TREATMENT FOR A RARE GENETIC SKELETAL DYSPLASIA
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Site-1 Protease (S1P) is encoded by membrane-bound transcription factor peptidase, site 1 (MBTPS1) gene

S1P, a key serine protease in the Golgi, is required for intracellular protein trafficking and for endoplasmic reticulum (ER) stress responses

MBTPS1 mutation leads to S1P deficiency causing ER retention of collagen in chondrocytes resulting in chondrocyte apoptosis and bone matrix degradation

While ER dysfunction is common in genetic skeletal disorders, to date, there is no treatment targeting ER stress responses
Methods for treating subjects harboring MBTPS1 mutations

Treatment with PBA, BIX and AMO reduces ER stress and enhances collagen secretion from ER.
FINDINGS

Left: Immunofluorescence images of collagen I in patient fibroblasts treated with or without the S1P inhibitor PF-429242, ER chaperone inducer BIX [BiP (immunoglobulin heavy-chain binding protein) inducer X] or chemical chaperone PBA (sodium phenylbutyrate) for 48 hours. TO-PRO, nuclear staining.

Right: Quantification of mean fluorescent intensity (MFI) of intracellular collagen I.

**PBA and BIX treatment diminishes collagen I accumulation in patient fibroblasts**
**FINDINGS**

Antisense Morpholino Oligo (AMO) treatment increased collagen I secretion in patient fibroblasts.

Left: the red box indicates AMO designed to block cryptic splice site and asterisk indicates the premature termination. AMO hampers pathogenic alternative splicing and promote correct mRNA splicing. Right: secreted procollagen I from maternal and patient fibroblasts, treated as indicated, was measured by ELISA.
Dr. Xia has discovered that the S1P defect causes impaired activation of GlcNAc-1-phosphotransferase and of the ER stress transducer BBF2H77, resulting in abnormal secretion of lysosomal enzymes and ER retention of collagens in chondrocytes.

Cartilage related disorders, that account for the majority of skeletal dysplasia, are associated with ER stress.

Dr. Xia’s data indicates that treatment of these cartilage related disorders with PBA, BIX or AMO would improve bone function by manipulating ER stress and result in enhanced collagen secretion and reduced chondrocyte apoptosis.

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