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(Article begins on next page)

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Title: NAMPT: a critical driver and therapeutic target for cancer

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Keywords: NAMPT, NAD, metabolism, cancer biology, tumor microenvironment, immune cell regulation, cancer therapy.

Running Title: The multiple roles of NAMPT in cancer biology

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Abstract

Nicotinamide phosphoribosyltransferase (NAMPT) possesses a vital role in mammalian cells due to its activity as a rate-limiting enzyme in the biosynthesis of nicotinamide adenine dinucleotide (NAD) from nicotinamide. NAD is an essential redox cofactor, but it also functions as a substrate for NAD-consuming enzymes, regulating multiple cellular processes such as DNA repair and gene expression, fundamental to sustain tumor growth and survival and energetic needs. A common strategy that several tumor types adopt to sustain NAD synthesis is to over-express NAMPT. However, beside its intracellular functions, this enzyme has a second life outside of cells exerting cytokine-like functions and mediating pro-inflammatory conditions activating signaling pathways. While the effects of NAMPT/NAD axis on energetic metabolism in tumors has been well-established, increasing evidence demonstrated the impact of NAMPT over-expression (intra-/extra-cellular) on several tumor cellular processes, including DNA repair, gene expression, signaling pathways, proliferation, invasion, stemness, phenotype plasticity, metastatization, angiogenesis, immune regulation, and drug resistance. For all these reasons, NAMPT targeting has emerged as promising anti-cancer strategy to deplete NAD and impair cellular metabolism, but also to counteract the other NAMPT-related functions.

In this review, we summarize the key role of NAMPT in multiple biological processes implicated in cancer biology and the impact of NAMPT inhibition as therapeutic strategy for cancer treatment.

Introduction

Hanahan and Weinberg in 2011 included the reprogramming of cellular metabolism among "next-generation" hallmarks of cancer that ultimately support tumorigenesis and cancer progression (Hanahan and Weinberg, 2011). A unique feature of cancer cells is the high demand for energetic molecules [i.e., adenosine triphosphate (ATP)] required to sustain their rapid growth rate and the biosynthesis of DNA and proteins (Pavlova and Thompson, 2016). For these reasons, metabolic pathways and enzymes are emerging as novel targets for cancer treatment.

Nicotinamide adenine dinucleotide (NAD) is a cofactor involved in many redox reactions essential to generate ATP. NAD functions as an electron carrier, cycling between the oxidized (NAD) and reduced (NADH) forms, and is fundamental in regulating the oxidative stress (Dolle et al., 2013; Houtkooper et al., 2010; Ruggieri et al., 2015). In addition, NAD is the substrate for different NAD-consuming enzymes [i.e., mono and poly-ADP-ribose polymerases (ARTs, PARPs), CD38/CD157 and sirtuins], orchestrating fundamental biological processes including DNA repair, apoptosis, calcium signaling, gene expression, transcription, immune regulation, circadian rhythm, and cell cycle progression (Chiarugi et al., 2012; Xie et al., 2020). Importantly, many of these cellular events were found to be implicated in malignant transformation and tumor progression (Audrito et al., 2021; Chiarugi et al., 2012). The homeostasis of NAD metabolism is therefore a critical element in tumor and is the result of a dynamic balance between its biosynthesis and consumption (Canto et al., 2015; Gasparrini et al., 2021). Cells maintain adequate NAD levels through multiple biosynthetic enzymatic pathways; however, a common strategy of several tumors is to sustain NAD production over-expressing the rate-limiting enzyme nicotinamide phosphoribosyltransferase (NAMPT) (Audrito et al., 2020a; Garten et

al., 2015; Heske, 2019). A link between NAMPT/NAD axis and cancer metabolism is clearly established, furthermore additional functions of NAMPT in tumor biology, not necessary connected with its enzymatic activity, are emerging as we discuss in this paper. For all these reasons, interfere with NAMPT activities in tumor is a valid therapeutic strategy as shown by anti-tumor properties of NAMPT inhibitors (i) in several models of cancers (Audrito et al., 2019a; Dalamaga et al., 2018; Galli et al., 2020; Ghanem et al., 2021; Xie et al., 2020; Yaku et al., 2018).

This review will summarize the main cancer features modulated by NAMPT, and its role as cancer therapeutic target.

NAMPT: enzyme and cytokine

NAMPT can function as NAD-biosynthetic enzyme, as well as growth factor, cytokine and adipokine as reviewed in (Audrito et al., 2019a; Garten et al., 2015; Heske, 2019) (**Figure 1**).

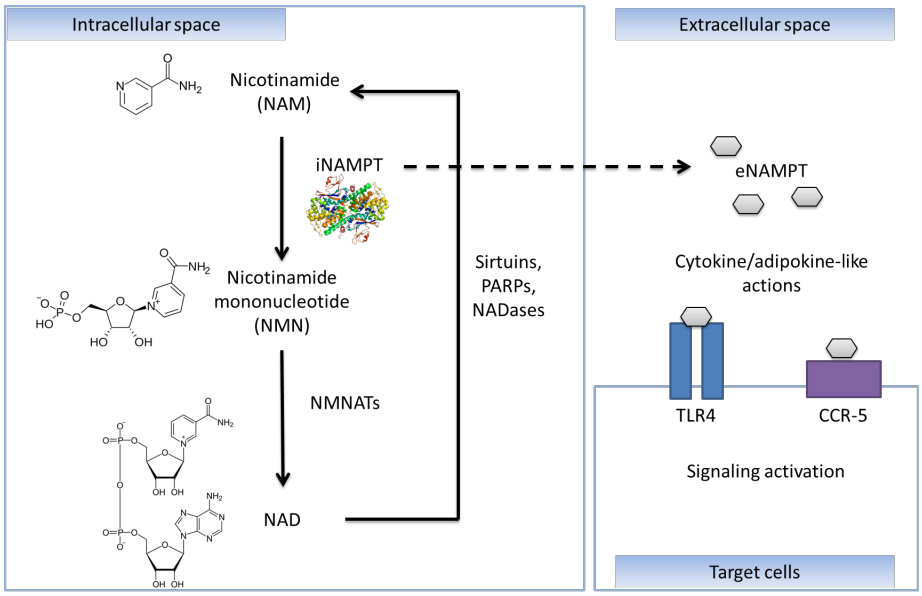


Figure 1. **Schematic representation of the intracellular and extracellular NAMPT activities.** Intracellular NAMPT (iNAMPT) converts NAM into NMN, which is then adenylated to NAD by NMNATs, sustaining NAD synthesis and energetic metabolism. Once secreted, the extracellular enzyme (eNAMPT) acts as a cytokine-like protein, regulating intracellular signaling pathways with different effects, directly binding to membrane receptors.
NMNATs: nicotinamide mononucleotide adenyltransferases; PARPs: poly-ADP-ribosyl polymerases; TLR4: toll-like receptor 4; CCR-5: C-C chemokine receptor type 5.

NAD biosynthesis is guaranteed by the presence of several metabolic routes. In addition to a *de novo* synthesis from the catabolism of the amino acid tryptophan, NAD can also be salvaged from the three forms of vitamin B3: nicotinamide (NAM), nicotinic acid (NA), and nicotinamide riboside (NR), metabolized by specific limiting enzymes. In the NAD-biosynthetic salvage pathway from NAM precursor, which represents the most relevant route of NAD production in mammalian cells, NAMPT is the first and rate-limiting enzyme promoting NAD biosynthesis. In turns, mostly PARPs and sirtuins release NAM during their enzymatic activities, increasing its availability for NAMPT-dependent NAD synthesis (Audrito et al., 2019b; Houtkooper et al., 2010; Ruggieri et al., 2015). NAMPT is ubiquitously expressed in all mammalian tissues and is a vital enzyme for the cells (Revollo et al., 2007; Rongvaux et al., 2003). It is primary located in the cytosol and in the nucleus (Kitani et al., 2003; Pittelli et al., 2010; Svoboda et al., 2019; Zhu et al., 2019) and converts NAM and 5-phosphoribosyl-1-pyrophosphate (PRPP) into nicotinamide mononucleotide (NMN), which is then adenylated to NAD, by the enzyme NMN adenylyltransferases (NMNATs), available in 3 different isoforms in different cell districts (Houtkooper et al., 2010; Ruggieri et al., 2015) (**Figure 1 and Table 1**).

