We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

3

Nicotinamide Phosphoribosyltransferase Inhibitors

Dan Wu[1], Dilyara Cheranova[1], Daniel P. Heruth[1], Li Qin Zhang[1] and Shui Qing Ye[1,2]
[1]*Department of Pediatrics, University of Missouri School of Medicine, Kansas City*
[2]*Department of Biomedical and Health Informatics, Children's Mercy Hospitals and Clinics, University of Missouri School of Medicine, Kansas City*
USA

1. Introduction

Nicotinamide phosphoribosyltransferase (NAMPT, EC 2.4.2.12) catalyzes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate (PRPP) to yield nicotinamide mononucleotide (NMN), a rate limiting enzyme in a mammalian salvage pathway of nicotinamide adenine dinucleotide (NAD) synthesis. Human NAMPT consists of 491 amino acids with a molecular weight of 52 kDa **(Samal et al., 1994)**. NAMPT was initially named pre-B-cell colony-enhancing factor (PBEF) for its growth factor like function on promoting pre-B-cell colony formation in the presence of stem cell factor plus interleukin 7 **(Samal et al., 1994)**. Martin et al. **(2001)** found that the gene encoding the bacterial *Haemophilus ducreyi* nicotinamide phosphoribosyltransferase (nadV) had a significant homology to the mammalian PBEF gene. Since then, Rongvaux et al.**(2002)**, Revollo et al. **(2004)** and others **(van der Veer et al., 2005)** have characterized the enzymological features of mammalian NAMPT. In 2005, NAMPT/PBEF was named visfatin, a "new visceral fat-derived hormone", which is an adipocyte-derived adipokine that induces insulin mimetic effects **(Fukuhara et al., 2005)**. To avoid the confusion, the name NAMPT will be used throughout this chapter since NAMPT was approved as the official name of this gene by the Human Genome Organization Gene Nomenclature Committee.

Because of NAMPT's pleiotropic functions in a variety of physiological processes, the dysregulation of NAMPT activity has been implicated in the pathogenesis of a number of human diseases or conditions such as acute lung injury, aging, atherosclerosis, cancer, diabetes, obesity related disease, rheumatoid arthritis and sepsis **(Borradaile & Pickering, 2009; Galli et al., 2010; Moschen et al., 2010)**. Therefore, targeted inhibition of NAMPT has become an attractive therapeutic strategy for these related diseases. Inhibition of NAMPT has been actively pursued as a potential new therapeutic modality to treat patients with cancer in clinical trials, to inhibit rheumatoid arthritis and to attenuate acute lung injury. The list of 'inhibition of NAMPT based therapy' is expanding rapidly. The initially tested inhibitors include FK866 (now called APO866, a small chemical molecule), antisense oligo, siRNA or shRNA and antibody.

This chapter will review the latest findings on NAMPT inhibitors in human clinical trials, animal studies and cell cultural experiments from published literature and our research findings. The first part will briefly cover the current understanding of NAMPT physiology. The second part will describe the pathological roles of NAMPT in various human diseases. The third and major component of this chapter will focus on the development, action mechanisms, and applications of various inhibitors of NAMPT. The biochemical and molecular characterization of various inhibitors to NAMPT looms large in this part. Perspective remarks at the end will provide some food for thought for future directions on the development of new and improved NAMPT inhibitors.

2. Physiology of NAMPT

This section deals with the three major functions of NAMPT: growth factor, cytokine and nicotinamide phosphoribosyltransferase. Accumulating evidence suggests that NAMPT can function as a growth factor or a cytokine though the underlying molecular mechanisms remain to be established. It is beyond dispute that NAMPT can function as a nicotinamide phosphoribosyltransferase.

2.1 Growth factor

Growth factor generally refers to a naturally occurring protein capable of stimulating cellular growth, proliferation and differentiation. Growth factors are important for regulating a variety of cellular processes. Several studies indicate that NAMPT may function as a growth factor. Samal et al. **(1994)** first found that NAMPT can enhance significantly the number of pre-B-cell colonies derived from normal human or mouse bone marrow by at least 70% in the presence of both IL-7 and stem cell factor. Thus, the authors first named this protein as pre-B-cell colony enhancing factor. Van der Veer et al. **(2005)** reported that NAMPT can promote vascular smooth muscle cell maturation. Human smooth muscle cells transduced with the NAMPT gene had enhanced survival. Fukuhara and co-workers **(2005)** proposed NAMPT as a visfatin, an adipokine produced by visceral fat that can engage and activate the insulin receptor (IR). Although this original publication was retracted **(Fukuhara et al., 2007)** because of questions regarding the reproducibility of the NAMPT/IR interaction from different preparations of recombinant NAMPT protein, Xie et al. found that NAMPT exerts an insulin-like activity as a growth factor for osteoblasts. They noticed that the effects of NAMPT, such as glucose uptake, proliferation, and type I collagen enhancement in cultured human osteoblast-like cells, bore a close resemblance to those of insulin and were inhibited by hydroxy-2-naphthalenylmethylphosphonic acid tris-acetoxymethyl ester (HNMPA-[AM]3), a specific inhibitor of IR tyrosine kinase activity **(Xie et al., 2007)**.

2.2 Cytokine

Cytokine is sometimes used interchangeably among scientists with the term growth factor. The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. Their actions may be grouped as autocrine, paracrine and endocrine. NAMPT may be added to the list of cytokines. The first NAMPT cDNA was screened out using a degenerate oligonucleotide probe designed on the basis of the similarity in the coding sequences of five different cytokines (GM-CSF, IL-2, IL-1β, IL-6 and IL-13), at the signal peptidase processing

site, though the DNA or protein sequence of NAMPT bears no homology to other known cytokines **(Samal et al., 1994)**. Ognjanovic and colleagues reported that recombinant human NAMPT (rhNAMPT) treatment of WISH cells and fetal membrane explants significantly increased IL-6 and IL-8 gene expression **(Ognjanovic et al., 2001; Ognjanovic & Bryant-Greenwood, 2002)**. We also found that an overexpression of NAMPT significantly augmented IL-8 secretion and mRNA expression in A549 cells, a human pulmonary carcinoma type II epithelial cell line, and in human pulmonary artery endothelial cells **(Li, H. et al., 2008; Liu, P. et al., 2009)**. It also significantly augmented IL-1β-mediated cell permeability. The opposite results were obtained with the knockdown of NAMPT expression. NAMPT expression also affected the expression of two other inflammatory cytokines (IL-16 and CCR3) **(Li, H. et al., 2008; Liu, P. et al., 2009)**. Hong et al. **(2008)** demonstrated that rhNAMPT functions as a direct rat neutrophil chemotactic factor in in vitro studies. They also detected a marked increase in bronchoalveolar lavage leukocytes after the intratracheal injection of rhNAMPT into C57BL/6J mice. Thus, NAMPT behaves like a chemokine.

2.3 Nicotinamide phosphoribosyltransferase

The clue that PBEF could be a nicotinamide phosphoribosyl transferase was first obtained by the work of Martin et al. **(2001)**. They found that the sequence of nadV gene is homologous to that of human NAMPT, suggesting that mammalian PBEF may also function as a NAMPT. Rongvaux et al. **(2002)** verified that similarly to its microbial counterpart, mouse PBEF is a NAMPT, catalyzing the condensation of nicotinamide with PRPP to yield NMN. Revollo et al. **(2004)** demonstrated further that NAMPT catalyzes a rate-limiting step in a salvage pathway of the mammalian NAD biosynthesis. Van der Veer et al. **(2005)** established that enhanced NAMPT activity is linked directly to the lengthening of the cellular lifespan of both human smooth muscle cells and fibroblasts. Recent work by Revollo et al. **(2007)** revealed that NAMPT regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. Because the salvage pathway of NAD synthesis has a faster rate and is more efficient than that of de novo NAD synthesis, it is conceivable that NAMPT plays an important role in a variety of physiological processes via the regulation of NAD synthesis.

3. Pathophysiology of NAMPT

This section presents potential roles of NAMPT in human diseases. The dysregulation of the NAMPT gene has been implicated in the susceptibility and pathogenesis of a number of human diseases and conditions because of its pleiotropic physiological functions. There is strong supporting evidence that both tissue and circulating NAMPT levels change in acute respiratory distress syndrome, aging, atherosclerosis, cancer, diabetes, rheumatoid arthritis, and sepsis.

3.1 Acute respiratory distress syndrome (ARDS)

ARDS is the severe form of acute lung injury (ALI). ALI is characterized by pulmonary inflammation, non-cardiogenic edema, and severe systemic hypoxemia **(Ware & Matthay, 2000; Wheeler & Bernard, 2007)**. One of the earliest manifestations of ALI is a diffuse, intense inflammatory process and damage to both endothelial and epithelial cell barriers, resulting in marked extravasation of vascular fluid into the alveolar airspace **(Matthay et al.,**

2003). A number of inflammatory cytokines including tumor necrosis factor-alpha (TNFα) and interleukin 8 (IL-8) can induce or aggravate the inflammation of endothelial and epithelial cells, leading to these barrier dysfunctions **(Frank et al., 2006)** and pathogenesis of ALI. The mortality and morbidity of ALI/ARDS remain high since the etiology and molecular pathogenesis are still not understood completely.

