



Physiopathology of rheumatic heart valve diseases

Romain CAPOULADE, PhD

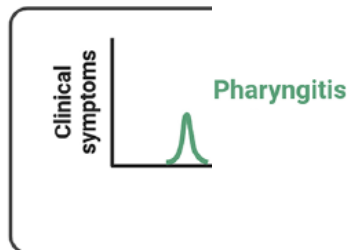
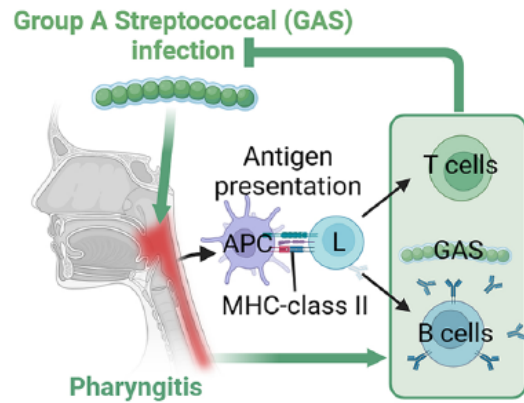
EuroValve 2025; September 26, 2025

CONFLICT OF INTEREST

➤ Nothing to declare

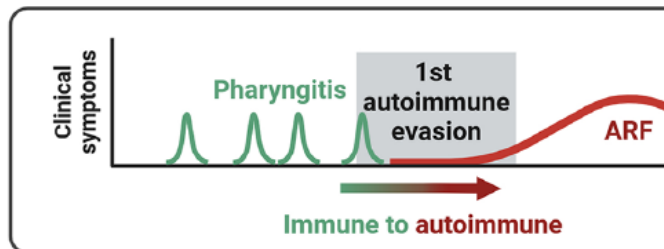
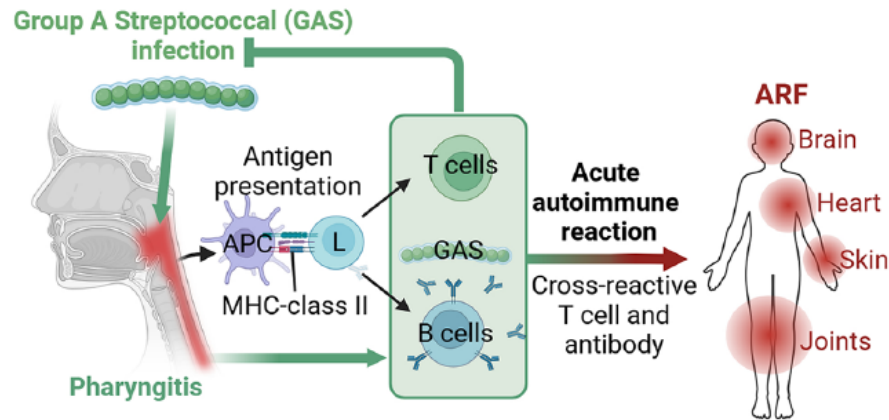
RHEUMATIC HEART VALVE DISEASES

NATURAL HISTORY



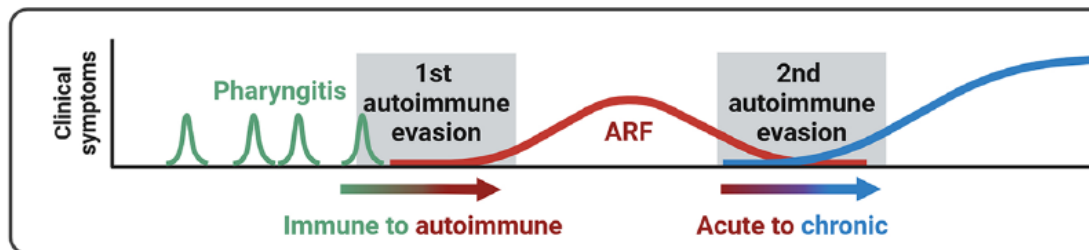
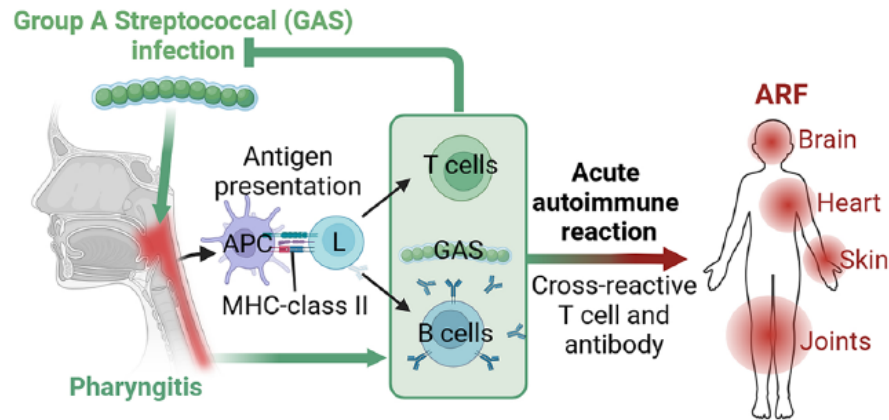
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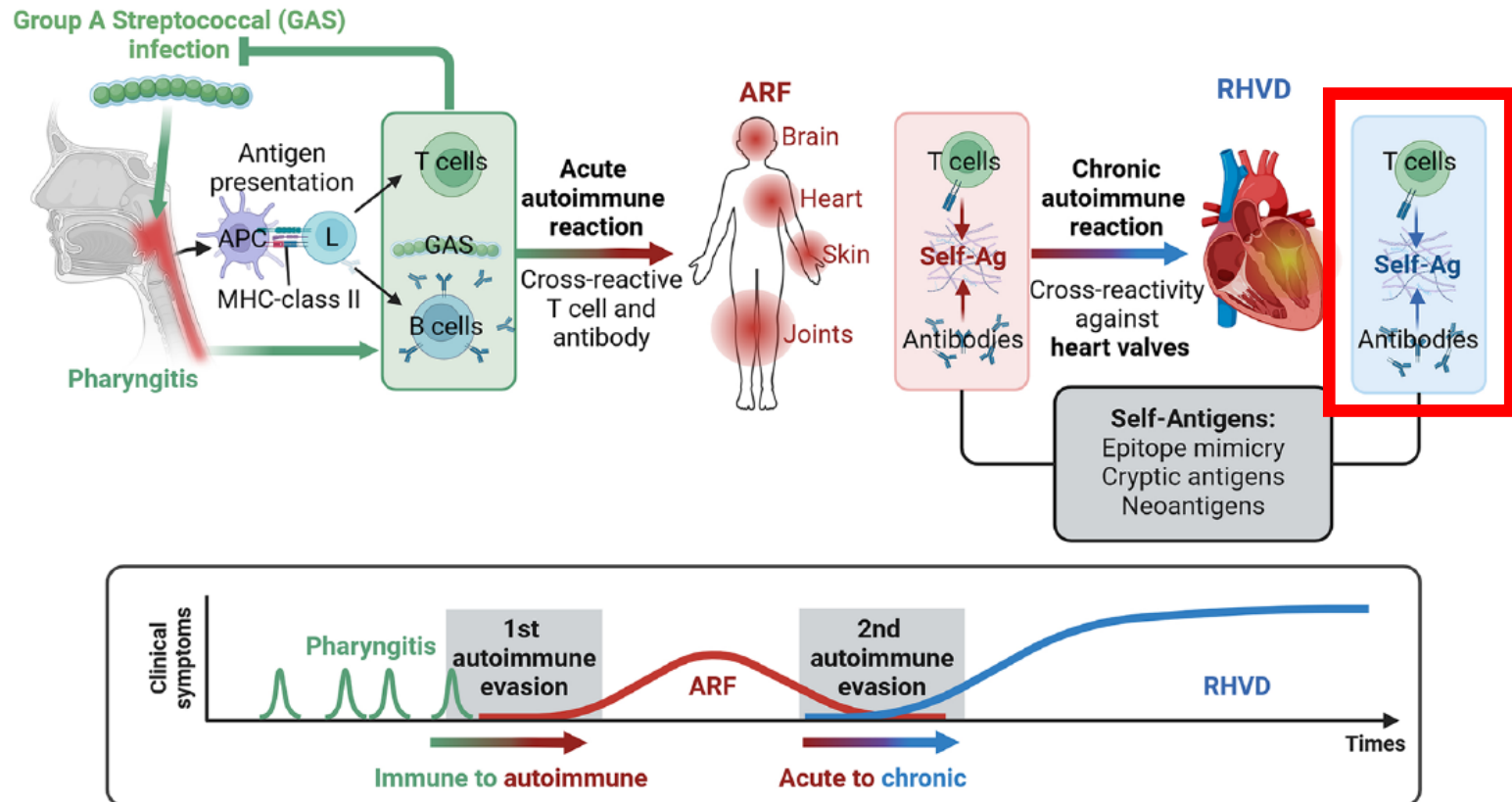
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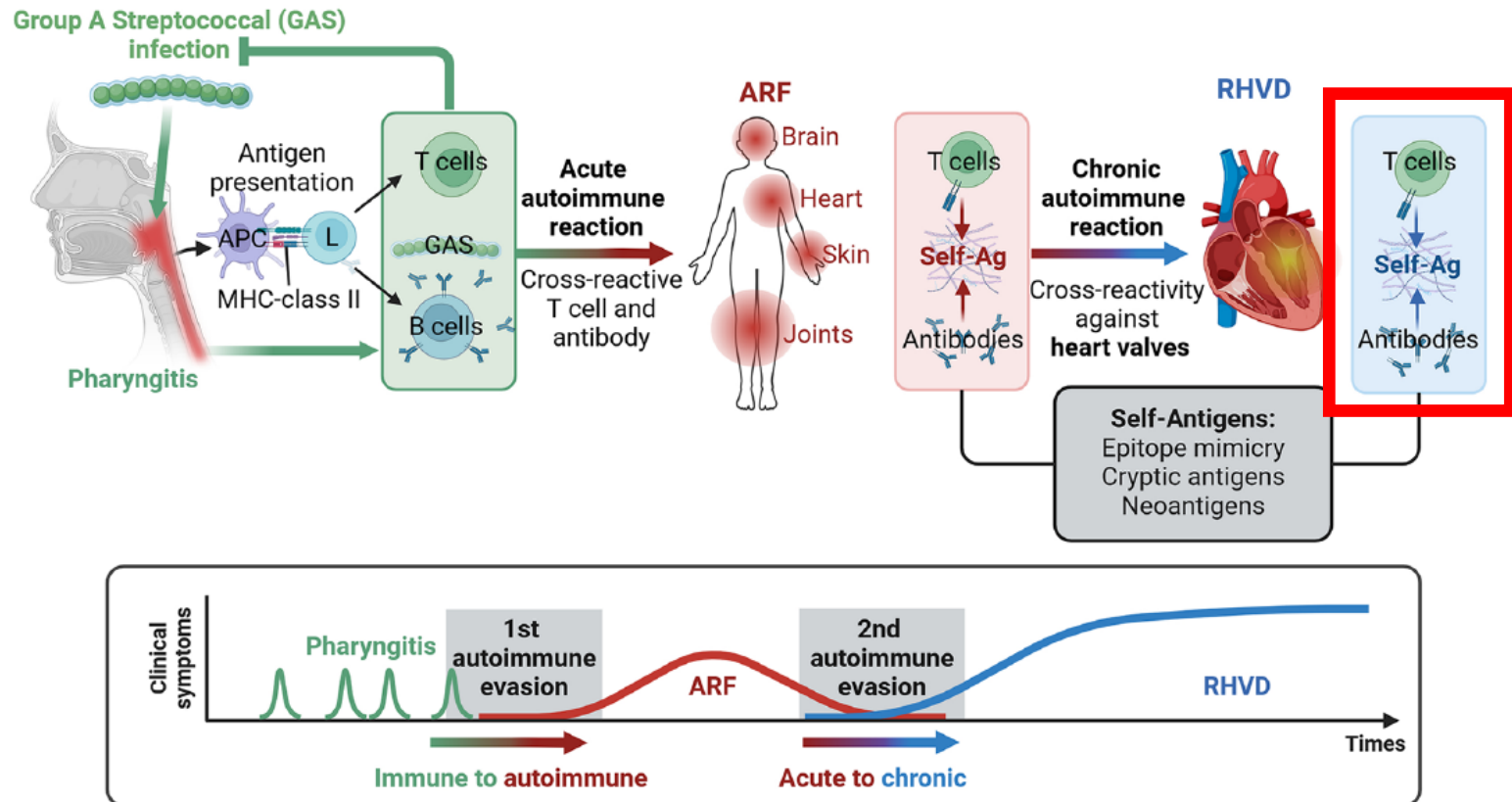
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RHEUMATIC HEART VALVE DISEASES

