

BREAKING THE PAIN BARRIER

A revolution is on the way for rheumatoid arthritis sufferers as a Brisbane-based researcher edges closer to a vaccine-like treatment that could have even wider applications

LEISA SCOTT

Fingers so nobbled and bent they look alien. Knees swollen and distorted, unable to bear weight. Muscles wasting. The young doctor saw the pain endured by rheumatoid arthritis patients in the late 1980s – the cruelty of acute disease – and a seed was planted. “There’s a big need here,” she thought.

The now 56-year-old Professor Ranjeny Thomas likes a challenge. As the eldest child of parents who thumbed their noses at convention, withstanding slurs because their union crossed racial boundaries, Thomas understands tenacity. She’s held on as the rollercoaster of medical research has taken her on dips and slides, climbing now to the cusp of a revolutionary, vaccine-like treatment for rheumatoid arthritis (RA).

It’s been 30 years since those crippled patients focused her attention. She remembers wards filled with the worst cases, people for whom a shower was agonising. “It was the bad old days,” Thomas says of her time doing physician training at Royal Perth Hospital. “A lot of patients had terrible, terrible disease.

“People were put on bed rest because there was nothing to be done apart from steroids or [injections of] gold. Steroids have side-effects,

like diabetes, osteoporosis and high blood pressure. And gold is very toxic and would take three to six months to work. Patients would be sitting in bed, waiting.”

Big advances in medications have been made since then to calm the disease that afflicts more than 450,000 Australians and 23 million people worldwide. But they treat the inflammatory symptoms once the disease has developed. Thomas’s approach targets the cause.

Thomas, now the Arthritis Queensland Chair of Rheumatology at the University of Queensland’s Diamantina Institute, has hit many milestones. Her work has opened up the field of immunology for other scientists to explore

further. With collaborators, she has secured patents, founded a commercialisation company and is awaiting the results of a groundbreaking clinical trial funded by Janssen Biotech, a pharmaceutical arm of multinational Johnson & Johnson.

Like her colleague and adviser Ian Frazer, the co-creator of the Gardasil vaccine now reducing cervical cancer rates around the globe, Thomas is at the forefront of big changes in disease control. Rheumatoid arthritis is only the beginning.

She's already investigating ways her work in the rapidly evolving world of immunotherapy can be applied to other auto-immune disorders, a curious family of diseases where the body turns on itself. Next target: type 1 juvenile diabetes.

GOING AGAINST THE NORM

The baby Rosemary Thomas was carrying was sure to have some form of abnormality. Lots of people told her that. It was 1961 and acquaintances, family even, would look at Rosemary, the Australian from Tasmania, then at her husband, CV Thomas, the Indian from Kerala, and let her know her first pregnancy would not end well. "She got a lot of flak; it was going against the law of nature," Thomas says.

Her medico parents met at Royal Hobart Hospital then moved to Perth after marrying. Neither of their families were happy about the union. "It was the first love marriage in [my father's] family," Thomas says. "It was a very big thing to do."

Three other high-achieving daughters would follow the perfectly formed Ranjeny: Cathy, now an occupational therapist with a string of clinics in Perth; Helen, a Melbourne-based immunologist, and Anna, a fashion designer with her own label in Melbourne. Their father comes from a "very paternalistic" society but eschews its ways. "There was never any limit to what we could do as girls."

Talented in the arts and science, Thomas blended both at the University of Western Australia, studying medicine but performing with the Western Australian Youth Orchestra. It was here, playing violin, that she met her husband, John Loneragan, the lead violinist who became a professional musician. You'll still hear the couple playing music together at their home in Hawthorne, in Brisbane's inner-east.

Thomas graduated in 1984, married the same year, and then began her internship and residency at the Royal Perth Hospital, before becoming a registrar. Her interest in immunology was nurtured during physician training, when doctors are exposed to a range of specialities. She zeroed in on rheumatology, treating the desperately diseased patients as well as doing research. "I started to get interested in why RA did what it did."

It's still unknown what sets rheumatoid arthritis off. A common belief among lay people that the disease is triggered by a virus is not proven, Thomas says. "We still haven't got to the bottom of whether there is a single trigger, or if there's even a trigger." Bacteria could play a role. Some sort of change in microbes in the lung and respiratory tract is suspected. Smoking elevates the risk, but there are also links to environmental factors such as pollution and coal dust exposure.

