Griseofulvin Analogues for Treatment of Cancer by Inhibition of Centrosomal Clustering (P-770 & P-844)

Key Facts
- Drug Candidate which Selectively Targets Cancer Cells only
- Mode of Action: Induction of Mitotic Catastrophe/ Apoptosis due to Inhibition of Centrosomal Clustering
- Possible Treatment of Several Cancer Types
- Analogue of Natural Compound Griseofulvin, Preliminary Hit to Lead Optimized

Background
Classical anti-cancer drugs use proliferation/cell division as a target, thereby killing all dividing cells without differentiating between cells belonging to the tumor that should be targeted and normal tissues. This lack of specificity causes most of the well-known and unavoidable side effects of classical chemotherapeutic agents.

Supernumerary centrosomes do almost exclusively occur in a wide variety of neoplastic disorders but not in non-transformed cells and lead to the formation of multipolar mitotic spindles and chromosome segregation defects. Many tumor cells regain mitotic stability after clonal selection by the coalescence of multiple centrosomes into two functional spindle poles. Therefore, inhibition of centrosomal clustering with consequential induction of multipolar spindles and subsequent cell death would specifically target tumor cells with no impact on normal cells with a regular centrosome content. To identify cell-permeable small molecules that inhibit centrosomal clustering in cells with supernumerary centrosomes, we developed a cell-based screening strategy founded on the visualization of microtubules and chromatin.

We screened a fungal extract library for compounds inhibiting centrosomal clustering. Fungal extracts were selected based on a chemotaxonomic screening approach, in order to increase the chemodiversity to be tested. An initial screening effort using extracts from different *Penicillium* species led to the identification of Griseofulvin, which induces multipolar mitotic spindles by inhibition of centrosome coalescence and subsequent cell death via mitotic catastrophe/apoptosis in several different tumor cell lines but not in normal cells with a regular centrosome content.

The Technology
The German Cancer Research Center (DKFZ) together with Technical University of Denmark (DTU) developed an analogue of Griseofulvin as a compound for cancer treatment, which selectively targets cancer cells only. Griseofulvin is a natural antibiotic produced by *Penicillium griseofulvum* as well as other microfungi and is still commonly used in humans for the treatment of dermatomycoses of skin, hair, and nails caused by *Microsporum*, *Trichophyton*, and *Epidermophyton*. The inhibiting function for cancer has been previously disclosed (WO 97/05870), but restricted to the natural product Griseofulvin only. The inhibiting effect of Griseofulvin is however not potent enough in doses necessary for cancer treatment in humans. Therefore, further hit to lead development of the natural compound was achieved by medicinal chemistry with corresponding biological activity tests. Basically, all human malignancies are potential targets for centrosomal cluster inhibitors (with griseofulvin analogues being first in class compounds) since almost all malignant neoplasias examined to date harbour centrosome aberrations.
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Advantages
• drug which selectively targets cancer cells only with little effect on normal tissues
• possible treatment of several cancer types
• analogue of natural compound (griseofulvin, orally available, almost no side effects in humans), thoroughly studied in biological tests

Commercial Opportunity
Development of a new drug against several cancer types inhibiting centrosomal clustering. In addition suitable for research applications as a centrosomal cluster inhibitor in-vitro and animal systems.

Development Stage
Hit to lead optimization. Activity of Derivatives tested in vitro and in animal studies.

Inventors
The invention was jointly conceived by Prof. Dr. Alwin Krämer and Ms. Blanca Rebacz of DKFZ and Dr. Thomas Ostenfeld Larsen and Dr. Mads Hartvig Clausen of Technical University of Denmark.

Intellectual Property
A first patent family was filed and published under WO 2009/000937. Subsequently a second patent application was filed December 22, 2008 based on new MedChem optimization findings with the number EP 08 172 542.6, which PCT equivalent was published as WO 2010/072770.

Reference:

http://pubs.acs.org/doi/pdf/10.1021/jm200835c

http://cancerres.aacrjournals.org/content/early/2012/08/30/0008-5472.CAN-12-2026.full.pdf

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Figure 1: Griseofulvin

Figure 2: Bipolar mitotic spindle with multiple centrosomes clustered at the spindle poles (left) and multipolar mitotic spindle after treatment with griseofulvin analogue (right).

Figure 3: Concentration-dependent induction of multipolar mitotic spindles by griseofulvin in multiple tumor cells lines but not in normal human cells (fibroblasts [BJ], keratinocytes [NHEK]).