Mieux comprendre la physiopathologie des amyloses pour mieux traiter

Christophe Sirac

Team BioPIC (Biology of Plasma cell, Immunopathology and Cancer)

CNRS UMR 7276 - INSERM U1262 - Control of the Immune Response B and Lymphoproliferations (CRIBL)

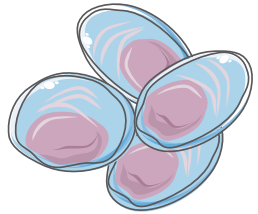
Université de Limoges

cnrs Inserm Université de Limoges

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

Liens d'intérêts

- Research grants from Attralus, Gate Bioscience, Sebia, AmylTherapeutics

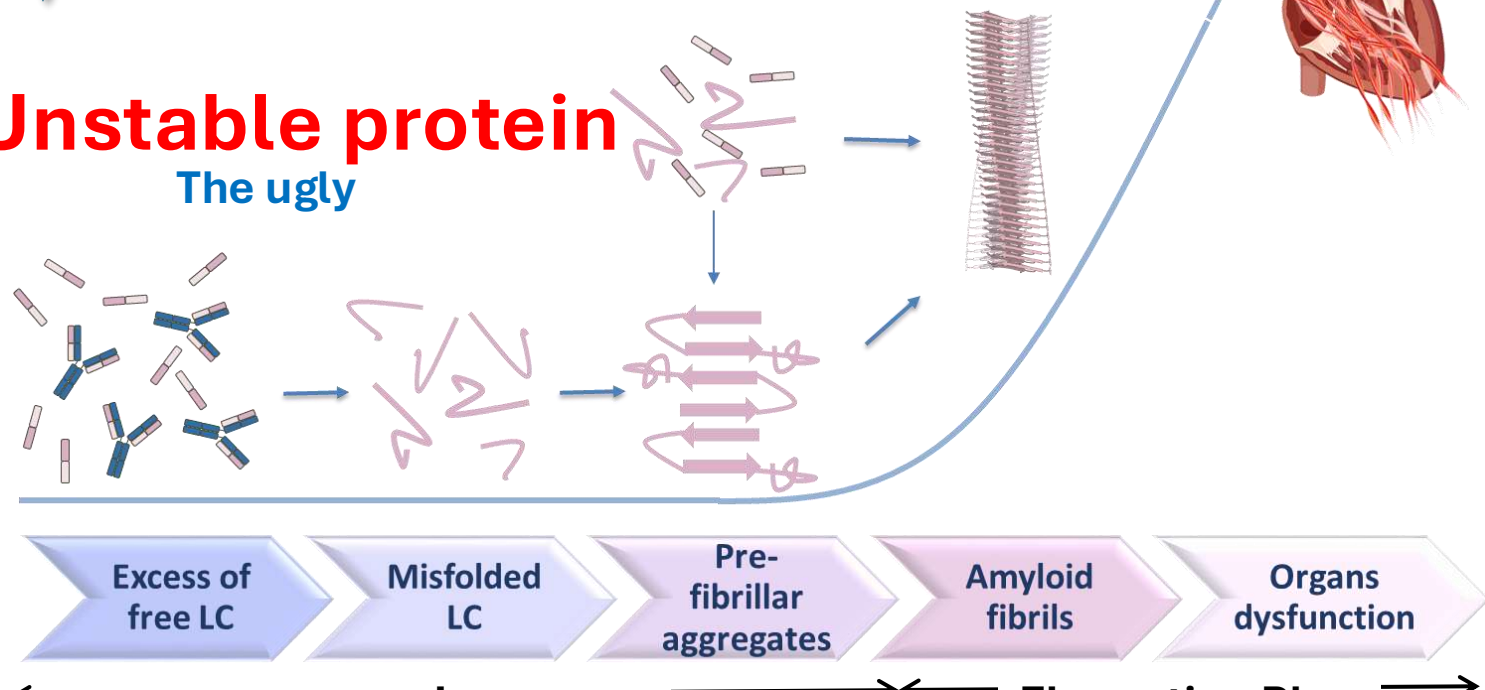


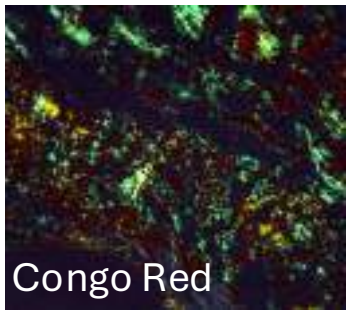
Producing cells

The (not) good

Unstable protein

The ugly

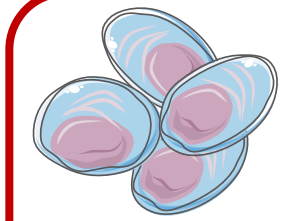




Deposits

The bad

Organ dysfunction



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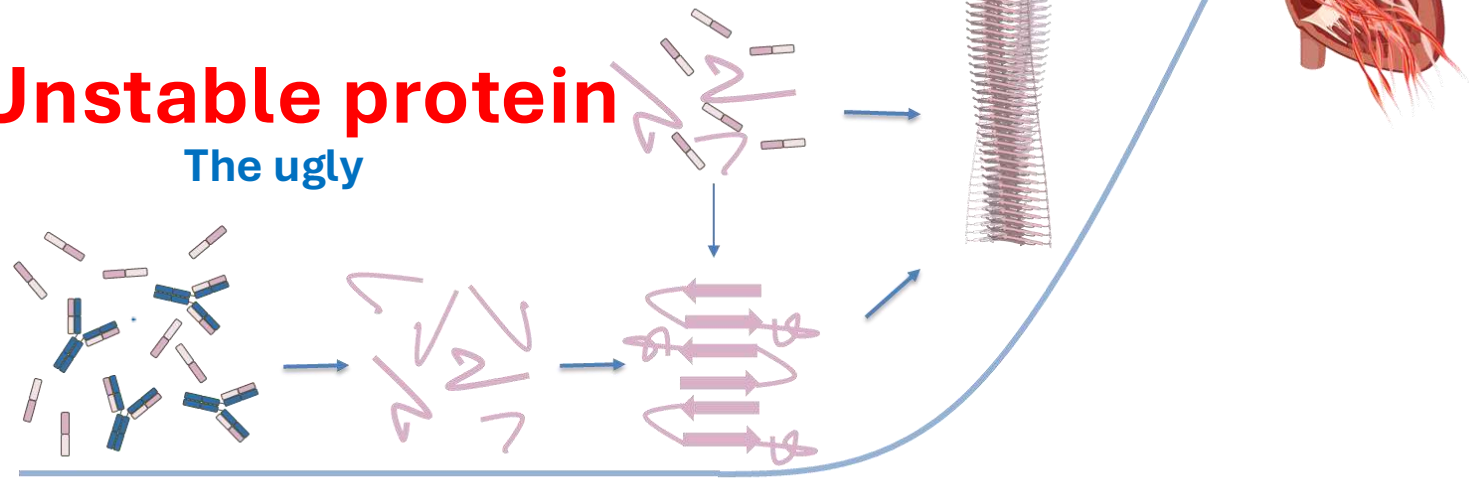
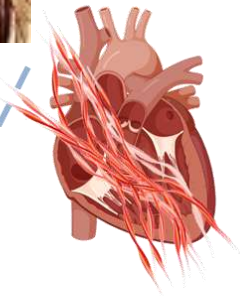
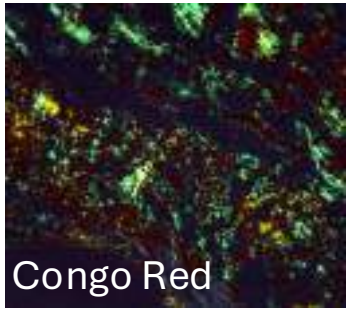






Deposits

The bad

Organ dysfunction

Amyloses ATTR, AA…

But: Réduire la production de la protéine amyloïdogène **mais** ne pas tuer la cellule productrice

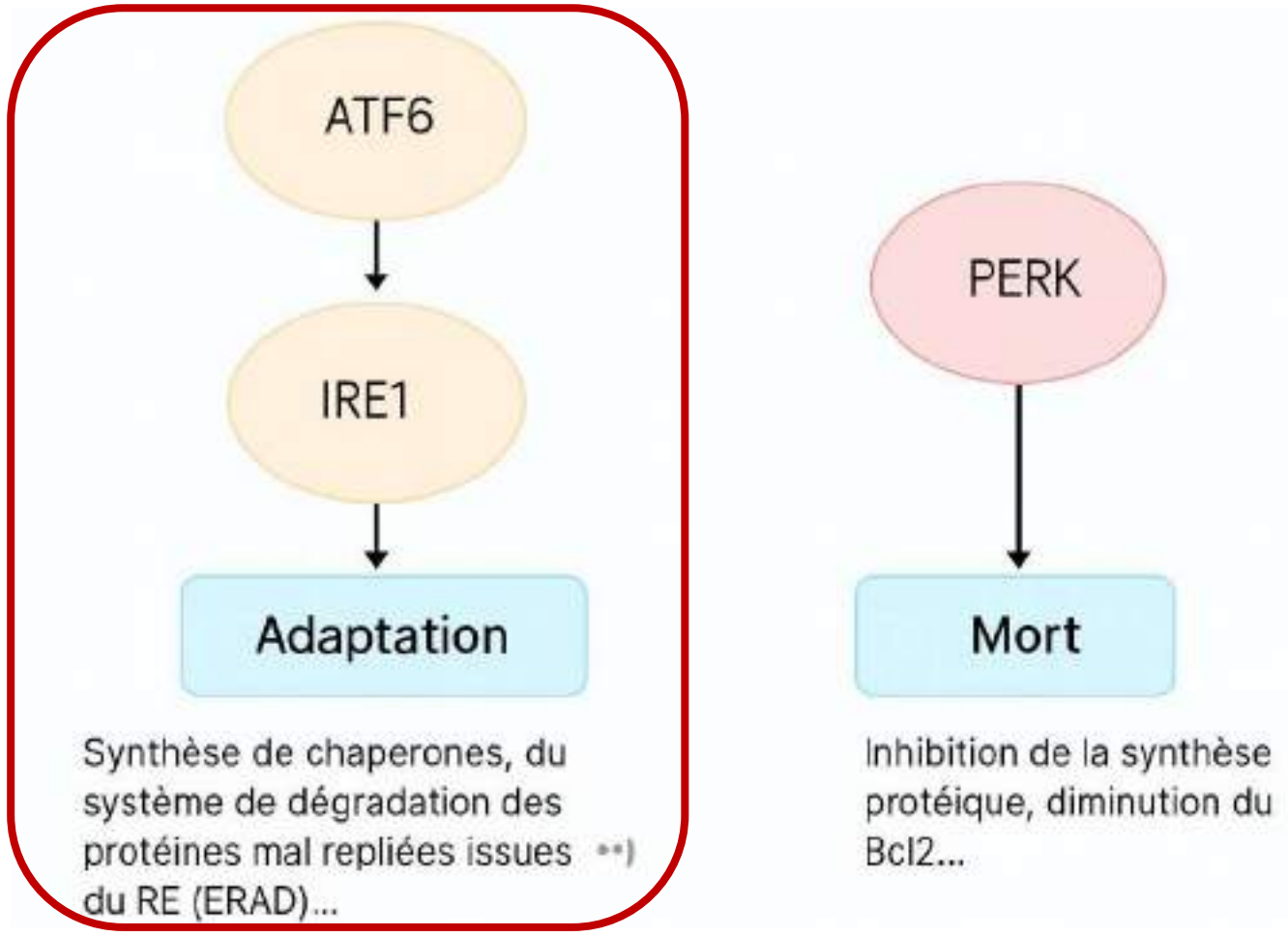
siRNA (patisiran), ASO (inotersen), Crispr-Cas9 (Nex-Z)…

- **Double avantage**: Ciblage du foie et peu de variabilité de séquences dans les protéines

