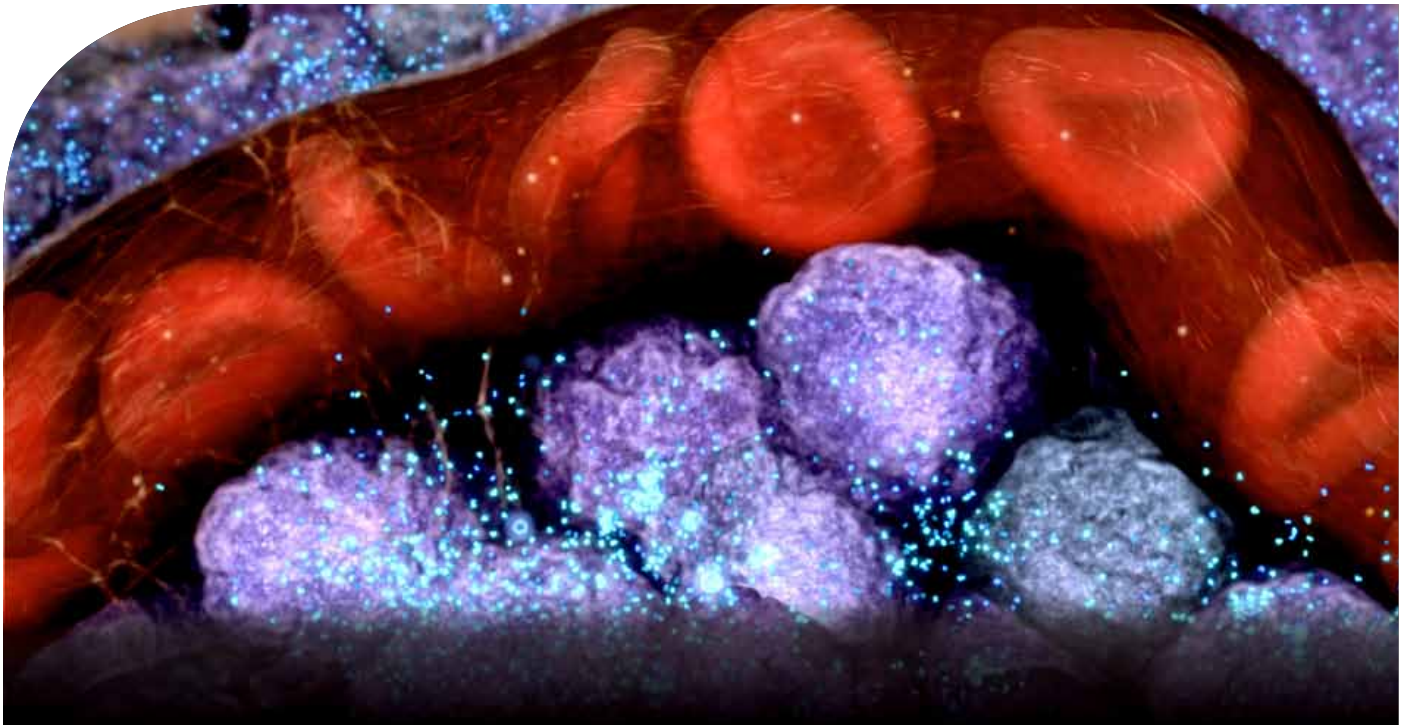

SHOWCASING EXCELLENCE in Biomedical Research

Australia-France Symposium

23 – 24 November 2011

Shine Dome,
Australian Academy
of Science, Canberra

PROGRAM

Australian Government
Department of Innovation
Industry, Science and Research

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RÉPUBLIQUE FRANÇAISE
Ambassade de France en Australie

Australian Academy of Science

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www.science.org.au/events/conferences-and-workshops/australiafrance/2011.html

Welcome Message

On behalf of the Australian Academy of Science and my colleagues in biomedical research in Australia, I am delighted to welcome you to the inaugural Australia-France Symposium.

A particular welcome to those of you who have travelled from France to be at this very special Symposium. The Australian Academy of Science is honoured to host what I hope will become the first of a series of bilateral events.

Showcasing Excellence in Biomedical Research is a topic in which I have a deep personal interest, having spent my career immersed in biomedical research.

Rapid advances in biomedical research have allowed us in recent years to improve diagnosis and treatment of disease in ways never previously imagined. Both Australia and France have made significant contributions to these advances. We are indeed fortunate to have at this Symposium global leaders and inspiring newcomers in the five main themes:

- Neuroscience;
- Cancer;
- Infection and immunity;
- Cardiovascular disease;
- Clinical translation.

We are also lucky to have with us experts in policy and strategy, both of which are crucial in bringing life-giving research outcomes to the people who need them.

I hope this Symposium marks the beginning of a fruitful series and that it lays the foundation for enhanced research collaboration between Australia and France.

I am particularly pleased to welcome the early and mid-career researchers attending this Symposium, some of whom will be making presentations. Many have strong connections with France and they will contribute strongly to future research relationships between France and Australia.

As the host organisation, the Australian Academy of Science is indebted to the French Embassy and the Australian Government Department of Innovation, Industry, Science and Research for their generous sponsorship, without which this event would not have been possible.

I do hope you find the next two days both productive and enjoyable, and that our French guests enjoy their visit to Australia.

Professor Suzanne Cory
President
Australian Academy of Science

Welcome Message

On behalf of The Embassy of France in Australia, I am honoured to welcome you to the Australia-France Symposium 'Showcasing Excellence in Biomedical Research'.

It has been a great pleasure for our team to work with the Australian Academy of Science to bring you this event, and we thank the Australian Government Department of Innovation, Industry, Science and Research for their support.

It was also a great pleasure to work with the French Organising Committee including AVIESAN, ARIIS and all the participating French medical institutions.

I would like to extend a special thank you to the speakers, both French and Australian, who have taken time out of their busy schedules and travelled great distances to attend this event.

The Embassy of France is committed to facilitating and strengthening the scientific and technological cooperation between Australia and France and has done so primarily through the French-Australian Science and Technology (FAST) Program developed in partnership with the Australian Government Department of Innovation, Industry, Science and Research. Over this program's 10 year lifespan, one in every five bilateral projects funded were in the area of Biology, Medicine and Health, making this the most popular field of research between the two countries.

This symposium will reunite renowned Australian and French scientists and serve as a platform for a fruitful dialogue tackling topics at the heart of biomedical research and addressing future challenges. This event is an opportunity for participants to consider bilateral cooperation, reinforce existing partnerships as well as highlight areas of potential future collaboration.

I hope that participants will enjoy the symposium and that this will be the first of many bilateral events which will promote Australian-French scientific relations.

His Excellency Mr Stéphane Romatet
Ambassador of France
Designated to Australia

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President of the Australian Academy of Science

Professor Moshe Yaniv
Fellow of the French Academy of Sciences
Department of Developmental Biology
Institut Pasteur, Paris

Workshop Day 1 – Wednesday 23 November 2011

Opening session

0830 – 0840	**Welcome:** Professor Suzanne Cory
	Official opening: His Excellency Mr Stéphane Romatet Ambassador of France Designated to Australia
	Professor Margaret Sheil, Chief Executive Officer, Australian Research Council
	Thanks: Professor Moshe Yaniv

Theme 1: Infection and Immunity
Chairs: Australia: Professor Peter Doherty
France: Professor Alain Fischer

0845 – 0915	Natural killer cells Professor Eric Vivier Centre d'Immunologie de Marseille-Luminy
0915 – 0945	An old enemy, a new battle plan: Combating the global scourge of malaria in the genomic era Professor Alan Cowman Walter and Eliza Hall Institute of Medical Research, Melbourne
0945 – 1015	Paving the way towards a cure for HIV Dr Monsef Benkirane CNRS Institut de Genetique Humaine, Montpellier

1015 – 1045	The role of BAFF in autoimmunity: A bench to bedside story Professor Fabienne Mackay Monash University, Melbourne
1045 – 1105	**Morning tea**
	Theme 2: Cancer **Chairs: Australia: Professor Jerry Adams** **France: Professor Jean-Marc Egly**
1105 – 1135	The anti-cancer immune response – indispensable for therapeutic success? Professor Laurence Zitvogel Institut Gustave Roussy, Villejuif
1135 – 1205	Alternative lengthening of telomeres in cancer Professor Roger Reddel Children's Medical Research Institute, Sydney
1205 – 1235	Immune contexture: A novel paradigm for cancer Dr Jerome Galon INSERM, Paris
1235 - 1305	Delineating the mammary stem cell hierarchy and its molecular regulators Professor Jane Visvader Walter and Eliza Hall Institute of Medical Research, Melbourne
1305 – 1405	**Lunch**
	Theme 3: Neuroscience **Chairs: Australia: Professor John Shine** **France: Dr Antoine Triller**
1405 – 1435	Super-resolutive and single molecule imaging: A new view on synapse biology Dr Antoine Triller Institute of Biology at Ecole Normale Superieure (IBENS), Paris
1435 – 1505	Activation of different neurogenic precursor populations in the hippocampus: Potential for dementia and depression therapy Professor Perry Bartlett Queensland Brain Institute, The University of Queensland

1505 – 1535	X-ray structure of general anesthetics bound to their principal target, pentameric channel receptors Dr Pierre-Jean Corringer Institut Pasteur, Paris
1535 – 1605	The natural history of Alzheimer's disease: Strategies for diagnosis and therapy Professor Colin Masters Mental Health Research Institute, Melbourne
1605 – 1625	**Afternoon tea**
	Early to mid-career researchers
1625 – 1640	Gata-3 negatively regulates the tumor-initiating capacity of mammary luminal progenitor cells and targets the putative tumor suppressor caspase-14 Dr Marie-Liesse Asselin-Labat Walter and Eliza Hall Institute of Medical Research, Melbourne
1640 – 1655	T cell receptors are as polymorphic as snails Dr Stephanie Gras Monash University, Melbourne
1655 – 1710	Involvement of lysophospholipids in stem cell biology and neurotrauma Dr Alice Pebay The University of Melbourne
1710 – 1725	Evaluation of the role of regulatory cells - mast cells, Treg cells and iNKT cells - in the regulation of immune responses to HPV-infected skin in mice Dr Anne-Sophie Bergot Diamantina Institute, The University of Queensland
1830	**Bus departs Diamant Hotel and University House for the National Gallery of Australia**
1845	**Guided tour of the Aboriginal and Torres Strait Islander Art Gallery**
1930	**Official gala dinner Gandel Hall, National Gallery of Australia**
2200	**Return to Diamant Hotel and University House**

Workshop Day 2 – Thursday 24 November 2011

Theme 4: Cardiovascular disease
Chairs: Australia: Professor Julie Campbell
France: Professor Alain Tedgui

