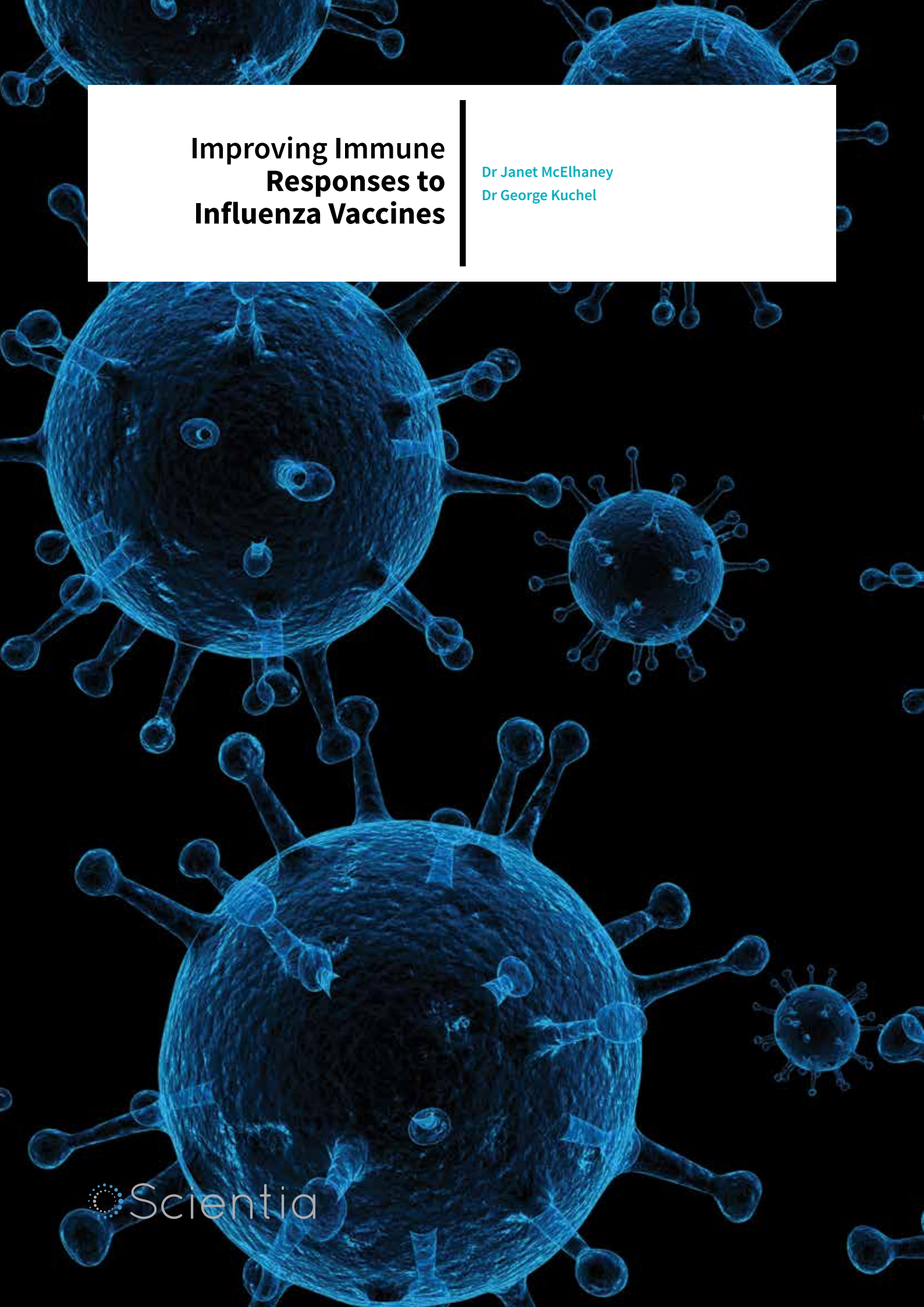

Improving Immune Responses to Influenza Vaccines

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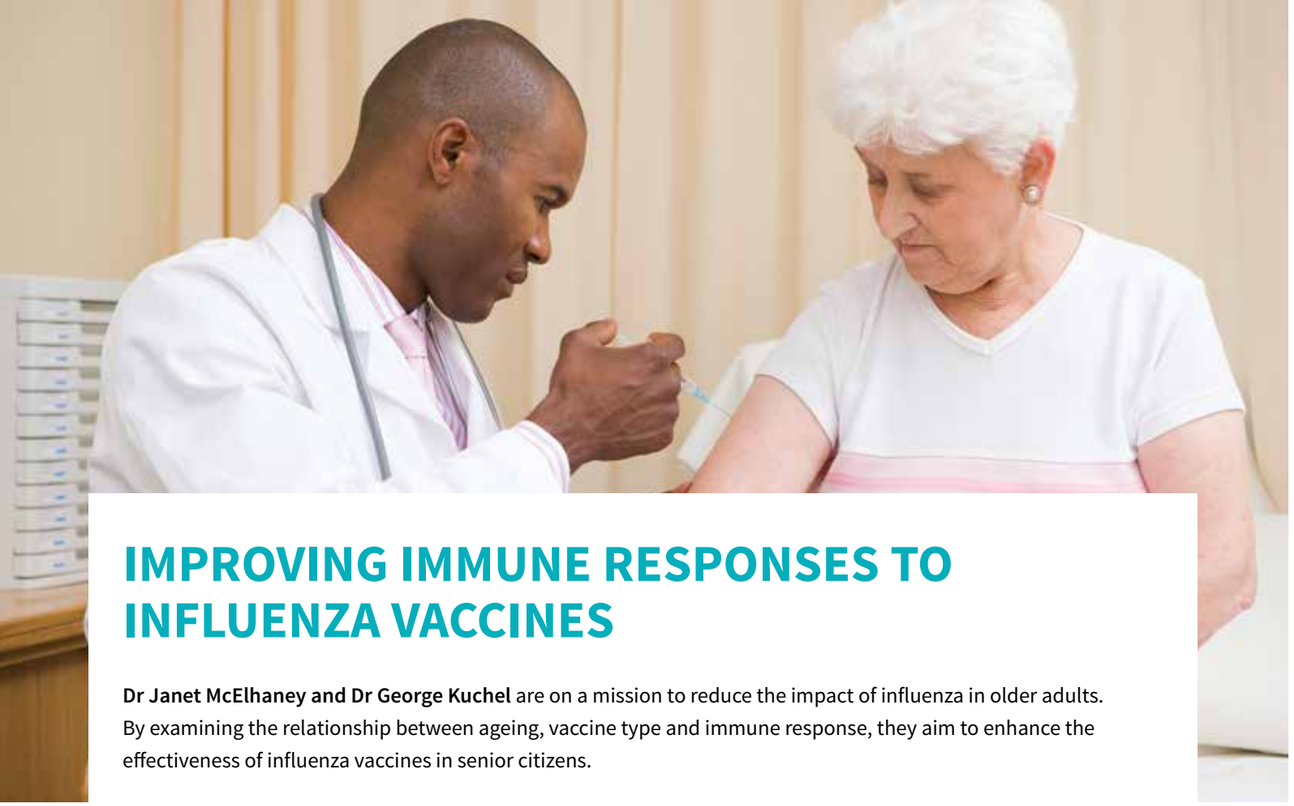

IMPROVING IMMUNE RESPONSES TO INFLUENZA VACCINES

Dr Janet McElhaney and Dr George Kuchel are on a mission to reduce the impact of influenza in older adults. By examining the relationship between ageing, vaccine type and immune response, they aim to enhance the effectiveness of influenza vaccines in senior citizens.

Preventing Flu Related Health Complications

Every year during winter, flu season comes upon us and we are often advised by healthcare professionals to be vaccinated with a flu shot. This is especially true for the older population – influenza causes 200,000 hospitalisations and 36,000 deaths per year in the United States, 90 per cent of which occur in those aged 65 or over. Influenza related morbidity and mortality increases when combined with factors such as age, chronic disease, dementia and history of pneumonia. Flu is also the most common cause of viral pneumonia in the elderly and has been linked to the development of heart disease, strokes and other illnesses which reduce quality of life. Therefore the goal of vaccinating senior citizens is to provide clinical protection and prevent future disability.

So how do vaccines work? Immunity is usually established by injecting a weak or inactive sample of a virus into the body. The body then produces strain-specific antibodies against the glycoproteins that are found on the surface of the pathogen. The immune system can do this in two ways: naïve T-cells and B-cells generate a response to the newly introduced pathogen, or memory T-cells (which have come in contact with the pathogen before) are boosted. With influenza, the latter is often what takes place as the majority of people have previously come in contact with the virus. However, this system doesn't always work, particularly amongst the elderly. Firstly, there may be a mismatch between the specific viral strains that are used in the vaccine and the influenza strains which are circulating in a particular flu season. This leads to a reduction in vaccine efficacy for all age groups. One randomised control trial estimated that influenza vaccines had only 50 per cent efficacy in a healthy cohort of older people, and this could be as low as 30 to 40 per cent for some members of the population. Secondly, older people do not always have the same level of immune functioning as their younger counterparts.

