Personalizing Amyloidosis Therapy with Real Time PET Imaging of Fibril-Reactive Chimeric Antibody CAEL-101

Jing Fu¹, Alan Solomon², Patrick Carberry³, John Castrillon³, Jongho Kim³, Suzanne Lentzsch¹, Akiva Mintz³

¹Division of Hematology and Oncology, Columbia University Medical Center, New York, NY; ²Graduate School of Medicine, University of Tennessee, Knoxville, TN; ³Department of Radiology, PET Center, Columbia University Medical Center, New York, NY
Disclosure

Jing Fu: No conflict of interest

Alan Solomon: Caelum Biosciences: Consultancy

Patrick Carberry: No conflict of interest

John Castrillon: No conflict of interest

Jongho Kim: No conflict of interest

Suzanne Lentzsch: Janssen: Consultancy. Caelum Biosciences: Consultancy, Shareholder for Caelum Biosciences, PI of the Phase 1a/b trial testing CAEL-101 until 11/2017. Bayer: Consultancy. BMS: Consultancy

Akiva Mintz: Caelum Biosciences: Research Funding
AL Amyloid Development

Mahmood et al, Haematologica 2014;99:209-221
Amyloidosis Mortality Remains High

Up to 80% ineligible for ASCT

Over 40% of these patients die within 1 year of diagnosis

Mutchar et al, Blood 2017
Delayed Organ Response (OR)

Median time to OR from start of treatment: 10.4 months (range, 8.7-12.8 mos)

Other variables influencing organ response:
- Features of chaperone proteins (polymorphisms)
- Organ and cell specific processes in proteolysis and phagocytosis

Kauffman et al, Am. J. Hematol. 2015;90:181-186
Urgent Need to Improve Organ Response!!

Targeting Amyloid Deposits Directly

Circulating free light chain
*NATIVE*

Tissue amyloid
*MISFOLDED*

Anti-Amyloid mAb

Courtesy of Jonathan Wall
Poly-reactivity of Murine 11-1F4 mAb with Human AL Amyloid Deposits

Congo red

11-1F4 mAb

AL Amyloid type

λ1

λ8

κ4

Courtesy of Jonathan Wall Lab
Murine 11-1F4 mAb Binds to a Conformational Epitope Common to All Light Chain Fibril

Native

Structure of soluble light chain in circulation → not reactive with 11-1F4 mAb

“Loop-Flip”

Structure of light chain in fibril → reactive with 11-1F4 mAb

Courtesy of Alan Solomon and Jonathan Wall Lab
Immunotherapy Using the Murine 11-1F4 mAb

11-1F4 mAb expedites the dissolution of human AL λ and κ amyloidomas in mice

Specificity of Murine 11-1F4 mAb Binding

Co-localization of $^{[124]}$I murine 11-1F4 with hepatosplenic and bone AL amyloid

Fused PET/CT image $^{[124]}$I murine 11-1F4 uptake in the myocardium
Phase 1a/b Study of Chimeric 11-1F4 mAb (CAEL-101) in Patients with AL Amyloidosis

- GMP-grade amyloid fibril-reactive chimeric 11-1F4 mAb (CAEL-101) was produced by NCI’s Biological Resource Branch

- Open-label, dose-escalation phase 1a/b study of CAEL-101
Phase 1a/b, Open-label Dose Escalation Study Completed in 2017

Patient criteria

Patients who received anti-plasma cell directed therapy in the past but with persistent organ dysfunctions

Primary endpoint

- Establish maximum tolerated dose (up to 500mg/m²) of CAEL-101
- Cardiac response (NT-proBNP)
- Renal response (24-hour Proteinuria)
- Pharmacokinetic profile (single dose vs. multiple weekly doses)

Secondary endpoints

- Well tolerated, MTD 500mg/m²
- 12 out of 18 patients (67%) with cardiac and/or renal involvement showed a response in Phase 1a/b
  - 67% Cardiac (8 of 12 evaluable for response)
  - 50% Renal (5 of 10 evaluable for response)
- 3 Patients responded with other organ system involvement (GI, liver, soft tissue)
- Overall Median Time to response was 3 weeks after the first dose of 11-1F4 mAb

958 BHUTANI et al, Improvement in Global Longitudinal Strain (GLS) Correlates with NT-ProBNP Response in Patients with Cardiac Amyloidosis Treated on a Phase 1b Study of Anti-Amyloid mAb CAEL-101

