Spyryx Biosciences Inc. is developing inhaled peptides for cystic fibrosis that inhibit the sodium channel responsible for regulating fluid volume in the lungs. The peptides could offer a pan-genotypic treatment that is more efficacious than therapies targeting CFTR.

CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) channel that result in depletion of airway surface liquid and abnormally adherent mucus. Spyryx's peptides target the epithelial sodium channel (ENaC), which conducts sodium and water away from the airway surface, and becomes hyperactive when CFTR is defective.

Scientific founder Robert Tarran discovered how defects in CFTR lead to excessive ENaC activity. Namely, the inability of defective CFTR to conduct chloride and bicarbonate ions results in the airway surface fluid becoming acidic. The acidity in turn causes a conformational change in SPLUNC1 (BPI fold containing family A member 1; BPIFA1; PLUNC; LUNX), a secreted protein that normally binds to and deactivates ENaC by causing its subunits to dissociate and internalize.

The conformational change in SPLUNC1 makes its ENaC binding domain inaccessible, which allows ENaC to be activated by proteases.

Spyryx is developing small peptides based on the SPLUNC1 ENaC binding domain to prevent ENaC activation.

"When you isolate the regulatory peptide from the rest of the protein, it maintains its binding affinity for ENaC, but it's pK independent," said CEO John Taylor.

In 2013, Tarran's group at the University of North Carolina at Chapel Hill and researchers from the University of Lausanne reported in the American Journal of Physiology Lung Cellular and Molecular Physiology that an 18-amino-acid peptide derived from SPLUNC1 inhibited ENaC conductance in CF human bronchial epithelial cultures and produced a mean airway surface liquid depth of 7.9 μm, which is comparable to non-CF bronchial cultures. Untreated CF bronchial cultures had a mean airway surface liquid depth of 4.2 μm.

Taylor said Spyryx is optimizing versions of the peptide that contain about 12 amino acids.

Spyryx has performed preliminary comparative testing that suggests the peptides could have greater efficacy than CFTR modulators, but also do not interfere with CFTR modulators' activity. Thus, the peptides may complement CFTR modulators the same way CFTR and ENaC work together to regulate airway hydration in the normal lung.

Unlike mutation-specific CFTR modulators, the peptides wouldn't be restricted to specific genotypes.

"Because we’re not working on the channel that’s mutated and are directly addressing airway fluid regulation, our belief is that our therapy should have a universal effect," he said.

At least one other ENaC inhibitor is in the clinic for CF. P-1037 from Vertex Pharmaceuticals Inc. and Parion Sciences Inc. is a small molecule in Phase IIa testing to treat CF regardless of genotype. Vertex and Parion declined to provide more information.
Taylor said small molecule inhibitors of ENaC risk causing diuresis and hyperkalemia if they enter circulation and reach ENaC in the kidney, which may be less likely with Spyryx’s peptides.

“It is our belief that they are not crossing into the bloodstream in a material way, and what does is rapidly cleaved and cleared from circulation,” he said.

He said Spyryx’s peptides also may have durable effects because they both inhibit and degrade ENaC.

Spyryx also plans to research the peptides’ ability to treat chronic obstructive pulmonary disease (COPD). Taylor said Tarran and others have shown that cigarette smoke may cause a CF-like condition by interfering with CFTR on airway epithelial cells.

Spyryx has an exclusive worldwide license to IP from UNC-Chapel Hill covering composition of matter and methods of treatment using SPLUNC1 and its derivatives. The university holds equity in Spyryx and is eligible for milestones and royalties.

In May, Spyryx raised an $18 million series A round to advance at least one candidate into the clinic. Spyryx also received an award of an undisclosed amount from Cystic Fibrosis Foundation Therapeutics Inc. in June to support development of the peptides. A timeline for entering the clinic is not disclosed.

COMPANIES AND INSTITUTIONS MENTIONED

Cystic Fibrosis Foundation Therapeutics Inc., Bethesda, Md.
Parion Sciences Inc., Durham, N.C.
Spyryx Biosciences Inc., Durham, N.C.
University of Lausanne, Lausanne, Switzerland
University of North Carolina at Chapel Hill, Chapel Hill, N.C.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Boston, Mass.

REFERENCES