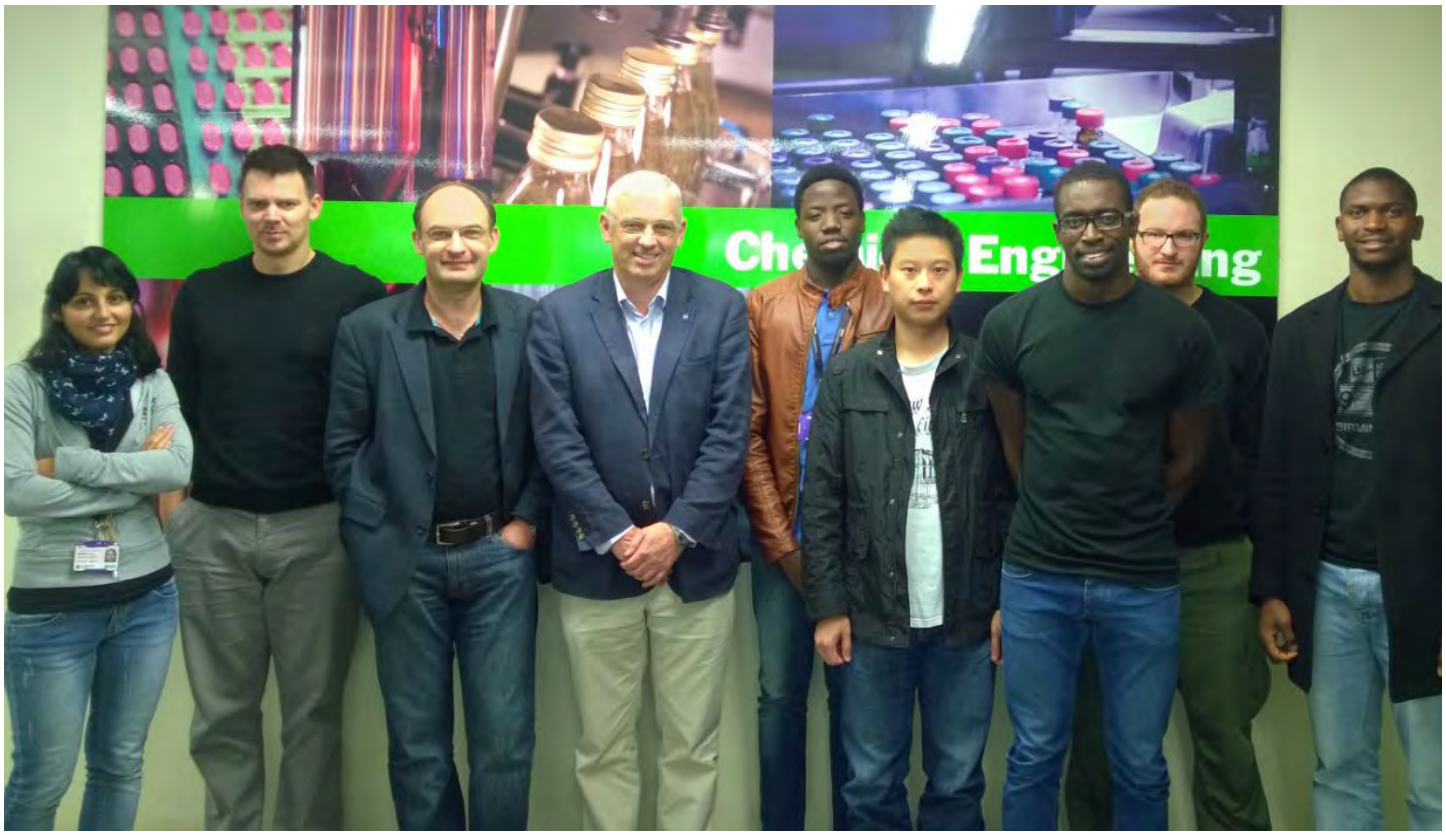
Iyke Onyemelukwe (2nd year DTC PhD student) is studying a different continuous crystallisation platform, namely the meso-scale oscillatory baffled crystalliser (meso OBC). This is a small scale (70 ml inventory) version of the OBC that could be very attractive for the early development stages of a new drug continuous manufacturing process. Recent work has obtained new experimental data for the tube side heat transfer coefficients and axial dispersion coefficients for the meso OBC, which is operated at much lower through flow and oscillatory Reynolds numbers than have been studied previously. A novel imaging technique has been developed to measure the residence time distributions (RTD) of both the solid and liquid phases in the meso OBC, allowing detailed checking of the assumption that the crystals are convected at the same velocity as the solution phase. The next stage in this study is to run some API crystallisation experiments in the meso-scale OBC to demonstrate the effect of oscillation conditions on the product crystal size distribution.

The latter project produces heat transfer, RTD information and kinetic data that are essential inputs to process models of the meso-OBC, which are currently being developed by Dimitris Fysikopoulos (1st year DTC PhD student). Initial models are based on one-dimensional population balance models, which will use empirical parameterised kinetic models for nucleation, growth and agglomeration; the kinetic parameters will be estimated from small scale batch experiments, as a starting point. A working and validated meso-scale OBC model may then be used to design suitable optimised temperature profiles to produce large, narrowly distributed crystals.

Emmanuel Kimuli (1st year DTC PhD student) is taking a different approach to mesoscale OBC modelling by developing detailed CFD simulations which will predict the unsteady-state flow behaviour of this crystallisation platform. The geometry of these simulations may be created as parametrised models within the CFD codes, allowing in silica optimisation of the baffle and tube dimensions and oscillation conditions to produce, for example, the narrowest RTD. These simulations may also be extended to predict tube-side heat transfer coefficients, to study solids transport and hence to identify problems of sedimentation. The next stage is to solve the detailed population balances within the CFD framework and hence to provide much more rigorous and assumption-free simulations of crystallisation processes; these detailed simulations can then be used to produce much better process understanding of the links between oscillation conditions, geometry, crystallisation kinetics and the product critical quality attributes, e.g. crystal size and shape distributions.

Sadly we said goodbye to Dr Ali Saleemi (CMAC PDRA) who has been recruited by GSK at Stevenage. Ali's work last year was mainly concerned with developing experimental cooling crystallisation protocols for manufacture of specific polymorphs of a co-crystal system (barbituric acid with urea as a coformer). Working with colleagues at Bath and using our fully PAT instrumented CryPRINS system we were successful in isolating both form 1 and form 3 co-crystals. A recent project student, Giulia Bartolini (University of Bologna) was then able to perform detailed characterisation of both polymorphic forms, using Raman, DSC, TGA, solubility and IR. She was able to show that both co-crystal forms provided improved solubility by around 30% compared to the pure barbituric acid crystals and moreover were much less susceptible to water absorption.

In the last year, our modelling expertise has been considerably strengthened through the appointment of Dr Qinglin Su, as the PDRA on the CMAC ICT project led by Prof Ivan Andonovic. Qinglin's research this year has been to develop simulation models for crystallisation and secondary downstream manufacturing processes which can be later used to test out plant-wide optimisation and control strategies. The next stage in his work is to assess the robustness of these models and to understand the effects of error propagation on the range of product qualities that are feasible. Qinglin has also worked extensively with other CMAC researchers to help them to estimate kinetics parameters from their experimental data, using his bespoke Matlab codes , as well as implementations within PSE's gCRYSTAL and gSOLIDS commercial simulation packages. This type of interaction is leading to better design of experiments to collect richer data sets that can be used for future optimised design of continuous crystallisers.



*The team at Loughborough*

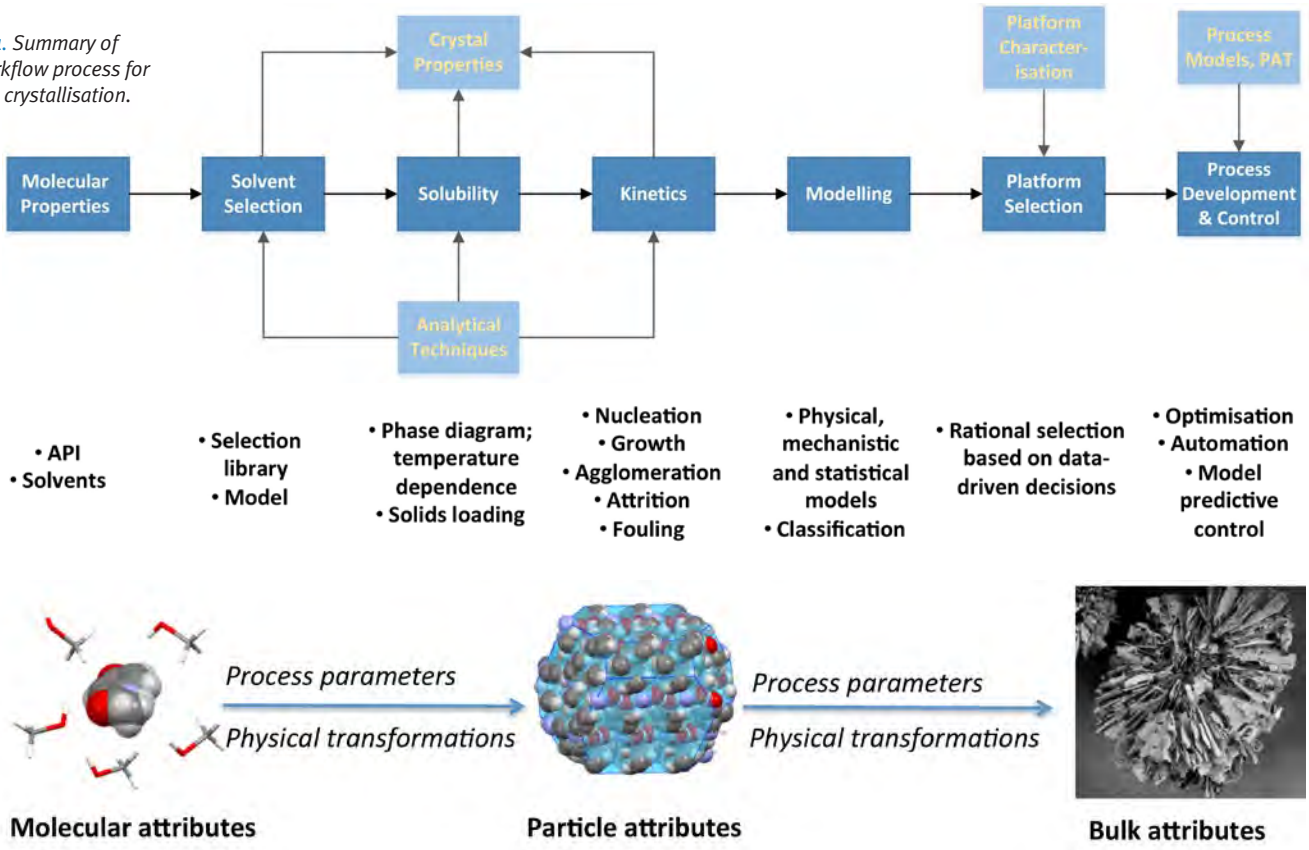



*Figure 1. Summary of the workflow process for cooling crystallisation.*

# Developing Workflows for Continuous Crystallisation

A detailed workflow for the delivery of a cooling crystallisation process has been developed, see Figure 1, potentially allowing rapid and accurate evaluation of feasibility with minimal requirements for material and researcher resource. The collection of relevant data at various stages throughout the workflow will inform decisions as to which subsequent steps should be taken whilst at the same time providing invaluable knowledge of the given process. Some specific examples are discussed:

## Solvent Screening

Based on the assumption that the molecular properties and solvent relationships are completely unknown, a rapid and reliable solvent screening tool is essential as part of potential system selection. Using the industry approved GSK solvent library,[1] a clustering approach was undertaken using a wide range of molecular descriptors, see Figure 2. This allowed a broad range of solvents to be grouped in order to reduce practical screening. An automated platform to generate subsequent experimental data is currently under development.

*Figure 2. Output of a solvent clustering model based on various molecular descriptors.*

## Automated MSZW Determination Using the FBRM Feedback Control

The integration of PAT techniques provides a basis for automation and feedback control, allowing useful data to be collected routinely, without the challenges of subsequent synchronisation. The MSZW for metformin hydrochloride in an ethanol-water solvent mixture has been determined for various cooling rates. This typically involved cooling at a given rate until primary nucleation occurred at which point the control system via FBRM particle counts would instruct a heating stage. This was repeated for additional cooling rates, see Figure 3.

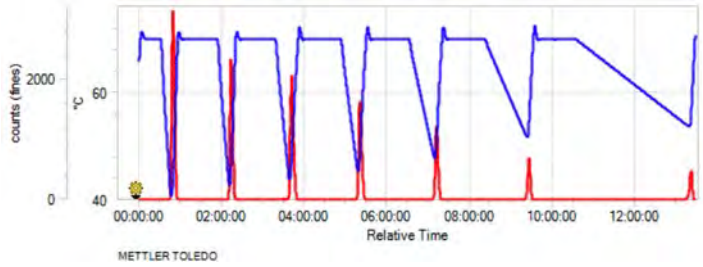



*Figure 3. Plot highlighting a heating/cooling cycle directed by FBRM control for metformin hydrochloride in an ethanol-water solvent system.*

When plotted with solubility, the predicted trend of increased MSZW with increased cooling rate can be clearly observed, see Figure 4. Such data can be used to provide an estimate of primary nucleation kinetics by applying selected models from the literature such as Nývlt,[2] Kubota[3] and population balance.[4]

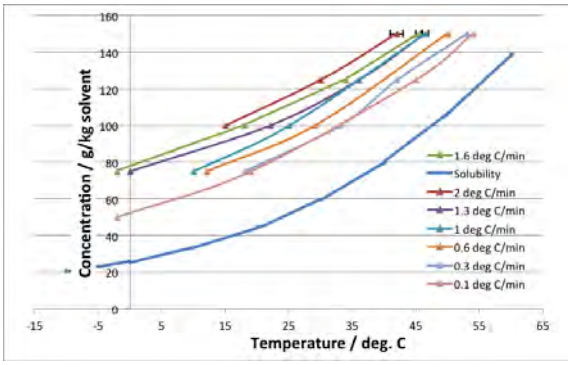



*Figure 4. Graph indicating the various MSZWs for metformin hydrochloride in an ethanol-water solvent system obtained via various cooling rates. The solubility curve is also shown.*

## Supersaturation Control in a Moving Fluid OBC Platform

Thermodynamic information such as solubility is scalable and can be readily transferred from batch to continuous platforms. However kinetic parameters such as nucleation, growth and fouling are heavily dependent on process conditions and the hydrodynamic environment. Moving fluid OBC platforms have shown promise in better simulating continuous process conditions when compared to STCs for example.[4] A PAT enabled moving fluid platform has been developed to allow rapid collection of data including solubility and MSZW, and to subsequently use this data to develop controlled cooling profiles which can inform continuous platform selection, see Figure 5.

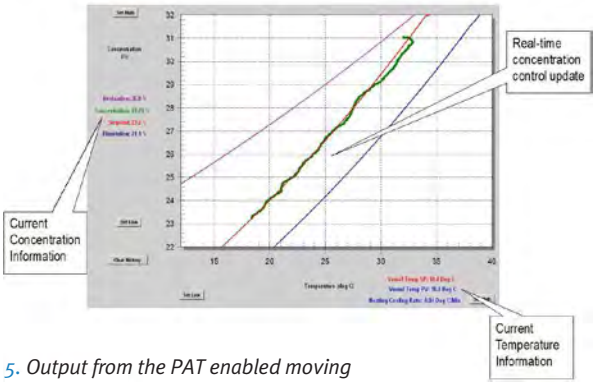



*Figure 5. Output from the PAT enabled moving fluid platform highlighting crystallisation within the metastable zone.*

## PAT Monitoring of a Continuously Seeded Crystallisation of Form III Carbamazepine in a COBC

The continuous cooling crystallisation of form III carbamazepine in a COBC was carried out using a controlled seeding approach allowing extended operation without evidence of fouling. Numerous in-line PAT techniques were employed including FBRM, mid-IR, PVM and non-invasive Raman, see Figures 5 and 6. A temperature profile was designed and employed to direct formation of only form III and this was verified by Raman in addition to off-line XRPD measurements.

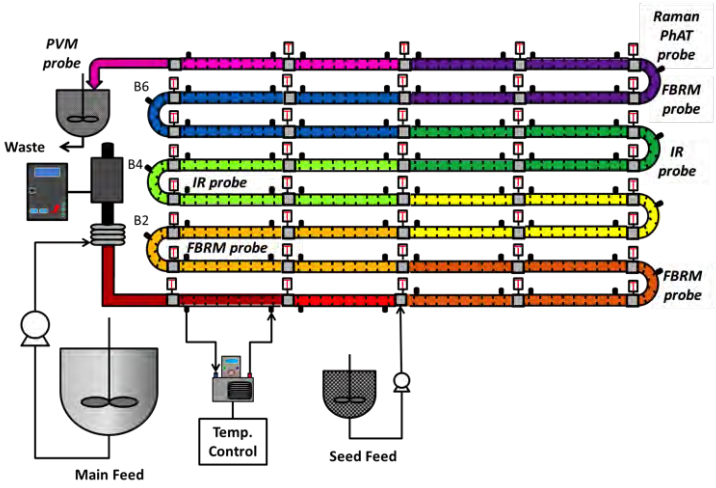



*Figure 6. Schematic showing the experimental setup for the continuously seeded crystallisation of carbamazepine in a COBC.*

The FBRM and IR techniques provide an indication of steady state operation.

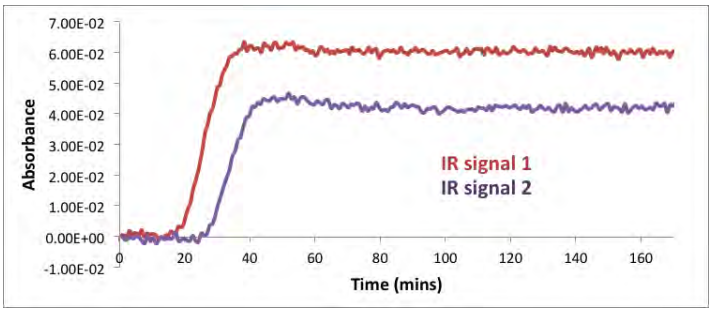



*Figure 7. IR data from the continuous crystallisation of carbamazepine.*


1. *Green Chemistry*, 2011, 18, 854
2. *J Cryst. Growth*, 1968, 3-4, 377
3. *CrystEngComm*, 2013, 15, 1199
4. *CrystEngComm*, 2014, 16, 8008

# Continuous Crystallisation and Solid-form Selectivity of a Multi-component Molecular Material

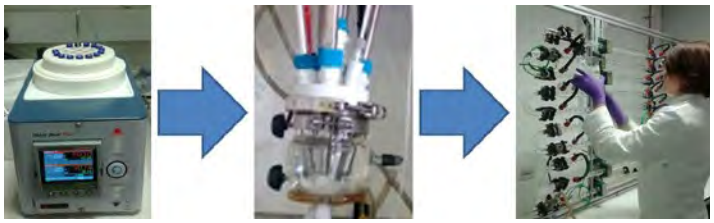
**Bath and Loughborough teams:**
Kate Wittering and Dr Ali Saleemi
with Prof Chick Wilson,
Prof Zoltan Nagy and Prof Chris Rielly

The polymorphic multi-component system urea-barbituric acid, in which the solubility of the target barbituric acid precursor is enhanced, has been optimised for processing in the continuous COBC crystalliser with selectivity in production of the kinetic form.

Within the pharmaceutical industry a range of strategies are used to improve physicochemical properties of active pharmaceutical ingredients (APIs). These include accessing different polymorphs, formation of hydrates, salts, solvates and co-crystals; the latter are all examples of multi-component systems. In recent years the number of co-crystals reported in the literature has increased significantly as a result of advances in crystal engineering and supramolecular chemistry. The creation of multi-component systems enable formation of new materials, with enhanced properties such as improved dissolution rate and hygroscopicity, without altering covalent bonding within the API.

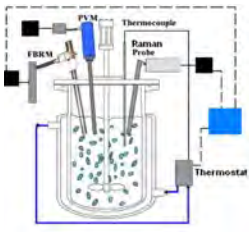
Existing methods for co-crystallization are largely based on slow evaporation or grinding, methods that are not readily translated for crystallization scale-up and are incompatible with many current crystallization technology platforms. The multi-component strand within CMAC is geared towards generating co-crystals via methods which are more viable for process scale-up, and implementing this in continuous environments. These underpinning methods include cooling crystallisation, one of the most dominant techniques in crystallization, but the challenge lies in implementing this at scale and translating it to continuous platforms.

A collaborative effort within CMAC, predominantly from the chemists in Bath and the chemical engineers in Loughborough, working with expertise and facilities at the CMAC hub at Strathclyde, has established control and scale-up of co-crystallisation of the target system urea barbituric acid (UBA) and implemented this in the continuous environment of the DN15 continuous oscillatory baffled crystalliser (COBC) in Bath. This breakthrough work has only been possible by using the opportunities offered by the multi-disciplinary collaborative environment within CMAC and represents an added value achievement within an exceptionally challenging area. UBA is a prime example of crystal engineering whereby the co-crystal demonstrates enhanced solubility over the barbituric acid target material. Barbituric acid is a known precursor for barbiturate pharmaceuticals and urea a common coformer molecule on the list of chemicals generally regarded as safe (GRAS). UBA is of particular



*Scale-up of urea-barbituric acid crystallisation from small scale cooling crystallisation in the PolarBear (Cambridge Reactor Design) through to continuous crystallisation using the COBC.*

interest as it has three known polymorphs, forms I, II and III and is thus an ideal candidate for investigating control of polymorphism in cocrystals, optimising the conditions for selective production of the various polymorphs in continuous crystallisation processes. Achieving single solid-form selectivity in such a complex system would be significant for CMAC core investigations.




By use of extensive Process Analytical Technology (PAT) methods at Loughborough, coupled with off-line characterisation at Bath and solubility measurements at Strathclyde, it was found possible to establish cooling regimes under which all three forms of UBA could individually be isolated. Moreover, the scaled-up cooling crystallisation (at substantial laboratory scale) was achieved and optimised. The highly metastable form II can also be isolated in small scale crystallisations, requiring a complex cooling regime; scale-up of this solid form is more challenging to achieve, but has been achieved in at-scale batch experiments. The scaled-up crystallisations tuned for selective production of either form I or form III under well defined conditions, are particularly suitable for transfer to high volume continuous processes ideally suited for CMAC applications.

In these experiments, polymorph-selective production of UBA has been initially implemented in the continuous environment. Using the underpinning scaled-up cooling experiments to establish the required parameters, high yield, high volume runs have been achieved in the DN15 COBC, optimised for the selective production of UBA Form I (verified by PXRD). This represents the first fully selective continuous scaled-up crystallisation of a polymorphic multi-component system and is a CMAC breakthrough. Ongoing work will establish continuous selective crystallisation of form III, tackle the even tougher target of production of the highly metastable form II, and establish multi-component continuous for UBA on a range of platforms, including Mixed Solvent Mixed Product Removal (MSMPR) which is currently underway. The experience gained in working with the complex system of UBA over a variety of platforms will be translated to other target systems and should prove valuable to all polymorphic systems, single component and multi-component alike.

# Continuous Generation and Growth of Seed Crystals


University of Strathclyde Glasgow

**Principal investigator:**
Prof Jan Sefcik
**Researcher:**
Dr Anna Jawor Baczynska


## The Challenge

Consistent particle attributes, such as solid form, particles shape and size distribution (PSD) are desirable for uniform dissolution time and good bioavailability of the drug as well as for optimising downstream processing steps. Moving from batch to continuous operation has the potential for significant increases in efficiency, flexibility and product quality. However, development of continuous crystallisation processes requires reliable control over crystal nucleation and growth as well as management of possible encrustation and fouling issues.

## The Technology

Particle engineering research group under the supervision of Prof Jan Sefcik has designed and investigated a novel continuous seed production unit (nucleator) wherein the particles are formed by the rapid antisolvent crystallisation process, see Figure 1. The control of crystal nucleation kinetics is achieved by adjusting the mixing efficiency, solvent-antisolvent ratio, supersaturation and residence time. The generated seed crystals can be directly transferred to the next crystallisation unit (growth unit) for example Continuous Oscillatory Baffled Crystalliser (COBC) or Mixed Suspension, Mixed Product Removal (MSMPR) crystalliser where crystals are grown to desired size while required purification/isolation objectives for an incoming upstream feed are achieved.

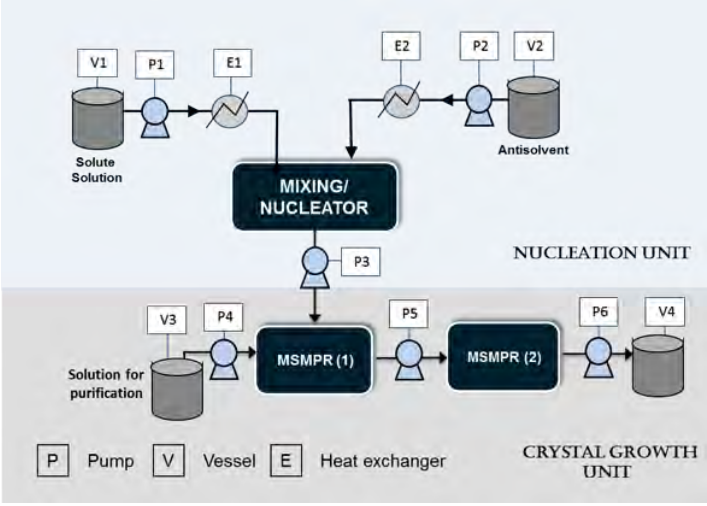



*Figure 1. Continuous seed crystals generation (nucleator) followed by two-step MSMPR cascade.*

## The Successful Outcome

The continuous nucleation unit was tested using several model compounds and good consistency in particles size, size distribution, morphology and yield was obtained (Figure 2). In subsequent step the seed crystals generated using the nucleation unit were directly transferred into a two-stage MSMPR where supersaturation was generated either by addition of another inlet stream (solution for purification) or by cooling, see Figure 1. As an illustration example, a two-stage MSMPR unit was used to grow paracetamol seed crystals from 190µm to 290µm during 30 minutes total residence time in the nucleation and MSMPRs seeds growth unit (Figure 3, 4).

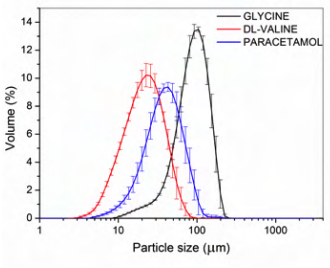



*Figure 2. Example of seed crystal size distributions (determined by laser diffraction) for several model compounds.*

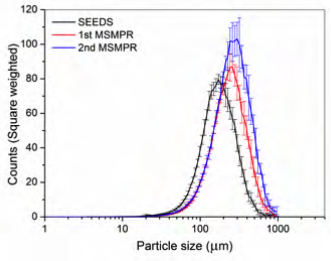



*Figure 3. Paracetamol crystal size distributions (determined by FBRM) for seed suspension together with crystals after 1st and 2nd MSMPR growth stages.*

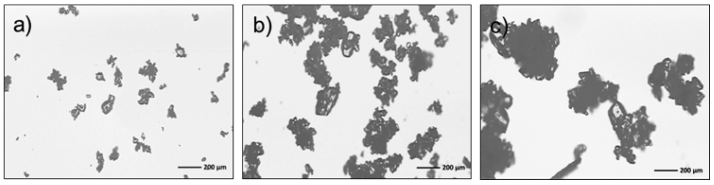
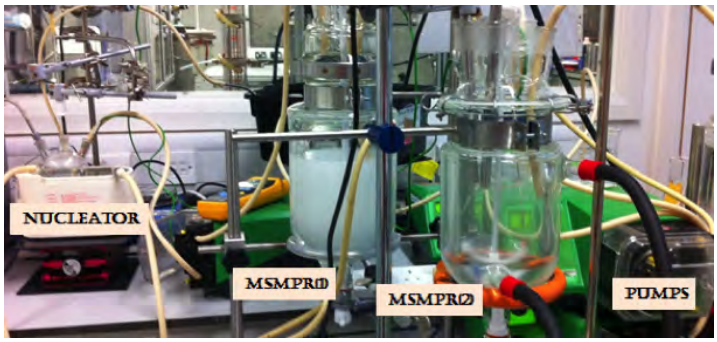



*Figure 4. Microscopic images of paracetamol seed crystals (a) and crystals after 1st (b) and 2nd (c) MSMPR growth stage.*




*Laboratory setup photo*

# CMAC: Industry Engagement

Sustainability is key to the Centre's success and ability to impact in this field through strong industry engagement and leadership. Following the award of the EPSRC Centre, an industry led membership organisation, CMAC, was created with three Tier 1 pharma companies (AstraZeneca, GSK and Novartis) to steer the development of user-led activities in this area informing basic research and develop activity at higher Technology Readiness Level (TRL). The first CMAC board meeting was held in April 2011 and the 13th board meeting recently took place in Boston. In accordance with the Centre's business plan, the aim is to populate the innovation landscape with parallel research activities across the TRLs using a range of appropriate funding mechanisms to address industry needs in a structured manner.

The membership organisation operates under a pre-competitive, collaborative research and development model with senior level company support. The CMAC board (Figure 1) is chaired by Dr Clive Badman, OBE. A separate Technical Committee comprising industrial experts and representatives of the EPSRC Centre defines the core programme. Alastair Florence & Craig Johnston are members of these committees to ensure that optimal alignment of the programmes across TRLs is maintained. In addition to our Tier 1 partners, we are also working with a range of technology providers and companies from other chemical sectors who are contributing to the technical programme, for example, through access to new processing and measurement technologies. An example is the relationship with Mettler Toledo, which involves the provision of a suite of equipment that will be used and developed across the programme. We are also continuing to develop further links with other companies that can contribute their expertise to advance the developing programme in continuous manufacturing research. Figure 2, illustrates the wide range of companies CMAC is currently engaging with as Tier 1 or Tier 2 members and collaborators on formal projects, including 2014 highlight, AMSCI Supply Chain Project.

AstraZeneca

**Founding Tier 1 member**

**"CMAC is providing...**

**Leverage;** knowledge, people, and expertise, greater return on investment
- Attracting leading academics, students and partners
- Highly successful in attracting funding
- Developing research portfolio with increasing impact

**Influence;** single voice, harmonisation, regulators and academics
- Industry open to new approaches

**Insight;** Industry led, new approaches, relevance

**Opportunities**
- Sustainability – to build on what has started and is working well
- Improved knowledge transfer to industry
  - Impact accelerators
- Demonstrable route to impact
- Providing a skills and talent pipeline;
  - blurred boundary between Industrial and Academic research

*Figure 1 (right).* *CMAC Tier 1 founding members. From left to right: Craig Johnston (Industry Director), Prof Sir Jim McDonald (Principal, University of Strathclyde), Dr Berthold Schenkel (Novartis, Switzerland), Prof Graham Wren (Strategic Projects, University of Strathclyde), Dr Jon-Paul Sherlock (AstraZeneca, UK), Dr Maureen O'Shea (GSK, Ireland), Dr Clive Badman, OBE (GSK, UK).*

## Tier 1

GlaxoSmithKline · AstraZeneca · NOVARTIS

## Tier 2

CAMBRIDGE REACTOR DESIGN · NiTech SOLUTIONS · AMTechnology · CLAIRET SCIENTIFIC LIMITED · PSE

AVANTIUM Crystallization Systems · METTLER TOLEDO · PERCEPTIVE ENGINEERING LTD · Alconbury Weston Ltd Design around you. · 25 yrs sirius analytical

## Collaborators

genzyme · FUJIFILM · AMRI GLOBAL SMARTSOURCING · TTP · Lubrizol · Johnson Matthey · syngenta · Pfizer · P&G

BRUKER · C-Tech INNOVATION · Dr. Reddy's Custom Technology Centre · Solid Form Solutions · syrris · cpi the future inspired · infinity automation · GILDEN photonics · CANCER RESEARCH UK

GEA · Britest · cogent Skills for Science Based Industries · INTERSYS · IntensiChem · CrystecPharma

# Knowledge and Technology Exchange

## Overview

The Centre's research direction is based on detailed knowledge exchange via academia-industry workshops, which develop industry problem statements and identify research targets. These have been updated and expanded over the past 12 months as the Centre progresses into Phase II. Further academia-industry links have been developed through faculty and researcher visits, workshops and secondments to industry. An innovative industry-mentoring scheme is underway for 50+ PhD students from the Centre and the Doctoral Training Centre. There has also been broad UK, European and International dissemination including conferences jointly organised with the Royal Society of Chemistry.

