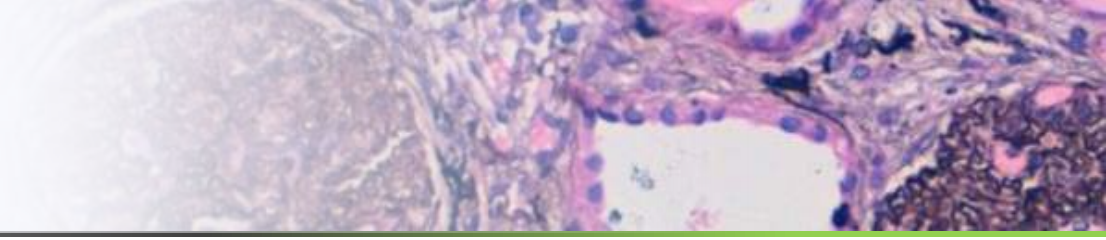

# Einteilung der GN nach Pathogenese, Aktivität und Chronizität

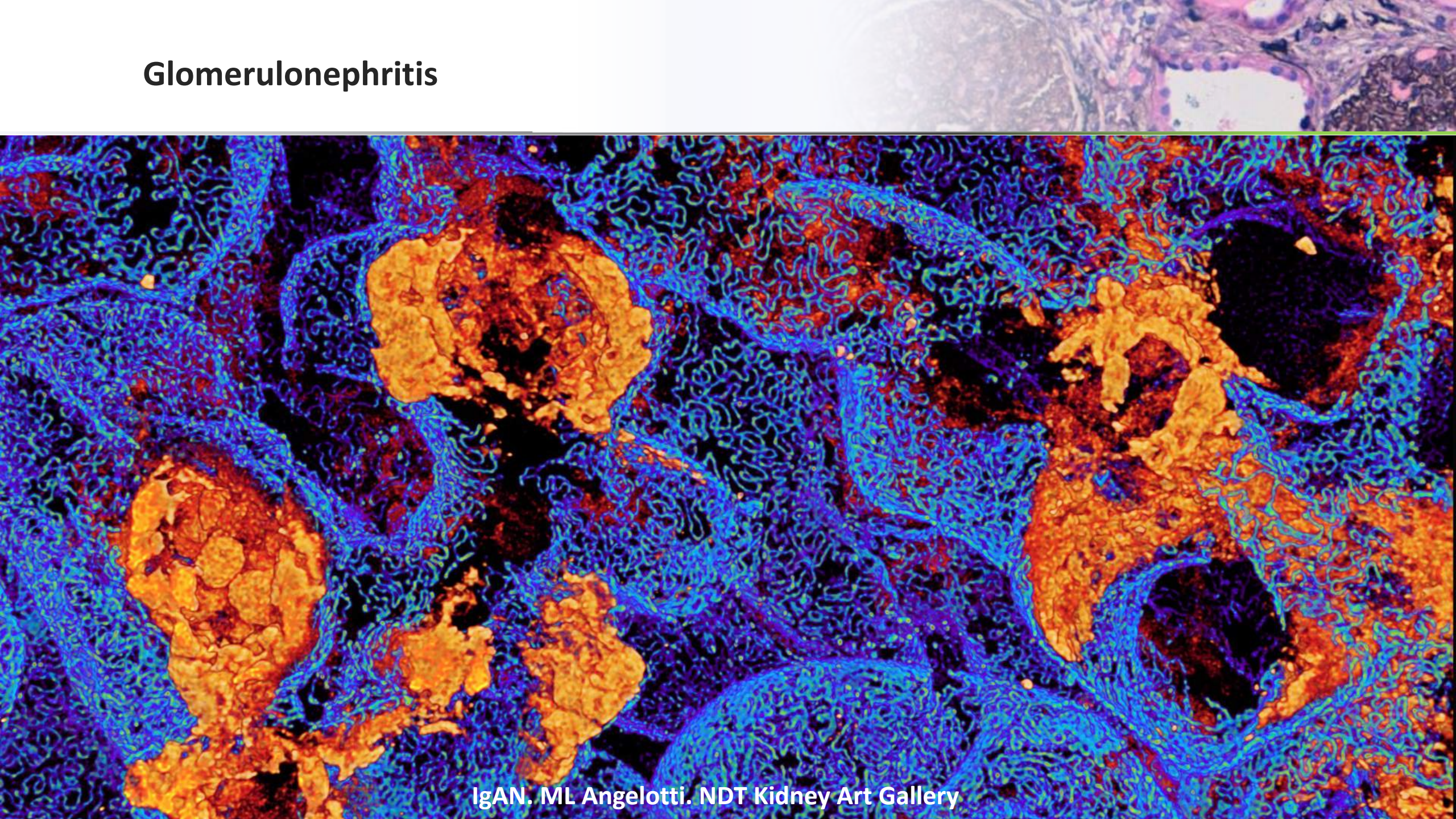
Hans-Joachim Anders
LMU München

# Interessenskonflikte



| | |
|---|---|
| Forschung: | Deutsche Forschungsgemeinschaft, Boehringer-Ingelheim |
| Honorare: | GSK, Otsuka, Novartis, Janssen, Kezar, AstraZeneca, Lilly, Vifor, Bayer Boehringer-Ingelheim |

# Glomerulonephritis



IgAN. ML Angelotti. NDT Kidney Art Gallery

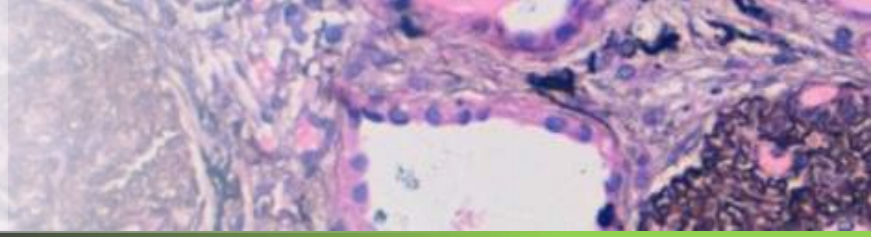
# Wie konnte es soweit kommen ?

# Schon mal versucht, Studenten GNs zu erklären?

# Haben Sie schon mal versucht einem Immunologen GNs zu erklären?

# Nephrologie + Nephropathologie

# Neulich…



**Traditionelle GN-Entitäten**

Nierenbiopsie = Pathologie

Primär: IgA Nephropathie
Membranöse GN
Membranoproliferative
C3GN
MCD, FSGS

Sekundär: Lupusnephritis
ANCA-GN
Post-infektiöse GN
Kryoglobulin GN
Transplantglomerulopathie
Monoklonale Gammopathie GN
(Diabetische Nephropathie)

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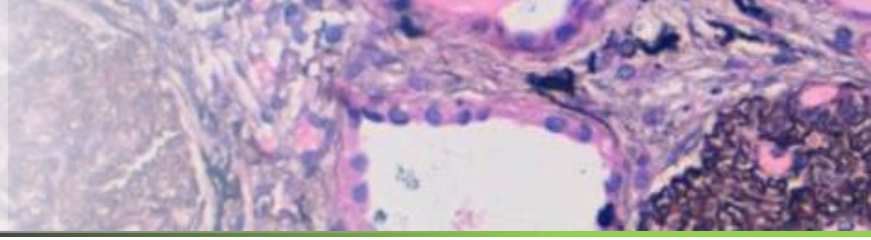

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**Pathogenetische GN-Entitäten**

Infektiöse GN

Autoimmune GN

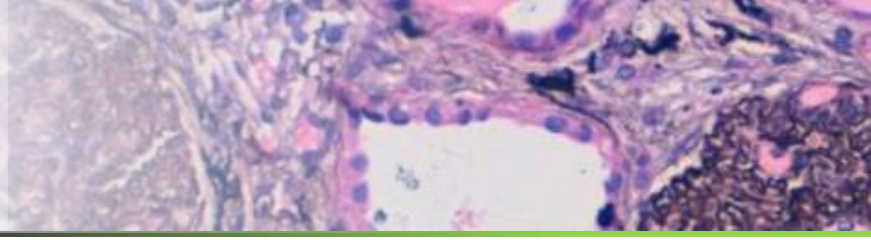
Alloimmune GN

Autoinflammatorische GN

Monoklonale Gammopathie GN

Anders, et al. Nat Rev Immunol 2023

# Neulich…



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Monoklonale Gammopathie GN
(Diabetische Nephropathie)