What is known for sure is that adult RA is a disease of an ageing immune system, women are more vulnerable and there is a big genetic component. In short, a patient's immune system attacks the lining surrounding the joints. The pain can be excruciating.

And while she's now at the spearhead of the next big thing in treatment, Thomas says there's one prescription that's timeless: look after yourself. "Reprioritise, get your diet and exercise consistent, control stress," she says. "The people I see doing the best – long term, really good remission – are people with control of their whole life."

“There was never any limit to what we could do as girls”



THE EUREKA MOMENTS

Thomas sat at home in despair. What was she doing here? She was alone on the other side of the world in Dallas, Texas. Her husband, now an architect, had to live three hours away in Austin to study. She'd stopped seeing patients to concentrate on research for her doctorate. And it was going nowhere. Nine months in and she was stumped.

"I just remember thinking, 'Argh,'" she says of that day in 1991. She refocused, picturing in her mind the commonly used chart of cell types in the blood and the markers that help identify

them. She went over old ground. Then, a eureka moment. "I just remember thinking, 'That's it!'"

In the lab the next day an experiment confirmed her belief. She had found the precursor to dendritic cells – the "orchestra conductors" of the immune system – and some markers. Before then, finding dendritic cells was hit and miss. Now scientists had a road map. "You could identify the cell with markers," Thomas says. "It opened up the field a lot."

The experience taught Thomas some big lessons: that from the nadir comes growth. That going back to basics is often the best way forward. And that she could do this research caper. "It was that kind of moment when you go, 'OK, I can do this'."

With a celebrated paper, a doctorate and further research into dendritic cells in joints under her belt, Thomas and her husband returned to Australia in 1994. She got a job with UQ as a senior lecturer, funded by Arthritis Queensland, a role that has advanced to the position of chair. "It gave me 70 per cent protected time for research,

20 per cent clinics (at Princess Alexandra Hospital), and 10 per cent teaching. It was perfect."

Thomas mourns the decline in clinician scientists, a rare breed who see patients as well as conduct research. "There are so few of us now but they're so important because they sit at this interface between the patient need, the discoveries that can be made and if you make a discovery, how you can use it."

One of the reasons for their decline, says Thomas, is the remuneration is not as good as in private rheumatology practice. "But it was what I wanted to do. You have to make priorities."

She also wanted a family and was pregnant with Sylvie, now 23, on arrival in Brisbane. Twins Asha and Bryn, now 18, followed. "You're really committing yourself to a huge undertaking." Nannies and child care helped but husband John Loneragan was her rock. "If you don't have a supportive partner, you really can't survive in research. It's a team."

Teamwork is vital in research, too, and Thomas gathered a good one around her in Brisbane to further her work on dendritic cells. These treelike cells are part of the immune system's early response to invasion. Thomas calls them the conductors because they instruct lymphocytes – a type of white blood cell integral to the immune system – on what to do. With an auto-immune disease such as RA, the conductor's baton goes rogue, causing the orchestra to play out of whack. What was going on in the cells to make that happen?

Years of lab work with mice, vaccines and dendritic cells followed, testing theories and re-testing before "the biggest eureka moment" came in 2000. Thomas's face lights up as she tells

of sitting in a lab meeting as a team member presented the results of experiments.

The data was unmistakable: a protein in dendritic cells known as RelB acted as a switch, making the immune system attack. "In the auto-immune disease, it was on where it should have been off," Thomas says. "At that moment, I knew we could 're-educate' through the dendritic cell."

Now for the next step: translating the discovery "from mouse to man". It took 10 years. In that time, a patent was secured through UQ's commercialisation arm, UniQuest; she became a director of a UniQuest-owned company, Dendright Pty Ltd, established to drive the business process and investment; a groundbreaking paper was published; a proof of concept clinical trial held; and another patent taken out on an improved delivery method, an injectable immunotherapy. But what was really needed was a pharmaceutical company with the financial and technological capacity to develop a product.