To identify novel candidate ALI genes, our lab employed a high-throughput functional genomics approach and found that NAMPT was a highly expressed gene in canine, murine and human ALI **(Ye et al., 2005a)**. These results suggest that NAMPT may be a potential biomarker in ALI. Analysis of single nucleotide polymorphisms (SNPs) in the NAMPT gene proximal promoter region indicated that a GC haplotype had a higher risk (nearly 8 fold) of ALI, while a TT haplotype had a lower risk of ALI **(Ye et al., 2005a)**. Our findings were confirmed and extended by Bajwa et al. **(2007)**. These results support that NAMPT is a genetic marker for ALI. To investigate further the role and molecular mechanism underlying NAMPT in the pathogenesis of ALI, we showed that heterozygous NAMPT (+/-) mice were protected significantly from severe ventilator associated lung injury (VALI) **(Hong et al., 2008)**. We also found that the NAMPT-specific siRNA would attenuate thrombin-induced decreases in human lung endothelial cell barrier function, increased cytoskeletal rearrangement, and secretion of the proinflammatory cytokine IL-8 **(Ye et al., 2005b)**. Overexpression of NAMPT significantly augmented IL-8 secretion and IL-8 mRNA expression in A549 cells and human pulmonary artery endothelial cells (HPAEC), respectively. NAMPT expression also affected the expression of two other inflammatory cytokines (IL-16 and CCR3) **(Li, H. et al., 2008; Liu, P. et al., 2009)**. These results reveal that NAMPT overexpression may adversely affect pulmonary cell barrier function, the deregulation of which is the well-recognized feature in the pathogenesis of ALI.

3.2 Aging

Aging is the accumulation of changes in an organism over time. Several evidences suggest that NAMPT may be an important regulator in aging. Axonal degeneration occurs in many neurodegenerative diseases. Sasaki et al. **(2006)** found that NAMPT can delay axon degeneration in the presence of nicotinamide in an in vitro Wallerian degeneration assay. These results suggest that increased activity of the NAD biosynthetic pathway stemming from nicotinamide promotes axonal protection. Van der Veer et al. **(2007)** reported that NAMPT can extend the lifespan of human smooth muscle cells. They found that replicative senescence of smooth muscle cells was preceded by a marked decline in the expression and activity of NAMPT. Furthermore, reducing NAMPT activity with the antagonist FK866 induced premature senescence in smooth muscle cells. NAMPT overexpression also reduced the fraction of p53 that was acetylated on lysine 382, a target of SIRT1, suppressed an age-related increase in p53 expression, and increased the rate of p53 degradation. Moreover, add-back of p53 with recombinant adenovirus blocked the anti-aging effects of NAMPT **(van der Veer et al., 2007)**. These data indicate that NAMPT is a longevity protein that can add stress-resistant life to human smooth muscle cells by optimizing SIRT1-mediated p53 degradation. Recently, Benigi et al. **(2009)** noticed that the longevity phenotype in angiotension II type 1 receptor knockout mice was associated with an increased number of mitochondria and up-regulation of the prosurvival genes NAMPT and sirtuin 3 (Sirt3) in the kidney. They postulated that disruption of angiotension II type 1

receptor promotes longevity in mice, possibly through the attenuation of oxidative stress and overexpression of prosurvival genes such as NAMPT and Sirt 3.

3.3 Atherosclerosis

Atherosclerosis is a disease affecting arterial blood vessels. In a microarray experiment, Dahl et al. **(2007)** identified that NAMPT expression was markedly enhanced in carotid plaques from symptomatic individuals compared with plaques from asymptomatic individuals. Zhong et al. **(2008)** also reported that serum NAMPT was increased in patients with carotid plaques. Cheng et al. **(2008)** noticed that NAMPT levels in epicardial and abdominal adipose tissues were significantly higher in coronary artery disease (CAD) patients relative to control subjects. In addition, significantly higher tissue NAMPT levels from abdominal fat depots were found compared to those from epicardial fat in CAD patients. These findings suggest that abdominal adiposity may play a more significant role than epicardial fat in the pathogenesis of coronary atherosclerosis. More studies are warranted to firmly establish the relationship between NAMPT and atherosclerosis and to elucidate the role(s) and molecular mechanisms of NAMPT in the pathogenesis of atherosclerosis.

3.4 Cancer

Molecular screening, epidemiological survey and pharmacological studies have indicated that NAMPT may be an attractive diagnostic and drug target for cancer therapy. Hufton et al. **(1999)** first noticed that NAMPT expression was increased 6 fold in primary colorectal cancer over the normal control using the suppression subtractive cDNA hybridization technique. This result was confirmed at the protein and tissue levels by both western blotting and immunohistochemical analyses **(Van Beijnum et al., 2002)**. Using cDNA microarray based expression profiling of different grades of astrocytomas, Reddy et al. **(2008)** identified several fold increased levels of NAMPT transcripts and protein in glioblastoma samples, suggesting that NAMPT could be a potential malignant astrocytoma serum marker and prognostic indicator in glioblastoma.

Through a chemical screen to find new antitumor drugs, Hasmann and Schemainda **(2003)** identified the first low molecular weight compound, designated FK866 {the chemical name: (E)-N-[4-(1-benzoylpiperidin-4-yl) butyl]-3-(pyridin-3-yl) acrylamide}, which induced apoptosis by highly specific and potent inhibition of nicotinamide phosphoribosyltransferase in HepG2 human liver carcinoma cells. Using ^{1}H-decoupled phosphorus (^{31}P) magnetic resonance spectroscopy, Muruganandham et al. **(2005)** observed that FK866 (also known as APO866) increased apoptosis and subsequent radiation sensitivity in the mammary carcinoma. FK866 has been shown to have anti-tumor, anti-metastatic and antiangiogenic activities in a murine renal cell carcinoma model **(Drevs et al., 2003)**. The three dimensional structural analysis of the NAMPT–FK866 complex by three groups revealed that the FK866 compound binds at the nicotinamide-binding site of NAMPT to competitively compete directly with the nicotinamide substrate to inhibit its activity **(Khan et al., 2006; Kim, M.K. et al., 2006; Wang et al., 2006)**. These structural analyses provided a molecular basis for the inhibition of FK866 on NAMPT and a starting point for the development of new anticancer agents.

Accumulated evidence indicates that at least three molecular mechanisms may implicate NAMPT in the pathogenesis of cancer. First, NAMPT inhibits apoptosis of tumor cells via its role as a key enzyme in NAD biosynthetic salvage pathway. Second, Li Y. et al. **(2008)** reported that NAMPT could activate an IL-6/STAT3 survival signaling pathway via a non-enzymatic mechanism. Third, increased NAMPT activity has been associated with angiogenesis and neovascularization. Kim et al. **(2008)** found that NAMPT potently stimulates in vivo neovascularization in chick chorioallantoic membranes and in implanted mouse Matrigel plugs. Furthermore, Bae et al. **(2009)** reported that NAMPT-induced angiogenesis is mediated by endothelial fibroblast growth factor-2 (FGF-2). Therefore, inhibition of NAMPT activity provides a important anticancer target, since neovascularization by angiogenesis is the prerequisite for tumor growth and expansion **(Chamberlain, 2008)**.

3.5 Diabetes mellitus

Diabetes mellitus, simply referred to as diabetes, is a syndrome of disordered metabolism with hyperglycemia as a hallmark phenotype. Its long and extensively-sought hereditary and environmental causes are not fully known. Initial attention brought to the relationship between NAMPT and Type 2 diabetes was due to the work by Fukuhara et al. **(2005)**. They found that NAMPT is a secreted factor produced abundantly by visceral fat. Plasma NAMPT levels in NAMPT gene heterozygous knockout mice were only 2/3 of those in wild type mice but their plasma glucose level were significantly higher. This suggests that like insulin, NAMPT may have a physiological role in lowering plasma glucose levels. The authors found that NAMPT bound to the insulin receptor (IR) but not to the same site to which insulin binds. Similar to insulin, NAMPT could stimulate insulin signaling, such as inducing tyrosine phosphorylation of the IR, insulin receptor substrate–1 (IRS-1), and IRS-2 in the liver. Taken together, the authors considered NAMPT as an insulin-mimetic and dubbed it as visfatin. Although this paper was withdrawn from *Science* due to the variation of different batches of recombinant NAMPT for their adipogenic and insulin-mimetic activities **(Fukuhara et al., 2007)**, this report has immediately and continuously drawn increased interest among biomedical researchers to the roles and mechanisms underpinning NAMPT in the pathogenesis of diabetes, obesity, insulin resistance, and metabolic syndrome.

The epidemiological survey of the relationship between NAMPT and Type 2 diabetes by Fukuhara et al. **(2005)** has been supported by a number of subsequent studies which reported that the level of plasma NAMPT and/or the amount of visceral fat NAMPT mRNA were increased significantly in or positively associated with Type 2 diabetes or obesity or insulin resistance or metabolic syndrome in patients under the baseline without any intervention of medication, surgery, and other reagents **(Berndt et al., 2005; Chen et al., 2006; Krzyzanowska et al., 2006; Dogru et al., 2007; Fernandez-Real et al., 2007; Lewandowski et al., 2007; Sandeep et al., 2007; Alghasham & Barakat, 2008; Botella-Carretero et al., 2008; Liang et al., 2008; Mazaki-Tovi et al., 2008; Retnakaran et al., 2008; Ziegelmeier et al., 2008; Hallschmid et al., 2009)**. Patients with Type 1 diabetes also had higher NAMPT concentrations than controls **(Haider et al., 2006; Lopez-Bermejo et al., 2006)**. However, other groups have obtained opposite findings **(Jian et al., 2006; Akturk et al., 2008; Kato et al., 2009)** or no changes of plasma NAMPT level in Type 2 diabetes **(Chan et al., 2006; Pagano et al., 2006; Takebayashi et al., 2007; Tsiotra et al., 2007; Palin et al., 2008)**. These conflicting findings on the correlation of plasma NAMPT level with diabetes

may stem from four major reasons: small sample sizes, variable phenotyping criteria, different populations and ethnicities and assay variation. The biological role and molecular mechanism of NAMPT related to diabetes remains to be fully elucidated.

