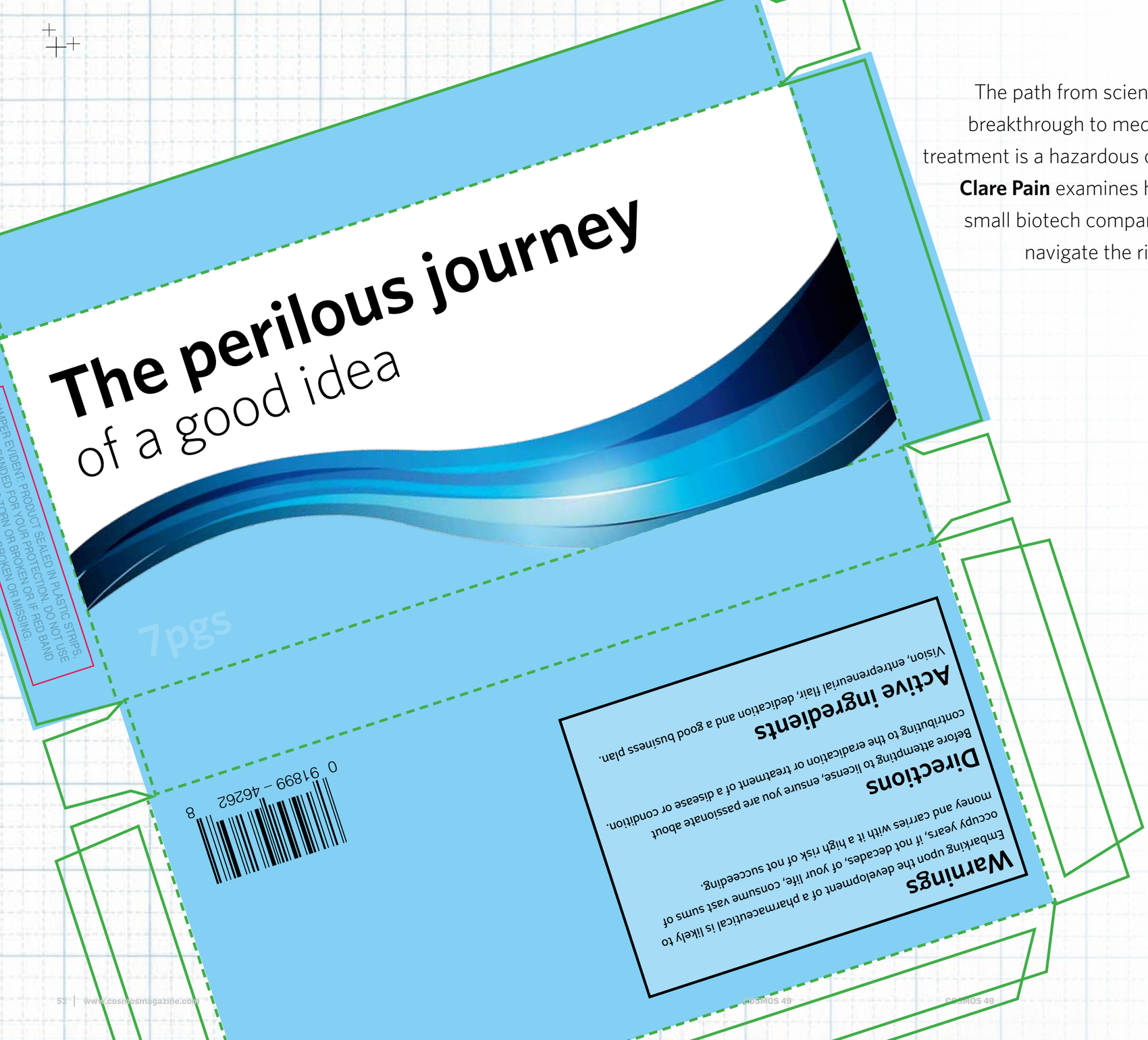
The perilous journey of a good idea

The path from scientific breakthrough to medical treatment is a hazardous one. **Clare Pain** examines how small biotech companies navigate the risks.



