Business Name

Australasian Gene Therapy Society Inc.

INSIDE THIS ISSUE:

Message from the President

Dear AGTS members,

Where does the time go? It seems like only yesterday we were running the 7th AGTS meeting at the Bio21 Institute in Melbourne. The meeting was a great success, and in times of general financial constraints on many people and organizations, it was amazing to have been able to invite seven international speakers, as well as so many high profile Australian researchers. Particular thanks again to our generous major sponsors for that meeting: Benitec, Sigma-Aldrich, FSH Global and Genzyme.

It is now 15 months later, and although many of us are still recovering from the grant-writing season*, planning is well underway for the 2013 meeting. The 8th AGTS meeting will be held 8-10 May, in the Ariel Function Centre, UTS, Sydney, and the proposed speakers will guarantee a most lively, informative and stimulating meeting.

* Some of us had more than grants to worry about; congratulations to Sam and Pete on the birth of Jethro James.

Best paper prize winners in 2011 were Dr Sharon Cunningham (Children's Medical Research Institute), Dr Michael Gantier (Monash Institute of Medical Research) and Shannen Lau (Monash Institute of Pharmacy) and, so far, in 2012 Associate Professor Frank Alderuccio (Monash University) and Dr Christopher Siatskas (Monash University). There has been a slight change in criteria in that AGTS members who are either first or corresponding authors are eligible for the prize. Hence, do not hold back if you are a member, submit your latest papers to Sam at sginn@cmri.org.au.

The AGTS aims to advance the growth and development of gene and genetic therapies to treat inherited and acquired disorders, and one of the most effective methods is the promotion of special seminars, meetings and events for the lay community, as well as specialist research institutions around Australia and internationally. Where possible, we promote presentations from our members as they travel to and from other meetings or conferences. Although we are a small society, we continue to explore links and associations with other like-minded groups to promote and publicize Australasian gene and genetic therapies on the national and international stage.

At the 2011 AGTS meeting, the Executive committee election resulted in Dr Sharon Cunningham joining the group, with Elizabeth Rakoczy stepping down. Hence the committee consists of Rose Martiniello-Wilks (Vice President), Ann Simpson (Treasurer), Samantha Ginn (Secretary) and Jim Vadolas,

Paul Gregorevic and Sharon Cunningham as Executive members. I am delighted Gerry Both has agreed to stay on in an ex-officio capacity, and although Gerry always seems to have too much time for golf and some grueling bike rides, his advice is always appreciated. My sincere thanks to the entire team, as their tireless efforts in face of ever increasing demands on their time will guarantee we remain a strong and vibrant society.

Professor Steve Wilton
Winthrop Professor, University of Western Australia

Director of Translational Research and Development The Australian Neuro-muscular Research Institute and Centre for Neuromuscular and Neurological Disorders

President, Australian Gene Therapy Society

"Best paper" Prize by an AGTS Member

Congratulations to AGTS members Dr Sharon Cunningham (Gene Therapy Research Unit of the Children's Medical Research Institute), Dr Michael Gantier (Centre for Cancer Research of the Monash Institute of Medical Research), Shannen Lau (Department of Medicinal Chemistry and Drug Action of the Monash Institute of Pharmacy), Associate Professor Frank Alderuccio (Department of Immunology, Central Clinical School, Monash University) and Dr Christopher Siatskas (Monash Immunology and Stem Cell Laboratories, Monash University) for their papers:

Cunningham *et al.* (2011). Induction and prevention of severe hyperammonemia in the spf^{ash} mouse model of ornithine transcarbamylase deficiency using shRNA and rAAV-mediated gene delivery. *Molecular Therapy* 19(5): 854–859

Gantier *et al.* (2011). Analysis of microRNA turnover in mammalian cells following *Dicer* ablation. *Nucleic Acids Research* 39(13): 5692-703

Lau et al. (2012). Enhanced extravasation, stability and *in vivo* cardiac gene silencing via *in situ* siRNA–albumin conjugation. *Molecular Pharmaceutics* 9(1): 71-80

Nasa *et al.* (2012). Nonmyeloablative conditioning generates autoantigen-encoding bone marrow that prevents and cures an experimental autoimmune disease. *American Journal of Transplantation, accepted for publication 01 March 2012*

Siatskas *et al.* (2012). Thymic gene transfer of myelin oligodendrocyte glycoprotein ameliorates the onset but not the progression of autoimmune demyelination. *Molecular Therapy, advance online publication 21 February 2012*

Don't Forget to Send us Your Papers!

To encourage our early career scientists and disseminate information among members, the AGTS Executive is offering two $250 awards twice a year. These will be offered in each 6 month period of a calendar year to the first or corresponding author of a gene therapy or RNA therapeutic publication. Only current AGTS members may apply and the award is open to all AGTS members (the young as well as the wise).

Please send your paper details to our Secretary at sginn@cmri.org.au for consideration.

Gene Therapy Fulfilling its Promise

A landmark trial for Haemophilia B

Researchers in a clinical trial, lead by Professor Amit Nathwani from the Department of Haematology, University College London Cancer Institute and performed in collaboration with Katherine High (Children's Hospital of Philadelphia), Mark Kay (Stanford University) and Andrew Davidoff and Arthur Nienhuis (St. Jude Children's Research Hospital), have treated six adult males suffering from severe Haemophilia B with gene therapy. Using a single peripheral vein infusion, patients were given one of three doses of a serotype-8-pseudotyped, self-complementary adeno-associated virus (AAV) vector expressing a codon-optimised human factor IX (FIX) controlled by a liver-specific promoter. Vector was delivered in the absence of immunosuppressive therapy and, at the time of publication, patients were monitored for between 6 and 16 months. AAV-mediated expression of FIX resulted in between 2 to 11% of normal levels in all patients. Furthermore, four of the six patients were able to discontinue FIX prophylaxis and remained free of spontaneous haemorrhage. For the other two, the time between prophylactic injections was increased. For the two patients receiving the high dose of vector, one had a transient elevation of serum aminotransferase levels with an associated detection of AAV8-specific T cells, and the other, a slight increase in liver-enzyme levels. Both were treated with a short course of glucocorticoid therapy that rapidly returned aminotransferase levels to normal, without the loss of transgene expression. Although long-term follow-up is required on more patients, this approach, despite the risk of transient hepatic dysfunction, has demonstrated the potential to convert the severe form of this disease into a mild form or to reverse it completely.

Full details can be found in their *New England of Journal of Medicine* paper:

Nathwani *et al.* (2011). Adenovirus-associated virus vector-mediated gene transfer in Hemophilia B. *New England Journal of Medicine.* **365 (25):** 2357-2365

Transfer of genetically modified T cells results in potent anti-tumour effects in three patients with chronic lymphoid leukaemia

Researchers from the Abramson Cancer Center in Philadelphia have recently described the treatment of three patients with chronic lymphocytic leukemia (CLL) with autologous T cells that were genetically modified to express a chimeric antigen receptor (CAR) with specificity for the B-cell antigen CD19. This publication builds on the earlier data published for one of these patients (Porter *et. al.,* 2011), in which complete remission was achieved following an infusion of 1.42×10^7 transduced T cells, modified to express the CAR (CART19 cells). For all three patients in the most recent report, all carrying considerable CLL tumour burden, CART19 cells were administered following conditioning chemotherapy designed for depletion of lymphocytes. The gene-modified cells were administered over three consecutive daily intravenous infusions, starting one to five days after the chemotherapy. Post-infusion complications were limited to a transient, and treatable tumour lysis syndrome occurring after between seven and twenty-one days post infusion.

At the time of publication, two of the three patients were in complete remission, at 10 and 11 months post-therapy, with the third patient showing a partial response at 7 months post-therapy. Persistence of CART19 cells was also demonstrated, suggesting that this strategy may provide sustained tumour control in these patients. This work highlights a promising new approach for treating chemotherapy-resistant cancers.

