Docket #: S07-154

Semi-Synthesis of Prostratin and Related Compounds

Protein kinase C (PKC) is a family of 10 signaling proteins. Different PKC isoforms have been implicated as targets for HIV/AIDS eradication (currently under clinical evaluation) while others figure as targets for the treatment of Alzheimer's disease (currently under clinical evaluation) as well as small molecule enhanced cancer immunotherapy, Fragile X syndrome, Niemann-Pick disease, cancers with K-Ras mutation, and Charcot-Marie-Tooth disease amongst others. Effective small molecule therapies for these diseases could provide real benefits to patients.
Prostratin, originally obtained in scarce and variable amounts from Samoan trees, is a natural product that exhibits potent PKC modulatory activity. Prostratin induces transcriptional activation of latent HIV reservoir cells through the PKC pathway. Activation of such latent cells, leading to their cytopathic or immune mediated death, when used in combination with antiretroviral therapy (ART) represents the most promising strategy to address an as yet unachieved goal, the eradication of HIV. Prostratin has also shown promise against other diseases. In recent studies, orally administered prostratin has been reported to repress pancreatic tumor growth by disrupting K-Ras-CaM interaction.

Researchers in Dr. Paul Wender's laboratory at Stanford University have developed an efficient five-step semi-synthesis for prostratin using an abundant, sustainable, and inexpensive source that also provides scalable quantities of superior analogs. This is the only synthetic route to such agents, and the lead analogs are over 130-fold more potent than prostratin itself but show the same PKC selectivity profile and a better therapeutic window as determined in animal studies. The lead analogs show superior activity in all binding, cell, biomarker activation, cell pathway, animal, and humanized animal (BLT mouse) studies and ex vivo studies on samples obtained from volunteers and HIV positive individuals. It is noteworthy that prostratin was discovered as an orally active agent used in traditional medical practices, and indeed orally administered prostratin has been shown to be active against

pancreatic tumor. While some PKC modulators such as phorbol esters are known as tumor promoters, prostratin is non-tumorigenic and in fact reverses the tumor-promoting effects of phorbol esters.

Stage of Research
Prostratin had been advanced independently up to and including multiple animal and ADME studies and a positive pre-IND meeting for HIV/AIDS eradication. It has also been evaluated for other indications. The more potent, more accessible and readily tunable analogs made possible by this invention now serve as superior therapeutic leads for development and advancement into clinical trials. The synthesis of prostratin and more potent and effective analogs has been completed as well as the evaluation of the analogs in binding to cell free PKC isoforms, in cell assays including U1 cells and J-Lat cells (with genomically encoded copies of HIV-1), in normal animals and humanized animals (BLT mice) for activation of genomically encoded HIV, and in ex vivo studies of samples from healthy volunteers and HIV positive individuals on suppressive therapy. The use of analogs to make cancer cells more immunogenic has also been evaluated. Preferred candidates have been selected for preclinical advancement.

Applications

- **Synthesis of the natural therapeutic lead and superior analogs:**
  - for HIV eradication
  - for neurological disease including Alzheimer's disease
  - for small molecule enhanced immunotherapy
  - for cancers with K-Ras mutations (pancreatic cancer, colorectal cancer, lung adenocarcinoma, etc.)
- **Research tools** – PKC is a family of proteins implicated in numerous diseases including Alzheimer's disease, Niemann-Pick disease, Fragile-X syndrome, cancer immunotherapy, Charcot-Marie Tooth disease, cancer and cardiovascular disease.

Advantages

- **Therapeutic leads:**

    - PKC modulators are now in the clinic for cancer, Alzheimer's disease and HIV/AIDS eradication. All work has been focused on natural PKC modulators. These prostratin PKC modulating analogs are more potent than the natural product, more effective, better tolerated, more readily tuned and more readily available.
- **Diverse products:**
    - gives access to both known and unknown structures for potential therapeutic agents
    - small synthetic changes allow a host of structural possibilities for the treatment of human disease
- **Inexpensive:**
    - the starting material is commercially available in multi-kilogram quantities
    - short synthetic sequence
- **Sustainable** - plants are not sacrificed to harvest for production of the starting material
- **High yield** - approximately two orders of magnitude greater yield of prostratin with semi-synthesis compared to mamala tree extraction and purification

Publications

- Wender et al. Practical Synthesis of Prostratin, DPP, and Their Analogs, Adjuvant Leads Against Latent HIV. *Science.* Vol 320 no 5876 pp 649-652. May 2008.
- Beans et al. Highly potent, synthetically accessible prostratin analogs induce latent HIV expression in vitro and ex vivo. *Proc Natl Acad Sci*USA 2013, 11698-11703.
- Khan et al. A cellular model of Alzheimer's disease therapeutic efficacy: PKC activation reverses A?-induced biomarker abnormality on cultured fibroblasts. *Neurobiology of Disease*2009, 34(2), 332-339.
- Shaha et al. Prolonging microtubule dysruption enhances the immunogenicity of chronic lymphocytic leukaemia cells. *Clinical & Experimental Immunology* 2009, 158, 186-198.

Patents

- Published Application: 20090187046

- Published Application: 20120101283
- Issued: 8,067,632 (USA)

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