GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

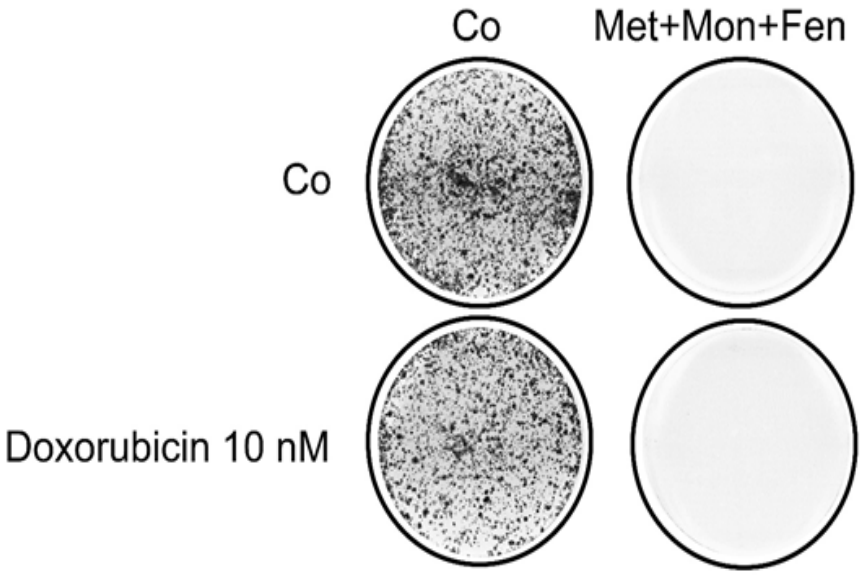
TECHNOLOGY OFFER

Cancer cell specific treatment by simultaneous targeting metabolism and intracellular pH (P-1271, P-1415)

Cancer cell specific inhibition of wnt/β-catenin signaling by forced intracellular acidification.

EXECUTIVE SUMMARY

Chemotherapy is the most effective treatment method for metastasis but it causes severe side effects such as organ toxicity and anaemia.
We have invented a new approach for cancer specific therapy that is based on utilizing treatment with combination of two / three drugs. One drug must be an inhibitor mitochondrial complex I and another could have property of H+ ionophore. The third drug is optional and is either also mitochondrial complex I inhibitor with different properties compared to first one, or inhibitor of lactate transport. In addition to a cooperative effect on cancer cell eradication in vitro and in vivo, the suggested combinations work as a strong wnt-signaling inhibitors. Examples: Meformin + Fenofibrate + Monensin; Simvastatin + Papaverine.



Effect of triple combined treatment on colony formation efficiency in DLD1 cancer cells

Category	Indication	Development stage	Seeking
Combination therapy	Cancer	In vivo and in vitro POC	Licensing, Development partner

BENEFITS

- All components are oral drugs. All drugs were tested on animals. Metformin, Fenofibrate Papaverine and Simvastatin are long in human use. The intracellular acidification happens only in cancer cells and strong inhibits Wnt signaling. Wnt signaling is characteristic feature of cancer stem cells.
- The drug combinations has no side effects and acts on cancerous tissues only.
- Metformin+Fenofibrate+Simvastatin combination was tested on humans for cancer unrelated purposes and found to have no side effects (DOI: 10.5603/EP.a2016.0021).

TECHNOLOGY BACKGROUND

Based on insights into a link between of mitochondrial respiration inhibitors and intracellular pH, the inventors suggested an auto-enhancing cycle inflicted by a combination of ionophore and of mitochondrial respiration inhibitor drugs, which would specifically entrap cancer cell, - a 'Warburg Trap'.
The combination disrupts the process of ATP production in mitochondria and shows a strong inhibitory effect on Wnt signalling in cancer cells. It is shown to be an effective treatment of cells showing a Warburg effect.
The data provide the mechanistic rationale for a combination drug-based cancer cell specific approach to inhibit Wnt signaling downstream of β-catenin. This approach offers a new strategy for cancer cell specific treatment, especially for Wnt-addicted tumors such as a colon and lung cancer.

DEVELOPMENT STAGE

Cancer cell viability has been successfully evaluated in cell culture experiments with examples of treatment using various cancer cell lines and combinations of compounds shows a synergistic effect of the triple combinations in killing cancer cells, but not in non-cancer cells.

APPLICATIONS

- Treatment of various kinds of tumors, especially in combination with routine chemo- and radio-therapies with potential to overcome multiple drug resistance caused by ATP-dependent extrusion pumps.
- Post-surgery treatment as a supportive therapy component, especially in cases of patients with tumors scored high for Wnt signaling, to prevent their tumor recurrence risk.

INTELLECTUAL PROPERTY

Priority patent application "Treatment of cancer targeting energy metabolism and intracellular pH" EP 19176166.7 filed on 23 May 2019
Patent applications "Cancer treatment by simultaneous targeting energy metabolism and intracellular pH" with priority date 15 June 2016 (EP, US, CN) and publication number WO 2017/216257.

PUBLICATIONS & REFERENCES

"Cancer cell specific inhibition of Wnt/β-catenin signaling by forced intracellular acidification." Melnik et al. Cell Discov. 2018 Jul 3;4:37. doi: 10.1038/s41421-018-0033-2.

"The beneficial effects of metformin on cancer prevention and therapy : a comprehensive review of recent advances" Published by Pouya saraei, Muhammad Azam Kakar, PMC6497052

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ABOUT THE DKFZ Innovation Management

Working at the interface of research and industry, the Innovation Management of the German Cancer Research Center (DKFZ) helps to get new cancer drug candidates, diagnostic tests, and research instruments onto the market as quickly as possible.

The DKFZ with its more than 3,000 employees is the largest biomedical research institution in Germany. At the Center more than 1,300 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.