Oligomerization improves endostatin as antiangiogenic and anticancer drug (P-1000)

Key facts

- Endostatin is well known and therefore approved in clinical trials
- Established endostatin has as monomer poor efficacy
- oligomerization of endostatin improves pharmacokinetics

Background

Endostatin is an antiangiogenic protein first discovered in Folkman's laboratory at Childrens Hospital, Harvard Medical School, and Boston. The antitumor properties of this protein are well established. However, the amount of protein required for injection in patients was beyond production feasibility due to the poor pharmacokinetics of endostatin monomer.

We have shown that the problem of poor pharmacokinetics can be solved by using the Fc domain of IgG being conjugated to endostatin, a component of all monoclonal antibodies approved for patients with a number of diseases including cancer. As a result of employing Fc-endostatin, the half-life in mice was increased to 2 weeks instead of 2 hours for endostatin alone, consistent with pharmacokinetics of monoclonal antibodies.

The Technology

We identified a novel molecule, NC1 rather than monomeric endostatin to be the key physiologic molecule exerting antiangiogenic effects. We further provide rational that synthetic dimerization of endostatin via fc-conjugation not only improve its pharmacokinetics and therefore the biologic efficacy but also better mimics the effects of the natural trimeric NC1 as compared to monomeric "conventional" endostatin.

We demonstrated that oligomerization of endostatin as observed in NC1 is important for its binding to a large number of extracellular matrix proteins including Fibronectin and cytokines such as VEGF, which are important ligands for exertion of an antiangiogenic property.

Development Stage

A clinical trial based on Fc-NC1 or Fc-endostatin will be carried out in order to enable us to evaluate the efficacy of antiangiogenic endostatin.

Advantages and Commercial Opportunity

Established endostatin resulted in poor efficacy in clinical trials. In contrast, oligomerization of endostatin toward the natural fragment of collagen 18 (NC1) can improve both, pharmacokinetic as well as the spectrum of targeting molecules for a broader use of endostatin as antiangiogenic and anticancer drug.

Inventors

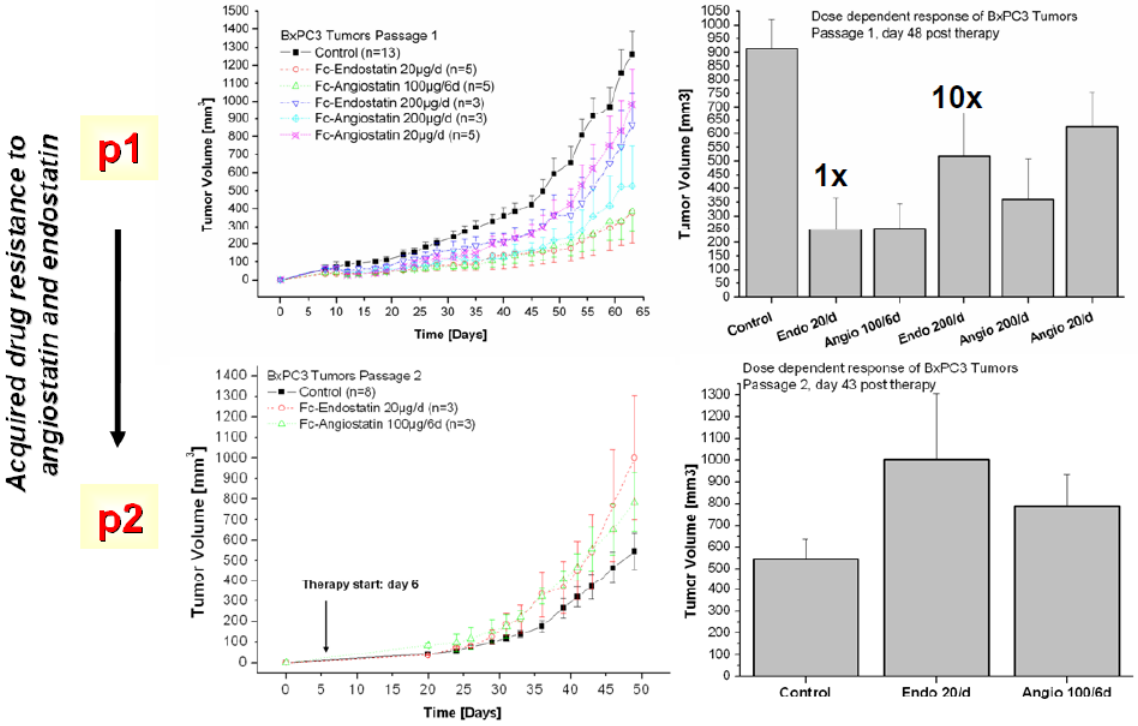
The invention was jointly conceived by Amir Abdollahi of German Cancer Research Center Heidelberg (DKFZ) as well as Kashi Javaherian (USA) and Tong-Young Lee (Taiwan).

Intellectual Property

Priority patent application EP2561888 and subsequently PCT application published as WO 2013026913.

DKFZ Contact:
Dr. Frieder Kern
Deutsches Krebsforschungszentrum
Office of Technology Transfer T010
Email: f.kern@dkfz.de
Tel.: +49-(0)6221-42-2952
Fax: +49-(0)6221-42-2956

Determining the optimum dose and therapy schedule



Acquired drug resistance to endogenous angiogenesis inhibitors: angiostatin and endostatin