Wnt pathway inhibitor: New Substance Class for Promising Novel Anti-Tumor Agent (P-916)

Key Facts

- **low** nM IC_{50} against colon cancer (stem) cell lines
- **Specificity** (in epistasis and suppression of double axis formation)
- **good** CYP/kinase & hERG-profiles, metab. stab., $t_{1/2}$/AUC (mice), solubility
- *in vivo* **efficacy** and **tolerability** of substance class (mouse)
- **solid** IP protection

Background

The Wnt signalling pathway plays an important role in the regulation of cell proliferation and differentiation. Aberrant activation of the Wnt signalling pathway is known to promote uncontrolled cell growth and survival and can therefore be a major driving force in a broad spectrum of human cancers and diseases such as colon, skin, liver and ovary cancer. For example, the inhibition of aberrant Wnt signalling pathway activity in cancer cell lines effectively blocks their growth[1]. Other disorders and diseases are considered to be influenced by an aberrant Wnt signaling pathway, too (see e.g. literature baker et al. below).

The Technology

The systematic evaluation of Structure Activity Relationships (SAR) of several 100 hit variants have been investigated to yield a lead structure. Intensive medicinal chemistry on the lead compound improved the pharmacologic profile (see Figure 1 below).

Development Stage

The lead compound shows low nM IC_{50} against colon cancer (stem) cell lines and specificity in epistasis and suppression of double axis formation. PD analyses revealed good CYP/kinase & hERG-profiles, metabolic stability as well as promising $t_{1/2}$/AUC in mice. Further optimization of *in vitro* & *in vivo* ADMET is ongoing.

Applications and Commercial Opportunity

Development of a small molecule drug candidate for chemotherapy of cancer types such as colon, skin, liver and ovary cancer.

Inventors

The invention was jointly conceived from researchers at Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ) and University of Heidelberg by R: Maskey, C. Koch, F. Fuchs, S. Steinbrink, D. Gilbert and M. Boutros.

Scientific References

1) N. Barker and H. Clevers "Mining the Wnt pathway for cancer therapeutics", Nature Reviews, vol. 5, 2007, pages 997-1014;

2) R. Nusse, "Wnt signalling in disease and in development", Cell Research, Vol. 15, 2005, pages 23- 32

Intellectual Property

DKFZ filed a priority patent application, which subsequently divided into two international patent families: WO 2012/062901 and WO 2012/062905 nationalized in USA, Europe, China, Canada (CA2817331), Australia (AU2011328074) and India.

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Table 1:
Pharmacologic Profile of current Lead candidate 80158:

Property	Value
MW	~ 450 D
Purity	> 95 %
Solubility	5 mg/L
Wnt-Inhibition (HEK293T)	IC_{50} = 1 nM
Cytotox (HCT116)	IC_{50} = 2 nM
PK (mice)	$t_{1/2}$ = 2,02 h
Metabolic Stability	$t_{1/2}$ (murine) = 33 min
	$t_{1/2}$ (human) = 82 min
CYP450 profile (5 isoforms)	IC_{50} > 25 µM
hERG	no inhibition up to 25 µM

Figure 1: The test compound 80158 inhibits efficiently Wnt-signalling and the viability of the colorectal cancer derived cell lines HCT116 and DLD1.