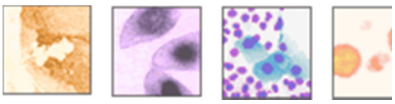

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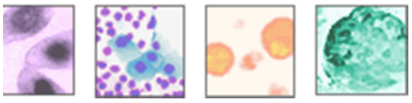

22nd NSW Stem Cell Network Workshop

Stem Cells and Genetic Muscle Disorders

Darlington Centre
City Rd, Sydney
Monday, April 13th, 2015

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WELCOME

Welcome to the 22nd Workshop of the NSW Stem Cell Network

Muscle research is a continuously expanding field in Australia, with numerous groups across the country working on treating the different pathologies that affect patients. In recent years, Australian innovations in muscle stem cell research have increased our understanding of the biology and pathology of muscle development and disease. However, in light of this, we are still faced with the dilemma of a large number of untreatable muscle disorders like muscular dystrophies. How can we move stem cell research forward towards therapies for the treatment of these debilitating, and often fatal pathologies?

In order to understand how muscle disorders arise, and therefore be able to treat them efficiently, it is important to bring together the diverse knowledge and skill sets from researchers of muscle development, stem cells, disease and therapeutics. This workshop, *'Stem Cells and Genetic Muscle Disorders'* aims to do just that.

Beginning with the history of muscle stem cells, the program will cover recent advances in the biology, pathology and therapeutic avenues of stem cells in both skeletal and cardiac muscle systems. The goal is to build discussion on how the field is progressing and how we can best move forward towards new solutions for, what are in many cases, untreatable diseases. By combining the areas of skeletal and cardiac muscle stem cell and disease research, our aim is to promote cross-disciplinary opportunities to find solutions for muscle disease.

Today, you will hear the latest findings from leading muscle researchers across Australia and you will have the opportunity to engage in what we hope will be a stimulating and thought-provoking event.

Our thanks go to Dr Heather Main, former NSW Stem Cell Network Manager, whose brain child this Workshop was, and to our sponsors without whose support it would not have been possible to run this event. Their names and crests appear on the opposite page.

We hope you enjoy the workshop.

Rachel Shparberg
NSW Stem Cell Network
Manager

Professor Bernie Tuch
NSW Stem Cell Network
Director

PROGRAM

9:00am	Registration opens/ Light refreshment
9:30am	**Professor Bernie Tuch—NSW Stem Cell Network** *Welcoming*
9.35am	**Bill Moss AO—Chairman and Founder of FSHD Global Research Foundation** *Opening Address*
Session 1	**Setting the Scene** **Chair: Professor Bernie Tuch**
9:45am	**Professor Miranda Grounds—University of Western Australia** *Skeletal muscle stem cell therapy: Where have we come from and where we are going?*
Session 2	**Developmental Biology and Regeneration** **Chair: Professor Edna Hardeman—University of NSW**
10:10am	**Dr David Elliott—Murdoch Childrens Research Institute** *The use of pluripotent stem cells to model heart development*
10:30am	**Dr Robyn Meech—Flinders University** *Control of Wnt signaling in muscle satellite cells*
10:50am	**Professor Peter Currie—Australian Regenerative Medicine Institute** *Asymmetric divisions coordinate regeneration via a genetically defined population of stem cells during muscle regeneration in zebrafish*
11:10am	Morning tea
Session 3	**Disease Identification, Mechanisms and Modelling** **Chair: Dr Adam Hill—Victor Chang Institute**
11:30am	**Dr Vesna Nikolova-Krstevski—Victor Chang Institute** *Modelling the mechano-electric feedback in the endocardium using a novel primary cell model*
11:50am	**Dr Leslie Caron—Genea Biocells** *A human pluripotent stem cell model of FSHD-affected skeletal muscles*
12:10pm	**Dr Robert Bryson-Richardson—Monash University** *Identifying the genetic basis and pathological mechanisms of myopathies using zebrafish*

PROGRAM

12:30pm	Lunch/ Poster session
Session 4	**Therapeutic Potential** **Chair: Dr Janet Macpherson—University of Sydney**
1:30pm	**Professor Gordon Lynch—University of Melbourne** *Functional assessments to evaluate therapeutic efficacy for skeletal muscle disorders*
1:50pm	**Dr Paul Gregorevic—Baker IDI** *Gene therapy technologies: Strategies to study muscle disease, and potentially enhance the efficacy of stem cell therapies*
2: 10pm	**Professor Robert Kapsa—University of Wollongong** *Autologous cell replacement therapies for hereditary muscle disease*
2:30pm	**Dr James Chong—Westmead Millennium Institute/University of Sydney** *Cell therapies to repair and regenerate the injured heart*
2.50pm	Afternoon tea
Session 5	**Panel Session – What is the best way to tackle muscle disorders?** **Chair: TBA**
3:10pm	**Lead Discussants:** Professor Miranda Grounds Dr Paul Gregorevic Dr Leslie Caron
4:00 pm	Refreshments / Networking

Professor Miranda Grounds—University of Western Australia

Professor Miranda Grounds graduated from the University of Western Australia (UWA) with a Bachelor of Science with Honours (Biochemistry) in 1969, gained a PhD from the University of London in 1978 and returned to UWA to become an independent researcher funded by the National Health & Medical Research Council of Australia from 1980 to 1994. In 1994, M Grounds became a Professor in the School of Anatomy, Physiology and Human Biology at UWA: the transition in 2013 to Emeritus Professor and Honorary Research Fellow allows for more intense dedication to the many ongoing projects and graduate research students. For over 40 years, the research of M Grounds has focussed on *in vivo* studies related to understanding factors controlling the damage, repair and maintenance of skeletal muscles and on potential treatments for muscle disorders such as muscular dystrophy and muscle wasting, including age-related loss of mass and function (sarcopenia), mainly using mouse models of normal and diseased muscles. There is an emphasis on translational applications to human clinical conditions, with long-standing involvement with parent groups for Duchenne muscular dystrophy (DMD) and pioneering studies using muscle stem cell therapy for DMD, as a strategy based on fusion of normal and dystrophic myoblasts into multinucleated cells to specifically replace the defective dystrophin gene in dystrophic myofibres. Although this approach has had limited success to date, M Grounds maintains a strong interest in strategies to optimise the efficacy of myogenic stem cell therapies for a range of applications. This research of M Grounds has generated over 180 publications and is widely recognised internationally: http://school.anhb.uwa.edu.au/personalpages/grounds/

Skeletal muscle stem cell therapy: Where have we come from and where are we going?

In many genetic diseases, the ideal scenario is to replace or correct the peccant gene or protein: this is attempted using a creative range of strategies. Duchenne Muscular Dystrophy (DMD) is a lethal inherited X-linked disease of skeletal muscles which manifests mainly in boys, with progressive severe loss of muscle mass and function during growth. DMD is due to defects in the dystrophin gene (identified in 1986), that result in myofibre fragility leading to necrosis, inflammation and subsequent myogenesis, regeneration and new muscle formation. These endogenous ongoing cycles of necrosis/inflammation lead to increasing fibrosis that progressively impairs myogenesis and results in replacement of muscle by fibrous-fatty connective tissue. It is important to emphasise that extrinsic factors such as fibrosis will determine stem cell capacity. One strategy to replace the defective dystrophin gene within myofibres, relies on replacing the dystrophic muscle nuclei (myonuclei) with normal myonuclei derived from myoblasts or stem cells. The two critical properties of a stem cell are self-renewal and plasticity, with the potential capacity to generate huge numbers of myoblasts. Such myoblast (or stem cell) therapy takes advantage of the fact that skeletal muscle is formed by fusion of myoblasts into multinucleated muscle cells, as routinely occurs during myogenesis and regeneration after muscle necrosis. The donor stem cells can fuse with the host myofibres only because there is ongoing n ecrosis/regeneration in the dystrophic host muscles. The first Myoblast Transfer Therapy conference was held in New York in 1989, human trials started in the 1990s, and many studies have been conducted using the mdx mouse and dystrophic dog models of DMD, combined with a diversity of sources for the normal donor myoblasts/ stem cells. Unfortunately, despite these efforts for almost 30 years, there has been little clinical success. The problems encountered will be outlined and future possibilities discussed. Brief comment will be made on other situations, including tissue engineering, where stem cells to enhance muscle formation have potential clinical applications.

