

## Therapeutics

### Identification and Characterization of Axl Inhibitors as Pharmaceutical Leads

#### Background

The Axl gene encodes for a receptor tyrosine kinase (Ufo or Ark) that is known to possess oncogenic potential. Axl/Gas6 overexpression has been found in a multitude of human cancers including glioblastoma, colon, prostate, melanoma, thyroid, breast and lung carcinomas. In addition Axl influences tumor metastasis formation and is involved in drug resistance. It has been shown that Axl represents a characteristic gene for invasive breast cancer and *in vivo* abrogation of metastasis could be achieved using Axl-siRNA. Furthermore an upregulation of Axl can be observed in drug-resistant leukemia as well as GIST cancer cells resistant to imatinib. Activation of this receptor is also seen in lapatinib-resistant cells.

Taken together these data emphasize that this receptor tyrosine kinase is a highly attractive target for the development of novel therapeutics to treat metastatic cancer.

#### Technology

In a collaborative approach between the Max-Planck Institute for Biochemistry, Vichem Kft. and the Lead Discovery Center (LDC) two small molecule lead series have been identified. Hit to lead optimization was guided by an Axl homology model. The structure-activity relationship of both series is fully understood and the nominated compounds show excellent potency and kinase selectivity. A representative of one lead series, LDC41267, is orally bioavailable and shows good *in vivo* tolerance (no adverse toxic effects, no impact on body weight; BALB/c mice, 30 and 100mg/kg, bidx7d p.o.). LDC41267 affects *in vivo* metastasis formation at high dosage (Figure 1) providing a platform for further lead optimization with derivatisation potential at three different sites of the molecule.

We are looking for interested parties that are willing to enter into collaboration and/or licensing discussions regarding our Axl inhibitor program.

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## Patent Information / Confidential package

Patent applications for both lead series have been filed recently in EP and US.

A confidential data set has been prepared and can be received upon request and signing a CDA.

## Literature

Zhang YX et al., Cancer Res. 2008, 68(6): 1905-15; AXL is a Potential Target for Therapeutic Intervention in Breast Cancer Progression.

Vajkoczy P et al., PNAS April 11, 2006 vol. 103 no.15 5799-5804; Dominant-negative inhibition of the Axl receptor tyrosine kinase suppresses brain tumor cell growth and invasion and prolongs survival.

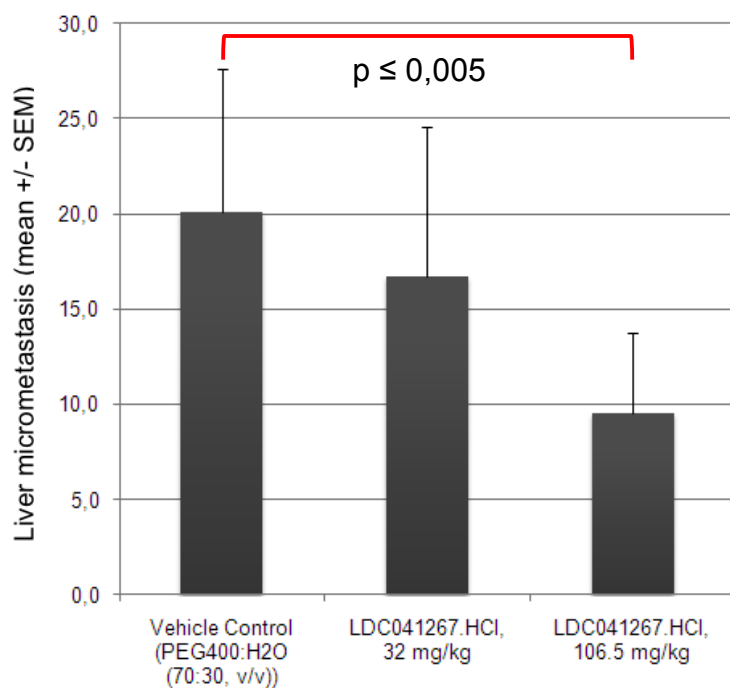


Figure 1: Compound LDC041267 affects *in vivo* metastasis formation in BALB/c mice. Treatment and dosage of LDC041267 was bidx14d p.o. at 30 and 100mg/kg.