

Inhibition of VEGF signaling

Disrupting the process of angiogenesis

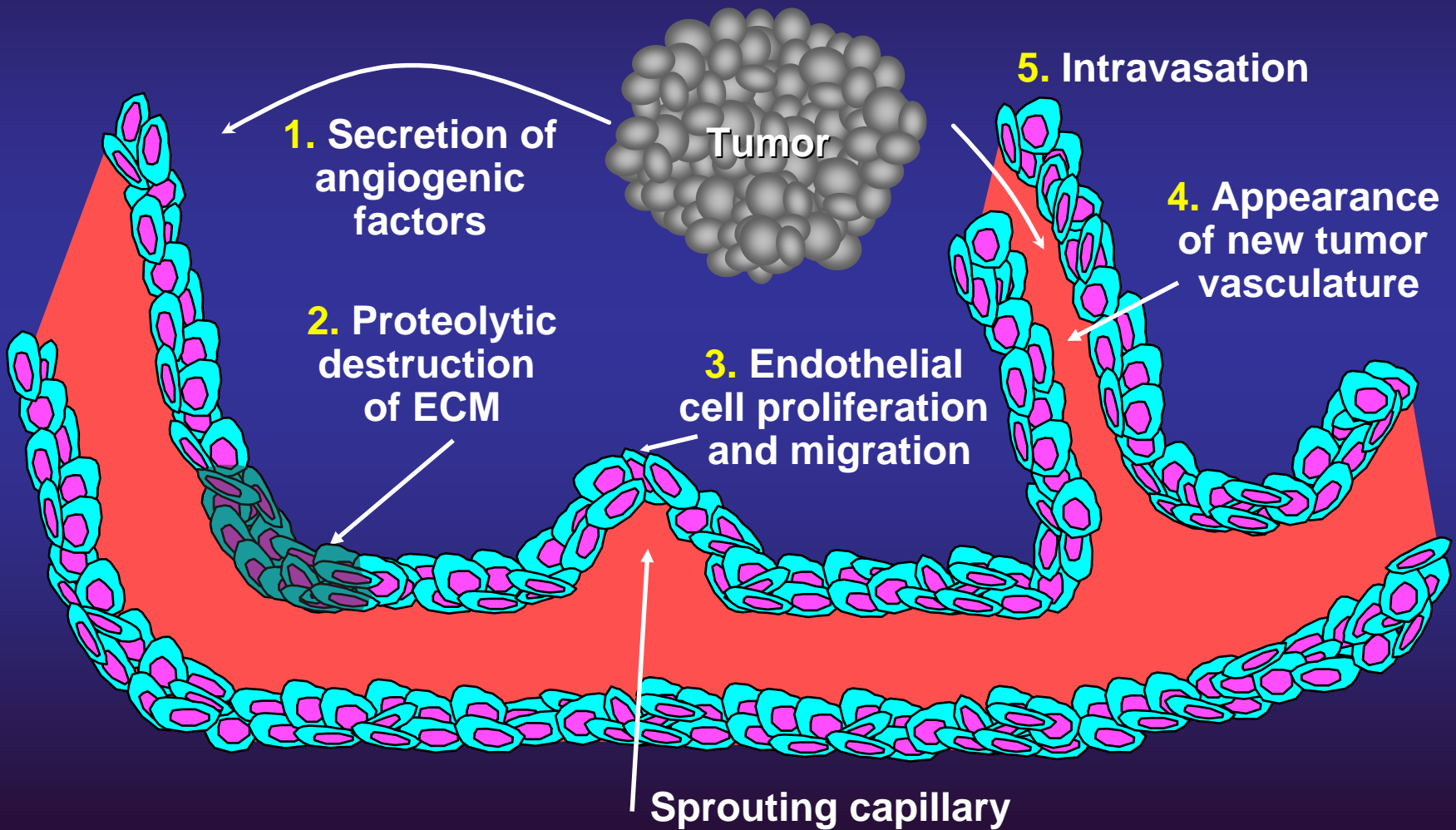


Putting progress into practice

Angiogenesis

- **Angiogenesis is the formation of new blood vessels from pre-existing vasculature**
- **Angiogenesis is highly dependent on the VEGF signaling pathway**
 - **VEGFR-2 is the most important VEGF signaling pathway for angiogenesis**
- **VEGF is frequently overexpressed in cancer and is associated with poor prognosis**
- **Without a blood supply, tumors do not grow larger than 1–2mm**
- **As tumors grow they become hypoxic, which leads to the up-regulation of angiogenic factors such as VEGF**
 - **Stimulates the production of new vasculature**

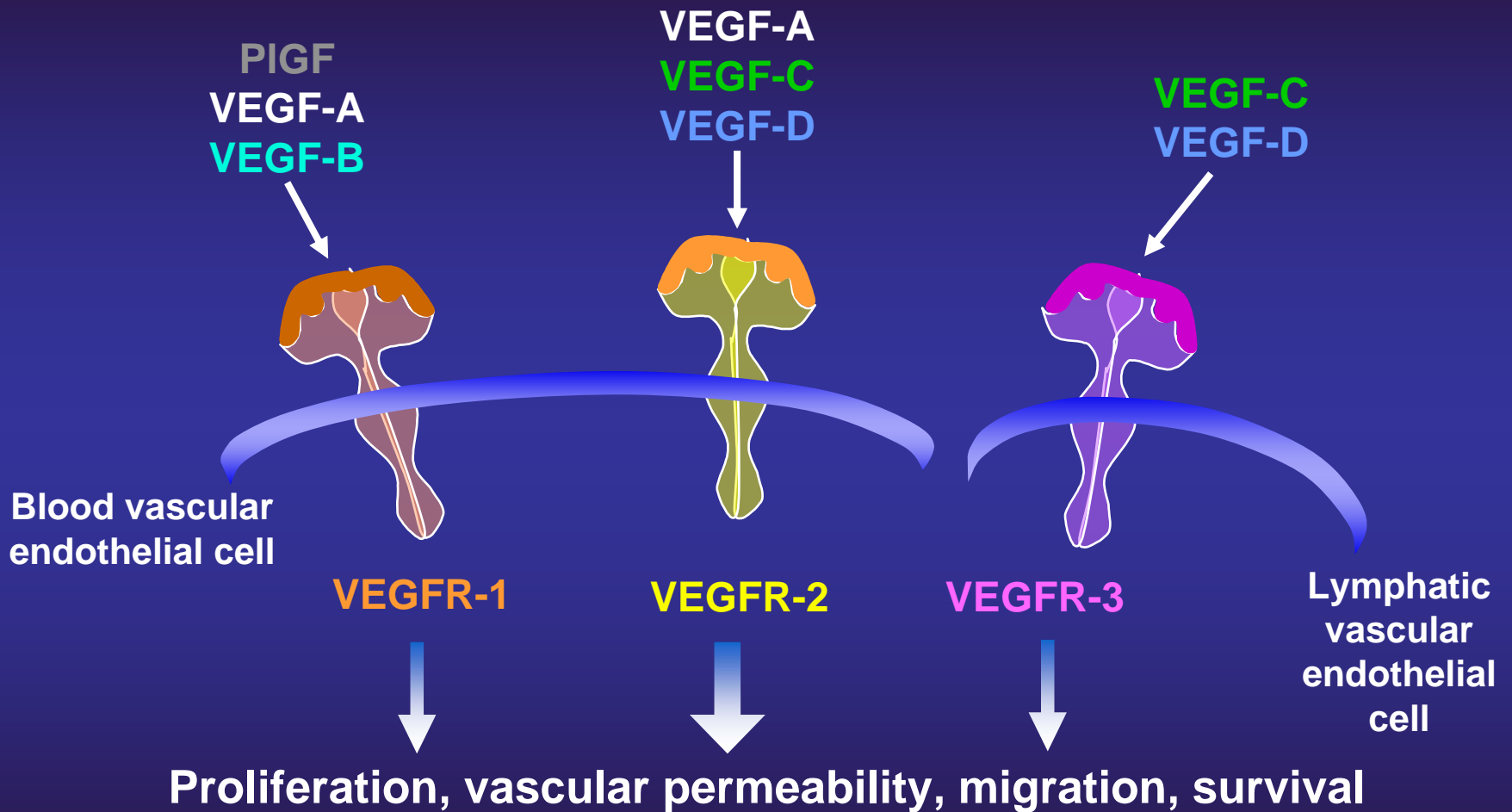
Tumor angiogenesis



Summary of VEGF function

- **VEGF is a key angiogenic regulator directly implicated in**
 - endothelial cell proliferation
 - endothelial cell migration
 - endothelial cell protease expression
 - endothelial cell adhesion
 - capillary tube formation
 - vessel maturation/pericyte recruitment
- **It also acts as**
 - a survival factor for newly formed vasculature
 - **Vascular Permeability Factor**

