

Immunothérapie anti-AL

Traitements non dirigés contre le clone B

Pr Arnaud Jaccard – CHU Limoges

Liens d'intérêt

- Honoraires : Janssen, Celgene, Takeda, Amgen
- Financement de la recherche: Celgene, Janssen, Sanofi

Traitement de l'amylose AL

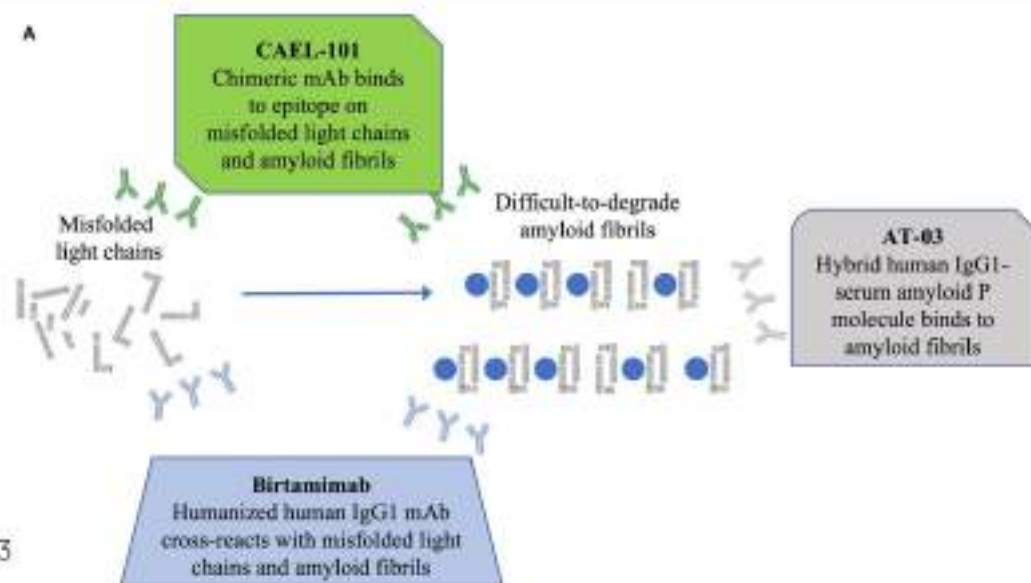
- Vise à renverser l'équilibre entre
 - la formation des dépôts d'amylose qui dépend du niveau des chaînes légères libres d'immunoglobulines monoclonales
 - et leur élimination lente par l'organisme
- 1) En faisant baisser le taux de chaînes légères en détruisant les cellules productrices (plasmocytes dans 90% des cas)
- 2) **En accélérant l'élimination des dépôts**
- **La chimiothérapie ne joue pas sur les dépôts eux-mêmes**

Traitements visants à éliminer les dépôts

- Anti-corps anti-SAP (dezamizumab)
et CPHPC (miridesap)
- Anticorps conformationnels
 - ▶ NEOD 001 (Birtamimab)
 - ▶ CAEL-101
- Protéines chimériques
 - ▶ AT-O1
 - ▶ AT-03

Changing paradigm in the treatment of amyloidosis: From disease-modifying drugs to anti-fibril therapy

C. Cristina Quarta^{1*}, Marianna Fontana², Thibaud Damy³, Julia Catini¹, Damien Simoneau¹, Michele Mercuri², Pablo Garcia-Pavia^{4,5}, Mathew S. Maurer⁶ and Giovanni Palladini¹



TYPE Mini Review
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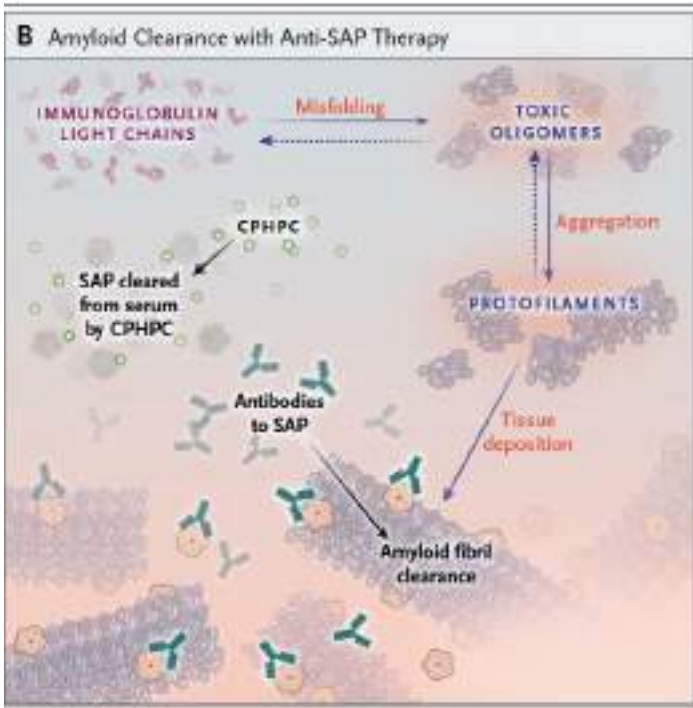
ORIGINAL ARTICLE

Therapeutic Clearance of Amyloid by
Antibodies to Serum Amyloid P Component

Duncan B. Richards, D.M., Louise M. Cookson, B.Sc., Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc., Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci., Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D., Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci., and Mark B. Pepys, Ph.D., F.R.S.