Dr David Elliott—Murdoch Childrens Research Institute

Dr David Elliott completed his PhD the laboratory of Professor Richard Harvey at The Walter and Eliza Hall Institute and The Victor Chang Cardiac Research Institute. The focus of David's PhD was the characterisation of transactivation domains of the homeodomain protein Nkx2-5 and their role in heart development and disease. For his post-doctoral studies David studied Drosophila neurogenesis in the laboratory of Prof. Andrea Brand at the Gurdon Institute, the University of Cambridge. David returned to Australia in 2007 to take up a post-doctoral position in the Embryonic Stem Cell Differentiation laboratory (jointly headed by Profs. Andrew Elefanty and Ed Stanley) at Monash University. During this time David developed a range of technologies and reagents to investigate human heart development using differentiating human pluripotent stem cells as a model system. In 2013 David started his laboratory at the Murdoch Childrens Research Institute. The focus of laboratory is to investigate the genetic control of early human heart development and develop pluripotent stem cell based models of congenital heart disease.

The use of pluripotent stem cells to model heart development

Congenital heart disease is the most common form of birth defect, with a prevalence approaching 1 in 100 children. Similarly, cardiovascular disease is a major cause of illness and death in the Western world and is considered "Australia's most costly disease" requiring an estimated annual expenditure of $5.9 billion. Although the etiologies underlying congenital heart disease and cardiovascular disease differ, the development of new treatments for either condition will be critically dependent on a detailed understanding of how the human heart is formed and how it functions at the cellular and molecular level. Human pluripotent stem cell (hPSC) derived cardiomyocytes are the only tractable platform for illuminating the fine detail of the genetic networks that control human cardiomyocyte cell biology. We have developed a cellular framework to investigate the genetic regulation of human cardiac cell lineage specification. We are now utilizing these reagents and technologies to study congenital heart disease using differentiating hPSCs. In particular, we are examining the role of the important cardiac transcription factor NKX2-5 to determine the molecular mechanisms underlying congenital heart disease in individuals with *NKX2-5* mutations. In addition, we have developed hPSC-based models of a number cardiovascular diseases including cardiac hypertrophy and pulmonary arterial hypertension.

Dr Robyn Meech—Flinders University

Dr. Robyn Meech is a stem cell biologist and pharmacologist with extensive experience in mechanisms of gene regulation, cell signalling and stem cell function in disease, development, and ageing. She trained at Flinders University of South Australia and the Scripps Research Institute in San Diego, California. She directs a program of study on muscle stem cells with particular focus on the Wnt and Notch signalling pathways, as well as cancer stem cells and drug metabolism and development. She has received 3 NIH grants in support of her work and currently holds an ARC Future Fellowship and directs an NHMRC project grant.

Control of Wnt signaling in muscle satellite cells

Satellite cells (SC) are the essential mediators of muscle growth and regeneration. Notch and Wnt signaling are key effectors of SC function with Notch controlling quiescence and activation, and canonical Wnt driving differentiation. A balance between these signals is essential to maintain the SC pool whilst mounting an effective regenerative response to injury/degeneration. Recent work suggests that inappropriate/sustained canonical Wnt signaling impairs muscle regeneration, and increased Wnt has also been linked to muscle aging and fibrosis. We have been studying how canonical Wnt signaling is controlled and have identified two novel effectors of this pathway: the homeobox factors Barx2 and Pax7. Barx2 is expressed in SC and myoblasts, nteracts with MyoD and promotes differentiation. Barx2 null mice have delayed muscle growth and repair as well as increased age-associated fibrosis. Barx2 is induced by canonical Wnt signals and acts as an effector of the Wnt pathway by direct interaction with b-catenin. Although Barx2 activates b-catenin-target promoters, various data suggest that the Barx2 null phenotype may be due to inappropriately sustained rather than reduced Wnt signaling. Specifically, Barx2 regulates genes that provide negative feedback to the Wnt pathway and Barx2 null myoblasts appear to have an extended period of Wnt signaling. In contrast to Barx2, Pax7 (which is induced by Notch) acts in SC and myoblasts to prevent precocious differentiation. Our data indicate that this involves direct inhibition of b-catenin function by Pax7. We have also found that Wnt signals post-transcriptionally suppress Pax7, likely via induction of miR133b/206 that bind to the Pax7 mRNA, thus creating a negative feedback loop. Overall, this work is developing a more comprehensive understanding of the Notch/Pax7–Wnt/Barx2 signaling network and its roles in the proliferation–differentiation switch as well as in the appropriate temporal control of signaling required for efficient muscle growth and repair.

