John EJ RASKO

BSc(Med), MBBS(Hons), PhD, MAICD, FFSc(RCPA), FRCPA, FRACP, FAHMS

I am a clinical hematologist trained as a physician (FRACP 1993) and pathologist (FRCPA 1993). In 1995 I received a PhD under Prof. Don Metcalf at WEHI studying autocrine leukaemogenesis, cytokines & first human clinical trials of thrombopoietin. My postdoc was at the Fred Hutchinson Cancer Research Centre in gene therapy and haemopoiesis under the pioneer Prof. Dusty Miller. In 1999, I established the Gene & Stem Cell Therapy Program, Centenary Institute, and Department of Cell & Molecular Therapies (CMT) at RPA Hospital. In 2005 I was promoted to a personal chair at the University of Sydney. In 2010 I was elected founding Fellow, Faculty of Science, RCPA, and in 2015 a founding Fellow of the Australian Academy of Health and Medical Sciences.

Funding (since 2016)

I have been awarded an NHMRC Investigator Grant (L3, 2020-4) for "Driving clinical cell and gene therapy in Australia". My Program at the Centenary Institute has been awarded $16.8M peer-reviewed funding from NHMRC (6 Project Grants (4 as CIA)), NSW government (2), Cancer Council NSW (4 Project, 1 Pathway Grants), Ramaciotti Foundation (1), Tour de Cure (5), Cure The Future (2). My clinical Department of CMT has received equipment, infrastructure and clinical trial funding of ~$18M from some of above & ACRF, NCRIS, Li Ka Shing Foundation, CSR and CRC-Cell Therapy Manufacturing.

Research Record (molecular genetics, stem cell biology, translational medicine).

My 179 publications in refereed international journals have received >14,000 citations (GS). I have 32 publications cited over 100 times, which evidences outstanding and enduring contributions. I have championed AAV-mediated gene transfer to cure haemophilia via control of immune mechanisms (*Nat. Medicine* 2006 Cit:1702; *Nat. Medicine* 2007; Cit:540). Gene therapy clinical trials comprise haemophilia (*NEJM* 2017 Cit 216:, thalassaemia (*NEJM* 2018 Cit:173), GVHD and B-cell malignancies. Prior to milestone iPS discoveries, we facilitate *ex vivo* expansion and gene transfer of blood stem cells *Nature Biotech.* (2010 Cit:213). I led and established the Australian Aminoaciduria Consortium to discover genes for Hartnup disorder (*Nature Genetics* (2004; Cit:202) iminoglycinuria & dicarboxylic aminoaciduria (*J. Clin. Invest*. 2008; Cit:75; 2011 Cit:79), thence showing they determine cancer progression & provide anti-cancer targets eg *Cancer Res* (2011; Cit:113), *IJC* (2014 Cit: 132), *Oncogene* (2016 Cit: 195). In 2001 I demonstrated tumour suppressor effects of CTCF (*Cancer Res*; Cit: 106) leading to an international standing in the biology of ZF transcription factors (most recently *Genome Biol* 2015 & *Oncogene* 2017). Our work in the biology and bioinformatics of RNA has evolved from a focus on microRNAs (*NEJM* (letter 2008), *Nature Methods* (2009), *Bioinformatics* (2010, 2012, 2013), *Haematologica* $\times$2 (2010)) and extends to identifying new small RNA types (*Nature Struct. Mol. Biol.* (2010; Cit:163) and gene regulation by intron retention [*Cell* 2013, see below 3; *Nature Comms* 2017, see below 4].

Collaborations

Through co-publications, collaborative grants and shared initiatives I have an extensive network of national and international collaborators. These include Andras Nagy (U Toronto), Gerd Blobel (CHOP, PA), William Ritchie (CNRS, Montpellier), Tim Hughes/Deb White (SAHMRI) and those specified in this grant proposal. As immediate Past President of ISCT I have strong and regular personal contact with global cell therapy leaders & collaborators; as well I serve on the Board of FACT for international quality accreditation in cellular therapies.

Awards, Prizes and Other Recognition

Recognition of my research and service includes 13 awards prior to 2012 and the following: RCPA Visiting Lecturer Award 2013; the Distinguished Fellow Award 2013, [highest award of the RCPA (~one pa since 1986)]. In 2012, I was appointed Officer, General Division, Order of Australia (AO) for "distinguished service to biomedical research in gene and cell therapy".

