

SYNTHETIC LIPOPEPTIDE INHIBITORS OF RAS ONCOPROTEINS

SUMMARY

It is well known that overactive Ras signaling is linked to many forms of cancer, and despite intensive efforts worldwide to develop effective inhibitors of Ras, to date there is no anti-Ras inhibitor in clinical use. Researchers at the NCI's Cancer and Inflammation Program, in collaboration with scientists at Vanderbilt University and the University of Illinois in Chicago, have identified a number of small peptidomimetic compounds that bind to Ras proteins with nanomolar affinity. NCI's Cancer and Inflammation Program seeks partners interested in licensing or co-development of synthetic, highly potent cell-permeable inhibitors of Ras that bind to the protein directly.

REFERENCE NUMBER

E-293-2010

PRODUCT TYPE

- Therapeutics

KEYWORDS

- colon
- lung
- multiple myeloma
- pancreatic cancer
- thyroid cancer
- Ras

COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

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DESCRIPTION OF TECHNOLOGY

It is well known that overactive Ras signaling is linked to many forms of cancer, and despite intensive efforts worldwide to develop effective inhibitors of Ras, to date there is no anti-Ras inhibitor in clinical use.

Researchers at the NCI's [Cancer and Inflammation Program](#), in collaboration with scientists at Vanderbilt University and the University of Illinois in Chicago, have identified a number of small peptidomimetic compounds that bind to Ras proteins with nanomolar affinity. The development of compounds was based on two previously unknown mechanisms of Ras regulation uncovered due collaborative efforts of the three groups. The researchers have found that hypervariable regions (HVR) of some isoforms of Ras proteins function as negative regulators of Ras activity. Rational design lead to generation of metabolically stable cell-permeable analogs of HVRs with much improved binding affinity and anti-tumor activity. The second class of inhibitory compounds targets Ras dimerization interface. Compounds inhibit RAS-dependent growth of cancer cells at low nanomolar and subnanomolar concentrations.

In vitro data indicate that the inhibitors are effective at inhibiting growth in a number of cancer cell lines including lung cancer. In addition, *in vivo* data indicate that the inhibitors are effective at inhibiting tumor growth in mouse xenograft models.

The inventors are interested in collaborations to help optimize PK/PD properties of Ras inhibitors and conduct preclinical *in vivo* studies.

POTENTIAL COMMERCIAL APPLICATIONS

- Novel cancer therapeutic (prostate cancer, colon cancer, pancreatic cancer, ovarian cancer, lung cancer, breast cancer, thyroid cancer, leukemia, bladder cancer, salivary gland cancer, melanoma, myeloid malignancy, or germ cell tumors)

COMPETITIVE ADVANTAGES

- Synthetic compounds binding to Ras proteins with high affinity
- Cell permeable peptidomimetics
- Membrane-anchored inhibitors

INVENTOR(S)

- [Nadya I. Tarasova, Ph.D.](#) (NCI)

DEVELOPMENT STAGE

- Pre-clinical (in vivo)

PUBLICATIONS

Jang, H., et al. [[PMID: 25713064](#)]

PATENT STATUS

- **U.S. Issued:** US Patent 9,328,142
- **U.S. Filed:** Application # 15/015,940 filed February 4, 2016

THERAPEUTIC AREA

- Cancer/Neoplasm