Aggregated LC-Mediated Cardiotoxicity Directly Upregulates BNP Production

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Summary of Moderated Poster #017
Reductions in NT-proBNP in Patients With AL Amyloidosis Predict Improved Survival

- AL amyloidosis is a rare, progressive, and typically fatal disease caused by misfolded immunoglobulin LC protein.

- Soluble toxic aggregates and deposited fibrils lead to failure of vital organs, including the heart.

- It has been proposed that elevated levels of NT-proBNP result in part from a direct cardiotoxic effect of misfolded LCs.

**Objective:** To investigate the mechanism of misfolded LC-induced cardiomyocyte toxicity and NT-proBNP production

*Progression was defined as ≥300 ng/L and 30% increase in NT-proBNP; response was defined as ≥300 ng/L and 30% decrease in NT-proBNP; patients with stable disease had neither response nor progression.*

AL, amyloid light chain; LC, light chain; NT-proBNP, N-terminal probrain natriuretic peptide.

Figure modified from Palladini G et al. J Clin Oncol. 2012;30:4541.

Aggregated LC induces oxidative stress in cardiomyocytes

Cardiomyocytes (rat)

± Light chain
(recombinant sequence derived from a patient with AL amyloidosis)

Assessment of Hmox-1 expression
(oxidative stress)

Hmox-1, heme oxygenase-1; LC, light chain.
Aggregated LC Increases Secreted NT-proBNP in an Hmox-1–Dependent Manner

NT-proBNP Protein Secretion

Hmox-1 inhibitor: 30 µM tin protoporphyrin IX

BNP, brain natriuretic peptide; LC, light chain.
Aggregated LC–Mediated Induction of Cellular Oxidative Stress Directly Upregulates BNP Expression

- NT-proBNP represents a direct measure of cardiotoxicity in AL amyloidosis that may not present in other forms of heart failure.

- These data support the use of NT-proBNP as a surrogate biomarker for therapeutic efficacy in clinical trials assessing treatments for patients with AL amyloidosis.

*Potential non-p38 MAPK pathways. Hmox-1, heme oxygenase-1; MAPK, mitogen-activated protein kinase; NT-proBNP, N-terminal probrain natriuretic peptide.