MoSMed CDT Newsletter

ISSUE 02

September 2020

A note from the Editors

Since the last issue of the MoSMed newsletter we have seen a transition from a national lockdown due to the COVID-19 pandemic to the reopening of our research facilities and a return to laboratory work.

This issue encapsulates the resolve and adaptability shown by the MoSMed CDT Doctoral Researchers, academics and partners, who have all dealt with the challenges posed by the pandemic exceptionally well. From online conferences to weekly cohort seminars and even a BBC Newshour interview, the CDT has certainly remained active!

We hope you enjoy reading about the experiences and achievements of the MoSMed CDT and its partners over the past three months. We would also like to thank those who have contributed to this issue and if you would like to be involved with the next issue please contact mosmed.cdt@ncl.ac.uk.

Olivia Gittins, Trudi Pemberton and Emma Worden

Contents

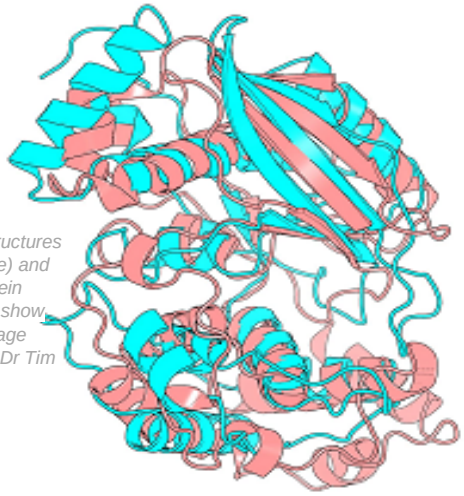
Tuberculosis Bacteria Waging War on Itself with Discovery of New Toxin MenT.

One of our MoSMed PIs, Dr Tim Blower (Durham University), is at the forefront of a significant new discovery concerning the toxin MenT, which could be utilised in developing drugs in the fight against tuberculosis (TB). As co-senior author of a new paper published in 'Science Advances' that outlines the discovery of the toxin, Tim and his collaborators constructed an extremely detailed 3-D picture of MenT which, combined with genetic and biochemical data, showed that the toxin inhibits the use of amino acids needed by the bacteria to produce protein. This finding has significant implications for the future potential development of drugs to treat and eradicate TB.

In the midst of a global pandemic it is often easy to forget about other deadly diseases that are prevalent worldwide and often have more fatalities than the coronavirus. Tuberculosis is an example of such a deadly disease that has plagued humanity for thousands of years having even been detected in Egyptian mummies from over three thousand years ago. It is thought that approximately a quarter of the planet are infected with a latent or dormant infection and that there are around ten million active cases of the disease annually resulting in 1.5 million deaths each year. Therefore, this exciting new study is a significant discovery in the quest to eradicate the disease.

While treatments do exist, usually with two courses of antibiotics for a period of six months, these have issues in terms of patient access to the drugs, increasing cases of antibiotic-resistant cases and difficulties in regimentation in ensuring patients complete the treatment. This latest study by an international team of researchers led by Dr Tim Blower at Durham University and Dr Pierre Genevaux at the Laboratory of Molecular Microbiology in Toulouse, France, has discovered a new way of killing the bacteria that cause TB. By using a toxin called MenT, which is produced by the TB bacterium Mycobacterium tuberculosis to effectively wage war against itself, it might be possible to destroy the bacteria that causes the disease.

Interviewed by the BBC 'Newshour' programme, Tim outlined the potential for Discovery Science Researchers to use this toxin to develop new drugs to treat TB. In identifying how these toxins operate and broadening understanding of what is an extremely complex pathogen it is hoped that in the future it may be possible to develop new ways of controlling their growth.



High resolution structures of the MenT3 (blue) and MenT4 (pink) protein toxins, overlaid to show their similarity. Image credit Ben Usher, Dr Tim Blower.

Explaining the significance of the discovery Tim comments that:

"Through the forced activation of MenT, or by destabilising the relationship between the toxin and its anti-toxin MenA, we could kill the bacteria that cause TB……..The remarkable anti-bacterial properties of such toxins make them of huge therapeutic interest."

As with all areas of Discovery Science, significant funding is required to ensure that the necessary progress is made and fully utilised to implement scientific knowledge in the development of drugs to combat the disease. While TB cases are decreasing by a rate of approximately 1.6% a year, there is much work to be done to meet the World Health Organisation target of all but eradication of TB cases by 2030.

Further tuberculosis research at Durham University

The recent findings in this article follow other existing projects linked to tuberculosis research where the researchers designed and validated a sub-micromolar lead compound that was found to kill tuberkels. The details of the findings related to these projects can be found in the following two papers:

Relative Binding Energies Predict Crystallographic Binding Modes of Ethionamide Booster Lead Compounds

Tatum NJ, Duarte F, Kamerlin SCL, Pohl E. J Phys Chem Lett. 2019 May 2;10(9):2244-2249.

New active leads for tuberculosis booster drugs by structure-based drug discovery

Tatum NJ, Liebeschuetz JW, Cole JC, Frita R, Herledan A, Baulard AR, Willand N, Pohl E. Org Biomol Chem. 2017 Dec 13;15(48):10245-10255

https://pubs.rsc.org/en/content/articlehtml/2017/ob/c7ob00910k?casa_token=hu-4b3wUCA8AAAAA:5Q9n8UoA_s6eF4QDi6roiYBz56DdSaIFI0CM2UQhrWz86FDqLobWilrjcOyt6zKj6q55d3sSaUQrXhk

Emma Worden – CDT Manager (Durham)

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ASMS Online Conference 2020.