**Pathogenetische GN-Entitäten**

Mikrobiologie, Serologie, Genetik, Biopsie = Nephrologie

Infektiöse GN (Erregernachweis)

Autoimmune GN (IgA, IgG, ANCA, PLA2R, NELL-1, FH…)

Alloimmune GN (Z.n. NierenTx)

Autoinflammatorische GN (Genetisch)

Monoklonale Gammopathie GN (FLC, KM-Biopsie)

Anders, et al. Nat Rev Immunol 2023

# Alle GNs sind Immunkrankheiten

- nur immunologisch zu diagnostizieren
- nur immunologisch zu verstehen
- nur immunologisch zu behandeln
- daher immunologisch zu klassifizieren

und nicht wie es unterm Mikroskop aussieht

**Ursache**

↓

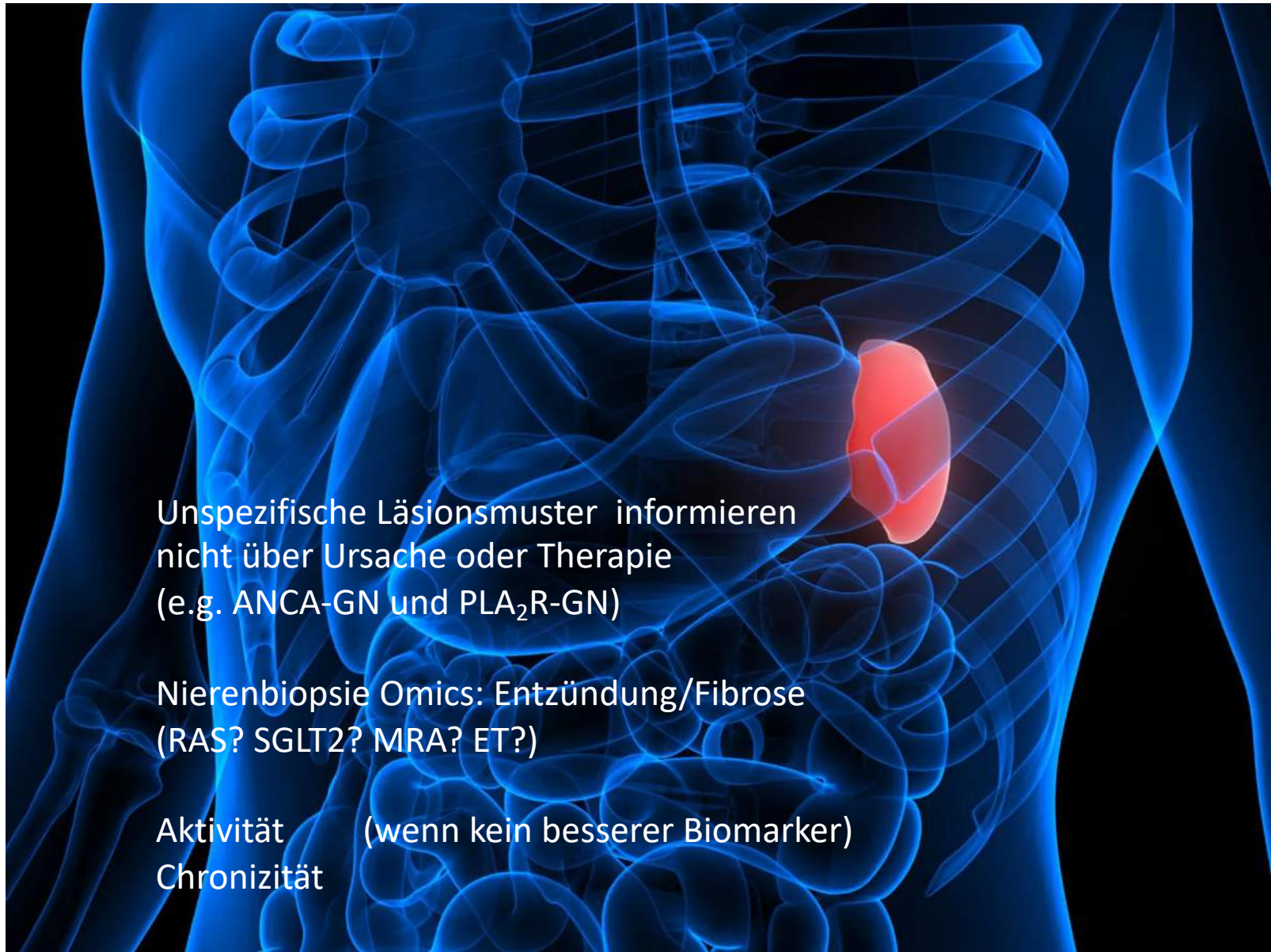
**Immunreaktion in Milz/LK/KM**

↓

**Zirkulierendes nephrotoxisches Agens**

↓

**Nierenschädigung**



# Wie GNs brauchbar klassifizieren?

**Eine Klassifikation muss sein:**

- Einfach — TNM, GOLD, NYHA, CKD G/A, AKI 1-3
- Intuitiv — Fundamentale Kategorien der Pathogenese oder Schwere
- ->Therapie — Pathogenese — Was behandeln?
  - Aktivität — Wie viel Immuntherapie?
  - Chronizität — CKD Therapie ?

# Wie GNs brauchbar klassifizieren?

## GN-A/C

| Typ der GN | Aktivität | Chronizität |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

Romagnani, *et al*. NDT 2023

# Monoklonale Gammopathie-assoziierte GNs

**Table 2 | Proposed classification of glomerulonephritis**

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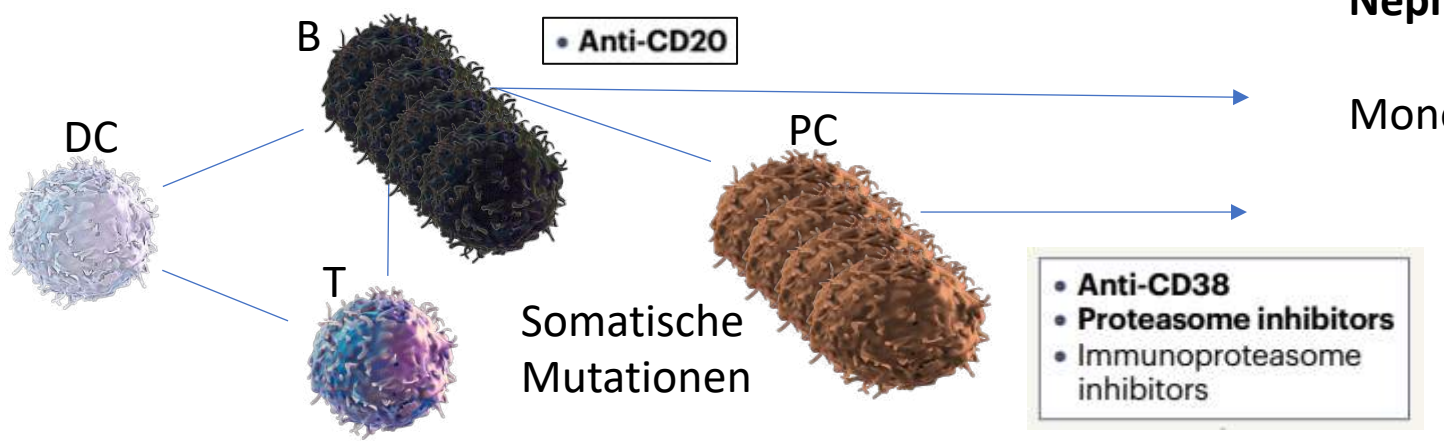
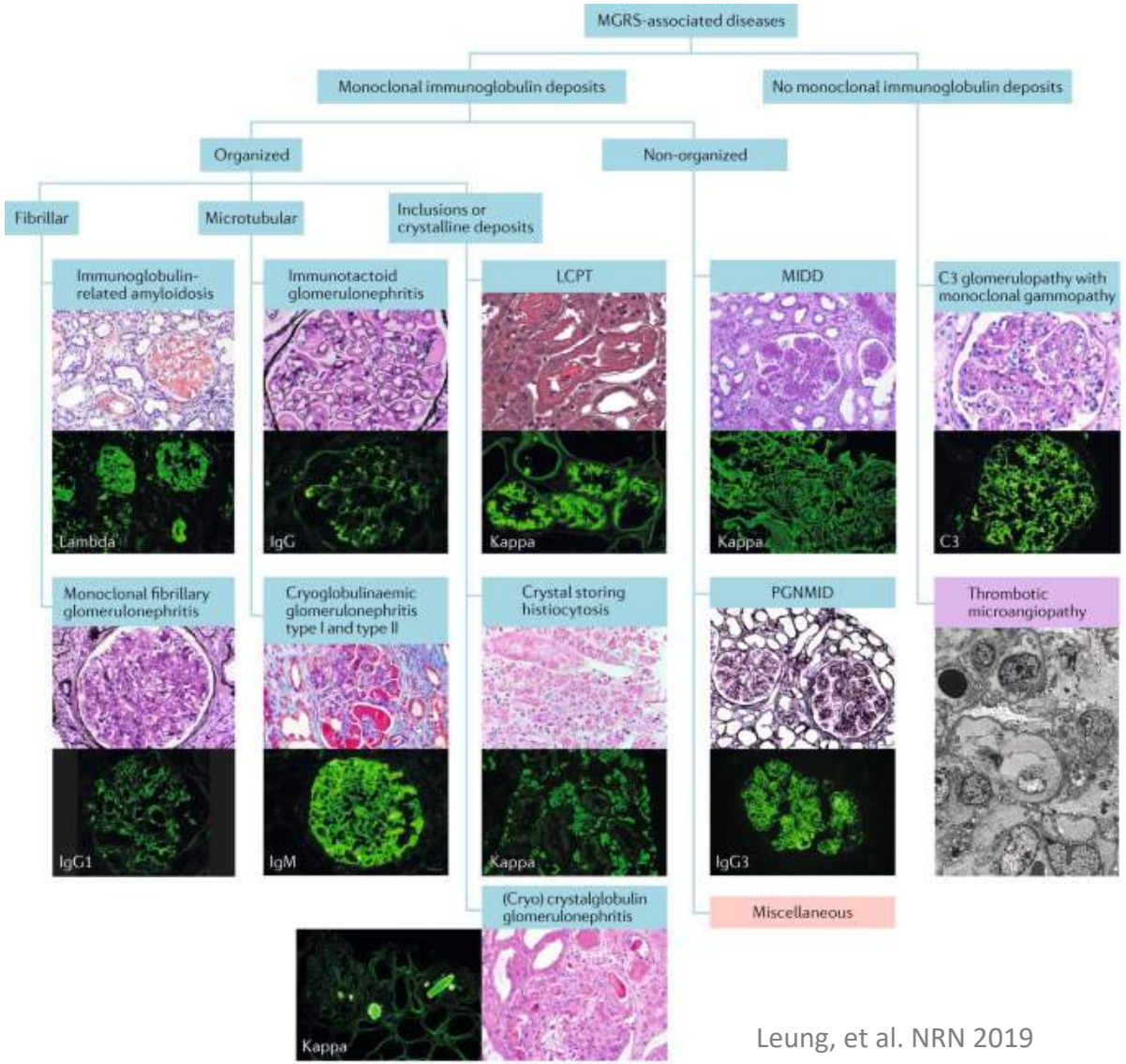



**Nephrotoxische Agens**

Monoklonale Paraproteine

# Infektion-assoziierte GNs




Leung, et al. NRN 2019

OXFORD ERA ndt

Nephrol Dial Transplant, 2024, 0, 1–5
https://doi.org/10.1093/ndt/gfae005
Advance access publication date: 8 January 2024

RESEARCH LETTER

## Proliferative glomerulonephritis with monoclonal immunoglobulin deposits in the native or posttransplant kidney

Margo Verbinnen[1], Ben Sprangers[2,†], Alferso C. Abrahams[3,†], Priyanka Koshy[4,5], Rob C.M. Van Kruijsdijk[6,†], Ester Philipse[7], Magdalena Michalak[8], Michel Delforge[9], Josephine M.I. Vos[10,†], Jack Wetzels[6,†], Amélie Dendooven[11,†] and Amaryllis H. Van Craenenbroeck[1,5,†]

[1]Department of Nephrology, University Hospitals Leuven, Leuven, Belgium
[2]Department of Nephrology, General Hospital Oost-Limburg, Genk, Belgium
[3]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands
[4]Department of Pathology, University Hospitals Leuven, Leuven, Belgium
[5]Department of Microbiology, Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, KU Leuven, Leuven, Belgium
[6]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands
[7]Department of Nephrology, General Hospital AZ Voorkempen, Antwerp, Belgium
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[9]Department of Hematology, University Hospitals Leuven, Leuven, Belgium
[10]Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam & LYMMCARE, Amsterdam, The Netherlands
[11]Department of Pathology, University Hospitals Gent, Gent, Belgium
Correspondence to: Amaryllis Van Craenenbroeck; E-mail: amaryllis.vancraenenbroeck@kuleuven.be
†Members of the Benelux MGRS expertise group.

# Autoinflammation-assoziierte GNs

**Table 2 | Proposed classification of glomerulonephritis**

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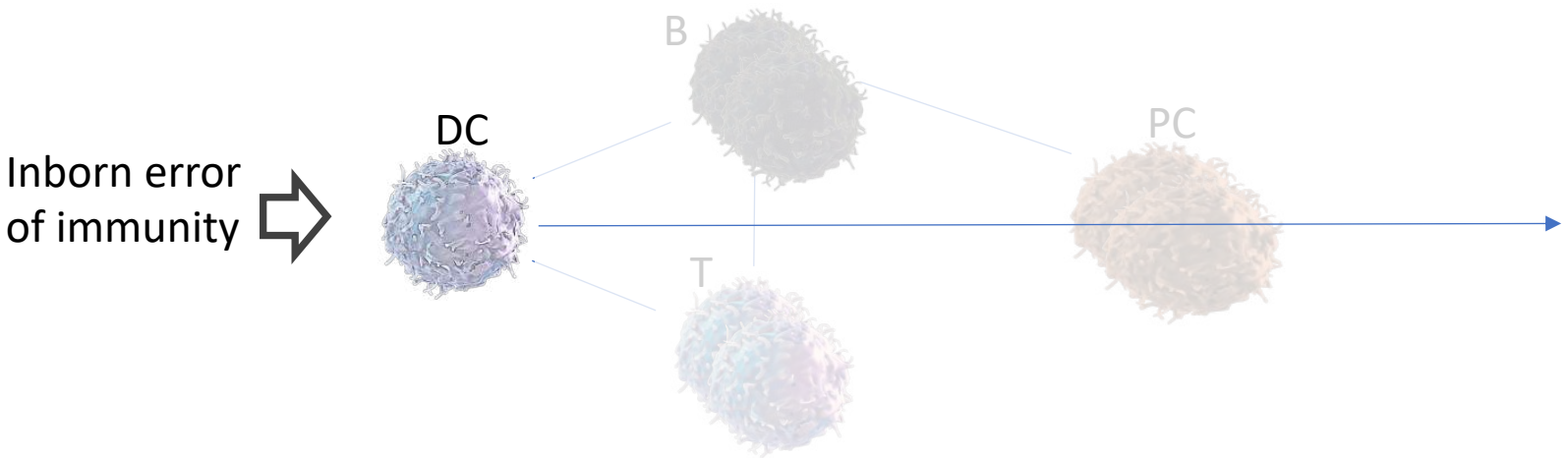


**Nephrotoxische Agens**

SAP, CRP, IL-6, TNF, IL-1

Lokale Komplementaktivierung

# Auto-/Alloimmune GNs

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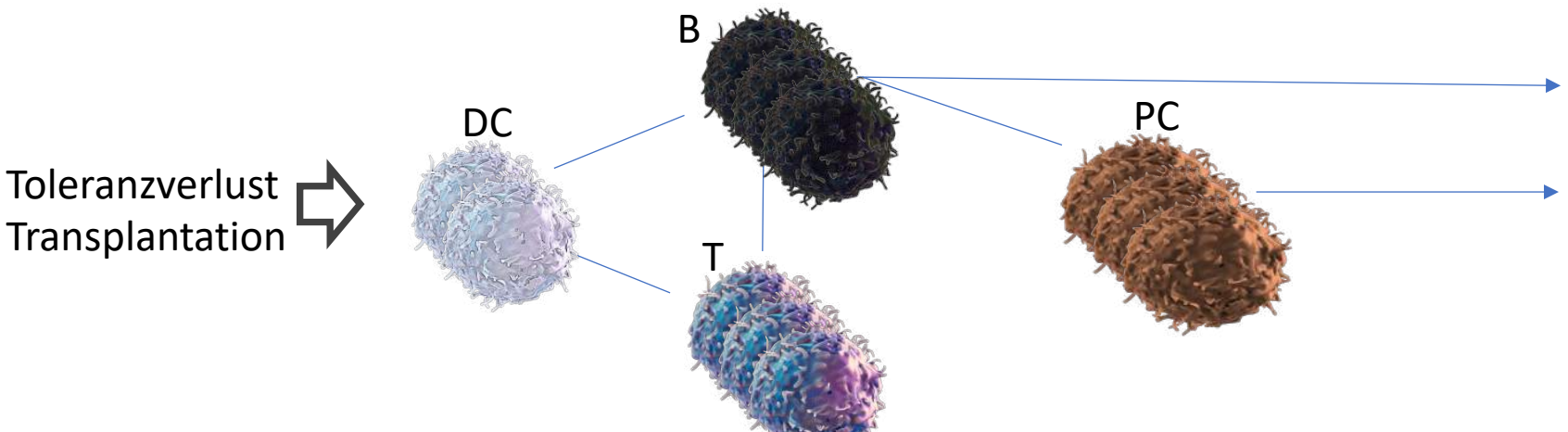


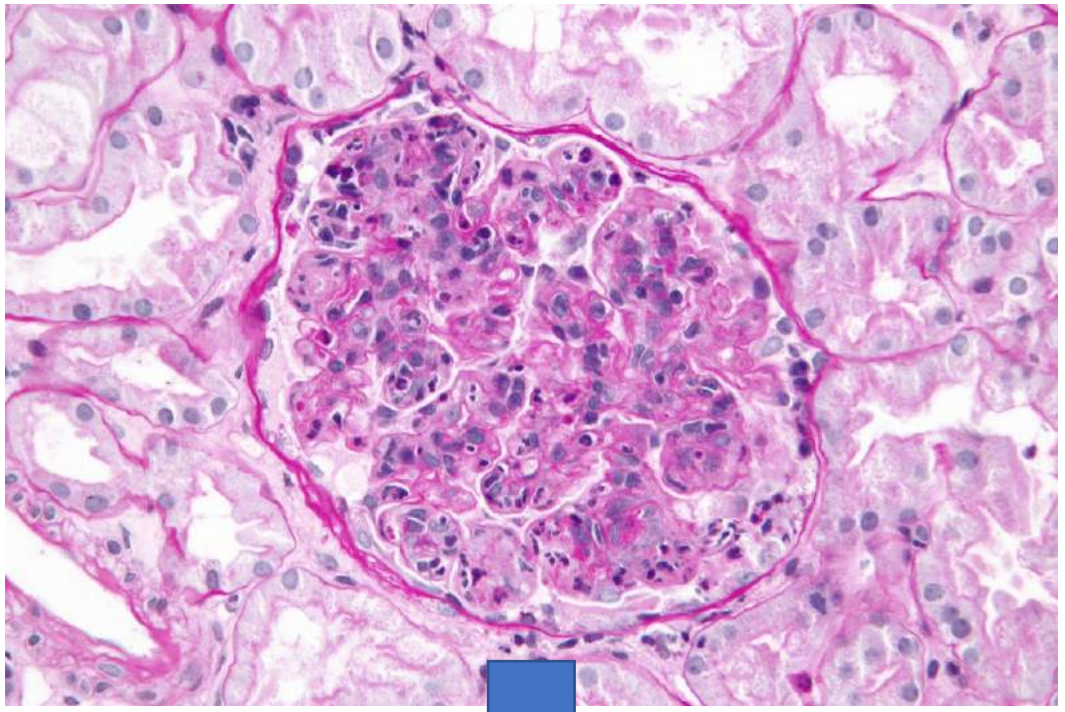

**Nephrotoxische Agens**

Autoantikörper Ein/wenige Ag
DSA Viele Ag

Immunkomplexe
C3, C4d

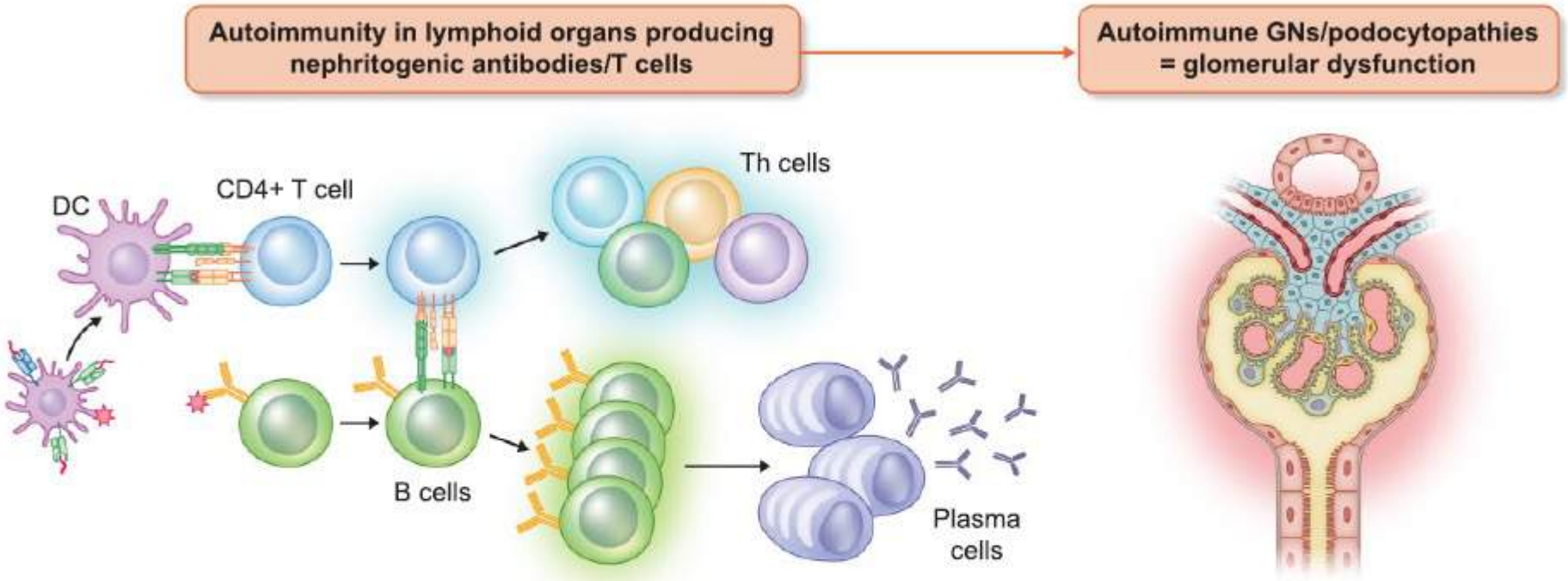
# Autoimmune GNs

| GN subtype | Underlying cause |
|---|---|
| **Autoimmune GN** | |
| IgA nephropathy | Anti-Gd IgA1 |
| Cryglobulinaemia | Cryoglobulins, RF |
| ANCA vasculitis (GPA)<br>ANCA vasculitis (MPA) | Cytoplasmic ANCAs, anti-PR3<br>Perinuclear ANCAs, anti-MPO |
| C3GN | Anti-C3, anti-C4, anti-C5, anti-factor B, anti-factor H |
| Lupus nephritis | Anti-dsDNA, anti-histone |
| Anti-GBM disease | Anti-type IV collagen α3 chain |
| Steroid-sensitive nephrotic syndrome | Anti-nephrin |
| Primary membranous GN | Anti-PLA2R, anti-TSHD7A, anti-semaphorin 3B, anti-PCDH7, anti-HTRA1, anti-contactin 1, anti-netrin G1, anti-NELL1 |
| **Alloimmune GN** | |
| Transplant glomerulopathy | Transplantation of cells or organ from a donor |



Kortison
RTX, MMF, et al.
Avacopan

# Auto-/Alloimmune GNs




| | | | | | | |
|---|---|---|---|---|---|---|
| **Antigen** | IgA, IgG | Neutrophils | Complement | Chromatin | GBM | Podocytes |
| **Antigen compartment** | Blood | Blood | Blood, cells | Ubiquitous | GBM | Glomerulus extracapillary |
| **Clinical presentation** | Vasculitis IC-GN | Vasculitis | TMA, C3GN | Vasculitis IC-GN | IC-GN | Nephrotic syndrome |

