



The Otago Institute, the Otago Branch of the Royal Society of New Zealand

NEWSLETTER

JULY 2002

A decade of Gene Therapy: has it enhanced the health of patients or simply the frustration of health researchers?

In June Warren P. Tate, of the Department of Biochemistry and Centre for Gene Research, University of Otago presented the Lunch-time Lecture.

Gene therapy was heralded in 1990 as a new technology of great promise for improving human health when it was first tried on a human patient. Its advent signalled an expectation of immediate therapeutic benefit, fuelled not only by the pioneering medical scientists and clinicians anxious to share their excitement with a wider public, but also by a media trying to satisfy our insatiable appetites for a healthier future.

Unfortunately, a large gulf existed between a 'drawing board' strategy for gene correction, and ultimate therapeutic benefit. For a start the process of delivering a new drug, must go through phased trials, and most trials in the first decade have been only at the first safety level. Despite this a small number have given indications of therapeutic success, a hint that this therapy does indeed have immense promise to deliver spectacularly in the future. Second there is a large vista of uncharted biology in the process of delivering a gene to a particular target in the human body, to securing the gene in a stable environment, and to expressing the gene as an effective level of a missing protein long term. Undoubtedly there has

been misplaced optimism that these problems would resolve easily. Nevertheless after a decade of learning, the enthusiasm and optimism for the technology remains high, but now with a much more realistic time line.

What is gene therapy? In practice it means the addition of a good copy of a gene to the existing genome as a 'nano drug'. It does *not* mean the replacement of the defective gene. Rather the bad copy is left in place and the replacement copy enters a new environment either on a chromosome or as a separate DNA element. When gene therapy was contemplated in the 1980's there was much debate about the best vehicle for delivery. Since viruses have been highly successful in transferring genetic material into human-like cells for millions of years they were attractive candidates. Counter to that, a minority view was that human cells have had millions of years to combat invading viral genes and therefore viruses may not be the best vectors for *in vivo* gene expression. An attractive alternative, bundling up the gene in a bag of cationic lipid, has been tried but it has resulted in relatively inefficient delivery to date. A compelling advantage of a virus is that it uses a specific receptor on human cells, for example, the commonly used modified retrovirus, derived from the Mouse Moloney Leuke-

mia Virus, attaches at a phosphate symport.

While the retrovirus has been the most frequently used in gene therapy trials other vehicles based on the human adenovirus, and the human adeno-associated virus have also been popular. Each has its own advantages and limitations, however, it is likely when this therapy becomes really effective the vehicle will have the best characteristics of several different viral systems, including HIV. The mouse retrovirus has efficient uptake into cells, with the gene integrated somewhere in the human genome, but it has the disadvantage that cells must be dividing (and most in the human body are not). Moreover the production of this modified virus results in a relatively low titre. This makes it only suitable for *ex vivo* transfer where specific cells are removed from the human body (for example, from bone marrow or from a lobe of liver) and the gene transfer to the specific cells occurs in culture. For *in vivo* gene transfer, at best only 1 in 50 000 cells could be affected with this system. Human adenovirus is a relatively benign human virus that in modified form can be produced at high titre and therefore is more suitable for *in vivo* application. It also affects non dividing cells, but the gene introduced is not integrated into the genome. Critical for its use severe inflammatory and immuno-

logical responses have been reported. The adeno-associated virus, against which 80% of us have antibodies, appears very safe with the modified virus having all its viral genes removed. Although the virus integrates into the human genome at a safe and specific site this key property seems to have been lost in the vehicle. Production of significant amounts of this virus for more routine use is also difficult.

There have been over 400 gene therapy trials in the first decade, with over 4000 patients. About half of the trials have targeted tumours, and the rest specific diseases, such as immunological deficiency disorders, cystic fibrosis, haemophilia, and neurological diseases. Remarkably the very first of the many trials may have been the most successful. The study was a safety trial in a 4 year old patient with adenosine deaminase (ADA) deficiency associated with Severe Combined Immune Deficiency (SCID) disease. As the first trial it was limited by the cautious regulatory authority to mature T cells only, that is restricted to cells responding only to antigens to which the young girl had already been exposed. The T cells were removed from the patient and the good gene copy was transferred to the cells by a retrovirus vehicle. The patient was continued on ADA *rtqvglp* therapy, and remarkably after 10 years she still had both relatively high T cell counts and a significant number still expressing ADA from the introduced gene. This degree of success and the girl's subsequent good health was not anticipated (and is still not completely understood). Ironically subsequent trials using haematopoietic stem cells (so a response to new, as well as pre exposed antigens was possible) proved ineffective through the decade. New millennium trials to correct an X linked SCID however, now look extremely promising.

Use of the human adenovirus has not been without problems. The gene is transferred effectively, but expression often lasts only for a short time. This may be a problem with the 'switch' used to turn on the gene, and more work is required to develop 'on' switches that contain the best combinations of normal human elements and powerful sub elements from other systems. The first major safety scare came about with this vector when a relatively healthy 18 year old male, Jesse Gelsinger, died in 1999 from a severe inflammatory response 48 h after treatment with a high dose of modified adenovirus carrying the gene for ornithine transcarbamylase (OTC). This reinforced problems that had been evident in animal studies, and it is puzzling that these warning signs did not preclude high doses in the human trial. A more highly modified 'gutless' adenovirus vector has now been produced that delivers genes equally well in animal studies but does not give the inflammatory response. Nevertheless there has been extreme reluctance to proceed with this vector while the stark memory of Jesse Gelsinger's death remains.

New Zealand has had its own drama in its brief controversial foray into gene therapy. There were a series of 'firsts' with Professor Matthew During's pioneering addition of a gene to the brains of two patients with the disease featured in the film 'Lorenzo's Oil', Canavan's disease. It used an adeno-associated vector, and a cationic lipid formulation. The trial was unusual and somewhat controversial in that the patients came from another country (USA) avoiding regulations of their own country, with the approval in the hands of New Zealand relatively inexperienced regulatory and advisory bodies. It brought to light the tension between the families of patients who are desperately looking for therapeutic benefit, and the health researcher and clinician who is essentially carrying out a safety trial with no promise of efficacy anticipated. It also brought into focus how difficult it is for the medical pioneer to advance practice by bold and perhaps high risk measures today, because regulatory bodies in approving protocols will inevitably adopt a precautionary principle when knowledge is incomplete.

Where will the next decade lead us? There is now a sense of anticipation that 'good news' stories will flow from existing and upcoming trials. Nevertheless with still much to be learned about the biology of delivering genes into human cells, improved outcomes will inevitably only follow from a better understanding of the fundamental biomedical science. Despite this there is already serious consideration of using the technology *kp'wgtq* so that correction can occur before irreversible effects of a disease take hold. Many of the same problems are to be overcome but with the added difficulties of manipulating cells or injecting directly into a fetus. As well the successes in isolating stem cells from both human embryonic and adult tissues has raised the spectre that current gene correction technologies could be combined with new advanced reproductive technologies for novel, but ethically problematical, strategies of gene correction. The pioneer of ADA gene therapy in 1990, W French Anderson, has since stated that until a gene can be delivered to a patient like insulin by simple injection gene therapy will be just too expensive, too complicated, and too dependent on specialists, to have major impact in medicine. Simple gene delivery appears closer, but perhaps still beyond the next decade.

Letter to the Editor from members of the Department of Zoology, University of Otago

Dear Editor,

It was with dismay that we read in the *Octej* '4224' *Qxi q'Kpukwng'Pgy urgwgt* that the CEO of the Royal Society of New Zealand, Dr Steve Thompson, is reported as saying that "the amount of public money going into scientific research at present was 'about right'." We sincerely hope that Dr Thompson's views were somehow misconstrued because, by almost any measure, the New Zealand government spends significantly less money on scientific research than most OECD countries: in 1998, 0.59% of GDP compared to the OECD average of 0.67% and 0.71% for Australia. In per capita dollars, this expenditure equates to \$231 compared to \$320 for the OECD average and \$383 for Australia. Figures like these (from the *QGEF* 'kp' *Li wt gu<Uc vkukeu'qp* 'yj g'o go dgt 'eqwpt kgu'4223) lead almost all New Zealand scientists (and even the editors of *Pcwtg*) to argue that more government funding is absolutely necessary for our science to be of international quality. We wonder, therefore, how Dr Thompson can apparently make such a statement. As the *QKPgy urgwgt* points out, the Royal Society has two major roles: service to society and service to scientists. In what sense does Dr Thompson's statement serve either?

