A VISION OF B CELL TARGETING FOR IGAN

Professor Jonathan Barratt, University of Leicester, UK

DISCLOSURES

Jonathan Barratt	
Consulting and Speaker Fees	Alexion, Alnylam, Argenx, Astellas, BioCryst, Biogen, Biohaven, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Otsuka, Takeda, Travere Therapeutics, Vera Therapeutics, Vertex, Visterra
Grant Support	Alexion, Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra

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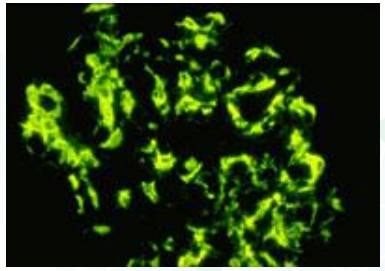


Address immune & inflammatory drivers of continued nephron loss

IN ALL PATIENTS THESE SHOULD BE CONSIDERED SIMULTANEOUSLY

Address generic CKD drivers of continued nephron loss

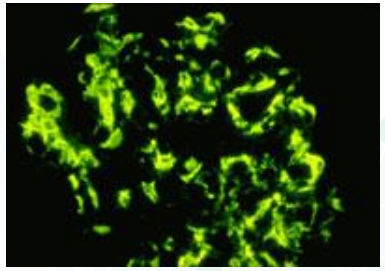
Cardiovascular risk reduction

Stop mesangial IgA-IC accumulation

Stop IgA-IC mediated injury

Reduce formation of circulating IgA-IC

Reduce inflammation & fibrosis



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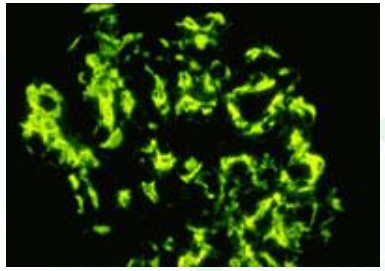

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Wiley Periodicals Inc.

doi: 10.1111/ajt.13393

Intrarenal B Cell Cytokines Promote Transplant Fibrosis and Tubular Atrophy

G. H. Tse[1,*], C. J. C. Johnston[2], D. Kluth[1], M. Gray[1], D. Gray[2], J. Hughes[1] and L. P. Marson[1]

[1]Medical Research Council/University of Edinburgh Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh, United Kingdom
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Introduction

Renal transplantation is the optimum treatment for many patients with end-stage renal failure (1). A major challenge of renal transplantation is chronic allograft damage (CAD) characterized by interstitial fibrosis and tubular atrophy. The pathophysiology is poorly understood and multiple cell mediators and mechanisms are involved (2).

B cells have been identified in biopsies of renal transplants with stable function (3), in the context of acute rejection (4,5), and chronic damage (6). However, other studies have not correlated the presence of B cells to be

Translational and clinical immunology

B lymphocytes directly contribute to tissue fibrosis in patients with IgG_4-related disease

Check for updates

Emanuel Della-Torre, MD,[a,b,c] Elena Rigamonti, PhD,[a] Cory Perugino, DO,[b,d] Simona Baghai-Sain, PhD,[e] Na Sun, PhD,[b] Naoki Kaneko, DDS, PhD,[b,f] Takashi Maehara, DDS, PhD,[b,f] Lucrezia Rovati, MD,[a,b] Maurilio Ponzoni, MD,[a,g] Raffaella Milani, MD,[h] Marco Lanzillotta, MD,[a] Vinay Mahajan, MBBS, PhD,[b] Hamid Mattoo, PhD,[i] Ivan Molineris, PhD,[e] Vikram Deshpande, MD,[j] John H. Stone, MD,[d] Massimo Falconi, MD,[a,k] Angelo A. Manfredi, MD,[a,c,*] and Shiv Pillai, MBBS, PhD[b,*]

Milan, Italy, Boston and Cambridge, Mass, and Fukuoka, Japan

Arthritis&Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

Full Length

B Cell Depletion Inhibits Fibrosis via Suppression of Profibrotic Macrophage Differentiation in a Mouse Model of Systemic Sclerosis

Hiroko Numajiri, Ai Kuzumi, Takemichi Fukasawa, Satoshi Ebata, Asako Yoshizaki-Ogawa, Yoshihide Asano, Yutaka Kazoe, Kazuma Mawatari, Takehiko Kitamori, Ayumi Yoshizaki, Shinichi Sato

Journal of Pathology
J Pathol 2017; **241**: 80–90
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4831

ORIGINAL PAPER

Renal recruitment of B lymphocytes exacerbates tubulointerstitial fibrosis by promoting monocyte mobilization and infiltration after unilateral ureteral obstruction

Hui Han,[1,2] Jinzhou Zhu,[1] Yaqiong Wang,[3] Zhengbin Zhu,[1] Yanjia Chen,[1,2] Lin Lu,[1,2] Wei Jin,[1] Xiaoxiang Yan[1,2,*] and Ruiyan Zhang[1,2,*]

[1] *Department of Cardiology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, PR China*
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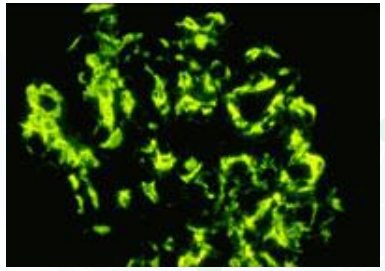
KDIGO IMPROVING GLOBAL OUTCOMES

