

Progen Technology Switches on Cancer Fighting Genes and Inhibits Tumor Growth

Brisbane, Australia 20 April 2009: Progen Pharmaceuticals Limited (ASX: PGL; NASDAQ: PGLA) has released data that shows its epigenetic technology successfully inhibits tumor growth.

The results of the pre-clinical experiments, presented by Progen's collaborators at the 100th Annual American Association for Cancer Research (AACR) Conference, revealed Progen's product was effective in 'switching on' important anti-cancer genes – a significant achievement in epigenetics research and cancer therapeutics.

Progen CEO Justus Homburg said the latest findings reinforced Progen's position at the forefront of anti-cancer drug research.

"Epigenetics represents an exciting new target for cancer therapeutics and is a focus of this AACR meeting. We are very proud to have achieved such promising results in this exciting area of research," he said.

Epigenetics technology represents one of the latest breakthroughs in cancer drug development which focuses on expression (switching on) or silencing (switching off) of certain genes.

Progen and its collaborators have focused their research on an enzyme known as lysine specific demethylase 1(LSD1), which contributes to the silencing of important tumor suppressor genes. They have successfully developed PG11144 that inhibits LSD1 and reactivates (expresses) the silenced genes that are inactivated in cancer.

Progen's Chief Scientific Officer Dr Laurence Marton said the results showed the product successfully inhibited tumor growth in test tubes and living organisms.

"We believe the use of LSD1 inhibitors represents a highly promising and novel approach to cancer prevention and therapy, and may be suitable for multiple indications."

In addition to its epigenetics findings, Progen also presented an update on its cell proliferation technology at the AACR Conference.

Progen's lead cell proliferation product, PG11047, targets hyper-proliferating cells specifically to inhibit tumor growth, and is currently undergoing two phase 1 clinical trials.

The pre-clinical research presented at the Conference showed the product provides a significant additive anti-cancer effect when combined with Cisplatin and Avastin when compared with either drug alone in lung cancer and prostate cancer models respectively.

Progen is currently progressing PG11047 through early clinical development in parallel to additional translational studies to determine the most promising indications.

Mr Homburg said to date, 44 patients had been treated in the monotherapy PG11047 Phase 1 trial, and over 130 patients in combination studies with approved anti-cancer therapies. The dosing regime in the monotherapy trial has been escalated far beyond Progen's original expectations.

"While we expect to find the maximum dose soon, we already have supporting data that the drug will have a large therapeutic window when given as a monotherapy," he said.

Mr Homburg said the latest findings in Progen's epigenetics and cell proliferation technologies represented another important milestone in the development of its anti-cancer portfolio.

"These latest findings prove we have the technology, the expertise and the resources to progress our strong product pipeline," he said.

"We have a fantastic team of collaborators, who have played a significant role in these achievements.

"We are very pleased to have had the opportunity to present these findings on the world stage, among leaders of the international scientific community."

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About Progen

Progen Pharmaceuticals Limited is a biotechnology company committed to the discovery, development and commercialization of small molecule pharmaceuticals primarily for the treatment of cancer. Progen has built a focus and strength in anti-cancer drug discovery and development. Progen targets the multiple mechanisms of cancer across its three technology platforms of angiogenesis, epigenetics and cell proliferation. Progen has operations in Australia and the United States of America. www.progen-pharma.com

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This release contains forward-looking statements that are based on current management expectations. These statements may differ materially from actual future events or results due to certain risks and uncertainties, including without limitation, risks associated with drug development and manufacture, risks inherent in the extensive regulatory approval process mandated by, amongst others, the United States Food and Drug Administration and the Australian Therapeutic Goods Administration, delays in obtaining the necessary approvals for clinical testing, patient recruitment, delays in the conduct of clinical trials, market acceptance of PI-88, PG11047, PG545, PG562, PG11122, PG11144 and other drugs, future capital needs, general economic conditions, and other risks and uncertainties detailed from time to time in the Company's filings with the Australian Securities Exchange and the United States Securities and Exchange Commission. Moreover, there can be no assurance that others will not independently develop similar products or processes or design around patents owned or licensed by the Company, or that patents owned or licensed by the Company will provide meaningful protection or competitive advantages.

Abstract Details

Novel oligoamine/polyamine analogues inhibit lysine-specific demethylase 1 (LSD1), induce reexpression of epigenetically silenced genes, and inhibit the growth of established human tumors *in vivo*

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Abstract:

Abnormal DNA CpG island hypermethylation and histone modifications are associated with the aberrant silencing of tumor suppressor genes and are thought to be a fundamental defect resulting in the genesis and progression of cancer. The recent identification of the flavin-dependent, lysine-specific demethylase1 (LSD1/KDM1) and the iron-dependent, Jumonji C (JmjC) domain lysine demethylases has demonstrated that histone lysine methylation is a dynamic, enzymatically-controlled process that, like other histone post-translational modifications, is critical to gene transcription. LSD1 specifically catalyzes demethylation of mono- and dimethyl-lysine 4 of histone H3, key positive chromatin marks associated with transcriptional activation. Here we identify a new class of polyamine analogues that are effective inhibitors of LSD1; specifically, long chain polyamine analogues known as oligoamines. As specific oligoamine compounds have been found in our earlier studies to be potent inhibitors of FADdependent polyamine oxidases that are structurally and functionally homologous to LSD1, we hypothesized that oligoamines would be potent inhibitors of LSD1 activity. In this study, we demonstrate that the specific oligoamines, PG-11144 and PG-11150, effectively inhibit the enzymatic activity of recombinant LSD1. Further, treatment of cultured human colorectal cancer cells with these oligoamines results in a global increase of H3K4me2/me1 and the re-expression of the aberrantly silenced Wnt signaling pathway antagonist genes, the secreted frizzled-related proteins (*SFRPs*), which are important in colon tumorigenesis. Chromatin immunoprecipitation analysis shows that the reexpression of *SFRPs* is associated with increased H3K4me2 and H3K4me1 active marks, and a decreased H3K9me2 repressive mark at the promoters of these genes. Additionally, combination treatment with low doses of oligoamines and the DNA methyltransferase inhibitor, 5'-deoxy-azacytidine (DAC), results in robust re-expression of the *SFRP2* gene. Finally, PG-11144 and the bisguanidine polyamine analogue, 2d, a previously identified potent LSD1 inhibitor, remarkably increase global H3K4me2 levels in human colon cancer cell xenografts in host nude mice, and exhibit significant synergy with DAC in inhibiting tumor growth *in vivo*. These results identify a novel class of polyamine analogue inhibitors of LSD1 that induce the re-expression of aberrantly silenced genes and result in significant growth inhibition of established human tumors *in vivo*. The use of these LSD1- inhibiting polyamine analogues represents a highly promising and novel approach to cancer prevention and therapy.

PG11047, A Polyamine Analog, Induces Potent Antitumor Activity in a Preclinical Model of Non-Small Cell Lung Cancer in Combination with Cisplatin.

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PG-11047 is a novel conformationally restricted analog of the polyamine N1, N12-bisethylspermine, currently in Phase I trials for advanced cancer as a monotherapy and in combination with a number of approved anti-cancer agents. The use of polyamines as a target for antiproliferative therapy is based on many studies indicating that cells synthesize more polyamines when induced to grow and polyamine metabolism is frequently dysregulated in cancers. A selective polyamine transport system provides access for PG-11047 into rapidly dividing cells to induce the rate limiting enzymes spermidine/spermine N¹-acetyltransferase (SSAT) and spermine oxidase (SMO) which could subsequently induce reactive oxygen species that contribute to tumor cell responses to PG-11047. Herein, we show the antitumor efficacy of PG-11047 as a single agent in lung (A549) prostate (DU-145)

models of cancer. When used in combination with bevacizumab or docetaxel (both in DU-145), the potency of the approved agents at the dose tested made it difficult to comment on any potential additive or synergistic effects with PG-11047. However, when combined with a standard dose of cisplatin, the combination therapy of PG-11047 and cisplatin led to a potent antitumor effect far superior to either agent alone. In all experiments, PG-11047 was well tolerated with no adverse effects on bodyweight gain. At least in the case of the cisplatin study, the preclinical data supports the rationale for the current Phase I which is assessing PG-11047 as a monotherapy and in combination with a number of approved anti-cancer agents including cisplatin, bevacizumab and docetaxel.

Pediatric Preclinical Testing Program (PPTP) evaluation of the novel polyamine analogue PG11047

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Background: PG11047 is a novel conformationally restricted analog of the polyamine, N1,N12-bisethylspermine. PG11047 demonstrated in vitro and in vivo activity against a range of adult cancer models, and it is currently in phase 1 evaluations in adults. Polyamine analogs are of particular interest for tumors with MYC overexpression, as MYC activates transcription of ornithine decarboxylase, a key regulator of polyamine synthesis. The activity of PG11047 was evaluated against the PPTP's in vitro and in vivo panels.

Methods: The PPTP includes an in vitro panel of cell lines (n=27) and an in vivo panel of xenografts (n=61) representing most of the common types of childhood solid tumors and childhood acute lymphoblastic leukemia (ALL). PG11047 (provided by Progen Pharmaceuticals) was tested in vitro at concentrations from 10.0 nM to 100 µM and was tested against the PPTP in vivo panel using a weekly x 6 schedule with IP administration at 100 mg/kg. Three measures of antitumor activity were used: 1) an objective response measure modeled after the clinical setting; 2) a treated to control (T/C) tumor volume measure; and 3) a time to event (4-fold increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

Results: Because the PG11047 activity pattern was primarily indicative of cytostasis, the in vitro data analysis focused on EC₅₀ values. The median EC₅₀ for PG11047 for the entire in vitro panel was 72.5 nM. Cell lines of the Ewing sarcoma panel had a lower median EC₅₀ value compared to the remaining cell lines in the panel, while cell lines of the neuroblastoma panel had a higher median EC₅₀ value (<21.5 nM versus 574.5 nM, respectively). In vivo, PG11047 induced toxicity in 11.9% of treated animals, indicating that the dose evaluated is at or slightly above the maximum tolerated dose for the weekly schedule employed. Thirty-nine xenograft models were considered evaluable for efficacy, with 6 xenografts excluded from reporting because of excessive toxicity. PG11047 induced significant differences in EFS distribution compared to control in 5 of 32 (15.6%) of the evaluable solid tumor xenografts and in 0 of 7 of the evaluable ALL xenografts. The 5 solid tumor xenografts showing significant growth delay were spread across 4 different tumor panels. The single case of tumor regression occurred in a slow growing ependymoma xenograft.

Conclusions: PG11047 demonstrated a cytostatic pattern of activity against the PPTP in vitro panel, with greater sensitivity for the Ewing sarcoma cell lines compared to the remaining PPTP cell lines. In vivo activity for PG11047 was limited against the pediatric models studied. Further preclinical studies will evaluate PG11047 activity against additional ependymoma models and will evaluate the activity of PG11047 in combination with standard agents against neuroblastoma xenografts.

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