During lockdown I had the opportunity to attend the American Society of Mass Spectrometry (ASMS) 2020 conference online, which I had not anticipated would be possible during the first year of my PhD. However, I found it an invaluable experience allowing me to access the recorded talks from mass spectrometry experts across the world.

How was the conference different from if it had been held in person? Advantages / disadvantages

Being an online conference, I had the opportunity to attend any sessions that interested me. The conference organisers recorded the sessions and have made the videos available until September, allowing me to catch up on sessions which I might not have caught in person. This has been an advantage allowing me to get more out of the conference from the seminars / workshops than if I had attended the sessions in person. Several other attendees also expressed that for various reasons having an online conference had benefitted them as they would not have been able to attend in person.

However, there were areas such as networking and poster presentations that were difficult in the online setting and had to be reimagined. Posters were presented with videos and questions could be submitted for answers as well as general poster Q&A sessions. Unfortunately many participants' questions were not answered and discussions were not as in depth as those which can be carried out in person. Having attended other online conferences since then and seeing posters presented in various formats, I have yet to see a method that presents the posters in a way that satisfies all attendees and presenters.

How was networking carried out?

One of the main reasons for attending a conference is networking, meeting people that are involved in similar research that you could maybe collaborate with in the future or gain inspiration from their research / insight. However, in an online conference these casual meetings by sitting next to someone in a seminar / workshop or bumping into someone at a bar or meeting someone at a mixer don't happen so conference organisers have had to come up with creative methods for allowing people to meet others.

ASMS online ran Kahoot trivia quizzes sponsored by different industrial partners of the event such as Waters, Bruker and Shimadzhu. They also had zoom networking sessions on several evenings, with Fridays dedicated to more informal sessions where participants were encouraged to bring a drink of their choosing and the organisers placed people into breakout rooms to introduce themselves.

There were also some interesting networking sessions starting with presentations by a panel, followed by Q&A and discussions run by Females in Mass Spectrometry (@FeMS) and a Black People Meet session run by Dr Christina Jones, Dr Michelle Reid and Dr Candice Ulmer. I really enjoyed attending these sessions because networking in an online setting was a very different experience and it gave me the opportunity to meet leaders in the field and learn more about their research.

What did I get out of the conference?

As the ASMS is such a broad mass spectrometry conference I had the opportunity to listen to many different fascinating talks from various research angles, providing me with an invaluable opportunity to learn more about mass spectrometry, cutting edge ideas and the different technology applications. It also helped me to broaden my knowledge of investigators in the field and other relevant seminars and opportunities which I can take advantage of. It was also inspiring to hear PhD students from across the world present at the conference as this is something I hope to achieve by the end of my PhD. After the conference, different members of my lab group, myself included, presented to each other a remarkably diverse range of talks and posters which we had found the most interesting and useful for our research.

Would you recommend attending online conferences?

I would highly recommend attending online conferences. The COVID-19 crisis has led to many conferences/meetings being held online and has prompted lots of scientists to reassess whether conference travel is truly essential. Recently, environmental concern has become a bigger and bigger influencer on policy, which might also influence these decisions. Despite this, whether conferences related to your area of research are online or not, I think that they play a key role in cutting edge research, collaborations, and knowledge transfer. Therefore, I cannot recommend enough attending an online conference or seminar series especially one where they offer the opportunity to network!

Ruth Walker – CDT Doctoral Researcher

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Interview with a Doctoral Researcher: Matthew Boutflower

After three months of lockdown everybody is keen to be back in the lab and continue their experimental work. This week I caught up with Matthew, who is working with Peter Chivers (Durham) and Paula Salgado (Newcastle) to unravel the secrets of metal-dependent enzymes. Here, he is checking his latest SDS Page gel (see above).

Lockdown time

Just like most PhD students, Matthew used the time during lockdown to catch-up on lab-books and to write up his results, including an extensive 1st year report (I know that, because I read it!). For Matthew, the lockdown provided a unique opportunity to delve much deeper into bioinformatics. His eyes were lighting up when he explained new functional clues from his detailed sequence analysis and it was obvious how much he enjoyed solving this piece of the puzzle. He now has new ideas for his experimental work and he is planning to learn a lot more about bioinformatics tools.

Last, not least, I was glad to hear that he enjoyed and appreciated our weekly MosMed CDT catch-ups – being part of the cohort is clearly important.

First days in the laboratory

Coming back into the new lab environment wasn't without challenges. Being in a multi-use lab shared by three research groups often collaborating across the boundaries required clear rules to maintain physical distancing (personally I don't like the term social distancing as we need to keep our social connection while maintaining sufficient physical space). The room layout allows for roughly 50% capacity which in Matthew's case is organised in a one-week-on / one-week-off rota. This works quite well for him because it gives him enough time to continue the theoretical and computational work in his week-off.

Matthew explains that possibly due to the fact that there are fewer (senior) people in the lab (and the building), he has made huge strides in improving his independence. The week in the laboratory is now more intense and more efficient than before the lockdown as work has to be planned better in advance – and there are fewer distractions. Coffee breaks in the Chemistry social rooms are no longer allowed….

