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Emerging Company Profile

Presidio: Penultimate NRTIs

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Staff Writer

Conventional nucleoside reverse transcriptase inhibitors are nucleoside analogs with modified structures that incorporate into viral DNA and block replication. However, HIV eventually mutates to become resistant to the drugs.

Presidio Pharmaceuticals Inc. is developing NRTIs that it believes will be active against the most common reverse transcriptase mutations and will present a high barrier to the development of new mutations. The company has exclusive, worldwide rights to PPI-801 and a series of prodrugs from **Medivir AB**.

Unlike other NRTIs, which bind to the end of viral cDNA, "PPI-801 inserts in the nascent cDNA chain at a penultimate position, allowing one additional nucleoside to be incorporated but with a modified orientation," President and CEO Omar Haffar told BioCentury.

This last nucleoside protects the compound from excision via common reverse transcriptase escape mutations such as those that develop under selective pressure from treatment with thymidine analogs and nucleoside analogs, which lead to removal of other NRTIs via pyrophosphorylation.

In both animals and human cell culture, according to the company, PPI-801 was effective against the M184V and K65R mutations, which are single amino acid substitutions within the HIV reverse transcriptase enzyme that renders the virus resistant to inhibition by cytidine analogs such as lami-

Presidio Pharmaceuticals Inc.

San Francisco, Calif.

Technology: Nuclear Exclusion Technology (NEXT)

Disease focus: Infectious

Clinical status: Preclinical

Founded: 2006 by Omar Haffar, Antoun Nabhan and David Jobs

University collaborators: Stanford University

Corporate partners: Cytokine PharmaSciences Inc., Medivir AB, Numerate Inc. and XTL Biopharmaceuticals Ltd.

Number of employees: 14

Funds raised: \$27.4 million

Investors: Panorama Capital; Baker Brothers Investments; Bay City Capital; Ventures West Capital; Nexus Medical Partners; Sagamore Bioventures; Peninsula Overview Fund and George Rathmann Investment Fund
CEO: Omar Haffar

Patents: 13 U.S. and 5 international patents issued covering 3 programs in HIV and HCV

vidine (3TC).

Haffar said PPI-801 has shown a good safety profile in *in vitro* toxicity assays, rodents and non-human primates.

Presidio has a prodrug of PPI-801 called

PPI-802 in preclinical development for patients failing existing NRTIs and as a potential first-line therapy for newly infected individuals. In animal studies, the prodrug is more orally bioavailable than the parent molecule, according to the company. PPI-802 is expected to start Phase I testing in 2009.

Presidio also has its Nuclear Exclusion Technology (NEXT) for developing compounds to treat HIV-1 and other viral diseases. NEXT is an *in silico* assay methodology for identifying and validating viral targets and specific small molecule inhibitors.

Presidio licensed NEXT from **Cytokine PharmaSciences Inc.**

Presidio uses NEXT to identify viral-specific small molecule inhibitors that bind to the nuclear localization sequences (NLS) of viral proteins and interrupt the binding of viral RNA and the host cellular cytoplasmic guide protein that mediates translocation across the nuclear membrane, thus preventing replication.

"When HIV attacks human cells, the virus releases its genetic material into the cytoplasm as part of a nucleoprotein complex called the preintegration complex, or PIC," said Haffar. "The nascent viral DNA is translocated into the nucleus in the PIC."

This translocation is mediated by a cellular cytoplasmic guide protein called karyopherin. "The interaction of the PIC and karyopherin is possible due to the presence of nuclear localization sequences, which are specific amino acid sequence tags that iden-

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Presidio,
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tify proteins destined to localize into the nucleus, on a viral protein component of the PIC," Haffar said.

Presidio has a series of NEXT-derived compounds in lead optimization.

Haffar said NEXT can be applied to other viruses such as herpes and HBV to identify inhibitors that target the specific viral protein implicated in localization of the viral genome into the nucleus of host cells. NEXT is not useful for viruses such as HCV, where the virus replicates solely in the cytoplasm and nuclear entry is not required.

Presidio is approaching HCV in other ways. Most recently, the company received exclusive worldwide rights to an HCV program targeting non-structural protein 5A (NS5A) from **XTL Biopharmaceuticals Inc.** The program is in late lead optimization.

Presidio also is collaborating with **Numerate Inc.** to identify selective HCV inhibitors and has exclusive, worldwide rights to HCV technology from **Stanford University**, including a screening assay and IP covering targets for a specific region found in the HCV proteins NS4B and NS5A, which are required for virus replication.

COMPANIES AND INSTITUTIONS MENTIONED

Cytokine PharmaSciences Inc., King of Prussia, Pa.

Medivir AB (SSE:MVIR B), Huddinge, Sweden

Numerate Inc., San Bruno, Calif.

Presidio Pharmaceuticals Inc., San Francisco, Calif.

Stanford University, Stanford, Calif.

XTL Biopharmaceuticals Ltd. (NASDAQ:XTLB), New York, N.Y.

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