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NUMBER ONE

Bart Somers has beat mayors from much larger cities to take the World Mayor Prize, based on Mechelen's handling of the refugee crisis

\ 4

PEOPLE POWER

A Brussels-based start-up has designed an interactive programme that lets citizens talk to local politicians – and they're listening

\ 7

THE PARTY LINE

It's Carnival time across Flanders, with a huge number of cities and towns dressing up and dancing through the streets

\ 15

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Think small

Nanoparticles offer fresh ammunition in battle against cancer

Senne Starckx
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Cancer research stands on the brink of a new revolution in Flanders, with novel diagnostic tools and nanoscale particles that battle tumours right at the source.

Cancer diagnostics and treatments have evolved significantly over the past two decades. But the way most patients are treated still follows the traditional model of "the big three": radiation, chemotherapy and surgery.

Each of these treatments has its own advantages and disadvantages. With surgery, for example, normal, healthy tissue is left alone, while with chemotherapy and radiotherapy, many healthy cells suffer as much as the targeted cancer cells.

One way to diminish side effects – which can sometimes be even more dreaded than the tumour itself – is to lower the dose of the cancer drugs or the radioactive substance. This is only possible if the chemicals are delivered more precisely to the malignant cells, sparing the normal tissue.

A promising method of doing this is the use of nanomedicines. These are toxic substances (in chemotherapy) or biomarkers (in radiotherapy) that are attached to nanoparticles, which put them where they need to be: in the tumour's bloodstream. Nanoparticles can be used to "lock up" therapeutic molecules until the cancer cells are reached.

About 10 nanocancer medicines are already in use today in hospitals around the world, but, in terms of the precise delivery of the toxic load, the main challenges remain.

"What is generally clear at the moment is that current nanomedicines aren't succeeding in delivering the substances into diseased tissues," says professor Stefaan De Smedt, who investigates the design, evaluation and fundamental understanding of "nanocages" for the delivery of biological drugs at Ghent University.

De Smedt was one of the speakers at the Nano World Cancer Day conference, held in Brussels earlier this month and organised by the European Technology Platform on Nanotechnology (ETPN). The platform aims to highlight the incorporation of "engineering on the smallest level" into the fight against cancer, a disease that kills more than eight million people a year.

Belgium has an elaborate network of researchers working on nanomedicines, a few of whom are working on nano cancer drugs specifically. The ETPN lists 58 hospitals, research groups and companies in Belgium.

But for De Smedt, the number of academic groups working on nanocarriers for cancer therapy is still limited. "It's true that there's growing interest from industrial players,

continued on page 5

Think small

A elaborate network of researchers is working on nanomedicines to tackle cancer

continued from page 1

as they start to recognise the strategic role nanotechnology plays in advanced products for the diagnosis and treatment of diseases in the future," he says.

But compared to existing drugs, "nanomedicines are very complex structures," he continues. "We will need skills and procedures to produce highly qualitative and safe nanomedicines, which will impose new challenges for the pharmaceutical industry as well."

It's clear that the nanomedicine revolution has to start with the "nano" part. And so a large part of the innovation can come from research that's not necessarily connected to cancer, or even to medicine.

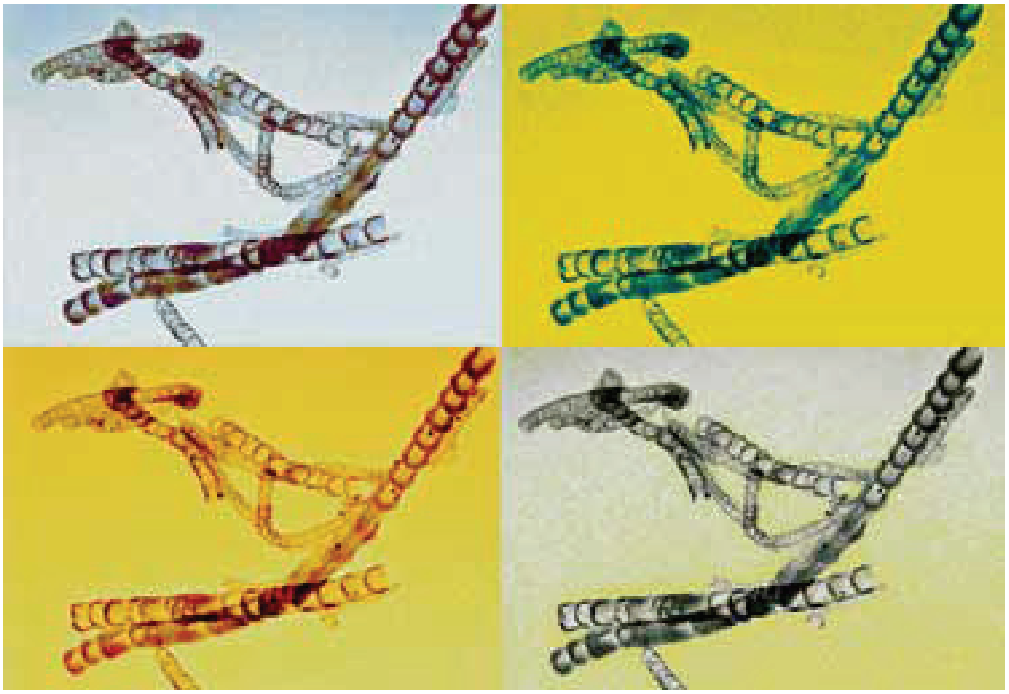
Another speaker at the ETPN conference was Franky Van Herreweghe, who works with nanoparticles as sensors in diagnostics tools at Phoreon, based in Leuven. The company aims to develop a miniature sensor for clinical diagnostics, based on a rapid but reliable identification of molecules.