3.6 Rheumatoid arthritis

Rheumatoid arthritis [RA] is a chronic, systemic autoimmune disorder that most commonly causes inflammation and tissue damage in joints. Despite that the first recognized description of rheumatoid arthritis was made in 1800 by Dr. Augustin Jacob Landré-Beauvais in Paris **(Landre-Beauvais, 2001),** its pathogenesis remains incompletely understood. Otero et al. **(2006)** first reported that patients with rheumatoid arthritis showed higher plasma levels of NAMPT, leptin, and adiponectin than healthy controls. These findings were confirmed by Nowell et al. **(2006)**, Bretano et al. **(2007)** and Matsui et al. **(2008)**. When compared with osteoarthritis (OA) patients, Nowell and colleagues detected elevated levels of NAMPT in synovial fluid from RA patients **(Nowell et al., 2006)**. In a large survey of 167 RA patients and 91 control subjects, Rho et al. **(2009)** found that elevated levels of NAMPT correlated with both radiological joint destruction and mediators of inflammation.

NAMPT is a pleiotropic protein which can induce the expression of a number of genes (e.g. CCR2, CCR3, Cox-2, IL-6, IL-8, IL-16, ICAM1, MCP-1, MMP-2, MMP-9, VCAM1, VEGF) **(Ognjanovic et al., 2001; Kim, S.R. et al., 2007; Adya et al., 2008; Adya et al., 2008; Kim, S.R. et al., 2008; Li, H. et al., 2008; Adya et al., 2009; Liu, P. et al., 2009; Liu, S.W. et al., 2009)**. It is suggested that NAMPT affects the innate immune system's inflammatory response in the pathogenesis of rheumatoid arthritis via regulating expression of those inflammatory cytokines or activators. However, the mechanism by which NAMPT mediates the cytokine signaling cascade has not yet been determined fully.

3.7 Sepsis

Sepsis, a life-threatening disorder characterized by a whole-body inflammatory state caused by infection, is a frequent cause of ALI/ARDS. Jia et al. **(2004)** reported that NAMPT functions as a novel inflammatory cytokine that plays a requisite role in the delayed neutrophil apoptosis of clinical and experimental sepsis. They found that transcription of the NAMPT gene is increased in neutrophils from septic patients, while the prevention of NAMPT translation through the use of an antisense oligonucleotide largely restored the normal kinetics of apoptosis. Moreover, the incubation of quiescent neutrophils from healthy volunteers with recombinant NAMPT results in dose-dependent inhibition of apoptosis, while antisense NAMPT prevents the inhibition of apoptosis that results from exposure to lipopolysaccharide (LPS) or to a variety of host-derived inflammatory cytokines **(Jia et al., 2004)**. The authors postulate that the prolonged survival of activated neutrophils may be linked to sustained inflammation and the organ injury of sepsis.

Because of its multiple functional roles in physiology, the list of NAMPT involvement in various human diseases is expected to grow.

4. NAMPT inhibitors

As summarized in the first part of this chapter, NAMPT is considered as a rate-limiting enzyme of a mammalian synthetic pathway of NAD synthesis. Thus, NAMPT may exert its

physiological and pathological roles by regulating the synthesis of NAD. NAD plays a major role in the regulation of several essential cellular processes. It's an essential coenzyme in metabolic pathways, and important in several biological processes including signal transduction **(Corda & Di Girolamo, 2003)**, DNA repair **(Menissier de Murcia et al., 2003)**, calcium homeostasis **(Lee, H.C., 2001)**, gene regulation **(Blander & Guarente, 2004)**, longevity **(Lin et al., 2000)**, genomic integrity **(Schreiber et al., 2006)** and apoptosis **(Wright et al., 1996)**. Additionally, as reviewed above, NAMPT is a pleiotropic protein which also functions via non-enzymatic mechanisms. Thus, NAMPT has become an attractive target in the treatment of many diseases. This section will focus on the development and progress of various NAMPT inhibitors and their applications.

4.1 Chemical inhibitors of NAMPT

4.1.1 FK866

The first NAMPT inhibitor, FK866 (also called APO866 or WK175, (E)-N-[4-(1-benzoylpiperidin-4-yl) butyl] acrylamide-3-(pyridin-3-yl), was reported by Hasmann and Schemainda, who found that FK866 induced apoptosis by a highly specific and potent inhibition of nicotinamide phosphoribosyltransferase in HepG2 human liver carcinoma cells **(Hasmann & Schemainda, 2003)**. FK866 has no primary effect on cellular energy metabolism and thus has no direct and immediate cytotoxicity, but rather gradually depletes the cells of a vital factor, NAD, by inhibiting NAMPT, which eventually triggers apoptosis. The authors proposed that FK866 may be used for treatment of diseases involving deregulated apoptosis, such as cancer, or as a sensitizer for genotoxic agents. Furthermore, FK866 may provide an important tool for investigation of the molecular triggers of the mitochondrial pathway leading to apoptosis through enabling temporal separation of decreased NAD levels from ATP breakdown and apoptosis **(Hasmann & Schemainda, 2003; Pittelli et al., 2010)**.

Depletion of cellular NAD levels leads to lowered ATP levels and the inhibition of poly (ADP-ribose) polymerases (PARPs) **(Khan et al., 2007)**. Cancer cells have a high demand of both PARP and ATP, and they also display higher energy requirements **(Hufton et al., 1999)**. Thus, cancer cells would be expected to be more sensitive than normal cells to the inhibition of NAD synthesis **(Hasmann & Schemainda, 2003; Billington et al., 2008; Nahimana et al., 2009)**. Therefore, since NAMPT acts as a key enzyme of NAD synthesis, its inhibitors could provide an effective cancer therapy. Additional reports have demonstrated that FK866 elicited massive cell death in primary leukemia cells and in numerous leukemia/lymphoma cell lines **(Nahimana et al., 2009; Zoppoli et al., 2010)**. FK866 has been shown to have anti-tumor, anti-metastatic and antiangiogenic activities in a murine renal cell carcinoma model. Nahimana et al. **(2009)** investigated the cytotoxic effects of FK866 in both in vitro and in vivo assays, using a cell panel of human hematologic malignancies and early and established human hematologic cancers, respectively. They observed in in vitro assays that FK866-induced apoptosis involved an initial decrease in intracellular NAD levels that were subsequently accompanied by decreases in intracellular ATP levels. In animal models of human acute myeloid leukemia, lymphoblastic lymphoma, and leukemia, FK866 as a single agent prevented and abrogated tumor growth without significant toxicity to the animals. These findings demonstrated that FK866 displayed strong anticancer activity in hematologic malignancies both in vitro and in vivo.

FK866 was also found to improve the sensitivity of other anticancer agents. The main objectives of combination chemotherapy are an increased response rate against the tumor and minimization of adverse effects of drugs without compromising efficacy of treatment. Using ^{1}H-decoupled phosphorus (^{31}P) magnetic resonance spectroscopy, Muruganandham et al. **(2005)** observed that FK866 increased cell death (apoptosis) and subsequent radiation sensitivity in the mammary carcinoma. Pogrebniak et al. **(2006)** treated THP-1 and K562 cells with FK866 and various cytotoxic agents: the antimetabolite Ara-C, the DNA-intercalating agent daunorubicin and the alkylating compounds 1-methyl-3-nitro-1-nitrosoguanidinium (MNNG) and melphalan. The results showed the anticancer activity of FK866 was particularly obvious in combination with substances like MNNG that cause NAD depletion chemo-sensitizing. Additionally, Yang et al. **(2010)** combined FK866 and the indoleamine 2,3-dioxygenase inhibitor L-1-methyl-tryptophan (L-1MT) in the treatment of mouse tumor models. The combination of FK866 and L-1MT had a better therapeutic effect than did either L-1MT or FK866 alone.