The Institute for Manufacturing at the University of Cambridge (CMAC academic partner) coordinated the road-mapping for the Pharma 'Deep Dive' report, both with direct active contribution and through engagement with CMAC companies. The Centre has worked very closely with the Technology Strategy Board (TSB) during Phase I and it is pleasing to note that there are initial examples of the development of new technologies for direct exploitation with industrial partners.

The Centre has also engaged with HVM Catapult - Centre for Process Innovation (CPI) exchange visits, common skills agenda and is involved in one of the current TSB Collaborative R+D projects, which is looking at developing links in complementary areas as well as building on the Centre capabilities at higher TRL that complement core CPI base.

A major highlight of the last year is the award of the £23m four-year Advanced Manufacturing Supply Chain Initiative (AMSCI) project, REMEDIES which will benefit from research expertise from the EPSRC Centre as well as a host of other partners. The aim of the Advanced Pharmaceutical Supply Chain Consortium, led by GSK and comprising 22 partners including 11 SMEs, is to modernise the manufacturing supply chain for pharmaceuticals, paving the way for increasingly personalised production, which is closer to patients and in response to need.


> “Working with CMAC they delivered key learning points relevant to subject area, ‘nucleation behaviour under different conditions’ with a high quantity of good quality data. There was excellent communication and information sharing throughout the 5 month project.”
>
> **Syngenta** – Project Partner

## The Talent Pipe-line

The success of the Centre has resulted in a two-way exchange between Academia and Industry with Dr Chris Price moving from GSK to take the position of EPSRC Industrial Fellow at the University of Strathclyde. This is coupled with researchers who have used their multi-disciplinary skills learned through the Centre to gain prestigious places in industry. This talent pipeline is a key centre output highly valued by industry

- Researcher Dr Peter Hamilton moved to work as a senior scientist at GSK, UK
- Researcher Rajan Talati (Strathclyde) moved to work at MacFarlane Smith, UK
- On completion of her PhD Laura Palmer (Strathclyde) secured a job at Johnson Matthey, UK.
- Researcher Ulrich Schacht (Strathclyde) commenced his career as a Technology & Application Consultant with Mettler Toledo following the completion of his PhD.
- Researcher Dr Ali Saleemi (Loughborough) secured a senior scientist position at GSK, UK.
- Researcher Dr Craig Callaghan (Heriot Watt) is now working for Solid Form Solutions, UK.

## Industrial Secondment - Development of Continuous Processes for Separating Nucleation and Growth in Crystallisation of Pharmaceutical Products

Through the successful award of funding from the EPSRC Impact Accelerator Account, Centre researcher, Dr Anna Jawor-Baczynska, spent an eight week secondment at Tier 1 member AstraZeneca commencing 3rd March 2014. During the project, a continuous nucleation system was implemented and tested using a live pharmaceutical compound, therefore allowing continuous generation of seed crystals of consistent quality to be used for further growth in a subsequent seeded crystallisation step under batch or continuous conditions. By using the same methodology that is actively being investigated within related EPSRC Centre funded projects using a range of model compounds, this collaboration allowed the further development of the method for active pharmaceutical ingredients to enhance successful product/process development in industry.

SPIRE
Sustainable Process Industry through Resource and Energy Efficiency

## A.SPIRE Membership

CMAC has joined A.SPIRE (**http://www.spire2030.eu**) as an academic member. A.SPIRE is an international non-profit association formed to represent the private sector as a partner in the Sustainable Process Industry through Resource and Energy Efficiency (SPIRE) Public-Private Partnership (PPP) launched as part of the European Horizon2020 framework programme. It represents more than 90 industrial and research process industry stakeholders from over a dozen countries and is a key influencing body for H2020 projects.

As a direct result of this membership, CMAC was one of 3 founding members in a (€5million) bid in the SPIRE 3 area for Solvent Selection for PI Applications involving 8 partners across 3 industry sectors. Further H2020 proposals will be submitted in relevant areas.

# Made to Order Processing Plants

## Advanced Process Control (APC) for Continuous Processing

The “Make To Order Processing Plants” (MOPPs1) project involving CMAC, CPI, AstraZeneca and led by Perceptive Engineering has the aim of designing a single, flexible control system software infrastructure and work process that will work across a whole range of equipment including reactors, crystallisers, spray driers etc. The system uses Advanced Process Control (APC) software to enable real-time control using multiple in-line analytics (PAT) utilising both feed forward and feedback control. Advanced control typically reduces off-spec production by 40% and re-work by 10% as demonstrated already in batch processes across a range of industries including pharma, fine chemicals, water and food. The project aims to leverage this knowledge in the new generation of novel continuous equipment and processes being developed.

Coupling APC with the new continuous technologies being brought to market offer the chance for producers to develop a new ‘manufacture at the point of need’ model for high value low volume products and reduce the delivered costs of products to the customer by up to 50% [2] through savings in the supply chain, increased stock turns and reductions in non-value adding activities. Further savings in waste product of 8-15% and energy by 40-70% are anticipated. These reactors can be used for multiple product lines by varying throughput, feed-rate and process conditions.

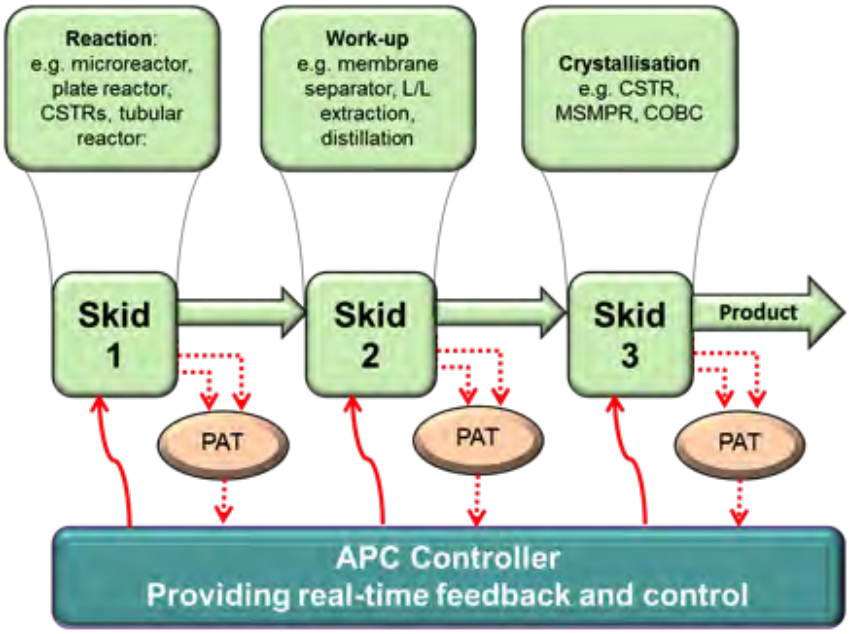
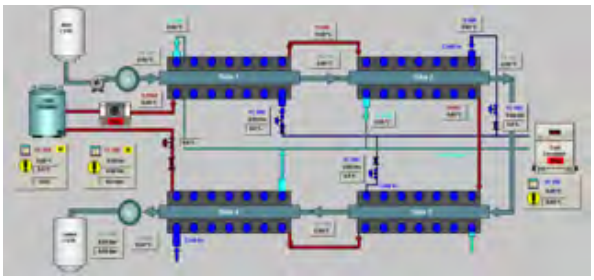



*Figure 1: Schematic for use of APC with flexible, plug-and-play production systems.*

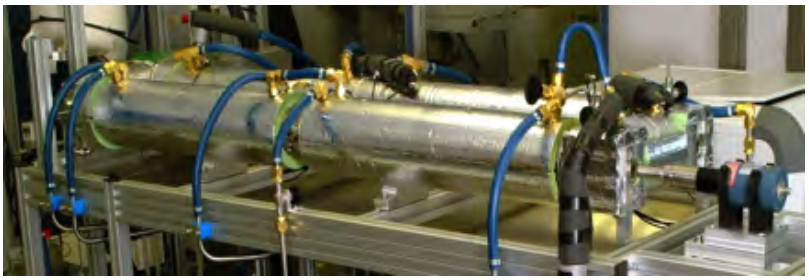
The project is demonstrating the control system on:

- Two chemical reactions in a continuous Corning plate reactor.
- The continuous crystallisation of lactose in 2 different types of crystalliser, Cambridge Reactor Design’s Rattlesnake and in Nitech’s DN15 continuous oscillatory baffled crystallisers (COBCs).

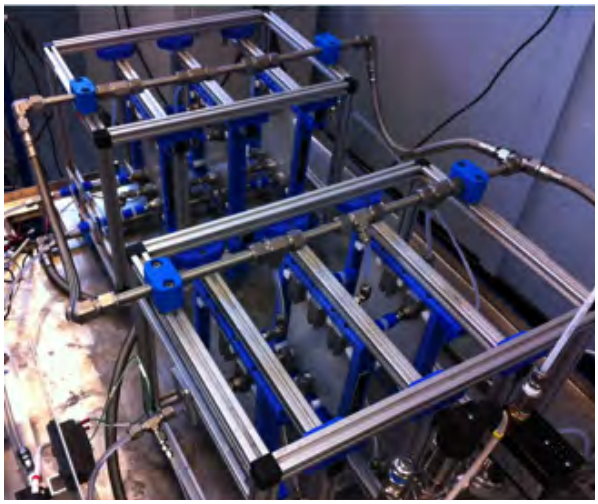
The development of model predictive control for these systems allows for the incorporation of DoE experiments at the same time, adding further flexibility and functionality to improve process understanding and reduce product development time. The agile, flexible single control system is expected to be used in plug and play environments where different skid mounted items can be rapidly (re-)configured and controlled using a common APC interface for on-demand manufacture and rapid scale-up/down as production requirements change or for multi-product plants.



*Rattlesnake APC system*



*CRD's Rattlesnake Continuous Crystalliser*



*Corning Advanced Flow Reactor*

*Nitech DN15 Continuous Crystalliser*

[1] *The MOPPs project team would like to thank the Technology Strategy Board and EPSRC for funding (project number 101334).*

[2] *Off Shoring" Lifecycle Production is not the only answer, Professor Roger Benson, FREng, Pharmaceutical Engineering , Q3 2007*

## CMAC Collaboration

**Benefits to Perceptive and CMAC**

PERCEPTIVE ENGINEERING LTD

*Tier 2 member*

Our Partnership benefits both parties:

**CMAC**

- PEL enables research by solving complex integration problems and delivering flexible platforms
- Access to leading-edge APC software and process control techniques used in the Pharma industry
- Accelerate progress with current Centre and DTC projects
- Support themes and activities within the scope of the Centre objectives and the CMAC-ICT project

**Perceptive Engineering Ltd**

- An opportunity to work with Tier 1 Pharma companies
- A pre-competitive environment for development and improvement of our software and solutions
- Closer integration with software and PAT provided by Tier 2 companies

*Team Building 2014 Summer School*

> "The Centre provides an excellent focus for training and skills development and students are clearly benefitting from the multi-centre nature of the DTC programme."
>
> **Centre Midterm Review Panel**

# Training

The Centre has a distinctive training programme on offer across all levels from the unique MSc in Advance Pharmaceutical Manufacturing, the innovative Doctoral Training Centre (DTC) cohort training programme and transferable skills development for all levels of the Centre. Collective training of the entire Centre has occurred at intensive creativity days, collaboration workshops and during our tailor-made DTC summer school which combines training of the two DTC cohorts with entire Centre team building exercises. The Centre is also pioneering the use of Electronic Lab Notebooks (ELNs) by all of its researchers.

## The Doctoral Training Centre

The CMAC Doctoral Training Centre (DTC) commenced in October 2012, and offers a vibrant, world-class, multi-disciplinary four-year training programme that will equip 45 graduates with leading edge skills in pioneering continuous processes. Funded through combined support, from a £4.2m award from EPSRC, a £501k contributions towards training costs from AstraZeneca, GSK and Novartis and significant support for studentships, training and infrastructure from the seven Centre universities, this DTC employs a novel approach to cohort building and training (Figure 1) whereby year 1 of the PhD encompasses residential training weeks throughout all of the partner institutions with visits and input from industrialists.

By embedding the DTC within our National Centre, our students are exposed to:

(i) Relevant fundamentals across each discipline,
(ii) Current state-of the-art in knowledge and the challenges in continuous manufacturing and crystallisation,
(iii) Existing research activities both within the Centre and internationally and
(iv) Unparalleled opportunities to engage in leading-edge research projects as part of a National team.

The formal training programme is co-ordinated by Prof Jan Sefcik and has three main elements:

(i) A range of taught modules covering the different aspects of the programme;
(ii) Individual and group miniprojects;
(iii) Transferable skills training.

To date two of the three cohorts have completed their first year residential training weeks and are now in the research phase of their project. The final cohort will commence their DTC studentships in October 2014.

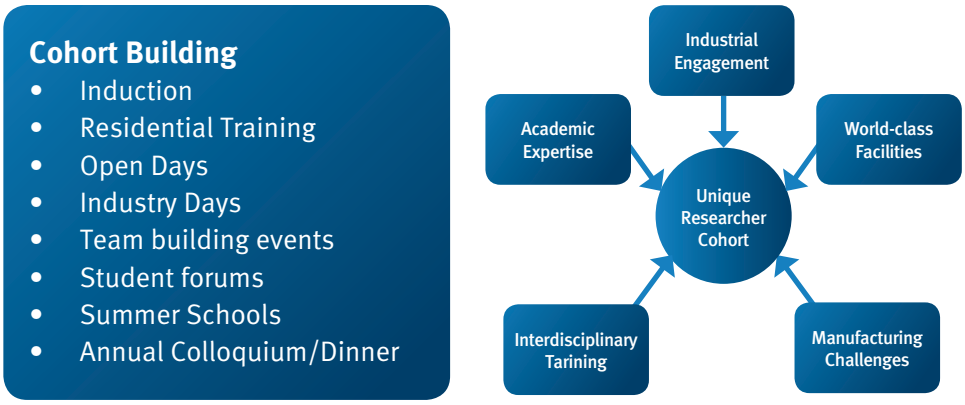



*Figure 1. The DTC will create a new community of continuous manufacturing researchers.*

## Industry Mentors

All Centre students and researchers benefit from support from internationally leading supervisors and expert industry practitioners and opinion leaders through the established industrial mentor scheme. Mentor groups meet regularly to enable industry experts to coach the students in their research and provide industrial relevance and context for their work. The meetings are a mixture of telecon/webex and face-to-face meetings and involve both Tier 1 members as well as several Tier 2 companies. These mentor meetings have already enabled a student to access industrial analytical equipment and it is anticipated that they will also facilitate placements within the companies as students move into their second and third year. This is a key avenue for the research and learning in CMAC to be transferred into industry and an efficient way for companies to access and influence the ongoing research.

## The MSc

The Scottish Funding Council (SFC) awarded CMAC at the University of Strathclyde 20 fully funded places for a new MSc in Advanced Pharmaceutical Manufacturing, commencing September 2014. This unique course will train graduates to Masters Level in key aspects of modern manufacturing approaches suitable for pharmaceuticals and high value chemicals. This bespoke course is designed to produce highly skilled graduates in continuous manufacturing science and technology that will meet the growing demands for expertise in this area and makes them ideally trained to take up jobs in the food, chemical and pharmaceutical industries. The programme curriculum was also designed with input from CMAC industry partners to deliver the practical skills required by scientists and engineers in their organisations.

The course combines taught material with practical classes running between October and April, following by a 10 week summer project in Industry or Academia.

