ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Session 3:
Drug Development with Emphasis on AI, Repurposing, and Animal Models

Chairs: Gareth Morgan, Ashutosh Wechalekar

Faculty: Angela Dispenzieri, Mathew Maurer, Jeff Kelly, Jing Fu, Christophe Sirac, Richard Giadone, Stefano Ricagno

MAYO CLINIC

NEW TARGETS OF THE PLASMA CELL FOR AL AMYLOIDOSIS

Angela Dispenzieri, MD

Serene and Francis During Named Professor of Medicine, Division of Hematology
Mayo Clinic, Rochester, Minnesota

October 13, 2025

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

Research $: Alexion, Alnylam, Bristol-Myers Squibb, Pfizer, AbbVie

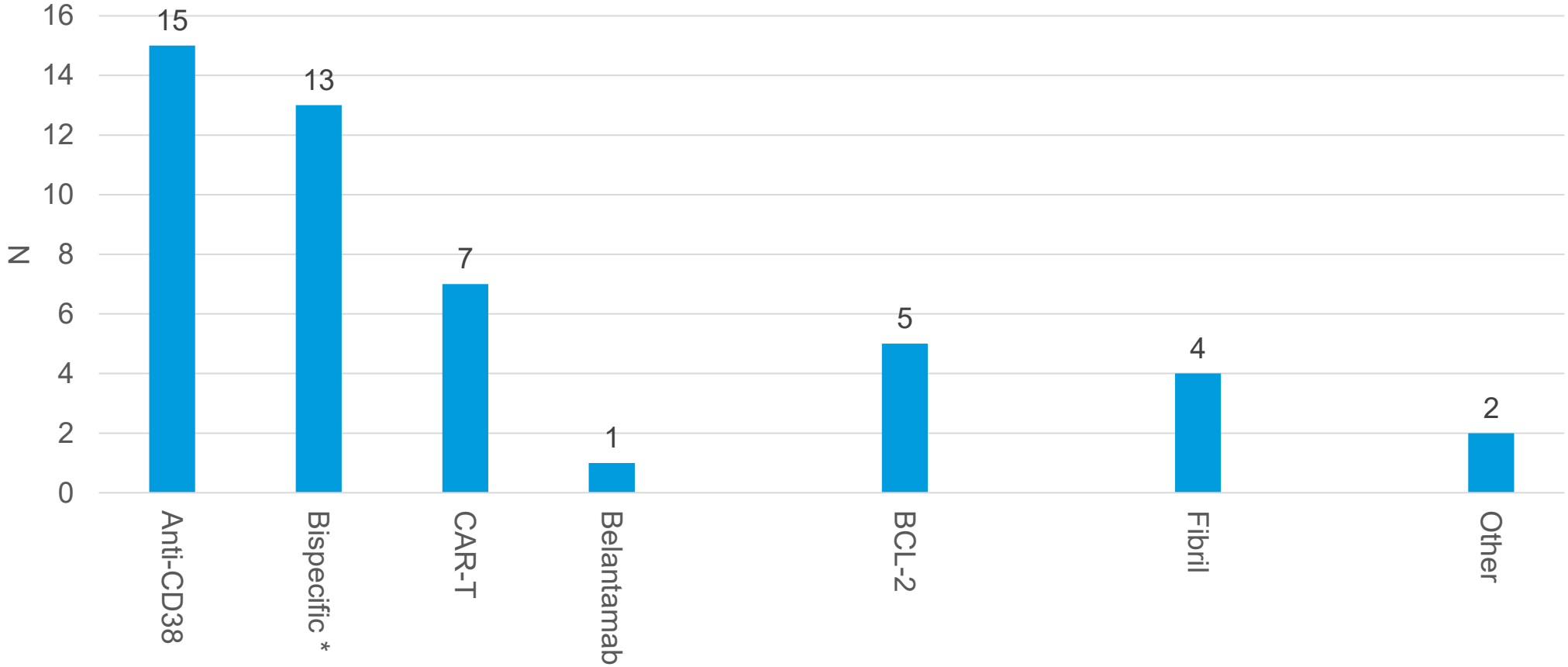
Consultant/advisor/speaker: Janssen; HaemaLogiX.

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

44 INTERVENTIONAL TRIALS AL AMYLOIDOSIS CLINICALTRIALS.GOV

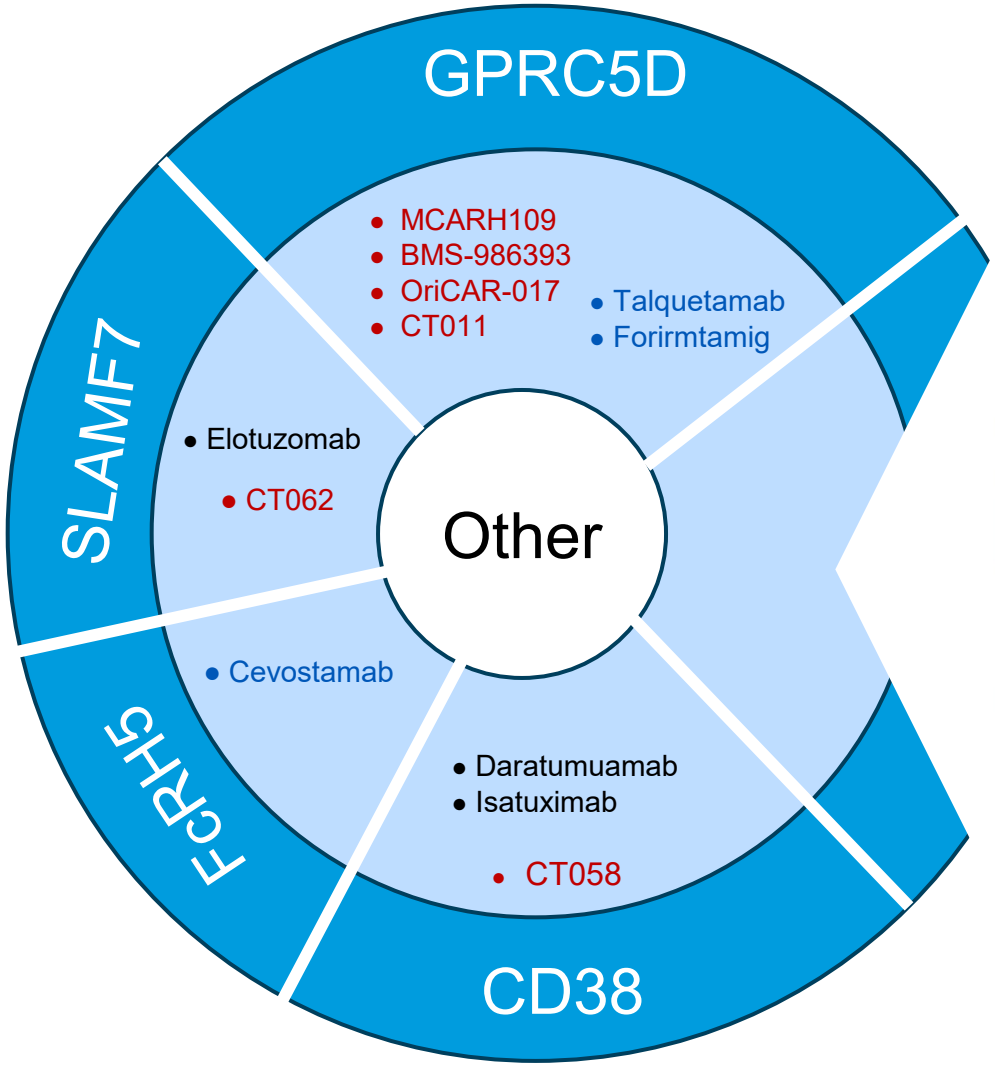


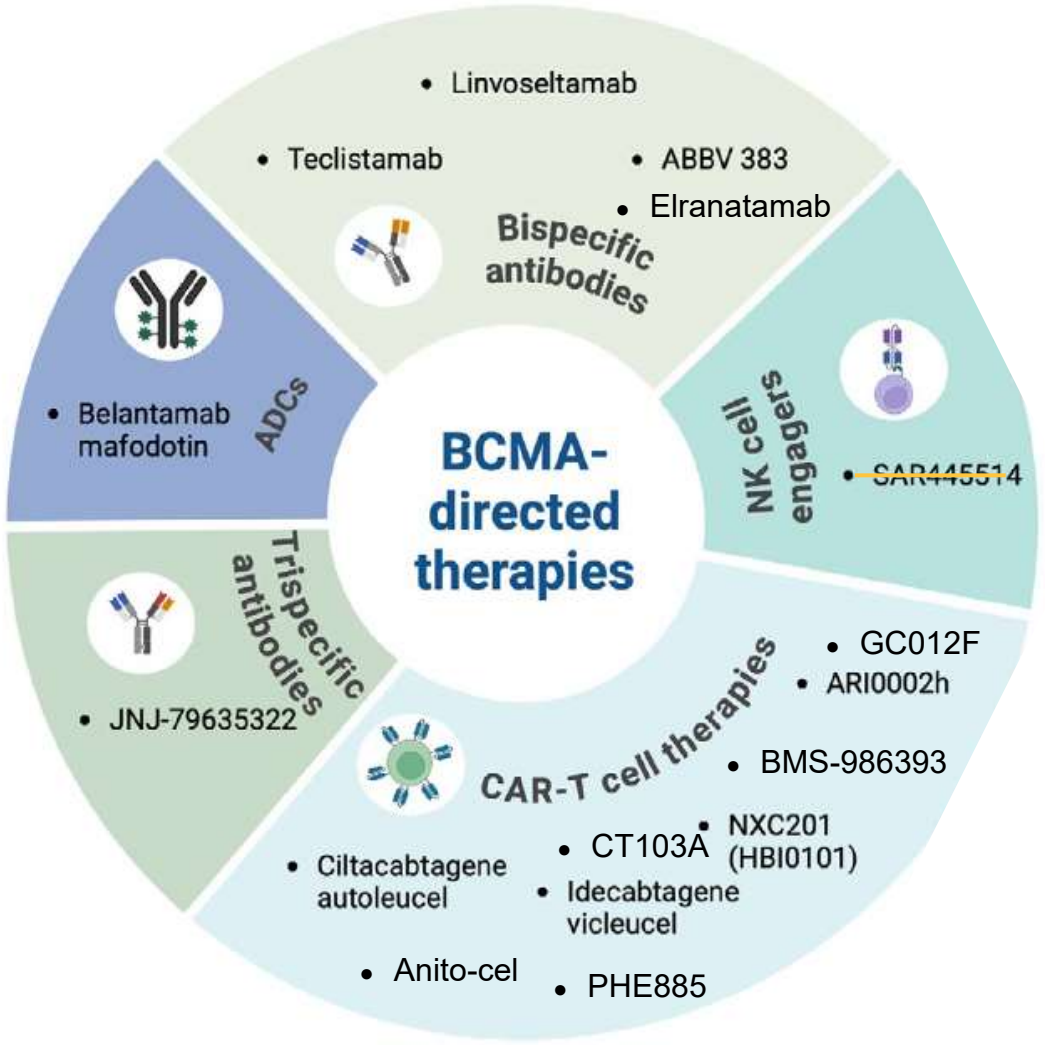
*1 trispecific

10/2/2025

DISCUSSION POINTS

- Targeting surface antigens
- Targeting pathways
- Targeting microenvironment?



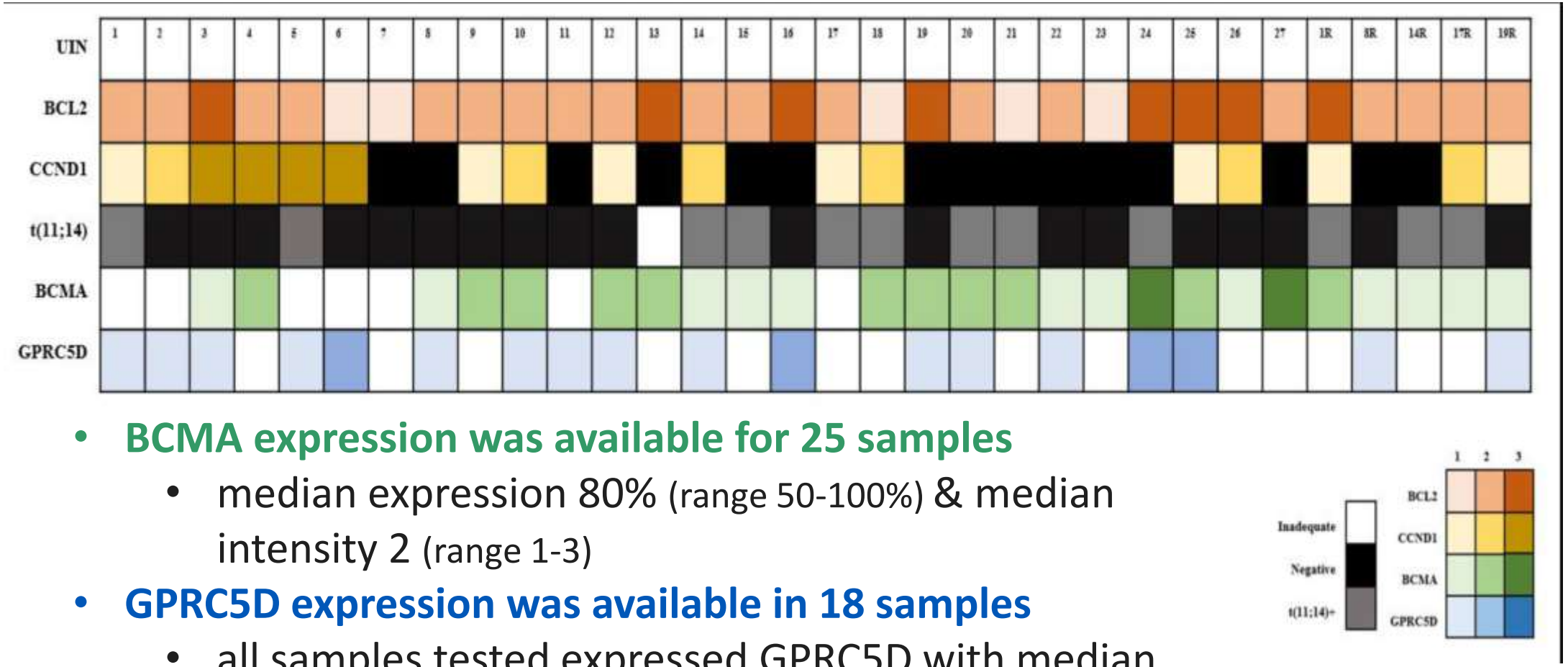


Blue=bispecific Red = CART Black = Naked Ab

Modified from: Jamroziak K. Br J Haematol. 2025 Mar;206(3):817-831.

BISPECIFIC T-CELL ENGAGERS

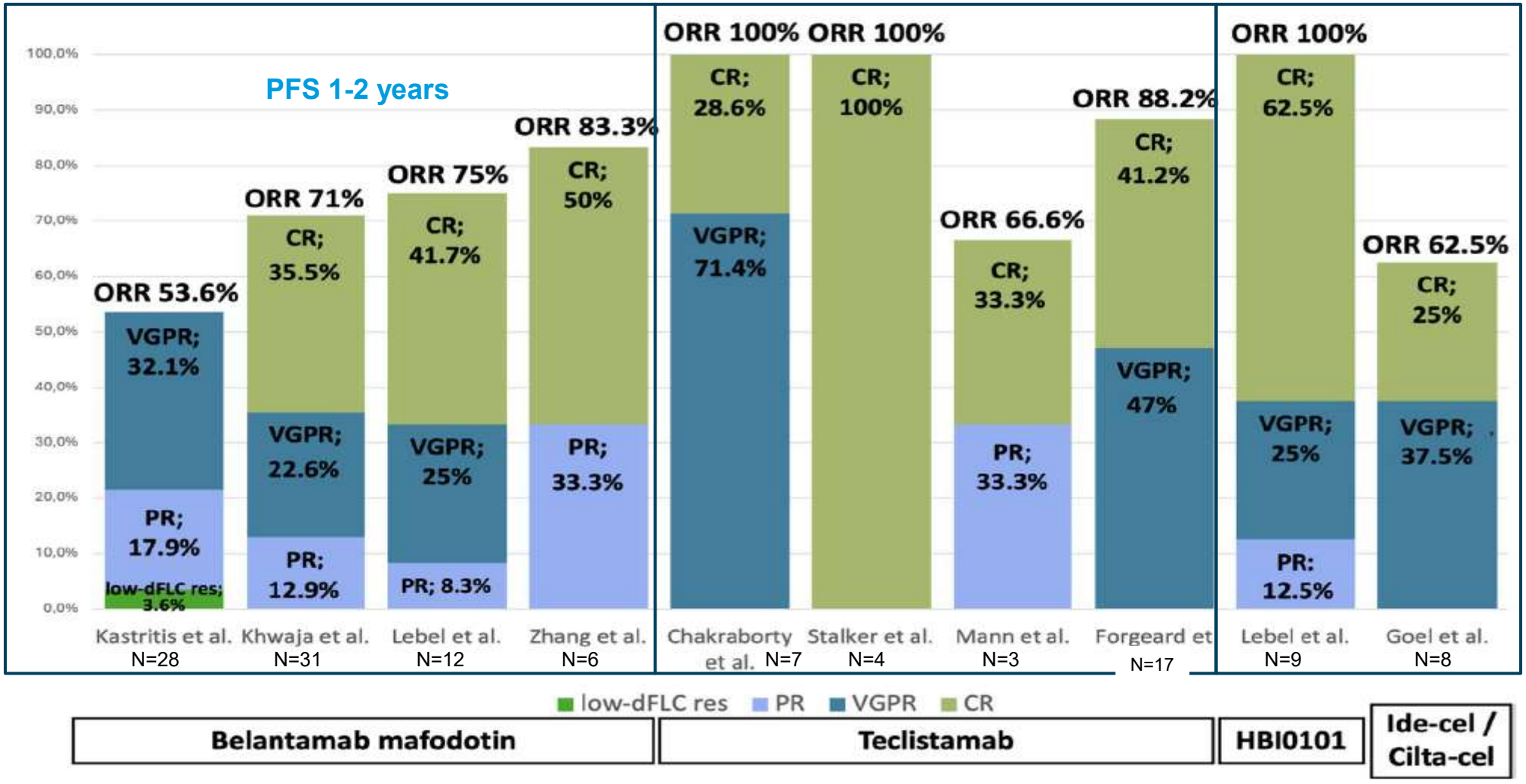
EPITOPE EXPRESSION ON AL PLASMA CELLS

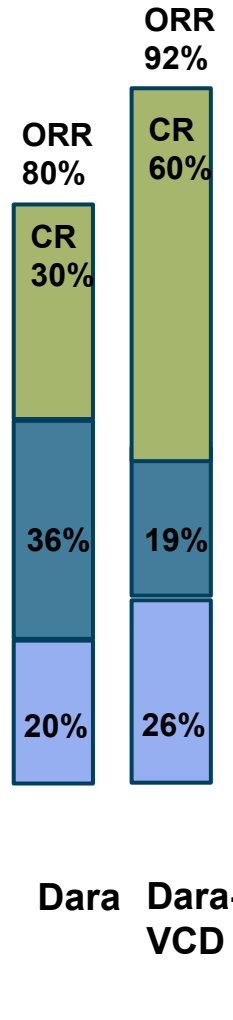


- **BCMA expression was available for 25 samples**
  - median expression 80% (range 50-100%) & median intensity 2 (range 1-3)
- **GPRC5D expression was available in 18 samples**
  - all samples tested expressed GPRC5D with median 80% (range 30-100%) & median intensity 1 (range 1-3)

Bal S. *Blood. 2021;138:4706.*

UPDATE ON B-CELL MATURATION ANTIGEN-DIRECTED THERAPIES IN AL AMYLOIDOSIS





Jamroziak K. Br J Haematol. 2025 Mar;206(3):817-831.

BELANTAMAB-MAFADOTIN IN AL AMYLOIDOSIS

	Kastritis	Khwaja	Lebel	Zhang [c]
N	35	31	12	6
Prior lines	3	3	3	6
FU, m	14	12	13	4.5
Hem ORR, %	54	71	75	83
>=VGPR (CR), %	31	58 (35)	67 (42)	50 (50)
DOR	--	--	Median 34 m	> 4; > 5 x 2; >7; >18 m
PFS / OS	10 m[a] / 22 m	TTNT 27 m / 1-yr 89%	Median 22 m / 29 m	--

a MOD-PFS
b Two patients received drug with other agents: Ven (1); Pom (1)
c Very myeloma-like population

Kastritis E. *Blood. 2024;144:1927-1928.*
Lebel E. *Acta Haematologica. 2025;148(4):419-426.*
Khwaja J. *Br J Haematol. 2024;204(5):1811-1815.*
Zhang YF. *Annals of Hematology. 2022;101(9):2119-2121.*

TECLISTAMAB IN AL AMYLOIDOSIS (14 DAYS TO RESPONSE)

	Forgeard 2024	Chakraborty 2023	Stalker 2025	Mann 2023	Leung 2023
N	17	7 [b]	8	3	1
Prior lines	4	4	7	4	7
FU, m	3	3	8	1.5	6
≥VGPR (CR), %	88 (41)	100 (29)	100 (80)	66 (33)	100 (100)
PFS / OS	-- / 2 died [a]	-- / 3-m 86%	--/ 8-m 100%		

[a] One IIIB; another died of infection
[b] 4 patients had prior BCMA exposure

Forgeard N. *Blood. 2024;143(8):734-737.*
Stalker M. *Eur J Haematol. 2025;114(3):443-447.*
Leung N. *EJHaem. 2023;4(4):1157-1159.*

Chakraborty R. *Blood Cancer J. 2023;13(1):172.*
Mann H. *Blood. 2023;142.*

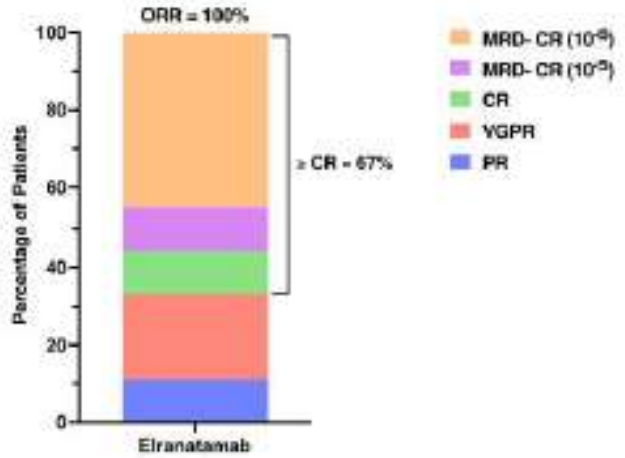
SAFETY AND EFFICACY OF ELRANATAMAB IN PATIENTS WITH RELAPSED AND/OR REFRACTORY AL AMYLOIDOSIS

- 9 patients treated with single agent elranatamab
- 100% response rate after 1st cycle
- Six cycles of therapy were planned upfront except for patient 4 with multidru RRMM/RRAL overlap who is currently receiving monthly elranatamab
- Median fu of 8.2 m, average of 9 Elra doses

Time from Initial Diagnosis to C1D1 (mo)	3.4	5.7	66.9	66.6	8.4	79.1	3.7	49.7	5.8

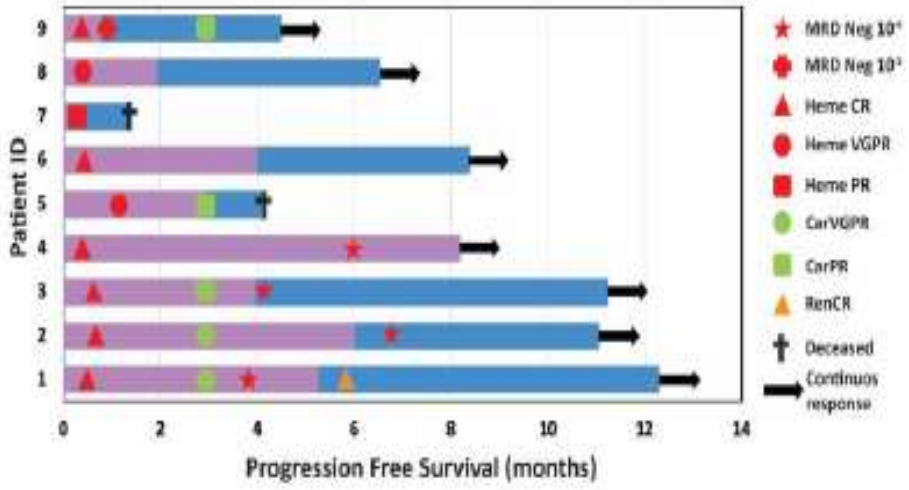
Vianna P. *Blood. 2025.*

E.



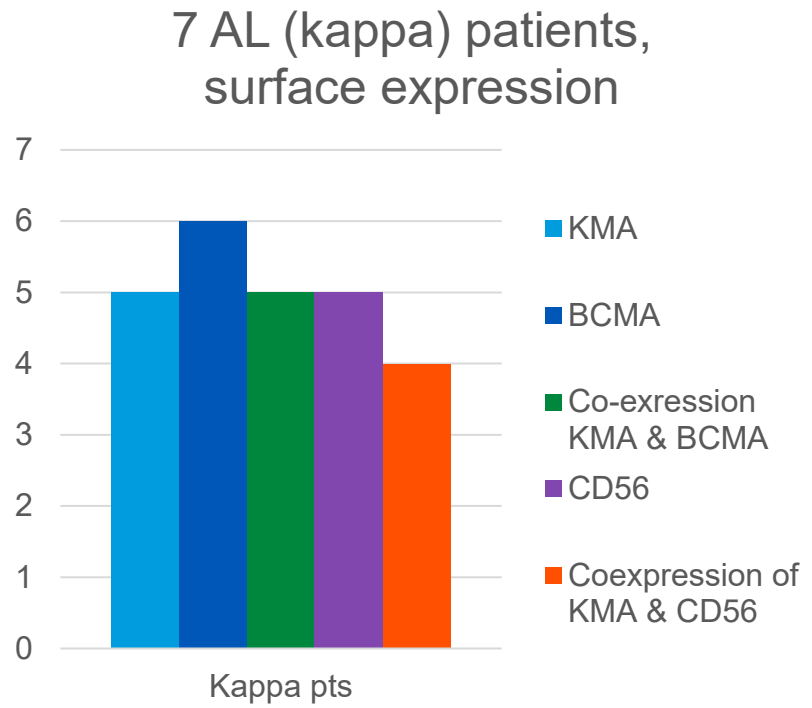
F.

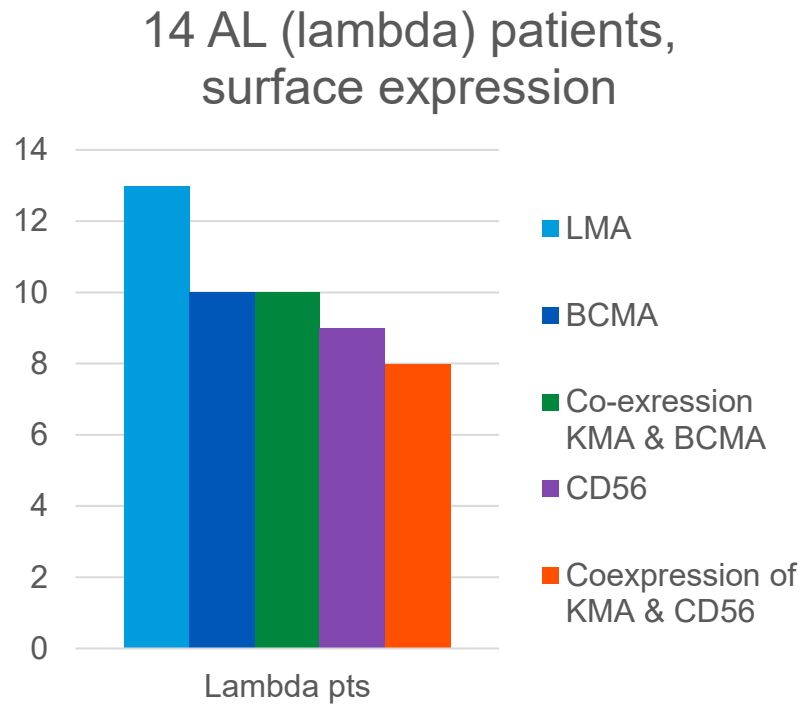
50% MRD negative



KAPPA MYELOMA ANTIGEN (KMA) AND LAMBDA MYELOMA ANTIGEN (LMA) AS NOVEL THERAPEUTIC TARGETS

- KMA has been shown to be expression by malignant PC's and not expressed on normal PCs or other cells in normal bone marrow or blood. LMA not assessed to date



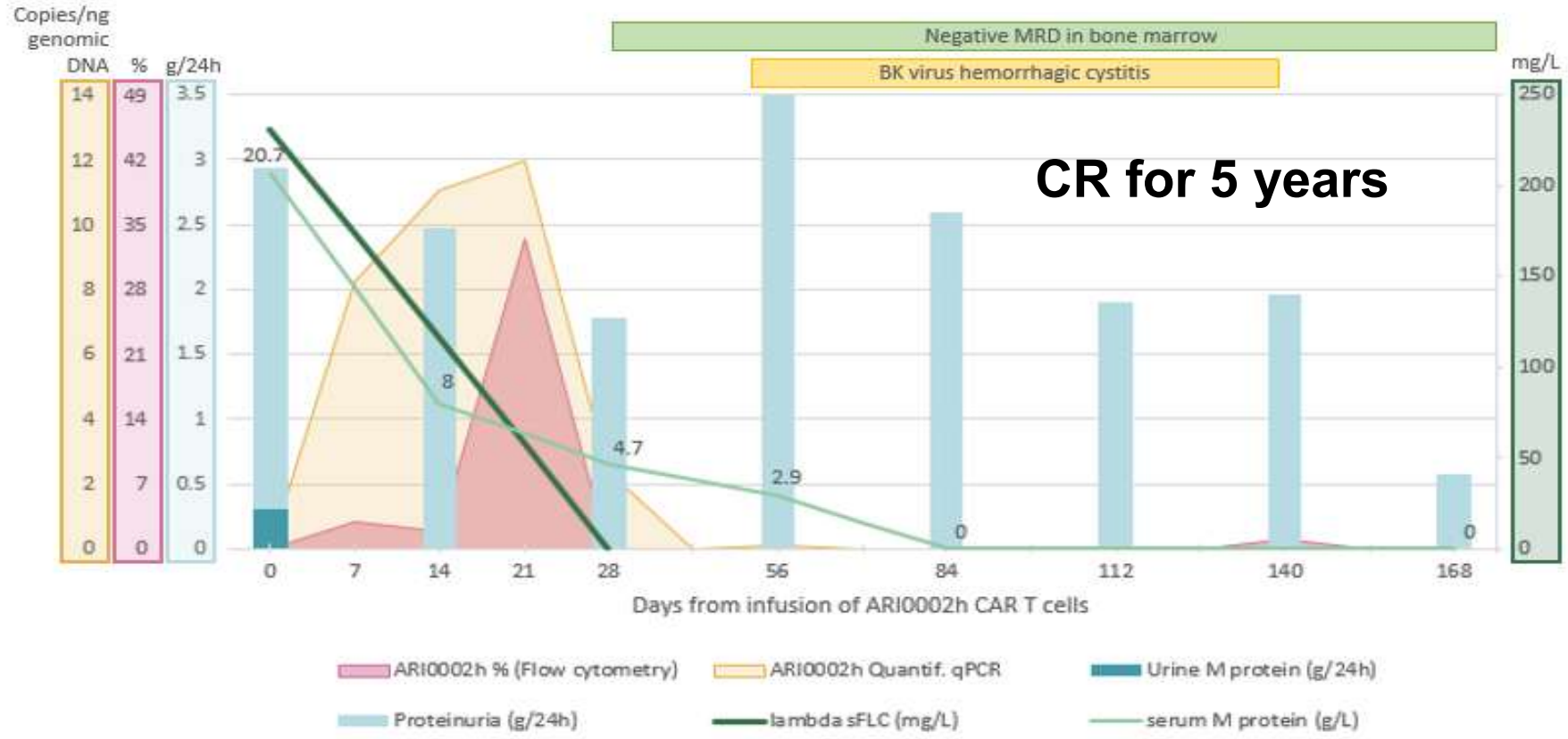


Kappa myeloma antigen (KMA); Lambda myeloma antigen (LMA)

Sartor M. *Clin Lymphoma Myeloma Leuk. 2025;25(10):e788-e798 e785.*

CAR-T

ARI0002h: first patient AL amyloidosis



Slide compliments of Carlos Fernandez de Larrea

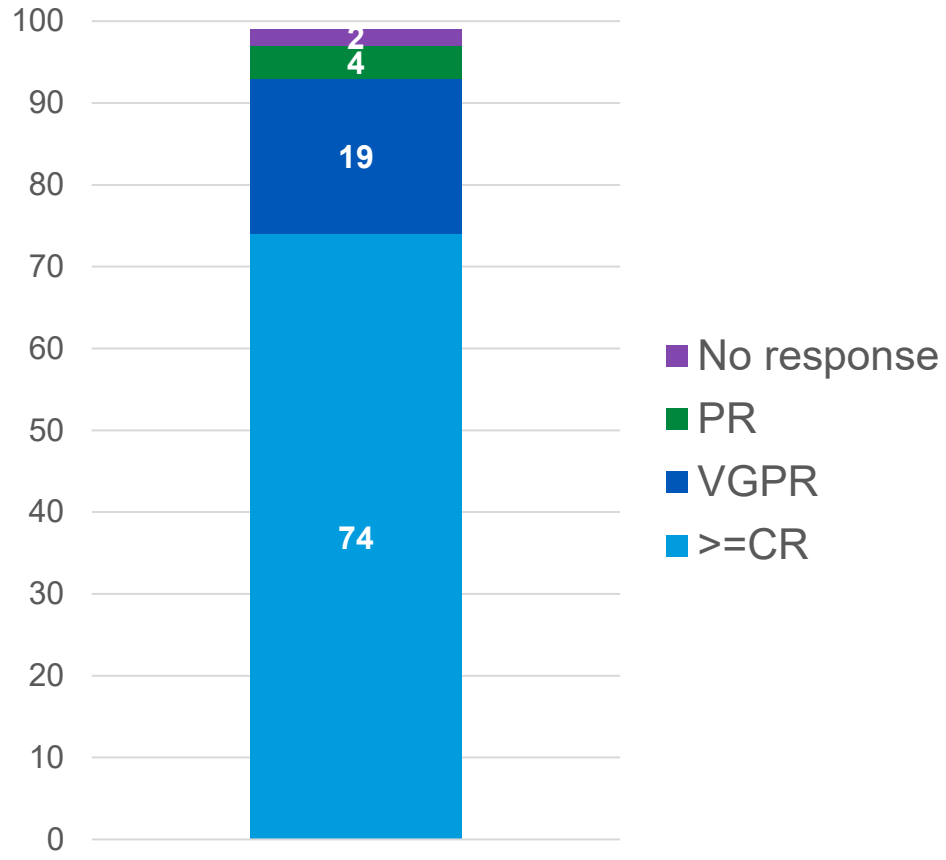
Oliver-Caldés *et al*. Journal for ImmunoTherapy of Cancer 2021

SUMMARY OF CAR-T, 43 EVALUABLE PATIENTS

NCX-201 (HB10101), n=26
Ide-Cel, n=10
Cilta-cel, n=9
AR10002h, n=1

Total: 46 patients

Short follow-up
Organ responses



1. Oliver-Caldes A. *J Imm Cancer. 2021;9(12).*
2. Das S. *Curr Oncol. 2023;30(11):9627-9633.*
3 Goel U. *EJH. 2024;113(6):817-823.*
4. Tan M. In press
5. Lebel E. *JCO. 2025;43(17):2007-16*
6. Landau H. ASCO 2025

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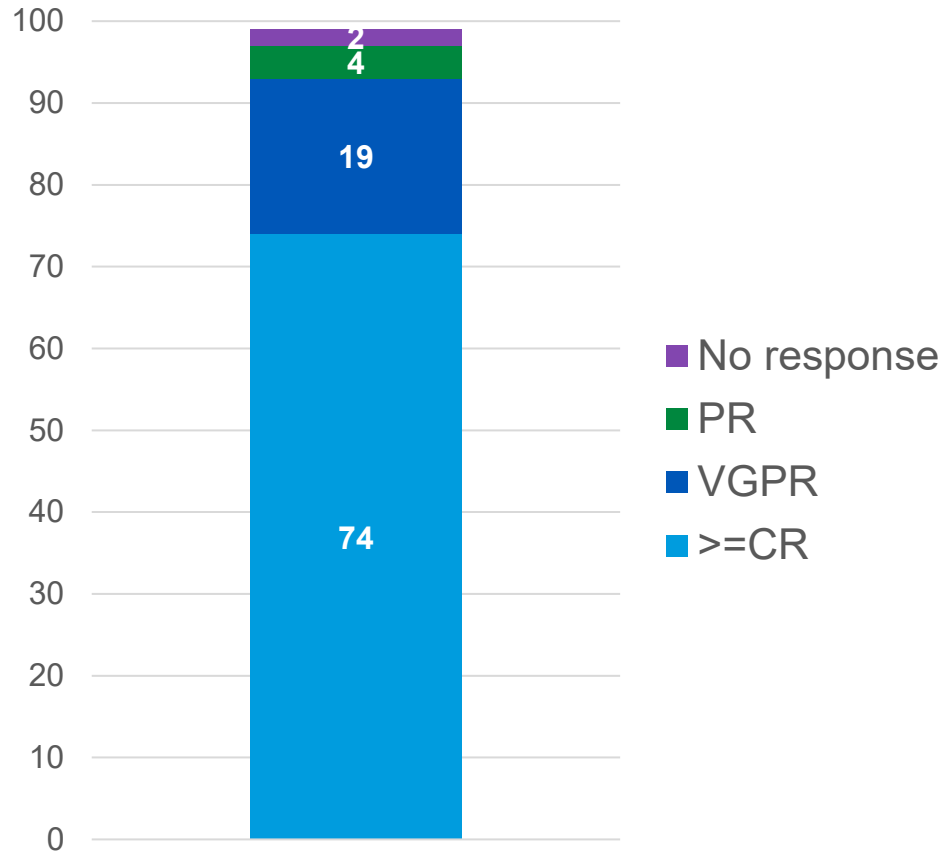

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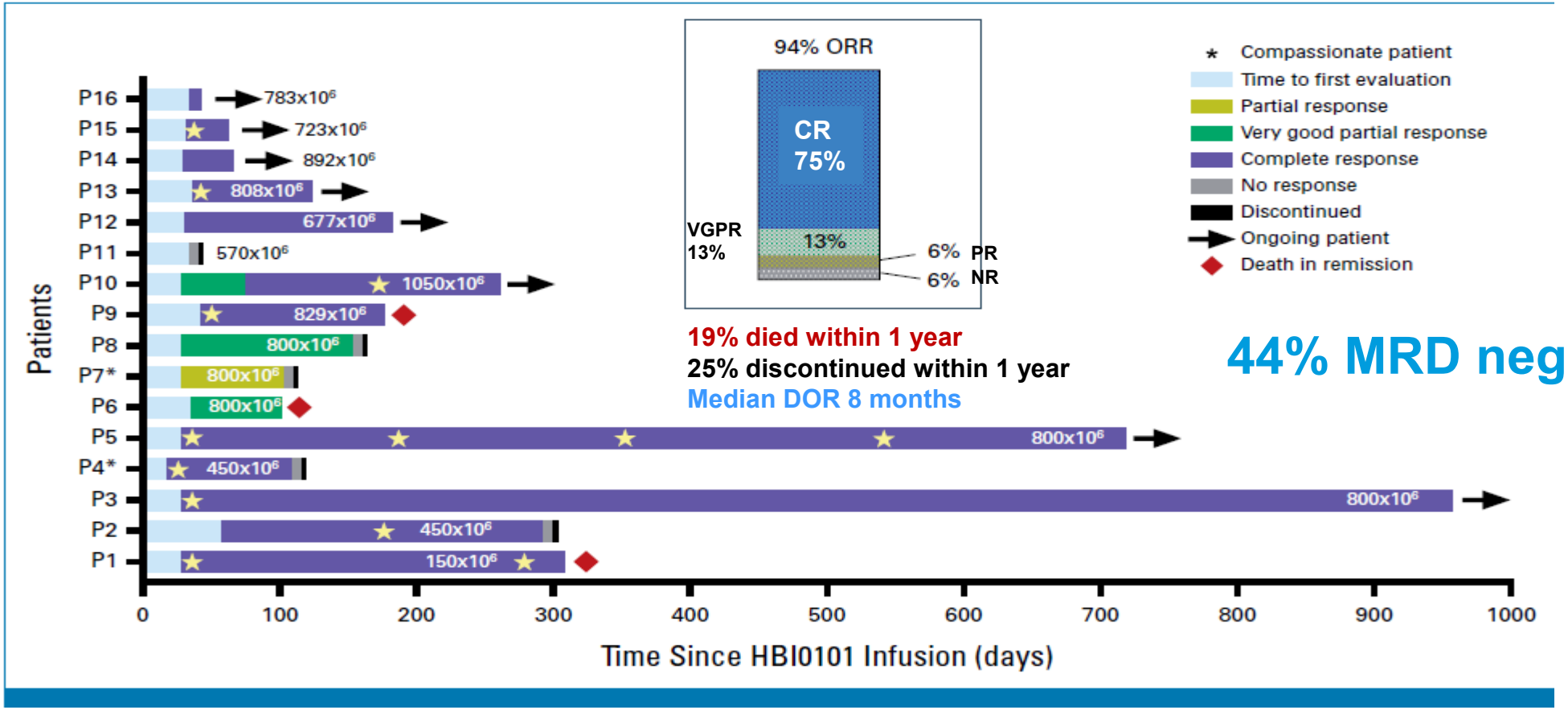
4. Tan M. In press
5. Lebel E. *JCO. 2025;43(17):2007-16*
6. Landau H. ASCO 2025

EFFICACY AND SAFETY OF BCMA CART FOR RELAPSED AND REFRACTORY AL AMYLOIDOSIS



D30 MRD neg: Pt# 1, 3, 4, 5, 9, 13, 15
Stage IIIA: Pt # 1, 2, 4, 12

D30 MRD pos: Pt# 6, 8, 10, 11, 12, 14
Stage IIIB: Pt #6

D30 MRD ND: Pt# 2, 7, 16

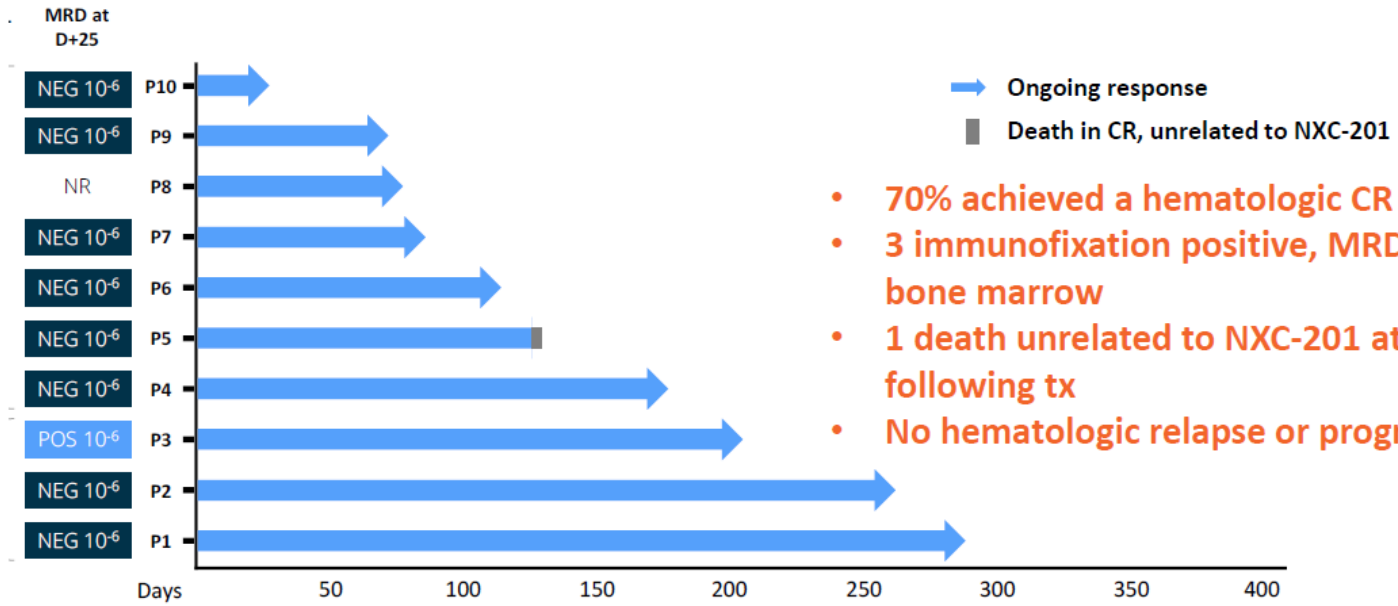
Lebel E. Journal of Clinical Oncology. 2025 Jun 10;43(17).