0830 – 0900	Role of adaptive immunity in atherosclerosis Professor Alain Tedgui INSERM, Paris
0900 – 0930	Characterisation and embryonic origins of MSC-like stem cells in the adult mouse heart Professor Richard Harvey Victor Chang Cardiac Research Institute, Sydney
0930 – 1000	Inhibition of mitochondrial permeability transition: From molecular aspects to clinical applications Professor Michel Ovize Inserm & Hospices Civils de Lyon, Lyon University
1000 – 1030	The emerging role of HDL in glucose metabolism Professor Bronwyn Kingwell Baker IDI Heart and Diabetes Institute, Melbourne
1030 – 1050	**Morning tea**

Theme 5: Translation for Health
Chairs: Australia: Professor John Chalmers
France: Professor Moshe Yaniv

1050 - 1120	Primary immunodeficiencies: From genes to therapy Professor Alain Fischer INSERM/University Paris Descartes
1120 – 1150	Translation of basic knowledge into clinical practice: Solutions for the 21st century Professor Ian Frazer Translational Research Institute Pty Ltd, Brisbane
1150 – 1220	Translational research towards therapies in progeria and defective prelamin A processing associated syndromes Professor Nicolas Levy Hospital of Children la Timone and University of Medecine, Marseille
1220 – 1250	Designed drugs for moving targets Professor Peter Colman Walter and Eliza Hall Institute of Medical Research, Melbourne

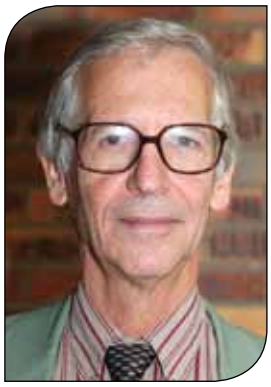
1250 – 1335	**Lunch**
	Early to mid-career researchers
1335 – 1350	Development and characterisation of new inhibitors the pro-survival protein BCL-XL Dr Guillame Lessene Walter and Eliza Hall Institute of Medical Research, Melbourne
	Can beta-blockers represent a novel therapeutic tool in medical oncology? Dr Eddy Pasquier Children's Cancer Institute Australia, Sydney
1405 – 1420	Realtime dosimetry in synchrotron x-ray microbeam radiation therapy Dr Michael Lerch University of Wollongong
1420 – 1435	Deciphering cardiac gene regulatory networks Dr Mirana Ramialison Victor Chang Cardiac Research Institute, Sydney
	Fostering Australia-France Research Collaboration **Chairs: Australia: Professor Bob Williamson**
1435 – 1600	Funding biomedical research in Australia and France/New initiatives Professor Warwick Anderson National Health and Medical Research Council, Canberra Professor Andre Syrota INSERM, Paris Professor Moshe Yaniv Department of Developmental Biology, Institut Pasteur, Paris
1600 – 1620	Closing remarks: Professor David de Kretser Sir John Monash Distinguished Professor Monash Institute of Medical Research and Monash University
1620 – 1650	**Afternoon tea**
1700	**Ground transportation to Canberra airport**

Symposium Chairs

Professor Suzanne Cory

President
Australian Academy of Science
president@science.org.au

Professor Suzanne Cory is one of Australia's most distinguished molecular biologists. She was born in Melbourne, Australia and graduated in biochemistry from The University of Melbourne. She gained her PhD from the University of Cambridge, England and then continued studies at the University of Geneva before returning to Melbourne in 1971, to a research position at The Walter and Eliza Hall Institute of Medical Research. From 1996 to 2009 she was Director of The Walter and Eliza Hall Institute and Professor of Medical Biology of The University of Melbourne. She is currently a Vice-Chancellor's Fellow at the University of Melbourne and Honorary Professorial Fellow at the Walter and Eliza Hall Institute, Her research has had a major impact in the fields of immunology and cancer and her scientific achievements have attracted numerous honours and awards. In 2010 she was elected President of the Australian Academy of Science.



Professor Moshe Yaniv

Emeritus Professor
Department of Developmental Biology
Institut Pasteur
moshe.yaniv@pasteur.fr

Moshe Yaniv is an Emeritus Professor at the Pasteur institut and Directeur de Recherche (CNRS). He received a Master degree in Chemistry from the Hebrew University in Jerusalem (1961) and a Ph.D in Molecular Biology from the University of Paris (1969). He was a postdoctoral fellow in LMB Cambridge and Stanford University.

He was head of the Gene Expression and Disease Unit at the Pasteur Institute (1975-2006), chair of the departments of Molecular Biology (86-88) and Biotechnology (92-94). He was a pioneer in the field of DNA tumour viruses and combined it with studies on chromatin, tissue specific gene expression and mouse models for human cancer. He is the author of more than 300 publications in the most prestigious scientific journals.

He is a member of the French Academy of Sciences, EMBO (chairman of the council, 1996), foreign honorary member of the American Academy of Arts and Sciences, Academia Europea, European Academy of Cancer Sciences etc.

Session Chairs

Professor Jerry Adams

Joint Head
Molecular Genetics of Cancer Division
Walter and Eliza Hall Institute of Medical Research
adams@wehi.edu.au

Jerry Adams is Joint Head of the Molecular Genetics of Cancer Division of the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne, Australia.

His PhD studies with James D Watson at Harvard revealed the role of methionine in initiating protein synthesis. In Frederick Sanger's lab at Cambridge and subsequently at the University of Geneva, he pioneered mRNA sequencing. With Suzanne Cory, in 1971 he established a laboratory at WEHI focussed on immunogenetics and later cancer genetics. Adams is known for his contributions to unravelling the role of chromosome translocation in tumorigenesis, for discoveries on the impact of impaired apoptosis in the development and therapy of cancer and for clarifying the mechanism by which the Bcl-2 protein family controls cell life and death. He was elected to the Australian Academy of Science in 1986, the Royal Society in 1992 and the US National Academy of Science in 2008.

Professor Julie Campbell

Director
Wesley Research Institute
jcampbell@wesleyresearch.com.au

Julie Campbell is a Director of the Wesley Research Institute at the Wesley Hospital and a Research Professor at the University of Queensland. Her major research interest over the last 40 years has been the cell biology of vascular smooth muscle in the normal artery wall and in diseased states such as atherosclerosis.

She was a founder (1992) and inaugural President of the Australian Vascular Biology Society. Her work has been recognized by the award of the Wellcome Australia Medal in 1995, and in 2000 she was elected to the Australian Academy of Science. In 2003 she was awarded a Centenary Medal for services to vascular biology, and in 2004 became a 'Queensland Great' awarded by the Queensland State Government. She was awarded an Order of Australia, Officer (AO) in the General Division in 2006, and in 2007 won the Queensland Business Women of the Year in the - Public & Not for Profit category.

Professor John Chalmers

Senior Director
The George Institute of Global Health
University of Sydney
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John Chalmers AC FAA is Emeritus Professor of Medicine at the University of Sydney and Senior Director of The George Institute for Global Health. His research has focused on hypertension and cardiovascular disease. It spans fundamental research on biogenic brain amines, amino acids and neuropeptides regulating blood pressure in animal models of experimental hypertension, through to leadership of large scale trials of blood pressure lowering for the prevention of strokes and coronary disease, including PROGRESS, ADVANCE and INTERACT. He is a past-president of the International Society of Hypertension. He was also chairman of the National Health and Medical Research Council (NHMRC) of Australia, in which capacity he forged an "Amicale Franco-Australienne" with INSERM, signed in 1991 and has led the Australian contingent at the quinquennial Franco-Australian meetings on hypertension held since that time. He was decorated as an Officer in the French National Order of Merit in 2010.

Professor Peter Doherty

Laureate Professor
Department of Microbiology and Immunology
University of Melbourne
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Peter Doherty shared the 1996 Nobel Medicine Prize for discovering the nature of the cellular immune defense. Based at the University of Melbourne and also spending part of his year at St Jude Children's Research Hospital, Memphis, he continues to be involved in research directed at understanding and preventing the severe consequences of influenza virus infection. In addition, he goes in to bat for evidence-based reality, relating to areas as diverse as childhood vaccination, global hunger and anthropogenic climate change. In an effort to communicate more broadly, he has published two "lay" books, and has two more in progress.

Professor Jean-Marc Egly

Genomique Fonctionelle et Cancer
Institute of Genetics and Molecular and Cellular Biology
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Jean Marc Egly's (JME) main achievement is the identification of TFIIH, a remarkable multiprotein complex that is not only essential in several key steps of transcription but also plays an equally pivotal role in DNA repair, thus revealing a striking connection between these two worlds. By systematically dissecting the key molecular mechanisms of TFIIH and testing their biochemical and physiological functions, JME and his collaborators revealed the extraordinary complexity of both transcription and DNA repair that are strongly connected. Moreover he also greatly contributed to the molecular description and understanding of the various phases of both protein coding gene transcription and nucleotide excision repair mechanisms. Importantly the work of JME has provided molecular insights into several human diseases, such as xeroderma pigmentosum, trichothiodystrophy, Cockayne syndrome which are all related to mutations in TFIIH subunits, or other associated disorders with mental retardation (found in Mediator subunits) as clinical features thus pioneering the field of Transcription Diseases.

Professor John Shine

Executive Director
Garvan Institute of Medical Research
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Professor Shine is Executive Director of the Garvan Institute of Medical Research, Professor of Medicine and Professor of Molecular Biology at the University of NSW.

Professor Shine obtained his PhD from the Australian National University in 1975 when he discovered the gene sequence (now listed in biology text-books as the "Shine-Dalgarno" sequence) responsible for the initiation and termination of protein-synthesis. During 1975-1978 at the University of California, San Francisco, Professor Shine was instrumental in the development of many of the techniques of genetic engineering. He was a central figure in the cloning of the insulin and growth hormone genes and was the first to clone a human hormone gene.

He was responsible for cloning the endorphin gene (the body's natural morphine) and was the first to demonstrate that hormone genes cloned in bacteria could be expressed in a biologically active form.

In 2010, Professor Shine was awarded the Prime Minister's Prize for Science.

Professor Bob Williamson

Secretary (Science Policy)
Australian Academy of Science
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Professor Bob Williamson became Professor of Molecular Genetics and Biochemistry at St Mary's Hospital Medical School, University of London, in 1976, where he remained until 1995 when he moved to Melbourne as Director of the Murdoch Institute and Professor of Medical Genetics. He retired in October 2004, and now is an Honorary Senior Principal Fellow of the Murdoch Institute, the University of Melbourne, and Monash University. Bob has over 400 refereed career publications, including about 40 in Nature, Nature Genetics, Cell and Lancet. He was involved in the identification of genes for cystic fibrosis, Friedreich ataxia, craniofacial abnormalities, heart disease and Alzheimer disease. More recently he has taken a major interest in national science policy and medical and scientific ethics, and has advised several Premiers, Health Ministers and Ministers for Innovation, and is still advising research groups wishing to use stem cells to treat genetic disorders. He is a Fellow of the Australian Academy of Science (where he is Secretary for Science Policy), a Fellow of the Royal Society, and an Officer of the Order of Australia.

