Patent highlights June–July 2018

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A snapshot of noteworthy recent developments in the patent literature of relevance to pharmaceutical and medical research and development.

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WO/2018/099933

Methods of modulating FAM64A

Inventors: Carayol J, Valsesia A, Hager J

Assignee: Nestec SA (Vevey, Switzerland)

In WO/2017/174716 the present inventors had reported that a protein quantitative trait *loci* (pQTL) analysis of data from DIOGenes (a pan-European randomized and controlled study investigating the effects of dietary protein and glycemic index on weight loss and its maintenance in obese and overweight families) [1] had revealed a link between branched-chain alpha-keto acid dehydrogenase and the physiological appetite suppressor, leptin (reviewed in *Pharm. Patent Anal.* 7(2)). The same analysis has found a much less likely link, with Fam64a (CATS), a protein that is overexpressed in malignant tissues [2] and acts as a cell cycle promoter in hypoxic fetal cardiomyocytes [3] but has never been mentioned in the context of obesity. In the DIOGenes data, Fam46a was highly correlated with *BAG6*, a Bcl2-associated gene for which alternative splicing of its mRNA in subcutaneous fat tissue is known to be strongly influenced by the body mass index [4]. In cultured preadipocytes, Fam64a expression decreases during maturation, to reach a minimum after 7 days while leptin levels rise. Fam64a knockdown did not impact expression of leptin, or of adipocyte differentiation markers. The surprise is the broad range of known molecules that decrease *FAM64A* expression: various antirheumatic agents, clofibrate, cuprizone, valproate, entinostat (a class I HDAC inhibitor) and even the insecticide fipronil – to name just a few from a long list.

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MeSH keywords: FAM46A protein, human • leptin • obesity

WO/2018/102751

IRE1 small molecule inhibitors

Inventors: Vacca JP, Li D, Bettigole S

Assignee: Quantis Therapeutics, Inc. (New York, NY, USA)

IRE1, an inositol-requiring enzyme that possesses both Ser/Thr kinase and RNase activities, is the most conserved of the three specific transmembrane receptors that sense accumulation of misfolded or unfolded proteins in the endoplasmic reticulum (the others are PERK and ATF6) and activate the stress-dependent signaling branches [5]. Kinase transautophosphorylation in the cytosol and subsequent RNase domain activation engages the unfolded protein response (UPR) which can either lead to apoptosis, or to an adaptive response that maintains the functionality of the secretory pathway in the endoplasmic reticulum, depending on the circumstances. Aggressive tumors utilize this pathway to shape their microenvironment to evade oxidative stress and high metabolic demand [6]; proapoptotic functions of the UPR are triggered in normal cells by immune responses [7], in neurodegeneration [8], organ ischemia/reperfusion and many other conditions that put tissues under severe stress. In all these cases IRE1 inhibitors might prove beneficial, either by enhancing the efficacy of standard chemotherapies, or by preventing cell death. Very few such small molecule inhibitors have been developed, for example, UPRM8 and the research compound 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (4 μ 8C) that work through covalent inactivation, and some others that exert allosteric inhibition through ATP-competitive binding. The compounds of this invention

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were assessed for IRE1 signaling disruption using a IRE1 α endoribonuclease nanoluciferase assay, and for cellular effects in T-cell activation assays and lipid accumulation assays. Some compounds had IC₅₀ or EC₅₀ values below 5 nM in some of these assays. In the most interesting embodiments, they have at least two distinct binding sites within the RNase domain, kinase domain, ATP-binding pocket or activation loop; their binding prevents the essential back-to-back dimerization of IRE1 α that is essential for UPR activation. For related work see Cubillos-Ruiz *et al.* [9].

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MeSH keywords: endoplasmic reticulum stress • IRE1 protein, human • neoplasms • unfolded protein response

WO/2018/104172

Compounds for treating Barth syndrome

Inventors: Tribouillard-Tanvier D, Lasserre J-P, Di Rago J-P

Assignee: CNRS (Paris, France); Université Bordeaux (Bordeaux, France); Association Française contre les Myopathies (Paris, France)

Barth syndrome, an ultrarare disease with less than 500 patients worldwide, is caused by mutations in *TAZ*, the tafazzin gene which encodes a mitochondrial phospholipid transacylase that promotes cardiolipin acyl chain remodeling. Its symptoms include lactic acidosis, excretion of organic acids in urine, muscle weakness and cardiomyopathy [10]. Barth syndrome has attracted only a few patentees, such as in US 9,55,0981 (University of Washington, modified tafazzins), WO/2014/134554 (Stealth Peptides International, Inc.) and WO/2007/121479 (Diobex, Inc. claiming ketoconazole). Reduced cytosolic protein synthesis suppresses membrane depolarization and mitochondrial defects in a yeast model system of mitochondrial ADP/ATP translocase mutations [11], which had suggested to the inventors that tafazzin mutations might respond in a similar way. Indeed, a yeast model for the Barth Syndrome that presents with proteostatic stress could be rescued by the eukaryote protein synthesis inhibitors cycloheximide and anisomycin, at doses that trigger a subtle metabolic adaptation with very little decrease of cytosolic protein synthesis. Hsp60, a mitochondria-specific molecular chaperone and marker of the mitochondrial unfolded protein response, and Ccp1, the cytochrome c peroxidase that modulates the antioxidant defense are overexpressed in *taz1A* mutant yeast in presence of cycloheximide. In HeLa cells in which *TAZ* was knocked down by RNA interference and cardiolipin maturation is defective, 50 pM cycloheximide prolonged continuous growth for 170 h, while untreated cells died after 72 h. For the peer review companion paper see de Taffin de Tilques *et al.* [12].

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MeSH keywords: Barth syndrome • cycloheximide • genetic diseases, X-Linked • TAZ protein, human

WO/2018/106636

SHMT inhibitor and uses thereof

Inventors: Mainolfi N

Assignee: Raze Therapeutics, Inc. (Cambridge, MA, USA)

SHMT1, a cytosolic serine hydroxymethyltransferase, and its mitochondrial isoform SHMT2 catalyze the reversible conversion of serine to glycine, with the concurrent generation of methylene-tetrahydrofolate, the latter of which is required for one-carbon unit anabolic reactions [13]. Many cancers depend on SHMTs [14]. Raze Therapeutics, a startup company that had focused on developing therapeutics that target such metabolic pathways, published several patent applications in this field, mostly claiming 3-phosphoglycerate dehydrogenase inhibitors (WO/2017/156181 and others) but also inhibitors of MTHFD2, an enzyme acting on methylene-THF (WO/2017/023894). The present application is the only one addressing SHMT2 inhibitors. Seventy-one compounds are specified by structural formula; about a third of these is said to show nanomolar IC₅₀ values in SHMT2 activity assays using the recombinant enzyme and mass spectroscopy detection of serine production. About half of the latter ones are comparably active against SHMT1. No *in vivo* data are presented. For other SHMT2 inhibitors from the University of Michigan see WO/2016/085990.

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MeSH keywords: SHMT protein, human • neoplasms

WO/2018/109198**Bicyclic O-GlcNAcase inhibitors compounds***Inventors: Bartolomé-Nebreda J, Triabanco-Suárez A, Martínez Viturro C, Tresadern G, Alcázar-Vaca M*

Assignee: Janssen Pharmaceutica NV (Beerse, Belgium)

O-GlcNAcase (OGA) is the only known enzyme that removes the post-translational O-Linked β -N-acetylglucosamine modifications (added by the respective transferase, OGT) from the hydroxyl groups of serine and threonine residues of target proteins. Perturbations in these reversible modifications are involved not only in cancer and in metabolic diseases including diabetes [15], but also in the formation of protein aggregates in Alzheimer's and Parkinson disease, and in various tauopathies [16–18]. Expression of O-GlcNAcase itself is sensitive to changes in this homeostasis [19], providing a feedback effect. The few relatively selective OGA inhibitors that are active *in vivo*, such as Thiamet G, are research tools. The inventors present OGA inhibitors bearing a 1,3-disubstituted piperidine or piperazine or a 2,4-disubstituted morpholine bound to the 5-membered ring of a 9-membered bicyclic heteroaryl. They were assessed in an enzyme inhibition assay, and in HEK293 cells inducible for P301L mutant human Tau (isoform 2N4R), with OGA inhibition evaluated through the immunocytochemical detection of O-GlcNAcylated proteins with a monoclonal antibody. Typical compounds had high-nanomolar IC₅₀ values for inhibition of free OGA, and mostly also in the cell assay. Also see WO2016/030443 (Asceneuron SA) for 1,4-disubstituted piperidine and piperazine OGA inhibitors.

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MeSH keywords: Alzheimer disease • beta-N-acetylhexosaminidases

WO/2018/112077**Inhibitors of dihydroceramide desaturase for treating disease***Inventors: Romero DL, McCall JM, Blitzer J*

Assignee: Centaurus Therapeutics, Inc. (San Francisco, CA, USA)

Dihydroceramide desaturases (DES1 and its less important isoform, DES2) catalyze the last step of ceramide formation by introducing a 4,5-*trans* double bond into the sphingoid base backbone of dihydroceramide, thus regulating the physiologically relevant balance between dihydrosphingolipids and sphingolipids. Accumulation of endogenous ceramides and glucosylceramides antagonizes insulin stimulated glucose uptake and anabolism (mimicking the effects of exogenous sphingolipid analogs) and is now appreciated as an important nutrient metabolite that accumulates in obesity [20]. Inhibition of their biosynthesis is considered to be insulin sensitizing. DES inhibitors might also be useful in lipid storage disorders, inflammatory autoimmune conditions, in neurodegenerative diseases [21], and also in cancer where they can induce autophagy [22]. Discovery of potent and selective DES1 inhibitors is difficult because of the configurational preferences of the enzymes, and has picked up only very recently [23]. In an assay based on Jurkat E6-1 cells loaded with dihydroceramide, a number of the compounds described herein exhibit IC₅₀ values <50 nM (significantly better than the reference inhibitor, fenretinide); for example, *N*-(5-hydroxypyridine-2-yl)-7-methyloctanamide and (1*R*,4*R*)-4-(4-chlorophenyl)-*N*-(5-hydroxypyridine-2-yl)cyclohexane-1-carboxamide had IC₅₀ values of 10 nM. *In vivo* models are described, but no data are presented.

Published: 21 June 2018

MeSH keywords: dihydroceramide desaturase • insulin resistance • neoplasms

WO/2018/114965**ClpX inhibitory compounds for the treatment of multiresistant *Staphylococcus aureus* virulence and for the treatment of leukemia***Inventors: Fetzner C, Korotkov V, Sieber S*

Assignee: Technische Universität München, München (Germany)

Staphylococcus aureus virulence is controlled by a complex network involving quorum sensing mediated by autoinducing peptides expressed by the accessory gene regulator (AGR) system [24]. These peptides initiate the production of toxins by binding to receptors of two component systems upon a threshold density. A caseinolytic protease, ClpP is the proteolytic component in the ClpXP complex that plays a central role in AGR-dependent toxin expression by *S. aureus* [25] and other bacteria. It is formed by association of ClpP with a chaperone, ClpX that recognizes and recruits the substrate proteins and unfolds them in an ATP-dependent reaction [26]. Deregulating ClpP activity either through overactivation or inhibition could offer a route to treat virulent and multiresistant bacterial strains

by small molecules [27]; however, ClpX might represent an even more interesting target for antivirulence strategies. To identify specific inhibitors of ClpX the inventors employed a high-throughput screen against over 40,000 compounds, based on the degradation of green fluorescent protein carrying an SsrA peptide-tag. ClpX binds, unfolds the tagged green fluorescent protein, then digests it within the proteolytic ClpP barrel; this abolishes the protein fluorescence. Among the 332 primary hits were 158 ClpXP-only inhibitors with a potency $<5 \mu\text{M}$. One of these (compound 334) collapsed the whole ClpXP proteolytic complex in response to (noncovalent) binding, and induced deoligomerization of ClpX. Synthesis of 34 derivatives and SAR studies revealed that the molecular scaffold is restrictive for diversification. Compound 334 downregulates several secreted *S. aureus* (strain NCTC 8325) virulence proteins in a concentration dependent manner. Serine protease A–F, gamma hemolysin component C and Staphopain A show a reduction with a mean EC_{50} of about $3 \mu\text{M}$. For the peer review companion paper see Fetzner *et al.* [28].

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MeSH keywords: bacterial toxins • endopeptidase Clp • methicillin-resistant *Staphylococcus aureus*

WO/2018/118711

Small molecule ferroptosis inducers

Inventors: Stockwell BR

Assignee: The Trustees of Columbia University in the City of New York (New York, NY, USA)

Ferroptosis is a necrotic form of regulated cell death which mainly affects membrane lipids, and can be suppressed by iron chelators [29,30]. Its natural inhibitor is ferrostatin-1. Periventricular leukomalacia, nephrotic tubular death and Huntington's disease are conditions where ferroptosis might be particularly important [31,32]. Ferroptosis can be induced by direct or indirect inhibitors of GPX4 (a glutathione peroxidase, which reduces lipid hydroperoxides), such as the cystine-glutamate antiporter inhibitor erastin. Ferroptosis inducers could synergize with cytotoxic drugs. Among 3169 lethally cytotoxic compounds tested by the inventors, 451 primary hits were identified as potential inductors of caspase-3 and -7 independent cell death in fibrosarcoma cells and transformed fibroblasts, and 56 structurally diverse and potent ones were further examined using a modulatory profiling strategy. In the mechanistic analysis, 10 compounds exhibited high modulatability, that is, their lethality was considerably suppressed by metal chelators, necrostatin-1 or iron chelators and lipophilic antioxidants. The last mentioned of these three classes (six compounds) were the desired ferroptosis inducers, three of which had novel chemical scaffolds. Characterization of the most promising molecule (FIN56, an almost symmetrically substituted tricyclic bis-sulfonyl compound) revealed degradation of GPX4 and activation of squalene synthetase as a dual mechanism. The last-mentioned activity depletes coenzyme Q_0 , an apoptosis inducer that might have potential in estrogen receptor-negative breast cancer and ovarian carcinoma.

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MeSH keywords: FIN56 compound • necrosis • neoplasms

WO/2018/125983

Oxypyridine derivatives useful as aminocarboxymuconate semialdehyde decarboxylase inhibitors

Inventors: Takahashi Z, Ji N

Assignee: Mitobridge, Inc. (Cambridge, MA, USA)

ACMSD is a zinc-dependent amidohydrolase that stands at a branch point of the NAD^+ biosynthetic pathway from tryptophan and determines the final fate of the amino acid, that is, either transformation into picolinic acid, or complete oxidation through the citric acid cycle [33]. If ACMSD is inhibited, its unstable substrate α -amino- ω -carboxymuconic acid semialdehyde is nonenzymatically converted to quinolinic acid (an NMDA receptor agonist), leading to the formation of NAD^+ . Therefore, ACMSD inhibitors might be useful in conditions where intracellular NAD^+ levels are low: diabetes, hyperlipidemia, neutropenia, kidney disorders, cancers and (as has recently been suggested) Parkinson's disease [34]. In this invention 2-(3-cyano-5-methoxy-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-2-ylthio)acetic acid and 3-(((5-chloro-3-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)thio)methyl)benzoic acid are two examples with low-nanomolar IC_{50} values in an enzyme immunoassay with human ACMSD. Many other compounds with comparable inhibitory activity contain a tetrazole substituent, which might confound their metabolic stability. Note the discovery of the ACMSD inhibitor, TES-1025 (TES Pharma s.r.l.), recently reported by researchers working in Italy and Switzerland [35], and presum-

ably disclosed in WO/2018/069532 or WO/2016/030534. Also, reduced ACMSD activity has been reported to correlate with suicidality [36].

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MeSH keywords: aminocarboxymuconate-semialdehyde decarboxylase • NAD • quinolinic acid

WO/2018/127689

Universal influenza vaccine compositions

Inventors: Philip R

Assignee: Emergex Vaccines Holdings Ltd (Abington, UK)

The fact that the extreme antigenic variability of the influenza virus forces manufacturers to design and produce different vaccines every year, based on the predicted prevalence of strains, is a huge logistic challenge and remains the Achilles heel in all pandemic preparedness plans. While several quadrivalent vaccines (protecting against two influenza A and two influenza B strains) have been approved, the 'universal' influenza vaccine [37,38] had not progressed to the level of clinical efficacy testing until late 2017, when Vaccitech's much publicized MVA-NP+M1 (a modified Vaccinia virus Ankara vector encoding viral nuclear protein and matrix protein 1, which are conserved among the major strains), designed to boost memory T-cell responses, entered Phase IIb trials. In its first international patent application, Emergex is taking a different path, using influenza peptide antigens comprising B-cell and CD8⁺ T-cell epitopes from two or more of H1N1, H5N1, H7H9 and H3N2 Influenza A virus strains, bound to anorganic, polymeric or gold nanocarriers; this is supposed to remove the requirement for an adjuvant. The inventors identified seven epitopes with the HLA-A2 binding motif from infected cells; five of the seven epitopes had a HLA-A24 cross binding motif. In addition, they identified several HLA-B7 and B44 motif containing epitopes. All the epitopes originate from regions of the proteins that are conserved between multiple influenza strains including pandemic ones. The known CD8⁺ T-cell peptides YINTALLNA, AIMDKNIL and LPFDRTTIM (conserved between influenza A and B) were also found during the search. The B cell epitope is around 5–20 amino acids in length and can be an influenza matrix 2 protein (M2e) epitope (whose extracellular domain is conserved among influenza A viruses). Planned animal studies are outlined. For some of the research supporting this patent document see Testa *et al.* [39].

Published: 12 July 2018

MeSH keyword: influenza vaccines

WO/2018/132383

Cry-Clock-Bmal1 complex-disrupting agents and methods of identifying and using same

Inventors: Parico GCG, Partch C, Michael A, Fribourgh J

Assignee: The Regents of the University of California (Oakland, CA, USA)

The molecular basis of circadian rhythms is based on a set of interlocked transcription/translation feedback loops that include a set of dedicated core clock proteins and are synchronized by the daylight cycle. At the center of the feedback loops, the primary circadian transcription factor Clock:Bmal1 binds to E-box consensus motifs in clock target genes to activate transcription. Two of the targeted genes encode its dedicated repressor proteins, cryptochrome (Cry) and period (Per). Cry and Per associate in the cytoplasm, undergo extensive post-translational modification, and re-enter the nucleus to inhibit Clock:Bmal1 activity [40,41]. The inventors identify a deep, druggable pocket on Cry1 that binds Clock:Bmal1 (a tryptophan side chain from Clock Pas-B is essential for this), and claim agents that disrupt the ternary complex by preventing interaction between this secondary pocket and the Pas-B domain of Clock. Some of these agents are peptides with a flavin moiety; others are folate derivatives. They could be useful to rapidly reset the circadian clock, or to shorten the circadian period, for example, in an individual having Delayed Sleep Phase Syndrome – caused by a recently discovered dominant mutation in Cry1 that removes an exon coding for a domain that acts as an autoinhibitory module to antagonize the interaction of Cry1 with Clock:Pas-B. In the inventors' experiments, the peptide encoded by this exon served as a positive control inhibitor of the complex. For the peer review paper discussing some of the findings see Michael *et al.* [42].

Published: 19 July 2018

MeSH keywords: ARNTL transcription factors • circadian clocks • cryptochromes • sleep disorders, circadian rhythm

WO/2018/136913

Inhibition of bone loss and inhibition of arthritis by Cthrc1

Inventors: Lindner V, Jin Y-R

Assignee: Maine Medical Center Research Institute (Scarborough, ME, USA)

The inventors have found that the circulating collagen factor Cthrc1, which is expressed at sites of tissue injury and remodeling [43,44], is secreted by osteoblasts and some osteocytes (but not osteoclasts). It inhibits osteoclast differentiation and collagen antibody-induced arthritis by blocking Rankl-stimulated NFκB activation via prevention on IκBα degradation, while also inhibiting ERK1/2 activation; this signaling pathway is critical for mediating inflammatory responses. This cell type-specific action in bone homeostasis could make Cthrc1 or its mimicking agonistic peptides promising antiarthritic and antiosteoporotic agents. Three-point bending tests and microcomputed tomography demonstrated that the mechanical and architectural properties of bones from 8-week-old male Cthrc1 null mice were inferior to those of their female counterparts, and also to those of the C57BL/6J wildtype. Proliferation of bone marrow stromal cells was not impacted by the presence or absence of Cthrc1. The invention also claims Cthrc1 inhibitors. Their therapeutic utility would be much narrower in bone metabolic diseases, but could be very significant in cancers [45]. For the peer review companion paper see Jin *et al.* [46].

Published: 26 July 2018

MeSH keywords: arthritis • CTHRC1 protein, human • neoplasms • osteoporosis

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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