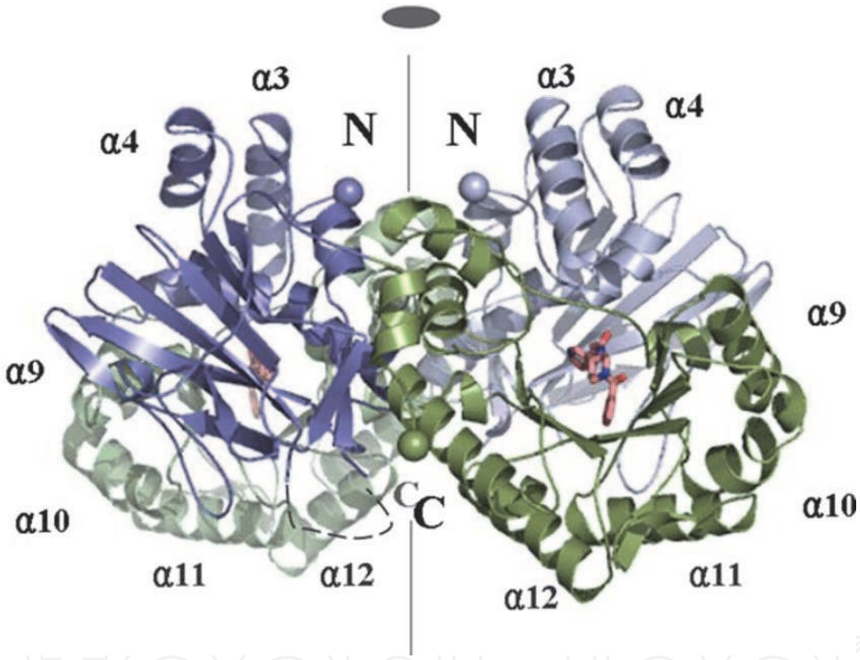


Fig. 1. Representative ribbon diagram of two FK-866 molecules binding to the NAMPT dimer. The two FK-866 molecules are shown in red. The two monomers are shown in slate and green (subunit A) and pale blue and green (subunit B), respectively. This figure is copied from Kim M.K. et al (2006) with permission from Elsevier.

The mechanism of FK866 inhibition of NAMPT has been well characterized. Three dimensional structural analyses of the NAMPT–FK866 complex revealed that FK866 binds at the nicotinamide-binding site of NAMPT, thus functioning as a competitive inhibitor of NAMPT enzymatic activity **(Khan et al., 2006; Kim, M.K. et al., 2006; Wang et al., 2006)**. A representative crystal structure of NAMPT-FK866 binding is shown in Figure 1 **(Kim, M.K. et al., 2006)**. FK-866 binds to the active site of NAMPT with higher affinity than either the substrate or the product does. The benzoylpiperidin group of FK-866 plays a key role in binding to NAMPT in hydrophobic interactions **(Kim, M.K. et al., 2006)**. These structural

analyses provided a molecular basis for the inhibition of FK866 on NAMPT and a starting point for the development of new anticancer agents.

The first human study of FK866 in the treatment of cancer was reported by Holen et al. **(2008)**. They collected serial plasma and blood samples from 24 patients, with advanced solid tumors, treated with increasing doses of FK866. The patient age ranged from 34-78 and the dose of FK866 ranged from 0.144 mg/m2/h to 0.018mg/m2/h. The recommended dose for phase II clinical trial was 0.126mg/m2/h, which was given as a continuous 96 h infusion every 28 days. Thrombocytopenia was the main toxicity of FK866. Plasma analysis showed that FK866 did not affect VEGF concentration. FK866 has been used in phase II and I/II clinical trials against cancer, including advanced melanoma, cutaneous T-cell lymphoma and B-chronic lymphocytic leukemia **(Holen et al., 2008; Olesen et al., 2010a, 2010b)**.

FK866 has also been applied to treat a mouse model of collagen induced arthritis (CIA). Busso et al. (2008) carried out a CIA curative experiment using the optimal dose of FK866. Twenty mice with CIA were treated twice daily with 10 mg/kg/ip of FK866 from the first day onward of appearance of clinical arthritis for 14 consecutive days. They found that FK866 effectively reduced arthritis severity with comparable activity to etanercept, and decreased proinflammatory cytokine secretion in affected joints. Paws from FK866-treated mice showed minimal signs of inflammation after 2 weeks of treatment whereas paws from placebo-treated mice were still inflamed (Figure 2). This study indicates that the inhibition of NAMPT might have therapeutic efficacy in immune-mediated inflammatory disorders.

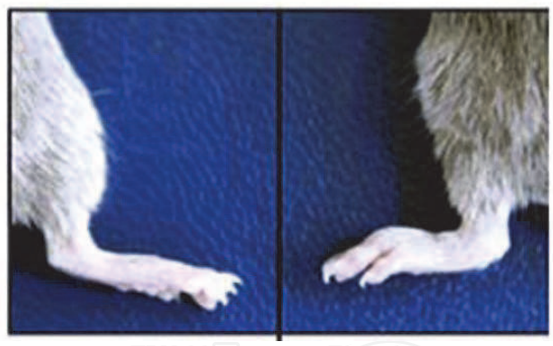


Fig. 2. FK866 treatment alleviated inflammation in a CIA mouse model. Collagen induced arthritis was initiated in male DBA/1 mice. Mice were treated for 14 consecutive days with two injections of 10 mg/kg/IP/day of APO866 from the first day onward of appearance of clinical arthritis (clinical score >1, mild swelling and/or erythema). Placebo mice received vehicle only. One of parameters to evaluate the FK866 therapeutic effect on arthritis is presented here with paws of FK866-treated (left) showing diminished swelling and inflammation compared to those in placebo-treated (right) arthritic mouse. This figure was copied from Busso et al. (2008).

4.1.2 CHS 828

CHS 828 (N-(6-chlorophenoxyhexyl)-N′-cyano-N″-4-pyridylguanidine, GMX1778, active form of GMN1777), a cyanoguanidine compound, which displayed promising preclinical anticancer activity, is another important NAMPT inhibitor currently in phase II clinical

trials in oncology **(Schoua C., 1997; Hjarnaa et al., 1999; Olesen et al., 2010b; von Heideman et al., 2010)**. Hjarnaa et al. **(1999)** first demonstrated the anticancer properties of CHS 828 both in vitro and in vivo using established cancer cell lines and in rodent models of tumor growth, respectively. The mechanism of this small molecular inhibitor has been hypothesized to function through NF-κB inhibition **(Schoua C., 1997; Hassan et al., 2006)**, but the exact mechanism was undefined. Olesen et al. **(2004)** originally found no common resistance mechanism between CHS 828 resistant human small cell lung carcinoma NYH cells (NYH/CHS) and NF-κB inhibitors resistant NYH cells. For FK866, it was observed that its cross-resistance was comparable to CHS 828 in NYH/CHS cells. CHS 828 was subsequently defined as an inhibitor of NAD synthesis as increasing cellular levels of NAD were able to completely block cytotoxicity of CHS 828, which is similar to FK866. Furthermore, crystal structure and in vitro biochemistry results showed that FK866 and CHS 828 shared a binding site in the active site of NAMPT **(Kim, M.K. et al., 2006; Olesen et al., 2008, 2010a)**. Thus, CHS 828 is conclusively identified as a competitive inhibitor of NAMPT.

4.1.3 Other chemical inhibitors

Kang et al. **(2009)** designed and synthesized IS001, in which a ribose ring was added to the FK866 pyridyl ring. The ribose ring of IS001 did not improve its solubility and binding interactions. The structures of the NAMPT-IS001 and NAMPT-FK866 complexes are nearly identical. You et al. **(2011)** replaced the pyridine ring of FK866 with various heteroaromatic rings for combination with a simple ribose-mimicking moiety containing a diol group. One analogue, compound 7, showed superior anti-cancer activity to FK866 (IC50 > 20μM) in human leukemia cells (K562) with an IC50 value of 1.4μM, but not in other cancer cell lines. Crystal structure of NAMPT-compound 7 demonstrated the binding site of compound 7 was nearly identical to that of FK866 and NMN.

TP201565, a potent analogue of CHS 828, displayed inhibition activity in xenograft models **(Hjarnaa et al., 1999)**. TP201565 shows more than 10 fold increased activity in sensitive cancer cell lines compared to FK866 and CHS 828. Additionally, computer modeling analysis predicted that TP201565 inhibits NAMPT by binding to the same site as FK866 and CHS 828. Myriad Pharmaceuticals (http://www.myrexis.com) is developing a series of NAMPT inhibitors, such as MPC-9528, CB30865, MPI0479883. These inhibitors, which are designed analogues of FK866 and CHS 828, potently inhibited NAMPT activity and cancer cell growth with lower IC_{50} values than previously reported inhibitors.

4.2 NAMPT siRNA/shRNA

RNA interference (RNAi) is a natural biological mechanism where gene expression is silenced in a highly specific manner through the addition of double stranded RNA (dsRNA). Once dsRNA enters the cell, it is cleaved by an RNase III –like enzyme, Dicer, into double stranded small interfering RNAs (siRNA). The resulting siRNA with 21-23 nucleotides in length, containing 2 nucleotide overhangs on the 3′ ends, integrate into a multi-subunit protein complex, RNAi induced silencing complex (RISC). The RISC-bound antisense strand then serves as a guide for targeting the activated complex to complementary mRNA sequences, resulting in subsequent mRNA cleavage and degradation. Small hairpin RNA or short hairpin RNA (shRNA) is a sequence of RNA that makes a tight hairpin turn that can be used for RNA interference**.** shRNA uses a vector introduced into cells and utilizes the U6

or H1 promoter to ensure that the shRNA is constitutively expressed. This vector is usually passed on to daughter cells, allowing the gene silencing to be inherited. The shRNA hairpin structure is cleaved into siRNA**,** which is then bound to the RISC. This complex binds to and cleaves target mRNAs which match the siRNA that is bound to it. Knock down of gene expression by siRNA and shRNA technology has become a popular and effective tool to dissect gene function in the current functional genomics era.

Ye et al. **(2005b)** employed NAMPT stealth siRNAs to explore the pathophysiological relevance of the altered NAMPT expression to the lung endothelial barrier dysregulation induced by thrombin and the pathogenesis of ALI. Acute lung injury (ALI) is characterized by a diffuse intense inflammatory process and by damage to both endothelial and epithelial cell barriers. The NAMPT gene was highly expressed in ALI and our group reported that NAMPT was a biomarker in ALI **(Ye et al., 2005a)**. We studied whether downregulation of NAMPT protein expression by the NAMPT-specific siRNA would affect thrombin-induced decreases in human lung endothelial cell barrier function **(Ye et al., 2005b)**. The results revealed that NAMPT expression was decreased significantly and the thrombin effect on cell barrier function was attenuated by NAMPT siRNA treatment in cultured human pulmonary artery endothelial cells (HPAEC), while siRNA had no effect on the protein expression level of β-actin, a house-keeping gene. Similar results were also obtained in A549 cells, a lung alveolar type II epithelial cell line.

NAMPT levels in serum and synovial fluid are elevated in RA patients. RA synovial fibroblasts (RASFs) were major NAMPT expressing cells. Brentano et al. **(2007)** used siRNA to silence NAMPT expression in RASF, which significantly inhibited basal and TLR ligand-induced production of IL-6, IL-8, MMP-1, and MMP-3. Van der Veer et al **(2005)** knocked down endogenous NAMPT in smooth muscle cells (SMC) to explore if the conversion of the SMC phenotype from a proliferative state to a nonproliferative state was accompanied by up-regulation of NAMPT. This shift of SMC phenotype is essential for conferring vasomotor function to developing and remodeling blood vessels. SMC, transfected with NAMPT siRNA, exhibited significant decrease in NAMPT mRNA and protein. Furthermore, they found that NAMPT siRNA treatment increased SMC apoptosis and reduced the capacity of synthetic SMCs to mature to a contractile state. NAMPT expression also increased during macrophage differentiation. To examine the role of NAMPT in macrophages differentiation, NAMPT siRNA was transfected into macrophages to silence NAMPT. Dahl et al. **(2007)** found that silencing of NAMPT increased lipid accumulation in THP-1 macrophages, increased ADRP (adipose differentiation-related protein) and cholesterol levels in oxidized LDL stimulated macrophages, and enhanced the binding of acetylated LDL in these cells. Cumulatively, these results indicate that NAMPT siRNAs could effectively and specifically inhibit the NAMPT expression and its function, which may be exploited as a promising strategy for NAMPT expression based therapy in relevant human diseases.

Sigma Company (http://www.sigmaaldrich.com/) now markets MISSION® NAMPT esiRNA. MISSION esiRNAs are endoribonuclease-prepared siRNA pools comprised of a heterogeneous mixture of siRNAs that all target the same mRNA sequence. These multiple silencing triggers lead to highly specific and effective gene silencing with lower off-target effects than single or pooled siRNAs. Although no experimental report on the true effectiveness of MISSION® NAMPT esiRNA to silence the NAMPT expression appears in the literature yet, MISSION® NAMPT esiRNA may gain steam over other NAMPT siRNA tools soon.

4.3 Antisense oligonucleotide to NAMPT

An antisense oligonucleotide is a synthesized strand of nucleic acid which binds to and inactivates its corresponding mRNA molecule effectively making the target gene silent. Generally, they are relatively short (13–25 nucleotides) and hybridize (at least in theory) to a unique sequence of target present in cells.

Jia et al. **(2004)** used a phosphorothioate-modified antisense oligonucleotide to block NAMPT mRNA expression in neutrophils. Neutrophils play an important role in sepsis. Activated neutrophils have been implicated in the increased micro vascular permeability of systemic inflammation **(Gautam et al., 2001)** and in the pathogenesis of inflammatory injury to the lung **(Lee, W.L. & Downey, 2001)**, liver **(Ho et al., 1996)**, gastrointestinal tract **(Kubes et al., 1992)**, and kidney **(Lauriat & Linas, 1998)**. The number and activity of neutrophils are tightly linked to infection and inflammatory injury, and regulated by apoptotic program. LPS and other inflammatory cytokines can inhibit neutrophil apoptosis. The research by Jia et al. demonstrated that NAMPT is synthesized and released by neutrophils in response to inflammatory stimuli and that it plays a requisite role in the inhibition of apoptosis in neutrophils **(Jia et al., 2004)**. The NAMPT antisense oligonucleotide prevented neutrophil apoptosis induced by either LPS or other inflammatory cytokines. In neutrophils of patients with sepsis, addition of NAMPT antisense oligonucleotide resulted in a greater than two fold increase in rates of apoptosis. This study demonstrated that the antisense oligonucleotide to NAMPT could effectively inhibit NAMPT expression, which could prove useful as a new therapeutic tool.

4.4 NAMPT miRNA

MicroRNAs (miRNAs), short ribonucleic acid (RNA) molecules, are post-transcriptional regulators, about 22 nucleotides long. miRNAs could bind to 3′ UTR of messenger RNA transcripts (mRNAs) resulting in translational repression and gene silencing. Gene silencing may occur either via mRNA degradation or preventing mRNA from being translated. It has been demonstrated that if there is complete complementation between the miRNA and target mRNA sequence, mRNA can be cleaved and degraded.

Elangovan et al. **(2011)** reported at the American Thoracic Society Annual Conference, 2011 that two miRNA hsa-miR-374a and hsa-miR-568 potentially bound to the 3′ UTR of NAMPT mRNA and thereby inhibited its expression. In human pulmonary artery endothelia cell (HPAEC) transfected with the luc-Nampt-3′UTR reporter construct and miRNAs, they found that hsa-miR-374a and hsa-miR-568 effectively reduced LPS- and cyclic stretch-stimulated NAMPT expression in cultured HPAEC cell by both dual luciferase assay and immunoblotting. This study indicates that synthetic NAMPT miRNAs have potential to be a novel class of therapeutic molecules.

Currently, several companies, such as Sigma (http://www.sigmaaldrich.com/) and Dharmacon (http://www.dharmacon.com/), offer the products of NAMPT miRNA mimics. MicroRNA mimics are double-stranded RNA oligonucleotides and are chemically modified. They effectively mimic endogenous mature miRNA functions with a superior performance in comparison to native double-stranded miRNA. Although there is yet a report about the application of NAMPT miRNA mimics, NAMPT miRNA mimics may gain an advantage over natural NAMPT miRNA as more effective inhibitors of NAMPT for the reasons as described above.

4.5 Antibody to NAMPT

An antibody, also known as an immunoglobulin, is produced by the immune system to identify and neutralize a foreign object by recognizing its antigen, a unique part of the foreign target. The current progress in biotechnology and genetic engineering has kindled a growing interest in antibody based therapy, which has quickly become incorporated into the therapeutic armamentarium for various human diseases. It will be no exception for the development of NAMPT antibody based therapy.

Our group has evaluated whether NAMPT antibody can block the function of NAMPT and thus attenuate ventilator induced lung injury (VILI) in a mouse model since NAMPT overexpression seemed to play a significant role in the pathogenesis of acute lung injury **(Hong et al., 2008)**. We found that simultaneous instillation of rhNAMPT (20 mg/mouse) and NAMPT neutralizing antibody produced dramatic reductions in rhNAMPT-induced PMN recruitment. The intratracheal delivery of NAMPT neutralizing antibody (30 min before mechanical ventilation) abolished VILI-induced increases in total BAL cell counts and significantly decreased PMN influx into the alveolar space as well as VILI-mediated increases in lung tissue albumin. This result indicates that NAMPT antibody based strategy may be a viable therapeutic modality to acute lung injury. Although this was only one case report **(Hong et al., 2008)**, it could ignite an increasing interest at NAMPT antibody based therapy to other diseases where a dysregulated overexpression of NAMPT gene is one of the key features.

4.6 NAMPT gene knockout

Gene knockout (KO), namely the inactivation of a specific gene within an organism, is a potential important gene therapy technique. In mouse experiments, typically, a gene target vector contains a selective marker in the center with both 5'- and 3'- arms, whose sequences are homologous to the targeted gene. This gene target vector is introduced into the mouse embryonic stem cell by electroporation. As the embryonic stem cell divides, the original gene segment is replaced through homologous recombination in a small number of the divided cells. After the target vector is integrated in the cognate position, the stem cells are then introduced into a female mouse. Subsequently, a knock-out mouse line would be engendered after further characterization.

To explore the effect of NAMPT to ventilator-induced lung injury (VILI) in vivo, Hong et al. **(2008)** generated a heterozygous NAMPT+/- mouse line and subsequently exposed the mouse to a model of severe VILI. The results were opposite between the rhNAMPT and NAMPT+/- mice when exposed to a model of severe VILI. In rhNAMPT mice, it was observed that dramatic increases in bronchoalveolar lavage (BAL) leukocytes, BAL protein, and cytokine levels (IL-6, TNF-a, KC). In contrast, NAMPT+/- mice exhibited significantly decreased expression of VILI associated genes, inflammatory lung injury and lower peak aspiratory pressures compared with control mice. These results suggest that NAMPT is a critical effecter in the development of ventilator induced lung pathobiology and it shows a promise that reducing NAMPT gene expression could protect lungs from VILI in human patients down the road.

5. Perspective

NAMPT has drawn an ever-increasing attention in biomedical fields because of its presumed pleiotropic physiological functions and its dysregulation implicated in a number

of human diseases and conditions. As of Aug 15, 2011, 836 publications have appeared in PubMed when searched with key words: NAMPT or PBEF or visfatin.

A growing interest has been to develop inhibitors of NAMPT as a potential new therapeutic strategy to several human diseases where the dysregulated overexpression of NAMPT is implicated in their pathogeneses. Although there have been several reported methods to effectively inhibit NAMPT activity, such as small molecular chemicals, siRNA, miRNA, antisense oligonucleotide, and gene knock out, further improvement of these inhibitors are warranted. These include improving the efficacy, reducing side effects and enhancing the specificity. For FK866, or other synthetic chemical inhibitors, the main obstacle to be overcome is toxicity. Enhancing the potency, lowering the effective dosage and reducing the side effects are necessary for the improvement of this NAMPT inhibitor class. Although RNA interference technology by siRNA and miRNA has become a standard research tool for genetic studies and a new class of drugs designed to silence disease-causing genes, it is still in the development stage. RNA in general is more unstable than DNA and tends to be degraded easily. siRNA or miRNA may also cause an immune response which causes the body to reject the foreign RNA. Transfection inefficiency is a problem both in treatment and in study of RNA interference. Off target effects are a major concern. The stability issue of antisense oligonucleotides in blood and tissue is still not satisfactorily resolved. Although our group demonstrated that antibody blocking of NAMPT could attenuate acute lung injury in a mouse model, antibody based inhibition of NAMPT is far from fully developed as a effective therapy to other diseases. Gene therapy still has a long way to go before clinical fruition. NAMPT aptamers or other forms of NAMPT inhibitors have yet come into the world. Nevertheless, it is anticipated that improved and new NAMPT inhibitors will be developed within next few years. NAMPT based strategy holds an immense promise in management of various human conditions.

6. Acknowledgements

Some cited studies in this chapter were in part supported by NIH grants (R01HL080042 and RO1 HL080042-S1, SQY) as well as the start-up funds of Children's Mercy Hospitals and Clinics, University of Missouri (SQY).

7. References

Adya, R., Tan, B.K., Chen, J. and Randeva, H.S. (2008). Nuclear factor-kappaB induction by visfatin in human vascular endothelial cells: its role in MMP-2/9 production and activation. Diabetes Care 31(4): 758-760.

Adya, R., Tan, B.K., Chen, J. and Randeva, H.S. (2009). Pre-B cell colony enhancing factor (PBEF)/visfatin induces secretion of MCP-1 in human endothelial cells: role in visfatin-induced angiogenesis. Atherosclerosis 205(1): 113-119.

Adya, R., Tan, B.K., Punn, A., Chen, J. and 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.

Akturk, M., Altinova, A.E., Mert, I., Buyukkagnici, U., Sargin, A., et al. (2008). Visfatin concentration is decreased in women with gestational diabetes mellitus in the third trimester. J Endocrinol Invest 31(7): 610-613.

Alghasham, A.A. and Barakat, Y.A. (2008). Serum visfatin and its relation to insulin resistance and inflammation in type 2 diabetic patients with and without macroangiopathy. Saudi Med J 29(2): 185-192.

Bae, Y.H., Bae, M.K., Kim, S.R., Lee, J.H., Wee, H.J., et al. (2009). Upregulation of fibroblast growth factor-2 by visfatin that promotes endothelial angiogenesis. Biochem Biophys Res Commun 379(2): 206-211.

Bajwa, E.K., Yu, C.L., Gong, M.N., Thompson, B.T. and Christiani, D.C. (2007). Pre-B-cell colony-enhancing factor gene polymorphisms and risk of acute respiratory distress syndrome. Crit Care Med 35(5): 1290-1295.

Benigni, A., Corna, D., Zoja, C., Sonzogni, A., Latini, R., et al. (2009). Disruption of the Ang II type 1 receptor promotes longevity in mice. J Clin Invest 119(3): 524-530.

Berndt, J., Kloting, N., Kralisch, S., Kovacs, P., Fasshauer, M., et al. (2005). Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 54(10): 2911-2916.

Billington, R.A., Travelli, C., Ercolano, E., Galli, U., Roman, C.B., et al. (2008). Characterization of NAD uptake in mammalian cells. J Biol Chem 283(10): 6367-6374.

Blander, G. and Guarente, L. (2004). The Sir2 family of protein deacetylases. Annu Rev Biochem 73: 417-435.

Borradaile, N.M. and Pickering, J.G. (2009). NAD(+), sirtuins, and cardiovascular disease. Curr Pharm Des 15(1): 110-117.

Botella-Carretero, J.I., Luque-Ramirez, M., Alvarez-Blasco, F., Peromingo, R., San Millan, J.L., et al. (2008). The increase in serum visfatin after bariatric surgery in morbidly obese women is modulated by weight loss, waist circumference, and presence or absence of diabetes before surgery. Obes Surg 18(8): 1000-1006.

Brentano, F., Schorr, O., Ospelt, C., Stanczyk, J., Gay, R.E., et al. (2007). Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. Arthritis Rheum 56(9): 2829-2839.

Busso, N., Karababa, M., Nobile, M., Rolaz, A., Van Gool, F., et al. (2008). Pharmacological inhibition of nicotinamide phosphoribosyltransferase/visfatin enzymatic activity identifies a new inflammatory pathway linked to NAD. PLoS One 3(5): e2267.

Chamberlain, M.C. (2008). Antiangiogenesis: biology and utility in the treatment of gliomas. Expert Rev Neurother 8(10): 1419-1423.

Chan, T.F., Chen, Y.L., Lee, C.H., Chou, F.H., Wu, L.C., et al. (2006). Decreased plasma visfatin concentrations in women with gestational diabetes mellitus. J Soc Gynecol Investig 13(5): 364-367.

Chen, M.P., Chung, F.M., Chang, D.M., Tsai, J.C., Huang, H.F., et al. (2006). Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 91(1): 295-299.

Cheng, K.H., Chu, C.S., Lee, K.T., Lin, T.H., Hsieh, C.C., et al. (2008). Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. Int J Obes (Lond) 32(2): 268-274.

Corda, D. and Di Girolamo, M. (2003). Functional aspects of protein mono-ADP-ribosylation. EMBO J 22(9): 1953-1958.

Dahl, T.B., Yndestad, A., Skjelland, M., Oie, E., Dahl, A., et al. (2007). Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. Circulation 115(8): 972-980.

Dogru, T., Sonmez, A., Tasci, I., Bozoglu, E., Yilmaz, M.I., et al. (2007). Plasma visfatin levels in patients with newly diagnosed and untreated type 2 diabetes mellitus and impaired glucose tolerance. Diabetes Res Clin Pract 76(1): 24-29.

Drevs, J., Loser, R., Rattel, B. and Esser, N. (2003). Antiangiogenic potency of FK866/K22.175, a new inhibitor of intracellular NAD biosynthesis, in murine renal cell carcinoma. Anticancer Res 23(6C): 4853-4858.

Elangovan, V.R., et al. (2011). Hsa-Mir-374a And Hsa-Mir-568 Attenuate LPS- And Cyclic Stretch-Induced Pbef Gene Expression In Human Lung Endothelium. American Journal of Respirator and Critical Care Medicine 183: A3523.

Fernandez-Real, J.M., Moreno, J.M., Chico, B., Lopez-Bermejo, A. and Ricart, W. (2007). Circulating visfatin is associated with parameters of iron metabolism in subjects with altered glucose tolerance. Diabetes Care 30(3): 616-621.

Frank, J.A., Parsons, P.E. and Matthay, M.A. (2006). Pathogenetic significance of biological markers of ventilator-associated lung injury in experimental and clinical studies. Chest 130(6): 1906-1914.

Fukuhara, A., Matsuda, M., Nishizawa, M., Segawa, K., Tanaka, M., et al. (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 307(5708): 426-430.

Fukuhara, A., Matsuda, M., Nishizawa, M., Segawa, K., Tanaka, M., et al. (2007). Retraction. Science 318(5850): 565.

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

Gautam, N., Olofsson, A.M., Herwald, H., Iversen, L.F., Lundgren-Akerlund, E., et al. (2001). Heparin-binding protein (HBP/CAP37): a missing link in neutrophil-evoked alteration of vascular permeability. Nat Med 7(10): 1123-1127.

Haider, D.G., Pleiner, J., Francesconi, M., Wiesinger, G.F., Muller, M., et al. (2006). Exercise training lowers plasma visfatin concentrations in patients with type 1 diabetes. J Clin Endocrinol Metab 91(11): 4702-4704.

Hallschmid, M., Randeva, H., Tan, B.K., Kern, W. and Lehnert, H. (2009). Relationship between cerebrospinal fluid visfatin (PBEF/Nampt) levels and adiposity in humans. Diabetes 58(3): 637-640.

Hasmann, M. and Schemainda, I. (2003). FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis. Cancer Res 63(21): 7436-7442.

Hassan, S.B., Lovborg, H., Lindhagen, E., Karlsson, M.O. and Larsson, R. (2006). CHS 828 kill tumour cells by inhibiting the nuclear factor-kappaB translocation but unlikely through down-regulation of proteasome. Anticancer Res 26(6B): 4431-4436.

Hjarnaa, P.J., Jonsson, E., Latini, S., Dhar, S., Larsson, R., et al. (1999). CHS 828, a novel pyridyl cyanoguanidine with potent antitumor activity in vitro and in vivo. Cancer Res 59(22): 5751-5757.

Ho, J.S., Buchweitz, J.P., Roth, R.A. and Ganey, P.E. (1996). Identification of factors from rat neutrophils responsible for cytotoxicity to isolated hepatocytes. J Leukoc Biol 59(5): 716-724.

