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Title:
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Date:
2021-04-01

Citation:
Borger, J. G., Nguyen-Robertson, C. V. & Harris, J. (2021). Trailblazing women immunologists of Australia and New Zealand. Immunology and Cell Biology, 99 (4), pp.338-343. https://doi.org/10.1111/imcb.12454.

Persistent Link:
https://hdl.handle.net/11343/298412

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Article type : Editorial

ICB Editorial – Free to View

(to accompany the *ICB* Virtual Issue on Trailblazing women immunologists of Australia and New Zealand

Title:

Trailblazing women immunologists of Australia and New Zealand

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/IMCB.12454

The topic of women in science usually draws immediate mention of Marie Curie, the first person to win two Nobel Prizes, first in physics in 1903 (with her husband Pierre), and then in chemistry in 1911. Or more recently, Jennifer Doudna and Emmanuelle Charpentier's ground-breaking work in gene editing, which won them the 2020 Nobel Prize in Chemistry. Their win marked the first time a science-related Nobel Prize was shared by women and no men. Many other remarkable women have made revolutionary contributions to the advancement of science over the years. In our 'Trailblazer Women Immunologists in Australia and New Zealand' Virtual Issue of *Immunology & Cell Biology (ICB)*, we celebrate the achievements of women who made ground-breaking discoveries, challenged the dogma of the time and left a formidable legacy within Australia and New Zealand.

Historically, many notable women in science, including chemist and noblewoman, Marie-Anne Paulze Lavoisier, were merely seen as the wives or sisters of male scientists. Indeed, up until the early 1900s, women were largely prevented from pursuing a tertiary education, with the Royal Society, the UK's most prestigious scientific establishment, not permitting membership for women by statute until 1945. Even after Marie Curie was awarded her second Nobel Prize, she was still refused membership of the French Académie de Sciences. A notorious example of an unrecognized female scientist is Rosalind Franklin, an x-ray crystallographer who played a central role in understanding the molecular structure of DNA, RNA, viruses, coal and graphite. She was only recognized posthumously for identifying the double helical structure of DNA, a fundamental biological discovery for which her male colleagues, James Watson and Francis Crick, were awarded the Nobel Prize in 1953. Although the number of women scientists is far greater today, disparities continue to exist in gender equality and women empowerment around the world.

Women represent approximately 50% of the global population. Yet, according to data from the United Nations' Gender Inequality Index, which measures gender disparity across reproductive health, empowerment and economic status, women continue to remain disadvantaged in political representation, access to healthcare, entry into education and participation in the labour workforce. These barriers significantly impact the development of their capabilities and can stunt their potential. Unfortunately, science is not immune to these inequalities. The United Nations has identified that women only make up 30% of the

global pool of academic researchers and often face gender-based discrimination and absence of equal opportunities to develop their research capabilities and scientific discoveries. Female academics are also often tasked with additional carer and household duties, and increased pastoral care at work, disproportionately impacting their academic output, grant funding and promotions compared to their male peers.

Currently, a disproportionate number of professors are men. Women in Science Parkville Precinct (WiSPP) reported that 80% of full professorships in the five foremost research institutes in Parkville, Victoria, are held by men, coming at the expense of the career advancement and retention of female academics. Despite marked advances towards bridging disparities in the past few decades, only 5 out of 27 recipients awarded the Australian Prime Minister's Prize for Science since 2000 have been women. Additionally, of the 923 Nobel laureates since 1901, including 25 immunologists, only 48 have been women (and none of these immunologists). Yet there have been many notable women immunologists, including Professor Eva Engvall, one of the scientists who invented the ELISA, Professor Phillippa Marrack who discovered superantigens during her foundational work on immunological tolerance and Professor Polly Matzinger who proposed the danger model theory of how the immune system works and always challenged the traditional scientific establishment – all three are still yet to be awarded for their fundamental discoveries.

The theme for the International Day of Women and Girls in Science 2021, 'Women Scientists at the forefront of the fight against COVID-19', celebrated the recent remarkable efforts of women in science. The outbreak of the pandemic clearly demonstrated the critical role of women researchers in different stages of the fight against COVID-19. Leading female Australian and New Zealander researchers, including Professors Katherine Kedzierska and Sharon Lewin and Dr Kylie Quinn, are helping to advance our knowledge of the virus through developing techniques for testing, vaccine development and participating at the forefront of community education, providing inspirational role models for current and future generations of scientists.

