STF-31 Inhibits NAD⁺ Production to Stop Tumorigenic Human Pluripotent Stem Cell Proliferation

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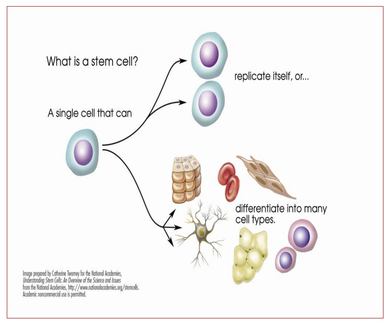
Abstract [1,2]

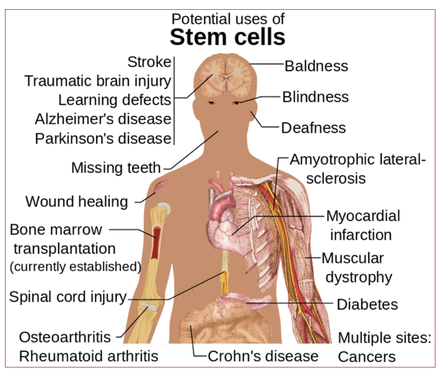
Human pluripotent stem cells (hPSC), which include human embryonic and induced pluripotent stem cells, have the ability to differentiate into any cell type. Recently, scientists have developed new techniques to differentiate hPSC into rarer and more desired cell types which are useful for drug targeting, drug toxicity testing, study of differentiation, and developmental diseases. Future hPSC-based clinical therapies will likely rely on the ability to create differentiated cultures free from tumorigenic pluripotent cells. A small molecule called STF-31 has been demonstrated to inhibit an important enzyme, nicotinamide phosphoribosyltransferase (NAMPT), in a metabolic process of hPSC development. This strategy is effective for eliminating potentially tumorigenic cells but spare new cell progeny. The Marquette University High School SMART (Students Modeling A Research Topic) Team has designed a model of NAMPT bound to STF-31 using 3D printing technology to investigate structure-function relationships. STF-31 is one of over 50 different inhibitors of NAMPT. What makes STF-31 unique is its ability to deliver potent effects on cells. The pyridine ring of STF-31 is situated between the Phe-193 and Tyr-188 sidechains of NAMPT and a hydrogen bond is observed between the compounds NH moiety and Asp-219 residue. The central phenyl ring of STF-31 occupies the tunnel region of NAMPT. Other binding sites between STF-31 and NAMPT include His 191, Arg 196, Ser 241, Val 242, Ala 244,Ser 275, Ile 309, and Arg 311. Further research into NAMPT inhibition will provide important advancements toward the development of clinically safe hPSC progeny for human stem cell based therapies, drug development, and toxicity testing.

Stem Cells

Embryonic (hESC): Pluripotent cells capable of becoming all cell types. These cells are acquired from the inner cell mass of the blastocyst before differentiation resulting in the death of the embryo.

Induced Pluripotent (hiPSC): Can be generated from many varying adult cell types, and can differentiate into any needed cell type. Since they can be obtained through the modification of donated adult cells, they offer an easily attainable supply of cells.

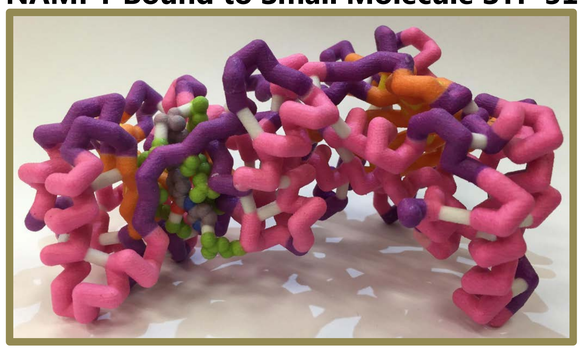




By studying stem cells, researchers can identify drug targets at early stages, run toxicity tests to experiment with the cellular reactions to different toxins, generate new tissues and organs for transplants, and study possible methods to prevent and treat varying birth defects. Through the study of stem cells, researchers gain a greater understanding of the process of human development, allowing them to develop treatment strategies for such diseases.

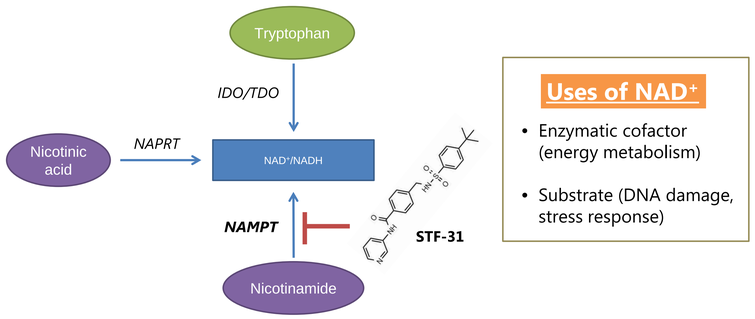
Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". Wikiversity Journal of Medicine 1 (2). DOI:10.15347/wjm/2014.008.