2



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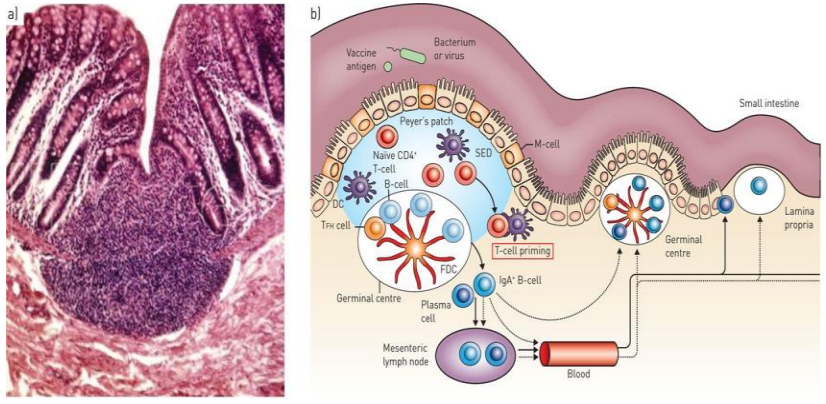
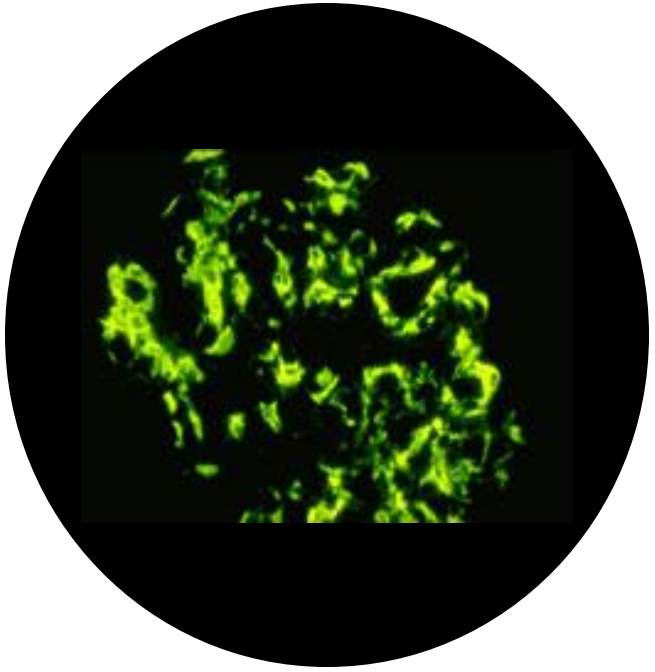
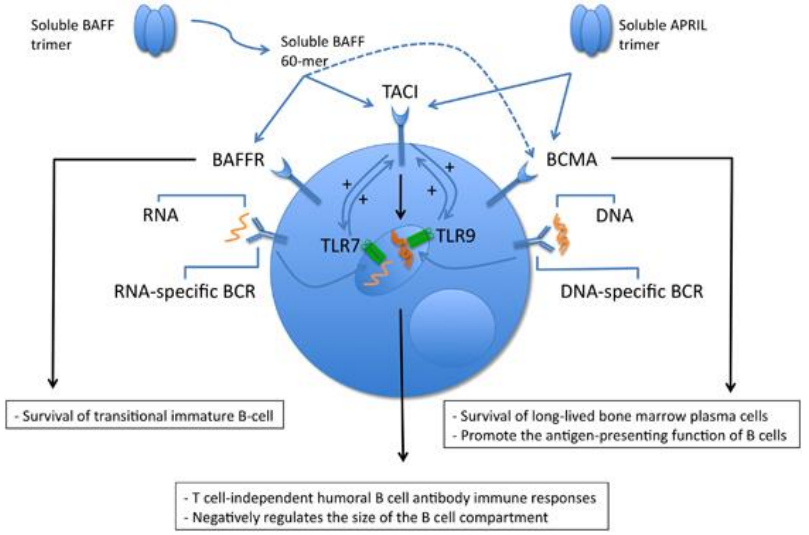
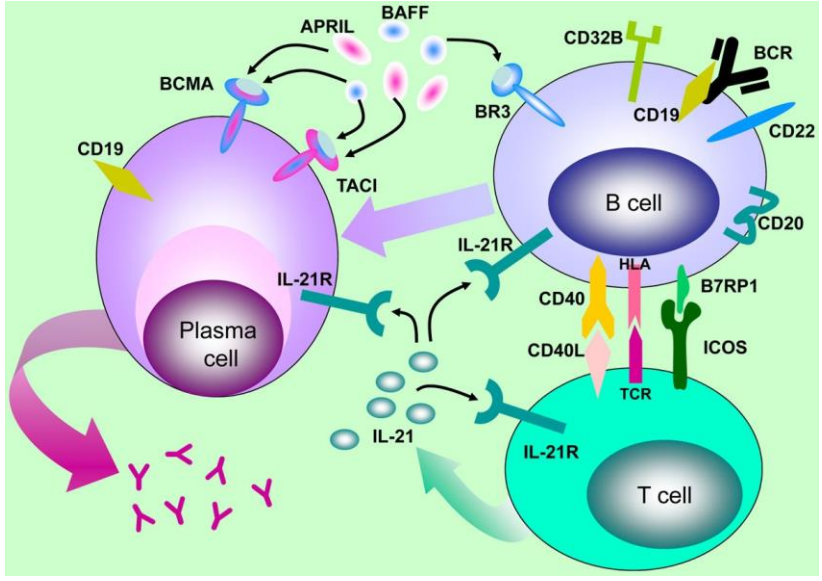
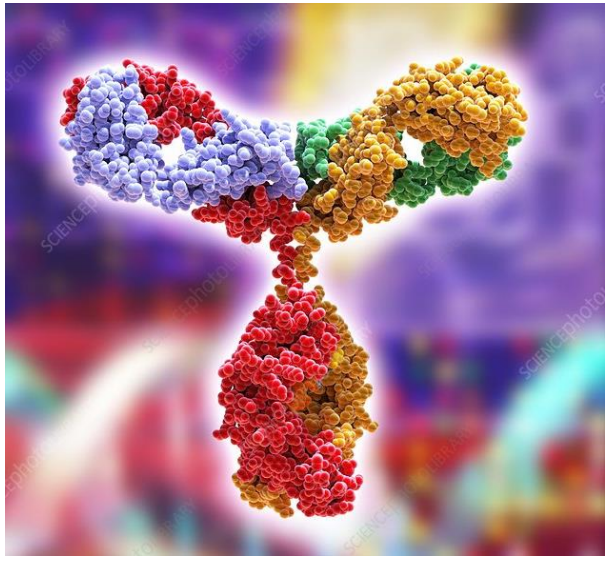
Mucosa Associated Lymphoid Tissue