In addition to this canonical intracellular (i) enzymatic activity, NAMPT was found to be present in the extracellular environment (eNAMPT) where it represents an important mediator of inflammatory response (Audrito et al., 2020a). NAMPT can be secreted in the extracellular space, in response to different stress conditions, such as oxidative stress and inflammatory signals, by various types of cells,

including cancer cells, immune cells (macrophages), hepatocytes, cardiomyocytes and adipocytes (Friebe et al., 2011; Garten et al., 2010; Grolla et al., 2016; Pillai et al., 2013; Schilling et al., 2012; Tanaka et al., 2007). The exact mechanism of secretion is still an open question in the field (Audrito et al., 2020a). Once secreted eNAMPT can acts as a cytokine-like protein that modulates the immune response, triggering intracellular signaling that promote differentiation/polarization of myeloid cells, activation of inflammosome and secretion of pro or anti-inflammatory cytokines (Audrito et al., 2015; Gasparrini et al., 2021). The molecular mechanism of eNAMPT signaling is still under investigation. Revollo and colleagues demonstrated that secreted eNAMPT in conditioned media of adipocytes can exist as a dimer, a condition required for enzymatic activity of NAMPT (Revollo et al., 2007). This aspect was further confirmed by Zamporlini et al. which highlighted that the extracellular protein is enzymatically active (Zamporlini et al., 2014). More recently, eNAMPT showed its enzymatic role to induce intracellular NAD biosynthesis in different mice tissues (Yoon et al., 2015; Yoshida et al., 2019) with the obvious implication of a sufficient enzyme's substrates concentration to support the catalytic activity at least in mice. In this case eNAMPT might catalyze NMN formation directly in the extracellular space, thus supplying cells with this NAD precursor. However, the presence in the extracellular space of substrates, activator and product of NAMPT enzymatic reaction was not confirmed by other groups (Hara et al., 2011). On the other side, probably the most accredited hypothesis demonstrated by several studies in different cellular models was that eNAMPT could exerts cytokine-like functions independently from its enzymatic activity, as reviewed in (Audrito et al., 2020a). It has been recently reported that eNAMPT could directly binds to membrane receptors, like C–C chemokine receptor type 5 (CCR-5), acting as receptor antagonist in cancer cells or promoting muscle stem cells mediated-repair in muscle injuries (Ratnayake et al., 2021; Torretta et al., 2020; Van

den Bergh et al., 2012), and Toll-like 4 receptor (TLR4), as demonstrated in different cellular models, through the activation of specific intracellular signaling cascade, like the NF-kB pathway, involved in pro-inflammatory mechanisms (Camp et al., 2015; Carbone et al., 2017; Manago et al., 2019; Romacho et al., 2020) (**Figure 1 and Table 1**). All these evidences fix eNAMPT as a novel damage-associated molecular pattern protein (DAMP) with a remarkable role in the inflammatory response and cancer promotion (Audrito et al., 2020a).

Table 1. **iNAMPT/eNAMPT specific functions.**

NAMPT localization	***Function***	***References***
INTRACELLULAR ENZYME ACTIONS (iNAMPT)	**NAD METABOLISM** iNAMPT converts NAM into NMN, which is then adenylated to NAD by NMNATs	(Gasparrini et al., 2021)
	REGULATION OF THE ACTIVITY OF NAD-CONSUMING ENZYMES (i.e. sirtuins and PARPs)	(Chiarugi et al., 2012)
	DNA TRANSCRIPTION AND REPAIR	(Zhu et al., 2012)
	TARGET IN CANCER CELLS cancer cells express high levels of NAMPT and are highly sensitive to NAMPT inhibitors	(Galli et al., 2020)

EXTRACELLULAR ENZYME ACTIONS (eNAMPT)	**EXTRACELLULAR NAD BIOSYNTHESIS?**	(Audrito et al., 2021)
	ACTIVATION OF INTRACELLULAR PATHWAYS acting as a cytokine-like protein, eNAMPT regulates intracellular signaling pathways with different effects, directly binding to membrane receptors, like CCR-5 and TLR4	(Gasparrini et al., 2021)
	MYELOID CELL DIFFERENTIATION AND POLARIZATION	(Audrito et al., 2015; Skokowa et al., 2009; Travelli et al., 2018)
	PRO-TUMOUR SIGNALS acting as DAMP with a remarkable role in the inflammatory response and cancer promotion	(Audrito et al., 2020a).
	CANCER BIOMARKER eNAMPT circulating level are useful in the monitoring of certain malignancies	(Audrito et al., 2020a).
iNAMPT and eNAMPT	The exact interplay between the intracellular and extracellular forms has still to be fully clarified	

NAMPT functions in tumor biology

iNAMPT over-expression as well as increased circulating levels of eNAMPT were documented in several solid tumors including colorectal, ovarian, breast, gastric, prostate, thyroid, pancreatic cancers, melanoma, gliomas, sarcoma, endometrial carcinomas and hematological malignancies, as reviewed in (Audrito et al., 2019a; Chowdhry et al., 2019; Dalamaga et al., 2018; Yaku et al., 2018). Several transcriptional and post-transcriptional mechanisms regulate NAMPT expression and activity in tumors, as well as multiple signals, including hypoxia, stress conditions, DNA damage, pro-inflammatory cytokines, can induce its released (Audrito et al., 2020a). NAMPT, as intracellular and extracellular factor, exerts a direct role on tumor cells increasing tumor aggressiveness, correlating with worse prognosis and regulating different processes including metabolic adaptation, DNA repair, gene expression, signaling pathways, cell growth, invasion, stemness, epithelial to mesenchymal transition (EMT) program, metastatization, angiogenesis, immune regulation, secretion of both pro-inflammatory and immunosuppressive cytokines, and resistance to genotoxic stress. Here we described the main cancer processes in which NAMPT is involved (**Figure 2**), as many papers highlighted during past years (Dalamaga et al., 2018; Galli et al., 2010; Garten et al., 2015; Jieyu et al., 2012; Navas and Carnero, 2021; Sampath et al., 2015; Shackelford et al., 2013).

Metabolic reprogramming

Cancer cells require high energetic needs to support their proliferation, rewiring their metabolism usually increasing glycolysis to produce lactate, the so-called “Warburg effect”. Increased demand of NAD, obtained through NAMPT overexpression, is therefore needed to finance cellular metabolism. NAD supports various metabolic pathways such as glycolysis, Krebs cycle (citric acid cycle), oxidative phosphorylation, and fatty acid oxidation (Audrito et al., 2019a; Canto et al., 2015; Dalamaga et al.,

2018; Garten et al., 2015). The block of NAD generation via NAMPT inhibition is a valid therapeutic strategy to switch off altered cancer cell metabolism reducing ATP levels (Kennedy et al., 2016; Tan et al., 2013). Inhibition of NAMPT decreases glucose up-take and subsequently glycolytic flux down-regulating activity of GAPDH and LDH (Tan et al., 2015; Tan et al., 2013; Tolstikov et al., 2014). Furthermore, NAMPT inhibition causes reduction in several TCA cycle intermediates and mitochondrial dysfunction with a drop in mitochondrial potential and oxygen consumption (Audrito et al., 2018; Kennedy et al., 2016; Tan et al., 2013). Interestingly, some tumors with oncogenic mutations in metabolic genes, as for example tumors carrying Isocitrate dehydrogenase (*IDH*) mutations, become highly sensitive to NAD depletion (Tateishi et al., 2015), and the combination of NAMPT and proteasome inhibitors induces a synergistic effects in metabolic disruption (Bergaggio et al., 2018). Additionally, NAD/NADH axis is very important to protect cells from oxidative stress. NAD is an important regulator of cellular reactive oxygen species (ROS), commonly increased in cancer cells (Heske, 2019; Hong et al., 2019). NAMPT inhibition altered mitochondrial ROS levels balance leading to decreased cancer cell viability in different tumors as reviewed in (Dalamaga et al., 2018; Heske, 2019). Recently for example, pharmacological NAMPT inhibition by novel NAMPTi KPT9274 potently targeted genetically heterogeneous gliomas by activating mitochondrial dysfunction (Sharma et al., 2021).

Overall, these studies provide a rationale for targeting the NAMPT/NAD axis as a novel strategy to induce metabolic dysfunctions leading to tumor cell death.

DNA repair and epigenetic regulation

Beyond its role in redox reactions and cellular metabolism, NAD possesses a prominent cell regulatory function. Through its function in NAD biosynthesis, NAMPT activity is crucial for regulation of the activity of NAD-consuming enzymes, such as sirtuins and PARPs (Chiarugi et al., 2012).

The maintenance of genome stability is crucial for preventing cancer. A functional connection between NAMPT and PARPs derived from the evidence that NAD depletion using NAMPTi impairs DNA damage repair. Decreased PARP activity upon treatment with NAMPTi has been reported in several cancer models, forming the basis for preclinical testing of NAMPTi plus PARP activity modulators (Bajrami et al., 2012; Chan et al., 2014; Lucena-Cacace et al., 2018; Silveira et al., 2020). Importantly, the finding that tumors with defects in DNA repair mechanisms may be selectively more sensitive to NAMPTi paved the rationale to combine NAMPTi with chemotherapies enhancing the efficacy of this class of agents in selected tumor types (Piacente et al., 2017; Touat et al., 2018). PARP1 is the better characterized DNA damage sensor, rapidly activated in a damage dose-dependent manner playing a critical role in the initial chromatin organization and DNA repair pathway (Gupte et al., 2017). Recently, it has been shown that nuclear NAMPT translocation is a regulated process induced by genotoxic, oxidative stress, mainly to finance NAD production for increased PARP1 activity (Grolla et al., 2020; Svoboda et al., 2019), linking NAMPT and PARP functions in cell survival and cancer development.

As for PARPs, a NAMPT-dependent NAD levels regulation impacts on sirtuins activity. Induction or inhibition of NAMPT leads to the increase or decrease of SIRT1 activity, respectively (Imai and Yoshino, 2013). In turn, SIRT1 and SIRT6 functions can regulate NAMPT secretion and activity (Sociali et al., 2019; Yoon et al., 2015). In cancer cells the SIRT1-dependent regulation of chromatin and transcription links NAD metabolism and signaling to the control of cellular functions (Chalkiadaki and Guarente, 2015). In turns, NAMPT expression is directly regulated by SIRT1 in a positive feedback loop also including c-MYC, a transcription factor driving many hallmark characteristics of cancer cells. c-MYC requires the function of NAMPT, that leads to increased NAD to mediate SIRT1 activation (Brandl

et al., 2018; Liu et al., 2019; Menssen et al., 2012). Additionally, c-MYC was found to be a transcriptional regulator of NAMPT expression (Chowdhry et al., 2019), sustaining a c-Myc/NAMPT/SIRT1 axis in tumors.

