MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

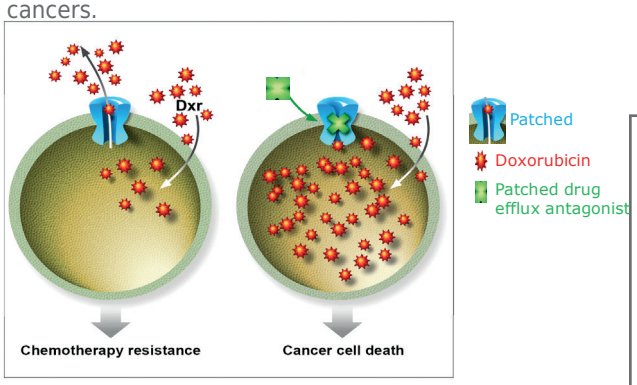
SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

PATCHEDTARGET

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. We recently discovered that the Hedgehog receptor Patched, which is overexpressed in many recurrent and metastatic cancers, is a multidrug transporter and contributes to the efflux of chemotherapeutic agents such as doxorubicin and to chemotherapy resistance in melanoma and in adrenocortical carcinoma cells. Remarkably, we 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. We 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. We 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 EP17306544.2-1462, Hasanovic et al. 2018).
We do believe 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.



SCOPE

Inhibition of cancer cell resistance to chemotherapy

KEYWORDS

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

INNOVATIVE COMPONENT & TECHNOLOGY

We 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
We discovered a Patched drug efflux inhibitor which
•Increases chemotherapy efficiency in vitro and in vivo
•Is metabolically stable and soluble
•Highly favorable for med chem optimization
The use of this molecule 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 our lead with chemotherapy treatment first on a cohort of patient suffering of adenocortical carcinoma and then to extend it to patients suffering from a Patched-expressing cancer

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

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

European Patent filed in November 2017 (EP 17306544.2) (CNRS Innovation)

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

STRENGHTS & 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 lead can be proposed in combination with doxorubicin in the treatment of adrenocortical carcinoma and other cancers treated with doxorubicin if the cancer presents an expression of Patched. The applicability to other standard-of-care / other tumors will be questioned in the forthcoming activity.

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