Hamish Spencer, Associate Professor

Mike Paulin, Senior Lecturer and Immediate Past President
of the Otago Institute

Carolyn Burns, FRSNZ, Professor

Gerry Closs, Senior Lecturer

Alison Cree, Senior Lecturer

Lloyd Davis, Associate Professor

Ian Jamieson, Senior Lecturer

Ailson Mercer, Associate Professor

Robert Poulin, FRSNZ, Associate Professor

Michael Roy, Senior Lecturer

Colin Townsend, FRSNZ, Professor

Graham Wallis, Associate Professor

David Wharton, Senior Lecturer

Graham Young, Associate Professor

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Dear Brendon,

A letter you have received has rightly pounced on a quote from my talk to the Otago Institute early this year, and reported in your March newsletter. The quote dealt with the amount of public funding available for RS&T in New Zealand, which stands now at about 0.63% of GDP. It seems that the letter was in reaction to the report of my talk, rather than the talk itself, so I hypothesise that I must have voiced different emphases in my actual talk.

Rather than try to recall my exact words at the meeting, perhaps I should amplify the points I usually make when asked to talk on the economic growth aspects of this topic. These points are generally in line with the Royal Society's "Manifesto for RS&T" which it published in December 2000.

My usual point here is that New Zealand is "in the pack" as far as government investment in RS&T is concerned, though on the low side. We are below the OECD average of 0.68%, but considerably above the UK's 0.52%. Discussion over a second decimal place, however, detracts from the main point I made, and that is that the overall funding of RS&T in New Zealand is catastrophically low! Private sector input to R&D runs at an abysmal 0.32% of GDP, compared with an OECD average of 1.52% - almost five times greater than New Zealand. Our old nemesis, Finland, runs at a whopping 2.86%. Much has been written on cause and effect when investing in S&T, but a strong association does show between total R&D investment and per capita income, and New Zealand is well below the OECD trend line. A key difference between countries with strong growth and us is their substantially higher industry investment in R&D. These countries have a strong belief that R&D investment is their key to future success.

In my Royal Society "ALERT" newsletter comments on this year's budget, I noted that some steps were being taken to use government money to leverage increased private sector investment. If all the measures are added together, I guessed that the extra investment from industry might total to \$90m annually - nothing like the quantum leap that New Zealand needs if it hopes to reach the OECD average of GDP invested from industry. I also noted

that, while the budget increased RS&T investment in New Zealand by 4.4% this year (in line with the general trend over the last ten years), this is unlikely to get us to that oft-repeated target of 0.8% of GDP in less than 20 years.

So I'm sorry that some readers pounced on one figure. As they rightly state, the Royal Society has a role of service to society, and that role requires a broad view of how science can contribute to New Zealand as a whole. Yes, the amount of public funding is low, though not the lowest. Yes, it should be increased, but increases must also be used effectively. A personal view is that New Zealand needs to simultaneously increase the relative amounts it invests at both the basic and applied ends of the spectrum, and use public funds to lever a strong increase in private sector investment. Recent budgets have made moves in that direction, though much more remains to be done. Now look at the Votes which lie either side of RS&T. Industry New Zealand is a new agency. It needs to do much more to stimulate a research mentality in industry, and it needs to coordinate its programmes very closely with RS&T. On the other side, tertiary research programmes need similar coordination - there is anecdotal evidence to suggest that money destined for university research never fully gets there! We all see movements in the right directions, but the pace of improvement is not yet strong enough to help us climb up, rather than continue our slide down, the OECD Snakes and Ladders board. Increasing government investment in RS&T will not, by itself, get us out of the hole. As scientists we often look exhaustively at one part of the picture. As citizens, we need to see the whole.

Yours sincerely, Steve Thompson, CEO, RSNZ.

“Ready to tackle Armageddon”

A space mission to knock a potential rogue asteroid off course is undergoing feasibility studies with money from the European Space Agency (Esa). A Spanish company, Deimos-Space, is designing the mission and hopes its plans will convince Esa to give the go-ahead for a full scale test on a real asteroid. The company has come up with a plan, which it calls the Don Quixote mission, to launch a pair of probe spacecraft called Hidalgo and Sancho at a far off asteroid. One would hit the asteroid at extremely high speed, deflecting it slightly from its orbit. The other would observe the asteroid and make highly accurate measurements of what happened to it after the impact.

The idea is that the mission would tell scientists how hard they would have to hit a real rogue asteroid heading for Earth in order to deflect it safely. Deimos plans to finish its study early in 2003 and hopes Esa will then come up with the cash for the actual mission. The company is optimistic. “We believe that the outcome of this mission would be good science,” Deimos-Space’s Jose-Antonio Gonzalez told BBC News Online. “And we are trying to demonstrate the feasibility of the mission, not only in terms of astrodynamics calculations or technology requirements but also financially,” he said. The company expects plenty of public and scientific interest in the project. “That’s why we expect this mission to go on with the next phases, or at least with even more detailed studies on the key aspects of the mission,” he said. If it does, a suitable asteroid will be selected and then Hidalgo will slam into it at extremely high speed, probably around 10 kilometres (six and a half miles) per second. Sancho will be orbiting the asteroid at a safe distance to see what happens. If all goes to plan, the asteroid’s orbit will be disturbed in the beginning by a few fractions of a millimetre. The idea is that Sancho will measure this tiny shift and feed the data back to Earth. Tiny changes in orbit can become much larger over time and Deimos wants to use the experiment to calculate how to knock a real rogue asteroid off course.

Whether such an approach to dealing with an asteroid threat would work would depend largely on how much warning there is. Hidalgo and Sancho would take many months to reach their target. Any Hidalgo-like satellite used to deflect an incoming hazard would have to hit it in just the right place and at just the right speed. Getting it right would involve great precision, but, as Mr Gonzalez points out, would not require the nuclear super-rockets of science fiction. If the project does get the go-ahead, the Don Quixote mission would provide valuable information about the composition of the target asteroid. “This mission would provide, for the first time, a look inside the asteroids,” said Mr Gonzalez. “The results of the experiment would either validate our proposed strategy or might mean we have to think of other solutions, such as placing a huge solar sail on the asteroid’s surface to use the solar wind to change its trajectory.”

**Edited from BBC news on-line
Science/Nature 9 August 2002**

Robot tests linguistic theory

A project to teach a robot to learn English the way a child does, may get a boost from New Zealand's first research consortium in information technology.

The project leader, Professor Albert Yeap, of the Auckland University of Technology (AUT), is using a robot, named Albot by his students, to challenge the theory of linguists such as Noam Chomsky that children are born with an innate "universal grammar".

Albot's computer programme uses the premise that children learn sentence structure starting with the simple idea of "left" and "right", and put words together using simple rules about which kinds of words come to the left or right (before and after) other words.

Malaysia-born Dr Yeap is using Albot to test his linguistics model. He also is teaching the robot to learn to move in the way a child does.

"I have developed a theory that people move around by first capturing a representation of local spaces, then joining them together to form a cognitive [learning] environment," he said. "We are testing that with the robot to understand how the robot can move about on its own and capture a representation of the environment without being told; without being given a map."

His project is part of a package of research ideas being proposed by a new consortium combining AUT, Auckland and Waikato Universities, a cluster of health software firms and, potentially, others, including Auckland firm Peace Software and a multinational telecommunications company.

The consortium will be one of the bidders for \$1 million in matching Government funding on offer to industry-research consortiums in information and communications technology (ICT).