Another important function mediated by the reciprocal regulation of NAMPT/SIRT1 is in aging/longevity process, strictly connected with tumor. This regulatory network, named the "NAD World" by Imai S. some years ago, orchestrates physiological responses to internal and external perturbations and maintains the robustness of the physiological system in mammals (Imai and Yoshino, 2013; Imai, 2016). A deregulation of this axis impacts on aging as a driver of different diseases, including cancer (Imai and Guarente, 2014; Navas and Carnero, 2021; Stromland et al., 2021; Yaku et al., 2018).

In addition to these functions, some of other tumor cellular processes in which NAMPT is involved include mechanistically a de-regulation of PARP and SIRT1 activities, as following described.

Epithelial-Mesenchymal Transformation and Stemness

NAMPT modulates phenotype plasticity of tumor conferring invasive features on cancer cells, by regulating EMT process, and supports stemness properties of tumor (Heske, 2019; Navas and Carnero, 2021). The first study that connected NAMPT with EMT/stemness highlighted that high NAMPT expression was associated with the presence of a high proportion of cancer-initiating cells in colorectal cancer (CRC) (Lucena-Cacace et al., 2018). High NAMPT expression was revealed in glioblastoma and glioma tumors and patient-derived stem-like cells (Gujar et al., 2016; Lucena-Cacace et al., 2017). NAMPT over-expressing melanoma cells increased their invasive and mesenchymal features, including expression of EMT markers such as vimentin, ZEB1, Twist, and ABC transporters. This association between an elevated NAMPT expression and aggressive melanoma features was

verified also in patients. Moreover, increased percentage of stem cell population was measured in melanoma with higher NAMPT levels (Audrito et al., 2018; Audrito et al., 2020b).

Pharmacological and genetic inhibition of NAMPT decreased cancer cell stemness and EMT markers expression in different cancer types including glioblastoma, hepatocellular carcinoma, melanoma, breast cancer (Gujar et al., 2016; Lucena-Cacace et al., 2018; Lucena-Cacace et al., 2017; Navas and Carnero, 2021; Soncini et al., 2014; Zhang et al., 2018). Additionally, NAMPT inhibition has also been shown to reverse the ability of cancer cells to dedifferentiate, as well as to reduce their capacity for invasion and metastasis formation (Lucena-Cacace et al., 2019; Soncini et al., 2014; Zhang et al., 2018).

Mechanistically, the impact of NAMPT on stemness and EMT process may be the result of the influence of NAMPT activity on transcriptional and functional regulation of stem cell signaling pathways mediated by SIRT1 and PARP as reviewed in (Heske, 2019; Navas and Carnero, 2021). In fact, perturbations of NAD levels affect gene expression also in stem cells, thus understanding the impact of NAMPT activity and expression on stemness properties of cancer cells could be relevant for optimal clinical translation of NAMPTi, but also PARPi and SIRTi.

Drug resistance and susceptibility to drugs

NAMPT is often associated with enhanced acquired resistance to chemotherapeutic agents, and more recently to targeted therapy. NAMPT overexpression confers resistance to specific drugs (chemotherapeutic agents and selective kinase inhibitors) in several tumor models, including melanoma (Audrito et al., 2018; Audrito et al., 2020a), breast cancer (Ge et al., 2019), glioma (Lucena-Cacace et al., 2017), colon cancer (Lucena-Cacace et al., 2018), sarcoma (Vora et al., 2016). On the contrary, its inhibition increases the susceptibility to different drugs. In prostate cancer, NAMPT is

overexpressed along with SIRT1. NAMPT knockdown sensitizes prostate cancer cells to oxidative stress caused by H_2O_2 or chemotherapeutic treatment. Overexpression of NAMPT increases prostate cancer cell resistance to oxidative stress, which is partially blocked by SIRT1 knockdown (Wang et al., 2011). Up-regulation of NAMPT in breast cancer patients is closely related to poor response to chemotherapeutic drugs such as doxorubicin (Folgueira et al., 2005); on the contrary, NAMPT inhibition by direct targeting by miR-154 led to reduction of breast cancer cells viability increasing their susceptibility to doxorubicin (Bolandghamat Pour et al., 2019). *IDH1*-mutant gliomas are dependent on NAD for survival. The combination of alkylating chemotherapeutic agent temozolomide with NAMPTi in an *in vivo IDH1*-mutant cancer model exhibited enhanced efficacy compared with each agent alone (Tateishi et al., 2017). In hematological malignances the inhibition of NAMPT sensitizes leukemia cells for chemotherapeutics. For example, NAMPT protein abundance, enzymatic activity and NAD concentrations were significantly higher in Jurkat and Molt-4 leukemia cell lines compared to normal peripheral blood mononuclear cells. Combination of etoposide and NAMPTi caused increased cell death in leukemia cell lines compared to etoposide alone (Grohmann et al., 2018). In myeloma, NAMPT knockdown significantly enhances the anti-myeloma effect of bortezomib, which can be rescued by ectopically NAMPT overexpression (Bergaggio et al., 2018; Cagnetta et al., 2013).

All these evidences support the targeting of NAMPT as a novel therapeutic strategy to enhance the efficacy of chemotherapeutic agents and targeted-therapy in tumors.

Immune modulation within the Tumor Microenvironment

It is now clear that a de-regulation of NAMPT expression and function strongly impacts on immune responses (Audrito et al., 2021). As previously described, NAMPT is also present in the extracellular environment, where it can be considered as an immunomodulatory agent mainly binding receptors

like TLR4 and CCR-5 (Camp et al., 2015; Carbone et al., 2017). On the contrary, the enzymatic function of eNAMPT is still under debate. Circulating eNAMPT was reported as a cancer biomarker, useful in the monitoring of certain malignancies (Audrito et al., 2020a; Dalamaga et al., 2018; Garten et al., 2015; Grolla et al., 2016). The role of eNAMPT directed on tumor cells is the promotion of tumor progression and aggressiveness. eNAMPT activates signaling pathways, including NF-KB, MAPK, STAT3, and increases secretion of cytokines, including IL-1α, IL-1β, IL-8, IL-6 and tumor necrosis factor- α (TNF-α), linking chronic inflammation with carcinogenesis (Kim et al., 2008; Moschen et al., 2007). Treatment with eNAMPT promotes tumor invasive and metastatic features stimulating matrix metalloproteinases (MMPs) activity and modulating EMT via transforming growth factor-β (TGF-β) (Adya et al., 2008; Soncini et al., 2014). In addition, eNAMPT exerts a pro-angiogenetic activity promoting expression of vascular endothelial growth factor (VEGF) through MAPK, phosphoinositide 3 kinases (PI3Ks)/Akt and STAT3 pathways (Adya et al., 2008; Kim et al., 2009).

The second function of eNAMPT within the tumor microenvironment is the modulation of immune response. eNAMPT acts mainly on myeloid cell populations (Sica et al., 2017) by promoting macrophage differentiation and polarization in tumor-supportive cells like tumor-associated macrophages (TAMs) (Audrito et al., 2015) and myeloid-derived suppressor cells (MDSCs) (Travelli et al., 2019) in hematological and solid tumors. However, the exact role of iNAMPT/eNAMPT in the process of myelopoiesis is incompletely elucidated so far (Audrito et al., 2015; Skokowa et al., 2009; Travelli et al., 2018). Additionally, NAMPT/NAD axis impacts also on metabolic switch of macrophages characterized by the transition from the early initiation phase of acute inflammation, which is anabolic and primarily requires glycolysis, to the later adaptation phase which is catabolic and relies on fatty acid oxidation (FAO) for energy (Liu et al., 2012). Effects of eNAMPT on other immune cell populations

included a priming of the pro-tumor functions and pro-angiogenic switch of tumor-associated neutrophils (TANs) in melanoma (Pylaeva et al., 2019). Intriguingly, very recently in liver carcinoma NAMPT/NAD was recently found to impinge on the interferon (IFN)γ-STAT1 axis, via NAD-dependent epigenetic mechanism potentiating IFN-induced programmed death-ligand 1 (PD-L1) expression and immune evasion (Huffaker et al., 2021). The impact of eNAMPT signaling in triggering IFN-like responses needs to be evaluated to investigate a potential NAMPT-dependent T cell function modulation.