Activation of VEGF receptor signaling



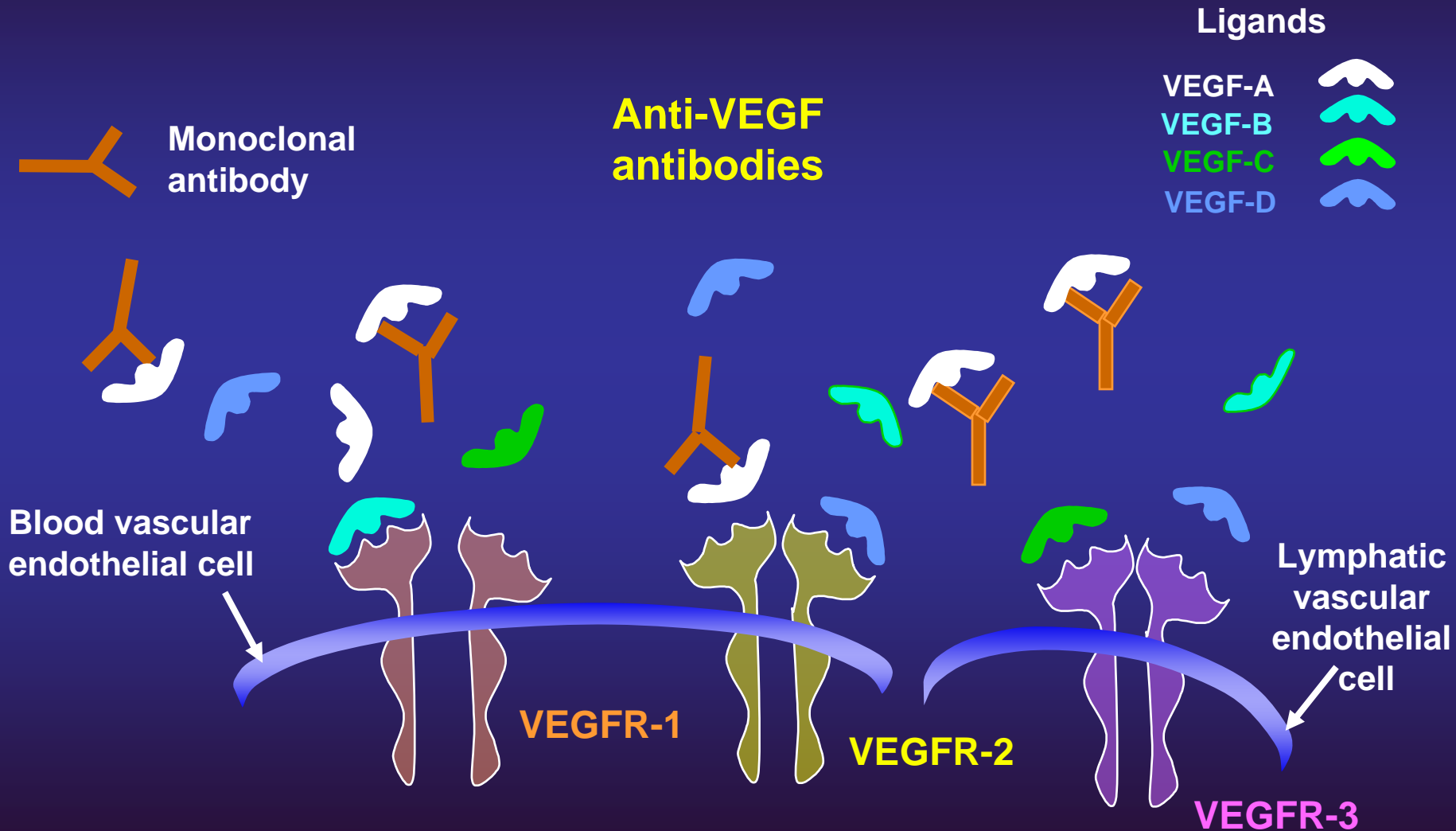
PIGF, placental growth factor

VEGFR, vascular endothelial growth factor receptor

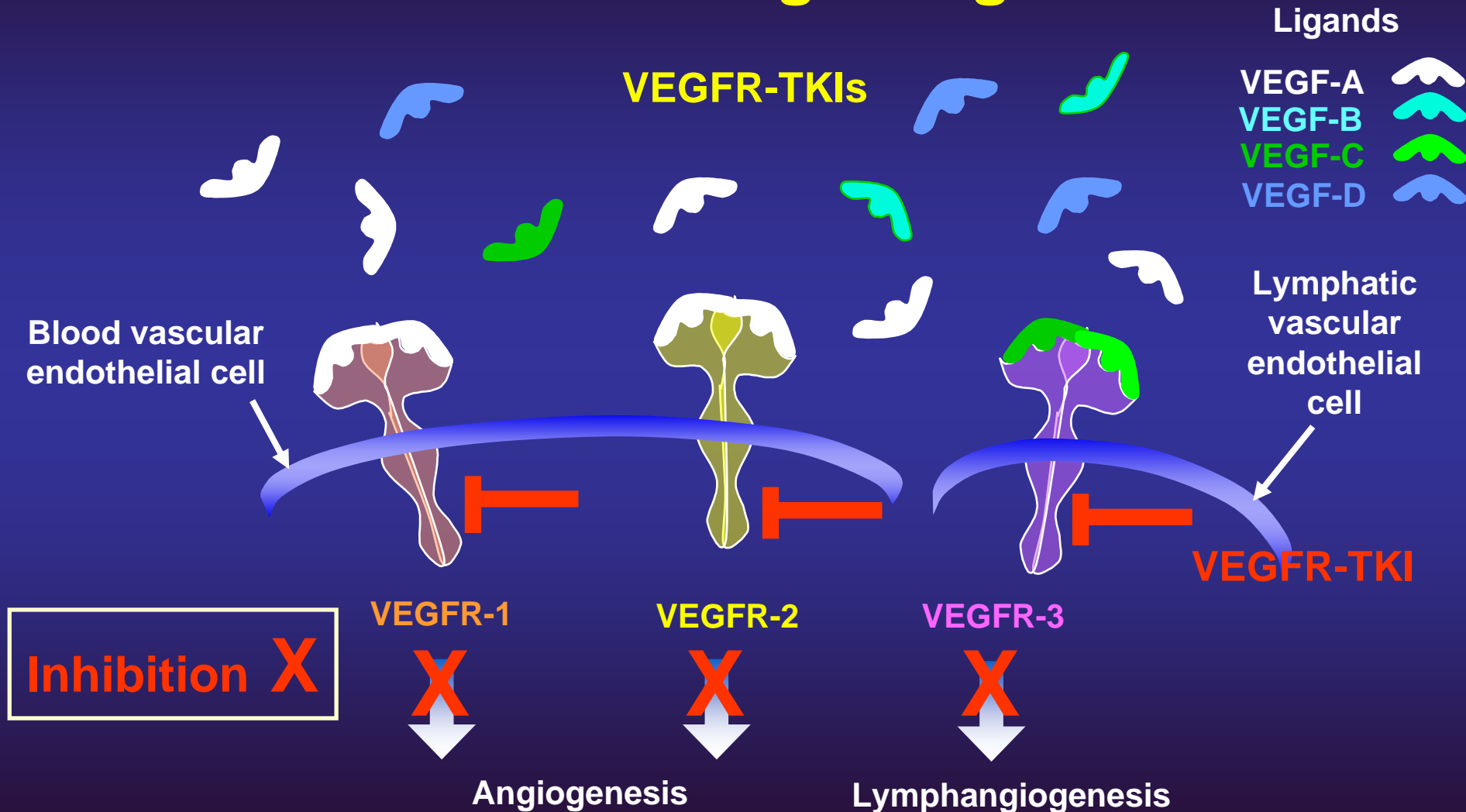
Inhibition of VEGF signaling

- **Inhibiting VEGF signaling**
 - inhibits growth of new tumor vessels
 - decreases vascular density, diameter and permeability
 - may induce regression of recently developed tumor microvessels
- **Therapeutic inhibition of tumor angiogenesis should be effective in a broad range of solid malignancies**
- **Target tissue is in direct contact with blood, facilitating drug delivery**

Approaches to the inhibition of VEGF signaling



Approaches to the inhibition of VEGF signaling



VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor

VEGFR tyrosine kinase research at AstraZeneca

- **Preclinical studies have evaluated the potency, selectivity, anti-angiogenic and antitumor activity of VEGFR tyrosine kinase inhibitors (VEGFR-TKIs) at AstraZeneca**
- **The lead VEGFR-TKI is currently in Phase II/III trials in NSCLC and CRC, and work is also ongoing to determine the activity in a wide range of other tumors**