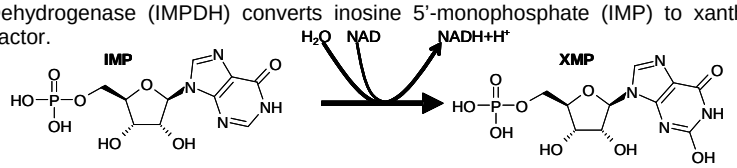
# IMPDH II, a choice target for major therapeutic applications

**Catalytic activity**

Inosine Monophosphate Dehydrogenase (IMPDH) converts inosine 5'-monophosphate (IMP) to xanthosine 5'- monophosphate (XMP) using $NAD^+$ as a cofactor.




The oxidation of IMP to XMP is considered as the pivotal step in the biosynthesis of guanine nucleotide, whose pool controls cell proliferation and many other major cellular processes[1]. The decrease in guanine nucleotide resulting from IMPDH inhibition interrupts the nucleic acid synthesis in proliferating cells. The involvement of IMPDH in *de novo* guanine nucleotide biosynthesis makes IMPDH a crucial enzyme in cell proliferation and differentiation[2]. IMPDH is recognized as a validated target for several major therapeutic areas. IMPDH inhibitors are exploited as antiviral (*e.g.* ribavirine), antiparasitic, antimicrobial, antileukemic and immunosuppressive agents[2]. IMPDH Type II is the predominant isoform of the enzyme and is selectively expressed in proliferating cells, including lymphocytes and tumor cells[2].

**IMPDH in immunology**

IMPDH is highly active in lymphocytes. It is a validated target to treat immunological diseases and to induce immunosuppression (CellCept®, a mycophenolic acid (MPA) prodrug - Roche – CHF1.85 Bn as an immunosuppressive agent in 2006, orphan drug designation in 2006 for Myasthenia Gravis, Phase III in Lupus Nephritis). IMPDH is also recognized as an excellent target for the treatment of psoriasis, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)[3].

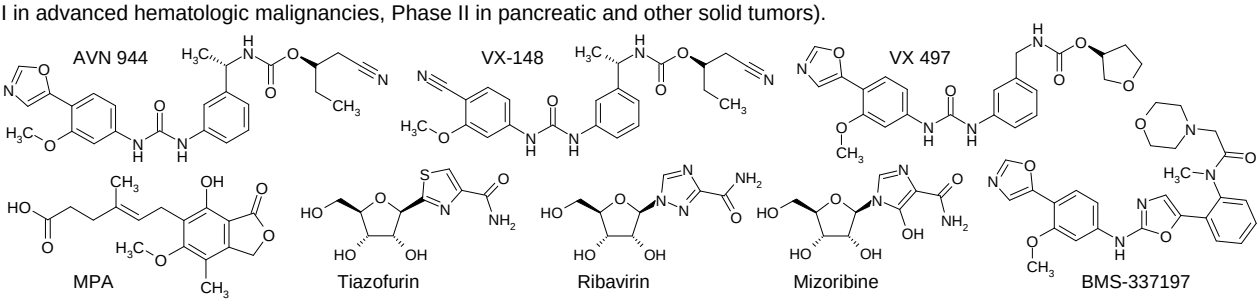
**IMPDH in oncology**

IMPDH, and particularly Type II, which is overexpressed in tumor cells, is considered as a highly potent target for cancer chemotherapy[1 2 4 5]. Several IMPDH inhibitors are under development for the treatment of Acute and Chronic Myelogenous Leukemia (AML, CML)[6], and other cancers (pancreas, colon, bladder…). Additionally, it has been shown that the use of IMPDH inhibitors counteracts the drug resistance[7] that may appear in certain tumors. For instance, methotrexate resistance is directly related to the overexpression of IMPDH, whose inhibition restores the drug efficacy[8]. Combination with other anti-cancer drugs extends the potential application of IMPDH inhibitors.

**Current development of IMPDH inhibitors**

CellCept®, ribavirin, mizoribine and tiazofurine are examples of currently used drugs that target IMPDH. Benzamide riboside, tiazofurine, MPA are under development in Phase II/III in leukemia: results are judged very encouraging[8].

The IMPDH II atomic structure has been resolved and it provides a valuable background for further leads optimization[9]. Besides nucleosides analogues, NCEs have been identified as IMPDH inhibitors[10 11 12 13 14] and enter development trials (*e.g.* AVN-944: Phase I in advanced hematologic malignancies, Phase II in pancreatic and other solid tumors).




All this demonstrates how promising the research of new IMPDH inhibitors is and why the inhibiting activity of compounds is worth being evaluated on such a highly pertinent target.

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