Despite the formidable societal and scientific challenges women continue to face in terms of gender inequality, we are proud to present our 'Trailblazer Women Immunologists in Australia and New Zealand' Virtual Issue. In this issue, we have highlighted the key works of eight Australian and New Zealander women immunologists, published in *Immunology & Cell Biology* (previously named *Australian Journal of Experimental Biology and Medical Sciences)*. Each have helped shape the field of immunology through their novel ideas, ground-breaking research, and determination to address the challenges of the decades, leaving a legacy to continue to uphold and contribute towards.

Last month, we farewelled the exceptionally talented and visionary scientist, Professor Katharina Gaus. Professor Gaus developed powerful and innovative single-cell super-resolution fluorescence microscopy techniques, winning her many accolades, including the Gottschalk Medal for outstanding research in the biomedical sciences from the Australian Academy of Science, the NSW Premier's Prize for Science and Engineering, the prestigious Elizabeth Blackburn Fellowship, and the Khwarimi International Award. These techniques enabled her to elegantly visualise the lipid structure and raft domains in living cells to investigate how actin and plasma membrane structural dynamics intricately control early T cell signalling events of lymphocyte activation[1-4]. The selected research article from Professor Gaus in this Virtual Issue of *ICB* identified the positioning and critical role of Annexin A6 within T-cell plasma membranes to support a lipid raft-like environment required for the regulation of signalling events that intricately balance IL-2 homeostasis and sensitivity[5]. These findings demonstrate that a single protein can act as a sensitive rheostat for cellular lipid and cholesterol content, and highlight the integrative relationship between plasma membrane organisation and signalling pathways.

Professors Barbara Heslop CBE and Margaret Baird were two leading immunologists at the University of Otago, both of whom gained recognition in the medical community for their pioneering research and teaching, at a time when women scientists and role models were scarce in New Zealand. Indeed, Professor Heslop was Baird's PhD supervisor and mentor. Together they co-authored almost 20 publications on the immunosuppressive activity of the class I major histocompatibility complex antigens and contributed to the understanding of how they regulate transfusion success[6-10].

Professor Heslop was a Fellow of the Royal Australasian College of Surgeons (RACS), a Fellow of the Royal Society of New Zealand and was appointed a Commander of the Order of the British Empire, for services to medical education. To commemorate Heslop's work and that of her husband, John Heslop, they were joint recipients of the Sir Louis Barnett Medal awarded by the RACS, and the Barbara and John Heslop Medal was established by the RACS in their name. Publishing more than 130 research papers, her major contributions to immunology reflected her investigations in prolonging organ graft survival, with a focus on allogenic lymphocyte cytotoxicity, the development of immunosuppressive regimens for organ transplant and the H-Y antigen. A seminal research paper of Professor Heslop's, selected for this *ICB* Virtual Issue, demonstrates her early investigation into identifying the histocompatibility antigens of the AS2 isohistogenic rat strain, to more fully appreciate the origin and antigenic inter-relationship of this newly developed strain and 3 other isohistogenic strains (AS, BS and HS). This came at a time when, although the development of inbred rat strains was incrementally advancing, relatively few systematic investigations on histocompatibility antigens had been undertaken. Her work provided integral knowledge required for the study of organ transplantation and the development of immunosuppressive therapies[11].

Following her postgraduate studies, where she was the only female and oldest person in the course, Professor Margaret Baird forged a luminary career investigating the role of dendritic cells (DCs) in infectious diseases and cancer. She was appointed as a lecturer at the University of Otago and quickly became a distinguished lecturer and role model to many female students due to her impassioned sustained drive for equity in science. Professor Baird is credited with coordinating the 1985 immunology meeting that led to the formation of the Australian and New Zealand Society for Immunology Inc. (ASI). This was acknowledged when she became the first New Zealander to receive the Derrick Rowley Medal, representing outstanding service to the immunology field and the ASI. In 2019, the establishment of the Margaret Baird Women in Immunology Award aimed to recognise the awardee's research and education achievements but also their passions for equity in science, emulating all that Professor Baird strived for throughout her career. Professor Baird's later research included deciphering how the tumor suppressor gene p53 regulates

DC function, along with its role in tumor suppression. Key to these investigations is her seminal paper in this *ICB* Virtual Issue, which defined a cross-presentation pathway in DCs, which operates independently of the proteasome and TAP, for the presentation of tumor antigens in virus-like particles (VLP) to $CD8^+$ T cells[12]. These VLP conduits have been shown to significantly inhibit tumor growth and thus her findings suggest that they could be tailored for specific tumors to generate greater tumor cytotoxicity and act as potential immunotherapeutics in the future.