All students shall undertake the following compulsory classes amounting to 120 credits:

- Continuous Manufacturing of Pharmaceutical Particles and Products
- Crystallisation and Formulation for Manufacture
- Generic Biomedical and Pharmaceutical Research Skills
- Industrial Pharmacy
- Pharmaceutical Project Management
- Process Analytical Technology (PAT) and Quality by Design in Continuous Pharmaceutical Manufacturing

*DTC 2013 cohort*

*Figure 1. Artist interpretation of the Technology and Innovation Centre.*

# Facilities

## The Strathclyde Technology and Innovation Centre

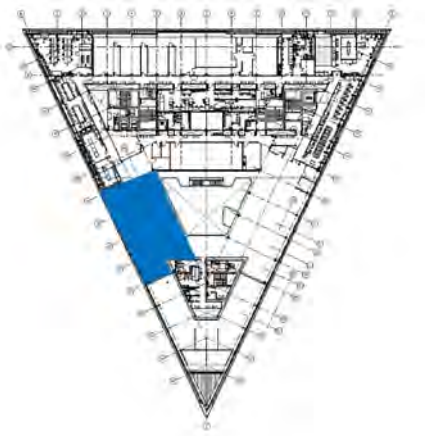
The EPSRC Centre has secured a dedicated purpose built 750m2 laboratory facility in the new £100m Technology and Innovation Centre (TIC) at the University of Strathclyde (Figure 1). This facility, which will open in February 2015, will act as the physical hub for the National Centre offering state-of-the-art processing, analysis control and characterization capabilities. A £34.2m capital investment composed of £11.4 million cash injection from the Higher Education Funding Council for England (HEFCE)'s UK Research Partnership Investment Fund (UKRPIF) scheme supported with £22.8 million industry and charity contributions will assist in establishing worldclass capabilities for crystallisation, process development, materials characterisation, secondary processing, and process and product analysis. Importantly, this new building will allow CMAC to co-locate multi-disciplinary teams of PhDs, RAs and academics across the Centre's projects. The facility will also have the capability to host industry research secondments to accelerate delivery on continuous manufacturing and crystallisation research.

The Technology and Innovation Centre will enable leading academics and researchers to partner in delivering groundbreaking and viable solutions for energy, manufacturing, health and smart cities.

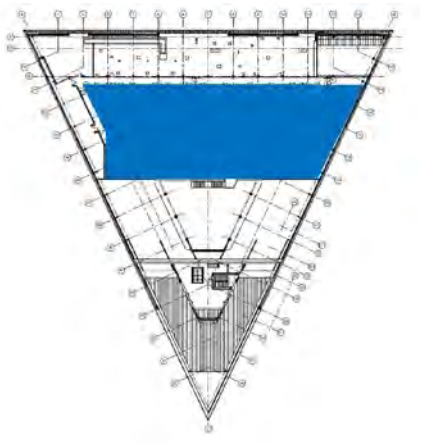
Currently, the construction work of the TIC building continues to progress with CMAC's location on Level 8 now 65% complete. This is on schedule for the move to the purpose built laboratory on week commencing 23rd February 2015.

# CMAC and TIC

TIC Level 6



TIC Level 7



TIC Level 8

The University of Strathclyde is on track to take ownership of TIC on Friday 28th November. The new centre is looking fantastic and the next 6 months ahead of us will be the most exciting stage in the project – we can finally move into the new facility. CMAC is scheduled to move into TIC at the start of 2015. Space planning for level 8 has been completed and signed off. Design of the bespoke fumehoods is in the final stages, with installation pencilled in for late September. CMAC has been allocated more space within TIC on level 6. This will greatly help us realise our potential for CMAC at Strathclyde by housing all our equipment under one roof. We are engaged with a design team for the space planning on level 6, this is in the initial stages but we are working towards a hand over date inline with the other TIC spaces.

CMAC is scheduled to occupy three levels within TIC. Level 8 will be main hub for CMAC activity, housing 4 main labs and occupying 500m$^2$. The main process lab will include the bespoke fumehoods to run the primary and secondary processing equipment. The fumehoods have been designed with modularity and flexibility in mind to accommodate various processing equipment in numerous configurations. Removable partitions and pass-throughs will allow bulky equipment and associated in-line PAT to be easily accomodated for each experiment undertaken. An open plan lab will allow maximum flexibility when running skid processing modules, aided by mobile benching and reconfigurable enclosures for local ventilation. A solvent pumping system has been comissioned that will sit in its own room, with a dedicated pipeline for solvent delivery to the fumehoods within the process lab. An analytical lab will house various chromatography instruments, and other at-line analytical techniques. There is also a vibrationally sensitive lab for machines where is this a site requirement, such as the IR and Raman mapping microscopes. Various storage rooms are located nearby for safe and convenient storage of equipment when not in use. Level 6 will house 4 labs, these being an X-ray suite, TOF-SIMS Wolfson Laboratory and two process labs. The process labs on level 6 will be used for experiments that are stand alone in nature, i.e. those just requiring a fumehood or bench space in order to run. Level 7 will accommodate all Strathclyde CMAC researchers, visiting researchers, technicians and management team. There will be 56 permanent desks, with 10 hot-desks for visiting researchers.

“

Strathclyde’s Technology and Innovation Centre will help transform Glasgow and Scotland. Based on our reputation for high quality research with industrial impact and relevance, it will attract millions of pounds of inward investment to the city, drive global businesses, and create jobs - helping develop highly-qualified graduates and postgraduates.

“We believe that this project will be in the vanguard of exciting new investments that fully realise our potential to capitalise on academic excellence, contribute to economic development and position Scotland as a global competitive player in key sectors. The Centre will raise Glasgow’s profile internationally and help restore the city’s reputation as an engineering and technology centre of excellence.

“But beyond that, this is about transforming the way we share knowledge and find solutions to challenges that affect every area of society – including energy, pharmaceuticals, manufacturing and economics”

**Professor Sir Jim McDonald, Principal of the University of Strathclyde**

# UK Research Partnership Investment Fund

On 6th June 2014 The Rt Hon George Osborne MP formally announced CMAC's award of £34.2m for capital investment from the Higher Education Funding Council for England (HEFCE)'s UK Research Partnership Investment Fund (UKRPIF) scheme. This award was composed of £11.4 million cash injection from UKRPIF, supported with £22.8 million industry and charity contributions. This substantial investment will further develop and enhance the world-leading facilities in our national research programme. With a move into a new £100m Technical Innovation Centre planned for February 2015 this award will provide state-of-the-art capabilities for researchers from academia and industry to work side-by-side to accelerate delivery on continuous manufacturing and crystallisation research.

*Figure 1. Picture of the official opening of Phase 1 of the UK Research Partnership Investment Fund (UKRPIF), pictured here is Vince Cable with Alastair Florence, Craig Johnston and Clive Badman (GSK).*

Phase 1 of the UKRPIF for Pharmaceutical Manufacturing Research award was formally opened by The Rt Hon Dr Vince Cable MP, Secretary of State for Business, Innovation and Skills, on Wednesday 8th January at the University of Strathclyde, Figure 1.

To date, high priority equipment items have been identified covering the following core areas:

- Advanced continuous processing equipment for laboratory scale manufacturing research
- A comprehensive suite of state-of-the-art at-line analysis capability
- A suite of complementary process analytical technologies (PAT) for on line analysis
- Data management and process control infrastructure
- Novel continuous process skids for process development
- A national centre PAT network across the Centre partner universities

Equipment purchasing is underway with the total equipment spend currently at £1.4m. The purchases include an initial suite of in line process analytical technologies, at-line particle analysis tools and a control infrastructure across several processing and crystallisation platforms.

## UKRPIF Award

The money from UKRPIF and Wolfson Award has given CMAC a unique opportunity to create a world-leading Centre located in the Technology and Innovation Centre (TIC) at the University of Strathclyde. The award has been spread across processing equipment, in-line process analytical techniques (PAT), analysis at-line, control systems, data management, and installation and move costs. In addition £1.15m has been allocated for our partners across the UK, these include Bath, Cambridge, Edinburgh, Glasgow, Heriot Watt and Loughborough Universities, to enhance continuous manufacturing and crystallisation capability. Glasgow University has completed its spend, Heriot Watt and Loughborough are making good progress and Edinburgh are about to begin their spend. The Department of Pure and Applied Chemistry at University of Strathclyde will benefit from a £400k contribution toward a brand new NMR spectrometer, capable of measuring solutions, gels and solids.

In accordance with procurement procedures at the University of Strathclyde, strict purchasing guidelines are being adhered to. Equipment over £50k and not on an APUC (Advanced Procurement for Universities and Colleges) framework will be tendered through Official Journal of the European Union (OJEU). Equipment less than £50k and those on APUC frameworks have a quicker route to market, facilitating shorter procurement exercises. To date OJEU tenders have been completed for a TOF-SIMS instrument (£1m), bespoke skid processing equipment, and an AFM instrument (£350k). Chromatography equipment (LC-MS and GC-MS) and a suite of pharmaceutical powder characterisation instruments will be evaluated soon. The next big OJEU tender to be advertised will involve approximately £1m of X-ray equipment. The bulk of spending has centered on analysis at-line instruments due to longer lead times. We are moving onto processing equipment with the help of a new appointee, John Robertson, who has great expertise in this area.

## Key Appointments at CMAC for the Successful Delivery of UKPRIF Equipment

### Roy T. McBurney

Roy T. McBurney was born and raised in Carnoustie, Scotland. He received a MChem in Chemistry at the University of Edinburgh (2000–2005) and later obtained his PhD under the supervision of Prof. David Leigh, investigating metal template strategies to interlocked architectures. In 2008 he took up a postdoctoral position at Durham University with Prof. David Parker studying responsive MRI probes. In 2010 he joined the group of Prof. John Walton at the University of St Andrews. His research interests included semiconductors for use as photocatalysts in organic synthesis and tin-free methods for the direct generation of organic radicals. In 2012, Roy took up a postdoctoral position in the Cronin group at Glasgow University before joining CMAC as a senior technician in May 2014. Roy is the lead on UKRPIF equipment specification and procurement, aiming to deliver all instruments to CMAC at Strathclyde and across all partner Universities.

### Scott McPhee

Originally from Stirling, Scott studied at Edinburgh and Glasgow Universities to receive a degree in Chemistry. After graduation he took up a position at the University of Dundee as Service Manager and Research Technician in the Nucleic Acids Structure Research Group. At Dundee Scott implemented a series of projects to improve operational and research efficiency leading to ground breaking capabilities in RNA research. During this time he was also involved in many research projects leading to a diverse range of publications in synthetic chemistry, bioinformatics and structural biology. As Lab Manager at CMAC, Scott will use his experience in facility management and multidisciplinary research to implement the equipment from the RPIF project, as well as coordinating the move to the TIC, increasing operational effectiveness and monitoring health and safety obligations.

## Processing Equipment – Skids

An identified key area to the success of CMAC is around processing equipment. An OJEU tender awarded a contract to MicroInnova (Austria) for the design, manufacture, supply and installation of skid mounted processing equipment, Zeton and Morgan Sindall are also on the framework. User specifications requirements are in the early stages but the first piece of skid equipment will be a Continuous Oscillatory Baffled Crystallizer (COBC). MicroInnova have a well-established track record for the design and supply of skid mounted processing equipment. With the Skids CMAC will be able to address various processing requirements, across different scale levels, to suit a whole range of projects. Reconfigurable skid modules will be an exciting area for CMAC to answer the specific research challenges. To help address the processing challenge, we are looking into a vast array of in-line PAT probes covering everything from UV/Vis to mid/near-IR, FBRM, PVM, and a variety of available processing analytical technologies.

## Pharmaceutical Materials Powder Characterisation Laboratory

To fully understand the properties of various pharmaceutical materials, a variety of different techniques need to be employed. An OJEU tender was advertised to address this need, incorporating nine separate analytical methods. The Surface Energy Analyzer (SEA) from Surface Measurement Systems (SMS) UK is the only commercial instrument based on the principal of inverse gas chromatography, see Figure 2. A powdered sample is loaded into a glass capillary and packets of known vapours are then passed though the sample. The different vapours retention times are recorded by a FID detector. The results obtained help the understanding of surface energy, diffusion and permeability plus an expanding portfolio of experimental techniques is being added by SMS. Feedback from both GSK and AZ has been very favourable for this machine and the information obtainable. A Dynamic Vapour Soprtion (DVS) instrument capable of looking at sorption of organic vapours will also add to our capability. We will be purchasing instruments to address porosity, pore size distribution, density measurements, and surface area measurements. Thermal analysis is also being addressed; we are keen to purchase a Simultaneous Thermal Analyzer (STA) capable of performing Differential Scanning Calorimetry (DSC) and Thermogravitmetric Analysis (TGA) at the same time. Dissolution testing instruments will also be purchased that conform to USP standards 1, 2, 4, 5 and 6. These will cover tablets in a basket, with and without stirring, and also flow through testing for low solubility tablets. The most recent purchase is an Instron Compression Testing machine, our aim with this instrument is to look at agglomerates and compressibility, see Figure 3.

## X-ray Instrument Suite

In addition to the existing X-Ray Diffractometers (XRD), (3 powder XRDs and 1 single crystal XRD), CMAC is looking to purchase additional capability that will extend the range of experiments that CMAC researchers can perform. The Centre is aiming to purchase a Small Angle X-Ray Scattering (SAXS) instrument. This instrument is sought to support a research program investigating the following aspects within CMAC's scope, namely: nanostructure and self-association in small molecule solutions - as a function of aqueous and organic solvents, concentration, function of pH/ionic strength, flow; nanoparticles/nuclei in suspension e.g. nuclei or other nano-scale/colloidal systems, mesoporous systems and other particulate systems – internal structure of particle; biopharmaceutical systems – structure; aggregation/protein-protein/ peptide-peptide interactions; liquid crystalline systems; and all across a scale range of ‹1nm up to 200 nm. In addition we are looking at state-of-the-art powder and single crystal XRDs, both with dual X-ray sources. The large floor standing X-ray machines will all be accommodated on Level 6 in TIC within one dedicated X-Ray Suite. In addition, the XRDs will be complimented by benchtop powder and single crystal instruments in the Process Lab on Level 8. This will facilitate routine analysis as part of the researchers workflow. CMAC is evaluating an X-ray Micro-CT instrument for 3D imaging through a material. Expectations for this instrument is that it will help understand the distributions of voids within filtercake, spray dried material, extrudate and tablets.

## Molecular Surface Imaging

CMAC awarded an OJEU tender to ION-TOF for the supply and installation of a time-of-flight secondary ion mass spectrometry (TOF-SIMS) instrument. Costing just under £1m, this will be the only TOF-SIMS instrument in Scotland and the third in the UK. We will have the highest specification in the country, with all available options installed on the machine. CMAC's vision is to build a research program around the machine to supplement understanding of continuous manufacture and crystallisation, e.g. the distribution of API from a spray-dried process. A Fast-Scan AFM instrument from Bruker, see Figure 4, will allow real time measurement of surfaces under environmental and physiological conditions. This instrument will be one of the few Bruker Fast-Scan AFM instruments with all available optional accessories included, making it one of the most powerful AFM instruments in Europe. IR and Raman microscopes will allow for a complete spectroscopic profile across the surface of a tablet or extruded material.

*Figure 2. A Surface Energy Analyzer (SEA) from Surface Measurment Systems (SMS) UK. The only commercially available instrument based on the principal of inverse gas chromatography..*


*Figure 3. An Instron compression tester will produce information about the compressibility of agglomerates and related powders.*

*Figure 4. A Bruker AFM Fast Scan, soon to be delivered to SIPBS and then located within a dedicated room within the new TIC building.*

# The Wolfson Foundation Award

In June 2013 the Centre at the University of Strathclyde was awarded £750,000 in funding from the Wolfson Foundation towards the purchase of a Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS), See Figure 1, to be housed in the new Technology and Innovation Centre. The provision of this facility went to tender with a contract awarded to ION-TOF GmbH in January 2014. Following this there has been discussions between ION-TOF and the University to clarify the exact specification of the instrument to maximise the research potential both for the EPSRC Centre and the wider research community of this highly specialised facility. It is proposed that following the delivery and installation of the TOF-SIMS, the instrument will be commissioned in March 2015 and the active research programme will start thereafter. As lead academic, Dr Dimitrios Lamprou has commenced engaging locally and across the wider academic community to develop a programme of initial research activity that is in support of the CMAC vision and that will simulate other areas of high quality research activity, including the health technologies arena. The location with TIC of the TOF-SIMS facility is still under review and the Centre have identified and put in a formal request for additional laboratory space on level 6 of the TIC building. The allocation of this space is awaiting final approval from the TIC steering committee, however if successful this will result in a designated TOF-SIMS laboratory space named in recognition of the support from the Wolfson Foundation.

