

News from GWAS on IgA Nephropathy



Molecular Diagnostics Symposium 2024, Zürich

Thursday, 07 March 2024

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**UNIVERSITÄT
BERN**

Disclosures

- multiples, multiples, multiples,**
- none related to this presentation**

nature genetics

Article

<https://doi.org/10.1038/s41588-023-01422-x>

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

Krzysztof Kiryluk and Ali G. Gharavi, et al.

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Nature Genetics | Volume 55 | July 2023 | 1091–1105

1. IgA Nephropathy

2. GWAS

3. Therapy ?

4. Dreaming of ... ?

Néphropathie à IgA

“IgA nephropathy”

GN à dépôts mésangiaux d'IgA

- **Maladie de Berger**

“Les dépôts intercapillaire d'IgA-IgG.”

Par J. Berger et N. Hinglais.

J Urol Nephrol (Paris) 74: 694-695, 1968

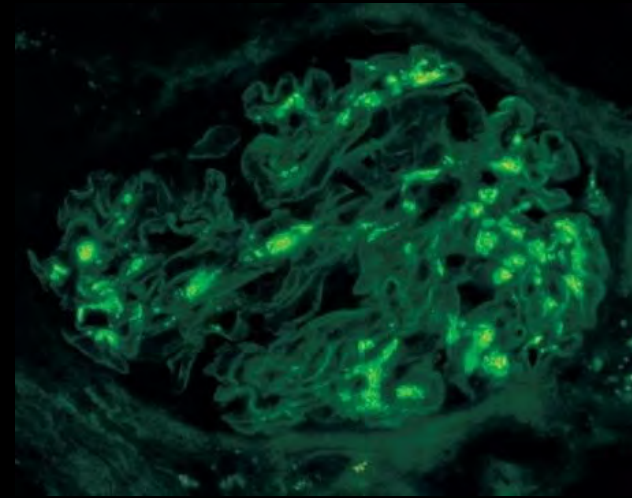
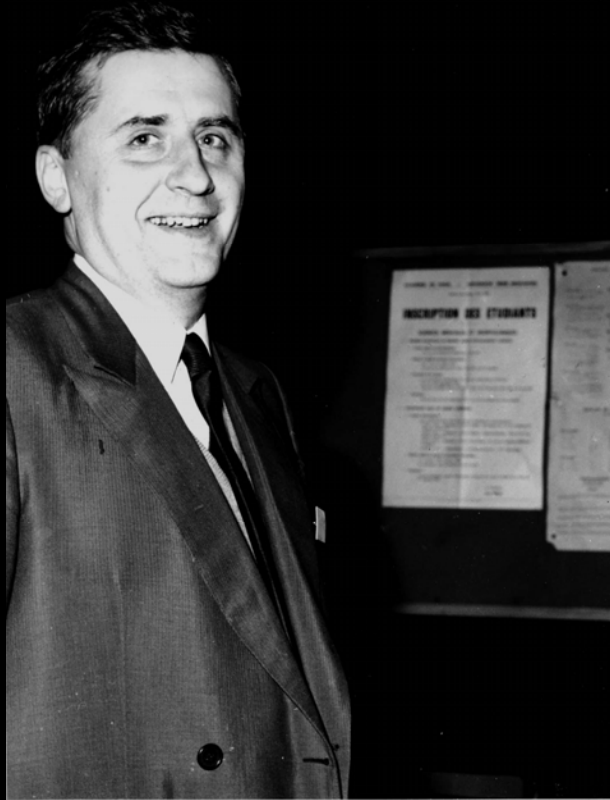
- **Purpura rhumatoïde de Schönlein-Henoch**



Hôpital des Enfants Malades. - Porte d'Entrée principale



JEAN BERGER



Les dépôts intercapillaire d'IgA-IgG

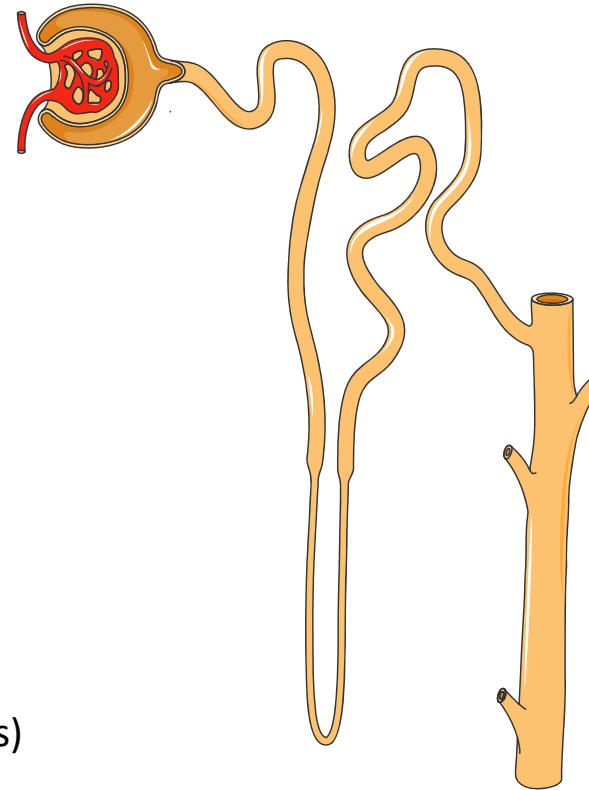
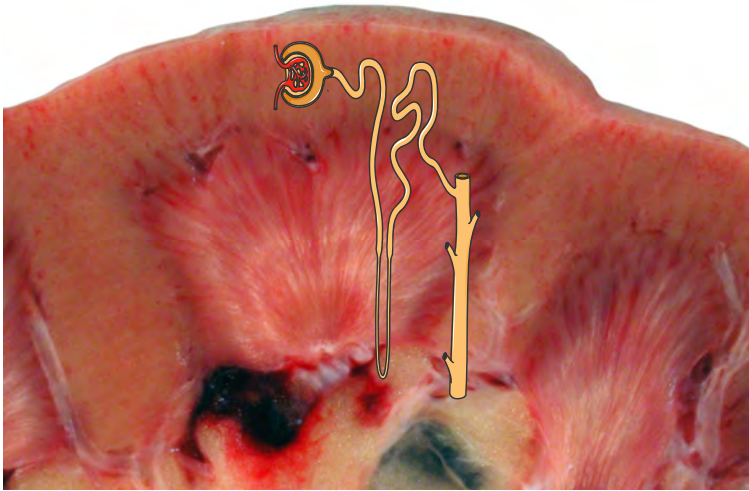
Par MM. J. Berger et N. Hinglais

J. Urol. Nephrol. (Paris) 74: 694-695, 1968

Résumé

Renée Habib (1924-2009)

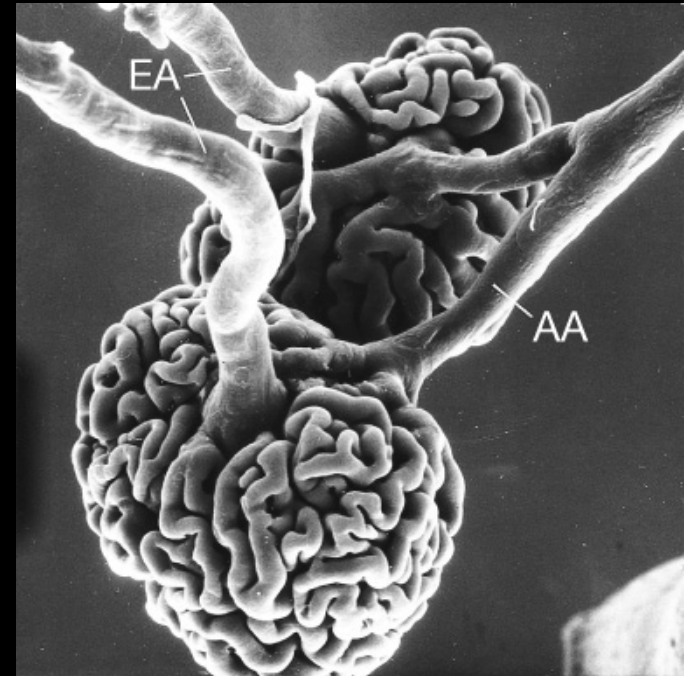




The KIDNEY

- Nephron (Glomerulus, Tubulus)
- Interstitium
- Vessels

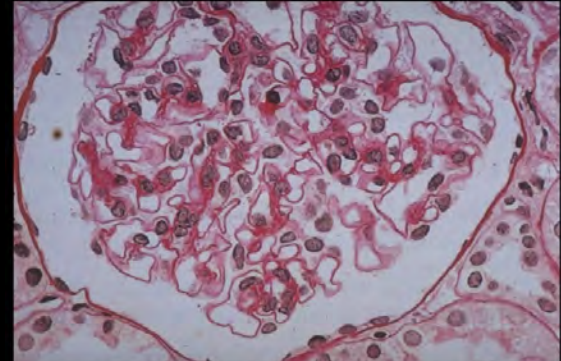
The kidney



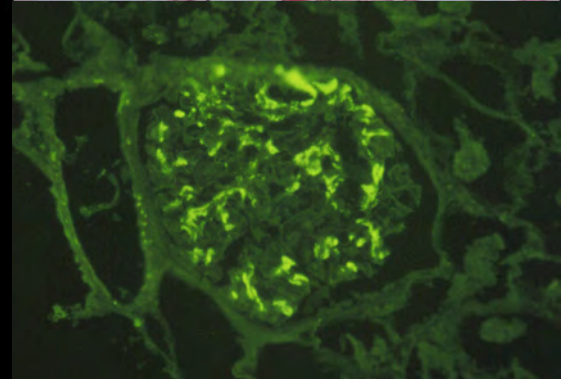
RENAL BIOPSY



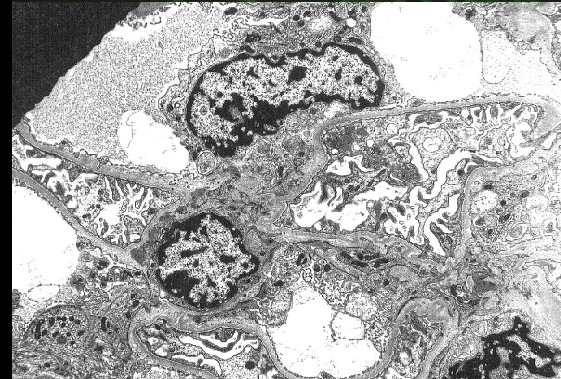
LM



IF

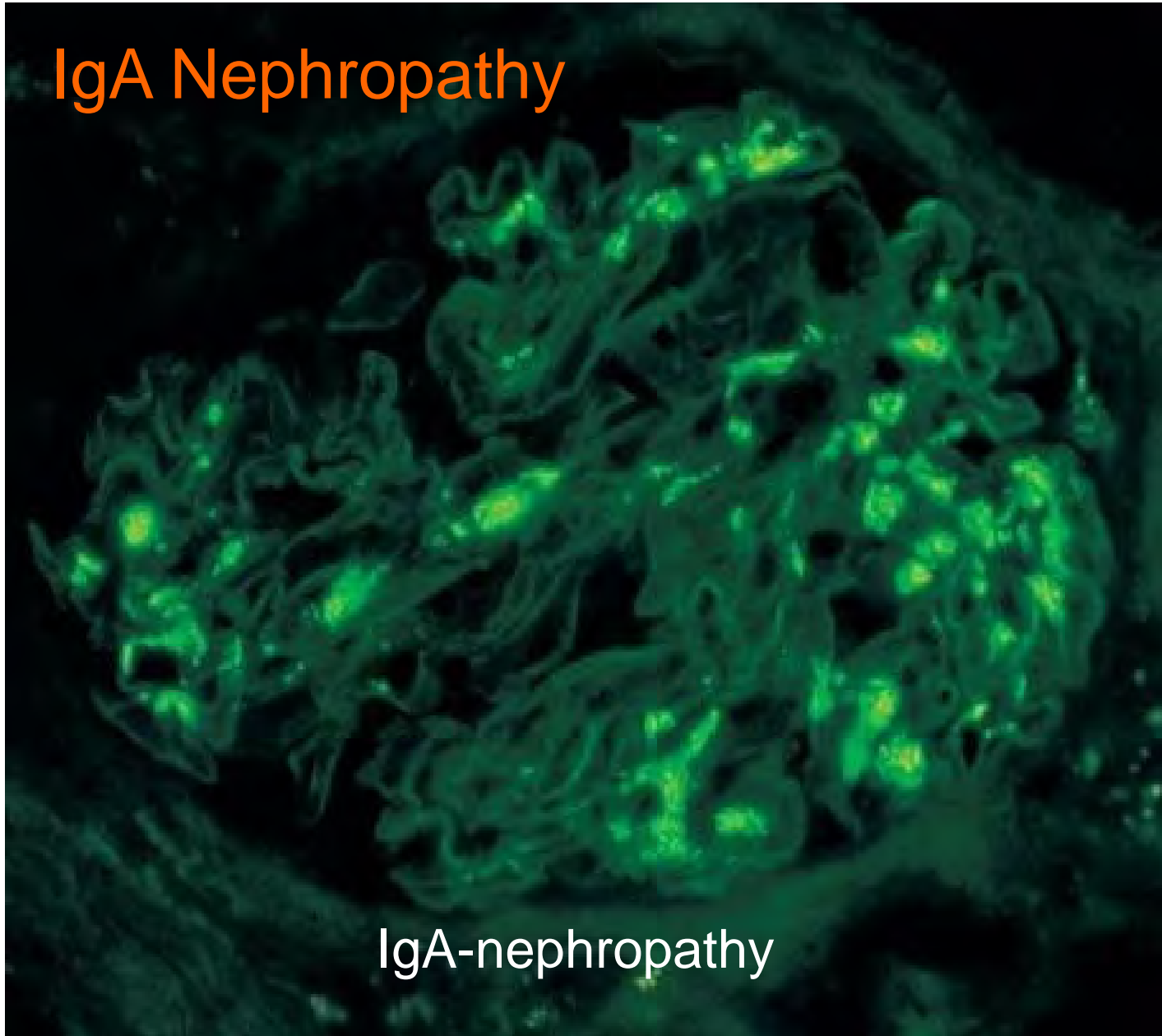


EM



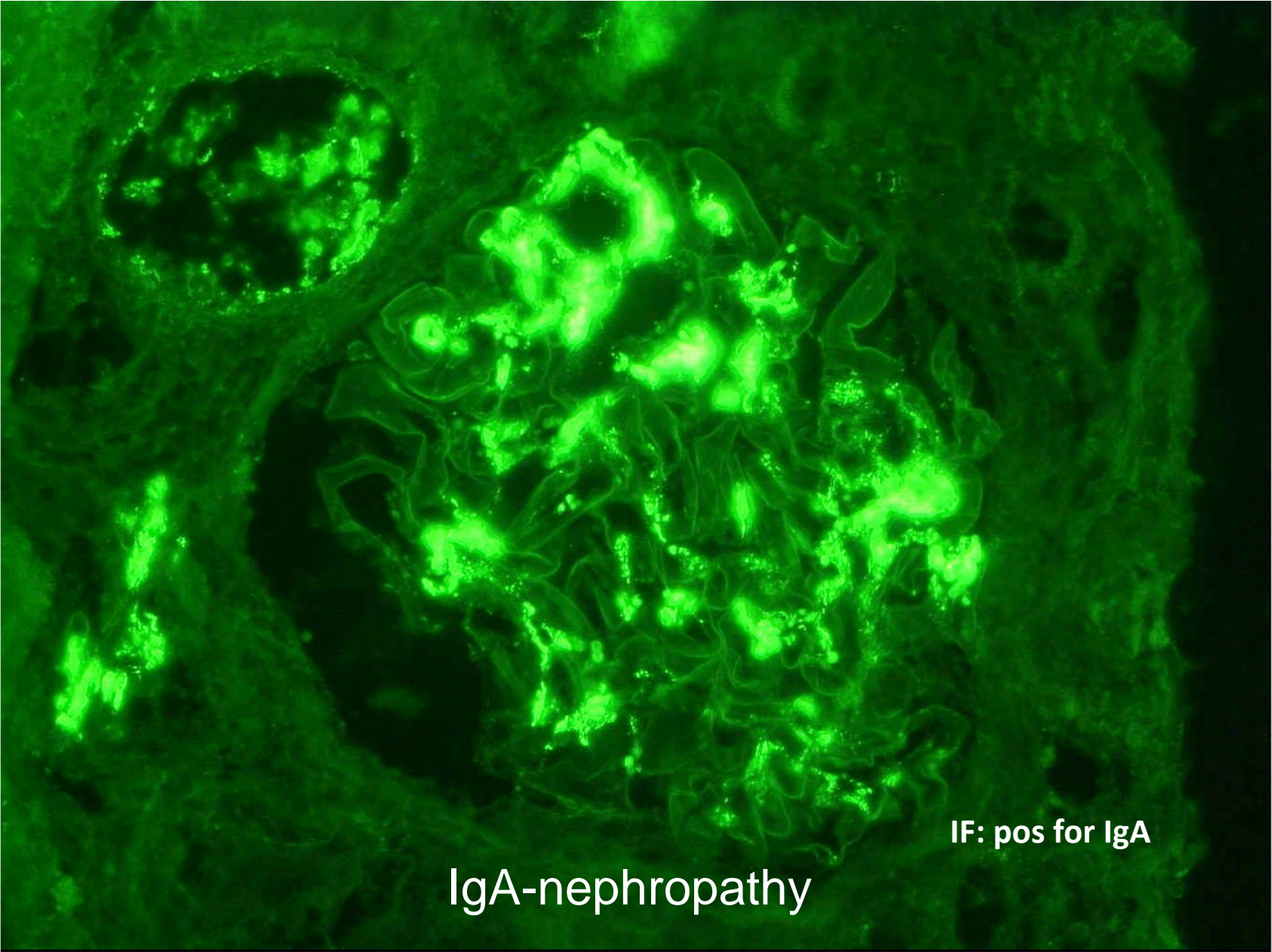
The renal biopsy gives the precise histologic diagnosis of renal disease !

IgA Nephropathy



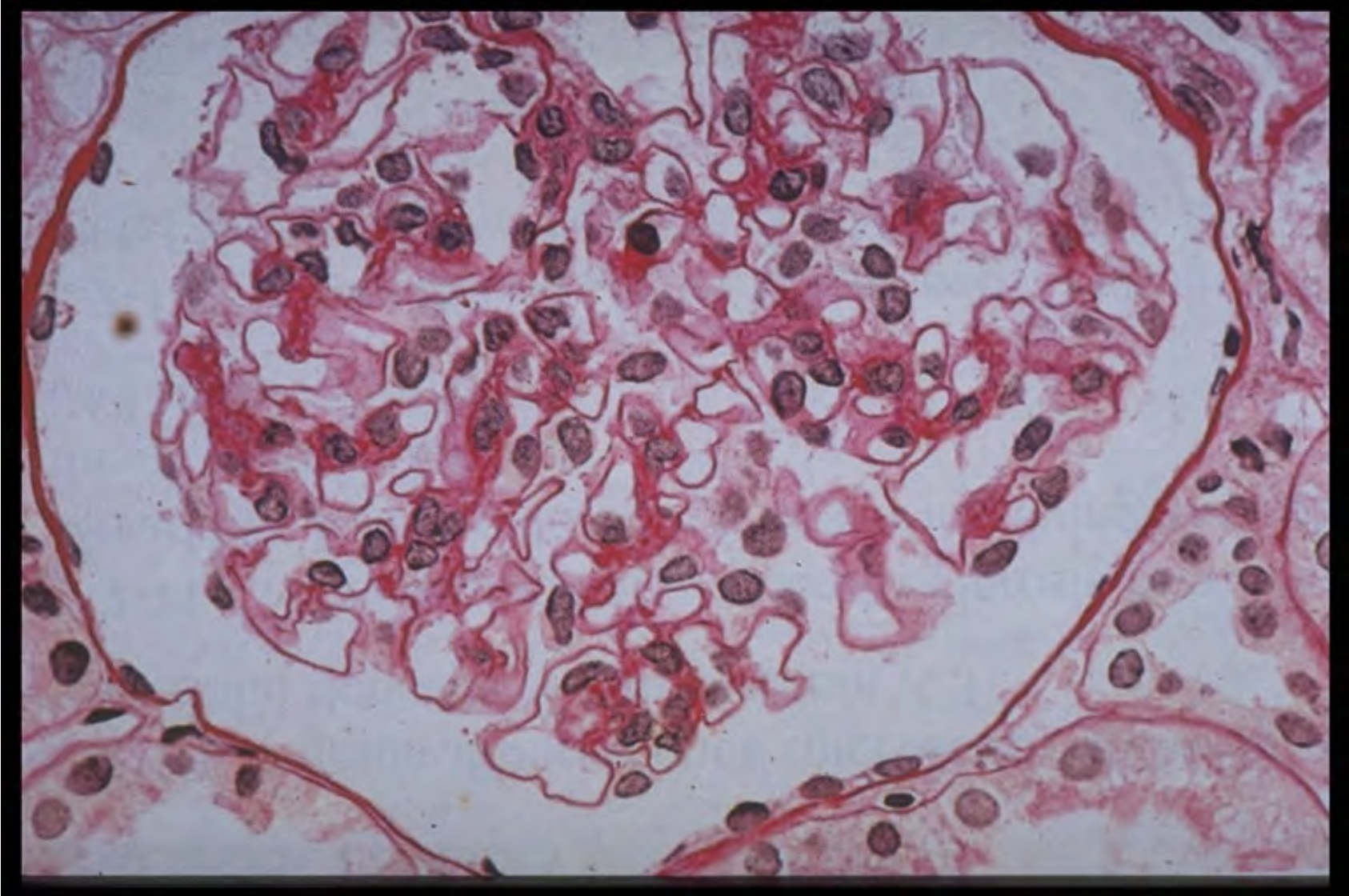
IgA-nephropathy

National
Kidney
Foundation

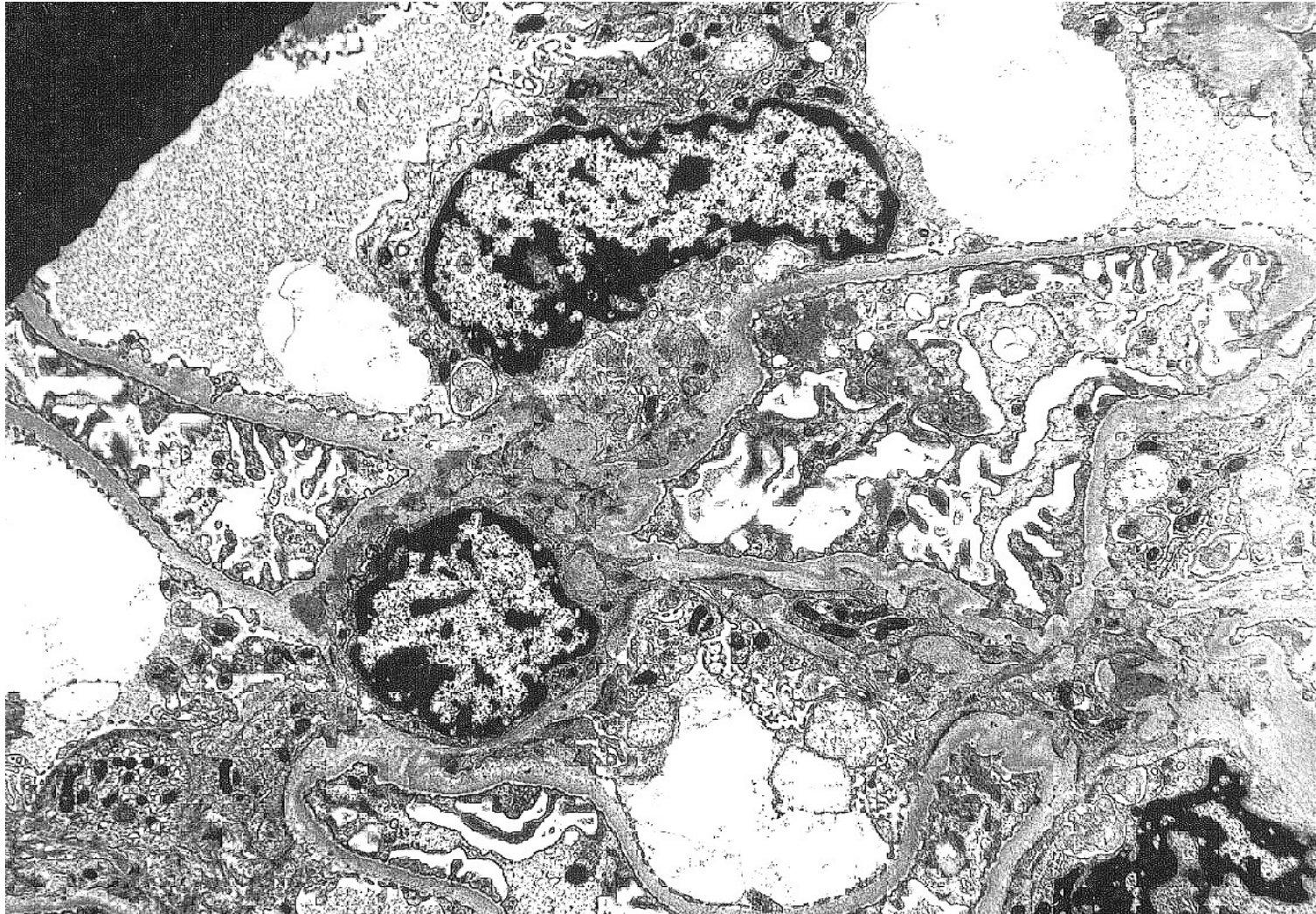


IgA-nephropathy

IF: pos for IgA



IgA-nephropathy



IgA-nephropathy

IgA nephropathy - summery

- IgA nephropathy is a mesangial proliferative glomerulonephritis characterized by **diffuse mesangial deposition of IgA.**
- IgA is unique among glomerular diseases in being defined by the **presence of an immune reactant rather than by any other morphological feature** found on renal biopsy, and the light microscopic changes are variable.

A classification of disorders associated with glomerular IgA deposits

Primary :

- IgA Nephropathy (Berger's disease)



Multi-system :

- Schoenlein-Henoch purpura (children and adults)
 - > drug side effect in adults



Secondary :

- Coeliac disease
- Crohn's disease
- Dermatitis herpetiformis
- Chronic liver disease
- Seronegative spondylarthropathies
- Psoriasis
- Sicca syndrome, etc.

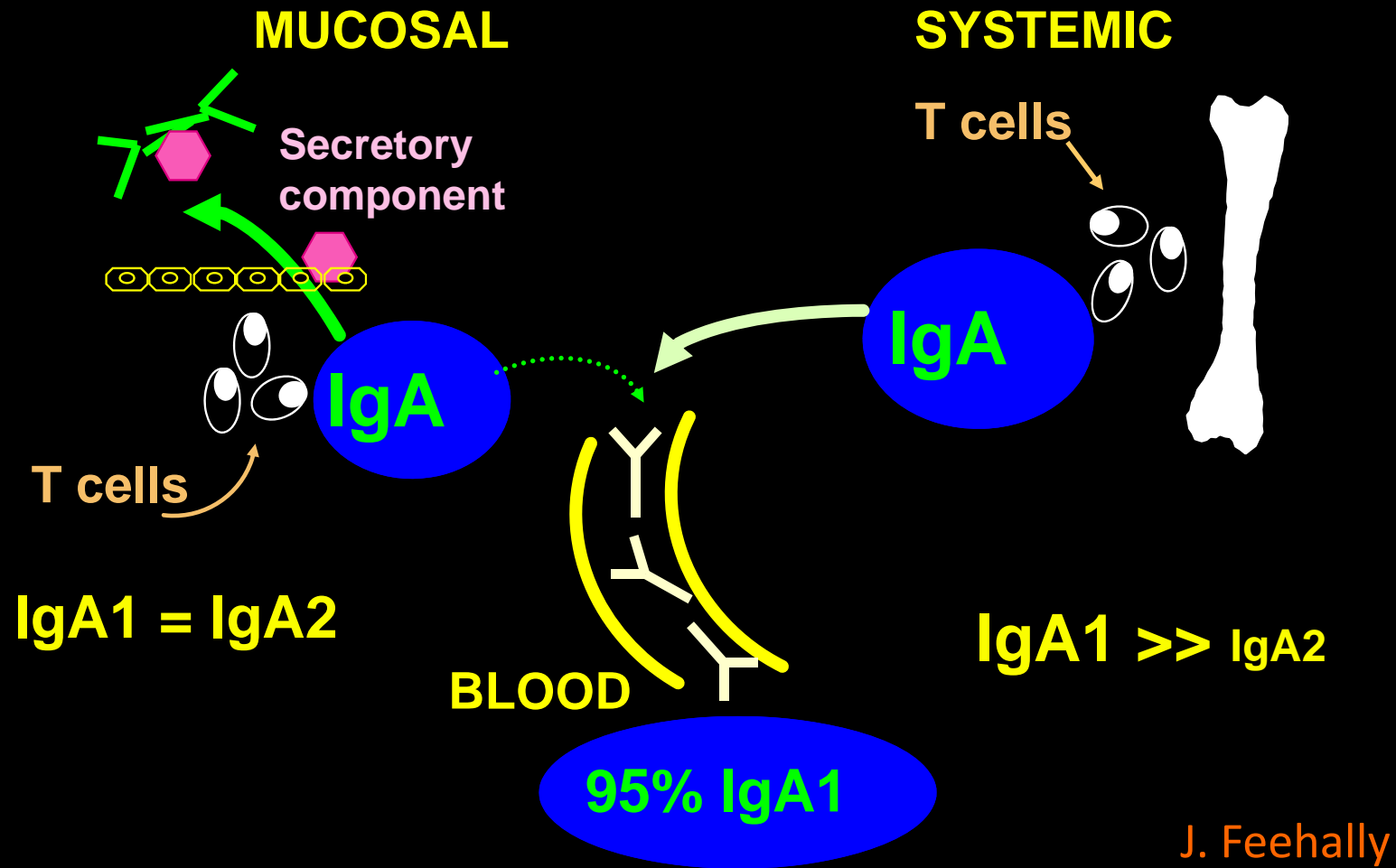


Pathogenesis of IgA nephropathy

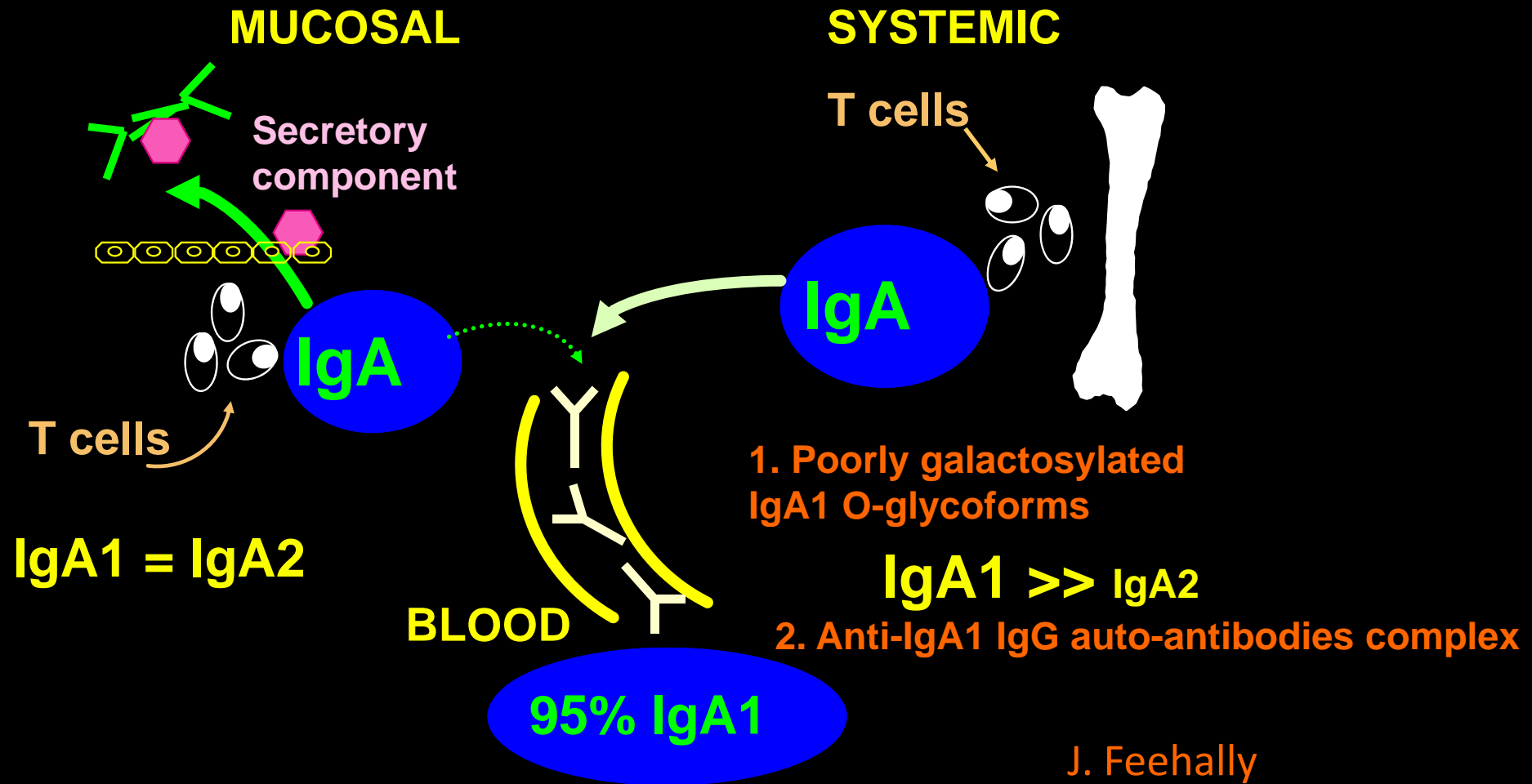
An abnormality in the glycosylation of the hinge region of the IgA1 isotype of IgA is fundamental to the origins of this very common form of glomerulonephritis.