The future

I asked Matthew what he thinks about how long this situation will continue, and unlike me, he doesn't expect any significant easing of laboratory restrictions before spring or summer next year. I am probably too optimistic hoping for some easing even before the new academic year is starting…. In any case, Matthew is clearly well on track, he has got plenty of plans for his project – and some really interesting ideas for future outreach, but you will learn about those another time.

Ehmke Pohl - MoSMed CDT Co-director

Thoughts from other Durham students about being back in the lab…

"It is good to be back in labs and continuing with my research. The current situation has changed how I work, I am now undertaking many simultaneous experiments given the challenges of accessing analytical equipment. I look forward to the return to normal work, whenever that may be.'"

Matthew Smith

"Coming back to the lab after lockdown has been on the whole a very positive experience but not one without its challenges. Learning to adapt to the new measures and restrictions here at Durham, as well as the limits on my work time (at 50%) has been difficult. However, it is great to be back focusing on my research and it has been lovely to see everyone I've missed the past 3 months."

Izzy Zawadski

"When I returned to the lab for a couple of weeks in the Summer I expected to be a bit rusty after 3 months away but it was still frustrating as I just wanted to get back to my reseatch. I've had to accept that when I return to the lab again it'll take me some time to readjust. But the silver lining of it all is that I've enjoyed and will continue to enjoy more time to think, read and develop new research skills!"

Laura Filipe

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MoSMed Industrial Partners – Working at Arcinova.

As MoSMed PhD Students we are lucky enough to benefit from industry partnerships with the CDT spanning a broad range of research areas. I decided to find out more about some of our partners, starting with one of our local industrial partners, Arcinova…

Arcinova are a multi-service contract development and manufacturing organisation (CDMO) serving global pharmaceutical and biotechology companies. Their expertise in drug development includes drug substance synthesis and manufacturing scale up, drug product manufacture, bioanalytical services and radiolabelling synthesis.

“Our ambition is to save our clients valuable time, enabling them to rapidly bring life-changing medicines to market.”

A friend of mine, Hannah Gent (pictured above), joined the Arcinova Bioanalytical Services team in 2018 after graduating from Newcastle University with a BSc Hons in Pharmacology. She has described how her studies shaped her decision to pursue a career with Arcinova and how she has found the past two years working for the company:

“Over the three years of my Pharmacology degree at Newcastle University I studied a wide range of modules which built upon each other across the years and gave me a good idea of which parts of pharmacology I both was and wasn’t interested in. My final year project was by far the highlight of my degree and gave me confidence to plan, organise and undertake experiments, interpret and analyse my own real life data. I am currently a bioanalyst for Arcinova, a CRO in Alnwick, and work predominantly in a lab-based environment using the practical skills and knowledge developed during my degree every day.

ARCINOVA

Even after working as a bioanalyst for over 2 years now I still find myself learning new things all the time and being given lots of opportunities to develop as a scientist within the pharmaceutical industry.”

With such a wide range of service areas involving many scientific disciplines, all based within one facility, Arcinova offers its employees opportunities for collaboration and development. Their teams of chemists, biologists and bioinformaticians deliver a “fully integrated” approach to drug development.

So it would seem that Arcinova would be a great working environment for those seeking a more inter-disciplinary role!

If you’d like to find out more about Arcinova, visit their website: https://arcinova.com/

Olivia Gittins – CDT Doctoral Researcher

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Recent Publications

Once again we would like to highlight and celebrate some recent published work from our academic team that is of relevance to the MoSMed CDT.

Cole DJ, Mones L, Csányi G**. A Machine Learning Based Intramolecular Force Field for a Flexible Organic Molecule**. Faraday Discussions 2020, in press.

"Quantum mechanical predictive modelling in chemistry and biology is often hindered by the long time scales and large system sizes required of the computational model. Here, we employ the kernel regression machine learning technique to construct ananalytical potential, using the Gaussian Approximation Potential software and framework, that reproduces the quantum mechanical potential energy surface of a small, flexible, drug-like molecule, 3-(benzyloxy)pyridin-2-amine. Challenges linked to the high dimensionality of the configurational space of the molecule are overcome by developing an iterative training protocol and employing a representation that separates short and long range interactions. The analytical model is connected to the MCPRO simulation software, which allows us to perform Monte Carlo simulations of the small molecule bound to two proteins, p38 MAP kinase and leukotriene A4 hydrolase, as well as in water. We demonstrate that our machine learning based intramolecular model is transferable to the condensed phase, and demonstrate that the use of a faithful representation of the quantum mechanical potential energy surface can result in corrections to absolute protein–ligand binding free energies of up to 2 kcal mol−1 in the example studied here."

