University of Otago
Te Whare Wananga o Otago

Centre for Gene Research
# NEWSLETTER

*Editor: Craig Marshall craigm@clutha.otago.ac.nz* *Volume 3 Number 1 March 1996*

## Centre for Gene Research News

### Activities for 1996

I am afraid that we have had a slow start to the year so far but your committee is looking to set up several activities for the year. One will be a repeat of our successful Poster Nights so keep those posters from meetings attended during the year. We are also looking to hold another one-day workshop in some selected field. Last year's workshop on yeasts and yeast technologies provided a very good model to follow up on. What we need, however, is a topic or topics to include and we would appreciate any input from members of the centre–after all, the goal is to find something for the benefit of centre members. We have budgeted to cover fares to bring someone to Dunedin from as far away as Australia as a keynote speaker at our workshop. Any ideas to me please.

Last year we held a successful hands-on course on the use of the GCG computer package. This was attended by around 20 people and the feed back was very positive. There is the opportunity to repeat this course this year but we would need to have something between 10 and 15 people to make it worthwhile. The likely date will be in the mid-year break. If you are interested please contact either myself or Mark Dalphin. There will be a charge of $100 per person ($50 for students) as there was last year.

Murray Grigor
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## Editorial[1]

Welcome to the first issue of the Centre for Gene Newsletter for 1996. As always we are looking for articles from members of the Centre: conferences attended, group profiles, techniques or equipment that look interesting, provocative articles to stimulate debate–all will be gratefully accepted.

The Research Management Plan is now a reality, at least in draft form. Although there are still doubts in some minds as to the value of managing research in such a way, a draft plan now exists and is expected to be in operation later in the year. Among the "current areas of research excellence" are *Gene Structure and Function* and *Oxidative Stress in Health and Disease* which are a reflection, in part at least, of the strength of the research within the Centre for Gene Research. How new areas will develop and how new researchers will establish niches for themselves remains to be seen.

Craig Marshall

[1] Editorial comment is not necessarily the official position of the Centre for Gene Research

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## Conference for Women in Science Coming Up

The following is a press release from the organisers of "SCIENCE-WOMEN AND OUR FUTURE", a conference organised by the Association for Women in the Sciences Inc (AWIS). The Dunedin-based National Executive of AWIS is pleased to report that more than a dozen Otago University women will be attending "Science–Women and our Future", thanks to the generous support of the Dean of the School of Medical Sciences and the AVC of the Division of Sciences.

PRESS RELEASE: WOMEN SCIENTISTS CHALLENGE

Genetic engineering, climate change, reproductive technology...what do we expect from scientists as they develop ideas that change our world? What do scientists expect of themselves?

New Zealand's women scientists are taking responsibility for asking the hard questions about established patterns in scientific thinking. In the 1996 Conference "Science–Women and our Future" in Wellington in May, speakers and participants are challenging the myth of objectivity, the way that the approach to science is constructed, and the philosophical and methodological underpinnings.

"We're taking up the challenge the public is laying down" says Conference Convener Karen Field. "Scientists are being asked to communicate about what they're doing, to think strategically about the effects, to be accountable for their impact on society. At the same time, we want to challenge the community to say what they really want from science."

"In 1993 the Association for Women in the Sciences ran a Conference for Suffrage Centennial Year. It was the first time that women scientists and technicians had heard the voices of other women in science in New Zealand. It was amazing! A lot of issues were raised about what women are doing with science in the community. The debate has continued in a variety of forums around the country. Now what we want to do is to address the question of where women want

to take science in the future. What are the issues for science to address? How? What are the ethical issues? What are the appropriate structures? Are there different ways of doing science? How do we get accessibility and dialogue with the community? Where does social responsibility come in? Those are the questions we want to address."

Karen Field says that of course there will also be a lot of "current work" discussed, as women scientists update each other about developments across the disciplines. "All the other scientific conferences in New Zealand are based in their own disciplines. This is the only cross-disciplinary scientific conference in New Zealand–and one where women who are not actually involved in science but interested in the philosophies and debates are also enthusiastically welcomed."

AWIS is pleased to report that more than a dozen Otago University women will be attending "Science-Women and our Future", thanks to the generous support of the Dean of the School of Medical Sciences and the AVC of the Division of Sciences.

For more information contact Jean Fleming, Physiology (ext 7320) or try the AWIS WWW Home Page, which you can access in the Recreation/Clubs section of the University of Otago Home Page.