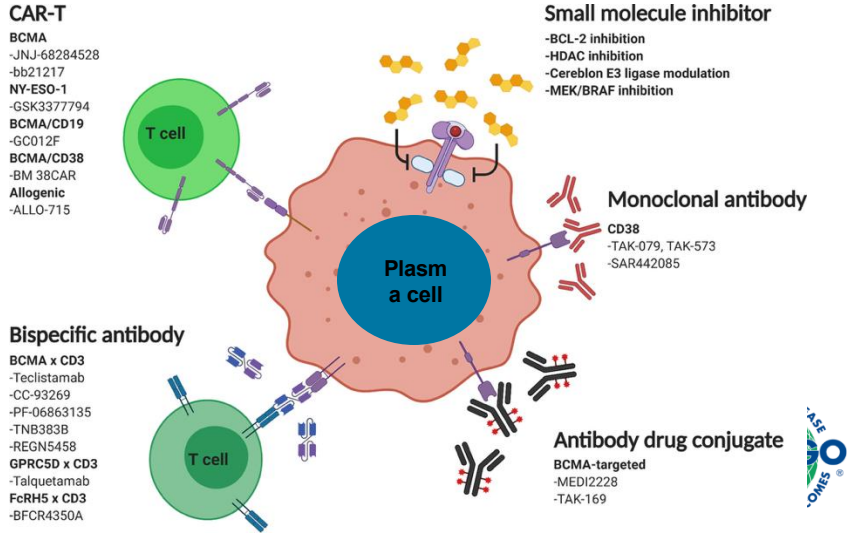












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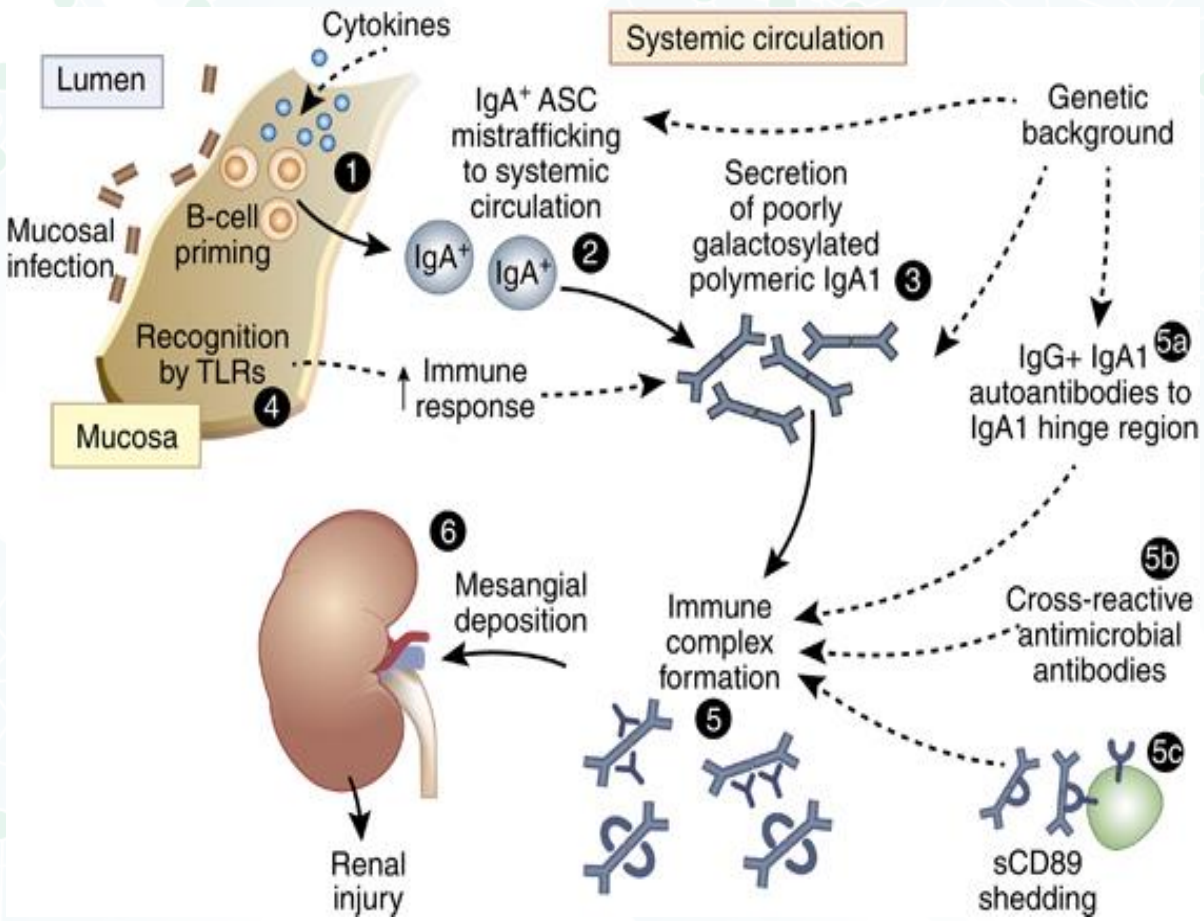
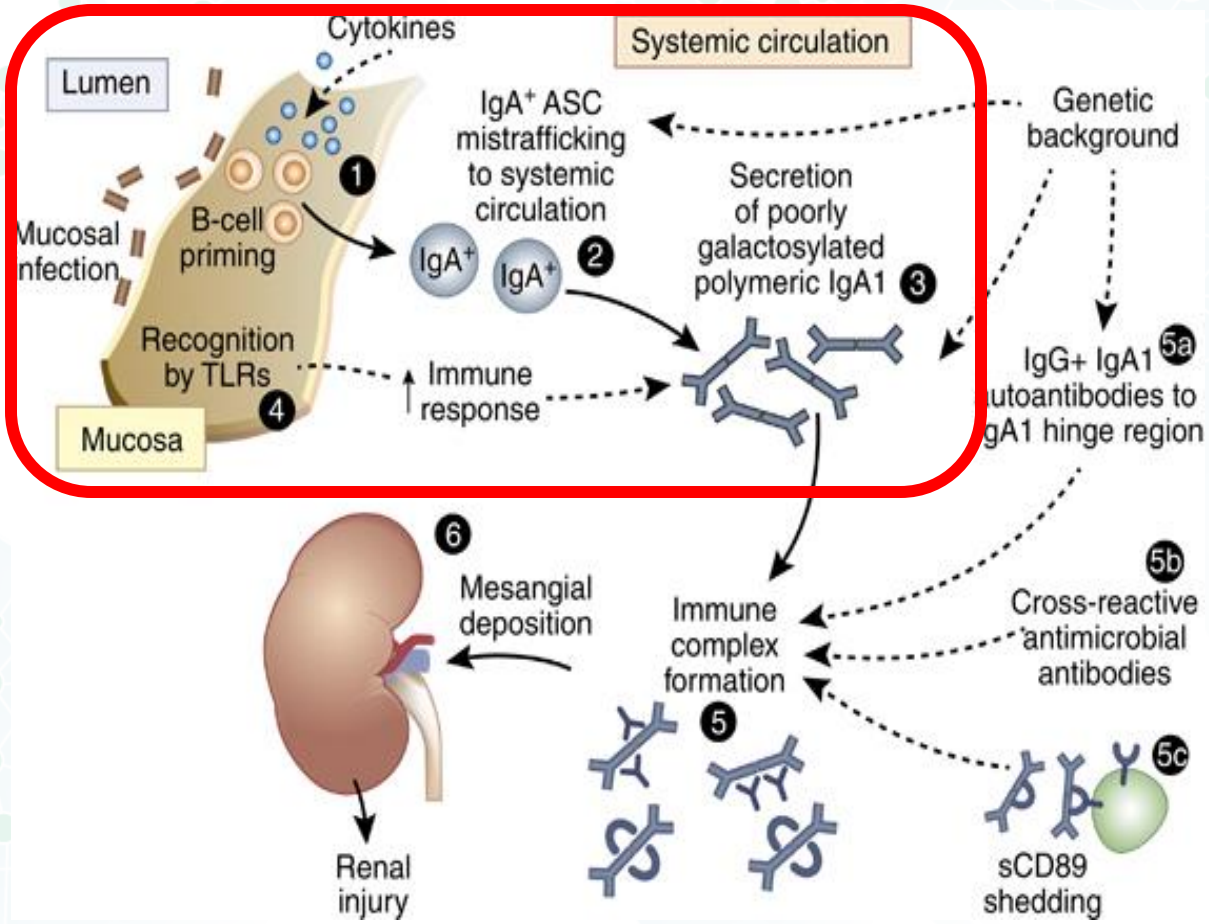

