NOVEL VEGF-ACTIVATED DEATH RECEPTOR LIGANDs

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INVENTION NOVELTY

This invention comprises novel recombinant fusion protein therapeutics for the treatment of cancer that combines VEGF inhibition with death receptor activation.

VALUE PROPOSITION

Two current approaches to targeted cancer drug development are VEGF inhibition and activation of pro-apoptotic death receptors such as Fas. The VEGF antibody bevacizumab is approved for the treatment of advanced colon, lung, renal and glioblastoma cancers, yet its clinical benefit has proven to be modest. Recombinant trimeric soluble death receptor ligands are in early clinical trials, but to date have only shown limited activity. This low activity derives in part from the fact that soluble ligand does not efficiently aggregate its receptors, which is required in triggering apoptosis. By fusing the VEGF binding domain of VEGFR1 with the trimerization and death receptor-binding domain such as FasL, these novel therapeutics are able to exploit elevated VEGF levels found in the tumor microenvironment in order to initiate death receptor-mediated apoptosis.

This novel invention provides the following advantages:

- **Specifically targets tumor cells** and kills them via their own VEGF
- Demonstrates ***in vitro* efficacy** against multiple cancer cell types
- Has a **validated mechanism of action**
- *In vivo* efficacy with **no initial indication of toxicity**

TECHNOLOGY DESCRIPTION

UCSF investigators have generated R1FasL (as well as other death receptor ligand) fusion proteins that are composed of the VEGF-binding domain of human VEGFR1 fused to the trimerization and receptor-binding domains of human FasL. In vitro studies demonstrated that these fusion proteins induced apoptosis in a variety of human renal, breast, glioblastoma and prostate cancer cell lines. This activity required the presence of VEGF, and was inhibited when VEGF was sequestered. Glioblastoma xenograft mouse studies revealed a significant tumor size reduction and extended survival in R1FasL injected animals. R1FasL induced

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OTHER INFORMATION

KEYWORDS

fusion protein cancer therapeutic, VEGF, death receptor, glioblastoma

CATEGORIZED AS

- Medical
- Disease: Cancer
- Therapeutics

RELATED CASES

2006-007-0

apoptosis is restricted to the tumor, and is not present in the normal CNS. Furthermore, R1FasL showed no apparent toxicity in mice after intratumoral delivery. Studies to examine R1FasL's effect after intravenous delivery are currently ongoing.

APPLICATIONS

- Development of novel therapeutics to treat renal cell, breast, glioblastoma and prostate cancers
- Development of novel therapeutics for other indications with unregulated angiogenesis such as rheumatoid arthritis, macular degeneration, and psoriasis

STATE OF DEVELOPMENT

Preclinical

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,056,102	06/16/2015	2006-007
United States Of America	Issued Patent	8,324,169	12/04/2012	2006-007

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