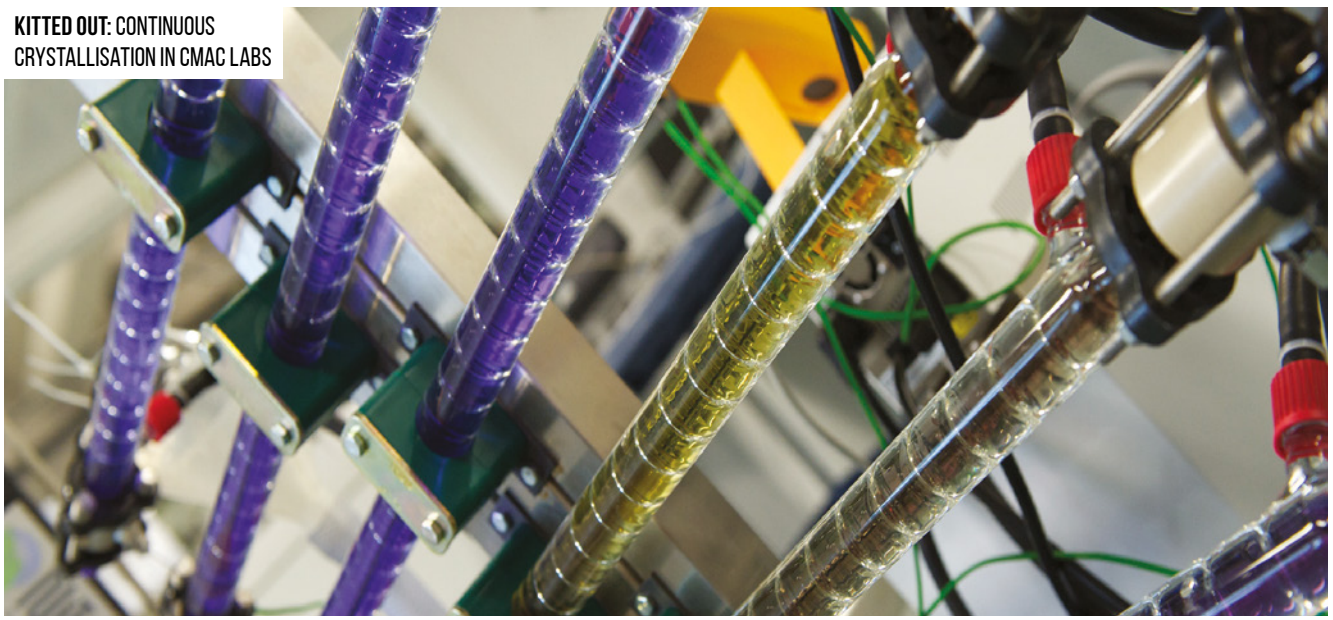

KITTED OUT: CONTINUOUS CRYSTALLISATION IN CMAC LABS

Continuous Collaboration

The Chemical Engineer visits the EPSRC Future Manufacturing Research Hub in Continuous Manufacturing and Advanced Crystallisation (CMAC)

STAFF, STUDENTS AND INDUSTRY PARTNERS
SPEAK TO HELEN TUNNICLIFFE

THE impression many have of industry is that it tends to be rather secretive, with individual companies jealously guarding proprietary information from each other. This, however, is not the only way to work successfully, and a centre at the University of Strathclyde, UK, is proving just that.

At the EPSRC Future Manufacturing Research Hub in Continuous Manufacturing and Advanced Crystallisation, better known as CMAC, collaboration is absolutely central – not just between companies, but between industry and academia, and between different academic disciplines.

CMAC was set up in 2011, to develop and implement continuous manufacturing processes in the pharmaceutical and fine chemicals industries. Many such high-value products are still made using batch processes, but continuous processes would make these products cheaper and more sustainable.

"Manufacturing research is a core focus of what we do and we have a portfolio of activities, from more fundamental research through to applied research into translation. Our mission is to lead the way in crystallisation and the adoption of continuous processing," says CMAC industrial director, Craig Johnston, who is an IChemE Fellow. He was involved on the industrial side in the early stages of the project, but says he liked it so much, he made the jump.

EPSRC Manufacturing Hubs are national UK centres which focus on early-stage research that can feed into industry. Led by Strathclyde's Institute of Pharmacy and Biomedical Sciences (SIPBS), CMAC brings together pharmacists, chemical engineers, chemists and operational management. Certain things, like molecules, remain proprietary, but everything else, from, as you might expect, active pharmaceutical ingredient (API) crystallisation techniques, to the supply chain, is covered. The research priorities and projects are set by industry.

