In what ways have your interests led to your current work at the US National Cancer Institute?

I was a radiologist before I gained my PhD. Radiologists are involved in both diagnosis and therapy, so I already knew about radiation therapy when I became a medical researcher. My current goal is to integrate physics and chemistry with medicine to achieve better diagnosis and therapy. As an example, in near-infrared photoimmunotherapy (NIR-PIT) we select the chemistry, target medical therapy to the antibody and then excite the photosensitiser with light.

How effective are molecular-targeted therapies in treating cancer?

Molecular-targeted drugs are specific to one type of cancer and address a complicated machinery – but we want to fix just the part that is cracked or damaged. The body is very complex and flexible, so even when there is a malfunction, this doesn’t stop the whole machine. Although the malfunction may become a type of cancer, the cell is still functional. It is very hard to fix a malfunction with a single-molecule drug.

The cell is extremely complex; the cell membrane is strong, so not much of the drug extends across the membrane to reach the target, and in addition the target is not very specific – even though the drug might be specific for the molecule, it is not specific for the cell. This means that there are many different side effects when we use molecular-targeted drugs.

Can you explain the potential uses of near-infrared fluorescent dyes phthalocyanine (IR700) in medicine?

These chemicals are called photosensitisers and are used for phototherapy, or photodynamic therapy (PDT). They are designed to be hydrophobic so that they can cross the cell membrane and enter the cell. When light is shone on them, this induces phototoxicity that kills the cell.

IR700 is a dye molecule that is minimally toxic when injected into the body or a cell. More than 99 per cent is excreted in urine within a day. It does not induce phototoxicity, unlike other PDT photosensitisers. Because it is designed to be very hydrophilic, it cannot cross the cell membrane and work inside the cell unaided. Once conjugated with cell binding vehicles such as antibodies and peptides, however, IR700 can induce strong phototoxicity to cancer cells.

Has the enhanced permeability and retention (EPR) effect been useful in nanoparticle cancer treatment?

Almost 100 per cent of the nanoparticles for cancer therapy rely on the EPR effect, which undermines the tumour vascular structure and allows nanoparticles to move into and accumulate within tumours more easily than in normal organs or tissues. Even under very good experimental conditions, however, the maximum effect obtained is no more than double.

Does NIR-PIT affect the EPR effect?

NIR-PIT can select specific cancer cells, cell by cell, in tissue. Using near-infrared light, we can target their cell surface molecules, and kill them without damaging any normal cells. This selectivity is unequalled by any other current cancer therapies.

We call the EPR effect the super (SUPR) effect when it is induced by NIR-PIT. NIR-PIT delivers up to 24 times more nano-agent accumulation than normal EPR. When you compare the accumulation in tumorous versus normal tissue, it can be huge: almost 50 times more. So we could minimise drug doses to achieve dramatically safer nano-cancer treatment.

What remains to be done for NIR-PIT to enter clinical trials?

We licensed our NIR-PIT technology with Aspyrian Therapeutics and helped them to raise US $8 million for the trial. They designed our first Phase I human trial, targeting head and neck cancer using cetuximab-IR700, which is due to start soon. This first trial does not include nanodelivery. However, we are planning to include nanodrugs in second and third trials with pancreatic, colonic and ovarian cancers.

Do you have any plans that you would like to highlight?

We are working on a way to improve our new cancer diagnostic and therapeutic approaches. And as NIR-PIT can selectively treat cancer cells, we are trying to apply this technique to personalised immunotherapy; that is, inducing host immunity against crashed patient cancer cells with NIR-PIT. Going forwards, I am also hoping to research new technology for cancer theranostics.
New light on cancer

Developed by the Laboratory of Theranostics at the US National Cancer Institute, one of the first non-toxic technologies for destroying cancer cells and tissues is poised to enter a clinical trial.

WHILE CANCER TREATMENTS have greatly improved over the last few decades, the disease persists as one of the leading causes of premature death worldwide. Though many patients with cancer now go on to live long after treatment, current approaches have undesirable physical or psychological side effects. Some, such as nausea after chemotherapy, are short-lived; others, such as breast removal or infertility, may be life-changing. But the greatest burden is often emotional: patients are faced with the knowledge that cancer has struck once, and may strike again at any time.

Dr Hisataka Kobayashi, Chief Scientist in the Molecular Imaging Program at the US National Cancer Institute, heads the Laboratory of Molecular Theranostics, which specialises in developing advanced imaging techniques. His particular research interest centres on novel molecular imaging and therapeutic agents and technologies for targeting cancers.

PRECISELY PINPOINTING PATHOLOGY
Better sensitivity and specificity are required if imaging techniques are to reliably detect and monitor cancer. However, because of the limitations in imaging technology, the therapeutic techniques currently available – surgery, chemotherapy, drugs, photodynamic therapy and radiotherapy – generally cannot be applied with sufficient precision to target only tumour cells and tissues while leaving the healthy ones unscathed: “The problem is that imaging is not sufficiently specific or selective, so we still make mistakes when diagnosing and detecting a pathologic region of the human body,” Kobayashi states.