Professional Activities

Having been a founding member in 2000 of The Gene Technology Technical Advisory Committee (GTTAC), I have been its Chair for over a decade. GTTAC provides scientific advice to The OGTR and Australian Legislative and Governance Forum on Gene Technology. I chair the RPA Hospital Institutional Biosafety Committee (2008-) &

am immediate past chair of the Advisory Committee on Biologicals to advise the Minister for Health and the TGA (2012-15). I am a regular reviewer for the ARC, with many years on GRPs & Assigners Panel (2015) for the NHMRC, Leukaemia Foundation, Cancer Council (>5 years), ACRF, SAHMRI and internationally the Wellcome Trust and CIRM. I was a founding member of the Cancer Institute of NSW Research Committee (2002-14). I serve on 3 medical philanthropic foundation Boards; biennial *New Directions in Leukaemia Research*; 2 ethics committees; and Haematology Committee, RCPA. I am co-founder/past President Australasian Cell & Gene Therapy Society (2000 onwards) and chaired the International Committee of the American Society of Gene & Cell Therapy (2004-11). In 2009 I founded the ANZ regional International Society for Cellular Therapy (ISCT), in my role as the elected ISCT Vice-President (2008-12). I was voted as ISCT President-Elect 2016-18, President 2018-20. Editorial positions include *Pathology* - Associate Editor 2000- and Guest Editor 2011; *J. Gene Med*; *Gene Therapy and Regulation*; *Human Gene Therapy*; and *Cytotherapy* - Associate Editor, 2008-.

Supervision and Mentoring

I have directly mentored >20 postdoctoral scientists and supervised ~20 PhD and fifteen MSc and BSc (Hons) completions since 2000. My medical PhD and postdoctoral mentees have become haematologist staff specialists or senior laboratory heads. Four postdocs have become Professors and one is a Deputy Dean. I deliver ~monthly national lectures, with ~10 paid international invitations pa. I regularly appear in print, radio and TV communicating science and medical research (Guardian; ABC Radio & Catalyst x5; Network Ten The Project; 2018 Boyer Lectures).

Five Best Publications (since 2016)

[1] George LA ... Rasko JEJ (4th of 28 authors) ... High KA. Hemophilia B Gene Therapy with a High Specific Activity Factor IX Variant. *New England J of Medicine* 2017, Cit: 344. In a ground-breaking clinical trial 10 haemophilia B patients infused IV with a liver-tropic AAV vector delivering an enhanced Factor IX gene variant had sustained therapeutic expression of Factor IX resulting in a near elimination of bleeding events and Factor IX prophylaxis. The Department of CMT at RPAH was the only non-US site administering AAV into patients.

[2] Thompson AA, ... Rasko JEJ (4th of 30 authors) ... Cavazzana M. Gene therapy for transfusion-dependent β-thalassemia. *New England J of Medicine* 2018, Cit: 287. In two international Phase1/2 clinical trials, mobilised autologous CD34+ stem cells were transduced ex vivo with a lentiviral gene therapy vector containing β-globin. Half of 22 transfusion-dependent β-thalassemia patients receiving gene modified cells were effectively cured, with the other half requiring fewer red blood cell transfusions. My Dept. at RPAH was the only non-US site where gene-corrected cells were infused into patients.

[3] Wong JJ, 10 authors, Rasko JEJ. Intron retention is regulated by altered MeCP2-mediated splicing factor recruitment. *Nature Comms* May 2017, Cit: 49. We have now dissected the epigenetic controls that direct this type of alternative splicing. Decreased DNA methylation near the splice junctions of retained introns corresponds with reduced MeCP2 occupancy and recruitment of splicing factors as well as increased RNA PolII stalling. This follows on from our groundbreaking discovery that intron retention (IR) is a previously overlooked, conserved mechanism of gene regulation in normal cellular differentiation. *Cell* 2013 (Cit: 298).

[4] Schmitz U, 8 authors, Rasko JEJ. Intron retention enhances gene regulatory complexity in vertebrates. Genome Biology, Nov 2017, Cit: 33. We revealed that IR is an evolutionarily conserved mechanism of gene expression regulation. We have since showed intron retention is a widespread alternative splicing event occurring in all tissues and 80% of coding genes. We established an IR database of 2000 RNAseq samples and provide the bioinformatics tool IRFinder to accurately detect IR from RNAseq data (Middleton R ... Rasko JEJ, Ritchie W. Genome Biology 2017, Cit: 86).

[5] Marshall AD, 14 authors, Rasko JEJ. CTCF genetic alterations in endometrial cancer are pro-tumourigenic. *Oncogene* 2017, Cit: 27. We functionally characterised the impact of CTCF haploinsufficiency in endometrial cancer and we were the first report to show some CTCF somatic mutations had a pro-tumourigenic rather than a loss-of-function effect.