Cytokines
Systemic circulation
Lumen
IgA+ ASC mistrafficking to systemic circulation
Genetic background
Mucosal infection
B-cell priming
1
IgA+
IgA+
2
Secretion of poorly galactosylated polymeric IgA1
3
Recognition by TLRs
4
Immune response
IgG+ IgA1 autoantibodies to IgA1 hinge region
5a
Mucosa
6
Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
5
5c
Renal injury
sCD89 shedding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Immune complex formation
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5c
Renal injury
sCD89 shedding

nature genetics

ARTICLES

Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens

Krzysztof Kiryluk[1], Yifu Li[1], Francesco Scolari[2,3], Simone Sanna-Cherchi[1], Murim Choi[4,5], Miguel Verbitsky[1], David Fasel[1], Sneh Lata[1], Sindhuri Prakash[1], Samantha Shapiro[1], Clara Fischman[1], Holly J Snyder[1], Gerald Appel[1], Claudia Izzi[2,6], Battista Fabio Viola[7], Nadia Dallera[2,3], Lucia Del Vecchio[8], Cristina Barlassina[9], Erika Salvi[9], Francesca Eleonora Bertinetto[9,10], Antonio Amoroso[9,10], Silvana Savoldi[11], Marcella Rocchietti[11], Alessandro Amore[12], Licia Peruzzi[12], Rosanna Coppo[13], Maurizio Salvadori[13], Pietro Ravani[14,15], Riccardo Magistroni[16], Gian Marco Ghiggeri[17], Gianluca Caridi[17], Monica Bodria[17], Francesca Lugani[17], Landino Allegri[18,19], Marco Delsante[18,19], Mariarosa Maiorana[18,19], Andrea Magnano[19,19], Giovanni Frasca[20], Emanuela Boer[21], Giuliano Boscutti[22], Claudio Ponticelli[23], Renzo Mignani[24], Carmelita Marcantoni[25], Domenico Di Landro[25], Domenico Santoro[26], Antonello Pani[27], Rosaria Polci[28], Sandro Feriozzi[28], Silvana Chicca[29], Marco Galliani[29], Maddalerlie Gigante[30], Loreto Gesualdo[31], Pasquale Zamboli[32], Giovanni Giorgio Battaglia[33], Maurizio Garozzo[33], Dita Maixnerova[34], Vladimir Tesar[34], Frank Eitner[35,36], Thomas Rauen[35], Jürgen Floege[35], Tibor Kovacs[37,38], Judit Nagy[37,38], Krzysztof Mucha[39], Leszek Pączek[39], Marcin Zaniew[40], Malgorzata Mizerska-Wasiak[41], Maria Roszkowska-Blaim[41], Krzysztof Pawlaczyk[42], Daniel Gale[43], Jonathan Barratt[44,45], Lise Thibaudin[46], Francois Berthoux[46], Guillaume Canaud[47,48], Anne Boland[49], Marie Metzger[50,51], Ulf Panzer[52], Hitoshi Suzuki[53], Shin Goto[54], Ichiei Narita[54], Yasar Caliskan[55], Jingyuan Xie[56], Ping Hou[57], Nan Chen[56], Hong Zhang[57], Robert J Wyatt[58,59], Jan Novak[60], Bruce A Julian[61], John Feehally[44,45], Benedicte Stengel[50,51], Daniele Cusi[8], Richard P Lifton[4,62] & Ali G Gharavi[1]

