Impact of COVID-19 on in vivo work and patient sample availability for cancer research

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The COVID-19 pandemic has destabilized the traditional bench to bedside workflow of cancer research. Particularly, in vivo experimentation plus the collection and distribution of patient samples has been significantly affected. Strategies are needed now to revolutionize current cancer research practices in order to avoid history repeating itself in future pandemics.

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As an early career academic who studies cancer genetics from both basic science and clinical perspectives, I have witnessed not only the impact the coronavirus disease 2019 (COVID-19) pandemic is having on the treatment of cancers, but also the influence it is having across the pan-cancer research sector. We are a year into this global pandemic, and the influences on fundamental cancer research have been severe. Immediate impacts were felt as research laboratories had to close and clinical trials cancelled, to align with national lockdown restrictions and to protect local health-care systems. Consequently, budgets for research are down with the Association of Medical Research Charities forecasting a sector-wide shortfall in UK research investment ranging between £252–368 million in 2020–2021 (REF.[1]). These trends are being mirrored across the globe[2], resulting in new research grants having postponed starting dates and also cuts to ongoing projects. For example, Cancer Research UK-funded schemes are faced with up to 10% reductions in awarded funds[3]. Together these immediate and long-term limitations are impacting key areas of cancer research, including animal experimentation and the availability of patient samples for analysis. These factors combine to destabilize the traditional bench to bedside workflow, hindering clinical advancement.

Animal models of cancer

The pre-clinical evaluation of cancers in animals is ritualistic in driving the discovery of novel genetic mechanisms and the development of new cancer treatments. For example, mice harbouring tumour xenografts are commonly used for treatment efficacy studies, and genetically engineered mouse models allow us to delve into the inner workings and cross-communications influenced by particular mutations.

However, in the face of COVID-19-related laboratory closures and work-from-home policies, institutions worldwide, including my own, were forced to make difficult decisions on their current animal stocks. In my experience, rapid responses and the establishment of contingency plans were crucial to ensuring minimal animal culling, a reality not realized everywhere. There are cases of mass culling of experimental mice in a plethora of institutions, with numbers reaching the 1,000s in some instances[4]. Factors influencing such decisions included the age of animals at the start of national lockdowns, with it being projected that many would be too old for experimentation by the time normal research could resume.

The take-home message from many universities was that swift and cooperative action would save as many animal lives as possible. The possibility of staff not being able to come into units for animal maintenance and care of remaining animals and/or ongoing experiments meant that decisions had to be made on which animals (and experiments) were worth continuing and which were not. This required clear communication and strong collegiality. This cooperative approach helped save animal lives and reduced the impact of lockdowns.

Although mice and rats make up the majority of animals used for research, we cannot forget that mammals such as dogs and cats are also used routinely. Autochthonous cancers in domesticated pet dogs and cats offer a distinctive model of human cancer biology, and thus translational therapeutic analysis. It seems, however, that companion animals such as these are not immune to COVID-19 (REF.[5]). Several reports have stated that human-pet transmission of the COVID-19 causative agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is possible and that these animals can develop COVID-19 symptoms. This of course would need to factor into the design of current and future animal experiments of this nature, from an ethical perspective but also as it could influence experimental outputs and tissue distribution. Indeed, members of the *Mustela* genus (ferret) are increasingly used

for models of cancer[6], and given the recent suggestions that mink (another member of the *Mustela* genus) can transmit SARS-CoV-2 to humans, it seems sensible that limitations should be put in place for the use of these animals for the time being, until we know more about the disease.

Perhaps, however, this pandemic has highlighted an even greater need for a necessary revolution in cancer research practices. Even before the COVID-19 pandemic, every year there were masses of experimental animals left 'unused'[7]. Conceivably, a greater need, now more than ever, is required to shift cancer research to more ex vivo and in silico models of disease. There have been some fantastic advances in recent years with the use of organoid models, for example. Organoids are derived from stem cells and can be cultured to replicate the intricacy of the tissue they originate from, thus are great physiological tools for cancer research. Many organoids can be cultured and expanded from a single mouse, which could include both cancerous and non-cancerous tissue. Organoids can also be derived from human patient tissue and could provide valuable insight into drug sensitivity of a particular patient's cancer, leading the way for a personalized medicine approach[8]. Animal models can be extremely useful, but their use is fraught with unreliability and high failure rates. With the translational success of animal models of cancer into human beings extremely unreliable, an overhaul seems prudent, and so why not now?

Patient-derived samples

It is estimated that in the UK alone there were approximately 12,750 people waiting for cancer surgery in June 2020, a result of a 60% reduction in procedures[9]. Cancer scientists, like myself, routinely utilize patient-derived samples. They provide invaluable insight not only into the mechanisms that make a cancer tick, but also how to treat it effectively. The reduced numbers of cancer surgeries will have an abrupt and enduring impact on tissue availability for scientific analysis. The potential knock-on effects for future studies give cause for alarm, as competition for tissues (in an already competitive environment) will be fierce.

Beyond tissue samples, many researchers require the collection of fluids (such as blood, serum and saliva) from patients with cancer. These samples are essential for the discovery of novel diagnostic and prognostic cancer biomarkers. Currently, there is a risk that biosamples collected from patients with cancer could be carrying SARS-CoV-2, resulting in a sharp decline in availability in addition to that brought about by delays and cancellations in sample collection[10]. The hope is that the fixation and embedding processes of tissue samples will inactivate the virus, however this does not extend to the surface of cassettes or bio-sample collection tubes, and so does not eradicate the risk of transmission.

Human tissue harbouring infection or potential infection with SARS-CoV-2 will require additional precautions. For example, working with SARS-CoV-2-positive human samples requires the use of biosafety class 2 workbenches. Regrettably, not all cancer biobanks or research facilities have access to such amenities, and to introduce them would be costly. Trackability of samples with potential or known SARS-CoV-2 contamination will be the critical factor in ensuring appropriate handling and distribution of tissues for cancer research moving forward. This of course will present further challenges in tissue availability, as well as significant financial investment to ensure accurate and robust compliance.

Conclusions

It is clear that a community approach among cancer researchers is indispensable to overcome the restrictions brought about by the COVID-19 pandemic. This approach will have many ethical and financial benefits in the immediate and distant future. We need to move forward from this pandemic assuming that it could very much happen again; there are new processes to be implemented, lessons to be learnt and mistakes to be remembered. In the face of the restrictions inflicted by the COVID-19 pandemic, cancer research should use this opportunity to revolutionize itself, so we can get back to investigating cancer with renewed strength.

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Competing interests
The author declares no competing interests.