Of days in lockdown...

... “the journey a ponderous one at times, long and slow but necessarily so”.

As Simon Armitage reminds us in his recent poem Lockdown, the last few months have been a journey like never before - one in which we have discovered the best in humanity as much as we have the fragility of all we took for granted. As we look ahead to returning to the workplace slowly, in this Newsletter we also look back through personal prisms at what the last few months have meant for researchers, both as people and as scientists. We take pride in the fact that we rallied round to support our doctors and nurses in the small ways we could- be it through cart-loading our PPE stocks to the hospital or ferrying across whatever our commercial collaborators were willing to donate or at other times by adapting tests we have created over a decade to aid patients at a time when cancer diagnosis had all but come to a standstill. Then there were the heroes who have continued to volunteer their expertise to help the national testing capacity – both at the Anne McLaren or as part of the Covid labs in the JCBC building. Yet others have creatively fundraised for cancer research or made us proud by winning prestigious contests. The post-doc and grad-socs have kept our virtual social calendars going through quizzes and bring -your-pint Zoom evenings. Last but not the least, we thank our support staff who have quietly looked after the building through this lockdown and are working tirelessly to ensure the Hutch can be back in business soon. Here’s saluting all of them and everyone else for lasting it out!
Lockdown musings

The Frezza lab

Although this lockdown has forced us to stay distant, the Frezza Lab members are closer than ever. Different countries, cultures, and personalities…, but we discovered we are not that different. Some went back home and found a “new reality” spending more time with their beloved ones. Sharing moments with their families, pets, and even enjoying some pineapple pizza, but not knowing when they will be able to come back. Some being woken up by their kids in the early morning, multitasking between yoga for kids, organizing the lab, writing manuscripts, and performing quite a new version of experiments at home. Some new to the city, are discovering it in a silent way, and realised that apparently even Midsummer Common cows need social distancing. Balancing work with walks and cycling in probably the most amazing weather we had in a while. Flowers blooming outside show that life goes on even in these tough times. Some trying to go back home and see their families and partners. Some missing the taste of traditional cuisine, preparing Italian coffee using the moka, or dreaming of having jamón serrano again. Either with family, alone, in the UK, Canada, Australia or Germany, we are all supporting each other during this tragedy. Trying to stay positive and even if being quite impossible, trying to get the best out of it. Things that we took for granted before will become the new most valuable pieces of our lives. Still, we know we can count on each other to make this situation just a little bit better.

We have adapted our homes and tiny studios to have the most comfortable workspace possible (desk picture, Lorea). Missing home, and trying to wake up in the morning, we went back to old habits (moka picture, Christian). We also got some free time to practise yoga for kids (quite a revelation during the quarantine, Tim) and go for a run or walk through the amazing Cambridge parks and fields (socially distanced cow, Marc).
Serena Nik-Zainal

Of mankind and his milieu

In the 1990s, when pig-farmers in a small village called Sungai Nipah in Malaysia decided to supplement their income by planting fruit trees, they inadvertently tipped the eco-balance in favour of a deadly zoonosis. The fruit trees attracted flying foxes, a type of jungle fruit-bat (Pteropus sp.) that carried a virus. The virus was passed on to the pigs when bat excretions dropped into pig pens. Humans then contracted the novel agent, Nipah virus, through close contact with pigs.

A seemingly innocuous act of planting fruit trees was a minor change to the local environment but had a massive impact on human health and the economy. The Nipah virus outbreak between Sept 1998 and May 1999 spread to other pig farms in Malaysia and Singapore, infecting 265 people, killing 105 (fatality nearly ~50%). Nipah virus targeted medium and small blood vessels in humans, resulting in diffuse, vasculitic, cerebral damage. Affected patients presented with varying symptoms including fever, sore throat, vomiting, myalgia, confusion and seizures. Apart from the human cost, the Nipah virus outbreak caused near-collapse of the pig-farming industry in Malaysia (~USD 500 million). One million pigs were culled in a 24-hour period to contain the epidemic. Although eventually eradicated, the incident served as a painful reminder of the importance of rapid recognition and management of such outbreaks.

With a population of ~31.5 million, expansive coastal borders that leak illegal immigrants and limited resources, Malaysian authorities initiated an aggressive strategy of contact-tracing, testing and strict quarantine in January 2020, at the first sign of SARS-CoV2. A depoliticised team handles the crisis, led by the Director General of Health with no agenda other than “breaking the chain of infection”. There have been mistakes: a religious event involving ~15,000 pilgrims took place on Feb 27. Duly acknowledged as an error, the authorities pursued attendees, performed 38,411 tests detecting 2,364 cases from this event alone, making it the biggest cluster of SARS-CoV2 cases in Malaysia.

Today, May 15 2020, Malaysia has recorded 6,855 infected individuals and 112 deaths. The attitude towards these outbreaks is one of healthy respect for the forces of nature, and a humbled acknowledgement that we (humans) are the orchestrators of these epidemics. As long as humans collide with their environment, health and economic sequelae may be inevitable; but we can and must be vigilant, decisive and clinical in managing these crises, to limit the extent of catastrophic consequences.

