Curing cancer is a difficult problem. Part of this is because cancer cells are very challenging to distinguish from our own healthy living tissue so it is difficult to create therapies that only target the cancerous cells. In addition, diagnosis of cancer at early stages is still a challenge in many cancer types. Prof Melpomeni Fani at University Hospital Basel, Switzerland may have one answer to this problem in the form of molecular probes – tailor-made chemicals that bind to cancerous cells and can act as ‘antennas’ for diagnostic imaging, while being lethal as endoradotherapy.

Every day, our body produces billions of new cells to replace dead ones. Each time this cell division, or replication, occurs there is a small chance of a mistake being made in the copying process, resulting in a mutation in the genetic code of the cell that regulates its functions. Normally, cells only divide as much as is required for replacement of the dead cells but one possibility during a mutation is that this regulatory function becomes switched off. When this happens, the cells then start to divide relentlessly, resulting in cancers.

While cancer treatments and diagnostic techniques are constantly advancing, with continual improvement in survival rates, there are still many cancers that are untreatable and we are still a long way away from a universal ‘cure’. Many treatments, although effective, such as chemotherapy and radiation therapy, come with debilitating side effects as well. As cancer cells are very hard to distinguish from our own healthy cells, many cancer treatments end up damaging healthy tissue alongside the cancerous cells. Chemotherapy, in particular, can be debilitating for patients’ immune systems, leading to additional health risks from infections and common illness during the treatment processes.

The benefits of targeted cancer treatments, that only affect cancerous cells, are obvious: fewer side-effects due to less collateral healthy cell damage, better prognosis and the possibility of treating more types of cancer. This is therefore, can be used for targeting the cancerous cells. The other advantage of designing tags for such proteins is that their chemical structure has the potential to bind specific types of molecular probes very strongly, which is essential for the probe to remain in place long enough for diagnosis and, more importantly, for treatment.

Chemical Beacons
A molecular probe is a chemical that can be attached to a target to study its properties. This technique is already commonly used in molecular biology labs for labelling and imaging cells under microscopes. The reason this technique is so useful is that the molecular probe can be designed in such a way that, when it binds to the target molecule, it strongly emits light, acting as a beacon for the researcher to pinpoint the target cells of interest. Different types of probes can also be designed to only react with specific types of cell or to emit light of different colours making the identification processes much easier.

Prof Fani is interested in designing such probes specifically for targeting cancerous cells inside the human body that can be used for both imaging and therapy purposes. Her work is in a highly interdisciplinary area of research, that draws upon aspects of chemistry, biology, pharmacology and medicine. Chemists need to be able to design and synthesise the probe molecules but a good understanding of the cancerous cell structure and biology is required to know which chemical entities will recognise and attach to the correct cell. It is also essential that these probes are safe for use in humans, with no toxic effects.

Finding a unique chemical signature that differentiates cancer cells from healthy ones so the molecular probes target the correct cells is a tricky problem. Prof Fani has been focusing on the compelling area of utilizing G-protein coupled receptors for this purpose. These proteins are produced in very large quantities in the surface of many human tumours and therefore, can be used for targeting the cancerous cells.

Radiopharmaceuticals
While imaging cells tagged with molecular probes under a microscope is fairly straightforward, imaging tumours in humans is a little more complicated. Common imaging techniques for cancer diagnosis include CT and MRI scans but it can be difficult to get a good contrast between the tumour and surrounding tissue for a clear, unambiguous diagnosis, while sensitivity at a cellular level can not be reached.

The benefits of targeted cancer treatments, that only affect cancerous cells, are obvious.
A number of radioactive metals are interesting for medical applications. While γ-rays or positron (β⁺) emissions are used for diagnosis, α- or β⁻ particles are used for therapy. By simply swapping one radiometal for another within a chelating unit of the same molecular probe (here X-Y-Z), diagnosis or therapy can alternatively be performed for specific cancer cells. These so-called theranostic probes are designed, produced and tested in Prof Fani’s lab, from the level of the single cancer cell (in vitro) to the level of imaged cancer in animal models (in vivo). The radioactive probes with the highest potential for improving patient care are brought into clinical trials (clinical translation).

One very sensitive and precise approach to succeed this is to use molecular probes that are radioactive for targeting specific tumour cells. The radiopharmaceutical is trapped in the area of interest and the emitted radiation can be used either for imaging or for the destruction of tumours, depending on the type of radioactive emission. Prof Fani is a specialist in the area of radiopharmaceuticals utilizing radiometals that are ideal for such purposes. She has developed techniques to incorporate these species into existing and newly developed molecular probes to establish precise radiopharmaceuticals that combine both aspects, diagnosis and therapy in what is known as a theranostic probe.

**DIAGNOSIS AND THERAPY**

Theranostics is a relatively new and developing area of medicine that combines a targeted therapy with a diagnostic test as part of offering treatments that are tailored to the patient’s specific tumour progression and needs, while also allowing therapy follow up. Prof Fani’s molecular probes are an example of theranostic probes as they utilize a combination of peptide structures and radiometals to achieve all-in-one diagnosis and treatment. Several of these probes have entered in early phase clinical trials and have already shown to be effective at detecting even small areas of abnormal cell growth that are invisible with other diagnostic tests or endoradiotherapy in metastatic diseases.

Prof Fani is further extending the versatility of these probes by taking advantage of hybrid imaging. This means that the probes can be used for imaging with a variety of diagnostic techniques such as CT or MRIs, in addition to the detection of the emitted radiation. In turn, this makes them well-suited to diagnosis of a variety of cancers by combining anatomical and functional information of the disease in one scan. Being able to swap the radiometals in the probes also means it is possible to finely switch between diagnosis and therapy using the same molecular probe and also adapt dosages to tumour size and stage. In addition to this, being able to deliver treatment exactly at the site of the cancer also means that overall dosage levels in the body can be reduced.

The adaptability of Prof Fani’s molecular probes and research is not just limited to cancer treatments, but can also find applications in neurological diseases, endocrinology, cardiology and other medical fields. The peptide structures Prof Fani uses are highly adaptable so it is possible to create many different variants as part of a more personalised and effective approach to medical care.

**References**

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**Personal Response**

What particular applications of this work are you most excited about? Radiopharmaceuticals are injected in tracer amounts, far beyond the amount of other pharmaceuticals are administered. This is only possible because radioactivity is a particularly sensitive “antenna” with excellent tissue penetration in the body. Even the least amount can be ‘seen’ and measured, making radiopharmaceuticals exceptionally sensitive tools in the hands of the physicians. They can be tracked and followed inside the body on real-time and monitor physiological or pathological processes on a cellular and molecular level.

Due to their ultra-high sensitivity, they can identify abnormalities at a very early stage of a disease. This allows early treatment and consequently, it may improve the prognosis of the patient. Even though the administration of radiopharmaceuticals may sound worrying, these procedures are among the safest diagnostic imaging exams available. It is a safe, painless, non-invasive way of gathering key information about the disease that allows the choice of the right treatment for the right patient.

Targeted radiopharmaceuticals provide very effective systemic treatment options for metastatic or unresectable cancer due to the specific delivery of lethal radioactive doses to the cancer cells, independent on their location in the body.

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Bio
Prof Fani studied Chemistry and she continued her education in Biochemistry (MSc) and Radiopharmacy (PhD) at the University of Athens, Greece. Since April 2018, she has been a clinical professor at the Medical Faculty of the University of Basel. Prof Fani is also the head of research and Division co-head of Radiopharmaceutical Chemistry at University Hospital Basel.

**Research Objectives**

Prof Fani’s research focuses on the development of radioactive peptides and other biomolecules as precision radio-theranostics for diseases for which there is a medical need, often due to the lack of alternatives.

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