"What we hope we provide in CMAC is a forum for us all to get together, and see what we can achieve collectively," says CMAC Hub director, Alistair Florence, a professor at SIPBS.

CMAC has seven 'tier one', or main, industry partners, GlaxoSmithKline, AstraZeneca, Novartis, Bayer, Eli Lilly, Roche and Takeda, and 17 tier two partners, including Siemens, PwC,

PSE, Mettler Toledo and Perceptive Engineering, and many other collaborators. Its seven core academic partners are the Universities of Strathclyde, Bath, Cambridge, Sheffield, and Leeds, Loughborough University and Imperial College London. It also collaborates with Heriot-Watt University and the Universities of Edinburgh and Glasgow.

More than 130 researchers are now associated with CMAC, with about 80 of these at the main hub in Strathclyde's £89m (US$107m) Technology and Innovation Centre. CMAC benefited from £34m in capital funding, from the UK RPIF Scheme, of which £11.4m was spent on an impressive range of equipment for x-ray diffraction, Raman microscopy, PAT, mobile processing units, and secondary processing such as hot melt and twin screw extruders, spray dryers and 3D printers. The X-ray laboratory alone has £5m of kit, including a brand new Xenocs small angle x-ray scattering (SAXS) beamline system for materials characterisation. In 2016 CMAC was named facility of the year by the International Society for Pharmaceutical Engineering (ISPE), the first time an academic institution has ever won the award.

CMAC is also an EPSRC Centre for Doctoral Training, which as the name suggests, trains PhD students with EPRSC funding.

"It is unique in that the students in their first year have training at all seven of the partner universities across the disciplines. The feedback on that from both students and industry has been absolutely fantastic. Part of the training includes trips to GSK and Syngenta," says Johnston.

The Centre also has a Master's programme and offers continuing professional development (CPD) to industry staff.

RESEARCH AND NETWORKING

Many of CMAC's collaborations are international. It has organised two continuous manufacturing symposia in conjunction with MIT in the US. CMAC has a research partnership with MIT and the Center for Structured Organic Particulate Systems (C-SOPS), led by Rutgers University, with Purdue University, the New Jersey Institute of Technology, and the University of Puerto Rico at Mayaguez. It has a partnership with the Research Center in Pharmaceutical Engineering (RCPE) in Graz, Austria, and has a joint PhD programme with Nanyang Technological University in Singapore. IChemE Fellow Paul Sharratt of the Institute of Chemical and Engineering Sciences (ICES), Singapore, chairs the CMAC Advisory Board.

CMAC is also involved in several multi-organisation major research projects including two under the umbrella of AMSCI – the Advanced Manufacturing Supply Chain Initiative. One of these, ReMediES, or Reconfiguring medicines end-to-end supply, has £23m in funding and aims to improve supply chains for drugs for clinical trials and commercial supply chains. ADDoPT – advanced digital design transforming pharmaceutical development and manufacture – looks to develop digital design techniques to improve efficiency of development and manufacture.

Joop ter Horst, who leads a CMAC research group on industrial crystallisation, coordinates the Europe-wide CORE Network – the European Training Network on Continuous Resolution and Deracemization of Chiral Compounds by Crystallization. It is developing a toolbox for manufacturers to separate enantiomers. It has seven academic partners, including ETH Zürich in Switzerland, the University of Rouen in France, and Otto-von-Guericke University in Germany, and seven industrial partners such as PSE and Merck.

He also won funding from the EU Horizon 2020 scheme for another project, AMECRYS, which aims to crystallise biopharmaceutical proteins more efficiently. Of more than 80 applicants, just 11 were funded.

"We are using electric fields to help crystallisation and particle separation. We take a solvent with a suspension of proteins and put electrodes in and increase the potential difference. You see the crystals begin to move around and collect at the electrodes. If the current is great enough, eventually when you turn off the electric fields, the crystals fall to the bottom. It was just a Friday afternoon experiment, we were surprised when it worked!" ter Horst says.

Ter Horst, a chemical engineer who joined CMAC from Delft University in the Netherlands, is concerned that the Brexit vote will mean it is more difficult to set up European research networks in the future. For now, though, he says they are "a nice success".