Julie-Ann Hulin[1], Shuang Cui[1], Bianca DeBelis[1], Helen P. Makarenkova[2], Michael Downes[3], Robyn Meech[1]

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[2] Department of Cell Biology, The Scripps Research Institute, La Jolla, CA 92037; [3]Gene Expression Laboratory, The Salk Institute, La Jolla, CA 92037

Professor Peter Currie—Australian Regenerative Research Institute

Professor Peter D. Currie received his PhD in Drosophila genetics from Syracuse University, New York, USA. He undertook postdoctoral training in zebrafish development at the Imperial Cancer Research Fund (now Cancer Research UK) in London, UK. He has worked as an independent laboratory head at the UK Medical Research Council Human Genetics Unit in Edinburgh, UK and the Victor Chang Cardiac Research Institute in Sydney, Australia where he headed a research programme focused on skeletal muscle development and regeneration. His work is centred on understanding how the small freshwater zebrafish is able to build and regenerate both skeletal and cardiac muscle. In 2008 he was appointed Deputy Director of the Australian Regenerative Medicine Institute at Monash University in Melbourne, Australia. He is a recipient of a European Molecular Biology Organization Young Investigators Award and a Wellcome Trust International Research Fellowship and currently is a Principal Research Fellow with the National Health and Medical Research Council in Australia.

Asymmetric divisions coordinate regeneration via a genetically defined population of stem cells during muscle regeneration in zebrafish

Zebrafish possess a broad capacity to regenerate tissues and organs via a variety of distinct mechanisms, capacitites that have been largely lost in the mammalian context. However, skeletal muscle is an intriguing example of a tissue that can regenerate in both zebrafish and mammals. In mammals a quiescent self-renewing stem cell, the satellite cell is deployed to effect repair to damaged muscle. In contrast the cellular basis of zebrafish muscle regeneration remains poorly defined. Despite the paradigmatic status of the satellite cell in stem cell mediated tissue repair many fundamental questions remain unanswered about its mode of activation and self-renewal *in vivo*. Here we reveal that zebrafish also deploy a morphologically and genetically definable muscle stem cell population analogous to the mammalian satellite cell system. Taking advantage of the optical accessibility of zebrafish muscle we have utilized timelapse microscopy to reveal that muscle regeneration in zebrafish deploys an asymmetric method of satellite cell division and self-renewal. We further reveal the existence of a highly dynamic set of morphogenetic interactions between the stem cell and injured and uninjured muscle cells that act to coordinate the regenerative process.

David Baruch Gurevich[1], Ashely Siegel[1], Phong Dang Nguyen[1] Heather Verkade[2] and Peter David Currie[1,3].

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Dr Vesna Nikolova-Krstevski—Victor Chang Institute

Dr Vesna Nikolova was awarded the PhD degree in Medicine from the University of New South Wales in December 2006. Her doctoral studies were conducted at the Victor Chang Cardiac Research Institute (VCCRI) in Sydney, where she worked on a project investigating the molecular basis of dilated cardiomyopathy (DCM) and conduction system disease caused by mutations in the *LMNA* gene encoding the nuclear lamin A/C proteins. Her studies provided novel insights into the molecular mechanisms involved in the pathogenesis of DCM and showed for the first time that abnormal connections between the nucleus and the cytoskeleton promoted defective force transmission and cardiac contractile dysfunction. Following the completion of her doctoral studies, Dr Nikolova moved to the United States in 2006 to commence postdoctoral at the Harvard Institutes of Medicine in Boston, Massachusetts. She used differentiating embryonic stem (ES) cells as a model system of endothelial differentiation. Dr Nikolova returned to Australia in November of 2009 to the lab of Prof. Diane Fatkin at the VCCRI in Sydney, where she is committed to a long-term career in the field of molecular cardiology. Her current research focuses on studying mechanical stress responses in the atrial wall and specifically the mechanosensing and mechanotransduction properties of the atrial endocardium and their involvement in the development of atrial fibrillation. Dr Nikolova is a recipient of the Allied Health and Technology Award from the Cardiac Society of Australia and New Zealand in 2013. She was also the Ralph Reader Basic Science Award Finalist at the World Congress of Cardiology in 2014.