July 15, 2015

15 patients
Elimination très rapide des
dépôts hépatiques:
Coeur et rein ?



C SAP Scintigraphy in Patient 8

Before

After



25.2



9.1

¹²⁵I-SAP Dose
in Liver (%)

D SAP Scintigraphy in Patient 13

Before

After

¹²⁵I-SAP Dose
in Liver (%)

61.1



17.4

SYSTEMIC AMYLOIDOSIS

Janvier 2018

Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

Duncan B. Richards,¹ Louise M. Cookson,¹ Sharon V. Barton,¹ Lia Liefwaard,¹ Thirusha Lane,² David F. Hutt,² James M. Ritter,³ Marianna Fontana,² James C. Moon,⁴ Julian D. Gillmore,² Ashutosh Wechalekar,² Philip N. Hawkins,² Mark B. Pepys^{2,5*}



Fig. 2. Effect on amyloid load of miridesap followed by dezamizumab. (A) Anterior views of radiolabelled serum amyloid P component (SAP) scintigraphy scans for amyloid in subject D14 with systemic immunoglobulin light chain (AL) amyloidosis. Images shown are for before treatment (left), 42 days after first dezamizumab dose (center), and 42 days after second dezamizumab dose (right). (B) Posterior views of radiolabelled SAP scintigraphy scans for amyloid in subject D17 with hereditary systemic fibrinogen A α -chain (AFib) amyloidosis. Images shown are before treatment (left) and 42 days after dezamizumab treatment (right).

- 23 patients, 15 de la précédente série
- Jusqu'à 3 injections (10 pts)
 - AL: 12 pts
 - Afib: 5 pts
 - ATTR: 3 pts
 - AA: 2 pts
 - AApoA1: 1 pt
- Demie vie courte
- Elimination amylose hépatique ++

RESEARCH ARTICLE

Open Access



Pharmacodynamic evaluation and safety assessment of treatment with antibodies to serum amyloid P component in patients with cardiac amyloidosis: an open-label Phase 2 study and an adjunctive immuno-PET imaging study

Ashutosh Wechalekar^{1*}, Gunnar Antoni², Wasfi Al Azzam^{3,9}, Mats Bergström⁸, Swethajit Biswas^{4,10}, Chao Chen⁴, Joseph Cherlyan⁵, Matthew Cleveland⁴, Louise Cookson⁶, Paul Galette³, Robert L. Janiczek⁴, Raymond Y. Kwong⁷, Mary Ann Lukas⁵, Helen Millns⁴, Duncan Richards^{4,10}, Ian Schneider^{4,11}, Scott D. Solomon⁷, Jens Sörensen⁴, James Storey⁴, Douglas Thompson⁴, Guus van Dongen⁸, Danielle J. Vugts⁸, Anders Wall², Gerhard Wikström³ and Rodney H. Falk⁷

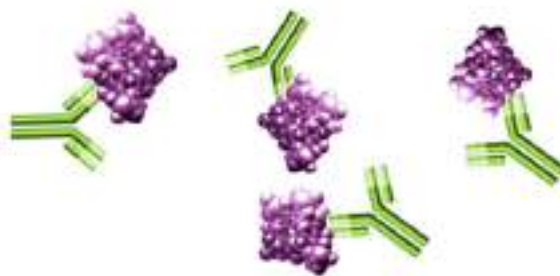
Conclusions: Unlike previous observations of visceral amyloid reduction, there was no appreciable evidence of amyloid removal in patients with cardiac amyloidosis in this Phase 2 trial, potentially related to limited cardiac uptake of dezamizumab as demonstrated in the immuno-PET study. The benefit-risk assessment for dezamizumab in cardiac amyloidosis was considered unfavourable after the incidence of large-vessel vasculitis and development for this indication was terminated.

Potential NEOD001 MOA: Neutralizes Soluble Toxic Aggregates and Clears AL Amyloid Deposits

Potential Mechanism of Action for NEOD001

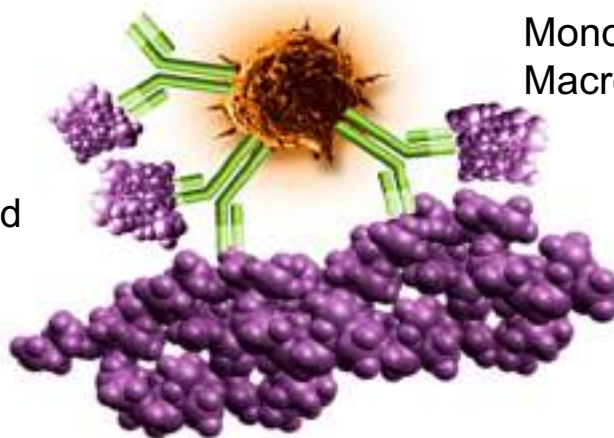
Neutralize or facilitate clearance of amyloid protein

Neutralization



Soluble Aggregates
of Amyloid Protein

Deposited
Amyloid



Monocyte/
Macrophage

Clearance

NEOD001 Demonstrates Organ Biomarker Responses in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction: Final Results From a Phase 1/2 Study

Morie A. Gertz,¹ Raymond L. Comenzo,² Heather Landau,³
Vaishali Santhorawala,⁴ Brendan Weiss,⁵ Jeffrey Zonder,⁶ Jackie Walling,⁷
Gene G. Kinney,⁸ Martin Koller,⁸ Dale B. Schenk,⁸ Spencer D. Guthrie,⁸
Enchi Liu,⁸ Michaela Liedtke⁹