Round Table Participants

Professor Warwick Anderson

Chief Executive Officer
National Health and Medical Research Council
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Professor Warwick Anderson is the Chief Executive Officer (CEO) of NHMRC, Australia's major governmental funding body for health and medical research. Previously, he was Head of School of Biomedical Sciences at Monash University and Deputy Director of the Baker Medical Research Institute, following research fellowships at the University of Sydney and Harvard Medical School.

Professor Anderson obtained his PhD from the University of Adelaide, South Australia. His research has focused on renal mechanisms in the pathogenesis of hypertension, including the roles of renal vascular remodeling and the renin-angiotensin system. He has published over 170 peer review articles.

For his contributions to medical research, Professor Anderson was made a Member of the Order of Australia in 2005.

Professor Andre Syrota

President and CEO
INSERM
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Andre Syrota is a professor of medicine, and research specialist in the development of non-invasive functional imaging methods in humans, based on positions emission tomography and nuclear magnetic resonance. His research has given rise to some 200 publications and 40 book chapters.

Director of Life Sciences at the French Atomic Energy Commission (CEA) from 1993, Andre Syrota was appointed Chief Executive Officer of INSERM in October 2007 and also became its President in March 2009. He presides over the French National Alliance for Life and Health Sciences (Aviesan), founded in 2009 for ensuring national strategic programming coordination in this research field. Aviesan aims at boosting the French potential of research, making it more visible at the national and international levels and more reactive to deal with emerging fundamental scientific questions or major public health issues.

Andre Syrota participates on various boards of national and international institutions and is also a member of scientific evaluation committees in the field of biophysics and medical technologies. Since April 2009, he has been one of the two Vice Presidents of EUROHORCs (European Heads of Research Councils), which works on promoting the European Research Area.

Speakers

Professor Perry Bartlett

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Professor Perry Bartlett, FAA was appointed Foundation Chair in Molecular Neuroscience at The University of Queensland in 2002, and inaugural Director of the Queensland Brain Institute in 2003 - the same year he was elected a Fellow of the Australian Academy of Science. He is internationally renowned in the field of cellular and molecular neuroscience. In 1992, his laboratory co-discovered the presence of stem cells in the adult brain that had the capacity to produce new neurons. His group was also the first to isolate and characterise these stem cells; they went on to reveal the presence of a latent hippocampal stem cell population that can be activated by synaptic stimulation and give rise to new neurons. These discoveries underpin the concept of functional stem cells in the adult mammalian brain and the burgeoning interest in their importance to learning and memory. Professor Bartlett has published extensively and received a number of prizes for neuroscience excellence.

Activation of different neurogenic precursor populations in the hippocampus potential for dementia and depression and depression therapy

The production of new neurons in the hippocampus is thought to underpin aspects of learning and memory. Defining how neurogenesis is regulated is central to our understanding of the learning process and to the future development of neurogenic-based therapeutics aimed at ameliorating cognitive loss.

Recently, we identified a large precursor pool in the dentate gyrus of the mouse hippocampus, including a small number of true stem cells, which is normally dormant but can be activated by depolarizing levels of K+ to produce large numbers of neurogenic neurospheres. In situ stimulation of the perforant pathway also activates this precursor population and leads to an increase in newly born neurons. Importantly, this population can be activated in the aged mouse, uncovering the potential for significant neurogenesis in the ageing brain.

Further, synaptic activity stimulates precursor activity through the release of a number of soluble factors and the neurotransmitter, norepinephrine (NE). These factors act directly on the precursors with NE activating through a novel adreno-receptor pathway. Interestingly, different stimuli led to the activation of different pools of precursors and stem cells, suggesting production of hippocampal neurons in the dentate gyrus with distinct properties reflective of a specific stimulation process. This provides a mechanism by which the functional capacity and the number of newly generated neurons can be directly influenced by the type and complexity of environmental stimuli.

Dr Monsef Benkirane

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Monsef Benkirane obtained his PhD in immunology from the University of Marseille Luminy (CIML) to understand the role of T-cell activation in HIV replication. Later, he did his postdoctoral training at the NIH (Bethesda, MD, USA) with Kuan-Teh Jeang where he focused on HIV gene expression. In 1998, he became principal investigator at the "Institut de Génétique Humaine CNRS" and head of the molecular virology laboratory. His main interest is to understand the interaction between HIV and its host with particular emphasis on viral persistence and restriction. He is associate editor of Retrovirology, president of the French National Agency for AIDS Research (ANRS) study section committee and member of the International AIDS Society working group on viral persistence. He is the recipient of an award from the French Medical Research Foundation for his contribution to virology, and was recently awarded an ERC advanced grant.

Paving the way towards a cure for HIV

HIV infection is characterized by a harmful chronic activation of the immune system. Major advances in HIV/AIDS treatment have altered the natural history of the disease and reduced HIV-related morbidity and mortality in countries where such treatments are accessible. The most notable advance is the use of combination antiretroviral therapy or ART. However, after 15 years of treatment it is clear that ART is unable to achieve complete virus eradication and is not a "sterilizing cure". Indeed, in most cases, viral rebound is rapidly observed after ART interruption. Thus, life-long treatment is needed to control HIV. Drug resistance, cumulative side effects, high cost and residual damaging inflammation represent major drawbacks of current treatments. The persistence of HIV results from the establishment of viral reservoirs insensitive to ART and poorly visible to the immune system. Thus, understanding HIV persistence and developing drugs able to flush out HIV, in order to achieve viral eradication or to decrease the need for continuous ART remain outstanding challenges.

We will discuss our recent discovery of the immune-modulator Samhd1 as the cellular factor restricting HIV-1 infection in myeloid cells and its impact on the balance between viral replication and persistence

Professor Peter Colman

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Peter Colman, Head, Structural Biology Division, The Walter and Eliza Hall Institute of Medical Research, has published widely in the field of structural biology. His main research discoveries have concerned the molecular structure of influenza viruses and their interactions with antibodies and small molecules. In 1983 his laboratory determined the structure of one of the surface proteins of this virus, neuraminidase. A major result of that work was the recognition that there exists a strain invariant feature on the surface of all influenza viruses which could serve as a target for drugs. This in turn led him to the discovery of a new class of medicines, the neuraminidase inhibitors. Zanamivir and Oseltamivir have been stockpiled by many governments as a first line of defence against pandemic influenza. His current research interests lie in the exploitation of the apoptotic machinery in the discovery of new drugs for cancer.

Designed drugs for moving targets

Zanamivir, the influenza virus neuraminidase inhibitor, is an early example of structure-based drug design. It is chemically very similar to the transition state of the enzyme reaction. Oseltamivir carboxylate, the second-in-class neuraminidase inhibitor, is chemically less similar to the natural substrate. This property can be correlated with an increased occurrence of drug resistant viruses selected by oseltamivir carboxylate as compared with zanamivir. Trends in second generation protease inhibitors for HIV indicate substrate-likeness as a desirable property for suppressing drug resistance.

Colman, PM (2009) AnnRev Biochem 78:95-118

Dr Pierre-Jean Corringer

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Pierre-Jean Corringer was trained as a chemist and did his PhD (Paris) and post-doctoral fellowship (Brighton) in organic synthesis. He then joined the Pasteur Institute as a CNRS researcher to work on the functional architecture and biosynthesis of nicotinic acetylcholine receptors, in the research unit of Jean-Pierre Changeux. His work contributed to the discovery of bacterial homologues of these neurotransmitter receptors. In january 2008 he created his own research group on Channel Receptors in the Pasteur Institute, which has notably produced, in collaboration with Marc Delarue, one of the first atomic resolution structures of the bacterial homologues of the nicotinic receptors, alone or in complex with general anesthetics. PJ Corringer was awarded the Pasteur Vallery-Radot price in 2009.

X-ray structure of general anesthetics bound to their principal target, pentameric channel receptors

Pentameric channel-receptors, including nicotinic acetylcholine and GABAA receptors, play a key role in fast excitatory and inhibitory transmission in the nervous system and are the target of numerous therapeutic and addictive drugs. They carry several neurotransmitter binding sites which govern the opening of a transmembrane ion channel. Extensively expressed in animals, they were recently found in several bacteria, especially the homolog from *Gloeobacter violaceus* (GLIC) which functions as a proton-gated ion channel, and the homolog from *Erwinia chrysanthemi* (ELIC). The simplified architecture of these archaic homologues, as well as their prokaryotic origin, allowed solving the first X-ray structures of integral membrane ELIC and GLIC in a closed and apparently open conformation, respectively. Comparative analysis of ELIC and GLIC suggests that receptor activation occurs through a symmetrical quaternary twist and tertiary deformation, according to a global transition that couples channel opening with reorganization of the binding pockets for neurotransmitters and allosteric effectors. In addition, recent co-crystallization of GLIC with allosteric inhibitors that are clinically used as general anesthetics reveals the mechanism of action at the membrane of these amphipatic molecules and will help designing new drugs targeted to pentameric channel-receptors.

Professor Alan Cowman

Division Head
Infection and Immunity
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Professor Alan Cowman is the Head of the Division of Infection and Immunity at the Walter and Eliza Hall Institute of Medical Research and is an NHMRC Australia Fellow. He is a Fellow of the Royal Society and the Australian Academy of Sciences. His work is aimed at understanding the function of proteins in Plasmodium falciparum, the causative agent of the most severe form of malaria in humans. He has made contributions to understanding drug resistance, elucidating the mechanism of resistance to important antimalarials. His laboratory concentrates on understanding how the malaria parasite invades human red cells and the remarkable remodeling of the host cell. This is mediated by the export of over 200 P. falciparum proteins and these alterations play a key part in pathology and virulence.

An old enemy, a new battle plan: Combating the global scourge of malaria in the genomic era

It has been over a hundred years since the discovery that 'the ague' (now commonly known as malaria) is caused by infection with the protozoan *Plasmodia,* which is transmitted between humans by the bite of a female mosquito. There are a number of *Plasmodia* species but the most severe form of malaria is caused by *Plasmodium falciparum.* Malaria has been a scourge of humanity since antiquity and remains so today. It is estimated that over a third of the world's population is at risk, with over three hundred million people developing clinical malaria each year and the loss up to a million lives. Recently there has been a strengthening of the political will to combat malaria including the vaccine initiatives funded by the Bill and Melinda Gates Foundation. This has coincided with an enhanced ability to genetically analyse the parasite as well as the availability of the *P. falciparum,* mosquito vector and human genome sequences. This has provided the information to not only utilise new approaches to understand pathogenesis of this disease but also to identify new drug and vaccine candidates. Malaria has been a companion of humans throughout recorded history and the numerous attempts to control it have been defeated by a combination of the ability of the parasite and the mosquito vector to adapt to the unsuccessful challenges by the host. It is hoped that the increased commitment to malaria together with the full exploitation of the scientific advances associated with our increased knowledge of the *P. falciparum* genome will eventually bring this old enemy under control.

Professor Alain Fischer

Director
INSERM & University Paris Descartes
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Alain Fischer has been a professor of pediatrics since 1986. He is Director of the department of Pediatric Immunology and Haematology at Necker Hospital, University Paris Descartes. He is the head of an INSERM research laboratory. He studied medicine in Paris and received the MD degree in 1979 and a PhD in Immunology the same year. He had a post doctoral training in Immunology at University College London 1980 and 1981. His main interests are development of the immune system, genetic diseases of the immune system and gene therapy. He is a member of Institut Universitaire de France, EMBO and the French Academy of Science. He is the Director of the Institute for genetic diseases (Imagine) on the Necker campus since 2009.

Primary immunodeficiencies from genes to therapy

Primary immunodeficiencies (PID) consist in more than 200 rare conditions mostly with mendelian inheritance. Their study has unraveled important key mechanisms of both innate and adaptive infectious immunity as well as of checkpoints of reactivity to self. New examples will be herein discussed. Their study also helped to design genetic therapy that turned out to be successful for several forms of PIDs, albeit initially at the cost in some cases of adverse events. These results serve today as a basis for the extension of gene therapy to other forms of genetic disorders of the hematopoietic system.

Professor Ian Frazer

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Professor Ian Frazer was trained as a renal physician and clinical immunologist in Edinburgh Scotland. Dr Frazer's research group studies the immunology of papillomavirus associated cancers. In 1991, along with Chinese colleague, Dr Jian Zhou, he developed the virus-like particle technology which has become the basis of vaccines to prevent cervical cancer. Dr Frazer has recently been appointed as CEO and Research Director of the newly created Translational Research Institute in Brisbane, Australia. He is the current chair of the Scientific Advisory Council of the International Agency for Research on Cancer.

Translation of basic knowledge into clinical practice: Solutions for the 21st Century

Biomedical research over the last 100 years has given us insights into the genetic and environmental factors promoting the chronic non-infectious diseases that cause most of the health burden in the developed world. We have some understanding of pathophysiological processes leading to chronic disease, including ineffective repair of tissue damage with associated chronic inflammation, and ineffective repair of somatic cell DNA damage with associated neoplasia. However, our ability to translate this knowledge into clinical practice is limited by our inability to communicate basic messages about health maintenance, and by diversion of health care resources away from development of effective health interventions towards commercially more popular health products. Progress in delivery of better health care requires a new approach to research and development of effective interventions driven by expert knowledge and public funding rather than commercial feasibility. I will discuss this proposition with examples from the fields of vaccine development and cancer immunotherapy.

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Dr Jérôme Galon is Research Director at INSERM (National Institute of Health and Medical Research) and leading an INSERM laboratory (Integrative Cancer Immunology) at the Cordeliers Research Center in Paris, France.

He was trained as an immunologist at the Pasteur Institute and at the Curie Institute (Paris, France). Between 1997 and 2001 he worked at the NIH (National Institute of Health, Bethesda, USA) on functional genomics, bioinformatics and immunology on fundamental and clinical research. In 1999, he received the fellow Award for Research Excellence at NIH (USA).

Recruited at INSERM, Dr Galon directed an interdisciplinary research team between 2001 and 2006. He demonstrated that the adaptive immune reaction within the tumor was a better predictor of survival than traditional staging based on a cancer's size and spread In 2009, he was awarded by the Avenir Research Program (France), and became Research Director at INSERM in 2007. Between 2007 and 2009, he was director of INSERM Avenir Team. In 2009, he became head of the INSERM Integrative Cancer Immunology laboratory (Paris, France). Dr Galon was awarded for his work on cancer research, by the French foundation (Schaeverbeke Award 2008), by the Medical Research Foundation (Rose Lamarca Award 2008). He received the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology (Cancer Research Institute, USA 2010), and the Cancer Research Award of Simone et Cino del Duca Foundation (2011).

Immune contexture: A novel paradigm for cancer

To date the anatomic extent of tumor (TNM classifications) has been by far the most important factors to predict the prognosis of cancer patients. We showed that tumors from human colorectal cancer with a high density of infiltrating memory and effector memory T-cells (TEM) are less likely to disseminate to lymphovascular and perineural structures and to regional lymph-nodes (NEJM 2005). We showed that the combination of immune parameters associating the nature, the density, the functional orientation and the location of immune cells within the tumor was essential to accurately define the impact of the local host immune reaction on patients prognosis (Science 2006). We proposed to define these immune criteria as "immune contexture". Investigation of the primary tumor microenvironment allowed us to uncover the association of favorable outcomes with efficient coordination of the intratumoral immune response. We described four major immune coordination profiles within primary tumors depending on the balance between tumor escape and immune coordination. Analysis of patients with early-stage colorectal cancer confirmed the major role of cyotoxic effector T cells in predicting the prognosis of the patients (JCO 2009).

In conclusion, the density and the immune-cell location within the tumor have a prognostic value that is superior of those of the TNM classifications. Tumor invasion is statistically dependent on the host-immune reaction (JCO 2011). Recent advances analyzing mechanisms responsible for lymphocytic infiltration will be discussed.

Professor Richard Harvey

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Professor Richard Harvey received his PhD in 1982 from the University of Adelaide, training in molecular biology. He undertook postdoctoral studies in embryology at Harvard University, then moved to the Walter and Eliza Hall Institute in Melbourne, establishing an independent group. In 1998, he relocated to the Victor Chang Cardiac Research Institute, where he is currently Co-Deputy Director and Head of the Developmental and Stem Cell Biology Division. He holds the endowed Sir Peter Finley Professorship of Heart Research at UNSW and an NHMRC Australia Fellowship, and is a member of EMBO and the Australian Academy of Science. His research has focused on the genetic basis of heart development and congenital heart disease, and more recently on the biology and origin of adult cardiac stem cells, and cardiac regeneration.

Characterisation and embryonic origins of MSC-like stem cells in the adult mouse heart

Richard Harvey, James Chong, Owen Prall, Vashe Chandrakanthan, Munira Xaymardan, Naisana Asli, Ish Ahmed, Joan Li, Cory Heffernan, Christine Biben, Amirsalar Rashidianfar, Chris Scarlett, Andrew Biankin, Bin Zhou, William Pu

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Identification of multi-potent stem cells in the adult mammalian heart has promoted a revision of the dogma that the heart is a post-mitotic organ with limited regenerative reserve. Stem cell and regeneration therapies may therefore have a significant clinical impact in patients with myocardial infarction and heart failure, the most significant cause of death in our society. Our laboratory has developed a quantitative framework for characterising a population of MSC-like stem cells from the adult mouse heart. Such cells (cardiac colony-forming units-fibroblast; cCFU-F) show long-term growth and are multipotent for a variety of mesodermal and transgerm layer lineages in vitro and in vivo, and have a gene expression and surface receptor profile resembling bone marrow (BM) MSCs. We will present our recent data on the characterisation of cCFU-F in vivo and in vitro, their lineage origins in development, their behaviour in disease and aging, and molecules regulating their cell cycle state and stemness.

Professor Bronwyn Kingwell

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Professor Bronwyn Kingwell received her PhD from the University of Melbourne in 1991. She is a National Health and Medical Research Council of Australia Principal Research Fellow, and at the Baker IDI Heart and Diabetes Institute in Melbourne is both Executive Director, Science Policy and Diabetes and Metabolism Theme Leader. She is current chair of the National Committee for Medicine of the Australian Academy of Science. An integrative physiologist, she heads a multi-disciplinary laboratory with a strong clinical translational flavour in metabolic and vascular disease. Her strengths include vascular biomechanical properties, predictors of unstable coronary heart disease and novel metabolic effects of high-density lipoproteins (HDL). She has recently returned from a sabbatical in the area of HDL and atherosclerosis with Professor John Chapman at the Hôpital Pitié Salpêtrière as an Honorary Professor of the University of Pierre and Marie Curie in Paris.

The emerging role of HDL in glucose metabolism

Low plasma high-density lipoprotein (HDL) is an atherosclerotic risk factor, however emerging evidence suggests that it may also contribute to the pathophysiology of type 2 diabetes mellitus (T2DM) through direct effects on plasma glucose. Recent animal and clinical studies from our laboratory and others have uncovered a previously undescribed spectrum of HDL actions indicating that HDL may control glucose homeostasis through mechanisms including insulin secretion, direct glucose uptake by muscle via the AMPK-activated protein kinase (AMPK) and enhanced insulin sensitivity.1 These effects are mediated by multiple cell types through mechanisms including both preservation of cell function via cellular lipid removal and also direct signaling events. This suggests a paradigm shift from HDL being a bystander to active player in diabetic pathophysiology and raises the possibility that HDL elevation could be a novel therapeutic avenue for T2DM. The recent entry of HDL-raising agents of the cholesteryl ester transfer protein inhibitor class into late phase clinical trials creates potential for rapid clinical translation. This presentation will discuss the emerging evidence for HDL-mediated glucose regulation in the context of both the pathophysiology of T2DM and the therapeutic potential for HDL elevation beyond vascular disease to the prevention and treatment of T2DM.

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Professor Nicolas Levy

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Nicolas Lévy is Professor of Human and Molecular Genetics. He is the head of the Medical Genetics department and of the Inserm research laboratory "Medical Genetics and Functional Genomics". In 2009, he was appointed as the director of the French national institute for rare diseases and has been nominated as the scientific director of the National Foundation for Rare Diseases, which will be created in 2011. Specialist in genetics of neuromuscular disorders and laminopathies, his team has provided the community with important achievements in these fields. After having identified the LMNA mutation causing Progeria, Nicolas Lévy's efforts have been dedicated to the identification of genes and pathophysiological mechanisms involved in Progeria and related progeroid. Taking advantage of European collaborations, his laboratory has developed and pre-clinically tested combinations of global prenylation inhibitors in human cells and living mouse models. Nicolas Lévy is the PI of of the first phase II trial using amino-bisphosphonates and Statins for Progeria, in progress at La Timone Hospital in Marseille, France. Recently, his work dedicated to the understanding of mechanisms, and to the development of therapeutic strategies in neuromusccular disorders, led his team to demonstrate the proofs of principle for exon skipping and minigene transfer as pertinent therapies in dysferlinopathies.

Translational research towards therapies in progeria and defective Prelamin A processing associated syndromes

Hutchinson-Gilford Progeria Syndrome (HGPS) is a very rare and severe genetic disease, characterized by segmental premature aging and accelerated atherosclerosis. It invariably leads to death in the teenage, due in most cases to myocardial infarction. No effective and validated treatment is available to date. In 2003, our group identified in the *LMNA* gene, encoding the ubiquitous nuclear proteins Lamins A/C, a recurrent, dominant mutation causing most HGPS cases. This *de novo* mutation activates a cryptic pre-mRNA splicing site leading to the production of a truncated Lamin A precursor called "progerin". Progerin cannot be fully post-translationally processed, remains aberrantly prenylated and accumulates in cells' nuclei, where it exerts several toxic effects. In the last years, we were able to demonstrate a link between other nosologic entities classified as progeroid syndromes and defective prelamin A processing, either caused by mutations *LMNA* or its main post-translational processing enzyme. Preclinical studies *in vitro* on patients' cells and on animal models of the disease provided proof-of-principle that the combined use of prenylation inhibitors, statins and amino-bisphosphonates (N-BPs), could improve the natural course of the disease, ameliorating several disease parameters, including growth, bone density and survival. The beneficial effects of these drugs could be ascribed to the reduction of Progerin prenylation levels, as well as, probably, to their specific pharmacological activities. These data allowed us to launch a phase II, open-label, single arm, monocentric trial that is conducted in La Timone Children's Hospital, in Marseille, France on 12 European children affected with Progeria. The trial aims to assess the safety and efficacy the identified combination on several disease parameters, including growth, bone density and turnover as well as cardiovascular risk parameters. We report the first therapeutic intervention that seems to favorably impact the natural course of this devastating disease, with potential wider impacts in the field of aging. Beside, our continuing work aimed to create a new KI mouse model carrying the typical and most common mutation associated to Progeria. In collaboration with Pr. C. Lopez-Otin, this model was recently validated for Splicing directed intervention that will lead to the setting up of a new trial in children affected with Progeria and associated disorders.

Professor Fabienne Mackay

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Prof Mackay obtained her Ph D in 1994 at the Louis Pasteur University in Strasbourg. Co-supervision: Dr. Werner Lesslauer (Hoffmann La Roche, Basel Switzerland) and Prof Diane Mathis. In 1994, Prof Mackay joined BiogenIdec Inc in Boston where she dissected the role of a TNF-like ligand lymphotoxin-alpha/beta in autoimmunity and cancer. This work led to many patents and the development of a new treatment currently tested in the clinic. In 2000, Prof Mackay joined the Garvan Institute in Sydney as a Wellcome Trust senior research fellow and was awarded a NHMRC program grant. Prof Mackay's lab at Garvan discovered the role of a new molecule named BAFF/BLyS as a key B cell survival factor essential for the maturation of B-lymphocytes but also playing a role in autoimmunity, and became one the leading group on BAFF research. In July 2009, belimumab, a therapeutic antibody neutralising BAFF has met the primary endpoints in a phase III clinical trial with lupus patients, run by GSK and Human Genome Sciences. This treatment was approved on March 9th 2011, the first new treatment in over 50 years. In March 2006, Prof Mackay was appointed to Director of the Autoimmunity Research Unit and adjunct full professor at the Faculty of Medicine of the University of New South Wales. In 2008 and 2009, she was a NSW director for the Australian Society of Medical Research (ASMR). In 2009, Professor Mackay became the 5th Chair of the Department of Immunology, Monash AMREP. Her current group has a program studying the role of B cell subsets and innate immunity in immune tolerance, autoimmunity and cancer. Her laboratory also discovered the function of the orphan chemokine receptor CXCR7 in fibrosis and she is the co-founder of MabDesign Ltd. for the development of CXCR7 inhibitors. Prof Mackay is a NHMRC Senior Research Fellow and has authored over 90 articles/reviews/book chapters, many in high impact factor journals such as Nature, J. Exp. Medicine and J. Clin. Invest. She is a consultant for several biotech and pharmaceutical groups. Her h-index is 44, with over 7000 citations, an average of 79 citations per article. In 2010, she was a member on a national ERA scoring panel for ARC.

The role of BAFF in autoimmunity: A bench to bedside story

The TNF-like ligand BAFF is a fundamental survival factor for B cells, essential during their maturation. However, overproduction of BAFF in transgenic (Tg) mice triggers autoimmune disorders similar to Systemic Lupus Erythematosus (SLE) and Sjögren's syndrome (SS), possibly as the result of abnormal self-reactive B cell survival. Elevated levels of BAFF have been detected in the serum of patients with various autoimmune conditions. Intriguingly, we showed that excess BAFF only mildly affected B cell immune tolerance, could not prevent deletion of high affinity self-reactive B cells but could rescue some low affinity self-reactive B cells, in particular marginal zone (MZ) B cells. As germinal center formation and antibody affinity maturation were not essential for disease in these mice, we questioned the real implication of low affinity autoreactive B cells in driving the disease. Indirect and direct effects of BAFF on T cell activation and expansion of the effector T cell compartment in BAFF Tg mice were then thought to perhaps contribute to nephritis in these animals. Surprisingly, BAFF Tg mice lacking T cells develop the same autoimmune disease as the original BAFF Tg mice. Interestingly, MyD88-/- B cells had impaired autoantibody production in BAFF Tg mice. Thus, this work revealed that autoimmunity in BAFF Tg mice is the result of an abnormal innate B cell response involving the combined effects of excess BAFF and Toll-like receptor signalling. Recently, Belimumab, an inhibitor of BAFF, has been approved by the FDA, as the first new treatment for SLE patients in over 50 years. This exciting outcome validated over ten years of work demonstrating the unique role of BAFF in autoimmunity with new lessons learned about mechanisms driving autoimmunity. References

Professor Colin Masters

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Professor Colin Masters is a leader in research into Alzheimer's disease and other neurodegenerative disease, including Creutzfeldt-Jakob and other prion diseases, and his work over the last 35 years is widely acknowledged as having had a major influence on Alzheimer's disease research world-wide. This work has led to the continued development of novel drugs and therapeutic strategies to treat these diseases. Professor Masters is currently the Director of the Mental Health Research Institute, and Laureate Professor at the University of Melbourne. He is the Chair of the NHMRC's Transmissible Spongiform Encephalopathies Advisory Committee, a consultant in neuropathology at the Royal Melbourne Hospital and a scientific advisor to Neurosciences Australia. His achievements have been recognised by the receipt of many international awards - including the King Faisal International Prize in Medicine (1996), the Grand Hamdan International Award for Medical Sciences (2006) and the Victoria Prize from the Minister for Innovation (2007).

The natural history of Alzheimer's disease: Strategies for diagnosis and therapy

Compelling evidence now shows that the Aβ-amyloid peptide is the central biochemical marker of Alzheimer's disease (AD), and is the most likely cause of the neurodegeneration manifest in synaptic dysfunction and eventual neuronal loss. Pathways up-stream of Aβ production provide therapeutic targets amenable to protease inhibition/modulation. Strategies which affect APP trafficking may also prove of value. Downstream, pathways promoting the degradation of Aβ or clearance from the brain also offer windows for therapeutic opportunity. Our central interest lies in the mechanism through which Aβ undergoes toxic gain-of-function, inducing neuronal damage. This provides the most direct route for therapeutic intervention, with least risk of therapeutic side-effects, since Aβ toxicity is unlikely to mimic any normal function. Two principal hypotheses have emerged to explain Aβ toxicity: redox chemistry associated with the Cu/Zn metal binding sites on Aβ, and lipid interactions associated with the α/β conformation of the hydrophobic C-terminus. The major genetic risk factor for sporadic AD is the APO E haplotype. Despite many years' investigation, the mechanism through which ApoE regulates the age of onset of AD remains uncertain: an effect on the clearance of Aβ from the brain is likely. To get a clearer idea on the natural history of AD, particularly in its preclinical phase, we developed the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, which has recruited over 1000 individuals to monitor the evolution of AD. Volunteers underwent a screening interview, had comprehensive cognitive testing, gave 80 ml of blood, and completed health and lifestyle questionnaires. One quarter of the sample also underwent structural MRI and amyloid PET brain imaging. At baseline a total of 1112 volunteers were recruited (211 subjects with AD, 133 with mild cognitive impairment (MCI) and 768 healthy controls). This cohort has now been assessed at 18 months and 36 months; the 54 month phase is about to commence. Using amyloid PET technologies, we can now define a subset of 30% healthy controls who are in the preclinical stages of AD. Other biomarkers, including blood Aβ and ApoE, are also emerging as potential indices of preclinical AD. Repeat measures of cognitive abilities in the preclinical and MCI groups is essential in establishing the correct statistical methodologies for assessing the rates of decline ("slope analysis"), a prerequisite for any future studies of interventions aimed at prevention or delay of onset of AD. Removing subjects with preclinical AD or risk factors for cerebrovascular disease may also define a group of true "super-normals" in whom brain neurodegeneration and cognitive impairment with aging will not occur. Therapeutic interventions targeting Aβ, aimed at disease modulation, are being vigorously pursued. Results so far are mixed.

Professor Michel Ovize

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Michel Ovize
Born on 7 September 1958 MD, PhD,
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Current Position

- *Director of the Research Team "Cardioprotection", Inserm U1060 (CARMEN)*
- *Chief of the Non-invasive and Stress Testing Cardiology Department at the L.Pradel Hospital in Lyon.*
- *Coordinator of the Centre for Clinical Investigation (CIC) of Lyon*
- *Chief of team 5 "Cardioprotection" of the Inserm unit 1060 (CarMeN) in Lyon*

Michel Ovize created the research unit "Cardioprotection" in 2002, mainly devoted to basic research in the field of myocardial ischemia-reperfusion, with specific attention to the role of mitochondrial permeability transition in cell death. He then created in the Hospices Civils of Lyon a clinical research group, in order to transfer basic knowledge to clinical practice; his group first demonstrated the existence and the treatment of lethal myocardial reperfusion injury in the clinical settings of acute myocardial infarction (ischemic and pharmacological postconditioning).

Inhibition of mitochondrial permeability transition: From molecular aspects to clinical applications

During the last two decades, reperfusion therapy has dramatically improved the clinical outcome of ST elevation myocardial infarction (STEMI) patients. However, little progress has been made to protect the myocardium from the acute reperfusion injury. The existence and the importance of the myocardial damage induced by reperfusion injury was first reported by Zhao et al. who showed that brief cycles of ischemia and reperfusion performed immediately after reflow could significantly reduce infarct size in a dog model. Accumulating experimental evidence suggests that inhibition of the opening of the mitochondiral permeability transition pore (PTP) at the time of reflow plays a key role in this type of protective mechanism. Our group is involved in understanding the regulation of the PTP under stress conditions, with specific attention to the role of a crucial chaperone, namely cyclophilin D. We further transfered this concept through a series of small-size proof of concept clinical studies showing that infarct size and contractile function could be improved by angioplasty postconditioning or cyclosporine, the reference inhibitor of the PTP. Current phase II studies are ongoing to confirm this protection in various clinical settings. We recently started a large-scale clinical trial (the CIRCUS study) aimed to determine whether cyclosporine may improve clinical outcome in STEMI patients. We will present during this meeting several aspect of this translational research program.