Full details can be found in their *Science Translational Medicine* paper:
Michael Kalos, *et al.* (2011) T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia *Sci Transl Med* **3 (11):** 95ra73

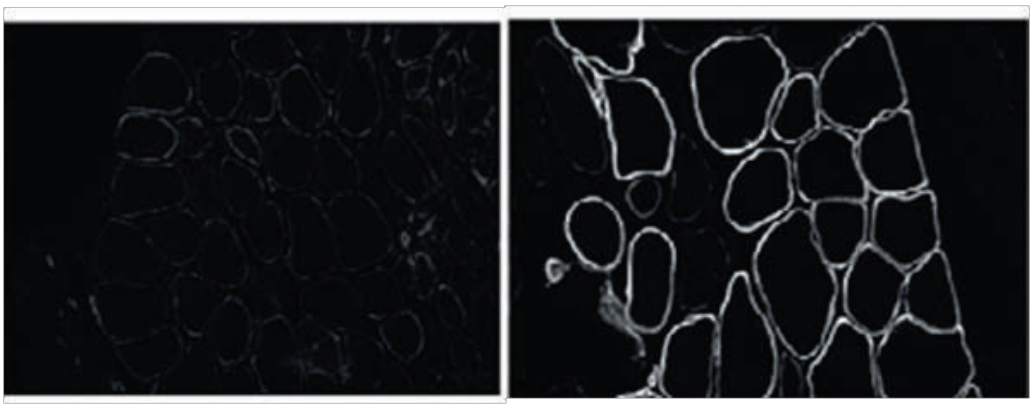
And their earlier *New England of Journal of Medicine* paper:

Porter *et al.* (2011). Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia. *New England Journal of Medicine.* **365 (8):** 725-733

Good News for Australian Gene Therapy

Results from the latest morpholino oligomer exon skipping trial have been published (The *Lancet*, 378: 595 - 605, 2011) and the title says it all: "Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study". The test compound, AVI-4658 was designed in Perth and found to induce exon 51 skipping, with expression of patient specific Becker muscular dystrophy dystrophin isoforms in a dose-dependent, but variable manner in participants in cohorts 3 to 6 (doses 2, 4, 10 and 20 mg/kg/week) onwards. The three patients who showed the greatest responses to treatment had 21%, 15%, and 55% dystrophin-positive fibres after 12 weeks treatment. Western blotting showed increases in dystrophin from 2% to 18%, from 0·9% to 17%, and from 0% to 7·7% of those in normal muscle. No clinical benefit was observed after the short safety and tolerability study, and extended higher dose studies are currently under way at Nationwide Children's Hospital Columbus, Ohio. Preliminary results from this study are expected towards the end of year.

Demonstration that splice switching morpholino oligomers are capable of more than exon skipping to address protein-truncating mutations in the dystrophin gene, Porensky and colleagues report "A single administration of morpholino antisense oligomer rescues spinal muscular atrophy in the mouse", in Human Molecular Genetics (Epub date 2011/12/22, December 20). Untreated pups die by day 15, whereas survival was increased markedly to over 100 days after a single intracerebroventricular injection of a morpholino oligomer targeting a strong intronic silencing element downstream of SMN2 exon 7. One animal survived to 165 days as a result of a single treatment, and such encouraging results have initiated discussions on how clinical trials could be conducted. Spinal muscular atrophy is one of the most common human autosomal recessive disorders and the leading genetic cause of death in children under the age of 2 years. This disease arises from the loss of the *SMN1* gene, and inappropriate splicing of the near identical *SMN2* gene only provides sufficient functional gene product to keep SMA Type 1 children alive for up to 2 years.



Sections of untreated (left) and treated (right) muscle specimens immunolabelled with an antibody against human dystrophin from one patient who responded to treatment

(from Cirak *et al.* 2011 *Lancet* 378: 595-605)

AGTS Notice Board

Congratulations to AGTS members...

Mr Jieyu Chung
Post-graduate scholarship from Multiple Sclerosis Research Australia
Title: Mechanisms of tolerance induction following genetically modified bone marrow transplantation in preventing experimental autoimmune encephalomyelitis
Total Funding $81,600

Associate Professor Frank Alderuccio
Incubator grant from Multiple Sclerosis Research Australia
Title: Regulatory T cells to treat experimental multiple sclerosis
Amount: $24,200

Dates for your Diaries

The XXth ESGCT and SFTCG Collaborative Congress will take place in the beautiful city of Versailles from 26th to 29th October 2012. Details are available on the ESGCT website at www.esgct.eu

The Australian Health & Medical Research Congress

The 5th AH&MR Congress will be held on the 25th-28th November 2012 at the Adelaide Convention Centre. Details are available on the congress website at www.ahmrcongress.org.au

Planning is now underway for the 8th biennial AGTS conference. Next year, the conference will be held in Sydney from the 8th to the 10th May. Please check the AGTS website for more details at www.agts.org.au

Australasian Gene Therapy Society Inc.

The 7th AGTS Conference

The time since our biennial meeting, held at the Bio21 Institute in Melbourne on 4th to 6th May 2011, seems to have flown by. With the help from our sponsors, we were able to invite an impressive lineup of International and National speakers; Professor Alexandra Belayew, Professor Melanie Ehrlich, Dr Dirk Grimm, Professor Doug Hilton, Professor David Kaye, Professor Maria Kavallaris, Professor Alan Mackay-Sims, Dr Tomoji Mashimo, Professor John Mattick, Professor John Rossi, Professor David Russell, Dr Dominic Wall and Professor York Zhu. Again, with help from our sponsors, we were able to award many prizes to our student members and Dr Nham Tran (Translational Cancer Research Group, University of Technology, Sydney) received the Panos Ioannou Young Investigator Award. Professor Doug Hilton presented an excellent Greg Johnson Memorial Oration, and we conducted a successful election to install a new Executive Council, with Elizabeth Rakoczy stepping down and Sharon Cunningham joining the Committee.

Delegates at the 7th Biannual Australasian Gene Therapy Society Meeting,
4th - 6th May 2011, Bio21 Institute, Melbourne, Australia.

Meeting Sponsors

Greg Johnson Memorial Oration by Professor Douglas Hilton

Pathways regulating blood cell production

Douglas Hilton & many generous and valued colleagues in the Divisions of Molecular Medicine, Cancer & Haematology, Molecular Immunology and Bioinformatics.

The Walter and Eliza Hall Institute of Medical Research and the Department of Medical Biology, University of Melbourne.

While an undergraduate and PhD student in the Cancer Research Unit at WEHI in the mid to late 1980s, I was privileged to work alongside Greg Johnson. Greg was a generous and warm teacher and was a wonderful example that great science could go hand-in-hand with having good fun. I have a copy of Greg's PhD thesis "Hepatic Haemopoiesis: A Developmental Study" on my bookshelf and refer to it regularly. I consider it a tremendous honour to be the 2011 Greg Johnson Orator.

My current research takes genetic, genomic and bioinformatic approaches to identify gene networks important in regulating haemopoiesis; the production of nine lineages of blood cells from multipotential, self-renewing stem cells. In this presentation I will discuss our most recent published and unpublished experiments that focus on stem cells and commitment to the megakaryocyte lineage.

"Greg was a generous and warm teacher and was a wonderful example that great science could go hand-in-hand with having good fun."

Dr Nham Tran Recipient of the 2011 Panos Ioannou Young Investigator Award

On April 14th, 2005 the Executive Members of the AGTS on behalf of its Members established the Panos Ioannou Young Investigator Award in recognition, appreciation and thanks to Panos for his founding, passionate and sustained support for young scientists in the society. At the closing session of the 7th AGTS meeting, Dr Nham Tran (Translational Cancer Research Group, University of Technology, Sydney) received the Panos Ioannou Young Investigator Award to be used for conference travel expenses up to the value of $2,500.