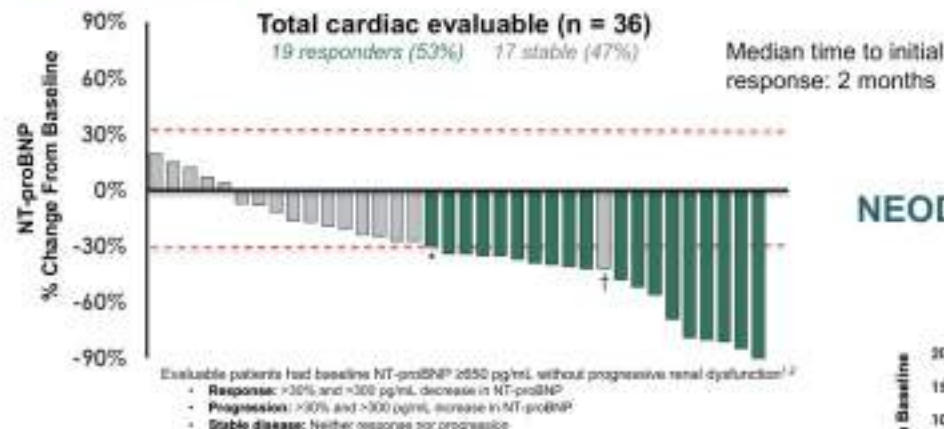
Organ Biomarker Responses in Patients With Light Chain Amyloidosis Treated With NEOD001 Are Independent of Previous Hematologic Responses

Michaela Liedtke,¹ Raymond L. Comenzo,² Heather Landau,³
Vaishali Santhorawala,⁴ Brendan Weiss,⁵ Jeffrey Zonder,⁶ Jackie Walling,⁷
Gene G. Kinney,⁸ Martin Koller,⁸ Dale B. Schenk,⁸ Spencer D. Guthrie,⁸
Enchi Liu,⁸ Morie A. Gertz⁹

ASH 2016

NEOD001: Cardiac Biomarker Response

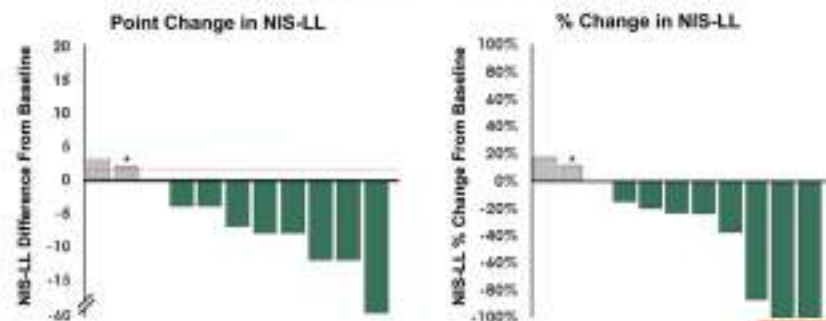
Best Response Analysis



NEOD001: Neuropathy Response at Month 10 (NIS-LL)

Peripheral Neuropathy Expansion Cohort (N = 11)

9 responders (82%) 2 progressors (18%)

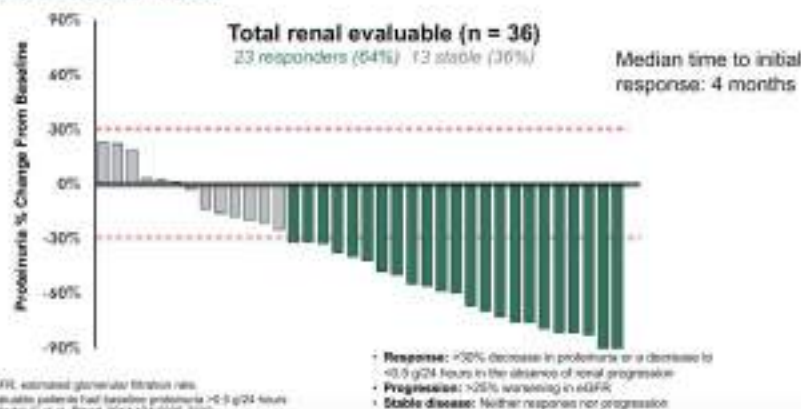


Response: <2 point increase in NIS-LL from baseline; response criteria established in patients with diabetic neuropathy and in use in clinical trials for diabetic neuropathy and transthyretin polyneuropathy.
* Patient discontinued at month 4, last observation carried forward for 2 patients without NIS-LL at month 10.