Incomplete understanding of the pathogenesis of IgA nephropathy has hampered development of targeted therapies.

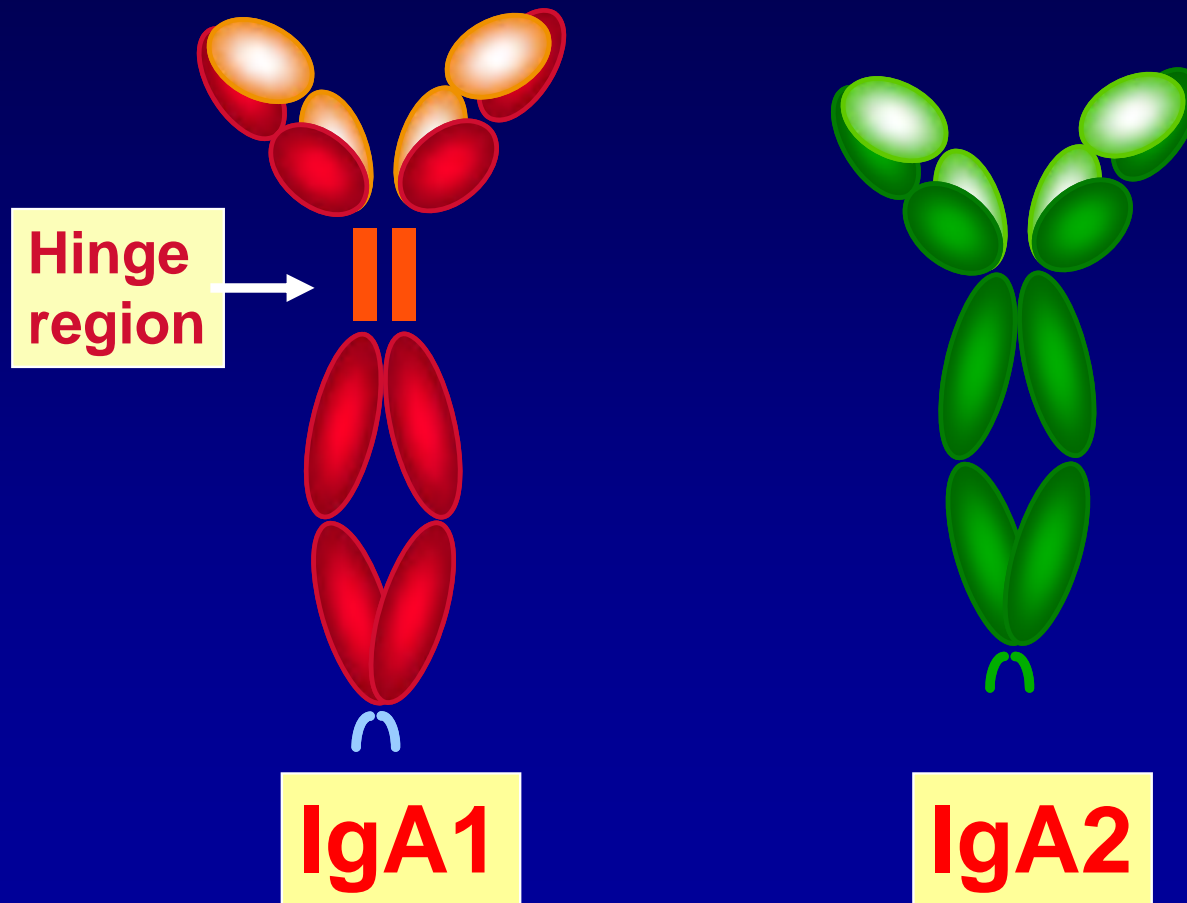
Human IgA Systems



IgA nephropathy



Human IgA subclasses



J. Feehally

Pathogenesis of IgA nephropathy

An abnormality in the glycosylation of the hinge region of the IgA1 isotype of IgA is fundamental to the origins of this very common form of glomerulonephritis.

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nature genetics

Article

<https://doi.org/10.1038/s41588-023-01422-x>

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Nature Genetics | Volume 55 | July 2023 | 1091–1105

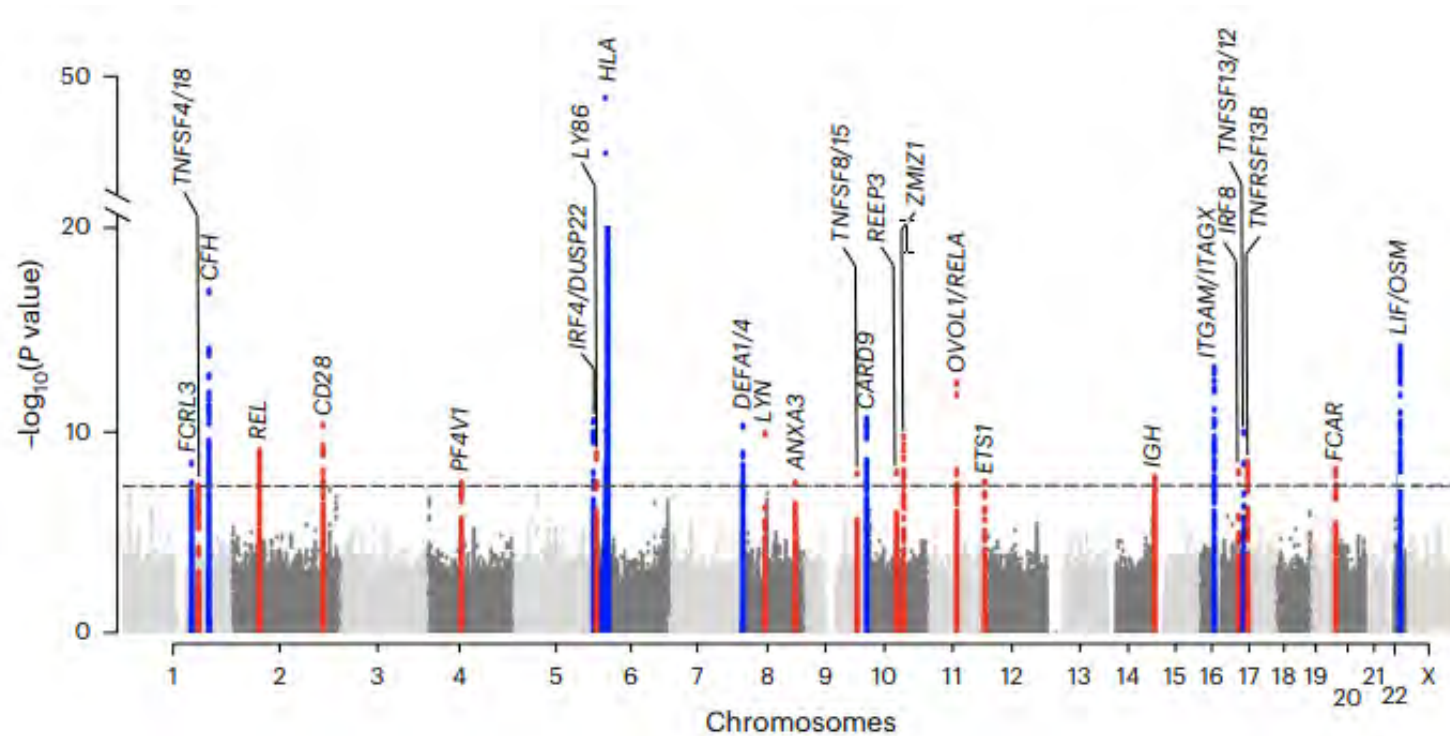
Methods

Genome-wide association study of 10,146 kidney-biopsy-diagnosed IgAN cases and 28,751 controls across 17 international cohorts.

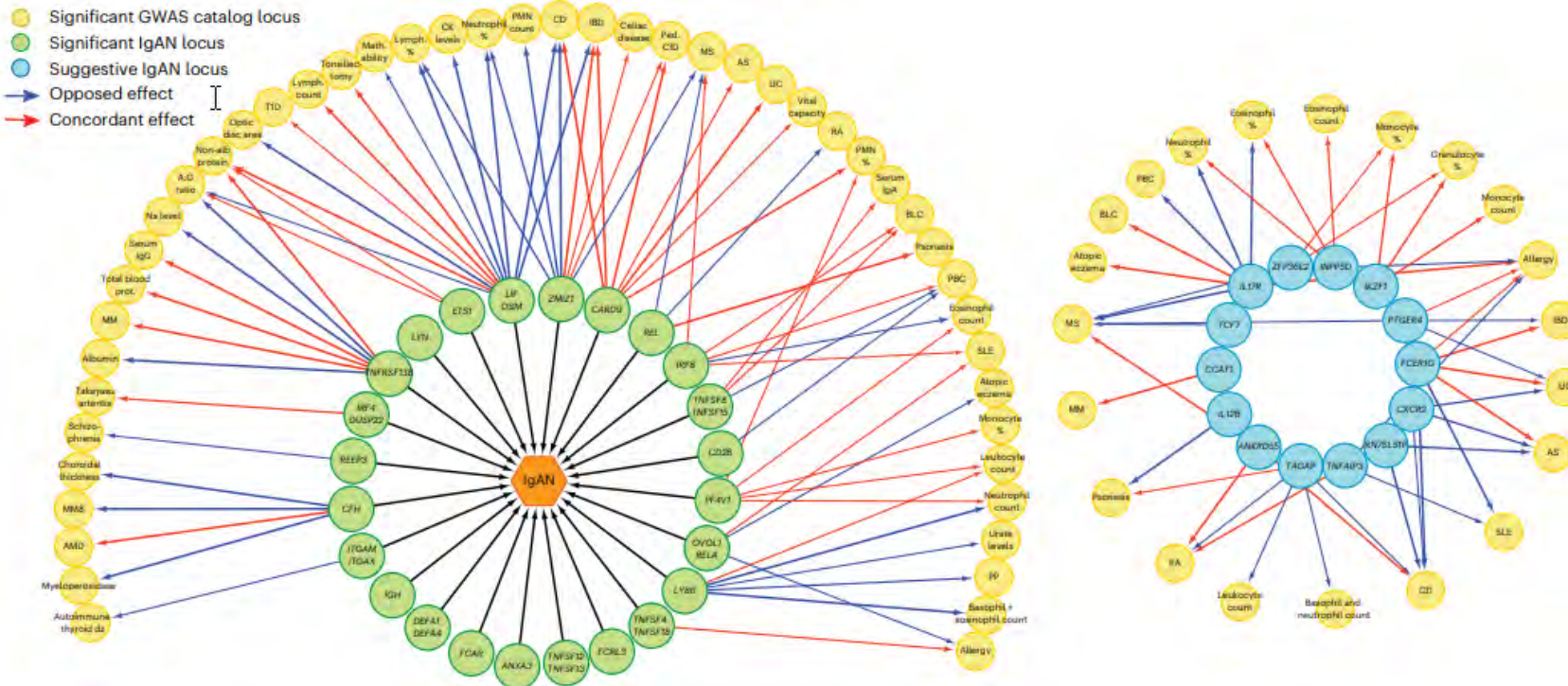
We defined 30 genome-wide significant risk loci explaining 11% of disease risk.

