Human tumor derived CANScript™ platform predicts molecular mechanism of sensitivity and resistance to Fragmin in pancreatic cancer


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Abstract

One of the formidable challenges in cancer therapeutics is developing and validating a highly effective preclinical testing platform. However, existing in vitro and in vivo testing platforms show limited success. In this context, we have developed CANScript™, a novel clinically relevant preclinical platform demonstrated to have very high correlation to clinical outcome for chemotherapeutics as well as targeted drugs in multiple solid and hematological cancers (with overall sensitivity of 88% and specificity of 90% in more than 500 patients). CANScript™ is a rapid reproducible ex vivo tumor explant system, developed to mimic native tumor microenvironment. By including autologous paracrine growth factors, cancer specific customized matrix support, autologous immune environment along with other growth promoting conditions, significant improvements were observed in viability, proliferation of tumors including retention of tumor/stroma, cancer phenotypes, integrity at microarchitecture level and maintenance of functional signaling network. Using this platform we assessed the anti-tumor efficacy of Fragmin (a low molecular weight heparin-LMWH) alone as well as in combination with various Standard-of-Care drugs (SOCs) and compared the outcome with efficacy derived from the use of SOCs alone in twenty patient derived pancreatic tumors. Clinical trial data indicates that Fragmin when administered in patients with advanced pancreatic cancer decreased levels of circulating-tissue factor antigen and attenuated induction of cellular invasion in their blood. CANScript™ data indicates that Fragmin has potent anti-angiogenic activity as a single agent (in ~77 tumor samples) and enhanced anti-proliferative and apoptotic effect in combination with SOC (Cisplatin and Gemcitabine) compared to SOC alone in ~ 30% of these pancreatic tumors. Our study has been powered to include 75-100 patient derived refractory pancreatic tumors for further evaluation. Detailed molecular profiling studies are underway to understand the mechanism of action of this drug to delineate the biology behind response in the responder sub-population.

Objectives

- Establishing a human tumor derived CANScript™ platform for low molecular weight heparins
- Understanding molecular mechanism of anti-tumor effect of Fragmin
- Application of CANScript™ technology for selecting best combination for Fragmin in human pancreatic cancer

Study Plan & Patient Selection

Experimental design to determine responders and non responders using CANScript™ platform technology

Results

Fragmin inhibits angiogenesis, tumor cell proliferation and induces activation of Caspase-3 when combined with SOC in primary pancreatic tumors

Summary

- Efficacy of low molecular weight heparin, Fragmin was tested in human pancreatic tumors derived CANScript™ platform.
- Fragmin exhibited anti-tumor effect in 30% of human pancreatic tumors.
- CANScript™ suggests Fragmin inhibits angiogenesis in these tumors
- Anti-tumor effect is also associated with the induction of Caspase activation
- Exome sequencing and transcriptome profiling are undergoing in these tumors to identify the genomic markers associated with these functional output

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