Modeling the mechano-electric feedback in the atrial endocardium using a novel primary cell model

Atrial fibrillation (AF) is the most common heart arrhythmia and a major risk factor for hearth failure. Atrial pressure and/or volume overload are the common features of the diseases that cause AF suggesting that mechanical stress has a major role in the pathogenesis of AF. The atrial endocardial endothelium (AE) is the interface between the myocardium and the circulating blood but its role in the mechanotransduction in the atrium is unknown. We investigated the AE responses to increased mechanical stress by subjecting novel primary AE cells to mechanical stretch. The mechanical stretch conditions included cyclic stretch of 30cycles/ min at 10% displacement. Changes in the cell shape with elongation, hypertrophy and re-alignment of the cells and their stress fibres in a direction perpendicular to the lines of stretch were first observed after 1h of stretch. Redistribution and changed levels of expression of the stretch-sensitive Ca2+ channel TRPC6 in the stretched AE was a major finding. The latter suggested changed TRPC6 activity in the stretched AE, which was evaluated by measuring the levels of intracellular Ca2+ in the cells under baseline and stretch conditions. We found that short-stretch (1-10min) increased TRPC6 activity, while the long stretch (1-24h) silenced it. These findings suggest that TRPC6 is an important mediator of mechanical stretch responses in the AE; the functional consequences of the altered channel activity are predetermined by the duration of the stretch-stimulus; and that TRPC6 changes in the stretched AE may cause AE dysfunction through altered Ca^{2+} signalling that contributes to AF development.

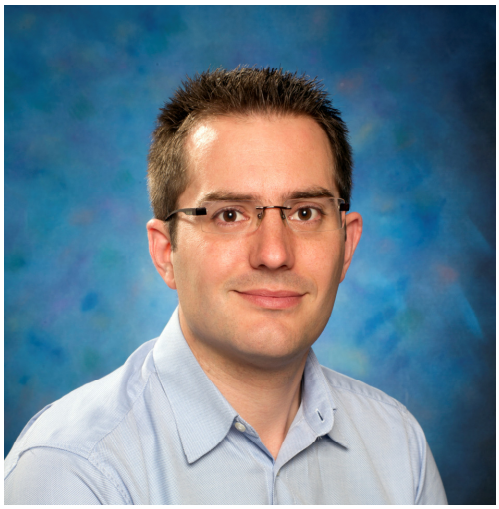
Dr Leslie Caron—Genea Biocells

Dr Leslie Caron has been working for Genea Biocells for the past 3 years. Prior to this Leslie worked at Harvard differentiating human embryonic stem cells into heart muscle and before this, carried out her PhD studies in France differentiating mouse embryonic stem cells into skeletal muscle. At Genea Biocells Leslie has put her expertise together and with FSHD global funding is the first in the world to efficiently make human skeletal muscle out of embryonic stem cells. Leslie's focus with this new system has been to develop a human disease model for FSHD, accelerating potential towards finding a cure.

A human pluripotent stem cell model of FSHD-affected skeletal muscles

Facioscapulohumeral muscular dystrophy (FSHD) represents a major unmet clinical need arising from the progressive weakness and atrophy of skeletal muscles. The dearth of adequate experimental models has severely hampered our understanding of the disease. To date, no treatment is available for FSHD. Human embryonic stem cells (hESC) potentially represent a renewable source of skeletal muscle cells (SkMCs) and provide an alternative to invasive patient biopsies. We developed an efficient monolayer system to differentiate hESCs into mature SkMCs within 26 days, without cell sorting or genetic manipulation. Here we show that SkMCs derived from FSHD1-affected hESC lines exclusively express FSHD pathogenic marker *DUX4*. FSHD-myotubes are thinner when compared to unaffected and Becker muscular dystrophy (MD) myotubes, and differentially regulate genes involved in cell cycle control and oxidative stress response. This unique cellular model will be a powerful tool for studying FSHD and will ultimately assist in the development of effective treatments for muscular dystrophies.

Dr Robert Bryson-Richardson—Monash University



Dr Robert Bryson-Richardson studied Human Genetics at the University of Nottingham before moving to the Medical Research Council's Human Genetics Unit in Edinburgh to complete his PhD and begin his work using the zebrafish model system. He completed his PhD in 2003 and continued his research at the Victor Chang Cardiac Research Institute in Sydney and the Australian Regenerative Medicine Institute at Monash University. He joined the School of Biological Sciences as a lecturer and principal investigator in 2010.

