SELECTED OPPORTUNITIES IN ONCOLOGY

Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) for the treatment of melanomas (BIO17393)

INHIBITION OF NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE (NAMPT) FOR THE TREATMENT OF MELANOMAS (BIO17393)

Product factsheet

Preclinical

Product:

- A NAMPT inhibitor such as Daporinad

Rational / POC:

- In BRAF ^{V600E} melanoma cells, a global metabolic analysis discloses a decrease in nicotinamide adenine dinuclotide levels upon PLX4032 treatment that is mediated by a transcriptional up-regulation of NAMPT gene.
- NAMPT inhibition decreases melanoma cell proliferation both *in vitro* and *in vivo.*
- Forced NAMPT expression renders melanoma cells resistant to PLX4032.
- NAMPT expression induces transcriptomic and epigenetic reshufflings that steer melanoma cells toward an invasive phenotype associated with resistance to targeted therapies and immunotherapies.

Patent and publication:

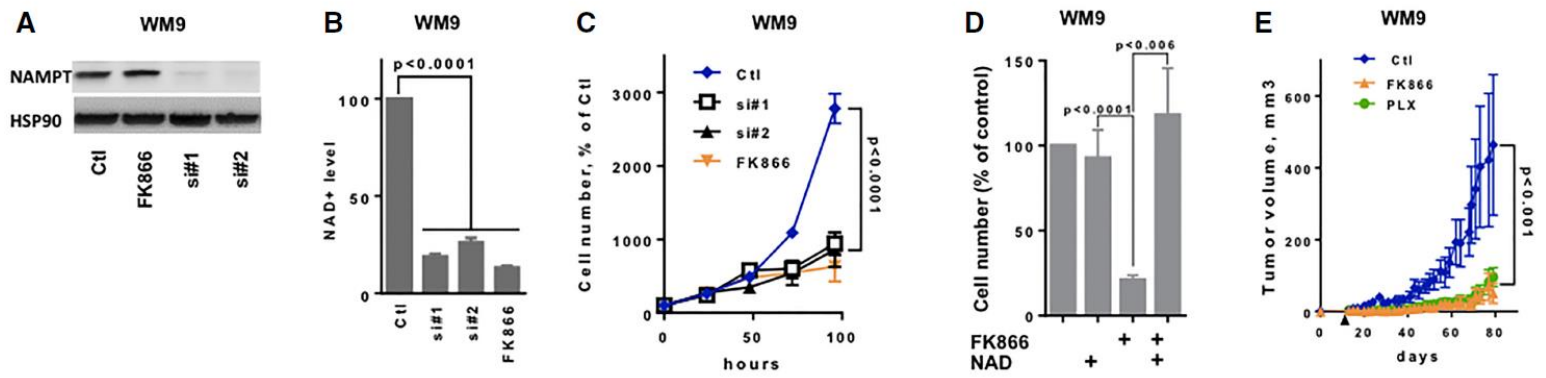
- METHODS AND COMPOSITIONS FOR TREATING MELANOMA RESITANT EP18305002
- ***Pivotal role of NAMPT in the switch of melanoma cells toward an invasive and drug-resistant phenotype*** Ohanna M, Cerezo M, Nottet N, Bille K, Didier R, Beranger G, Mograbi B, Rocchi S, Yvan-Charvet L, Ballotti R, Bertolotto C. *Genes Dev.* 2018 Mar 22. doi: 10.1101/gad.305854.117.

InsermTransfert
Your partner in health innovation

INHIBITION OF NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE (NAMPT) FOR THE TREATMENT OF MELANOMAS (BIO17393)

Proof of concept

NAMPT inhibition decreases melanoma cell proliferation and xenograft development and restores PLX4032 sensitivity



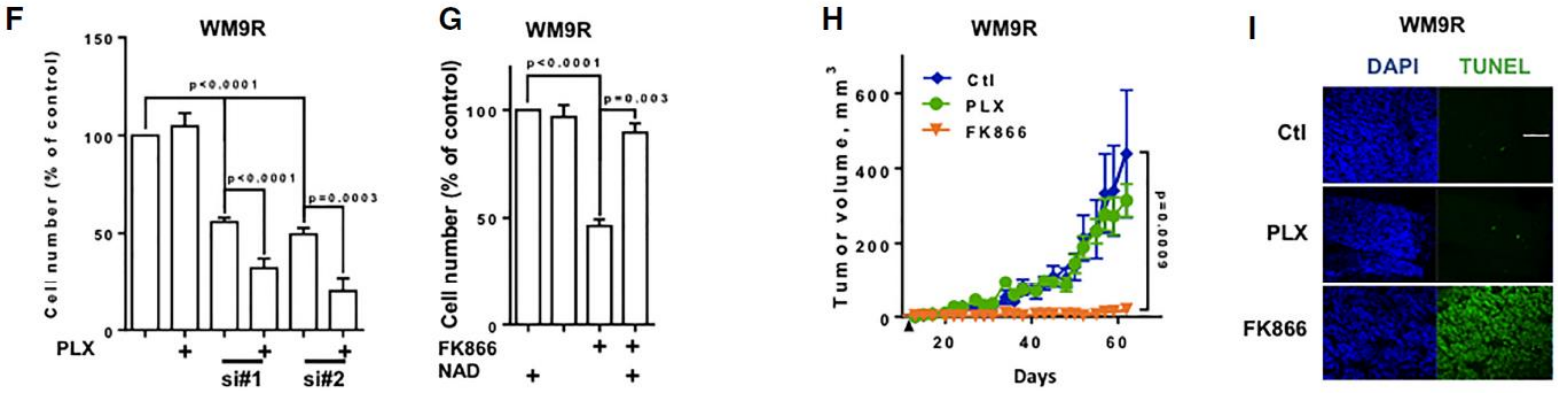
(A) Western blot analysis of NAMPT expression in WM9 melanoma cells transfected with control (Ctl) siRNA or two different NAMPT siRNAs (si#1 and si#2) or exposed to a NAMPT inhibitor (FK866). HSP90 was used as loading control. (B) Intracellular NAD+ levels in WM9 melanoma cells treated as in A. Values represent the means + SD of three independent experiments. (C) Proliferation of WM9 melanoma cells treated as in A. Cells were trypsinized and counted each day. Values represent the means ± SD of three independent experiments. (D) Cell number of WM9 melanoma cells exposed to 5 µM FK866 or 500 µM FK866 plus NAD+ for 72 h. Values represent the means + SD of three independent experiments. (E) Growth curve of tumor xenografts after subcutaneous injection of WM9 cells. Mice (six per group) were treated or not with PLX4032 or FK866. Data are shown as the means ± SD of tumor volume. The black arrow indicates the beginning of the treatment.