Romagnani, *et al*. NDT 2023

# Autoimmune GNs

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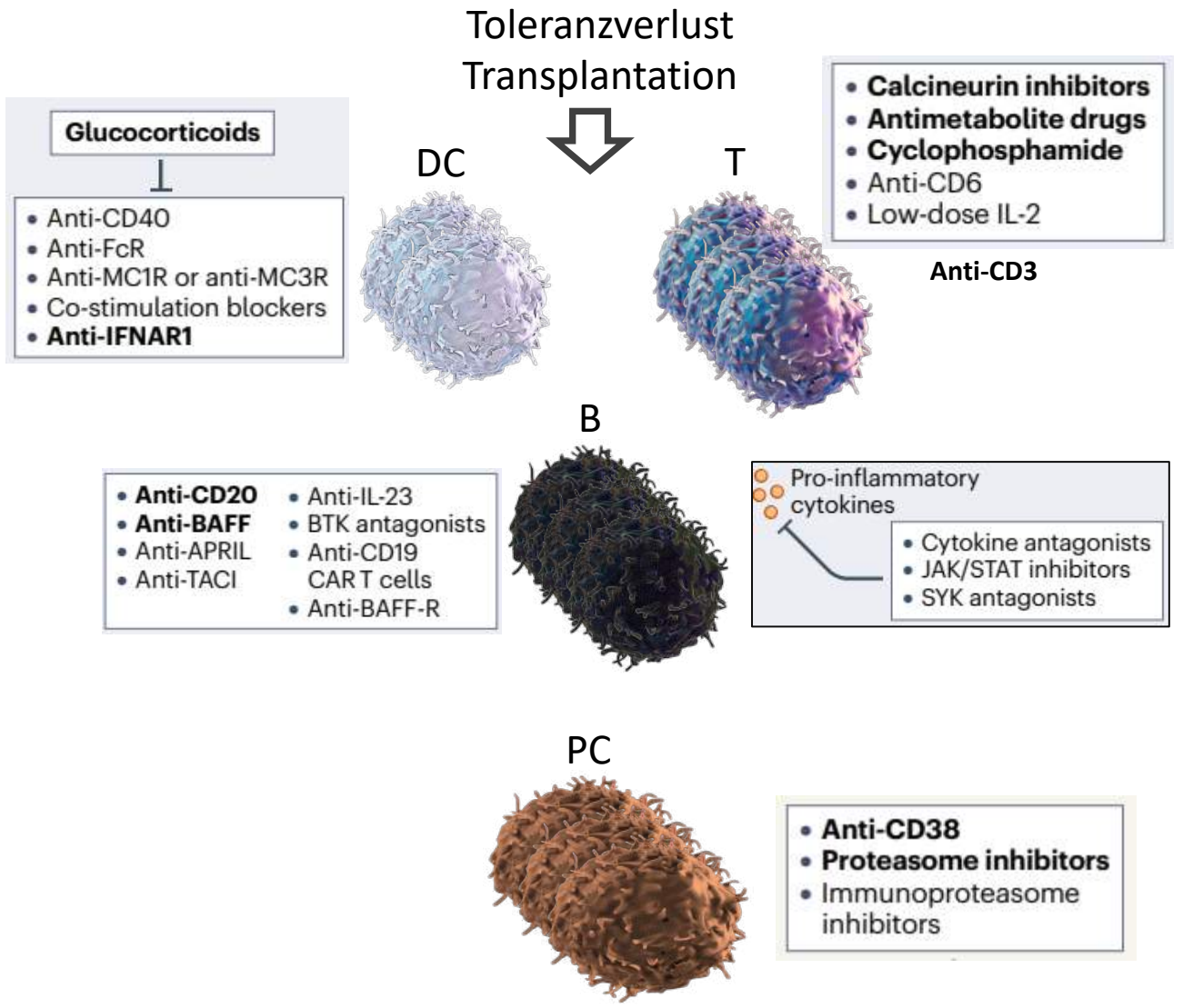
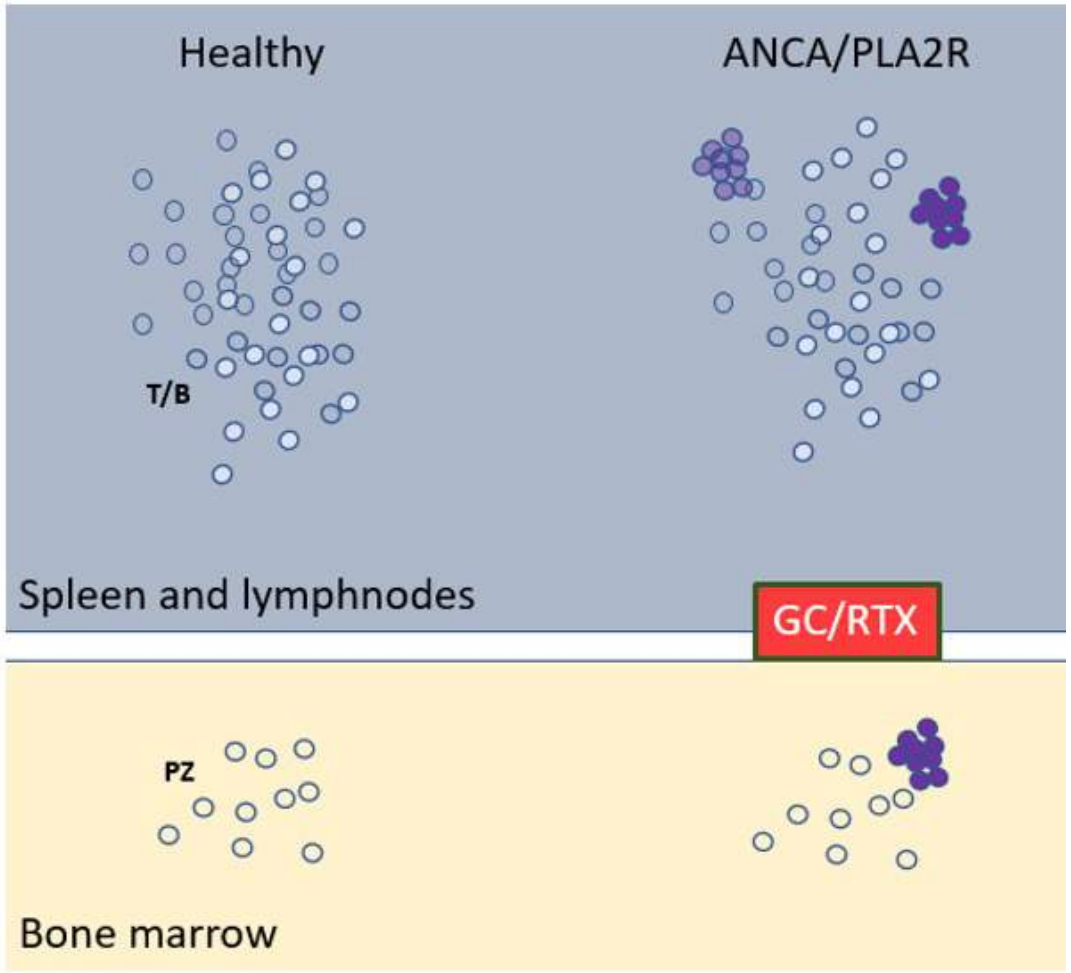


# GNs: Auto-/alloreaktive Lymphozytenklone produzieren das nephrotoxische Agens




Parodis, … Anders HJ. Autoimmun Rev 2023

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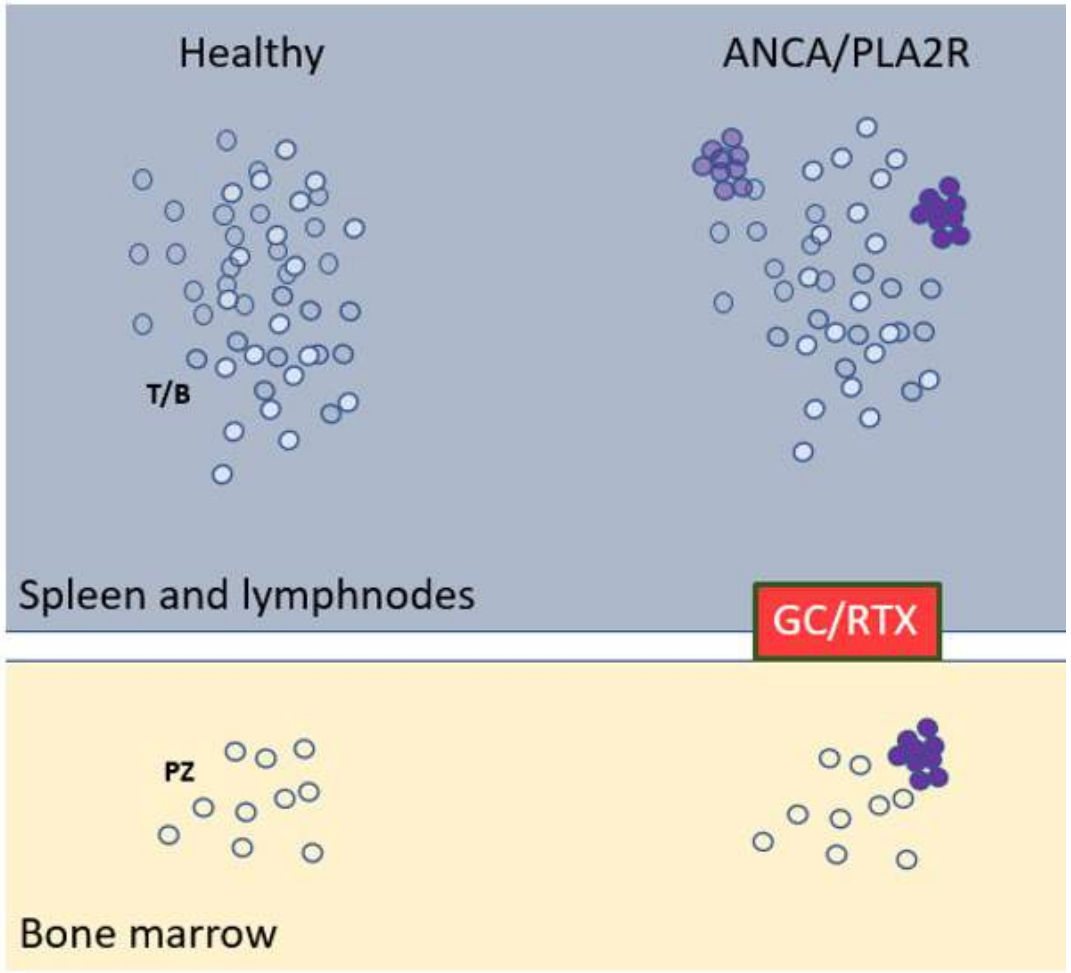


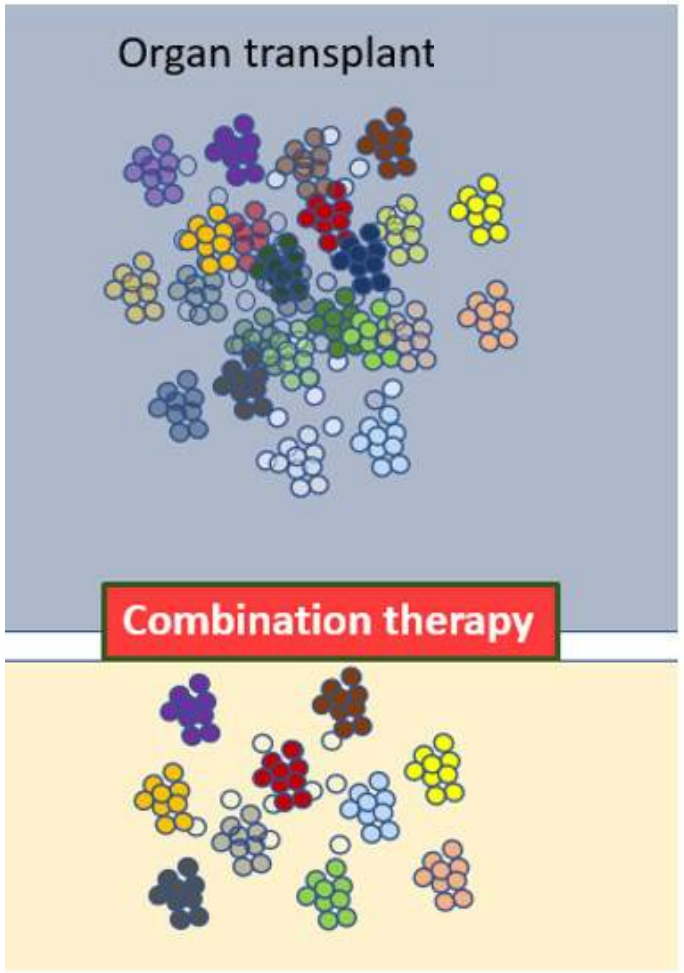


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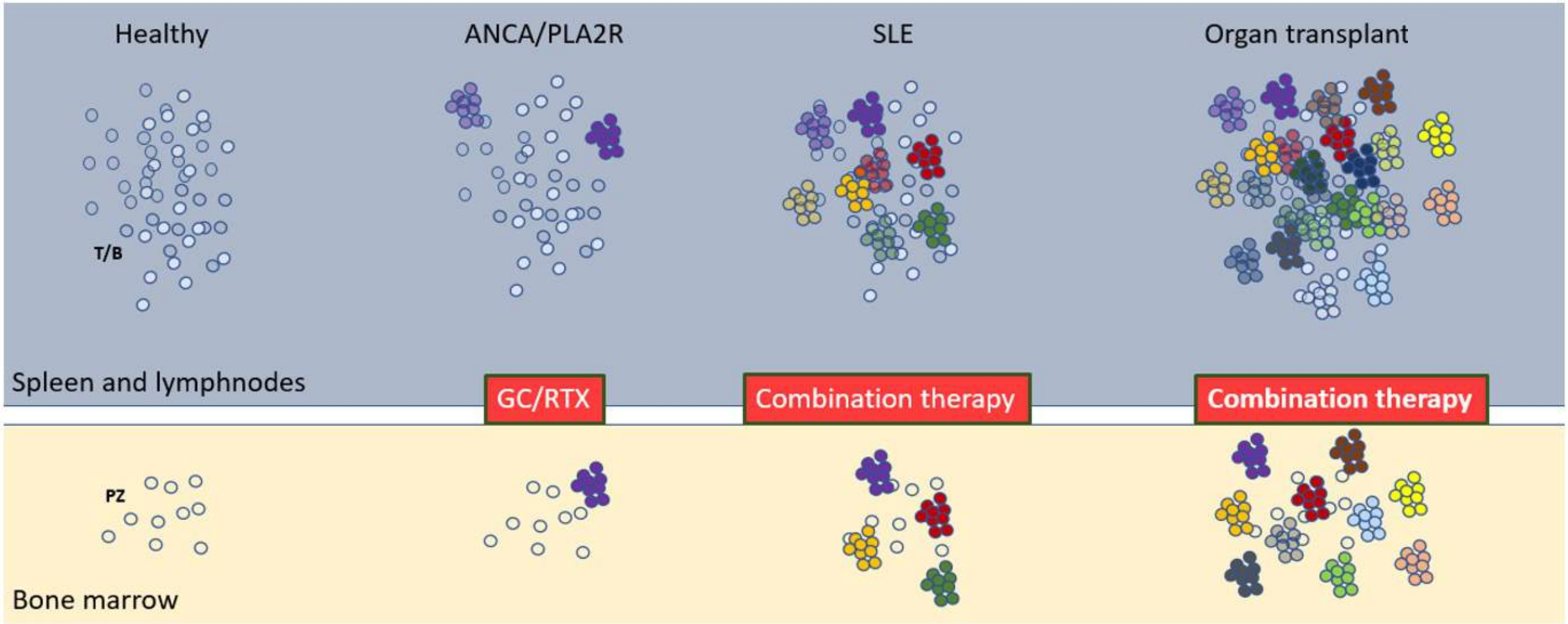


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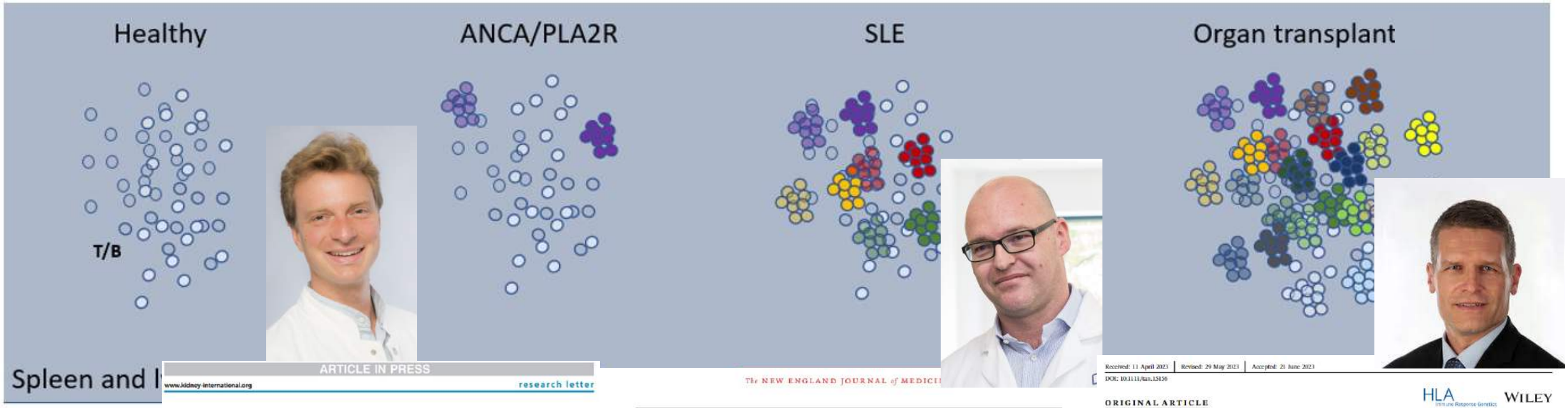