IN THE 1970s, two young women used to horse-ride together in Dural, then a rural Sydney suburb. As they laughed and chatted at dressage and cross-country events, they never imagined their friendship would spur on the birth of an Australian biotech company that would go on to develop a novel compound designed to combat hepatitis C and HIV. But the path to commercialisation has been anything but smooth.

One of those women, Angela Dulhunty, became a university biochemist and the partner of Peter Gage, an electrophysiologist at the Australian National University (ANU) in Canberra. Gage, who died in 2005, was fascinated by ion channels, the tunnels through proteins that marshal the flow of charged atoms into and out of cells. Common in muscle and nerve cells, ion channels had just been found in some viruses, and Gage's team was investigating these.

In 1996, the team was excited to discover that a protein produced by HIV (the virus that can cause AIDS) formed sodium channels. Viruses hijack the cells they invade, turning them into replication factories – the enslaved cells spend the rest of their lives manufacturing, packaging and exporting viruses. Clearly, if HIV was creating a sodium channel protein, sodium channels must in some way be important for its survival, the scientists reasoned.

Soon afterwards, they found that some of the chemical compounds they kept in their laboratory fridge completely incapacitated the channel. At the time, exactly how a sodium channel might be helping the virus was not known. It's still not certain, but it is now clear that the protein, known as VPU, straddles the membranes of the HIV-infected cells. This VPU channel enables control of sodium ions passing through those membranes – probably to create an environment that's ideal for virus replication. Clearly, Gage and his team were onto something that might have potential in fighting HIV.

THE OTHER HORSE-RIDING devotee was Gail Snedaker, who married businessman Peter Scott and along with him started several companies producing and directing film, multimedia and conference events. The four used to meet frequently.

"The two Peters would sit down with their drinks and Peter Scott would ask 'now what's happening in the lab?'," says Dulhunty. When Scott heard about Gage's work on HIV, he immediately thought it must have commercial potential, she says.

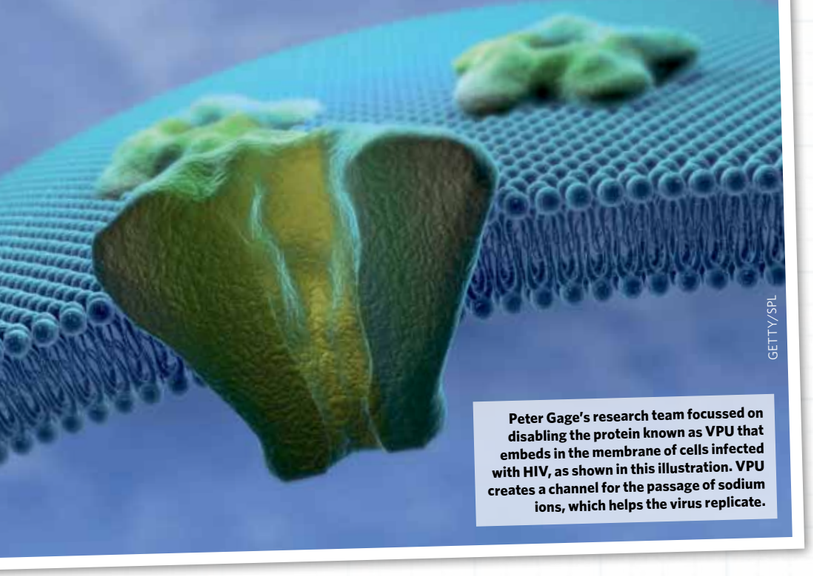
"Peter had this new approach to attacking viruses," says Scott. "I told him, 'This is incredible stuff. You must be able to get money to develop it.' He was spending so much time trying to get grants – and was getting peanuts."

And so, in 1997, Scott embarked on a journey that was to occupy him full-time, unpaid, for the next four years. Little did he know they were entering a phase described by Simon McKeon, who chaired a strategic review of health and medical research in Australia, released in December 2012, as "the valleys of death". These twin valleys are the 'preclinical' and 'early clinical' testing phases (see 'The trials of taking a drug to market', p56), which cost drug developers millions of dollars as they take a compound with potential in the lab to the point where a multinational pharmaceutical company will buy or license it.

"I was born in the Middle East, so I know how to drive a hard bargain. You learn how to negotiate, make deals and, when you are ready, to compromise."

