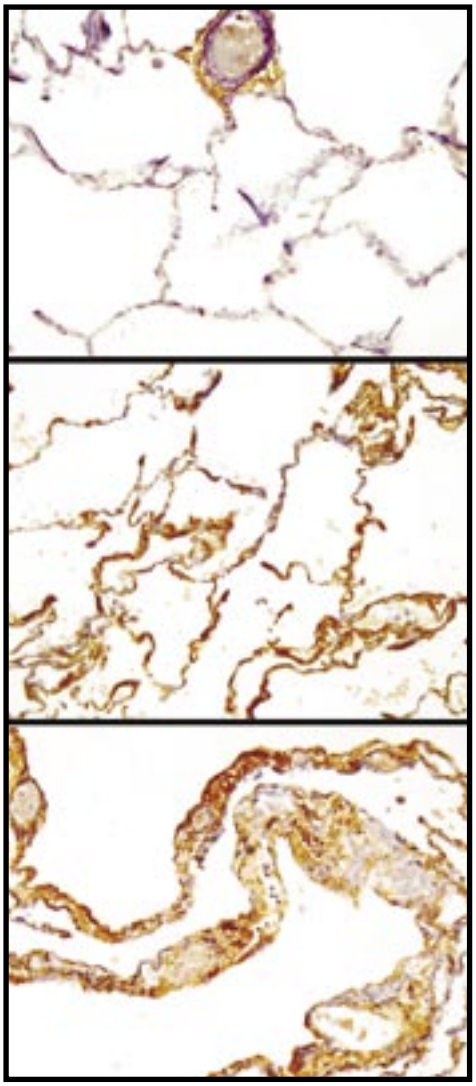
Dying to breathe



Why is one of the University's leading heart researchers on a quest to find a cure for a rare lung disease? Tess Redgrave investigates.

Ever heard of Lymphangioleiomyomatosis (LAM) – a rare lung disease that knocks young women down in their reproductive prime?

No? Well you're in fine company then because five years ago neither had Associate-Professor Mervyn Merrilees (Anatomy with Radiology). Yet now he is at the forefront of an international research effort urgently trying to understand and find a cure for this devastating (and often fatal) condition, which spurns all familial links, choosing its victims at random.

As the *News* goes to print, Dr Merrilees is in Cincinnati, Ohio, at the 10th annual conference of the USA LAM Foundation, giving a platform presentation on the findings of cutting edge research he and his postgraduate team have been undertaking. If the Auckland research is on the right track, it will add an important piece to the puzzle that is LAM, offering hope to thousands of women around the world and to 14 women in New Zealand, including one 37-year-old Auckland family lawyer.

The story of why one of the University's foremost heart researchers is on a quest to understand LAM is irrevocably linked with Auckland woman Bronwyn Gray and her daughter, Lisa.

Let's rewind here a moment back to February 1997: 29-year-old Lisa, after weeks of looking tired, wheezing, coughing and even spattering tissues with blood, is sent by her GP to Greenlane Hospital's respiratory department. A few days later the results of a bronchoscopy and CT scan show that the exercise-induced asthma she thought she had suffered since her early 20s is in fact something far more insidious: LAM – a rare disease (caused by a defect in a gene called TSC2) which affects only women – usually between the onset of puberty and menopause – and is characterised by the growth of an unusual type of smooth muscle cell around lymph channels and blood vessels resulting in an increase in the amount of tissue in the lung and a loss of airspace.

"I went into a blind panic when I heard Lisa's diagnosis," remembers Bronwyn Gray, when we meet at her Freemans Bay villa. "In 1997 no one in New Zealand could tell us anything about LAM except that Lisa was unlikely to live to be an old lady." (Early reviews of the disease, which affects about one or two per million, reported a dire prognosis: most patients died of progressive respiratory failure within 4-10 years of onset).

Not a mother to lie down and watch her daughter slowly die, Bronwyn Gray, a former Auckland Girls' Grammar English and history teacher – determined, articulate and focused – abandoned retirement plans to live half of each year in France, and set out to find out as much as she could about LAM, garnering whatever help she could find along the way to save her daughter's life.

Her quest took her to London, Paris, America, Australia, back to New Zealand, and finally to a meeting on November 13, 2000, in the conference room on the fifth floor of Auckland's Medical and Health Sciences Faculty.

"I was invited to that meeting even though I'd never heard of LAM," remembers Mervyn, "because at the time I was working on smooth muscle cells in blood vessels of the heart. It's the change in the function of these vessel smooth muscle cells that leads to coronary artery disease."

There were six people at the November meeting but Bronwyn Gray "beamed in" on Mervyn. Eighteen months earlier she had set up the NZ LAM Charitable Trust and begun a mammoth fund-raising effort; now she was looking for someone in New Zealand to be part of an international research effort to find a cure for LAM. Mervyn's work on smooth muscle cells was the closest she'd come.

"I didn't make any promises," remembers Mervyn, "but I was interested so I went away and read up on LAM."

LEFT: Tissue sections of normal lung (top panel) and LAM lung (middle and lower panels). The spongy architecture of normal lung is lost in the LAM lung and the walls of the air pockets (alveoli) become thickened. The orange-brown (antibody) staining of the LAM lung is due to an increase in a matrix molecule called versican that binds water, occupies space and helps cells proliferate.

BELOW: Mounted jigsaw pieces like this were distributed at a LAM conference to signify the "puzzle" of LAM.

Then early in 2001 Bronwyn, via the Trust, offered to pay for Mervyn's flights to attend the 2001 USA LAM conference in Cincinnati.