Ashok Venkitaraman

An Outsider on the Inside

The Covid-19 lockdown has been paradoxically clarifying. Amidst the chaos, I find myself busier than ever – yet strangely, more focused on what I do, and why I do it. Writing for the Newsletter at this curious time has therefore sparked some curious reflections.
I never intended to be a cancer researcher. I trained in infectious disease medicine and molecular immunology. My research interests when starting my lab (then at the MRC Laboratory of Molecular Biology) concerned programmed DNA rearrangement in the immune system. However, the trajectory of my subsequent work changed radically when we first discovered, with several Cambridge colleagues, that the breast cancer gene BRCA2 is essential for genome stability. I have spent the last twenty years trying to understand why some people are more susceptible to cancer than others, and how that understanding can help to detect, treat or prevent the disease at an early stage. Nevertheless, my earlier experience in immunology, then near the peak of its conceptual maturation, has left an indelible intellectual mark.

These influences, both developmental and philosophical, have kept me an outsider on the inside of cancer research. This self-construed status carries both advantages and challenges. The advantages are simpler to distil. I often remark to my lab colleagues, “A little unhappiness goes a long way”, meaning that discontent with the status quo is a powerful spur to imaginative thinking. Such discontent in any research discipline comes more naturally, more easily to the outsider – as does, I think, reasoning less constrained by disciplinary dogma. I have not for a moment regretted this hair shirt, not least because it has emboldened me to take paths that might otherwise be left untrodden.

However, scientific research is a uniquely communal endeavour. Progress stands on the shoulders of many preceding insights or discoveries. At its most positive, communality stimulates open communication and the free-flowing exchange of important insights. Each of us achieves far more, together, than we might otherwise have done, alone. On the other hand, the negative aspects of scientific communality are increasingly evident. The scientific complexity and segmented funding of fields like cancer research fragments us into ever-smaller scientific guilds. These guilds too often disregard work that falls outside their mainstream, to everyone’s cost. Groupthink can obscure, or even rewrite, the narrative behind scientific discoveries. The laudable push to highlight research in the public sphere regrettably often descends into banal slogans, over the thoughtful dissection of ideas. Thus sadly, the struggle for recognition in crowded fields like cancer research has distorted in many ways what – in its essence – should be a quest for discovery.

In such a milieu, you might well ask, how far does being an outsider on the inside get you? I am largely upbeat. Remaining unaligned with particular schools of thought, or the guilds sponsoring them, has helped me question the received wisdom. Discontent with the narrow confines of unidimensional approaches to complex problems has stimulated discussions with colleagues from different fields. In consequence, I have frequently been forced to re-evaluate what (I thought) I knew and impelled to make the difficult effort to familiarize myself with different technical perspectives and scientific areas. Not unwillingly, being an outsider on the inside has motivated me to spend more time on prosecuting research, than managing or promulgating it. This has had what might be regarded as negative consequences, by those who see scientific research as a means to other ends. However, I have not felt any need to compromise my own aspirations in research and beyond, and so I would unhesitatingly commend outsider status to anyone with congruent ambitions. If you never rock the boat, when do you learn to swim?

I accept, of course, that my views will not be universally palatable – nor should they be! But if, like me, you are essentially concerned with scientific understanding and its application to improve the outcome of human disease, I hope that these reflections will resonate or provoke. Ideas, after all, are the engines of our progress.
MRC Cancer Unit: Research successes

Why the microenvironment matters

Single cell RNA-sequencing reveals a dynamic stromal niche that supports tumour growth

Cancer cells are surrounded by a diverse range of “normal cells” known as the stroma. The stroma includes immune cells, endothelial cells, fibroblasts and the extracellular matrix scaffold they produce. Together cancer cells and stroma form the tumour microenvironment. Crosstalk between the tumour and stroma is critical to help a tumour form and grow, but the complex relationships that exist within such a rapidly changing microenvironment remain unclear. In their recent paper published in Cell Reports, Davidson et al from the Shields lab, in collaboration with Sarah Teichmann’s lab (Wellcome Trust Sanger Institute) used single cell RNA sequencing (scRNAseq) to resolve stromal heterogeneity at the single-cell level, and to characterize how the function of stromal cells is temporally regulated during carcinogenesis. They showed that immune cells enter the tumour in a naïve state, where they are educated to develop immune suppressive functions. Researchers also identified the existence of fibroblast populations with distinct functions; immune regulatory, desmoplastic (laying down and remodelling extracellular matrix) and contractile. Contractile populations dominated in later, more established tumours. However, fibroblasts with immune regulatory function were prevalent at earliest stages of tumour development examined, producing factors to attract immune cells and change their function.

