Natural product avrainvillamide and its analogs as targeted anticancer agents

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Technology description

MARKETS ADDRESSED:
In vitro and in vivo validation:
In the NCI 60 cancer cell assay, an avrainvillamide analog has exhibited specific growth inhibition at near nanomolar levels against myeloma, and hence supports a likely biomarker strategy aimed at patient pre-selection. Avrainvillamide and this analog were advanced into colorectal cancer xenograft studies. Pharmacokinetics and maximum dose tolerability studies are in progress to prepare for pre-clinical testing in animal models.
First-in-class targeted agents with nanomolar GI50 in many cell lines
Compounds validated by NCI 60 cancer cell assay and mouse xenograft model
Novel cancer target that is overexpressed in multiple cancers; modulates p53 and c-Myc
May be opportunity to develop patient preselection biomarker strategy
Total synthesis of avrainvillamide and simplified analogs with SAR data

Avrainvillamide and analogs: First-in-class nucleophosmin inhibitors:
Using avrainvillamide as a lead structure, the Myers group has successfully synthesized ~130 avrainvillamide analogs with simplified structures, and some achieve comparable potency to the parent molecule. Through the support of the Harvard Accelerator Fund, the Myers group has made considerable progress on the optimization of the synthesis and scale-up production of the compounds. Our chemists have generated structure activity relationship (SAR) data that will be invaluable for the design of potential drug leads. Computer models of avrainvillamide-nucleophosmin interaction have also been used to fine-tune the design of the analogs.

Nucleophosmin: Novel and selective oncology target:
The Myers group has shown that avrainvillamide interacts directly with the pro-oncogenic protein nucleophosmin (NPM) in cancer cells. Nucleophosmin is a nucleolar phosphoprotein that shuttles between the nucleus and cytoplasm, and has a critical role in cell proliferation and cell death. NPM expression is tightly regulated during cell proliferation and is overexpressed in several types of cancer. It is implicated in the regulation of the tumor suppressors ARF and p53, and most recently, the proto-oncogene c-Myc. Overexpression of NPM dramatically stimulates c-Myc-induced hyperproliferation

and oncogenic activities (PNAS 2008, 105, 18794-18799). NPM is also a major regulator of ribosome biogenesis. Upon growth factor stimulation, NPM forms a protein complex with the serine/threonine protein kinase Akt, together they regulate cell cycle progression and cell survival (PNAS 2008, 105, 16584-16589).

Because nucleophosmin is overexpressed in tumor cells, compounds which exert their function predominantly by binding to nucleophosmin have the potential to be selective anticancer agents by inhibiting tumor growth without harming healthy tissue. In assays developed in the Myers' laboratory, avrainvillamide has shown a 10-fold selective toxicity against human melanoma cells over non-cancerous fibroblast cells from the same donor.

Advantages

INNOVATIONS & ADVANTAGES:
Organic chemists at Harvard University led by Prof. Andrew Myers have a longstanding interest in the synthesis of structurally and biologically interesting anticancer agents of natural origin. The Myers' laboratory has pioneered the total synthesis of the antiproliferative agent avrainvillamide, a compound originally isolated in trace quantities from marine fungi.

Institution

Harvard University

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com