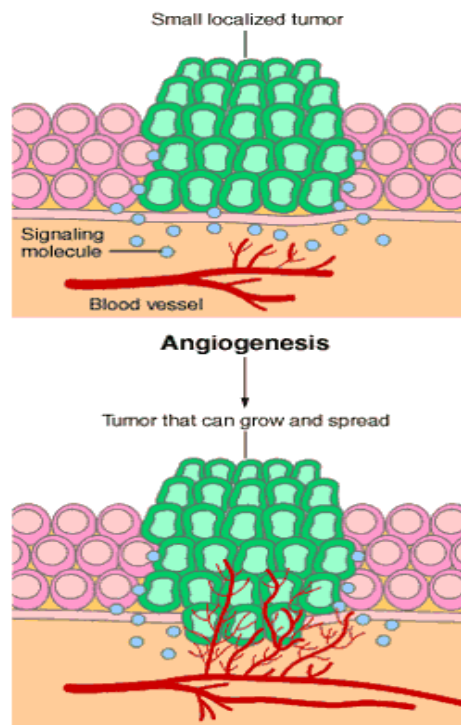


### TARGET RATIONALE

The formation of new blood vessels from preexisting vasculature supports primary tumor growth and coincides with the development of metastasis, and vascular endothelial growth factor receptor 2 (VEGFR2) plays a pivotal role in both processes. As a result, inhibition of this receptor's interaction with vascular endothelial growth factor (VEGF) has been an attractive strategy for fighting cancer. Moreover, VEGFR2 is a clinically validated target, with several inhibitors in late-stage clinical trials or already on the market.



**Fig. 1.** Tumor angiogenesis art work created for the [National Cancer Institute](#) by Jeanne Kelly. © 2000.

### VEGFR2 INHIBITORS DISCOVERED by TRAP®

- Structurally novel VEGFR2 inhibitors were discovered by Telik's proprietary drug discovery technology TRAP®.
- These compounds demonstrated VEGFR2 kinase inhibition *in vitro* at nanomolar concentrations.
- We confirmed the mechanism of action in cell-based secondary assays.
- A selective kinase profile was ascertained.
- Select compounds demonstrated significant tumor-growth inhibition after oral administration to nude mice bearing HCT-116 human colon carcinoma xenografts.

### ACTIVITY PROFILE

#### *In Vitro* Activity

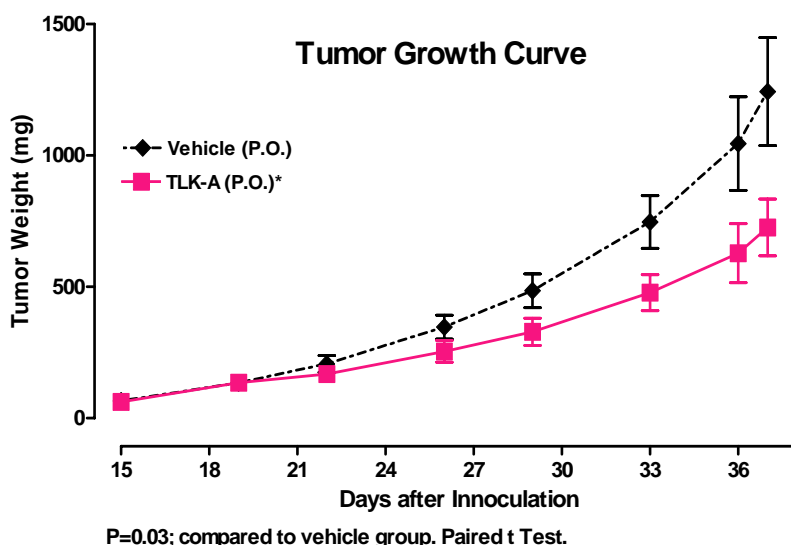
TRAP® screening identified several structurally novel inhibitors of VEGFR2 kinase with  $IC_{50}$  between 0.3 and 7  $\mu$ M *in vitro*. Medicinal chemistry optimization of these hits provided compounds with  $IC_{50}$  lower than 10 nM, and a kinase selectivity panel showed these compounds to be potent inhibitors of Ret kinase as well.

**Cellular Activity**

Compounds inhibited VEGF-induced phosphorylation of VEGFR2 in HUVEC cells and VEGF-dependent proliferation of these cells, both at nanomolar concentrations.

**In Vivo Activity**

Compounds inhibited tumor growth by more than 40% without loss of overall body weight when administered orally (200 mg/kg, q.d. x 13) to athymic nude mice bearing an HCT-116 human colon carcinoma xenograft (Fig. 2).



*Fig. 2. In vivo activity of a representative compound in the mouse HCT-116 xenograft model*

**CONTACT INFORMATION**

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