Three operational modes are available using TOF-SIMS: surface spectroscopy, surface imaging and depth profiling. A brief schematic of the physical processes behind the TOF-SIMS techniques is depicted in Figure 2. Analytical capabilities of ToF-SIMS include:

- Mass resolution of 0.00x amu. Particles particles with the same nominal mass (e.g. Si and $C_2H_4$, both with amu = 28) are easily distinguished from one another because as Mr. Einstein predicted there is a slight mass shift as atoms enter a bound state.
- Mass range of 0-10,000 amu; ions (positive or negative), isotopes, and molecular compounds (including polymers, organic compounds, and up to ~amino acids) can be detected.
- Trace element detection limits in the ppm range.
- Sub-micron imaging to map any mass number of interest.
- Depth profiling capabilities; sequential sputtering of surfaces allow analysis of the chemical stratigraphy on material surfaces (typical sputtering rates are ~100 A/minute).
- Retrospective analysis. Every pixel of a ToF-SIMS map represents a full mass spectrum. This allows an analyst to retrospectively produce maps for any mass of interest, and to interrogate regions of interest (ROI) for their chemical composition via computer processing after the dataset has been instrumentally acquired.

*Figure 1. An indication of the complexity of a TOF-SIMS instrument. This instrument will be housed in a dedicated facility on Level 6 in TIC.*

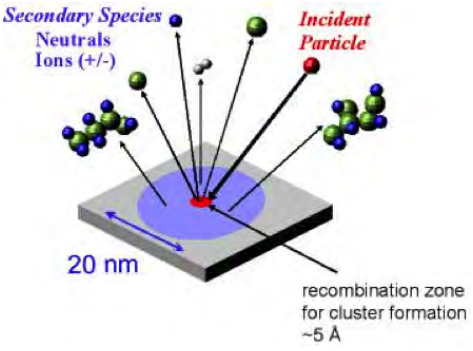
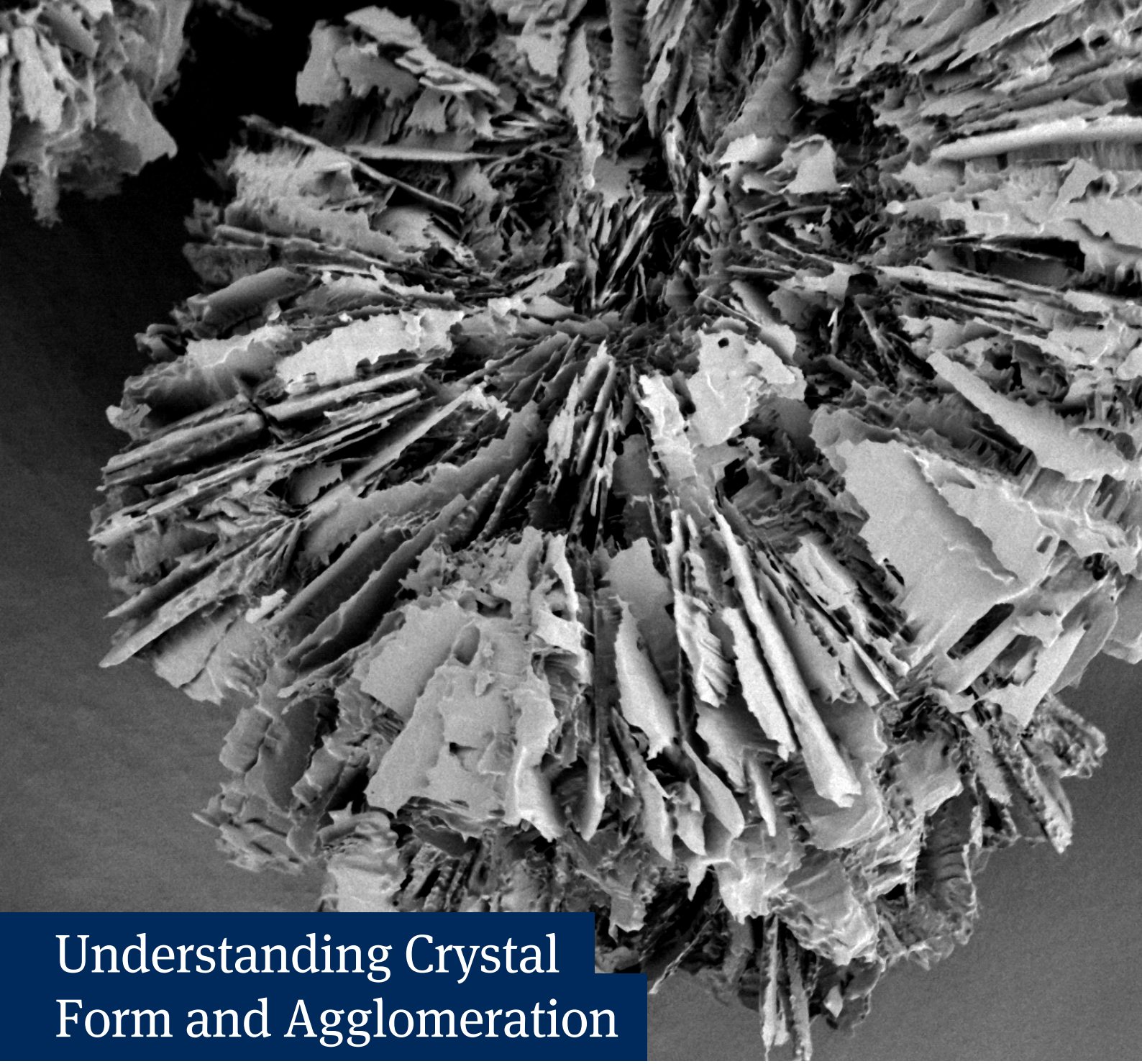



*Figure 2. A brief diagram depicting the collision of a primary incident particle onto a surface with the subsequent ejection of secondary ions that are then detected with the time-of-flight detector.*



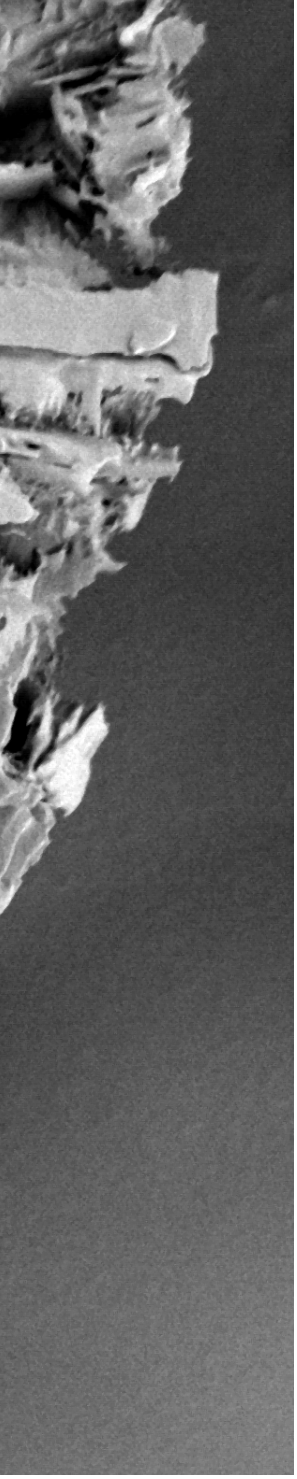
# Understanding Crystal Form and Agglomeration

## The Challenge

A fundamental aspect of the research at the Centre is understanding the processes behind different crystal forms and looking at nucleation, aggregation and agglomeration. To address this need, CMAC undertook a series of demos to test all commercially available benchtop scanning electron microscopes.

## Agilent 8500 FE-SEM

CMAC placed an order with Keysight, formerly Agilent's Nanoscale Measurement Operations, for a field emission (FE) SEM the 8500 FE-SEM. This instruments offers CMAC researchers resolution and imaging equivalent to that of conventional FE-SEMs. Variable low voltage eliminates charging and the need for sample coating. The compact size of the instrument enables easy installation in our research laboratory and does not require special facilities. CMAC researchers will be able to take any sample and acquire instant high magnification images revealing surface detail, texture, composition. We have opted to install the Energy-dispersive X-ray spectroscopy (EDS) option will allow a complete elemental map of sample under investigation.



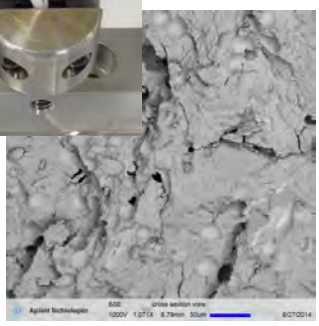
## Case Study 1:
## Co-crystals of Lipoic Acid and Nicotinamide

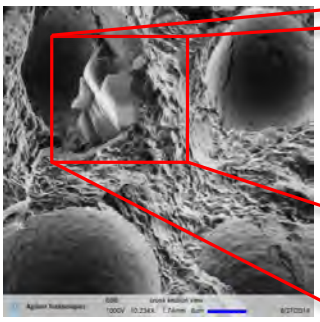
α-Lipoic acid-nicotinamide co-crystals were identified from a small-scale (~100 mgs) experimental co-crystal screen of α-lipoic acid. These co-crystals display enhanced thermal stability and differences in aqueous solubilities compared to α-lipoic acid. For the first time, scale-up of the co-crystallisation process of α-lipoic acid with nicotinamide was then carried out in a continuous oscillatory baffled crystalliser (COBC) supported by a systematic approach to process design. Over 1 kg of solid co-crystals was produced using a continuous antisolvent crystallisation process (1: 1 isopropyl alcohol:hexane system) in a COBC at a throughput of 350 g/hr yielding a purity of 99% . SEM images of the α-lipoic acid nicotinamide co-crystals produced in the COBC showed that the co-crystals were spherical agglomerates comprising multiple small thin plates. SEM images also highlighted the relatively narrow particle size distribution of the co-crystals.

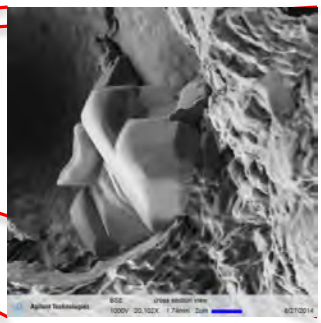
## Case Study 2:
## Extruded Paracetamol Rods

The SEM has already proved useful for the examination of paracetamol extruded rods that were prepared using the Thermo Process twin-screw extruder. This insight on the microscale will help contribute towards the understanding of the influence of solid form properties on formulation and extrusion. Images of the rods were obtained side on and of cross sections through the extrudate. Cross section analysis revealed voids containing intact paracetamol crystals. Side on views revealed the smooth nature of this formulation, also a few intact paracetamol crystals were observed.

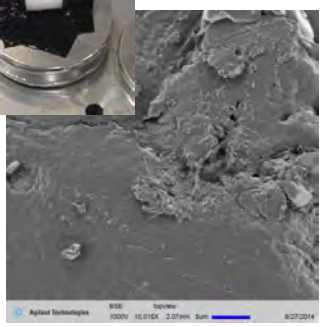
*Cross Section*

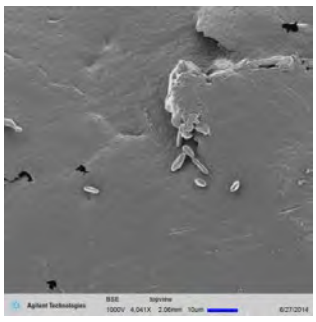


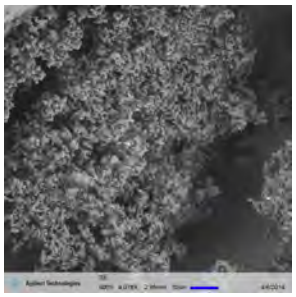


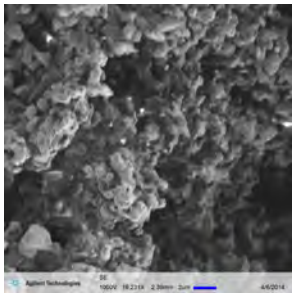


*Side on*









## Case Study 3: Crystal Form

For research into using spray drying to engineer particles of pharmaceutical compounds, the Agilent SEM enables the imaging and analysis of particles that can be as small as 1 micron in size. As these particles are so small, optical microscopy cannot provide a suitable image to measure the size, morphology and sphericity. The Agilent SEM can achieve this through the high magnification as seen in both images using 4078x and 16231x magnifications. These images show clearly that the sample particles are homogeneous and they are roughly 1 – 5 µm in size. The technique is easy to use and is non-destructive.

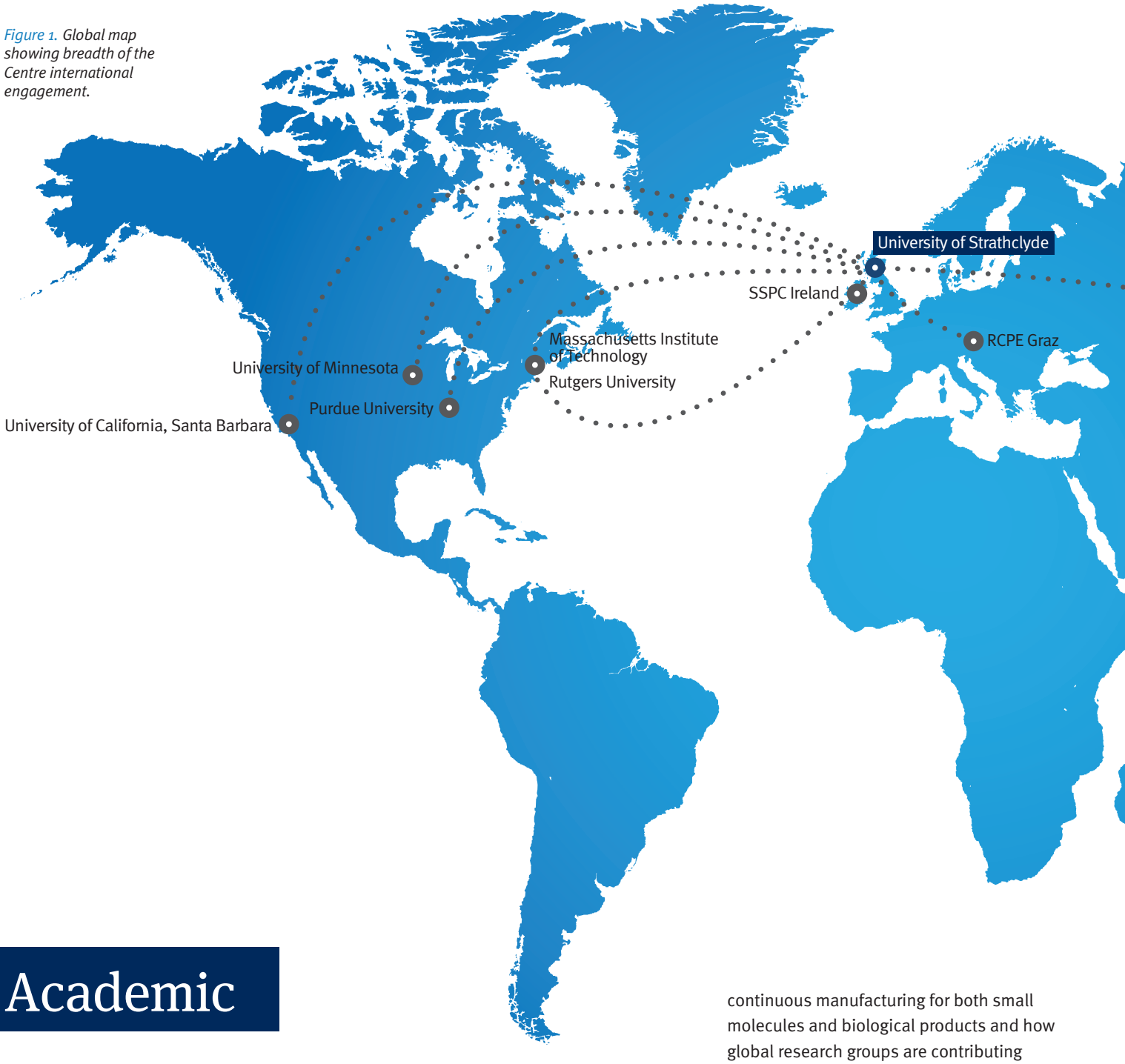



*Figure 1. Global map showing breadth of the Centre international engagement.*

# Academic

Since the launch of the Centre in October 2011 the outreach activities and events have escalated in-line with the accelerated growth and success of the Centre. This activity includes putting the EPSRC Centre on the global map as a leader in the area of continuous manufacturing and crystallisation. Figure 1 illustrates the breadth of the Centre and the international collaborations that have taken place including researcher and academic exchanges, international workshops, hosting conferences and a symposium, and establishing a joint international PhD programme.