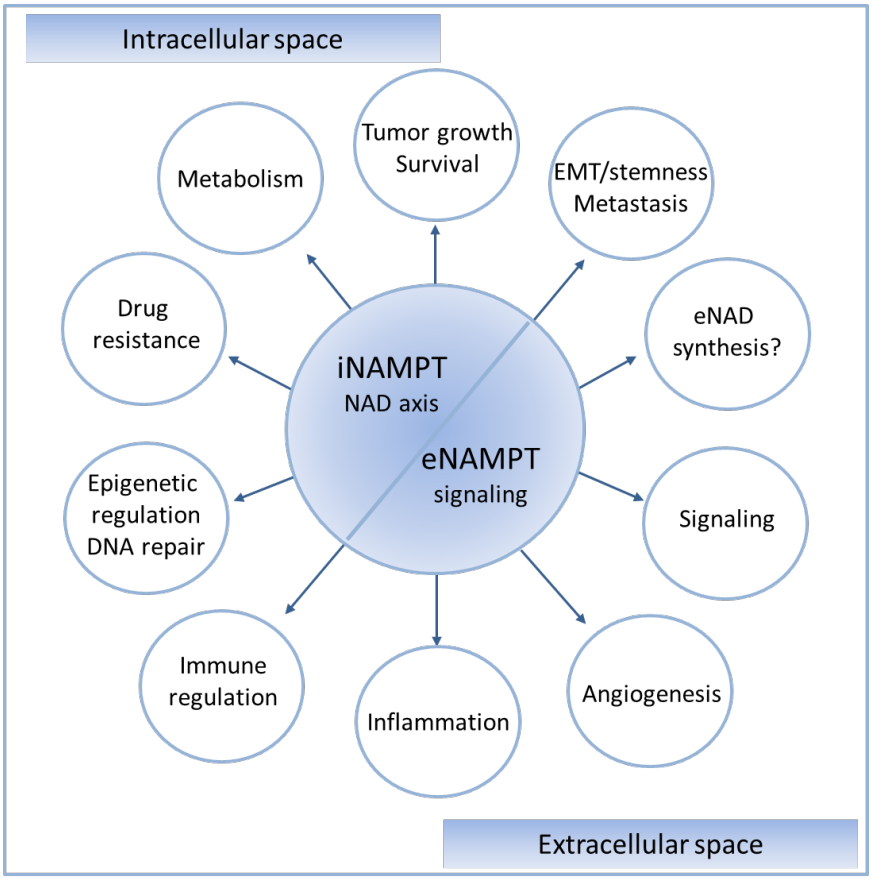


Figure 2. NAMPT in cancer biology. NAMPT is a multifunctional protein regulating NAD generation mainly in the intracellular (i) space (iNAMPT) and a cytokine-like protein binding receptors like TLR4 and/or CCR-5 in the extracellular (e) space (eNAMPT). The up-regulation of NAMPT in cancer affects several processes involved in tumor development and progression, as well as modulating the tumor microenvironments and the crosstalk with immune and stromal cells. The synthesis of eNAD in the extracellular space remains an open question that needs more investigations.
EMT: epithelial-mesenchymal transition.

NAMPT inhibition as a therapeutic strategy in cancer

Increasing number of pharmacological NAMPTi have been developed, considering the key role of NAMPT as rate-limiting enzyme in the NAD salvage pathway [www.clinicaltrials.gov; (Galli et al., 2020; Xie et al., 2020)].

The first chemical compound studied as NAMPT inhibitor was FK866 (also known as APO866), which demonstrated important cytotoxicity and tumor regression activity both *in vitro* and *in vivo* models, mainly in leukemia and liver cancer cells (Galli et al., 2020; Ghanem et al., 2021; Xie et al., 2020). A similar role was exerted by GMX1778 (also known as CHS-828), which highlighted beneficial effects in breast and lung cancer *in vitro* and *in vivo* (Ghanem et al., 2021). Despite these important results obtained with these compounds, phase I clinical trials in advanced solid tumors and leukemia showed no objective tumor remission and toxicity (Audrito et al., 2020a; Galli et al., 2020; Xie et al., 2020). One possible explanation of the partial failure of NAMPTi treatment could be linked to the concomitant expression of others NAD-biosynthetic enzymes [i.e. nicotin acid prosphoribosyltransferase (NAPRT)] that can overcome NAMPT inhibition ensuring NAD production from NA and restricting the use of NAMPTi as single agents (Audrito et al., 2020a; Galli et al., 2020; Ghanem et al., 2021; Xie et al., 2020).

In order to overcome this limit, different approaches have been identified to re-sensitize cancer cells to NAMPTi and reduce their toxicities, as recently reviewed in (Ghanem et al., 2021; Xie et al., 2020): (i) combining NAMPTi with specific anti-cancer agent or therapy to achieve a synergistic therapeutically effect; (ii) combining NAMPTi with NAPRTi in NAPRT-overexpressing tumors. The competitive inhibitor 2-Hydroxy Nicotinic Acid (a NAPRT enzymatic inhibitor), in particular, might represent a useful tool to sensitize cells to FK866 in pancreatic and ovarian cancer cells. Other NAPRTi

include non-steroidal anti-inflammatory compounds and different metabolites involved in glucose and fatty acid metabolisms (Galassi et al., 2012). (iii) Developing less toxic and more effective NAMPTi: among these the novel specific NAMPTi OT-82 demonstrated stronger activity towards hematopoietic malignancies compared to non-hematopoietic cancers, and it is currently evaluated in phase I clinical trials; (iv) developing dual NAMPTi, like STF-31, an hybrid inhibitor of NAMPT and glucose transporter 1 used in renal cell carcinomas, chidamide, a histone deacetylase inhibitor useful for the T-cell lymphoma treatment, or KPT-9274 (ATG-019, **Table 2**). This one is a dual inhibitor of NAMPT and of the serine/threonine p21-activated kinase 4, it is used in renal cell carcinoma and, such as OT-82, it is under phase I clinical trials evaluation (**Table 2**). Finally, considering the controversial aspect related to the enzymatic role of eNAMPT, it is not clear if these inhibitors could also affect eNAMPT activity. In this sense there is a new research goal focused to the (v) development of blocking antibody able to neutralize eNAMPT and reduce its "cytokine-like activity" in the tumor microenvironment. Different polyclonal and monoclonal antibodies (Abs) have been created and used to block the inflammatory and cancer development activity mediated by NAMPT, in different models, like lung injury and prostate cancer (Garcia et al., 2022; Oita et al., 2018; Sun et al., 2020), endothelial cells inflammation (Quijada et al., 2020) and in different models of induced-colitis (Colombo et al., 2020). The main activities of these Abs, currently all in pre-clinical stages, are summarized in **Figure 3**.

Altogether these different approaches could improve the overall performance of NAMPT-blocking strategies.

Table 2. NAMPTi under evaluation in clinical trials (https://www.clinicaltrials.gov)

Compound	Study type	Brief description	Condition	Intervention	Clinical trials.gov

	and pahse				**number and results**
OT-82	Interventional, phase 1	Determine the safety and tolerability and the maximum tolerated dose (MTD) or the maximum tested dose of OT-82 administered orally to participants	Relapsed or Refractory Lymphoma	<u>Dose Escalation</u> The starting OT-82 dose level will be16.5mg/m^2 given orally as an oral suspension once daily on days 1-3, 8-10, and 15-17 of each successive 28-day cycle. Dose escalation will follow a modified 3+3 design. There is no maximum duration of OT-82 treatment	NCT03921879, Actually no results posted (estimated study completion date: June 2021)
KPT-9274	Interventional, phase 1	Evaluate the safety and tolerability (MTD) of oral KPT-9274 administration	Relapsed and Refractory Acute Myeloid Leukemia	<u>Dose escalation</u> Patients will receive oral KPT-9274 three times a week every other day (days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle, and the first	NCT04914845, Actually no results posted (estimated study completion date: February 2027)

				dose cohort will be 30 mg. Subsequent dose escalation cohorts, as well as a de-escalation cohort, will be administered. Dose escalation will continue until the MTD is determined	
KPT-9274 ± niacin ER	Interventional, phase 1	Evaluate the safety and tolerability (MTD) of oral KPT-9274 administration alone or in combination with niacin ER	solid tumors or non-Hodgkin's lymphoma	<u>Dose escalation</u> Oral KPT-9274 will be taken three times a week every other day (days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle alone or in combination with a starting dose of 500 mg niacin ER co-administered with each dose of KPT-9274	NCT04281420, Actually no results posted (estimated study completion date: November 2023)

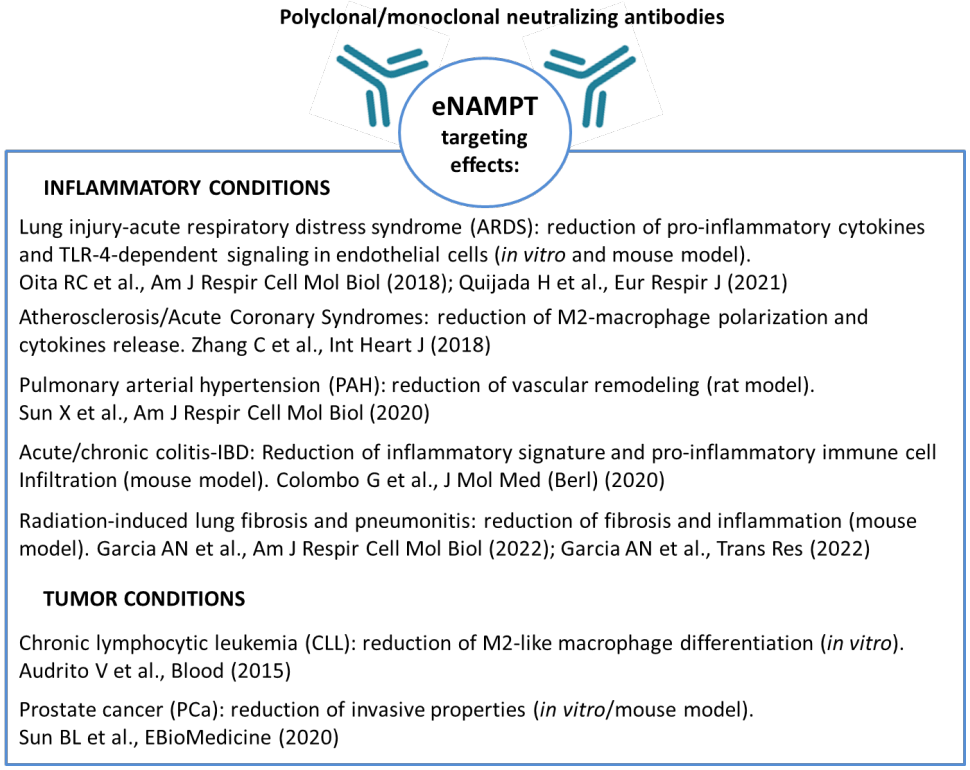


Figure 3. eNAMPT targeting. eNAMPT functions within the extracellular space in inflammatory and tumor conditions can be counteracted exploiting polyclonal or monoclonal neutralizing antibodies. These antibodies were used in pre-clinical setting in different diseases models, as reported.