The miniaturisation process has brought Van Herreweghe and his colleagues into the realm of the nano world. Their technology is based on "nanogold rods" – golden cylinders that measure 15 by 45 millionths of a millimetre – which they use as a sensor.

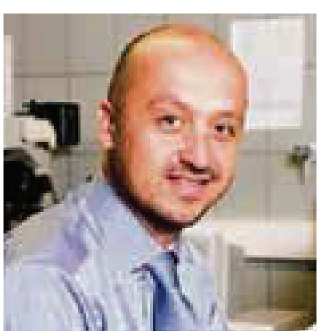
"This requires us to make gold of an exact – and incredibly small – size and shape, and to put different sorts of molecules on top of it." Phoreon's unique nanogold expertise is catching the eye of more and more scientists who are investigating the potential use of gold in next-generation cancer therapies.

Van Herreweghe: "That's why we've decided to commercialise some of our gold nanorod products for academic cancer research." The idea that one of the most desirable materials in the world could play a major role in cancer treatment seems a little bizarre, but if you look closer at the properties of this noble metal, everything becomes clear.

"First of all, golden nanoparticles are extremely small," says Van Herreweghe. "They're small enough to pass through the blood supply system of a tumour. Secondly, the nanogold can be coated with molecules that recognise cancer cells. Those help to ensure that the nanogold will only stick to or enter cancer cells, leaving healthy cells untouched."



Nitrogen-doped carbon nanotubes, to which 10-nanometre spherical gold particles have been linked. The nanotubes can be detected in the body by using X-rays and heat produced by lasers. This may allow more accurate intervention in cancers that are inaccessible to current surgical techniques



Professor Stefaan De Smedt investigates "nanocages" for the delivery of biological drugs at Ghent University

Finally, nanogold inside the body also reacts to light or X-rays, "which has interesting diagnostic – and even tracking – possibilities".

So what will a future cancer treatment based on nanogold look like? Van Herreweghe: "When it's loaded with chemotherapeutic molecules, nanogold becomes lethal to cancer cells, just like a precision bombardment."

The key challenge here for companies like Phoreon is to coat the nanogold in such a way that the therapeutic molecules still work when they are put on to it. "But in principle, the nanogold can be coated with all molecules imaginable," says Van Herreweghe.

Two categories are important, he explains: the cancer drugs themselves and antibodies. In many cases, the nanogold is coated with both types of molecules. Antibodies recognise specific structures on the surface of tumour cells – known as biomarkers – to allow exclusive targeting to tumour cells.

"The antibodies on the surface of the nanogold act as a key that fits in the lock of the biomarker," he says. "Once the key-lock connection is made, the nanogold will not come off easily anymore. This intimate contact between the nanogold and cancer cells allows the hitch-hiking cancer drug to exert its tumour-killing effect."

Nanogold also has the potential to infiltrate the other two treatments of "the big three". A surgeon could light up the golden nanoparticles with a CT scan, which helps localise and visualise the tumour. Or a radiologist could use infrared laser light to heat the nanogold locally so the tumour cells are literally burned away.

But, as Van Herreweghe emphasises, all these cancer therapies are preclinical – read: experimental, and still far from being introduced.

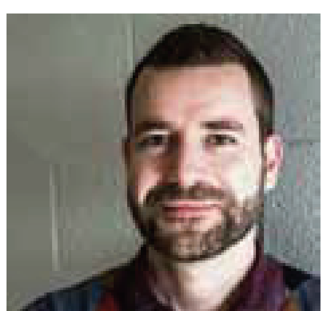
If one evolution has contributed significantly in recent decades to a decrease in the number of cancer deaths and to better survival rates, it's early diagnosis. And it seems that the nanoworld can also provide a new weapon in this area.

Professor Inge Mertens investigates extracellular vesicles, or EVs, which are secreted by both healthy and malignant cells. These nano-size blisters end up in our bodily fluids, carrying a tiny part of the molecular content of their mother cell.

The ultimate goal of Mertens and her colleagues at the Flemish Institute of Technology (Vito) and Antwerp University (UAntwerp) is to create an extremely powerful tool to diagnose and identify tumours, based on the molecular content of the EVs.

> "Nanogold will only stick to or enter cancer cells, leaving healthy cells untouched

"It's important to realise that these EVs are actually responsible for what makes cancer so deadly, namely the metastasis process," says Mertens. "They abuse the normal method of communication between cells and encourage growth, progression and even drug resistance of the tumour." But there's also a positive aspect about EVs: They betray the presence of the enemy within.



Franky Van Herreweghe develops nanogold rods to carry toxins directly to cancer cells

Mertens sees two main challenges in her work. "First, we need to learn how we can isolate an EV from other complex body fluids, like blood. And second, we have to identify the molecules that can be used as specific and sensitive biomarkers for certain types of cancer."

In the meantime, a research network has been developed to tackle these two challenges. Mertens works at the Centre for Proteomics, run by Vito/UAntwerp, which focuses on the protein content of the EVs. Other private partners are looking at the lipid and nucleic acid content, while the Antwerp University Hospital is collecting blood samples to see if valuable EV fractions can indeed be derived from blood.

If Mertens and her colleagues succeed in identifying the right biomarkers for specific cancer types, a next step is designing a test that can be used for preventive screening campaigns.

"The current tests, like the one used to detect colorectal cancer in stool samples, have major flaws, such as false positives. If we could replace these tests with a routine blood test that can be incorporated in a yearly check-up at the GP, this would be an enormous step forward."