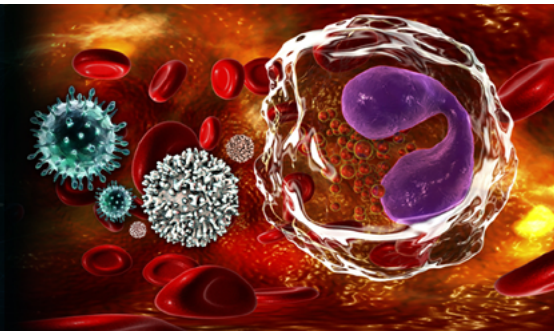
# Immunology Research Review™



Making Education Easy

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## In this issue:



### Abbreviations used in this issue:

**AAT** = α1-Antitrypsin; **ACE2** = angiotensin-converting enzyme 2; **AIV** = avian influenza virus; **COVID-19** = coronavirus disease 2019; **GR** = glucocorticoid receptor; **HIV** = human immunodeficiency virus; **HPV** = human papillomavirus; **IBD** = inflammatory bowel disease; **IFN** = interferon; **Ig** = immunoglobulin; **IL** = interleukin; **LLPC** = long-lived plasma cell; **MOG** = myelin oligodendrocyte glycoprotein; **SARS-CoV-2** = severe acute respiratory coronavirus 2; **TLR5** = Toll-like receptor 5; **Treg** = regulatory T cells; **TSLP** = thymic stromal lymphopoietin.



# Welcome to the latest issue of Immunology Research Review.

This review begins with a Chinese study that explicates the mechanisms by which commensal bacteria dysbiosis contributes to Crohn's disease pathogenesis, which is followed by a publication from the Human Immunology Project Consortium that aimed to identify a biological signal predictive of universal vaccine efficacy and revealed an innate immune endotype predictive of humoral response to vaccination. The Novavax 2019nCoV101 Study Group reports a safe profile and good immunogenicity for a six-month homologous booster dose of their severe acute respiratory coronavirus 2 (SARS-CoV-2) recombinant spike protein vaccine in an ongoing trial and our armamentarium to combat coronavirus disease 2019 (COVID-19) may continue to expand with phase 1 results from an ongoing Australian trial of a spike protein subunit vaccine (SCB-2019) reporting a durable immunogenicity and cross-reactivity of neutralising antibodies to variants after a two-dose primary vaccination regimen in healthy adults. Other publications in this issue detail a second case of human infection with a reassorted avian influenza (AIV) A H3N8 virus in China emphasising the need to closely monitor for further zoonoses, and a meta-analysis highlights the need for high quality research into the efficacy of human papillomavirus (HPV) vaccines in people living with human immunodeficiency virus (HIV).

We hope you enjoy this update in Immunology research, and we welcome your comments and feedback.

Kind Regards,


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## *Roseburia intestinalis* stimulates TLR5-dependent intestinal immunity against Crohn's disease

**Authors:** Shen Z et al.


**Summary:** Researchers from the Third Xiangya Hospital, Central South University Changsha in China expand on their previously published work that identified reduced commensal bacteria such as *Roseburia intestinalis* (*R. intestinalis*) as part of the intestinal microbiota dysbiosis contributing to Crohn's disease pathogenesis and the bacteria's protective anti-inflammatory role in inflammatory bowel disease (IBD) to elucidate the molecular pathways by which this activity is achieved (Shen Z et al. *J Gastroenterol Hepatol* 2018;33[10]:1751-60). Utilising *in vivo* murine modelling with colitis induced by trinitrobenzenesulfonic acid and various knockout variants plus *in vitro* experiments in human intestinal epithelial cell lines and human monocyte-derived dendritic cells with short interfering RNA the researchers demonstrated that *R. intestinalis* restored intestinal immune function in IBD primarily by promoting increased differentiation of regulatory T cells (Tregs). Specifically, *R. intestinalis* upregulated secretion of the cytokine thymic stromal lymphopoietin (TSLP) from intestinal epithelial cells through Toll-like receptor 5 (TLR5). The researchers posited that their findings may lay the groundwork for new therapeutic strategies for Crohn's disease.