The genome-wide association analysis was performed in each of the 17 cohorts using imputed dosage data under an additive model with adjustment for significant PCs in PLINK v1.9. Only high-quality ($R^2 > 0.8$) common ($MAF > 0.01$) SNPs were included in GWAS.

Cross-ancestry GWAS for IgAN. Manhattan plot for the combined meta-analysis across 38,897 individuals



Pleiotropic effects of non-HLA GWAS loci for IgAN based on the NHGRI GWAS catalog



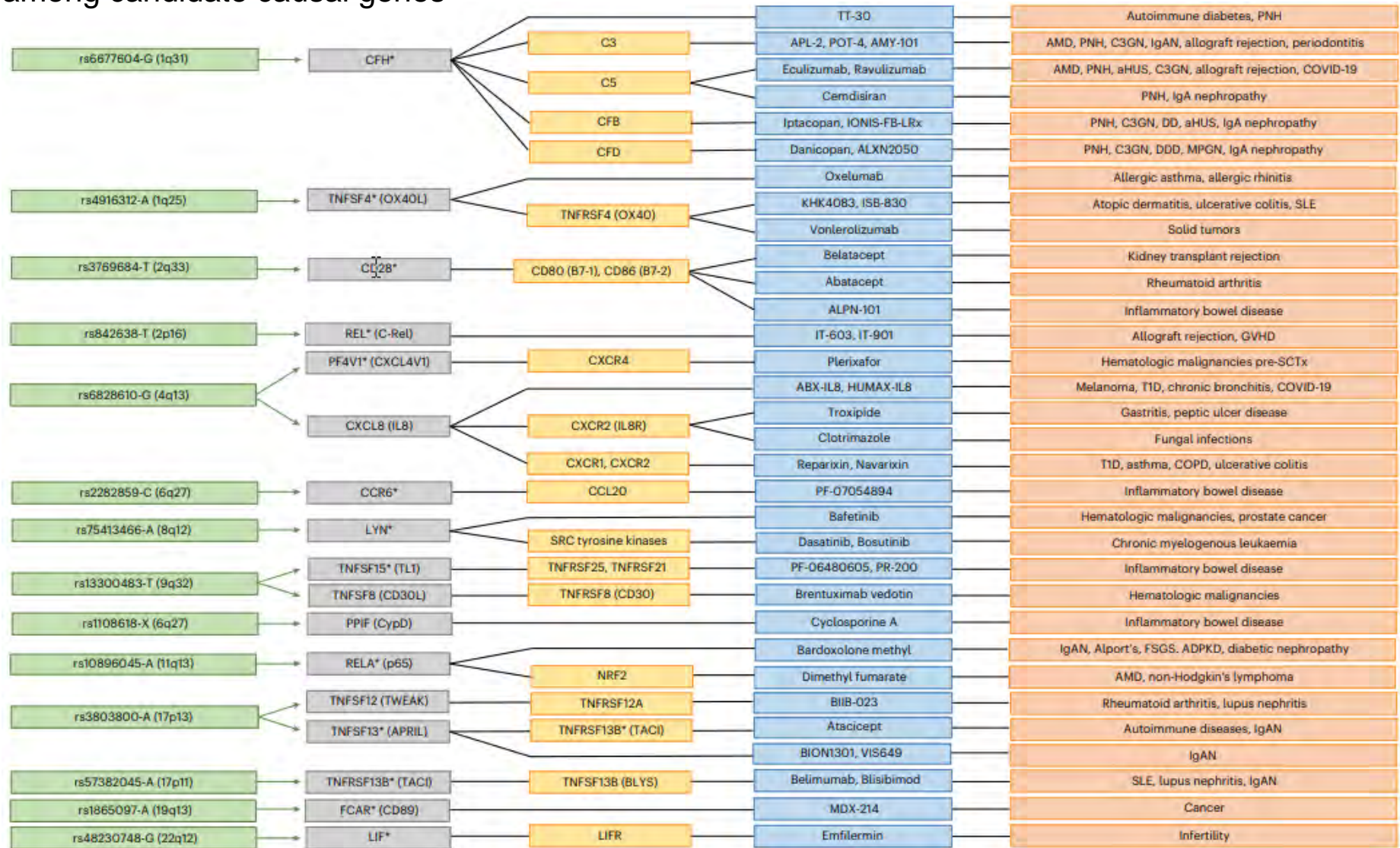
Yellow are diseases and traits sharing at least one locus with IgAN.

Concordant effects are indicated in red, and opposed effects are indicated in blue.

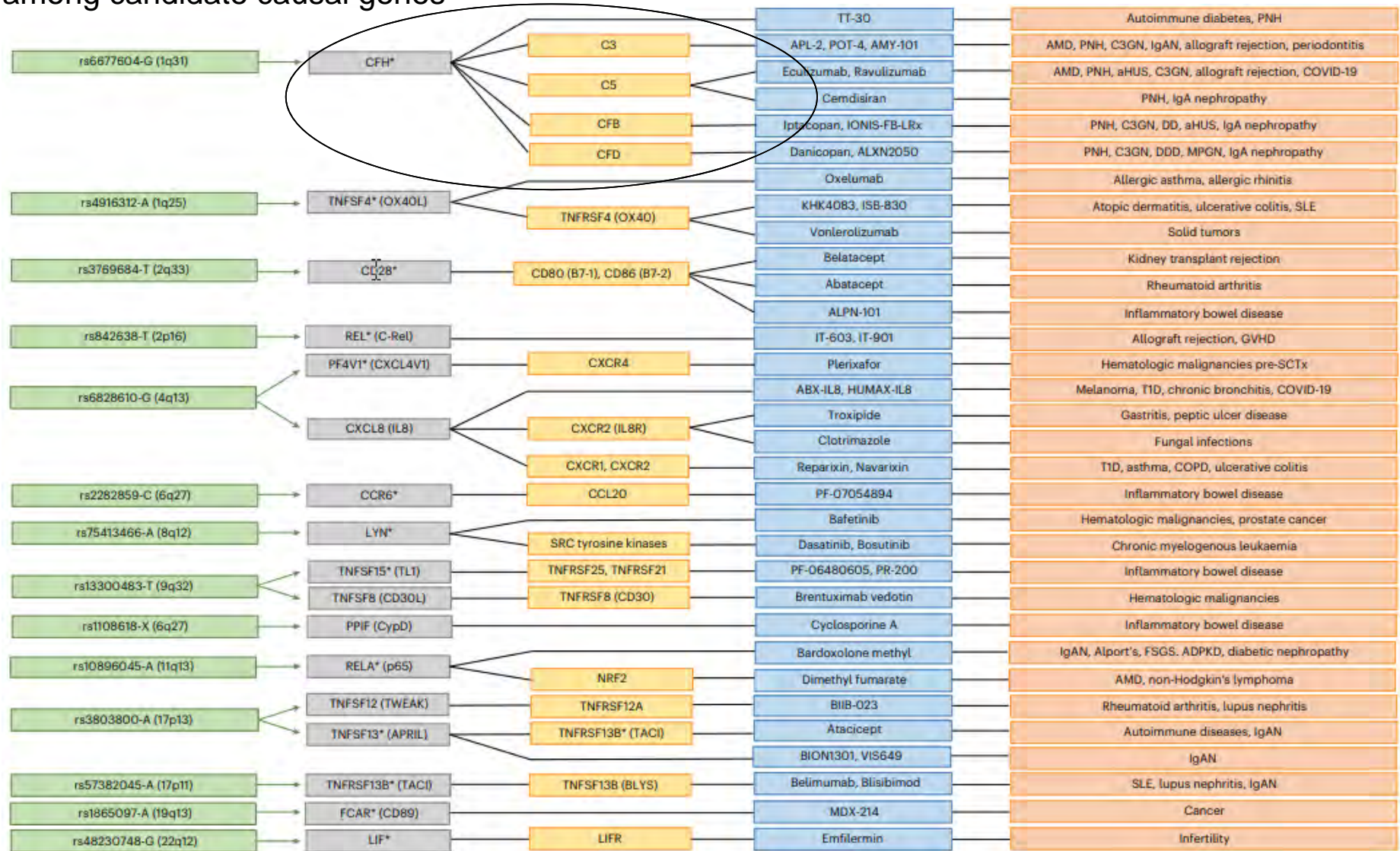
Green nodes represent IgAN GWAS loci, and light-blue nodes are IgAN-suggestive loci.

Only 14 suggestive loci sharing at least one pleiotropic association with a genome-wide significant IgAN locus are depicted.

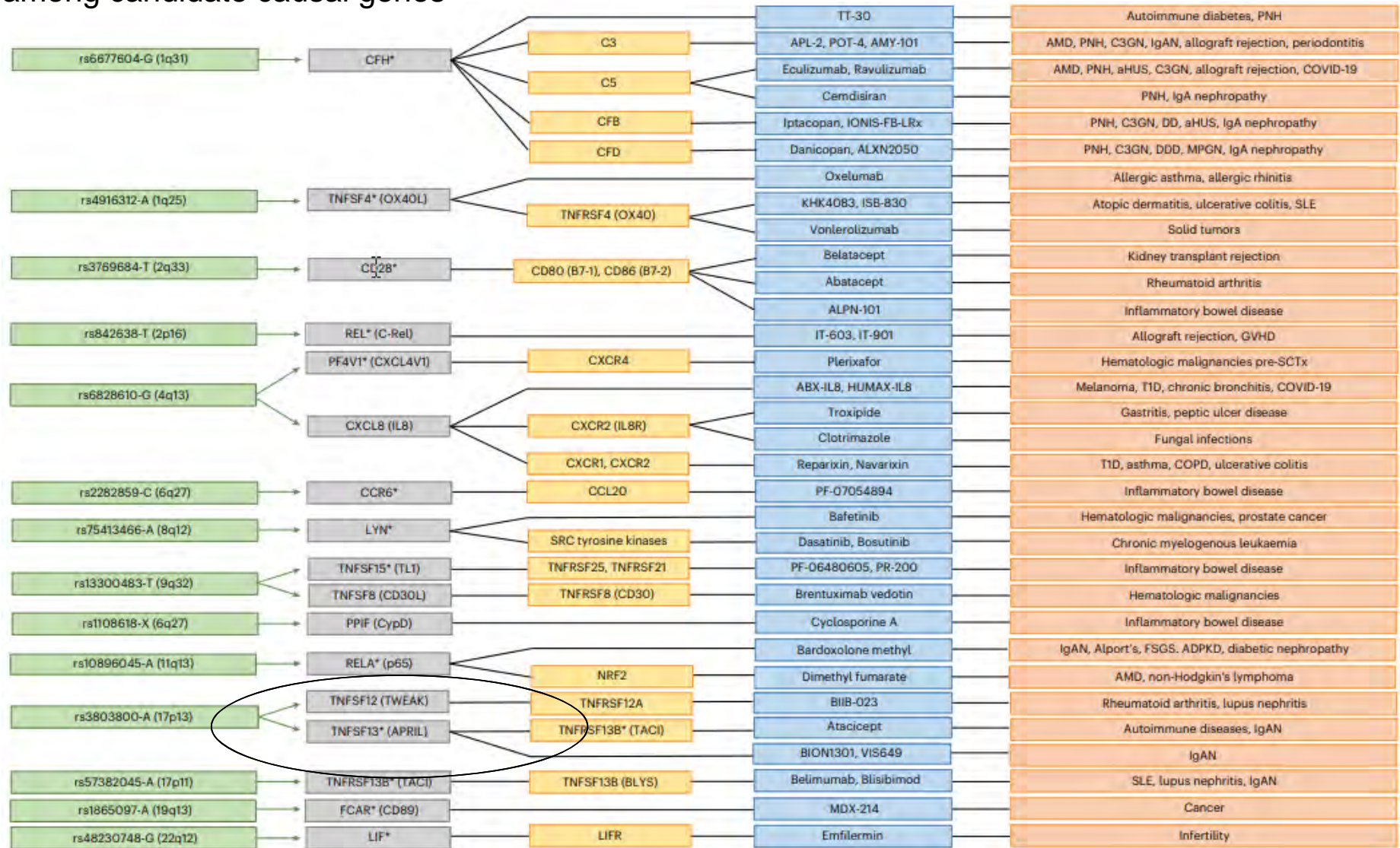
Drug targets among candidate causal genes