Efficacy in AL amyloidosis

NEXICART-2: hematologic responses as reviewed by an independent review committee

Data available as of cut-off April 11, 2025. Median follow up 121 days (range 29-289).

	Subject #	NX2-001	NX2-002	NX2-003	NX2-004	NX2-005	NX2-006	NX2-007	NX2-008	NX2-009	NX2-010
	NXC-201 Dose (million CAR+T cells)	150	150	150	450	450	450	450	450	450	450
AL Amyloidosis Disease Markers	Status as of data cutoff	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Time to normalization (days)	14	7	15	7	7	7	7	7	7	7
	Hematologic response	CR	CR	CR	VGPR MRD(-) 10^{-6}	CR	CR	Low dFLC PR MRD(-) 10^{-6}	CR	VGPR MRD(-) 10^{-6}	CR

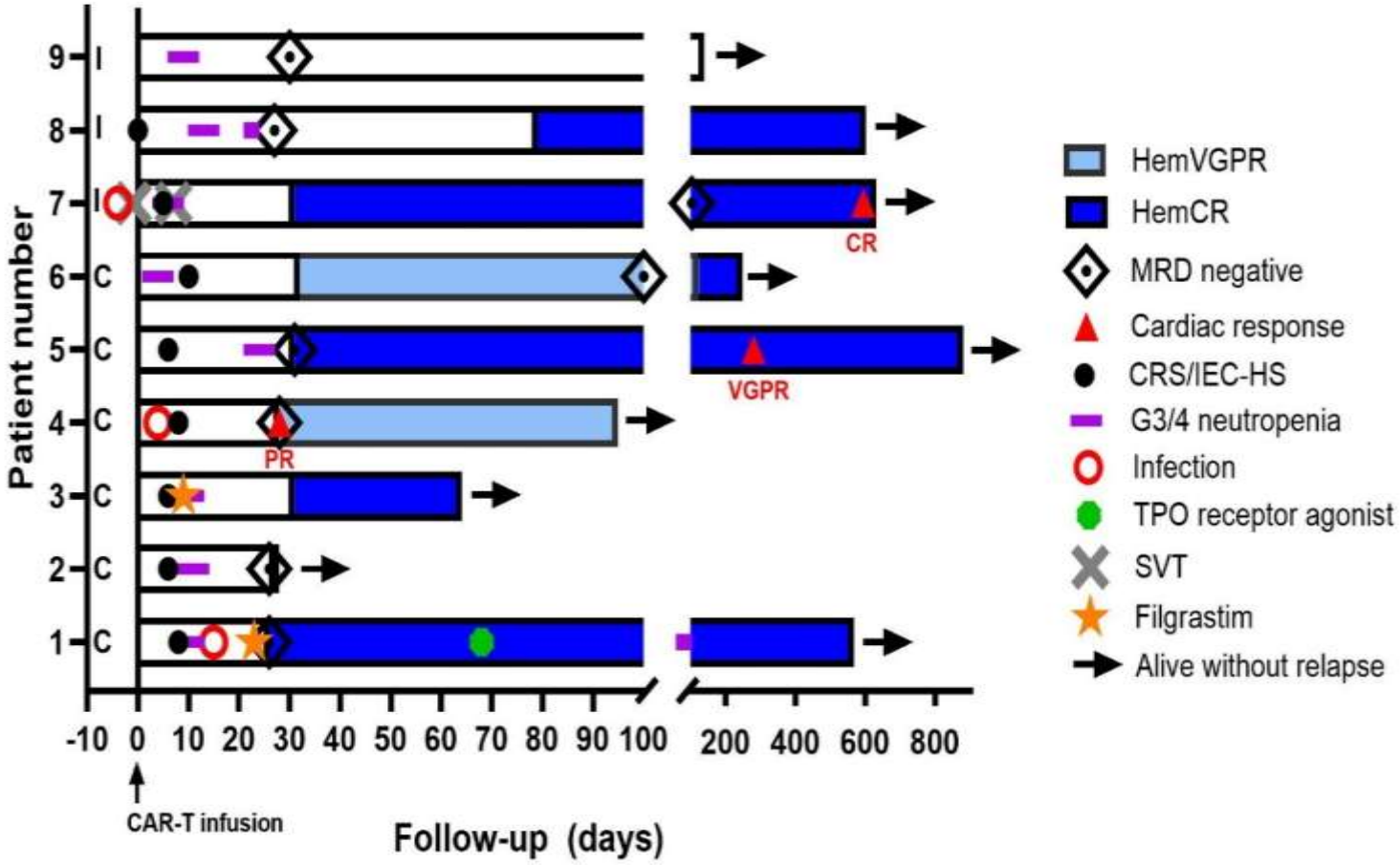


- 70% achieved a hematologic CR
- 3 immunofixation positive, MRD – in the bone marrow
- 1 death unrelated to NXC-201 at 5 mos following tx
- No hematologic relapse or progression

Minimal residual disease (MRD) negativity was assessed by 10-color flow cytometry or clonoSEQ with sensitivity 10^{-6}

Landau *et al*. ASCO 2025

MAYO CART EXPERIENCE (N=9)



Tan M. (in press)

All had heme response
3 Ida-cel and 6 Cilta-cel
Median fu 21 months

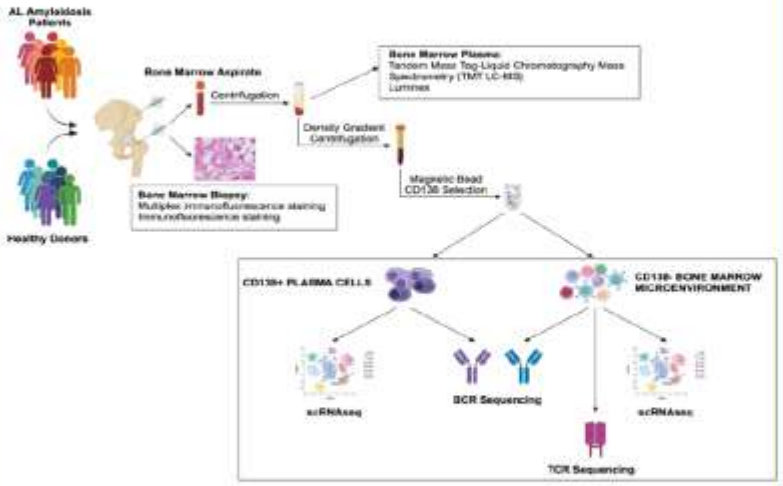
Response	N=9
MRD neg	9 (100%)
Cardiac	3 / 7= 43%
Renal	2 / 4=50%

PATHWAYS AND MICROENVIRONMENT

OTHER TARGETS? SINGLE-CELL AND CLONAL ANALYSIS OF AL AMYLOIDOSIS PC & THEIR BM MICROENVIRONMENT

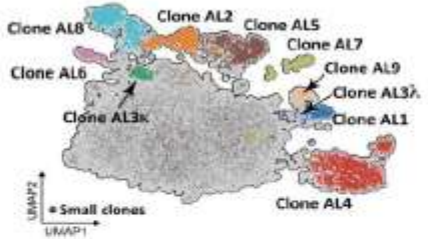
Approach

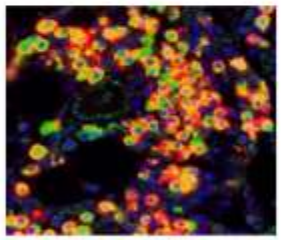
STUDY POPULATION: Newly diagnosed, treatment naïve AL amyloidosis patients.
CONTROLS: Age- and gender-matched healthy donors



In AL Amyloidosis Patients We Observed:

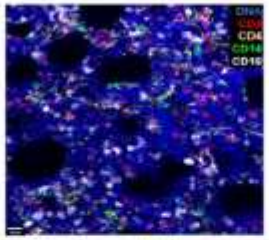
Transcriptionally distinct clonal AL-PCs with increased expression of proteostasis network genes

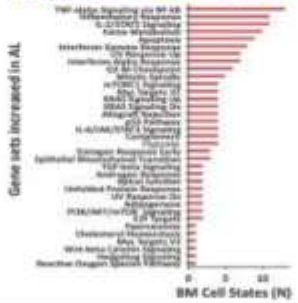




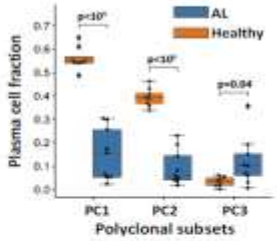
Red= CD138 Green= FKBP2

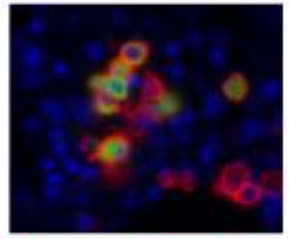
Monocyte expansion and inflammatory signature of bone marrow niche





Expanded CRIP1+ non clonal plasma cells



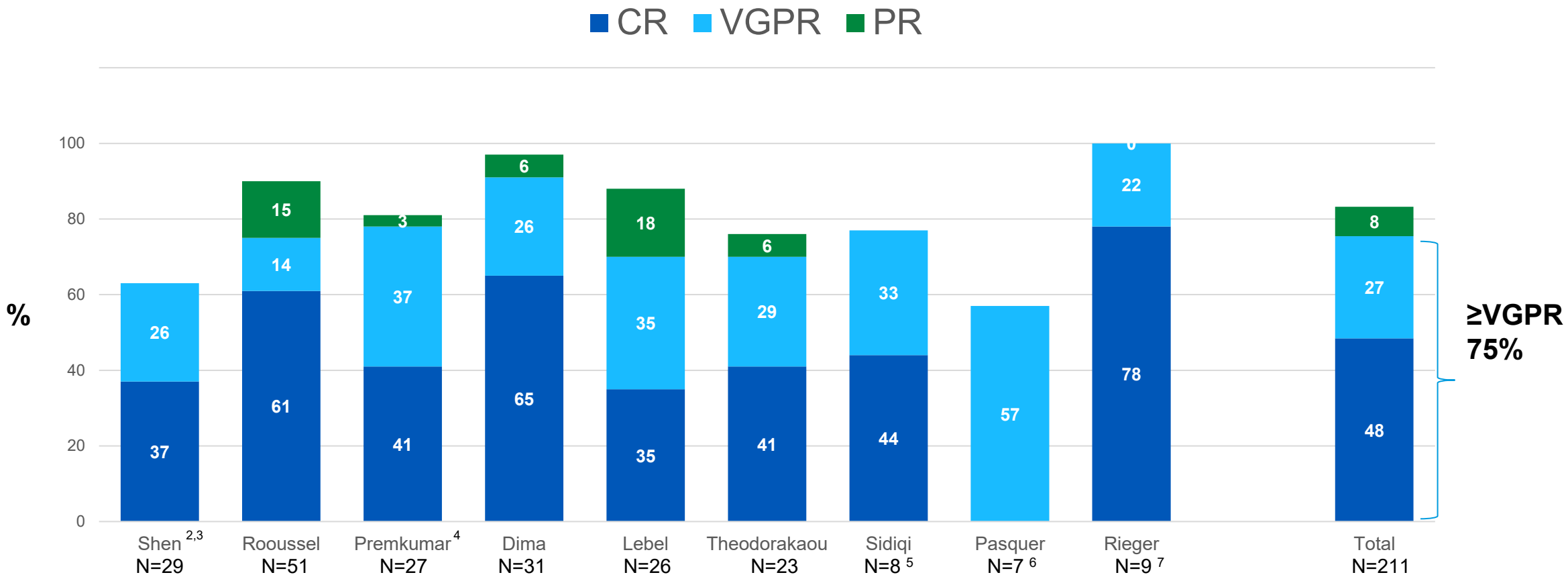


Red= CD138 Green= CRIP1

CONCLUSIONS: 1- AL amyloidosis plasma cells are transcriptionally distinct from non clonal plasma cells. 2- Monocyte expansion and a TNF-α and inflammatory signature characterize the bone marrow microenvironment. 3- A population of non clonal plasma cells with a distinct transcriptional program is paradoxically expanded in patients with AL amyloidosis.

Gort-Freitas NA. *Blood. 2025.*

VENETOCLAX[1] RESPONSE RATES IN T(11;14) AL



[1] Mono and combo therapy
[2] Prospective trial in newly diagnoses; all with Ven-Dex
[3] Of 29 evaluable of 36
[4] Study included 43 pts, but table limited to t(11;14), n=30, and for heme evaluable only 27 pts
[5] Of 8 evaluable of 12 in study
[6] t(11;14) only, n=7 of 10 in study; authors listed >=VGPR w/o calling out CR
[7] Advanced cardiac

Shen KN. *Blood. 2024;144:893-893.*
Dima D. *Amyloid. 2024;31(3):195-201.*
Sidiqi MH. *Blood Cancer J. 2020;10(5):55.*
Roussel M. *HemaSphere. 2023;7(S2):4-4.*
Lebel E. *Cancers (Basel). 2023;15(6).*
Pasquer H. *Br J Haematol. 2021;193(3):674-677.*
Premkumar VJ. *Blood Cancer J. 2021;11(1):10.*
Theodorakakou F. *Blood. 2024;144:4675-4675.*
Rieger MJ. *Ann Hematol. 2024;103(10):4163-4170.*

VENETOCLAX FOR AL AMYLOIDOSIS

Study / Source	N	Mono[1] / Combo, %	T(11;14), %	Dx to Ven / prior lines	ORR, %	CR / VGPR, %	FU, mo	PFS	OS	DOR
Shen (2024)	36	M: 100 [2]	100	1st line	--	37 / 26 [3]	NA	--	--	--
Roussel (2023)	51	M: 30 C: 21	94	24 m / --	90	61 / 14	17	Med 40 m	3-yr 68%	12.7 m
Premkumar (2021) [4]	30	M: 17 C: 13	100	-- / 3	81 [4]	41 / 37 [4]	14	12-m 90%	12-m 97%	--
Dima (2024)	31	M: 11 C: 20	100	10 m / 1	97	65 / 26	22	TTNT: 2 yr 56%	2-yr 85%	--
Lebel (2023)	26	M: 18 C: 8	88	12 m / 3	88	35 / 35	33	EFS 25 m	33 m 77%	25 m
Theodora-kakou (2024)	23	Ven-based	91	7 m / --	76	41 / 29	12	2 relapses	2-yr 61%	--
Sidiqi (2020)	12	M: 7 C: 5	92	--/ 2	87 [5]	50 / 37 [5]	11	2 progs	0 deaths	--
Pasquer (2021)	10	M: 3 C: 7	70	34 m / >3	67 [6]	≥ VGPR 57 [6]	9	NA	10.5 m	8 m
Rieger et al. (2024) [7]	9	M: 3 C: 6	100	-- / 3	100	78 / 22	35	2 progs	3-yr 89%	NR

[1] Mono counts as with or w/o dex. [2] Prospective trial in newly diagnoses; all with Ven-Dex
[3] Of 29 evaluable
[4] Study included 43 pts, but table limited to t(11;14), n=30, and for heme evaluable only 27 pts
[5] Of 8 evaluable
[6] t(11;14) only, n=7
[7] Advanced cardiac

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Dima D. *Amyloid. 2024;31(3):195-201.*
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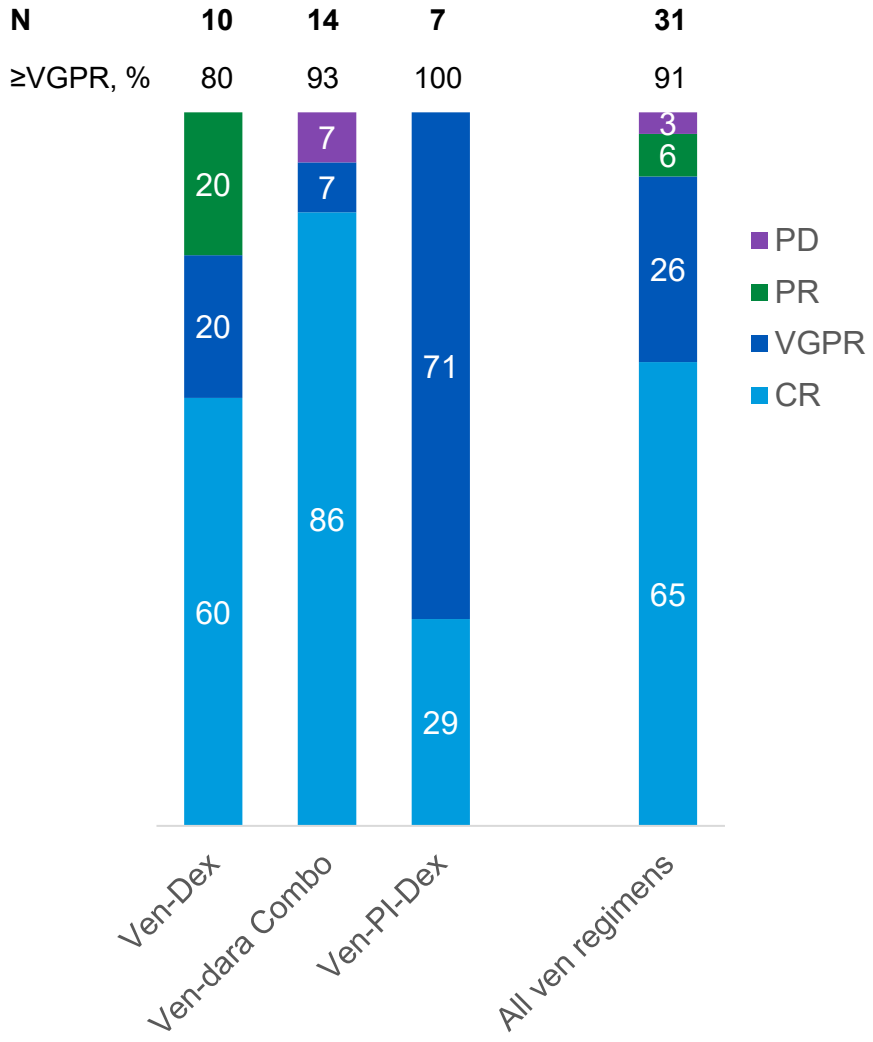
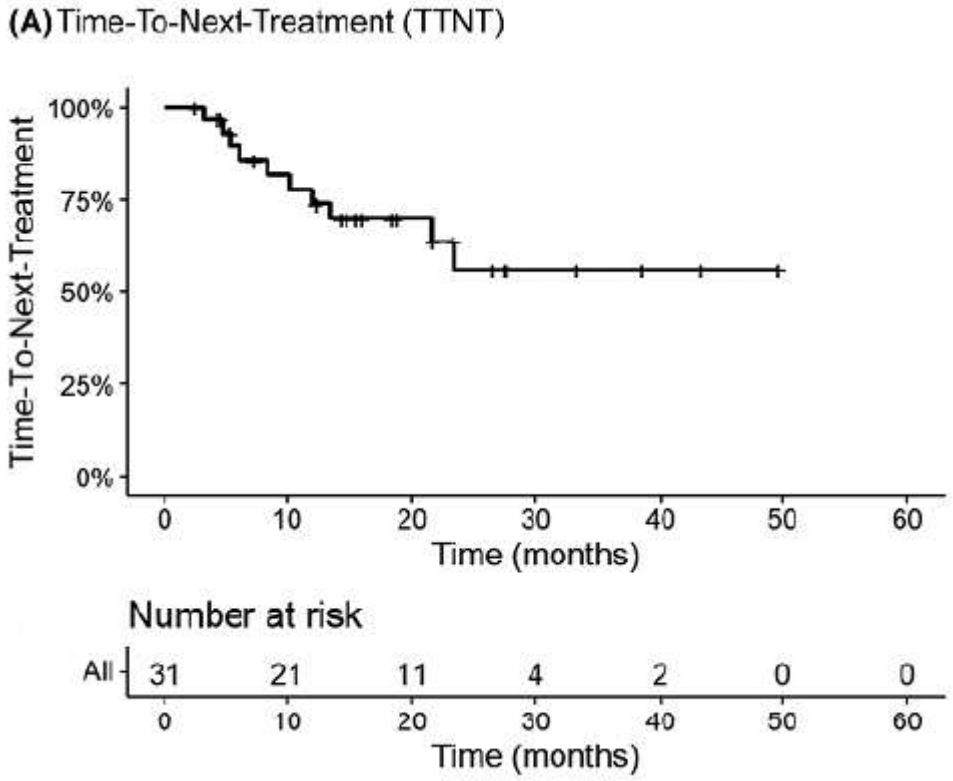
Premkumar VJ. *Blood Cancer J. 2021;11(1):10.*
Theodorakakou F. *Blood. 2024;144:4675-4675.*
Rieger MJ. *Ann Hematol. 2024;103(10):4163-4170.*

VENETOCLAX AFTER DARATUMUMAB FAILURES

Median time from diagnosis to Ven initiation 10 (IQR 4-38)

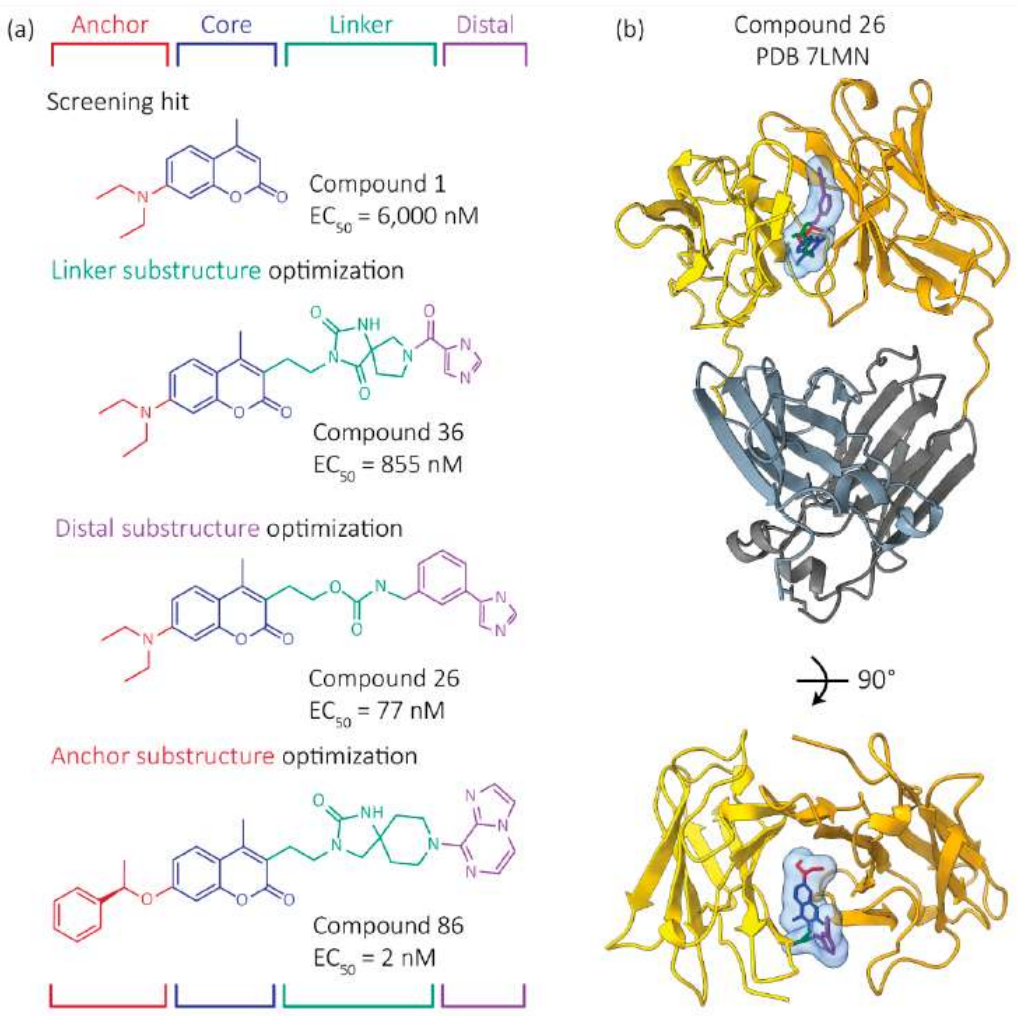




Median follow up 22 months
4 deaths: 2 HF, 1 cardiac arrest; 1 ESRD

Dima D. *Amyloid. 2024;31(3):195-201.*

LIGHT CHAIN STABILIZERS



Morgan GJ, Buxbaum JN, Kelly JW. *Hemato. 2021;2(4):645-659.*

ELSEVIER

Blood 144 (2024) 3372–3373

The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

654.MULTIPLE MYELOMA: PHARMACOLOGIC THERAPIES

Small Molecule Kinetic Stabilizers Reduce Amyloidogenicity of Free Light Chain Proteins of Diverse Sequences in λ Light Chain Amyloidosis

Bo Qin, PhD[1], Alexander B Jackman[1], Yao-Cheng Li, PhD[1], Jianying Wang[1], Huang Qiu, PhD[1], Nathan Onpaeng[1], Steven Wilkens, PhD[1], Virginia Grant[1], Robyn L Stanfield, PhD[2], Ian Wilson, PhD[2], Imani Rogers[1], Richard Labaudiniere, PhD[1], Jeffery W Kelly, PhD[3], H Michael Petrassi, PhD[1], Xin Jiang, PhD[1]

protego

CONCLUSIONS

- BCMA
  - ADC → ≥VGPR in 30-67% pts with PFS 1-2 yrs
  - Bispecific T-cell engagers
    - Teclistamab→ ≥VGPR 80-100%; PFS ?
    - Elranatamab→ ≥VGPR 90%; PFS ?
  - CAR-T → ≥VGPR 80%; PFS ?
  - High rates of favorable MRD with TCE & CAR-T
- For t(11;14) pts, venetoclax ≥VGPR 60-90%; PFS 2-3 yrs
- Other targets: KMA/LMA; GPRC5D; light chain stabilizers

AMYLOIDOSIS AT MAYO CLINIC ROCHESTER

Hematology

- Nadine Abdallah, MD
- Moritz Binder, MD
- Francis Buadi, MD
- Joselle Cook, MD
- David Dingli, MD
- Angela Dispenzieri, MD
- Amy Fonder, PA
- Morie Gertz, MD
- Wilson Gonsalves, MD
- Ronald Go, MD
- Suzanne Hayman, MD
- Miriam Hobbs, CNP
- Lisa Hwa, CNP, PhD
- Prashant Kapoor, MD
- Taxiarchis Kourelis, MD
- Shaji Kumar, MD
- Robert Kyle, MD
- Yi Lin, MD, PhD
- Eli Muchtar, MD
- Vincent Rajkumar, MD
- Rahma Warsame, MD

Nephrology

- Nelson Leung, MD

Cardiology

- Martha Grogan, MD
- Kyle Klarich, MD
- Omar Abou-Ezzeddine, MD
- Allan Jaffe, MD

Neurology

- P. James Dyck, MD
- Michelle Mauermann, MD
- Peter J. Dyck, MD
- Christopher Klein, MD
- Elie Naddaf, MD

Laboratory

- David Murray, MD
- Surendra Dasari, PhD
- Ellen McPhail, MD

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Targeting the production of TTR

Mat Maurer, MD
Columbia University Medical Center
Arnold and Arlene Goldstein Professor of Cardiology
October 14, 2025

Disclosures

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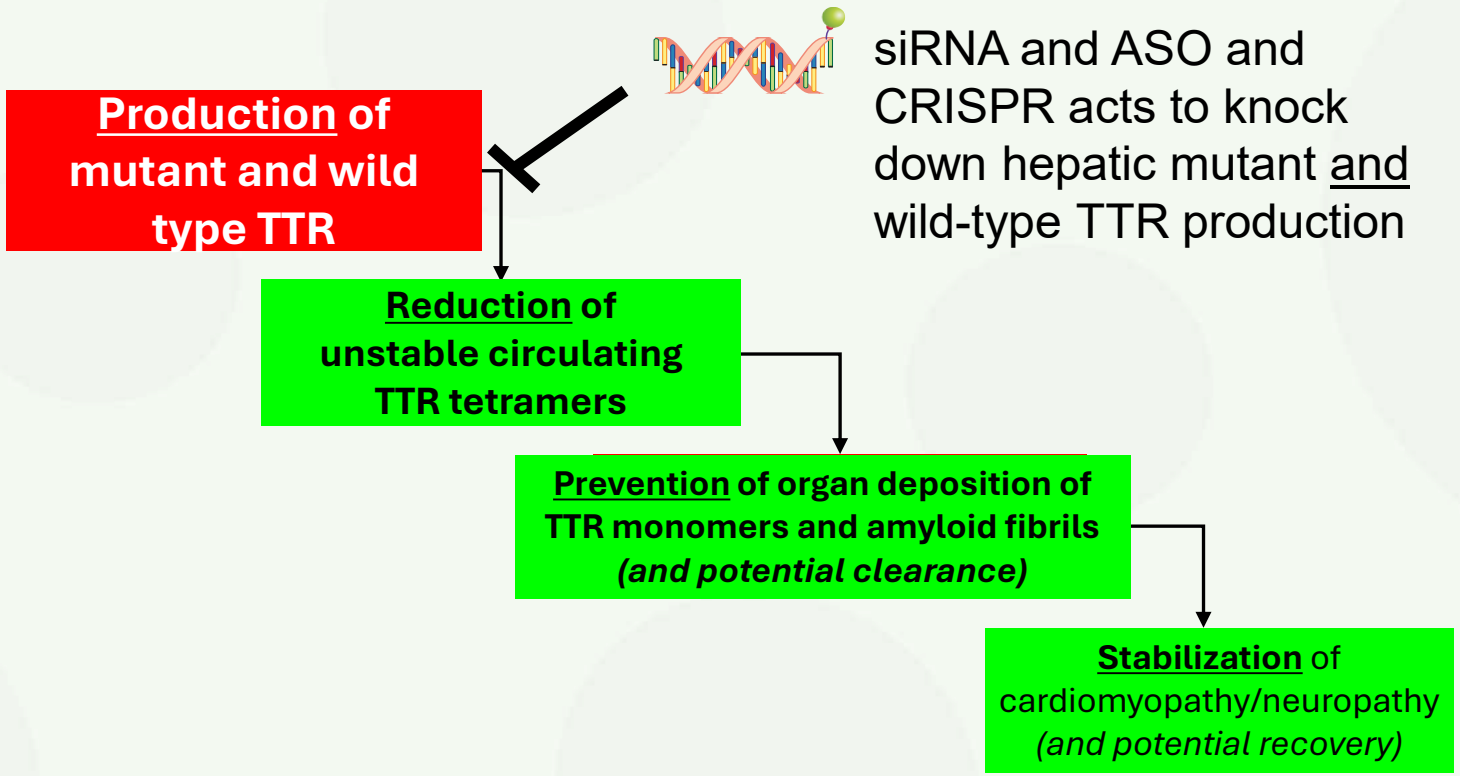
- I have support from several pharmaceutical companies and the NIH:
  - NIH/NIA
  - Novo-Nordisk
  - Ionis Pharmaceuticals
  - Pfizer, Inc.
  - BridgeBio
  - -Astra-Zeneca
  - -Intellia
  - -Alnylam
  - -Attralus
  - -Bayer
- Will discuss a novel and investigational products for transthyretin cardiac amyloidosis.

Therapeutic Efficacy of TTR reduction in Transthyretin Amyloidosis

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Approaches to Silencing Hepatic Transthyretin Production (Knockdown)

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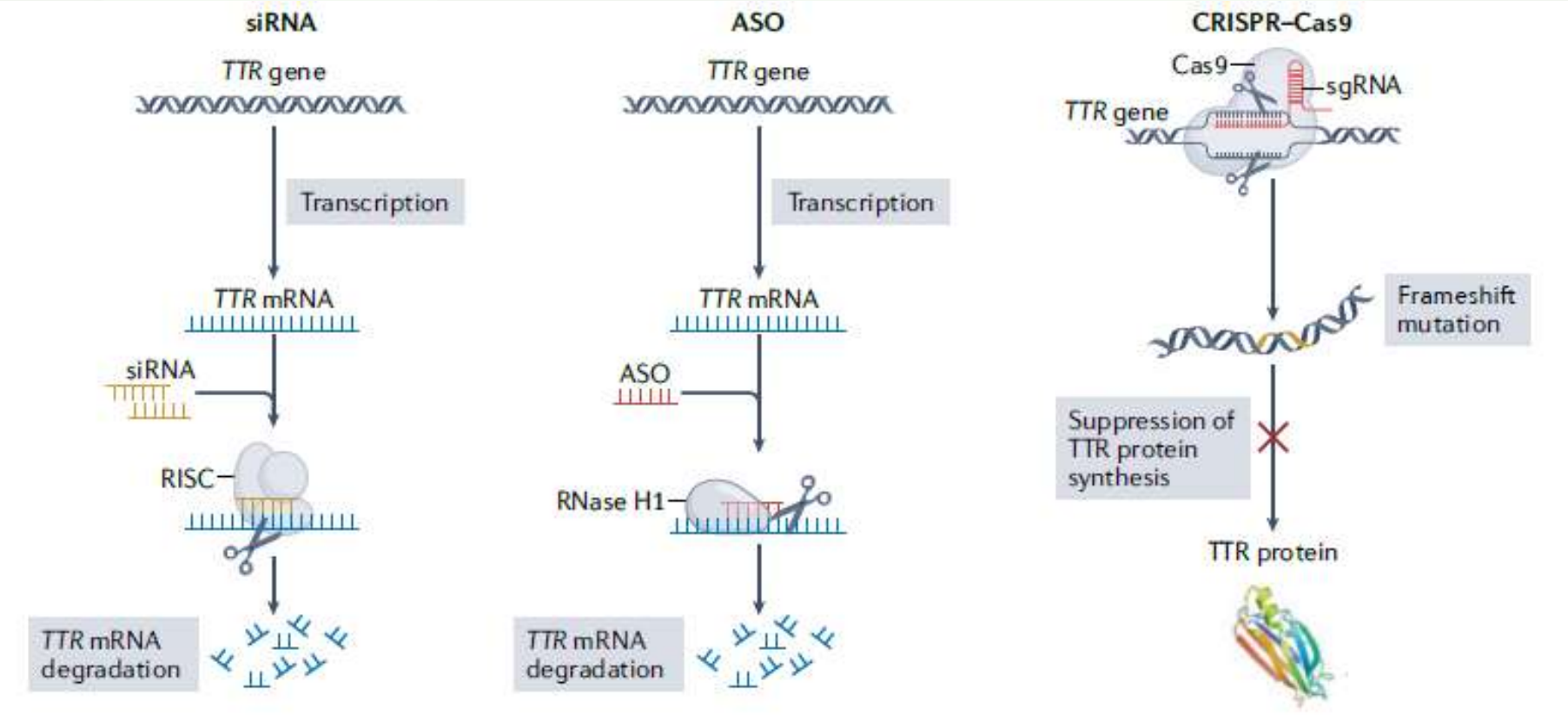

Nat Rev Cardiol. 2022;19(10):655-667.

Mean TTR knockdown of approved therapies

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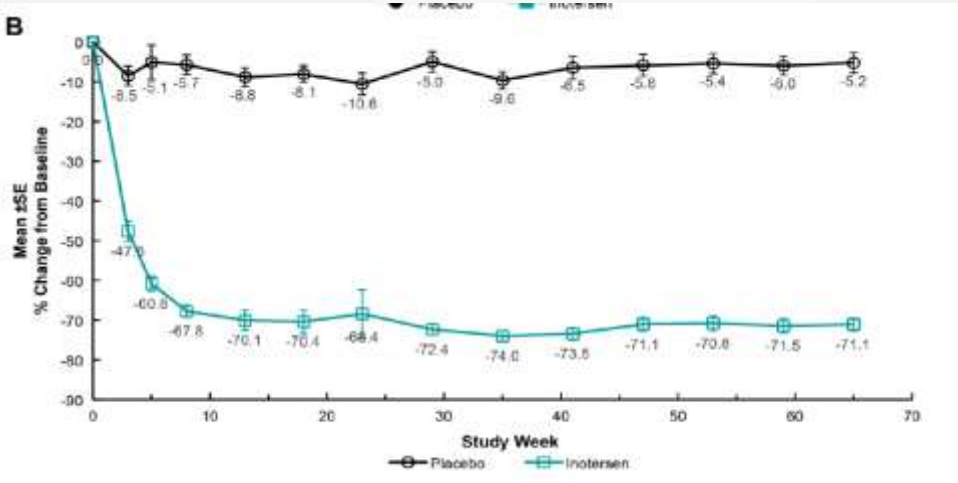
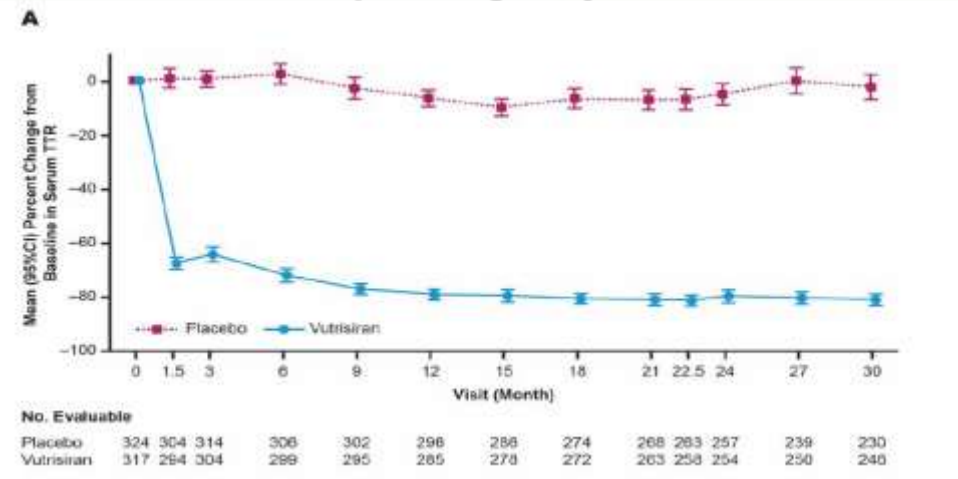
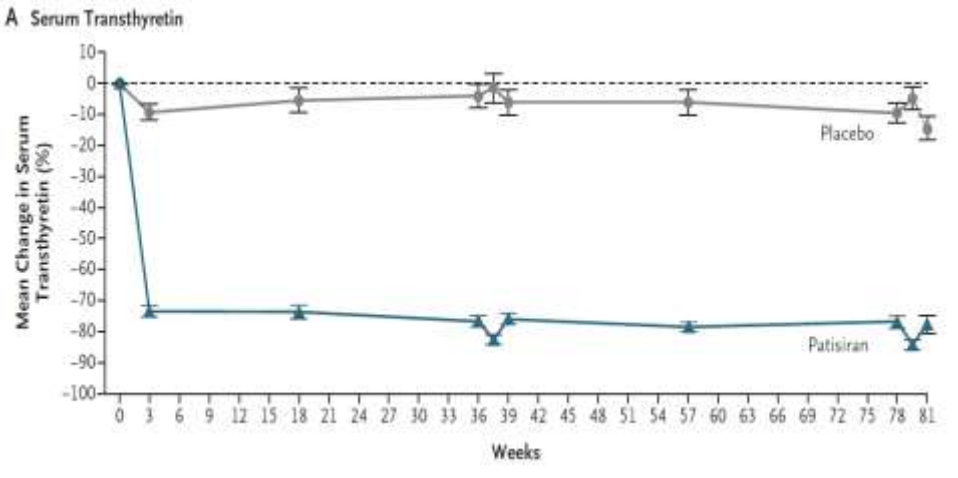
Inotersen



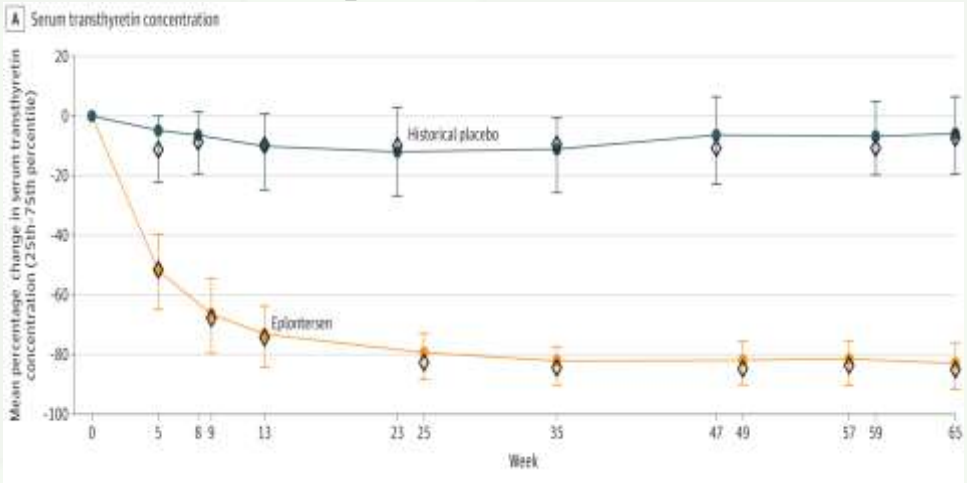
Vutrisiran



Patisiran



Eplontersen



NEJM 2018 Jul 5;379(1):11-21; NEJM 2018;379(1):22-31; NEJM 2025 Jan 2;392(1):33-44; JAMA 2023;330(15):1448-1458

Efficacy of Targeting TTR production in ATTRv-PN

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Drug	Study	TTR knockdown		mNIS+7 mean difference (95% CI)	Norfolk QOL-DN mean difference (95% CI)
		Mean	Median		
Inotersen	Neuro-TTR	71.1%	74.6%	-19.7 points (-26.4 to -13.0)	-11.7 points (-18.3 to -5.1)
Patisiran	APOLLO	78%	81%	-34.0 points (−39.9 to −28.1)	-21.1 points (−27.2 to −15.0)
Vutrisiran	Helios-A	81%	86.2 %	-28.6 points (-34 to -23.1)	-21.0 points (–27.1 to -14.9]
Eplontersen	NEURO-TTRansform	83%	85%	–24.8 points (–31.0 to –18.6)	–19.7 points (–25.6 to–13.8)

NEJM 2018;379(1):22-31; N Engl J Med 2018;379:22-31; Amyloid. 2023 Mar;30(1):1-9; JAMA 2023;330(15):1448-1458;

Efficacy of Targeting TTR production in ATTR-CM

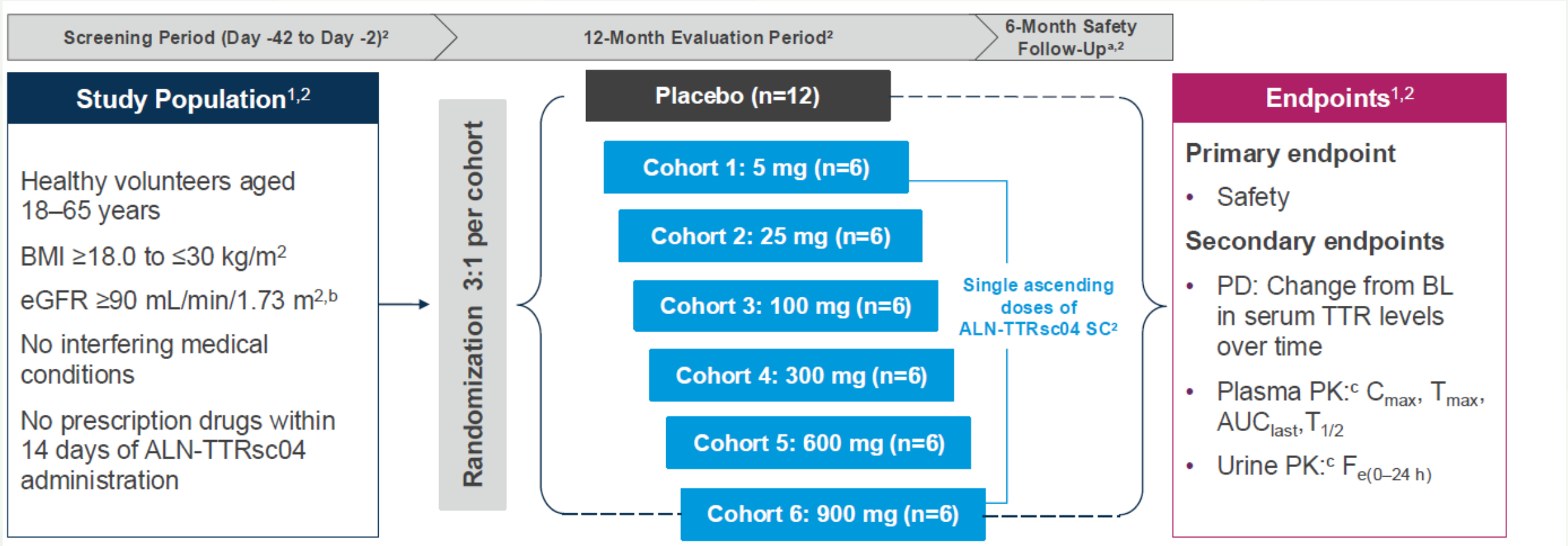
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Drug	Study	TTR knockdown Mean	Morbidity Reduction	Mortality Reduction	6MWT Difference	KCCQ Difference
Patisiran	APOLLO-B	86.8%	0.88 (95% CI, 0.58 to 1.34)		14.7 meters (95% CI, 0.7 to 28.7)	3.7 points (95% CI, 0.2 to 7.2)
Vutrisiran	Helios-B	81.0% (95% CI, 79.0 to 83.0)	0.73 (95% CI, 0.61 to 0.88)	0.69 (95% CI, 0.49 to 0.98)	26.5 meters (95% CI, 13.4 to 39.6)	5.8 points (95% CI, 2.4 to 9.2)
Eplontersen	CardioTTR ansform	**UNKNOWN – RESULTS ANTICIPATED IN 2026**				

N Engl J Med. 2023 Oct 26;389(17):1553-1565: N Engl J Med 2018;379:22-31; Amyloid. 2023 Mar;30(1):1-9; JAMA 2023;330(15):1448-1458;

Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study of nucresiran

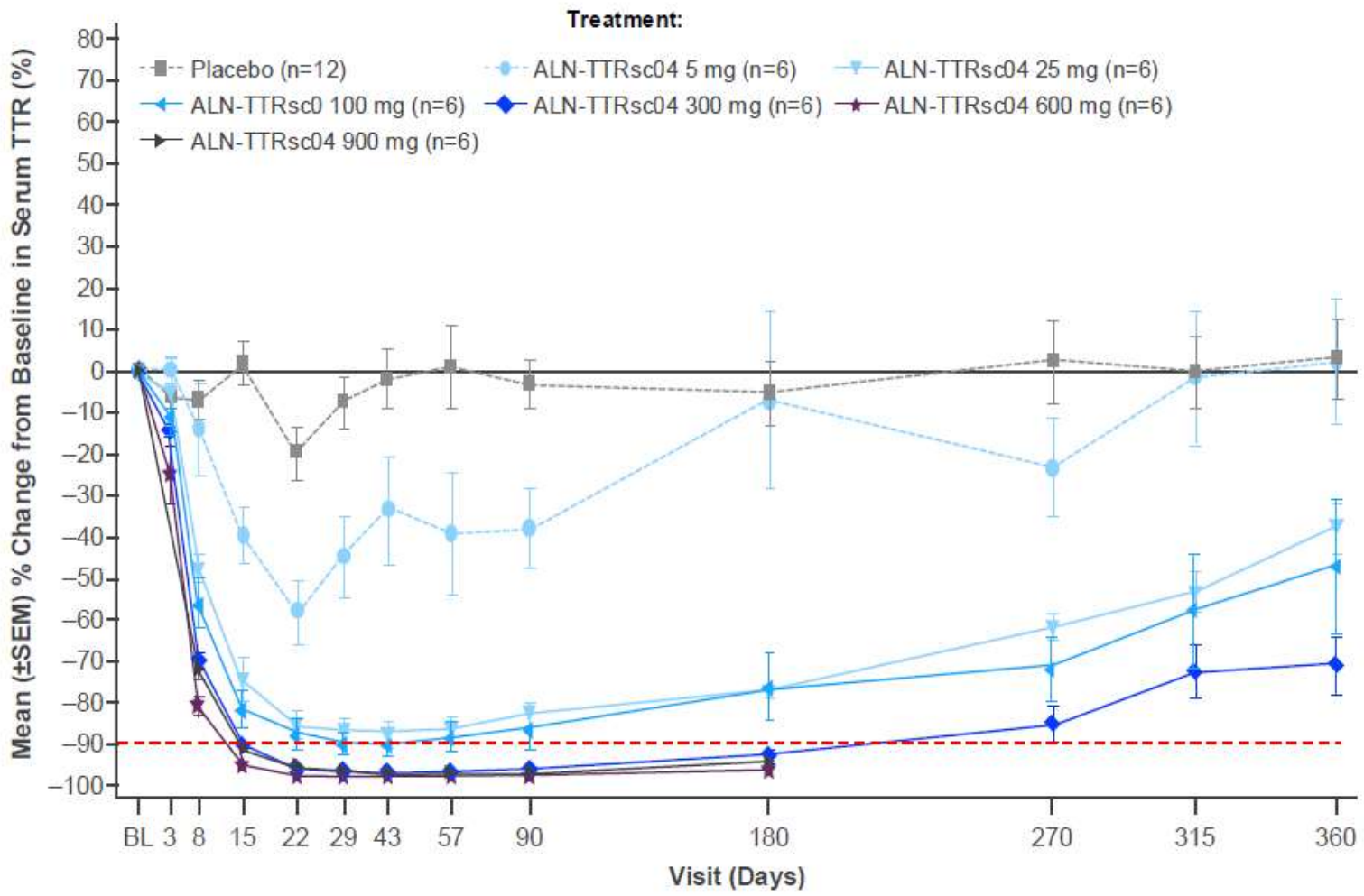
ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



Murad A, Presented at AHA 2024 Congress

Mean Percent Change from Baseline in Serum TTR Levels over Time with nucresiran

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

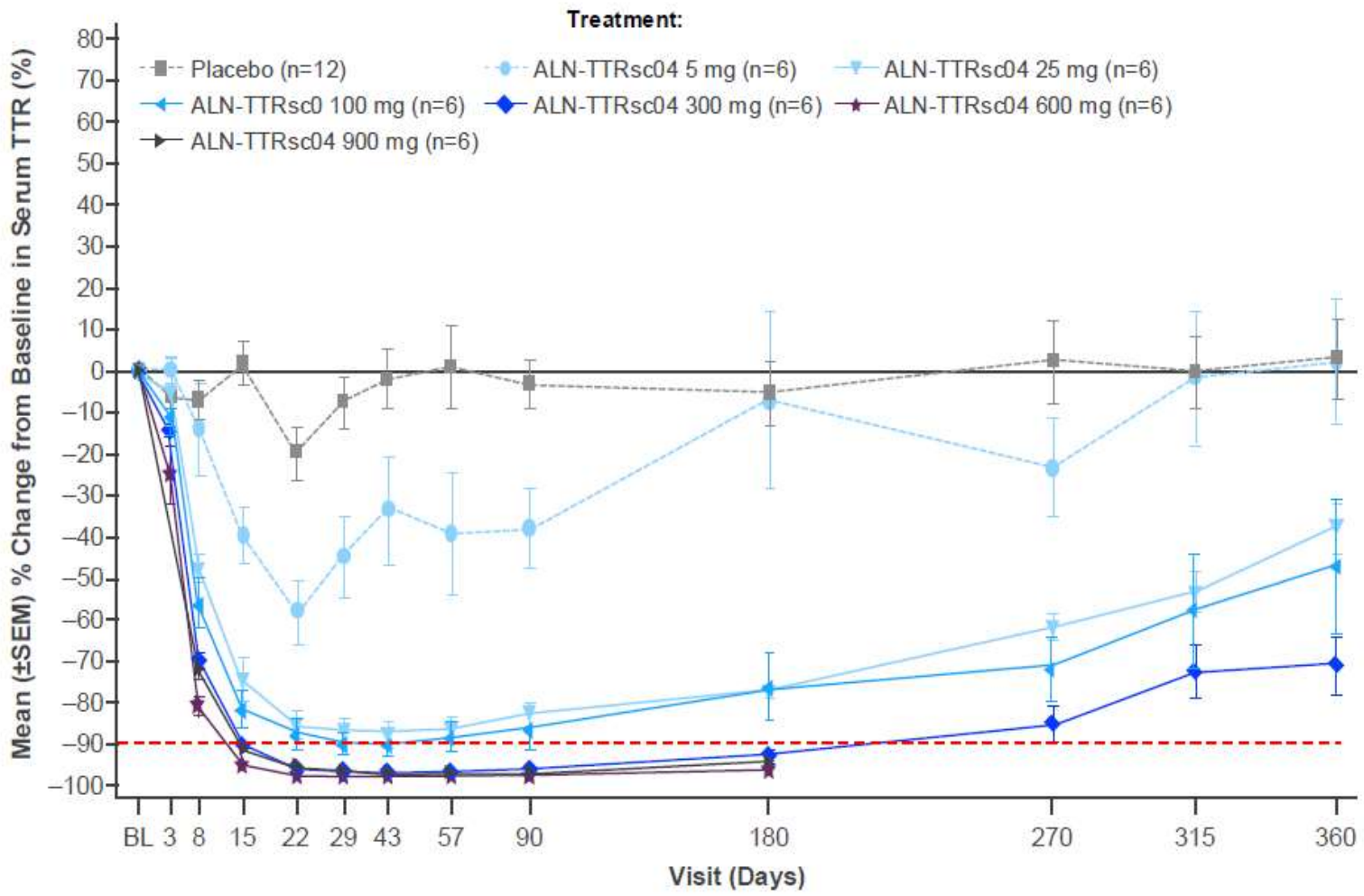


- **Rapid** knockdown in serum TTR at Day 15; mean reductions of 90.3% (300 mg), 95.0% (600 mg)
- **Deep** knockdown of TTR by Day 29; mean reductions of 96.5% (300 mg), 97.8% (600 mg)
- **Sustained** knockdown of TTR through Day 180; mean reductions of 92.6% (300 mg), 96.0% (600 mg)
- **Low variability** of TTR knockdown on Day 29 (% TTR reduction range): 96.0–96.7% (300 mg), 96.6–98.6% (600 mg)

Murad A, Presented at AHA 2024 Congress

Mean Percent Change from Baseline in Serum TTR Levels over Time with nucresiran

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



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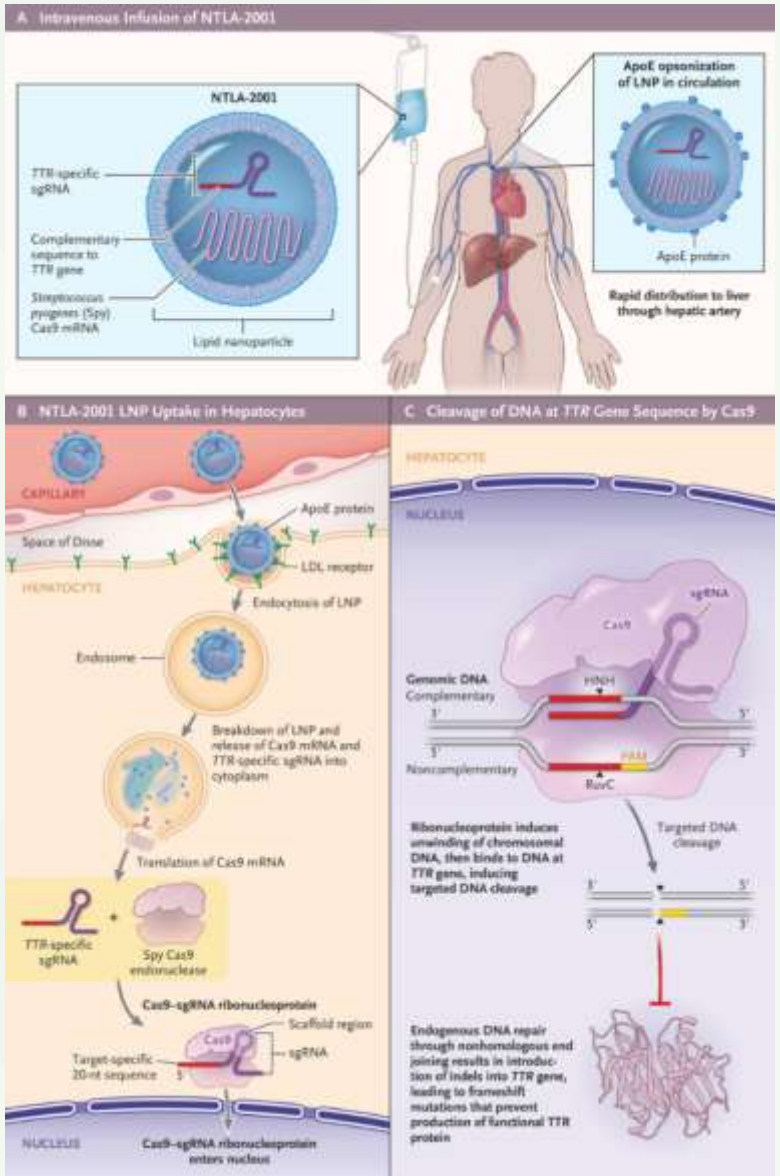
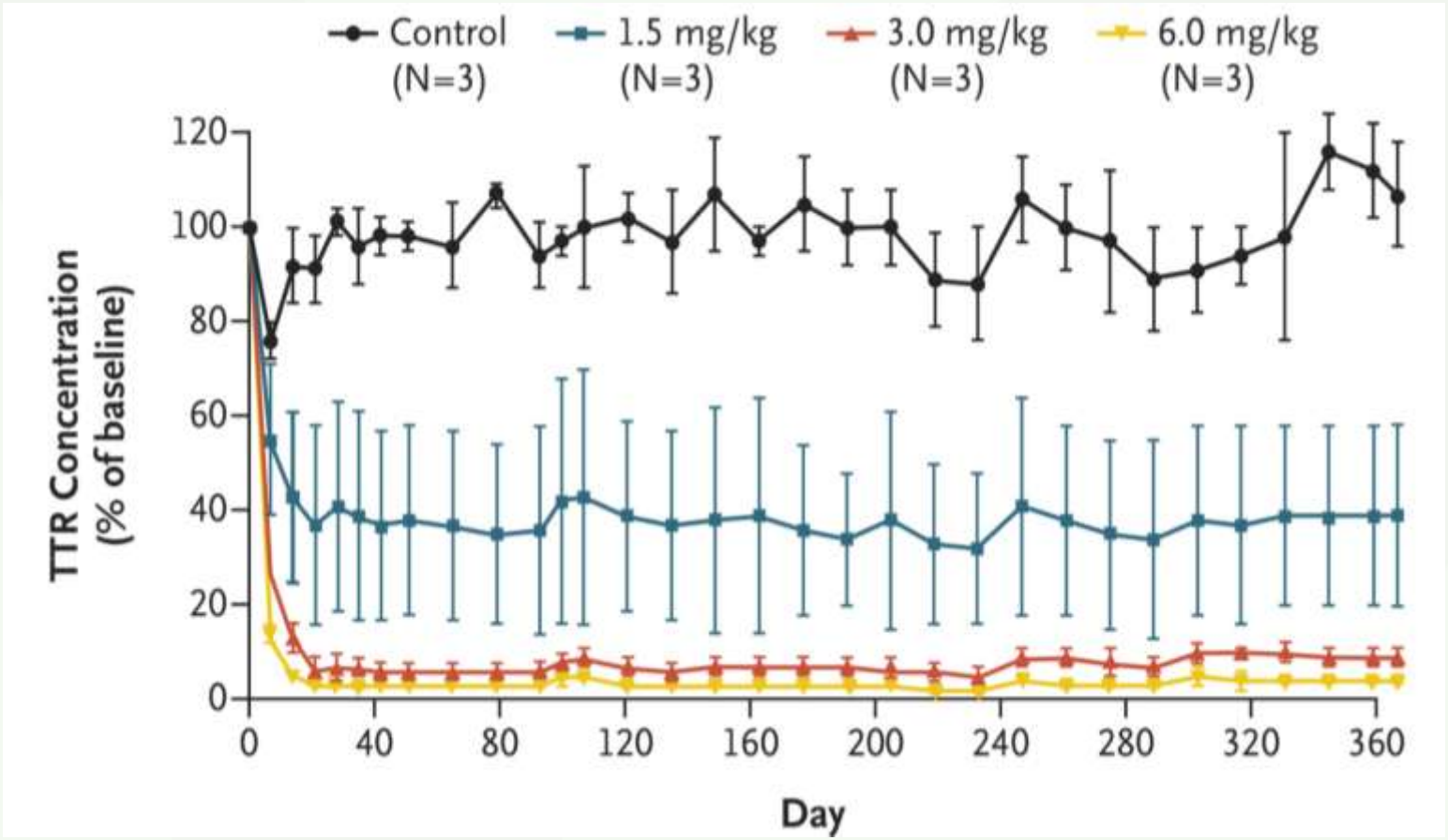
Murad A, Presented at AHA 2024 Congress

TTR Gene Editing via CRISPR-Cas9

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

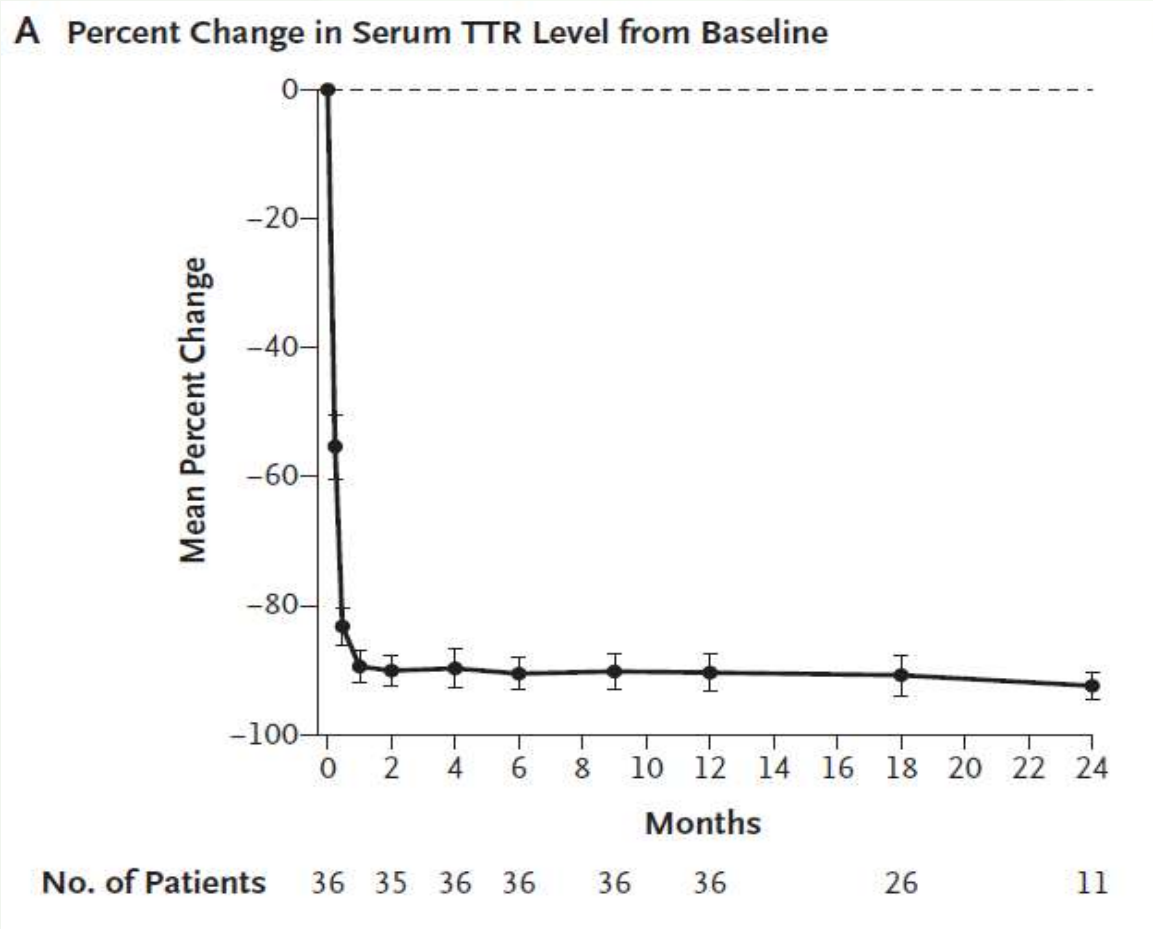


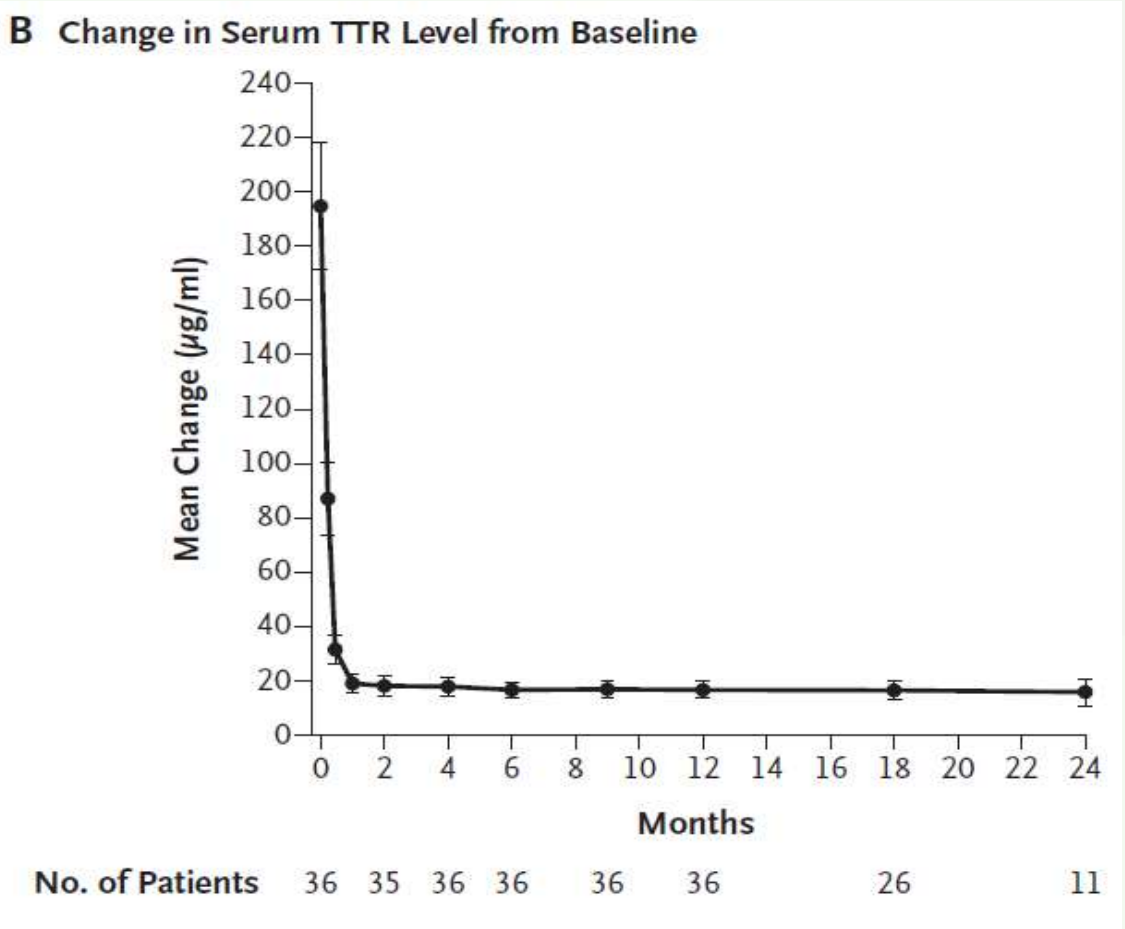


N Engl J Med 2021;385:493-502

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR-CM

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

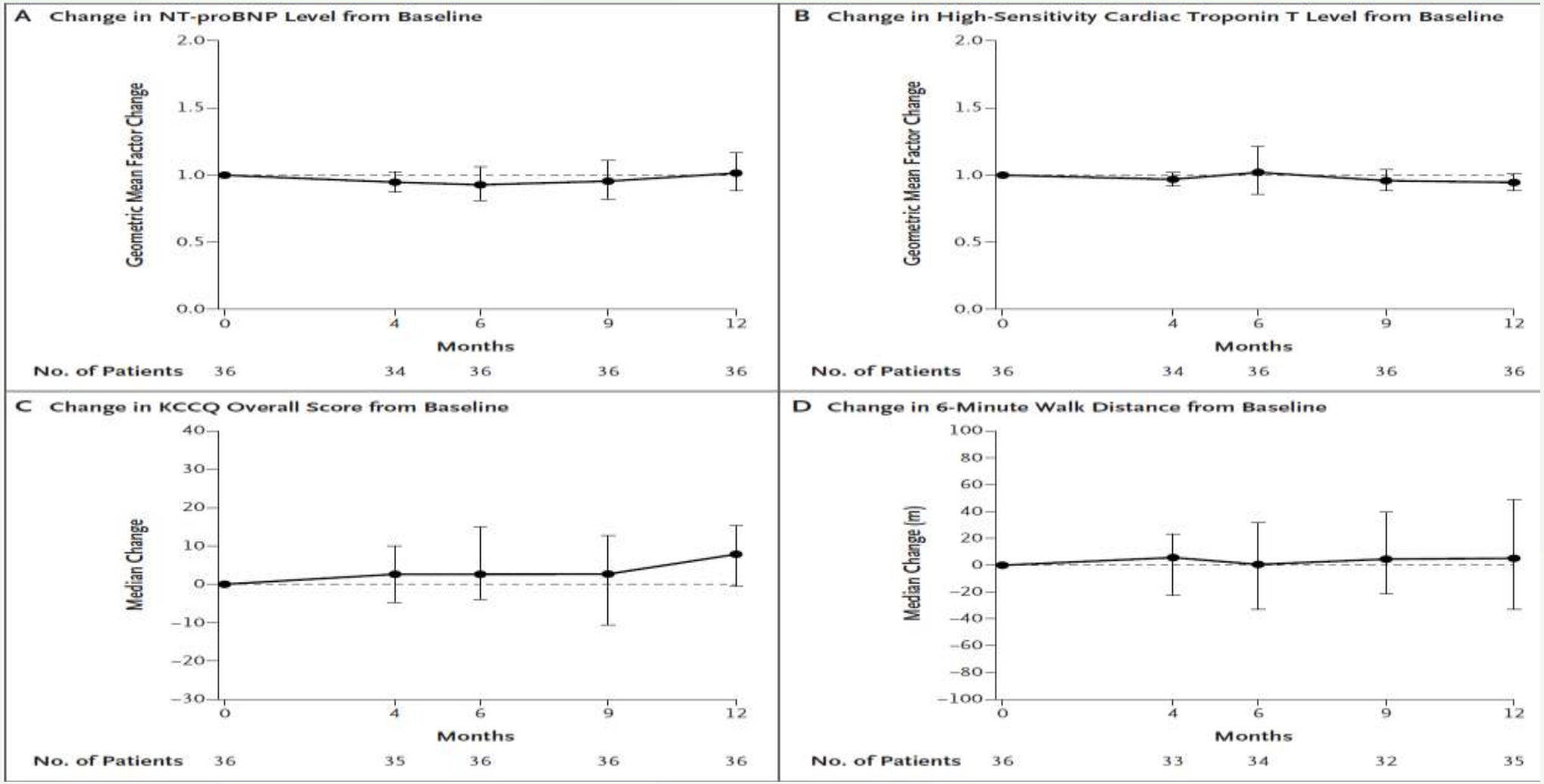




N Engl J Med. 2024 Dec 12;391(23):2231-2241

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR-CM

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS



N Engl J Med. 2024 Dec 12;391(23):2231-2241

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

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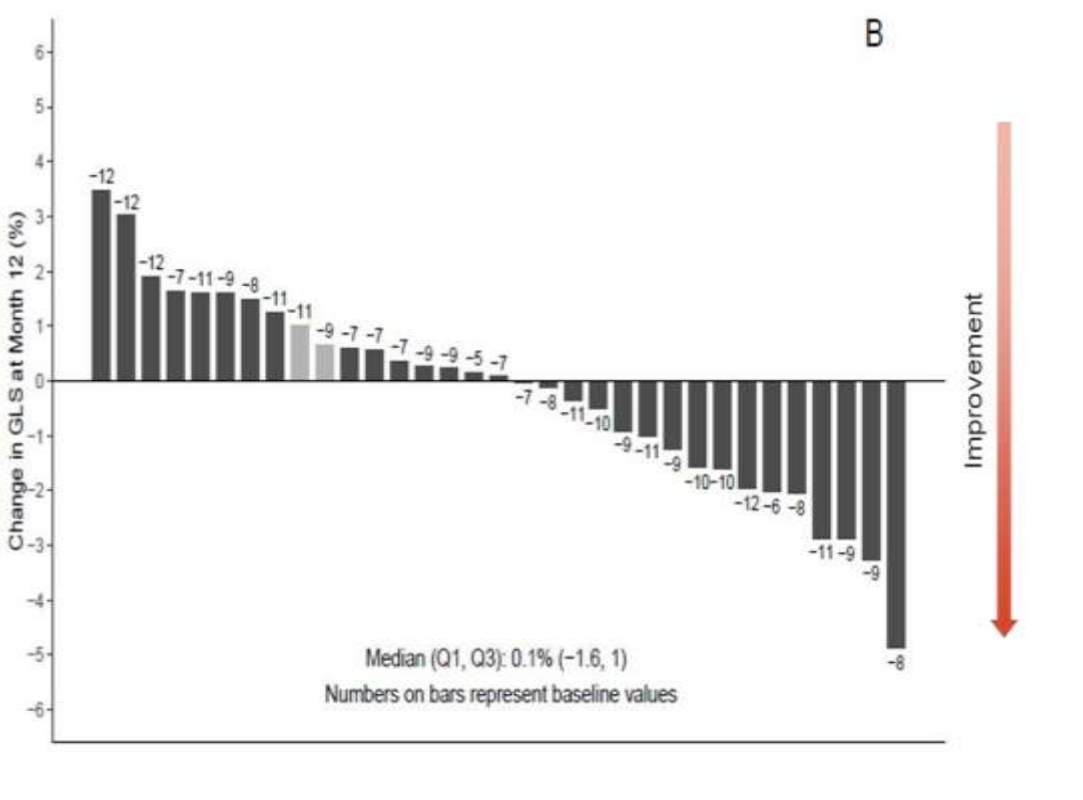
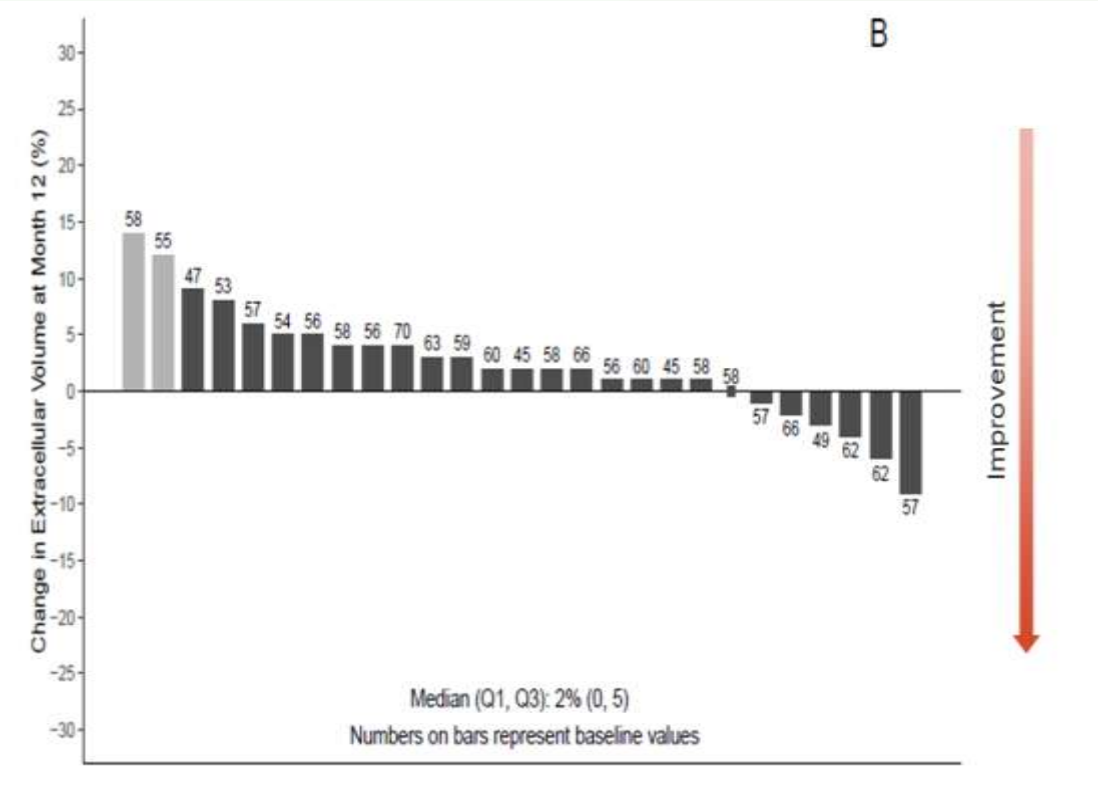
Changes in GLS (%)



Change in ECV (%)



N Engl J Med. 2024 Dec 12;391(23):2231-2241

Magnitude – Phase 3 Trial of CRISPR in ATTR-CM

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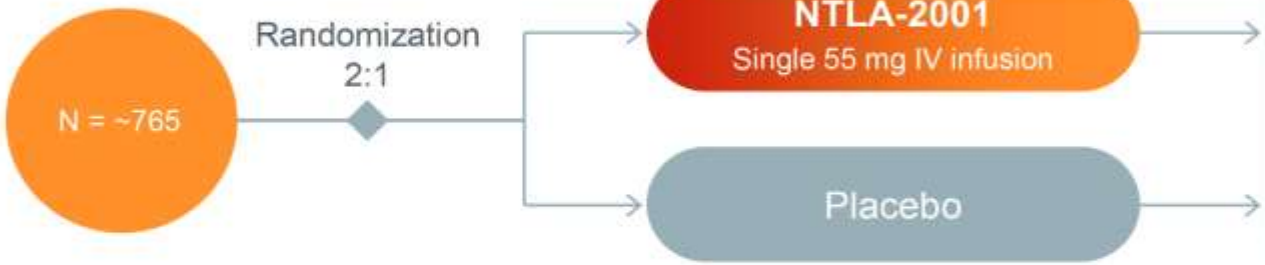
MAGNITUDE
ATTR-CM

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 in Patients with ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)



Primary Endpoint

- Composite endpoint of CV-related mortality and CV-related events

Key Secondary Endpoints

- Serum TTR
- KCCQ-OS score

Key Eligibility Criteria:

- Adult patients with diagnosis of either hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/mL

Stratification:

- NAC stage
- TTR genotype: wild-type vs. mutant
- Concomitant tafamidis use vs. no tafamidis

Study Duration:

- Dependent on occurrence of pre-specified number of CV events and a minimum of 18 months follow-up
- Majority of patients are expected to have ≥ 30 months of follow-up for the primary analysis

Summary

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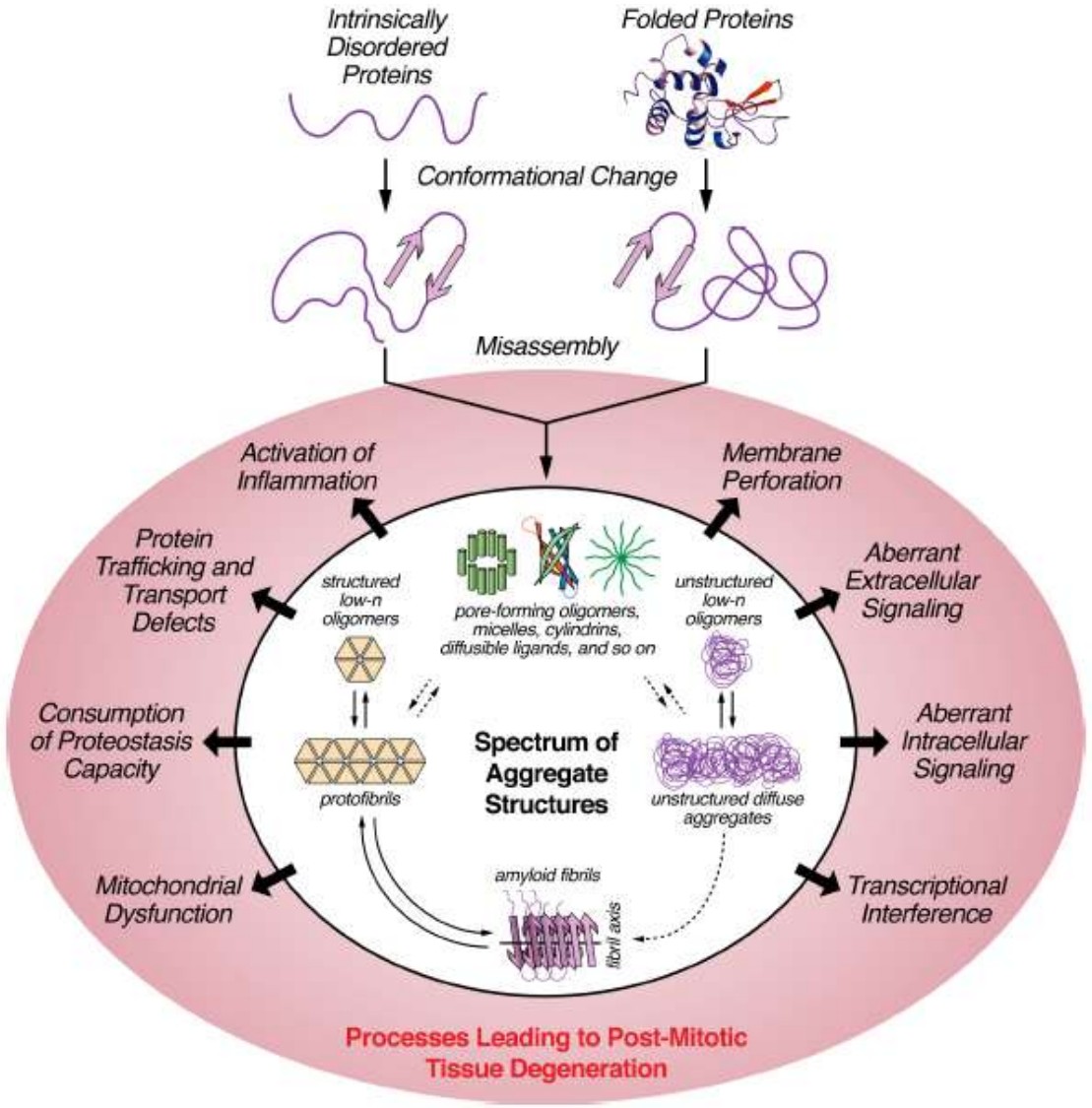
- Reductions in hepatic produced TTR is achieved with various agents.
- Data from trials in ATTRv-PN patients have established TTR reduction as highly effective.
- Initial phase III clinical trial (Helios B) demonstrated the clinical efficacy of this approach using vutrisiran in ATTR-CM.
- Several other TTR lowering agents are in phase III clinical trials with favorable results anticipated.