**Comment:** This study identifies a coherent signal pathway that links *R. intestinalis* to TLR5-mediated upregulation of intestinal regulatory T cells via TSLP, ultimately inducing an anti-inflammatory interleukin (IL)-10 and transforming growth factor (TGF)-β cytokine phenotype. This model – explored comprehensively in a mouse model and recapitulated in human Crohn's disease samples – identifies a significant role for *R. intestinalis* deficiency/dysbiosis in disease pathogenesis and highlights the potential benefits of correcting this imbalance as a treatment strategy. This contributes to a body of evidence implicating flagellin-induced, TLR-5-mediated immune responses in Crohn's disease (Cook L et al. *Cell Mol Gastroenterol Hepatol* 2020;9[3]:485-506), capable of mediating harmful type 1 T helper (Th1)/type 17 T helper (Th17) effector cell-skewed immune responses (notably by *Escherichia coli* and Bacteroides species) as well as protective anti-inflammatory effects of intestinal Treg populations revealed here. This is another small, but important, step on the road to precision modulation of the gut microbiome in human disease.

***Reference: EBioMedicine 2022;85:104285***
Abstract

## Pan-vaccine analysis reveals innate immune endotypes predictive of antibody responses to vaccination

**Authors:** Fourati S et al.

**Summary:** In an effort to elucidate a biological signal predictive of universal vaccine efficacy as a step toward improving vaccine responses, especially in people who mount an ineffectual protective humoral response, a research group from Emory University in the USA conducted a meta-analysis. The study, part of the Human Immunology Project Consortium, analysed matched pre- and post-vaccination transcriptomic profiles from 820 adult patients who received a vaccine against one of 13 pathogens comprised of either a live or inactivated virus (yellow fever, smallpox, influenza; and influenza, Hepatitis B, respectively), a glycoconjugate vaccine (meningococcus, pneumococcus), or a vaccine created using recombinant viral vector (Ebola, HIV, tuberculosis) or recombinant protein technologies (malaria). Unsupervised hierarchical clustering analysis identified three longitudinally stable pre-vaccination inflammatory transcriptional profiles (endotypes; high, medium and low) independent of sex, age or pre-existing antibody levels to the immunogen. Further analysis revealed that 12.5% of differential gene expression both prior to and after vaccination was attributable to endotype and that a significantly stronger humoral response to vaccination was attained in patients with the high inflammatory endotype versus either the medium or low endotypes. It was concluded that the wide heterogeneity observed between individuals in vaccine efficacy may be driven by variations in the transcriptional state of the immune system.

**Comment:** This is one of a pair (Hagan T et al. *Nat Immunol* 2022;23[12]:1788-98) of large-scale analyses that have set out to provide a meaningful overview of vaccine responsiveness across 13 vaccine platforms. While it may be argued that vaccine effectiveness may not always be well-represented by the endpoint of higher antibody responses at one month, the analysis does offer some very interesting insights in that the common immune 'signature' that predicted month was characterised by higher levels of NFkB- and interferon-dependent innate immune activation enriched within monocyte and myeloid dendritic cell populations. Adding to this potentially counterintuitive result, further analysis suggested that pathogen-driven immune activation – rather than non-infectious inflammation – may well provide advantages to those with a 'naturally adjuvanted immune system'. The authors also speculate that the gut microbiome may contribute to the endophenotype, based on previous work on influenza vaccine responsiveness (Oh J et al. *Immunity* 2014;41[3]:478-92), providing an interesting link to the previous commentary.

***Reference: Nat Immunol 2022; Oct 31 [Epub ahead of print]***
Abstract

## Heterogeneous plasma cells and long-lived subsets in response to immunisation, autoantigen and microbiota

**Authors:** Liu X et al.

**Summary:** A research group affiliated with Tsinghua-Peking Centre for Life Sciences and Tsinghua University, both in Beijing, China, conducted a preclinical murine study to elucidate the cell and molecular biology underlying the differentiation and maintenance of long-lived plasma cells (LLPCs) following immunisation. The study first longitudinally evaluated the heterogeneity of the transcriptome and surface B-cell receptors in splenic and bone marrow plasma cells prior to and following immunisation with 4-hydroxy-3-nitrophenylacetyl hapten conjugated to keyhole limpet hemocyanin (NP-KLH) compared to vaccine-naïve mice using fluorescence-activated cell sorting cytometry and single-cell messenger RNA (mRNA) sequencing with antigen-specific plasma cells identified using a transgenic Blimp1–enhanced yellow fluorescent protein reporter strain. The durability of plasma cell subsets was investigated using genetic pulse-chase animal models. Immune profiling results demonstrated development of transcriptionally distinct LLPC immunoglobulin (Ig) subsets after immunisation, primarily derived from somatically hypermutated cells, with IgG and IgM plasma cell surface phenotypes characterised by high levels of the adhesion molecule EpCAM and an absence of the chemokine receptor CXCR3 ($EpCAM^{hi}CXCR3^{-}$) and IgA plasma cells by high levels of the lymphocyte antigen 6 complex (Ly6A) and an absence of the immune checkpoint receptor Tigit ($Ly6A^{hi}Tigit^{-}$). Mice bone marrow niches were found to also contain unmutated IgM long-lived plasma cell subsets that may play a role in innate immunity to self and microbial-derived antigens.

**Comment:** Harnessing the power of single-cell RNA sequencing analysis to investigate LLPCs that are scarce in accessible samples, Liu et al have identified distinct subsets of IgG/IgA/IgM LLPCs that highlight their functional attributes and the transcriptional regulation of their longevity. Interestingly, IgM LLPCs appear to respond primarily to antigens within the gut microbiome without requiring germinal centres or T-cell help, often involving public clones. In contrast, IgG LLPCs induced by vaccination are highly germinal centre-experienced with prominent somatic hypermutation and $EpCAM^{hi}CXCR3$- surface expression likely to promote long-term survival within bone marrow stromal niches. These data suggest considerable heterogeneity within LLPC populations, with links to germinal centre-dependent humoral immunity as well as more 'innate-like' responses to self and commensal antigens. As we seek to understand the basis of durable humoral immune responses – particularly in response to vaccination – these numerically small LLPC populations are likely to emerge further as key orchestrators.

***Reference: Nat Immunol 2022;23(11):1564-76***
Abstract

## Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373)

**Authors:** Mallory R et al., on behalf of the Novavax 2019nCoV101 Study Group

**Summary:** A secondary analysis of a randomised, placebo-controlled, phase 2 trial reports the safety and immunogenicity of a six-month booster dose of NVX-CoV2373, a recombinant SARS-CoV-2 vaccine containing full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant in COVID-19 naïve adults. A total of 210 adults aged 18-59 years at enrolment with a body mass index of between 17 and 35 kg/$m^2$ and without any prior SARS-CoV-2 infection who received a two-dose primary vaccination regimen with 5 µg NVX-CoV2373 plus 50 µg Matrix-M adjuvant (the globally authorised dose) in the first part of the trial received either a single intramuscular booster injection at the same dose as the primary dose (n=104) or placebo (n=106) at six months. Safety analysis revealed a higher incidence of both local and systemic adverse events after the third vaccine dose compared to the primary regimen, most commonly mild to moderate and transient tenderness and pain at the injection site or fatigue or headache. Per-protocol analysis of immunogenicity demonstrated that the vaccine booster elicited increases in serum anti-SARS-CoV-2 spike IgG antibody concentrations and neutralisation titres compared to pre-booster and approximately four-fold higher than that elicited by the primary vaccine regimen. The trial is ongoing and will assess further booster doses as well as cross-reactive immunity to SARS-CoV-2 variants.

**Comment:** The Novavax-produced SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) entered the Australian COVID-19 vaccine armamentarium with Therapeutic Goods Administration approval in January 2022, and is currently the only recommended protein-based vaccine. NVX-CoV2373 has a simplified adjuvant strategy (soapbark-derived Matrix M) and provides an alternative to mRNA vaccination, particularly among individuals who have experienced adverse effects. However, despite reassuring effectiveness and safety data from a large phase 3 study (Dunkle L et al. *N Engl J Med* 2022;386[6]:531-43), the evidence base for NVX-CoV2373 use is comparatively sparse. In this relatively small study of booster dosing in a phase 2 trial, involving 105 participants who received three doses of NVX-CoV2373, there were no concerning vaccine safety signals, and booster dosing was associated with elevated antibody binding and neutralisation titres that appear to be comparable with those elicited by mRNA vaccines. It is hoped that evidence around NVX-CoV2373 vaccine effectiveness will now accrue rapidly, filling an evidence gap that needs to be closed as we enter a new era of increasing vaccine resistance.

***Reference: Lancet Infect Dis 2022;22(11):1565-76***
Abstract

## Human infection of avian influenza A H3N8 virus and the viral origins: a descriptive study

**Authors:** Yang R et al.

**Summary:** Yang et al detail the second case of zoonotic novel AIV A H3N8 transfer in China in 2022. A human infection with a reassorted AIV A H3N8 was identified in a five-year old boy who attended the fever clinic of The First Hospital of Changsha on May 10, 2022 with confirmation of H3N8 virus subtype by real-time reverse transcription–polymerase chain reaction and avian origin by next-generation sequencing. Clinical symptoms were mild and predominantly cold-like with a fever zenith of 40ºC plus sore throat and runny nose that resolved within 48 hours. Epidemiological investigation suggested zoonotic transfer from poultry, possibly from a local fresh market where several chickens tested positive for H3N8 AIV. Lack of contact between this case and the previously reported case (Bao P et al. *Nat Commun* 2022;13[1]:6817) in the non-neighbouring Henan Province eliminated human-to-human transmission as the source of infection but emphasised the risk of interspecies transmission of this AIV variant. Serological surveillance of 81 poultry workers (51 in Hunan province) failed to identify any anti-H3N8 antibodies. Evolutionary and genotypic analyses of the novel variant revealed that it originated from reassortment of three strains and was comprised of a possibly-duck Eurasian avian *H3* gene, a North American avian *N8* gene possibly from migratory birds and internal genes from chicken H9N2 viruses with mammalian adaption permitting binding to human receptors. Despite the rarity of zoonotic cases presently the authors cautioned that the pandemic potential warranted close monitoring.

**Comment:** Recent investigations of SARS-COV-2 have illustrated how rapidly human-adapted infection and transmission can occur (within weeks), and how a small number of founder infections involving animal-to-human transmission can determine pathways that lead to epidemics or extinction (Pekar J et al. *Science* 2022;377[6609]:960-66). In this context, this case study which documents the second known human infection with H3N8 AIV A, is illuminating. It reinforces the message that multiple genetic recombination events that lead to human adaptation – here involving local Chinese domestic bird populations (*H3* gene from ducks; internal genes from chickens) as well as migratory birds (*neuraminidase* gene from North America waterfowl; *N8* from Russian/Japanese waterfowl) – are likely to occur frequently under favourable conditions, creating human-adapted viral strains with epidemic potential. Reassuringly, H3N8 exposure was not evident among local poultry workers based on serological surveillance, but there is a clear message regarding awareness and management of zoonotic viral pathogens, and the rapid evolution of viral pathogens via genetic reassortment events.

***Reference: Lancet Microbe 2022;3(11):e824-34***
Abstract

## Immunogenicity, safety, and efficacy of the HPV vaccines among people living with HIV

**Authors:** Staadegaard L et al.

**Summary:** A systematic review and meta-analysis was conducted to elucidate the effectiveness and immunogenicity of HPV vaccines in people living with HIV. A total of 43 reports (32 published articles plus 11 online trial records) published prior to February 2021 that provided prospectively collected longitudinal data on one of three licensed HPV vaccines (Gardasil quadrivalent HPV vaccine, Cervarix bivalent HPV vaccine or Gardasil nine-valent vaccine), from 18 independent studies including just over 3,900 individuals were identified from online databases. Pooled DerSimonian-Laird random effects modelling analysis found that all three vaccines elicited robust humoral immune response in people living with HIV with seropositivity rates of 99%-100% against the HPV-16 strain and 94%-100% against the HPV-18 high-risk strain (plus high rates of seropositivity against the five other HPV types in individuals vaccinated with the nine-valent vaccine) after three doses that was durable for at least 28 weeks. Lower antibody titres and lower rates of seropositivity in HIV-positive individuals over time was noted compared to HIV-negative individuals (72% HPV-18 seropositivity at 29-99 weeks after quadrivalent vaccine vs 94% in HIV-negative controls). The vaccine efficacy for protection against HPV infection in this population was precluded by low quality evidence. Immunogenicity or outcomes after vaccination stratified by HIV disease indicators or treatment were sparce but an inverse trend between CD4 cell counts and seroconversion was detected. HPV vaccination was safe in this population but it was concluded that establishment of efficacy and clinical benefit requires further study.

