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Media release, 2 March 2021

Predicting success in therapy with individualized cancer models

Scientists at Urology Research Laboratory of the Department for BioMedical Research (DBMR), University of Bern and Urology Department of the Inselspital of Bern, have established organoid culture models from prostate tumor biopsies. These are small clusters of cells which can be used to test the efficacy of various drugs. In this way, it is possible to test which treatment will most likely benefit individual patients.

In the EU alone, 78,800 men died of prostate cancer last year. While tumors discovered at an early stage can often be completely removed by surgery and radiation therapy, the prospects of successful treatment is reduced if the cancer has further metastasized. At present, physicians cannot predict drug response or therapy resistance in patients.

Three-dimensional structures

The team led by PD Dr. Marianna Kruithof-de Julio at the Urology Research Laboratory at the Department for BioMedical Research (DBMR) of the University of Bern and Inselspital Bern, has developed a new strategy for the generation of prostate cancer organoids that can contribute to assess therapy response, their work is published in the latest issue of *Nature Communications*. Drs Sofia Karkampouna and Federico La Manna, the two lead co-authors of the paper, spent over one and a half year in optimizing and efficient protocol for the generation of the patient derived organoids and their detailed characterization. Moreover, in collaboration with the NEXUS Personalized Health Technologies, they have meticulously developed a medium-throughput screen fir drug testing.

The researchers led by PD Dr. Kruithof-de Julio have demonstrated that patient-derived organoids retain relevant characteristics of the prostate carcinoma from which they have been originated: not only are they characterized by the same genetic mutations, but they also exhibit similar gene activity patterns.

Paving the way for personalized medicine

PD Dr. Kruithof-de Julio and her collaborators first generated a novel early stage, patient derived xenograft that is treatment naïve, then tested 74 different drugs on organoids from this and other experimental tumor models - identifying 13 compounds that reduced prostate cancer cell viability. The researchers then tested the efficacy of these compounds on organoids from five prostate cancer patients - two with early-stage tumors and three with advanced metastatic tumors. Interestingly, among the hits ponatinib, so far approved for the treatment of leukemia, proved to be

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particularly effective in reduction of organoid viability and tumor growth in vivo.

However, for PD Dr. Kruithof-de Julio, the significance of these results lies not only in the drug repurposing but more importantly in promoting an approach that the medical community can undertake. "Our results pave the way for personalized medicine. In our study we only analyzed data from five patients retrospectively," says Kruithof-de Julio. "But we clearly showed that the method would be in principle feasible. Growing the organoids and drug testing can be accomplished in two weeks, a time frame that is compatible with clinical decision making. In collaboration with the Urology Department of the Inselspital, lad by Prof Thalmann, we have now already been able to prove this in several cases."

"In my clinical activity, I am regularly confronted by tumors that do not respond to therapy or for which we do not know which therapy to use", says Thalmann. "This is a further step in the direction of individualized medicine, where we might be able to tailor the treatment to the tumor during the course of the disease and better understand its biology." With this approach, the researchers hope to treat patients more efficiently with less side effects and diminished costs.

Publication details:

Karkampouna, S.and La Manna, F., et al. Patient-derived xenografts and organoids model therapy response in prostate cancer. *Nat Commun* **12**, 1117 (2021).
https://doi.org/10.1038/s41467-021-21300-6

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The Bern Center for Precision Medicine (BCPM)
The Bern Center for Precision Medicine was founded in 2019 on the initiative and with the support of the canton, the University of Bern and the Insel Group. The center is dedicated to advancing precision medicine and developing new medicines to help patients for whom standard care fails. The BCPM provides an interdisciplinary network for researchers and clinicians from different fields and faculties and brings together more than 70 members.
Further information

The Insel Gruppe
The Insel Gruppe is Switzerland's leading group of hospitals for university and integrated medicine. It offers comprehensive health care based on groundbreaking quality, research, innovation and education. The six Insel Gruppe hospitals (Inselspital, Aarberg, Belp, Münsingen, Riggisberg and Tiefenau) carried out around 864 000 outpatient consultations and treated about 65 000 in-patients in the financial year 2019. The Insel Gruppe employs almost 10 800 members of staff from 100 nations. It provides training for a large number of professions and is the most important institution for the further training of young physicians.
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INTERVIEW: MARIANNA KRUITHOF-DE JULIO / ORGANOIDS

"Our efforts are devoted to convert cancer from a lethal to a chronic disease"

Marianna Kruithof-de Julio and her team are developing methods to grow small clusters of cells from tumor biopsies. In this way, the researchers hope to customize treatment for each individual patient. Their goal is perhaps still five to ten years away, the expert estimates.

Interview: Ori Schipper

Dr. Kruithof-de Julio, you head the "Organoid Core Facility" at the University of Bern. What should I envisage this as?

Marianna Kruithof-de Julio: We are developing methods to grow and multiply cells from biological samples taken from cancer patients. In doing so, we try to create favorable conditions for the cells so that they join together to form spherical cell clusters - so-called organoids. These organoids are a fairly accurate representation of the tumor from which they were derived, this cannot be achieved by conventional cell line models. Currently, we are optimizing and standardizing the procedures so that we can use the patient-specific organoids in broader tests.

What for?

To be able to test which drugs are most effective for each individual patient. At the moment we have tested patient derived organoids in primary and advanced cancer stages, after the course of standard of care. My vision is that organoid testing would be incorporated in the initial clinical decision making, favored by the collaboration between the clinics and research laboratories. Pathological evaluation and organoid testing would be carried out in parallel, to identify the most promising personalized therapy.

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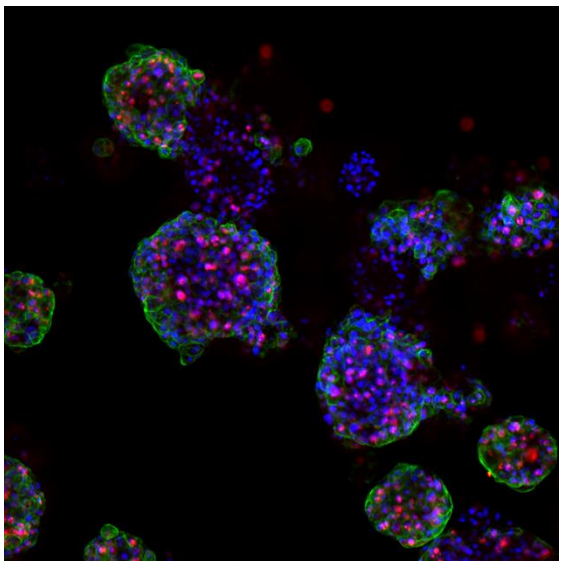

Proliferating prostate cancer organoids: A) Cell Surface Stem Cell Marker (green), dividing cells (red) and DNA (Blue) © Marianna Kruithof-de Julio and Marta De Menna.

You have just published a study in which you show that the approach with patient-derived organoids is feasible in principle.

Yes, we have setup a routine platform for the derivation and testing of patient-derived organoids. Prof. George Thalmann, MD, and his colleagues at the University Department of Urology at the Inselspital in Bern, have played a crucial role in this process. In our paper we have used prostate cancer specimens to derive a novel experimental mouse model, which has allowed us to setup a medium throughput screen with FDA-approved drugs. This has resulted in the selection of 13 drugs which we then tested on patient-derived organoids. In this proof of principle approach, we have used patient-derived organoids, 2 primary and 3 advanced cases. Interestingly, from the drug testing, we could discriminate among primary non-treated versus advanced therapy resistant cases in terms of drug response. Larger cohorts and patient follow-up are needed to make our findings translatable to clinical practice which makes it challenging for prostate cancer.

Our efforts are devoted to convert cancer from a lethal to a chronic disease, which can be solely achieved by the collaboration between the researchers and the clinicians.

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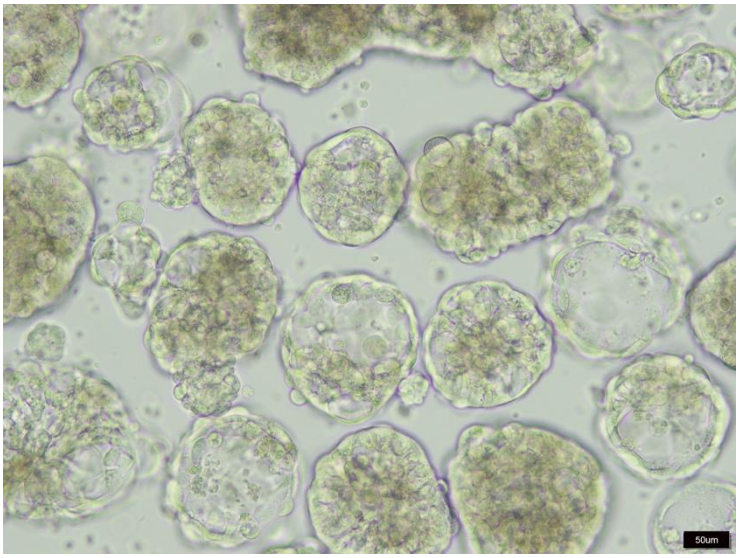

Bright Field image of Prostate cancer organoids © Marianna Kruithof-de Julio and Sofia Karkampouna.

Organoids should also help reduce animal testing. Why are they better suited than animal models?

Organoids allow the study of biological processes, such as cell behavior, tissue repair and response to drugs or gene mutations, in an environment that mimics endogenous cell organization and organ structures. Starting as a major technological breakthrough they are now firmly established as an essential tool in biological research and also have important implications for clinical use. As evident from our study, organoids allow for high and medium throughput screen of drugs already in use for other cancer types, resulting in drug repurposing bypassing the need of additional animal experiments. Major advantages include that they can be grown from a limited supply of starting material, e.g. biopsies; the rapid growth compared to PDXs (patient-derived xenografts) where tissue biopsies from patients are transferred into an animal model - in this case mice. Other advantages include renewal resources for biomedical research; the potential to model 3D growth, the ability to be manipulated with gene editing tools (e.g., CRISPR-Cas9) to create model systems with similar complexity as experienced in a population of cancer patients; the direct application to precision oncology management to anticipate next or best therapies – all this will lead to a significant reduction of animal experimentation.

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ABOUT HER:

PD Dr. Marianna Kruithof-de Julio has been a research group leader at the Department for BioMedical Research (DBMR) and Inselspital since 2016 and member of the Bern Center for Precision Medicine (BCPM) of the University of Bern. Her main research is on the development and application of tools for precision medicine. In recent years, she has obtained several highly competitive grants, such as the USA Congressionally Directed Medical Research Program (CDMRP) and the Swiss 3R Competence Center (3RCC).

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