Jean S Fleming

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## The Health Research Council Virus Research Unit

**Department of Microbiology, University of Otago.**

### A brief history

The Virus Research Unit originated from initiatives by the Dean of the Otago Medical School, Sir Charles Hercus, and the Professor of Biochemistry, Dr Norman Edson, to broaden the School's research base in the postwar period. In 1945 the Medical Research Council of New Zealand established a Committee for Research in Immunology and Viruses and appointed Dr Max Richardson to set up a Virus Laboratory. Four years later he was succeeded by his colleague, Dr Lyle Fastier, who continued the development of a dedicated Virus Laboratory. Professor John Miles became Honorary Director of the Virus Laboratory in 1955 and saw it restyled the Virus research Unit in 1962. After Professor Miles retired in 1979, Dr Tony Robinson was appointed Director, a position he occupied from 1983 until he resigned in 1993. Dr Andrew Mercer has been Programme Director since that time. The Unit is currently working with three viruses, dengue virus, human papilloma virus and orf virus. In each case a molecular approach is being taken to work towards the development of vaccines. Funding is provided by grants from the Health Research Council, the Foundation for Research Science and Technology and the New Zealand Lottery Grants Board.

The **dengue viruses** are being studied by Terry Maguire with the technical help of Yvonne Coughlan. Dengue is a serious, insect-transmitted disease of tropical regions, including the Pacific islands. Dengue viruses are responsible for millions of cases of dengue fever and dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) worldwide each year. Dengue fever is an acute illness characterised by fever, headache, pain in the joints, prostration, rash, lymphadenopathy and leukopaenia. DHF is a severe febrile illness producing abnormalities of haemostasis and increased vascular permeability, which in some cases leads to hypovolemic shock and death. DHF and DSS are responsible for thousands of deaths in countries where the *Aedes* mosquitoes which transmit these viruses abound. Dengue thus represents a major public health problem and is certainly the most important arthropod-borne viral disease in terms of human morbidity and mortality. Although the vector for this disease does not yet occur in New Zealand, the disease is widespread in the Pacific and cases are regularly imported into New Zealand. The recent accidental introduction to New Zealand of a vector mosquito in tyres imported from Japan, the possible effects of global warming on vector distribution, increased urbanisation and rapid air travel by infected individuals, together make arthropod-borne viruses an increasing threat to this country.

In an effort to assist in rational decisions in the development of an effective vaccine, we are studying functional epitopes (antigenically reactive sites) within the surface envelope glycoprotein (E) of dengue type 2 virus. We are interested in those individual amino acids or peptide sequences which are involved in antibody binding and neutralisation of viral infectivity. Identification of important amino acids in these sites is being made through the isolation of neutralisation escape mutants which occur when the parent virus population is grown in the presence of neutralising amounts of an E-specific monoclonal antibody. These mutants have lost the abi-

lity to bind with the selecting antibody. This loss usually involves a single amino acid change which can be located by sequencing the RNA of the mutant. We have so far obtained and sequenced eight such mutants and we are able to compare the epitopes with those found in other flaviviruses. Such information is helping to build up a map of the important binding sequences of these viruses - maps which will assist in the design of protein sub-unit or engineered vaccines against these agents. We are also looking at cell receptors for dengue virus in collaboration with Dr R. Marks, University of Michigan.

**Human papillomaviruses** (HPV) comprise a group of over 70 genotypes that are known to infect both human skin and mucosa. A subset of these viruses is specific for the anogenital tract, where some types (HPV6 and HPV11) usually induce benign proliferation of the genital skin and mucosa, while other types (particularly HPV16 and also HPV18) are linked to premalignant lesions and carcinoma of the cervix. It is possible to isolate HPV DNA from around 80% of cases of *in situ* and invasive cervical cancer, though it is currently unknown whether HPV has a role in the development of the remainder of cases.

The incidence of cervical carcinoma is high world-wide. The World Health Organisation estimates that half a million women die from this disease each year and the incidence of HPV infection has been increasing over the last twenty years. This disease is costly to control through cervical screening programmes which are often unavailable in poorer countries. The development of an effective vaccine against the causal virus may control a serious world health problem.

