LETTER TO THE EDITOR

Proteomic shifts post-plasma cell therapy in AL amyloid plaques and potential implications for light chain-directed anti-fibril monoclonal antibodies

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Supplement to proteomic shifts post plasma cell therapy in AL amyloid plaques and potential implications for light chain directed anti-fibril monoclonal antibodies

Supplementary Table 1. Best organ response for eligible patients, stratified according to hematological response at time of repeat bone marrow biopsy.

Characteristic	**Non-responder** N = 9	**Responder** N = 54
Eligible for cardiac response, n (%)	1 (11%)	24 (44%)
Best cardiac response, n (%)		
CR	0 (0%)	5 (21%)
VGPR	0 (0%)	8 (33%)
PR	0 (0%)	5 (21%)
NR/progression	1 (100%)	6 (25%)
Eligible for renal response, n (%)	3 (33%)	35 (65%)
Best renal response, n (%)		
CR	1 (33%)	13 (37%)
VGPR	0 (0%)	9 (26%)
PR	1 (33%)	4 (11%)
NR/progression	1 (33%)	9 (26%)
Eligible for hepatic response, n (%)	1 (11%)	12 (22%)
Hepatic response, n (%)		
R	1 (100%)	9 (75%)
NR	0 (0%)	3 (25%)

CR, complete response; VGPR, very good partial response; PR, partial response; NR, no response.

Supplementary Table 2. Differential expression of immunoglobulin related proteins amongst responders and non-responders in diagnostic and post-treatment bone marrow biopsy samples.

BONE MARROW BIOPSIES OF RESPONDERS

Gene	Protein Name	Log2 fold change	FDR p-value
IGKC	Immunoglobulin Kappa Constant	0.1824	0.024
IGLC7	Immunoglobulin Lambda Constant 7	0.2884	0.016
IGHG3	Immunoglobulin Heavy Constant Gamma 3	0.3303	0.0044
IGHG4	Immunoglobulin Heavy Constant Gamma 4	0.3875	0.0053
IGHG2	Immunoglobulin Heavy Constant Gamma 2	0.4016	<0.001
IGHG1	Immunoglobulin Heavy Constant Gamma 1	0.4311	<0.001
IGLV3-21	Immunoglobulin Lambda variable 3-21	-1.1694	<0.001

BONE MARROW BIOPSIES OF NON-RESPONDERS

Gene	Protein Name	Log2 fold change	FDR p-value
IGHM	Immunoglobulin Heavy Constant Mu	1.2726	0.00021

Supplementary Table 3. Proteins with the highest fold increase amongst responders and non-responders in diagnostic and post-treatment bone marrow biopsy samples.

UPREGULATED IN DIAGNOSTIC BONE MARROW BIOPSIES OF RESPONDERS

Protein (gene symbol)	Log2 fold change	FDR p-value	Function in human biology and role in amyloidosis (if previously described).
EVPL, Envoplakin	3.1704	<0.0001	Crucial in the formation of the cornified envelope. Reinforces the epidermal barrier, providing structural integrity and protection against environmental stressors.
PPL, Periplakin	2.6729	<0.0001	Role in wound healing and cell migration by interacting with signalling molecules and regulating the dynamics of the cytoskeleton, contributing to epithelial resilience and repair.
ACAN, Aggrecan	1.8087	<0.0001	Major proteoglycan found in the extracellular matrix of cartilage, with key role in bone/cartilage tissue homeostasis. Aggrecan fragments can trigger inflammatory pathways through toll-like receptors amplifying the cellular stress response.
IDE, Insulin-degrading enzyme	1.7628	<0.0001	A zinc-metalloprotease that degrades amyloid-beta plaques. Key role in preventing toxic protein aggregates in cells.
A2ML1, Alpha-2-macroglobulin like 1	1.4712	<0.0001	Protease inhibitor, protects tissues from protein degradation. Key role in wound healing, and maintaining tissue integrity by trapping proteases and facilitating their clearance.
CILP2, Cartilage intermediate layer protein 2	1.3622	<0.0001	A glycoprotein which contributes to the structural integrity and biochemical properties of the extra-cellular matrix. No known function in cellular stress response and amyloidosis.
DYNC1H1, Dynein Cytoplasmic 1 Heavy Chain 1	1.3198	<0.0001	Powers intracellular transport by facilitating dynein-based motor movement along microtubules. While not directly involved in the endocytosis, has role in post-endocytic trafficking of amyloid.
CHAD, Chondroadherin	1.3006	<0.0001	Supports cartilage structure and interacts with collagen for matrix stability. Can activate stress-related pathways in chondrocytes.
COL2A1, Collagen type II alpha 1 chain	1.2962	<0.0001	Major structural component of cartilage. With cartilage damage, COL2A1 degradation can lead to secondary changes where fibrosis like changes occur at the cartilage-bone interface.