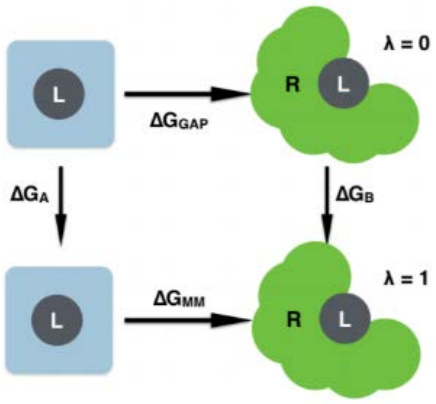
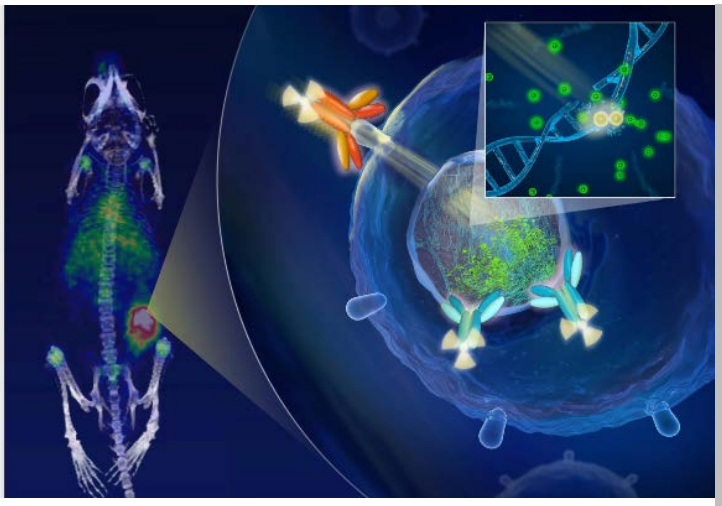


Fig. 2 Free energy cycle used to compute the GAP correction to the MM binding free energy. Simulations are performed of the ligand (L) in water and bound to the receptor (R).



Poty S, Mandleywala K, O'Neill E, Knight JC, Cornelissen B, Lewis JS. **89Zr-PET imaging of DNA double-strand breaks for the early monitoring of response following α- and β-particle radioimmunotherapy in a mouse model of pancreatic ductal adenocarcinoma.** Theranostics 2020; 10(13):5802-5814. doi:10.7150/thno.44772.

(Featured on July 2020 cover of Theranostics, pictured above)

Rationale: The evaluation of early treatment response is critical for patient prognosis and treatment planning. When the current methods rely on invasive protocols that evaluate the expression of DNA damage markers on patient biopsy samples, we aim to evaluate a non-invasive PET imaging approach to monitor the early expression of the phosphorylated histone γH2AX in the context of pancreatic cancer targeted radionuclide therapy. Pancreatic ductal adenocarcinoma has a poor patient prognosis due to the absence of curative treatment for patients with advanced disease. There is therefore a critical need for the fast clinical translation of new therapeutic options. In line with these observations, our group has been focusing on the development of radiotheranostic agents based on a fully human monoclonal antibody (5B1) with exceptional affinity for CA19.9, an antigen overexpressed in PDAC. Two on-going clinical trials resulted from these efforts, one with 89Zr (diagnosis) and one with 177Lu (β-particle therapy). More recently, we successfully developed and evaluated in PDAC mouse models a targeted α-therapy strategy with high clinical translation potential. We aim to expedite the clinical translation of the developed radioimmunotherapy approaches by investigating the early therapeutic response and effect of radiation therapy in a PDAC mouse model via PET imaging.

Conclusions: PET imaging studies with [89Zr]Zr-DFO-anti-γH2AX-TAT following α- and β-particle PRIT in a BxPC3 PDAC subcutaneous xenograft mouse model allowed the monitoring of tumor radiobiological response to treatment.

(See article for full abstract)

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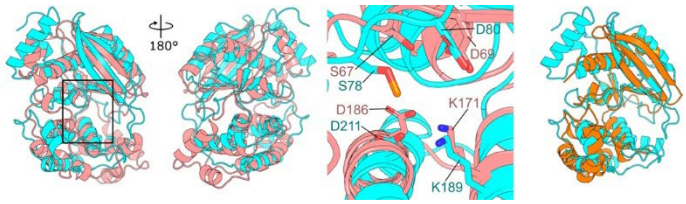
Oliver R. Maguire, Bethany Taylor, Eleanor M. Higgins, Matthew Rees, Steven L. Cobb, Nigel S. Simpkins, Christopher J. Hayes, Ann Marie C. O'Donoghue. **Unusually high α-proton acidity of prolyl residuesin cyclic peptides.** *Chem. Sci.*, 2020, 11, 7722. DOI: 10.1039/d0sc02508a.

"Proline is unique amongst the proteinogenic amino acids in its ability to induce structural and conformational modifications in proteins. The proliferation of prolyl residues in the enzymes of thermophilic organisms has been linked to enhanced protein stabilities in more extreme host environments. The unique chemistry of proline is not confined to influences on protein structures and stabilities. Proline and small molecule derivatives have been widely shown to be efficient, stereoselective catalysts for a range of (bio)organic transformations. Co-authored by AnnMarie O'Donoghue and Steven Cobb, this paper demonstrates a new unique property for the chemistry of proline derivatives: the enhanced acidity of prolyl residue α-protons. These data provide new insight to inform synthetic and biological applications of prolyl-containing cyclic peptide systems for which the α-proton stereochemical integrity, both in solution and in vivo, is crucial."

This article was chosen to be included also in a Chemical Science anniversary issue marking the 10th anniversary of the journal.



Yiming Cai, Ben Usher, Claude Gutierrez, Anastasia Tolcan, Moise Mansour, Peter C. Fineran, Ciarán Condon, Olivier Neyrolles, Pierre Genevaux, Tim R. Blower. **A nucleotidyltransferase toxin inhibits growth of Mycobacterium tuberculosis through inactivation of tRNA acceptor stems**. Science Advances29 Jul 2020 : eabb6651. DOI: 10.1126/sciadv.abb6651

Toxin-antitoxin systems are widespread stress-responsive elements, many of whose functions remain largely unknown. We characterized the four DUF1814-family nucleotidyltransferase-like toxins (MenT$_{1-4}$) encoded by the human pathogen, *Mycobacterium tuberculosis*. Toxin MenT$_3$ inhibited growth of *M. tuberculosis* when not antagonized by its cognate antitoxin, MenA$_3$. We solved the structures of toxins MenT$_3$ and MenT$_4$ to 1.6 Å and 1.2 Å resolution, respectively, and identified the biochemical activity and target of MenT$_3$. MenT$_3$ blocked *in vitro* protein expression and prevented tRNA charging *in vivo*. MenT$_3$ added pyrimidines (C or U) to the 3'-CCA acceptor stems of uncharged tRNAs and exhibited strong substrate specificity *in vitro*, preferentially targeting tRNA^{Ser} from amongst the 45 *M. tuberculosis* tRNAs. Our study identifies a previously unknown mechanism that expands the range of enzymatic activities employed by bacterial toxins, uncovering a new way to block protein synthesis and potentially treat tuberculosis and other infections.

See page 1 of this issue for more about this research.

Upcoming events

Delivering Innovative Medicines: small changes can have a large effect

5pm (GMT) on Thursday 29th October, via Zoom

Wendy Young - Senior Vice President, Small Molecule Drug Discovery, Genentech INC.

To register to attend this event, please see our website: https://research.ncl.ac.uk/mosmed/impact/events/

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The effects of COVID-19 on a scientific researcher

When the COVID-19 pandemic first hit the UK, I was in the sixth month of my PhD and I had just come into my stride with respect to my research; I had gained experience in the lab, I had developed confidence in myself and most importantly, I had built up momentum. It was then a great shock to the system when I was told to swiftly stop all reactions, pack up my things and to prepare to work from home indefinitely as part of the nation-wide lockdown.

The 15 weeks of lockdown gave me an opportunity to take a step back from the hustle and bustle of lab work and to focus more on the background literature and the long-term strategy of the project. Fortunately for me, lockdown also coincided with my first year report deadline – so I had the extra time to put further detail into my introductory chapters and explore the literature more widely. In particular, working from home enabled me to dig deep into the rationale behind my project and get a better understanding of the biology. For me this was extremely useful, as I had not formally studied biology since my GCSEs, so I used the extra time to understand the disease pathogenesis and how my biological target was implicated.

As a so-called “bench chemist” I am heavily dependent on experimental data and so as the lockdown began to lengthen, I felt an ever-growing presence of falling behind. Lockdown had placed almost all aspects of my life on hold, apart from my thesis submission deadline. As with most other post-graduate students, I will have effectively lost more than 3 months of research due to the lockdown, with no indication of whether an extension will be granted in the future. Having spoken to other PhD students across institutions and disciplines, I discovered that this feeling of increased pressure was universal and that for some students, it became debilitating and demoralising.

Our group was fortunate enough to be able to return to the lab on June 17th, much sooner than most other academic groups at the university and other institutions. However, we would not be returning to the way things used to be, as many changes were needed in order to allow a continuation of our research whilst adhering to strict social distancing guidelines outlined by the government.

The most significant change has been the introduction of social ‘bubbles’ and shift working. Work bubbles were introduced at a university-wide level in order to minimise disruptions from possible COVID outbreaks, but this also enabled social distance to be maintained in labs and offices by reducing the number of people onsite at any given time. For my group, we adopted a morning-afternoon shift pattern system, which enabled us to maintain a consistent 5-day work week at the expense of shorter 4.5 hr lab rotations.

The reduced lab hours have resulted in big changes to how we operate. Where typically we would often jump between the lab and office throughout the day, we must now maximise the time spent in the lab during the reduced hours. For example, I am on the afternoon shifts so I spend my mornings at home planning reactions, writing COSHH forms and analysing data so that when my lab shift starts, I can focus solely on the practical work. The end result is a huge improvement to efficiency. Despite not having the luxury of time, most researchers have now reached a point where they can achieve the same amount of work in a day as they would have previously, but in a shorter period of lab time.

Shorter days can also have an impact on the type of reactions you can set up. Some reactions require a long time and can often be difficult to manage in a single half-shift. This has resulted in great improvements to teamwork and communication skills as you often need to help each other out.

Thoughts from other Newcastle students about being back in the lab…

"It's great to be back in the lab. As scientists conducting primary research; carrying out experiments and pursuing new information is what we are all driven to do and it was strange to be entirely desk based for 3 months. Returning to the lab did require some big adjustments to working practices but we've managed to pull together as a team to make it work. I do worry about the impact that the hiatus may have on my progress; but we're all trying to take each day as it comes and focus on delivering good quality research with the time we have."

Catherine Salvini

"Although I was able to spend time during lockdown learning new molecular modelling and data analysis techniques, getting back to the lab is certainly a relief! I am now working in shifts and managing my day in order to finish experiments in a shorter time frame. I feel I have become more resourceful and independent as a result of the changes imposed due to COVID-19."

Olivia Gittins

"I have loved being back in the lab and getting back on track with my research. It was a little shock to the system working reduced hours, but you quickly adapt to your new situation and it's certainly better than the alternative**. "**

Jessica Graham

In my case, there is an MPhil student who works on the same project as myself but is now on the morning shift. We often meet (virtually) to discuss our plans: she is then able to set up reactions in the morning that I can subsequently deal with later in the afternoon.

However, this improved operational efficiency comes with a price; the lab has lost its soul. While the concept of bubbles has great benefits in terms of social distancing, it also means that you are literally detached from any real social interaction with other bubbles. Thus, we are more than simply physically distanced.

