



THERAPY

PATCHTARGET

Targeting the multidrug transporter Patched potentiates chemotherapy efficiency



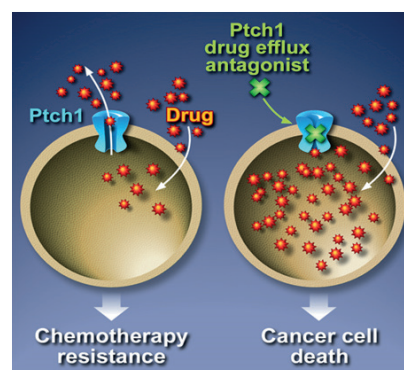
CONTEXT & BACKGROUND

One of the crucial challenges in the clinical management of cancer is the resistance to chemotherapeutics. Multidrug resistance (MDR) has been intensively studied, and one of the most prominent mechanisms underlying MDR is overexpression of ATP-binding cassette (ABC) transporters. Despite research efforts to develop compounds that inhibit the efflux activity of ABC transporters and increase classical chemotherapy efficacy, to date, the Food and Drug Administration (FDA) has not approved the use of any ABC transporter inhibitor due to toxicity issues.

The team recently discovered that the Hedgehog receptor Patched (Ptch1), which is overexpressed in many recurrent and metastatic cancers, is a multidrug transporter and contributes to the efflux of chemotherapeutic agents such as doxorubicin, vemurafenib, docetaxel and other standards-of-care, and to chemotherapy resistance in multiple type of cancer cell lines like adrenocortical carcinoma, BRAF mutated melanoma, prostate and colorectal cancer cells. Remarkably, they have shown that Patched is not an ABC transporter but uses the proton motive force to efflux drugs. Indeed, the "reversed pH gradient" that characterizes cancer cells allows Patched to function as an efflux pump. This makes Patched a particularly relevant therapeutic target for cancers expressing Patched such as lung, breast, prostate, ovary, colon, brain, ACC, and melanoma.

The team developed screening tests that allowed us to identify several molecules able to enhance the cytotoxic effect of doxorubicin on different cancer cell lines which endogenously overexpress Patched by inhibiting Patched drug efflux activity. They showed that, in mice, the combination of one of these compounds with doxorubicin prevents the development of xenografted adrenocortical carcinoma tumors more efficiently than doxorubicin alone without obvious undesirable side effect (patent application PCT/EP2018/080510, Hasanovic et al. 2018).

It is believed that the use of a Patched drug efflux inhibitor in combination with classical or targeted therapy could be a promising therapeutic option for Patched-expressing cancers.



INNOVATIVE COMPONENT & TECHNOLOGY

The team discovered that the membrane receptor Patched is a new target for cancer treatment.

- Patched is overexpressed in many cancers (lung, breast, prostate, ovary, colon, brain, melanoma, ACC, ...)
- Patched transports chemotherapeutic agents out of cells thanks to the proton motive force
- Patched drug efflux activity is specific of cancer cells (due to the reversed pH gradient of cancer cells)
- Targeting Patched drug efflux activity should have no toxicity for healthy cells and no side effect

They discovered Patched drug efflux inhibitors showing the following profile :

- Increased chemotherapy efficiency in vitro and in vivo
- Great phys-chem and DMPK properties
- Highly favorable small molecule structures for med chem optimization and rapid analoging

The use of these molecules in combination with classical or targeted therapy should improve treatment efficacy in Patched-expressing cancers, and risk of decrease relapse and metastasis.



OBJECTIVES

To perform a clinical proof of concept of the advantage of combining a Patched drug efflux inhibitor such as the lead with chemotherapy treatment first on a cohort of patient suffering of adrenocortical carcinoma, and then to extend it to patients suffering from a Patched-expressing cancer such as BRAF mutated melanoma, prostate, colorectal, lung or breast cancer.

SCOPE

Inhibition of cancer cell resistance to chemotherapy

KEYWORDS

Chemotherapy resistance,, small molecule, drug efflux pump, Patched



DEVELOPMENT & MATURATION STAGE

Pre-clinical proof-of-concept in vivo is obtained on adrenocortical carcinoma. More in vivo proof-of-concept must be performed on breast and colorectal cancer cells xenografts. Optimization of the drug candidate is in progress



TARGET POPULATION

Patients which present a Patched-expressing cancer treated with chemotherapy.



TARGET PROFILE

Route : IV or oral delivery
Positioning : synergy with the standard-of-care chemotherapy



STRENGTHS & COMPETITIVE ADVANTAGES

- Specificity of Patched for cancer cells in comparison to ABC transporters which are ubiquitous
- No competition on the target (Patched drug efflux activity first described by IMV)
- PoC in-vitro and in-vivo that Patched is a particularly relevant new target for cancer treatment
- PK and PD properties of the lead
- Large optimization possibilities
- The expected impact is to increase the efficacy of the current standard-of-care in patients whose cancer expresses the target Patched.



INDUSTRIAL APPLICATIONS & OPPORTUNITIES

The industrial potential is very important based on the unmet medical need and the large profile of expression of Patched in multiple cancer types. The team proved the relevance of our approach in combination with most of the chemotherapy standards-of-care in in-vitro models and adrenocortical carcinoma in-vivo model as first intention.

Other in-vivo studies are on-going. A major increase in efficacy is expected with the molecules. Combination approach is also a great opportunity in term on life cycle management as most of the chemotherapy drugs are generics with poor toxicology profile and low general efficacy.



INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

European Patent filed in Nov. 2017 (EP 17306544.2), PCT in Nov. 2018 (PCT/EP2018/080510) (CNRS Innovation)