Complete resolution

NEOD001: Renal Biomarker Response

Best Response Analysis

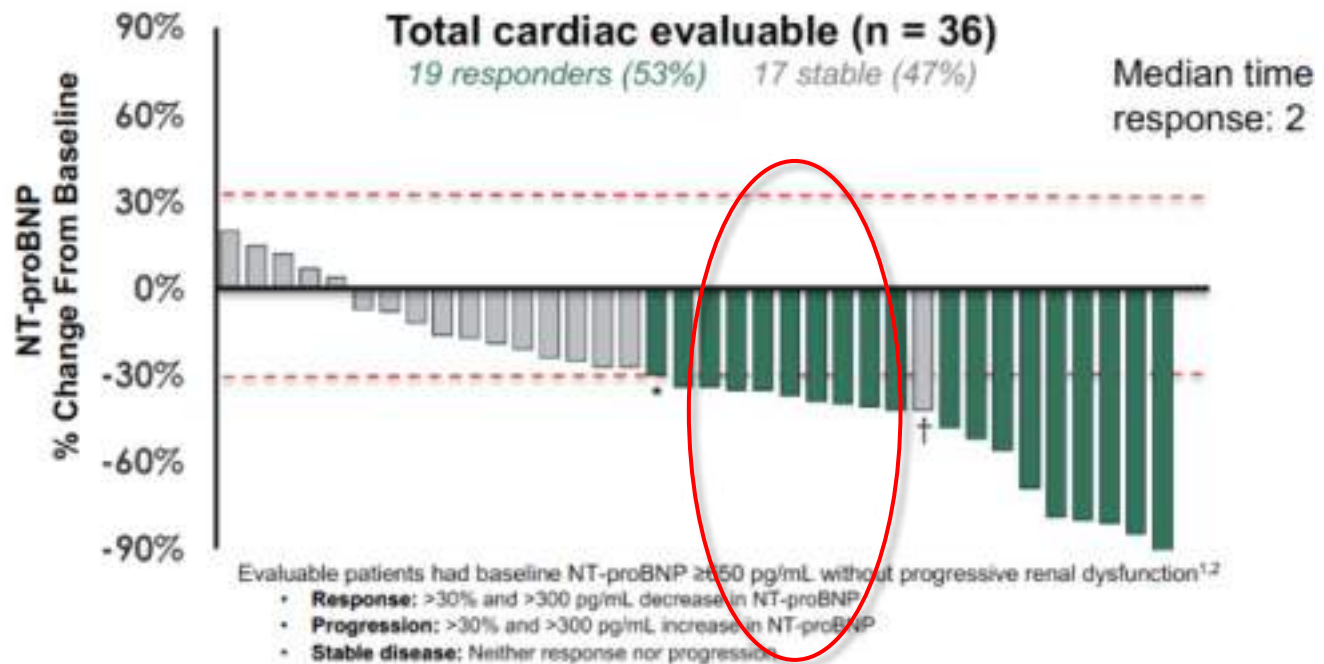


ANDROMEDA: Réponse cardiaque à 6 et 18 mois

■ Cardiac responses :

- in patients with NT-proBNP ≥ 650 ng/l or NYHA III or IV (D-VCd, n = 118 ; VCd, n = 117)
- ≥ 30 % drop in NT-proBNP serum level (> 300 ng/l) or NYHA, (drop > 2 classes in patients NYHA III or IV)

NEOD001: Cardiac Biomarker Response Best Response Analysis



Phase 2b:

THE

Pas de différence avec placebo

116 pts / 100 prévus

Phase 3:

THE

Etude de futilité négative

236 pts / 236

Prothena Reports Results from the Phase 3 VITAL Amyloidosis Study of NEOD001 (birtamimab) in AL Amyloidosis

April 18, 2019

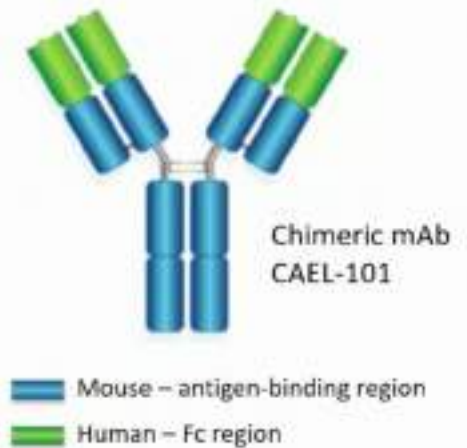
- Results from final analysis of the composite primary endpoint were consistent with the futility analysis reported in April 2018
- Results from post hoc analyses revealed a potential survival benefit with NEOD001 in the category of patients at the highest risk for early mortality (Mayo Stage IV)

	NEOD001 + SOC (n=130)	Placebo + SOC (n=130)	Total (N=260)
Mayo Stage N (%)			
I	11 (8%)	10 (8%)	21 (8%)
II	34 (26%)	28 (22%)	62 (24%)
III	47 (36%)	53 (41%)	100 (38%)
IV	38 (29%)	39 (30%)	77 (30%)



CAEL-101

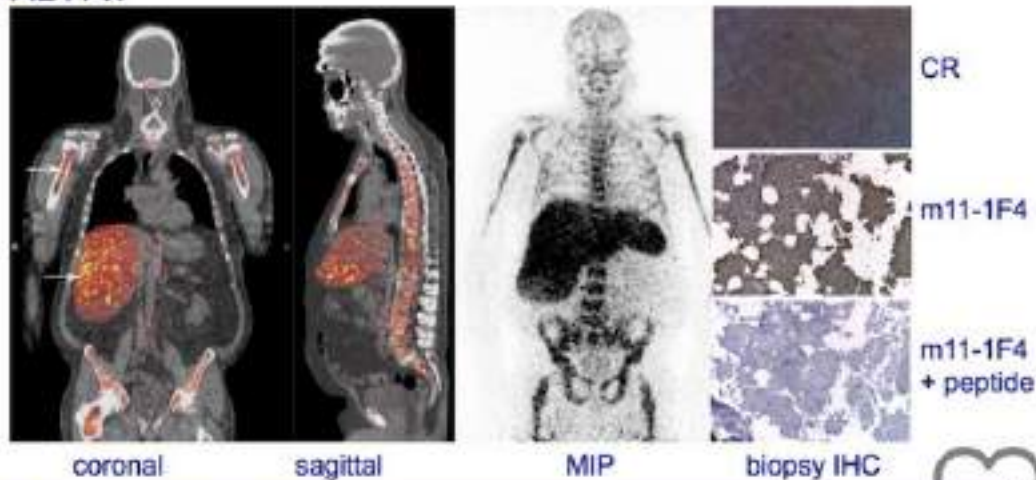
CAEL-101 est un anticorps monoclonal IgG1k qui se lie directement à un épitope conformationnel présent sur les fibrilles amyloïdes, quel que soit l'isotype (κ ou λ)