Dr Bryson-Richardson's laboratory utilises the zebrafish model to investigate disease mechanisms and potential therapies for a range of muscle diseases including nemaline and myofibrillar myopathy. In addition to the work on skeletal muscle the team is also interested in the patterning of the embryonic heart and the role of blood flow in regulating its shape and gene expression.

Identifying the genetic basis and pathological mechanisms of myopathies using zebrafish

We are interested in identifying the genetic causes of muscle disease and the molecular basis for pathology. I will present how the zebrafish model can contribute to the identification of novel disease genes and illustrate this with an example from our work on nemaline myopathy. I will focus on the application of zebrafish to understand the mechanisms of muscle disease. I will describe the generation and characterisation of models for ACTA1 nemaline myopathy and FLNC and BAG3 myofibrillar myopathies that have contributed to our understanding of disease, and highlighted potential therapeutic approaches.
In nemaline myopathy we have identified the subcellular origins of the characteristic protein aggregates, identifying multiple subtypes, explaining conflicting reports in the literature as to their composition, and suggesting multiple factors that contribute to muscle weakness.
In myofibrillar myopathy we have demonstrated that muscle weakness results from protein insufficiency resulting from a toxic gain of function. In contrast to the previously established theory we demonstrate that mutant protein is capable of preserving muscle structure but its sequestration in the cytoplasm limits its sarcomeric function. Furthermore, we examine potential approaches to treat myofibrillar myopathy, presenting preliminary results promoting autophagic clearance of protein aggregates.

Professor Gordon Lynch—University of Melbourne

Professor Gordon Lynch is Head of the Department of Physiology at The University of Melbourne (UoM). His research investigates mechanisms and treatments for muscle wasting and weakness in muscular dystrophy, ageing, and cancer. He completed his BSc Honours at La Trobe University (1988), his Ph.D. at UoM (1992), and postdoctoral training at the University of Michigan, U.S.A. (1995-1997) while a C.J. Martin Research Fellow (NHMRC, Australia). Gordon was awarded the Australian Physiological Society's *A.K. McIntyre Medal* (1995) and research fellowships from the Australian Research Council (1998) and the NHMRC (1998) before becoming a Lecturer in Physiology at UoM (1999). He was promoted to Professor in 2008 and appointed Head of Department in 2011. Gordon has published more than 170 papers in leading journals, including *Nature* and *Physiological Reviews*. His sole edited textbook on *Sarcopenia* is a definitive resource on age-related muscle wasting and weakness. Gordon's passion for mentoring has been recognised through the UoM's Research Higher Degree Mentoring Award (2008), a national Citation from the ALTC (2009), the Smorgon Families Award for mentoring the winner of the Victorian Premier's Award (2012), and UoM's Grimshaw Award for Mentor Excellence (2013). In the corporate world, Gordon was co-Founder, Director and Chairman of *Fitness2live* (2000-2009), one of the world's first online health and fitness companies; later sold to Medibank, Australia's leading health insurer. He has authored ~1000 health monographs and his weekly national broadcast media work on ABC Radio for the last 13 years has seen him interviewed on more than 700 occasions, and featured in newspapers, magazines, and TV news/lifestyle shows. Gordon won a National Journalism Award from Australia's National Asthma Council (2002) and he was a Finalist for Australia's *Eureka Prizes* for Promoting Understanding of Science (2006) and for Scientific Research (2013).

Functional assessments to evaluate therapeutic efficacy for skeletal muscle disorders

Many claims are made about the therapeutic potential of different pharmacologic, gene, cell and bioengineering strategies for muscle diseases like Duchenne muscular dystrophy (DMD) and other muscle wasting conditions. Many of these approaches, even some which proceed to clinical trials, sadly fail because their therapeutic potential cannot be realised. Their lack of success can often be traced to a lack of rigorous pre-clinical evaluation, specifically the absence of comprehensive evaluations of muscle function that can ultimately determine whether an intervention will translate to improvements in quality of life.

Muscle function can be assessed through simple measures of overall muscle strength and physical capacity (like walking, running, climbing and swimming) to more sophisticated analyses at the level of working muscle groups, isolated intact muscles and muscle strips *in situ* or *in vitro*, as well as cellular preparations that allow for manipulation of organelle (sarcoplasmic reticulum) function and cross-bridge cycling. Even simple measures like voluntary running performance (in dystrophic mice) can provide important information about whether an intervention is likely to provide (clinically) meaningful improvements in physical capacity and performing activities of daily living.

Functional measures include assessments of muscle force (strength) and power, fatigue and susceptibility to contraction-mediated muscle damage. For DMD and related diseases where muscle fibres are inherently fragile, interventions that can improve the relative susceptibility to muscle injury may confer sufficient protection to attenuate muscle fibre breakdown, preserve muscle mass and slow the progression of the dystrophic pathology – ultimately to improve lifespan and functional independence.

Dr Paul Gregorevic—Baker IDI

Dr Paul Gregorevic gained his PhD from the University of Melbourne Department of Physiology in 2001. He subsequently trained as a postdoctoral research fellow within the University of Washington Department of Neurology, Seattle USA, where he acquired expertise in molecular biology and the design of recombinant viral vectors as gene delivery technologies for studying and treating muscle diseases. In 2008, Dr Gregorevic relocated his research program to Baker IDI Heart and Diabetes Institute, Melbourne, where he is Head of the Laboratory for Muscle Biology and Therapeutics Development, and Director of the Recombinant Viral Vector Core. His research interests focus on elucidating the mechanisms underlying the development and regulation of the skeletal muscle phenotype, and the development of novel therapeutic interventions to combat loss of muscle function associated with heritable and acquired diseases and the aging process. Dr Gregorevic has authored numerous papers, reviews and book chapters concerning the mechanisms of skeletal muscle function and adaptation, neuromuscular disorders, and intervention strategies for their treatment. He has served as an elected member of the Executive Committee of the Australian Gene Therapy Society since 2009.

Gene therapy technologies: Strategies to study muscle disease, and potentially enhance the efficacy of stem cell therapies

Skeletal muscle is a highly adaptive tissue, the attributes of which are influenced by stimuli emanating from other cell types. Similarly, skeletal muscle is an important source of secreted factors that impact on the functions of other tissue/organ systems. Recombinant viral vectors have been developed as tools for admin istering gene therapies to combat medical conditions, including neuromuscular disorders. These gene delivery technologies can also be used to interrogate the mechanisms that control skeletal muscle homeostasis and adaptation, and the aetiology of disease. We propose that gene delivery-based interventions could also prove valuable to manipulate interactions between skeletal muscles and other cell types. Such approaches could conceivably enhance the efficacy of stem cell-based therapies targeting muscle and other tissue systems. Using these gene delivery technologies, we have identified important new roles for the Transforming Growth Factor- beta (TGFb) and Hippo signalling networks in skeletal muscle. These pleiotropic signalling pathways are also involved in the regulation of organogenesis and remodeling, with implications for stem cell function and manipulation. This presentation will examine how muscle-directed gene delivery strategies targeting the TGFb and Hippo signalling networks in muscle, and other mechanisms, could potentially aid the development of new interventions for muscle-related disease, including stem cell therapies.

Professor Robert Kapsa—University of Wollongong

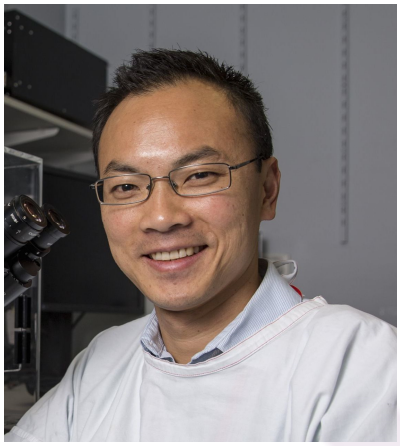
Professor Robert Kapsa received his PhD in 1996 in mitochondrial polymorphisms' contribution to human disease. He has produced 91 published communications (>1626 citations, H index of 21) and been the lead investigator on a number of National (Australia) and international (USA and Europe) projects dealing with neuromuscular disease, nerve and muscle regeneration and gene editing of hereditary mutations. His 91 published outputs include two book chapters and one book. He is currently the Principle Scientist (Bionics) at University of Wollongong, Intelligent Polymer Research Institute, which features a role as CI within the Synthetic BioSystems platform of the ARC Centre for Electromaterials Science (ACES). He holds a joint appointment as Head of Research at the Department of Neuroscience, St Vincent's Hospital Melbourne. Professor Kapsa has extensive experience in tissue regeneration, cell and molecular biology, gene therapy, biochemistry and the use of polymers for tissue engineering, specifically in the area of muscle/nerve regeneration and has conducted a number of projects investigating regeneration and gene therapy in Muscular Dystrophy, and nerve regeneration.