Holen, K., Saltz, L.B., Hollywood, E., Burk, K. and Hanauske, A.R. (2008). The pharmacokinetics, toxicities, and biologic effects of FK866, a nicotinamide adenine dinucleotide biosynthesis inhibitor. Invest New Drugs 26(1): 45-51.

Hong, S.B., Huang, Y., Moreno-Vinasco, L., Sammani, S., Moitra, J., et al. (2008). Essential role of pre-B-cell colony enhancing factor in ventilator-induced lung injury. Am J Respir Crit Care Med 178(6): 605-617.

Hufton, S.E., Moerkerk, P.T., Brandwijk, R., de Bruine, A.P., Arends, J.W., et al. (1999). A profile of differentially expressed genes in primary colorectal cancer using suppression subtractive hybridization. FEBS Lett 463(1-2): 77-82.

Jia, S.H., Li, Y., Parodo, J., Kapus, A., Fan, L., et al. (2004). Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. J Clin Invest 113(9): 1318-1327.

Jian, W.X., Luo, T.H., Gu, Y.Y., Zhang, H.L., Zheng, S., et al. (2006). The visfatin gene is associated with glucose and lipid metabolism in a Chinese population. Diabet Med 23(9): 967-973.

Kang, G.B., Bae, M.H., Kim, M.K., Im, I., Kim, Y.C., et al. (2009). Crystal structure of Rattus norvegicus Visfatin/PBEF/Nampt in complex with an FK866-based inhibitor. Mol Cells 27(6): 667-671.

Kato, A., Odamaki, M., Ishida, J. and Hishida, A. (2009). Relationship between serum pre-B cell colony-enhancing factor/visfatin and atherosclerotic parameters in chronic hemodialysis patients. Am J Nephrol 29(1): 31-35.

Khan, J.A., Forouhar, F., Tao, X. and Tong, L. (2007). Nicotinamide adenine dinucleotide metabolism as an attractive target for drug discovery. Expert Opin Ther Targets 11(5): 695-705.

Khan, J.A., Tao, X. and Tong, L. (2006). Molecular basis for the inhibition of human NMPRTase, a novel target for anticancer agents. Nat Struct Mol Biol 13(7): 582-588.

Kim, M.K., Lee, J.H., Kim, H., Park, S.J., Kim, S.H., et al. (2006). Crystal structure of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase, free and in complex with the anti-cancer agent FK-866. J Mol Biol 362(1): 66-77.

Kim, S.R., Bae, S.K., Choi, K.S., Park, S.Y., Jun, H.O., et al. (2007). Visfatin promotes angiogenesis by activation of extracellular signal-regulated kinase 1/2. Biochem Biophys Res Commun 357(1): 150-156.

Kim, S.R., Bae, Y.H., Bae, S.K., Choi, K.S., Yoon, K.H., et al. (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.

Krzyzanowska, K., Krugluger, W., Mittermayer, F., Rahman, R., Haider, D., et al. (2006). Increased visfatin concentrations in women with gestational diabetes mellitus. Clin Sci (Lond) 110(5): 605-609.

Kubes, P., Hunter, J. and Granger, D.N. (1992). Ischemia/reperfusion-induced feline intestinal dysfunction: importance of granulocyte recruitment. Gastroenterology 103(3): 807-812.

Landre-Beauvais, A.J. (2001). The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. Joint Bone Spine 68(2): 130-143.

Lauriat, S. and Linas, S.L. (1998). The role of neutrophils in acute renal failure. Semin Nephrol 18(5): 498-504.

Lee, H.C. (2001). Physiological functions of cyclic ADP-ribose and NAADP as calcium messengers. Annu Rev Pharmacol Toxicol 41: 317-345.

Lee, W.L. and Downey, G.P. (2001). Leukocyte elastase: physiological functions and role in acute lung injury. Am J Respir Crit Care Med 164(5): 896-904.

Lewandowski, K.C., Stojanovic, N., Press, M., Tuck, S.M., Szosland, K., et al. (2007). Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. Diabetologia 50(5): 1033-1037.

Li, H., Liu, P., Cepeda, J., Fang, D., Easley, R.B., et al. (2008). Augmentation of Pulmonary Epithelial Cell IL-8 Expression and Permeability by Pre-B-cell Colony Enhancing Factor. J Inflamm (Lond) 5: 15.

Li, Y., Zhang, Y., Dorweiler, B., Cui, D., Wang, T., et al. (2008). Extracellular Nampt promotes macrophage survival via a nonenzymatic interleukin-6/STAT3 signaling mechanism. J Biol Chem 283(50): 34833-34843.

Liang, Y., Xu, X.M., Wang, H.S. and Wang, P.W. (2008). [Correlation between the expression of gastrocolic omentum visfatin mRNA and gestational diabetes mellitus]. Zhonghua Fu Chan Ke Za Zhi 43(11): 824-827.

Lin, S.J., Defossez, P.A. and Guarente, L. (2000). Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science 289(5487): 2126-2128.

Liu, P., Li, H., Cepeda, J., Zhang, L.Q., Cui, X., et al. (2009). Critical role of PBEF expression in pulmonary cell inflammation and permeability. Cell Biol Int 33(1): 19-30.

Liu, S.W., Qiao, S.B., Yuan, J.S. and Liu, D.Q. (2009). Visfatin stimulates production of monocyte chemotactic protein-1 and interleukin-6 in human vein umbilical endothelial cells. Horm Metab Res 41(4): 281-286.

Lopez-Bermejo, A., Chico-Julia, B., Fernandez-Balsells, M., Recasens, M., Esteve, E., et al. (2006). Serum visfatin increases with progressive beta-cell deterioration. Diabetes 55(10): 2871-2875.

Martin, P.R., Shea, R.J. and Mulks, M.H. (2001). Identification of a plasmid-encoded gene from Haemophilus ducreyi which confers NAD independence. J Bacteriol 183(4): 1168-1174.

Matsui, H., Tsutsumi, A., Sugihara, M., Suzuki, T., Iwanami, K., et al. (2008). Visfatin (pre-B cell colony-enhancing factor) gene expression in patients with rheumatoid arthritis. Ann Rheum Dis 67(4): 571-572.

Matthay, M.A., Zimmerman, G.A., Esmon, C., Bhattacharya, J., Coller, B., et al. (2003). Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. Am J Respir Crit Care Med 167(7): 1027-1035.

Mazaki-Tovi, S., Romero, R., Kusanovic, J.P., Erez, O., Gotsch, F., et al. (2008). Visfatin/Pre-B cell colony-enhancing factor in amniotic fluid in normal pregnancy, spontaneous labor at term, preterm labor and prelabor rupture of membranes: an association with subclinical intrauterine infection in preterm parturition. J Perinat Med 36(6): 485-496.

Menissier de Murcia, J., Ricoul, M., Tartier, L., Niedergang, C., Huber, A., et al. (2003). Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. EMBO J 22(9): 2255-2263.

Moschen, A.R., Gerner, R.R. and Tilg, H. (2010). Pre-B cell colony enhancing factor/NAMPT/visfatin in inflammation and obesity-related disorders. Curr Pharm Des 16(17): 1913-1920.

Muruganandham, M., Alfieri, A.A., Matei, C., Chen, Y., Sukenick, G., et al. (2005). Metabolic signatures associated with a NAD synthesis inhibitor-induced tumor apoptosis identified by 1H-decoupled-31P magnetic resonance spectroscopy. Clin Cancer Res 11(9): 3503-3513.

Nahimana, A., Attinger, A., Aubry, D., Greaney, P., Ireson, C., et al. (2009). The NAD biosynthesis inhibitor APO866 has potent antitumor activity against hematologic malignancies. Blood 113(14): 3276-3286.

Nowell, M.A., Richards, P.J., Fielding, C.A., Ognjanovic, S., Topley, N., et al. (2006). Regulation of pre-B cell colony-enhancing factor by STAT-3-dependent interleukin-6 trans-signaling: implications in the pathogenesis of rheumatoid arthritis. Arthritis Rheum 54(7): 2084-2095.

Ognjanovic, S., Bao, S., Yamamoto, S.Y., Garibay-Tupas, J., Samal, B., et al. (2001). Genomic organization of the gene coding for human pre-B-cell colony enhancing factor and expression in human fetal membranes. J Mol Endocrinol 26(2): 107-117.

Ognjanovic, S. and Bryant-Greenwood, G.D. (2002). Pre-B-cell colony-enhancing factor, a novel cytokine of human fetal membranes. Am J Obstet Gynecol 187(4): 1051-1058.

Olesen, U.H., Christensen, M.K., Bjorkling, F., Jaattela, M., Jensen, P.B., et al. (2008). Anticancer agent CHS-828 inhibits cellular synthesis of NAD. Biochem Biophys Res Commun 367(4): 799-804.

Olesen, U.H., Petersen, J.G., Garten, A., Kiess, W., Yoshino, J., et al. (2010a). Target enzyme mutations are the molecular basis for resistance towards pharmacological inhibition of nicotinamide phosphoribosyltransferase. BMC Cancer 10: 677.

Olesen, U.H., Thougaard, A.V., Jensen, P.B. and Sehested, M. (2010b). A preclinical study on the rescue of normal tissue by nicotinic acid in high-dose treatment with APO866, a specific nicotinamide phosphoribosyltransferase inhibitor. Mol Cancer Ther 9(6): 1609-1617.