UPREGULATED IN POST-TREATMENT BONE MARROW BIOPSIES OF RESPONDERS

Protein (gene symbol)	Log2 fold change	FDR p-value	Function in human biology and role in amyloidosis (if previously described).
TTN, Titin	-6.7507	<0.0001	Tissue regeneration, through sarcomeric stability, mechanosensing, and signalling. Ensures sarcomere reassembly by acting as a scaffold for myofibril formation.
CKM, Creatine kinase, M-type	-4.5261	<0.0001	Buffers and rapidly regenerates ATP during muscle contraction, ensuring a continuous energy supply for high-demand activities. Elevated levels are often observed post-injury, and its activity supports the metabolic demands of tissue remodelling.
MYH1, Myosin heavy chain 1	-4.1062	<0.0001	Component of the thick filament in the sarcomere. It also plays a role as a structural component in muscle regeneration.
MYH2, Myosin heavy chain 2	-3.9943	<0.0001	Powers fast, fatigue-resistant type IIA skeletal muscle contractions.
NEB, Nebulin	-3.6734	<0.0001	Regulates actin filament length and stabilizes thin filaments in skeletal muscle. Role in muscle regeneration by contributing to the structural organization and functional restoration of sarcomeres in regenerating muscle.
MYH8, Myosin heavy chain 8	-3.6625	<0.0001	Drives contraction in fetal and regenerating skeletal muscle.
MYH4, Myosin heavy chain 4	-3.5027	<0.0001	MYH4 fuels rapid, powerful type IIB skeletal muscle contractions. No known association with amyloid.
PYGM, Glycogen phosphorylase, muscle associated	-3.4255	<0.0001	PYGM breaks down glycogen for energy during muscle activity.
MYH7, Myosin heavy chain 7	-3.2291	<0.0001	MYH7 powers slow, endurance-based contractions in type I skeletal and cardiac muscle.