Drug targets among candidate causal genes



Drug targets among candidate causal genes



APRIL (protein)

A proliferation-inducing ligand (APRIL), also known as tumor necrosis factor ligand superfamily member 13 (TNFSF13), is a protein of the TNF superfamily recognized by the cell surface receptor TACI. It is encoded by the TNFSF13 gene.

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doi:10.1016/j.jmb.2004.08.040

J. Mol. Biol. (2004) 343, 283–290

JMB

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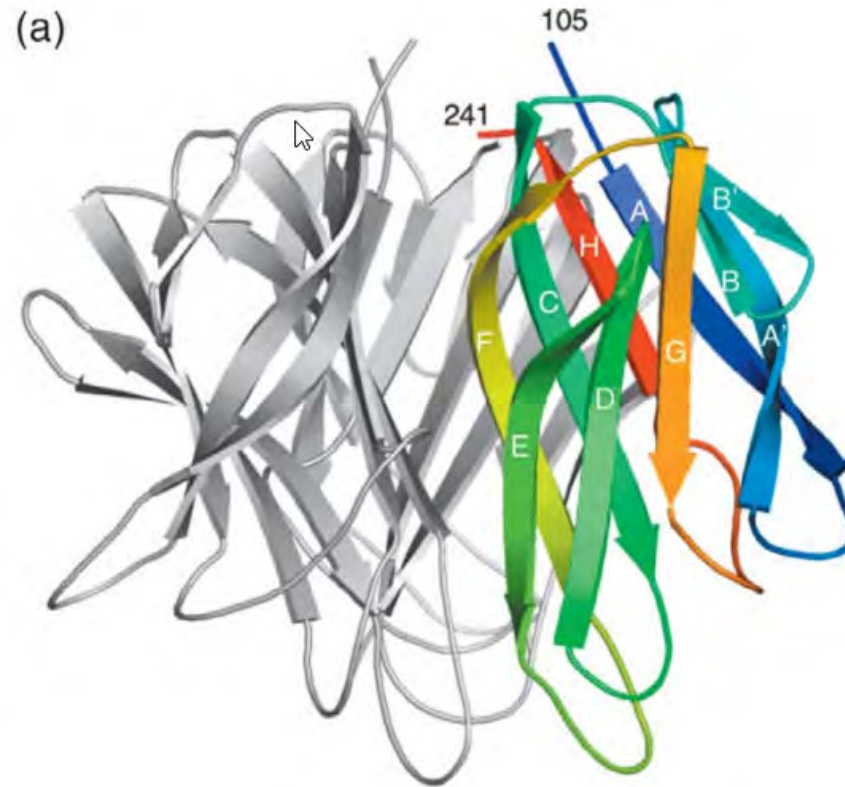


COMMUNICATION

The Crystal Structure of A Proliferation-inducing Ligand, APRIL

Heidi J. A. Wallweber, Deanne M. Compaan, Melissa A. Starovasnik
and Sarah G. Hymowitz*

The crystal structure of APRIL



(a) Cartoon of the APRIL trimer from the C2 crystal form. The A chain is colored in gradations from blue (N terminus) to red (C terminus) with strands labeled. The other two protomers are colored white.

J. Mol. Biol. (2004) 343, 283–290
doi:10.1016/j.jmb.2004.08.040

IgA nephropathy (IgAN) is characterized by a dysregulation of the mucosal IgA system.

A proliferation-inducing ligand (APRIL) is a B cell–stimulating cytokine that increases mucosal IgA production.

APRIL has been implicated in the pathogenesis of IgAN by genome-wide association studies (GWASs) with 2 loci, **TNFSF13 (encoding APRIL)** and **TNFRSF13B (encoding TACI, an APRIL receptor)**, reported to be significantly associated with IgAN susceptibility.

Moreover, serum levels of APRIL are known to be elevated in IgAN.

Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL.

The NEW ENGLAND JOURNAL of MEDICINE

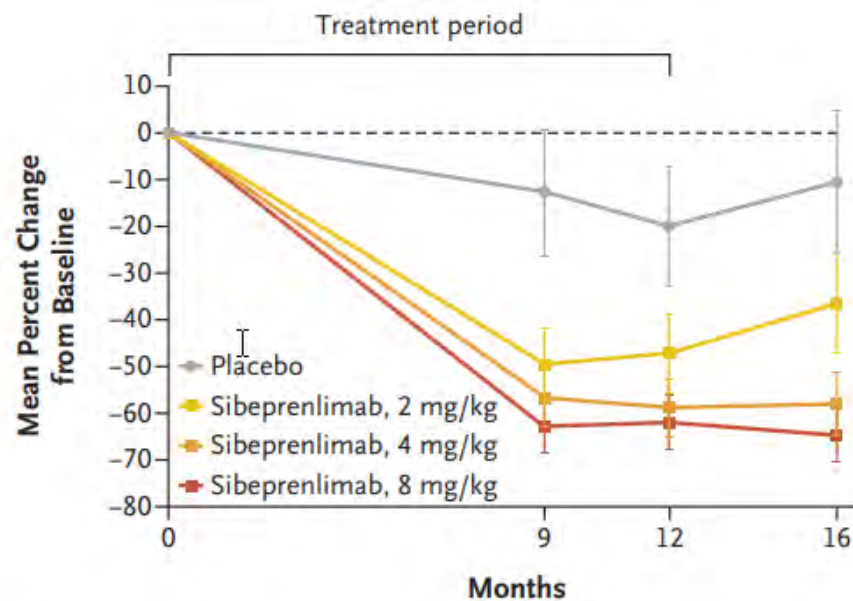
ORIGINAL ARTICLE

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mohit Mathur, M.D., Jonathan Barratt, Ph.D., Bobby Chacko, M.D., D.M.,
Tak Mao Chan, M.D., D.Sc., Laura Kooienga, M.D., Kook-Hwan Oh, M.D., Ph.D.,
Manisha Sahay, M.D., Yusuke Suzuki, M.D., Ph.D., Muh Geot Wong, M.B., B.S., Ph.D.,
Jill Yarbrough, B.A., Jing Xia, Ph.D., and Brian J.G. Pereira, M.D.,
for the ENVISION Trial Investigators Group*

N Engl J Med 2024;390:20-31.
DOI: 10.1056/NEJMoa2305635

Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL.



No. of Patients

Placebo	38	35	35	35
Sibeprenlimab, 2 mg/kg	38	35	35	35
Sibeprenlimab, 4 mg/kg	41	40	38	38
Sibeprenlimab, 8 mg/kg	38	36	37	37

Percentage change in the 24-hour urinary protein-to-creatinine ratio from baseline by treatment group.

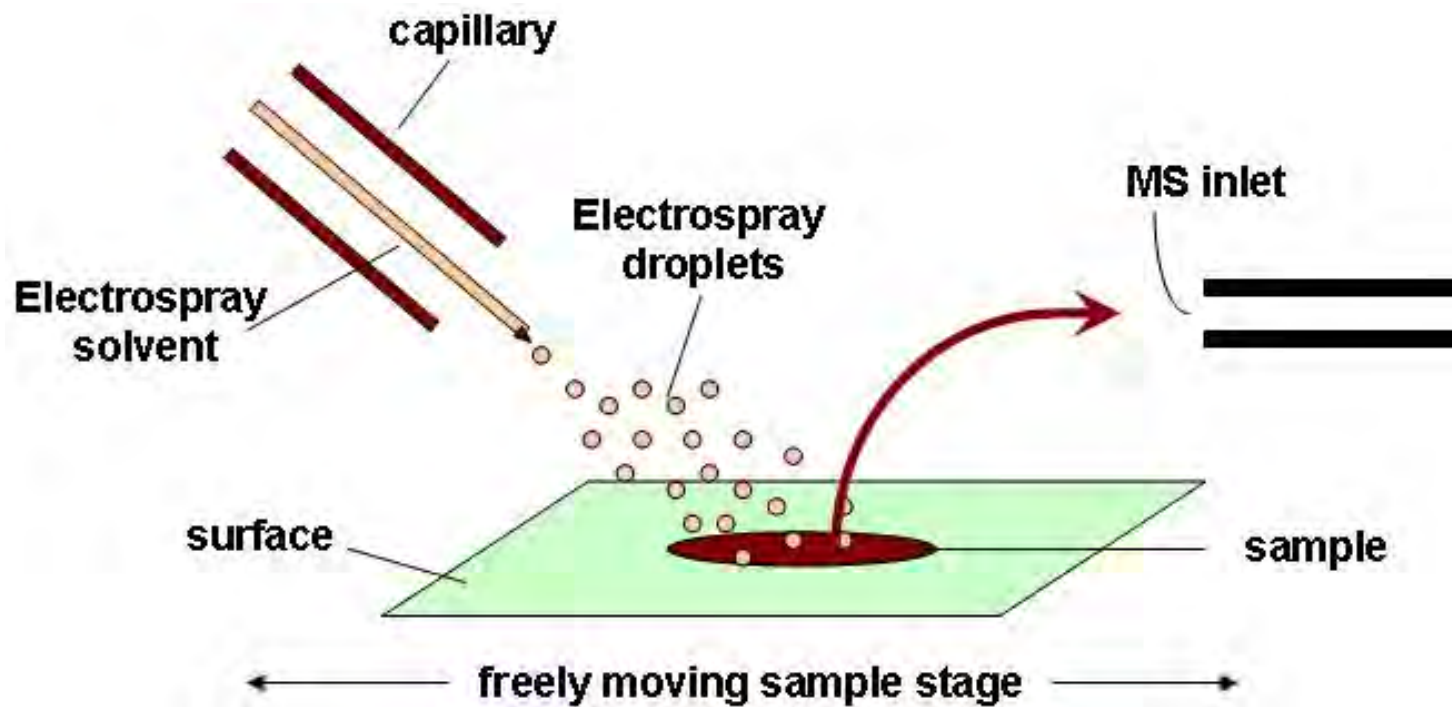
N Engl J Med 2024;390:20-31.
DOI: 10.1056/NEJMoa2305635

Some personal thoughts on the future

-> go to activity when ever possible.