NATURAL HISTORY



**Symptomatic
infections**

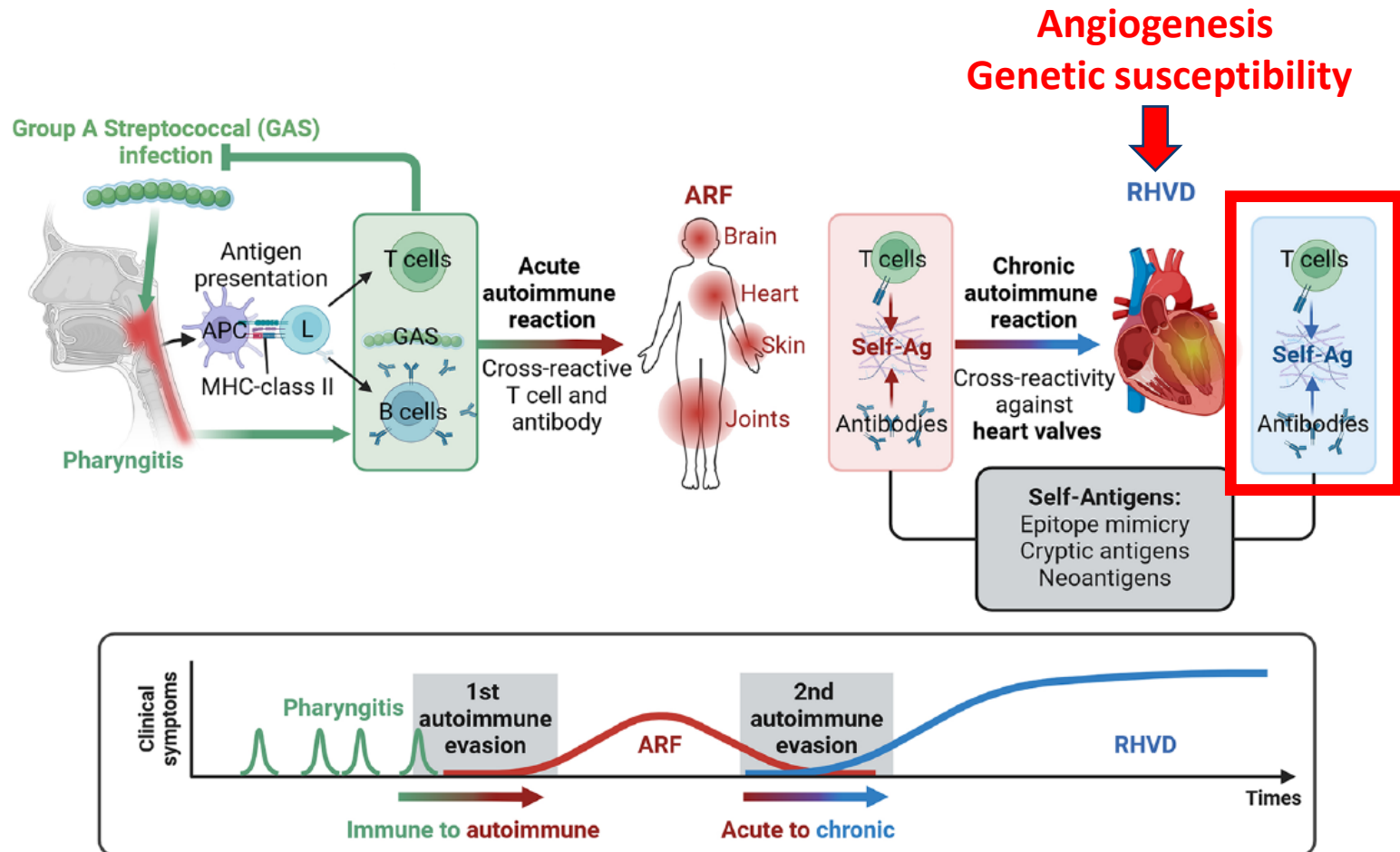
3-6%

**>40 million
affected with RHVD**

Lupieri et al., Front. Cardiovasc. Med. 2025;12:1537104
Carapetis et al., Lancet Infect Dis. 2005;5:685–94.
Dougherty et al., J Am Coll Cardiol. 2023;81:81–94.