Professor Roger Reddel

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Roger Reddel is the Lorimer Dods Professor at Sydney Medical School, University of Sydney, and also Director of the Children's Medical Research Institute. He trained as a medical oncologist at Sydney's Royal Prince Alfred Hospital, obtained a PhD in the cellular biology of breast cancer at the University of Sydney, and undertook post-doctoral training in molecular carcinogenesis at the National Cancer Institute in Bethesda, Maryland. His research focusses on the molecular genetics of cellular immortalization, especially the role of telomere length maintenance. He and his team discovered the Alternative Lengthening of Telomeres (ALT) mechanism, and have made major discoveries regarding the enzyme, telomerase. He was awarded the Ramaciotti Medal for Excellence in Biomedical Research in 2007, elected as a Fellow of the Australian Academy of Science in 2010, and this year received the NSW Premier's Award for Outstanding Cancer Researcher.

Alternative lengthening of telomeres in cancer

Normal somatic cells have a finite proliferative capacity that is imposed by the gradual attrition of chromosome ends (telomeres) that accompanies DNA replication. Cancer cells escape from this normal limitation on proliferation by activating a telomere length maintenance mechanism. In the majority of human cancers, this occurs by the dysregulated activity of telomerase, but a substantial minority use a different mechanism referred to as Alternative Lengthening of Telomeres (ALT). New telomeric DNA is synthesised by ALT in a process involving homologous recombination-mediated DNA replication. ALT is common in tumour types including osteosarcomas, specific subtypes of soft tissue sarcomas, and glioblastoma multiforme. Cells that utilise the ALT mechanism contain many copies of an unusual type of DNA molecule that we have called "C-circles": partially single-stranded circles of telomeric DNA in which the C-rich (CCCTAA)n strand is intact, and the G-rich (TTAGGG)n strand is partially gapped. We developed an assay that detects C-circles in nanogram quantities of genomic DNA from ALT[+] cell lines. C-circle Assay levels were significantly elevated in whole blood from ALT[+] osteosarcoma patients. We will this assay to screen for genes involved in the ALT mechanism and to find chemical compounds that inhibit ALT and could be developed as novel anti-cancer treatments.

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Alain Tedgui obtained his PhD thesis in Fluid Mechanics. After his post-doctoral fellowship at the Imperial College, London, he joined the French Institute of Health and Medical Research (INSERM) in 1983. He has been heading an INSERM laboratory at Paris Hospital Lariboisière from 2000 to 2004. His is currently the Director of the PARCC (Paris-Cardiovascular research Center) at the Georges-Pompidou European Hospital. He coordinated the European Network of Excellence EVGN (European Vascular Genomics Network) from 2004 to 2008. His current primary research is aimed at elucidating the role of apoptosis and inflammation in atherosclerosis. More recently, he bridged the interface between vascular biology and immunology in showing that a subset of immune cells, regulatory T cells, limits the development of atherosclerosis and can be used as a promising anti-atherosclerotic strategy to curtail inflammation. He is the European Editor of Arteriosclerosis Thrombosis and Vascular Biology.

Role of adaptive immunity in atherosclerosis

Atherosclerosis is a chronic disease of the arterial wall where both innate and adaptive immuno-inflammatory mechanisms are involved. Inflammation is implicated in the formation of early fatty streaks, when the endothelium is activated and expresses chemokines and adhesion molecules leading to monocyte/lymphocyte recruitment. It also acts at the onset of adverse clinical vascular events, when activated cells within the plaque secrete matrix proteases that degrade extracellular matrix proteins and weaken the fibrous cap, leading to rupture and thrombus formation. Recent advances in our understanding of the mechanisms of atherosclerosis provided evidence that the immuno-inflammatory response in atherosclerosis is modulated by regulatory pathways involving the two anti-inflammatory cytokines IL-10 and TGFβ, which play a critical role in counter-balancing the effects of pro-inflammatory cytokines. Interestingly, IL-10 and TGF-β are also the two cytokines that mediate the immune regulatory functions of regulatory T (Treg) cells, a sub-population of T cells that control autoimmune disease. We demonstrated that natural CD4+CD25+ Treg cells play an important role in the control of atherosclerosis in apoE-/- mice. Moreover, modulation of the peripheral immune response is achievable by transfer of regulatory T cells. It is therefore believed that atherosclerosis results from an imbalance between pathogenic T cells, mostly Th1, producing pro-atherogenic mediators, and Treg cells with immunosuppressive properties, and that promotion, expansion or exogenous administration of Treg cells, ideally specific of plaque-derived antigens, might limit disease development and progression. More recently, we showed that loss of suppressor of cytokine signaling (SOCS) 3 in T cells increases both interleukin IL-17 production, induces an antiinflammatory macrophage phenotype, and leads to unexpected IL-17-dependent reduction in lesion development and vascular inflammation. This better understanding of the regulation of adaptive immunity should pave the way for new approaches in the prevention and treatment of atherosclerosis. Immunological treatment strategies include interference with cytokine signaling, inhibition of pathogenic T-cell functions, and promotion of regulatory immunity associated with TREG cells. A number of these immunotherapies are being evaluated in ongoing clinical trials to treat autoimmune diseases. Knowing whether or not these therapies affect cardiovascular risk will provide important information on the actual role of T cells in human atherosclerotic disease.

Dr Antoine Triller

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Antoine Triller obtained his M.D. in 1978, and his D.Sc. in 1985, while being at the Pasteur Institute. He worked initially on synaptic inhibitory neurotransmission, correlating quantal parameters of release with the ultrastructure of the synapse. In 1985, he gave the first description of the structural organization of a synaptic receptor. In 1995 he joined the Ecole Normale Supérieure.

He now focuses on the cell biology and molecular mechanisms of receptor accumulation at synapses during development and plasticity. Combining cell biology with physical methods, he could access high-resolution real-time imaging of receptor movements. This structural and dynamic approach allows the correlation between molecular diffusion dynamics and the organization of the plasma-membrane not only at steady state but also during modifications of the synaptic composition observed during the so-called synaptic plasticity, as well as in pathological conditions such as epileptic status or in more complex synaptopathies such as in Alzheimer disease.

Super-resolutive and single molecule imaging: A new view on synapse biology

Single molecule imaging has emphasized that synapses are not static entities but result from the continuous assembly and disassembly of molecules. Furthermore, single molecule and super-resolution imaging allows an access to molecular interactions that are implicated within the synapse. Measuring association and dissociation rates and determining equilibrium constants is particularly important for the investigation of supra-molecular structures such as the synapse, which represent a mesoscale intermediate between the molecular and the cellular scale. Using a combination of dynamic imaging and biochemical approaches we have characterized the molecular mechanisms that link the inhibitory glycine receptor-gephyrin interaction with glycine receptor diffusion and synaptic receptor number. This ultimately sets the strength of inhibition. We have identified a PKC phosphorylation site in the cytoplasmic domain of the β-subunit of the glycine receptor that reduces the interaction between the receptor and gephyrin. In consequence, the receptor's diffusion in the plasma membrane is accelerated, consequently, the number of synaptic glycine receptors as well as inhibition are reduced. We propose that the regulation of glycine receptor levels by protein kinase C contributes to the plasticity of inhibitory synapses and may be involved in maladaptive forms of synaptic plasticity seen during spasticity and neuropathic pain.

Professor Jane Visvader

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Jane Visvader is Joint Head of the Division of Stem Cells and Cancer, and the Breast Cancer Laboratory at The Walter and Eliza Hall Institute. She carried out her PhD studies in the Department of Biochemistry at the University of Adelaide, and held subsequent positions as a postdoctoral fellow at the Salk Institute and Research Associate at the Children's Hospital, Boston. She was awarded a NHMRC Australia Fellowship in 2011. Visvader serves on the Medical and Scientific Advisory Committee of the Cancer Council Victoria and the Scientific Advisory Council of the National Breast Cancer Foundation. She is a Senior Editor for Cancer Research and a member of the Editorial Boards of Cell Stem Cell, Molecular Oncology and Breast Cancer Research. Her laboratory focuses on understanding the epithelial hierarchy in normal and cancerous breast tissue, as well as identifying genes important for regulating mammary development.

Delineating the mammary stem cell hierarchy and its molecular regulators

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To understand relationships between breast tissue, 'cells of origin' and cancer stem cells in breast tumors, it is necessary to dissect the normal mammary epithelial hierarchy. We have isolated discrete populations of mouse and human mammary epithelial cells on the basis of cell surface markers and identified subsets that are highly enriched for mammary stem (MaSC), luminal progenitor and mature luminal cells. Recent studies have revealed that MaSCs are highly responsive to steroid hormones despite lacking expression of the estrogen and progesterone receptors. Transcriptome analyses of mouse and human mammary epithelial populations have led to the identification of multiple conserved genes/pathways and potential effectors of hormone action. The RANKL/RANK signaling pathway emerged as an important mediator of paracrine signaling to stem cells. In addition, the roles of a number of transcription factors have been pinpointed along the mammary hierarchy using targeted mice. We are currently determining the global epigenomes of the different mammary epithelial subtypes in order to gain further insight into the molecular mechanisms that control cell-fate and differentiation decisions. Finally, analysis of different mouse models of mammary tumorigenesis as well as primary human breast tissue has been instrumental in revealing potential 'cells of origin' of breast cancer.

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Natural killer cells

Abstract: Natural killer (NK) cells were originally defined as effector lymphocytes of innate immunity endowed with constitutive cytolytic functions. More recently, a more nuanced view of NK cells has emerged. NK cells are now recognized to express a repertoire of activating and inhibitory receptors that is calibrated to ensure self-tolerance while allowing efficacy against assaults such as viral infection and tumor development. Moreover, NK cells do not react in an invariant manner but rather adapt to their environment. Finally, recent studies have unveiled that NK cells can also mount a form of antigen-specific immunologic memory. NK cells thus exert sophisticated biological functions that are attributes of both innate and adaptive immunity, blurring the functional borders between these two arms of the immune response.

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Pr L. Zitvogel, MD (clinical oncology), PhD (tumor immunology), PU-PH Faculty Paris Sud, University Paris XI (Clinical Biology), graduated in Medical Oncology from the School of Medicine of the University of Paris in 1992. She started her scientific career when she was at the University of Pittsburgh in the USA in Michael Lotze's laboratory. She became Research Director at Institut National de la Santé et Recherche Médicale U805, in a laboratory located at Institut Gustave Roussy, a large cancer Center in Villejuif/France and the Head of the Center for Clinical Investigations CICBT 507 for vaccine developments at Villejuif. She has been actively contributing to the field of cancer immunology and immunotherapy, and she brought together basic and translational research, including the design of cancer therapies through combined animal studies and Phase I patient trials. Her expertise is mainly dendritic cell and innate effector biology and relevance during tumour development as well as exosome-based vaccine designs. She pioneered the concept of immunogenic cell death and showed that chemotherapy, radiotherapy and inhibitors of tyrosine kinase mediate their tumoricidal activity, at least partly through the immune system.

The anti-cancer immune response - indispensable for theraputic success?