We performed a genome-wide association study (GWAS) of IgA nephropathy (IgAN), the most common form of glomerulonephritis, with discovery and follow-up in 20,612 individuals of European and East Asian ancestry. We identified six new genome-wide significant associations, four in *ITGAM-ITGAX*, *VAV3* and *CARD9* and two new independent signals at *HLA-DQB1* and *DEFA*. We replicated the nine previously reported signals, including known SNPs in the *HLA-DQB1* and *DEFA* loci. The cumulative burden of risk alleles is strongly associated with age at disease onset. Most loci are either directly associated with risk of inflammatory bowel disease (IBD) or maintenance of the intestinal epithelial barrier and response to mucosal pathogens. The geospatial distribution of risk alleles is highly suggestive of multi-locus adaptation, and genetic risk correlates strongly with variation in local pathogens, particularly helminth diversity, suggesting a possible role for host–intestinal pathogen interactions in shaping the genetic landscape of IgAN.

IgAN is the most common form of primary glomerulonephritis and the leading cause of end-stage kidney failure in China[1]. Diagnosis is made by kidney biopsy, which shows predominant deposition of IgA-containing immune complexes in the glomerular mesangium, leading to glomerulosclerosis, glomerular sclerosis and progressive loss of kidney function. The etiology of IgAN is poorly understood, and the genetic architecture is complex. The disease is most prevalent in East Asians, less frequent in individuals of European ancestry and relatively rare in individuals of African ancestry. For example, Asian Americans have a fourfold higher incidence of end-stage renal disease (ESRD) due to IgAN in comparison to European Americans and a nearly sevenfold higher risk in comparison to African Americans[2].

IgAN affects individuals in all age groups, with a peak incidence in the second or third decade of life; the factors determining age of onset are unknown.

Thus far, there have been three GWAS for IgAN[3–5]. The results of these studies demonstrate a strong contribution of the major histocompatibility complex (MHC) locus to disease risk. The two largest studies, both based on Asian discovery cohorts, detected four additional non-HLA (human leukocyte antigen) loci, including chromosome 1q32, comprising a common deletion of the complement factor H–related *CFHR3* and *CFHR1* genes (*CFHR3-CFHR1* deletion); chromosome 8p23, comprising the *DEFA* gene cluster (encoding α-defensins); chromosome 17p13 (including *TNFSF13*);

A full list of author affiliations appears at the end of the paper.

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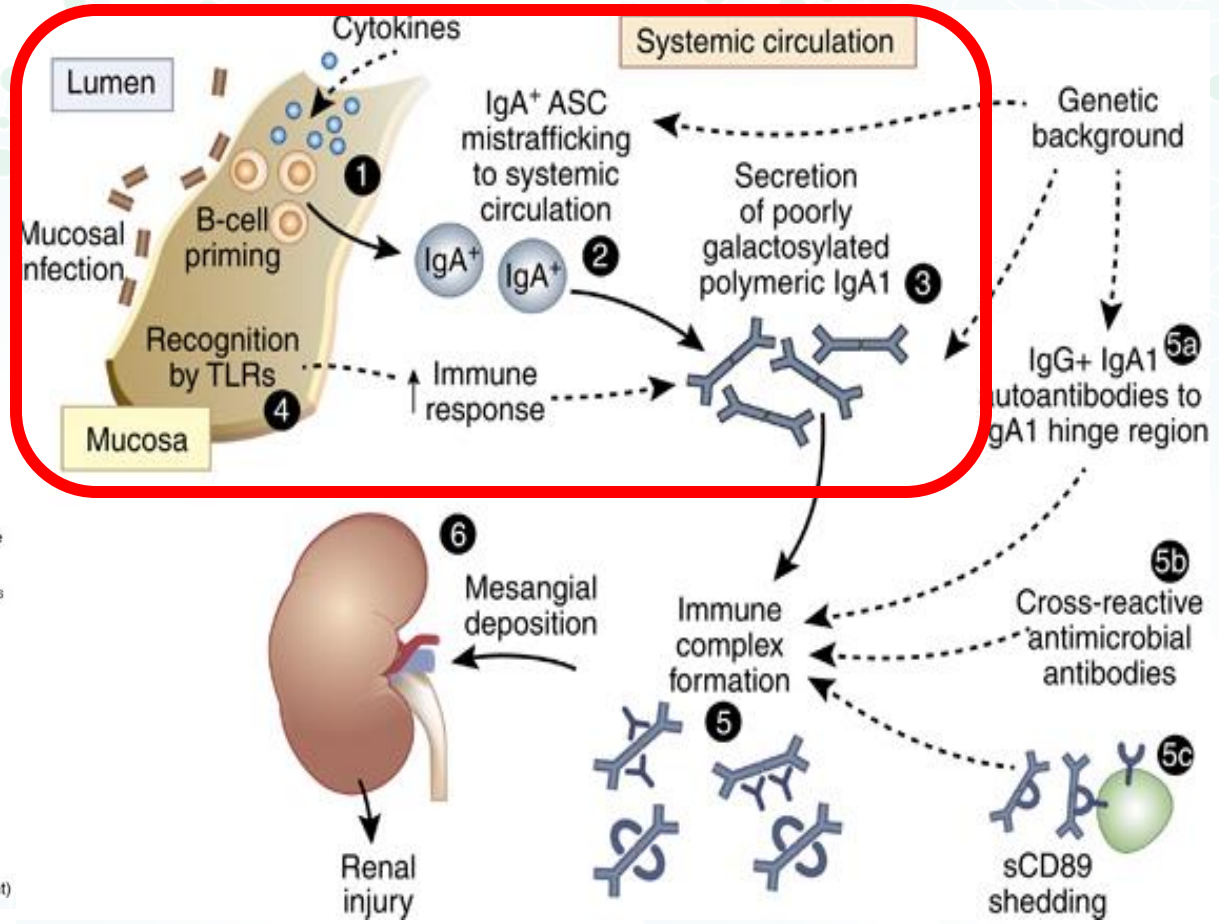