Conclusion and perspectives

In the last 20 years increasing evidence has supported a prominent role of NAMPT in tumor biology, not only as biomarker due to its general over-expression in several tumor types, but also as a driver in modulating tumor-associated properties. The recent finding of its genetic amplification in tumors (Chowdhry et al., 2019) prompts to consider this enzyme as a proto-oncogene involved in tumor transformation, even if this hypothesis needs to be experimentally confirmed. Targeting NAMPT in cancer may be a valid strategy, also considering that tumor cells are in general more sensitive to

NAMPTi compared to normal cells. However, old NAMPTi showed no objective tumor remission in the first round of clinical trials due to the appearance of side effects that limited their use in patients and, most probably, due to the concomitant expression of other NAD-biosynthetic enzymes (NBEs) that could compensate for NAMPT inhibition. It is now clear that is essential to select tumors addictive to the NAD salvage pathway controlled by NAMPT, to avoid rescue mechanisms. However, in our opinion, the future of NAMPTi will be in combination with other drugs with complementary activities, rather than used as single agents, to target simultaneously different critical tumor features. This strategy could lead to obtain a more durable clinical remission and exclude or postpone drug resistance mechanisms. Finally, the increasing idea of targeting eNAMPT in tumors, to counteract the extracellular functions of this protein, could be a goal imaging to combine eNAMPT neutralization and immunotherapy. At this moment these are only speculative hypotheses, but we hope that in the next few years some new NAMPTi and/or antibodies in combination with other compounds will enter in clinical trials for cancer therapy.

Commentato [MG1]: Non mi pare venga riutilizzata questa abbreviazione, forse conviene toglierla.

Author Contributions

VA designed and reviewed the work. VA and MG wrote the paper. All authors approved the final version of the manuscript for publication.

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References

Adya, R., Tan, B.K., Punn, A., Chen, J., Randeva, H.S., 2008. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. Cardiovasc Res 78(2), 356-365.

Audrito, V., Manago, A., Gaudino, F., Deaglio, S., 2019a. Targeting metabolic reprogramming in metastatic melanoma: The key role of nicotinamide phosphoribosyltransferase (NAMPT). Semin Cell Dev Biol (18), 30203-30209.

Audrito, V., Manago, A., Gaudino, F., Sorci, L., Messana, V.G., Raffaelli, N., Deaglio, S., 2019b. NAD-Biosynthetic and Consuming Enzymes as Central Players of Metabolic Regulation of Innate and Adaptive Immune Responses in Cancer. Front Immunol 10, 1720.

Audrito, V., Manago, A., La Vecchia, S., Zamporlini, F., Vitale, N., Baroni, G., Cignetto, S., Serra, S., Bologna, C., Stingi, A., Arruga, F., Vaisitti, T., Massi, D., Mandala, M., Raffaelli, N., Deaglio, S., 2018. Nicotinamide Phosphoribosyltransferase (NAMPT) as a Therapeutic Target in BRAF-Mutated Metastatic Melanoma. J Natl Cancer Inst 110(3).

Audrito, V., Messana, V.G., Brandimarte, L., Deaglio, S., 2021. The Extracellular NADome Modulates Immune Responses. Front Immunol 12, 704779.

Audrito, V., Messana, V.G., Deaglio, S., 2020a. NAMPT and NAPRT: Two Metabolic Enzymes With Key Roles in Inflammation. Front Oncol 10, 358.

Audrito, V., Messana, V.G., Moiso, E., Vitale, N., Arruga, F., Brandimarte, L., Gaudino, F., Pellegrino, E., Vaisitti, T., Riganti, C., Piva, R., Deaglio, S., 2020b. NAMPT Over-Expression Recapitulates the BRAF Inhibitor Resistant Phenotype Plasticity in Melanoma. Cancers (Basel) 12(12).

Audrito, V., Serra, S., Brusa, D., Mazzola, F., Arruga, F., Vaisitti, T., Coscia, M., Maffei, R., Rossi, D., Wang, T., Inghirami, G., Rizzi, M., Gaidano, G., Garcia, J.G., Wolberger, C., Raffaelli, N., Deaglio, S., 2015. Extracellular nicotinamide phosphoribosyltransferase (NAMPT) promotes M2 macrophage polarization in chronic lymphocytic leukemia. Blood 125(1), 111-123.

Bajrami, I., Kigozi, A., Van Weverwijk, A., Brough, R., Frankum, J., Lord, C.J., Ashworth, A., 2012. Synthetic lethality of PARP and NAMPT inhibition in triple-negative breast cancer cells. EMBO Mol Med 4(10), 1087-1096.

Bergaggio, E., Riganti, C., Garaffo, G., Vitale, N., Mereu, E., Bandini, C., Pellegrino, E., Pullano, V., Omede, P., Todoerti, K., Cascione, L., Audrito, V., Riccio, A., Rossi, A., Bertoni, F., Deaglio, S., Neri, A., Palumbo, A., Piva, R., 2018. IDH2 inhibition enhances proteasome inhibitor responsiveness in hematological malignancies. Blood.

Bolandghamat Pour, Z., Nourbakhsh, M., Mousavizadeh, K., Madjd, Z., Ghorbanhosseini, S.S., Abdolvahabi, Z., Hesari, Z., Ezzati Mobasser, S., 2019. Suppression of nicotinamide phosphoribosyltransferase expression by miR-154 reduces the viability of breast cancer cells and increases their susceptibility to doxorubicin. BMC Cancer 19(1), 1027.

Brandl, L., Kirstein, N., Neumann, J., Sendelhofert, A., Vieth, M., Kirchner, T., Menssen, A., 2018. The c-MYC/NAMPT/SIRT1 feedback loop is activated in early classical and serrated route colorectal cancer and represents a therapeutic target. Med Oncol 36(1), 5.

Cagnetta, A., Cea, M., Calimeri, T., Acharya, C., Fulciniti, M., Tai, Y.T., Hideshima, T., Chauhan, D., Zhong, M.Y., Patrone, F., Nencioni, A., Gobbi, M., Richardson, P., Munshi, N., Anderson, K.C., 2013. Intracellular NAD(+) depletion enhances bortezomib-induced anti-myeloma activity. Blood 122(7), 1243-1255.

Camp, S.M., Ceco, E., Evenoski, C.L., Danilov, S.M., Zhou, T., Chiang, E.T., Moreno-Vinasco, L., Mapes, B., Zhao, J., Gursoy, G., Brown, M.E., Adyshev, D.M., Siddiqui, S.S., Quijada, H., Sammani, S., Letsiou, E., Saadat, L., Yousef, M., Wang, T., Liang, J., Garcia, J.G., 2015. Unique Toll-Like Receptor 4 Activation by NAMPT/PBEF Induces NFkappaB Signaling and Inflammatory Lung Injury. Sci Rep 5, 13135.

Canto, C., Menzies, K.J., Auwerx, J., 2015. NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus. Cell Metab 22(1), 31-53.

Carbone, F., Liberale, L., Bonaventura, A., Vecchie, A., Casula, M., Cea, M., Monacelli, F., Caffa, I., Bruzzone, S., Montecucco, F., Nencioni, A., 2017. Regulation and Function of Extracellular Nicotinamide Phosphoribosyltransferase/Visfatin. Compr Physiol 7(2), 603-621.

Chalkiadaki, A., Guarente, L., 2015. The multifaceted functions of sirtuins in cancer. Nat Rev Cancer 15(10), 608-624.

Chan, M., Gravel, M., Bramoulle, A., Bridon, G., Avizonis, D., Shore, G.C., Roulston, A., 2014. Synergy between the NAMPT inhibitor GMX1777(8) and pemetrexed in non-small cell lung cancer cells is mediated by PARP activation and enhanced NAD consumption. Cancer Res 74(21), 5948-5954.

Chiarugi, A., Dolle, C., Felici, R., Ziegler, M., 2012. The NAD metabolome--a key determinant of cancer cell biology. Nature reviews. Cancer 12(11), 741-752.

Chowdhry, S., Zanca, C., Rajkumar, U., Koga, T., Diao, Y., Raviram, R., Liu, F., Turner, K., Yang, H., Brunk, E., Bi, J., Furnari, F., Bafna, V., Ren, B., Mischel, P.S., 2019. NAD metabolic dependency in cancer is shaped by gene amplification and enhancer remodelling. Nature 569(7757), 570-575.

Colombo, G., Clemente, N., Zito, A., Bracci, C., Colombo, F.S., Sangaletti, S., Jachetti, E., Ribaldone, D.G., Caviglia, G.P., Pastorelli, L., De Andrea, M., Naviglio, S., Lucafo, M., Stocco, G., Grolla, A.A., Campolo, M., Casili, G., Cuzzocrea, S., Esposito, E., Malavasi, F., Genazzani, A.A., Porta, C., Travelli, C., 2020. Neutralization of extracellular NAMPT (nicotinamide phosphoribosyltransferase) ameliorates experimental murine colitis. J Mol Med (Berl) 98(4), 595-612.

Dalamaga, M., Christodoulatos, G.S., Mantzoros, C.S., 2018. The role of extracellular and intracellular Nicotinamide phosphoribosyl-transferase in cancer: Diagnostic and therapeutic perspectives and challenges. Metabolism 82, 72-87.

Dolle, C., Skoge, R.H., Vanlinden, M.R., Ziegler, M., 2013. NAD biosynthesis in humans--enzymes, metabolites and therapeutic aspects. Curr Top Med Chem 13(23), 2907-2917.

Folgueira, M.A., Carraro, D.M., Brentani, H., Patrao, D.F., Barbosa, E.M., Netto, M.M., Caldeira, J.R., Katayama, M.L., Soares, F.A., Oliveira, C.T., Reis, L.F., Kaiano, J.H., Camargo, L.P., Vencio, R.Z., Snitcovsky, I.M., Makdissi, F.B., e Silva, P.J., Goes, J.C., Brentani, M.M., 2005. Gene expression profile associated with response to doxorubicin-based therapy in breast cancer. Clin Cancer Res 11(20), 7434-7443.

Friebe, D., Neef, M., Kratzsch, J., Erbs, S., Dittrich, K., Garten, A., Petzold-Quinque, S., Bluher, S., Reinehr, T., Stumvoll, M., Bluher, M., Kiess, W., Korner, A., 2011. Leucocytes are a major source of circulating nicotinamide phosphoribosyltransferase (NAMPT)/pre-B cell colony (PBEF)/visfatin linking obesity and inflammation in humans. Diabetologia 54(5), 1200-1211.

Galassi, L., Di Stefano, M., Brunetti, L., Orsomando, G., Amici, A., Ruggieri, S., Magni, G., 2012. Characterization of human nicotinate phosphoribosyltransferase: Kinetic studies, structure prediction and functional analysis by site-directed mutagenesis. Biochimie 94(2), 300-309.

Galli, M., Van Gool, F., Rongvaux, A., Andris, F., Leo, O., 2010. The nicotinamide phosphoribosyltransferase: a molecular link between metabolism, inflammation, and cancer. Cancer Res 70(1), 8-11.

Galli, U., Colombo, G., Travelli, C., Tron, G.C., Genazzani, A.A., Grolla, A.A., 2020. Recent Advances in NAMPT Inhibitors: A Novel Immunotherapic Strategy. Front Pharmacol 11, 656.

Garcia, A.N., Casanova, N.G., Kempf, C.L., Bermudez, T., Valera, D.G., Song, J.H., Sun, X., Cai, H., Moreno-Vinasco, L., Gregory, T., Oita, R.C., Reyes Hernon, V., Camp, S.M., Rogers, C., Kyubwa, E.M., Menon, N., Axtelle, J., Rappaport, J., Bime, C., Sammani, S., Cress, A.E., Garcia, J.G.N., 2022. eNAMPT is a Novel DAMP that Contributes to the Severity of Radiation-Induced Lung Fibrosis. Am J Respir Cell Mol Biol.

Garten, A., Petzold, S., Barnikol-Oettler, A., Korner, A., Thasler, W.E., Kratzsch, J., Kiess, W., Gebhardt, R., 2010. Nicotinamide phosphoribosyltransferase (NAMPT/PBEF/visfatin) is constitutively released from human hepatocytes. Biochem Biophys Res Commun 391(1), 376-381.

Garten, A., Schuster, S., Penke, M., Gorski, T., de Giorgis, T., Kiess, W., 2015. Physiological and pathophysiological roles of NAMPT and NAD metabolism. Nat Rev Endocrinol 11(9), 535-546.

Gasparrini, M., Sorci, L., Raffaelli, N., 2021. Enzymology of extracellular NAD metabolism. Cell Mol Life Sci 78(7), 3317-3331.

Ge, X., Zhao, Y., Dong, L., Seng, J., Zhang, X., Dou, D., 2019. NAMPT regulates PKM2 nuclear location through 14-3-3zeta: Conferring resistance to tamoxifen in breast cancer. J Cell Physiol 234(12), 23409-23420.

Ghanem, M.S., Monacelli, F., Nencioni, A., 2021. Advances in NAD-Lowering Agents for Cancer Treatment. Nutrients 13(5).

Grohmann, T., Penke, M., Petzold-Quinque, S., Schuster, S., Richter, S., Kiess, W., Garten, A., 2018. Inhibition of NAMPT sensitizes MOLT4 leukemia cells for etoposide treatment through the SIRT2-p53 pathway. Leuk Res 69, 39-46.

Grolla, A.A., Miggiano, R., Di Marino, D., Bianchi, M., Gori, A., Orsomando, G., Gaudino, F., Galli, U., Del Grosso, E., Mazzola, F., Angeletti, C., Guarneri, M., Torretta, S., Calabro, M., Boumya, S., Fan, X., Colombo, G., Travelli, C., Rocchio, F., Aronica, E., Wohlschlegel, J.A., Deaglio, S., Rizzi, M., Genazzani,

A.A., Garavaglia, S., 2020. A nicotinamide phosphoribosyltransferase-GAPDH interaction sustains the stress-induced NMN/NAD(+) salvage pathway in the nucleus. J Biol Chem.

Grolla, A.A., Travelli, C., Genazzani, A.A., Sethi, J.K., 2016. Extracellular nicotinamide phosphoribosyltransferase, a new cancer metabokine. Br J Pharmacol 173(14), 2182-2194.

Gujar, A.D., Le, S., Mao, D.D., Dadey, D.Y., Turski, A., Sasaki, Y., Aum, D., Luo, J., Dahiya, S., Yuan, L., Rich, K.M., Milbrandt, J., Hallahan, D.E., Yano, H., Tran, D.D., Kim, A.H., 2016. An NAD+-dependent transcriptional program governs self-renewal and radiation resistance in glioblastoma. Proc Natl Acad Sci U S A 113(51), E8247-E8256.

Gupte, R., Liu, Z., Kraus, W.L., 2017. PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes. Genes Dev 31(2), 101-126.

Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144(5), 646-674.

Hara, N., Yamada, K., Shibata, T., Osago, H., Tsuchiya, M., 2011. Nicotinamide phosphoribosyltransferase/visfatin does not catalyze nicotinamide mononucleotide formation in blood plasma. PLoS One 6(8), e22781.

Heske, C.M., 2019. Beyond Energy Metabolism: Exploiting the Additional Roles of NAMPT for Cancer Therapy. Front Oncol 9, 1514.

Hong, S.M., Hwang, S.W., Wang, T., Park, C.W., Ryu, Y.M., Jung, J.H., Shin, J.H., Kim, S.Y., Lee, J.L., Kim, C.W., Yoon, G., Kim, K.H., Myung, S.J., Choi, K.Y., 2019. Increased nicotinamide adenine dinucleotide pool promotes colon cancer progression by suppressing reactive oxygen species level. Cancer Sci 110(2), 629-638.

Houtkooper, R.H., Canto, C., Wanders, R.J., Auwerx, J., 2010. The secret life of NAD+: an old metabolite controlling new metabolic signaling pathways. Endocr Rev 31(2), 194-223.

Huffaker, T.B., Ekiz, H.A., Barba, C., Lee, S.H., Runtsch, M.C., Nelson, M.C., Bauer, K.M., Tang, W.W., Mosbruger, T.L., Cox, J.E., Round, J.L., Voth, W.P., O'Connell, R.M., 2021. A Stat1 bound enhancer promotes Nampt expression and function within tumor associated macrophages. Nat Commun 12(1), 2620.

Imai, S., Guarente, L., 2014. NAD+ and sirtuins in aging and disease. Trends Cell Biol 24(8), 464-471.

Imai, S., Yoshino, J., 2013. The importance of NAMPT/NAD/SIRT1 in the systemic regulation of metabolism and ageing. Diabetes Obes Metab 15 Suppl 3, 26-33.

Imai, S.I., 2016. The NAD World 2.0: the importance of the inter-tissue communication mediated by NAMPT/NAD(+)/SIRT1 in mammalian aging and longevity control. NPJ Syst Biol Appl 2, 16018.

Jieyu, H., Chao, T., Mengjun, L., Shalong, W., Xiaomei, G., Jianfeng, L., Zhihong, L., 2012. Nampt/Visfatin/PBEF: a functionally multi-faceted protein with a pivotal role in malignant tumors. Curr Pharm Des 18(37), 6123-6132.

Kennedy, B.E., Sharif, T., Martell, E., Dai, C., Kim, Y., Lee, P.W., Gujar, S.A., 2016. NAD(+) salvage pathway in cancer metabolism and therapy. Pharmacol Res 114, 274-283.

Kim, J.Y., Bae, Y.H., Bae, M.K., Kim, S.R., Park, H.J., Wee, H.J., Bae, S.K., 2009. Visfatin through STAT3 activation enhances IL-6 expression that promotes endothelial angiogenesis. Biochim Biophys Acta 1793(11), 1759-1767.

Kim, S.R., Bae, Y.H., Bae, S.K., Choi, K.S., Yoon, K.H., Koo, T.H., Jang, H.O., Yun, I., Kim, K.W., Kwon, Y.G., Yoo, M.A., Bae, M.K., 2008. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-kappaB activation in endothelial cells. Biochim Biophys Acta 1783(5), 886-895.

Kitani, T., Okuno, S., Fujisawa, H., 2003. Growth phase-dependent changes in the subcellular localization of pre-B-cell colony-enhancing factor. FEBS Lett 544(1-3), 74-78.

Liu, H., Liu, N., Zhao, Y., Zhu, X., Wang, C., Liu, Q., Gao, C., Zhao, X., Li, J., 2019. Oncogenic USP22 supports gastric cancer growth and metastasis by activating c-Myc/NAMPT/SIRT1-dependent FOXO1 and YAP signaling. Aging (Albany NY) 11(21), 9643-9660.

Liu, T.F., Vachharajani, V.T., Yoza, B.K., McCall, C.E., 2012. NAD+-dependent sirtuin 1 and 6 proteins coordinate a switch from glucose to fatty acid oxidation during the acute inflammatory response. J Biol Chem 287(31), 25758-25769.