We are currently investigating ways of stimulating protective immunity against HPV16. Our interests are concentrated primarily on using one of the early proteins of HPV16, E2 as a target. Merilyn Hibma, currently an HRC Repatriation Fellow, is conducting the study of immunity to HPV. Lucy Heinemann is studying the role of cytokines in protection against HPV and Lauren Woodfield is determining whether HPV16 E2 is a target for cytotoxic T cells.

**Orf virus** is a poxvirus that causes a highly contagious, eruptive disease in sheep and goat populations worldwide and is readily transmitted to humans. It is our goal to characterise the interaction between orf virus and infected hosts. We have adopted a multi-faceted approach aiming both to identify orf virus antigens that induce protective immunity and to investigate virulence determinants of the virus with the possibility of exploiting this information in vaccine development.

Protection against orf virus is thought to be mediated by cytotoxic T cells with antibody playing little or no part. Characterisation of the targets of the protective immune response to orf virus and investigating noninfectious modes of immunisation will provide important information relevant to infection by this and other viruses. We have approached this goal by using vaccinia virus recombinants containing multigene fragments of orf virus DNA to identify genes encoding candidate antigens.

The recent identification of numerous poxvirus-encoded factors which interfere with the immune response of the infected host has resulted in widespread interest in the opportunities provided by these viruses for the discovery of novel therapeutic agents, for the gaining of new insights into the operation of mammalian immunity and for the directed attenuation of pathogens. We have evidence of four orf virus factors with potential to influence the responses of an infected individual. Three of these have not been reported in other poxviruses, and all are encoded by genes found in a 30 kb region of the orf virus genome which we postulate is unique to the parapoxvirus genus.

These investigations of orf virus are being conducted by Steve Fleming and Andrew Mercer with the technical assistance of Cathy McCaughan and Ellena Whelan, and the participation of postgraduate students, Loreen Savory and Georgie Roberts. Loreen is investigating the activities of an orf virus-encoded homologue of vascular endothelial growth factor, while Georgie has mapped and sequenced the gene encoding an orf virus envelope protein. A separate orf virus project is the responsibility of David Lyttle and Chris Moore. That project is attempting to apply to orf virus the potential various poxviruses have shown as vaccine vectors. We believe that orf virus may become a very useful vehicle for the delivery of antigens able to induce immunity against appropriate pathogens of sheep.

This year three further postgraduate students will join us: Dave Reeve to study the expression of a viral encoded homologue of interleukin–10; Garry Jenkins to establish a cytotoxic T lympho-

cyte assay for orf virus infected cells; and Trudie Bateman to sequence and analyse a region of the orf virus genome that appears to not be represented in other related poxviruses.

**The Lighter Side of Laboratory Life**

Members, partners and children of the Unit staff and students have always enjoyed an active social life outside working hours, with numerous activities being organised over the years. Very successful and happy Christmas parties, Midwinter parties, and any-other-excuse parties are frequently held, along with week-end retreats, Unit expeditions to the mountains (otherwise known as mobile parties), cricket matches and golf tournaments. Virology rarely enters the conversation at these times, but social activity has been an important part of building up a very happy working relationship within the group. As one individual said after a recent Unit outing to a particularly sleazy film, 'people who can sit through that together can do anything together'. We try.

Andy Mercer

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## Gordon Research Conferences

**Oxygen Radicals in Biology**
**11-16 February 1996**

**Ventura, California, USA**

The range of topics covered at the 9th biennial Gordon Conference on oxygen radicals reflected the many different areas of biology for which oxygen radicals are significant. The Conference started with a session (appropriate, considering the proximity of LA) on radicals and air pollution, focusing on the lung damage caused by the ozone and oxygen and nitrogen radicals in air pollution. The next sessions considered the potential health benefits of plant derived antioxidants in our diets. This research stems from the well established findings that fruit and vegetables protect us from cancer and other diseases–hence the recommendation for "five servings of fruit or vegetables a day". However, it is unclear which are the actual active constituents in fruit and vegies. A combination of lab and epidemiological intervention studies has failed to come up with definite answers: at the moment carotenoids are losing favour but flavonoids have attracted some interest. However, it may be impossible to mimic *in vivo* the effects of a complex mixture with a single component. Furthermore, it is still unclear if the efficacy of fruits and vegetables are due to their antioxidant properties–flavonoids, for example, have many other pharmacological effects.

