BioCentury
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EMERGING COMPANY PROFILE

PICKING A PCSK9

BY EMILY CUKIER-MEISNER, SENIOR WRITER

As the first mAbs against PCSK9 are making their market debuts, several companies are vying to replace them with oral candidates. Liphorus Pharmaceuticals Inc. has assembled a test kitchen of screens for small molecules with different PCSK9-targeting mechanisms — including one mechanism that stymied other companies.

PCSK9 binds to and enhances the degradation of LDL receptors, which are responsible for clearing LDL from the circulation. PCSK9 must cleave itself to exit the endoplasmic reticulum and leave the cell, where it circulates and binds to the LDL receptor to target it for lysosomal degradation.

Scientific founder Nabil Seidah said developing an oral small molecule that directly inhibits the interaction of PCSK9 and LDL receptors has been challenging because the proteins interact at a large, flat surface. Seidah is director of the Laboratory of Biochemical Neuroendocrinology at the Institut de Recherches Cliniques de Montréal (IRCM), and was part of the team that discovered PCSK9 in 2003.

In addition, at least two companies, the now-defunct Index seed company Purple Therapeutics Ltd. and the Genentech Inc. unit of Roche, ran into problems identifying small molecule inhibitors that would be highly selective for PCSK9 over other proprotein convertases that have critical functions. The compounds inhibited PCSK9 from binding external substrates but were unable to inhibit PCSK9 from activating itself via autocleavage.

Liphorus chose to study molecules that interfere with many different activities of PCSK9 — such as preventing PCSK9 autocleavage or oligomerization, or reinternalization of the PCSK9-receptor complex.

"We have to find out which mechanism is most specific and least toxic," Seidah said.

His group developed multiple screens for interference with PCSK9, including a mechanism-agnostic platform to identify molecules that prevent PCSK9 secretion. Seidah said Liphorus is using CROs to explore structural-activity relationships of its hits, and expects to nominate a lead molecule in about two years.

LIPHORUS PHARMACEUTICALS INC.
Montreal, Quebec

Technology: Small molecule inhibitors of PCSK9

Disease focus: Cardiovascular

Clinical status: Preclinical

Founded: 2014 by Sanderling Ventures, Nabil Seidah, Institut de Recherches Cliniques de Montréal (IRCM)

University collaborators: IRCM

Corporate partners: None

Number of employees: None

Funds raised: C$6.4 million ($5.6 million)

Investors: Sanderling Ventures, IRCM

CEO: Peter McWilliams

Patents: None

Liphorus has a license from IRCM to IP

covering cell-based assays and molecules targeting PCSK9.

Seidah hypothesized that a small molecule might be both more convenient for patients, and safer. He noted patients can develop antibodies to mAb therapeutics, and they could burden the kidneys when given over the long term.

"When you take an antibody all your life, the kidney has to get rid of about 100 mg every two weeks," he said.

Patients have used other mAbs chronically for at least a decade in other indications without kidney problems. However, doses of PCSK9 mAbs are pretty high.

Sanofi and Regeneron Pharmaceuticals Inc.'s Praluent alirocumab requires twice-monthly injections of 75 or 150 mg. Amgen Inc.'s Repatha evolocumab may be dosed at 140 mg twice a month, or 420 mg once a month. By contrast, the routine maintenance dose of Humira adalimumab from AbbVie Inc. for adult indications is 40 mg every other week.

Amgen said no adverse effects on kidney function have been seen in clinical trials. Sanofi did not respond to BioCentury's request for comment.

Seidah added that Liphorus' molecules might be useful in indications anti-PCSK9 mAbs cannot treat — such as hepatitis and kidney disease — by disrupting intracellular interactions between PCSK9 and proteins other than LDL receptor.

There are at least three other oral PCSK9 inhibitors in preclinical development, and next-generation injectable PCSK9 inhibitors are seeking to reduce dosing frequency. In the latter group, ALN-PCSsc could achieve mAb-like LDL reduction dosing two to four times per year. The Medicines Co. has rights to the subcutaneous formulation of small interfering RNA (siRNA) against PCSK9 from Alnylam Pharmaceuticals Inc. and plans to begin Phase II studies in patients with familial hypercholesterolemia and atherosclerotic cardiovascular disease this year.

In the small molecule group, Shifa Biomedical Corp. is developing inhibitors of autocatalytic cleavage and antagonists of the PCSK9/LDL receptor interaction and plans to begin IND-enabling studies next year.

Serometrix LLC has allosteric ligands that disrupt PCSK9 folding in ways that hinder its activity. The company declined to discuss the program for this story, but said it plans to out-license it for clinical development.

Pfizer Inc. plans to begin clinical trials of a small molecule that down-regulates PCSK9. bc

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NASDAQ:ABBV), Indianapolis, Ind.
Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Cambridge, Mass.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Genentech Inc., South San Francisco, Calif.
Institut de Recherches Cliniques de Montréal (IRCM), Montreal, Quebec
Liphorus Pharmaceuticals Inc., Montreal, Quebec
The Medicines Co. (NASDAQ:MDCO), Parsippany, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Serometrix LLC, Pittsford, N.Y.
Shifa Biomedical Corp., Malvern, Pa.

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