Policy Health & Education Cancer

'Liquid radiation' promises new gen cancer treatment

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It's described as "liquid radiation" and it promises to be a new pillar in the treatment of cancer. And among the groups around the world working on this technology, Australia is a leader.

Professor Michael Hofman, a nuclear physician-scientist at the Peter McCallum Cancer Centre in Melbourne, is a pioneer of this highly technical nuclear therapy.

"It's not very often that a new pillar of treatment comes along," says Professor Michael Hofman. **Jesse Marlow**

Unlike conventional radiation that fires beams into a tumour, it involves injecting radioactive molecules into the arm, hence the term "liquid radiation".

These smart molecules act like heat seeking missiles. They travel through the blood stream, find their way to a target on a cancer cell, hit it, and destroy the cell in the process.

This already works in some neuroendocrine and prostate cancers, and now a global race is under way to design smart molecules and targets for other cancers.

"I think the success with treatment-resistant prostate cancer woke up the cancer industry," says Hofman.

"It's not very often that a new pillar of treatment comes along. Immunotherapy was the last game changer, now many laboratories

around the world are looking at different ways of using nuclear medicine to target any number of cancers. More than 200 trials in humans are already underway."

Hofman translated this treatment from bench to bedside, [https://www.afr.com/policy/health-and-education/one-man-s-mission-to-make-prostate-cancer-fix-open-to-all-20220127-p59rnb] when he ran clinical trials that led the US FDA to approve it for prostate cancer last year. But, can it possibly work in other cancers too?

"With advances in chemistry, targeting, and radioactive molecules, I think the answer is yes, and I think we might be able to use the same platform," he says.
In December, Hofman and his team won a $15 million discovery grant [https://www.pcf.org/news/the-prostate-cancer-foundation-announces-inaugural-30-million-tactical-awards-program-for-innovative-prostate-cancer-research/] from the US Prostate Cancer Foundation that included two moon shots.

The first was to develop a visionary treatment to "intercept the lethality" of prostate cancer.

The second was to build foundation blocks for using liquid radiation in other cancers.

Collaboration is essential

Gone are the days when discovery science could be done by a person sitting alone, or with a small crew in a laboratory.

In this age of bio-informatics, complex biology and constantly evolving technologies, collaboration with experts in other disciplines has become essential.

As it takes a village, Hofman pulled together a multidisciplinary international team of 28 people from the Peter Mac and three other institutions: Essen University Hospital in Germany and the universities of California Los Angeles and San Francisco in the US.

The field, which is formally called theranostics, is a combination of "therapeutics" and "diagnostics" and reflects the two stages of the treatment.

In stage one, a radioactive drug identifies the cancer on a scan, so the extent of disease can be diagnosed. Then, for stage two, another radioactive drug is weaponised and sent in to kill the cancer cells.

The FDA approval was for a first generation of this treatment for men with prostate cancer who had run out of options.

Now, the team is creating generation two, which it expects will produce a quantum leap in effectiveness.

While generation one uses beta radiation as the weapon, generation two will use alpha radiation, which is precise and far more powerful.

"Beta is delivered in the form of Lutetium-177 which targets to 1mm, affecting an area the size of a grain of rice," Hofman says.

"Alpha, in the form of Lead-212, targets to 1/10th of a millimetre, the width of a human hair, which spares nearby healthy cells.

"The difference in power is akin to the difference between going into the sun and getting sunburnt, and going into a microwave oven and getting really burnt.

"Lead 212 has 100-to-1000-fold higher energy than the Lutetium-177."

Another advantage is that alpha has supply chain gains as it does not need a nuclear reactor.

Research excellence

Supply has proved a major headache for the multinational corporation Novartis, which purchased the gen one molecule for $US2.1 billion

[https://www.afr.com/life-and-luxury/health-and-wellness/billiondollar-molecule-may-extend-life-in-men-with-prostate-cancer-20180507-h0zq1w].

It has had trouble meeting demand because of complications with the specifications of global regulators.

By special arrangement, the Peter Mac gets its beta supplies from the Lucas Heights reactor in NSW and then formulates its injectables in its own radio-pharmacy.