"It takes a small village to get a drug to the clinic and eventually become successful," says Raymond Schinazi, a hugely successful entrepreneur and pharmacist based at Emory University in Atlanta in the USA. He negotiated the valleys of death many times, and has created, run and sold three biotechnology companies to so-called 'big pharma' at handsome profits. Worldwide, 90% of people with HIV use a drug that was developed by his group.

"You have to have an entrepreneurial flair, a good business plan and follow the vision," says Schinazi. "In my case, I was born in the Middle East, so I know how to drive a hard bargain. You learn how to negotiate, make deals and, when you are ready, to compromise." >>



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Peter Gage's research team focussed on disabling the protein known as VPU that embeds in the membrane of cells infected with HIV, as shown in this illustration. VPU creates a channel for the passage of sodium ions, which helps the virus replicate.

>> **SCOTT HAD A HARD** road ahead. In the late 1990s, he used his entrepreneurial flair to persuade three other ANU professors whose research had commercial potential (including Angela Dulhunty), as well as the ANU itself, to form a private company along with Gage. "I asked Peter how much money we would need to progress all the research," says Scott. "He said between two and three million – which was a huge sum of money to him. In terms of the funding they normally get for research, it was enormous."

But science researchers rarely think commercially, Scott knew. Pricing it himself, he came up with a ballpark goal of $12 million. "Then I had the intellectual property of the company valued. We had just one patent at that stage – for a method of testing ion channel activity – but that and the researchers' know-how came back valued at about $31 million."

Once formed, the company needed to attract investors. But private companies aren't allowed to advertise for shareholders from the general public, so Scott was after the 'sophisticated investors' – those who could put up a cool half a million. The husband-and-wife team and the PR arm at ANU went to the press to try to develop some interest in the fledgling product.

"That night in early 2000, we were on the television news of every major channel and had a seven-minute segment on the ABC's *7.30 Report*. We were pretty close to the front page of virtually every newspaper in Australia," says Scott. A total of about $3.5 million was offered – but none was from the required 'sophisticated investors'. So, Scott then knocked on the doors of venture capitalists around Australia. "I quickly learned why they are called 'vulture capitalists'," he says. "They are either not interested because it is not big enough or far enough along, or they want so much of it for peanuts. We decided the only way forward was to float the bloody thing on the ASX [Australian stock exchange]."

SCHINAZI HAS ALSO overcome plenty of hurdles in taking drugs through the valleys of death. Universities are great environments for making discoveries, he says, because curiosity and innovation are the drivers, rather than monetary reward. But at some stage you have to translate what you've done into something useful. "What's the point of these wonderful studies if you are going to leave the drug you discovered sitting on the shelf where it's not going to help anybody?" he asks.

So how do you get the research out there in public view? "This was the frustration," Schinazi admits. In 1990, during the burgeoning AIDS epidemic, Schinazi was championing his research into drugs to combat HIV. "I don't think Emory University understood – at first they wouldn't even file the patents. In those days entrepreneurship was a dirty word."

Schinazi says he and chemistry colleague Dennis Liotta had to push very hard to get their first HIV patent filed for blockbuster drugs lamivudine and emtricitabine (which now earn big pharma more than US$1 billion per year). "Even if you have the best drug in the world, people don't believe you. You have to be a champion for your molecule. You have to do everything you can – even pulling out your credit card to pay all the bills."

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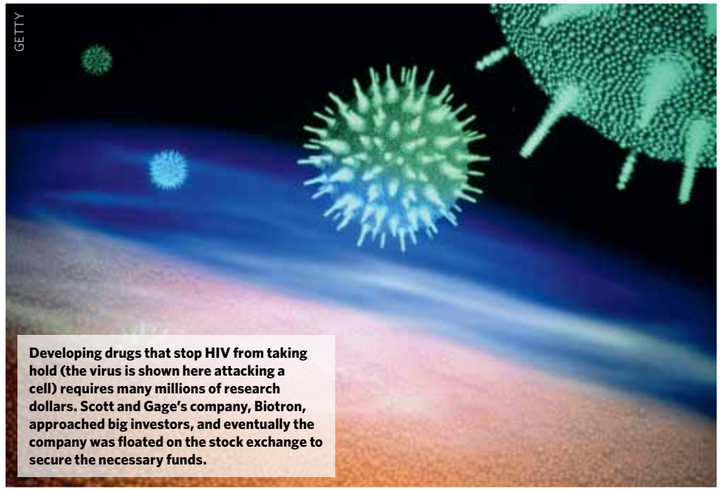

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Developing drugs that stop HIV from taking hold (the virus is shown here attacking a cell) requires many millions of research dollars. Scott and Gage's company, Biotron, approached big investors, and eventually the company was floated on the stock exchange to secure the necessary funds.