Lucena-Cacace, A., Otero-Albiol, D., Jimenez-Garcia, M.P., Munoz-Galvan, S., Carnero, A., 2018. NAMPT Is a Potent Oncogene in Colon Cancer Progression that Modulates Cancer Stem Cell Properties and Resistance to Therapy through Sirt1 and PARP. Clin Cancer Res 24(5), 1202-1215.

Lucena-Cacace, A., Otero-Albiol, D., Jimenez-Garcia, M.P., Peinado-Serrano, J., Carnero, A., 2017. NAMPT overexpression induces cancer stemness and defines a novel tumor signature for glioma prognosis. Oncotarget 8(59), 99514-99530.

Lucena-Cacace, A., Umeda, M., Navas, L.E., Carnero, A., 2019. NAMPT as a Dedifferentiation-Inducer Gene: NAD(+) as Core Axis for Glioma Cancer Stem-Like Cells Maintenance. Front Oncol 9, 292.

Manago, A., Audrito, V., Mazzola, F., Sorci, L., Gaudino, F., Gizzi, K., Vitale, N., Incarnato, D., Minazzato, G., Ianniello, A., Varriale, A., D'Auria, S., Mengozzi, G., Politano, G., Oliviero, S., Raffaelli, N., Deaglio, S., 2019. Extracellular nicotinate phosphoribosyltransferase binds Toll like receptor 4 and mediates inflammation. Nat Commun 10(1), 4116.

Menssen, A., Hydbring, P., Kapelle, K., Vervoorts, J., Diebold, J., Luscher, B., Larsson, L.G., Hermeking, H., 2012. The c-MYC oncoprotein, the NAMPT enzyme, the SIRT1-inhibitor DBC1, and the SIRT1 deacetylase form a positive feedback loop. Proc Natl Acad Sci U S A 109(4), E187-196.

Moschen, A.R., Kaser, A., Enrich, B., Mosheimer, B., Theurl, M., Niederegger, H., Tilg, H., 2007. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 178(3), 1748-1758.

Navas, L.E., Carnero, A., 2021. NAD(+) metabolism, stemness, the immune response, and cancer. Signal Transduct Target Ther 6(1), 2.

Oita, R.C., Camp, S.M., Ma, W., Ceco, E., Harbeck, M., Singleton, P., Messana, J., Sun, X., Wang, T., Garcia, J.G.N., 2018. Novel Mechanism for Nicotinamide Phosphoribosyltransferase Inhibition of TNF-alpha-mediated Apoptosis in Human Lung Endothelial Cells. Am J Respir Cell Mol Biol 59(1), 36-44.

Pavlova, N.N., Thompson, C.B., 2016. The Emerging Hallmarks of Cancer Metabolism. Cell Metab 23(1), 27-47.

Piacente, F., Caffa, I., Ravera, S., Sociali, G., Passalacqua, M., Vellone, V.G., Becherini, P., Reverberi, D., Monacelli, F., Ballestrero, A., Odetti, P., Cagnetta, A., Cea, M., Nahimana, A., Duchosal, M., Bruzzone, S., Nencioni, A., 2017. Nicotinic Acid Phosphoribosyltransferase Regulates Cancer Cell Metabolism, Susceptibility to NAMPT Inhibitors, and DNA Repair. Cancer Res 77(14), 3857-3869.

Pillai, V.B., Sundaresan, N.R., Kim, G., Samant, S., Moreno-Vinasco, L., Garcia, J.G., Gupta, M.P., 2013. Nampt secreted from cardiomyocytes promotes development of cardiac hypertrophy and adverse ventricular remodeling. Am J Physiol Heart Circ Physiol 304(3), H415-426.

Pittelli, M., Formentini, L., Faraco, G., Lapucci, A., Rapizzi, E., Cialdai, F., Romano, G., Moneti, G., Moroni, F., Chiarugi, A., 2010. Inhibition of nicotinamide phosphoribosyltransferase: cellular bioenergetics reveals a mitochondrial insensitive NAD pool. J Biol Chem 285(44), 34106-34114.

Pylaeva, E., Harati, M.D., Spyra, I., Bordbari, S., Strachan, S., Thakur, B.K., Hoing, B., Franklin, C., Skokowa, J., Welte, K., Schadendorf, D., Bankfalvi, A., Brandau, S., Lang, S., Jablonska, J., 2019. NAMPT signaling is critical for the proangiogenic activity of tumor-associated neutrophils. Int J Cancer 144(1), 136-149.

Quijada, H., Bermudez, T., Kempf, C.L., Valera, D.G., Garcia, A.N., Camp, S.M., Song, J.H., Franco, E., Burt, J.K., Sun, B., Mascarenhas, J.B., Burns, K., Gaber, A., Oita, R.C., Reyes Hernon, V., Barber, C., Moreno-Vinasco, L., Sun, X., Cress, A.E., Martin, D., Liu, Z., Desai, A.A., Natarajan, V., Jacobson, J.R., Dudek, S.M., Bime, C., Sammani, S., Garcia, J.G.N., 2020. Endothelial eNAMPT Amplifies Preclinical Acute Lung Injury: Efficacy of an eNAMPT-Neutralising mAb. Eur Respir J.

Ratnayake, D., Nguyen, P.D., Rossello, F.J., Wimmer, V.C., Tan, J.L., Galvis, L.A., Julier, Z., Wood, A.J., Boudier, T., Isiaku, A.I., Berger, S., Oorschot, V., Sonntag, C., Rogers, K.L., Marcelle, C., Lieschke, G.J., Martino, M.M., Bakkers, J., Currie, P.D., 2021. Macrophages provide a transient muscle stem cell niche via NAMPT secretion. Nature 591(7849), 281-287.

Revollo, J.R., Korner, A., Mills, K.F., Satoh, A., Wang, T., Garten, A., Dasgupta, B., Sasaki, Y., Wolberger, C., Townsend, R.R., Milbrandt, J., Kiess, W., Imai, S., 2007. Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. Cell Metab 6(5), 363-375.

Romacho, T., Valencia, I., Ramos-Gonzalez, M., Vallejo, S., Lopez-Esteban, M., Lorenzo, O., Cannata, P., Romero, A., San Hipolito-Luengo, A., Gomez-Cerezo, J.F., Peiro, C., Sanchez-Ferrer, C.F., 2020.

Visfatin/eNampt induces endothelial dysfunction in vivo: a role for Toll-Like Receptor 4 and NLRP3 inflammasome. Sci Rep 10(1), 5386.

Rongvaux, A., Andris, F., Van Gool, F., Leo, O., 2003. Reconstructing eukaryotic NAD metabolism. Bioessays 25(7), 683-690.

Ruggieri, S., Orsomando, G., Sorci, L., Raffaelli, N., 2015. Regulation of NAD biosynthetic enzymes modulates NAD-sensing processes to shape mammalian cell physiology under varying biological cues. Biochim Biophys Acta 1854(9), 1138-1149.

Sampath, D., Zabka, T.S., Misner, D.L., O'Brien, T., Dragovich, P.S., 2015. Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) as a therapeutic strategy in cancer. Pharmacol Ther 151, 16-31.

Schilling, E., Wehrhahn, J., Klein, C., Raulien, N., Ceglarek, U., Hauschildt, S., 2012. Inhibition of nicotinamide phosphoribosyltransferase modifies LPS-induced inflammatory responses of human monocytes. Innate Immun 18(3), 518-530.

Shackelford, R.E., Mayhall, K., Maxwell, N.M., Kandil, E., Coppola, D., 2013. Nicotinamide phosphoribosyltransferase in malignancy: a review. Genes Cancer 4(11-12), 447-456.

Sharma, P., Xu, J., Williams, K., Easley, M., Elder, J.B., Lonser, R., Lang, F.F., Lapalombella, R., Sampath, D., Puduvalli, V.K., 2021. Inhibition of nicotinamide phosphoribosyltransferase, the rate-limiting enzyme of the nicotinamide adenine dinucleotide salvage pathway, to target glioma heterogeneity through mitochondrial oxidative stress. Neuro Oncol.

Sica, A., Strauss, L., Consonni, F.M., Travelli, C., Genazzani, A., Porta, C., 2017. Metabolic regulation of suppressive myeloid cells in cancer. Cytokine Growth Factor Rev 35, 27-35.

Silveira, S.C., Buhagiar-Labarchede, G., Onclercq-Delic, R., Gemble, S., Bou Samra, E., Mameri, H., Duchambon, P., Machon, C., Guitton, J., Amor-Gueret, M., 2020. A decrease in NAMPT activity impairs basal PARP-1 activity in cytidine deaminase deficient-cells, independently of NAD(.). Sci Rep 10(1), 13907.

Skokowa, J., Lan, D., Thakur, B.K., Wang, F., Gupta, K., Cario, G., Brechlin, A.M., Schambach, A., Hinrichsen, L., Meyer, G., Gaestel, M., Stanulla, M., Tong, Q., Welte, K., 2009. NAMPT is essential for the G-CSF-induced myeloid differentiation via a NAD(+)-sirtuin-1-dependent pathway. Nat Med 15(2), 151-158.

Sociali, G., Grozio, A., Caffa, I., Schuster, S., Becherini, P., Damonte, P., Sturla, L., Fresia, C., Passalacqua, M., Mazzola, F., Raffaelli, N., Garten, A., Kiess, W., Cea, M., Nencioni, A., Bruzzone, S., 2019. SIRT6 deacetylase activity regulates NAMPT activity and NAD(P)(H) pools in cancer cells. FASEB J 33(3), 3704-3717.

Soncini, D., Caffa, I., Zoppoli, G., Cea, M., Cagnetta, A., Passalacqua, M., Mastracci, L., Boero, S., Montecucco, F., Sociali, G., Lasiglie, D., Damonte, P., Grozio, A., Mannino, E., Poggi, A., D'Agostino, V.G., Monacelli, F., Provenzani, A., Odetti, P., Ballestrero, A., Bruzzone, S., Nencioni, A., 2014.

Nicotinamide phosphoribosyltransferase promotes epithelial-to-mesenchymal transition as a soluble factor independent of its enzymatic activity. J Biol Chem 289(49), 34189-34204.

Stromland, O., Diab, J., Ferrario, E., Sverkeli, L.J., Ziegler, M., 2021. The balance between NAD(+) biosynthesis and consumption in ageing. Mech Ageing Dev 199, 111569.

Sun, B.L., Sun, X., Casanova, N., Garcia, A.N., Oita, R., Algotar, A.M., Camp, S.M., Hernon, V.R., Gregory, T., Cress, A.E., Garcia, J.G.N., 2020. Role of secreted extracellular nicotinamide phosphoribosyltransferase (eNAMPT) in prostate cancer progression: Novel biomarker and therapeutic target. EBioMedicine 61, 103059.

Svoboda, P., Krizova, E., Sestakova, S., Vapenkova, K., Knejzlik, Z., Rimpelova, S., Rayova, D., Volfova, N., Krizova, I., Rumlova, M., Sykora, D., Kizek, R., Haluzik, M., Zidek, V., Zidkova, J., Skop, V., 2019. Nuclear transport of nicotinamide phosphoribosyltransferase is cell cycle-dependent in mammalian cells, and its inhibition slows cell growth. J Biol Chem 294(22), 8676-8689.

Tan, B., Dong, S., Shepard, R.L., Kays, L., Roth, K.D., Geeganage, S., Kuo, M.S., Zhao, G., 2015. Inhibition of Nicotinamide Phosphoribosyltransferase (NAMPT), an Enzyme Essential for NAD+ Biosynthesis, Leads to Altered Carbohydrate Metabolism in Cancer Cells. J Biol Chem 290(25), 15812-15824.

Tan, B., Young, D.A., Lu, Z.H., Wang, T., Meier, T.I., Shepard, R.L., Roth, K., Zhai, Y., Huss, K., Kuo, M.S., Gillig, J., Parthasarathy, S., Burkholder, T.P., Smith, M.C., Geeganage, S., Zhao, G., 2013. Pharmacological inhibition of nicotinamide phosphoribosyltransferase (NAMPT), an enzyme essential for NAD+ biosynthesis, in human cancer cells: metabolic basis and potential clinical implications. J Biol Chem 288(5), 3500-3511.

Tanaka, M., Nozaki, M., Fukuhara, A., Segawa, K., Aoki, N., Matsuda, M., Komuro, R., Shimomura, I., 2007. Visfatin is released from 3T3-L1 adipocytes via a non-classical pathway. Biochem Biophys Res Commun 359(2), 194-201.

Tateishi, K., Higuchi, F., Miller, J.J., Koerner, M.V.A., Lelic, N., Shankar, G.M., Tanaka, S., Fisher, D.E., Batchelor, T.T., Iafrate, A.J., Wakimoto, H., Chi, A.S., Cahill, D.P., 2017. The Alkylating Chemotherapeutic Temozolomide Induces Metabolic Stress in IDH1-Mutant Cancers and Potentiates NAD(+) Depletion-Mediated Cytotoxicity. Cancer Res 77(15), 4102-4115.

Tateishi, K., Wakimoto, H., Iafrate, A.J., Tanaka, S., Loebel, F., Lelic, N., Wiederschain, D., Bedel, O., Deng, G., Zhang, B., He, T., Shi, X., Gerszten, R.E., Zhang, Y., Yeh, J.J., Curry, W.T., Zhao, D., Sundaram, S., Nigim, F., Koerner, M.V.A., Ho, Q., Fisher, D.E., Roider, E.M., Kemeny, L.V., Samuels, Y., Flaherty, K.T., Batchelor, T.T., Chi, A.S., Cahill, D.P., 2015. Extreme Vulnerability of IDH1 Mutant Cancers to NAD+ Depletion. Cancer Cell 28(6), 773-784.

Tolstikov, V., Nikolayev, A., Dong, S., Zhao, G., Kuo, M.S., 2014. Metabolomics analysis of metabolic effects of nicotinamide phosphoribosyltransferase (NAMPT) inhibition on human cancer cells. PLoS One 9(12), e114019.

Torretta, S., Colombo, G., Travelli, C., Boumya, S., Lim, D., Genazzani, A.A., Grolla, A.A., 2020. The Cytokine Nicotinamide Phosphoribosyltransferase (eNAMPT; PBEF; Visfatin) Acts as a Natural Antagonist of C-C Chemokine Receptor Type 5 (CCR5). Cells 9(2).

Touat, M., Sourisseau, T., Dorvault, N., Chabanon, R.M., Garrido, M., Morel, D., Krastev, D.B., Bigot, L., Adam, J., Frankum, J.R., Durand, S., Pontoizeau, C., Souquere, S., Kuo, M.S., Sauvaigo, S., Mardakheh, F., Sarasin, A., Olaussen, K.A., Friboulet, L., Bouillaud, F., Pierron, G., Ashworth, A., Lombes, A., Lord, C.J., Soria, J.C., Postel-Vinay, S., 2018. DNA repair deficiency sensitizes lung cancer cells to NAD+ biosynthesis blockade. J Clin Invest 128(4), 1671-1687.

Travelli, C., Colombo, G., Mola, S., Genazzani, A.A., Porta, C., 2018. NAMPT: A pleiotropic modulator of monocytes and macrophages. Pharmacol Res 135, 25-36.

Travelli, C., Consonni, F.M., Sangaletti, S., Storto, M., Morlacchi, S., Grolla, A.A., Galli, U., Tron, G.C., Portararo, P., Rimassa, L., Pressiani, T., Mazzone, M., Trovato, R., Ugel, S., Bronte, V., Tripodo, C., Colombo, M.P., Genazzani, A.A., Sica, A., 2019. Nicotinamide Phosphoribosyltransferase (NAMPT) acts as a metabolic gate for mobilization of myeloid-derived suppressor cells. Cancer Res 79(8), 1938-1951.

Van den Bergh, R., Morin, S., Sass, H.J., Grzesiek, S., Vekemans, M., Florence, E., Tran, H.T., Imiru, R.G., Heyndrickx, L., Vanham, G., De Baetselier, P., Raes, G., 2012. Monocytes contribute to differential immune pressure on R5 versus X4 HIV through the adipocytokine visfatin/NAMPT. PLoS One 7(4), e35074.

Vora, M., Ansari, J., Shanti, R.M., Veillon, D., Cotelingam, J., Coppola, D., Shackelford, R.E., 2016. Increased Nicotinamide Phosphoribosyltransferase in Rhabdomyosarcomas and Leiomyosarcomas Compared to Skeletal and Smooth Muscle Tissue. Anticancer Res 36(2), 503-507.

Wang, B., Hasan, M.K., Alvarado, E., Yuan, H., Wu, H., Chen, W.Y., 2011. NAMPT overexpression in prostate cancer and its contribution to tumor cell survival and stress response. Oncogene 30(8), 907-921.

Xie, N., Zhang, L., Gao, W., Huang, C., Huber, P.E., Zhou, X., Li, C., Shen, G., Zou, B., 2020. NAD(+) metabolism: pathophysiologic mechanisms and therapeutic potential. Signal Transduct Target Ther 5(1), 227.

Yaku, K., Okabe, K., Hikosaka, K., Nakagawa, T., 2018. NAD Metabolism in Cancer Therapeutics. Front Oncol 8, 622.

Yoon, M.J., Yoshida, M., Johnson, S., Takikawa, A., Usui, I., Tobe, K., Nakagawa, T., Yoshino, J., Imai, S., 2015. SIRT1-Mediated eNAMPT Secretion from Adipose Tissue Regulates Hypothalamic NAD+ and Function in Mice. Cell metabolism 21(5), 706-717.

Yoshida, M., Satoh, A., Lin, J.B., Mills, K.F., Sasaki, Y., Rensing, N., Wong, M., Apte, R.S., Imai, S.I., 2019. Extracellular Vesicle-Contained eNAMPT Delays Aging and Extends Lifespan in Mice. Cell Metab 30(2), 329-342 e325.

Zamporlini, F., Ruggieri, S., Mazzola, F., Amici, A., Orsomando, G., Raffaelli, N., 2014. Novel assay for simultaneous measurement of pyridine mononucleotides synthesizing activities allows dissection of the NAD biosynthetic machinery in mammalian cells. FEBS J.

Zhang, B., Shi, D., Zhang, X., Liang, G., Liu, W., Qiao, S., 2018. FK866 inhibits the epithelial-mesenchymal transition of hepatocarcinoma MHCC97-H cells. Oncol Lett 16(6), 7231-7238.

Zhu, B., Deng, X., Sun, Y., Bai, L., Xiahou, Z., Cong, Y., Xu, X., 2012. Nampt is involved in DNA double-strand break repair. Chin J Cancer 31(8), 392-398.

Zhu, Y., Liu, J., Park, J., Rai, P., Zhai, R.G., 2019. Subcellular compartmentalization of NAD(+) and its role in cancer: A sereNADe of metabolic melodies. Pharmacol Ther 200, 27-41.