ARTICLE IN PRESS

www.kidney-international.org research letter

**An antigen-specific chimeric autoantibody receptor NK cell strategy for the elimination of anti-PLA2R1 and anti-THSD7A antibody-secreting cells**

OPEN

Larissa Seifert[1,2,6], Kristoffer Riecken[3,6], Gunther Zahner[1,2], Julia Hambach[4], Julia Hagenstein[1,2], Gudrun Dubberke[4], Tobias B. Huber[1,3,5], Friedrich Koch-Nolte[4], Boris Fehse[3,5] and Nicola M. Tomas[1,2,5]

[1]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Hamburg Center for Kidney Health, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Research Department Cell and Gene Therapy, Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]Institute of Immunology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; and [5]Hamburg Center for Translational Immunology (HCTI), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Kidney International (2024) ■, ■–■; https://doi.org/10.1016/j.kint.2024.01.021

KEYWORDS: ■ ■ ■



Membranous nephropathy (MN) is an antibody-mediated disease of the kidney, typically resulting in nephrotic syndrome with urinary loss of high amounts of albumin and other plasma proteins. Phospholipase A2 receptor 1 (PLA2R1) and thrombospondin type-1

The NEW ENGLAND JOURNAL of MEDICI

CORRESPONDENCE

**CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus**

Received: 11 April 2023 | Revised: 29 May 2023 | Accepted: 21 June 2023

DOI: 10.1111/tan.15136

ORIGINAL ARTICLE

HLA Immune Response Genetics WILEY

**Chimeric HLA antibody receptor T cells for targeted therapy of antibody-mediated rejection in transplantation**

Sergi Betriu[1] | Jordi Rovira[2,3] | Carolt Arana[2,4] | Ainhoa García-Busquets[2] | Marina Matilla-Martinez[2] | Maria J. Ramirez-Bajo[2,3] | Elisenda Bañon-Maneus[2,3] | Marta Lazo-Rodriguez[2] | Ariadna Bartoló-Ibars[1] | Frans H. J. Claas[5] | Arend Mulder[5] | Sebastiaan Heidt[5] | Manel Juan[1] | Beatriu Bayés-Genís[2,4] | Josep M. Campistol[2,4] | Eduard Palou[1] | Fritz Diekmann[2,3,4]

# Infektion-assoziierte GNs

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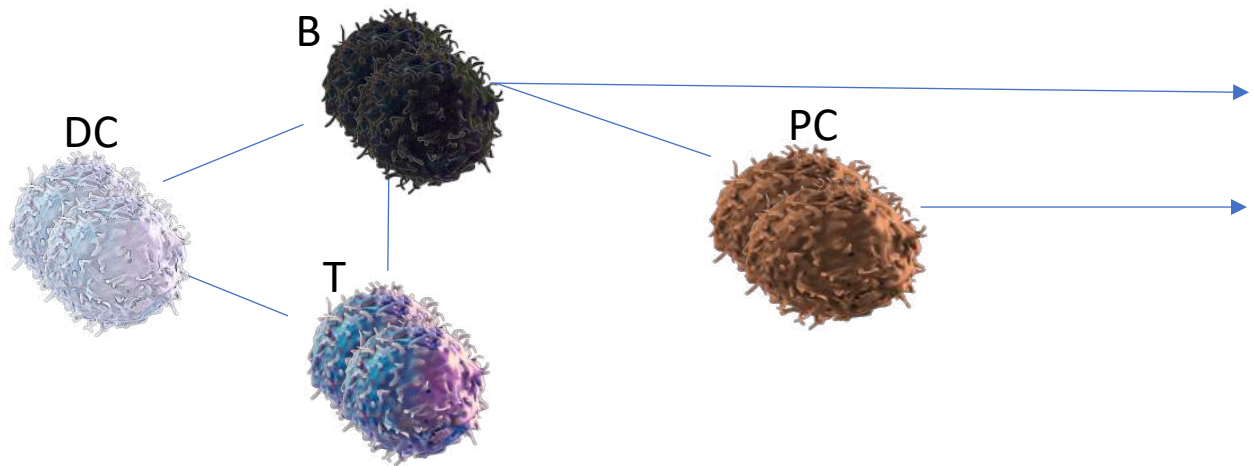
Bakterielle Infektion



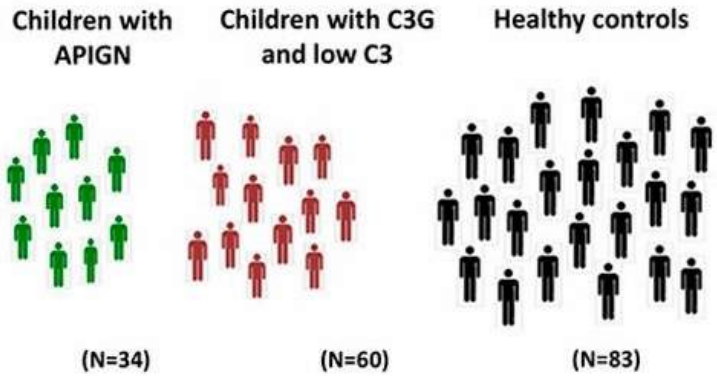

**Nephrotoxische Agens**

Niedrig-affine IgM
Hoch-affine IgG
IgA bei Schleimhautinfektionen
Immunkomplexe
C3, C4d

# Auto-/Alloimmune GNs

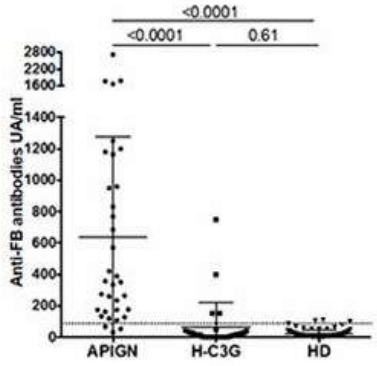
## Anti-Factor B antibodies in acute post infectious glomerulonephritis in children

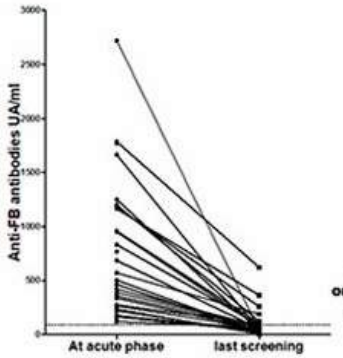
### METHODS

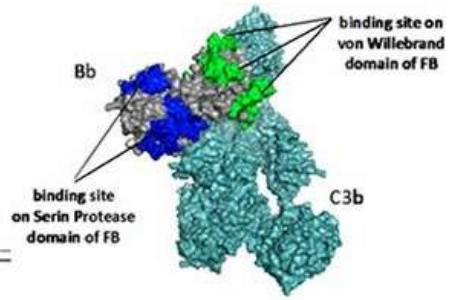



1-Study of complement biomarkers
2-Screening for complement antibodies at acute phase and follow up.
3-Complement genetic screening

### RESULTS



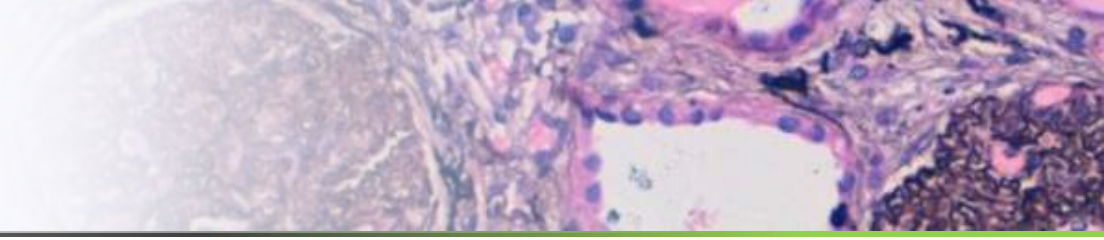

-Transient anti-Factor B antibodies are found in 91% of patients with APIGN and are specific of APIGN compare to C3G (14%)
-Anti-FB antibodies recognized area of FB involved in C3b binding (Von Willebrand domain) and in enzymatic activity (Serine protease domain).