Olsen, L.S., Hjarnaa, P.J., Latini, S., Holm, P.K., Larsson, R., et al. (2004). Anticancer agent CHS 828 suppresses nuclear factor-kappa B activity in cancer cells through downregulation of IKK activity. Int J Cancer 111(2): 198-205.

Otero, M., Lago, R., Gomez, R., Lago, F., Dieguez, C., et al. (2006). Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 65(9): 1198-1201.

Pagano, C., Pilon, C., Olivieri, M., Mason, P., Fabris, R., et al. (2006). Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. J Clin Endocrinol Metab 91(8): 3165-3170.

Palin, M.F., Labrecque, B., Beaudry, D., Mayhue, M., Bordignon, V., et al. (2008). Visfatin expression is not associated with adipose tissue abundance in the porcine model. Domest Anim Endocrinol 35(1): 58-73.

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

Pogrebniak, A., Schemainda, I., Azzam, K., Pelka-Fleischer, R., Nussler, V., et al. (2006). Chemopotentiating effects of a novel NAD biosynthesis inhibitor, FK866, in combination with antineoplastic agents. Eur J Med Res 11(8): 313-321.

Reddy, P.S., Umesh, S., Thota, B., Tandon, A., Pandey, P., et al. (2008). PBEF1/NAmPRTase/Visfatin: a potential malignant astrocytoma/glioblastoma serum marker with prognostic value. Cancer Biol Ther 7(5): 663-668.

Retnakaran, R., Youn, B.S., Liu, Y., Hanley, A.J., Lee, N.S., et al. (2008). Correlation of circulating full-length visfatin (PBEF/NAMPT) with metabolic parameters in subjects with and without diabetes: a cross-sectional study. Clin Endocrinol (Oxf) 69(6): 885-893.

Revollo, J.R., Grimm, A.A. and Imai, S. (2004). The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyltransferase regulates Sir2 activity in mammalian cells. J Biol Chem 279(49): 50754-50763.

Revollo, J.R., Korner, A., Mills, K.F., Satoh, A., Wang, T., et al. (2007). Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. Cell Metab 6(5): 363-375.

Rho, Y.H., Solus, J., Sokka, T., Oeser, A., Chung, C.P., et al. (2009). Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 60(7): 1906-1914.

Rongvaux, A., Shea, R.J., Mulks, M.H., Gigot, D., Urbain, J., et al. (2002). Pre-B-cell colony-enhancing factor, whose expression is up-regulated in activated lymphocytes, is a nicotinamide phosphoribosyltransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur J Immunol 32(11): 3225-3234.

Samal, B., Sun, Y., Stearns, G., Xie, C., Suggs, S., et al. (1994). Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol 14(2): 1431-1437.

Sandeep, S., Velmurugan, K., Deepa, R. and Mohan, V. (2007). Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians. Metabolism 56(4): 565-570.

Sasaki, Y., Araki, T. and Milbrandt, J. (2006). Stimulation of nicotinamide adenine dinucleotide biosynthetic pathways delays axonal degeneration after axotomy. J Neurosci 26(33): 8484-8491.

Schoua C., O.E.R., Petersena H.J., Björkling F., * Latinib S., Hjarnaac P.V., Brammc E. and Binderup L. (1997). Novel cyanoguanidines with potent oral antitumour activity Bioorganic & Medicinal Chemistry Letters 7(24): 3095-3100.

Schreiber, V., Dantzer, F., Ame, J.C. and de Murcia, G. (2006). Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol 7(7): 517-528.

Takebayashi, K., Suetsugu, M., Wakabayashi, S., Aso, Y. and Inukai, T. (2007). Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. Metabolism 56(4): 451-458.

Tsiotra, P.C., Tsigos, C., Yfanti, E., Anastasiou, E., Vikentiou, M., et al. (2007). Visfatin, TNF-alpha and IL-6 mRNA expression is increased in mononuclear cells from type 2 diabetic women. Horm Metab Res 39(10): 758-763.

Van Beijnum, J.R., Moerkerk, P.T., Gerbers, A.J., De Bruine, A.P., Arends, J.W., et al. (2002). Target validation for genomics using peptide-specific phage antibodies: a study of five gene products overexpressed in colorectal cancer. Int J Cancer 101(2): 118-127.

van der Veer, E., Ho, C., O'Neil, C., Barbosa, N., Scott, R., et al. (2007). Extension of human cell lifespan by nicotinamide phosphoribosyltransferase. J Biol Chem 282(15): 10841-10845.

van der Veer, E., Nong, Z., O'Neil, C., Urquhart, B., Freeman, D., et al. (2005). Pre-B-cell colony-enhancing factor regulates NAD+-dependent protein deacetylase activity and promotes vascular smooth muscle cell maturation. Circ Res 97(1): 25-34.

von Heideman, A., Berglund, A., Larsson, R. and Nygren, P. (2010). Safety and efficacy of NAD depleting cancer drugs: results of a phase I clinical trial of CHS 828 and overview of published data. Cancer Chemother Pharmacol 65(6): 1165-1172.

Wang, T., Zhang, X., Bheda, P., Revollo, J.R., Imai, S., et al. (2006). Structure of Nampt/PBEF/visfatin, a mammalian NAD+ biosynthetic enzyme. Nat Struct Mol Biol 13(7): 661-662.

Ware, L.B. and Matthay, M.A. (2000). The acute respiratory distress syndrome. N Engl J Med 342(18): 1334-1349.

Wheeler, A.P. and Bernard, G.R. (2007). Acute lung injury and the acute respiratory distress syndrome: a clinical review. Lancet 369(9572): 1553-1564.

Wright, S.C., Wei, Q.S., Kinder, D.H. and Larrick, J.W. (1996). Biochemical pathways of apoptosis: nicotinamide adenine dinucleotide-deficient cells are resistant to tumor necrosis factor or ultraviolet light activation of the 24-kD apoptotic protease and DNA fragmentation. J Exp Med 183(2): 463-471.

Xie, H., Tang, S.Y., Luo, X.H., Huang, J., Cui, R.R., et al. (2007). Insulin-like effects of visfatin on human osteoblasts. Calcif Tissue Int 80(3): 201-210.

Yang, H.J., Yen, M.C., Lin, C.C., Lin, C.M., Chen, Y.L., et al. (2010). A combination of the metabolic enzyme inhibitor APO866 and the immune adjuvant L-1-methyl tryptophan induces additive antitumor activity. Exp Biol Med (Maywood) 235(7): 869-876.

Ye, S.Q., Simon, B.A., Maloney, J.P., Zambelli-Weiner, A., Gao, L., et al. (2005a). Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 171(4): 361-370.

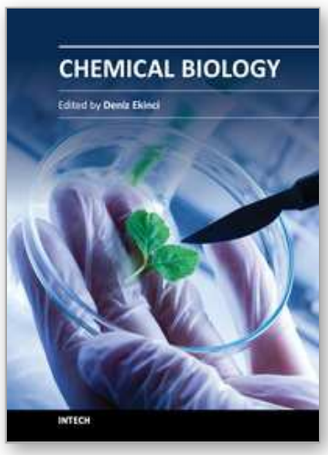
Ye, S.Q., Zhang, L.Q., Adyshev, D., Usatyuk, P.V., Garcia, A.N., et al. (2005b). Pre-B-cell-colony-enhancing factor is critically involved in thrombin-induced lung endothelial cell barrier dysregulation. Microvasc Res 70(3): 142-151.

You, H., Youn, H.S., Im, I., Bae, M.H., Lee, S.K., et al. (2011). Design, synthesis and X-ray crystallographic study of NAmPRTase inhibitors as anti-cancer agents. Eur J Med Chem 46(4): 1153-1164.

Zhong, M., Tan, H.W., Gong, H.P., Wang, S.F., Zhang, Y., et al. (2008). Increased serum visfatin in patients with metabolic syndrome and carotid atherosclerosis. Clin Endocrinol (Oxf) 69(6): 878-884.

Ziegelmeier, M., Bachmann, A., Seeger, J., Lossner, U., Kratzsch, J., et al. (2008). Adipokines influencing metabolic and cardiovascular disease are differentially regulated in maintenance hemodialysis. Metabolism 57(10): 1414-1421.

Zoppoli, G., Cea, M., Soncini, D., Fruscione, F., Rudner, J., et al. (2010). Potent synergistic interaction between the Nampt inhibitor APO866 and the apoptosis activator TRAIL in human leukemia cells. Exp Hematol 38(11): 979-988.



Chemical Biology

Edited by Prof. Deniz Ekinci

ISBN 978-953-51-0049-2
Hard cover, 444 pages
Publisher InTech
Published online 17, February, 2012
Published in print edition February, 2012

Chemical biology utilizes chemical principles to modulate systems to either investigate the underlying biology or create new function. Over recent years, chemical biology has received particular attention of many scientists in the life sciences from botany to medicine. This book contains an overview focusing on the research area of protein purification, enzymology, vitamins, antioxidants, biotransformation, gene delivery, signaling, regulation and organization. Particular emphasis is devoted to both theoretical and experimental aspects. The textbook is written by international scientists with expertise in synthetic chemistry, protein biochemistry, enzymology, molecular biology, drug discovery and genetics many of which are active chemical, biochemical and biomedical research. The textbook is expected to enhance the knowledge of scientists in the complexities of chemical and biological approaches and stimulate both professionals and students to dedicate part of their future research in understanding relevant mechanisms and applications of chemical biology.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen