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Product Development

Amira's lipid love affair

By Aaron Bouchie
Senior Writer

Spurred by academic research linking LPA1 to idiopathic pulmonary fibrosis, **Amira Pharmaceuticals Inc.** used its medicinal chemistry expertise in bioactive lipids to design antagonists for preclinical studies. The company presented proof-of-concept data in a mouse model of IPF last week and hopes to enter the clinic next year with the first candidate it could take to market on its own.

Lysophosphatidic acid (LPA) is an anionic bioactive lipid that acts through EDG receptors to mediate cell proliferation, platelet aggregation, smooth muscle contraction, inhibition of neuroblastoma cell differentiation, chemotaxis and tumor cell invasion. LPA also elicits angiogenesis.

Lysophosphatidic acid receptor 1 (LPAR1; EDG2; LPA1) is an EDG receptor that is part of the phosphatidic acid/lysophosphatidylcholine pathway.

In January 2008, researchers from **Harvard Medical School** published a study in *Nature Medicine* linking LPA1 to IPF. They first showed that bleomycin mice, a model of pulmonary fibrosis created by administering the glycopeptide antibiotic bleomycin, had elevated levels of LPA in the bronchoalveolar lavage fluid, and that LPA mediated fibroblast migration. LPA1 was the most highly expressed LPA receptor in mouse lung fibroblasts.

Next they showed LPA1 knockout mice were protected from fibrosis and mortality after challenge with bleomycin. At 21 days after challenge with the highest dose of bleomycin (3 units/kg), mortality was 0% in knockout mice and 50% in wild-type mice (n = 10 mice/group).

The authors also showed that bronchoalveolar lavage samples from IPF patients had elevated LPA, and that fibroblast migration in these samples was dependent on LPA1.

Amira, which already was working on FLAP and prostaglandin D2 receptor subtype DP2 in the arachidonic acid bioactive lipid pathway, liked the target and the indication.

"IPF is a perfect indication for biotechs to pursue. It's a small market, so big pharma is not interested," said CEO Bob Baltera. **NIH's** National Heart Lung and Blood Institute estimates there are 200,000 patients with IPF in the U.S., with 50,000 new cases diagnosed each year.

"LPA1 is under the umbrella of phospholipid pathways, which we've been working on. Our strength is medicinal chemistry, so we began synthesizing compounds and screening last spring," he said.

The company last week presented data on its lead LPA1 inhibitor, AP2966, at the FASEB Lysophospholipid Mediators in Health and Disease meeting in Carefree, Ariz.

Mice given AP2966 and bleomycin together had a 40-60% reduction in lung inflammation and fibrosis compared with

mice given bleomycin alone. Inflammation and fibrosis were measured by Ashcroft score after 14 days.

"We saw results similar to the knockout model. That is really exciting because we have shown pharmacologically what was shown in the knockout setting," Baltera said.

Baltera and CSO Peppi Prasit said Amira has seen similar trends when AP2966 is given five days after bleomycin challenge, but those data are not yet disclosed.

The company also presented data from CHO cells, in which
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Bob Baltera, Amira Pharmaceuticals

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AP2966 demonstrated high potency and greater selectivity for mouse LPA1 and recombinant human LPA1 than for LPA2, LPA3 and LPA5.

Baltera expects AP2966 to start Phase I testing in 1H10. He said Amira intends to develop and market the compound itself, because the IPF market is small enough for the company to handle on its own.

The biotech's AM803 and AM103, both 5-lipoxygenase activating protein (FLAP) inhibitors in Phase II testing to treat inflammatory disease, are licensed to **GlaxoSmithKline plc**.

Amira also plans to out-license AM211, a prostaglandin D2 receptor subtype DP2 antagonist that is in Phase I testing to treat asthma and chronic obstructive pulmonary disease (COPD). Interim results announced last week showed a single dose produced a sustained pharmacodynamic effect at blood concentrations much lower than the highest safe concentration in animals.

Baltera said Amira has enough cash to last well into 2010, and the company expects more milestone payments from GSK this year.

COMPANIES AND INSTITUTIONS MENTIONED

Amira Pharmaceuticals Inc., San Diego, Calif.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Harvard Medical School, Cambridge, Mass.

National Institutes of Health (NIH), Bethesda, Md.