Amylose AL

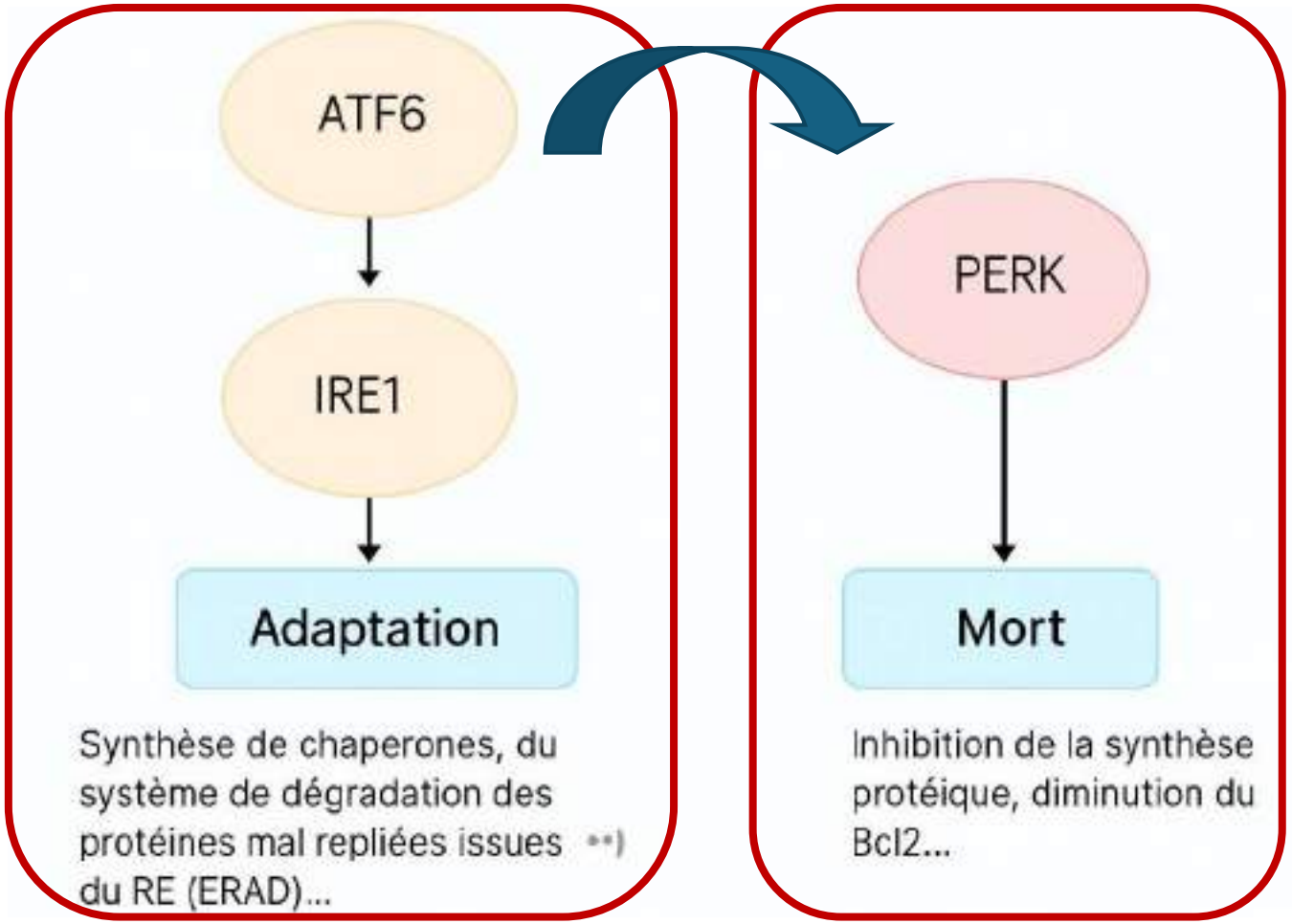
Buts: Réduire la production de la LC amyloïdogène **et** tuer le clone plasmocytaire

Comment supporter la production massive de protéines = système UPR (unfolded protein respo



Talon d'Achille des plasmocytes = Protéostase intracellulaire

Les cellules productrices privilégient les voies d'adaptation (ATF6, IRE1, XBP1)



Perturbation du système de protéostase

↓

Inhibiteurs du protéasome, autres...

↓

MORT

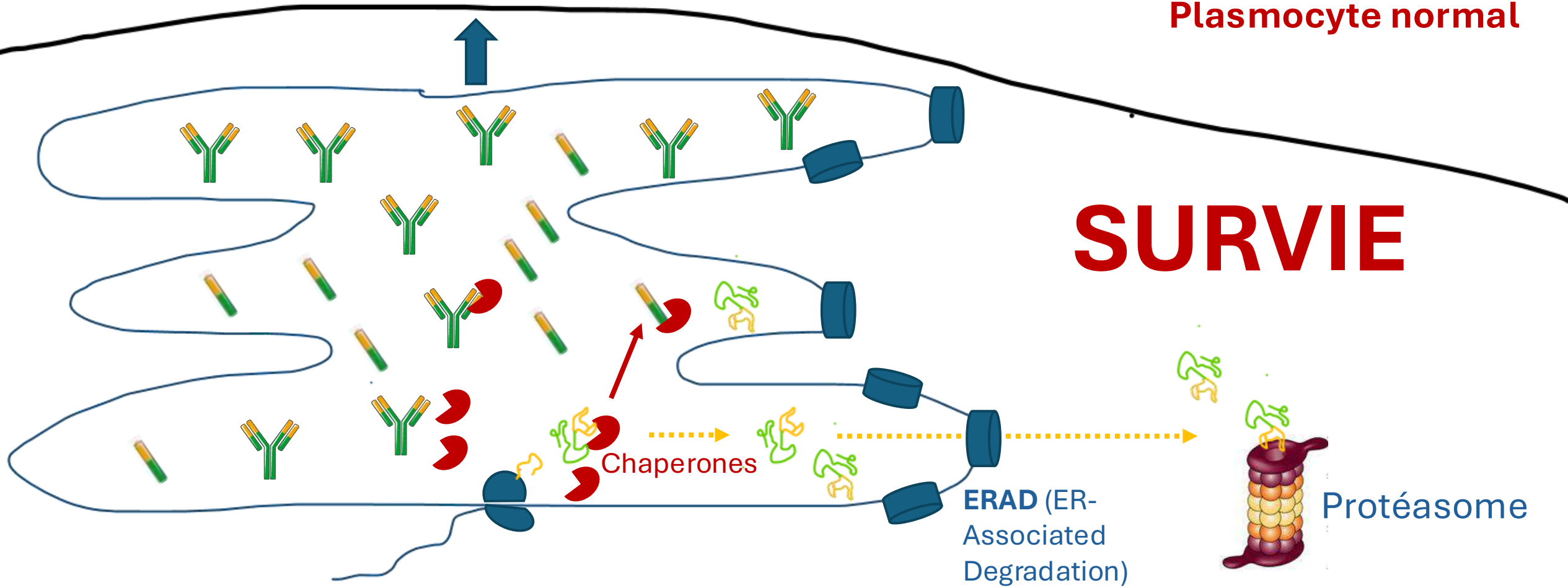
NEOPLASIA

Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells

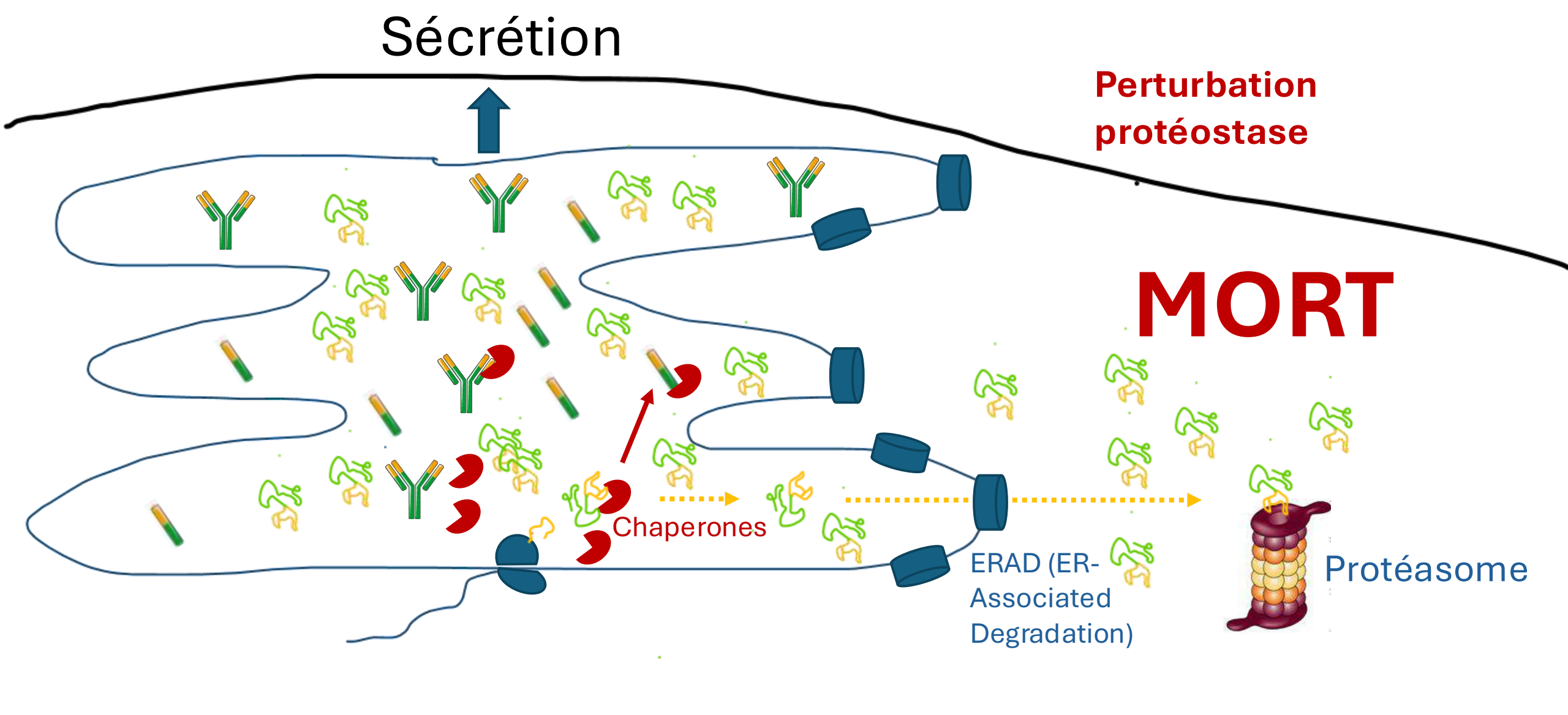
Esther A. Obeng, Louise M. Carlson, Delia M. Gutman, William J. Harrington Jr, Kelvin P. Lee, and Lawrence H. Boise

Sécrétion

Plasmocyte normal



SURVIE


Sécrétion
Perturbation protéostase
MORT
Chaperones
ERAD (ER-Associated Degradation)
Protéasome

Blocage LC par siRNA: Accumulation chaînes lourdes dans ER → **terminal ER s**

LYMPHOID NEOPLASIA

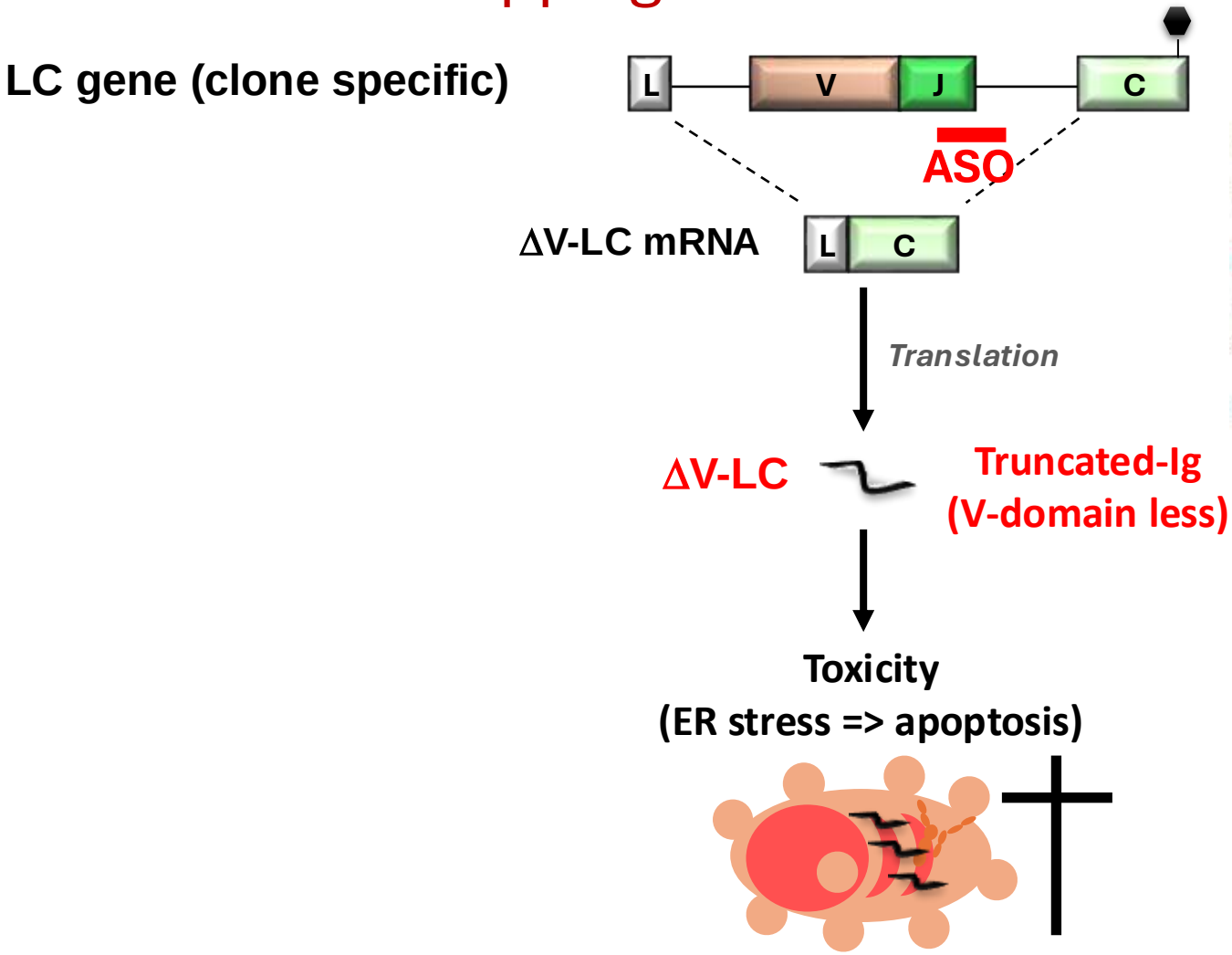
One siRNA pool targeting the λ constant region stops λ light-chain production and causes terminal endoplasmic reticulum stress

Ping Zhou,[1] Xun Ma,[1] Lakshmanan Iyer,[2] Chakra Chaulagain,[1] and Raymond L. Comenzo[1,2]

[1]Tufts Medical Center, Boston, MA; and [2]Tufts University School of Medicine, Boston, MA

- Peut être clone-spécifique (médecine personnalisée)

LC exon skipping: Accumulation CH dans ER → **terminal ER stress**



Physiological and druggable skipping of immunoglobulin variable exons in plasma cells

Mohamad Omar Ashi, Nivine Srour, Jean-Marie Lambert, Anne Marchalot, Ophélie Martin, Sandrine Le Noir, Eric Pinaud, Maria Victoria Ayala, Christophe Sirac, Jérôme Saulière, Jérôme Moreaux, Michel Cogné & Laurent Delpy

Cellular & Molecular Immunology 16, 810–819 (2019) | Cite this article

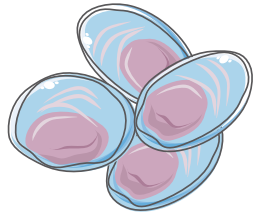
Delpy et al. patent WO2017089359

- Peut être clone-spécifique (médecine personnalisée)

Amylose AL

But: Réduire la production de la LC amyloïdogène **et** tuer le clone plasmocytaire

> Traitements anti-myélome font très bien le job (Dara, Bispé, Car-T…)



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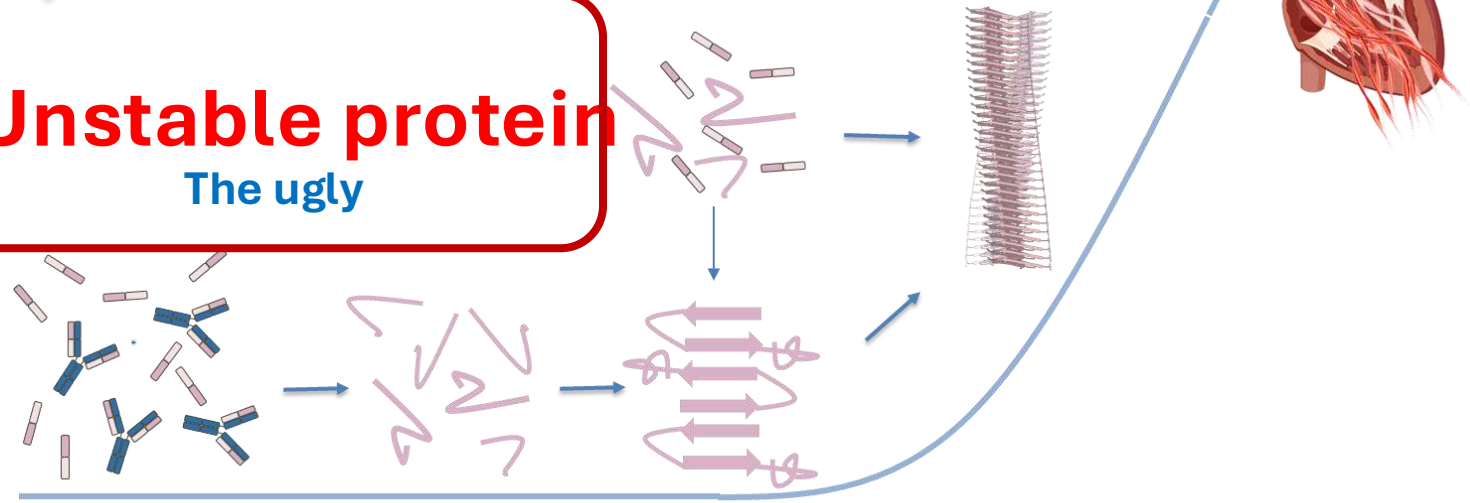
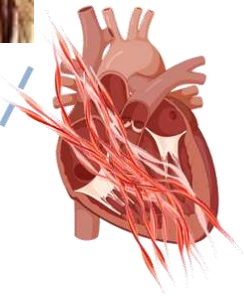
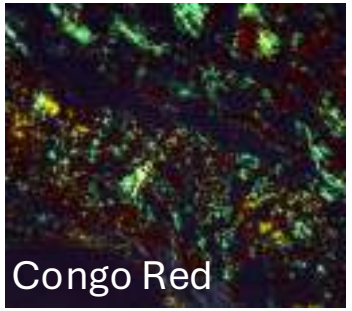






Deposits

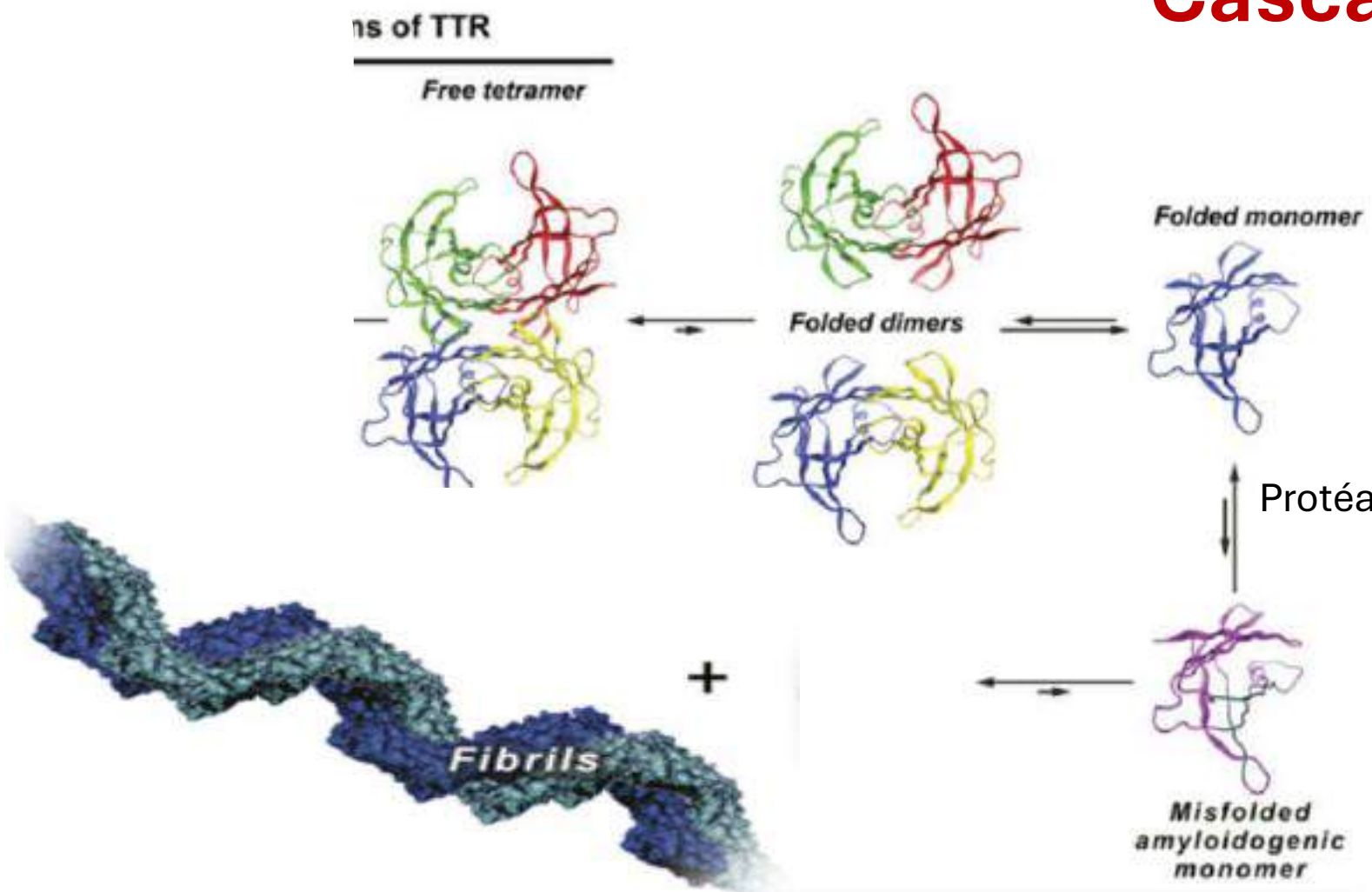
The bad

Organ dysfunction

Cascade amyloïde de la TTR

Accélérée par certaines mutations

Travaux de Jeff Kelly (depuis 1992)



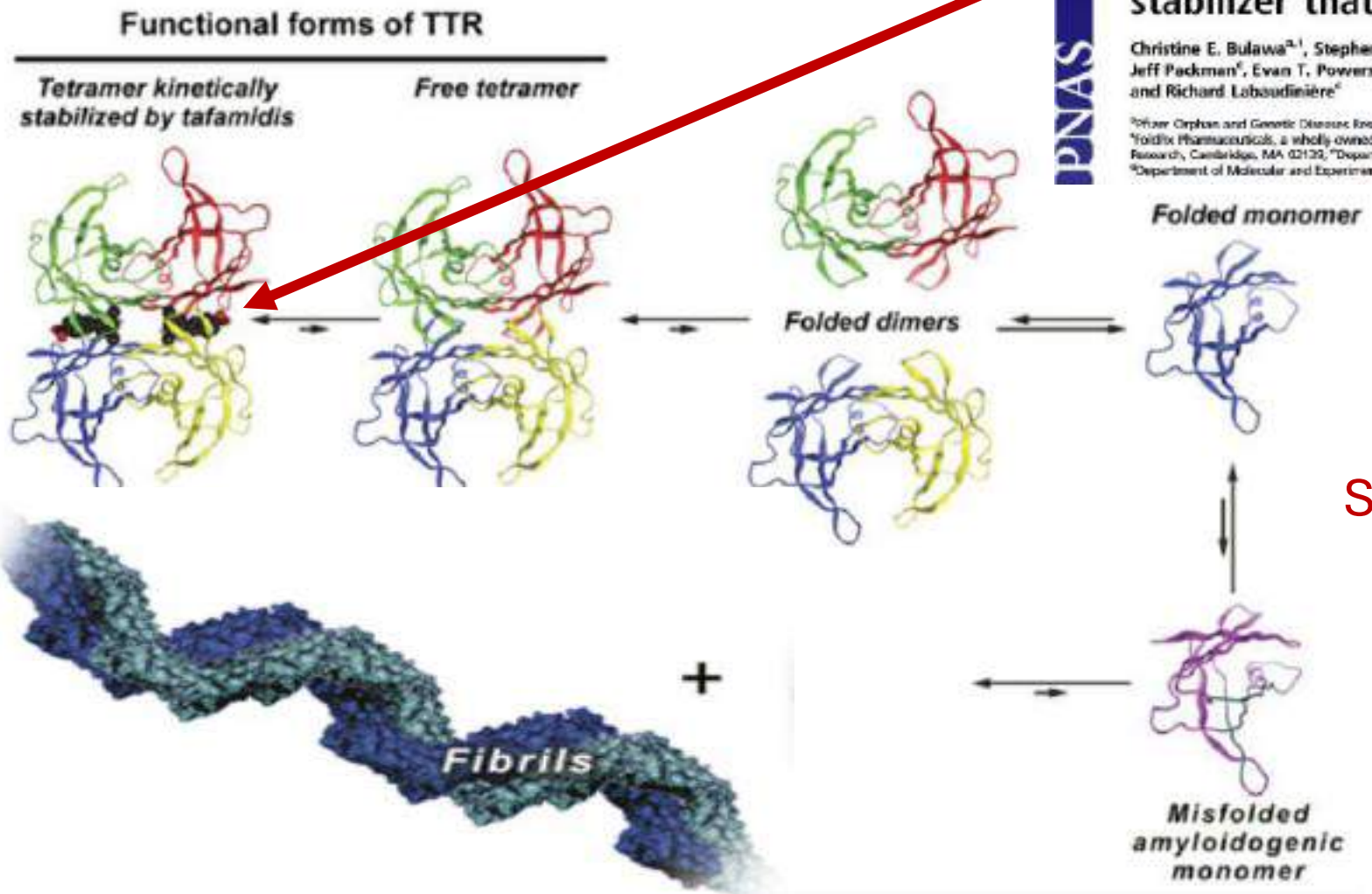
nature COMMUNICATIONS

ARTICLE

OPEN

Plasmin activity promotes amyloid deposition in a transgenic model of human transthyretin amyloidosis

Ivana Stanova[1], Rozita Adib[1,2], Stephan Elmerich[1], Michal R. Golos[1,4], Janet A. Gilbertson[1], Nicola Botcher[1], Diana Canetti[1], Graham W. Taylor[1], Nigel Rendell[1], Glenys A. Tennent[1], Guglielmo Verona[1], Riccardo Porcari[1], P. Patrizia Mangione[1,2], Julian D. Gillmore[1], Mark B. Pepys[1], Vittorio Bellotti[1,2], Philip N. Hawkins[1], Raya Al-Shawi[1] & J. Paul Simons[1]



PNAS

Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade

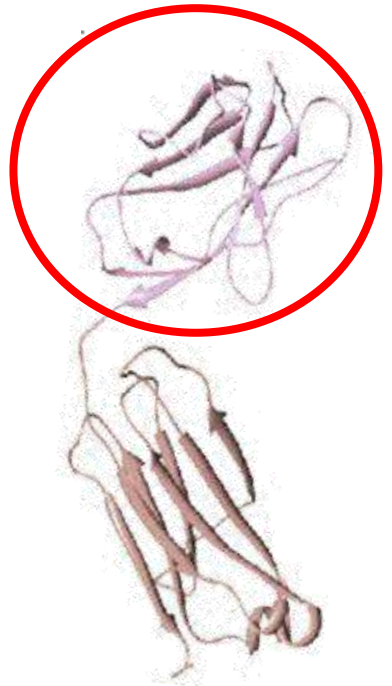
Christine E. Bulawa[a-i], Stephen Connelly[b], Michael DeVit[c], Lan Wang[c], Charlotte Weigel[a], James A. Fleming[a], Jeff Packman[c], Evan T. Powers[e,f], R. Luke Wiseman[g], Theodore R. Foss[h], Ian A. Wilson[b,f], Jeffery W. Kelly[e,f,g], and Richard Labaudinière[c]

[a]Pfizer Orphan and Genetic Diseases Research Unit, Cambridge, MA 02140; [b]Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037; [c]Foldrx Pharmaceuticals, a wholly owned subsidiary of Pfizer, Cambridge, MA 02140; [d]Cardiovascular and Metabolic Diseases, Novartis Institutes for BioMedical Research, Cambridge, MA 02139; [e]Department of Chemistry, The Scripps Research Institute and [f]The Skaggs Institute for Chemical Biology, La Jolla, CA 92037; [g]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA 92037; and [i]Life Technologies, Genetic Systems, Beverly, MA 01915

Stabilise tous les mutants et WT

Amylose AL: ça se complique…

- Role of the V domain: Not all LC are amyloidogenic
- 100 papers about specific mutations reducing stability of LC *(Ramirez-Alvarado, Wall, Kelly, Eisenberg, Merlini, Lavatelli, Buel, Buchner, Fandrich, Pozo-Yauner, Stevens, etc…)*
- ALbase with ~900 AL LC – Limoges ~350 AL LC



- No common mutations
- Multiple mutations in each VL

Emergence d'outils de prédiction d'amyloidogénicité par machine-learning

VICTOR

Garofalo et al. 2021

83%

VLAmY-Pred

Rawat et al. 2021

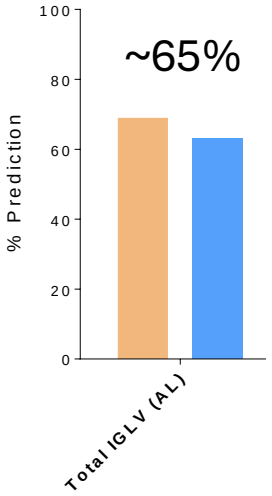
79%

HLAB AB—AmY Antibody Amyloidosis

Zhou et al. 2023

93%

Limoges database, 350 IGLV AL, 580 IGLV other monoclonal diseases



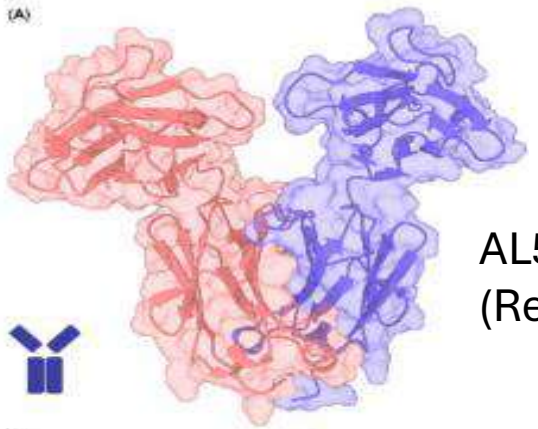
Nombreux biais (contrôles, données cliniques)

BUT:

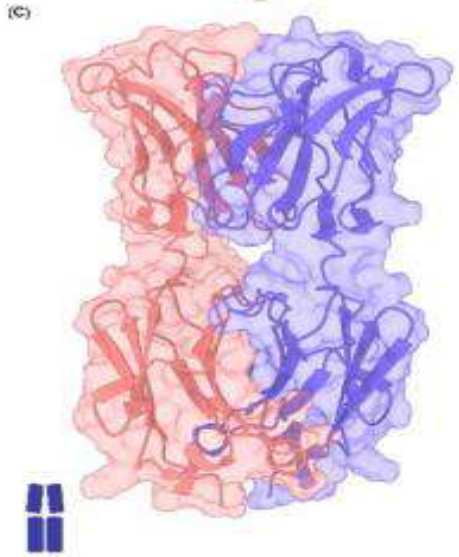
- Prédire évolution dans MGUS ou MM
- Evaluer la dangerosité de la LC

Présentation Virginie Pascal

Dimère VL ouvert



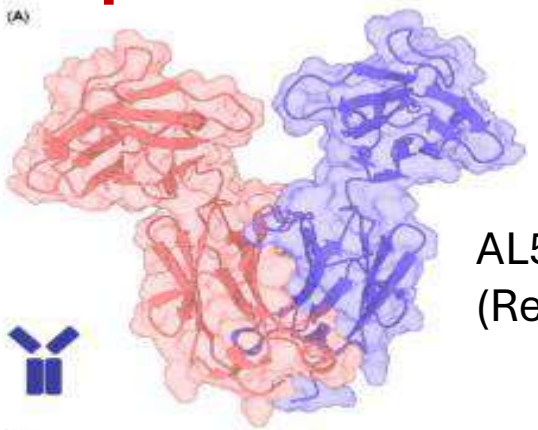
AL55 structure
(Real crystal)



AL55 structure
(Predicted
Alphafold)

Puri et al. JMB 2025

Open VL dimer



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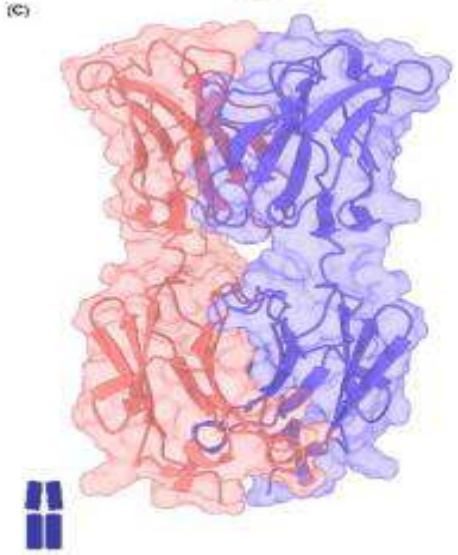
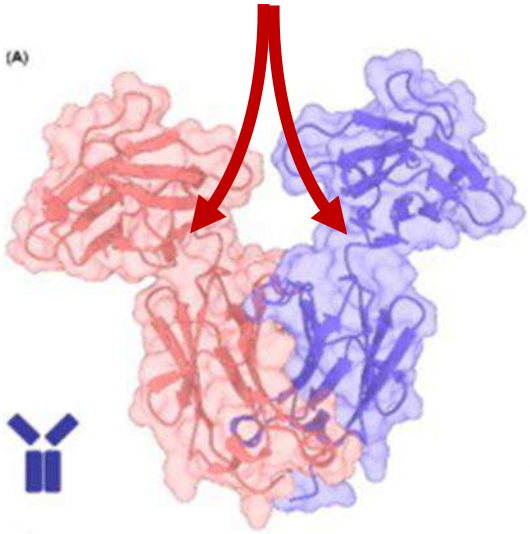


AL55 structure
(Predicted
Alphafold)

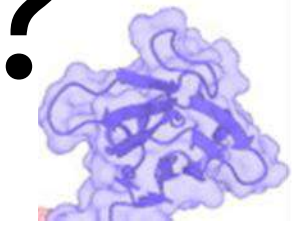
Puri et al. JMB 2025

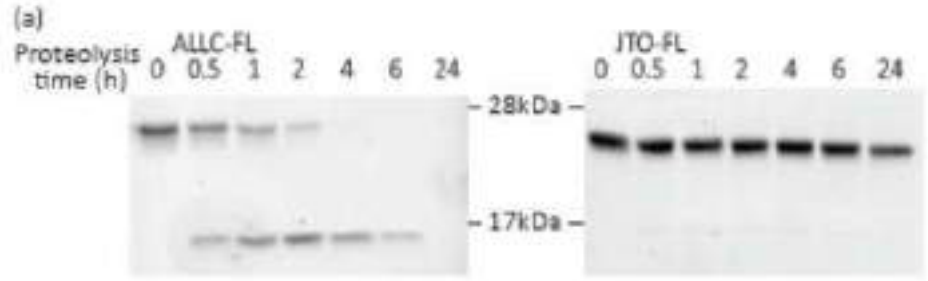
Protéases

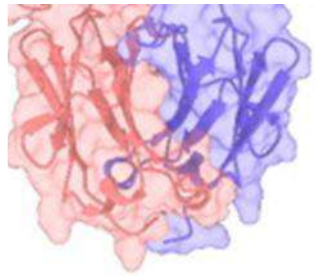


Morgan et al, JMB 2016

?







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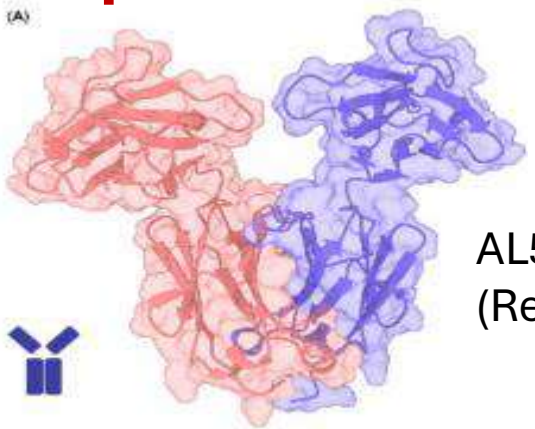

AL55 structure
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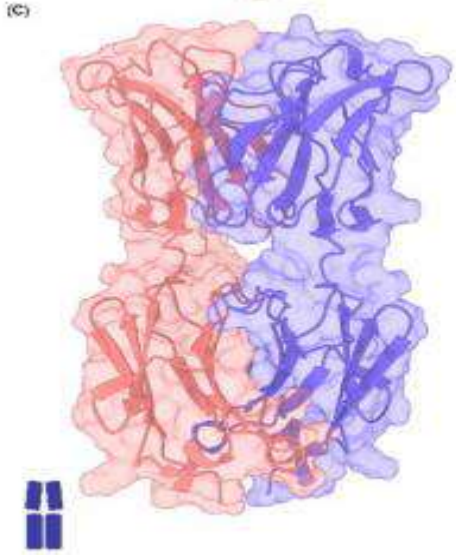

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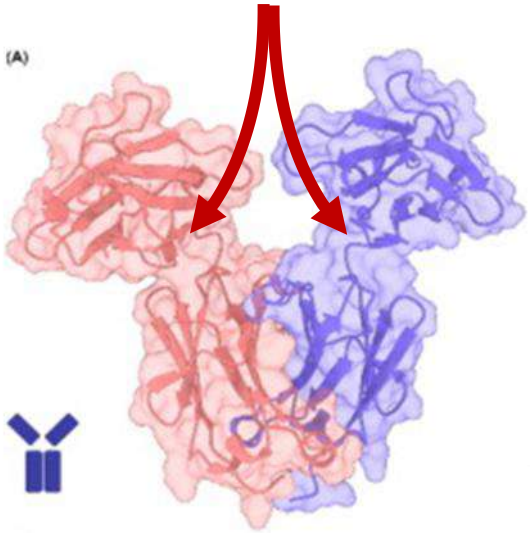

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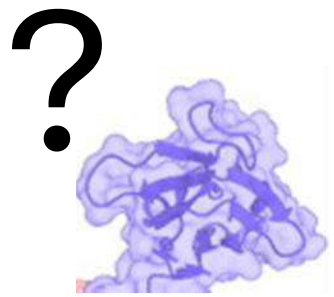
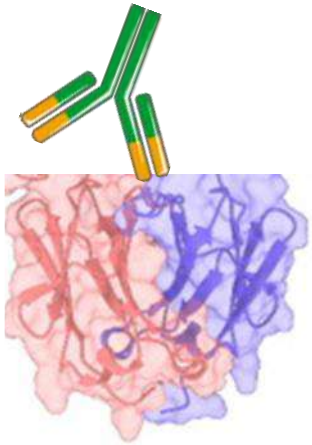




Diagnostic
Prédiction

protego

protego

536 Blood-Based Diagnostic Assay for λ Light Chain Amyloidosis through Quantification of an Amyloidogenicity-Indicating Neo-Epitope

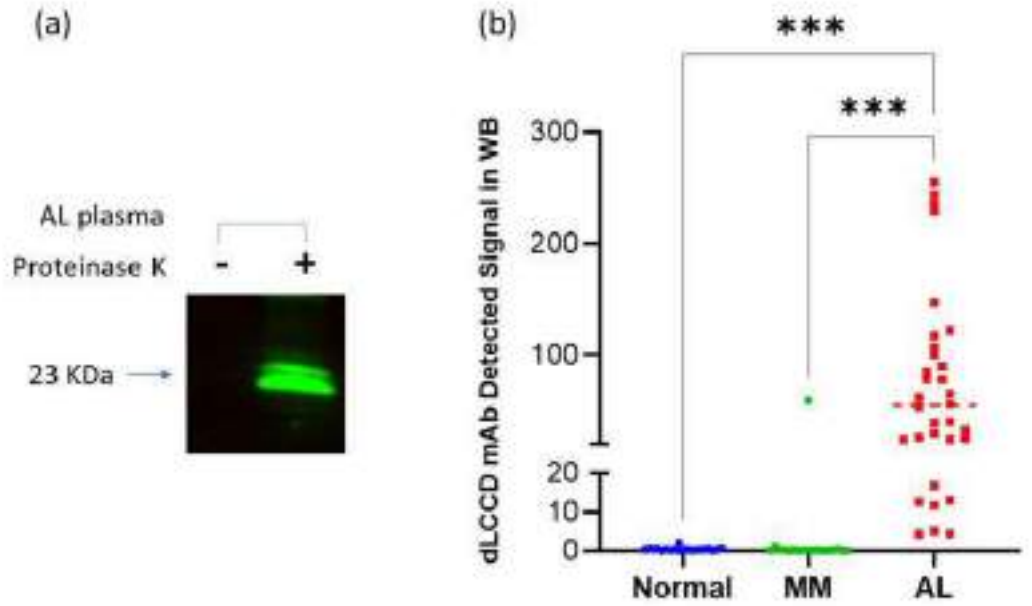


Fig. 1. dLCCD mAbs quantify dLCCD fragment specifically in monoclonal λAL patient plasma samples after limited proteolysis with Proteinase K. (a) Example of an AL plasma sample before and after limited proteolysis, ran on a Western blot, and detected with a dLCCD mAb targeting the neo-epitope on dLCCD. A fluorophore-tagged secondary antibody was used for the detection and quantification. (b) dLCCD signal of protease-treated λFLC in plasma samples from healthy normal donors (N=23), MM (N=19) and AL (N=32) patients. One-way ANOVA was used to compare normal or MM to AL samples, resulting in p=0.0007 and 0.0008, respectively.

Test sérique pour prédire et suivre l'amyloïdogénicité d'une LC monoclonale
(uniquement lambda LC)

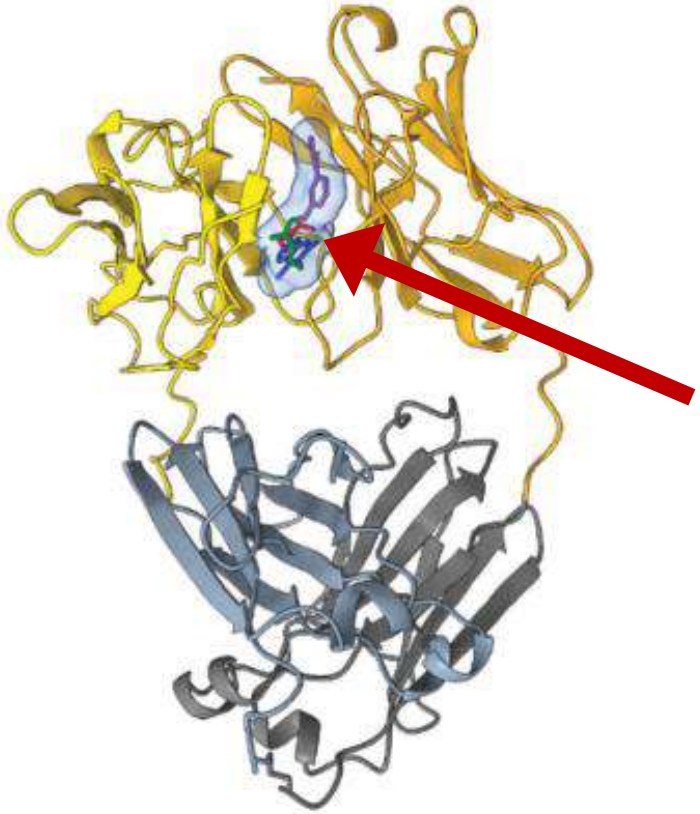
PNAS

Stabilization of amyloidogenic immunoglobulin light chains by small molecules

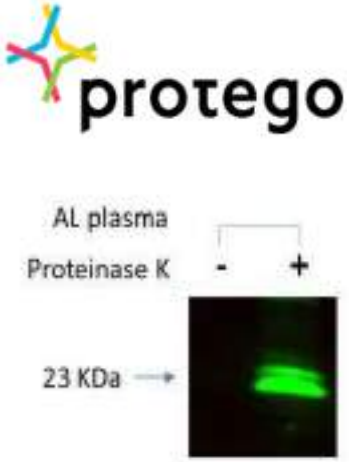
Gareth J. Morgan[a,b,1,2,3], Nicholas L. Yan[a,b,1], David E. Mortenson[a,b], Enrico Rennella[c,d,e], Joshua M. Blundon[a,b], Ryan M. Gwin[a,b], Chung-Yon Lin[a,b], Robyn L. Stanfield[f], Steven J. Brown[e], Hugh Rosen[e], Timothy P. Spicer[g], Vimeliz Fernandez-Vega[g], Giampaolo Merlini[h,i], Lewis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

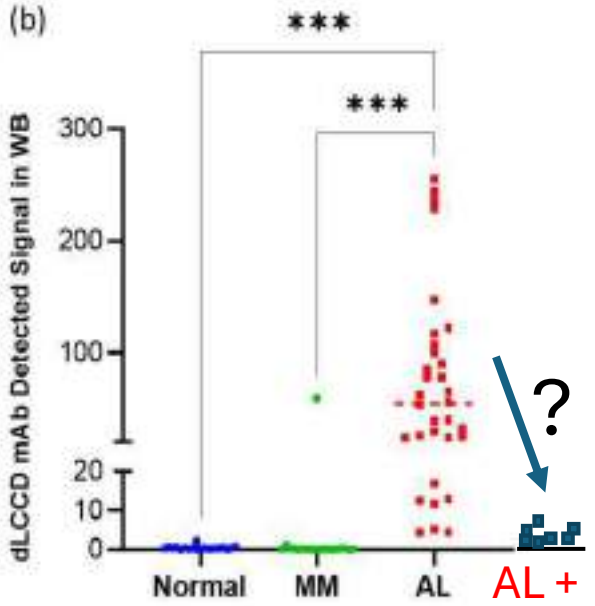
[a]Department of Molecular Medicine, The Scripps Research Institute, La Jolla, CA 92037; [b]Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037; [c]Department of Molecular Genetics, The University of Toronto, Toronto, ON M5S1A8, Canada; [d]Department of Biochemistry, The University of Toronto, Toronto, ON M5S1A8, Canada; [e]Department of Chemistry, The University of Toronto, Toronto, ON M5S1A8, Canada; [f]Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA 92037; [g]Department of Molecular Medicine, The Scripps Research

Stabilizing amyloid LC (?)



Stabilisateur du dimère

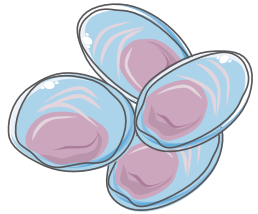




Stabilizing amyloid LC (?)

Utile?

(à l'heure des bi-spécifiques, CAR-T…)



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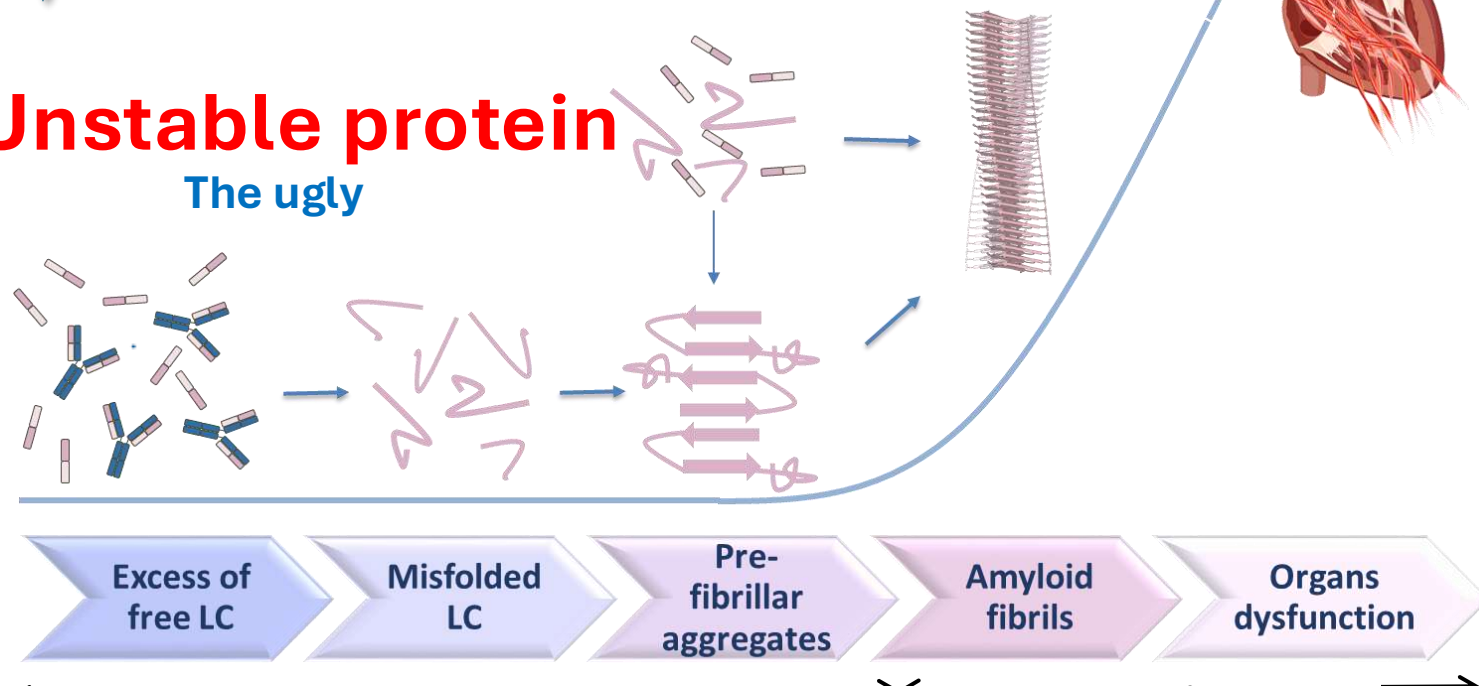
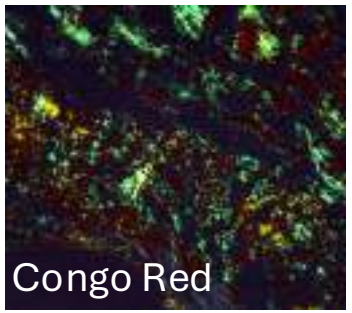




Deposits

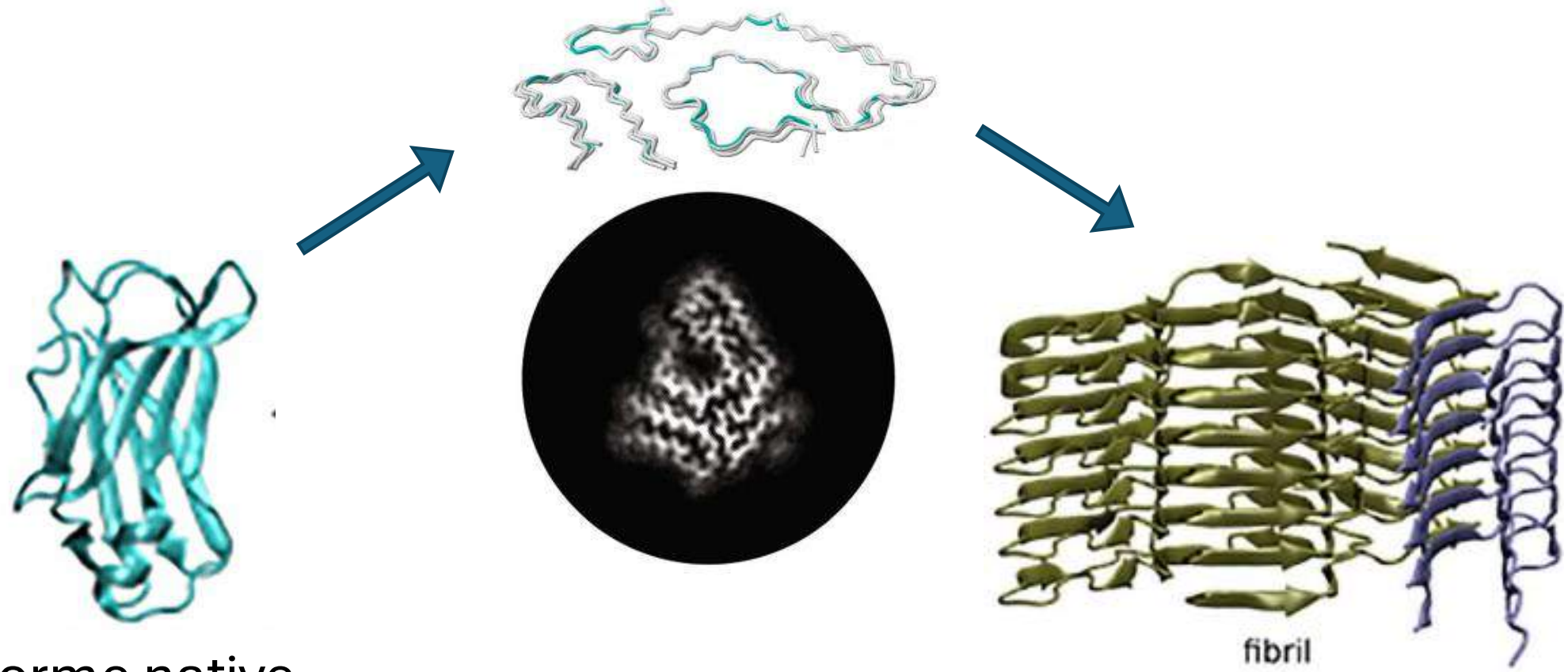
The bad

Organ dysfunction

Avant la Cryomicroscopie electronique (CryoEM)

Forme native circulante

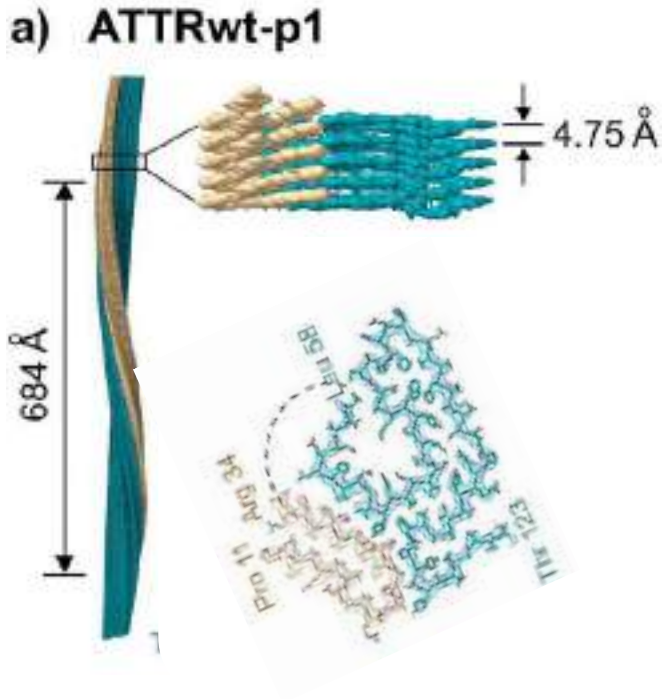
Avec la Cryomicroscopie electronique (CryoEM)

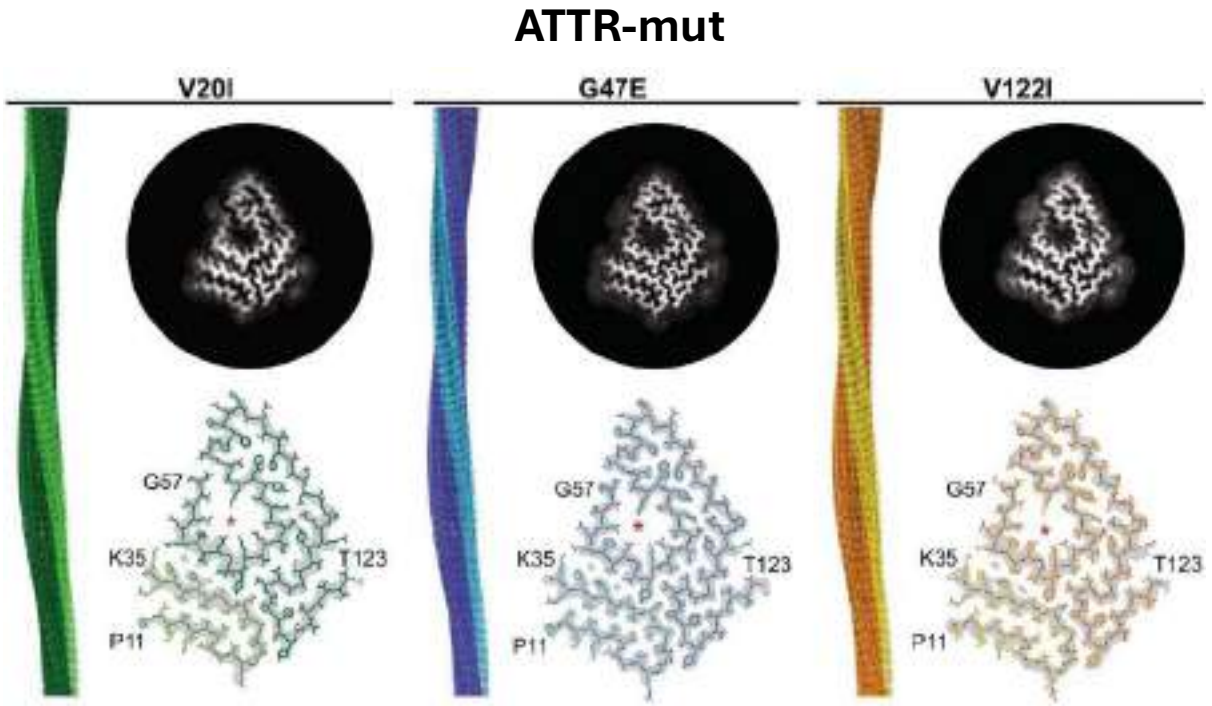


Forme native circulante

ATTR (mais aussi la plupart des amyloses systémiques)

- Homogénéité inter-organes
- Homogénéité inter-patients
- Homogénéité inter-mutants





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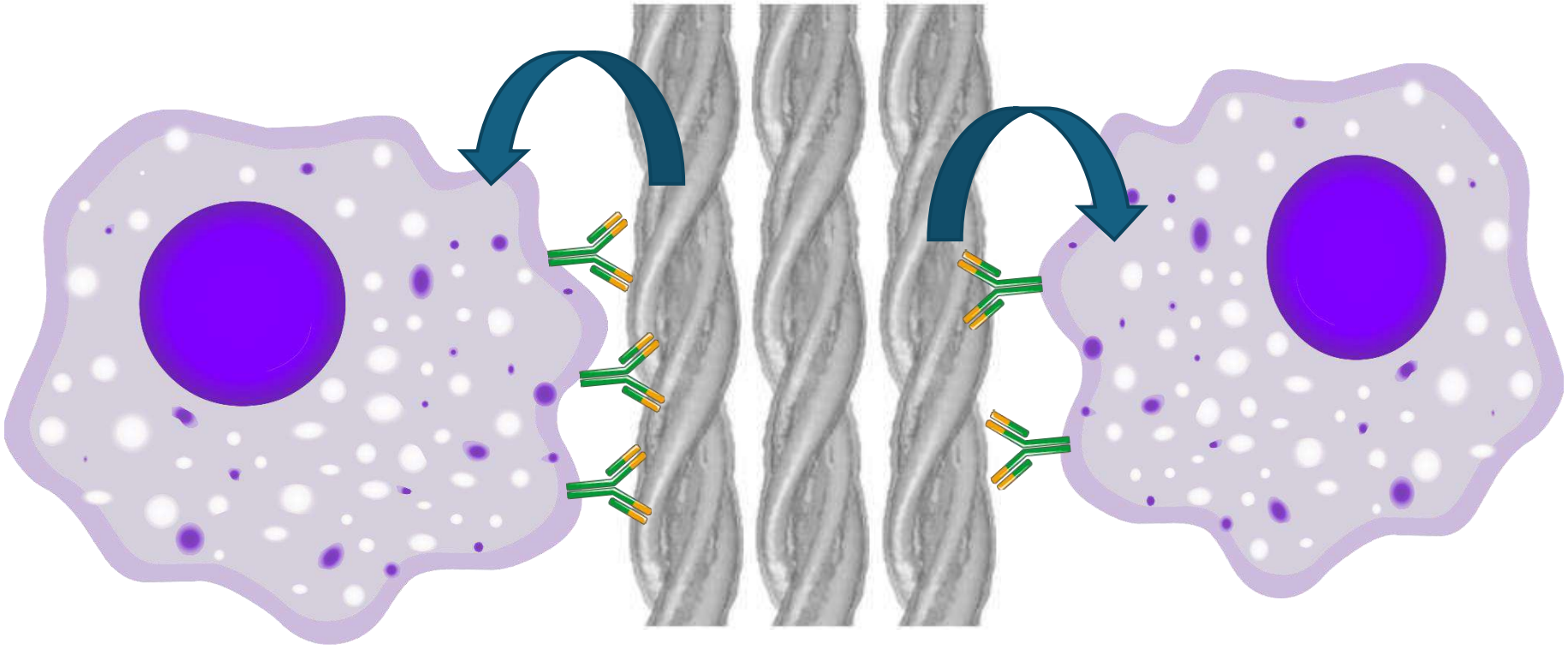
Rationnel pour les nouvelles générations d'anticorps anti-amyloide

« Nettoyer » les organes

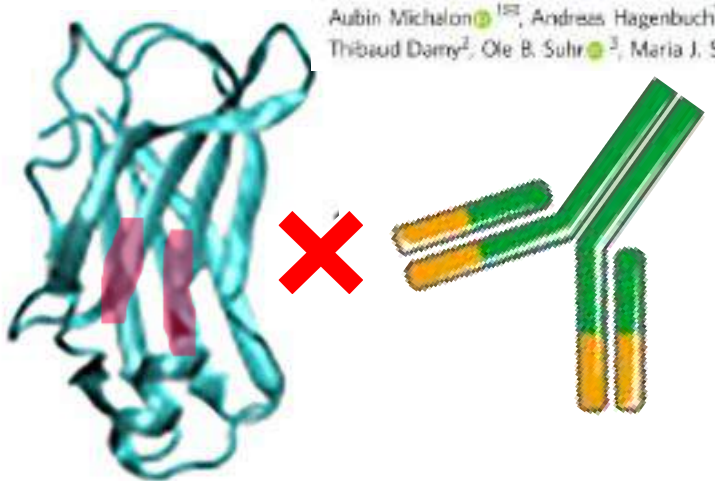


En complément des autres thérapies

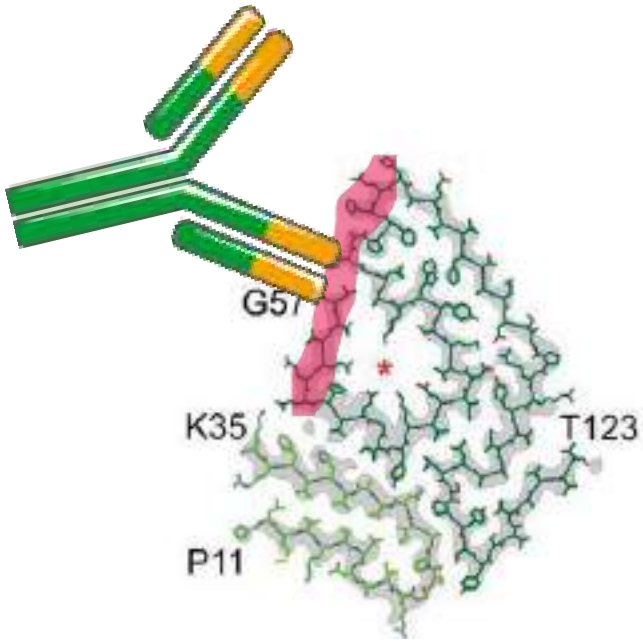
Rationnel pour les nouvelles générations d'anticorps anti-amyloide

A human antibody selective for transthyretin amyloid removes cardiac amyloid through phagocytic immune cells

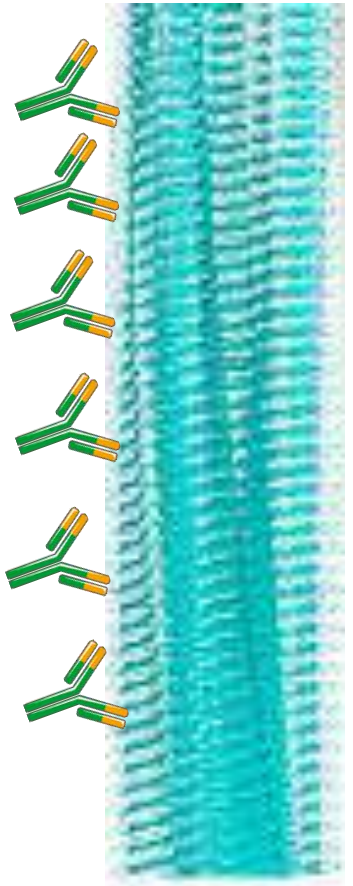
Aubin Michalon[1,2], Andreas Hagenbuch[1], Christian Huy[1], Evita Varela[1], Benoit Combaluzier[1], Thibaud Damy[2], Ole B. Suhr[3], Maria J. Saraiva[4], Christoph Hock[1,5], Roger M. Nitsch[1,5] & Jan Grimm[1]



Forme native circulante



Forme fibrillaire



Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.

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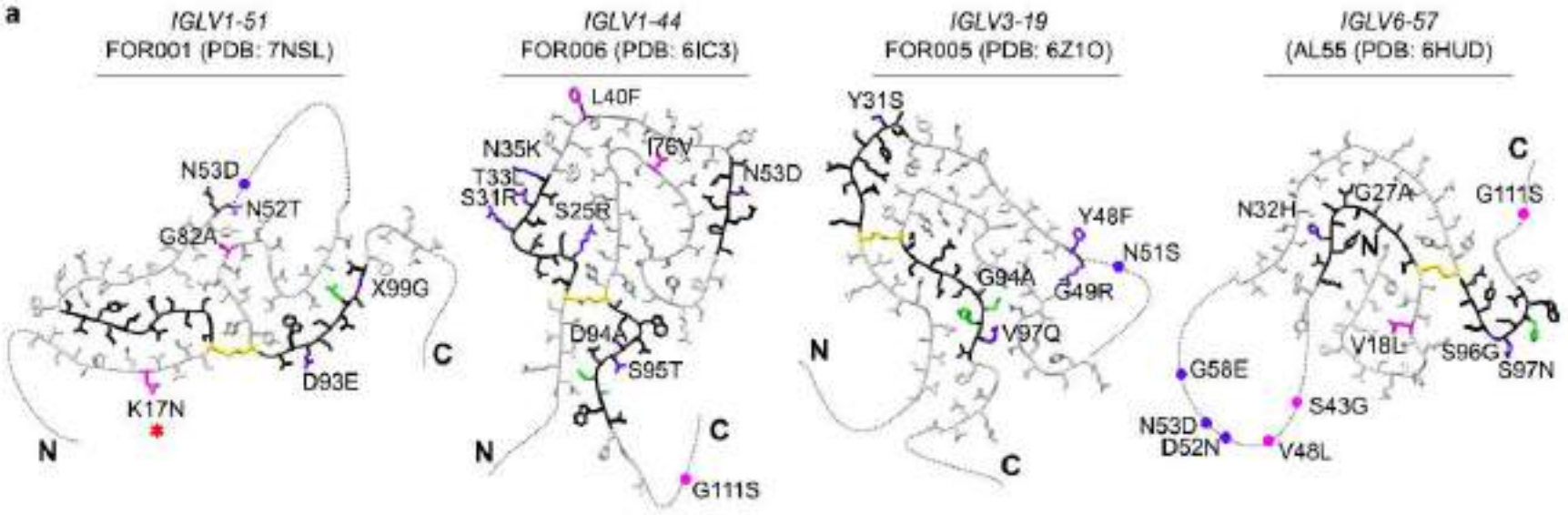
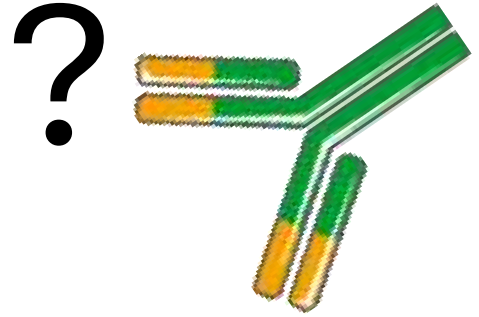
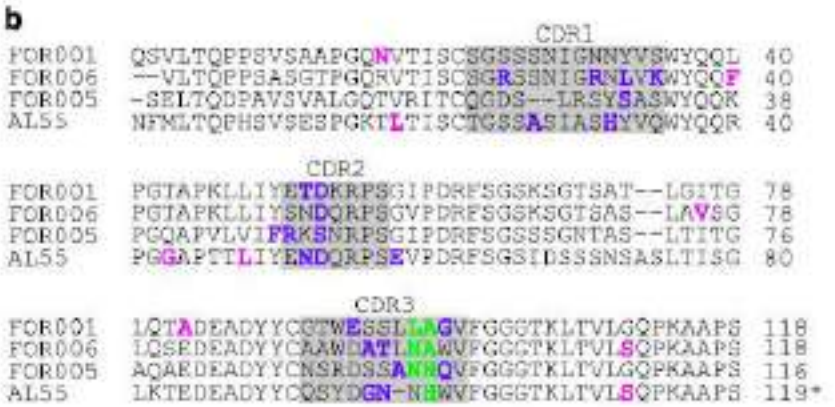
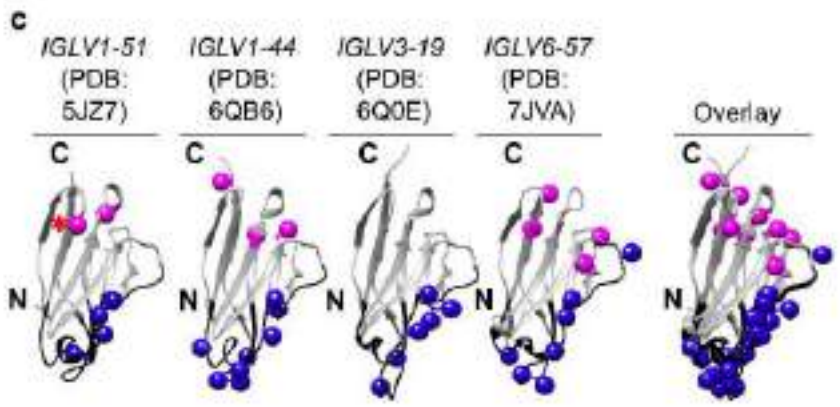
Et dans l'amylose AL…