As there is no point during the workday in which both bubbles are in the office or at home, it means that even virtually you are removed from the other half of your colleagues for extended periods of time. For me there are many colleagues that I haven't seen, physically or virtually, since March due to the limitations of the shift pattern system. So although I mentioned earlier that you learn to communicate effectively with team members on other shifts, it means that unfortunately you are forced to meet in unsociable hours - either after the evening shift has returned home or at weekends. This often feels demoralising and infringes on a healthy work-life balance, especially when certain routine tasks require liaising with people from the other shift, such as our weekly progress meetings.

Because of these scheduling difficulties it has also meant that we have lost wider group activities such as group seminars. These events are crucial to acquiring wider knowledge as well as developing confidence and presentation skills. I fear that if these measures continue for an extended period of time, the scientific community may become too insular and lose its tight network and multidisciplinary edge.

I understand that the measures put into place are necessary to protect us and allow the continuation of our research in these unprecedented times, but it has had a noticeable personal impact on morale. Concentrated lab hours means that there is little time for socialising with your colleagues, especially when there are no longer any communal breaks. This can cause a group to feel distant and divided, and thus potentially threatens to stifle innovation and motivation.

However, I must stress that not all is doom and gloom: rather it has been incredibly reassuring for many people, myself included, to be able to return to work and to regain some sense of routine and normality. Despite these operational changes, we are still able to perform new and exciting research which is both rewarding and motivating. The flood of online journal submissions over the past few months is a testament to the resilience of the scientific community and if anything, the COVID-19 crisis has highlighted to the whole world just how important scientific research is to society.

Alex Hallatt – CDT Doctoral Researcher

The first of our Doctoral Researchers began returning to the labs in June, and we are delighted that they are now all back, albeit still on reduced hours. As the scheduling rules are decided locally, based on the type of work being carried out in each particular lab, and in conjunction with the government regulations, this has resulted in the MoSMed students being on a range of different shift patterns. Some are on mornings or afternoons, others are on one week on and one week off, some are able to come in for half the week, while others have to book time in the lab on a rota-system.

Although this has meant some necessary changes to the way they work and socialise, we are glad that their important research is able to progress once again, and we continue to be incredibly proud of how well they are all coping with the challenges they face.

We recognise the added pressure that the lockdown and subsequent restrictions have brought. We would encourage anybody who is struggling with stress, or feelings of isolation to reach out to their supervisor or CDT Manager for support.

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MoSMed Industrial Partners: Boehringer Ingelheim

The MoSMed CDT involves an extensive, regional, national, and international network of partners from large companies to smaller biotechnology organisations and national facilities. Partners bring industrial relevance to the CDT, operating across a diverse innovation spectrum and are involved in the conception and supervision of research projects.

As a MoSMed PhD student, I am fortunate to work in collaboration with my industrial partner Boehringer Ingelheim Pharma GmbH & Co.KG (BI). BI is a global, family-owned research-driven pharmaceutical company focused on improving the health and quality of life of patients. It focuses on six key areas of human pharmaceuticals (Cardio-/ Metabolic Diseases, Central Nervous System Diseases, Immunology, Oncology, Respiratory Diseases, Retinal Health), animal health and biopharmaceuticals and works in collaboration with many other companies to develop innovative therapies to extend the lives of patients.

Having BI as an industrial partner affords me the opportunity to undertake a year-long placement at their research site in Germany. This will allow me to apply my research in an industrial setting, benefiting from diverse experimental approaches in an applied / translational dimension whilst undertaking cutting-edge research relevant to the organisations' priorities and objectives. My co-supervisor for my PhD is Dr Frank H. Büttner who is head of a laboratory doing assay development, undertaking medium to high-throughput screening and compound profiling and has established the use of high-throughput MALDI-TOF mass spectrometry at BI. Dr. Büttner kindly agreed to be interviewed about how he came to be in his role and his motivations for being a partner of the MoSMed CDT and funding my studentship.

What is your research background and how did it bring you to work at BI? How did getting your PhD prepare you for this job?

"I studied Biology with a main focus on Biochemistry, Immunology, Genetics and Zoology; during my Master thesis I was already asked to join a pharmaceutical company (former Hoechst AG, then known as Hoechst Marion Roussel, then known as Aventis, now known as Sanofi) to do my PhD thesis on drug discovery projects for osteoarthritis, which was at this point of time quite unusual. During that time, I stayed also for several months in two different laboratories in the USA increasing my knowledge and gained experience in working with international teams. Finally, after my PhD in Biochemistry, I stayed in this company for a Postdoc and was already supervising drug discovery projects and then moved to Boehringer-Ingelheim."

What is your role at BI and how long have you worked there?

"I have been at BI for 20 years and 6 months now. I recently got promoted to a Senior Principal Scientist and I am head of a laboratory doing assay development, medium to high-throughput screening and compound profiling. I also established high-throughput MALDI-TOF mass spectrometry (MS) at BI and I am now responsible for MS-based projects in our group. I am involved in several drug discovery projects, and I am working together with colleagues from different disciplines (Chemistry, Chemoinformatics, Therapeutic areas, etc.)."

What are your highlights from working at BI?