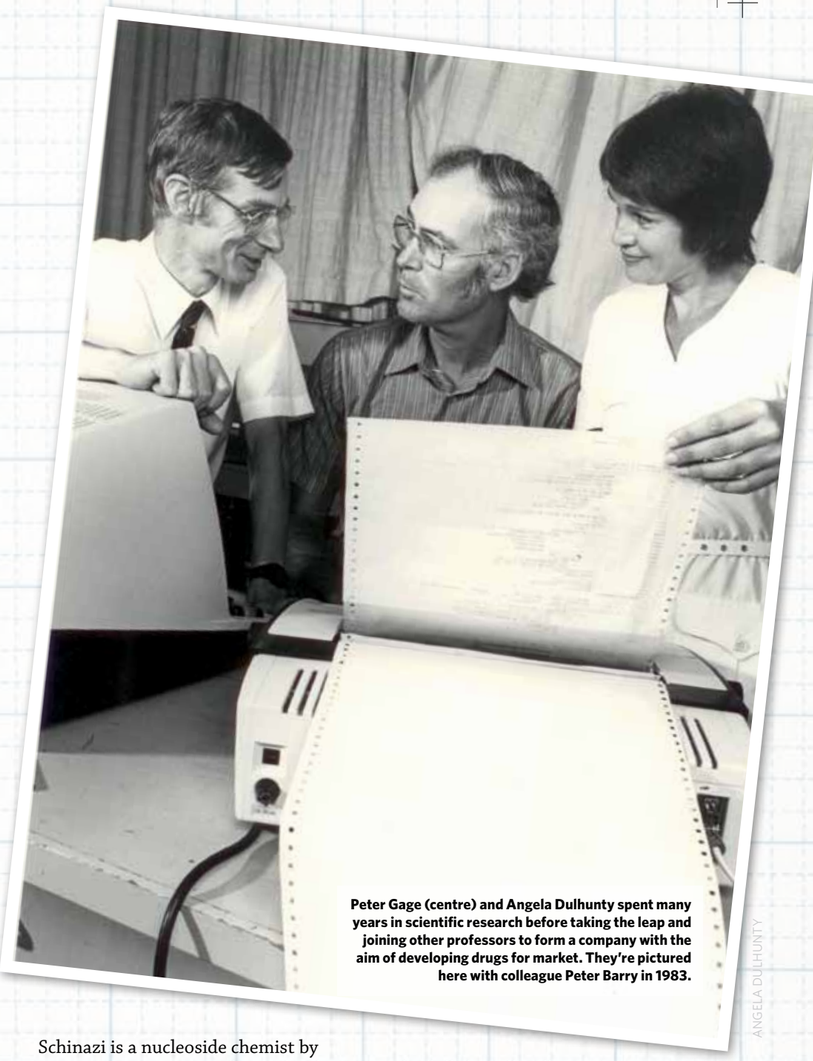
Things have changed a lot at Emory University since those days, says Schinazi. "I think they've woken up and realised that this is a fantastic new source of revenue. Not only that, but it also provides prestige – you can say 'this drug was invented here'. Emory's technology transfer office is very professional now."

Drugs are an industry with big money attached. Michelle Miller, who sports a PhD in retroviruses, research experience in big pharma and time as a biotechnology venture capital fund manager, is now the managing director of Biotron Ltd, the company born of Scott and Gage's labours.

Some of the recent big pharma deals have been "just extraordinary", she says. In November 2011, Gilead, a U.S.-based big pharma company, bought biotech company Pharmasset for US$11.4 billion – "a phenomenal amount of money," says Miller. In January 2012, Bristol-Myers Squibb (BMS) paid US$2.5 billion to acquire drug development company Inhibitex, primarily for a promising drug that targets hepatitis C.