The next session looked at oxidative stress and aging–a field in which the urgency of research effort seemed to increase dramatically as workers enter their late fifties! A number of studies in lower organisms, notably those of Raj Sahal on Drosophila, suggest a definite link between increased oxidative stress and aging, although which was cause and which was effect was unclear. However, the only proven way to live longer (for mice, at least) was shown by Rick Wein to be by caloric restriction–in practice this means a very low calorie diet, supplemented with all necessary vitamins and micro-nutrients. This causes mice to live 30-40% longer, in excellent health, until they finally die of boredom. Most delegates reckoned living a life of perpetual hunger was too big a price to pay for an extra 20 years. However, as this research does suggest that a decrease in oxidative stress may be partly responsible for the life extension, caused by caloric restriction, pharmacological interventions may be possible to decrease the stress without starving. One other possibility suggested was the pharmacological modulation of the recently discovered leptin pathway to suppress hunger and thereby make caloric restriction bearable.

The next few sessions looked at the role of oxidative stress in a host of pathologies; inflammation, ischaemia/reperfusion injury and cancer. The final session on the role of oxygen radicals in apoptosis was interesting, with some new data showing early modulation of GSTs in apoptosis, however the rationale or consequences for the cell of this was unclear. The final report by Sten Orrenius on the rapid efflux of glutathione from cells very early during apoptosis suggested a range of possible interactions between oxidative stress and apoptosis.

Overall, the conference gave a good overview of current research, although there were no major new data or breakthroughs. It was also an excellent opportunity to meet some of the big names in the field in a pleasant environment.

Mike Murphy

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**Gordon Conference on Angiotensin**

**Ventura, California, USA**

This meeting was held in Ventura, California in mid-February. Because of the diverse roles of angiotensin, this meeting attracted people from

the cardiovascular and nephrology fields. Unfortunately neither group seemed to want to talk to each other and it was left for the general biologists to hold things together. There have been some exciting developments in the angiotensin cell signalling field over the last couple of years particularly in terms of the control of gene expression. The pathway from the receptor at the cell surface to the cell nucleus has become immensely more complicated and inhabited by multiple protein kinases and their substrates. Several groups have taken advantage of the availability of new monoclonal antibodies to many of these proteins to map their involvement in the signalling sequence. Overall this is proving to be a powerful technology. Other new developments relate to the cloning and analysis of several ion channels and the elucidation of several genetic disorders relating to the ion channel function. Overall this was an interesting meeting at the interface between the disciplines of physiology and molecular biology. It is clear that the complementation of these techniques has accelerated progress in this field greatly.

Murray Grigor

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## Computer Corner

New Software: a number of new versions of software are available from Information Technology Services (formerly CSC). Most of these are significant improvements on the old software particularly if you are one of those lucky enough to have a PowerMac. The software can be found on the server CWIS in the Central Services zone. Log in as guest and select the CWIS disk. In here you will find a number of item of which the Network items are of particular interest to us. NetScape Navigator™ v2.01, NCSA Telnet v2.7b4 and Fetch v3.0 are all available here. On this disk is also the most recent version of the Macintosh operating system, System v7.5 Update v2.0 which can be found inside the Site Licensed Software. Also at this site is server called ITS_public which has a wide variety of Macintosh software of various sorts.

With your newly updated Netscape you might to look around the Internet. For those who did not see it last year, an excellent site for molecular biology is Pedro's Research Tools (http://www.public.iastate.edu/~pedro/research_tools.html) which has a tremendous collection of sites useful and interesting to molecular biologists. Wilbur's Hotlist (http://sunset.bph.jhu.edu/~kuo_wy/index.shtml) is also a useful site with a slightly broader focus.

ITS are running a computer expo on April 11 and 12. As well as a number of talks, there will be displays of various equipment and services. It might be worth your while to wander over there for an hour or two. Last year rather nice muffins were available if you turned up at the right time.

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## Hot Tip

A recent paper suggests that transformations of *E. coli* can be done in 5 minutes with no heat shock steps and at a higher efficiency than with the conventional approach. The new method suggests that adding DNA to cells, keeping them on ice for 5 minutes and then plating them out onto pre-warmed plates provides better results than the usual heat shock and recovery. Pre-warming the plates is apparently very important. Full details of the method can be found in Pope, B. & Kent, H.M. (1996) "High efficiency 5 min transformation of *Escherichia coli*" Nucleic Acid. Res. 24:536–537. Herman Pel has tried it and found it to be good, and so have we.

Craig Marshall