## The International Symposium on Continuous Manufacturing of Pharmaceuticals

On 20th – 21st May 2014, CMAC co-hosted the first International Symposium on Continuous Manufacturing of Pharmaceuticals at MIT, US (**https://iscmp.mit.edu**). This prestigious event was attended by the world leaders in continuous processing, with pharmaceutical end users, suppliers, regulators and academics who discussed accelerating the adoption of continuous manufacturing for both small molecules and biological products and how global research groups are contributing towards the new technology and approaches. Dr Clive Badman (CMAC Chair) was Co-host. The key outputs from the symposium were eight white papers. Alastair Florence, Craig Johnston, Jag Srai, Clive Badman, Jon-paul Sherlock and the wider CMAC Network contributed to the papers entitled: Technologies and Approaches for Synthesis Work-Up and Isolation of Drug Substance (Alastair Florence lead author), Equipment and Analytical Companies Meeting Continuous Challenges (Craig Johnston lead author) and Future Supply Chains Enabled by Continuous Processing - Opportunities and Challenges (Jag Srai and Craig Johnston co-authors). The event was also attended by four Centre researchers who presented posters of their work to the esteemed audience.



*Figure 2. Craig Johnston delivering his white paper to the symposium at MIT .*

*Figure 3. Alastair Florence delivering his white paper to symposium at MIT, Jon-Paul Sherlock and Paul Sharratt, centre Advidory Board are also featured.*

| White paper title | Authors |
|---|---|
| Introductory White Paper: Achieving Continuous Manufacturing | Clive Badman and Bernanrd L. H Trout |
| Technologies and Approaches for Synthesis Work-Up and Isolation of Drug Substance | Ian R. Baxendale, Richard D. Braatz, Benjami K Hodnett, Klavs F. Jensen, Martin D Johnson, Paul Sharratt, Jon-Paul Sherlock and Alastair Florence |
| Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them | Stephen Byrn, Maricio Futran, Hayden Thomas, Eric Jayjock, Nicola Maron, Robert F. Meyer, Allan S. Myerson, Michael P. Thien, and Bernhardt L. Trout |
| Regulatory and Quality Considerations for Continuous Manufacturing | Gretchen Allison, Yanxi Tan Cain, Charles Cooney, Tom Garcia, Tara Gooen Bizjak, Oyvind Holte, Nirdosh Jagota, Bekki Komas, Evdokia Korakianiti, Dora Kourti, Rapti Madurawe, Elaine Morefield, Frank Montgomery, Moheb Nasr, William Randolph, Jean-Louis Robert, Dave Rudd and Diane Zezza |
| Continuous Bioprocessing | Konstantin B Konstantinov and Charles L. Cooney |
| Equipment and Analytical Companies Meeting Continuous Challenges | Trevor Page (GEA), Henry Dubina (Mettler Toledo), Gabriele Fillipi (IMA), Roland Guidat (Corning), Saroj Patnaik (Emerson) Peter Poechlauer (DSM) and Craig Johnston (CMAC) |
| Control Systems Engineering in Continuous Pharmaceutical Manufacturing | Allan S. Myerson, Markus Krumme, Moheb Nasr, Hayden Thomas and Richard D. Braatz |
| Future supply chains enabled by continuous processing – opportunities and challenges | Jag Srai, Clive Badman, Mauricio Futran, Markus Krumme and Craig Johnston |
| How Development and Manufacturing Will Need to be Structured – Heads of Development/Manufacturing | Kevin Nepveux, Jon-Paul Sherlock, Mauricio Futran, Michael Thien and Markus Krumme |

# Collaborative Projects

## CMAC AND C-SOPS

In May of this year the Centre led a joint international workshop on behalf of the UK community with US colleagues from Purdue and Rutgers universities. The two-day workshop, which was at the request of EPSRC and NSF, was held in Puerto Rico with the purpose of identifying opportunities for internationally leading research collaboration to advance current practices in continuous manufacturing of pharmaceuticals via new, sustained joint activity. The international collaborative team comprising members of two major national manufacturing research centres (CMAC and C-SOPS, Centre for Structured Organic Particulate Systems) and global industry developed a shared vision to establish an International Institute for Advanced Pharmaceutical Manufacturing GSK, Pfizer, BMS, AZ - Industry representatives.

## Who's involved?

Particpants at the workshop in Puerto Rico:

**UK**

- Clive Badman, GSK
- Ian Baxendale, Durham
- Antony Chapman, EPSRC
- Richard Creekmore, Astra Zeneca (US)
- Alastair Florence, CMAC (Strathclyde)
- Gavin Halbert, CMAC (Strathclyde)
- Svetlana Ignatova, Brunel
- Blair Johnston, CMAC (Strathclyde)
- Craig Johnston, CMAC (Strathclyde)
- Alexei Lapkin, Cambridge
- Chris Reilly, CMAC (Loughborough)
- Stephen Ross, RCUK (US)
- Jan Sefcik, CMAC (Strathclyde)
- Jag Srai, CMAC (Cambridge)
- Zoltan Nagy, Purdue

**US**

- Alberto Cuitino, Rutgers
- Rajesh Dave, NJIT
- Fritz Fiesser, GSK
- Douglas Hausner, Rutgers
- Keith Jensen, MIT
- Charanjeet Kaur, Rutgers
- Bruce Kramer, NSF
- Eduardo Misawa NSF
- Christine Moore, FDA
- Fernando Muzzio, Rutgers
- Jose Perez Ramos, Pfizer
- Rex Reklaitis, Purdue
- Rodolfo Romanach, Puerto Rico
- Zoltan Nagy, Purdue

## The SAVI Award

**'International Institute for Advanced Pharmaceutical Manufacturing'**

### US investigators

- Prof Alberto Cuitino
- Prof Fernando Muzzio

### UK investigators

- Dr Blair Johnston
- Prof Alastair Florence
- Prof Jan Sefcik
- Dr Andrea Johnston (Coordinator)

This International Institute will bring together world-leading academic expertise to deliver new end-to-end continuous manufacturing capabilities that will transform the global supply chain for medicines. The joint programme leverages existing extensive investments in the UK and US and by creating a vibrant international manufacturing research community that will accelerate progress through excellence in research. Furthermore, by engaging with regulators the research will be targeted to maximise impact for end users.

## Key Steps in Forming the Collaboration

- Establishing a team to form The International Institute for Advanced Pharmaceutical Manufacturing.
- Meeting face to face for a 2 day workshop in Puerto Rico for academic engagement.
- Interacting as a community of practice by conducting monthly web based meetings.
- Using the MIT-CMAC ISCMP symposium in Boston in May as a 2nd face-to-face meeting to secure wider industry participation.
- Obtain seed funding for initial support of activities and future exchanges as major funding proposals are developed.

The initial key steps identified to establish the collaboration have already been completed with the award of a circa $1m SAVI seed fund in September of this year. This award will fund an 18 month PDRA in the UK in addition to providing the resource for academics to increase face to face interactions for workshops and meetings.

## A Joint International Doctoral Training Centre in Continuous Manufacturing and Crystallisation Of Pharmaceuticals

As part of an EPSRC Global Engagements award in 2012/2013, the Centre established links with Nanyang Technological University (NTU) in Singapore via workshops and exchanges. This year we have built on these links and established a joint doctoral training programme due to commence in October 2014. The first year of this unique PhD scheme will commence with a cohort of 6 students 3 based at the university of Strathclyde and 3 at NTU.

## The Projects

| Strathclyde-NTU Collaborative theme | Strathclyde-Led Projects (supervisors) | NTU-Led Projects (supervisors) |
|---|---|---|
| Pharmaceutical Particle Formation | Experimental continuous crystallization in a continuous oscillatory baffled reactor (COBR)<br><br>(A Florence, Joop Ter Horst) | CFD/PIV modelling of continuous crystallization in a COBR<br><br>(K Ong, R. Lau) |
| Novel particles for optimised pharmaceutical performance | Particle engineering for high density constructs<br><br>(I Oswald, G Halbert) | Covalent adducts for API-excipient constructs<br><br>(Zaher, K Ong) |
| Multi-scale Pharmaceutical Systems | Pharmaceutical investigations of Silk: a biopolymer for engineering defined nanomedicines<br><br>(B Johnston, Philip Seib) | Modeling (GROMACS) and drug excipient interactions<br><br>(S Mushrif) |

# Being a National Centre

**Dr Andrea Johnston**
**National Centre Manager**

As a National Centre we have a role to work with and on behalf of the wider community and to act as a focus for the wider research community in this area. We engage with the wider community, acting on their behalf e.g. to influence policy, facilitate and support workshops, meetings on topics within scope, support feasibility studies, develop national expertise and facility registers. The Centre holds an important position in the collaborative Research and Innovation Landscape in the UK and has an abundance of engagements including those with EPSRC Grand Challenge networks, iCON PI's, CPI (HVM catapult), KTNs and collaborative TSB R&D projects. As a National Centre there has been a high degree of developing strategy and influencing policy in the area of continuous manufacturing. To date the Centre is enthusiastically engaged with TSB, SCI, IChemE, KTNs, CIA, RSC, MMIP and is a member of APSIRE. We have received press coverage from announcements from Rt Hon David Willets and Rt Hon Vince Cable visited our facilities to officially open Phase I of our RPIF award. More recently we have been visited by the Swiss Ambassador Dominik Furgler, to discuss potential UK – Swiss opportunities. Also in Januray the Foreign and Commonwealth Office's Chief Scientific Adviser (CSA), Prof Robin Grime, visited CMAC. The UK Chief Scientific Adviser is responsible for providing advice to the Foreign Secretary, Ministers and officials on science, technology and innovation. His role is to ensure that our work on key issues undergoes proper scientific challenge, and to strengthen the scientific and engineering capacity within the Foreign Office. The CSA works closely with the cross-government community of Chief Scientific Advisers and the wider UK and international academic science community.


**"EPSRC Centres for Innovative Manufacturing will provide a national focus for areas of early stage basic research that will feed through to Catapult Centres and industry."**

## Open Day

The second Open Day was an international event which took place on September 12th 2013 at Glasgow's Science Centre. It was a vibrant event with over 180 delegates in attendance from industry and academia as well as numerous technology exhibitors. Key note presentations were given from Prof Paul Sharratt, Head of Process Science and Modelling, Institute of Chemical and Engineering Sciences, Singapore; Dr Amy Robertson, AstraZeneca, UK, and; Dr Ali Hassanpour, University of Leeds. Alongside the keynotes were presentations from researchers across all seven of the CMAC universities and over 50 posters on show. Feedback from the event has been extremely positive from all involved and we look forward to our next Open Day in September 2015.

## MANUFACTURING THE FUTURE

The Centre are proud organisers and hosts of the 2014 EPSRC Manufacturing the Future Conference. The Conference to be held in September 2014 at the Glasgow Science Centre, is set to be the largest since it started running in 2012. It is expected to attract around 400 delegates including academics, industrialists and government stakeholders. The programme is packed with oral and poster presentations, work-shops and debate sessions covering all priority themes in the UK manufacturing research landscape. For further information please visit http://www.ukmanufacturing.org/index.php

> "...the premier national manufacturing research conference focusing on the leading edge of science and engineering for manufacturing."
>
> Prof Phil Nelson
> Chief Executive EPSRC

**Business Secretary opens Phase 1 of the £34M UK Research Partnership Investment Fund for Pharmaceutical Research at CMAC, University of Strathclyde**

## Artist in Residence

**Public engagement**

Following an eight-month residency with CMAC, artist Fiona McGurk created a multidisciplinary installation of visual artworks. The works - inspired by the TIC build project and observations of continuous manufacturing research and data collection – were showcased at Hidden Door Festival, Market Street Vaults, Edinburgh (28th March – 5th April 2014).

The event attracted over 7500 visitors and gained national press reviews.




## CMAC Press Highlights

In January, CMAC received two high profile press announcements, the formal announcement of EPSRC's Manufacturing with Light Award by Rt Hon Dr Vince Cable MP, Secretary of State for Business, Innovation and Skills and the official opening of RPIF phase 1 by Rt Hon Dr Vince Cable MP, resulted in major press converge including articles in:

- The Times
- The Scottish Daily Mail
- The herald
- The Manufacturer
- BBC news
- MSN News

For further information and more details of these stories please visit, http://www.cmac.ac.uk/news.html

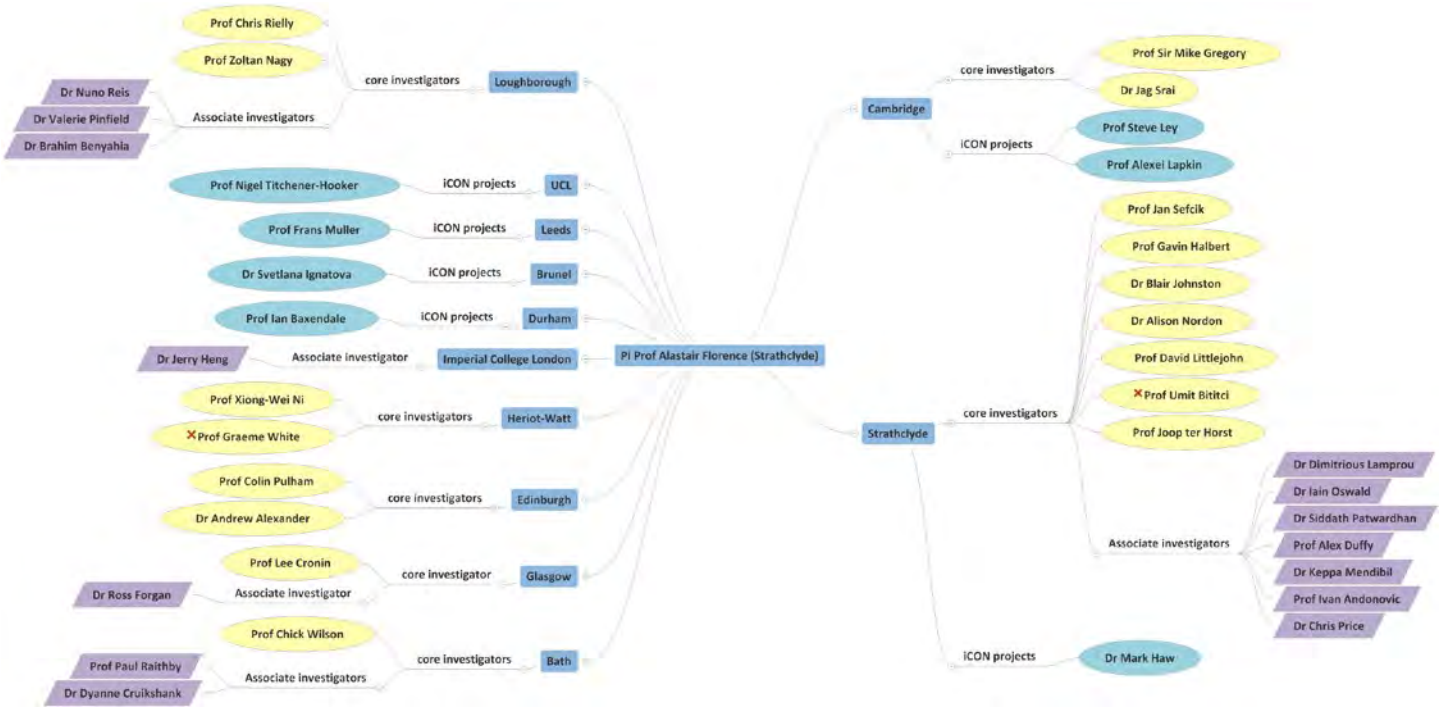



*Figure 2. Academic partner network, core investigators shown in yellow, associated investigators in purple and iCON project investigators in green.*

# Academic Engagement

The Centre supports an exceptional multi-disciplinary academic team, harnessing skills and expertise in Chemistry, Crystallisation Science, Material Science Process Analytical Technology, Chemical and Process Engineering, Pharmaceutical Science and Manufacturing and Business Operations Management. When the Centre was launched in Oct 2011 there were 13 academic investigators, 8 RA's, 8 PhDs and three management personnel. Staff numbers have grown across all institutions (Figure 1) and with the intake of this years DTC cohort staff numbers will grow to circa 100. The current academic partner network is shown in Figure 2. There have been several new developments in this network over the last 12 month period with new academics, Dr Andrew Alexander, Prof Joop Ter Horst and Dr Blair Johnston joining the core investigator team and Dr Chris Price joining the Centre as an EPSRC research fellow. A further development are the new external academic partnerships that have been established through a call for feasibility studies (iCON projects).

