

Profectus NF- κ B Inhibitors

- Unique Small Molecule Inhibitors for Canonical and Non-canonical Paths
- Under Pre-clinical Development to Treat Cancer and Inflammation

Summary

Activation of the NF- κ B pathway mediates a broad spectrum of diseases including cancer, inflammation and viral infections. Profectus has discovered several series of small molecule inhibitors that directly inhibit the binding of NF- κ B components, p65 (RelA), RelB and c-Rel to DNA. As a result, our proprietary compounds can block both the canonical and the non-canonical paths of NF- κ B. The dual inhibition is distinct from I κ B β kinase inhibitors that affect only the canonical path. We have demonstrated the efficacy of the PBS compounds in animal models of multiple myeloma and rheumatoid arthritis. We are seeking drug development partners to unlock the potential of our NF- κ B inhibitors as cancer chemotherapeutics, anti-inflammatory agents and treatments for viral diseases.

Background

NF- κ B (nuclear factor κ -light-chain-enhancer of activated B cells) is a family of transcription factors that consists of hetero- or homo-dimers of p65 (RelA), c-Rel, RelB, p50 (NF- κ B1), and p52 (NF- κ B2). In the classical, or canonical pathway of NF- κ B, stimulation of a variety of cell membrane receptors leads to phosphorylation, ubiquitination, and proteasomal degradation of the I κ Bs (inhibitor proteins), which results in the nuclear translocation of the p65/50 hetero-dimer that turns on transcription. The canonical path can be effectively blocked by inhibition of I κ B β kinase, 26S proteasome, or p65 binding to DNA. The alternative, or non-canonical path, is regulated through proteolysis of the inhibitory ankyrin containing protein NF- κ B2/p100 to release p52, which typically dimerizes with RelB. In addition, there is a “hybrid” path that activates p52/c-Rel and p52/p65. The non-canonical or “hybrid” paths are not susceptible to I κ B β kinase or proteasomal inhibitors. These paths are most effectively inhibited by antagonizing RelB or c-Rel binding to DNA. The canonical and non-canonical paths are associated with different aspects of specific diseases through activations of distinctive groups of genes. Thus, selective inhibition of either the canonical, or non-canonical pathway, or both, under different disease states,

is believed to be a most effective approach to ameliorate the underlying disease conditions.

Profectus Approach

Profectus focuses on targeting a “down-stream” event of NF- κ B activation, - preventing p65, RelB and c-Rel from binding to DNA enhancer sequences and activating transcription. This approach makes it possible to modulate both canonical and non-canonical pathways, either together or separately with different compounds. In addition, our “down-stream” NF- κ B inhibitors may avoid the side effects observed for many “up-stream” NF- κ B inhibitors. We have established a drug screening paradigm to identify novel and proprietary NF- κ B inhibitors of the Rel family. Profectus has taken three parallel approaches to identify suitable lead molecules: (1) an *in-silico* screen of 5,000,000 compounds using the crystal structure of p65, (2) a broad high-throughput screen of a diversified compound library using a cell based screen, and (3) modification to improve existing inhibitors of p65.

We have filed several composition-of-matter patent applications to cover our proprietary small molecule NF- κ B inhibitors. In comparison to known p65 antagonists, e.g. the natural product pathenolide and the synthetic molecule, dehydroxymethylepoxyquinomicin (DHMEQ), our compounds, e.g. PBS-1086, display a significant improvement in potency against p65 (RelA) (Fig. 1).

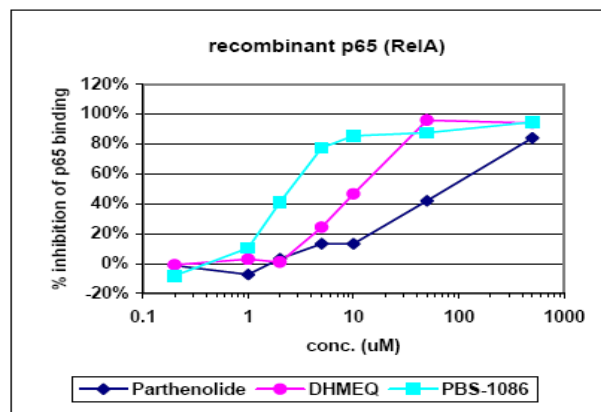


Fig. 1 PBS-1086 inhibits p65 (RelA) binding to DNA in the canonical pathway more potently than DHMEQ and parthenolide. In addition, unlike DHMEQ or pathenolide, Profectus

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compounds have been discovered to also inhibit RelB (Fig. 2) and *c*-Rel (data not shown). Thus, we have dual inhibitors of canonical and non-canonical paths, as well as sole inhibitors.

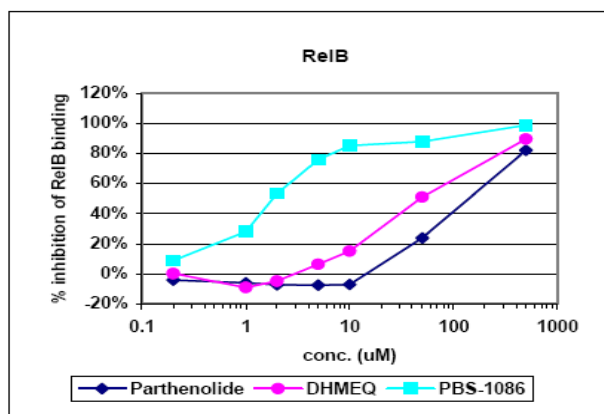


Fig. 2 PBS-1086 inhibits RelB binding to DNA in the non-canonical pathway, while DHMEQ and parthenolide do not.

To our knowledge, Profectus' NF- κ B program is unique in targeting both the canonical and non-canonical pathways.

Pre-clinical Data

In a series of *in vitro* experiments, Profectus NF- κ B inhibitors prevented cytokine releases and the growth of a broad spectrum of cancer cell lines. These compounds did not inhibit cytochrome P450's activities or block hERG channel. Several compounds have been assessed for efficacy studies in rodent disease models.

We first sought to obtain *in vivo* efficacy of Profectus NF- κ B inhibitors in multiple myeloma which has high incidence of constitutive activation of both the canonical and non-canonical pathways. In a xenograft model of human RPMI8226 multiple myeloma, PBS-1086 attained the same level of tumor growth reduction as PS-341 (bortezomib, Velcade®), which is approved as a first line therapy for this indication (Fig. 3). In addition, PBS-1086 was better tolerated than PS-341.

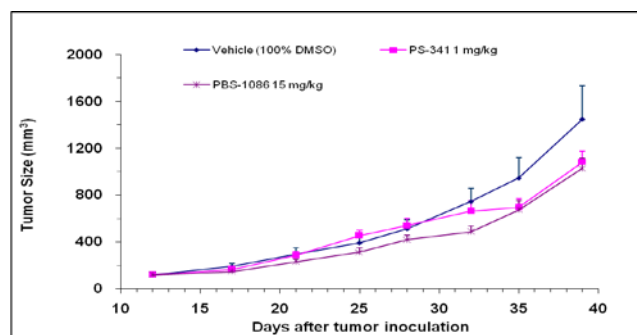


Fig. 3 PBS-1086 reduced RPMI8226 tumor growth as bortezomib in xenograft mice

After confirming the *in vitro* anti-inflammatory activities of Profectus NF- κ B inhibitors, which inhibit *c*-Rel, we sought to attain *in vivo* efficacy of our compounds in rheumatoid arthritis, where *c*-Rel is known to be a risk factor. In a mouse model of collagen-induced arthritis, PBS-1086 treatment significantly slowed the progression and reduced the magnitude of inflammatory damage to mouse hind paw joints to the same level as etanercept (Enbrel®) treatment achieved (Fig. 4). Etanercept belongs to a family of tumor necrosis factor α antagonists, approved for rheumatoid arthritis and colitis indications, that inhibits the NF- κ B pathway.

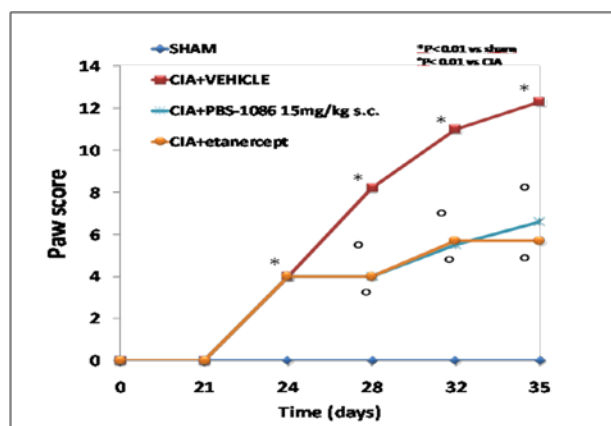


Fig. 4 PBS-1086 exhibited anti-inflammatory efficacy as etanercept in a mouse model of rheumatoid arthritis

In parallel, Profectus NF- κ B inhibitors are being tested as anti-inflammatory agents in animal models of colitis, as a radiosensitizer for irradiation treatment of solid tumors, as chemotherapeutic agents either alone or in combination with various approved cancer drugs. Both dual inhibitors for the canonical and non-canonical paths and sole inhibitors for the canonical path are being characterized.

Broad Market Indications

The activation of NF- κ B has been implicated in a large number of human diseases. Among these are cancer, arthritis, inflammatory bowel disease, AIDS, atherosclerosis, heart disease, asthma, catabolic disorders, type 1 and 2 diabetes, aging, skin diseases, renal diseases, gut diseases, pancreatitis, neuropathological diseases, pulmonary diseases, chronic obstructive pulmonary disease, sepsis and sleep apnoea. We have selected a lead series for further development. One lead from this series is undergoing a rapid optimization program to achieve maximal efficacy and optimize the pharmacokinetic and toxicity profiles.

Profectus is seeking partners to develop the lead drug candidates through IND-enabling studies and clinical development for the key indications.

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