GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

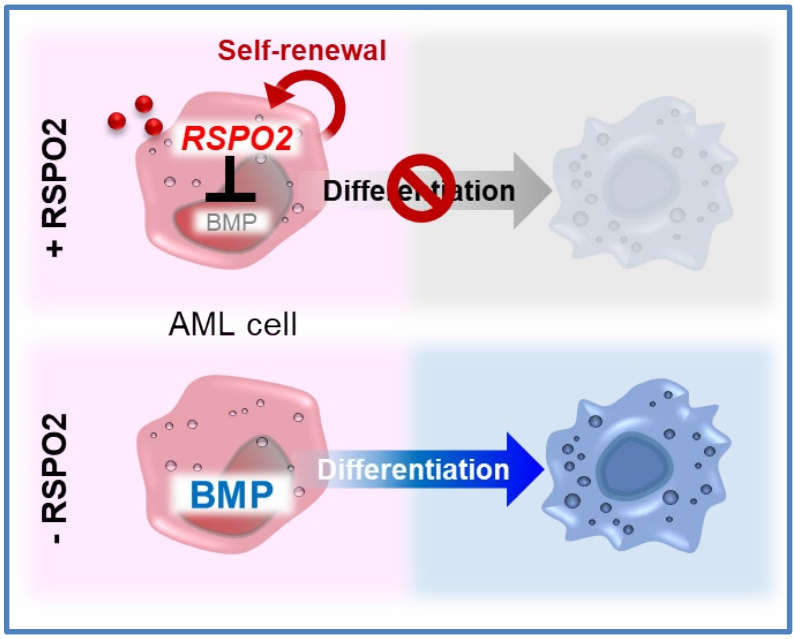
TECHNOLOGY OFFERS

Treatment of acute myeloid leukemia (AML)

R-spondin 2 (RSPO2) as a novel target in AML

EXECUTIVE SUMMARY

Acute myeloid leukemia (AML) is a malignancy of the hematopoietic system and arises from uncontrolled proliferation and impaired differentiation of myeloid precursors. Current therapeutic approaches have shown limited success rates, stressing the urgency to identify genes as potential new AML biomarkers or for direct AML therapy. Novel WNT-independent functions of R-spondins (RSPOs) in inhibition of bone morphogenetic protein (BMP) signaling were investigated, identifying the role of RSPO2 in growth and differentiation of AML cells. High RSPO2 expression was also identified to associated with poor prognosis, highlighting its potential for identification of AML risk patients. The present invention relates to an inhibitor of R-spondin 2 mediated BMP receptor inhibition for use in treating and/or preventing AML.



Category	Indication	Development stage	Seeking
Therapeutic / Prognostic	AML therapy & diagnosis	*in vivo* POC	Development partner / licensee

BENEFITS

- High Rspo2 expression as superior predictor for poor prognosis compared to widely reported biomarkers.
- Adjustment of chemotherapeutic approaches based on Rspo2 expression could improve chances of recovery.
- Direct AML therapy possibilities via anti-Rspo2 antibody therapy.

TECHNOLOGY BACKGROUND

RSPO-2 is a high affinity ligand for the BMP receptor ALK3 and engages the E3 ligase ZNRF3 to trigger membrane clearance of ALK3 via endocytosis and lysosomal degradation. The RSPO-2 target specificity for ALK3 binding is mediated by its TSP1 domain which differs from other RSPO proteins. RSPO-2 decreased phosphorylation of Smad1 and expression of ID1 (hallmarks of BMP signal activation) and has been shown to prevent macrophage differentiation and maintain cell proliferation via the described pathway of WNT-independent BMP pathway inhibition. Deficiency of RSP0-2, for example mediated by anti-RPSO2 antibody, reduces disease in AML cells.

DEVELOPMENT STAGE

Preclinical; Inhibitory antibodies and inhibitory dendrimers have been validated to reduce AML stemness in vitro; Rspo2 shRNA reduces tumor burden in a mouse xenograft model in vivo.

APPLICATIONS

Application as superior prognostic biomarker to identify high risk acute myeloid leukemia patients.
Direct targeting of endogenous Rspo2 protein with neutralizing anti-Rspo2 antibody in AML cells.

INTELLECTUAL PROPERTY

PCT Patent application “Treatment of acute myeloid leukemia (AML)” PCT/EP2020/087065 with priority application filed on 19 December 2019.

PUBLICATIONS & REFERENCES

- Kazanskays, O. *et al.* R-spondin2 is a secreted activator of Wnt/beta-catenin signaling and is required for Xenopus myogenesis. *Dev Cell* **7**, 525-534, doi:10.1016/j.devcel.2004.07.019 (2004)
- Sun *et al.*, RSPO2 inhibits BMP signalling to promote self-renewal in acute myeloid leukemia (in revision)

DKFZ Contact:

Lana Semykina
Deutsches Krebsforschungszentrum
Innovation Management T010
Email: s.semykina@dkfz.de
Tel.: +49-(0)6221-42-2953
Fax: +49-(0)6221-42-2956