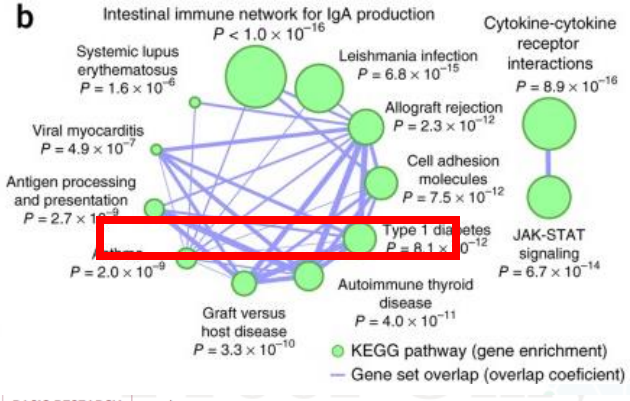

BASIC RESEARCH www.jasn.org

Galactosylation of IgA1 Is Associated with Common Variation in *C1GALT1*

Daniel P. Gale,* Karen Molyneux,† David Wimbury,† Patricia Higgins,† Adam P. Levine,‡ Ben Caplin,* Anna Ferlin,* Peiran Yin,§ Christopher P. Nelson,‖ Horia Stanescu,* Nilesh J. Samani,‖ Robert Kleta,* Xueqing Yu,§ and Jonathan Barratt†

*Centre for Nephrology and ‡Division of Medicine, University College London, London, United Kingdom; †Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom; §Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; and ‖Department of Cardiovascular Sciences, University of Leicester and National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Leicester, United Kingdom

PLOS | GENETICS

RESEARCH ARTICLE

GWAS for serum galactose-deficient IgA1 implicates critical genes of the *O*-glycosylation pathway

Krzysztof Kiryluk[1]*, Yifu Li[1], Zina Moldoveanu[2], Hitoshi Suzuki[3], Colin Reily[2,4], Ping Hou[5], Jingyuan Xie[5], Nikol Mladkova[1], Sindhuri Prakash[1], Clara Fischman[1], Samantha Shapiro[1], Robert A. LeDesma[1], Drew Bradbury[1], Iuliana Ionita-Laza[7], Frank Eitner[8,9], Thomas Rauen[9], Nicolas Maillard[10], Francois Berthoux[10], Jürgen Floege[9], Nan Chen[5], Hong Zhang[5], Francesco Scolari[11,12], Robert J. Wyatt[13,14], Bruce A. Julian[2,4], Ali G. Gharavi[1], Jan Novak[2]

nature genetics

Article

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Genome-wide association analyses define pathogenic signaling pathways and prioritize drug targets for IgA nephropathy

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Published online: 19 June 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

IgA nephropathy (IgAN) is a progressive form of kidney disease defined by glomerular deposition of IgA. Here we performed a genome-wide association study of 10,146 kidney biopsy-diagnosed IgAN cases and 28,751 controls across 17 international cohorts. We defined 30 genome-wide significant risk loci explaining 11% of disease risk. A total of 16 loci were new, including *TNFSF4/TNFSF18*, *REL*, *CD28*, *PFHY1*, *UBK*, *LYN*, *ANXA3*, *TNFSF8/TNFSF15*, *RELF3*, *ZMIZ1*, *OVOL1/RELA*, *ETS1*, *IGH*, *IRF8*, *TNFRSF13B* and *FCAR*. The risk loci were enriched in gene orthologs causing abnormal IgA levels when genetically manipulated in mice. We also observed a positive genetic correlation between IgAN and serum IgA levels. High polygenic score for IgAN was associated with earlier onset of kidney failure. In a comprehensive functional annotation analysis of candidate causal genes, we observed convergence of biological candidates on a common set of inflammatory signaling pathways and cytokine ligand–receptor pairs, prioritizing potential new drug targets.

IgA nephropathy (IgAN) is a common form of immune-mediated glomerulonephritis characterized by glomerular deposition of IgA-containing immune complexes. Examination of kidney biopsy tissue and demonstration of glomerular IgA deposits are required to establish the diagnosis. No approved targeted therapies presently exist for IgAN, and a large fraction of cases progress to kidney failure requiring kidney transplantation or dialysis.

Because the diagnosis requires a kidney biopsy, genetic discoveries have been hindered by small patient cohorts. Approximately 15 independent risk loci have been previously identified, implicating defects in the complement pathway, intestinal network of IgA production and innate immunity against mucosal pathogens[1–7]. These findings have led to the reformulation of the disease pathogenesis model, with most candidate mechanisms mapping to the immune system rather than the kidney[8]. Nevertheless, prior genome-wide association studies (GWASs) had a two-stage design, with the sample size of the discovery stage limiting the power to identify new loci.

Here we report a large GWAS discovery study for IgAN, involving 38,097 individuals (10,146 kidney biopsy-defined cases and 28,751 controls) recruited across 17 international cohorts. With the discovery of 16 new non-HLA (human leukocyte antigen) risk loci, we provide strong support for a highly polygenic architecture of IgAN. We assess the functional consequences of the risk alleles, define causal cell types and pathways and explore genetic correlations and pleiotropic associations of the risk loci. Notably, we report the convergence of multiple risk loci on a set of common signaling pathways and ligand–receptor pairs involved in the regulation of IgA production, prioritizing plausible new molecular drug targets.

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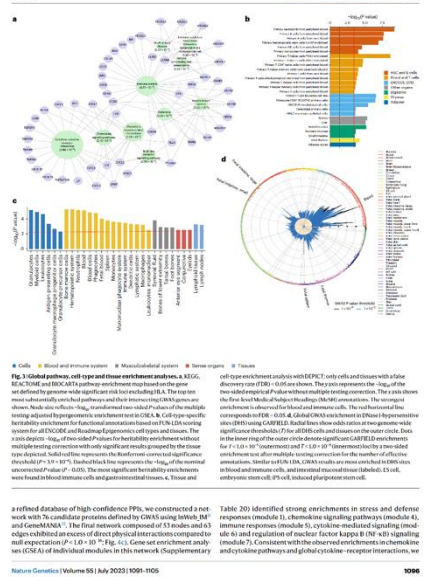
Results

Study design

We performed GWAS and meta-analysis of 17 independent international case–control cohorts (12 newly genotyped and five published cohorts) comprising 38,997 individuals (10,146 cases and 28,751 controls). All cases were defined by dominant mesangial IgA staining by immunofluorescence of kidney biopsy tissue. We excluded any cases with suspected secondary causes (for example, liver, autoimmune or malignant disease). The patient characteristics are summarized in Supplementary Table 1. The controls were unrelated to the cases, were derived from the same populations or geographic regions as the cases and had no known kidney disease. Of the 17 cohorts, 11 were of European ancestry, with participants from Italy, Poland, Germany, France,



Article

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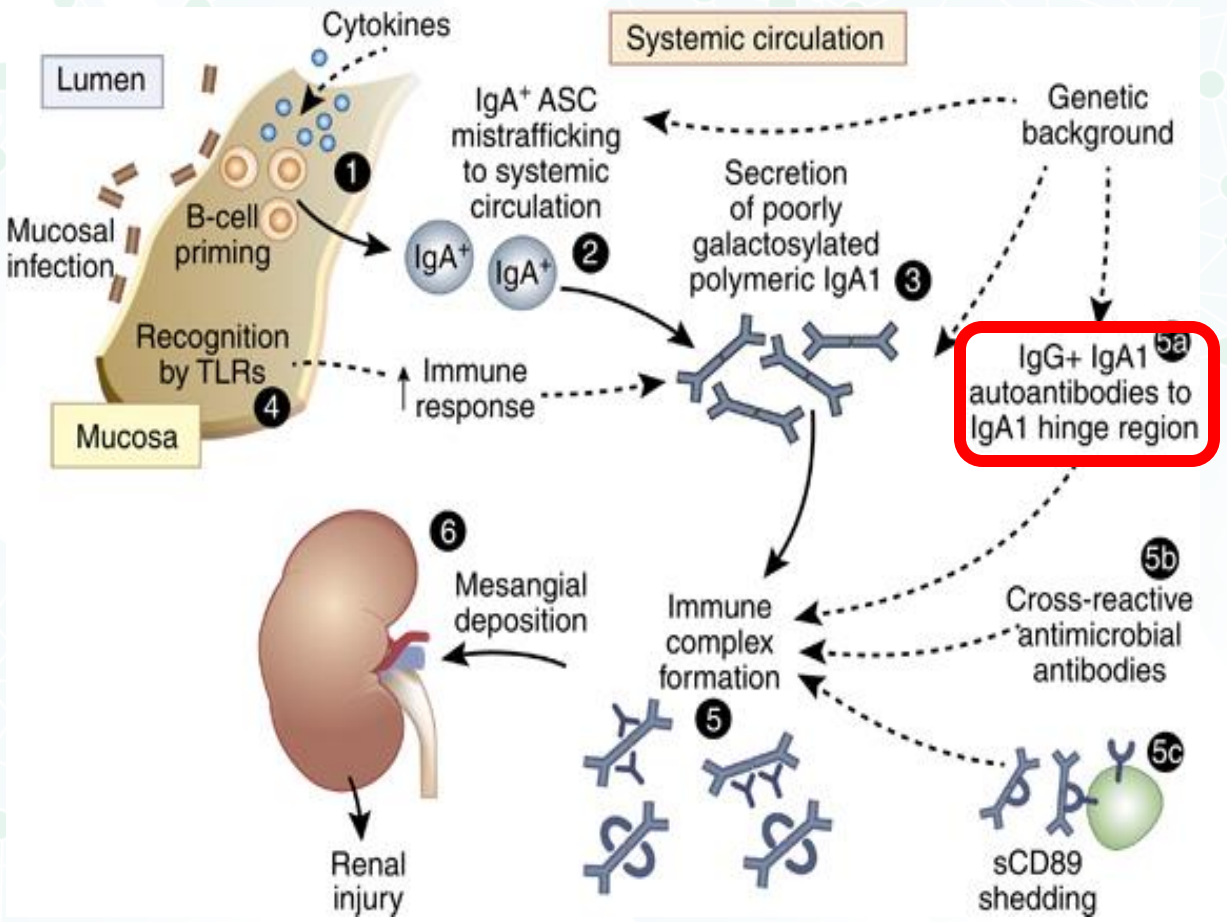
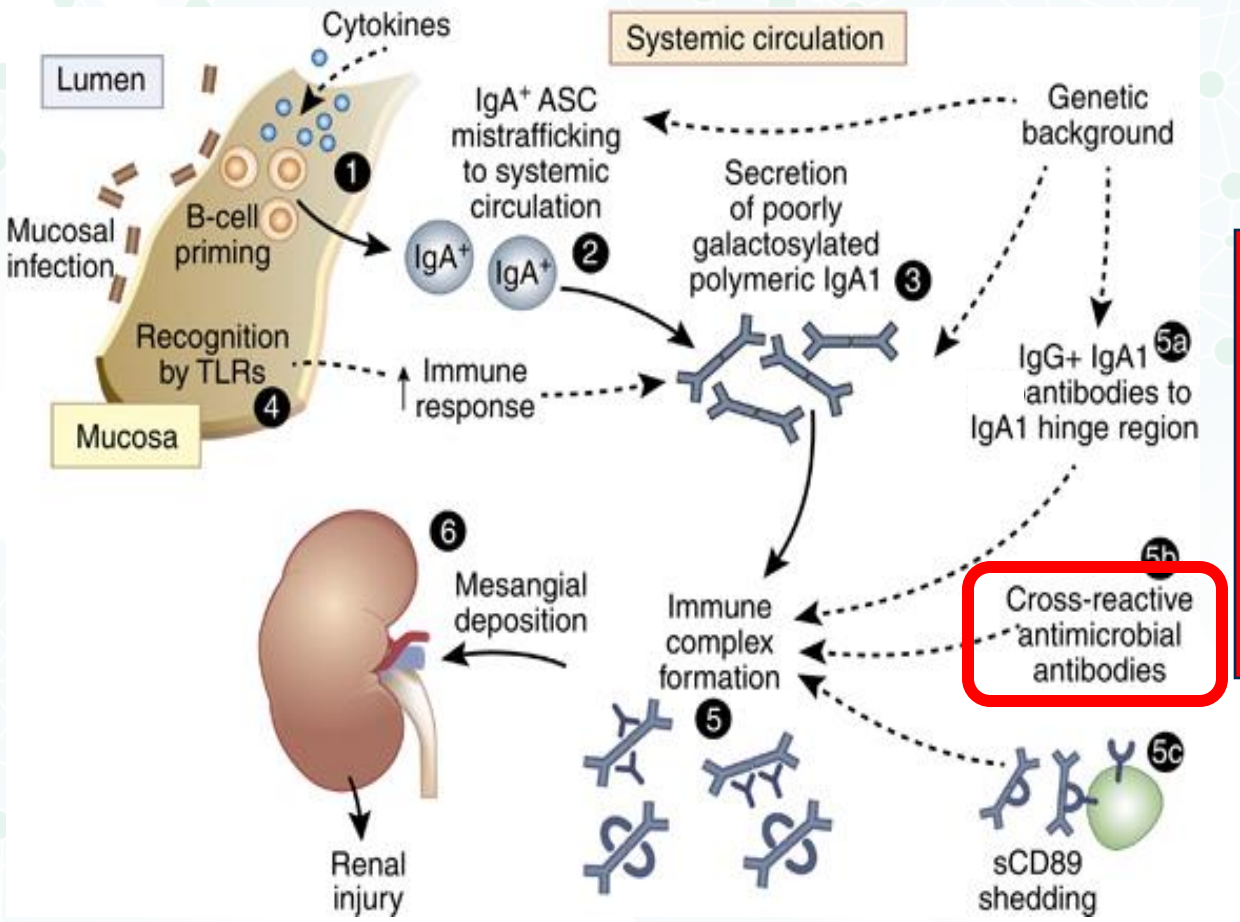