"Helping patients is a key aspect in our daily work by developing new medicines. I am in the lucky situation to have contributed and participated in two projects within which we could develop drugs that are now on the market for BI. I also enjoy educating and training young people. It is great that I have the chance to introduce and develop new technologies, which allows us to set up more physiologically relevant assays, e.g. using Mass Spectrometry. Working together in international teams, bringing in my expertise and driving projects to success makes me happy."

Do you have any tips for someone wanting to work in the pharmaceutical industry?

"Be enthusiastic about your work, have a broad education, be focused and concentrated during your education, be interested in new technologies, publish and give talks at international meetings to get awareness."

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How did you come to be a partner with MoSMed? And what do you get out of it?

"I was in touch with Prof. Matthias Trost working together on MALDI-MS when this initiative was started, and we agreed that we should intensify our cooperation and participate. As I have already pointed out, training and educating young scientists is quite important for me, also giving students the possibility to work for some time in a pharmaceutical company showing the "different world" and understanding the different focus compared to academia is a useful aspect – it gives the students the possibility to decide for themselves what they like most and should help them to make their decision on how to proceed with their career. Also having the scientific aspect of such a collaboration is important – one can focus on new and different aspects of a technology, of a disease and gain new knowledge at all. Further, the collaboration allows me to focus on scientific aspects while I do not have the time to work on during daily business."

It is valuable for me to hear about the experiences of an esteemed research scientist and how the different aspects of his career have helped him to reach the role that he holds today. I am also enjoying learning more about the work of BI and how one's career can develop with them. I hope to continue to learn more about this during my PhD alongside my research. As Dr. Büttner said, it is a fantastic opportunity to get training with BI outside of the university laboratory context. This will be an excellent chance to develop on many levels, with both my research skills as well as personally through working in Germany and experiencing a different culture and expanding my knowledge, and I am really looking forward to undertaking my placement at BI.

Ruth Walker – CDT Doctoral Researcher

Boehringer Ingelheim

Here are some recent publications by Dr Büttner which are related to Ruth's project:

Simon, R.P.,Winter M., Kleiner C., Wehrle, L. Karnath, M., Ries, R., Zeeb, M., Schnapp, G., Fiegen, D.,Häbe, T.T., Runge, F., Bretschneider, T., Luippold, A.H., Bischoff, D., Reindl, W., **Büttner, F.H.** MALDI-TOF-based Affinity-Selection Mass Spectrometry for Automated Screening of Protein-Ligand Interactions at High-Throughput (2020) SLAS Discovery (2020) submitted

Häbe, T.T., Liu, C., Covey, T.R., Simon, R.S., Reindl, W., **Büttner, F.H.**, Winter M., Bischoff, D., Luippold, A.H., Runge, F. Ultrahigh-Throughput ESI-MS: Sampling pushed to six Samples per Second by Acoustic Ejection Mass Spectrometry (2020). Analytical Chemistry (2020) accepted

Simon, R.P., Winter M., Kleiner C., Ries C., Schnapp, G., Heimann, A., Li J., Zuvela-Jelaska, L., Bretschneider T., Luippold, A.H., Reindl W., Bischoff, D., **Büttner, F.H.** MALDI-TOF Mass Spectrometry-based High-Throughput Screening for Inhibitors of the Cytosolic DNA Sensor cGAS (2020). SLAS Discovery 25(4)372-383

Bretschneider, T.,Ozbal C., Holstein M., Winter M., **Büttner F.H.**,Thamm S., Bischoff D., Luippold A.H. RapidFire BLAZE-Mode Is Boosting ESI-MS Toward High-Throughput-Screening (2019) SLAS Technology 24(4) 386-393

Winter M., Bretschneider T., Thamm S., Kleiner C., Grabowski D., Chandler S., Ries R., Kley J.T., Fowler D., Bartlett C., Binetti R., Broadwater J., Luippold A.H., Bischoff D., **Büttner F.H.** Chemical Derivatization Enables MALDI-TOF Based High-Throughput Screening for Microbial Trimethylamine (TMA) Lyase Inhibitors (2019) SLAS Discovery 24(7)766-777

Winter M., Ries R., Kleiner C., Luippold, A.H., Bischoff D., Bretschneider T., **Büttner, F.H.** Automated MALDI Target Preparation Concept: Providing Ultra-High-Throughput Mass Spectrometry-Based Screening for Drug Discovery. (2019). SLAS Technology 24(2) 209-221

Winter M., Bretschneider T., Kleiner C., Ries R., Hehn J.P., Redemann N., Luippold, A.H., Bischoff D., **Büttner, F.H.** Establishing MALDI-TOF as Versatile Drug Discovery Readout to Dissect Enzymatic Reactions. (2018). SLAS Discovery 23(6): 561-573

MoSMed Molecular Sciences for Medicine

What is lacking? Lessons from the “mother of modern medicine”

HeLa. Most researchers in the biomedical sphere will have heard the term, if not read studies that utilise this immortal cell line, or otherwise used them in their own research. HeLa cells were the first immortal human cell line and they form the backbone of much of modern medicine. What many people do not know, however, is their unexpected history.

The cells originate from an African-American woman by the name of Henrietta Lacks, from which the name ‘HeLa’ also originates. I came across a couple of articles from last month commemorating the centenary of Lacks’ birth. Not only are they interesting, but these articles highlight the long-standing controversy surrounding HeLa cells and raise important questions about consent, ethics, acknowledgement and even racial inequality in modern-day science. While I cannot, in a short article, give each point the full consideration it deserves, I will give a brief history of HeLa cells and highlight some of the issues that most struck me from reading these articles.