**Comment:** This timely review and meta-analysis demonstrates the overall effectiveness and safety of HPV vaccination in people living with HIV, with high rates of HPV-18 seropositivity after three doses (99% and 94%-99% for quadrivalent and bivalent vaccines, respectively), and limited impact of HIV treatment status or CD4 T cell counts. Perhaps more importantly, this meta-analysis highlights many gaps in the evidence base – particularly around vaccine-associated protection from incident infection as well as HPV-associated complications – that need to be addressed. This is particularly relevant in the current era, in which simplified single-dose HPV vaccine regimens are emerging as a non-inferior option for HPV vaccine delivery in at-risk populations (Baisley K et al. *Lancet Glob Health.* 2022;10[10]: e1485-93). More data relating to optimal HPV vaccine choice and dosing strategy (i.e., bivalent, quadrivalent, nonavalent), potential role of adjuvanted vaccines (e.g., TLR4 agonist), and durability of vaccine effectiveness in people living with HIV, are all awaited with interest.

***Reference: EClinicalMedicine 2022;52:101585***
Abstract

## Persistence of the immune responses and cross-neutralizing activity with variants of concern following 2 doses of adjuvanted SCB-2019 coronavirus disease 2019 vaccine

**Authors:** Richmond P et al.

**Summary:** Richmond et al report six-month results from the ongoing Australian phase 1 trial of the COVID-19 spike protein subunit SCB-2019 vaccine in healthy adults. The placebo-controlled trial, conducted at the Linear Clinical Research Centre in Perth, enrolled 151 adults and assessed a two-dose primary vaccination schedule with SCB-2019 dosed at between 3-30 µg and administered in one of three formulations – no adjuvant (spike-trimer protein alone) or with either AS03 or CpG/Alum adjuvant. Vaccine induced humoral response was durable with anti-SCB-2019 IgG antibodies, angiotensin-converting enzyme 2 (ACE2) competitive binding antibodies and neutralising antibodies against wild-type SARS-CoV-2 (Wuhan-Hu-1) detectable at six-months but at titre levels approximately one-quarter to one-third of their zenith. Cross-reactivity of neutralising antibodies against three variants of concern - Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1) – was also observed one-month after primary vaccination.

**Comment:** This paper presents encouraging phase 1 study results of the SCB-2019 vaccine (Clover Biopharmaceuticals, Chengdu), initially described in *The Lancet* (Richmond P et al. *Lancet* 2021; 20;397[10275]:682-94). This protein-based vaccine presents a stabilised trimeric S protein utilising a clamp method similar in concept to the University of Queensland vaccine that showed great promise in early development. In this case, Trimer-Tag (derived from human type I procollagen) provides trimer stabilisation, with a TLR9 agonist CpG + Alum adjuvant. This study presents further evidence of ACE-2 binding and neutralisation antibody titres that would suggest clinical utility, with peak responses between seven to nine weeks post-vaccination that waned to 25%–35% of peak levels at day 184. Testing day 36 (peak) sera against Alpha, Beta and Gamma SARS-COV-2 variants also yielded results that would be comparable with currently available vaccines. In this respect, investigating vaccine responses against increasingly antibody-resistant Omicron SARS-COV-2 variants will be a challenge for candidate vaccines such as this, which are still to find their place in clinical practice.

***Reference: J Infect Dis 2021;224(10):1699-1706***
Abstract

## Pre–germinal centre interactions with T cells are natural checkpoints to limit autoimmune B cell responses

**Authors:** Parham K et al.

**Summary:** This preclinical study from a Canadian research group utilised murine models to investigate T cell mediated control of pathogenic B cells and the pathways that regulate response to self-antigens and whose dysregulation may, therefore lead to autoimmune disorders. The study compared B cell activation between T cells specific to the self-antigen myelin oligodendrocyte glycoprotein (MOG) versus T cells specific for the foreign antigen nitrophenyl-haptenated OVA. Their study reported that self-antigen-specific T cells induced a lower quality interaction with B cells characterised by lower expression of interaction molecules on the B cell and lower responsiveness of B cell receptors. The authors hypothesised that the novel MOG-specific B cell phenotype observed in this study may mean that B cell response to self-antigens may be regulated via alternate energy pathways to that of B cells tolerised via regular exposure to systemically expressed self-antigens.

**Comment:** This intriguing research is perhaps more nuanced than the title suggests, as this does not redefine general principles of antigen-specific autoimmunity but rather offers a novel finding that MOG-specific T cells encounter a degree of B cell hypo-responsiveness that is regulated on the B cell side of the interaction and does not depend on known tolerance mechanisms. This does not reflect a lack of B cell receptor avidity or affinity (and cannot be overcome by optimising these parameters), but rather a reduced ability to upregulate B cell surface markers in response to MOG-specific T cell stimulation (e.g., ICAM-1 and CD150) with subsequent reduced B cell clonal expansion, plasmablast differentiation and class switching. It is interesting to note that therapeutic B cell depletion appears to be less effective for central nervous system syndromes associated with MOG versus aquaporin-4 antibodies (Barreras P et al. *Neurology* 2022;99[22]:e2504-16), perhaps suggesting that these observations may be antigen-specific even within the spectrum of central nervous system-specific autoimmunity.