Edwards, V. et al, Blood Abstract, 2017;130:509
Preliminary Radio-imaging Study of CAEL-101 in AL Amyloidosis

• To explore the diagnostic potential of radio labeled CAEL-101 for systemic amyloidosis

• To explore its use as a companion biomarker to stratify patients for CAEL-101 immunotherapy

• To explore its use in monitoring/assessing the response to the treatment
CAEL-101 Binds to Human λ and κ Amyloidosis *in vitro*

In dot blot assay, CAEL-101 binds to all the amyloid extract derived from patient heart, spleen, liver and kidney consisting of both κ and λ subtypes. BSA protein was used as negative control.
Mice Imaging Study Design

Day 0
s.c. injection of human Amyloidosis extract from:
Patient 1 (Cardiac κ1)
Patient 2 (Hepatic κ1)
Patient 3 (Splenic λ1)
Patient 4 (Renal λ6)

Day 5
i.v. injection with 200μCi of [¹²⁴I]CAEL-101

Day 6
Imaged by Inveon microPET scanner
T:B ratio was analyzed

Day 9
[\textsuperscript{124}I]CAEL-101 PET/CT at Day 4

P1 (cardiac k1)  P2 (hepatic k1)

P3 (renal \lambda 6)  P4 (splenic \lambda 1)

A: Amyloidoma  B: Bladder

PET  PET/CT  CT
[\textsuperscript{124}I]CAEL-101 Images Amyloidomas Regardless of the Original Organ and the LC Subtype

Amyloidoma Source
- Patient 1 (cardiac origin k1)
- Patient 2 (hepatic origin k1)
- Patient 3 (renal origin λ6)
- Patient 4 (splenic origin λ1)

* Clinically Significant

[\textsuperscript{124}I]CAEL-101 Target-To-Background Ratio (Mean)
[\textsuperscript{[124]}]CAEL-101 Target-to-Background Ratio (Mean) at Day 4

Target-to-Background Ratio (Mean) at Day 4

* Clinically Significant
\[ {^{124}\text{I}}\text{CAEL-101 Target-to-Background Ratio (Mean) at Day 4} \]

* Clinically Significant
$[^{124}\text{I}]\text{CAEL-101 Target-To-Background Ratio (Mean)}$

**Amyloidoma Source**
- Patient 1 (cardiac origin $k_1$)
- Patient 2 (hepatic origin $k_1$)
- Patient 3 (renal origin $\lambda_6$)
- Patient 4 (splenic origin $\lambda_1$)

* Clinically Significant
Summary

- $[^{124}]$CAEL-101 successfully imaged 100% of mice bearing human amyloid extracts ($\kappa1$, $\lambda1$ and $\lambda6$ subtypes derived from heart, liver, spleen, and kidney).

- Human amyloidomas were visualized at 1, 4 and 7 days post tracer infusion, with significantly increasing T:B ratio by day 4 in kappa subtype and day 7 in lambda subtype.

- We successfully used PET imaging to visualize cardiac derived amyloid fibrils from AL amyloidosis patients.
Future Outlook

• $[^{89}\text{Zr}]\text{CAEL-101}$ imaging study

• Radiolabeled CAEL-101 as a companion diagnostic to image real-time targeting of human amyloidosis \textit{in vivo}

• Use CAEL-101 PET imaging to stratify patients for CAEL-101 immunotherapy

• Use CAEL-101 PET imaging to quantify peripheral organ amyloid fibril deposition pre and post anti-amyloid therapy
Acknowledgements

Columbia Multiple Myeloma and Amyloidosis Program
Suzanne Lentzsch, MD, PhD
Shirong Li, PhD
Hsin S Wang

Boston University School of Medicine
Vaishali Sanchorawala, MD
Lawreen H. Connors, PhD

University of Tennessee
Alan Solomon, MD
Johnathan Wall, MD

Columbia PET center
Akiva Mintz, MD, PhD
Patrick Carberry, PhD
John Castrillon
Jongho Kim, MD, PhD
Andrei Molotkov

Funding
NCI Experimental Therapeutics (NExT) Grant
R01 FD005110-01 PI
Columbia Technology Ventures
Caelum Biosciences
Thank you!