### CONCLUSION

Anti-FB antibodies contribute to complement activation in APIGN and allow distinguishing typical APIGN from C3G at acute phase.

*JASN* 31(4):p 829-840, April 2020. | *DOI:* 10.1681/ASN.2019080851

# Wie GNs brauchbar klassifizieren?



## GN-A/C

| Typ der GN | Aktivität | Chronizität |
|---|---|---|
| Infektion: Erreger | | |
| Autoimmun: Antigen oder Systemkrankheit | | |
| Alloimmun: Transplantat | | |
| Autoinflammation: Mutation | | |
| Monoklonal Gammopathie: B Zell oder PZ Klon | | |

Romagnani, *et al*. NDT 2023

# Wie GNs brauchbar klassifizieren?

| Components of the activity index | Score | Calculating the activity score<br>Extent of lesion | Points |
|---|---|---|---|
| • Endocapillary hypercellularity | 0–3 | Not present | 0 |
| • Neutrophils and/or karyorrhexis | 0–3 | Present in <25% | 1 |
| • Fibrinoid necrosis | (0–3) × 2 | Present in 25%–50% | 2 |
| • Hyaline deposits (wire loop and/or hyaline thrombi) | 0–3 | Present in >50% | 3 |
| • Cellular/fibrocellular crescents | (0–3) × 2 | | |
| • Interstitial inflammation (interstitial leukocytes) | 0–3 | | |
| | **Total: 0–24** | | |
| **Items included into the NIH chronicity score** | **Score** | **Calculating the chronicity score**<br>**Extent of lesion** | **Points** |
| • Total glomerulosclerosis (global + segmental) | 0–3 | Present in <10% | 0 |
| • Fibrous crescents | 0–3 | Present in 10%–25% | 1 |
| • Interstitial fibrosis | 0–3 | Present in 25%–50% | 2 |
| • Tubular atrophy | 0–3 | Present in >50% | 3 |
| | **Total: 0–12** | | |
| **Other histologic findings not included in the activity or chronicity score** | | | |

Austin, Kidney Int 1984 Weening, JASN 2003 KDIGO 2021

# Wie GNs brauchbar klassifizieren?

## GN-A/C

| Typ der GN | Aktivität | Chronizität |
|---|---|---|
| Infektion: Erreger | 0 | |
| Autoimmun: Antigen oder Systemkrankheit | 1 Gering | |
| Alloimmun: Transplantat | 2 Moderat | |
| Autoinflammation: Mutation | 3 Hoch | |
| Monoklonal Gammopathie: B Zell oder PZ Klon | Serum Biomarker, +/- NS, Aktivität in der Nierenbiopsie | |

Romagnani, *et al*. NDT 2023

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## GN-A/C

| Typ der GN | Aktivität | Chronizität |
|---|---|---|
| Infektion: Erreger | 0 | 0 |
| Autoimmun: Antigen oder Systemkrankheit | 1 Gering | 1 Früh |
| Alloimmun: Transplantat | 2 Moderat | 2 Spät |
| Autoinflammation: Mutation | 3 Hoch | 3 Nierenversagen |
| Monoklonal Gammopathie: B Zell oder PZ Klon | Serum Biomarker, +/- NS, Aktivität in der Nierenbiopsie | CKD G1-3 A1-3 Sklerose + IFTA in der Nierenbiopsie |

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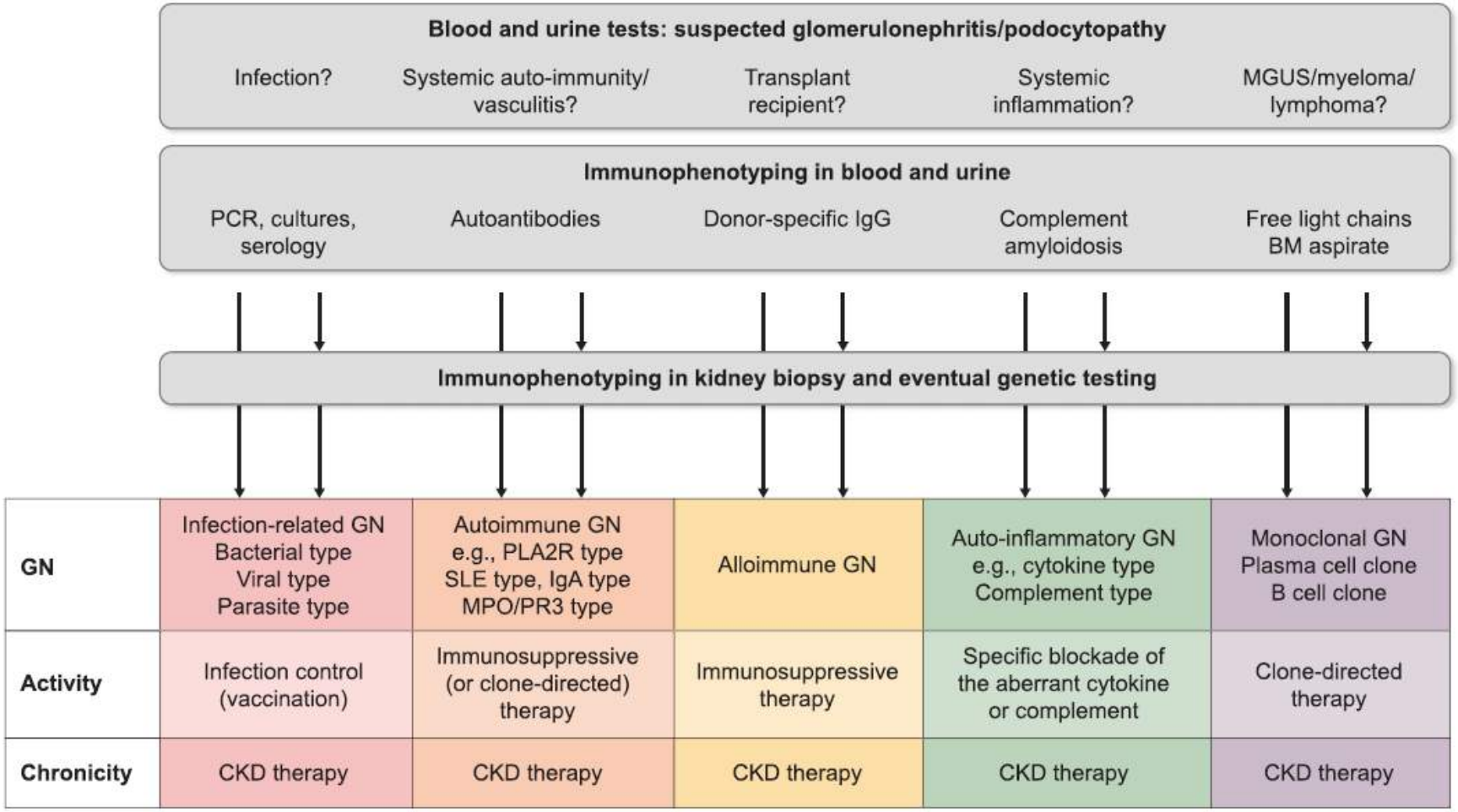
# Zusammenfassung GN-A/C Klassifikation




| | | | | | |
|---|---|---|---|---|---|
| **GN** | Infection-related GN<br>Bacterial type<br>Viral type<br>Parasite type | Autoimmune GN<br>e.g., PLA2R type<br>SLE type, IgA type<br>MPO/PR3 type | Alloimmune GN | Auto-inflammatory GN<br>e.g., cytokine type<br>Complement type | Monoclonal GN<br>Plasma cell clone<br>B cell clone |
| **Activity** | Infection control (vaccination) | Immunosuppressive (or clone-directed) therapy | Immunosuppressive therapy | Specific blockade of the aberrant cytokine or complement | Clone-directed therapy |
| **Chronicity** | CKD therapy | CKD therapy | CKD therapy | CKD therapy | CKD therapy |

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Nephrol Dial Transplant; 2023, Nov 8

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