Laurence Zitvogel[1,2,3,4,] Lionel Apetoh[1,3,4,] François Ghiringhelli[1,2,3,] Yuting Ma[3,4,5] Stephen Matarollo[6], Laetitia Aymeric[1,3,4,] Dalil Hannani[1,3,4,] Takahiro Yamazaki[1,3,4,] Oliver Kepp[3,4,5,] Antonella Sistigu[1,3,4,] Mark J. Smyth[6,] and Guido Kroemer[3,4,5]

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Although the impact of tumor immunology on the clinical managements of most cancers is still negligible, there is increasing evidence that anti-cancer immune responses may contribute to the control of cancer after conventional chemotherapy. Thus, radiotherapy and some chemotherapeutic agents, in particular anthracyclines, oxaliplatine and X Rays can induce anticancer protective CD4+ and CD8+ T cell-based immune responses (Obeid et al. Nat. Med 2007, Apetoh et al. Nat Med 2007) that result either in immunogenic cancer cell death. Other regimen of chemotherapy also result in tumor sensitization to effector attack, in immunostimulatory "side effects" or in suppression of regulatory cells. This anti-cancer immune response then helps to eliminate residual cancer cells (that failed to be killed by chemotherapy) or maintains micrometastases in check, keeping them in a stage of dormancy.

In collaboration with MJ Smyth at the Peter Mac Callum Cancer Center, we delineated the molecular mechanisms underlying the recognition of dying tumor cells by dendritic cells (DC) and found four major checkpoints that dictate the immunogenicity of cell death. First, optimal phagocytosis of chemotherapy or radiotherapy-treated tumor cells by DC requires the translocation of ER-resident calreticulin (CRT) and disulfide isomerase ERp57 to the plasma membrane of dying tumor cells (Obeid et al. Nat Med 2007, Panaretakis et al. CDD 2008, Panaretakis et al. EMBO J 2009). Second, the chromatin-binding high mobility group box 1 protein (HMGB1) must be released by dying tumor cells and bind to its receptor toll-like

receptor 4 (TLR4) on DC to facilitate antigen processing of the phagocytic cargo (Apetoh et al Nat Med 2007). Third, ATP has to be emitted by dying cells to engage P2RX7 on DC, triggering the activation of a cascade (Nlrp3 inflammasome>ASC>casp-1 cleavage>IL-1β maturation and secretion) leading to IL-1β-dependent Tc1 polarization of antigen-specific T cell responses. It is important to stress that the antitumor effects of anthracyclines, oxaliplatine and X Rays are abrogated in mice devoid of T cells, of a IFNγ/IFNγR functional pathway, of an IL-1β/IL-1R1 intact signaling while IL-12Rβ, perforine/TRAIL are dispensable for the tumoricidal effects of these compounds (Ghiringhelli et al. Nat Med. 2009). Fourth, the contexture of the tumor post-chemotherapy revealed that a precise T cell orchestration is required for the immune effectors to reject the tumor burden. Hence, IL-1β-dependent γδT17 cells precede the Tc1 CTL infiltrate and are indispensable for the efficacy of chemotherapy (Ma et al. JEM 2011, Matarollo, Cancer Res 2011). The IL-17/IL-17Ra pathway is mandatory for the immunogenicity of cell death and the success of chemotherapy. Overall, these molecular requirements dictating the efficacy of chemotherapy may promote the investigators to modify the routine management of cancer patient. Immunogenetics will help defining the immunological defects inherent to each individual patients prior to therapy urging for a distinct compensatory treatment while mapping the defects in the CRT exposure pathway may allow to predict tumor intrinsic defects that could be counteracted by defined therapies. Integrating immunological predictors in the current prognosis signatures may lead to personalization of anticancer clinical management. Based on these premises, we will discuss how it may be possible to ameliorate conventional therapies by stimulating the anti-cancer immune response. Moreover, we will discuss the rationale of clinical trials to evaluate and eventually increase the contribution of anti-tumor immune responses to the therapeutic management of neoplasia.

Early to Mid-Career Researchers

Dr Marie-Liesse Asselin-Labat

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Marie-Liesse Asselin–Labat is a Group Leader in the Stem Cells and Cancer division at the Walter and Eliza Hall Institute (WEHI) in Melbourne.

After completing her PhD (University Paris XI) Dr Asselin-Labat was awarded in 2005/2006 a Fondation pour la Recherche Medicale and INSERM/NHMRC fellowship for her post-doctoral studies in the Breast Cancer Laboratory at the WEHI. She was subsequently awarded a 3-year ARC Discovery Project post-doctoral fellowship to further her work on mammary stem cells and breast cancer. Her most significant contribution to the field was the identification of RANKL as a paracrine signal mediating steroid hormones regulation of mammary stem cells (Nature 2010).

In 2010, Dr Asselin-Labat won the L'Oreal For Women In Science Fellowship and was awarded an ARC Queen Elisabeth II fellowship before being appointed Group Leader in 2011. Her laboratory is interested in lung development, lung stem cells and lung cancer.

Gata-3 negatively regulates the tumor-initiating capacity of mammary luminal progenitor cells and targets the putative tumor suppressor caspase-14

Marie-Liesse Asselin-Labat, Kate D. Sutherland, François Vaillant, David E. Gyorki, Di Wu, Sheridan Holroyd, Kelsey Breslin, Teresa Ward, Wei Shi, Mary L. Bath, Siddhartha Deb, Stephen B. Fox, Gordon K. Smyth, Geoffrey J. Lindeman and Jane E. Visvader

The transcription factor Gata-3 is a definitive marker of luminal breast cancers and a key regulator of mammary morphogenesis. Here we have explored a role for Gata-3 in tumor initiation and the underlying cellular mechanisms using a mouse model of 'luminal-like' cancer. Loss of a single *Gata-3* allele markedly accelerated tumor progression in MMTV-PyMT mice while overexpression of *Gata-3* curtailed tumorigenesis. Through the identification of two distinct luminal progenitor cells in the mammary gland, we demonstrate that *Gata-3* haplo-insufficiency increases the tumor-initiating capacity of these progenitors but not the stem cell-enriched population. Overexpression of a conditional *Gata-3* transgene in the PyMT model promoted cellular differentiation and led to reduced tumor-initiating capacity as well as diminished angiogenesis. Transcript profiling studies identified caspase-14 as a novel downstream target of Gata-3, in keeping with its roles in differentiation and tumorigenesis. A strong association was evident between GATA-3 and caspase-14 expression in pre-invasive ductal carcinoma *in situ* samples, where GATA-3 also displayed prognostic significance. Overall, these studies identify GATA-3 as an important regulator of tumor initiation through its ability to promote the differentiation of committed luminal progenitor cells.

Dr Anne-Sophie Bergot

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During my PhD in France, I studied the physiobiology of regulatory T cells in cancer in mice and more precisely of memory Tregs (amTregs). We proposed that amTregs are the key cells of the tumor immunity, which explained the old paradigm of cancer immunology that preventive immunization is more effective than therapeutic immunization. We therefore suggested that preventive vaccination against cancer in humans should be reconsidered.

I moved to Brisbane last year and I continue working on cancer immunotherapy in a model that mimics papillomavirus infection in mice, virus known to be the leading cause of cervical cancer in women. The actual vaccines (Gardasil, Cervarix) are used for prophylaxis, but are not working as therapeutics. We thus would like to know what regulatory mechanisms are protecting the virus from clearance. I'm focusing my research in Tregs and mast cells.

Evaluation of the role of regulatory cells - mast cells, Treg cells and iNKT cells - in the regulation of immune responses to HPV-infected skin in mice

Anne-Sophie Bergot, Michelle Yong, Deepak Mittal, and Ian H. Frazer

Cervical cancer is the second most common cancer of women worldwide and the first cancer shown to be entirely induced by a virus, the human papillomavirus. As no natural papillomavirus infection occurs in mice, we developed a murine model that can mimic HPV infection, with the expression of the HPV16-E7 oncoprotein in skin and using a skin graft model. Activated iNKT have been identified cells as the key regulatory population, but the full mechanism of immunosuppression still remains undefined.
I hypothesized that other upstream regulatory populations could be involved, such as regulatory T cells and mast cells. 1) Treg cells are CD4+CD25+Foxp3+ T cells that play a major role in the suppression of immune responses. Preliminary data show that Tregs are increasing over the first 10 days after the E7-graft, to reach half of the infiltrating CD4+ T-cells. 2) Mast cells are a 'tunable' population that induces inflammation or immunosuppression depending of the immune context. Preliminary results show that E7-expressing ear skin contains two-times more MC than C57 ears and that those MC have a higher response to passive cutaneous anaphylaxis in vivo compared to MC in normal ears. Other experiments need to be addressed to assess a possible role for these 2 populations, individually or together.

Dr Stephanie Gras

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I've done my PhD in Grenoble (France) in X-ray Crystallography in Dr Housset's laboratory on the structural basis of the human T cell response to the CytoMegalovirus. I've been privileged during my PhD to work with well-know French immunologist Bernard Malissen. My passion for immunology and protein structure, naturally led me to join, in 2007, the Prof Rossjohn's laboratory at Monash University (Clayton, Australia) to pursue my post-doctoral training. My biomedical research focus on viral response and escape as well as understanding the basis for allo-recognition, crucial for organ transplantation. I've been invited to talk at both international & national conferences and so far published 20 articles in high quality journals such as Nature, Immunity, JEM and PNAS. My research group comprises 1 PhD student , 1 honours student, 1 post-doc and 1 RA and my laboratory is currently supported by an ARC discovery grant.

T cell receptors are as polymorphic as snails

Authors: Gras S1, Chen Z2, Miles JJ3, Liu YC1, McCluskey J2, Rossjohn J1, Burrows SR3.

In comparison to human leukocyte antigen (HLA) polymorphism, the impact of allelic sequence variation within T cell receptor (TCR) loci is much less understood. Particular TCR loci have been associated with autoimmunity, but the molecular basis for this phenomenon is undefined. We examined the T cell response to an HLA-B*3501–restricted epitope (HPVGEADYFEY) from Epstein-Barr virus (EBV), which is frequently dominated by a TRBV9*01+ public TCR (TK3). However, the common allelic variant TRBV9*02, which differs by a single amino acid near the CDR2b loop (Gln55→His55), was never used in this response. The structure of the TK3 TCR, its allelic variant, and a nonnaturally occurring mutant (Gln55→Ala55) in complex with HLA-B*3501HPVGEADYFEY revealed that the Gln55→His55 polymorphism affected the charge complementarity at the TCR–peptide-MHC interface, resulting in reduced functional recognition of the cognate and naturally occurring variants of this EBV peptide. Thus, polymorphism in the TCR loci may contribute toward variability in immune responses and the outcome of infection.