Lacks was a tobacco farmer from Virginia. In 1951 she was diagnosed with an aggressive cervical cancer and died a few months later, aged 31. During her diagnosis and treatment, doctors at the Johns Hopkins Hospital in Maryland took a biopsy of her cancerous tissue. Then, without Lacks’ knowledge or consent, some of the tissue was given to a researcher and cultured in the laboratory. At that time no one had found a way to keep human cells alive outside the body for long, so when Lacks’ cells were found to survive and replicate in culture (essentially acting ‘immortal’ – the holy grail of cellular biology at that time), it was hailed as a major scientific breakthrough. The cells were shared widely in the scientific community, without consent from Lacks or her family and without attributing credit or compensation. HeLa cells became the workhorse of biological research and remain the most widely used human cell line, with scientific reproducibility presumably being a driving factor. These cells have been fundamental to advances in areas as diverse as immunology, cancer, vaccine development and in vitro fertilisation.

Lacks’ family were only made aware of the existence of the cells in 1973 when Johns Hopkins requested blood samples from her children. Doctors and researchers consistently failed to seek Lacks’ family’s consent when disclosing personal information, such as her name and medical records; and the final straw came in 2013 when the European Molecular Biology Laboratory in Heidelberg published the HeLa genome unilaterally, which could have revealed sensitive genetic information about Lacks’ decedents, sparking an outcry that resulted in the genome’s removal. Following this, the HeLa Genome Data Use agreement was established between Lacks’ family and the US National Institutes of Health to control access to HeLa sequence information.

The Lacks case was a catalyst for changes to the Bioethics field. Indeed, most countries now have specific laws pertaining to informed consent in order to protect a patient’s privacy. However, given that personalised medicine (the tailoring of treatment to a patient’s genetics) is gradually becoming the norm, there is an increasing need for regulation, transparency, and communication between researchers and patients or donors. But the story of Henrietta Lacks does more than underline the need for consent and better scientific policy, it highlights historical injustices on which modern science is built, which should not be forgotten. In the wake of the #BlackLivesMatter movement for racial justice, some have called for an end to the use of HeLa cells in research, arguing that their use sustains an injustice. But, like much of her family, Lacks’ granddaughter Jeri Lacks-Whye wants to see a celebration of her life and legacy: “I want scientists to acknowledge that HeLa cells came from an African-American woman who was flesh and blood, who had a family and who had a story”.

The articles referred to above can be found at: https://www.nature.com/articles/d41586-020-02494-z and https://www.newscientist.com/article/2250449-genetic-privacy-we-must-learn-from-the-story-of-henrietta-lacks/

For another interesting read, see the international bestselling book by Rebecca Skloot, The Immortal Life of Henrietta Lacks (2010). Skloot founded the Henrietta Lacks foundation, which offers financial support to individuals and families in cases similar to Henrietta Lacks’.

Laura Filipe – CDT Doctoral Researcher

MoSMed Molecular Sciences for Medicine

News and Updates

Welcome to Our new Cohort

We are really excited that it is almost time to welcome the second Cohort of Doctoral Researchers to our CDT. Despite the disruptions as a result of Covid-19 we have had a wonderful year with our first cohort and look forward to welcoming our new Cohort of 14 Doctoral Researchers across our two institutions in a few weeks' time. We look forward to further developing our MoSMed community with our first cohort sharing their expertise and experiences regarding all things MoSMed with our new Doctoral Researchers. We are hoping that some of our new members will wish to contribute to the future editions of our Newsletter so that you will be able to learn more about them and their work.

Details regarding our current and new Cohort can be found on our webpage at:

https://research.ncl.ac.uk/mosmed/people/students/

Update on the 2020 MoSMed Conference – 15th-16th December 2020:

Unfortunately due to the ongoing restrictions related to the Covid-19 pandemic, we will be unable to hold our second Annual Conference in Durham this year. However we are instead planning to deliver our Conference online via Zoom and are committed to including a diverse and interesting range of speakers and exciting opportunities for networking and ideation in conjunction with our partners. As they did at our inaugural Conference earlier this year, our Doctoral Researchers will be making a significant contribution to the event with presentations and posters detailing their projects. In addition some members of our second year cohort will be directly involved in the planning and delivery of the event. We look forward to confirming further details concerning the speakers and sessions at this event in due course.

Recent online seminars and presentations given at weekly cohort meeting:

Will Britain (PDRA) - Fluoropyridines; Applications in Organic Synthesis, Peptide and Peptoid Chemistry
Paul Denny - Protozoan 'drug' discovery: old drugs, new targets and mining for novelty
Steven Cobb - 19F NMR applications in Medicinal Chemistry and Chemical-Biology
Andrew Unwin – Networking Skills
Roy Sandbach - Research & Innovation in a Multinational… insights from a lifetime
AnnMarie O'Donoghue - Dynamics of Proton Transfer in Peptide Systems: The Prolyl Effect
Tim Blower - A nucleotidyltransferase toxin inhibits growth of *Mycobacterium tuberculosis*through inactivation of tRNA acceptor stems
Peter Chivers - Bacterial metalloregulation - a nickel tour
Martin Noble - Developing computational and experimental methods to support structure-based drug discovery

Thank You

A huge thank you to Olivia Gittins - one of our talented Doctoral Researchers who has taken the lead on editing the second edition of our Newsletter. I'm sure you will agree that she has done a fabulous job. Thank you for all your hard work, Olivia!

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