NAMPT Bound to Small Molecule STF-31 [1]



Primary model Color: Purple, **STF-31:** CPK, **Active Site:** Green, **Beta Sheets:** Orange, **Alpha Helix:** Pink, **H-Bonds:** Yellow, **Struts:** White

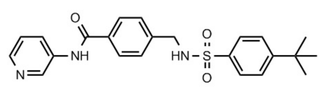
NAD⁺ Synthesis and Salvage Pathways



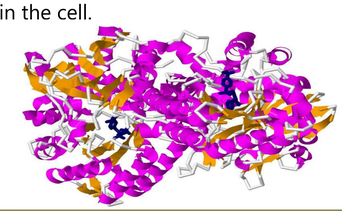
The biosynthesis of the dinucleotide Nicotinamide adenine dinucleotide, NAD⁺, takes place over ***de novo synthesis pathways*** from small molecules and by ***salvage pathways*** from preformed purine or pyrimidine bases. The salvage synthesis recycles, or *salvages*, its precursors – saving a lot of energy in the cell as a result. Tryptophan, an essential amino acid in the human diet, starts as a precursor for the de novo synthesis pathway where, through several steps, it forms into Nicotinic acid mononucleotide (a substrate for NMN/NaMN adenylyltransferase) and finally into NAD⁺. The *de novo synthesis pathway* is inadequate to meet the NAD⁺ demand for most cell types.
Niacin, a dietary vitamin, contains a mix of nicotinic acid (Vitamin B_3) and nicotinamide. These molecules serve as the substrate for the NAPRT and NAMPT mediated NAD⁺ salvage pathways, respectively. For most cell types, the NAMPT pathway is thought to serve as the major source of NAD⁺.

Why Use STF-31 to Inhibit NAMPT in Stem Cells? [1]

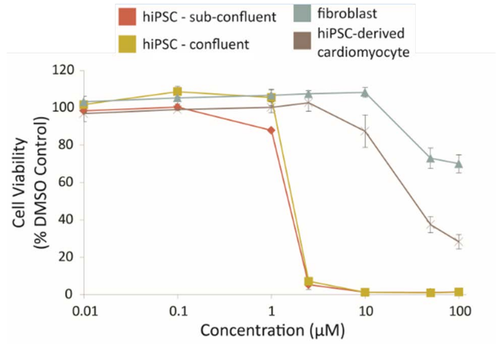
Until recently, Nicotinamide Phosphoribosyltransferase (NAMPT) was an enzyme suspected to be only involved in maintaining NAD⁺ levels. We now know that it also promotes stem cell differentiation. A drug known as STF-31 (below in blue) has been shown to inhibit NAMPT within the salvage pathway. The inhibition of the salvage pathway results in a remarkable loss in NAD⁺ production affecting, among many processes, energy metabolism in the cell.



STF-31



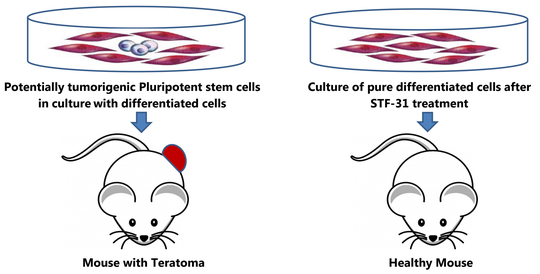
Selective Toxicity of STF-31 [2]



Study data shows selective toxicity of the NAMPT inhibitor STF-31. The x-axis represents concentration of STF-31 and the y-axis represents cell viability . STF-31 is toxic to human induced pluripotent stem cells (hiPSC) at a much lower concentration than differentiated cells (the cardiomyocytes and fibroblasts).

Potential Applications of NAMPT Inhibition [1,2]

The study of NAMPT inhibition may help scientists identify new drug targets and test novel therapeutics. An important key to such drug discovery is toxicity testing on stem cell and differentiated cell populations. The Gundry Lab study illuminates the value of such testing. Cellular replacement therapy (transplantation) to restore functionality to damaged organs and tissues is yet another potential application of study findings. Formulating pure differentiated cell culture for transplant is critical to potential applications. While stem cell development and reproduction is necessary to promote metabolic growth, unchecked growth of stem cells leads to the tumorous reproduction of these cells, teratoma, a form of cancer. Knowledge of the control mechanism of NAD⁺ synthesis and recovery could provide key insights into potential therapy towards highly proliferative cells.



Potential prevention of teratoma formation through selective toxicity of STF-31 [2]

Conclusion [2]

Researchers from the Gundry Lab at the Medical College of Wisconsin have effectively utilized the small molecule STF-31 to inhibit Nicotinamide Phosphoribosyltransferase (NAMPT), a key enzyme in the NAD⁺ salvage pathway of human pluripotent stem cells (hPSC). Researchers discovered that STF-31 exposure showed selective toxicity for hPSC and differentiated cell populations. This knowledge may lead to important advancements in the development of clinically safe hPSC progeny for human stem cells. Potential applications include drug development, toxicity testing, and hPSC based therapies including those that are susceptible to teratoma tumor formation.

References

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