Yet even when big pharma has taken on a drug, there are still risks. In August 2012, BMS's new drug became a casualty of the second valley. Phase II clinical trials were stopped on safety grounds, with nine people hospitalised, one of whom died of heart failure. "That shows you it's a very risky business. That drug would presumably have been fine all along until that stage. Every drug's fine until the day it's not," says Miller.

Pharmasset was one of Schinazi's companies. It was bought for its hepatitis C drug, now called GS-7977, which is widely touted as the front runner in the race for effective 'direct-acting antivirals' targeted at hepatitis C, and is undergoing the final stage of clinical trials (phase III). Schinazi says getting a big pharma to buy your drug is like fishing. "You have to have a good bait first of all, and then a good line helps, and being able to reel in slowly but surely, keeping your line straight is important – and you can bring in a fish." One gets the feeling he enjoys this and is a master of his game.



ANGELA DULHUNTY

Peter Gage (centre) and Angela Dulhunty spent many years in scientific research before taking the leap and joining other professors to form a company with the aim of developing drugs for market. They're pictured here with colleague Peter Barry in 1983.

Schinazi is a nucleoside chemist by training – an expert at making what he calls 'fraudulent' nucleosides, similar to the natural nucleotide bases of DNA and RNA. These interloper bases will stop DNA or RNA replication dead in their tracks and this strategy has been at the heart of his successful antiretroviral drugs for HIV.

"Bill Prusoff at Yale University was my mentor. He should have won a Nobel Prize because he really came up with the idea of selective antiviral agents – meaning a drug that doesn't affect the host cells but stops the virus replicating. Things like strong acid will kill the virus for sure, but it will also kill the cell. Bill taught me the antiviral business.

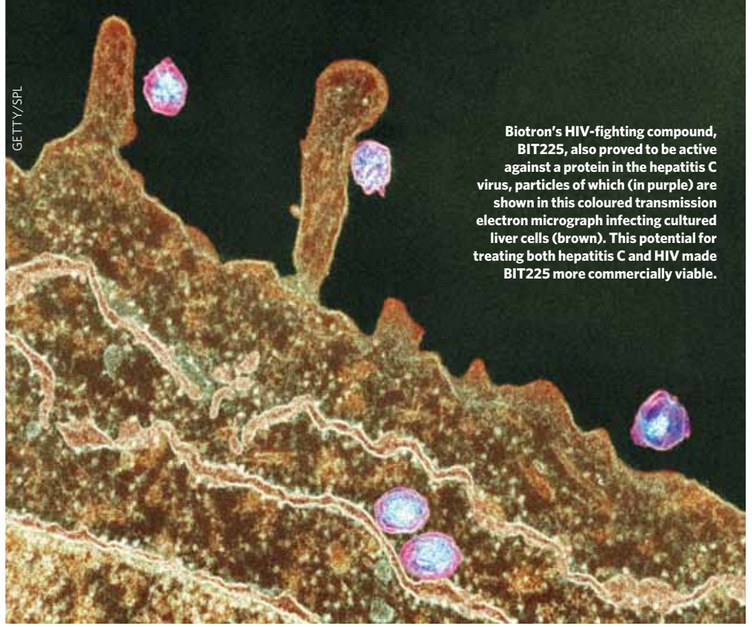
"I learned that the key was to be able to add value to the technology to the point where you can bring in, as I say, the big fish." Finding the right time to reel in that 'fish' is vital. "What you want to do is to add the value at the time when the research costs become very expensive but you have reduced the risk. You don't want to sell too early... and you don't want to sell too late – because you'll be broke, and it's never a good thing to negotiate from a weak position!" >>

>> Although he has created and sold biotech companies, Schinazi thinks it's better to license technology than form a company so scientists can "get on and invent something else". He adds: "We're not trained as businessmen, we're not trained to raise money, we're not trained to manage people in industry but we had to learn all this. It's a lot of hard work!"

WHILE SCHINAZI REAPS the rewards of his labours, Biotron has been making progress through the valleys, hoping the journey will pay off.