About the Ageing Immune System

Immunosenescence can be defined as the gradual deterioration of the immune system as a consequence of ageing. This affects both the body's response to infections and the development of immune memory after illness or vaccination. Immunosenescence therefore increases susceptibility to influenza while also reducing the effectiveness of the vaccine. The degree of immunosenescence experienced by an individual is also influenced by any underlying chronic illnesses they may have, their functional dependence and their level of frailty. All of these factors then contribute to the risk of serious outcomes from influenza. Frailty was of particular interest to the research team, who utilised the Frailty Index in their studies. The Frailty Index is a 40 point clinical tool based on clinical and laboratory markers of health variables such as medical conditions, cognitive and emotional health, and functional status amongst others.

Inflammaging is a chronic elevation of inflammatory cytokines in the blood due to the ageing process and is also associated with increased frailty. Such inflammation and other age related changes in tissues, can increase susceptibility to infection. As we age, changes occur in our mucosal barrier functions (which act as a protective barrier against pathogens), making them less effective. The loss of mucosal barrier function in the lungs makes older people particularly susceptible to influenza and other respiratory infections so any vaccine-induced protection also has to overcome this hurdle.

Finally, age-related changes in immune cells known as T-cells are involved in reduced responses to vaccines. As we age, the thymus (where T-cells are made) shrinks and the output of naïve T-cells declines leading to poorer immune responses and poorer vaccine efficacy. There is also a proportional increase of memory T-cells, specifically a subset known as CD8+ T-cells, and to a lesser extent, CD4+ T cells. These are the dominant effectors against the influenza virus. CD4+ (helper) T cells produce cytokines that stimulate B cells to produce antibodies in response to the surface glycoproteins, which are strain-specific. CD4+ T cells also stimulate CD8+ (cytotoxic) T cells that recognize the internal proteins of the virus and kill virus-infected cells and so are able to protect against different subtypes of influenza A. However, age related changes in these cells contribute to poor vaccine response and an increased risk of complications.

'The findings of this research will lead to a new way of testing vaccines much earlier in the process. Ultimately it will bring new vaccines for an aging population to market quickly and more cost-effectively.'

Cytomegalovirus (CMV) infection is common in older adults with around 90 per cent of those aged 80 and above being seropositive for CMV infection. Although CMV is generally an asymptomatic infection in older adults, the immune response that contains CMV replication leads to an expansion of CMV-specific T cells, and has been associated with a general decline in immune responsiveness, and also linked to functional decline.

Therefore, it is evident that T-cell mediated clearance of the influenza virus is an important pathway to explore in providing clinical protection against infection.

Difficulties in Development

It is clear that there is a need to develop more effective vaccines, so why is this so difficult to achieve? For one, results can be confounded by a number of factors, such as functional status, frailty, chronic disease burden, vaccination history and previous exposure to the virus. The interaction of immunosenescence, inflammaging and reduced immune responses also lead to major challenges in effective vaccine development.

Even establishing a suitable sample population can prove troublesome as researchers must enrol adequate numbers of subjects and retain them over a number of years due to the high variability in influenza attack rates. Influenza infection can also present itself atypically in older adults, therefore surveillance and documentation must be rigorous. This may involve making weekly phone calls to participants, taking note of any and all acute respiratory symptoms and analysing nose and throat swabs to confirm infection in those suspected of being ill.

Earlier research has shown that the serum antibody titres which are used to test the efficacy of vaccines do not distinguish between older adults who develop influenza from those who do not. Dr McElhaney explains: 'The tests we have now to evaluate a vaccine's effectiveness do not work very well with older adults. The findings of this research will lead to a new way of testing vaccines much earlier in the process. Ultimately it will bring new vaccines for an aging population to market quickly and more cost-effectively.' Therefore, they determined that it was essential to include other immunologic measures when assessing vaccine efficacy in the older population.

Drs McElhaney and Kuchel had several long term goals for this innovative five-year research project. The first was to identify T-cell responses which could act as biomarkers (indicators of biological processes) for serious complications of influenza in older adults. The second aim was to develop a clinical tool and set of biomarkers which could be used at the point of care to predict how the patient would respond to the influenza vaccine. They also sought to develop more useful tests to gauge the effectiveness of new vaccines.

A number of novel methods were involved in the investigation. This research project will be the first to use transcriptome sequencing to evaluate and analyse T-cell responses to identify a set of biomarkers that predict vaccine failure. This investigation into the correlates of effective T-cell response when compared to ineffective responses can help researchers understand at a population level how and for whom new vaccines should be developed.

The research team also investigated granzyme B activity as a biomarker for vaccine response. Granzyme B is an enzyme found in granules along with perforin, which when released by immune cells, enters the virus-infected cells through perforin and kills the cell to clear the pathogens. They found that increased granzyme B activity induced by influenza virus could predict a positive response to the vaccine which in turn prevented infection.

Other biomarkers proved more complicated

to pin down. One cytokine, IL-6, has both pro- and anti-inflammatory properties. On one hand, it has been linked to inflammaging, frailty and poorer clinical outcomes. On the other hand, IL-6 plays a key role in mounting an immune response to the influenza vaccine and infection. While it is a valid predictor of clinical outcomes when measured from peripheral blood samples, it can be a more difficult determinant within specific tissues and organs where levels tend to be more tightly regulated. Therefore, the ways in which the dysregulation of such biomarkers contribute to vaccine responses require further investigation.

Predicting Vaccine Efficacy

Taking the above into account, Drs McElhaney and Kuchel sought to establish Frailty Index scores and positive CMV status as correlates of disease severity and vaccine efficacy by analysing cytokine and granzyme B responses to the influenza vaccine in 150 older adults and 20 young adults. They postulate that CMV seropositivity and high levels of frailty predict an increase in the damaging effects of extracellular granzyme B which in turn affected the body's overall response to the vaccine. This may be due to the abnormally high baseline levels of GrzB in the resting T-cells of CMV positive individuals, which do not express perforin in response to influenza and are thus associated with a dysfunctional memory response to an influenza challenge. Previous results have shown that low GrzB activity in influenza-stimulated cells was correlated with developing influenza infection and increased disease severity. Current work is further defining how inflammation or anti-inflammatory responses, levels of frailty and CMV status could predict vaccine efficacy and risk for functional decline during influenza illness in older adults.

With the same sample of 150 older adults, the team explored whether a high dose vaccine induced a protective response in more subjects than a standard dose. Within each group, levels of frailty, inflammatory cytokines and GrzB activity were compared between those who developed influenza symptoms and those who did not. It was found that the increased dose of the vaccine boosted the immune response more effectively in older adults.

The project is still in its early days, but the results so far are impressive. The team have succeeded in developing and validating highly sensitive assays of T-cell responses to the influenza vaccine and identifying biomarkers of protection against disease. The development and manufacture of a new vaccine could cost up to 1 billion US dollars, therefore the industry requires robust means of confirming the effectiveness of new vaccines in as short a period as possible.

The project thus far has made it clear that vaccines that stimulate enhanced T-cell responses will improve primary prevention of influenza in older adults. The research suggests that the age related decline in immune function is reversible and it would be possible to improve protection through vaccination strategies which improve presentation of the internal proteins of the virus to the defence system.

Future Project Goals

The next steps of the project involve taking a closer look at the source of IL-10 production, a cytokine which impedes immune response when in excess. There will also be greater emphasis on the effects of adjuvants to the influenza vaccines and there potential to enhance protection.

They also hope to focus on developing a point of care test to vaccine responsiveness so as to develop clinician's knowledge of how to assess and modify disease risk. With such knowledge, healthcare providers can advise appropriate prevention strategies to their patients in addition to vaccination so as to reduce influenza related disability. With such high morbidity and mortality related to influenza infection in adults over 65, Dr McElhaney and Dr Kuchel's research is a major step in protecting the years and quality of life of our older population.

DR JANET MCELHANEY AND DR GEORGE KUCHEL

Meet the researchers

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Dr Janet McElhaney is the VP Research and Scientific Director of the Health Sciences North Research Institute and Professor in Clinical Sciences Division at the Northern Ontario School of Medicine. She is also Health Sciences North Volunteer Association Chair in Healthy Aging. After completing her medical degree in the University of Alberta, she completed her fellowship in geriatric medicine. Her research interests include the impact of immunosenescence on immune responses to vaccination, immunological biomarkers of protection mediated by vaccination and how vaccination plays a role in preventing disability in older adults. Her 13-year collaboration with Dr Kuchel has synergised the expertise in inflammation and frailty, and its impact on immune function and functional decline related to infectious diseases.

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Dr George Kuchel is Professor of Medicine in the University of Connecticut. After completing his medical degree in McGill University, Kuchel specialised in Geriatric Medicine at Harvard Medical School. He currently serves as director of the UConn Centre on Ageing, Division Chief of Geriatric Medicine and Citicorp Chair in Geriatrics and Gerontology. His research interests include pathophysiology of common geriatric syndromes, the role of inflammatory molecules in mediating muscle loss and sarcopenia in older adults, and the design of targeted interventions capable of altering the natural history of common geriatric syndromes.

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