AGTS President Steve Wilton presenting the Panos Ioannou Young Investigator Award

O13: Co-Regulation of the Programmed Cell Death Protein 4 (Pdcd4) by miR-21 and miR-499

Nham Tran [1, 2, 3], Xiaoying Zhang [1, 2], Barbara Rose [1, 2], and Rosetta Martiniello-Wilks[3]

[1.] The Sydney Head and Neck Cancer Institute, Sydney Cancer Centre, Royal Prince Alfred Hospital and University of Sydney, Sydney, NSW, Australia. [2.] Department of Infectious Diseases and Immunology, University of Sydney, Sydney, NSW, Australia. [3.] Translational Cancer Research Group. School of Medical & Molecular Biosciences. University of Technology Sydney, NSW, Australia

MicroRNAs are small non coding RNA molecules which control gene expression and dysregulation of the miRNA milieu is associated with head and neck cancer. Several studies have reported on the expression profiles in head and neck cancer but one of the main challenges is to understand the role of these dysregulated miRNAs in head and neck tumorigenesis. Here we report on a non-coding miRNA profiling study using oropharyngeal squamous cell carcinoma, a common subtype of head and neck cancer. Eleven miRNAs were dysregulated by more than 2-fold including miR-499 and miR-21. We demonstrated that both miRNAs temporally regulate PDCD4 at the post-transcriptional level. The initial suppression of PDCD4 was mediated by miR-21 whilst sustained suppression was mediated by miR-499. Moreover the single miR-21 site was able to elicit the same magnitude of suppression as the three miR-499 sites. Immunohistochemistry showed that PDCD4 expression was significantly reduced in cancers relative to normal cells. Our findings have added a new level of complexity to miRNA mediated gene regulation and suggests that the dual downregulation of the tumour suppressor PDCD4 by miR-499 and miR-21 acting in concert may be an important molecular event in the development of head and neck cancer.

Prizes for Best Abstracts by Students

The AGTS has awarded student prizes at each biennial conference since the inaugural meeting. The poster sessions have grown over the years, with the recent meeting exhibiting 27 posters in a new poster "walk-about" format. At the closing session five prizes were awarded to student members in recognition of their excellence in research.

(O16) TRANSFER OF AAV-SPECIFIC MATERNAL ANTIBODIES IN BREAST MILK IMPEDES VECTOR DELIVERY TO JUVENILE MICE

Cindy Y. Kok[1], Sharon C. Cunningham[1], Ian E. Alexander[1,2], *[1]Gene Therapy Research Unit, Children's Medical Research Institute and The Children's Hospital at Westmead, NSW, Australia; [2]Discipline of Paediatrics and Child Health, University of Sydney, NSW, Australia* ($250 Journal of Gene Medicine Student Prize)

(O17) ENHANCED NUCLEAR TRANSPORT IN TRANSFORMED CELLS; PROPECTS FOR ANTI-CANCER GENE THERAPY?

Henna V. Kuusisto, Kylie M. Wagstaff, Gualtiero Alvisi and David A. Jans, *Nuclear Signalling Laboratory, Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia* ($500 Genzyme Student Prize)

(P15) INVESTIGATING GENE THERAPY RESEARCHERS' ASSESSMENT OF RISKS IN CLINICAL TRIALS

Claire T. Deakin,[1,2] Ian E. Alexander,[1,3] and Ian Kerridge[2,4], *[1]Gene Therapy Research Unit, Children's Medical Research Institute and the Children's Hospital at Westmead; [2]Centre for Values, Ethics and the Law in Medicine, Faculty of Medicine, University of Sydney; [3]Discipline of Paediatrics and Child Health, University of Sydney; [4]Department of Haematology, Westmead Hospital*

(P21) ENHANCING HISTONE-MEDIATED GENE DELIVERY THROUGH INCREASED NUCLEAR TARGETIN

Michael Nastasie[1], David A. Jans[1], Helmut Thissen[2] and Kylie M. Wagstaff[1], *[1]Nuclear Signalling Laboratory, Dept. of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, Australia; [2]Molecular and Health Technologies, CSIRO, Clayton, Victoria, Australia* ($250 Journal of Gene Medicine Student Prize)