-> and if not possibe then go to expression such as Metabolomics, i.e. what is really fabricated

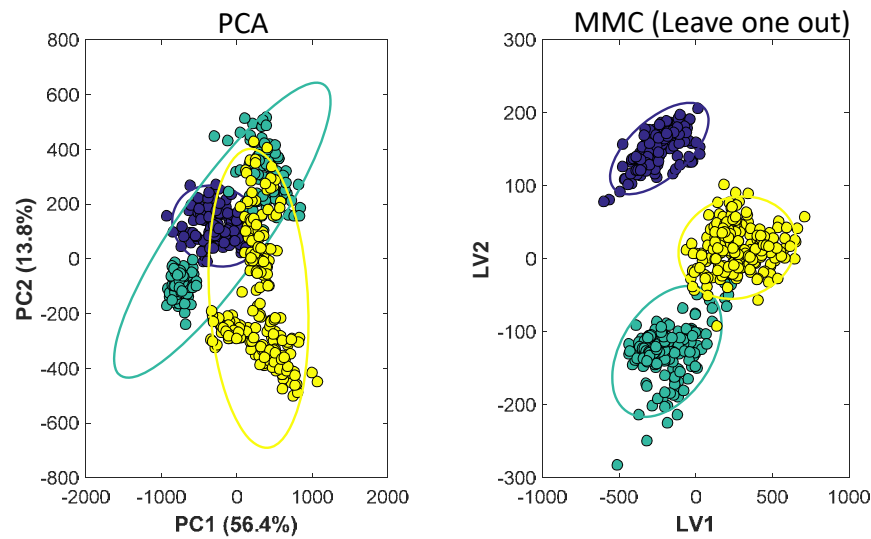
DESI-LC/MS: Desorption ElectroSpray Ionization LC/MS



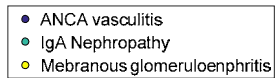
MALDI LC-MS: Matrix-Assisted Laser Desorption/Ionization LC/MS

Multivariate Statistical analysis – per disease grouping

Mass range (m/z): 600-900
Polarity: Negative ion mode



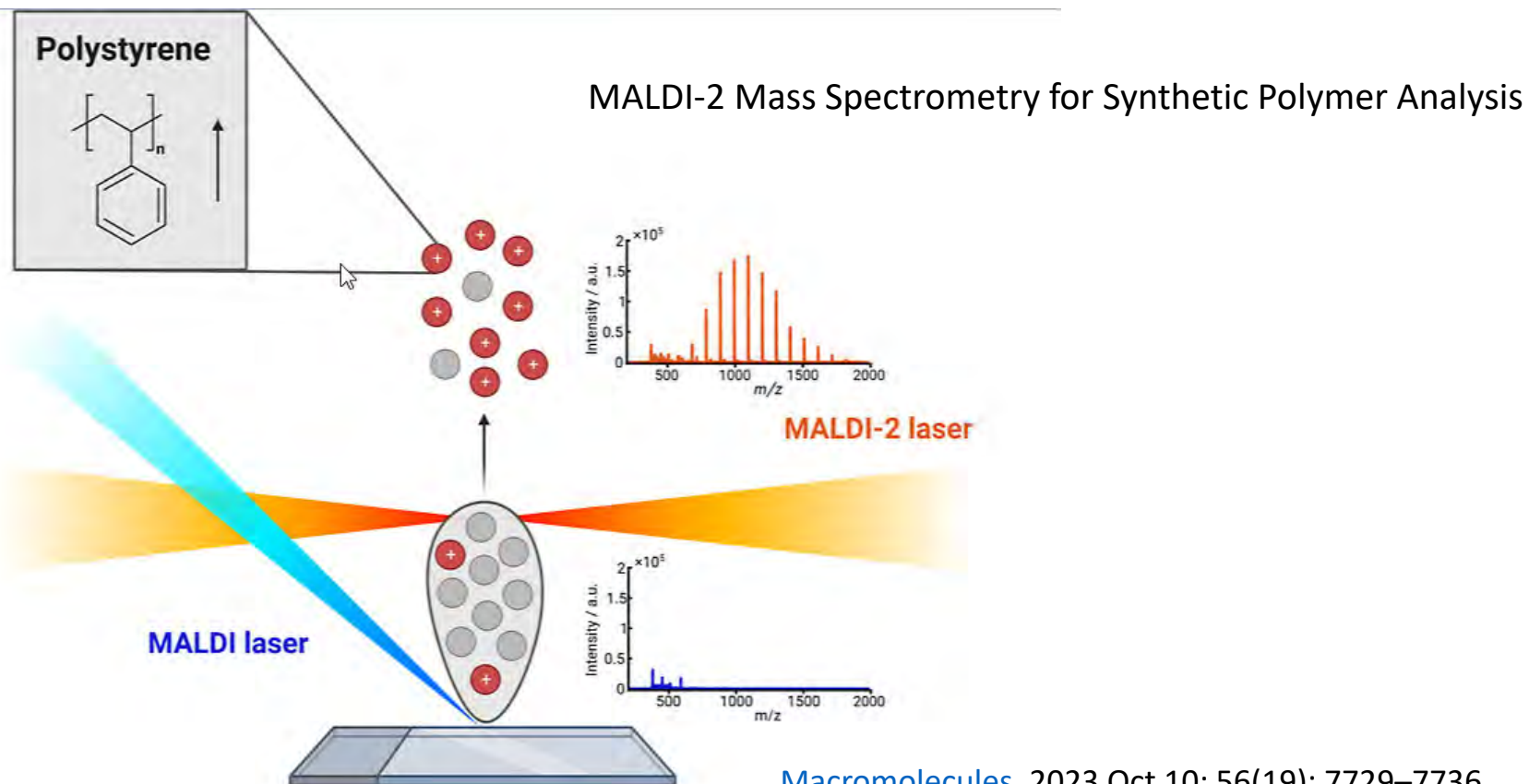
n=5



Cross validation accuracy

ANCA vasculitis	100.0% 121	
IgA Nephropathy	96.4% 163	3.6% 6
Membranous glomerulonephritis	0.4% 1	99.6% 222

Matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI) with MALDI-2 postionization



[Macromolecules](#), 2023 Oct 10; 56(19): 7729–7736.

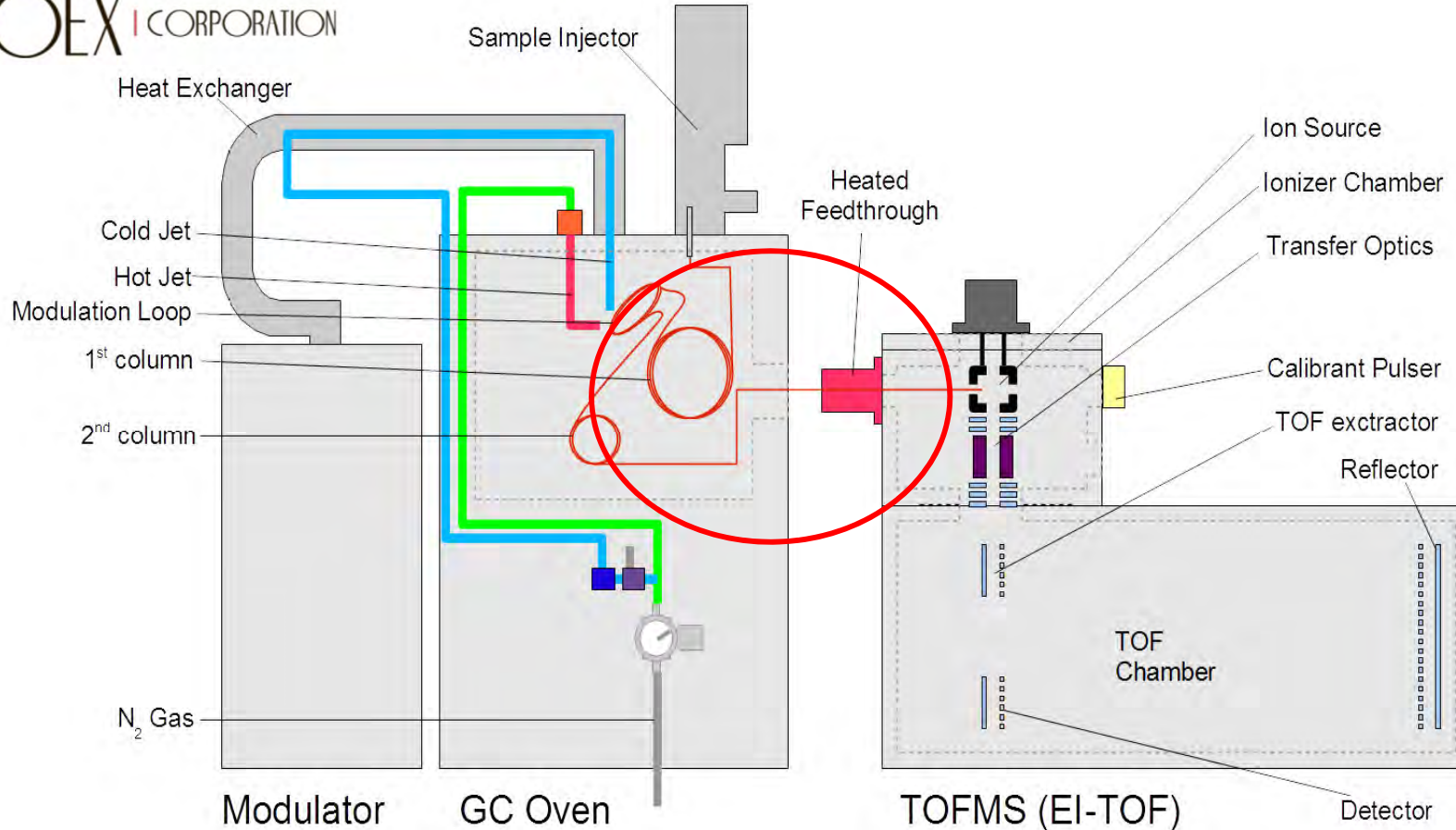
Published online 2023 Sep 22. doi: [10.1021/acs.macromol.3c01401](https://doi.org/10.1021/acs.macromol.3c01401)

PMCID: PMC10569092

PMID: [37841532](https://pubmed.ncbi.nlm.nih.gov/37841532/)

