Nicotinamide Phosphoribosyl Transferase (NAMPT) inhibitors are novel modulators of myeloid-derived suppressor cells

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Nicotinamide phosphoribosyl transferase (NAMPT) is a pleiotropic player in cell signalling as a key regulator of NAD synthesis in cells. NAD is an important cofactor for redox reactions and essential substrate for NAD- consuming-enzymes, including sirtuins and PARPs. Maintaining NAD levels in cells is essential in order to produce energy (ATP) and to maintain all functions regulated by NAD dependent enzymes such as, gene expression, calcium signalling, immune response and DNA damage and repair.

NAMPT has been found over-expressed in all cancer tested, and now is a well accepted cancer biomarker. Several inhibitors have been developed and two of them, FK866 and CHS828 have entered clinical trials (www.clinicaltrails.gov). However, the results of the trails have never been published, maybe due to the bad pharmacokinetic properties of these agents. There is an interest in finding new molecules and different companies (*e.g. Genentech, Eli Lilly*) have recently published and patented some new NAMPT inhibitors.

We have now synthetized a panel of novel NAMPT inhibitors (patent number WO 2014/178001 A1_06-11-2014), among them we found at least 7 molecules that have similar potency and efficacy in vitro, but with a marked increase in in vivo efficacy. In a fibrosarcoma mouse model NAMPT inhibitors are able to reduce tumour growth, delay spontaneous metastasis formation and angiogenesis. The efficacy of our new molecule, called MV87, is high compared to FK866. Moreover, *in vivo* NAMPT inhibitors are able to marked decrease the expansion of a subpopulation of tumour associated myeloid cells c called myeloid-derived suppressor cells (MDSCs). MDSCs are immature myeloid cells that act as pro tumoural cells by killing the cytotoxic CD8 lymphocytes. NAMPT inhibitors block MDSCs expansion and migration within the bone marrow and interfere with MDSCs suppression activity on cytotoxic CD8 cells. Similar results were obtained using fibrosarcoma resistant cells, demonstrating a direct effect of NAMPT inhibitors on MDSCs. Furthermore, when mice were subjected to thymectomy the efficacy of NAMPT inhibitor was reduced.

Here, we have demonstrated that NAMPT inhibitors act not only on cancer cells, but also in tumour microenvironment and in cancer-related inflammation and are novel modulator of anti-tumour immunity.