"There are several valleys of death in commercialisation," Thomas says, with a wry grin. "Research is a rollercoaster to start with, and commercialisation is truly a rollercoaster. You're up, then you're down; there's money, then there's no money." She had a template, though: as she chipped away, her colleague, Professor Ian Frazer, was further down the track with trialling the vaccine that would become Gardasil. "I really got an inside view around commercialisation," says Thomas, who is based at the Translational Research Institute, aimed at moving scientific discoveries from "bench to bedside". "I saw what was possible."

Thomas is passionate that more Australian scientists should take their work out of the lab

and into the marketplace. "We're competitive in publishing great research papers at a very high level but we're very, very bad at getting those into products," she says. Some researchers believe the altruism of their research will be tainted by dealing with drug companies. "It's just wrong thinking," she says. "It's not that we don't have the ability, it's just about making this a priority and something we're proud to do rather than somehow being ashamed that we're going to the dark side."

Thomas also knows it's risky to devote the time needed to do the work that will attract pharmaceutical companies, with research and publications more likely to receive grants – a scientist's lifeblood.

"I took a big hit when I did this translation ... But it's just what I felt I had to do."

She was tenacious. She pitched her discovery here and overseas. She pitched to venture capital firms and pharmaceutical companies. "I pitched to 26 different entities over a number of years.

We didn't get any investment." The newest form of treatment, biologics [see breakout] was still to the fore and nobody was that interested in her concept – an antigen-specific therapy. "An idea has to have the right timing."

A few years passed. Then, in late 2010, as she sat in a convention hall at an international rheumatology conference in Atlanta, US, her research displayed behind her, a scout from Janssen stopped for a chat. "By this stage, companies are starting to look for technologies that are going to push the boundary beyond biologics." Interest was sparked.

A year later at the UniQuest offices in St Lucia, Brisbane, Thomas stood with her slide show in front of Janssen's worldwide chairman of R&D, Dr Paul Stoffels, and pitched again. At the end, there was silence. "I'm thinking, 'Another failed pitch,'" Thomas says. Then Stoffels

spoke. "We better get on board before someone else does." A deal was done.

FROM BENCH TO BEDSIDE

The long, long road towards a vaccine-like treatment for rheumatoid arthritis climbed a steep rise when human trials of DEN-181 began at the Princess Alexandra Hospital in Brisbane last year. Finally, Thomas took a back seat, unable to be involved because, as an inventor, she stands to gain financially from any new treatment.

It's an exciting but delicately poised time. Contractual agreements with Janssen prohibit speculation about the results of this, or future trials. But Thomas's goal is clear: to provide a targeted immunotherapy, offering longer benefit with less reliance on other drugs and less toxicity.

Those days in rheumatoid arthritis wards, when a young specialist was moved by patients' suffering, set Thomas on a journey of discovery that now has the potential to go beyond helping those with the crippling disease. "What's happened in the last five years," says Thomas, "is the world has caught the vision that antigen-specific therapy can be a reality. Prior to that, people were saying to me, 'Nobody has been able to achieve this, why do you think you can? Now it's a real possibility ... for many auto-immune diseases like multiple sclerosis, type 1 diabetes, even coeliac."

A whole new field is opening up: Thomas is now working on a clinical trial for type 1 diabetes in children, after receiving a grant from the US-based philanthropic Helmsley Trust in collabor-

ation with JDRF Australia. "There's a lot of people looking at antigen-specific therapy, a lot of money floating around so there will be a lot more research in the area. I'm just happy to have contributed my bit," says Thomas. "To put this big piece in the jigsaw." ■

**“If you
don’t
have a
supportive
partner,
you really
can’t
survive in
research”**



FAMILY AFFAIR:

(Clockwise from right) Ranjeny Thomas as a child with her mother, Rosemary; with husband John Loneragan and daughters Sylvie (left) and Asha and Thomas with (left-right) Asha, Bryn and Sylvie in India in 2006.





IN HARMONY:
Professor Ranjey Thomas with her husband John Loneragan, who has been vital to her success, at their Hawthorne home; and (*opposite page*) Thomas at the Translational Research Institute at Woolloongabba. Pictures: Ric Frearson, Sarah Marshall/AAP Image