Multidimensional, high-resolution GC-MS

ZOEX CORPORATION



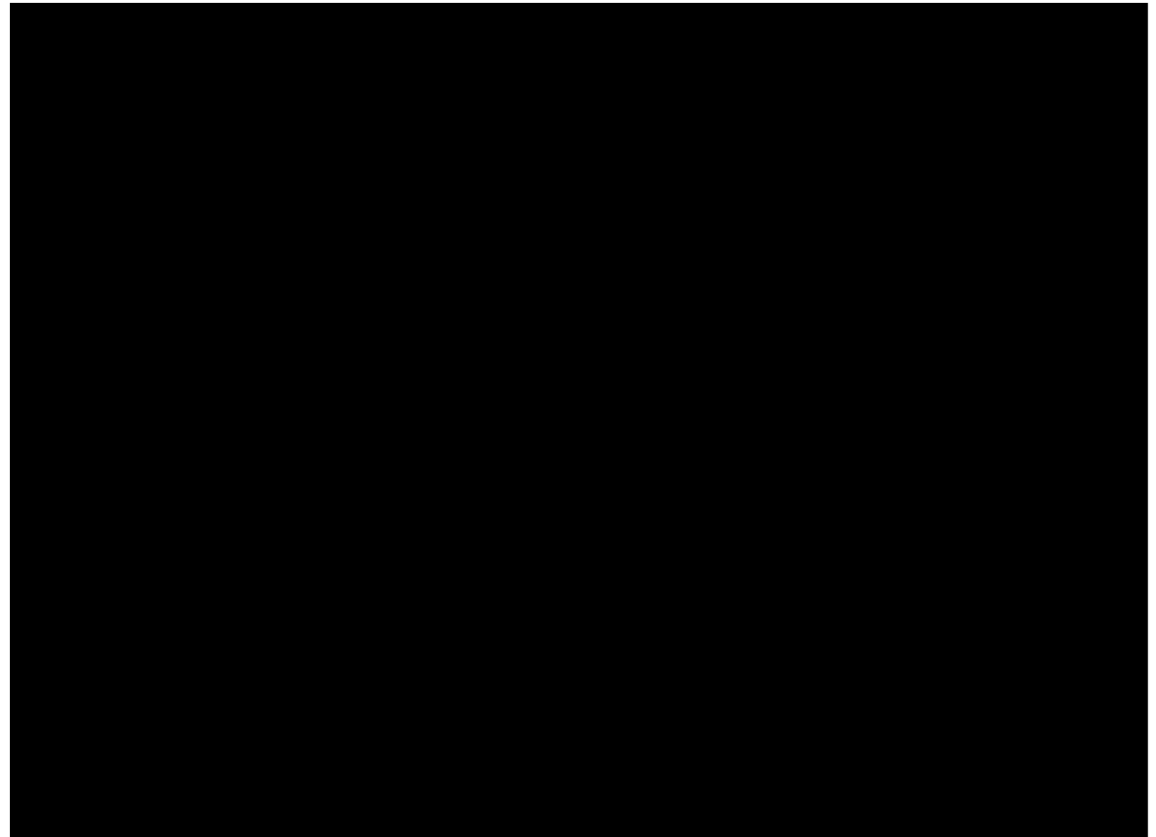
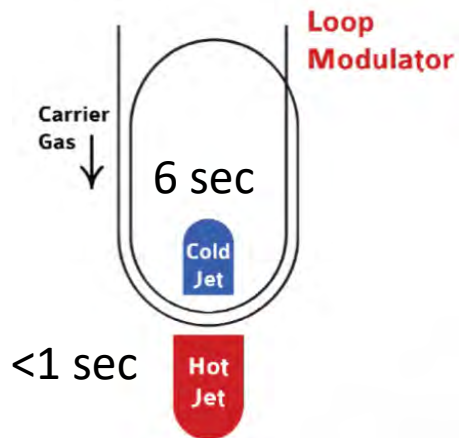
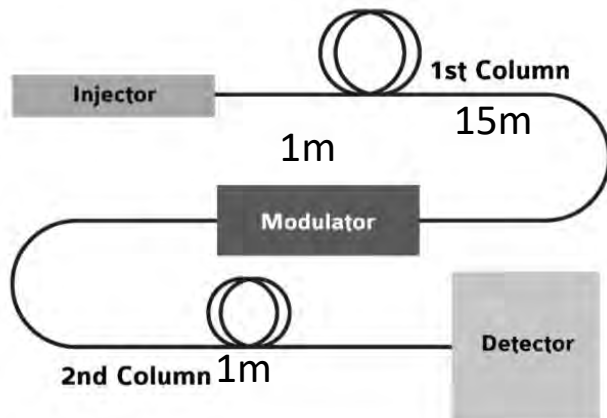
GCxGC-TOF MS
2 instead of 1 GC column
High-resolution MS

 **Agilent Technologies**

TOFWERK

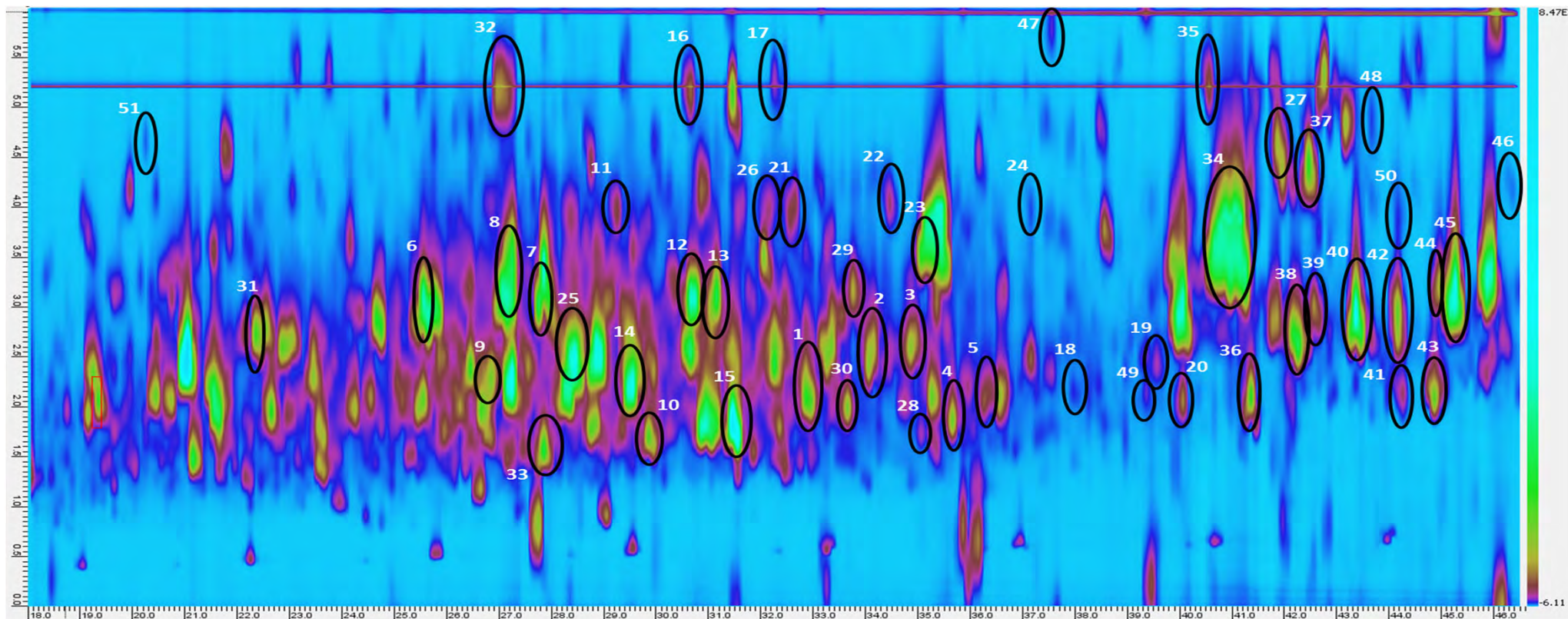
GCxGC

Two GC columns with different separation properties



<https://www.youtube.com/watch?v=Xc3vMSU9yIU>

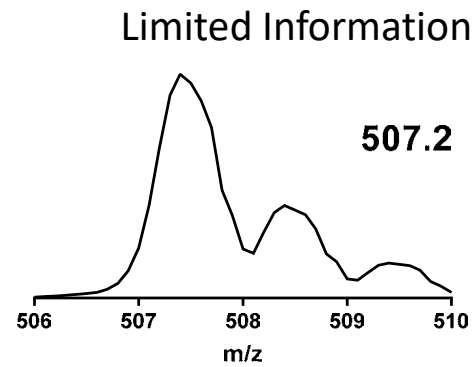
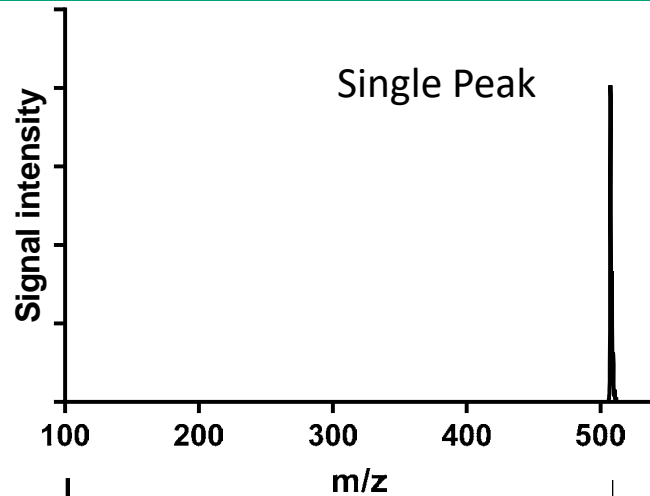
How many steroids are there?



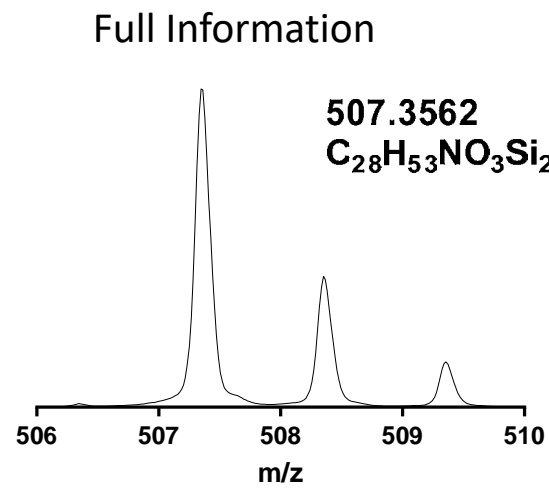
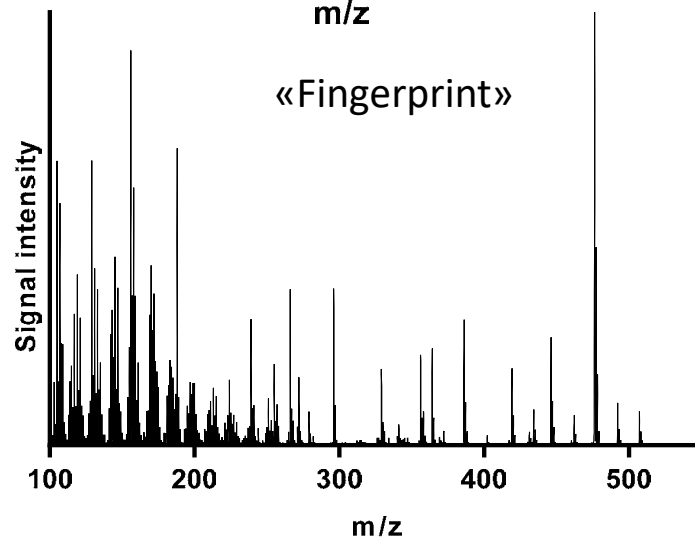
Assignment of > 90 steroid and steroid-like substances on spectral characteristics (exact mass, isotopic pattern, characteristic fragments) in human urine

Low versus high resolution MS

Low
Resolution



High
Resolution



Cross-ancestry GWAS for IgAN. Manhattan plot for the combined meta-analysis across 38,897 individuals

