UKCRC Tissue Directory and Coordination Centre of BioBanking

The UK Clinical Research Collaboration (UKCRC) Tissue Directory and Coordination Centre (the Centre) aims to coordinate Biobanking activities in the UK. The Centre represents a first step in integrating national biobanking infrastructure to support research activity. ***You can read more about the project and how to get involved at https://www.biobankinguk.org***

A joint vision

Biomedical researchers rely on human tissue samples for a multitude of research projects; cancer is of particular note as it such a heterogeneous disease. Given the development of precision medicine and the need for more reliable disease models in other fields, the demand for high quality samples and associated data will increase over time. Until now, there has been no coordinated effort to catalogue or coordinate human biosample acquisition and storage. The Centre was established in 2014 by the UK Clinical Research Collaboration (UKCRC) Experimental Medicine Funders Group in order to achieve their Vision for Human Tissue Resources.

The funder's vision

"Funders aim to maximise the value of human tissue samples and resources while minimising duplication of effort. This requires better characterisation of tissue samples, asking for generic consent, and increased linkage to accurate clinical data. Sample collections must then be made more easily discoverable and accessible for use in high quality, ethical research."

The Centre has therefore been established to promote best practice, harmonisation and standardisation, and increase sample visibility in the hope that this will lead to increased sharing of samples, creating a more efficient research environment in the UK.

The UKCRC Tissue Directory

Launched in 2016, the UK-wide Tissue Directory, is a first step in promoting access to samples for research. The directory contains the details of biological samples and data held across >80 biobanks in the UK. The directory aims to facilitate communication between researchers and biobanks, providing a quick and efficient route for researchers to access appropriate samples and data to match their research needs.

Researchers can search the online directory and locate appropriate tissue samples held by a specific biobank, based on the associated datasets giving age and gender of donors, and sample type. It is possible to search the directory using the specific disease term by viewing the list of diseases or the A-Z of Biobanks.

The Centre does not facilitate sample access; it acts as a platform for promoting visibility of existing resources.

An ethical duty to share

The UK Ethics Committee Authority (UKECA) has now made registration in the UKCRC Tissue Directory a condition of the Research Ethics Committee (REC) favourable opinion for research tissue banks (RTB). Patients gift their samples, under the impression that they will be used for scientific medical research. This change in the terms of REC favourable opinion should lead to a shift in the culture of research. Dr Philip Quinlan has said: "It is fantastic that the UKCRC Tissue Directory and Coordination Centre has been recognised as the best centre to do this work; tissue banks will have an ethical obligation to ensure their sample collections are visible to the community and we hope this will lead to better coordination between biobanks ensuring more samples are contributing directly to medical progress." Indeed, this is the first ever defined expectation for researchers to register the existence of the samples they hold.

Award winning engagement

The Centre actively engages with all stakeholders through events, campaigns and communications to ensure the development of the project provides plenty of information. The centre works with people and organisations to promote best practice, governance and public engagement.

The Centre has run a number of successful road-shows at institutions around the country to promote its work and encourage feedback. The Centre's most recent annual meeting was held on the 16th November at the Oval in London. UK Biobanking Showcase was a unique opportunity to bring together all stakeholders in the field and featured debates, give talks and award the prestigious "Biobank of the Year".

2016 saw the centre in parliament at a Biobanking event: "The Biobanking time-bomb; maintaining public trust in medical research". The aim of this event was to address the future risks to biobanking if certain issues were not addressed. These risks include the reducing contributions from Research grants to Biobanks, cost recovery being insufficient to recover financial deficits, particularly due to the increasing cost of running biobanks. Reward mechanisms and access to clinical data are also important issues that were discussed. Find out more about the event on our website.

As well as engaging with Biobanks and policy makers, The Centre has an active public engagement programme. Project and Engagement manager, Jessica Sims, has developed a Board game to explain biobanking to the public. This innovative approach to a complex and sensitive issue has won public engagement awards in the past. Ms Sims says "public understanding is vital to tissue donation. I wanted to develop a way of really engaging with people in a format they can understand". Contact Ms Sims at j.sims@ucl.ac.uk to learn more about the game,

BBMRI.uk

The Biobanking and BioMolecular Resources Research Infrastructure (BBMRI) – European Research Infrastructure Consortium (ERIC; BBMRI-ERIC) – is one of the largest research infrastructures for health in Europe today. It provides services and expertise for its members, including expert centres, events, and a European sample locator. They have also coordinated a number of research projects within Europe and beyond.

The Centre represents the UK and engages with this network on ethical, legal and societal issues (ELSI), IT and Quality common service groups. It has also contributed to the drafting of sample quality standards along with BBMRI-ERIC. Visit their website or get in touch to find out more about getting involved with this network.

To get involved

The Centre in the UK relies on the research community to shape our work; it is therefore keen to engage with pathologists, particularly those involved in biobanking on

how you can help (contact in email below). You can register your samples online at https://directory.biobankinguk.org. There are more resources including the latest biobanking news and advice at https://www.biobankinguk.org. Finally, you can also sign up to The Centre's Newsletter for all the latest news and events.

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Breaking bad: cancer cell drug addiction solved

From The Netherlands Cancer Institute

Cancer cells can become not only resistant to, but addicted to the drugs that try to kill them. A research team led by Professor Daniel Peeper from the Netherlands Cancer Institute has now discovered the underlying mechanism, which may guide the development of more rational alternating therapies.

Because cancers can become resistant to therapy, this presents a major challenge to patient care. Sometimes, however, cancers are not only resistant to, but can become addicted to the very drugs used to treat them. Indeed, research on patients, animal models and cultured cells have suggested that this dependency is a double-edged sword in that it can work against tumours; drug-addicted cells can die massively when treatment is suddenly stopped. Although this is a potential new approach, the mechanism of addiction was unknown, at least until now.

Breaking addiction

To understand the mechanism of cancer drug addiction, it is probably best to try to break it, argued group leader Daniel Peeper and his postdoc Xiangjun Kong at the Netherlands Cancer Institute. They used melanoma cells that were both resistant and addicted to a treatment based on the inhibition of BRAF, a common driver of malignancy. With a technique called CRISPR-Cas9, they knocked out all individual genes in the cancer cell genome one by one. They searched for cells carrying a mutation that had broken the addiction, which were those that had managed to survive when treatment was discontinued, whereas all others died. With this strategy, the researchers identified a signaling pathway vital for drug addiction, involving the proteins ERK2, JUNB, and FRA1. Peeper said "Interestingly, all resistant tumour cells we examined used this same drug addiction mechanism, irrespective of how they had become resistant. When this pathway is disrupted, cancer cells overcome their drug addiction. We have demonstrated this in both cell culture and tumour-bearing mice, and we have indications of the same phenomenon is seen in patients with drug-resistant melanoma. This mechanism was active in lung cancer cells that were addicted to another drug. This suggests that the pathway we uncovered may be important for various cancer types and treatments."

Rational alternating treatments

Unfortunately, cancer cells are very flexible and can often reverse their addiction themselves. The new findings may be used to target those addicted cancer cells that fail to die upon stopping the treatment. "Instead of giving addicted cells a break, we should probably immediately switch to another treatment", says Peeper. "Now that we understand how cancer cells can overcome their drug addiction, we have a solid basis for identifying the most effective second treatment for this so-called alternating therapy approach."

His team have started with melanoma cells addicted to a BRAF-inhibitor. They stopped this treatment and subsequently treated the cells with the chemotherapeutic agent, dacarbazine. This combination of sudden drug withdrawal and a second treatment turned out to be more effective than just discontinuing the first treatment. Peeper remarked that "This was a proof-of-principle experiment in cultured cells demonstrating how effective these alternating treatments may be. It sets the stage for systematic studies identifying which treatments cooperate best with drug withdrawal for therapy-addicted cancers."

The work was financially supported by the Dutch Cancer Society and the European Research Council. ***For more information or interview requests, please contact Sanne Hijlkema, Science Information Officer at the Netherlands Cancer Institute (communicatie@nki.nl, +31 20 512 28 50).***

About The Netherlands Cancer Institute

The Netherlands Cancer Institute has been at the international forefront of cancer care and research for more than a century. The unique combination of healthcare and scientific research within the same institute offers great benefit for cancer patients. Specialised cancer care professionals work together in multidisciplinary teams to set up and carry out treatment plans tailored to the needs of individual patients because no two tumours are alike. Cancer patients or people suspected of having cancer can come to our hospital, known as the Antoni van Leeuwenhoek, to make use of this personal approach, and the state-of-the-art research and treatment facilities. The research institute employs more than 600 scientists investigating many aspects of cancer development, diagnosis, treatment and epidemiology. Scientists at the Netherlands Cancer Institute have excess to state-of-the-art research facilities supporting their basic, translational and clinical research. This scientific research could not be carried out without the institutional support of the Dutch Cancer Society, the Ministry of Health, Welfare and Sport, the many research grants obtained by our researchers from international funding agencies, and the generous donations made by individuals that support our research program. The Netherlands Cancer Institute is the only OECI designated Comprehensive Cancer Centre in the Netherlands. ***For more information visit our websites: www.nki.nl and www.avl.nl.***

Technical University of Munich

– Corporate Communications Centre

A safety switch that automatically stops the device for example before it overheats has been built into many electrical appliances. The body's cells are equipped with this kind of "emergency stop". They make sure that a defective cell does not grow uncontrollably to become transformed as a tumour cell. A team from the Technical University of Munich (TUM) has now discovered such a switch in immune T cells. In the future it will be possible to use these results in new therapies for the treatment of T cell non-Hodgkin's lymphoma triggered by defective immune cells.

In the body T cells are usually responsible for immediately detecting and killing cancer cells. However, problems can arise when a T cell itself develops a defect in its genome, the DNA. If the defect affects areas of the genome which are responsible for cell growth, referred to as oncogenes, the T cell itself can become an uncontrollably growing tumour cell. T cell, an important part of the body's immune system against cancer, can also fail.

This is exactly what occurs in T cell non-Hodgkin's lymphoma. This aggressive form of lymphoma has a very low rate of successful treatment and afflicts approximately one out of every 100,000 persons in Germany. Prof Jürgen Ruland, Director of the TUM Institute for Clinical Chemistry and Pathobiochemistry, and Principal Investigator at the TUM Central Institute for Translational Cancer Research (TranslaTUM) and the German Cancer Consortium (DKTK), is working together with his team to better understand the molecular mechanisms of these cancers to find ways of treating them more effectively.

PD-1 as the shut-off switch in tumour formation

In their study, currently published in "Nature", the scientists succeeded in a very important step by showing that the defective T cells also have an emergency shut-off switch, referred to as a tumour suppressor. They ascertained that the protein PD-1 can turn off defective T cells at an early stage and thus prevent them from becoming malignant. They discovered this function of PD-1 in a mouse model for T cell non-Hodgkin's lymphoma, and could also explain the mechanism. PD-1 is activated by defects in genes for cell growth, i.e. oncogenes, and then suppresses the effect of these genes using other proteins. Thus it functions as a shut-off switch to prevent the uncontrolled growth of defective T cells.

Tumour analysis helps in deciding the therapies that should be used

The scientists also successfully resolved the question of why many T cell non-Hodgkin's lymphomas are so aggressive, in spite of this protective function. They investigated genetic data sets from 150 patients: "Based on our previous results, we intentionally focused closely on PD-1. In individual groups of >30 % of the patients showed changes in the regions of the genome that interfered with the production of PD-1. This has disastrous consequences in the tumour; PD-1 no longer functions as an 'emergency shut-off'. The diseased T cells can reproduce uncontrollably," explains Tim Wartewig, lead author of the study.

"These patients could be helped by medications that reverse the loss of PD-1 signalling and thereby destroy tumour cells. This type of medication already exists for other forms of cancer – in our opinion, use with T cell non-Hodgkin's lymphoma should also be considered," says Jürgen Ruland. The scientists therefore recommend investigating individual differences in tumours before making decisions about which medication is to be administered.

Original publication
T. Wartewig, Z. Kurgyis, S. Keppler, K. Pechloff, E. Hameister, R. Öllinger, R. Maresch, T. Buch, K. Steiger, C. Winter, R. Rad and J. Ruland, PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis, Nature, November 2017, DOI: 10.1038/nature24649
https://www.nature.com/articles/nature24649

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Pancreatic cancer: specific protein promotes development of pancreatitis and tumours

Pancreatic cancer is one of the most aggressive forms of cancer and is currently very difficult to treat. However, the last few years have seen advances in the scientific understanding of how this cancer develops at a molecular level. For example, as well as certain risk factors, genetic changes also play a role. In a study published in leading journal "Cancer Cell", a team led by laboratory medicine specialist Jelena Todoric from MedUni Vienna's Institute of Laboratory Medicine and molecular biologist Michael Karin from the University of California in San Diego were able to show that disrupted cell autophagy can be a precursor for these genetic changes. This gives rise to an abnormal amount of the protein p62/SQSTM1, which negatively affects pancreatic cells and consequently causes the tissue changes that then progress into pancreatic cancer.

Approximately 1,500 people a year develop pancreatic cancer in Austria, accounting for around 4% of all malignant cancers. Initially, pancreatic cancer is virtually asymptomatic and that is why it is usually only diagnosed when it is well advanced. By this point fewer than 20% of patients are operable.

It is a known phenomenon in medical research that 16% of healthy people and 60% of patients suffering from pancreatitis, that is to say inflammation of the pancreas, exhibit so-called precursor lesions in the pancreas. There is a 1% probability that these might develop into cancer. However, genetic factors also play a role, as do risk factors such as smoking, obesity, diabetes and chronic pancreatitis. However, it was hitherto not understood how all these factors interrelate and what mechanisms lie behind them.

In a study using an animal model and human cell material, the team led by laboratory medicine specialist Jelena Todoric from MedUni Vienna's Institute of Laboratory Medicine and molecular biologist Michael Karin from the University of California in San Diego has now shown that a disruption to cell autophagy is involved in the development of pancreatic cancer. Autophagy is one of those

essential bodily processes whereby cells operate a form of recycling: breaking down and reutilising their own constituents and eliminating bad proteins and cellular waste. When the process is disrupted, for example due to smoking or obesity, this aggravates the existing genetic lesions on the pancreatic cells, the function of which is to produce digestive enzymes. This then results in an extraordinary accumulation of the protein p62/SQSTM1, which is typically elevated in chronic pancreatitis or in the precursor lesions (Pancreatic Intraepithelial Neoplasia PanIN).

The study showed that accumulation of p62/SQSTM1 promotes the development of early precursor lesions, so-called acinar ductal metaplasia. A subsequent cascade of molecular activities then go on to produce pancreatic cancer. In this process, the protein p62 first of all causes the displacement of a second protein known as NRF2 into the nucleus. This in turn stimulates production of the protein MDM2. Elevated MDM2 levels transform acinar cells, which exhibit certain carcinogenic gene mutations, into vigorously proliferating duct cells. This ultimately leads to the growth of the malignant pancreatic tumour, pancreatic ductal adenocarcinoma.

The results of the study suggest that a new therapeutic approach could be to treat autophagy, since most of the known risk factors disrupt this process. The development of targeted MDM2 medications could, in future, prevent the development of malignant pancreatic cancer in people with a high risk of the disease.

Medical University of Vienna

Medical University Vienna (MedUni Vienna) is one of the most traditional medical education and research facilities in Europe. With around 8,000 students, it is currently the largest medical training center in the German-speaking countries. With 5,500 employees, 27 university hospitals and three clinical institutes, 12 medical theory centres and numerous highly specialised laboratories, it is also one of Europe's leading research establishments in the biomedical sector.

Service: Cancer Cell: Stress Activated NRF2-MDM2 Cascade Controls Neoplastic Progression in Pancreas. Todoric J, Antonucci L, Di Caro G, Li N, Wu X, Lytle NK, Dhar D, Banerjee S, Fagman JB, Browne C, Umemura A, Valasek MA, Kessler H, Tarin D, Goggins M, Reya T, Diaz-Meco M, Moscat J, Karin M. Cancer Cell. 2017, in press. http://www.cell.com/cancer-cell/fulltext/S1535-6108(17)30464-6; DOI: http://dx.doi.org/10.1016/j.ccell.2017.10.011

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Postmenopausal breast cancer: sufficient to extend treatment by two years

– from the Medical University of Vienna – ABCSG study: 5+2 years is the optimum length of treatment with aromatase inhibitors

Standard treatment for postmenopausal breast cancer is to give a hormonal (endocrine) breast cancer drug for five years following surgical removal of the tumour. The results of the recent study (ABCSG 16/S.A.L.S.A) conducted by the Austrian Breast & Colorectal Cancer Study Group (ABCSG) now show that two years of follow-on treatment with the aromatase inhibitor anastrozole is sufficient. Further extension of treatment to five years is not helpful, because it does not improve the treatment outcome, but can worsen the side effects.

Anti-hormone therapy suppresses the female sex hormones oestrogen and/or progesterone, since they can stimulate the growth of hormone-receptor-positive tumours and thus lead to relapse (recurrence). Earlier studies suggested that extended endocrine therapy has a positive impact upon disease-free survival but the question of the optimum length of treatment has hitherto remained unanswered. ABCSG 16/S.A.L.S.A has now tested this important clinical question.

Seven or ten years of endocrine therapy?

A total of 3,484 postmenopausal breast cancer patients at more than 70 Austrian centres took part in the investigation between 2004 and 2010 – making it one of the largest clinical studies so far conducted in Austria. The participants had an early hormone-receptor-positive breast cancer (Stage I-III) and, after five years of standard adjuvant anti-hormone therapy (endocrine therapy) they received an additional two or five years of the aromatase inhibitor anastrozole by way of extended endocrine therapy. "We discovered that two years on an aromatase inhibitor following endocrine therapy are sufficient and that prolonging the treatment offers no benefit but increases side effects," says Michael Gnant, coordinating investigator for the study.

Clear results

Anastrozole blockades oestrogen synthesis, thereby preventing recurrence but has a different mode of action and a more favourable toxicity profile than tamoxifen, which has been used for many years. It has now been demonstrated in this and similarly designed international studies that patients do not benefit from extending endocrine therapy to five years but they do suffer more side effects, such as fractures. There is therefore no indication for a total treatment time of 10 years. Studies also show that patient compliance diminishes with longer treatment. "Up until now, we were unable to say whether there is a subgroup of patients that might benefit from extended treatment. We hope that the new molecular testing methods, which we are currently trialling, can bring more clarity in this respect," says Gnant, with an eye to the future.

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