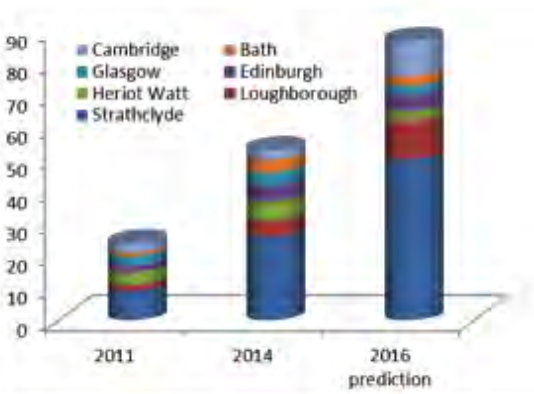



*Figure 1. Illustration of number of researchers per institution at start, mid-point and projection to end of Centre funding.*

## New Investigators

### Dr Andrew Alexander

Andy Alexander is a Senior Lecturer in chemical physics in the School of Chemistry at the University of Edinburgh. His research interests are in nucleation, dynamics of reactions and light–matter interactions. His recent 18-month project funded under EPSRC Manufacturing with Light initiative, "Laser-induced nucleation for crystallisation of high-value materials in continuous manufacturing processes" is in collaboration with Colin Pulham (Edinburgh), Jan Sefcik & Iain Burns (Strathclyde).

### Prof Joop Ter Horst

Joop ter Horst is Professor of Industrial Crystallisation at the University of Strathclyde within the Strathclyde Institute for Pharmacy and Biomedical Sciences. He studied chemical engineering at the University of Twente. As a PhD student at the Delft University of Technology (TU Delft), he investigated crystallization processes by a combination of experimental studies and molecular simulations. After a postdoctoral position, he became assistant professor and later associate professor at the TU Delft, where his research was focused on application-oriented fundamental aspects of crystallization processes, in particular, the elucidation of crystal nucleation and growth to enable the predictable and controlled synthesis of organic materials.

He joined University of Strathclyde in August 2014 where he will provide the fundamental knowledge needed to enable continuous manufacturing. His research approach is aimed towards fundamental understanding of crystallization processes in complex, multicomponent systems that will lead to new process opportunities in pharmaceutical manufacturing. He will identify new driving forces, new hybrid processes and new multicomponent materials for separations by targeting key scientific questions on the interplay between solution thermodynamics, mass transfer limitations, and complex products. He will further exploit his biotechnological experience to enable continuous manufacturing in the biotechnological realm.

### Dr Blair Johnston

Blair Johnston is a senior lecturer in the Strathclyde Institute of Pharmacy and Biomedical Sciences at the University of Strathclyde. His research is focused on the development of computational tools which expedite scientific and manufacturing process-development within CMAC. Configurable modular workflows fuse experimental and theoretical data to provide better understanding of the design space and to drive intelligent decision support for the further optimisation of processes. Process data are captured and made searchable within electronic lab notebooks, and web-based tools are being developed to allow for retrospective analysis of data by the wider research community. Blair is also a co-investigator in the EPSRC Manufacturing Informatics award, 'Intelligent Decision Support and Control Technologies for Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals' which is led by Prof Ivan Andonovic (Strathclyde).

### Dr Chris Price

Dr Chris Price FRSC CChem is one of the four individuals awarded a prestigious EPSRC Manufacturing Fellowship this year. http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/L014971/1 Chris' fellowship award of £1.2M will fund research to address the challenges of impurity incorporation in industrial crystallization. Crystallization is the principal purification technique in the pharmaceutical, fine chemical and agrochemical sectors. Current practice accepts that impurities bind to active growth sites on crystal faces where they inhibit growth reducing process yield and product purity. The research will focus on the impact of ultrasonic intervention at the growing crystal surface to actively displace impurity molecules accelerating growth, enhancing yield and purity. Chris joins the department of Chemical and Process Engineering, University of Strathclyde from GSK where he held project and line leadership roles in drug development and innovation, his recent projects include leading particle science and process engineering aspects of the newly launched HIV treatment Tivicay® and leading GSK's continuous particle formation team which secured their CEO's award for sustainable manufacture. Whilst at GSK Chris was a visiting professor in Chemical & Process Engineering and was involved in CMAC from its inception representing GSK on the Technical Board. In addition to his fellowship program which is funded independently of CMAC but which sits alongside and complementary to the CMAC research program, Chris' main involvement in CMAC will focus around the isolation of crystalline particles, where his experience in developing GSKs automated filtration and washing platforms in partnership with Cambridge Reactor Design will provides a useful basis from which to develop appropriate continuous isolation technology.

## iCON Projects

The Centre launched a call in June 2013 for funding "iCON" projects and the launch of this scheme stimulated the Centre's engagement with the wider UK research community under the Continuous Processing Work-Up Theme. Continuous work-up is an area outside the Centre's core research but was identified as a key gap in enabling the uptake of continuous processing at the initial industry workshop held at Novartis, Basel to identify key problem statements. This allows the project outputs to expand the Centre's knowledge and understanding of the pre-crystallisation supply chain. On 25th October 2013 seven successful iCON project awards were announced, which included two small scale equipment projects and five longer term research projects ranging from six to twelve months duration. Industrial mentors have been identified to provide steering and stimulate interest in this area (one project has 5 industrialists!). In February and March 2014, project kick-off meeting took place for all seven projects as detailed below. A workshop will be held at the end of 2014 in this area where all the projects will present their work.

## Sucessful iCON Feasibility Projects

| Name | Institution | Title | Duration |
|---|---|---|---|
| Dr Svetlana Ignatova | Brunel University | Counter-current liquid-liquid processes for continuous manufacture APIs | 6 months |
| Prof Alexei Lapkin | University of Cambridge | Telescoping continuous synthesis of APIs to work-up | 6 months |
| Prof Ian Baxendale | Durham University | Extracting and delivery procedures using phase transfer strategies | 12 months |
| Pro Frans Muller | Leeds University | Recirculating slurry hydrogenation in tandem with continuous product recovery | 6 months |
| Prof Nigel Titchener-Hooker | University College London | An ultra scale-down investigation of the impact of continuous crystallisation performance and recovery by depth filtration | 12 months |
| Prof Steve Ley | University of Cambridge | In-line flow solvent evaporator | Equipment Award |
| Dr Mark Haw | University of Strathclyde | OMNIFLOW: Optical and Magnetic Non-Invasive Flow and manipulation platform for controlling nucleation using local flow | Equipment Award |

# Meet the Teams

*The management team from left to right Dr Andrea Johnston, National Centre Manager, Jacqueline Brown, DTC Administrator, Lorna Grey, Centre Administrator, Rebecca O'Hare apprentice administrator, (top) Craig Johnston, Industry director, Prof Alastair Florence, Centre director, Dr Ian Houson, technical project manager*

## Management Team

**Professor A Florence**
**Centre Director**
Overall responsibility for delivery of Centre and DTC vision, academic leadership and scope and pace of research.

**Mr Craig Johnston**
**Industrial Director**
Centre sustainability; manage industry collaborations/engagement; business plan development and implementations; outreach.

**Dr Andrea Johnston**
**Centre Manager**
Planning and implementation of Centre activities; outreach; Centre/DTC finance. Manage Centre/DTC Administrative Staff.

**Dr Ian Houson**
**Technical Project Manager**
Provide support for Industrial Director. Project management of industry/academia projects; identify European funding/collaborative opportunities; organise Technical Committee and Industrial Mentor Groups; ensure high levels of knowledge transfer from academic research to industrial application.

**TBC**
**Assistant Centre Manager**
Support Centre Manager. First point of contact for all researchers on Centre related matters; co-ordinate/manage four communities of practice and cross centre forums; modelling/monitoring Centre budgets and reporting.

**Miss Jacqueline Brown**
**DTC Administrator**
Provide administrative support to the Centre Director, DTC Academic Director, DTC Programme and MSc Co-ordinator. Recruitment/marketing; organisation of training programme (i.e. handbook, timetables) travel, meetings, annual summer school; reconciling expenditure, modelling/monitoring DTC budgets; maintenance of student database; assist with media management.

**Miss Lorna Gray**
**Centre Administrator**
Provide administrative support to the Management Team and Centre. Organisation of travel, meetings; diary management; reconcile monthly expenditure; assistance with event planning; maintenance of a contacts database.

**Miss Rebecca O'Hare**
**Assistant Centre Administrator**
Assist with administrative support to the Centre. Book travel, catering, rooms; update records (finance and holidays); ordering stationery, printing supplies; photocopying, filing and scanning.

**Principle Investigator:**
**Professor Alastair Florence**
**Home Institution:**
University of Strathclyde
**E-mail:** alastair.florence@strath.ac.uk

**Researchers:**

- Dr Lihua Zhao, Senior Research Associate, Quick Win Projects Centre Platform RA. Feasibility studies and continuous crystallisation projects.
- Dr Thomas McGlone, Senior Research Associate, Centre Platform RA Feasibility studies and continuous crystallisation projects.
- Dr Cameron Brown, Senior Research Associate, Constructing Exquisite Particles (growth, transport, fouling and controlling agglomeration)
- Dr Humera Siddique, Research Associate on TSB funded projects, Made to order process plants (Perceptive Engineering, CPI and AstraZeneca) and Development of an innovative modular system for continuous chemical processing (Syrris, GSK and AMRI)
- Dr Huaiyu Yang, Research Associate, Quick Win Projects
- Naomi Briggs, PhD Researcher, Controlling nucleation, growth and polymorphism in continuous oscillatory baffled crystallisers.
- Francesca Perciballi, PhD Researcher, Continuous formation of optimised particles for formulation and processing.
- Vishal Ravel, Centre Platform Technician/PhD Researcher, Integrated lab scale continuous manufacturing of Pharmaceutical products
- Rebecca Halliwell, DTC Researcher, Lab scale continuous crystallisers for control of pharmaceutical polymorphs and critical particle attributes.
- Fraser Mabbott, DTC Researcher, The exquisite particle – Understanding fouling.
- Rajesh Gurung, DTC Researcher, Development and Testing of a Synthetic Design Approach for Continuous Crystallisation Process Design
- Stephanie Yerdelen, DTC Researcher, Lab-scale equipment for continuous crystallisation for control of particle attributes
- Bilal Ahmed, DTC Researcher, Lab-scale equipment for continuous crystallisation for control of particle attributes: seed production via slurry media milling approaches

**Co-Investigator:**
**Professor Joop ter Horst**
**Home Institution:** University of Strathclyde
**E-mail:** Joop.terHorst@strath.ac.uk

**Researchers:**

- DTC Researcher to be appointed

**Co-Investigator:**
**Dr Blair Johnston**
**Home Institution:** University of Strathclyde
**E-mail:** blair.johnston@strath.ac.uk

**Researchers:**

- Dr Murray Robertson, ICT-CMAC Research associate, Work package 5 People and Processes
- DTC Researcher to be appointed

**Co-Investigator:**
**Professor Lee Cronin**
**Home Institution:** University of Glasgow
**E-mail:** l.cronin@chem.gla.ac.uk

**Researchers:**

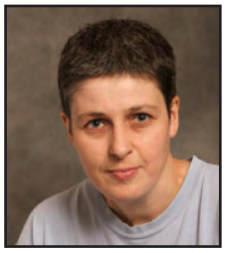
- Andreu Ruiz de la Oliva, PhD Researcher, Inorganic reactions in networked flow systems.
- Maria Vincencza Anna Dragone, PhD Researcher, Pathway Dependent Organic Syntheses.
- Sergio Martin, DTC Researcher, Coupling molecular synthesis with continuous crystallisation in organic and inorganic synthesis

**Co-Investigator:**
**Professor Gavin Halbert**
**Home Institution:** University of Strathclyde
**E-mail:** g.w.halbert@strath.ac.uk

**Researchers:**

- Research Associate to be appointed
- Laura Martinez-Marcos, DTC Researcher, Influence of solid form properties on formulation and extrusion processing.
- Elanor Brammer, DTC Researcher, Saleable oral dosage formulations
- Albarah Al-Afandi, DTC Researcher, Development of quality by design and regulatory parameters for continuous manufacturing
- Alice Turner, DTC Researcher, New methods for the production of oral dosage forms

**Co-Investigator:**
**Professor David Littlejohn**
**Home Institution:** University of Strathclyde
**E-mail:** d.littlejohn@strath.ac.uk



**Co-Investigator:**
**Dr Alison Nordon**
**Home Institution:** University of Strathclyde
**E-mail:** alison.nordon@strath.ac.uk

**Researchers:**

- Jaclyn Dunn, Research Associate, Filtration and Drying
- Denise Logue, PhD Researcher, In-Situ and non-invasive measurement techniques for the monitoring and control of continuous manufacturing processes.
- Joanna Lothian, DTC Researcher, In situ imaging and optical spectroscopic monitoring of crystallisation processes.
- DTC Researcher x 2 to be appointed

**Co-Investigator:**
**Professor Zoltan K Nagy**
**Home Institution:** Loughborough University
**E-mail:** z.k.nagy@lboro.ac.uk

**Co-Investigator:**
**Professor Chris Rielly**
**Home Institution:** Loughborough University
**E-mail:** c.d.rielly@lboro.ac.uk

**Researchers:**

- Keddon Powell, PhD Researcher, Improving continuous crystallisation using process analytical technologies.
- Iyke Onyemelukwe, DTC Researcher, Comparative investigation of continuous crystallisation approaches using process analytical technology.
- Emmanuel Kimuli, DTC Researcher, Coupled CFD/PBE modelling of continuous crystallisation
- Dimitrios Fysikopoulos, DTC Researcher, Comparative investigation of continuous crystallisation approaches using process analytical technology.
- DTC Researcher x 3 to be appointed
- Research associate to be appointed

**Co-Investigator:**
**Professor Xiong-Wei Ni**
**Home Institution:** Heriot-Watt University
**E-mail:** x.ni@hw.ac.uk

**Researchers:**

- Natalia Falenta, PhD Researcher, A study of the effect of mixing mechanisms in cooling crystallisation of adipic acid.
- Hannah McLachlan, PhD Researcher, Investigations into parameters affecting purity in OBC and STC.
- Juliet Adelakun, DTC Researcher, Characterisation of profiles and steady states in a continuous oscillatory baffled crystalliser (COBC) using cooling crystallisation process.
- Guillermo Jimeno Millor, DTC Researcher, Continuous Crystallisation under pressure in a continuous oscillatory baffled crystalliser
- DTC Researcher to be appointed

**Co-Investigator:**
**Professor Colin Pulham**
**Home Institution:** University of Edinburgh
**E-mail:** c.r.pulham@ed.ac.uk

**Researchers:**

- Craig Henderson, PhD Researcher, Co-crystals of energetic materials – a new route to insensitive munitions.
- Paul Coster, PhD Researcher, Investigating the polymorphism of energetic materials.
- Alasdair MacKenzie, PhD Researcher, Crystallisation using laser-induced nucleation for polymorph control.
- Fraser Keir, DTC Researcher, Combined experimental and computational studies of nucleation and crystallisation processes under continuous and non-ambient conditions
- Daniel Ward, DTC Researcher, Continuous crystallisation of energetic materials
- Adam Michalchuk, DTC Researcher, Applications of resonant acoustic mixing for the processing of powders and particles

**Co-Investigator:**
**Dr Andrew Alexander**
**Home Institution:** University of Edinburgh
**E-mail:** a.alexander@ed.ac.uk

**Researchers:**

- Martin Ward, Research Associate, Laser-induced nucleation for crystallisation of high-value materials in continuous manufacturing processes

**Co-Investigator:**
**Professor Sir Mike Gregory**
**Home Institution:**University of Cambridge
**E-mail:** mjg@eng.cam.ac.uk

**Researcher: Dr Jag Srai**
**Home Institution:** University of Cambridge
**E-mail:** jss46@cam.ac.uk

**Researchers:**

- Leila Alinaghian, PhD Researcher, Manufacturing operations and supply chain management challenges in continuous manufacturing.
- Dr Tomás Harrington, Researcher Associate, Manufacturing operations and supply chain management challenges in continuous manufacturing.
- Mark Phillips, DTC Researcher, Exploring supply network reconfiguration opportunities arising from more continuous processing in pharma

**Co-Investigator:**
**Dr Jan Sefcik**
**Home Institution:** University of Strathclyde
**E-mail:** jan.sefcik@strath.ac.uk

**Researchers:**

- Dr Anna Jawor-Baczynska, Research Associate, Modular test bench for continuous crystallisation
- Research Associate to be appointed
- Rachel Sheridan,PhD Researcher, Understanding and mitigation of fouling in continuous crystallisation.
- John McGinty, DTC Researcher, Constructing exquisite particles in continuous processes – effects of flow and mixing on fouling in continuous crystallisation.
- Maria Briuglia, DTC Researcher, Development of laboratory test bed for assessing effects of flow conditions on agglomeration/deagglomeration and attrition/breakage in continuous crystallisation
- Thomas Kendall, DTC Researcher, Laser induced nucleation in continuous crystallisation
- Vaclav Svoboda, DTC Researcher, Scale down of modular test bed for continuous crystallisation process development: continuous mixing, nucleation/seeding and solution/slurry transfer

**Co-Investigator:**
**Professor Chick Wilson**
**Home Institution:** University of Bath
**E-mail:** c.c.wilson@bath.ac.uk

**Researchers:**

- Dr Karen Robertson, Research Associate, Multi-component crystallisation of agrichemicals and development of flow crystallisers.
- Kate Wittering, PhD Researcher, crystallisation of multi-component materials within the continuous flow environment.
- Anneke Klapwijk, DTC Researcher, Inducing layered solid-forms and controlling crystalline defects in multi-component continuous crystallisation.
- Lauren Agnew, DTC Researcher, Multi-component templating approaches to polymorph selection, elusive form discovery and crystallisation.
- Alex Cousen, DTC Researcher, Scale-up, yield, purity and selectivity in continuous production of micronized API's

**Associated Investigator:**
**Professor David Watson**
**Home Institution:** University of Strathclyde
**E-mail:** d.g.watson@strath.ac.uk

**Researcher:**

- Natalia Dabrowska, DTC Researcher, Measurement of impurities in pharmaceutical crystallization using chromatographic techniques

**Associated Investigator:**
**Professor Alex Duffy**
**Home Institution:** University of Strathclyde
**E-mail:** alex.duffy@strath.ac.uk

**Researcher:**

- Leda Todorova, DTC Researcher, Optimisation of Supply Chain Configuration

**Associated Investigator:**
**Dr Kepa Mendibil**
**Home Institution:** University of Strathclyde
**E-mail:** k.mendibil@strath.ac.uk

**Researcher:**

- Georgi Aleksiev, DTC Researcher, Sustainable Supply Chain in the pharmaceutical sector

**Associated Investigator:**
**Professor C Price**
**Home Institution:** University of Strathclyde
**E-mail:** chris.price@strath.ac.uk

**Researcher:**

- Sara Ottoboni, DTC Researcher, Continuous Isolation

**Associated Investigator:**
**Dr Dimitrios Lamprou**
**Home Institution:** University of Strathclyde
**E-mail:** dimitrios.lamprou@strath.ac.uk

**Researcher:**

- Areti Tsigkinopoulou, DTC Researcher, Process and Product understanding of rapid and continuous wet granulation

# The Year Ahead

The objective of the Centre is to become a world-leading manufacturing research Centre in continuous manufacturing and the year ahead will play a vital role in achieving this. Two key elements of the upcoming year will be the successful furbishing and colocation into the technology and Innovation Centre at the University of Strathclyde (Figure 1) and staff appointments to commence the new Advanced Manufacturing Supply Chain Initiative (AMSCI) REMEDIES (RE-configuring MEDIcines End-to-end Supply).

**September 2014**
Final details passed to TIC for office move

**September/October 2014**
Installation of bespoke fumehoods into TIC

**January 2015**
Phased decomissioning of equipement in current labs

**January 2015**
Installation of solvent pumping system in TIC

**9th February 2015**
Research ceases in SIPBS

**28th February 2015**
CMAC Moving day

**16th March 2015**
Research commences in TIC

**31st March 2015**
Completion of the RPIF Project

**April 2015**
Opening of the Wolfson TOF-SIMS Suite

*Figure 1. Timeline of the CMAC move into TIC.*

The aim of the Advanced Pharmaceutical Supply Chain Consortium, led by GSK and comprising 22 partners including 11 SMEs, is to modernise the manufacturing supply chain for pharmaceuticals, paving the way for increasingly personalised production, which is closer to patients and in response to need. Below is an extract from the press release: CMAC Industry Director Craig Johnston, who coordinated all the industry partners said: "This project fully aligns with CMAC's vision of accelerating the introduction of continuous manufacturing. In addition to the involvement of GSK and AstraZeneca, a key element will be to help develop and demonstrate novel technologies in an industrial environment from our strong SMEs and academic research base."

**CMAC Director Professor Alastair Florence said: "This award, involving Cambridge and Strathclyde universities, builds on our national Centre collaborative consortium and will enable us to work with partners to exploit our leading technology, from reaction through to formulated pharmaceutical products."**

**Roger Connor, President, Global Manufacturing and Supply, GSK, who led the bid on behalf of the sector, said: "This bid, which will focus on areas such as continuous manufacturing and new technology platforms, creates and safeguards jobs across the partnership and helps keep the UK at the forefront of life sciences."**

The £23 million project was among nine winners from round four of the Advanced Manufacturing Supply Chain Initiative, which in total received £129 million of support – including £53 million of government funding and more than £75 million of private money. Dr Cable said: "Britain is starting to win back business on the basis of hard headed business decisions based on quality and good performance. Through our industrial strategy the government is working in partnership with business to nurture these encouraging signs."

### Consortium Partners

- 22 partners at kick-off

### Indirect Partners

- Regulators: MHRA
- Knowledge Transfer Networks: Health KTN, Office for Life Sciences
- Health Providers: NHS Area Academic Health Service Networks (AHSNs)

## Project Structure

The project is structured around 2 advanced manufacturing supply chain 'platform projects', each underpinned by 3 'technology strand projects', and 5 workstream project activities.

The 2 major platform projects have an End-to-End Supply Chain (SC) focus in terms of delivering an enhanced;

- E2E Clinical Trials SC - led by GSK (including both the physical and regulatory supply chain)
- E2E Commercial SC - led by University of Cambridge, IfM (from raw materials, production right through to the patient)

These 2 platform projects are underpinned by 3 technology strands, e.g.

- CMO-focused API technology projects
- Formulation, linking primary to secondary
- Packaging/Distribution

Finally a series of 5 application projects have been defined, Figure 2.

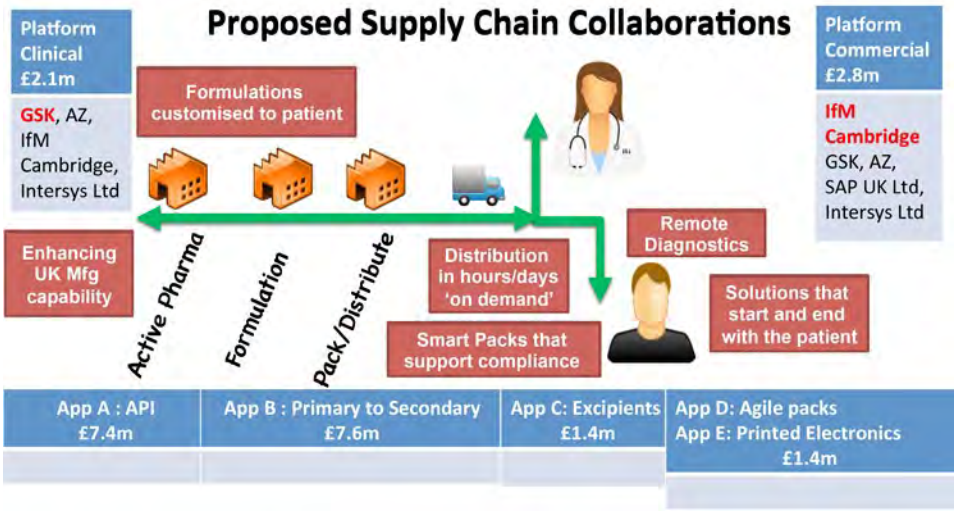



*Figure 2. Schematic showing REMEDIES project structure.*

# Centre Boards and Committees

The Centre's key activities are overseen by the Advisory Board and the Centre Management Committee. The Centre **Advisory Board** is chaired by Prof Paul Sharratt from ICES Singapore. Full membership is shown below. Centre representation on the board includes the Director, Industry Director and EPSRC. Additional members of the board are an experienced grouping of academics and industrialists. The board meets three times per year with at least two meetings face to face. Responsibilities of the board include:

1) Provide independent input from leading academics and industrialists not directly involved in the Centre;
2) Gather views that will influence the running of the research of the EPSRC Centre and DTC;
3) Advise on strategy, reporting, project monitoring etc.;
4) Provide input from researchers from different fields and from stakeholders from sectors other than pharmaceuticals;
5) Carry out an annual review of Centre performance.

| Name | Institution | Status |
|---|---|---|
| **Chair** | | |
| Prof Paul Sharratt | ICES, Singapore | International independent academic |
| Dr Clive Badman OBE (deputy-chair) | GSK | Non-independent industry |
| **EPSRC Centre Representatives** | | |
| Prof Alastair Florence | EPSRC Centre | Centre Director |
| Craig Johnston | EPSRC Centre | Industry Director |
| Dr Andrea Johnston | EPSRC Centre | Centre Manager |
| **Independent Academic Members** | | |
| Prof Brian Glennon | University College Dublin (SSC) | International independent academic |
| Prof Nigel Titchener-Hooker | UCL | Independent academic; EPSRC Centre Emergent macromolecular therapies |
| Prof Kevin Roberts | Leeds University | Independent academic |
| Prof William Jones | Cambridge University | Independent academic |
| **Non-independent Industrial Members** | | |
| Dr Jon-Paul Sherlock | AZ | Non-independent industry |
| **Independent Industrial Members** | | |
| Kenny Gilmour | Victrex | Independent industry |
| Dr Colin Groom | CCDC | Independent non-academic |
| Dr Kevin Girard | Pfizer (US) | International Independent industry |
| Ian Laird | Moorbrook Textiles | Independent industry |
| Dr Paul Stonestreet | Roche | Independent industry |
| **EPSRC/TSB Members** | | |
| Dr Richard Bailey | EPSRC | EPSRC representative |
| Dr Malcom Hannaby | TSB | TSB representative |

The **Management Committee** consists of the core management team plus co-investigators. The committee meets monthly and responsibilities of the committee include:

1) Review project progress against milestones;
2) Refine and shape the vision and research programmes in line with user needs;
3) Conduct an annual review and assess proposals for future work packages/DTC themes;
4) Responsible for wider functions such as ensuring that the work of the Centre is appropriately disseminated/published and ensure exploitation pathways are optimised;
5) Oversee the financial aspects of the programme;
6) Grow activities and secure future funding towards delivering the Centre vision.

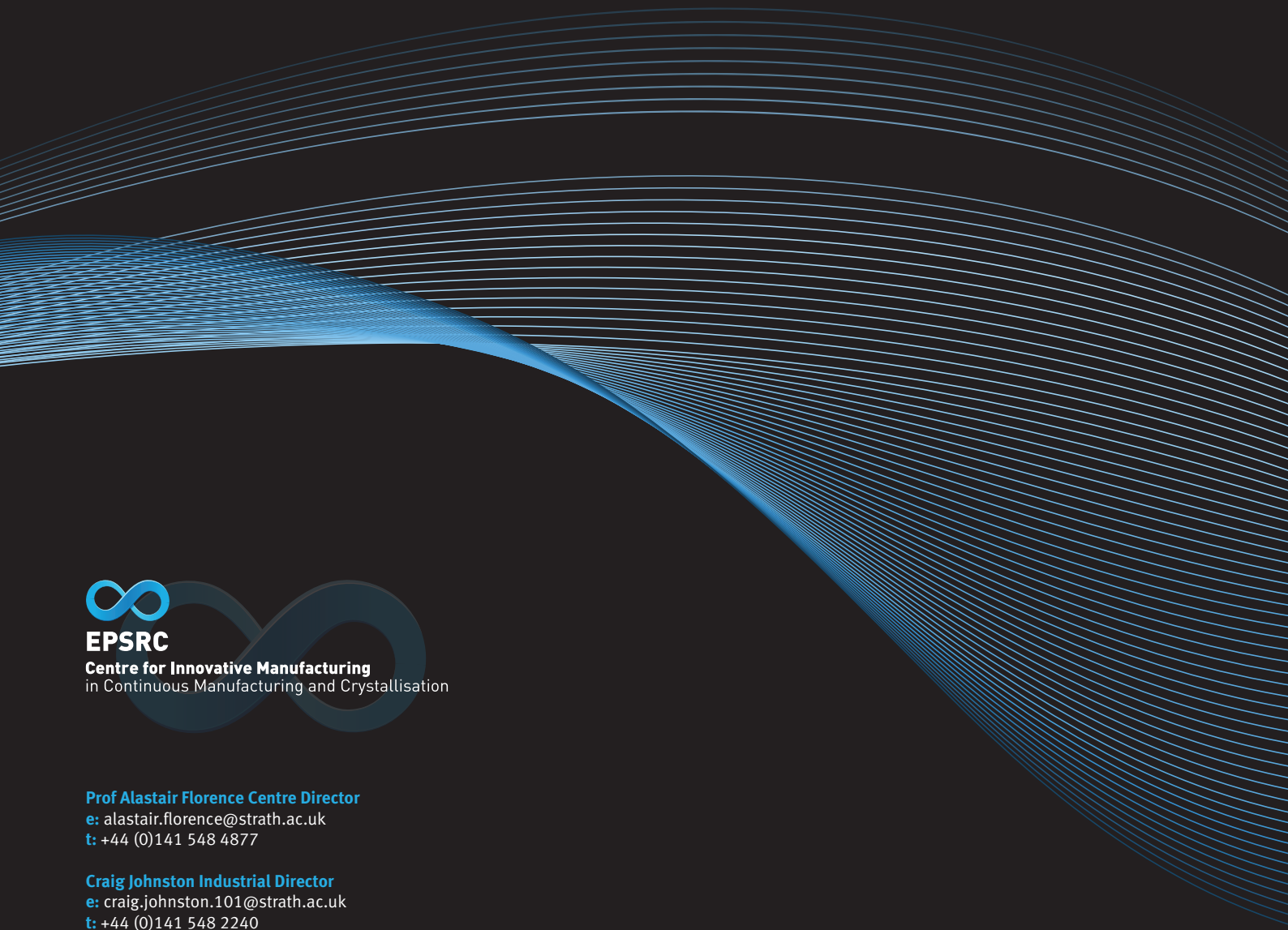
# Final Words

"The last year has been both busy and successful with increased industrial project work and a very successful symposium jointly sponsored by CMAC and MIT/Novartis. CMAC continues to grow both internationally and in its goal of accelerating the introduction of continuous manufacturing to industry"

Dr Clive Badman, OBE
(Chair of the CMAC Board)

"It's exciting to see CMAC continuing to evolve, with both a growing body of valuable research outputs and an increasingly influential position in defining research agendas in the UK and internationally. CMAC is demonstrating itself adept at bridging the gap between academic interest and industrial need, as well as training scientists and engineers whose distinctive skills are in great demand."

Prof Paul Sharratt,
(Chair of EPSRC Centre Advisory board)



**EPSRC**
**Centre for Innovative Manufacturing**
in Continuous Manufacturing and Crystallisation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