Specificity of Antibody Binding

Co-localization of ^{124}I -m11-1F4 with Hepatosplenic and Bone AL Amyloid

AL11 λ



Safety and Tolerability of CAEL-101, an Anti-Amyloid Monoclonal Antibody, Combined With Anti-Plasma Cell Dyscrasia Therapy in Patients With Light-Chain Amyloidosis: 18-Month Results of a Phase 2 Study

Michaela Liedtke¹, Jason Valent², Jeffrey Zonder³, Maria Angélica Molina⁴, Chandrasekhar Udata⁵, Juliana Janus⁶, John TrippTREE⁷, Julia Catini⁸, Candida Cristina Quarta⁹

¹Stanford University Medical Center, Palo Alto, CA, USA; ²Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; ³Karmanos Cancer Center, Detroit, MI, USA; ⁴IQVIA, Durham, NC, USA; ⁵Alexion, AstraZeneca Rare Disease Inc., Boston, MA, USA

Date: June 11, 2023

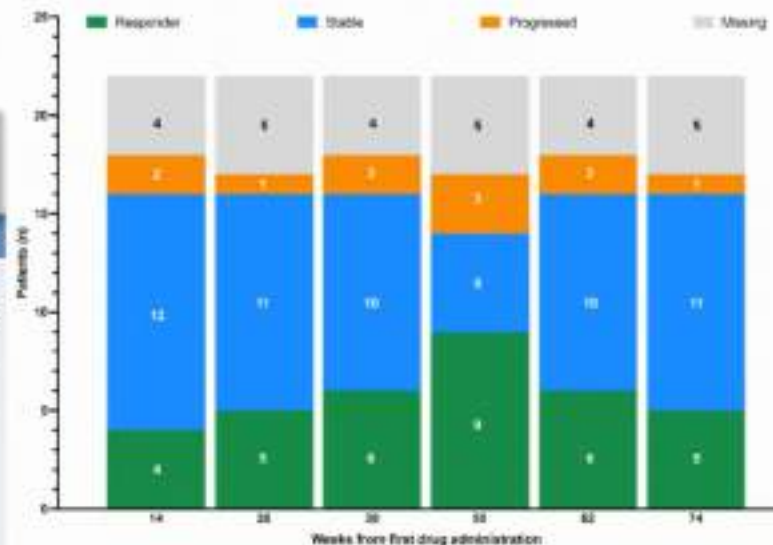
Program section: MM and CLL final analyses/long term follow up of clinical trials

Cardiac Response

- The overall analysis of serum NT-proBNP levels over time shows improvement or stabilization of cardiac function
- Response was observed even after cessation of anti-PCD therapy

Response	Criteria
Responder	>30% decrease from baseline AND a decrease of NT-proBNP >300 ng/L in patients with a baseline NT-proBNP of ≥650 ng/L
Stable disease	Neither responder nor progression
Disease progression	>30% increase from baseline and ≥300 ng/L NT-proBNP, in the absence of decline in estimated glomerular filtration rate (eGFR) ≥25% from baseline

NT-proBNP, N-terminal pro-brain natriuretic peptide; PCD, plasma cell dyscrasia.



Caelum CARES Phase 3 Program Initiated



Mayo Stage IIIb Newly Diagnosed Treatment Naive

CAEL-101 + CyBorD
74 Patient

Placebo + CyBorD
37 Patients

4 weekly doses followed by a maintenance
dose every 2 – 4 weeks

Primary endpoint: Overall Survival
Secondary endpoints: 6MWT, QoL, NT-
proBNP, GLS, Cardiac MRI, Proteinuria

Mayo Stage IIIa Newly Diagnosed Treatment Naive

CAEL-101 + CyBorD
178 Patient

Placebo + CyBorD
89 Patients

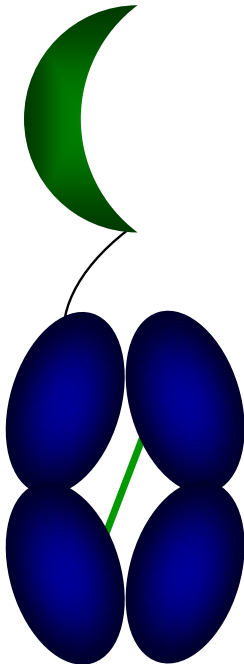
4 weekly doses followed by a maintenance
dose every 2 – 4 weeks

