

Nicotinamide Phosphoribosyl Transferase (NAMPT) inhibitors: anti-cancer agents and modulators of cancer-related inflammation

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Nicotinamide phosphoribosyl transferase (NAMPT) is 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, PARPs and CD38/CD157. Maintaining NAD levels in cells is essential in order to produce energy 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 has been accepted as cancer biomarker. Several inhibitors have been developed and two of them, FK866 and CHS828 have entered clinical trials (www.clinicaltrials.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 synthesized 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. Moreover, *in vivo* NAMPT inhibitors are able to marked decrease the expansion of a myeloid-derived suppressor cells (MDSCs), 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. 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.