Dr Michael Lerch

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Positions and Professional

- *Senior Lecturer, School of Engineering Physics, University of Wollongong (UOW)*
- *Head of the Radiation Detection and Instrumentation Theme, Centre for Medical Radiation Physics (CMRP), UOW.*
- *University Research Committee Member*
- *Chair, Australian Institute of Physics (NSW Branch) 2007-2009*

Research

- *Expertise in semiconductors for the design and development of novel, solid state based, instrumentation for application in radiation medicine.*
- *Over 50 peer reviewed articles*
- *Recent invited talk "Dosimetry of Intensive Synchrotron Microbeams", 16th International Conference on Solid State Dosimetry, Sydney 2010*
- *Supervised over 20 postgraduate research students since 1999*
- *Leader, experimental dosimetry program for the international collaboration between the CMRP and the Biomedical Beamline at the European Synchrotron Radiation Facility, France.*

Patents

- *M.L.F. Lerch, et.al, "Dual Detector" USA, WO2008095257 (A1), 2008 PCT*
- *A. Rozenfeld, M. Lerch, M. Petasecca, "PET Detector" PCT App. No. 2010904210.*

Grants

- *Secured over $3M in research funding since 2006, e.g. Lead Chief Investigator, NHMRC Development grant "X-Tream: A realtime X-ray treatment monitoring and dosimetry system for submillimetric radiosurgery" 2011-2013 $400k.*

Realtime dosimetry in synchrotron x-ray microbeam radiation therapy

M.L.F. Lerch[a], M. Petasecca[a], A. Cullen[a], H. Requardt[b], E. Brauer-Krischb[2], A. Bravin[b], V. L.Pervertaylo[c], A.B. Rosenfeld[a]
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According to the Australian Institute of Health and Welfare, the number of cancer cases in Australia continues to grow every year and around 50% of cancer patients currently receive some form of radiotherapy.
The treatment of some cancers (e.g. glioblastoma multiforme) is very challenging. The treatment outcomes of surgery, chemotherapy or radiotherapy are not always ideal, and for certain variants, the long term prognosis is very poor. Synchrotron X-ray Microbeam Radiation Therapy (MRT), an exciting and very novel form of radiosurgery uses submillimetre X-ray beams and offers new hope for such cancer treatment. MRT is under development at the European Synchrotron Radiation Facility (ESRF), Grenoble, France uses extremely high dose rates (~20 kGy/sec), laterally fractionated radiation fields and steep dose gradients, making real-time patient dosimetry a significant challenge. In order for this treatment to advance to the clinical trial stage of development real-time dosimetry systems are required. This talk will highlight the successful collaboration between the ESRF and the Centre for Medical Radiation Physics, University of Wollongong, by demonstrating the capabilities of a new real-time patient dosimetry system for MRT. The system combines high spatial resolution and real time readout and is able to measure the lateral dose profile of the MRT radiation field incorporating 59 X-ray microbeams.

Dr Guillaume Lessene

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Dr Guillaume Lessene is a drug discovery expert in the field of apoptotic regulation. He trained as a chemist at the Ecole Nationale Supérieure de Chimie de Paris and was awarded a PhD from the University of Bordeaux, before undertaking a postdoctoral fellowship at Pennsylvania State University. Since joining the Walter and Eliza Hall Insitute in 2001, Dr Lessene's research has focused on identifying and developing small molecules that target oncogenes (such as BCL-2 and SRC), helping to define their role in the development of cancer. This knowledge contributed to the successful research collaboration between WEHI, Genentech and Abbott, and is guiding current efforts to target pro-apoptotic proteins for cancer therapy. Dr Lessene was awarded the Biota Award for Medicinal Chemistry from the Royal Australian Chemical Institute in 2009, and the WEHI de Burgh Fellowship in 2010. Dr Lessene is a Laboratory Head in the Chemical Biology Division at WEHI.

Development and characterisation of new inhibitors the pro-survival protein BCL-XL

Biological regulation of cells' life/death decision is crucial to the normal functioning of the human body. The BCL-2 protein family plays a key role in this mechanism, and deregulation of its members is a known contributing factor to many forms of cancer. Specifically, proteins that promote cellular survival are often over-expressed allowing the rogue tumorigenic cells to proliferate. Targeting these "pro-survival BCL-2 proteins" with small molecules allows us to reinstate the normal cell death process, and represents a highly attractive chemotherapeutic strategy.

Our team applies chemical biology strategies to develop small molecules that selectively target members of the BCL-2 family. Here, we present compounds that mimick the interactions between proteins of the BCL-2 family, and provide X-Ray structures as well as biochemical evidence of their direct interaction with the pro-survival BCL-2 proteins. These new compounds provide a unique set of molecular probes to further study the role of the BCL-2 family of proteins in tumorigenesis, and represent a starting point for the development of novel chemotherapeutics.

Dr Eddy Pasquier

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Dr Eddy Pasquier completed his PhD in Oncology at the University of Aix-Marseille in October 2006 and joined the Children's Cancer Institute Australia as a research officer shortly after. His research has provided major insights into the mechanisms involved in tumour angiogenesis and drug resistance, thus contributing to the development of innovative treatment schedules and novel anti-cancer agents. He is now combining functional and pharmacological analyses to define the role and therapeutic implications of beta-adrenergic receptors in childhood cancer. Aged 29, Dr Pasquier has contributed to 28 publications including articles in leading journals such as Cancer Research and Nature Reviews Clinical Oncology, and participated in 32 conference presentations at national and international meetings. He also attracted >AUD$ 1.2 million in peer-reviewed funding and received a number of awards, including the Dean's Rising Star Award 2010 from the Faculty of Medicine, University of New South Wales.

Can beta-blockers represent a novel therapeutic tool in medical oncology?

Eddy Pasquier[1,6], Charlotte Pouchy[1], Joseph Ciccolini[2], Manon Carre[3], Janine Street[1], Jayne Murray[1], Toby Trahair[1,4], Nicolas Andre[5,6] and Maria Kavallaris[1]

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Drug repositioning, which consists of testing already approved drugs for new medical indications, has recently emerged as a strategy to fast track innovative cancer therapies into the clinic. Based on recent clinical data in infantile haemangioma and breast cancer, we hypothesized that β-blockers, which are commonly used in the management of hypertension, may be able to increase the efficacy of chemotherapy. A wide panel of human cancer and vascular endothelial cell lines was used to evaluate the combination of 7 different β-blockers with 5 classes of chemotherapeutics. Our results revealed a powerful synergism between β-blockers and microtubule-targeting agents at inhibiting cell proliferation and angiogenesis *in vitro*. Non-toxic and clinically relevant concentrations of β-blockers thus increased the sensitivity of breast cancer and neuroblastoma cells to vincristine, vinblastine and paclitaxel by up to 40-fold and increased their anti-angiogenic activity by up to 2-fold. Combination treatments were well tolerated *in vivo* when transposed into an orthotopic mouse model of triple negative human breast cancer and resulted in increased anti-tumour efficacy and extended survival. Our data thus suggest that β-blockers could potentially be used in the clinic to increase the efficacy of chemotherapy, thus warranting further fundamental and clinical investigation.

Dr Alice Pebay

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Dr Pébay trained with Prof Glowinski at the Collège de France (Paris) and obtained her PhD (with highest distinction) from the University of Paris VI in 2001, studying the role of lysolipids in the striatum. She subsequently joined Prof. Martin Pera at Monash University, the first Australian research group to undertake research on human embryonic stem cells (hESC). She established the first animal product-free, chemically-defined culture medium for the growth of hESC, and provided the first evidence of a role of lipid mediators in hESC growth. In 2007, she was recruited to the University of Melbourne to establish hESC biology to study human neuronal differentiation. In 2010, while retaining her appointment at Melbourne University, she joined the O'Brien Institute (Melbourne) to continue her research into the role of inflammatory lipids in stem cells and neurotrauma, funded by the award of a prestigious NHMRC-CDA Fellowship.

Involvement of lysophospholipids in stem cell biology and neurotrauma

Lysophosphatidic acid (LPA) is a bioactive lipid that acts on a wide range of cells and regulates numerous cellular functions. LPA has a wide range of physiological and pathophysiological actions, controlling events within the nervous, reproductive, gastrointestinal, vascular, respiratory and immune systems. It also has a prominent role in cancer, early mammalian embryogenesis and stem cells. LPA concentrations increase during inflammation and trauma, as it is synthetised by platelets and released upon platelet activation. In the brain, LPA levels increase when the integrity of the blood brain barrier is damaged, making it a significant player contributing to inflammatory response during neurotrauma. We are investigating how this inflammatory lipid modulates neural responses to injury and regeneration. To this end, we are assessing the role of LPA in stem cell, glial and neuronal responses to injury using a combination of *in vitro* and *in vivo* approaches with human embryonic stem cells (hESC), hESC-derived neural stem/progenitor cells (NS/PC), mouse adult NS/PC, and in vivo models of neurotrauma. Modulating LPA signaling might have a significant impact on injury, providing new avenues in the development of specific therapeutics for neurotrauma.

Dr Mirana Ramialison

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From the French Caribbean island Martinique, I moved to Marseilles –not so far from the sea- to study Bioinformatics and received my engineering degree from the Ecole Supérieure d'Ingénieurs de Luminy in 2002. I joined the laboratory of Prof. Kondoh in Japan (Kyoto) –still staying close to the sea- to develop an expression pattern database for medaka fish. It inspired me to start a PhD at the European Molecular Biology Laboratory (EMBL) in Germany (Heidelberg) with Prof. Wittbrodt to study eye development using bioinformatics approaches and experimental validation in medaka. In 2007, I received my PhD summa cum laude, but decided to move away as Heidelberg was not exactly close to any coastline. Since 2010, I work in Prof. Harvey's laboratory at the Victor Chang Cardiac Research Institute in Sydney as an EMBO and Human Frontiers post-doctorate fellow to work on cardiac gene regulatory networks using bioinformatics and zebrafish model system, and I'm very glad to be close to the ocean again…

Deciphering cardiac gene regulatory networks

Mirana Ramialison, Romaric Bouveret, Tram Doan, Danielle de Jong, Nicole Schonrock and Richard P. Harvey

The heart is a complex organ which successful development relies in part on complex feedback loops and cross-regulation between cardiac genes. Any alteration in these combinatorial interactions can be detrimental to the embryo and lead to congenital heart disease. Understanding which, how and when cardiac developmental genes interact with one another is key to comprehend disease mechanisms. Therefore, to gain insight into the complex interplay of genes governing heart development, we investigated the targets of cardiac transcription factors Nkx2-5, Gata4 and Tbx5 using DNA methyltransferase identification (DamID) in mouse cardiomyocytes at a genome-wide level. Using bioinformatics methods, we reconstructed the cardiac gene regulatory network centered on these key players. By applying *de novo* motif discovery to the components of this network, we provide evidence that Elk transcription factors are novel players in cardiac development. We demonstrate that these proteins physically interact with cardiac core transcription factors *in vitro*. Finally, by using zebrafish as a model system, we provide *in vivo* functional evidence that Elk factors are essential for proper heart formation. Our systems levels approach led us to identify novel genes implicated in heart development and potentially responsible for heart malformations.

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