Yet better quality imaging in and of itself is insufficient justification for the substantial economic investment required for the development of tools. Kobayashi has therefore worked on developing more sophisticated imaging technology and tools that not only better detect cancerous cells and tissues, but that can also be used to kill cancer selectively, ultimately excising the disease completely: “Current therapies all cause damage to some extent. Surgery removes more normal than cancerous cells, while radiation and chemotherapy damage normal as well as cancer cells,” he observes.

Because imaging does not cure patients, the challenge for Kobayashi was to develop a highly specific and selective imaging technique that would also lend itself to delivering therapy more precisely. After a series of investigations over the last few years, he has succeeded in developing a technology, using near-infrared light, to produce highly targeted cancer cell death: near-infrared photoonmunotherapy [NIR-PIT].

HIGHLIGHTING CANCER
In some cancers, such as lung and breast cancer, epidermal growth factor...
receptors (EGFRs) are overexpressed on cellular membranes. Kobayashi’s NIR-PIT method therefore employs light to detect a photosensitiser that is conjugated with established monoclonal antibodies (mAbs) for cancer treatment that targets the EGFRs on the surfaces of tumour cells.

The photosensitiser is a highly stable, water-soluble organic near-infrared fluorescent dye, phthalocyanine (Ir700), which can be used to label biomolecules. It is hydrophilic so it cannot penetrate cell membranes and its absorption of near-infrared light is high, so that under irradiation it induces strong cytotoxicity on contact with cell membranes. Thus, when anti-EGFR mAbs conjugated with Ir700 bind with the EGFRs on the tumour cell membrane, NIR-PIT targets that cancer cell specifically, by exciting the Ir700 with near-infrared light and activating its cytotoxicity. Though the details of these mechanisms are yet unclear, Kobayashi attributes its success primarily to the strong binding between the mAb/Ir700 conjugate and the cell membrane, and to a lesser extent on mAb internalisation and the generation of reactive oxygen species.

A FLEXIBLE THERANOSTIC PLATFORM

The ability to covalently conjugate any number of different antibodies to Ir700 means that NIR-PIT with mAb/Ir700 represents a highly flexible theranostic platform. Yet the platform has a number of other desirable features, too. One is that a substantially lower dosage can be administered in initial explorations for cancerous lesions, minimising the unnecessary exposure of adjacent tissues to potential harm. In addition, when mAb-Ir700 conjugates are not bound to the cell membrane, no phototoxicity occurs on NIR-PIT administration.

There are also other significant benefits. First, the near-infrared light excitation wavelength allows a penetration of at least several centimetres into tissues, enabling delivery even to relatively inaccessible tumours. Second, after NIR-PIT therapy, the fluorescent marking of the treated tumours decreases and eventually disappears, providing a means of non-invasively monitoring the effectiveness of treatment. Third, NIR-PIT has the potential to treat not only solid tumours but also those circulating in the blood. Finally, as Ir700 is quickly excreted and there is no risk of it accumulating in the body, and as near-infrared irradiation bears minimal risk of toxicity, repeated treatments would be feasible if there was a need for long-term cancer treatment.

To date, Kobayashi has tested NIR-PIT using mAb/Ir700 on mice with rapid and dramatic effects, even after a single dose, and now the technology is entering its first human trial.

NIR-PIT, NANOAGENTS AND THE SUPR EFFECT

Nanotreatments rely on the enhanced permeability and retention (EPR) effect, which augments the effects of drugs by enabling their accumulation in tumour vascular tissues. However, the scale of enhancement of accumulation is usually slight and the EPR effect does not change the fact that current nanoscale treatments are not strong enough to cure cancer completely. Kobayashi has, however, found that the application of NIR-PIT to nanodrugs enhances their accumulation massively, an effect he calls the super (SUPR) effect: “With NIR-PIT, the SUPR effect delivers 24 times more drug accumulation than the conventional non-NIR-PIT EPR effect,” he enthuses. This huge augmentation, constituting a 50-fold increase in drug effectiveness, provides opportunities for redefining the way nanodrug dosages are devised and delivered.

Kobayashi anticipates that the NIR-PIT/mAb/Ir700 technology currently under evaluation will need refining. Yet he is planning to extend it to other contexts, such as creating cancer immunity and suppressing the re-emergence of this disease. “Through combining surgery with NIR-PIT and nanodrugs, we could deliver nanoagents much more efficiently to residual cancers to suppress recurrence,” he points out.

Of course, nanotreatment formulation is complicated to get right structurally and practically, especially in terms of engineering combinations of nanomaterials capable of both molecular targeting and of carrying drugs. Looking ahead, Kobayashi has his work cut out for him as nanotreatments require extensive verification that they are effective and do not induce toxicity at either the component or holistic level. However, he remains resolute in the face of these challenges, and is currently planning to include nanodrug delivery in future NIR-PIT clinical trials.

Kobayashi has developed a technology, using near-infrared light, to produce highly targeted cancer cell death: near-infrared photoimmunotherapy.