InsermTransfert
Your partner in health innovation

INHIBITION OF NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE (NAMPT) FOR THE TREATMENT OF MELANOMAS (BIO17393)

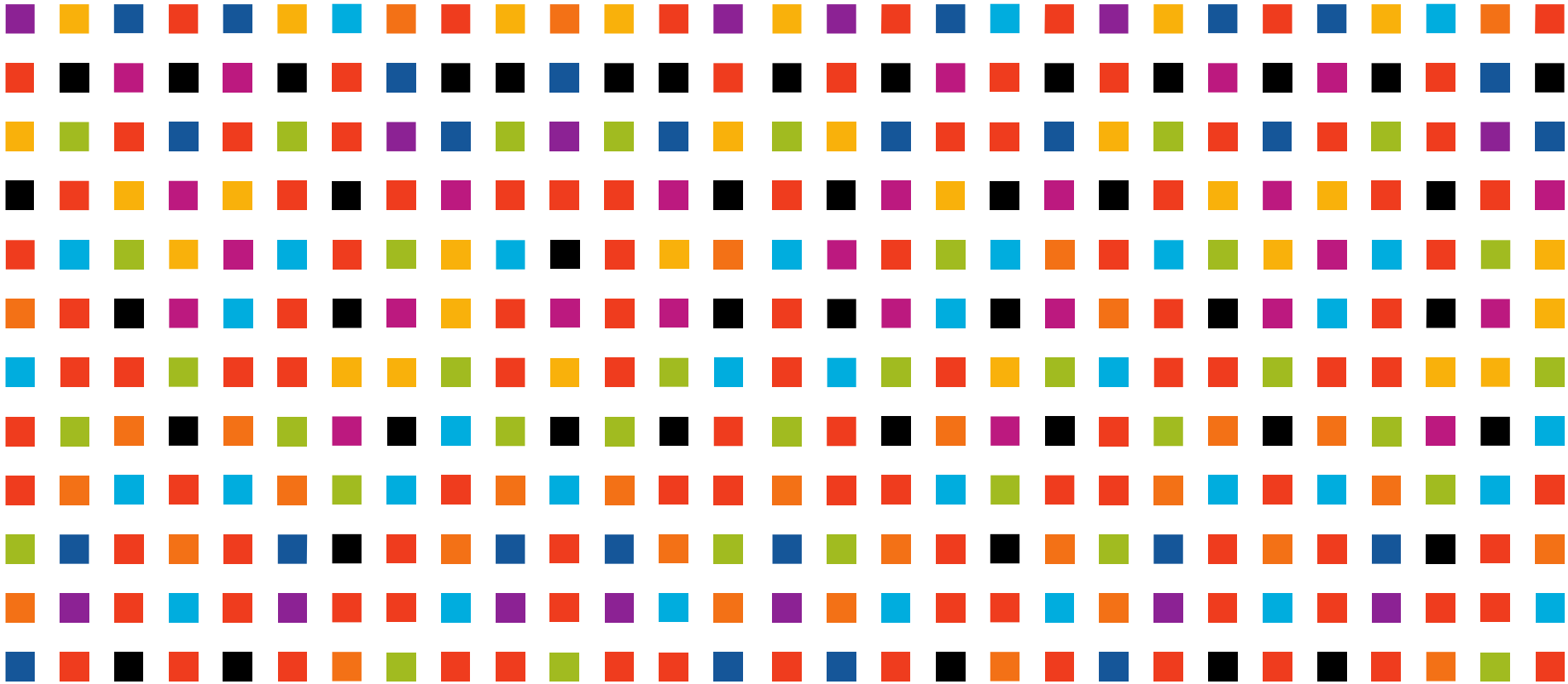
Proof of concept

NAMPT inhibition decreases melanoma cell proliferation and xenograft development and restores PLX4032 sensitivity



(F) PLX4032-resistant WM9 melanoma cells were transfected with control or NAMPT siRNA (si#1 and si#2) and subsequently exposed to 5 µM PLX4032. After 72 h, the cells were counted. The histogram represents the means + SD of three independent experiments. (G) Cell number of PLX4032-resistant WM9 melanoma cells exposed to 5 µM FK866 or 500 µM FK866 plus NAD+ for 72 h. Data are presented as the means + SD of three independent experiments. (H) Growth curve of tumor xenografts after subcutaneous injection of WM9 cells resistant to PLX4032. Mice (six per group) were treated with vehicle, PLX4032, or FK866. Data are shown as the means ± SD of tumor volume. The black arrow indicates beginning of the treatment. (I) Frozen sections of xenografts were stained with DAPI and subjected to transferase-mediated UTP nick end labeling (TUNEL).

InsermTransfert
Your partner in health innovation



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr