Why did you decide to devote your career to anticancer research, specifically developing chemotherapeutic approaches?

I work in organic chemistry as part of the Programmed Molecular Systems group at the University of Poitiers in France. A few years ago, we attempted a new molecular programming concept. We wanted to develop molecules with a chemical programme built into their structures that pilots their behaviour in different environments. To illustrate this concept, we decided to apply these ‘smart’ molecules to cancer chemotherapy. Selectivity in chemotherapy is a big problem, and we thought we could solve it with molecular programming by developing a smart drug delivery system.

What are these smart molecular systems, and how are you designing them for the selective delivery of anticancer drugs?

We define smart molecules as molecules composed of distinct units that collaborate in order to act in an autonomous manner. Smart drug delivery systems are defined as molecular systems that transport anticancer drugs in the body, in an iniquitous manner. Such a system should recognise malignant specificities located at the surface of cancer cells or in the tumour microenvironment. Finally, it should allow the controlled release of the drug exclusively at the tumour site.

How have you programmed the delivery system to allow the safe transport of potent anticancer agents?

Most clinically used anticancer drugs are toxic once inside cells, and therefore have the ability to penetrate the cell membrane. However, such compounds can often enter the membrane of healthy cells, causing undesirable toxicity. Thus, we have constructed highly hydrophilic molecular systems that include an anticancer drug, but cannot penetrate cells. As a result, toxicity in normal cells is considerably reduced.

You were recently awarded the Pierre Fabre Award for Therapeutic Innovation. Can you briefly discuss the award, highlighting how this will help your efforts to further cancer therapeutics?

This prize was awarded for the first time last year, dedicated to the memory of Pierre Fabre and in partnership with the French Medicinal Chemistry Society, in recognition of innovative technology which has contributed to the field of therapeutics.

I was honoured for my contribution to the field of cancer, particularly for my work on drug delivery systems. Our drug improves target specificity in the tumour microenvironment. In fact, tests in mice have shown successful selective treatment of pancreatic, breast, head and neck tumours, and this versatile approach was valued by the Pierre Fabre Company.

Being awarded this prize was important for my research, and provided my group with better visibility. As a result, I have received numerous emails from companies hoping to discuss the results and further develop the system.

Finally, can you highlight your greatest achievement to date?

I consider my greatest achievement to be the last compound we designed and evaluated, which is able to treat tumours in mice. This compound is highly efficient for the treatment of pancreatic tumours, especially those that are large and implanted, and there is as yet no equivalent.

What sets your group apart from others working to improve cancer chemotherapy?

Our main innovation is the way we trigger the release of the anticancer drug. There are two main methods of delivering an anticancer agent once the compound has reached the tumour site. The first technique involves releasing the drug through chemical activation, which is generally not very selective. The other, more recently developed method, is to activate the compound enzymatically. However, most enzymes explored in this context have been peptidases, which are not always very efficient. We have achieved specificity in our triggering system, as our drug delivery system is activated by galactosidase and glucuronidase. These two enzymes are extremely selective, and enable the drug to be delivered either to the tumour site or inside the tumour cell itself.

The Pierre Fabre Award for Therapeutic Innovation

www.internationalinnovation.com
MOST DRUGS USED in chemotherapy are not fully effective against cancer. This is evidenced by the fact that, despite major advances in prevention and detection, cancer remains a leading cause of death worldwide. The reason for this is poor selectivity; most anticancer agents act by generally inhibiting cellular proliferation, without any antitumour selectivity. This means normal, healthy tissues are destroyed alongside cancerous ones, causing severe side effects. In turn, doses administered must be limited, and are usually not sufficient to kill the tumour. As non-selective administration can also breed tumour cell resistance, it is clear that more selective chemotherapeutic approaches are needed. Working towards this important goal is Professor Sébastien Papot. With his team at the Institute of Chemistry of Poitiers: Materials and Natural Resources (IC2MP), Papot is designing smart molecular systems that could change the face of cancer chemotherapy.

ANTIBODY-BASED APPROACHES Over the years, many approaches have been explored to improve the efficacy of anticancer agents. Perhaps the most promising are drug carriers, which can deliver therapeutics when inside tumour cells and thus avoid the dose-limiting effects of traditional chemotherapy. Within this, the best studied approach is antibody-drug conjugates (ADCs), which work by targeting tumour-associated antigens. However, there are holes in this concept, and the downsides of using antibodies to deliver drugs are rapidly becoming clear. Because they are large, antibodies often struggle to penetrate tumours fully. They can elicit an undesirable immune response, and the time they remain in the body can lead to unselective drug release. Practically speaking, their production is costly and time-consuming. So, while the initial results have been encouraging, ADCs are clearly not the panacea. Smaller (low molecular weight) drug delivery systems may be the necessary alternative.

CONTROLLED RELEASE Papot’s team has been following these developments closely, and recently devised two new methods of drug delivery based on them. The first delivers an anticancer agent directly to the cell. The central premise of this ‘Trojan horse’ approach is a drug in an inactive (pro) form, which is delivered to the tumour cell by a ligand with tumour-affinity, and later activated by an enzyme inside the tumour cell. This compound is composed of a galactoside trigger, a tumour-targeting ligand, and a potent anticancer drug, all built around a linker that breaks apart on activation. The system is programmed to be selectively activated by an enzyme called β-galactosidase, present in the lysosome of cancer cells. However, because β-galactosidase is also present in healthy cells, the ligand is critical in avoiding drug release in healthy tissues. To prove the concept, Papot developed a system that can be activated only in tumour cells expressing the folate receptor (FR), which is overexpressed in many cancer types but largely undetectable in normal tissues. The team designed the system such that β-galactosidase would catalyse the release of monomethyl auristatin E (MMAE), a potent inhibitor of cell division.

