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Santhera becomes third group to buy into novel respiratory mechanism

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Today's licensing deal with the little-known private Swiss group Polyphor could signal a change of tack for Santhera, but it also highlights a pharmacology mechanism – neutrophil elastase inhibition – that has quietly generated significant deal interest of late.

Indeed, the Santhera/Polyphor tie-up is the third alliance involving neutrophil elastase inhibitors in less than a year (see table below). The mechanism of action appears to be involved in maintaining lung structure, hence its potential in respiratory disease, though industry has tried to target it more broadly.

Perhaps the most unusual possible use is diabetes. This stems from the finding that some patients with type 1 diabetes were found to have elevated levels of neutrophil elastase, and that this might have contributed to the self-destruction of insulin-producing β-cells.

Astrazeneca, one of two big pharma groups to have looked seriously at neutrophil elastase inhibition, had carried out early work with alvelestat as an adjunctive therapy in diabetes, in addition to its more obvious respiratory focus. However, it shelved the asset, which was then was picked up by Mereo Biopharma last October (*Interview – Mereo's quest for diamonds in the rough, January 2, 2018*).

Mereo's aim is to reposition alvelestat in alpha-1 antitrypsin deficiency. Strictly speaking, Mereo's focus here seems to be the pulmonary emphysema that can result from alpha-1 antitrypsin deficiency.

Cystic fibrosis

This morning Santhera said it would pay Polyphor CHF6.5m ($7m) up front in stock for rights to POL6014, which it will take forward in cystic fibrosis.

Santhera was hit hard last September when the EMA joined the US FDA in saying that phase III data were insufficient to back the efficacy of its lead asset, Raxone, in Duchenne muscular dystrophy. The company remains committed to running a US study that does not read out until next year, so POL6014 could give it a useful added focus.

Santhera and Polyphor thus join Chiesi in targeting cystic fibrosis with neutrophil elastase inhibition. For its part, Polyphor wants to focus on advancing phase III development of a novel antibiotic, murepavadin; the private group is also developing balixafortide, a CXCR4 antagonist, for combination treatment in oncology.

Selected neutrophil elastase inhibitors in development			
Product	**Company**	**Therapy focus**	**Note**
Marketed			
Sivelestat sodium	Ono Pharmaceutical	Acute lung injury	Lilly deal signed in 2000, terminated in 2003.
Phase II			
PHP-303	pH Pharma/Bayer	Inflammation in metabolic diseases	Licensed from Bayer in Mar 2017.
Alvelestat/AZD9668	Mereo/Astrazeneca	Alpha-1 antitrypsin deficiency	Licence (including option to acquire) signed in Oct 2017
Phase I			
CHF6333	Chiesi	Cystic fibrosis	NCT03056326 trial completed in Nov 2017
POL6014	Santhera/Polyphor	Cystic fibrosis	Deal signed in Feb 2018
Source: EvaluatePharma.			

Before Santhera and Mereo bought into this mechanism the South Korean group pH Pharma licensed PHP-303, Bayer's asset targeting neutrophil elastase. The focus of this project remains somewhat vague, pH only saying it will be developed to treat inflammation in metabolic diseases.

And while the licensing deals suggest growing interest in neutrophil elastase, the mechanism is not exactly novel: the first neutrophil elastase inhibitor, Ono's sivelestat sodium, was launched in 2002 in Japan as Elaspol 100 for acute lung injury.

However, development does not seem to have been pursued in the west, and a deal with Lilly, struck in 2000, was canned three years later. Renewed big pharma interest could help validate this target, but Astrazeneca's stance suggests that this might be some way off.

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