(P22) MICRORNAS AS TOOLS TO TARGET BONE MARROW MEDIATED TUMOUR ANGIOGENESIS

Prue N. Plummer[1], R. Taft[2], J. Mattick[2], N. McMillan[3], A. Swarbrick[4], R. Brink[4], V. Mittal[5], A.S. Mellick[1], *[1]Host Response to Cancer Lab, School of Medical Science, Griffith University, Gold Coast; [2]Institute of Molecular Biosciences, University of Queensland, Brisbane; [3]Diamantina Institute, University of Queensland, Brisbane; [4]Garvan Institute of Medical Research, Sydney; [5]Medical College, Weill Cornell University, New York, NY, United States*

Henna Kuusisto receiving the $500 Genzyme student prize, presented by Genzyme representative Linda Rigby

Cindy Kok (Children's Medical Research Institute, Sydney) is awarded the $250 Journal of Gene Medicine student prize by AGTS Vice-President Rosetta Martiniello-Wilks

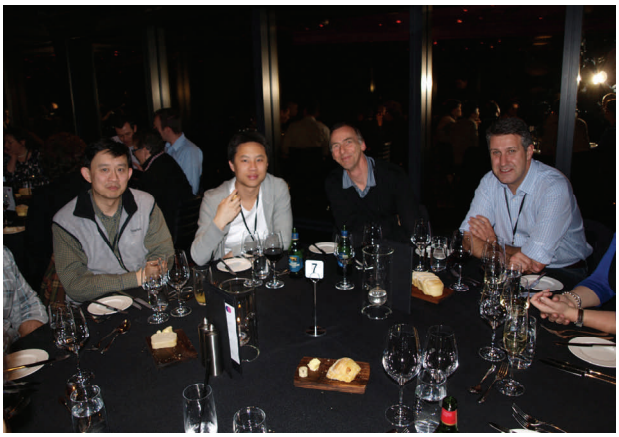
Claire Deakin (Children's Medical Research Institute, Sydney) is awarded a $250 student prize by AGTS President Steve Wilton

Prue Plumber (Griffith University, Gold Coast) is awarded a $250 student prize by AGTS President Steve Wilton

Michael Nastasie (Monash University, Melbourne) is awarded the $250 Journal of Gene Medicine student prize by AGTS President Steve Wilton

Conference Dinner at Eureka 89, Southbank Melbourne

From the left, Dr Glen Reid, Professor Melanie Ehrlich with partner (to her right), AGTS life-member Dr Gerry Both and Professor Sue Fletcher



From the left, Dr James Chan, Jie-Yu Chung, Associate Professor Frank Alderuccio and Committee member Dr Jim Vadolas

From the left, Dr Belinda Kramer, Anya Krattenmacher, Committee member Dr Sharon Cunningham, Amanda Skulte and Cindy Kok

From the left, Gustavo Alencastro, Dr Susan Siew, Claire Deakin and Sophia Liao

From the left, Lucy Barrett, Robyn Luo and Soma Amin with her husband (to her left)

From the left, Dr Heidi Peters, AGTS President Professor Steve Wilton, Associate Professor Robert Kapsa and AGTS life-member Professor Ian Alexander

From the left, Sue Alexander, Professor David Russell, Margot Latham and Roli Hirata

From the left, Dr Claus Hallworth, Dr Leszek Lisowski, Allison Dane, Dr Rachael Richardson and Maolin Zheng

From the left, Treasurer Professor Ann Simpson with Professor Alexandra Belayew, Vice President Dr Rosetta Martinello-Wilks and David Wilks

Thank you

The AGTS Executive would like to thank David Wilks for his generosity in photographing the 7th AGTS meeting in Melbourne

AGTS Executive Committee

President:	Professor Steve Wilton
Vice-president:	Dr Rosetta Martiniello-Wilks
Treasurer:	Professor Ann Simpson
Secretary:	Dr Samantha Ginn
Executive members:	Dr Sharon Cunningham Dr Paul Gregorevic Dr Jim Vadolas
Ex-officio member:	Dr Gerry Both