A FAMILIAR FACE FROM INDUSTRY

One of CMAC's main industrial sponsors is AstraZeneca. Its representative on the industrial board is none other than IChemE technical vice-president Jon-Paul Sherlock. He was

CMAC'S HOME: STRATHCLYDE'S TECHNOLOGY AND INNOVATION CENTRE

instrumental in securing AstraZeneca's tier one funding for CMAC.

"This pre-competitive collaborative space within pharma is something that's relatively new. Ten years ago, there were few examples of scientific collaboration between pharmaceutical companies. More recently the value of open innovation has been realised. There are still core areas of our business where IP is essential. However, the value of collaborating where we can, is that it de-risks the investment."

Sherlock says that there are three main reasons for AstraZeneca's involvement in CMAC. The first is the focus on crystallisation, and the education, training and research surrounding it, a key part of the company's science and technology strategy.

The second factor is the investment in continuous manufacturing, which is still an emerging technology in pharma.

"The opportunity we had was through this pre-competitive, collaborative approach, pooling our collective knowledge and building on that foundation to accelerate adoption of these technologies and overcome some of the major barriers," says Sherlock.

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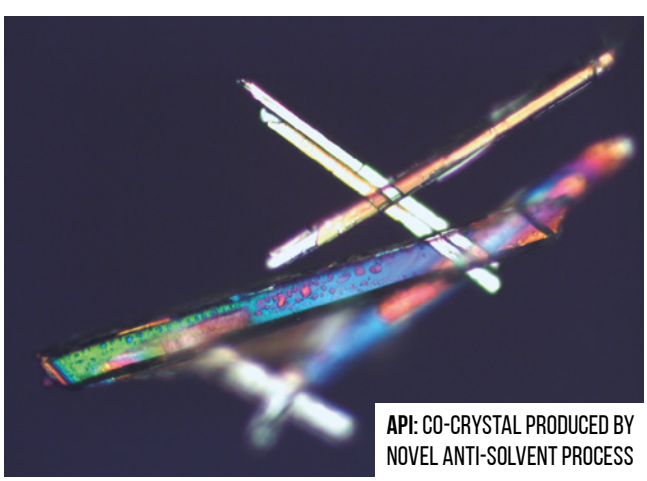
The final factor is the talent pipeline. CMAC, of course, is not just about research but about training the next generation of scientists and engineers.

"CMAC is training engineers and chemists to effectively work across these disciplines and boundaries. Chemists are emerging with an appreciation of chemical engineering concepts. They understand from day one what is required of them. We've recruited a number from CMAC over the last five years and we see it as a source of well-trained, highly capable talent," says Sherlock.



API: CO-CRYSTAL PRODUCED BY NOVEL ANTI-SOLVENT PROCESS

What has been particularly refreshing, he says, is the level of engagement with people at CMAC, making for a very different industry-academic relationship that they've encountered previously. AstraZeneca staff interact regularly with CMAC researchers and the boards and committees mean that the research aligns with industry needs. CMAC researchers work on live industry projects, and their work feeds directly back into AstraZeneca.

AstraZeneca's investment has multiplied substantially, through other investment from EPSRC, the government, fellow sponsors, the university and various other routes. In short, it has got far more out of it than it put in, and of course, all of the investors benefit.

"I've got a real passion for wanting to see industry and academia work well together. The experience at CMAC has really opened my eyes to what can happen and how effectively that can work," says Sherlock, adding: "There are a lot of people at AstraZeneca who have invested significant time and effort and there have been no boundaries between the scientists and engineers involved. The collaboration has been incredibly strong and it's down to that, I think, that it has been so successful."

THE STUDENT EXPERIENCE

CMAC is keen to make the experience positive for everyone, not just its researchers and industry partners. The four PhD students who spoke to *The Chemical Engineer*, quite simply, love it.

The industry links are a big draw for many of them in choosing to study at CMAC. Clarissa Forbes is working on a PhD to use ultrasound to promote crystallisation processes, and find a way to use this in continuous processes. Her first degree, in chemistry at Strathclyde, was a sandwich course.

"Spending a year in the pharmaceutical industry really helped to give me experience there. It was where I got experience of chemical engineering, and working with chemical engineers, and understanding how it went from lab-scale to plant, as a chemist, for me was really interesting. CMAC just seemed like a good option because of the industrial links," she says.

