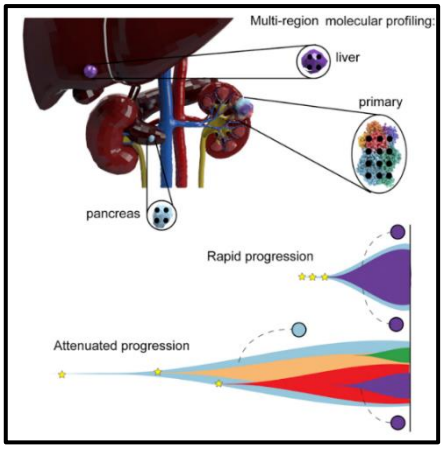
Turajlic lab – Cancer Dynamics Laboratory
TRACERx Renal Research Network 2023 Update

What is translational research?

We are a team of researchers working on renal cell carcinoma (RCC) aiming to improve the understanding of the biology of this often-overlooked cancer. To test this in the laboratory, we require samples from patients with kidney cancer: tissue from surgical resections or biopsies and blood tests. Using anonymised samples, we can explore many components of kidney cancer biology: from the structure of kidney cancer cells under a microscope and how this may predict their behaviour, to the underlying genetics and the involvement of the immune system.

The aim is to understand what factors drive kidney cancer growth, to target them when developing more effective treatments. We are also searching for markers in blood tests to allow us to monitor treatment response more accurately. Ultimately, our goal is to translate the research we do in the laboratory to provide better care to patients with kidney cancer. We are so grateful to all those who have supported and participated in our research to date.

The TRACERx Renal Study



One third of patients who undergo surgery with curative intent will go on to develop metastatic disease. To improve patient outcomes, we need to better understand what factors drive metastatic disease and resistance to treatment. We have shown that within a single kidney tumour, different areas of the tumour may have diverse characteristics meaning different areas of the tumour may respond differently to treatments. This "intra-tumour heterogeneity" shapes how tumours change and grow over time and is involved in how they spread to other parts of the body.

Research is ongoing, but we feel it is important to share some of the work we are currently doing with our patients, whom we hope one day will benefit from our research.

TRACERx Renal projects:

Genomic Analysis – Alice Martin

In our previously published work, we discovered an association between the clinical progression of a tumour (i.e. the rate of growth and risk of metastatic spread), and the genetic events that determine cancer evolution. We described seven distinct evolutionary pathways, each of which with different risk of disease progression following surgery. Since then, we have recruited more than double the number of patients to the TRACERx study and have access to newer, more sensitive research tools. We hope with extra numbers and more detailed analysis we can fill the gaps in current research. We hope to identify rarer, previously uncharaterised evolutionary pathways to enable us to predict the course of kidney cancer more accurately in the clinic.

Bacteria in tumours – Alice Martin

Scientists have recently discovered that tumours can contain bacteria within their cells. These bacteria can influence tumour progression through interactions with the immune system, and antibiotics (which are given to kill bacteria causing infections), may affect the outcome of cancer therapies. We are the first research group to look at the microbiome of kidney tumours in more detail. The aim is to find out more about the bacteria that are specific to kidney cancer, as well as identifying species that might be associated with aggressive disease or treatment resistance.

Newsletter compiled by Charlotte Grieco, Clinical Research Fellow, and reviewed by Rose Woodward, Founder of Action Kidney Cancer.

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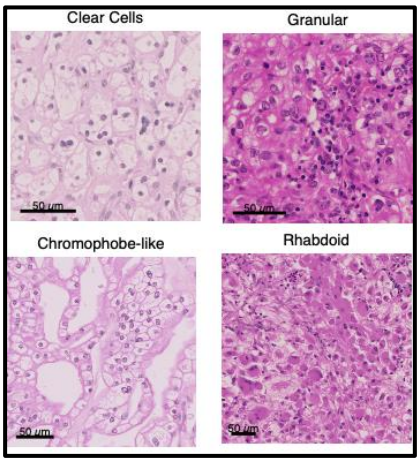
Pre-clinical modelling: organoids – Geoffrey Feng, Daqi Deng, Annika Fendler

We are building a biobank of model organs (organoids) grown in the laboratory to better understand the behaviour of kidney cancer cells. These are being made from normal kidney tissue and clear cell RCC (ccRCC) tissue donated by patients participating in TRACERx. We are manipulating the organoids with genetic engineering tools to identify the genetic changes associated with why ccRCC starts, how it progresses and how it might metastasise. With subsequent in-depth research, we aim to understand the fundamental mechanisms by which these genetic changes contribute to how ccRCC behaves in patients. We will also explore if such genetic changes may result in vulnerabilities in kidney cancer cells that we could target with new treatments for ccRCC patients to achieve better outcomes.