***Reference: J Immunol 2022;209(9):1703-12***
Abstract

## Modern clinical *Mycobacterium tuberculosis* strains leverage type I IFN pathway for a proinflammatory response in the host

**Authors:** Shankaran D et al.

**Summary:** A research group from the US National Institute of Allergy and Infectious Diseases employed human and mouse macrophage models of *Mycobacterium tuberculosis* (*M. tuberculosis*) infection to investigate how different strains leverage the flexibility of the host innate defence mechanism to improve intracellular survival. They showed that *M. tuberculosis* lineage 3 may control the host innate pro-inflammatory response by augmenting an early type 1 interferon (IFN) response that enhances macrophage 25-hydroxycholesterol and interleukin (IL)-6 expression.

**Comment:** The continuing evolution of *M. tuberculosis* is a fascinating topic in light of its ancient origins at least 70,000 years ago and its historical dominance as a human pathogen between the 17th and 19th centuries. Here, Shankaran and colleagues provide evidence that modern evolutionary lineages elicit substantially (five to 10-fold) higher type I IFN responses as well as IL-6 production in macrophages compared to circulating ancient lineages, in a manner that depends on pathogen viability and which involves mycobacterial DNA as the initiator of cGAS-STING signalling, most likely through enhanced access to the endolysosomal pathway. What advantage is given to a modern *M. tuberculosis* lineage with enhanced powers to induce a pro-inflammatory host response remain to be determined, although it may be speculated that this adaptation favours early active infection rather than a latent phenotype (Cliff J et al. *Immunol Rev.* 2015;264[1]:88-102).

***Reference: J Immunol 2022;209(9):1736-45***
Abstract

## α1-antitrypsin binds to the glucocorticoid receptor with anti-inflammatory and antimycobacterial significance in macrophages

**Authors:** Bai X et al.

**Summary:** This preclinical study from Bai and colleagues reveals that several properties of the serine protease inhibitor α1-Antitrypsin (AAT), may be driven by its binding to the cytoplasmic glucocorticoid receptor (GR) in human macrophages, a novel mechanism. The study provides evidence to support the physical interaction between AAT and the GR in differentiated THP-1 macrophages first by utilising a co-immunoprecipitation-immunoblot approach with an anti-AAT polyclonal antibody with subsequent validation in mass spectrometry and in a cell-free system with microscale thermophoresis methods. *In silico* molecular modelling analyses revealed multiple possible docking configurations between AAT and the macrophage GR primarily though the C-terminal ligand binding domain of the GR. Finally, the study found that AAT complexed with the GR in both the nucleus and cytoplasm and investigated the biological consequences of this interaction in GR-depleted cell lines using short hairpin RNA sequences encoded in a lentiviral vector and demonstrated a role in protection against mycobacteria.

**Comment:** Based on this study, it would appear that AAT has been hiding in plain sight as a natural GR binding protein, providing ligand-receptor complexes that can be identified in both cytoplasmic and nuclear compartments and which can elicit functional cellular responses including NF-kB inhibition and enhanced mycobacterial control in macrophages. This AAT-GR interaction appears to involve a site distinct from the canonical glucocorticoid binding domain, opening discussions around the development of small peptide AAT mimics that could promote GR-dependent immunomodulation with reduced risk of the adverse effects commonly associated with glucocorticoid therapy.

***Reference: J Immunol 2022;209(9):1746-59***
Abstract


### Independent commentary by Dr David Nolan

Dr David Nolan is a Consultant Physician and Head of Department in the Royal Perth Hospital Department of Immunology. After undergraduate training at the University of Melbourne and Austin Hospital (1990) and registrar appointment at Royal Darwin Hospital (1995-1996), David moved to Perth to work at Sir Charles Gairdner Hospital (1997-1998) before commencing work at Royal Perth Hospital in 1999 with a Clinical Research Fellow position from 2000-2006, followed by Consultant appointment that has been ongoing since that time. He also served as the Director Research at Royal Perth Hospital, and an adjunct Associate Professor at the Institute for Immunology and Infectious Diseases at Murdoch University.