Miller came on board, "intrigued" by Gage's novel approach, but her big pharma experience soon told her they needed to develop a new drug, to maximise the commercial potential. Gage's compounds were known compounds that Biotron had 'use patents' for – types of patents that give a company the right to use someone else's compound in a particular way – and they weren't human-approved drugs. What Biotron needed was a 'composition of matter' patent on a drug that stopped the VPU protein's ion channels from working in HIV. They needed to own a molecule.

"If you design a drug, you make it, and nobody else has made it before and described it, and you can show what it does – you own it for 20 years," says Miller. So Miller initiated a program to develop about 250 potential new drugs that were related to, but not the same as, Gage's compounds and then set about selecting the best one to progress.



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Biotron's HIV-fighting compound, BIT225, also proved to be active against a protein in the hepatitis C virus, particles of which (in purple) are shown in this coloured transmission electron micrograph infecting cultured liver cells (brown). This potential for treating both hepatitis C and HIV made BIT225 more commercially viable.

Choosing the drug the company will go forward with is a big decision, Miller says. "You only get one chance at it – it's a bit scary actually – it's a big roll of the dice." The compound they eventually picked, called BIT225, is currently undergoing phase II clinical trials. Although they selected it for its activity against the VPU protein of the HIV virus, it also has activity against a protein called p7, which is important in the hepatitis C virus, and recently much of their attention has been focussed on this market.

"Hepatitis C is a more straightforward disease than HIV," says Miller. The existing standard treatment drugs – interferon and ribavirin – don't have much success in patients infected with the most common form of the virus, Miller points out. So there's been a push for new drugs that could work in combination with the current treatments.

Currently, Biotron is near the end of the 'second valley' after successfully undergoing preclinical testing and phase I trials of BIT225. Preclinical testing (the first valley) includes testing the drug in animals for toxicity. "Every single drug on the planet is toxic. If you do these studies and you show there's no toxicity, the FDA [Food and Drug Administration] will throw your drug out. You have to keep going until there's toxicity because you need to show that it's a long way from the doses that you're going to be using," says Miller. The type of damage found – perhaps to the kidney or heart – will be a useful warning of what to look out for when the drug finally comes to be tested in humans.

Next come studies in healthy human volunteers, known as phase I clinical studies (the second valley). The volunteers take a single dose of the drug. The first cohort of volunteers takes an extremely low dose, and each successive cohort takes a slightly higher amount. "You go up to the level you feel comfortable with – making sure you are covering the levels your drug would be prescribed at," says Miller.

All the trials are carried out by a contract research organisation that works to 'good clinical practice standards'. "It takes a long time and it costs a lot of money," says Miller. "This area is *so* regulated – but it is what all drugs have to go through for regulatory approval in major markets."

Before a drug is released onto the market, it must go through three phases of human trials to determine its safety, effectiveness and potential side effects.

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In October 2012, Biotron announced the encouraging results of its latest phase II trials in people with hepatitis C, carried out in Bangkok. In a trial of 24 patients, no virus was detected in the blood of any patient who took the highest dose of BIT225 for a month at the start of almost a year of dosage by the standard treatment. In comparison, 25% of patients on the standard treatment alone still had detectable virus when treatment ended. Miller is currently running another Bangkok phase II trial, testing BIT225's efficacy against HIV, and anticipates the results in early 2013. She's also just announced the start of phase II trials on people who are 'co-infected' – those who have both hepatitis C and HIV.

WHILE THE VAST sums paid by big pharma have lured Biotron into hepatitis C trials for BIT225, Miller is particularly excited about the drug's potential for HIV. Comparatively little is known about the VPU protein, which is targeted by BIT225. It is thought to be important in the 'budding off' of viruses as they leave the subjugated human cell that has been turned into a virus-factory.

"It was challenging for us when we started," says Miller. "People in HIV research said 'why are you bothering with VPU?'." Nowadays, thanks to Schinazi's and >>

The trials of taking a drug to market

Discovery

Identification of a drug target and selection of promising drug candidates.

First valley of death – preclinical trials

Lab and animal testing to determine how the drug works and safety profile.

Second valley of death – early clinical trials

Phase I
Done with small numbers of healthy volunteers. These are short-term studies aiming to determine whether the drug is safe and how it behaves in the human body.