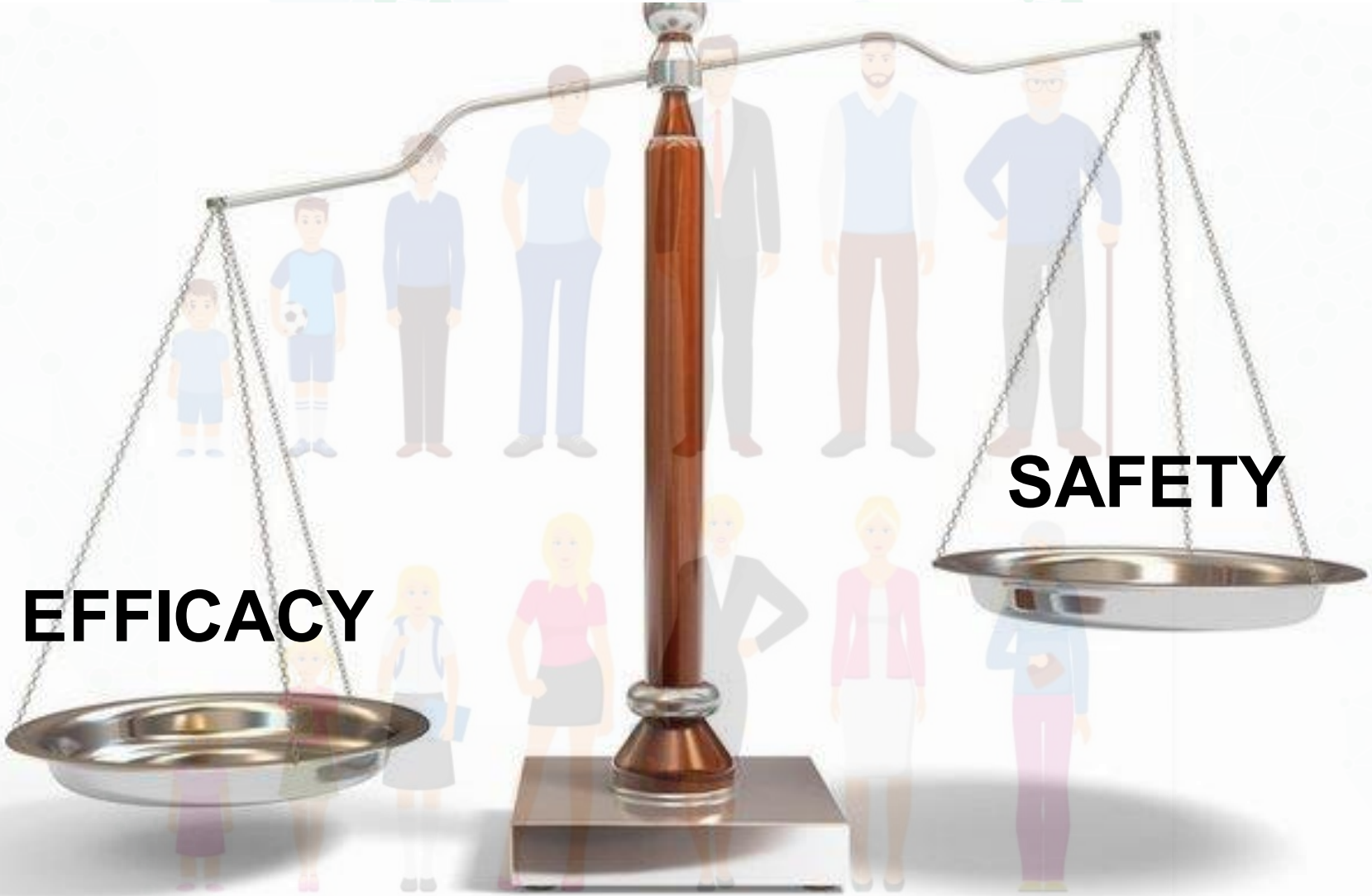
Autoimmune disease

Oligoclonal B cell expansion

Loss of tolerance



Polyclonal physiological antibody responses to encountered pathogens


SAFETY
EFFICACY