It has to attach the weapon to a vehicle that will find the target.

"The research excellence at Peter Mac has been on our radar screen for a very long time," says Dr Howard Soule, executive vice president and chief science officer of the US Prostate Cancer Foundation.

A few years ago, the foundation granted $US5 million to Hofman to establish the Prostate Theranostics and Imaging Centre of Excellence (ProsTIC).

Earlier this month, Soule made his first post-COVID-19 trip to Melbourne to check the progress.

"It was everything you'd want to see from a philanthropic investment. It almost brings tears to my eyes to see how far they have come in a relatively short period," he says.

Soule was most impressed by the number of trials under way, and by the way Peter Mac produces its own radioactive injectables.

"This is very expensive clinical science. It's not the largest radio-pharmacy in the world, but there's no more intelligent facility.

"I watched them make 30 to 40 doses in a relatively small laboratory. This is a unique capability, and no small investment from this hospital."

Soule says researchers from the four institutions have worked together in some ways before.

"But this is the first time they've been corralled. We've pulled the fence and the diameter of the corral has been greatly reduced. Now, with $15 million, they have the opportunity to do something big for patients.

"We'll be looking at this every six months or more often because sometimes this requires care and feeding."

Associate Professor Sze Ting Lee, president of the Australasian Association of Nuclear Medical Specialists, says: "It's fair to say that this next generation of targeted alpha therapy is potentially revolutionary.

"It's a very exciting development, and I'm optimistic about its possible application in a wide range of cancers.

"It's fair to say that this next generation of targeted alpha therapy is potentially revolutionary, "says associate professor Lee .

"The fact that it is an Australian innovation is also exciting. Australia is definitely punching above its weight in developing nuclear medicine technology for the world."

For alpha therapy, Brisbane company AdvanCell is developing a desktop device the size of a kitchen blender that would enable Lead-212 to be made on-demand daily, in Peter Mac's radio-pharmacy.

Targets of interest

On the broader moon shot for other cancers, the team's challenge is to find new targets for the alpha radiation. Traditionally, finding a protein that binds to a new target has been a slow and cumbersome process.

But new mRNA technology has radically accelerated this, enabling trillions of sequences to be tested against a target to see which has the strongest bond.

Dr Mohammad Haskali, a radiopharmaceutical scientist at Peter Mac who co-leads the research, says this technology is akin to having "a pharmaceutical company in a test tube".

Within weeks, it is possible to find high affinity proteins that bind to targets of interest.

He says the team is considering pan-tumour therapy proteins that tend to be expressed by a large range of cancers.

They are expressed at the stage where cancer transforms from benign to becoming very aggressive. Sometimes they are over expressed further when the cancer becomes treatment-resistant.

This technology is like having “a pharmaceutical company in a test tube”, says Dr Haskali.

Haskali believes alpha therapy could become a new pillar of cancer treatment that would stand among existing pillars. With its technical complexity, he doesn’t see it becoming as big as chemotherapy.

He explains its effectiveness in terms of sinking a ship. While beta radiation is the equivalent of crossfire, alpha radiation hits the hull with a cannonball.

“One hit is more than enough to cause double-stranded DNA damage, from which a cell cannot recover. We propose that this will transform the discipline of theranostics.”

It may be that a combination of alpha and beta is optimal. Although crossfire works for many tumours, Alpha is more effective, especially for micrometastases – small nesting cells – which may be missed by beta.

Haskali says the idea is to devise sequences using both to give the patient the best of two worlds.

"This project could provide the much-needed chemical and biological foundation to develop first-in-kind theranostics and targeted therapy against the range of cancers. We are trying to create a whole platform that can be utilised for future developments in this space."

Hofman says that in a way, this new paradigm is going back to the past.

Some 80 years ago, iodine radiation was injected for thyroid cancer. As the thyroid is the only human organ that absorbs iodine, a targeting technology was not needed, nor was it available.

He is hoping the alpha therapy for new targets that treat a range of cancers can be moved from the laboratory to clinical trials in less than three years.

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