Phase II
Done with small numbers of patients with the disease. These studies aim to evaluate preliminary data on the drug's effectiveness and short-term side effects.

Late clinical trials

Phase III
Done with a large number of patients with the disease. These studies confirm safety and effectiveness of the drug.

Marketable drug

Phase IV
After the drug is approved and released on the market, studies are conducted to determine long-term safety in the population.

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Patents allow drug companies to retain a 20-year monopoly on the revenue from drugs for which they've funded development, which can push up prices.

The price of a cure

THE WESTERN WORLD develops drugs by relying on what's called a 'patent rent'. Drug companies aim to patent a drug and retain monopoly on the drug's revenue for 20 years. Because it's a monopoly, they can charge a lot; the income they make covers the costs of developing the drug in the first place and provides their profit. But, from the point of view of getting effective treatments out to patients, is this really the best way? Dean Baker, co-director of the Centre of Economic and Policy Research in Washington in the U.S., has a string of reasons why it's not.

Firstly, he says, there is the issue of affordability. Because of their monopoly position, drug companies can charge hundreds or even thousands of dollars for drugs that cost less than $10 to make. These high prices rule out treatment for people in the developing world, for a start. He acknowledges that drug companies have to cover the high costs of developing their drugs, but estimates they could do so even if prices were 70% lower than they are today.

Secondly, high patent rents create "enormous incentives for drug companies to promote their drugs in cases where they may not be appropriate or may even be harmful", says Baker.

"Another big issue is the secrecy," Baker says. "Science advances best when it is open but when drug companies are going for patents, the incentive is to keep as much secret as possible."

Plus, there's a tendency for drug companies to concentrate on developing 'copycat' drugs, he argues. "If there's been a breakthrough drug such as Prozac, then that provides a big incentive to develop Prozac equivalents because it's clear there's a big market there. So companies may well choose to cash in on somebody else's patent rents rather than trying to develop a new breakthrough drug of their own," he says.

Having patents also biases research towards developing patentable products. There isn't any money in researching the treatment of a disease with a better diet, for instance, he says.

Finally, there's an incentive not to cure. If there is choice a between developing a one-off cure or a drug that has to be taken for 20 years for a chronic condition such as diabetes or a heart condition, the arithmetic is likely to favour the drug needed long term. "It's not a conspiratorial thing," says Baker, "they just take the best opportunity."

>> other antiretroviral drugs, most patients with HIV have very well controlled disease. But if patients go off the drugs, the virus rebounds. Miller says BIT225 is active in the monocyte macrophages (a type of white blood cell that migrates into tissue), which seem to be an important reservoir for HIV. The hope is that tackling the virus here may prevent the rebound.

"The C word (for cure) is a word you don't like using," says Miller, explaining that the idea of curing HIV has been ridiculed in the past. But she's now detecting a shift to a new optimism. "Now the buzzword among HIV academics is 'strategies for elimination'."

Miller says the Biotron story is typical of drug development. "People think drug development happens in the big pharma companies," she says. But trials are expensive, and big pharma relies more and more on a feed chain. Drug development is risky. Biotech companies are more cost-effective – particularly in Australia – and we're more flexible than the big pharma. We're carrying the risk, but that means that there is a pay-off when we on-sell the drug to pharma companies."

She's confident Biotron has enough cash to get through the second valley of death and is focussing on making her bait sufficiently enticing to be bought or licensed at the "right price". She says it's challenging because BIT225 works in a different way from other drugs under development. "We've been talking to potential partners for a long time. They want to see some really robust data, and we are getting it. It is tricky being at our end – it really is dancing with elephants."

Schinazi has obviously mastered the dance. He sounds utterly confident that the drug Gilead acquired from his company Pharmasset for a legendary US$11.4 billion will be a winner. Not only that, he believes the drug will effectively cure hepatitis C and claims it "could lead to global eradication" of the disease. Of course, he has reeled in the fish – a very big fish – and the risk (and rewards) lie with big pharma now.

Sadly, Peter Gage did not live to see whether his research on ion channels will result in his company landing a big pharma investment and making a marketable drug. But Miller is fishing hard.

Clare Pain is a Sydney-based science writer and is a regular *COSMOS* contributor.