SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

Melather
PRECLINICAL validation of new anti-melanoma compounds

2013_Rocchi

SCOPE	**Cancer in general, Melanoma in particular**
KEYWORDS	***Melanoma, therapy, resistance, solid and liquid tumors, reticulum endoplasmic stress, GRP78, apoptosis, autophagy***

CONTEXT & BACKGROUND

The melanoma, a malignant tumor developed from melanocytes is one of the most lethal cancers among young adults. Melanoma has a high capability of invasion and rapid metastasis to other organs (lymph node, lung, liver, brain...). The prognosis of metastatic melanoma is extremely pejorative, as the various protocols of chemotherapy or immunotherapy have not shown real survival benefit.
Even if recently encouraging results were obtained with the PLX 4032 (Vemurafenib), an inhibitor of BRAF, these responses remain transitory. Regrettably, after a short period of remission, the melanoma acquires in all the cases, a drug resistance and the metastases develop again increasing about 6 months the life expectancy of the patient. Another therapy, with Ipilimumab (anti-CTLA4), which reactivates the immunity response of the patient, was recently developed. However, this therapy gives an objective response in only 10 to 15 % of patients. Thus, it appears necessary to develop new approaches enabling the discovery of new drug candidates for specific biotherapy treatment of melanoma.

INNOVATIVE COMPONENT & TECHNOLOGY

Our main research theme is to develop new molecules with anti-melanoma properties. In collaboration with the Chemical Institute of Nice (Rachid Benhida, chemist leader of the Bioactive Molecules team), we identified a new family of active molecules on melanoma and other cancer cells such as breast, colon, pancreas, and prostate. Interestingly, these molecules overcome resistance in Vemurafenib and Dabrafenib resistant melanoma cells. The process of preparation, the identity and purity of molecules were clearly established. The synthetic pathway is well mastered and can be performed on a large scale (scale-up) for a possible industrial transfer **(Cerezo *et al.*, Cancer cell, 2016, in press)**.

OBJECTIVES

To improve the efficacy of a selected drug candidate and to clinically validate this drug in melanoma and in other cancers.

TARGET POPULATION

Melanoma patients including patients resistant to B-Raf inhibitors, Vemurafenib and Dabrafenib
Other cancers

TARGET PROFILE

Identification and validation of specific target

DEVELOPMENT & MATURATION STAGE

Using structure activity relationship studies, we selected candidate exhibiting strong death-promoting effects in melanoma cells and xenografts both sensitive and resistant to BRAF inhibitors. The biological evaluations were performed according to techniques and protocols well established in the team 1 at C3M, which has a recognized expertise in this domain. These studies allowed determining the in vitro and in vivo biological activities. We also performed studies to decipher the signaling pathway, the mechanism of action and the target of the best candidates. We identified the GRP78 (Bip) an endoplasmic reticulum protein, as the target. We demonstrated that the potential interaction between our compound and GRP78 increases Endoplasmic Reticulum Stress and leads to melanoma cell death by autophagy and apoptosis mechanisms. Even though little is known about the expression and the regulation of the target in melanoma, its overexpression in various cancers is described. Moreover, endoplasmic reticulum stress has already been involved as a drug resistance mechanism in melanoma suggesting an interest to combine those new molecules with already used therapies in melanoma.

INTELLECTUAL PROPERTY & PATENT CO-OWNER(S)

S. Rocchi, R. Ballotti, M. Cerezo, Rachid Benhida, Maria Duca, New benzene sulfonamide thiazole compounds, Brevet EP N° 12306391 patented 2012 November 9th in the name of INSERM. PCT/EP2013/073439

STRENGHTS & COMPETITIVE ADVANTAGES

- Discovery of new molecules with original structure
- Active molecules on all melanoma cells independently of mutational status
- Active molecules on melanoma cells freshly isolated from patients sensitive or resistant to B-Raf inhibitors
- New and original mechanism of action with molecular target identified
- No apparent toxicity in mice
- Exhibited a strong efficacy in xenograft mice models
- These molecules were also found to be active against other liquid and solid tumors including prostate, pancreas, Breast, colon and chronic myeloid leukemia.

INDUSTRIAL APPLICATIONS & PARTNERSHIP OPPORTUNITIES

Melanoma and other cancer therapies

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