In the early 20th century, although some women were able to practice as individual scientists, many were employed as female assistants of male scientists, which enabled their significant contributions to science. Miss Dora Lush, an accomplished bacteriologist, was one such female assistant, working as a close collaborator of Sir MacFarlane Burnett, researching infectious diseases including influenza, herpes infections and myxomatosis. She was investigating scrub typhus during the Second World War, which had become a significant health problem among Australian service men, when she accidentally pricked her finger with a needle containing scrub typhus. She tragically died four weeks later, yet today her extensive efforts in infectious disease research in Australia have been recognised by the National Health and Medical Research Council, who named the Dora Lush Basic Science Research Scholarship for postgraduate students in her honour. In this *ICB* Virtual Issue, we highlight Miss Lush's primary research on the 1939 Influenza epidemic in Melbourne. Although this was a mild flu epidemic, by isolating four different virus strains from four patients at Bundoora mental hospital, a hospital staff member, two family members and a Walter and Eliza Hall Institute (WEHI) staff member, she discovered that what appeared to be a homogenous epidemic of influenza could be caused by several antigenically different strains of virus[13]. The conclusions of this work reflect what the scientific community is observing in the current pandemic, in the isolation of numerous antigenic strains of SARS-CoV-2. Miss Lush concluded the impossibility that all antigenic varieties are imported from overseas, and that, instead, widespread dissemination and multiplication of a single strain within a population could give rise to numerous minor antigenic variants. Indeed, to quote Miss Lush's work "It would be a natural extension of this idea to believe that in pandemic periods even wider variation might result, that in this way a reasonable explanation of the

multiple waves in a pandemic as that of 1918–19 (H1-N1 influenza pandemic) may be obtained"[13]. This is reflected again in the current COVID-19 pandemic.

Another eminent woman immunologist under the mentorship of MacFarlane Burnett at the WEHI was Dr Margaret Holmes, who discovered that that immune cells are responsible for initiating autoimmune conditions. The leadership of Dr Holmes in both research and management was recognised when she became General Manager of the WEHI under Director, Sir Gustav Nossal. In recognition of her achievements at the Institute, it now awards an annual Margaret Holmes Emerging Leader prize in recognition of younger staff who have made significant contributions to the Institute and demonstrate the potential for leadership and continuing service. The research from 1964 by Dr Holmes in this *ICB* Virtual Issue laid the foundations of her extensive research that led to the identification that genetic predispositions can underlie the development of autoimmunity. To understand the immunological significance and pathology of the thymic lesions New Zealand Black (NZB) mice were predisposed to, Dr Holmes transplanted infant NZB thymus or spleen into NZB/C3H hybrids [14]. Although the transfer experiments did not induce or accelerate symptoms, there was a correlation between the intensity of lesions in the host thymus and graft, suggesting that the development of germinal centres in the thymus and subsequent B-cell hyperactivity (as we now understand) contribute to pathology. In addition, Dr Holmes identified that female mice were more susceptible to thymic lesions than males, now a commonly known preponderance in a number of autoimmune diseases.

During World War II, women immunologists came to the forefront in Australia, most notably Dr Lucy M Bryce CBE and Miss F Eleanor Williams MBE ARRC, for their distinguishable efforts with the Australia Red Cross Society and their extensive research into blood transfusion and understanding epidemic viral infections of the time. During the war, Dr Bryce, an Australian haematologist, immunologist and medical researcher, held the rank of major in the Australian Army Medical Corps. Dr Bryce went on to establish the first blood transfusion service in Australia, becoming the Founding Director of the Victoria Red Cross Blood Transfusion Service. Her work involved planning how donors should be screened, and how blood should be typed and stored, as well as supervising the establishment of a blood reserve. In 1951 she was named a Commander of the Order of the British Empire and, 50

years later, was inducted into the Victorian Honour Roll of Women. In this *ICB* Virtual Issue, we present a study carried out by Dr Bryce and Miss Williams in 1924 that was integral to the understanding of the antigenic properties of hydatid antigen preparations, routinely used in diagnostic tests for hydatid disease, a condition caused by cysts containing a parasitic tapeworm[15]. They found that hydatid fluid could be used as a universal diagnostic antigen but could also function as an anaphylactic antigen – a reaction which is now a known complication due to the rupturing of cysts in the lung and peritoneal cavity.

At the war's end, Miss Williams became one of the first three staff members of the WEHI, and notably, first female. As a bacteriologist and serologist who had never enrolled in a university degree, she managed her own laboratory studying infectious diseases, including hydatid disease, dysentery and syphilis. She was considered an expert in dysentery due to her research during the war and was awarded the Associate Royal Red Cross for her work. Along with Dr Ian Wood, Williams established Australia's first blood bank in 1939. This facility went on to become the centre for Red Cross blood transfusion services in the first years of World War II, where she also developed techniques for blood storage and administering blood products. Miss Williams extensively researched the venoms of Australian snakes to understand how they drove haemolysis and endeavoured to identify their antigenic variability. A seminal study presented in this *ICB* Virtual Issue identified the serological and blood relationships of common Australian snakes, critical for the generation of snake venom anti-serum[16]. Miss Williams compared different diagnostic tests – precipitin test, complement fixation and haemagglutination reactions – to assess their specificity in differentiating venomous snake species. The study, while only preliminary, suggested the haemagglutination reaction, which was favoured at the time (and is still used today), was not necessarily more specific than complement fixation in terms of differentiating between snake species' venom.

Dr Hildred Butler contributed significantly to research into maternal mortality following childbirth or abortion as a result of severe infections, working at both the Baker Medical Research Institute and the Royal Women's Hospital. She notably established a twenty-four-hour, seven-day-week bacteriological service at the Royal Women's Hospital to aid diagnosis of infections in pregnant women. It is estimated that in over 30 years at the Royal Women's

Hospital, Dr Butler investigated almost 250,000 women with infections during childbirth and some 64,000 who had aborted. From 1931, Butler examined material from patients at the Royal Women's Hospital, discovering the importance of anaerobic streptococci. She determined that severe infections were due to that group of organisms, together with haemolytic streptococci, *Staphylococcus pyogenes* and *Clostridium welchii*. As Group A streptococci and *C. welchii* infections could kill faster than they could be grown in culture, she developed a novel technique to rapidly microscopically assess stained smears from vaginal and cervical discharge. A fundamental paper underlying the application of these tests is published in this *ICB* Virtual Issue, where Dr Butler described the use of stained smears for the rapid diagnosis of *Str. Haemolyticus* Group A infection, a method that became the basis for routine clinical diagnosis[17].

Although not featured in this Virtual Issue, other notable trailblazing women in immunology include Professors Diana Martin and Margo Honeyman. Professor Martin was a microbiologist by training and did not claim expertise in immunology. Yet, having realised that a vaccine was the best way to control increasing numbers of meningococcal infections in New Zealand, Professor Martin collaborated with immunologists and the pharmaceutical industry to design, manufacture, and test a vaccine specific to the New Zealand meningococcal strain and ensured it was made available to the New Zealand population[18]. This monumental effort saw rates of infection greatly reduced, with research published in 2017 identifying that the same vaccination also reduced the number of cases of gonococcal infection, demonstrating for the first time that this disease is controllable by vaccination[19]. Professor Honeyman was an immunologist and expert in autoimmunity, focussing her work at the WEHI on the immunological triggers that influence the progression autoimmunity in type 1 diabetes[20]. Her research uncovered many immunological processes triggered at the earliest stages of disease and contributed to the discovery of predetermining markers, now applied diagnostically to children in the clinic [21].

In putting together this *ICB* Virtual Issue, our aim was to celebrate of the fundamental discoveries made to biomedical research by esteemed women immunologists that have, at many times, been overshadowed by the accomplishments of male colleagues. The selected original research papers in this collection showcase their novel observations and the impact

of their contributions to immunology that marked their careers in research. Finally, we hope that our readers will find the legacy of these trailblazing women immunologists inspiring and that it challenges us all to continue to contribute to immunological discoveries and strive towards attaining diversity and equality in science.

L–R: Professor Katharina Gaus, Professor Barbara Heslop, Professor Margaret Baird, Miss Dora Lush, Dr Margaret Holmes, and Miss F Eleanor Williams MBE ARRC. Note that photos of Dr Lucy M Bryce CBE and Dr Hildred Butler could not be obtained.

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