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Organoids: the new kid in cancer research

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Cancer is a major health burden, and is expected to rank as the leading cause of death in every country in the 21st century[1]. Despite extensive research and advances in cancer care, there is significant limitation in translation of bench to bedside treatments, largely due to the nature of current cancer models used in research.

Current cancer models include cell lines and mouse xenografts (PDXs). Cancer cell lines are 2D models of cells grown in vitro. They have variable success in establishment, often undergo substantial in-vitro genetic changes and fail to recapitulate the heterogeneity of the native tumour. Xenografts on the other hand retain the biology of the tumour better than cell lines. However, they are expensive, time and resource intensive, have variable success in establishment and may develop mouse specific tumour changes over time[2]. While both have been immensely useful in basic science, they have significant limitations in their clinical applicability. Recently, the development of a more physiological pre-clinical model that overcomes many of the deficiencies of cell lines and PDXs has come to the fore. Dubbed by Nature magazine as '*the method of the year'*, novel cancer models called "organoids" have the potential to revolutionise cancer care .

Organoids are three-dimensional cultures of cancer cells grown in the laboratory that recapitulate tumour heterogeneity and maintain genomic integrity far better than cell lines and animal models. Tumour specific stem cells can grow from small pieces of tumour embedded in a synthetic extracellular matrix in a cell culture plate with a cocktail of growth factors into self organising and self sustaining 3D structures called organoids[3]. Organoids represent the native cancer in their mutations, physiology and their cellular interactions. These 'mini tumours' can be rapidly grown in a matter of days, with greater success rates than cell lines or mouse models[4]. Organoids have enormous clinical applicability and potentially represent the next frontier in changing cancer care for patients.

Organoids can be grown with high success rates from simple needle biopsies. To date, organoids have been successfully developed from numerous cancers, including colorectal, pancreatic, gastric, oesophageal, liver, lung, glioblastomas and testicular cancers[5]. They can be used to develop a 'living tumour biobank' wherein replenishable organoids can be stored for each cancer.

Organoids can be used to help predict and prognosticate patient responses to therapy. Early studies with rectal cancer have shown that organoids can help predict rectal cancer responses to chemoradiotherapy[6]. This could potentially change how we treat rectal cancer in the future. They can be used to model and study various diseases, from genetic disorders like cystic fibrosis to inflammatory conditions like Clostridium colitis[7]. The ability to also grow matched "normal" tissue organoids allows one to interrogate the genetic

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alterations that lead to cancer, with gene editing tools like CRISPR-Cas9 that can be used to switch genes on and off[8].

Immunotherapy has transformed the treatment landscape of cancers such as melanoma and renal cell carcinoma. Currently there are no reliable biomarkers to predict responses to immunotherapeutic drugs. Organoids provide a valuable strategy to evaluate the response to immunotherapy in patients, thereby selecting those likely to respond to immunotherapy, and avoiding immunotherapy related complications in non-responders[9].

One of the most promising areas for the utilisation of organoids is in drug development and personalised medicine. Many drugs fail, or take years to reach the clinic due to regulations regarding evaluation of the drugs toxic profile. With the ability to grow normal tissue organoids alongside matched tumour derived organoids, a thorough in vitro assessment of drug toxicity on normal and tumour derived tissue can be undertaken to identify optimal doses that are toxic to the tumour, with minimal harm to normal tissue.

Organoids can aid in personalising treatment for patients with metastatic or low survival cancers such as pancreatic or colorectal peritoneal metastases. As surgeons, we are in a unique position, where fresh tumour tissue from surgical biopsies or resections can be shared with scientists for growing organoids. The ongoing development of high-throughput organoid drug screening can help identify novel drug targets that can be offered to patients who have failed other lines of treatment. This model of treatment offers a chance for surgeons to work alongside scientists, pathologists and researchers, encouraging development of translational research collaborations.

While the potential value of organoids in surgical oncology is immense, many limitations still remain. Being an in vitro model, they lack the tumour microenvironment and interactions with cells such as fibroblasts and other stromal elements cannot be well assessed. Cancers are generally vascular. However, organoids lack the ability to grow blood vessels, with angiogenesis mediated interactions unable to be evaluated. Despite these limitations, recent studies have successfully shown that organoid-drug interactions accurately predict and mirror patient drug responses in vivo[10, 11]. Future clinical trials may evolve into a more 'adaptive' nature similar to the *zero childhood cancer program*, where patients are offered drugs based on each tumours unique sensitivities, rather than generic guidelines.

. These are still early days, but there is already real hope that harnessing the true potential of these exciting tools may help turn the tide in the fight against cancer.

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The presumed myth of real time bench top to bedside treatment can very soon become reality.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018;0:1-31.
2. Kamb A. What's wrong with our cancer models? Nature Reviews. 2005;4:161-5.
3. Sato T, Vries R, Snippert H, van de Wetering M, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. Nature. 2009;459(7244):262-U147.
4. Clevers H. Modeling Development and Disease with Organoids. Cell. 2016;165(7):1586-97.
5. Li M, Izpisua Belmonte J. Organoids - Preclinical Models of Human Disease. N Engl J Med. 2019;380(6):569-79.
6. Kong J, Guerra G, Millen R, Roth S, et al. Tumor-Infiltrating Lymphocyte Function Predicts Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer. JCO Precision Oncology. 2018(2):1-15.
7. Drost J, Clevers H. Organoids in cancer research. Nat Rev Cancer. 2018;18(7):407-18.
8. Adli M. The CRISPR tool kit for genome editing and beyond. Nat Commun. 2018;9(1):1911.
9. Jenkins R, Aref A, Lizotte P, Ivanova E, et al. Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids. Cancer Discov. 2018;8(2):196-215.
10. Pauli C, Hopkins B, Prandi D, Shaw R, et al. Personalized In Vitro and In Vivo Cancer Models to Guide Precision Medicine. Cancer Discov. 2017;7(5):462-77.
11. Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. Science. 2018;359(6378):920-6.

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