RHEUMATIC HEART VALVE DISEASES

NATURAL HISTORY



**Symptomatic
infections**

3-6%

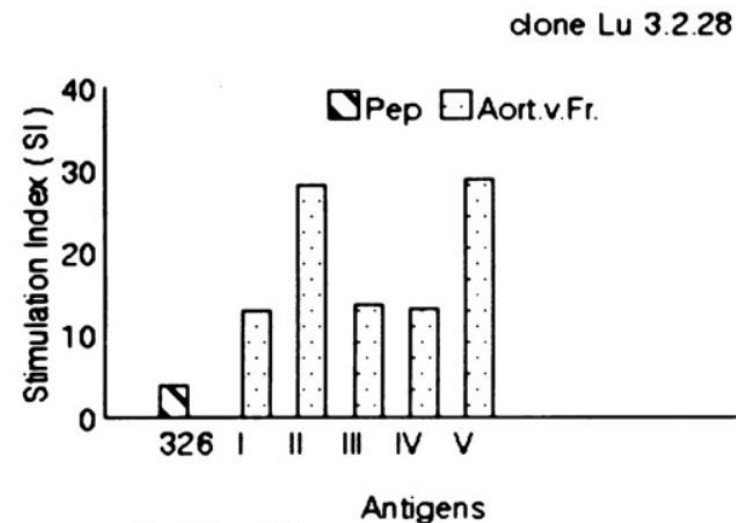
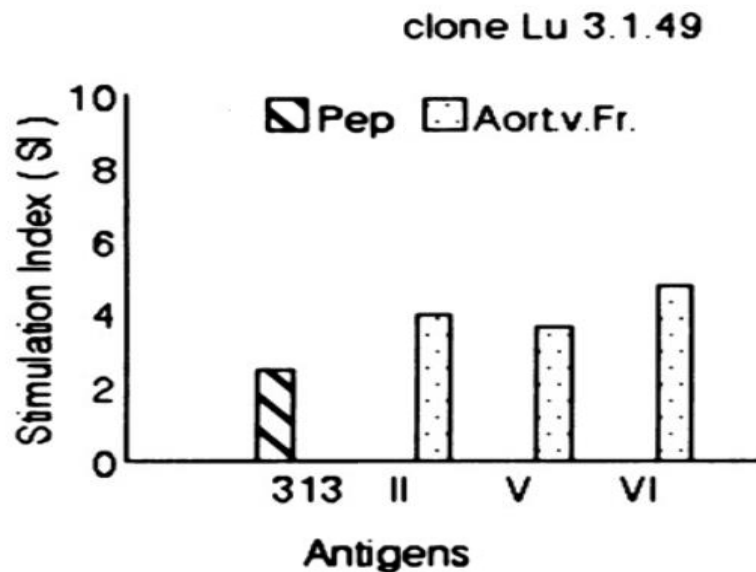
**>40 million
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Lupieri et al., Front. Cardiovasc. Med. 2025;12:1537104
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RHEUMATIC HEART VALVE DISEASES

MOLECULAR MIMICRY – CROSS-REACTIVITY

In vitro evidence of T cell cross-reactivity with both GAS-M protein and proteins from valve tissue



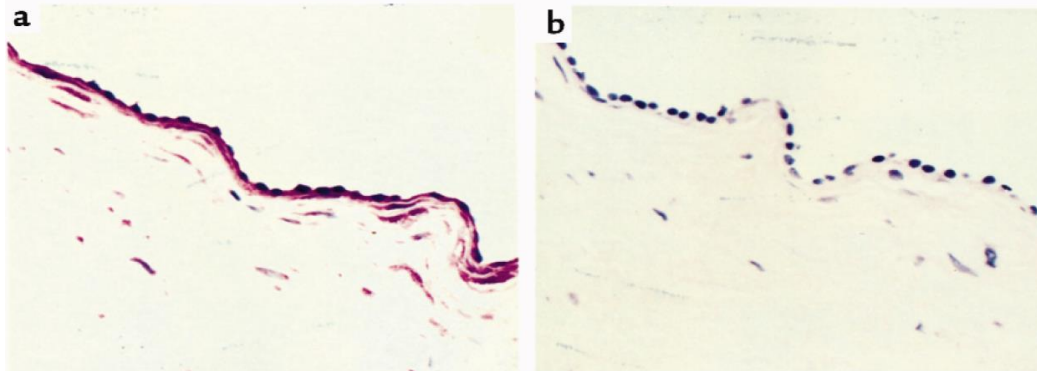
T cells from RHVD cross-reactivity with:

- recombinant **streptococcal M protein**
- fragments of **valve tissue**

RHEUMATIC HEART VALVE DISEASES

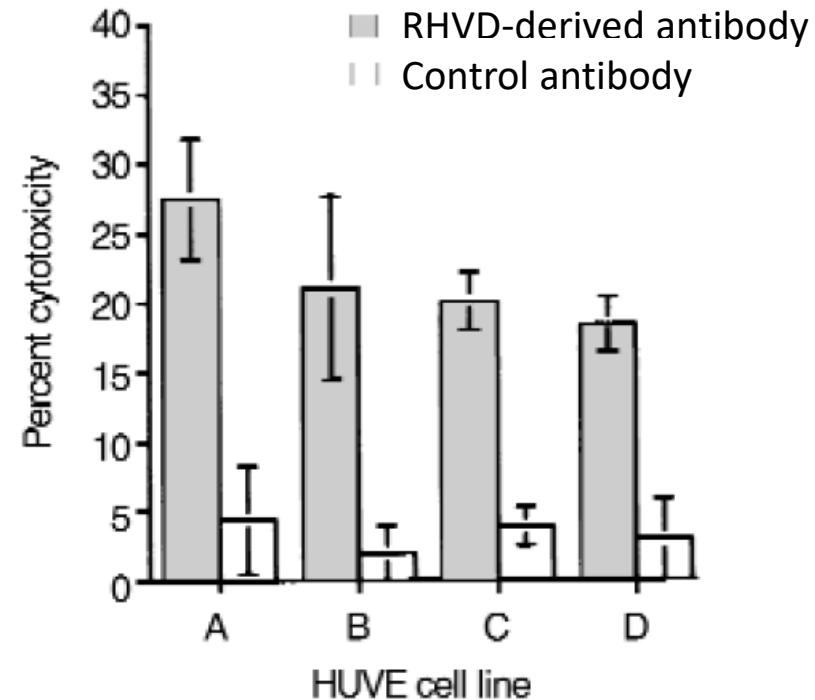
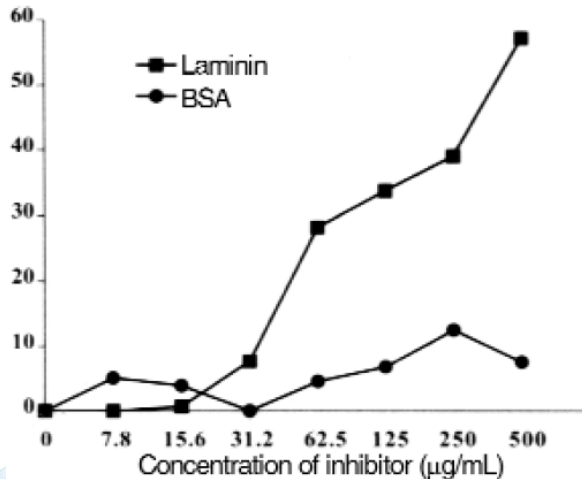
MOLECULAR MIMICRY – CROSS-REACTIVITY

RHVD-derived antibodies and valvular endothelial cells



RHVD-derived antibody

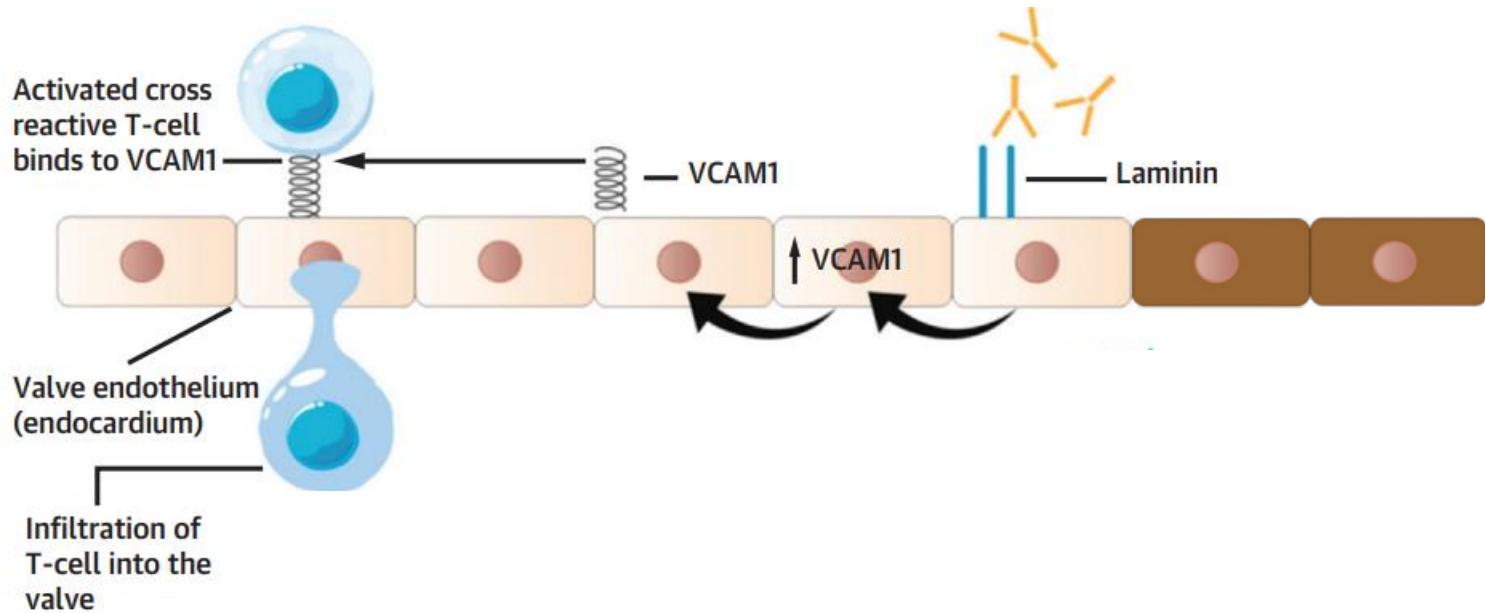
Control human IgM



Galvin et al., J Clin Invest. 2000;106(2):217-224

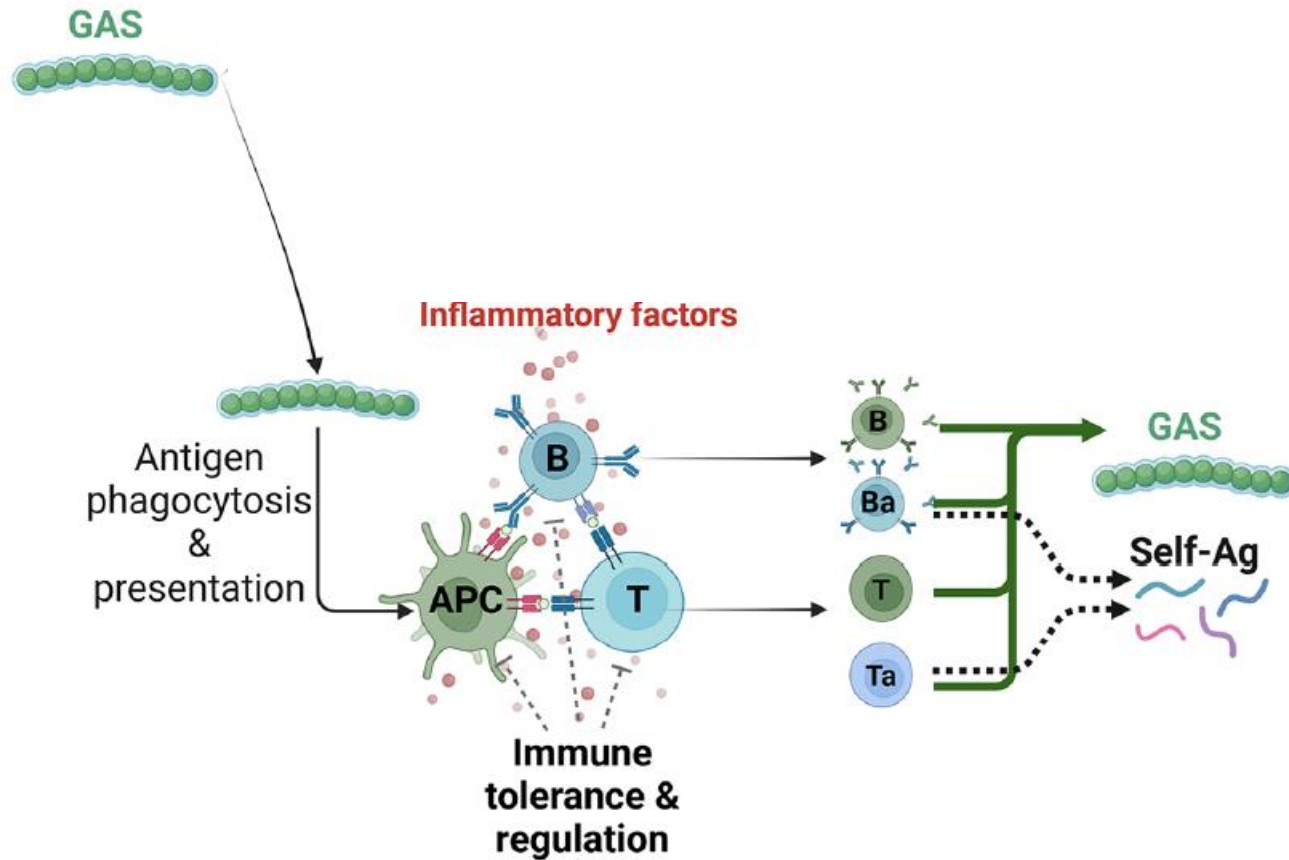
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MOLECULAR MIMICRY – CROSS-REACTIVITY



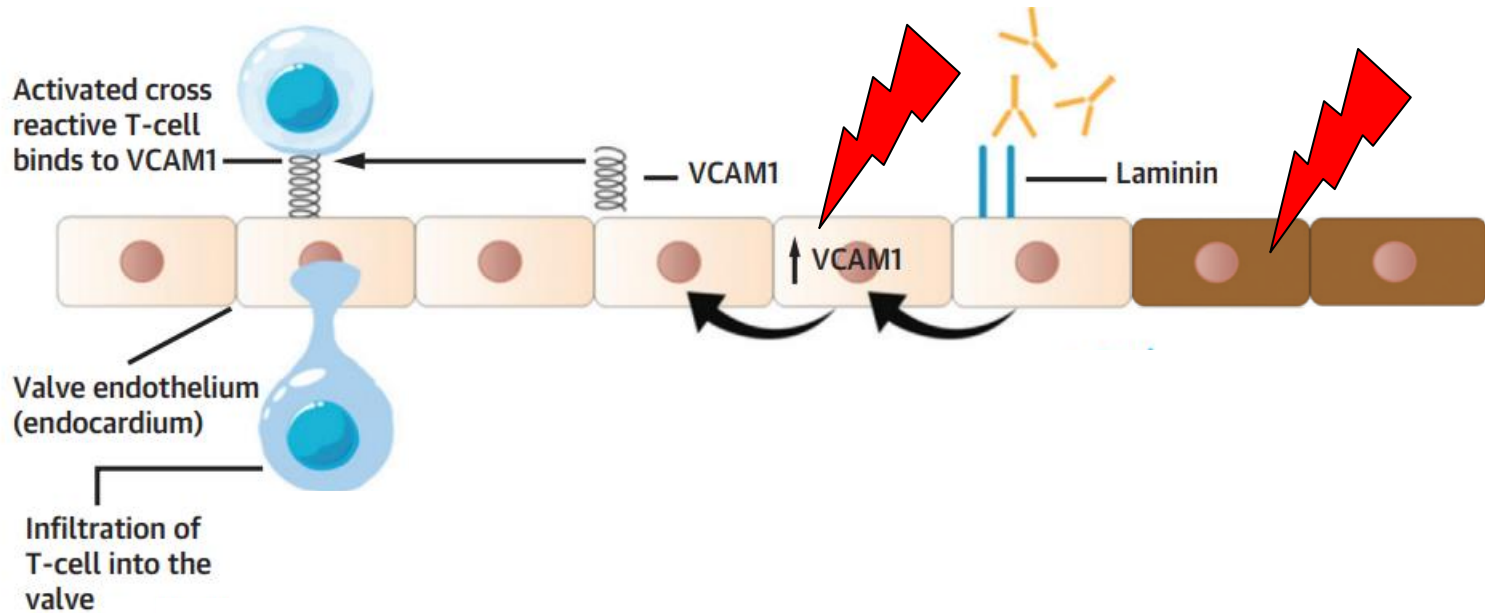
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MOLECULAR MIMICRY – CROSS-REACTIVITY



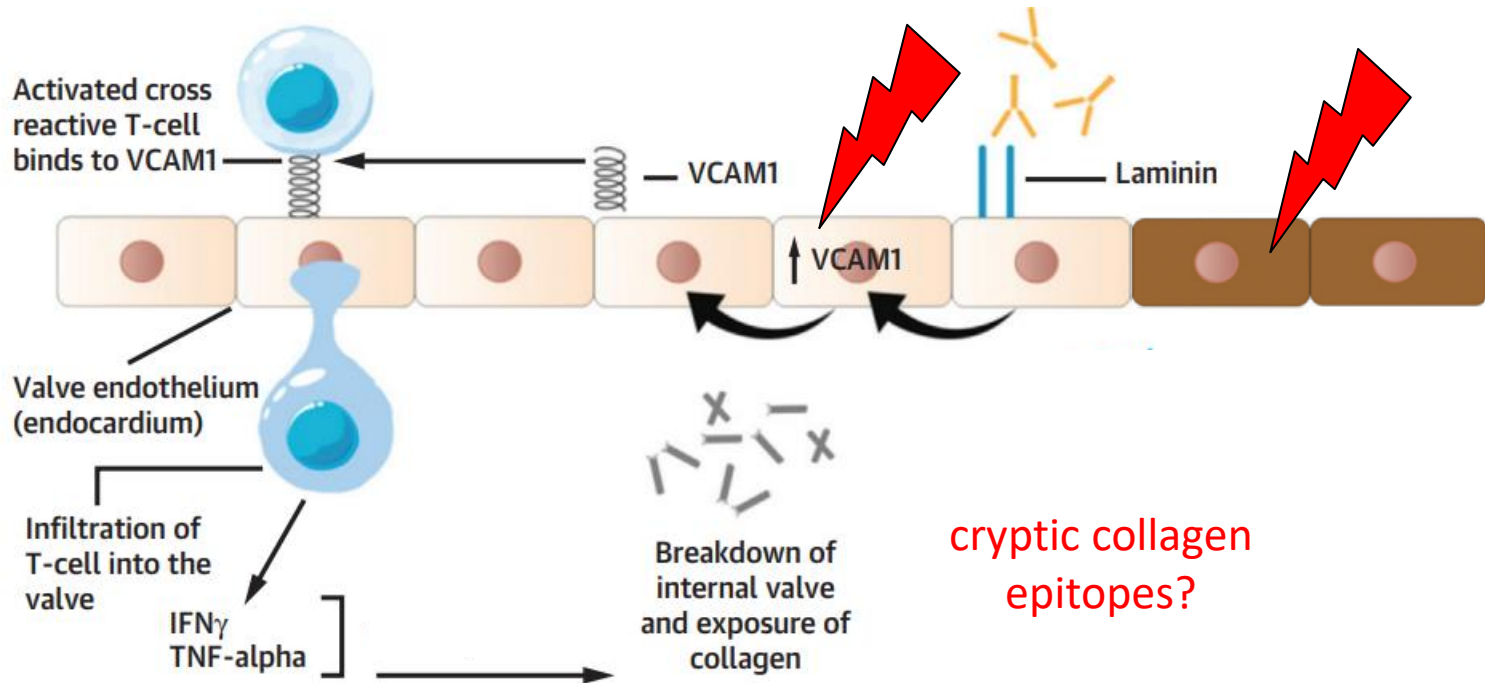
RHEUMATIC HEART VALVE DISEASES

MOLECULAR MIMICRY – CROSS-REACTIVITY



RHEUMATIC HEART VALVE DISEASES

MOLECULAR MIMICRY – CROSS-REACTIVITY



RHEUMATIC HEART VALVE DISEASES

MOLECULAR MIMICRY – CROSS-REACTIVITY

Non disease vs rheumatic MV proteome

Gene	UniProt	Description	q value
Human heart valve proteomes			NDMV vs RMVD
COL1A1	P02452	Collagen alpha-1(I) chain	0.085
COL3A1	P02461	Collagen alpha-1(III) chain	0.054
COL4A1	P02462	Collagen alpha-1(IV) chain	NS
COL6A1	P12109	Collagen alpha-1(VI) chain	0.035
COL12A1	Q99715	Collagen alpha-1(XII) chain	NS
COL14A1	Q05707	Collagen alpha-1(XIV) chain	NS
COL15A1	P39059	Collagen alpha-1(XV) chain	NS
COL16A1	Q07092	Collagen alpha-1(XVI) chain	NS
COL18A1	P39060	Collagen alpha-1(XVIII) chain	NS
COL5A2	P05997	Collagen alpha-2(V) chain	0.026
COL6A2	P12110	Collagen alpha-2(VI) chain	NS
COL6A6	A6NMZ7	Collagen alpha-6(VI) chain	NS
CTHRC1	Q96CG8	Collagen triple helix repeat-containing protein 1	0.084
COL1A2	A0A0S2Z3H5	Collagen type I alpha 2 isoform 1	0.076
COL4A2	A0A024RDW8	Collagen, type IV, alpha 2, isoform CRA_a	NS
COL5A1	A0A024R8E5	Collagen, type V, alpha 1, isoform CRA_a	NS
COL6A3	D9ZGF2	Collagen, type VI, alpha 3	0.084

Homologue epitope regions

Human heart COL1A1/COL1A2 vs *S. pyogenes* Collagen-like surface protein

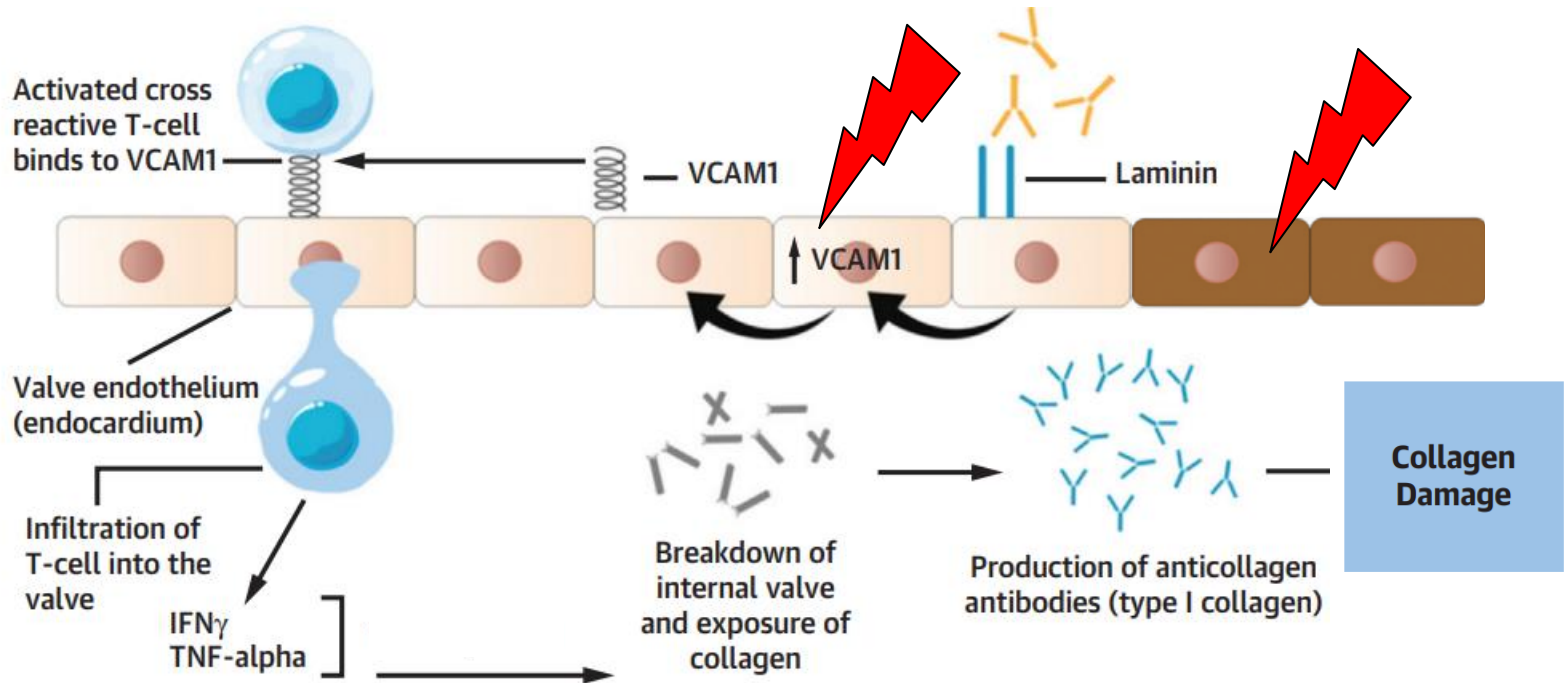
Epitope 6

<i>S. pyo</i>	GDRGETGAQGPVGPQGEKGETGAQGPAG
Hum	GERGRPGAGPAGARGNDGATGAAGPPG
	GERGRVGPAGPAGARGSDGSVGPVGPAG
	*: * * . * * * * : * . * . * * *

Passos et al., Circulation. 2022;145:531-548

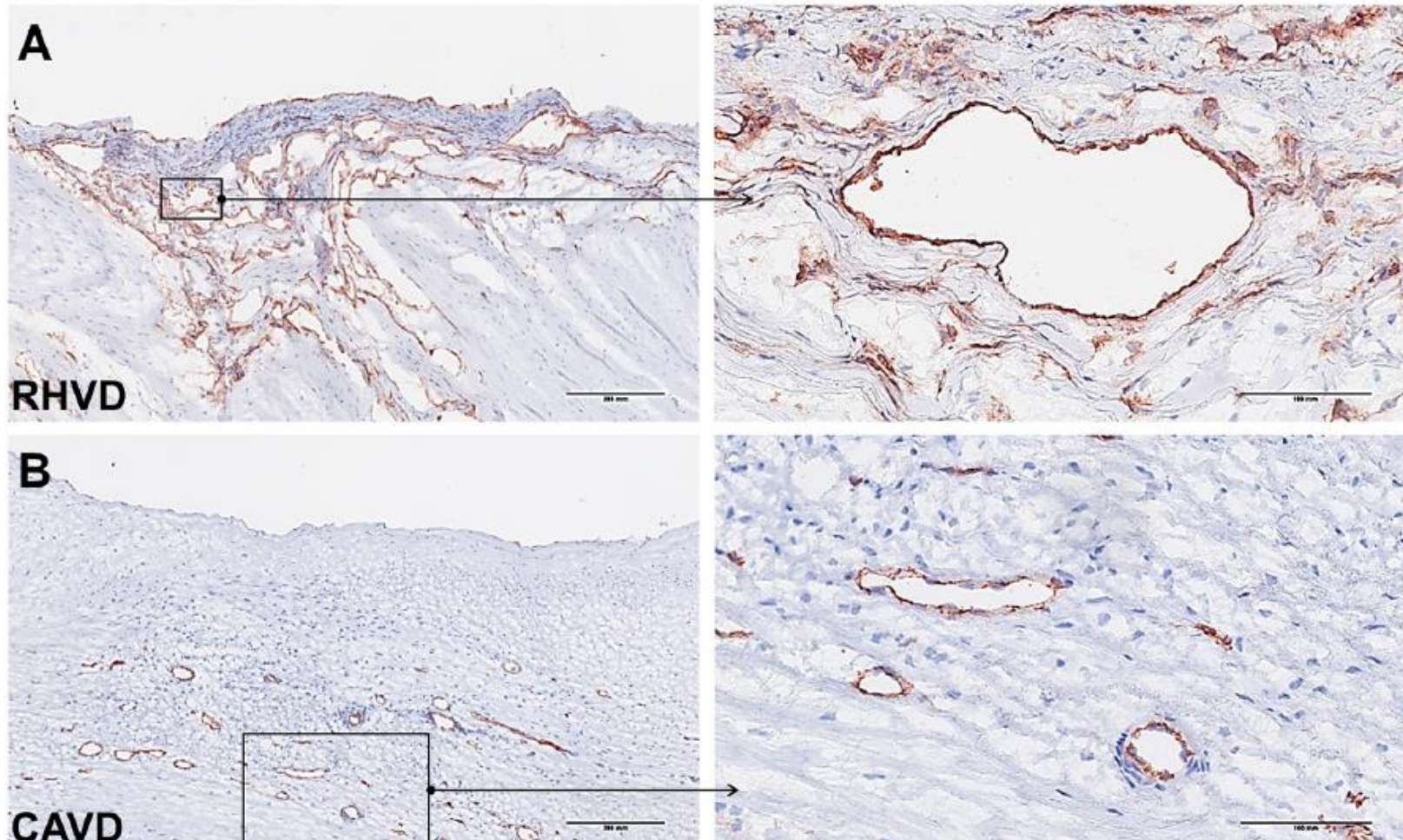
RHEUMATIC HEART VALVE DISEASES

MOLECULAR MIMICRY – CROSS-REACTIVITY



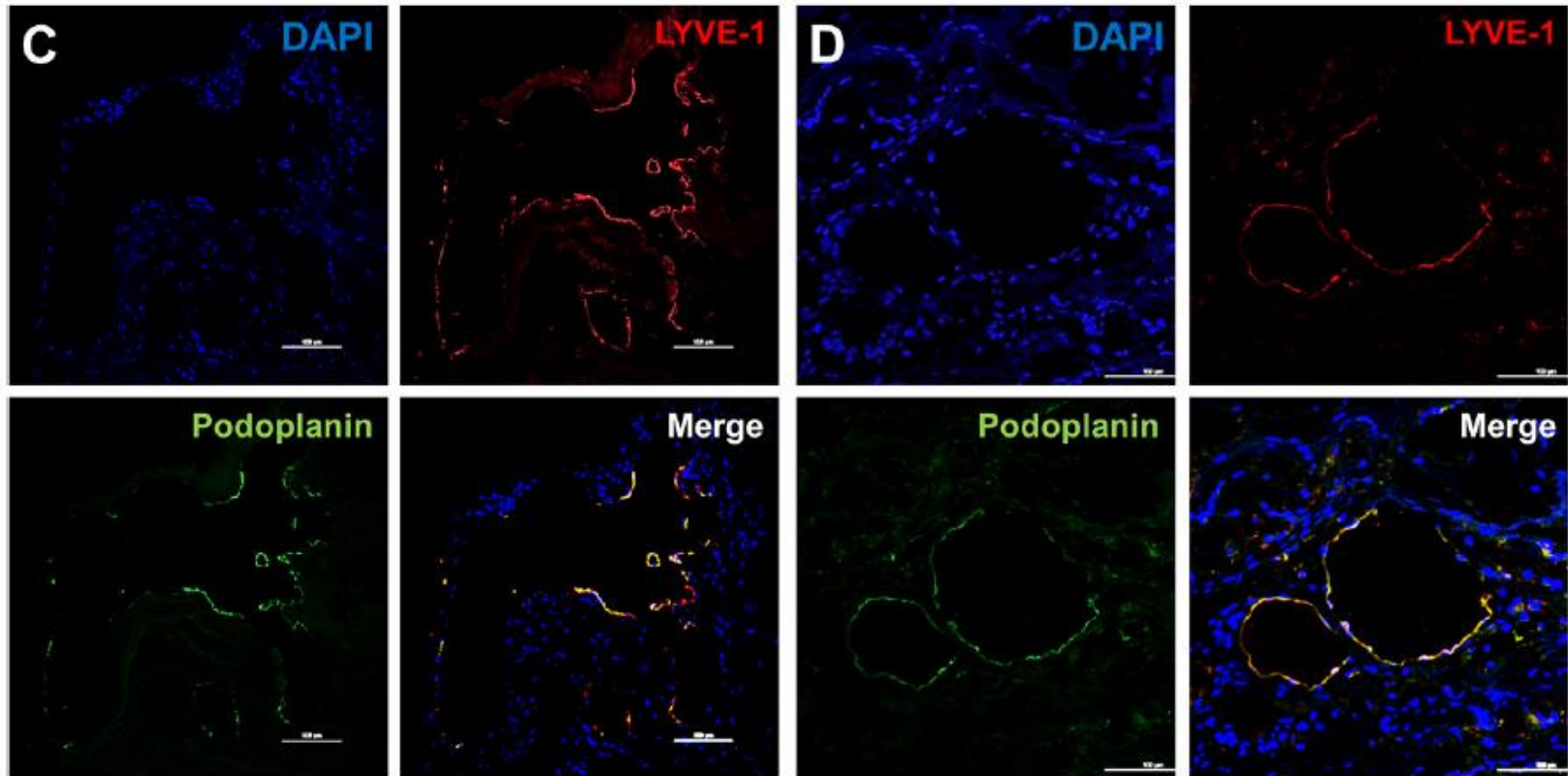
RHEUMATIC HEART VALVE DISEASES

NEO ANGIOGENESIS - LYMPHANGIOGENESIS



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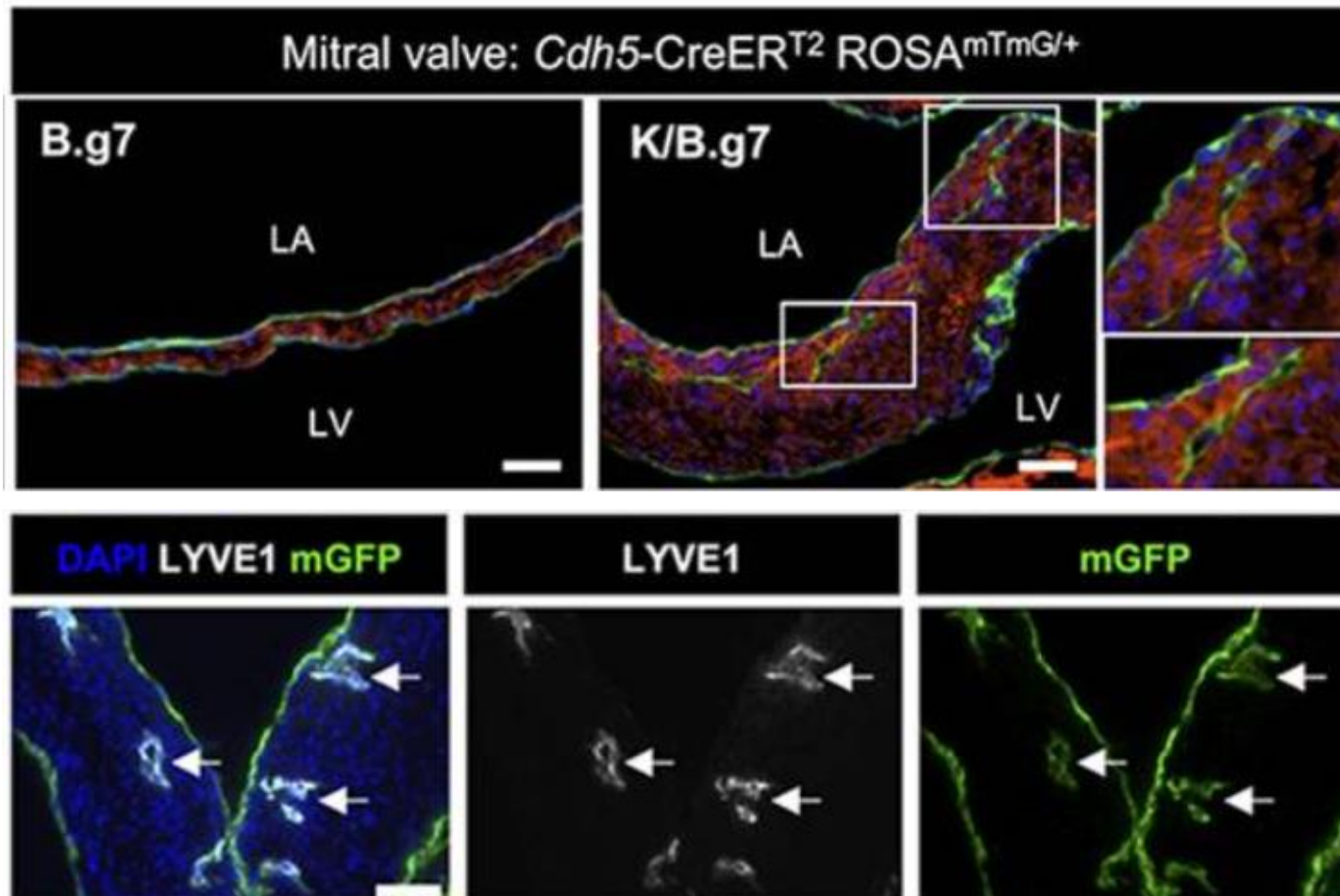


RHEUMATIC HEART VALVE DISEASES

NEO ANGIOGENESIS - LYMPHANGIOGENESIS



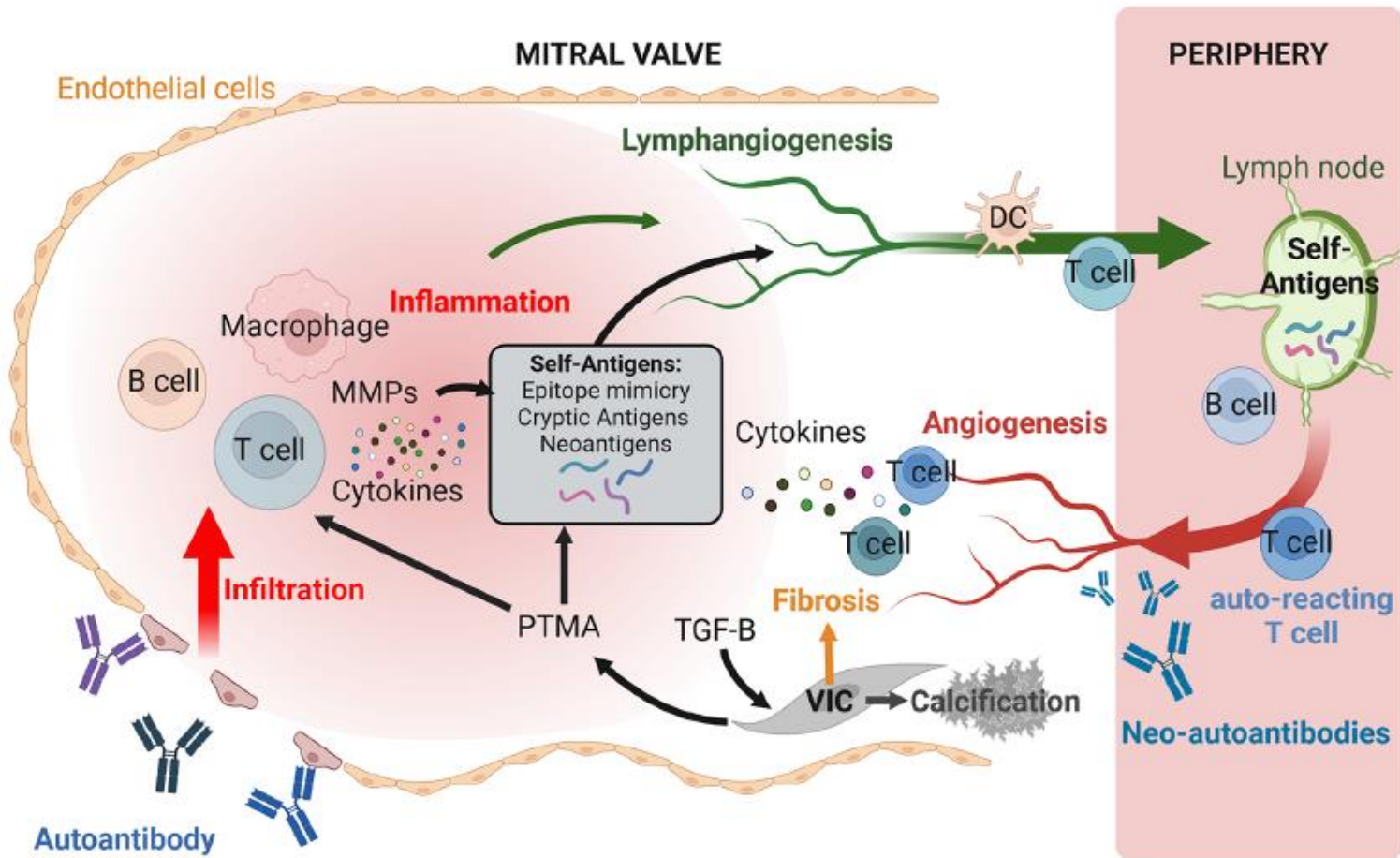
Endothelial cell lineage-tracing



Osinski et al. Arterioscler Thromb Vasc Biol. 2024;44:807-821

RHEUMATIC HEART VALVE DISEASES

MAIN MECHANISMS RELATED TO RHVD



RHEUMATIC HEART VALVE DISEASES

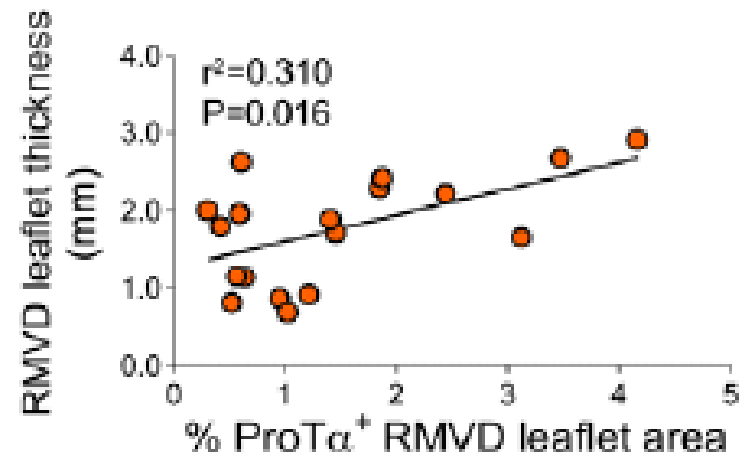
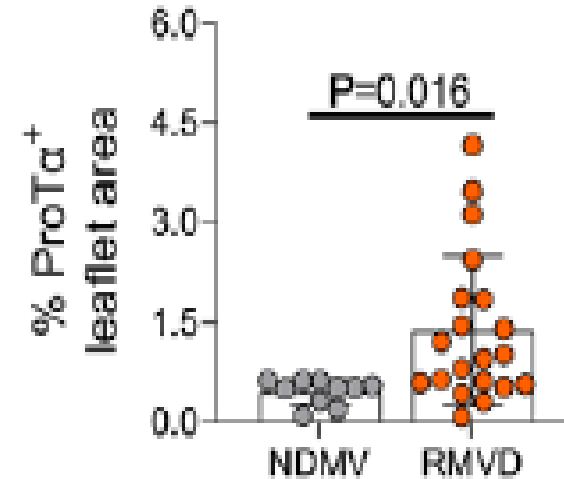
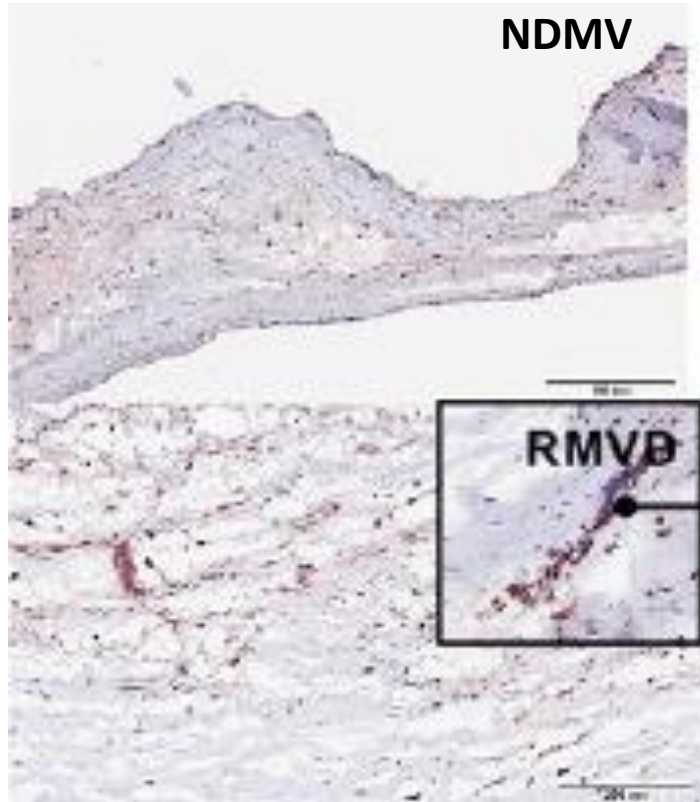
GENETIC SUSCEPTIBILITY

Gene/variant	Cohort	No. of studies	No. of participants	No. of cases	No. of controls	OR (95% CI)	Heterogeneity (I_2)	Year	References
ACE (I/D)	RHD	9	2,545	1,333	1,212	1.04 [0.81, 1.43]	77%	2016	Tian, Ge, Xing, Sun, and Ying (2016)
ACE (I/D)	RHD	6	1,882	981	901	0.76 [0.58, 0.99]	0%	2016	Shang et al. (2016)
ACE (I/D)	RHD	4	1,169	636	533	1.22 [1.02, 1.45]	0%	2013	Gupta et al. (2013)
IL-1 β (rs2853550)	RHD	2	978	515	463	1.35 [1.02, 1.78]	0%	2018	Bhatt, Kumar, Siddiqui, Garg, and Mittal (2018)
IL-6 (-174)	RHD	3	1,202	600	602	0.68 [0.32, 1.45]	69%	2018	Bhatt et al. (2018)
IL-10 (rs1800896)	RHD	4	1,196	588	608	1.01 [0.43, 2.34]	84	2018	Bhatt et al. (2018)
IL-10 (rs1800896)	RHD	3	820	318	502	0.62 [0.28, 1.39]	78%	2018	Dai et al. (2018)
TGF- β 1 (rs1800469)	RHD	3	1,043	588	455	1.83 [1.39, 2.41]	0%	2018	Bhatt et al. (2018)
TGF- β 1 (rs1982073)	RHD	3	1,043	588	455	2.41 [0.83, 7.01]	86%	2018	Bhatt et al. (2018)

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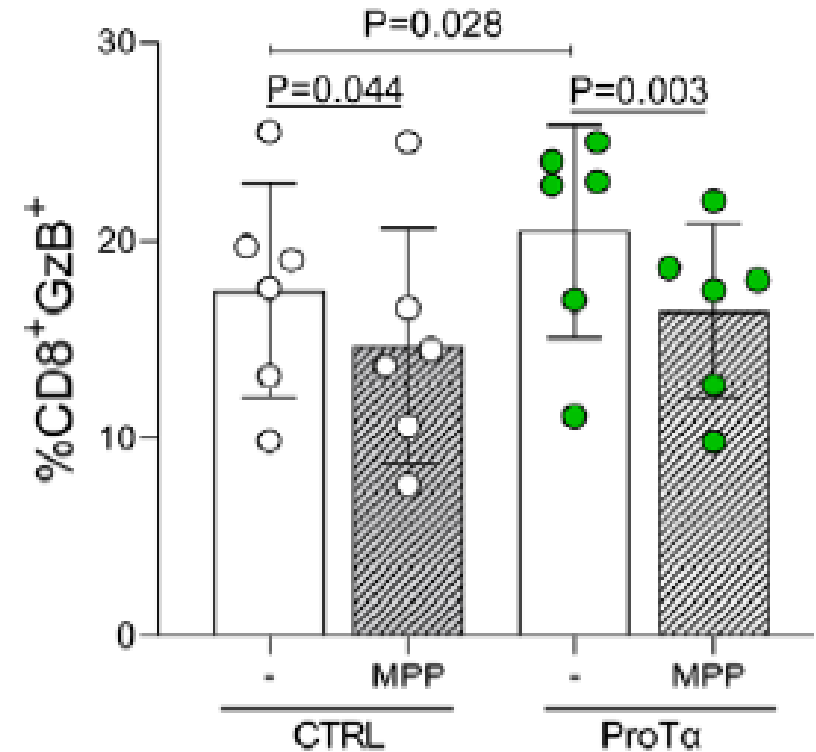
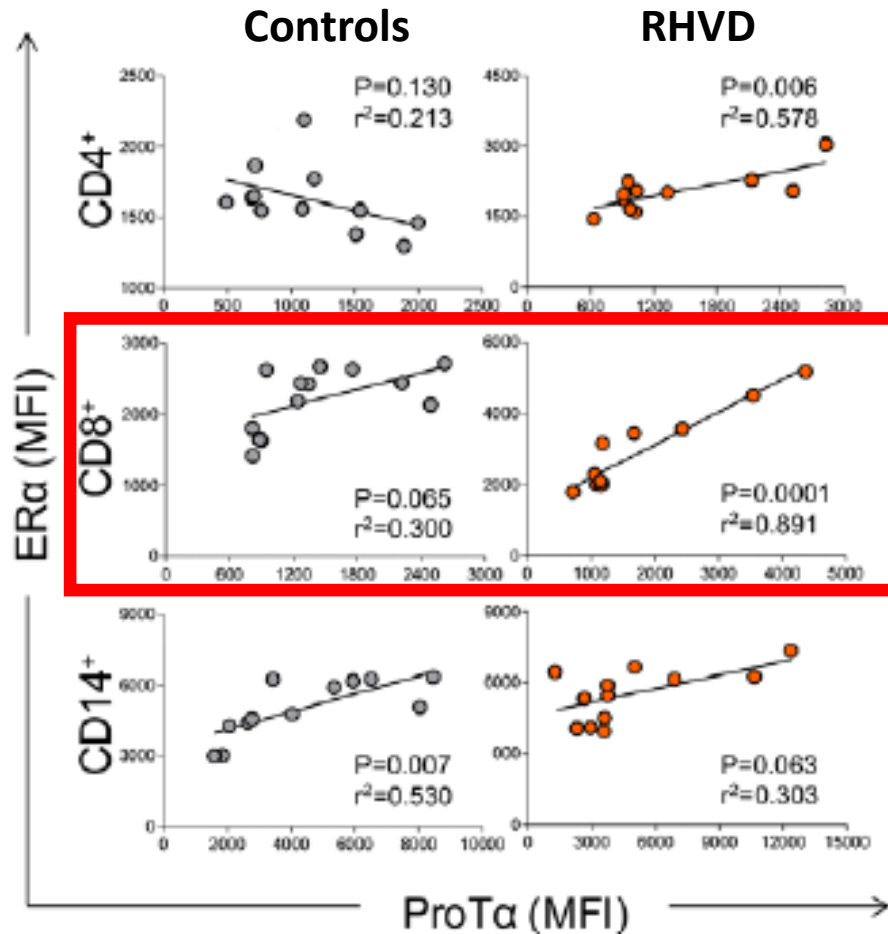
SEX-DIFFERENCES

Prothymosin Alpha (ProT α)



RHEUMATIC HEART VALVE DISEASES

SEX-DIFFERENCES



RHEUMATIC HEART VALVE DISEASES

TAKE HOME MESSAGE

- Complex pathophysiological mechanisms:
 - Molecular mimicry and cross-reactivity
 - Mechanical stress imposed to the left-side valves
 - Neo-angiogenesis and lymphantogenesis
 - Genetic susceptibility variants
 - Sex-related differences mediated by ER α

- Still important **gaps in knowledge** regarding the mechanisms involved in RHVD



Unité de Recherche

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Benjamin Le Vely

Marine Sallé

Th Le Tourneau

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Claire Toquet

Team 4

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CH David

G Guimbretiere

B Cariou

S Hadjadj

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E Bigot

M Carpentier



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O Gauthier



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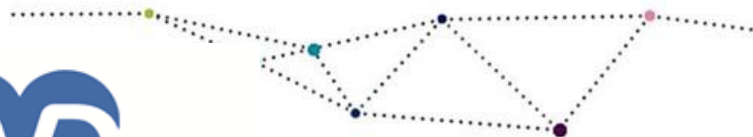
Elvira Mass



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