The in vivo efficacy of the galactoside prodrug was assessed in mice. Not only was it well tolerated, it also induced marked antitumour activity. At the end of the 31 day study, all the mice in the group treated with the prodrug were still alive, while over half of those treated with free MMAE died. The results, published in the international edition of Angewandte Chemie as a ‘Very Important Paper’ (VIP), make the system a strong candidate for the selective treatment of FR-expressing tumours. Excitingly, this approach could be generalisable to other tumours based on the receptors they express.

ENVIRONMENTAL FEATURES While still targeting the tumour, Papot’s second drug delivery method also targets the environment in which the tumour exists. The tumour microenvironment possesses characteristic properties that are not found in healthy tissues. Targeting these features can lead to the selective delivery of drugs.

The tumour vasculature is particularly unique, characterised by twisting, irregularly shaped and leaky blood vessels. Together with the lack of lymphatic drainage, it enables the accumulation and retention of macromolecular drugs, which are too large to pass through the blood vessel walls of healthy tissues. Exploiting this enhanced permeability, Professor Felix Kratz – who works in the Tumor Biology Clinic at the University of Freiburg – and his colleagues developed prodrugs that bind albumin (a protein found in blood) to researchers at the University of Poitiers, France, have developed smart molecular systems that selectively deliver anticancer drugs. As the systems are programmable, they can be adapted to target many different types of disease.
MOLECULAR SYSTEMS PROGRAMMED FOR SELECTIVE DELIVERY OF ANTICANCER DRUGS

OBJECTIVES

• To use molecular programming to enhance the selectivity of anticancer drugs
• To develop effective drug delivery systems targeted to the tumour cell surface or microenvironment

KEY COLLABORATORS

Professor Jean Guillon, University of Bordeaux, France
Dr Alain Le Pape, National Center for Scientific Research (CNRS) Orléans, France

FUNDING

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La Ligue contre le cancer

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INTELLIGENCE

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PROFESSOR SÉBASTIEN PAPOT works at the University of Poitiers within the Organic Synthesis Group of the Institute of Chemistry of Poitiers. Materials and Natural Resources (IC2MP). He currently heads the Programmed Molecular Systems team and has previously held postdoctoral positions at the University of Cork, Ireland, and the University of Orléans, France.

POWER OF THREE

The smart molecular systems allow:

1) Safe transport of potent anticancer agents
2) Efficient recognition of malignancies via the surface of cancer cells or the tumour microenvironment
3) Controlled release of the anticancer drug exclusively at the tumour site

create a drug carrier. These macromolecules only accumulate in malignant tissues, and – because of the prolonged half-life of albumin, they have an excellent pharmacokinetic profile.

Building on Kratz’s framework, the team led by Papot was the first to develop a β-glucuronidase-responsive albumin-binding prodrug. Similar to the first compound, it contains a glucuronide trigger (the substrate of β-glucuronidase), doxorubicin (an anticancer drug) and a labile linker. After it is administered intravenously, the prodrug binds albumin in the blood to produce the macromolecular drug carrier. Once the carrier has entered the tumour tissues, β-glucuronidase (an enzyme expressed in the tumour microenvironment) catalyses cleavage of the glycosidic linker, triggering the release of doxorubicin. “The compound does not penetrate the cells, but is activated to release the anticancer agent when it reaches the tumour microenvironment,” Papot explains. This allows it to reach multiple tumour cell types.

The prodrug was recently assessed in a mouse model of lung cancer, alongside a well-characterised doxorubicin prodrug that cannot bind albumin. While the latter was poorly active, the prodrug produced by Papot showed a good antitumour response, comparable even to doxorubicin – which has been used clinically for over 40 years. Free doxorubicin used at its maximum tolerated dose induced significant weight loss, while the prodrug was well tolerated. Based on these promising results, the team extended the concept to deliver MMAE, which they had used previously to good effect. Striking evaluations in mouse pancreatic cancer models led to the total and lasting removal of the tumours, while treatment with MMAE alone only minimally inhibited tumour growth.

INNOVATIVE MOLECULAR SYSTEMS

In both approaches, the group has delivered highly selective activation. Tests on various tumour models in mice have shown striking anticancer activities, without the side effects that come with free drugs. Astoundingly, the team’s second approach is more effective than an anticancer drug that has been used for decades. Thus, the ‘smart’ prodrugs developed by Papot’s group represent a valuable tool for selective chemotherapy – a sorely needed development. As they are easily modifiable, the potential is almost unlimited. The versatility of the system means it can be developed to target specific cancers. In the future, Papot hopes to design drug delivery systems ‘on demand’ by altering the anticancer drug, the target unit and the enzymatic trigger.

Not limited to his success so far, Papot’s next step is to develop another tumour targeting method – combining the power of the two he has already devised. “We had the idea to develop selective cancer polychemotherapy, a combination of the drug delivery system that can recognise specificities of tumours located at the surface of cancer cells and in the tumour environment. We believe with this kind of approach we will be able to achieve a synergetic effect, and to use different types of anticancer drugs,” he concludes.