Autologous cell replacement therapies for hereditary muscle disease

Autologous regenerative cell replacement is precluded as a viable therapeutic approach in hereditary degenerative muscle disorders such as Duchenne Muscular Dystrophy (DMD), due to the presence of the |disease-causing mutation in all cells from the affected individual. On the other hand in order to be ***functionally effective***, cell replacement therapy needs to target at least 20% of the 40% of total body mass representative of muscle tissue in any individual with degenerative muscle disease. Autologous cell replacement therapy for hereditary muscle disease thus requires:- i) accurate corrective gene editing (cGE) strategies to remove the disease-causing mutation from ii) a relevant myoregenerative cell derived from non-muscle tissue which needs iii) effective delivery to maximise corrected loci within the target muscle tissue. Improvement of several cGE technologies combined with developments in induced pluripotent stem cell (iPSC) technology over the past 2 decades can be integrated with polymer-based cell delivery approaches to make feasible autologous cell replacement therapies for hereditary muscle disease. This presentation communicates the development of a multi-component cGE/iPSC/polymer system by which to deliver autologous myoregenerative cells to dystrophic muscle in the *mdx* mouse model of DMD. Specifically, this consists of the application of cGE to skin-derived iPSCs from *mdx* mice, their differentiation and expandison *ex vivo* to robust myoregenerative phenotype and delivery to recipient *mdx* muscle within a soft gel Cell/Fibre microtissue construct (MTC) format to restore functional dystrophin in *mdx* muscle. This forms the basis of an autologous regenerative cell therapy for DMD and other hereditary muscle diseases.

ARC Centre for Electromaterials Science (ACES), University of Wollongong and St Vincent's Hospital, Melbourne, Fitzroy, Victoria 3165, Australia

Dr James Chong—Westmead Millennium Institute/University of Sydney



Dr James Chong MBBS, FRACP, PhD is a Consultant Cardiologist at Westmead hospital and leads a research group at the University of Sydney School of Medicine/Westmead Millennium Institute. His clinical cardiology focus is on Interventional Cardiology. His research group aims to translate findings from the field of Cardiac Regeneration into viable clinical therapies for patients with heart failure.

Dr Chong trained in cardiology at Westmead Hospital before completing a PhD at the Victor Chang Cardiac Research Institute under the mentorship of Prof Richard Harvey. This doctoral training in cardiac development and stem cell biology focused on a previously unidentified population of cardiac stem cells. With the support of a Fulbright fellowship and a NHMRC Biomedical Training fellowship he undertook post-doctoral training at the University of Washington, Seattle, USA with Prof Charles (Chuck) Murry. During this period he extended his interests in translational cardiac regeneration to include the use of pluripotent stem cells in small and large animal models of myocardial infarction.

Cell therapies to repair and regenerate the injured heart

Cell therapies specifically targeting heart failure could greatly decrease morbidity, mortality and burgeoning health care costs worldwide. These novel therapies can be broadly grouped into two categories. The first, Adult Stem/Progenitor Cells (ASCs) have a limited ability to form down-stream differentiated cells (termed plasticity). Nevertheless, ASCs have already been used in many clinical trials investigating cardiac repair. Results have shown a favourable safety profile but inconsistent results regarding efficacy. The second category, Pluripotent Stem Cells (PSCs) have an unquestionable ability to form bonafide, spontaneously contracting, cardiomyocytes. However, as a cardiac regenerative strategy PSCs currently remain in the preclinical arena. This presentation will discuss recent work on a Platelet Derived Growth Factor Receptor-Alpha expressing ASC population[1-2] and on human PSC derived cardiomyocytes (hPSC-CM). Particular focus will be made on recent non-human primate experiments demonstrating feasibility of human hPSC-CM as a potentially viable strategy for cardiac regeneration[3].

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Poster Presentations

1. **In-vitro model using equine articular cartilage explants for investigation of adipose-derived stem cell kinetics with Hyaluronan**
   Peter Succar, Michael Medynskyj, Edmond J. Breen, Tony Batterham, Benjamin R. Herbert

2. **Long-term impact of ionizing radiation on skeletal muscle in mice – toward an understanding of Metabolic Syndrome**
   Nádia Amorim, Sarah Bould, Anthony Kee, Christine Lucas, David Simar, Edna Hardeman

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