For Andrew Dunn, who is researching how to shorten startup times for continuous pharmaceutical processes, supervised by ter Horst, the PhD offered the best of both worlds – the pharmaceutical industry he finds so fascinating and the academic environment.

CMAC at Strathclyde holds regular internal research days where everyone can come together and discuss their research, which Forbes says quite often leads to new collaborations. There is also a summer school where researchers from every CMAC institution come together to present their research.

"We have regular mentor meetings where we present our work to industry representatives and you hear directly from them, suggesting that you try this, or you look at that. In fact

their suggestions have already helped me to solve a problem in my project," says Thomas Kendall, who is investigating non-photochemical laser-induced nucleation mechanisms, supervised by Jan Sefcik.

All this means that if a student gets stuck on a particular problem, they'll probably know someone who can help.

"I'm a chemist. When I started here I knew squat about chemical engineering, but you can come to anyone here and ask. You don't struggle here. Everyone is doing different things, so if you want to start exploring things you just start talking to them," says Dunn.

Students are encouraged to attend conferences all over the world, recently in Japan, the US and Spain, to publish research papers in peer-reviewed journals, and to participate in outreach programmes, eg Really Small Science.

Some students are already starting to see their research translate into industry. Sara Ottoboni, who came to CMAC from Italy, worked with an industrial partner to develop a continuous filtration unit to purify crystals.

"We are now in the prototyping stage, so the idea is to launch the machine into the market in the next year or so. Me and my supervisor also developed, with another company, another continuous filtration unit, so we have another prototype working," she says.

Generally, around 2/3 of students are recruited into industry and the remainder stay in academia. The centre gives ample opportunity to discover which environment they like best. Ottoboni has discovered a love of teaching, through supervising Bachelor's and Master's students, and wants to stay in academia. Dunn loves research and also wants to stay in academia. Forbes and Kendall, however, are keen to embark on industrial careers.

"It was industry that attracted me here in the first place," says Kendall. "I'm currently preparing for a two-month placement with Bayer in Leverkusen in Germany. I'm bringing my project back here afterwards. Working with industry has had some impact on my project already. Going back into industry is my goal."

According to Dunn, one of the best aspects of CMAC is the atmosphere. "It's just great banter," he says. "I find it a very relaxed environment, everyone's always having a laugh and it's a lot of fun. I do like coming here. You've obviously still got the stresses and deadlines of a PhD, but it's a great environment to do it in."

WHY IT WORKS

One thing you notice about CMAC is the genuine friendliness and respect. The spirit of collaboration, on a personal as well as a corporate level, seems to be a major part of its success.

"The real beneficiaries are students and researchers because they are exposed to an environment which is really unique. They can collaborate and talk to people," says Jan Sefcik, a chemical and process engineering professor, adding: "The good thing is, this is how it is in industry, you collaborate and you work in teams, you don't have your own project and get on with it with no one else. We prepare them better."

CMAC PHD TRAINING: PROCESS ANALYTICAL TESTING (PAT) CHALLENGES

Industry's willingness to be involved has paid dividends. Sefcik says that this sort of pre-competitive collaboration has taken some courage. Of course, the potential financial benefits stack up.

"If we can make savings in process development, time and cost of goods, that's worth more than a good number of new products for industry," says EPSRC manufacturing Fellow Chris Price. "If we can take 25% off the cost of a new product, that's transformational for industry. The hope is that industry will take this and use it to reshore in the UK."

Some of this translation can be small, according to Sefcik, such as routine ways of working or investigating, which will be picked up by industry as simply as through student placements. Johnston adds that they have already seen some companies implement CMAC discoveries, including Novartis, which is using CMAC crystal seeding technology in its continuous plant in Basel, Switzerland.

The initial five-year funding may be up, but in December, CMAC found out that EPSRC had awarded it another £10m as part of a programme to set up hubs for advanced manufacturing.

"Moving forward, our themes will be in digital design, microfactories and future supply chains. We have £10m from EPSRC and an initial £40m cash and in kind from industry, academic and business partners. Our business plan is to grow that to £150m over the next seven years. Looking backwards we created £100m over five years so that's definitely feasible," says Johnston. That is a lot of money to continue building on the success of CMAC.

Price sums up the reasons for that success: "We've blurred a lot of the boundaries. We span chemistry, physics, pharmacy, engineering, quite hardcore mathematics and the biological component as well. The real innovations come at the interfaces, and particularly when you put the pieces together, that's when you can do something that hasn't been done before." ■