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*Emerging Company Profile*

# PledPharma: Catalytic cytoprotection

**By Michael J. Haas**
**Senior Writer**

Toxicities associated with chemotherapy often prevent cancer patients from completing treatment or reaching the recommended dose, limiting the drugs' efficacy. **PledPharma AB** is developing mangafodipir to protect healthy cells from chemotherapy-induced toxicities, with the aim of increasing survival and quality of life and reducing overall costs for cancer patients.

Mangafodipir is a pyridoxyl ethyldiamine (PLED) analog first developed in the 1980s as an MRI contrast agent. **General Electric Co.**'s GE Healthcare unit marketed Teslascan mangafodipir as an MRI agent until it was withdrawn from the market due to low demand in October 2003 in the U.S. and July 2010 in the EU.

An academic study published in 1999 showed mangafodipir mimicked the antioxidant activity of superoxide dismutase (SOD), protecting normal rat heart tissue from damage by superoxide radicals. Because oxidative damage to the heart is a side effect of anthracyclines, study co-author Jan Olof Karlsson speculated mangafodipir might protect normal cells from toxic side effects of those drugs.

Karlsson is assistant professor of pharmacology at **Linkoping University** and co-founder and CSO of PledPharma, which spun out of the university in 2007.

## PledPharma AB

Stockholm, Sweden

Technology: Pyridoxyl ethyldiamine (PLED) analogs

Disease focus: Cancer, cardiovascular

Clinical status: Phase II

Founded: 2007 by Torsten Almen, Ingemar Lundstrom, Louis Ignarro, Jan Olof Karlsson, Per Jynge, Heidi Brurok and Rob Towart

University collaborators: Linkoping University

Corporate partners: None

Number of employees: 5

Funds raised: Not disclosed

Investors: Accelerator Nordic AB

CEO: Jacques Nasstrom

Patents: 4 issued covering broad therapeutic use of PLED analogs

Unpublished data from PledPharma's preclinical studies showed mangafodipir (PP-095) protected mouse models of colorectal, mammary and ovarian cancer from hematotoxicities and neurotoxicities associated with anthracyclines, taxanes, 5-fluorouracil (5-FU) or platinum-based chemotherapies, CEO Jacques Nasstrom told BioCentury.

Moreover, Karlsson said, mangafodipir monotherapy reduced tumor growth in those models and had additive effects in combination with doxorubicin or oxaliplatin.

The mechanism of mangafodipir's effect on tumor growth is unknown. But *in vitro* and mouse studies have shown normal cells and cancer cells regulate reactive oxygen species (ROS) differently. Nasstrom and Karlsson thus think mangafodipir's SOD-mimicking activity is sufficient to protect healthy cells — but not cancer cells — from oxidative stress.

PledPharma's lead indication is colorectal cancer. "It is a big indication, and about 50% of patients cannot complete the full 12-cycle course of standard FOLFOX treatment due to dose-limiting or dose-delaying hematotoxicities, neurotoxicities" and other side effects, Karlsson said.

In a Phase II trial completed in July, seven advanced colorectal cancer patients treated with mangafodipir before each of their first three cycles of FOLFOX (5-FU, leucovorin and oxaliplatin) experienced less severe neutropenia and neurosensory adverse events than seven patients pretreated with placebo. Consequently, delays between FOLFOX cycles totaled 8 days in the mangafodipir group and 21 days in the placebo group.

Through the subsequent nine cycles of FOLFOX therapy — when patients received no pretreatment — dosing had to

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PO Box 1246
San Carlos CA 94070-1246
Voice: 650-595-5333
Fax: 650-595-5589
www.biocentury.com

DAVID FLORES
President & CEO

KAREN BERNSTEIN, Ph.D.
Chairman & Editor-in-Chief

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***PledPharma AB,***
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be reduced in every patient. And treatment delays totaled more than 120 days, both in the cohort who had received mangafodipir prior to the first three cycles and in the cohort who had received placebo.

"We expect that PP-095 treatment during all 12 cycles will significantly reduce the number of delays and, at the same time, enable administration of FOLFOX much closer to the intended total dose," thus increasing patient survival, Karlsson said.

The Phase II trial used the same formulation of mangafodipir that had been used for MRI. Because it releases manganese, which is toxic, it is not suitable for long-term therapeutic use. PledPharma will thus develop a new formulation for subsequent clinical studies, Nasstrom said.

PledPharma plans to take the compound into Phase III testing in advanced colorectal cancer after finding a partner, and is in discussions with several contenders, Nasstrom said.

The company also hopes to develop mangafodipir as an adjuvant to chemotherapies to treat breast, lung and other cancers, but "whether we do this on our own or with a partner depends on timing of a partnership," Nasstrom said.

According to Nasstrom, mangafodipir is the only catalytic cytoprotectant in development. This should make it more effective than other cytoprotectants on the market and in development, which can exert their protective effects only once per molecule.

For example, he said mangafodipir is almost 100 times more effective at protecting mice against doxorubicin-induced cardiotoxicity than dexrazoxane. The iron chelator was approved in 1995 to protect against doxorubicin-induced cardiotoxicity, and in 2007 as Totect from **TopoTarget A/S** to treat accidental extravasation of anthracycline chemotherapeutics.

At least one other SOD mimetic is in development as a cytoprotectant: AEOL 10150 from **Aeolus Pharmaceuticals Inc.** is a catalytic manganoporphyrin antioxidant in preclinical testing to treat radiation poisoning. The compound has completed Phase I human safety testing and the company hopes to start Phase I or II testing of the compound as an adjunct to radiation in non-small cell lung cancer (NSCLC) patients in mid-2011.

PledPharma also has the PLED analog PP-099 in preclinical development to prevent ischemic damage following percutaneous coronary intervention (PCI) and plans to develop other PLED analogs as adjuvants to radiotherapy and to treat radiation exposure, acetaminophen-induced liver failure, iron and copper overload, and other indications involving oxidative stress.

PledPharma is a portfolio company of biobusiness accelerator **Accelerator Nordic AB**.

COMPANIES AND INSTITUTIONS MENTIONED

**Accelerator Nordic AB** (SSE:ACCE-B), Stockholm, Sweden
**Aeolus Pharmaceuticals Inc.** (OTCBB:AOLS), Mission Viejo, Calif.
**General Electric Co.** (NYSE:GE), Fairfield, Conn.
**Linkoping University**, Linkoping, Sweden
**PledPharma AB**, Stockholm, Sweden
**TopoTarget A/S** (CSE:TOPO), Copenhagen, Denmark