Echec ou succès relatif des anticorps anti-AL

prothena

NEOD001 = 2A4 (Anti-AA fibrils)

Prothena Announces Phase 3 AFFIRM-AL Clinical Trial for Birtamimab in Patients with AL Amyloidosis Did Not Meet Primary Endpoint

2025-05-23

attralus

652. MGUS, Amyloidosis, and Other Non-Myeloma Plasma Cell Dyscrasias: Clinical and Epidemiological

Renal responses in a phase 1/2 study of at-02, a novel pan-amyloid depleter ig fusion protein for the treatment of patients with AL amyloidosis

Gregory Bell [1], Claire Sherman [1], Matt Meldorf [1], Mazen Hanna [2], Vasvi Singh [3], Graham Hillis [4], Olga Motorna [5], Brett Sperry [6], Brian Drachman [7], Ahmad Masri [8]

CAELUM BIOSCIENCES AstraZeneca

CAEL101 = 11-1F4 (Anti-Vk4 soluble)

Results did not achieve statistical significance for the primary endpoint in overall patient population

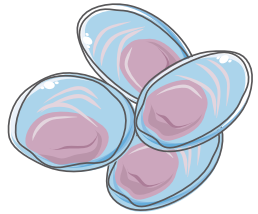
PUBLISHED
16 July 2025

CARES Phase III demonstrated anselamimab's potential to improve survival and cardiac outcomes in patients with advanced AL-kappa amyloidosis

Neurimmune expands collaboration with AstraZeneca to develop and commercialize fibril depleter NI009 for AL amyloidosis

Zurich, Switzerland - 04.12.2025

> Anti-Lambda : immunisation effectuées avec des fibrilles amyloïdes lambda de patients

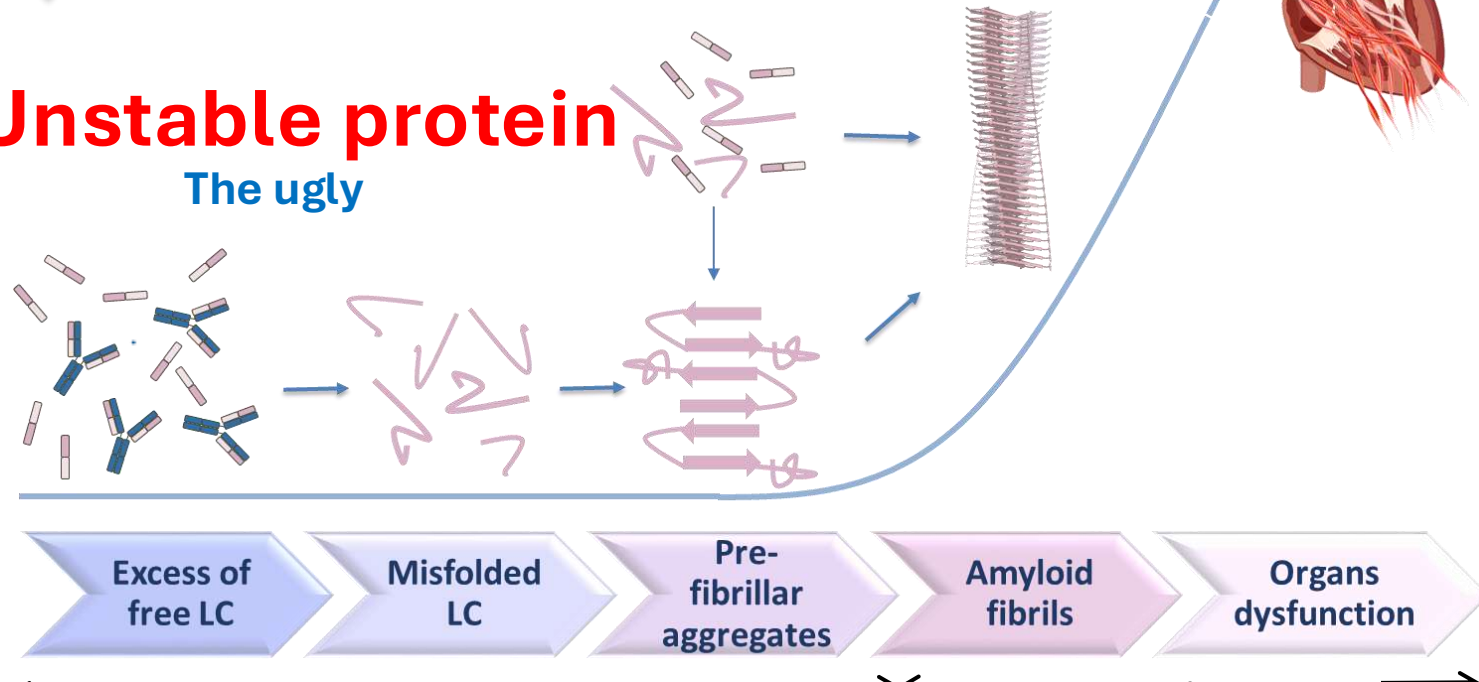


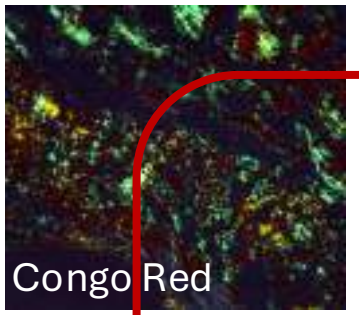
Producing cells

The (not) good

Unstable protein

The ugly





Deposits

The bad

Organ dysfunction

Toxicité

Tropisme

- Déclencheur

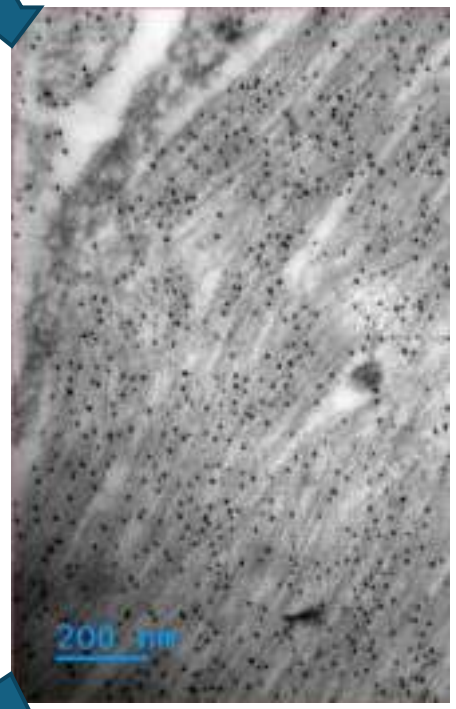
Toxicité

Fragmentation

Stacking

ApoE, ApoA4, SAP…

Maturation/deposition



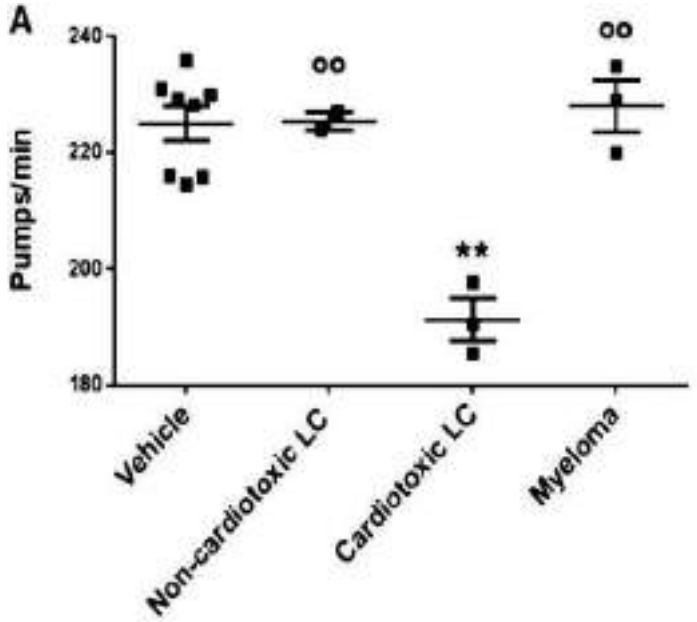
Toxicité

Toxicité

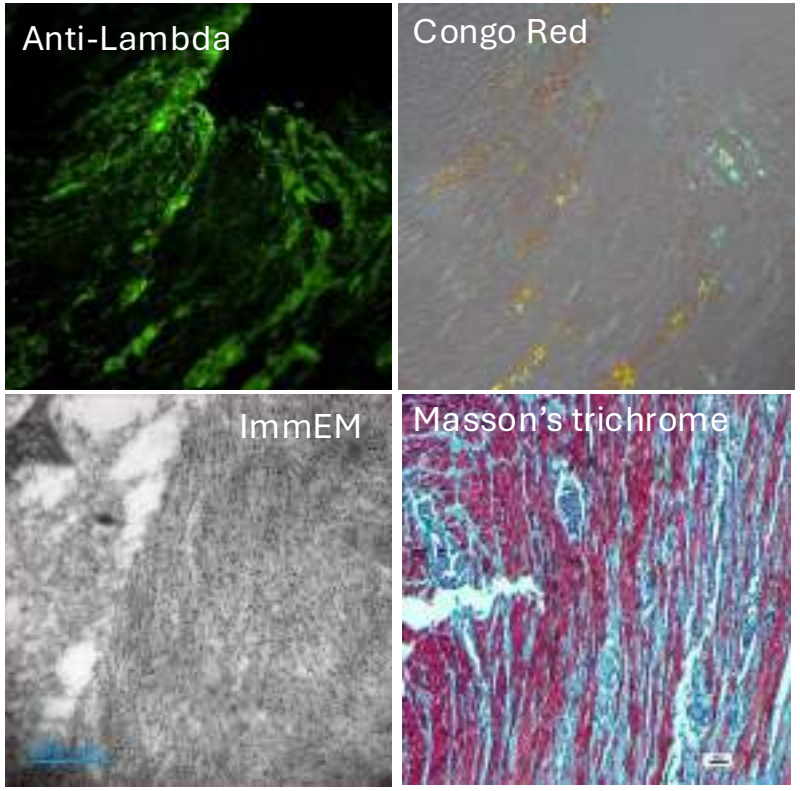
Difficulté à faire des modèles expérimentaux

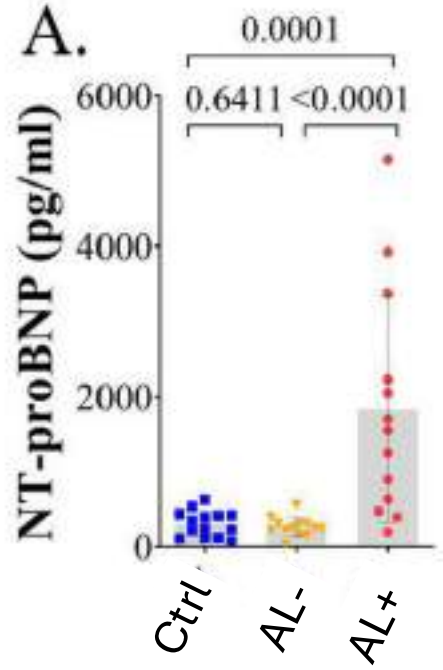
- Composition cellulaire complexe
- Matrice extracellulaire
- Flux/Force
- Système immunitaire

Modèles expérimentaux



Diomede et al, Blood, 2010





Martinez-Rivas et al, Nat Comm, 2024

Conclusion

Fais de la recherche fondamentale

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criBL lymphoproliférations

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CRIBL Lab
Lab retreat
2023

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

THANKS

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