TECHNOLOGY

NEU1-Selective Sialidase Inhibitors for Treatment of Idiopathic Pulmonary Fibrosis

OVERVIEW

Idiopathic Pulmonary Fibrosis (IPF) is an unrelenting, uniformly fatal disease in which lung architecture is distorted and replaced by scar tissue, thereby compromising pulmonary function. IPF patients only survive 2 to 3 years after diagnosis. Although numerous host factors have been implicated in IPF pathogenesis, no unified mechanistic model or life-saving therapy has been established. UMB investigators demonstrated elevated Neuraminidase-1 (NEU1) sialidase expression in the lung tissues of IPF patients, including in the airway epithelium, vascular endothelium, and lung fibroblasts.Furthermore, NEU1-selective sialidase inhibitors can dramatically protect in animal models of IPF suggesting a promising new therapeutic path for this fatal disease.

TECHNOLOGY

NEU1 is one of four mammalian neuraminidases, each with overlapping tissue distributions, substrates, and functions. This present invention is a method of treating IPF with NEU1-targeted small-molecule inhibitors. UMB investigators discovered that expression of the sialidase, NEU1, is elevated in the lungs of IPF patients. Further, forced NEU1 overexpression in the lungs of mice recapitulates the intra-pulmonary lymphocyte infiltration and collagen deposition that are hallmarks of IPF pathophysiology. To protect normal physiology, the sole isozyme, NEU1, implicated in IPF must be targeted. Lead candidate C9-BADANA represents the most promising approach to stopping – even reversing – the course of IPF (Fig 1). Backup compound III-32B5 (C5-hexanamido-C9-acetamido-DANA) has a similar profile.

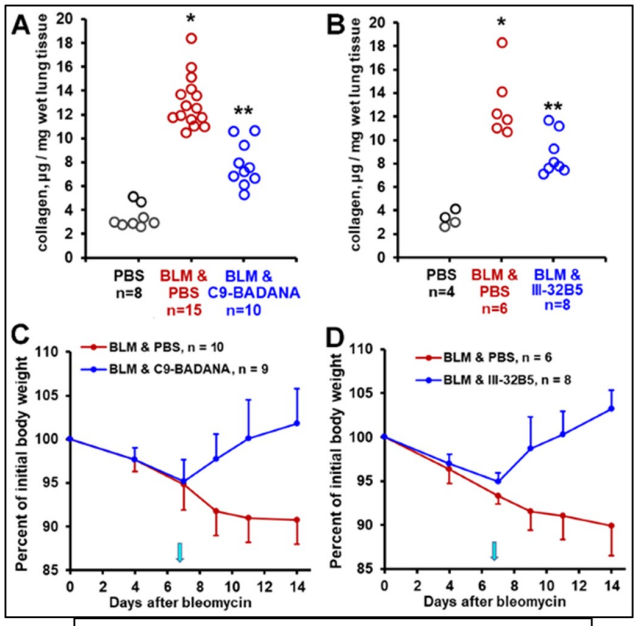

Fig. 1. NEU1 Inhibition Protects the Lungs of Mice from Bleomycin-Induced Fibrosis. Mice were challenged with BLM (day 0), then daily given i.p. C9-BADANA, III-32B5, or saline on days 8 through 14. **A and B:** At day 14, collagen (scar material) was low in naive mice (PBS, black circles), very high in BLM mice (red circles), and significantly decreased in BLM mice treated with NEU1 inhibitors (blue circles). **, significantly decreased at $p<0.05$ compared to BLM alone. **C and D:** Lung fibrosis is associated with decreased body weight (red lines). It is counteracted by NEU1 inhibition (blue lines). SEM shown.

APPLICATIONS

IPF has an estimated prevalence of 13 to 20 per 100,000 people worldwide. About 100,000 people are affected in the United States, and 30,000 to 40,000 new cases are diagnosed each year. The IPF Foundation places the tally higher, up to 200,000 people with mild, moderate, or severe cases. 50% die within two years of diagnosis, and 80% within five years. Treatment had been largely supportive in nature (e.g. O2 therapy), but two agents that slow disease progression were cleared in 2014, pirfenidone (Roche) and nintedanib (Boehringer). U.S. sales of pirfenidone topped $800 million in 2018; nintedanib's were slightly higher. Each is prescribed to about 10,000 patients (pirfenidone-nintedanib combination therapy is unproven and uncommon). The two FDA-approved drugs, pirfenidone (Esbriet) and nintedanib (Ofev), slow progression but do not improve survival. Each comes with multiple severe side effects that impact quality of life, e.g. diarrhea (62% of patients) and nausea (24%) for nintedanib. For the "advanced" stage, lung transplant, which is often unavailable, is the only cure.

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PATENT STATUS

Patent Pending (PCT/US2020/041212)

LICENSE STATUS

Available for licensing

CATEGORIES

- Therapeutics
- Methods of Treatment

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ATTACHMENTS

- Download SG-2019-090 Marketing Sheet.pdf

EXTERNAL RESOURCES

- Luzina IG, Lillehoj EP, Lockatell VK, et al. J Pharm Exp Ther. (2021) PMID: 33139318

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