While previous single cell studies have examined the tumour from individual time points, this study uses this technology to characterise the changing stromal landscape within a developing tumour microenvironment and associated lymph nodes in real time. This approach has given rise to a new level insight into the populations, dynamics and interactions occurring in order to meet the changing requirements of a rapidly growing tumour. As part of the study, having collected such a large dataset, the researchers employed a unique database of known ligand-receptor interactions developed in the Teichmann Lab. With this approach, they were able to identify potential interactions across stromal and immune populations to predict interactions that support tumour growth. Indeed, these predictions were used to disrupt specific interactions between fibroblasts and macrophages in preclinical cancer models and showed a slowing of tumour growth. All data is freely available at data.teichlab.org.

Collectively, the results highlight the power of scRNAseq to identify complex interplays and increasing stromal diversity as tumours develop, and serve as a resource for identifying candidates with therapeutic potential. This sets the foundation for further investigation of stromal kinetics in human tumours to develop potential patient stratification approaches and identification of novel stromal focussed-therapeutic strategies.
The expansion of ‘mutant’ cells that could lead to cancer is often restricted by their neighbours

Spatial competition shapes the dynamic mutational landscape of normal oesophageal epithelium

Some DNA mutations, particularly those affecting known ‘cancer genes’ such as TP53 and NOTCH1, confer a competitive advantage on cells that acquire them. This allows these mutant clones to expand more rapidly than normal cells and can lead to disease. By middle age, most cells in tissues such as the oesophagus and the skin are mutant clones. But despite this, the vast majority do not go on to form cancers. A previous study from the same groups has shown that clones competing against each other helps to prevent cancer formation, but until now the ‘rules of the game’ for clonal competition were unknown. To discover how mutant clones interact, the researchers combined genetic lineage tracing and ultradep sequencing and modelling.

This recent paper published in Nature Genetics from Phil Jones’ group and involving Ben Hall’s group shows how mutated clones in morphologically normal oesophageal epithelium compete with one another. The mutational landscape generated in mice resembles that seen in aging humans with several of the same genes under strong genetic selection. By tracking cohorts of clones over a year following diethylnitrosamine (DEN) treatment in this mutationally diverse tissue, the authors see how strongly competitive mutations, such as Notch1 come to take over the tissue through a proliferative advantage. However, when clones of similar fitness collide, their proliferative behaviour reverts towards normal. This ‘neighbour constraint’ behaviour is consistent with findings in human skin and oesophagus. Understanding the rules that constrain mutant clones in normal tissues is an important step in discovering interventions to reshape the mutational burden of clones in normal tissues to cut the chances of later developing cancer.

The study thus describes the ‘rules of the game’ of competition between oesophageal cells for the first time. By understanding these rules, the hope is that therapies can be developed to reduce the competitiveness of mutant clone cells that are more likely to become cancerous.
Recent arrivals & departures

We welcome Connor Rogerson, Omid Siddiqui, Vasiliki Kostiou, Ming Yang, Marc Segarra Mondejar (Research Associates), Junfan Huang (Research Assistant), Douglas van Niekerk (visiting PhD student), Alex Moelwyn-Hughes (PA to Professor Fitzgerald) and Chris Darke (IT Specialist). We would like to wish Carol Grenz, Clare Atherton, Claire Jefferies, Simon Stockwell, Sarah Leith Russell, Estrella Gaurino Almeida, Apostolos Pappas and Laura Tronci, all the best in their future careers.

Recent events

The Hutch Virtual Quiz (May 2020): Congratulations to all participants – a great mixture of students, post-docs, Group Leaders and support staff - and to the winning team NERD IMMUNITY (from the Shields lab)!

Other News

The MRC CU Art trail

The Art of Science – 2020. As part of the annual MRC Festival of Medical Research, the Unit was hoping to again host the Art Meets Science competition - till lockdown got in the way. However, thanks to the gradsoc this will now still take place online with the creating of a Hutch virtual gallery. Entries are now open.

The Dryathlon for CRUK

At a time when great personal hardships for the general public have meant a great hit to the income of charities that are vital for cancer research, doctors and researchers are doing their bit - like Massi (Dr Massimiliano De Pietro) who has taken the dryathlon challenge for a month in the hope of raising a grand!

Upcoming events

Work In Progress talks – this series will resume online from 28 May and continue in this format for the rest of this term

The MRC Max Perutz Science Writing competition 2020 - deadline 30 June
In April 2020 Annie Howitt, PhD student in the Esposito and Frezza labs won the regional Fame Lab competition in Cambridge. Fame Lab is an international competition run by Cheltenham Science Festival where competitors give 3 minute talks on their research, with only props and your own voice to help you. After submitting a video on cellular decisions in a tumour for her heat, Annie was excited to be selected for the Cambridge regional final which took place on the 27th of April via a video call. Instead of the normal event with a large public audience, Annie delivered her talk from her own work from home office, speaking only to her webcam and her dogs, explaining that it may take a village to raise a tumour, i.e. different cells present may have different functions and tumours require their collective action to survive. After an evening of very enjoyable and informative talks, she was selected to go to the UK final and will be receiving a ‘masterclass’ in science communication from a UK expert. The UK final will be streamed on YouTube on the 3rd of June as part of the Cheltenham Science Festival @ Home.

We wish Annie the very best for the nationals!
Recent publications