The Foundation for Research, Science and Technology (www.frst.govt.nz) is seeking proposals for the money. Its manager of investment operations, Peter Benfell, said the move was in line with the Government's growth and innovation package in February, which picked ICT, biotechnology and creative industries as the country's three best hopes for growth.

Three of the five industry/research consortiums approved in the foundation's last funding round, and two of the five university-based "centres of research excellence" chosen by the Royal Society in March, involve biotechnology. So far, none has involved ICT, and Tertiary Education Minister Steve Maharey has said the next two or three centres of excellence will be chosen from the other six March finalists - ruling out ICT.


Waikato University Professor Ian Graham, who would have been director of an ICT centre of excellence proposed by Waikato, Auckland and AUT in the March round, finds it "a bit ironic" that no university ICT proposal made the March shortlist.

Auckland University head of computer science Professor John Hosking said the Waikato-Auckland-AUT bid apparently had too much industry involvement rather than being a pure research "centre of excellence".

"We are hoping to get it right this time." Health software cluster member Ian McCrae, of Orion Systems, has hopes the consortium will solve how to keep records of all the tests and observations for patients with chronic diseases such as diabetes and asthma.

Sourced from The New Zealand Herald (<http://www.nzherald.co.nz/>)

13 August 2002



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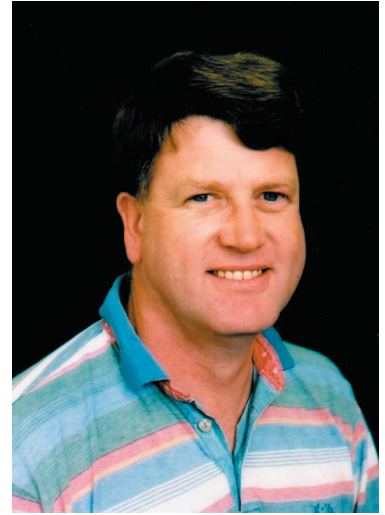
Contains:

- Updated events calander for this year.
- Hot links to other website full of information on science and technology.

<http://otagoinstitute.otago.ac.nz>

A word from the President

The purpose of the Otago Institute is to promote Research and Technology in the Otago & Southland area. The degree to which we can do that is strongly influenced by our financial resources. At a recent meeting of branches in Wellington, I was interested to be told by our Canterbury colleagues that they were the recipients of large amounts of money through endowments. This allowed them to offer a number of scholarships to young, promising researchers. For several years now we have recognised that if the Otago Institute is to thrive we need to involve more of our young researchers. Vince George has been very generous in funding the Vincent George travel award which allows one of our best young people to attend their first overseas conference. But anyone that has sat on the selection committee for this award is aware that each year of the 20-30 applications we have 4-5 excellent young people who miss out. They would all deserve and benefit from such an award. Each year the standard seems to improve and one is left feeling that we need to do more. I think that it is very important that we as an Institute should be seen to make every effort to support our outstanding young researchers. We need to involve them more in the Otago Institute and awards are a way of making them more aware of the Institute and making it more relevant to them.



Over the next few months the committee will be investigating ways to attract funding for at least 2 more travel awards. We would be grateful for any suggestions that members might have on the subject.

In closing, I wonder how many of you heard the item on the National programme this morning (13/08/02) in which an individual spoke against the AgResearch bid to have Human genes expressed in cows milk. He stated that although the cows would be contained under quarantine, in double fenced paddocks, everyone knew that microbes could not be contained by such barriers. One is left with a sense of exasperation about peoples level of basic understanding of the issues and reminded of the old proverb” A fool can raise more questions than seven wise men can answer”.