Artificial Intelligence in Cancer Evolution – Charlotte Spencer



Previous TRACERx Renal research has established which genetic events can predict disease progression in clear cell RCC. Testing for these genetic events in the clinical setting is not possible because they rely on DNA sequencing of multiple samples of fresh tumour tissue, which is both impractical and costly. However, multiple regions of tumour tissue are routinely taken for diagnostic pathology workflows. This presents the opportunity to predict important genetic events from routine samples using artificial intelligence. We are working closely with the Artificial Intelligence team at the Francis Crick Institute, as well as collaborating with Owkin (a biotechnology company) to develop a clinically implementable tool to improve the prediction of patient prognosis and treatment response in the clinic.

Radiomics – Matt Orton

We are exploring whether CT and MRI scan images can tell us more about the activity of kidney cancer than simply the size of tumour lesions. We are using artificial intelligence technology to analyse scan images in more detail, looking at the specific shapes and densities within tumour areas. We are then comparing this information to genetic data we have analysed from the tumours, looking for links between genetic changes and how tumours may appear on scans.

Tumour microenvironment – Anne-Laure Cattin

The survival of a tumour depends upon its environment in the body where it must compete with other cells for nutrients and space, as well as trying to evade the body's immune system which tries to kill cancer cells. This results in only the fittest and most aggressive tumour cells surviving to spread around the body.

Currently available drug treatments for metastatic kidney cancer target either the blood vessels to prevent nutrients getting to the tumour or boost the immune system to fight the cancer cells. However, response to drug therapy is variable and we lack tests to understand which patients will respond to specific treatment, which can result in significant side effects. We aim to bridge the gap between understanding the genetic alterations of tumour cells and how they behave within the pressures exerted by the environment they live in.

We are mapping tumour cells and other cell components of the surrounding environment, including blood vessels and immune cells in their three-dimensional context. This will allow better understanding of the behaviour and interactions between tumour cells and their environment, associated with (1) the severity of the disease and (2) the response to treatment, which will be vital in directing future drug therapies to help treat patients with kidney cancer.

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Adjuvant therapy – Zayd Tippu

Some patients who have a primary kidney tumour removed benefit from a year of drug treatment (immunotherapy) following nephrectomy to reduce the risk of their cancer returning. Work is still needed to identify which patients are most likely to benefit from this treatment, whilst also identifying patients who won't need treatment and thus minimising their risk of potential side effects, affecting their quality of life.

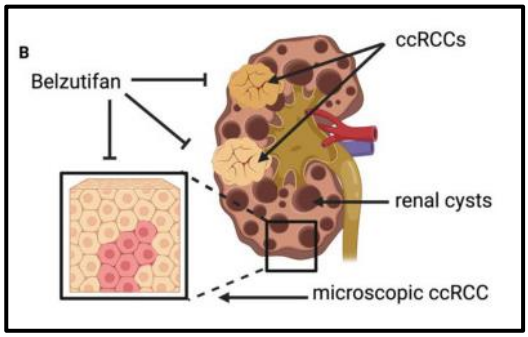
Using the cancer samples obtained through the TRACERx Renal study we are aiming to look at patterns of DNA, RNA and protein expression to determine risk of disease returning, and crucially identify which patients are most likely to benefit from treatment. This we hope will help guide decision making in the clinic.

Representative sequencing – Brian Hanley

Special tests (e.g. for DNA or RNA) are often applied to cancer samples in hospital to predict how tumours will behave and respond to treatment. However, test results vary according to the region of the tumour sampled and are typically limited to a single sample. From previous work we know that different regions of a tumour can be vastly different, so biopsy samples do not accurately reflect the tumour's overall characteristics. To address this, we are developing a novel technology called "Representative Sequencing". This blends solid tumour samples into a well-mixed liquid, which is subsequently sampled for special tests. Sampling of cancers in this way increases the number of mutations identified and reduces the over-interpretation of mutations present in only a single region of the tumour.

Von Hippel-Lindau disease – Scott Shepherd

Kidney cancer that affects multiple generations of a family is called hereditary kidney cancer. Hereditary kidney cancer is rare and accounts for around 1 in 20 patients with kidney cancer with at least 10 different genes implicated in affected families. The most commonly-affected gene – VHL – causes Von Hippel-Lindau (VHL) Disease which causes an inherited predisposition to kidney tumours and cysts as well as tumours affecting the adrenal gland, pancreas, retina, and central nervous system.



Management typically involves lifelong surveillance of tumours with scans and repeated surgical intervention which causes significant physical and psychological ill health over a patient's life. A new drug – belzutifan- has been shown to be effective in management of VHL-related tumours and could revolutionise the way VHL disease is treated and improve outcomes for patients, while also serving as a blueprint for managing other hereditary kidney cancer syndromes.

We are developing a national clinical network and research infrastructure to reach these patients with rare kidney cancer syndromes to i) help provide access to new therapies ii) collect research samples with a view to understanding why treatments work well in some and not well in others iii) establish a clinical trial infrastructure to test new therapies.

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