"It was a real eye-opener," he says. "The LAM conferences are driven by patient advocate groups so you've got clinicians, scientists and patients working together – a whole community working on LAM. You meet the patients and you see the urgency. They're all women in the prime of life, some mothers, some of them very ill. Many sit at the conference connected to portable oxygen tanks…."

LAM had got under the skin of this quiet, unassuming Auckland academic. Back in New Zealand, just as Bronwyn had hoped, and with help from his technical officer Brent Beaumont and a masters student, Elyshia Hankin, he began a research project studying LAM lung tissue samples from six patients who had had transplants in America, and three in Australia.

Studying the cell structure of these under a microscope he came up with a radical new perspective on the disease: that smooth muscle cells may not be the only culprit in LAM! "We discovered that some of the normal cells, without the TSC2 gene defect, get stimulated to proliferate too, and actually take up much more space in the lung than the abnormal smooth muscle cells. Presumably the smooth muscle cells send out a message to the normal cells which makes them start proliferating – the end result is the lungs run out of airspace."

Mervyn published this finding in the prestigious *UK Journal of Pathology* last year and it forms the basis of one of the papers he is now presenting at Cincinnati. But his research hasn't stopped there. In 2003, he again accompanied Bronwyn to the annual USA LAM conference and heard a presenter suggest that a drug called rapamycin (made from a soil fungus found on Rapa Nui, part of the Easter Island group, and originally used as immune suppressant to control rejection of transplanted tissue) might be able to stop the growth of smooth muscle cells.

In an interesting piece of serendipity, back in New Zealand, Mervyn discovered that of the two pharmaceutical companies in the world that manufacture Rapamycin, one is based in the USA, and the other, Industrial Research Limited (IRL), is in Wellington. Already interested in testing rapamycin on "normal" lung tissue, Bronwyn, on Mervyn's behalf, approached IRL; the Lower Hutt-based company has since got in behind the Auckland research and donated two milligrams of rapamycin (it costs about $800 per milligram to import from the USA).

In 2004 Mervyn and his team began observing rapamycin's impact on normal lung cells in culture imported from the US.

"We found the drug significantly decreased the growth of these cells and also decreased the matrix material which gets laid down outside the cell. It's these matrix molecules [the same molecules that bind cholesterol in the blood vessel wall, and that the heart researcher had discovered also stop the formation of elastic fibres] that bind a lot of water and make the LAM tissue swollen and puffy, slowly smothering the lungs."

While Mervyn has been beavering away in Auckland, researchers in the US have begun to trial rapamycin on LAM patients, with early results indicating the drug may indeed be beneficial.

"So rapamycin may well offer an opportunity and the best hope for LAM we've ever had," he says. "Like some cancers, in which cells start to proliferate when a tumour suppressor gene is damaged, LAM seems to occur when TSC2, also a tumour suppressor gene, malfunctions, allowing cells to grow. So basically rapamycin reasserts control; its very effective at stopping cells growing."

As a result of both the Auckland research and research in Australia and America, an international double blind rapamycin trial is likely to get underway later this year. Bronwyn Gray is playing a key role in organising the Australasian arm of the trial and is hopeful her daughter may be a candidate.

At the moment Lisa works in a family law chambers in Ponsonby (she is a Counsel for Child) but her lung function is "slowly but progressively decreasing.

"Every three months she has FEV1 (forced expiratory volume in one second) tests to measure how much breath she can get out in one second and every time it's a little less," says Bronwyn.

Lisa was not interviewed for this story (though happily photographed). "She just wants to get on with her life," explains Bronwyn. "But she gets very irritated and angry with this disease, she's so healthy, she doesn't drink, she doesn't smoke; she's in the prime of her life; she wants to have a child but is worried about further deterioration [much of the anecdotal evidence indicates that the hormonal changes of pregnancy, in particular raised estrogen levels, are likely to heighten the symptoms of LAM: some women only find out they have the disease when they experience difficulty breathing during pregnancy]; she doesn't know what the future holds."

So while Lisa gets on with her life, her mother and greatest advocate works from her Freemans Bay home raising awareness about LAM, organising conferences, helping other New Zealand patients, collaborating on the international trial, and finding funds so Dr Merrilees can continue investigating his perspective on LAM.

"Mervyn is absolutely pivotal," she stresses. "He and the team in his lab are the only people in New Zealand doing any work on LAM and I believe that after his presentation in Cincincatti [Bronwyn is going too] there will be quite a major response to what he is saying. "

Mervyn in turn has obviously been personally touched by Bronwyn Gray, her daughter Lisa, and LAM. "It's always struck me that LAM patients are extraordinary women with enormous courage," he says "There's a sense of being closely involved with this disease – often as a researcher you don't meet the recipients of your research, but with LAM, you meet the patients, you see the urgency – it focuses your mind."

After Cincinnati Mervyn will continue to work on LAM in tandem with his heart research; he is currently making a three-dimensional model of the elastic fibres in LAM lungs using a pair donated from a New Zealand patient who recently had a lung transplant at Auckland hospital.

"The understanding of this disease has happened very quickly," he says. "The US LAM foundation was only formed ten years ago and since then there have been huge strides in understanding but it's a hard road to solve a disease, we have to be realistic…"

As the international quest to find a cure for lymphangioleiomymomatosis continues you can bet that Mervyn and the work he is doing at the University will be a part of the mix. LAM has left an indelible mark on this academic and he is not likely to let the puzzle of it go.

To find out more about LAM see: www.lam.org.nz