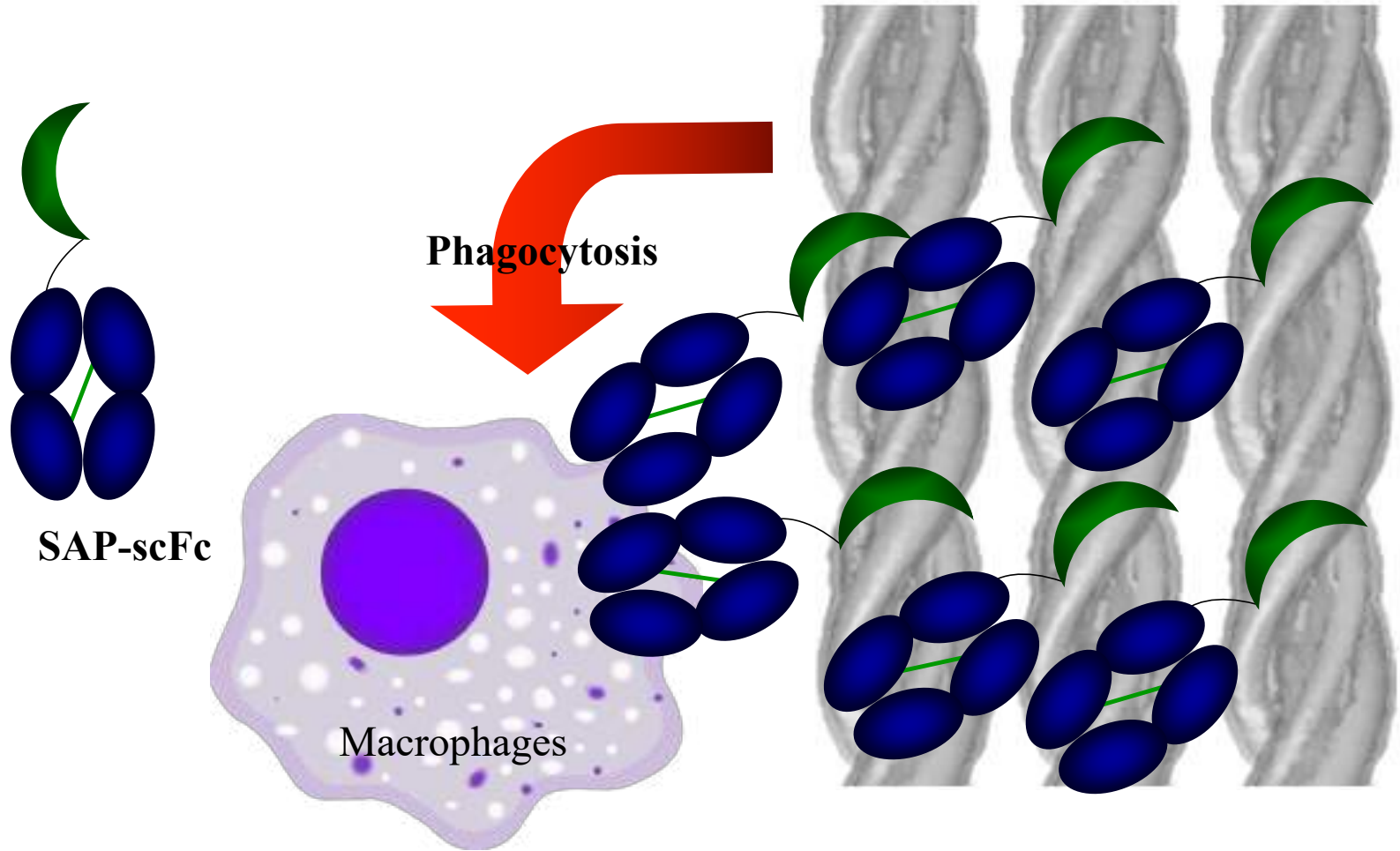
Primary endpoint: Overall Survival
Secondary endpoints: 6MWT, QoL, NT-
proBNP, GLS, Cardiac MRI, Proteinuria



SAP-Fc

Utilisant l'avidité de la SAP (sérum amyloid protein) pour les dépôts d'amylose





Preclinical Characterization of a Novel Fusion Protein, AT-03, With Pan-Amyloid Binding and Removal

Christophe Sirin,¹ Amal Jaccard,¹ Rayane Codo,¹ Sébastien Bender,¹ Gemma Martinez-Rivas,¹ Frank Dridoux,¹ Gregory Bell,¹ Spencer Guthrie,² Supriya Selvarajah,³ Stephen J. Remick,⁴ Angela D. Williams,⁴ James S. Foster,⁴ Jonathan S. Webb¹

¹CIRB, Laboratory, CHU d'Orlèans, National Reference Center for AL, Angers, France; ²CIRB, Laboratory, CHU d'Orlèans, National Reference Center for AL, Angers, France; ³UCSF, Laboratory, UCSF, University of California, San Francisco, CA, USA; ⁴University of Tennessee Health Science Center, Memphis, TN, USA

Figure 1. AT-03 SAP-scFc fusion protein designed to promote opsonization of amyloid. AT-03 pentamer consists of 5 AT-03 monomers. The peripheral blue regions represent human IgG1 Fc (CH2 and CH3), and the central purple regions represent SAP.

