Small Molecule Anti-cancer Agents that Stabilize the MYC-G-Quadruplex

Summary (1024-character limit)

The proto-oncogene c-Myc is deregulated and overexpressed in ~70% of all cancers. Thus, c-Myc is an attractive therapeutic target. Beyond cancer, Myc is also a positive effector of tissue inflammation, and its function has been implicated in the pathophysiology of heart failure. Researchers at the National Cancer Institute (NCI) developed novel small molecules that target c-Myc at the transcriptional level, thus enabling a potential pan-cancer therapeutic. Specifically, these compounds stabilize the transcription repressing quadruplex in the c-Myc gene promoter region. The National Cancer Institute seeks parties interested in licensing or collaborative research to co-develop these therapeutic targets.'

NIH Reference Number

E-053-2015

Product Type

- Therapeutics

Keywords

- c-Myc, G-Quadruplex (G4), Multiple Myeloma, Schneekloth

Collaboration Opportunity

This invention is available for licensing and co-development.

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Description of Technology

The proto-oncogene c-Myc is deregulated and overexpressed in ~70% of all cancers. Thus, c-Myc is an attractive therapeutic target since disrupting c-Myc activity could be used as pan-chemotherapy. Beyond cancer, Myc is also a positive effector of tissue inflammation, and its function has been implicated in the pathophysiology of heart failure. Because c-Myc is a transcription factor, a rationally designed small molecule targeting c-Myc would be required to exhibit significant specificity. Unfortunatly, several physical characteristics of Myc make it a very difficult protein to target and, to date, there are no approved drugs targeting c-Myc.

The invention is directed to small molecules that stabilize the transcription repressing quadruplex in the

c-Myc gene promoter region. Invention compounds target c-Myc at the transcriptional level are shown to inhibit c-Myc expression. Invention compounds are effective in selective killing in a variety of c-Myc driven cancer cell lines, including leukemia, non-small-cell lung cancer, colon, central nervous system, melanoma, ovarian, renal prostate and breast. Minimal unwanted activity is observed in peripheral blood mononucleocytes or cancer cell lines that resist inhibition of c-Myc protein expression.

Current efforts are focused on developing more potent molecules with improved ability to decrease c-Myc expression and superior bioavailability. Through synthesis of a focused library of analogs, we have identified inhibitors with improved Kd values for the quadruplex, improved toxicity towards c-Myc-driven cancer cells, and improved efficacy for decreasing c-Myc expression. By solving an NMR structure of the quadruplex in complex with the small molecule, we have begun to establish a molecular basis for selectivity observed in cell-based and biophysical assays and are working to use this information to design improved inhibitors. Additionally, we show that one compound of interest is orally bioavailable, albeit with a Cmax in oral dosing slightly below the concentration required for oral efficacy.

This technology is available for licensing and co-development to qualified entities.

Potential Commercial Applications

- Therapeutic for multiple myeloma, carcinoma of the cervix, colon, breast, lung and stomach
- Tissue Inflammation

Competitive Advantages

- First in class drug since no c-Myc drugs have been approved for any cancer indication
- Drug-like in nature, satisfying all of Lipinski's rule of five parameters
- Orally bioavailable
- Decreasing c-Myc expression without affecting expression from other quadruplex-driven genes
- Compound has significant potential for improvement with very minor structural alternations
- The methodologies used by the lab have explored the biological potential of c-Myc G-quadruplex-stabilizing agents to a degree of complexity greater than what has ever been done before.

Inventor(s)

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Development Stage

- Discovery (Lead Identification)

Publications

Kenneth M. Felsenstein et al. [PMID 26462961]

Patent Status

- **Foreign Filed:** Foreign Filed - Patent Application PCT/US2016/012222, Filed 05 Jan 2016

Therapeutic Area

- Cancer/Neoplasm