The Scientific Origins of Drugs That Slow Neurodegeneration–Targeting the Precursors for AL

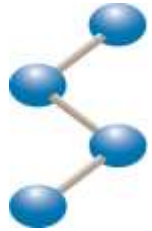
ISA Pavia October 2025

Jeffery W. Kelly
Scripps Research Institute

Amyloid Disease Etiology–Myriad Abnormal Conformations in Proteins Lead to Gain of Proteotoxicity

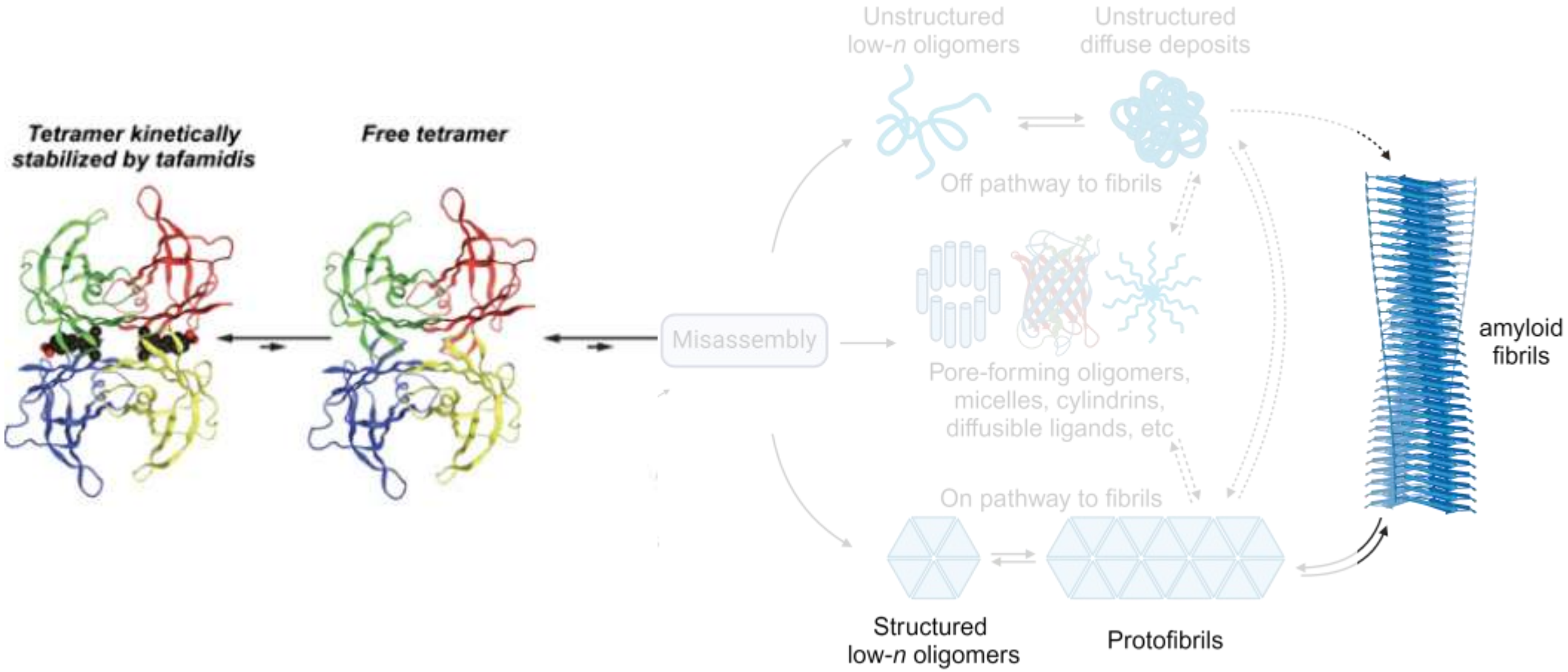


Category 1 Drugs Stop Newly Synthesized Protein Aggregation, But do Not Clear Amyloid Fibrils

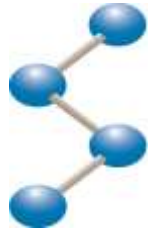


- Kinetic Stabilizers
  - Tafamidis
  - Diflunisal
  - Acoramidis
- mRNA Degraders
  - Inoteresen, and Eplontersen–Antisense Oligonucleotides
  - Patisiran and Vutrisiran–RNAi-based drug
  - Tofersen–Antisense Oligonucleotide (Ionis 1st Drug for ALS)

Stabilizer Binding to the Properly Folded Full-length Transthyretin or Transthyretin mRNA degradation Prevents Aggregation Enabling Non-native Transthyretin Clearance Slowing Neurodegeneration



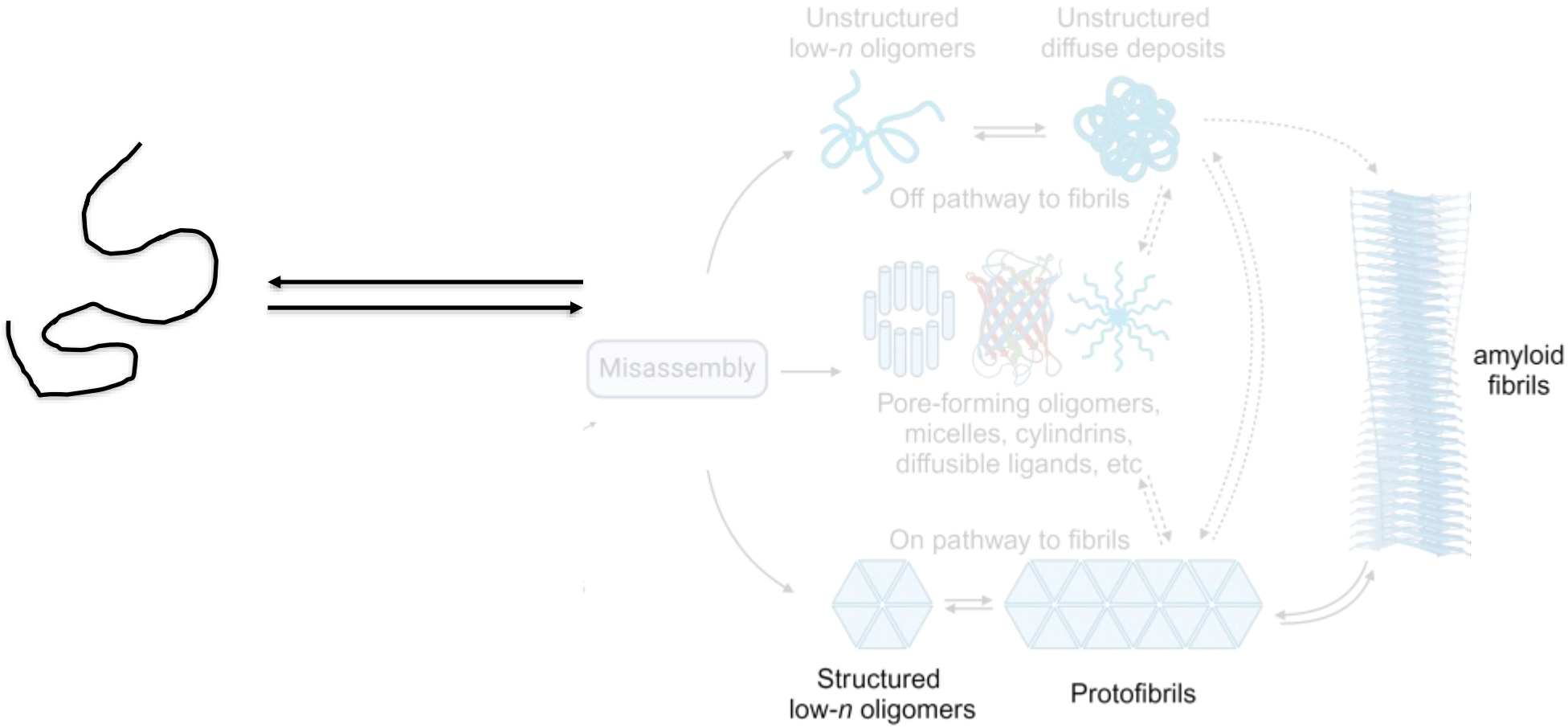
Category 2 Drugs Clear Amyloid Fibrils, and Stop the Aggregation of Newly Biosynthesized Proteins



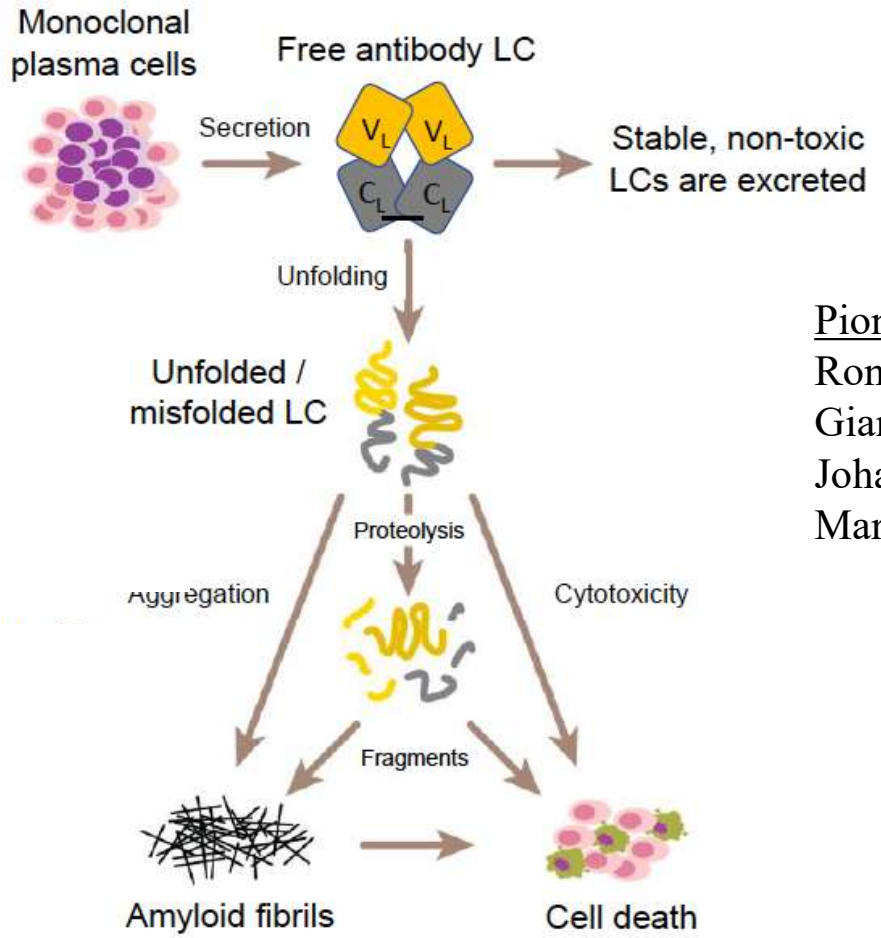
- Aducanumab-FDA Approved–Abandoned
- Lecanemab- Actively being used in the AD patient setting
- Donanemab-FDA Approved

These Monoclonal Antibodies bind amyloidogenic proteins and recruit Microglial Cells and Macrophage Cells to degrade the cross–β–sheet Amyloid Fibrils and structurally heterogeneous aggregates by cellular endolysosomal uptake and an autophagy-lysosome mediated degradation

Monoclonal Antibody Binding to Aβ Oligomers / Amyloid Fibrils Followed by Microglial Recruitment Likely Clears All Misassemblies. Thus Structure–Proteotoxicity Relationship Unclear

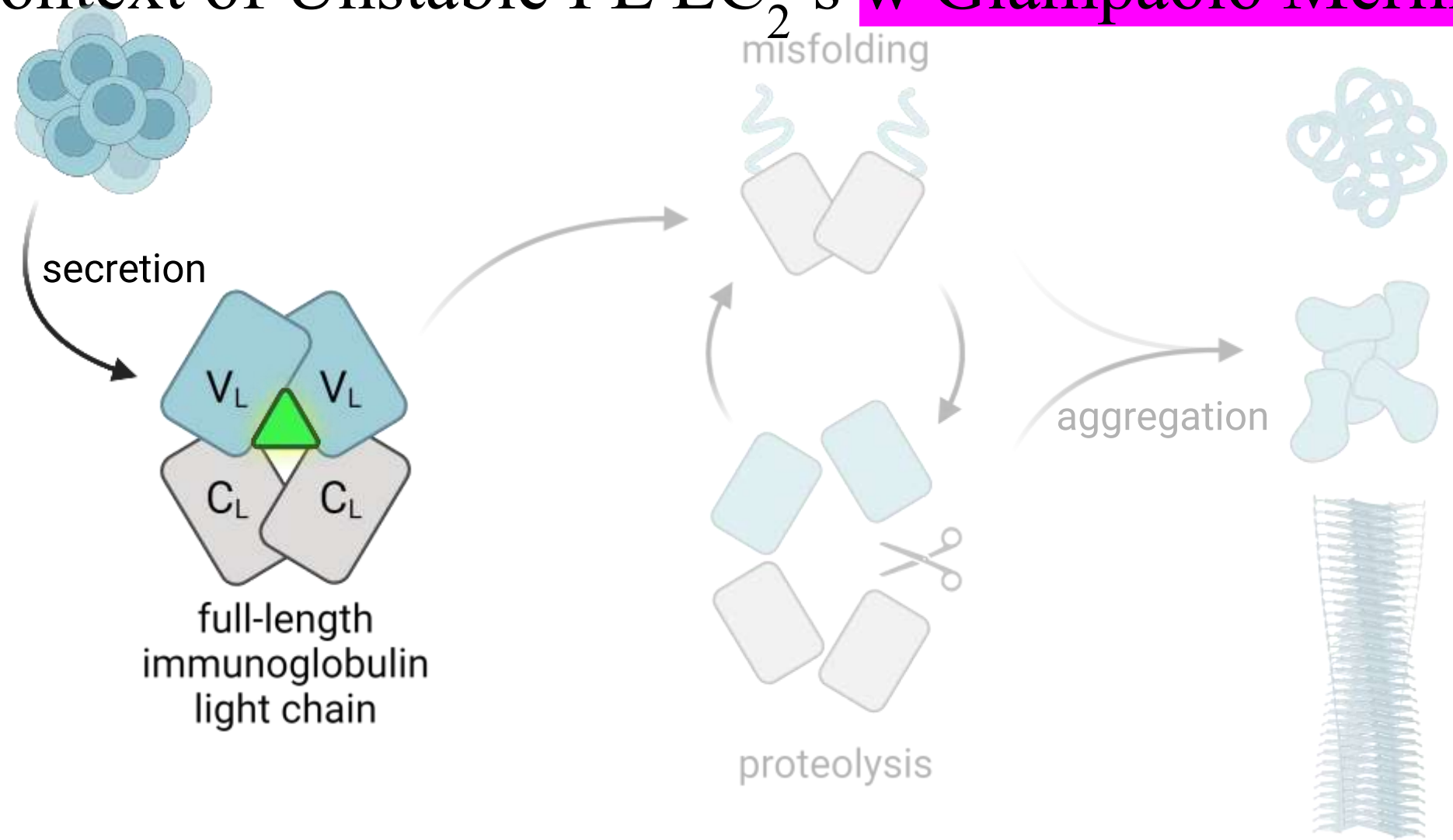


Light Chain Amyloidosis is a Both a Plasma Cell Cancer and a Proteinopathy–Treated Pharmacologically as a Cancer so far…



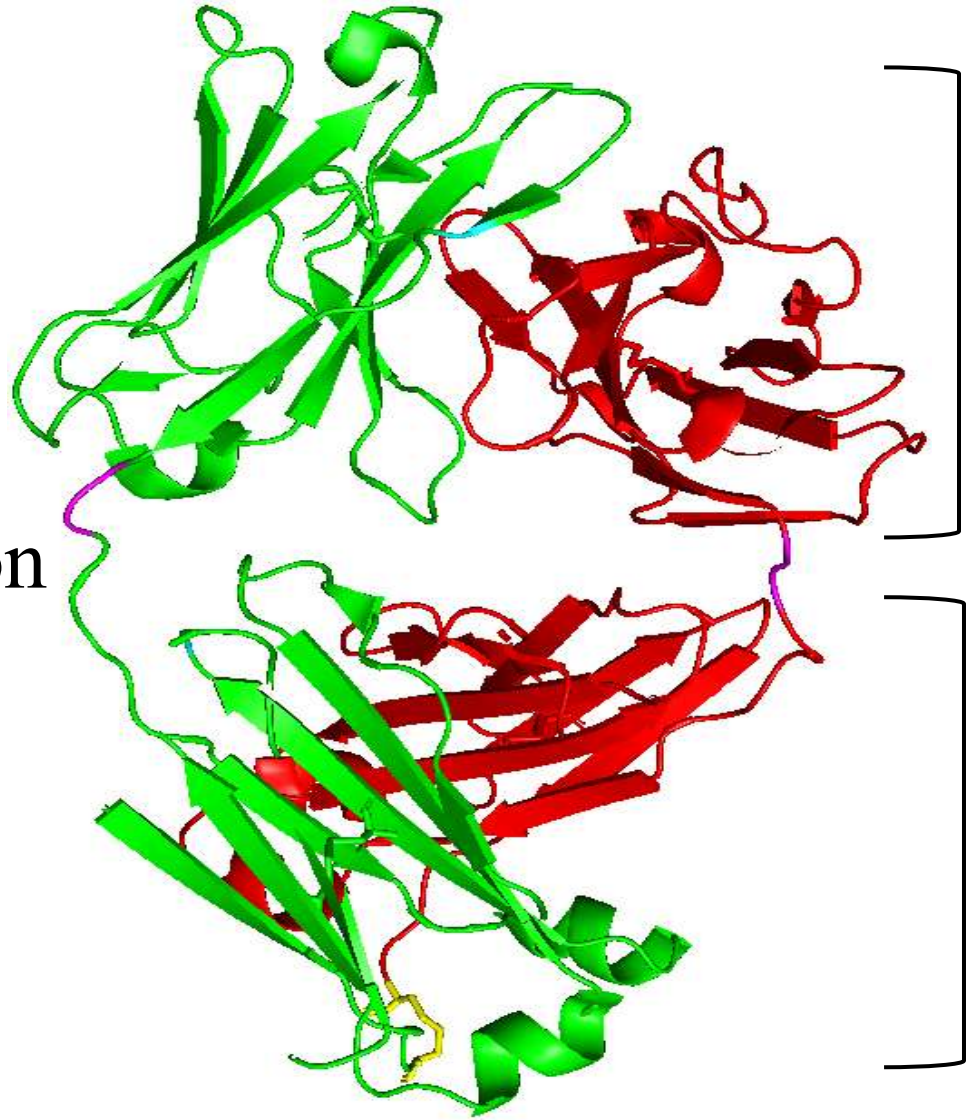
Pioneers in Light Chain Amyloidosis
Ron Wetzel
Giampaolo Merlini
Johannes Buchner
Marina Ramirez Alvarado

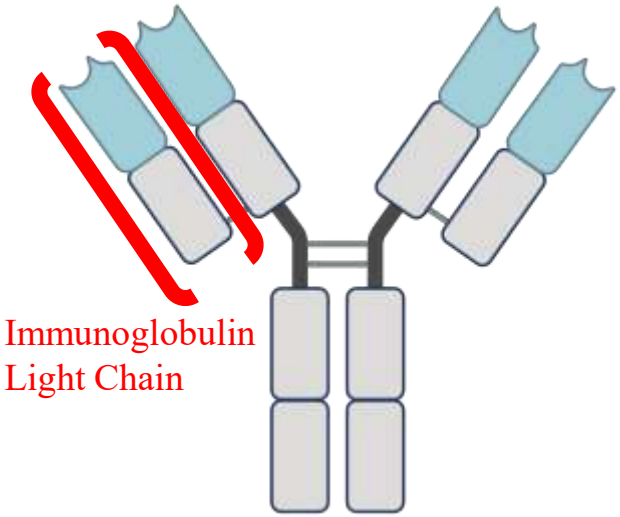
Kinetic Stabilizers Prevent V_L Dissociation, Misfolding and Aberrant Proteolysis of FL LCs in Context of Unstable FL LC_2's w Giampaolo Merlini



Native Full-length Light Chain Dimers Adopt a Well-defined β-Sheet-rich Structure with no known Function–Also Left over From Antibody Secretion

Full-length light Chain Concentration = 1 uM

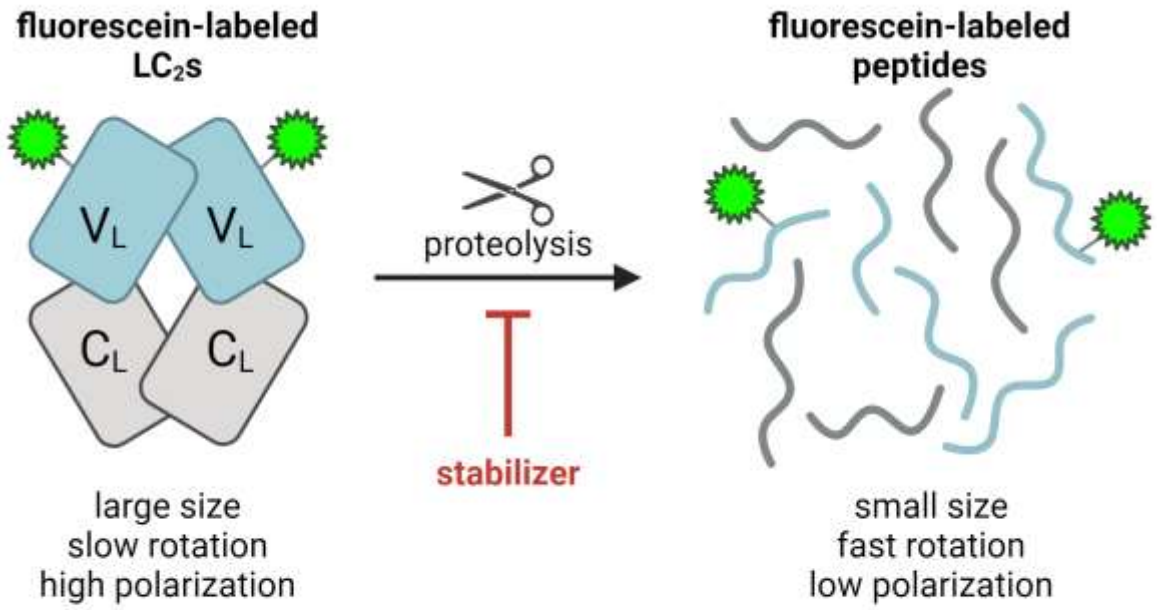




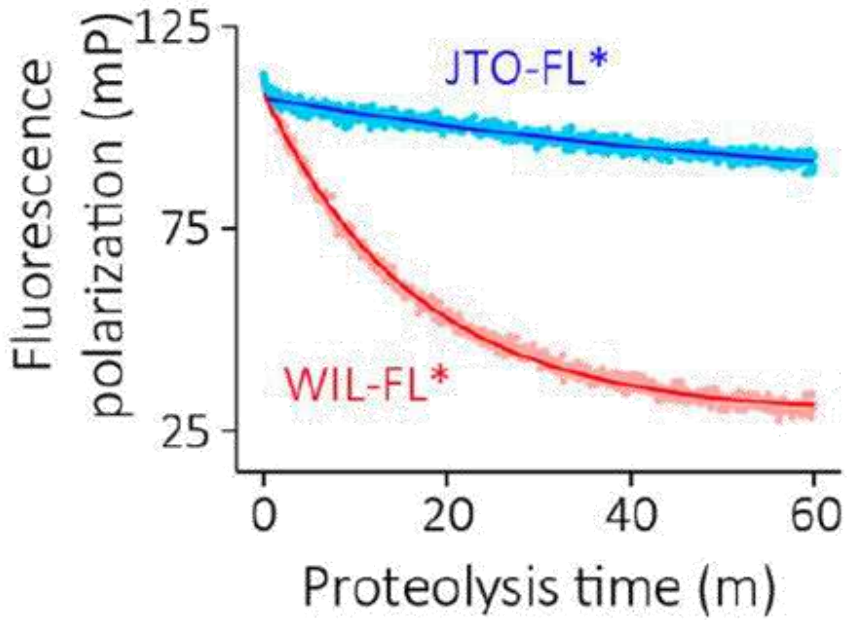
Antibody

A High-throughput FL LC Protease Sensitivity Screen Read Out by Fluorescence Polarization Identified Stabilizers with Micromolar K_D's–Gareth Morgan

Partial Unfolding of Full-length Light Chains is Rate-limiting for Proteinase K Cleavage



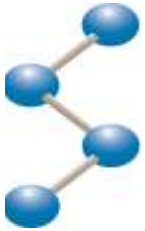
Protease-Coupled Fluorescence Polarization



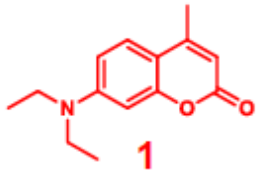
Morgan and Yan, et al. *Proc Natl Acad Sci*, 2019.

Created with BioRender.com

We identified 16 validated hits from 5 structural classes (chemotypes) K_D's in uM Range

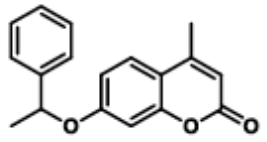


Coumarins



1

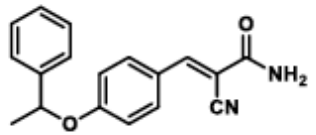
EC_{50} = 3.3 µM



3

2.0 µM

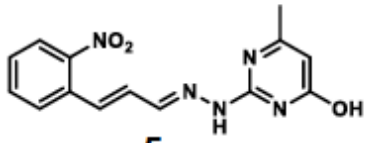
Aryl cyanoacrylamide



4

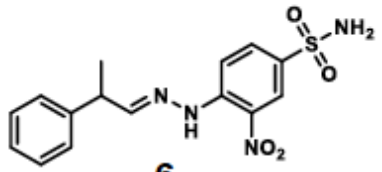
2.6 µM

Diaryl hydrazones



5

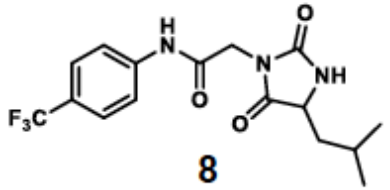
1.9 µM



6

1.3 µM

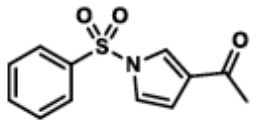
Hydantoins



8

2.9 µM

Sulfones



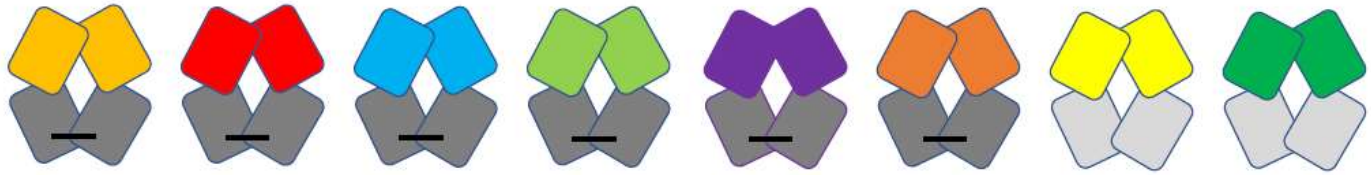
17

18.5 µM

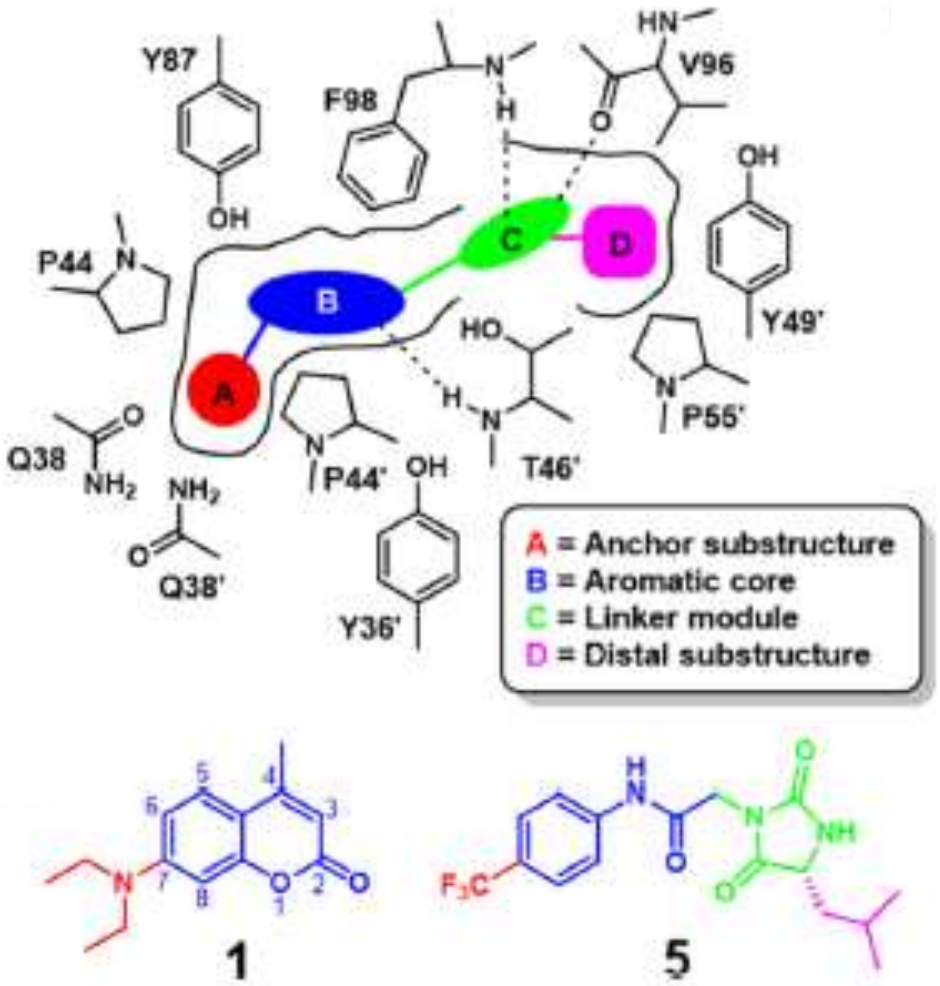
Scripps Research

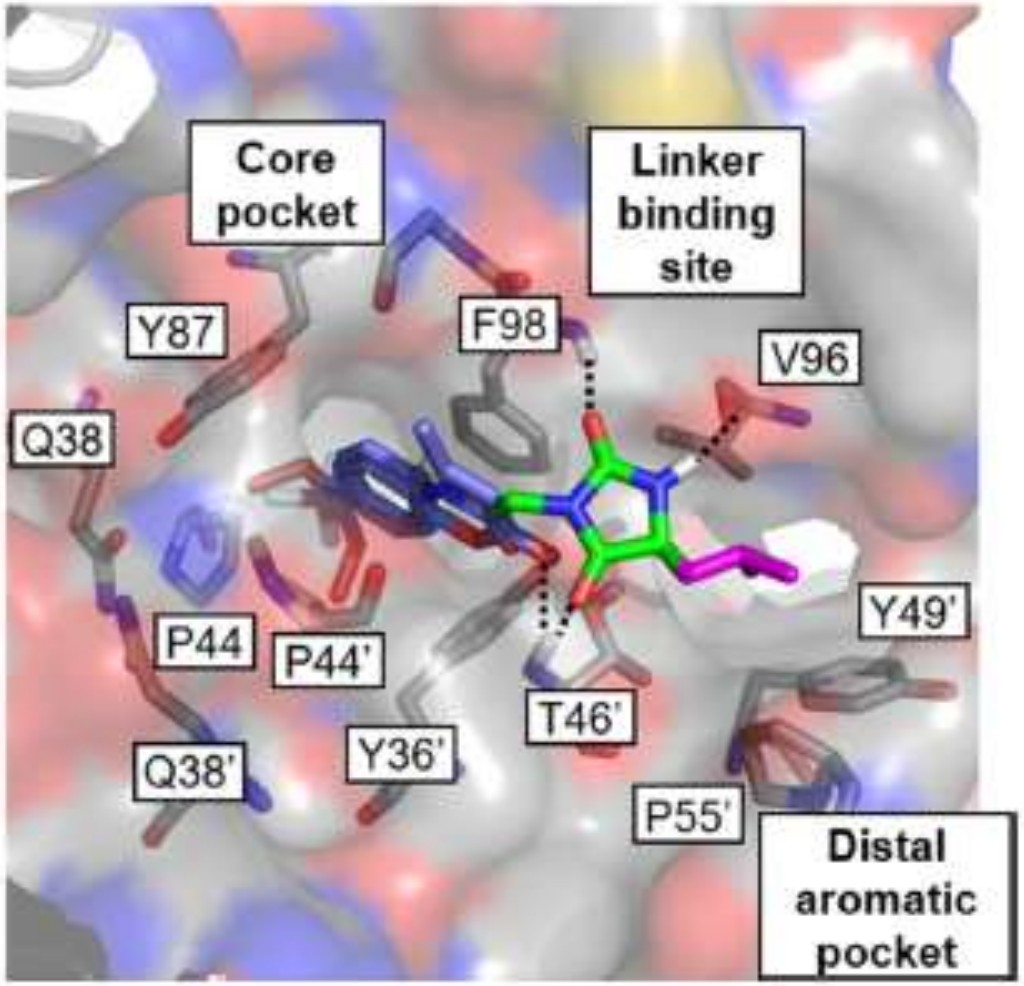
Morgan and Yan, et al. *Proc Natl Acad Sci*, 2019.

- **Each AL patient has a unique LC sequence**

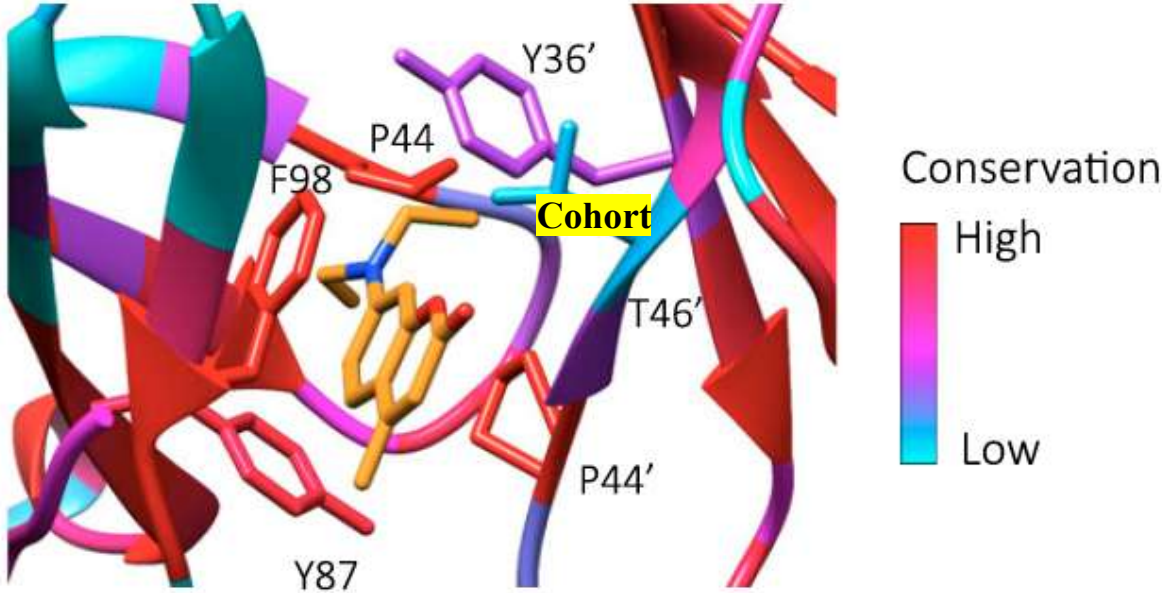


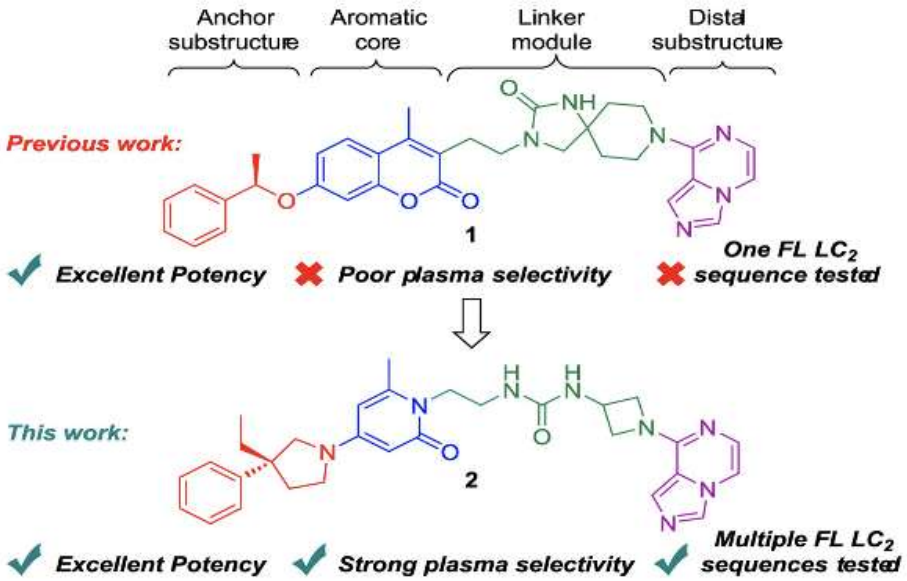
We Solved Co-crystal Structures of All of the Hits from the High Throughput Screen Which Mapped out the Conserved Small Molecule Binding Site





Kelly Lab Designed and Syntheized 1000+ Kinetic Stabilizers and Protego Mike Petrassi/Steve Wilkens Designed Made 2000+ Kinetic Stabilizers to Arrive at PROT001 = lambda Selective Clinical Trial Drug

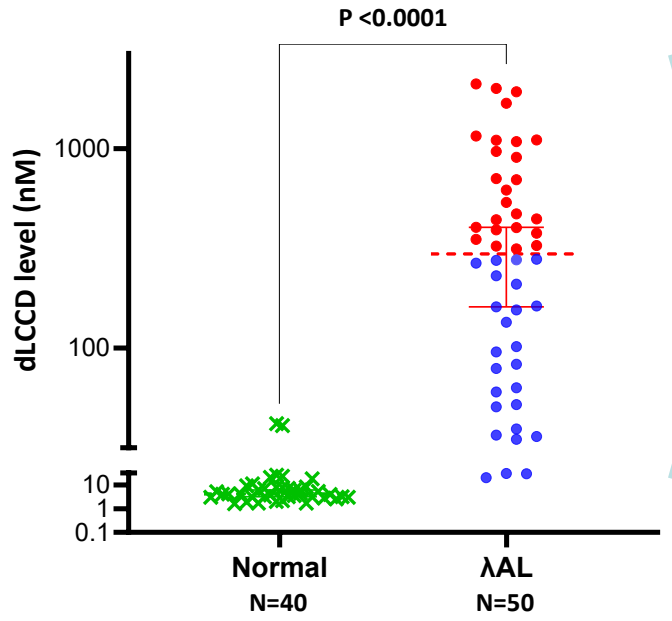




Protego Biopharma Phase 1 Clinical Trial on 5th SAD Cohort & First Multiple Dose Cohort

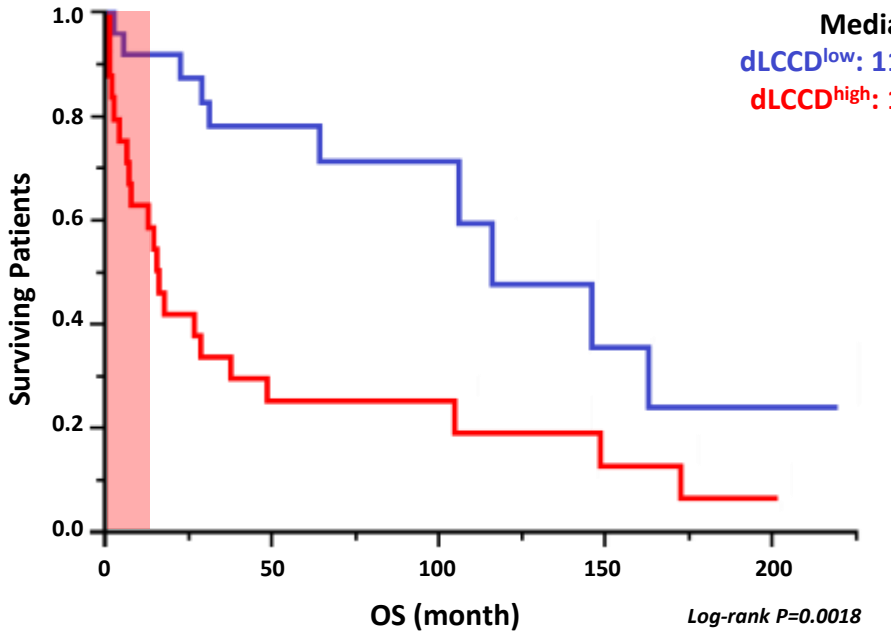
Kelly lab / Protego / Mayo Clinic Establish Correlation Between FL LC Kinetic Stability via Protease Sensitivity and Prognosis

AmyLite assay (dLCCD)
Plasma samples post proteolysis[1]



Proprietary dLCCD signal is specific for toxic FLC and is detected across AL patient samples

Poor survival outcomes in patients with high dLCCD (toxic FLC)[1]

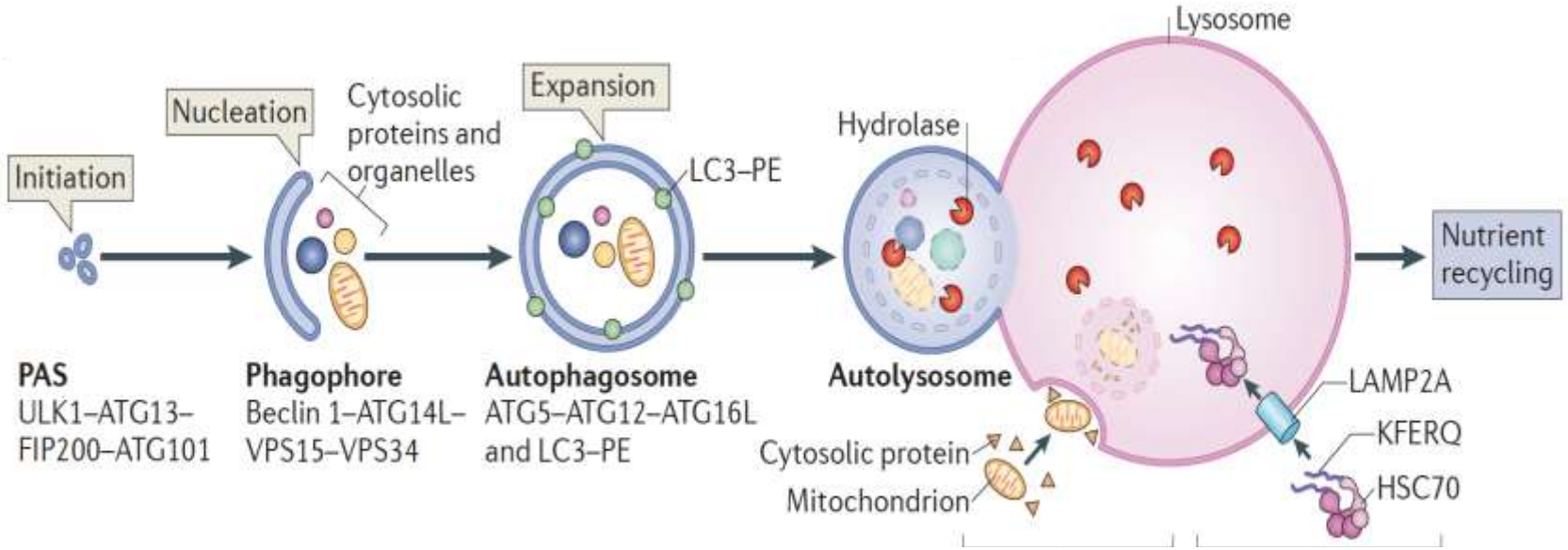


Stabilizing and reducing toxic FLC should address early and long-term mortality

1. Data analysis through collaboration with Mayo Clinic and Eli Muchtar, M.D., first group to generate this dataset 2. Median level of dLCCD in the 50 pre-treatment AL plasma samples FLC = free light chain dLCCD – protein fragment following proteolysis SOC = standard of care nM = nanomolar OS = overall survival

Autophagy: A cellular recycling pathway

Lysosomal degradative process used to recycle obsolete cellular constituents and eliminate damaged organelles, protein aggregates, and lipids–there is also constitutive turnover of cellular constituents



> 400 proteins support basal autophagy network

***Nature* 2010, *466*, 68-76.**

***Nat Rev Drug Disc* 2007, *6*, 304-312.**

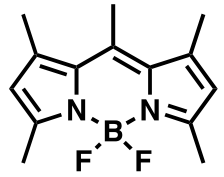
***Nat Rev Mol Cell Bio* 2015, *16*, 461-472.**

Lipophagic Lipid Droplet Degradation as the Basis for HTS for Discovery of Lysosomal Flux Activators

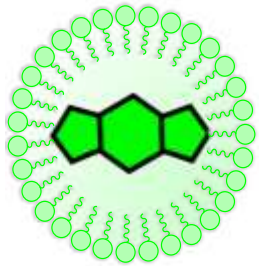
Fluorogenic lipid probe:

BODIPY 493/503

Hydrophilic environment

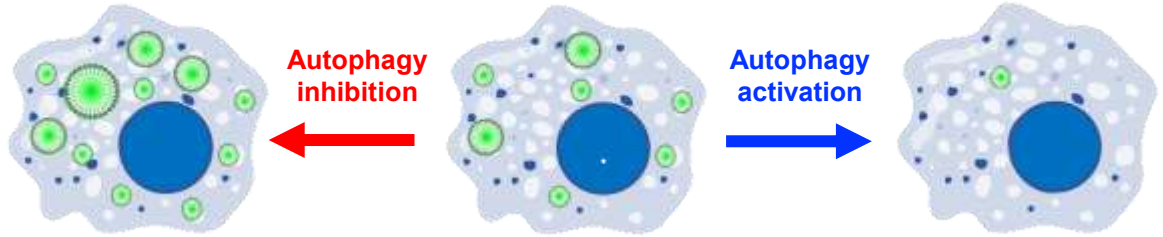


Hydrophobic environment (lipid droplet)



Rachel Botham
Kristen Johnson

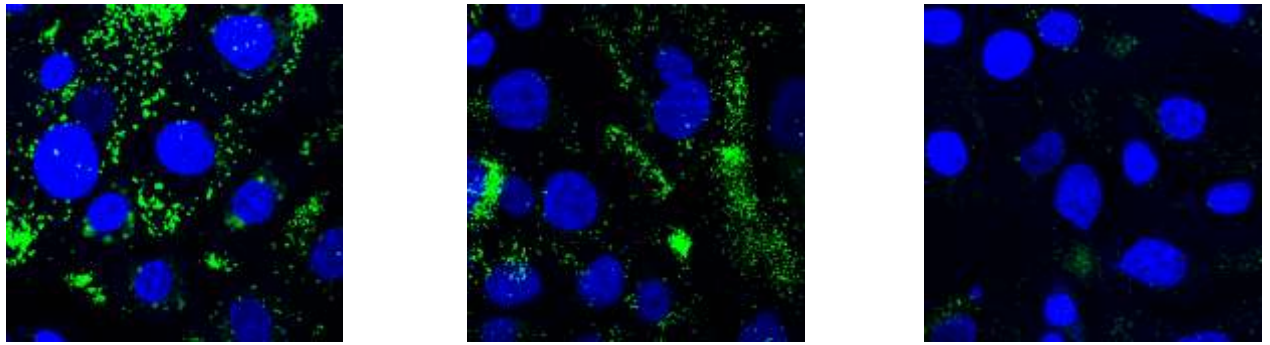
In cells:



Increased cellular fluorescence

Feed cells 10 µM oleic acid

Decreased cellular fluorescence



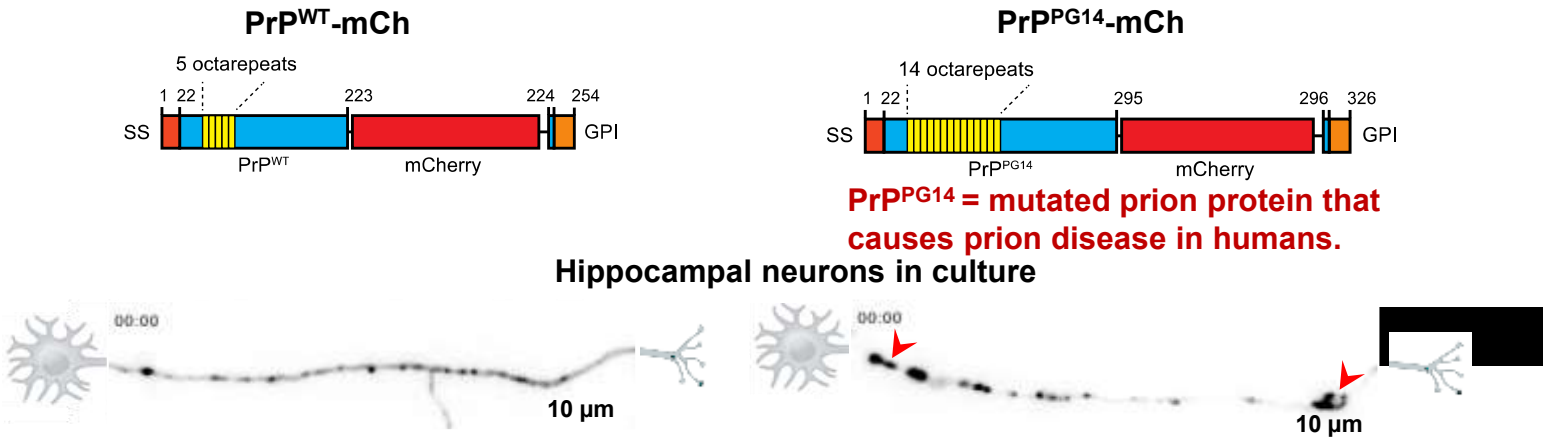
+ Lysosomal neutralizing agent

Control

+ Autophagy activator

Inspired by a low-throughput pilot, high content imaging screen by Lee et al. – *Chem Sci* 2013, *4*, 3282 and Singh, R.; Kaushik, S.; Wang, Y. J.; Xiang, Y. Q.; Novak, I.; Komatsu, M.; Tanaka, K.; Cuervo, A. M.; Czaja, M. J. "Autophagy regulates lipid metabolism" Nature 458, 1131.

Adriaan Verhelle Encalada Laboratory has Demonstrated that Expression of Disease-causing Mutant PrP in Primary Hippocampal Neurons Results in Axonal Aggregates



In collaboration with Encalada Laboratory

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Joel Buxbaum, M.D.

THE JPB FOUNDATION
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The Development of Anti-Amyloid Fibril Immunotherapy

Jing Fu, PhD

Assistant Professor of Medical Sciences

Columbia Multiple Myeloma and AL Amyloidosis Program

Columbia University Irving Medical Center

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Failure of Pan-anti-AL Amyloid Mabs?

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- **NEOD001 (Birtamimab)**
  - Humanized IgG1 antibody (mouse 2A4)
  - Developed **against AA amyloid**
  - Cross-activity to AL amyloid *in vitro*
  - Failed in AFFIRM-AL trial
- **CAEL-101 (Anselamimab)**
  - Chimeric IgG1 antibody (mouse 11-1F4)
  - Developed **against kappa 4 AL amyloid (Len)**
  - Cross-activity to lambda and other amyloids *in vitro*
  - Promising Phase ½ trials data
  - Phase III trial, CAEL101 **ONLY** showed highly clinically meaningful improvement in a prespecified subgroup of patients→ kappa AL?

→ **Has the pan-anti-amyloid mAb strategy failed?**

MOA of Amyloid-Targeting MAbs

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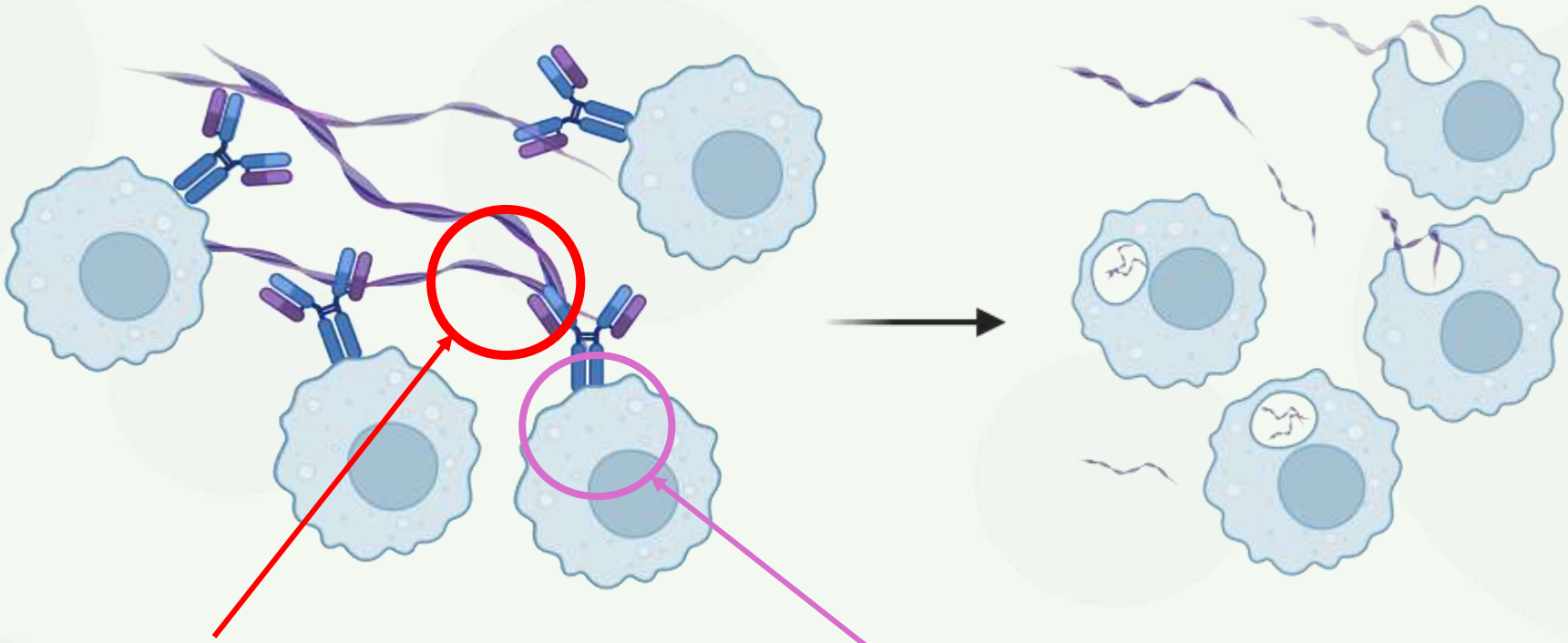

AL Amyloid targeting ?

The predominant lambda amyloid is not addressed

Antibody-Dependent Phagocytosis ?

Largely suppressed by endogenous IgG competition and potentially other monoclonal antibodies

New MAb 1F10 to Target Lambda Amyloid

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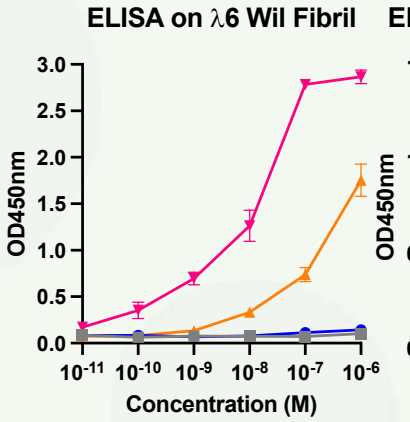

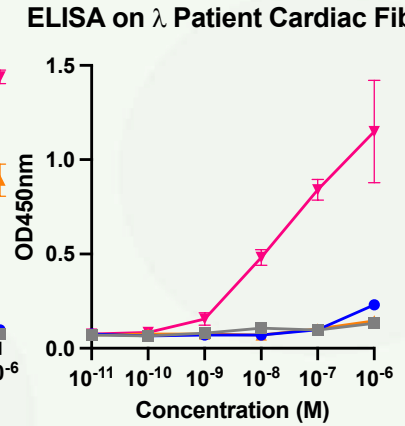

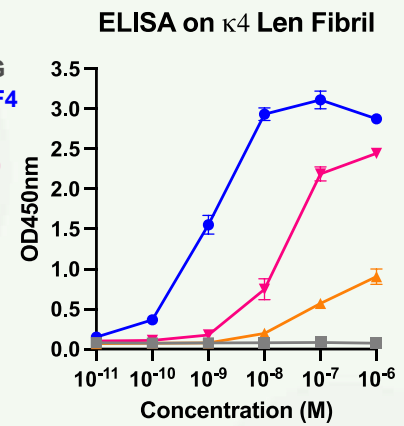

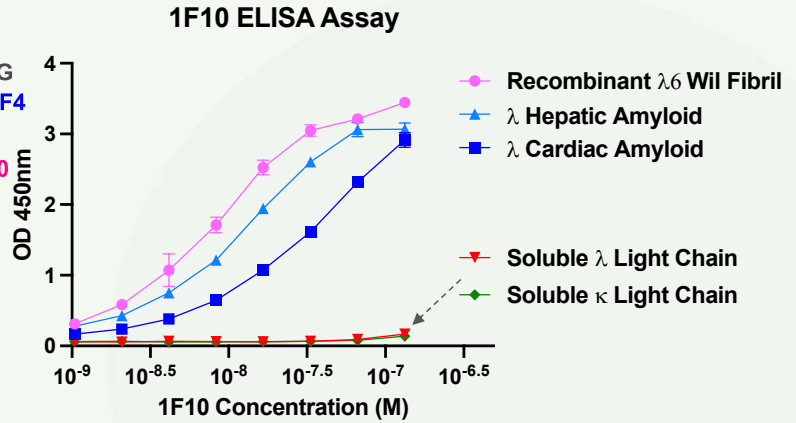

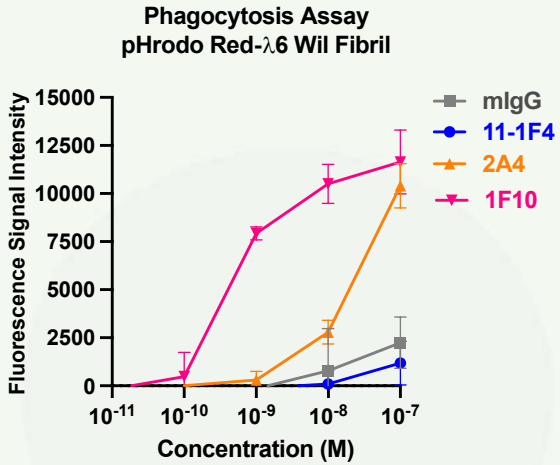

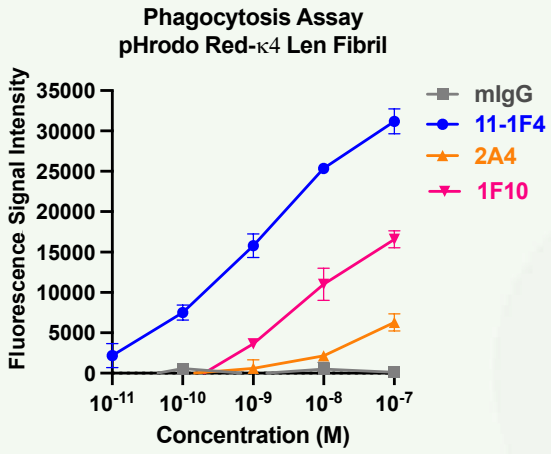

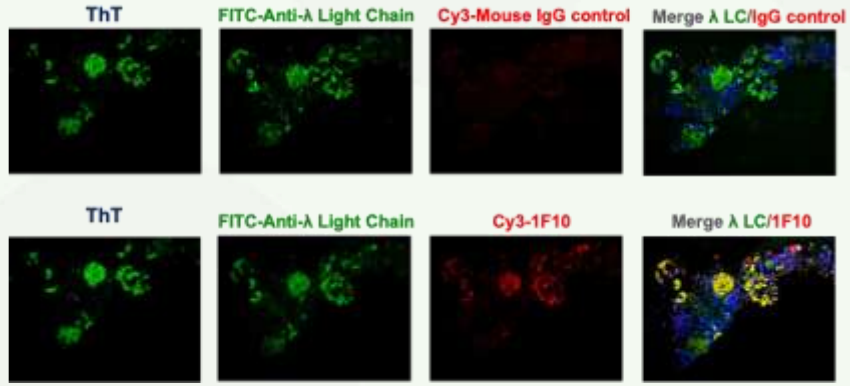

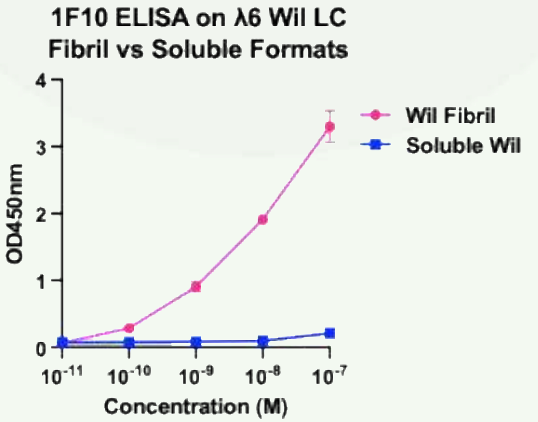

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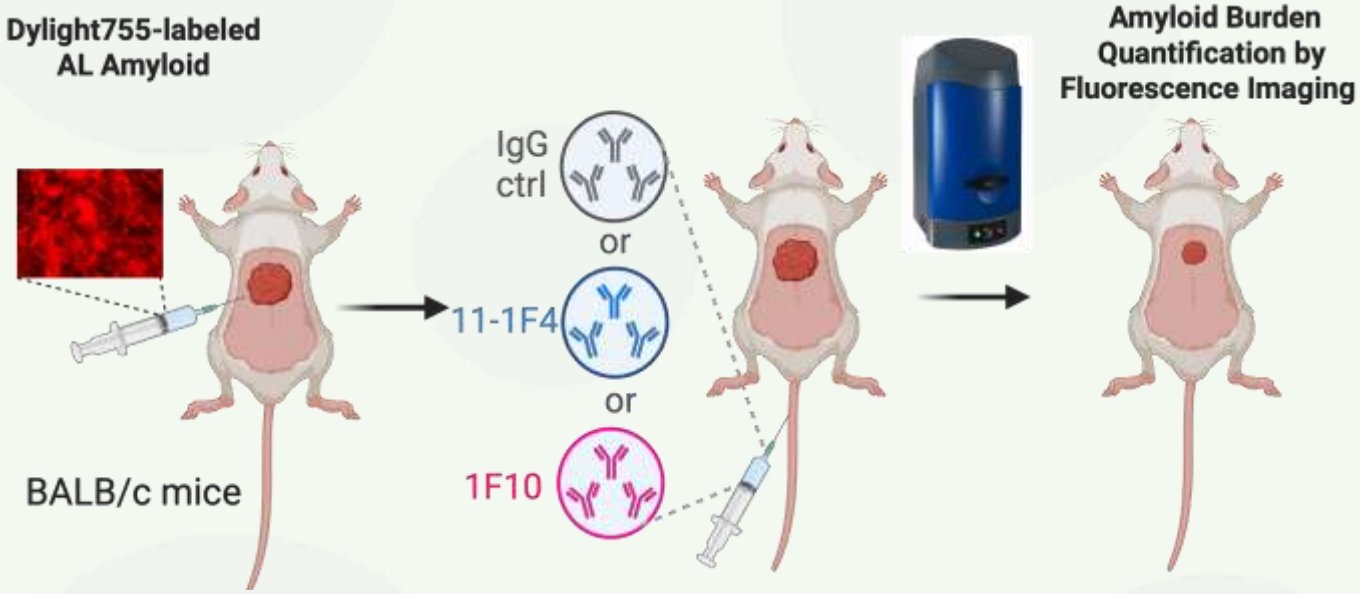
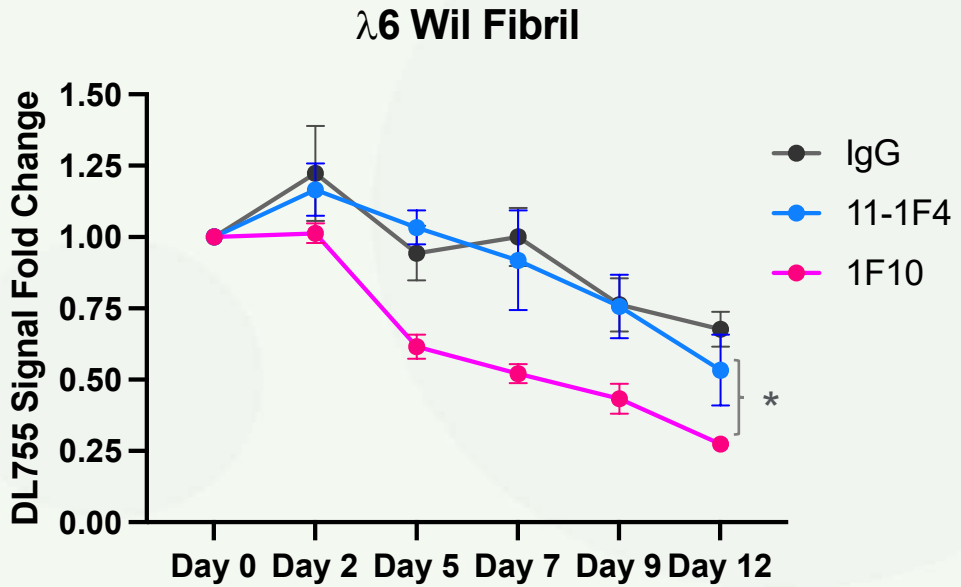
1F10 Induces Lambda Amyloid Clearance *in vivo*





Serum IgG Competes for FcR Binding Sites

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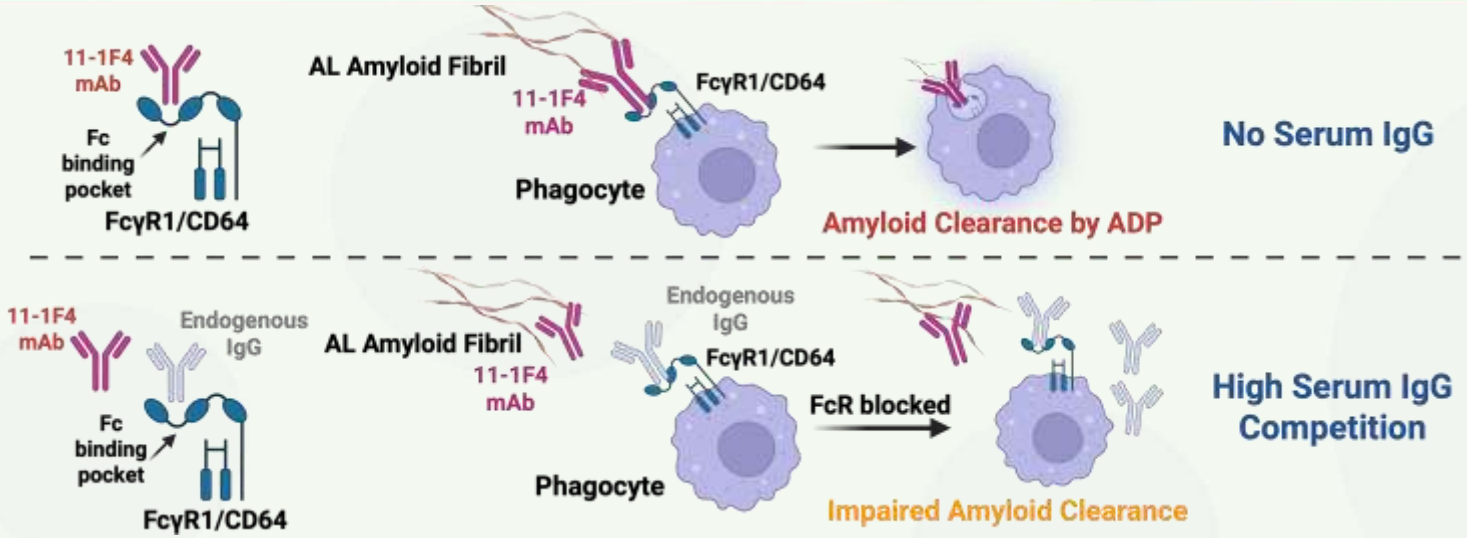

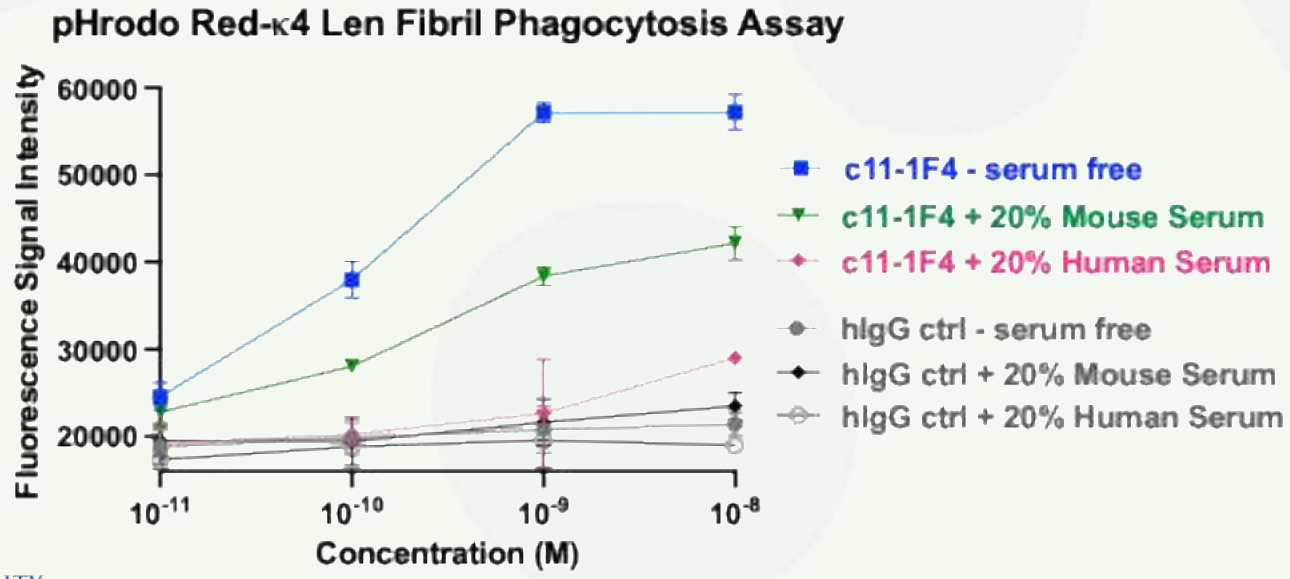

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Serum IgGs Compete for FcR Binding Sites

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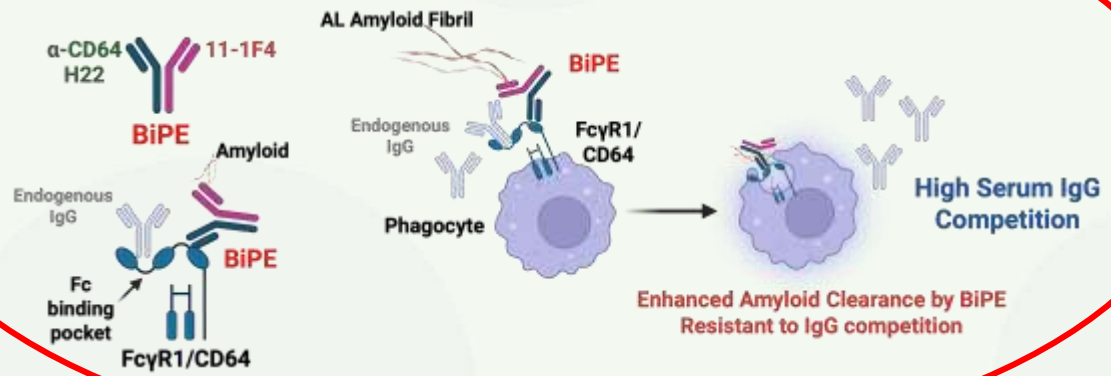
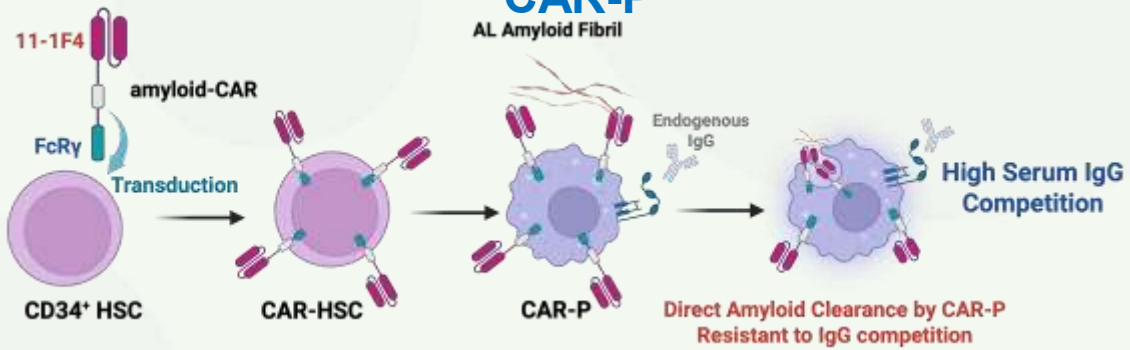
How to circumvent the serum IgG competition?

1. Bispecific phagocyte engager BiPE



2. CAR-Phagocyte CAR-P



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BiPE Bypasses Endogenous IgG Competition

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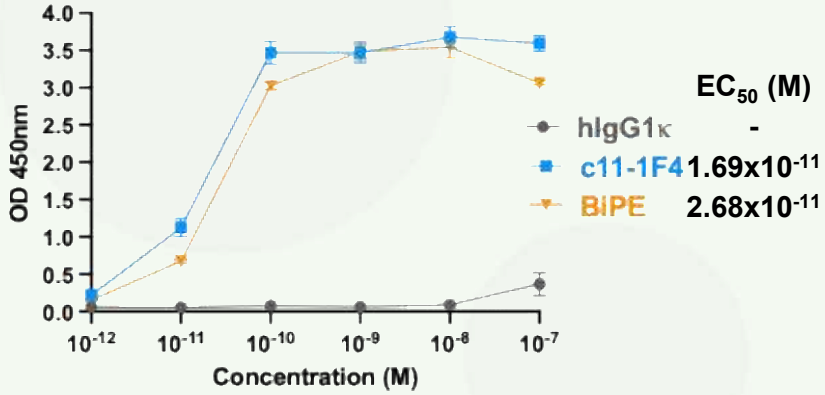
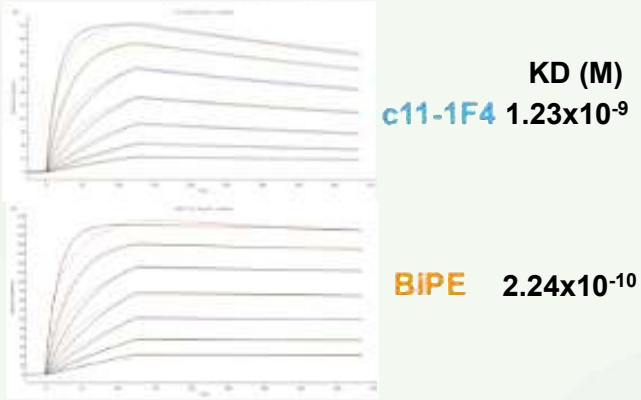
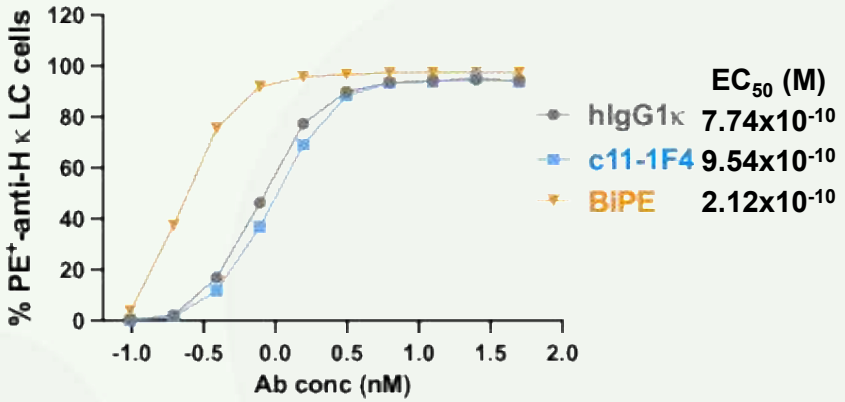
ELISA on Len Amyloid Fibril

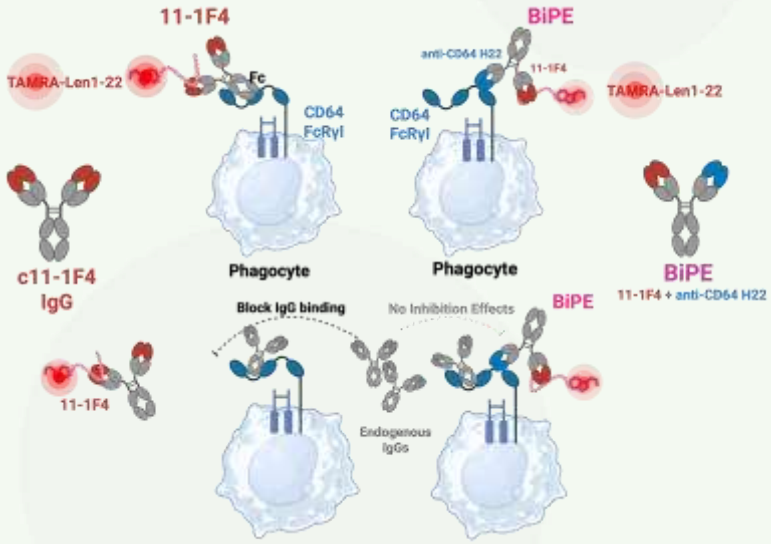


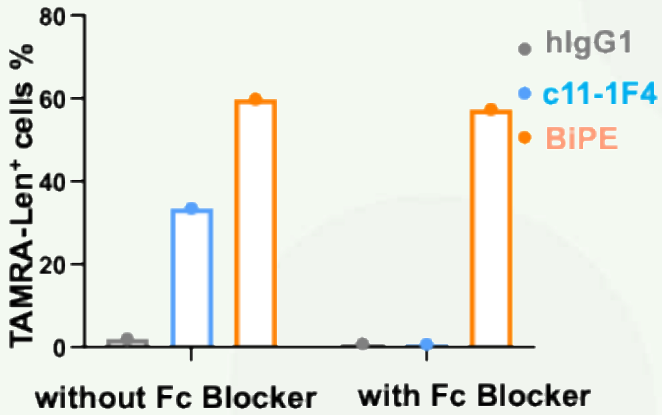
hFcγRI /CD64 SPR

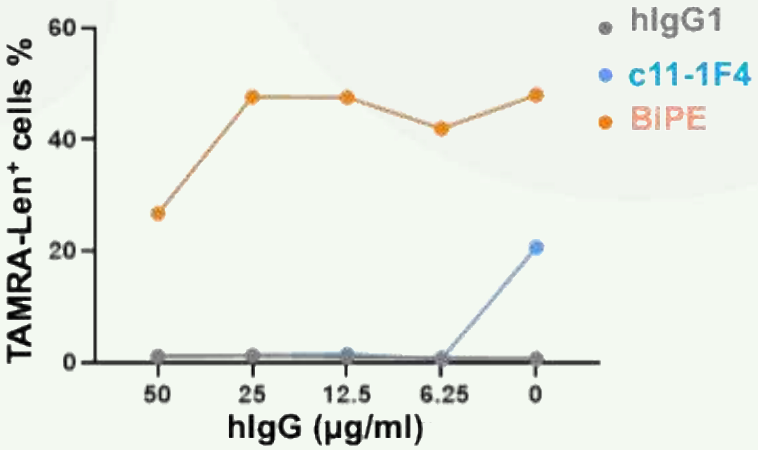


THP1 Cellular Binding









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BiPE Induces Robust ADP in Serum Conditions

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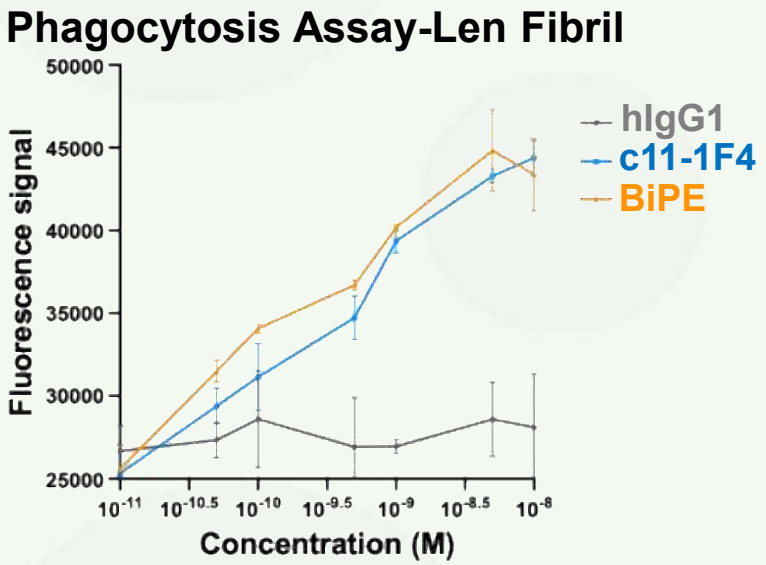
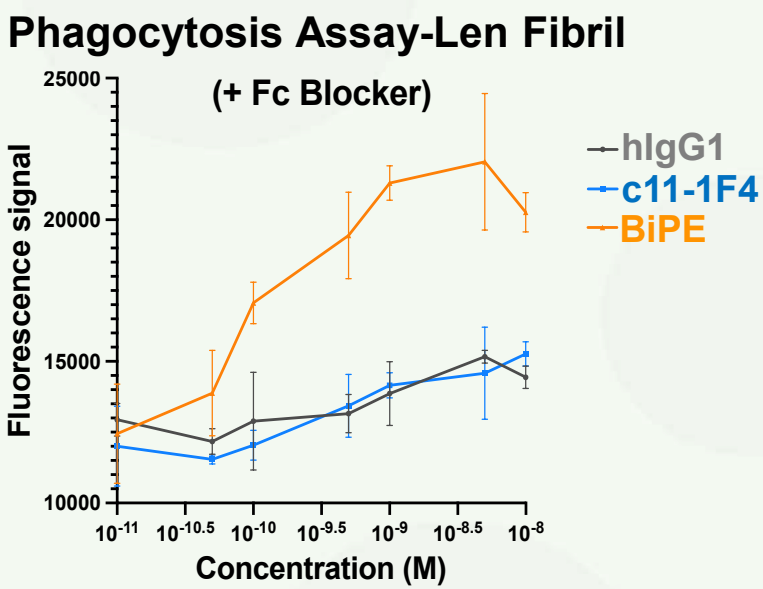
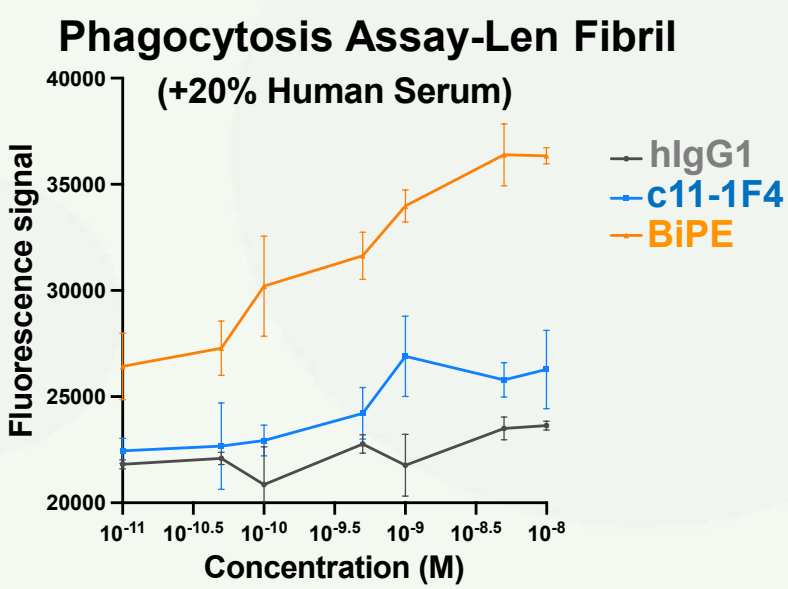


Serum Free



+ Fc Blocker



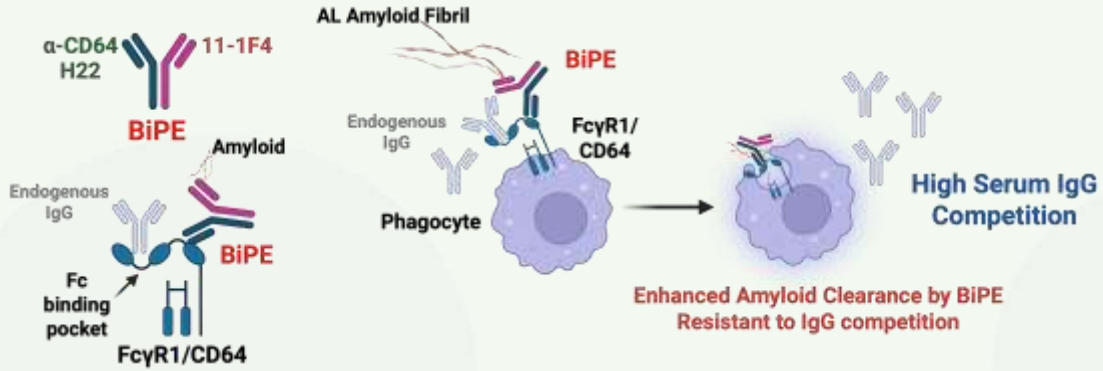
+ 20% Human Serum

Serum IgG Competes for FcR Binding Sites

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

How to circumvent the serum IgG competition?

1. Bispecific phagocyte engager BiPE



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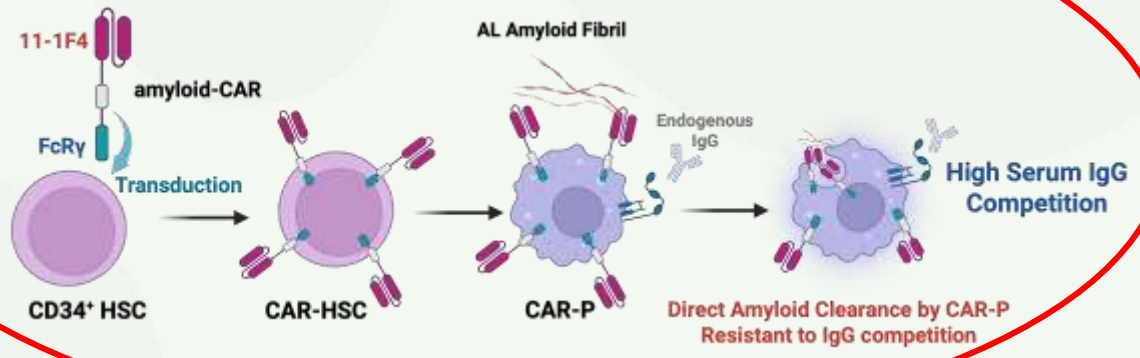

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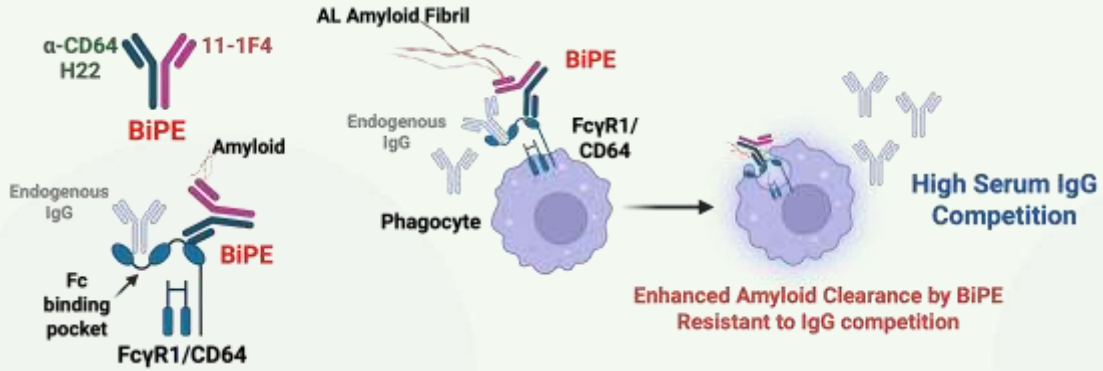

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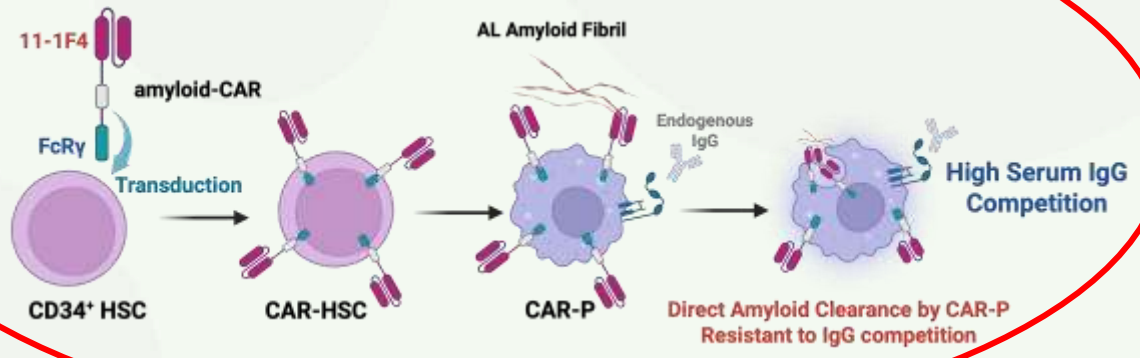

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Conclusions

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- Current clinical data does not support the pan-amyloid antibody concept.
- 1F10 antibody for the predominant lambda subtype in AL amyloidosis
- Monoclonal Ab's FcR binding and phagocytosis activities are suppressed by high concentrations of endogenous IgG.
- BiPE engages FcR independently of Fc and is resistant to endogenous IgG competition, achieving efficient amyloid phagocytosis.
- CAR-P bypasses the Fc engagement step for direct amyloid clearance and efficiently clears amyloid despite of IgG competition.

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NIH National Cancer Institute

International Myeloma Society

amyloidosis foundation

Emerson Collective

Cancer Research Institute

Conquer Cancer® The ASCO Foundation

CDMRP
Rare Cancers Research Program

Columbia | Columbia University Irving Medical Center

Strengths and limitations of animal models for research and drug development in amyloidosis: the case of AL amyloidosis

Christophe Sirac, CRIBL lab, BioPIC team, University of Limoges, France

Experimental models of (AL) amyloidosis

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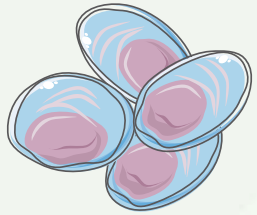
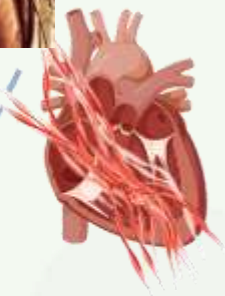


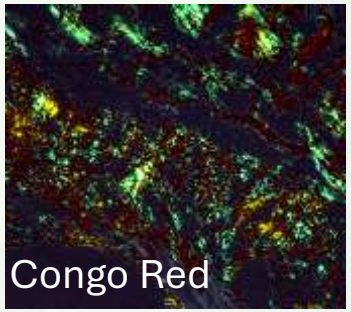
Producing cell

The (not) good

Unstable protein

The ugly





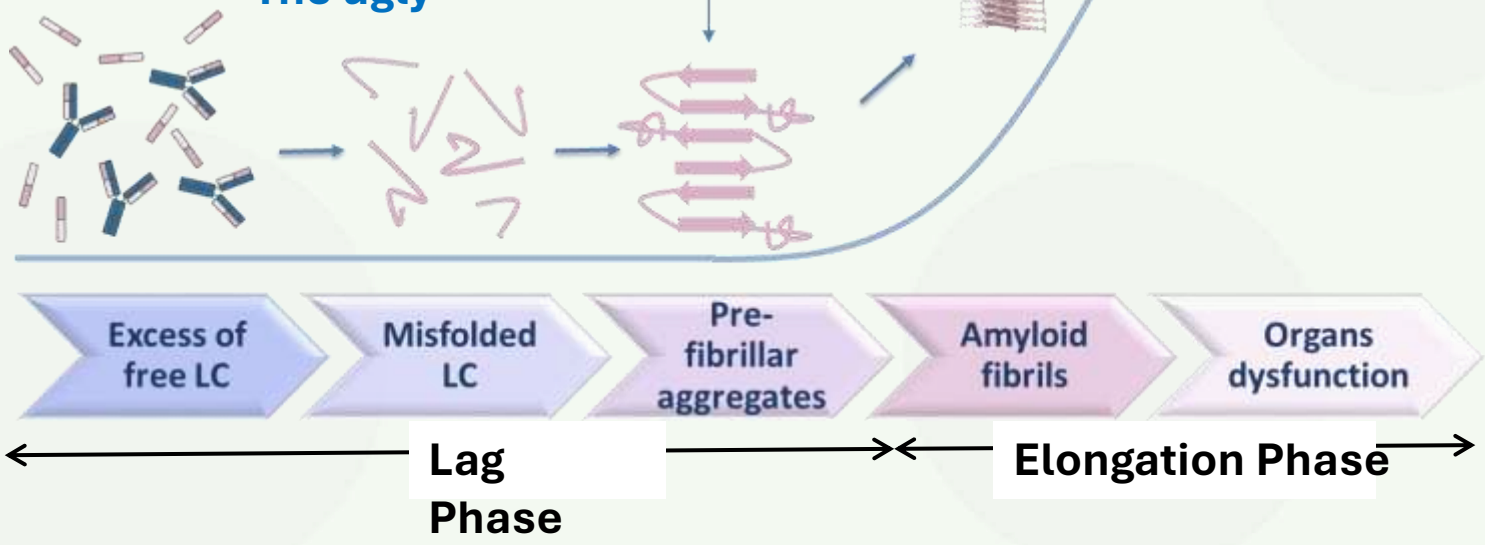
The bad

Deposits

(Scientists)

Organ dysfunction

(Physicians)



Experimental models of (AL) amyloidosis

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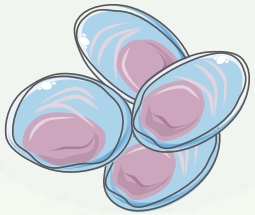
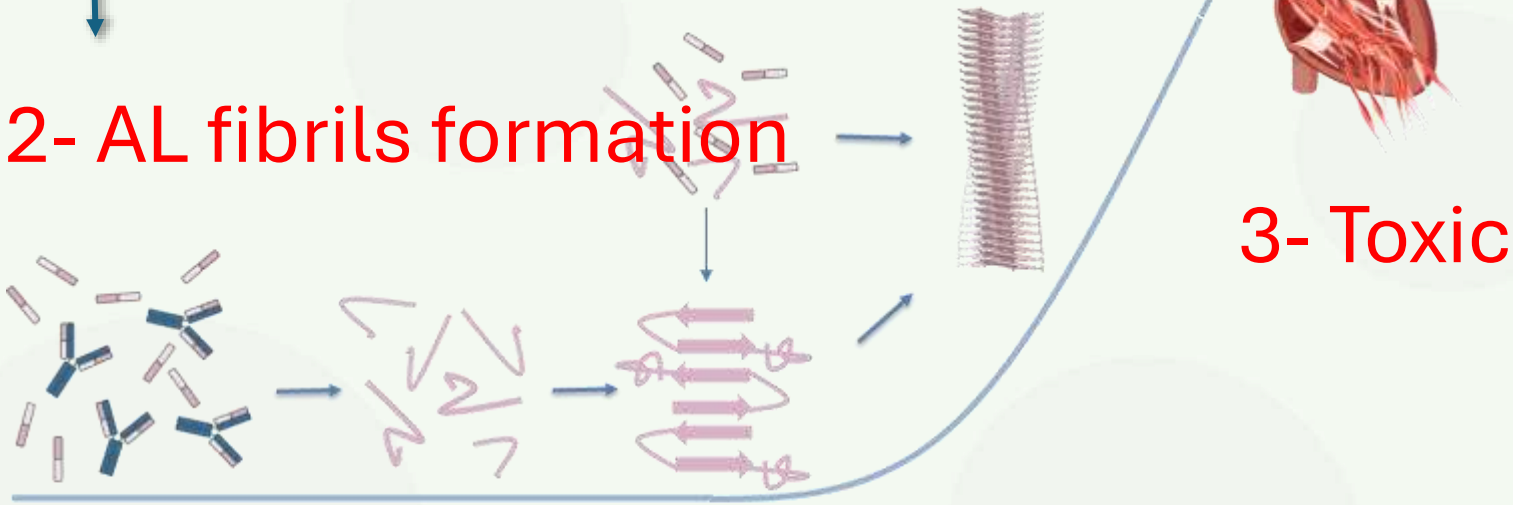
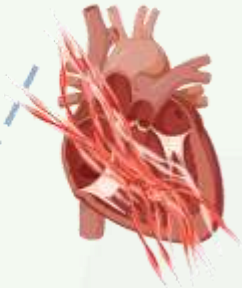
Why do we need *in vivo* experimental models of AL amyloidosis ?

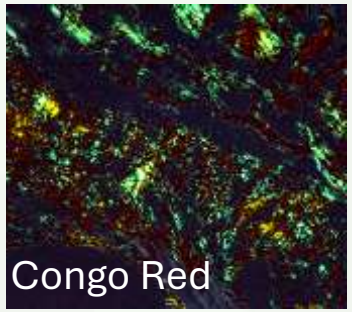
***in vivo* context**



1- Cell transformation







3- Toxicity for organs

- **1000s of other proteins**
- **Dozens of different cells**
- **ECM**

The perfect experimental model of AL amyloidosis

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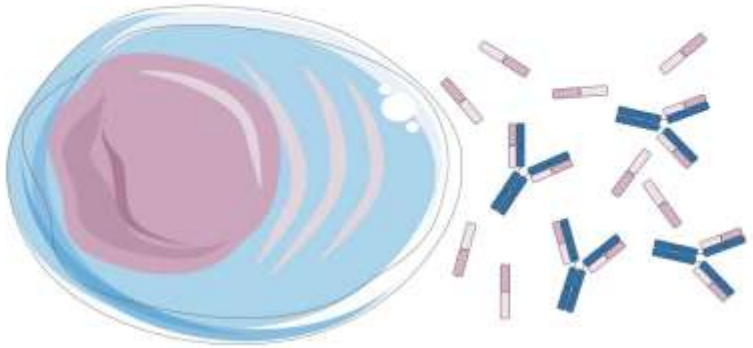
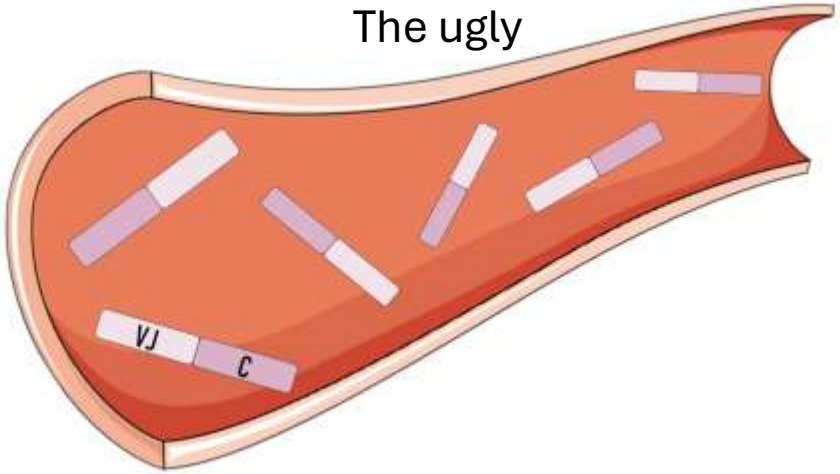
Producing cells

The (not) good



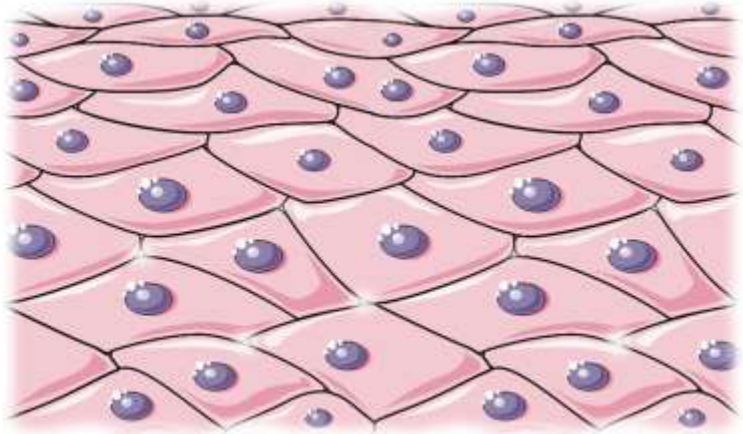
Unstable protein

The ugly



Deposits

The bad



Organ dysfunction

Enhancing factors

- Stress related to the unstable LCs
- Secretion of misfolded LCs
- Disability to dimerize LCs

- Lack of stabilization of LCs by chaperones
- Cleavage of LCs by circulating proteases
- Formation of oligomers ?

- Destabilization and misfolding of the LCs
- Digestion of LCs by tissue-specific proteases
- Endocytosis of LCs and cleavage by intracellular proteases

Inhibiting factors

- Stabilization of LCs by chaperones

- Stabilization of LCs by chaperones

- Stabilization of LCs by chaperones
- Clearance of misfolded LCs
- Digestion of amyloid fibrils by extracellular enzymes
- Tissue regeneration

The perfect experimental model of AL amyloidosis

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No, the perfect experimental model does not exist

We have to deal with it!

- To model each player independently
- To make use of each one

Right question ⇔ Right model

Published models to study AL amyloidosis

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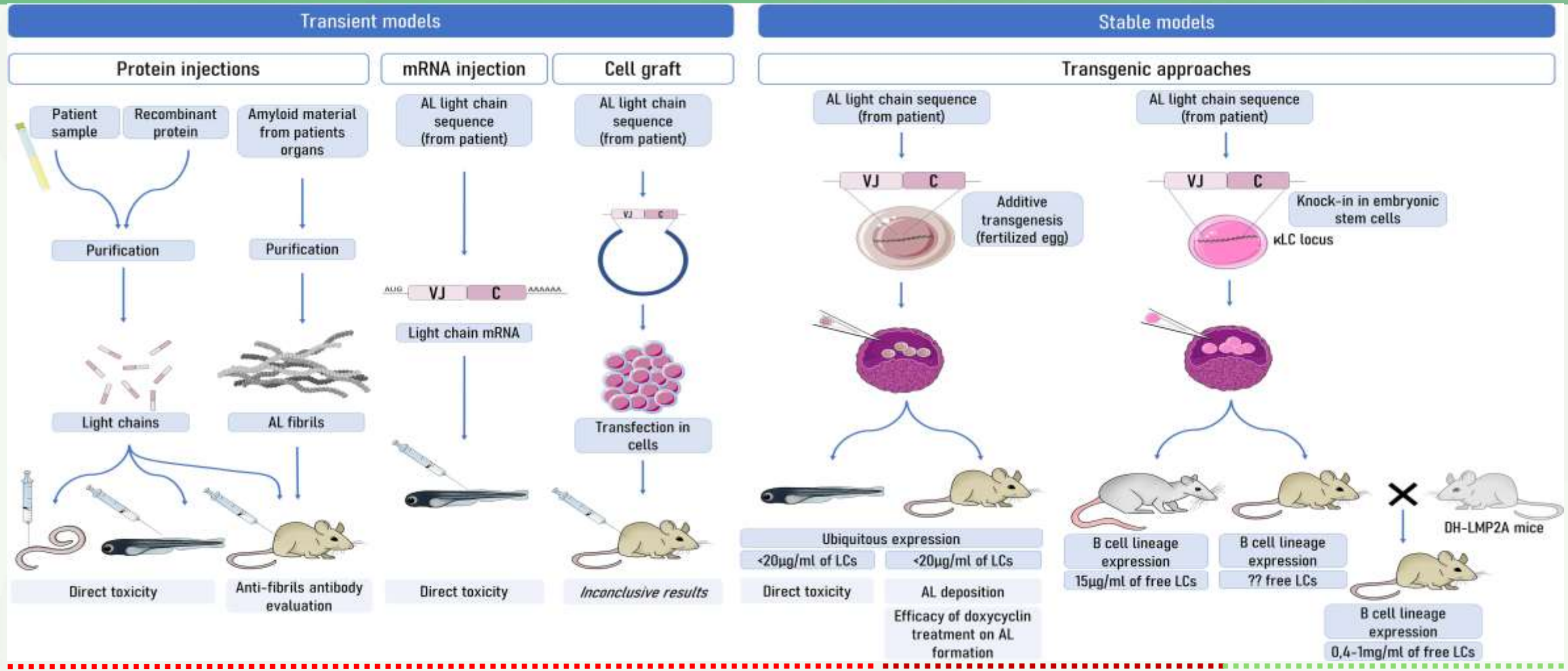

No congo-red deposits
Direct toxicity (in some of them)

Congo-red deposits

Congo-red deposits
Organ dysfunction

Adapted from Martinez-Rivas et al. 2023

Transgenic mouse model of AL amyloidosis

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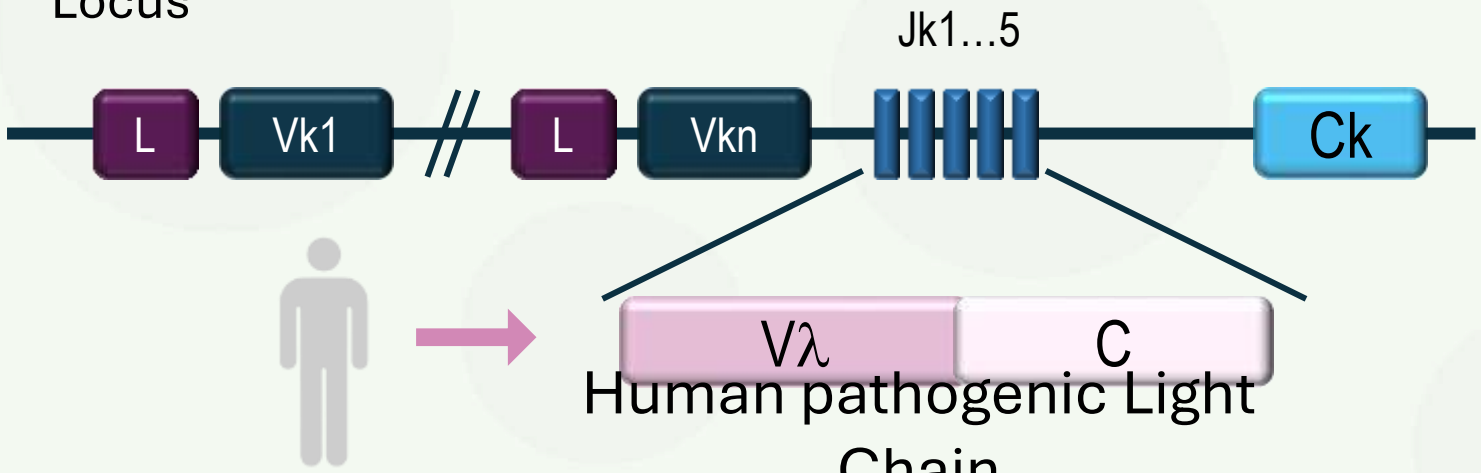
Kappa knock-in + LMP2A strategy

Mouse Kappa Light Chain Locus

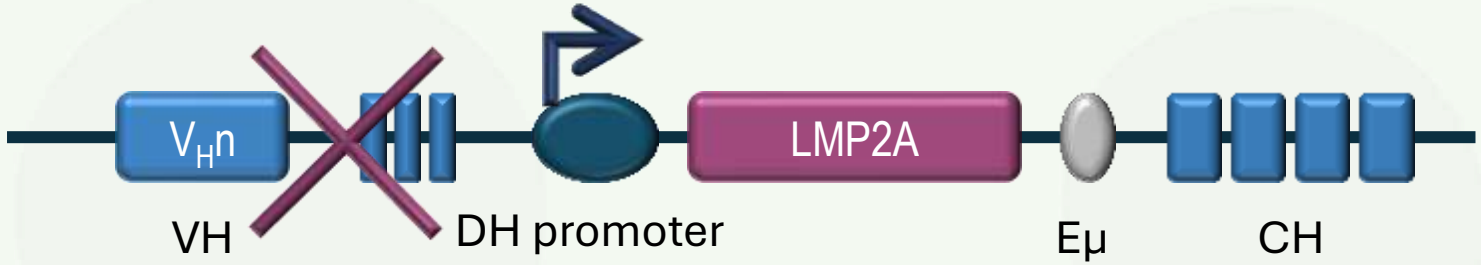


Human pathogenic Light Chain

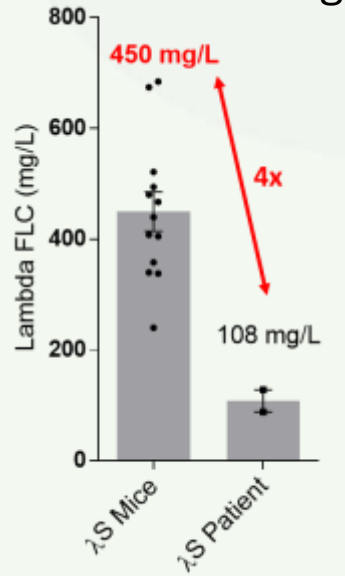
(VL or Full length LC)

Human pathogenic Free Light Chains

Mouse Heavy Chain Locus



~5% plasma cells (MGUS like)



Bender et al, Blood 2020

Transgenic mouse model of AL amyloidosis

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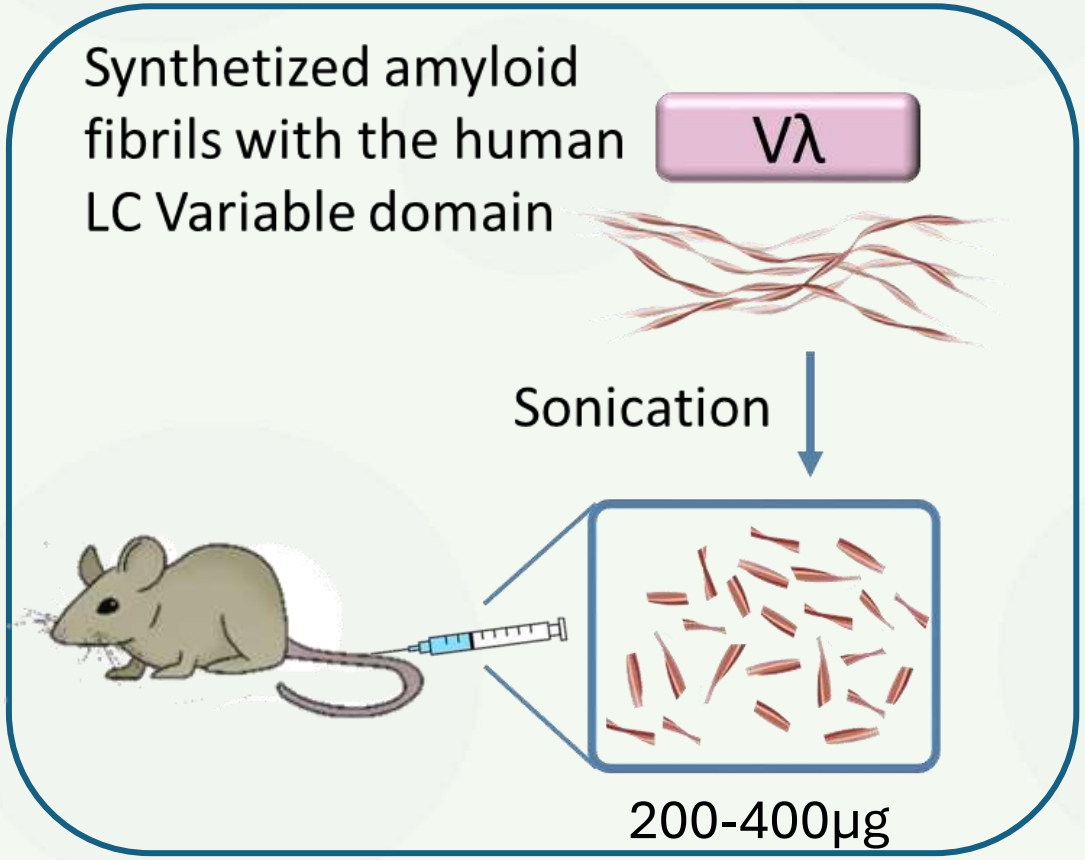
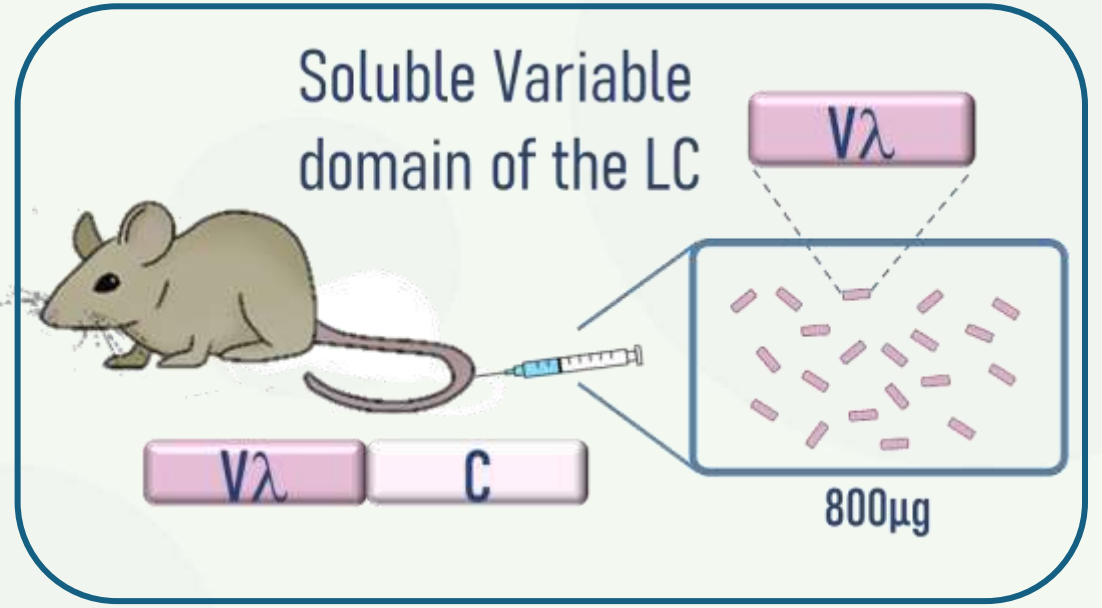
« Fast protocol »

Seeds: *in vitro* fibrils



« Physiological protocol »

Seeds: *soluble VL*



Few spontaneous AL amyloidosis *(5-10% in aged*

Transgenic mouse model of AL amyloidosis

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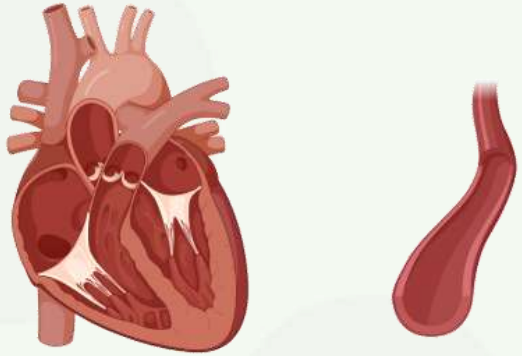
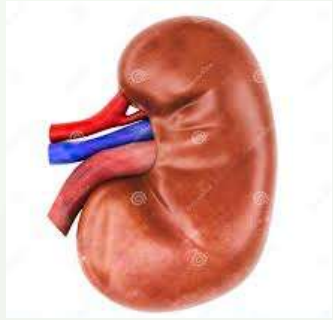
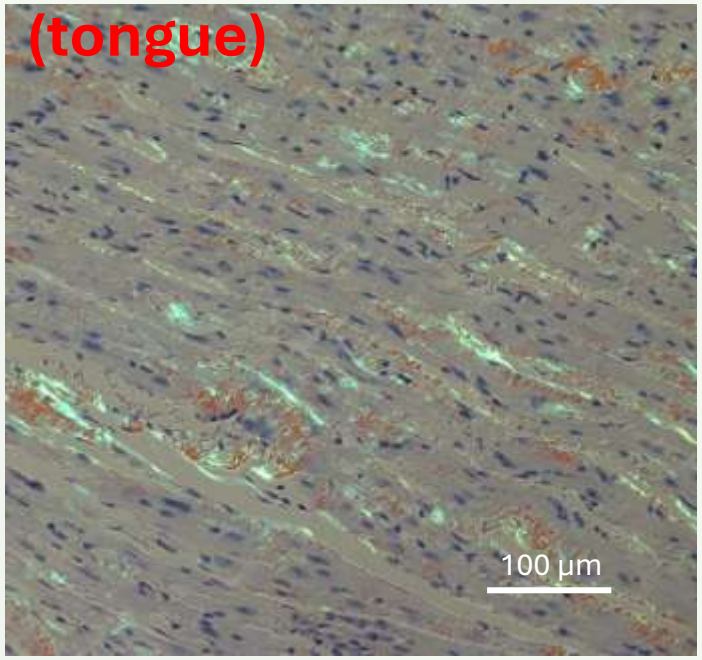


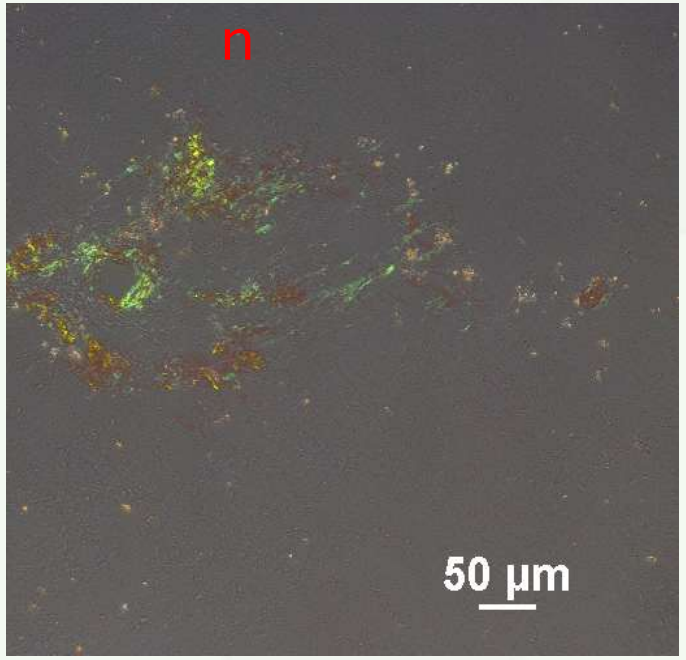
Heart, Vessels (tongue)

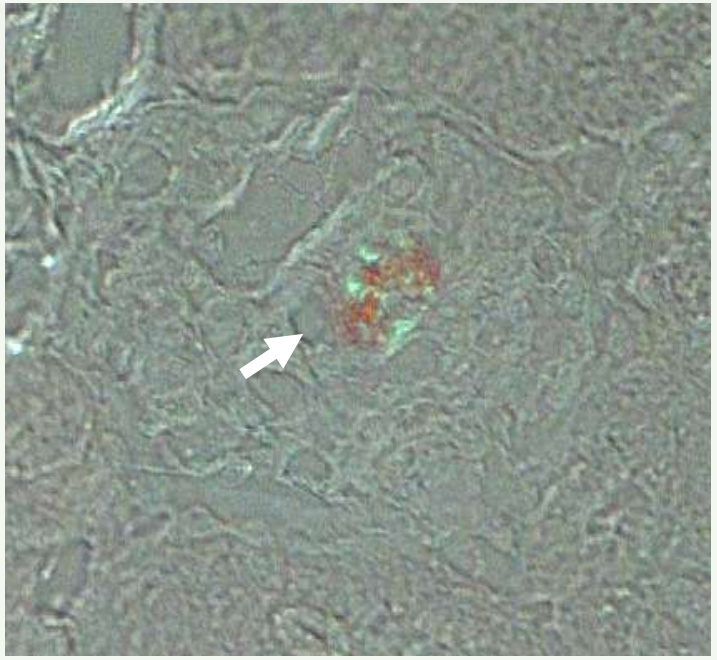
Splee n



Kidney, liver, fat





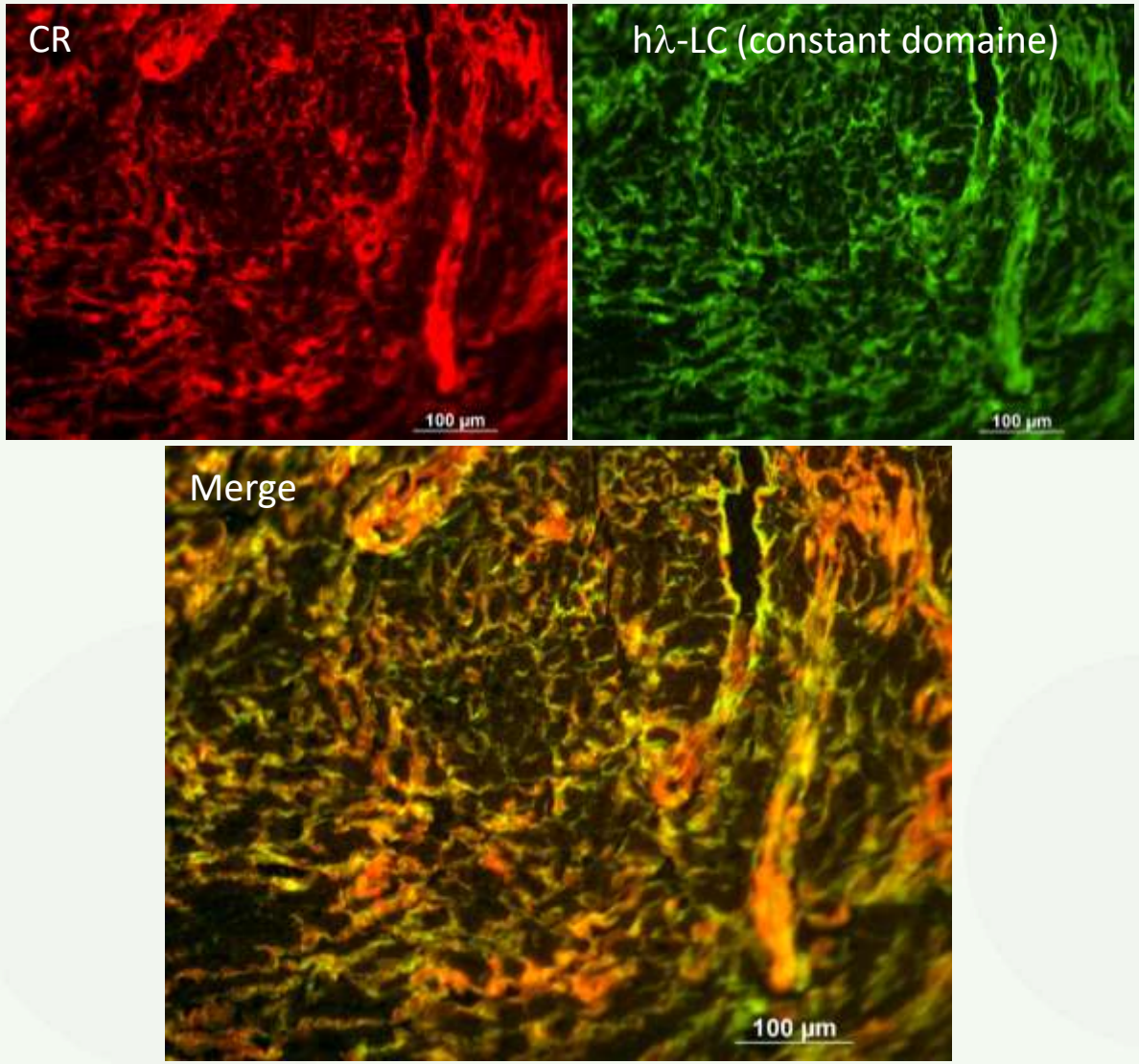


Martinez-Rivas et al. 2025

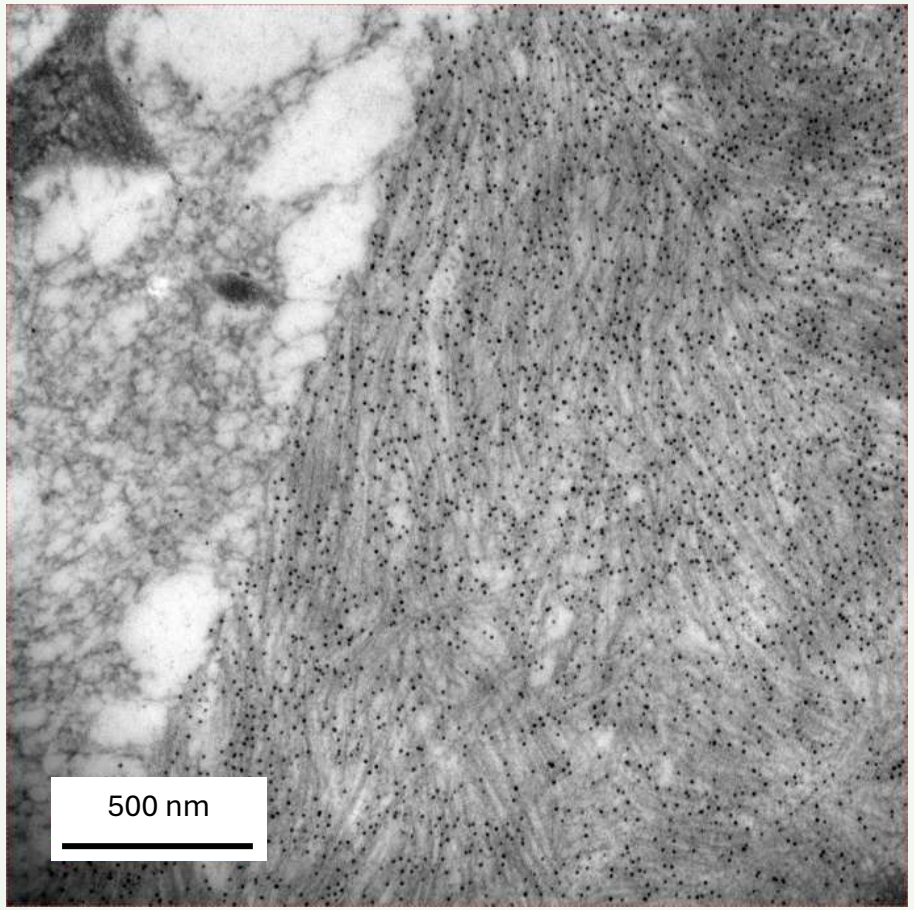
Transgenic mouse model of AL amyloidosis

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

Heart



Heart



@human lambda (gold)

Martinez-Rivas et al. 2025

Transgenic mouse model of AL amyloidosis

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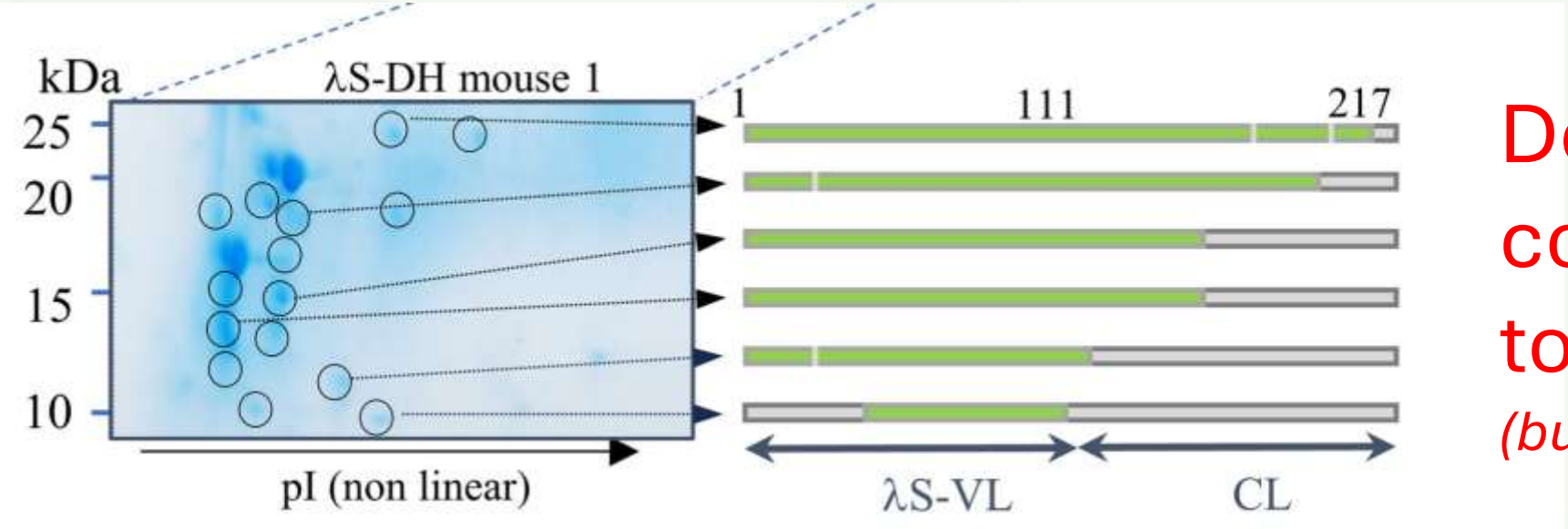
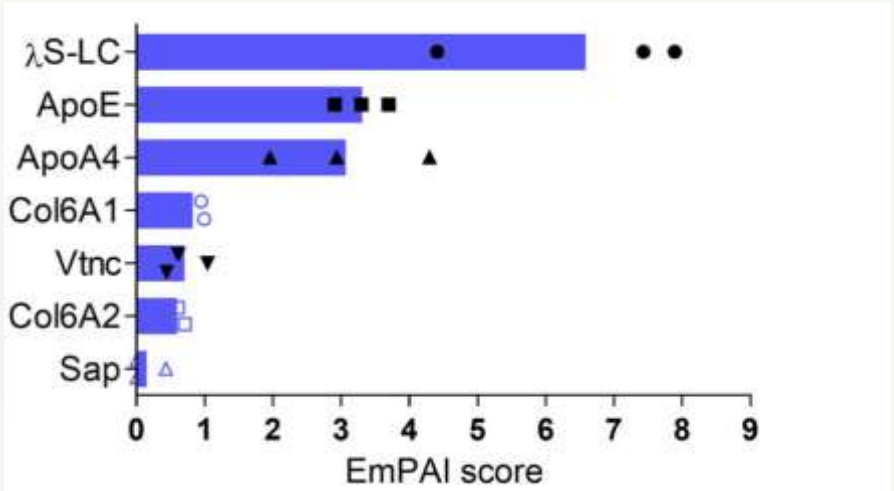


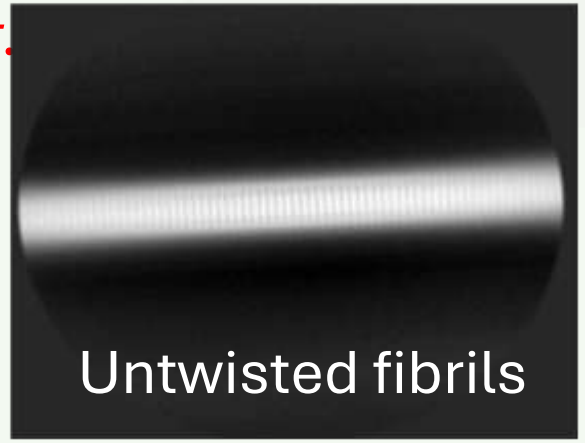
Deposits composition similar to human

(but no SAP)

But…



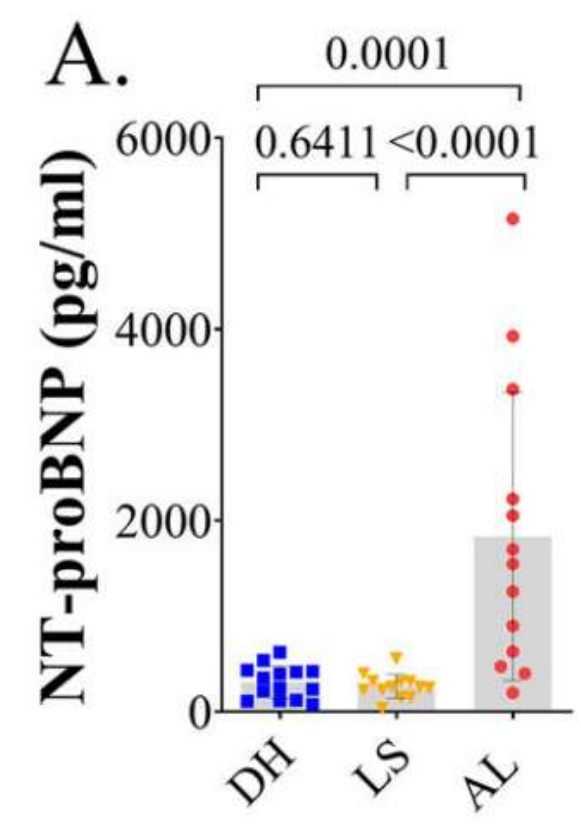
Martinez-Rivas et al. 2025

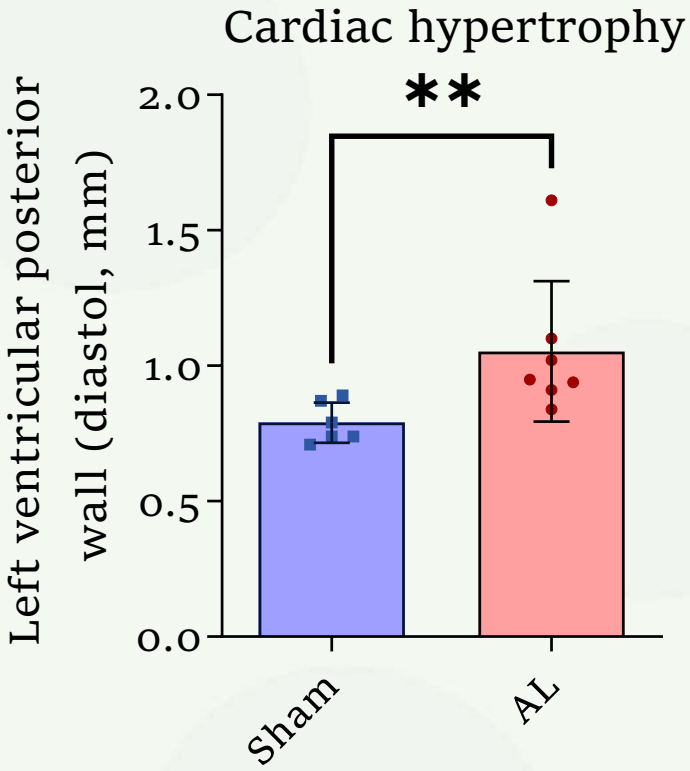


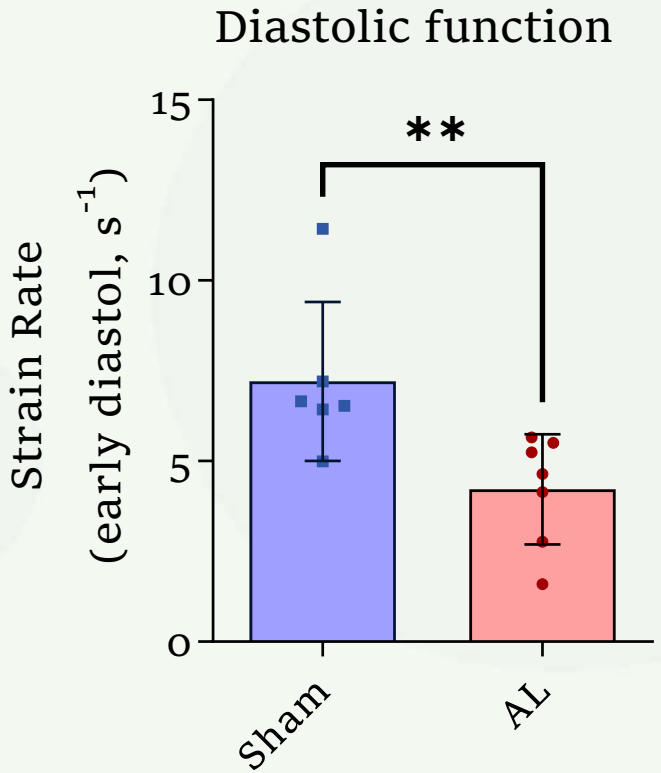
Stefano Ricagno's lab, manuscript in preparation

Transgenic mouse model of AL amyloidosis

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS







- Cardiac dysfunction
- Only in mice with extensive amyloid deposits

Martinez-Rivas et al. 2025

Transgenic mouse model of AL amyloidosis

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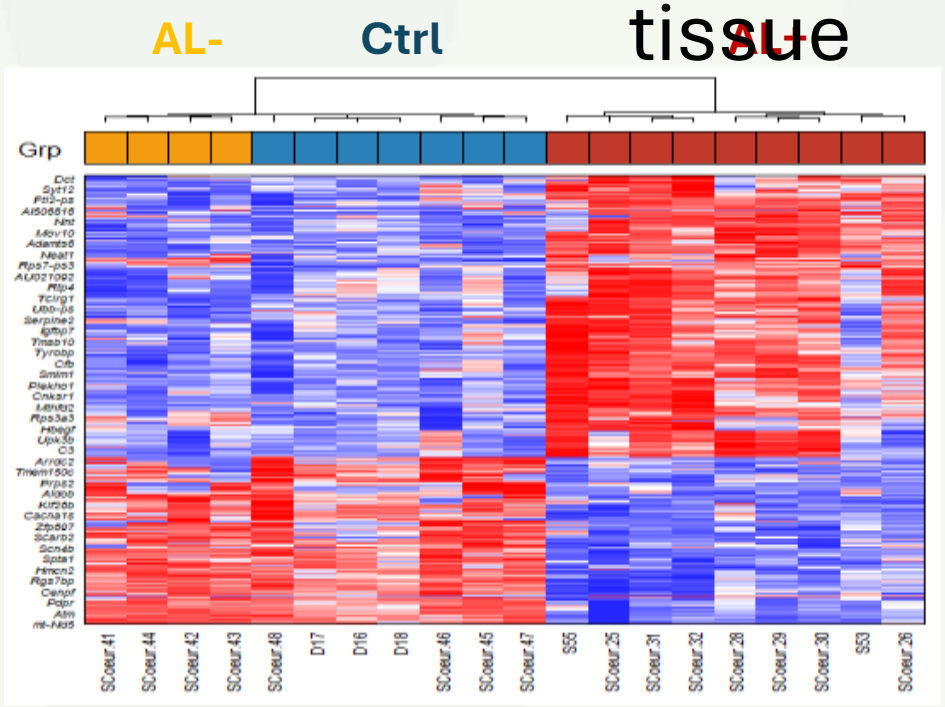
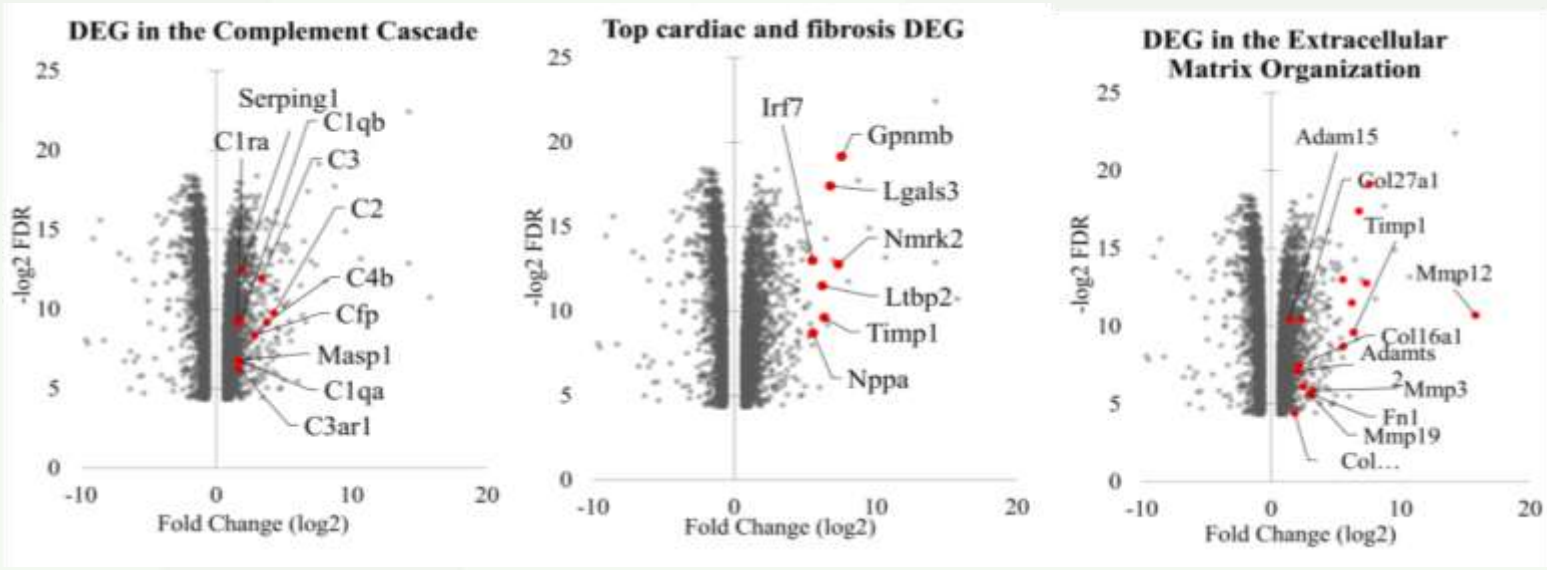
Transcriptomic analysis on heart tissue





- No change in transgenic mice **without deposits** (vs negative controls)
- Cardiac toxicity and fibrosis biomarkers
- Complement and remodeling of extracellular matrix

Martinez-Rivas et al. 2025

Transgenic mouse model of AL amyloidosis

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Strengths

- ✓ Elevated amyloid LC production
- ✓ Congo red positive deposits in relevant organs
- ✓ Toxicity for organs
- ✓ Organ dysfunction

Limitations

Produced by normal PC (stable?)

Upon seeding / ≠ Tropism / Same fibril structure?

(Not with soluble free LC)
No apoptosis

Incomplete

Incomplete

What can we do with that?

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What can we do with that?

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Targeting LC production

No need for specific amyloidosis models to test therapies targeting the production of the amyloid protein

Crispr/Cas9 in ATTR

What can we do with that?

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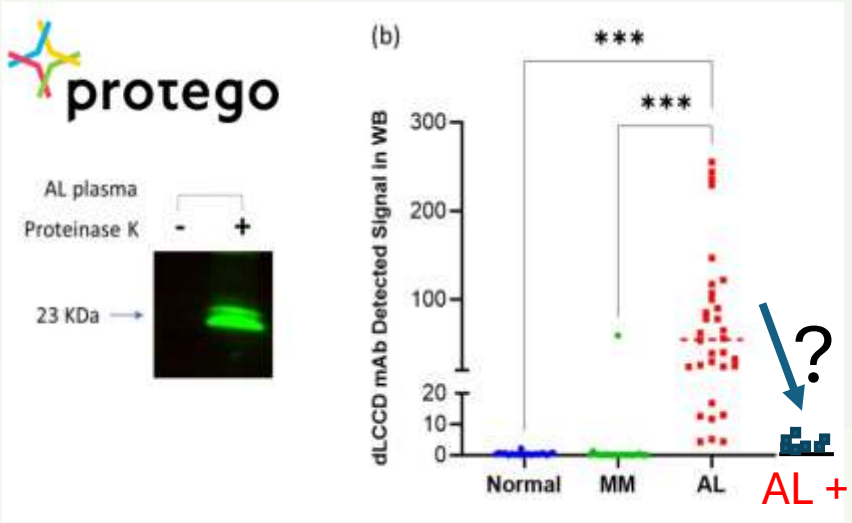
Stabilizing amyloid LC (?)

LC stabilizers (similar to tafamidis in ATTR)

Stabilization of amyloidogenic immunoglobulin light chains by small molecules

Gareth J. Morgan[a,b,1,2,3], Nicholas L. Yan[a,b,1], David E. Mortenson[a,b], Enrico Rennella[c,d,e], Joshua M. Blundon[a,b], Ryan M. Gwin[a,b], Chung-Yon Lin[a,b], Robyn L. Stanfield[f], Steven J. Brown[a], Hugh Rosen[a], Timothy P. Spicer[g], Virneliz Fernandez-Vega[g], Giampaolo Merlini[h,i], Lewis E. Kay[c,d,e,j], Ian A. Wilson[f,k], and Jeffery W. Kelly[a,b,k,2]

PNAS 2014



What can we do with that?

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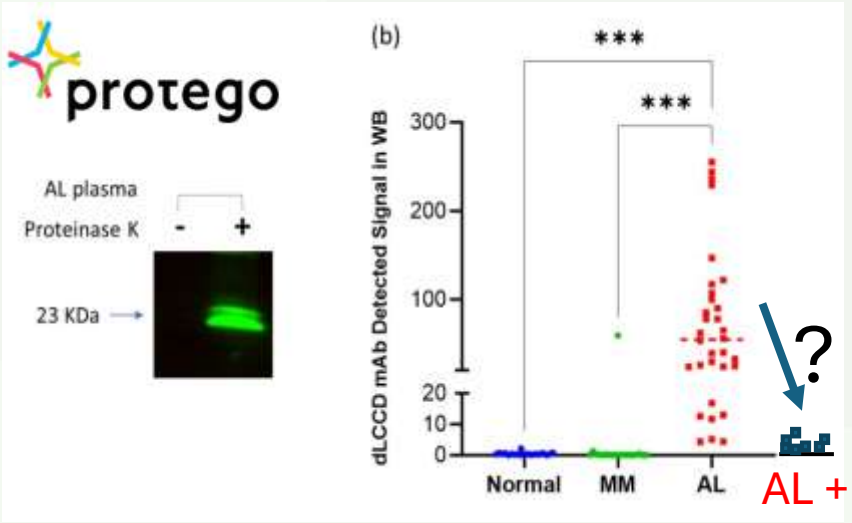
PNAS 2014



What can we do with that?

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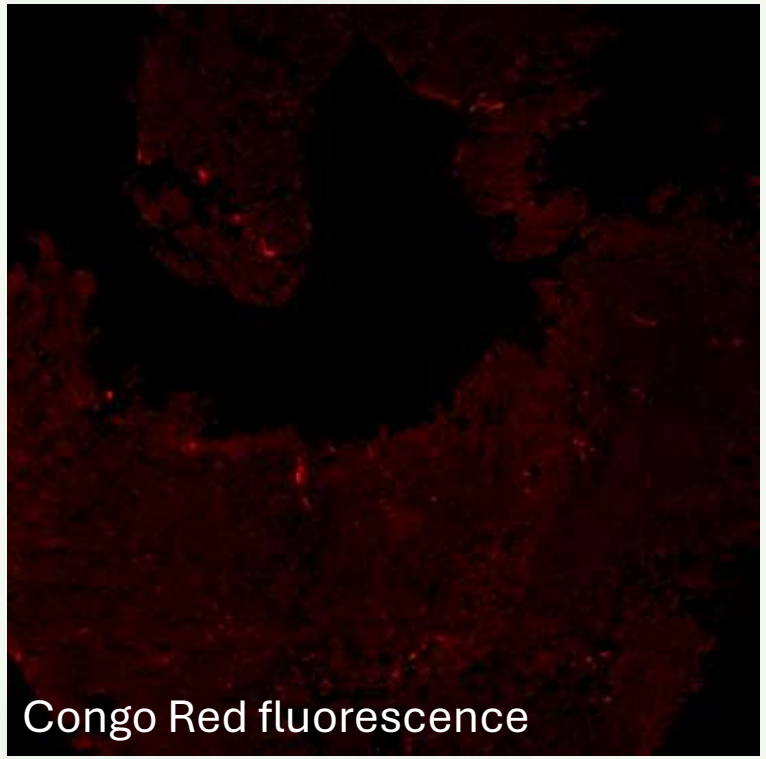
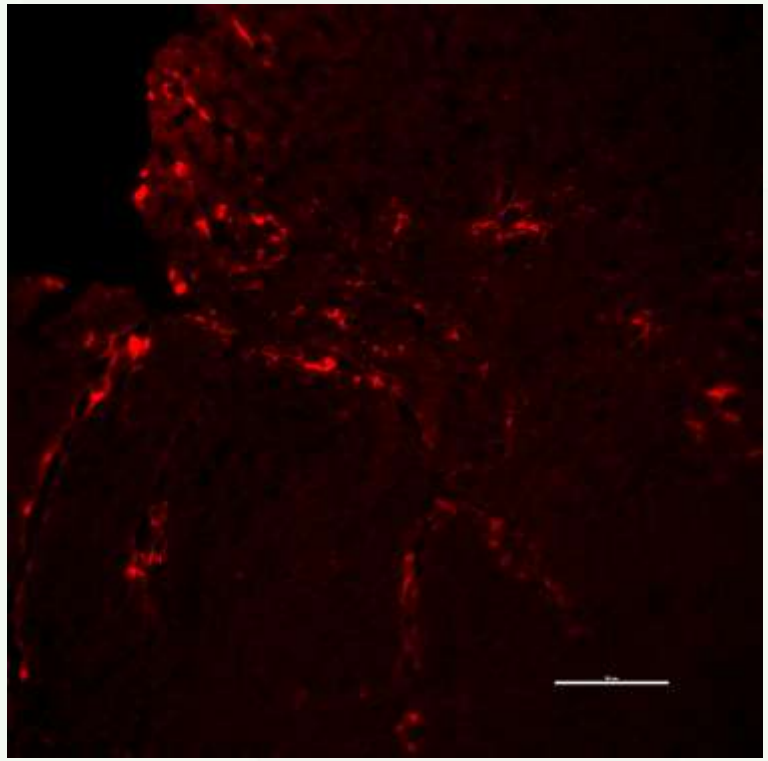
Fibril formation / Toxicity → New biomarkers (?)

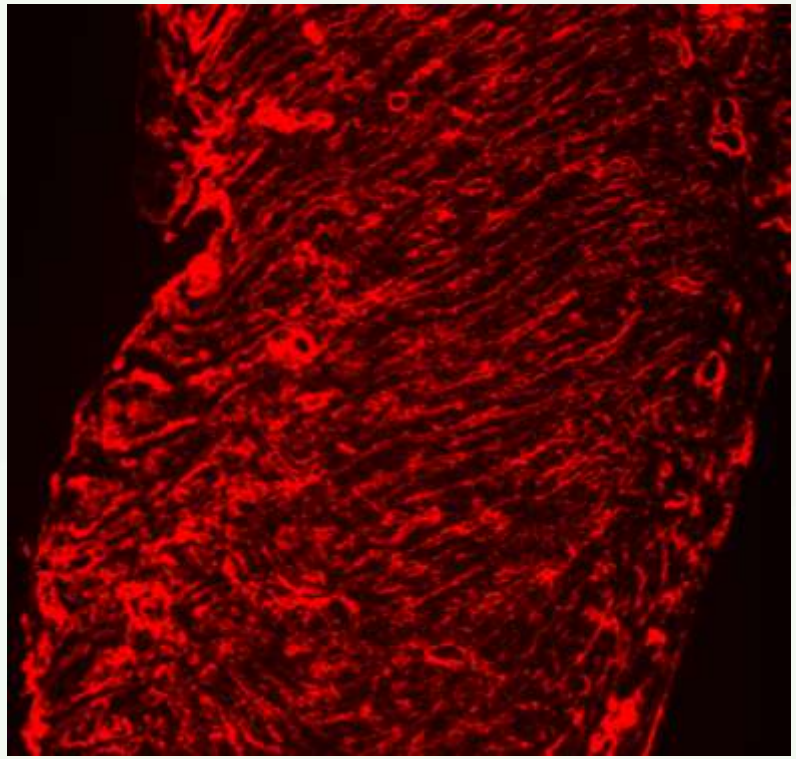
Low



Mid



High



Multiomic / Spatial analysis of amyloid microenvironment

What could we (potentially) do with that?

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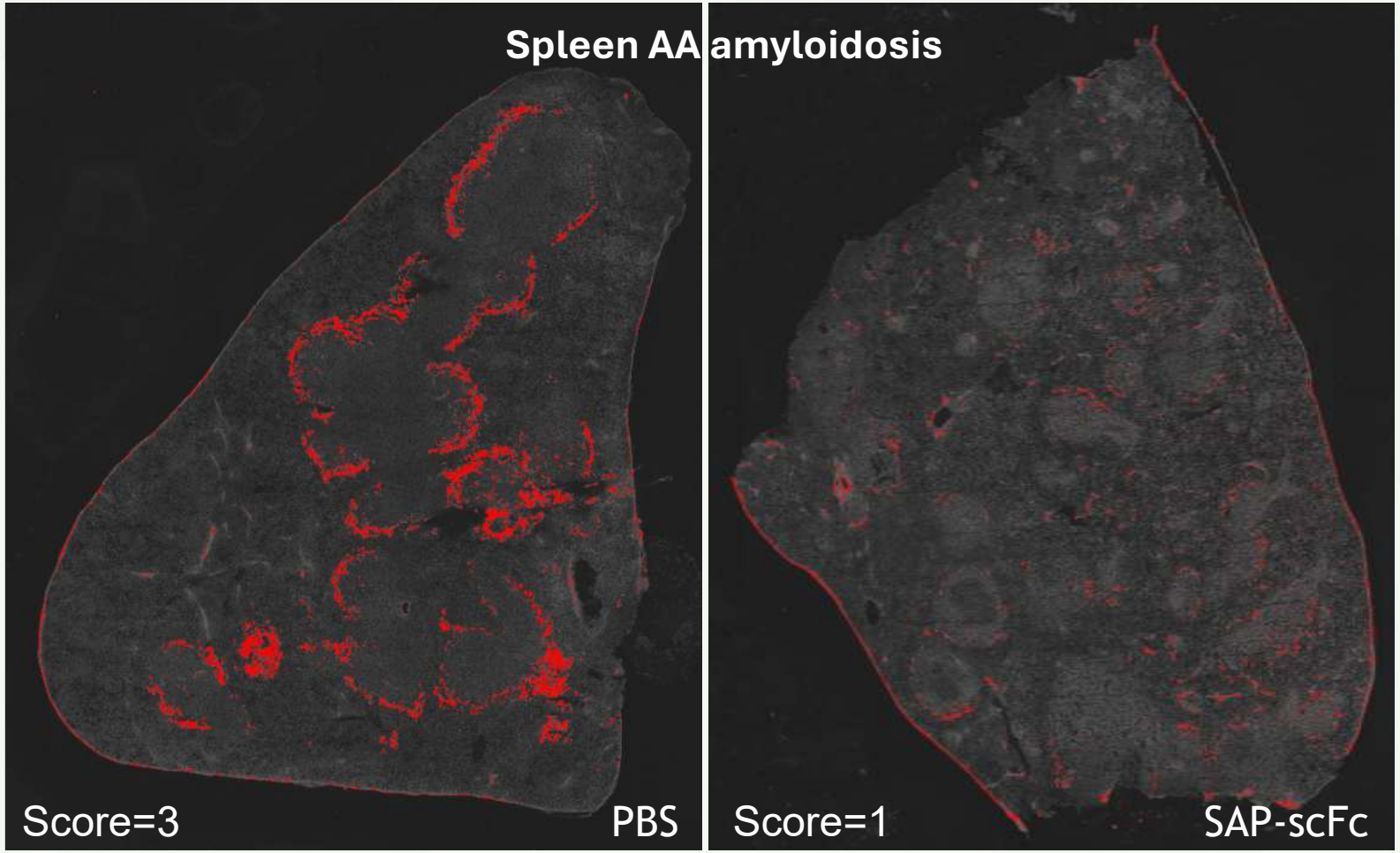
Amyloid removal



Best proof of concept for amyloid removers

But…

- Incomplete penetrance
- 1 LC!

Sirac et al. P284, ISA symposium 202

What could we (potentially) do with that?

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Organ dysfunction and recovery

Is it really necessary?

Centre national de référence
Amylose AL
& autres maladies par dépôts d'immunoglobulines monoclonales

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criBL lymphoprolifératives

Lab Task Force

Gemma Martinez-Rivas
Roussine Codo
Karolina Swiderska
Alessio Lampis
Sébastien Bender
Pauline Duchatelet

Clinical Task Force

Arnaud Jaccard
Virginie Pascal
Murielle Roussel
Vincent Javaugue
Frank Bridoux

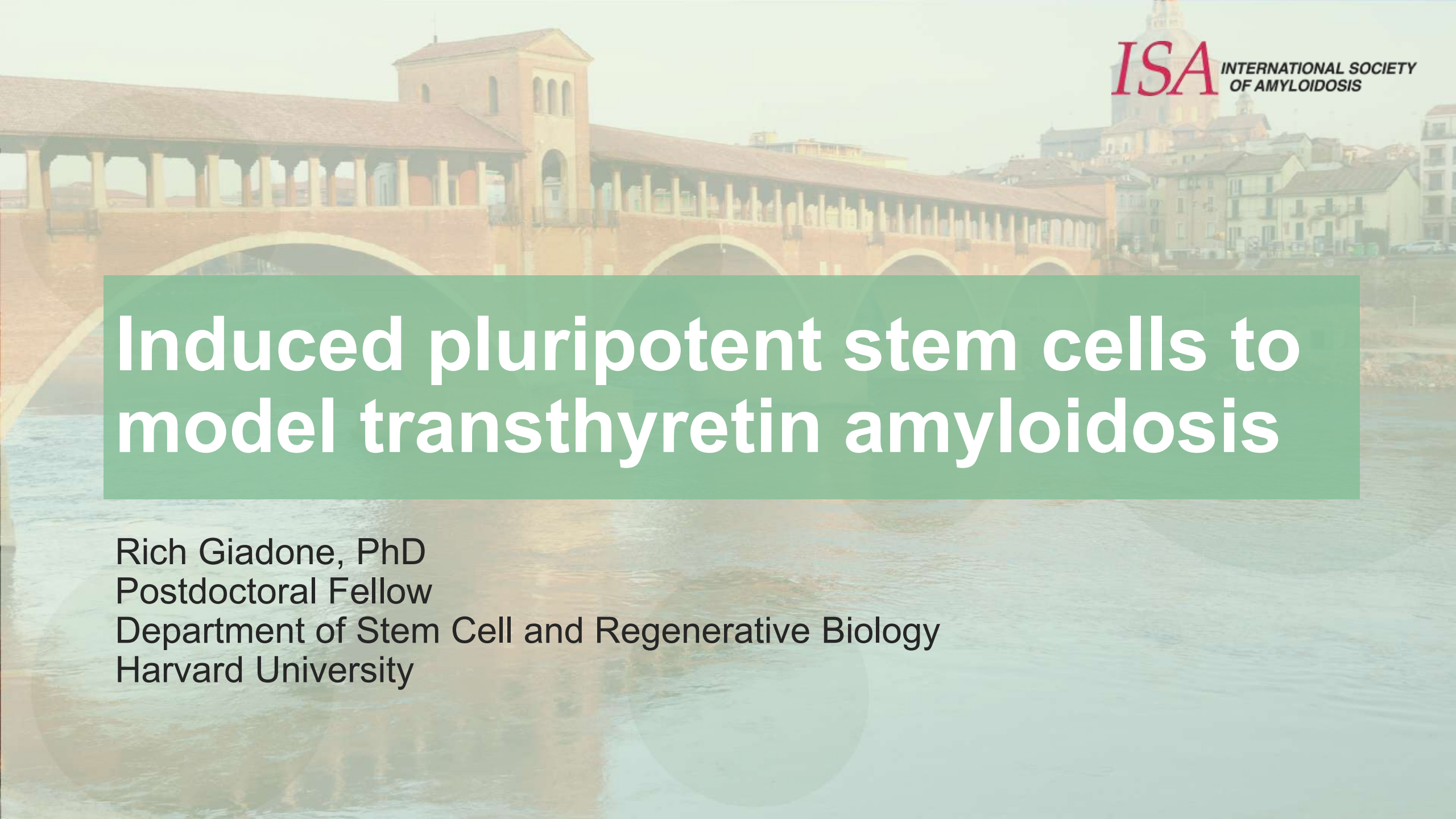
CRIBL Lab
Lab retreat
2023

+ Pathology crew: Sihem Kaaki, Cécile Ory, Alexia Rinsant, Oumayma Hachani, Laurence Richard, Emilie Pinault, Aurore Danigot

F.Lavatelli and coll.
M.Ehrmann and coll.
P.Sicard
S.Ricagno and coll.

ERA4Health Partnership

THANKS



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Induced pluripotent stem cells to model transthyretin amyloidosis

Rich Giadone, PhD
Postdoctoral Fellow
Department of Stem Cell and Regenerative Biology
Harvard University

Overview

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- Induced pluripotent stem cells
- What we've done:
  - Developed an iPSC-based model for ATTR amyloidosis
  - Generated a diverse library of ATTR amyloidosis patient iPSCs
  - Defined endogenous signaling altered in ATTR amyloidosis hepatic cells
- Where can we go from here?

Induced pluripotent stem cells (iPSCs) for studying complex diseases

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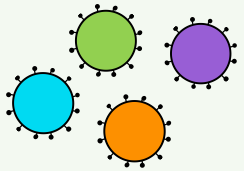
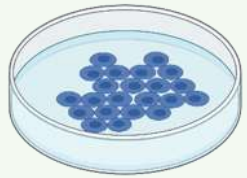
Genetically diverse patients

PBMCs

Reprogramming virus



Indefinite self-renewal



iPSCs

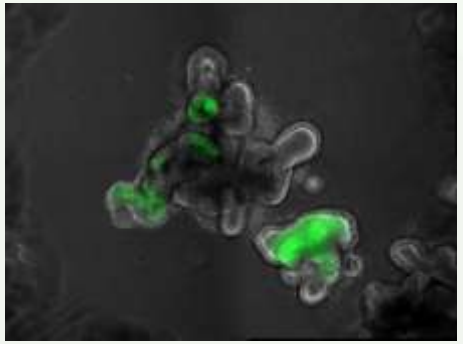
Differentiation

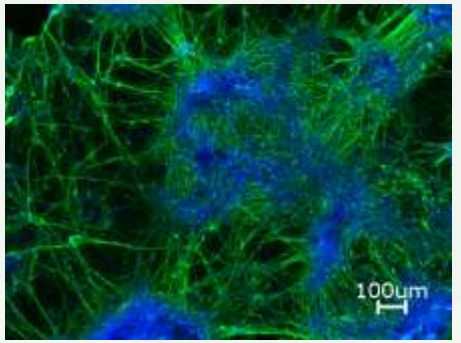
Diverse cell types

endoderm

ectoderm

mesoderm





Recapitulating aspects of human ATTR amyloidosis peripheral neuropathy

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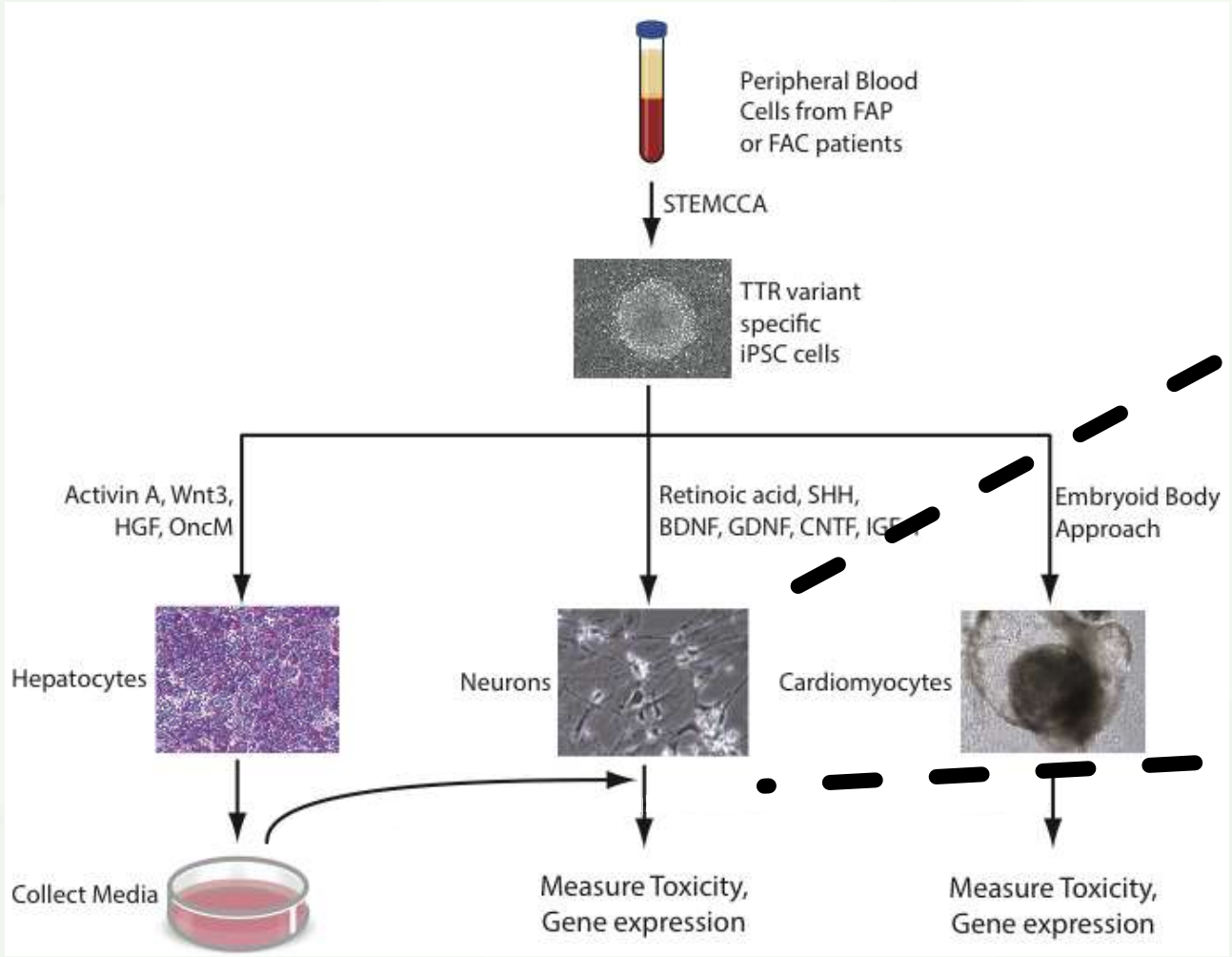

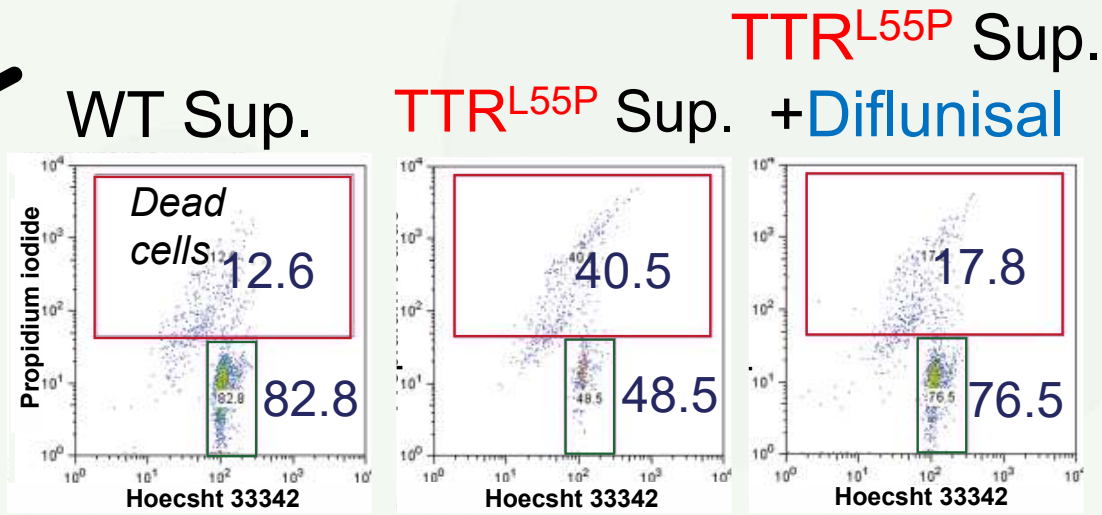

Adapted from Leung et al. 2014, *Stem Cell Reports*

An extensive, genetically diverse bank of ATTR patient-derived iPSCs

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Reprogrammed Lines	V30M (x3), V122I (x3), T60A, L55P, L58H, I107M, WT ATTR
PBMCs	V30M, WT ATTR (x10), V122I (x3), T60A (x2), L58H

Giadone et al. 2018, *Amyloid*

Are ATTR amyloidosis and wild-type hepatocytes different?

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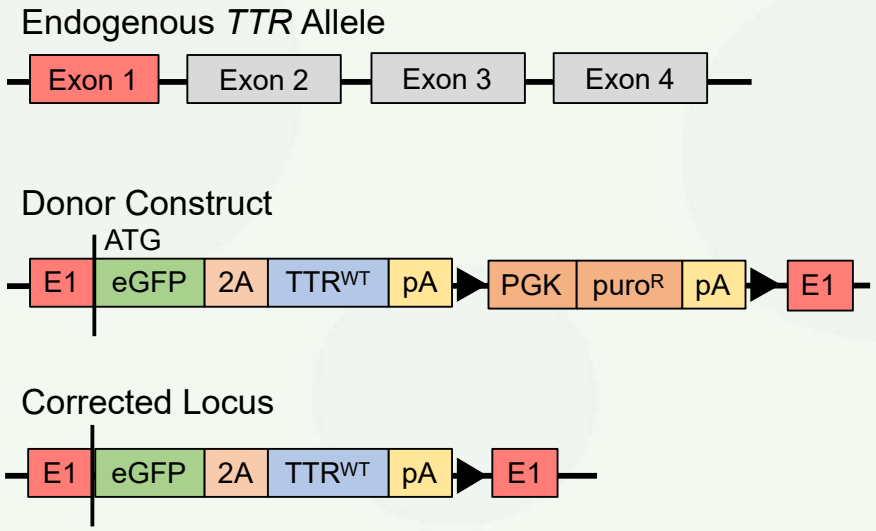
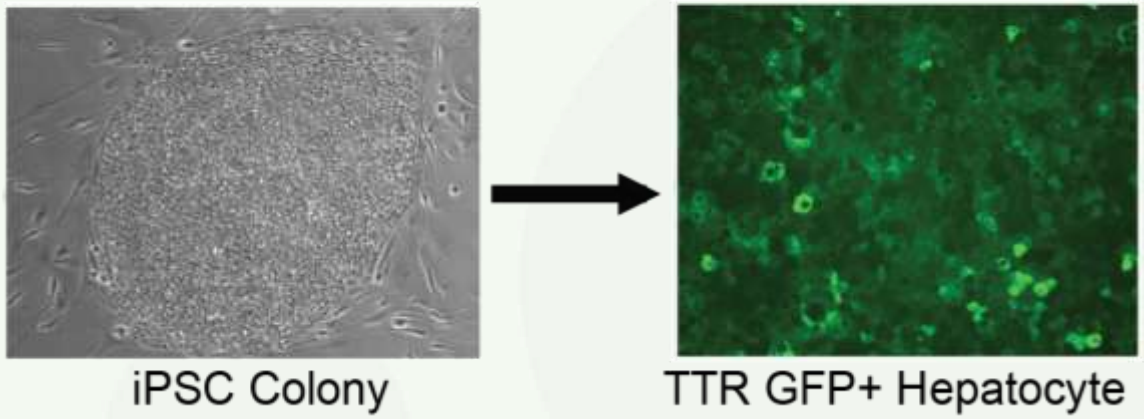
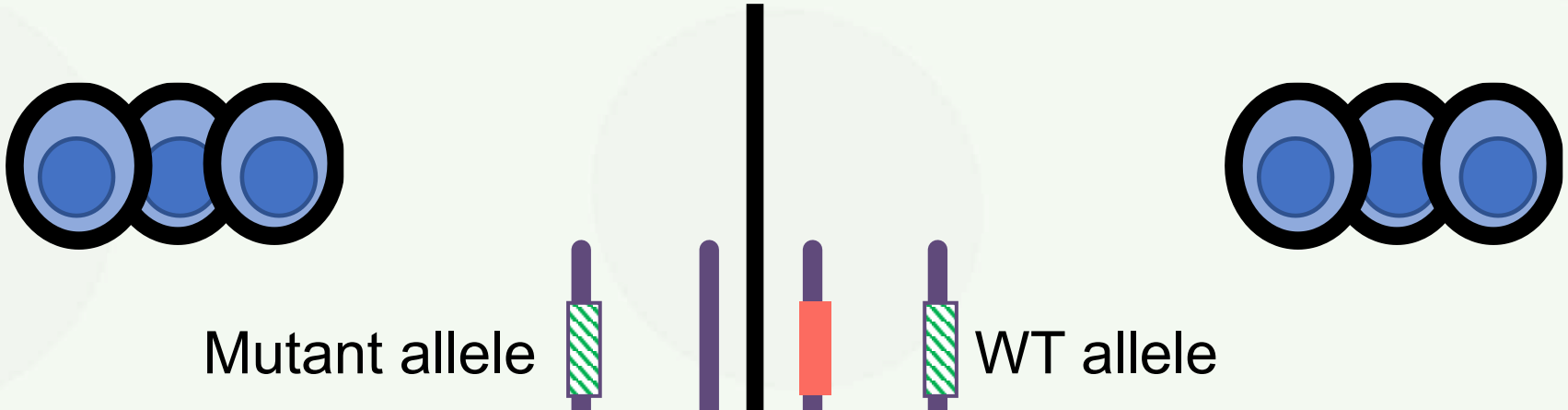




Corrected TTR reporter line

Uncorrected TTR reporter line



Hepatic expression of TTR^{L55P} correlates with expression of UPR genes

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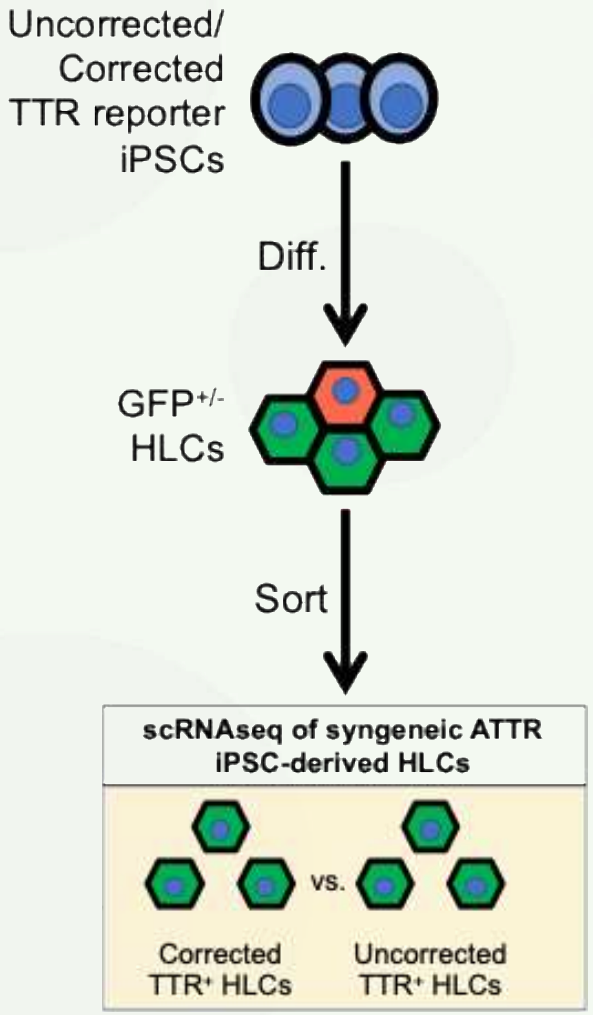

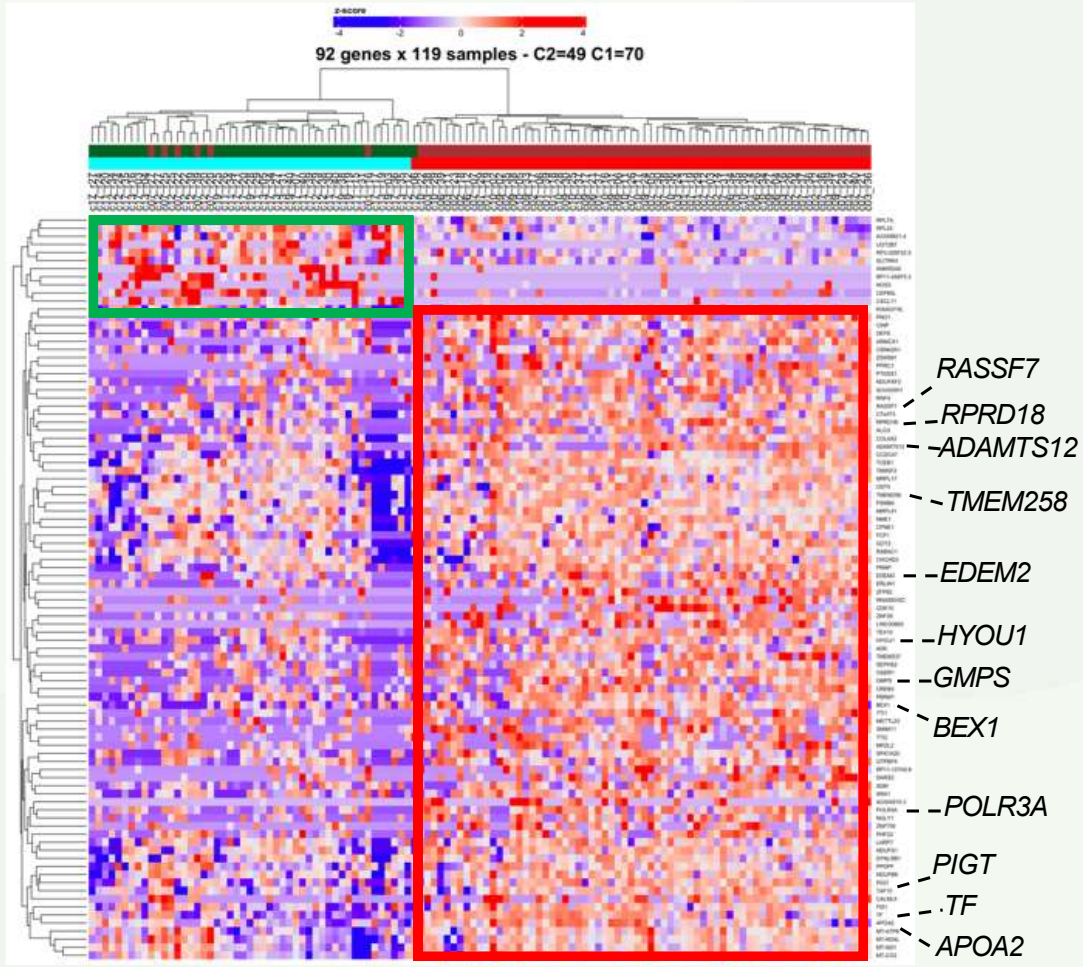

Corrected/Uncorrected

Giadone et al. 2020, *Stem Cell Reports*

Summary & Future Directions

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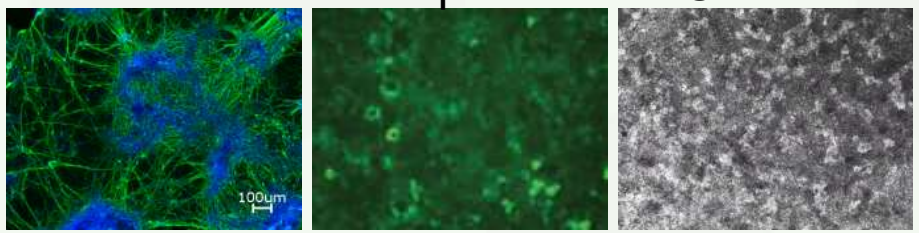
1. iPSC-based model encapsulating multiple cell types

Neuronal Hepatic Cardiac



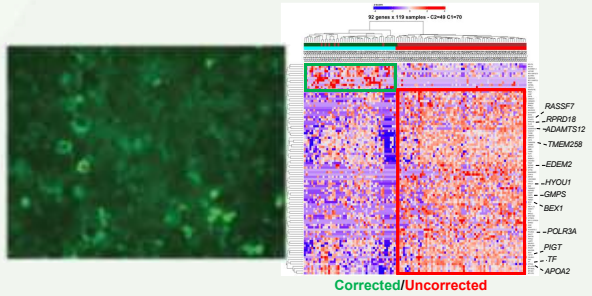
Leung et al. 2014, *Stem Cell Reports*

2. A library of ATTR amyloidosis patient-specific iPSCs

Reprogrammed Lines	V30M (x3), V122I (x3), T60A, L55P, L58H, I107M, WT ATTR
PBMCs	V30M, WT ATTR (x10), V122I (x3), T60A (x2), L58H

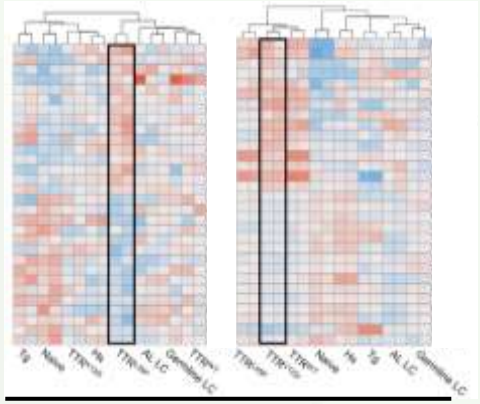
Giadone et al. 2018, *Amyloid*

3. Hepatic gene signature for ATTR amyloidosis



Giadone et al. 2020, *Stem Cell Reports*

How can we better measure toxicity in response to TTRs?

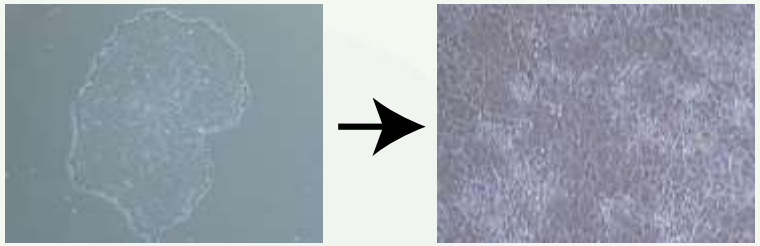


TTRs/Stress

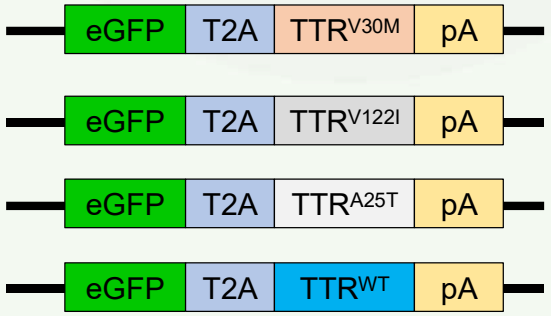
Ghosh et al. 2023, *Amyloid*

How can we model WT ATTR amyloidosis using iPSCs?

hiPSCs → Hepatic Cells



Can we dissect mechanisms of organ tropism?



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Contributions of AI into the research on Systemic Amyloidoses

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Examples of AI applications

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- Three examples:
- Prediction of protein structures and protein complexes
- Prediction of pathogenicity of point mutations in proteins
- Analysis of large datasets to reveal new applications for known drugs

Example 1:
AlphaFold 3 (AF3)

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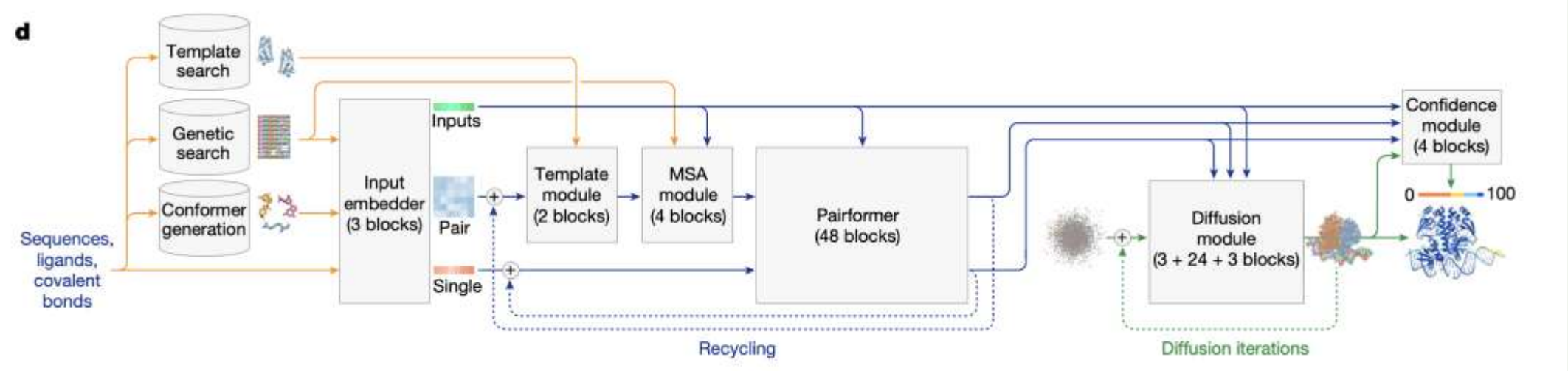

AF3 is a generative program capable to predict with high accuracy protein structures as well as protein complexes.
The AlphaFold project benefits from training on almost 250000 protein structures to date available.

Abramson et al Nature 2024

Example 1:
AlphaFold 3 (AF3)

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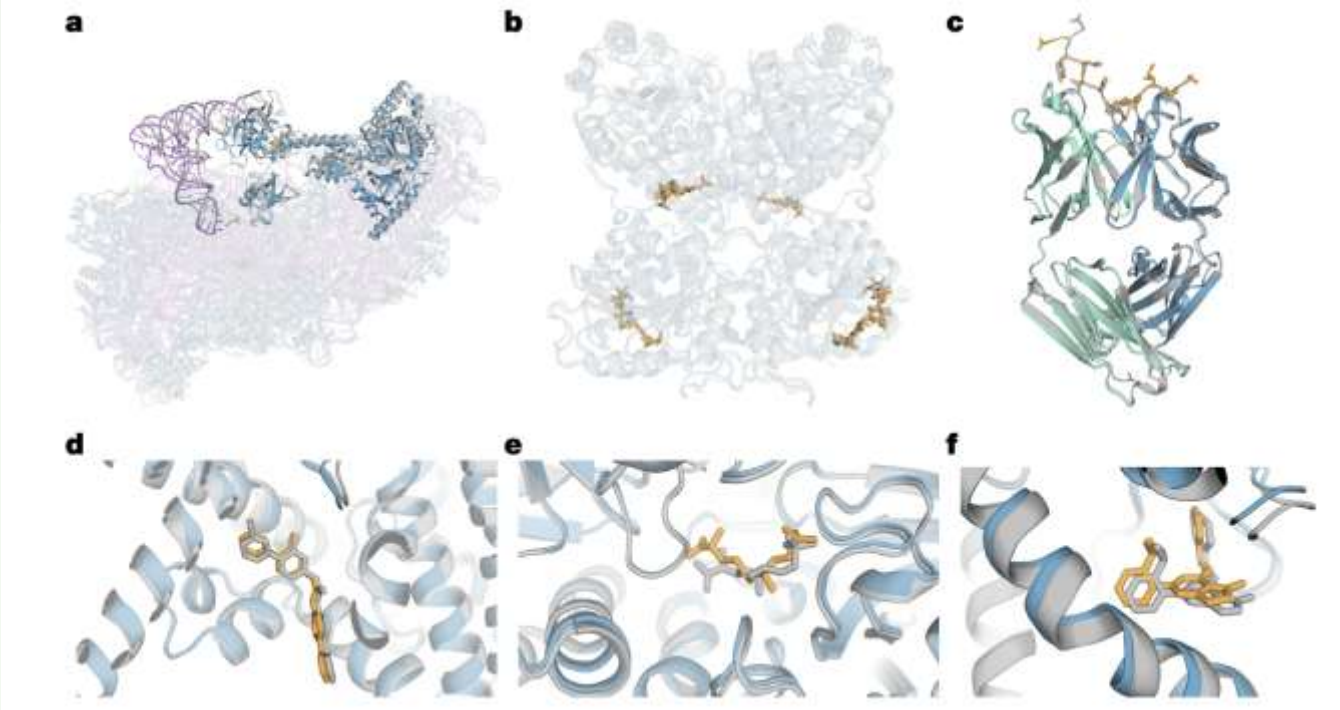
- AF3 can evaluate the formation of a complex between a drug and its target protein/receptor.
- AF3 can evaluate the formation of a complex between an antigen and a putative specific antibody.



Abramson et al Nature 2024

Example 2: AlphaMissense

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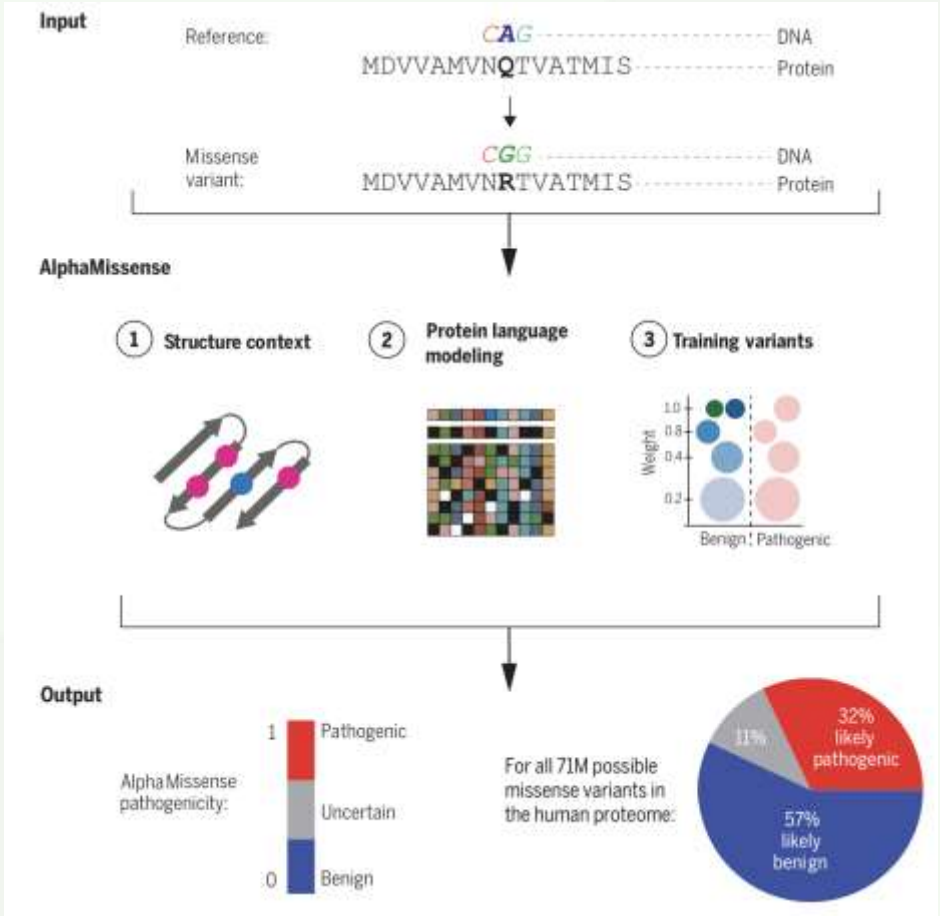
- First AlphaMissense predicts the protein structure and evaluates the impact of a given mutation
- Training sets: 1) benign are mutation frequently observed in human or primates, 2) pathogenic ones are never observed in populations,
- Test set: repository of genetic mutations (e.g. ClinVar)
- AlphaMissense database with all human proteins and predictions of all possible missense mutations: click here
- Human TTR UniProt code: P02766



Cheng et al Science 2023

Example 3:
Drug repurposing based on neural network

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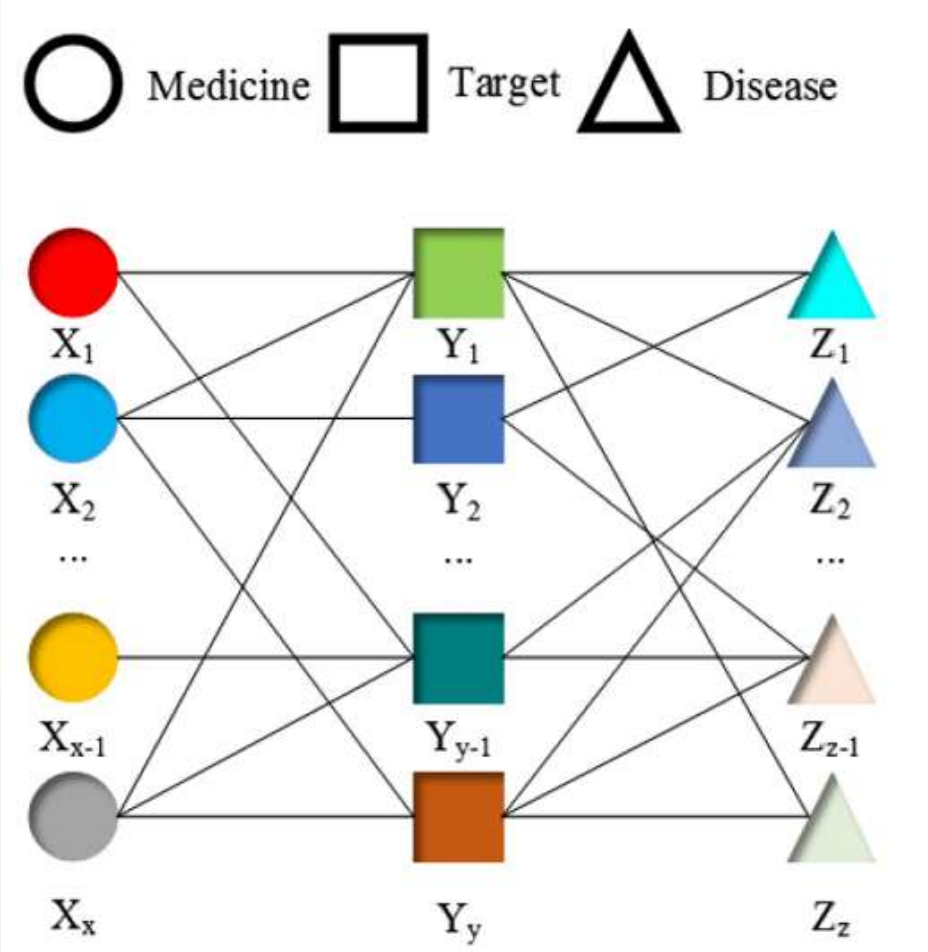
- BioSNAP dataset (Stanford University) provides:
- 15140 drug-target pairs
- 466658 drug-disease pairs
- 15509620 target-disease pairs

- Ternary relationships were created (drug-disease-target relationships)



Li et al. BMC Genomics 2024

Example 3:
Drug repurposing based on neural network

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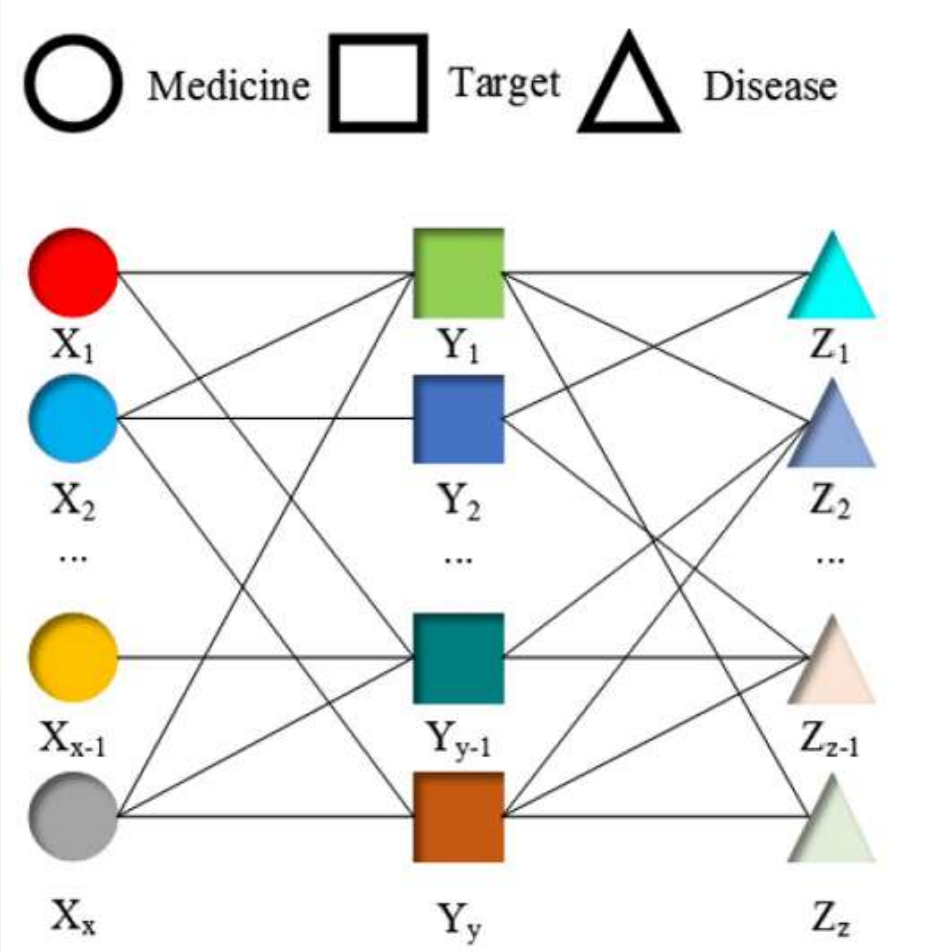
- The idea of binary relationships between drug – target – disease is over-simplifying medical experience
- Drug repurposing is based on possible effects of a drug on other targets / targets involved in several diseases
- Often drug repurposing efforts are also binary approaches



Li et al. BMC Genomics 2024

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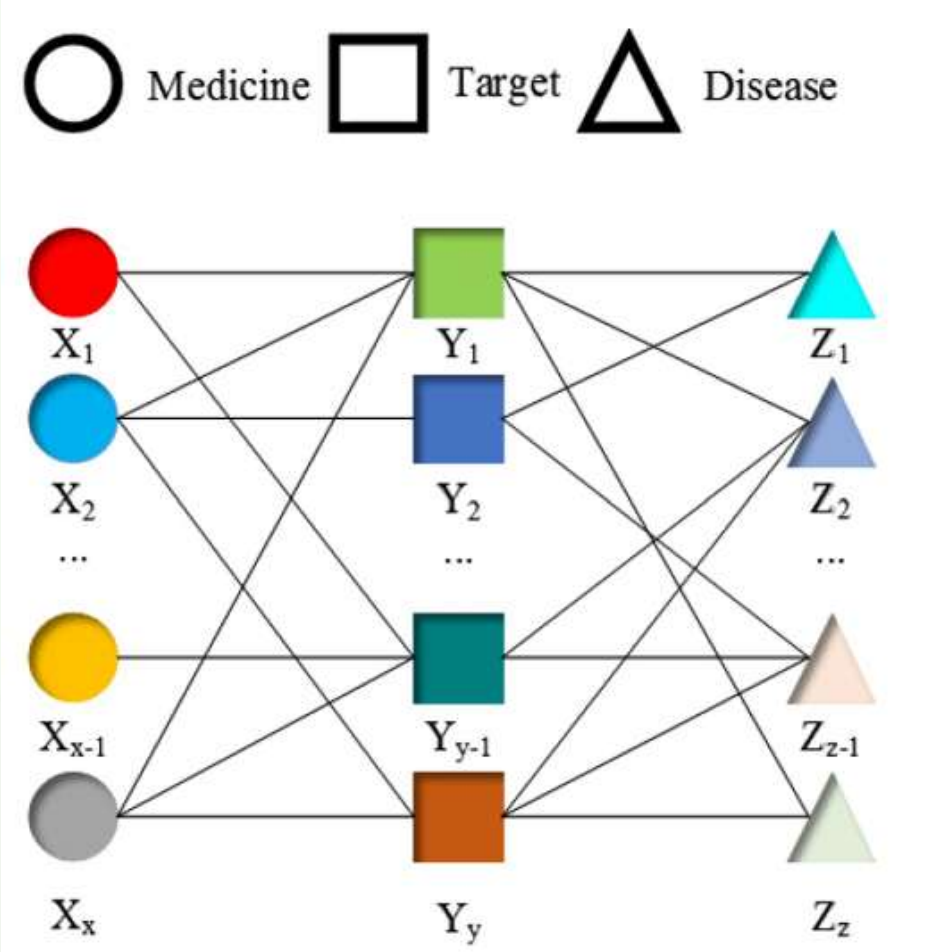

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Conclusions

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- Examples 1 and 2 show that AI can deliver tools with great predictive power
- Example 3 shows a promising proof-of-principle
- In all cases, the performance of AI-based tools depends on the size of the training set(s)

Li et al. BMC Genomics 2024