Glenn Buchan (PhD)
Department of Microbiology
University of Otago

Mincing Their Way Through France

A New Zealand company’s innovative approach to the humble mince has won it a place at SIAL, the world’s largest food exhibition, in France. Aria Farms, based in Hamilton, has cracked the code of how to make frozen mince flow freely from the freezer bag and their unique process will be New Zealand’s only entrant in the ‘most innovative meat, poultry and delicatessen meats’ category at this year’s SIAL. A grant of \$27,000 from Technology New Zealand’s Grants for Private Sector Research and Development scheme (GPSRD) helped find the solution to ‘de-clumping’ minced meat. Owner Erik Arndt has developed a way to deactivate amino acids, allowing the flakes of meat to remain separate while frozen and during cooking. Anna Arndt, of Aria Farms, says the research aimed to find ways of adding value to meat, particularly to lower grade cuts. “We also wanted to find a more user friendly and healthy product, and the free flow mince is much lower in fat than usual minced meat (around 1.5%).”

Ms Arndt says the product is already selling well in supermarkets, at a price similar to premium grade and she expects it to be popular in the food service industry, because of the convenience of free flow. “The Technology New Zealand funding was pivotal in helping us develop this process, which has led to being chosen for SIAL. It’s hard to find the time and energy to develop new products and we’re very pleased to be able to represent New Zealand innovation. Hopefully this will be good for the food industry as a whole,” she says. Ms Arndt says that while beef is the main product, the process can also be used to make lamb and pork free flow frozen mince.

From <http://www.frst.govt.nz/news/2002/MinceMeat-Jun02.cfm>

Lunchtime Lecture Series

The next lunchtime lecture is will be by Dr William Harris of the Political Studies Department at the University of Otago. His talk entitled "Middle Eastern Politics" is topical and sure to inform those present on this important global issue. The talk will be at 12 noon, Wednesday 14 August at the Hutton Theatre, Otago Museum.

Editorial



In the December 1999 issue of the *Otago University Gazette*, former editor Michele Coleman, speculated on what the incoming government would offer in terms of science and science education.

Less than three years later and it has become very apparent that initiatives dealing with the concept of the "knowledge economy" have been central to the government's involvement in the promotion of science and technology.

As I have mentioned in my previous editorial, we must maintain the momentum that has been generated in this area.

By the time you read this editorial you will be in the process of selecting a new government to take New Zealand into 2005.

Let's hope that New Zealanders as a whole realise that creating a society of "mental wealth" as well as financial wealth is just as important and they make this issue clear in the minds of their respective representatives for their electorate.

This is one means by which we can ensure that the "knowledge economy" thrives over the next few years and that science and science education continually develops.

Brendon J. Woodford
bjwoodford@infoscience.otago.ac.nz



Winner of the 2002 Vincent George House of Travel Award

Winner was Zane Andrews, who has just submitted his Ph.D. thesis working under the supervision of Dr. Dave Grattan, Department of Anatomy and Structural Biology, University of Otago. Zane's thesis involved an investigation of the regulation of prolactin secretion during late pregnancy in rats. He has published 3 papers in international journals on the basis of his research to date, with another paper currently under consideration. Zane is planning to attend the 5th International Congress on Neuroendocrinology in Bristol, UK in September, to present a paper entitled "Opioid receptor regulation of prolactin secretion during pregnancy and lactation".

Annual Otago Institute/Friends of the Museum Dinner

Where: Otago Museum Atrium
When : Thursday 19th September 2002 at 6:30pm for 7:00pm
Cost: \$35 per person (includes pre-dinner drinks, dinner, and wine or fruit juice with dinner)
RSVP: Return slip with payment by Tuesday 10th September to PO Box 6373, Dunedin North

After the dinner, Brian Patrick will speak to us about the setting up of the Southern Land/Southern People Gallery. The talk will be followed by a tour of the gallery with either Brian or one of the communicators who have been specifically trained to take tours of the gallery.

Please return the following slip with payment of \$35 per person by 10th September if you wish to attend. The Otago Institute/ Friends of the Museum Dinner 19th September 2002

Name(s)

Contact number

Number of persons attending

Return to the Secretary:
PO Box 6373, Dunedin North.

Next Otago Institute Talk

Dr Bill Harris
(Political Studies,
University of Otago)

Speaking on the theme
"Middle Eastern Politics"

12 Noon
Wednesday 14 August

Hutton Theatre
Otago Museum

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