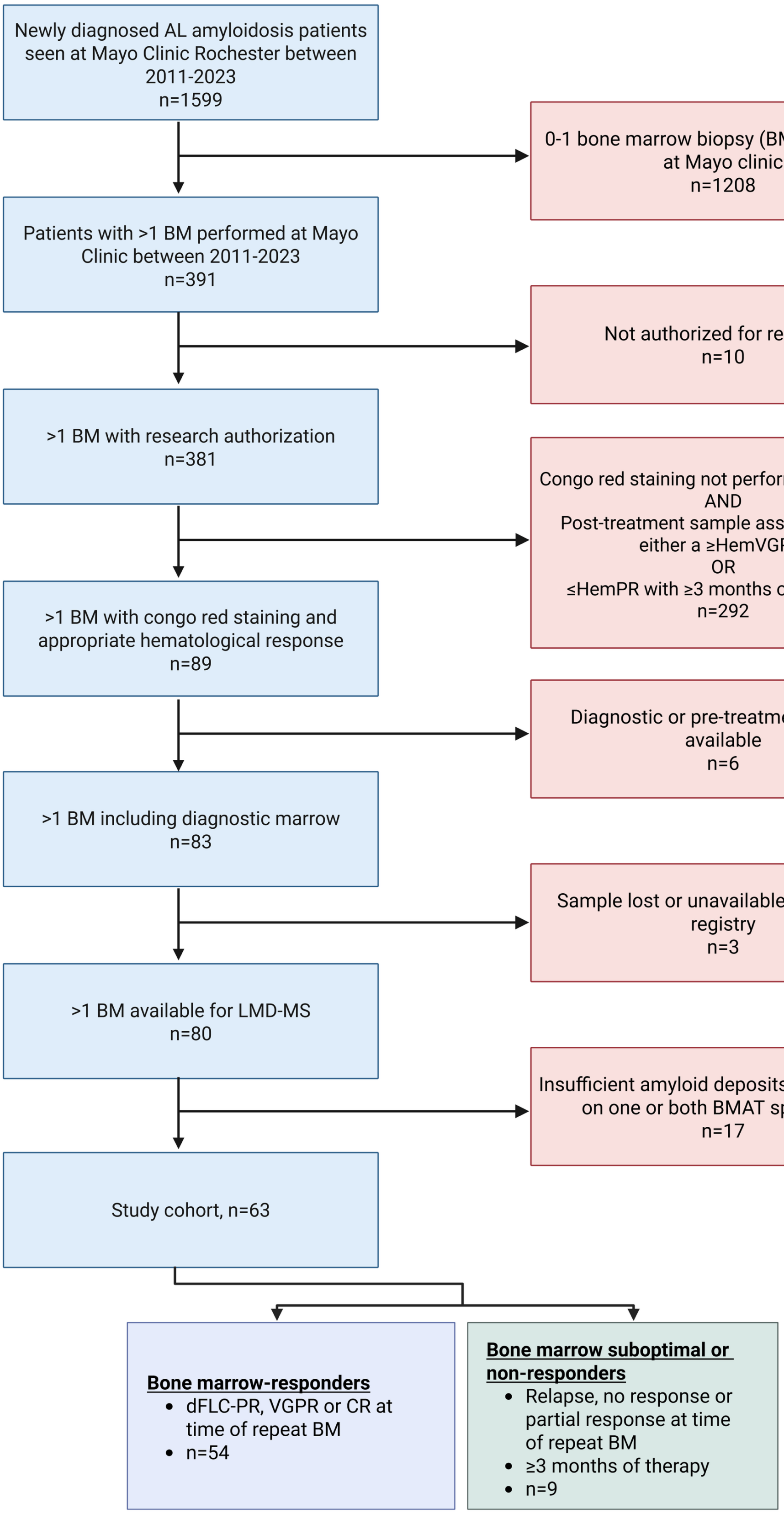
UPREGULATED IN DIAGNOSTIC BONE MARROW BIOPSIES OF NON-RESPONDERS

Protein (gene symbol)	Log2 fold change	FDR p-value	Function in human biology and role in amyloidosis (if previously described).
AGL, Amylo-Alpha-1,6-Glucosidase, 4-Alpha-Glucanotransferase	28.0015	<0.0001	Bifunctional enzyme involved in glycogen breakdown in muscle and liver.
MYOM1, Myomesin-1	27.7177	<0.0001	A structural protein in the M-band of striated muscle sarcomeres, anchoring thick filaments and titin.
RYR1, Ryanodine Receptor 1	27.5161	<0.0001	A calcium release channel in the sarcoplasmic reticulum of skeletal muscle, critical for excitation-contraction coupling.
MYOM2, Myomesin-2	27.3640	<0.0001	Another M-band protein in striated muscle, similar to MYOM1 but predominantly expressed in fast-twitch fibers and cardiac muscle.
MYBPC1, Myosin-Binding Protein C, Slow-Type	27.3640	<0.0001	A regulatory protein in the sarcomere, stabilizing thick filaments and modulating contraction in slow-twitch skeletal muscle.
TNNT1, Troponin T, Slow Skeletal Muscle (Isoform-Specific)	27.3640	<0.0001	Part of the troponin complex, it binds tropomyosin to regulate contraction in slow-twitch skeletal muscle; isoforms vary by splicing (e.g., TNNT1 has multiple splice variants)
PFKM, Phosphofructokinase, Muscle Type	27.3060	<0.0001	A key glycolytic enzyme (also called PFK-1) that catalyzes the phosphorylation of fructose-6-phosphate to fructose-1,6-bisphosphate in muscle.
MYBPC2, Myosin-Binding Protein C, Fast-Type	26.8389	<0.0001	Similar to MYBPC1, but expressed in fast-twitch skeletal muscle, regulating myosin structure and contraction speed.
TTN, Titin	8.6967	<0.0001	A giant sarcomeric protein providing elasticity and structural support in striated muscle, spanning from Z-disc to M-line.

UPREGULATED IN POST-TREATMENT BONE MARROW BIOPSIES OF NON-RESPONDERS

Protein (gene symbol)	Log2 fold change	FDR p-value	Function in human biology and role in amyloidosis (if previously described).
IDE, Insulin-Degrading Enzyme	-28.09836	<0.0001	A metalloprotease that degrades insulin, amyloid-beta, and other small peptides in various tissues. Known role in amyloid degradation.
SPTB, Spectrin Beta, Erythrocytic	-27.1390	<0.0001	A cytoskeletal protein forming part of the spectrin network in red blood cells, providing membrane stability.
PPL, Periplakin	-26.7743	<0.0001	A component of desmosomes and cornified envelopes in epithelial cells, aiding cell adhesion and barrier formation.
SPTA1, Spectrin Alpha, Erythrocytic 1	-26.1702	<0.0001	Partners with SPTB in the erythrocyte cytoskeleton to maintain cell shape and flexibility.
EVPL, Envoplakin	-5.01646	<0.0001	A plakin family protein involved in the cornified envelope of stratified squamous epithelia, linking cytoskeletal elements.
A2ML1, Alpha-2-Macroglobulin-Like Protein 1	-3.3884	<0.0001	Protease inhibitor, protects tissues from protein degradation. Key role in wound healing, and maintaining tissue integrity by trapping proteases and facilitating their clearance.
POF1B, Protein POF1B	-2.7770	<0.0001	An actin-binding protein implicated in cell adhesion and ovarian function, with less clear roles elsewhere.
PKP1, Plakophilin-1	-2.0445	<0.0001	A desmosomal protein in epithelial and cardiac tissues, stabilizing cell-cell junctions.
CLTC, Clathrin Heavy Chain 1	-1.7770	<0.0001	The major protein of clathrin-coated vesicles, essential for endocytosis and intracellular trafficking.

Figure 1. Cohort selection from the total number of newly diagnosed AL amyloidosis patients seen at the Mayo Clinic, Rochester, within 90 days of diagnosis for the period of 2011-2023.



HemPR, hematological partial response; HemVGPR, hematological very good partial response; dFLC-PR, difference in free-light chains partial response; CR, complete response; LMD-MS, laser microdissection mass spectrometry.