# TGF-β biologic targeted therapy for oncology, cardiovascular disease and nephrology indications (L-11817 and L-12074)

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## Technology description

The TGF-β super family is one of the most complex groups of cytokines with widespread effects on many aspects of growth and development. TGF-β signaling has been shown to control a range of cellular responses and has therefore been implicated in a number of diseases, including cancer, kidney disease and cardiovascular disease. The activated TGF-β signaling pathway is an emerging and attractive target but as yet unexploited for therapy in these diseases. The technology is a single-chain multivalent ligand trap that is able to offer the affinity and specificity of a monoclonal antibody, coupled with the size and ease of handling of a small molecule. It has the potential to be developed as a platform technology for all growth factors that are implicated in a variety of diseases. A TGF-β ligand trap has been developed which can be used in a number of conditions including breast and prostate cancer and glioblastoma.

## Description

Receptor-based antagonists that bind and sequester ligands are being tested in a range of cancers as a method to control their respective signaling pathways. The most common antagonists are monoclonal antibodies. However, due to their large molecular size they are less able to access ligands expressed within tumours and target tissues. In addition, they are costly to develop and often cause adverse reactions. Receptor ectodomain-based ligand traps therefore present an alternative approach to molecular targeted therapies. However, these are usually dimerized via an IgG Fc domain or a coiled-coil domain. Both of these have limitation due to their size and potency, respectively. The single-chain multivalent soluble receptor trap aims to overcome these issues and therefore is potent, diffusible, less toxic and inexpensive to produce. Furthermore, due to it being a single-chain protein, it can be more easily engineered thereby reducing development costs and time. No TGF-β signal transduction inhibitors are currently available on the market. Given TGF-βs role in tumour metastasis, the ligand trap is most likely to be used in combination with other therapeutic agents. The single-chain multivalent ligand trap is a TGF-β anatagonist, neutralizing the ligand and preventing it from binding with its receptor, thus disabling the consequential signaling pathway.
Numerous potential indications

TGF-β signaling has been associated with a number of diseases, including cancer, kidney disease and cardiovascular disease. It has been implicated in the metastasis of breast and prostate cancer and glioblastoma.

Validated target

TGF-β has been shown to be overproduced in all human tumours playing a role in promoting invasiveness and metastasis. Furthermore, TGF-β suppresses the immune surveillance of the developing tumour. The current approaches therefore aims to develop a drug whose mechanism of action is to target the TGF-β pathway.

## Application area

•A targeted approach to inhibit TGF-β which has been implicated in a number of diseases indications including breast and prostate cancer, glioblasotoma, kidney fibrosis and cardiovascular disease.
•A therapy to be used in combination with others to reduce metastasis in a range of tumours including breast, prostate and glioblastoma.
•The development of a platform technology to produce single-chain multivalent soluble receptor traps for a range of growth factors implicated in a variety of diseases.

## Advantages

Improved technology

The technology has two main benefits over current technologies that are similar of have similar mode of actions. It has (1) lower molecular mass therefore reducing issues with diffusion to tumour sites and (2) compared to other ligand traps there are no multimerizing moieties. The linkers contain primary natural sequences which should reduce the likelihood of an adverse immunogenic reaction. Furthermore, the technology is based on a single-chain protein that can be more easily engineered and cloned than a monoclonal antibody, thereby potentially reducing the time and cost of development.

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