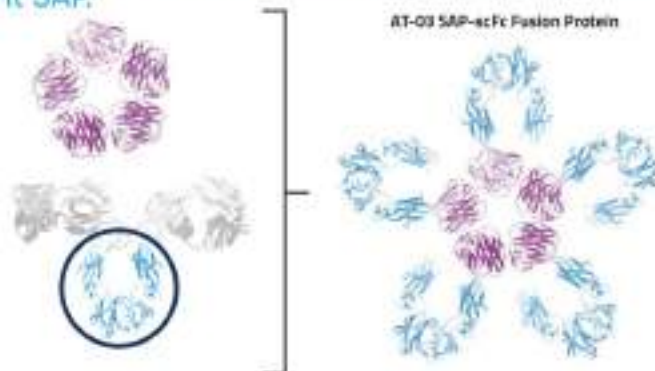
Serum Amyloid Protein (SAP)

- Naturally occurring protein
- Binds to all amyloid fibril types
- Circulates in pentameric form



Fc Portion of Antibody

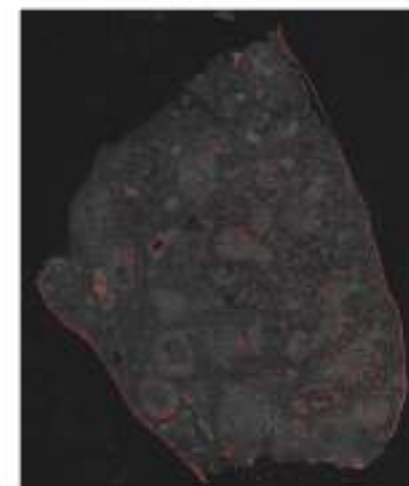
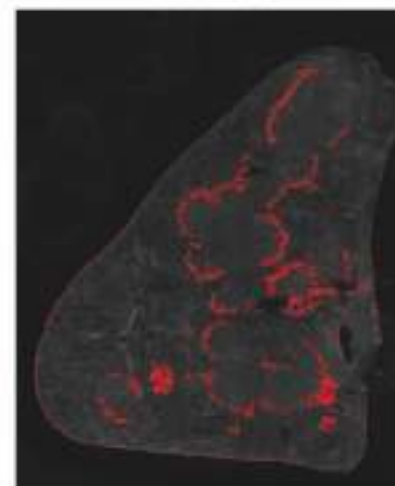
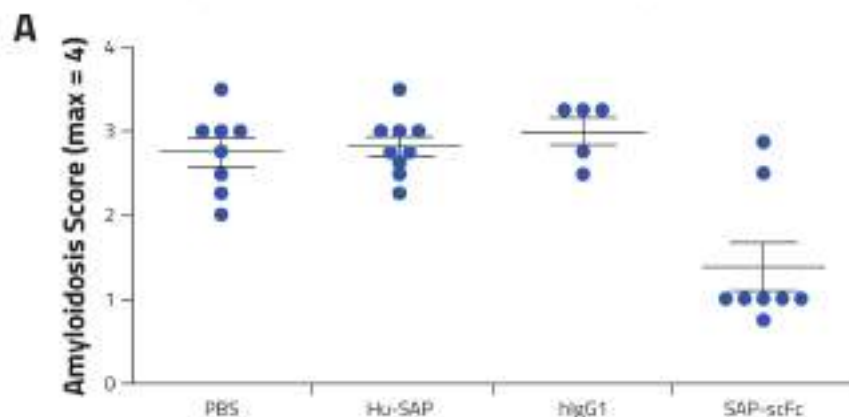
- Engages Fc receptor on macrophages
- Facilitates engulfment and removal of the amyloid fibril by phagocytosis



IgG1, immunoglobulin G1
Molecular weight of AT-03 is 410 kD

PBS
Score 3

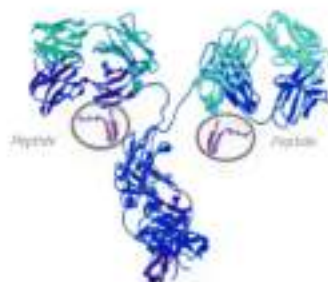
SAP-scFc
Score 1



ASH dec 2021

OUR PIONEERING PAN-AMYLOID PIPELINE

	PROGRAM	INDICATION	PRECLINICAL	IND ENABLING	PHASE 1	PHASE 2	PHASE 3	OPEN TO PARTNERSHIP
Therapeutics	AT-02 <i>PAR-peptide + Antibody</i>	SYSTEMIC AMYLOIDOSIS						
	AT-03 <i>PAR-peptide + TGF-βRI</i>	SYSTEMIC AMYLOIDOSIS						
	AT-04 <i>PAR-peptide + Ig</i>	SYSTEMIC AMYLOIDOSIS, NEURODEGENERATIVE/ CNS DISORDERS						
	AT-06 <i>PAR-peptide + CAR-T</i>	SYSTEMIC AMYLOIDOSIS						
	AT-07 <i>AT-04 + UNUS/BB-2516</i>	NEURODEGENERATIVE / CNS DISORDERS						
Diagnostics	AT-01 <i>Isoline (1-124) oxazolinide PAR-peptide + i-124</i>	SYSTEMIC AMYLOIDOSIS						
	AT-05 <i>PAR-peptide + MRI</i>	SYSTEMIC AMYLOIDOSIS						



AT-02

PAR-Peptide + IgG1 Antibody

AT-02 is a fusion of our PAR-peptide with an IgG1 antibody. The proprietary peptide binds to all types of amyloid and delivers the antibody to the site of disease to stimulate the immune system to remove amyloid.



XVIII, International Symposium on Amyloidosis 4th – 8th September 2022 | Heidelberg

Development of CAR-Macrophages (CAR-M) as a Potential Therapeutic to Facilitate Amyloid Clearance

Mansel Balachandran

James S. Foster, Joseph W. Jackson, Yoko Kikuchi, Emily Morris, Stephen Stewart, Angela Williams, Sallie Kays, Craig Wadler and Jonathan S. Wolf

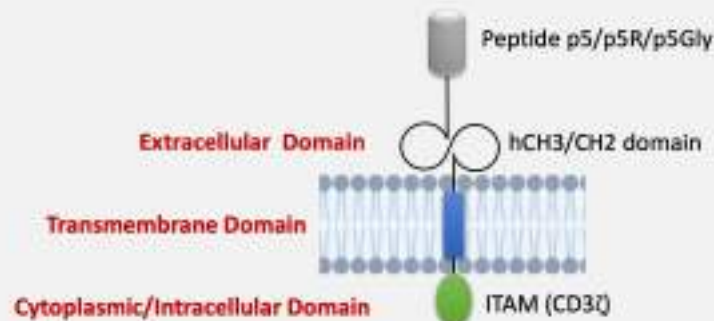
Amyloidosis and Cancer Therapeutics Program
Department of Medicine, University of Tennessee Medical Center
Knoxville, Tennessee, USA



The Exemplary CAR Structure for Amyloid Binding

- CAR technology originally developed for cancer immunotherapy (CAR-T and CAR-M)
- The amyloid-reactive CAR incorporates the pan amyloid-reactive peptide p5 (lysine version) or p5R (arginine version). The uncharged p5Gly (glycine version) serves as a negative control

Amyloid-binding CAR

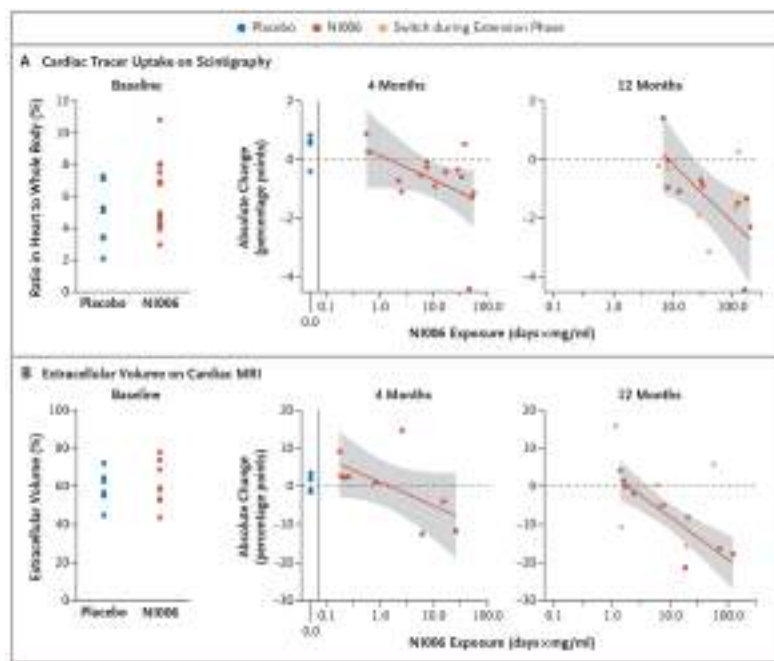


- The IgG1 heavy chain domains, hCH3 and hCH2, provide rigidity to the structure and may facilitate complement activation
- The intracellular signal activation domain CD3ζ has three ITAMs and is a phagocytosis signal enhancer

ORIGINAL ARTICLE

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.



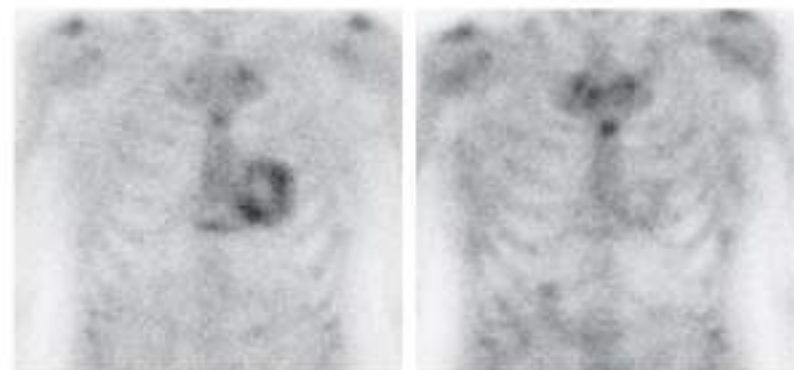
CORRESPONDENCE



Antibody-Associated Reversal of ATTR Amyloidosis–Related Cardiomyopathy

We investigated the possibility that the 3 patients had had an anti-amyloid immune response, and we identified high-titer circulating polyclonal IgG antibodies to human ATTR amyloid in each of the patients.

The cause and clinical significance of the anti-ATTR amyloid antibodies are intriguing and presently unclear. However, the clinical recovery of these patients establishes the unanticipated potential for reversibility of ATTR-CM and raises expectations for its treatment.



DPD Scintigraphy

Remerciements

- Tous les centres participants au réseau du Centre de référence Amylose AL et autres maladies par dépôt d'IG monoclonales
- L'association Française contre l'amylose
- Equipes de recherche clinique à Limoges et Poitiers
- UMR CNRS 7276 INSERM 1262 CRIBL

