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Article Reprint • Page 1 of 2

## Product Discovery & Development

# Roche goes shopping for staples

By Stephen Hansen  
Staff Writer

Targeting intracellular protein-protein interactions is difficult because small molecules lack sufficient specificity, while molecules with higher specificity such as antibodies are too big to enter the cell. **Aileron Therapeutics Inc.** says its Stapled Peptide technology creates cell-penetrating peptides that provide antibody-like specificity.

A year after **Roche's** venture arm invested in the biotech's series D round, the pharma has placed a second bet on the technology in a collaboration to develop and market Stapled Peptide therapeutics.

Aileron and Roche now will discover, develop and commercialize Stapled Peptide therapeutics against up to five undisclosed targets for cancer, virology, inflammation, metabolism and neurology. Aileron will receive \$25 million in technology access fees and R&D support.

The companies declined to break out how much of the money will go to FTEs, but Aileron will be responsible for the majority of discovery and preclinical development. Roche will have primary responsibility for further development and commercialization.

Aileron is eligible for up to \$1.1 billion in milestones if products against all five targets reach the market. The company also is eligible for royalties.

For Roche, the deal provides a second way of approaching its long-term focus on intracellular protein-protein interactions. Scientists on the company's Nutlin program have spent the last eight years developing small molecules that disrupt these inter-

actions.

The first of these is RG7112, an Mdm2 p53 binding protein homolog (MDM2; HDM2) antagonist that entered Phase I testing for cancer in 2008.

"It took us eight years to get to a molecule that is now in Phase I. It was a long journey, and you cannot afford to always take so many years," Klaus Strein, head of research therapeutic modalities at Roche, told BioCentury. "We have here another methodology that I expect will go faster than small molecules."

According to co-founder, President and CEO Joseph Yanchik, Aileron's technology overcomes two limitations associated with using peptides as drugs: isolated peptides lose their function and are quickly degraded, and peptides do not typically enter cells.

"Peptides are the keys to the locks that turn on and off most of the functions in the

body. The problem is that peptides are not designed to last very long in the body," Yanchik told BioCentury. "Also, they are not designed to enter through cell membranes, which creates a problem since many, if not most, of the very important and high value targets are inside the cell."

In the body, a peptide is connected to a protein that acts as a stabilizing scaffold to maintain the peptide in a biologically active alpha helix conformation. When the peptide is separated from this scaffold, it loses its shape, which results in a loss of biological activity and rapid degradation.

Aileron's technology uses an all-hydrocarbon linker to "staple" peptides in their alpha helix conformation. The linker also makes peptides resistant to protease degradation.

*See next page*

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**Klaus Strein, Roche**

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**Product Discovery & Development,**  
*from previous page*

Yanchik said an isolated, unmodified peptide will be degraded within minutes, but a Stapled Peptide has a half-life suitable for at least once-daily dosing.

Stapled Peptides also can penetrate the cell via mechanisms that are still under study. According to Yanchik, one mechanism is through endocytosis, similar to the way in which a virus would enter the cell.

“We think there are probably multiple ways that these peptides are getting into the cell, but we are just not sure yet. In terms of the different sequences we have tried at Aileron, and we’ve now tried thousands, there isn’t one that we cannot get into the cell,” he said.

Strein said Roche was attracted to the technology’s ability to penetrate the cell and by the specificity of the peptides.

To block protein-protein interactions in the cell with a small molecule, “you usually have to go with a very lipophilic molecule. Then you have the risk that this lipophilic molecule also blocks other protein-protein interactions, that they are not very specific, and that can lead to side effects,” he said.

“I think Stapled Peptides are in between antibodies and small molecules,” Strein added. “Let me say a little bit closer to antibodies than small molecules, because we can more specifically inhibit targets.”

A typical Stapled Peptide has a molecular weight of 2 kD, making it much smaller than standard antibodies.

Yanchik noted that individual Stapled Peptides can engage multiple targets. For instance, Aileron’s lead internal program is a BIM-BH3 stapled peptide in preclinical testing for cancer. The peptide hits up to five different targets including B-cell lymphoma 2 (Bcl-2), Bcl-XL, myeloid leukemia cell differentiation protein (Mcl-1), Bcl-2-associated X protein (BAX) and Bcl-2 homologous antagonist/killer (BAK).

Besides Roche Venture Fund, three other pharma investment funds have backed Aileron. These include SR One, Lilly Ventures and Novartis Venture Funds, which are the venture capital arms of **GlaxoSmithKline plc**, **Eli Lilly and Co.** and **Novartis AG**, respectively (see *BioCentury*, June 8, 2009).

**COMPANIES AND INSTITUTIONS MENTIONED**

- Aileron Therapeutics Inc.**, Cambridge, Mass.
- Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.
- GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
- Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland
- Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland