Patent Highlights June–July 2017

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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/2017/089453**Iminotetrahydropyrimidinone derivatives as plasmepsin V inhibitors***Inventors: Charlton RL, De Haro Garcia T, Lowe MA et al.**Assignee: UCB Biopharma sprl, Brussels (Belgium)**MeSH Keywords: aspartic acid endopeptidases • malaria • plasmodium • protein interaction domains and motifs*

The plasmepsins are the hemoglobin-degrading aspartic proteases of *Plasmodium* spp. Plasmepsin V is involved in the export of approximately 400 proteins containing the conserved *Plasmodium* export element motif (PEXEL). Most exported proteins must traverse two membranes to their destination in the infected erythrocyte cytosol, the parasite plasma membrane and surrounding parasitophorous vacuole membrane. Interactions and cleavage of PEXEL proteins by plasmepsin V is necessary for export, which in turn is required for the erythrocytic stage development of malaria parasites [1,2]. This makes plasmepsin V an attractive antimalarial drug target, but – as with all inhibitors of pathogen proteases – the candidate compounds must be highly specific. The inventors present a series of 2-imino-6-methyltetrahydropyrimidin-4(1*H*)-one derivatives, substituted in the 6-position by a phenyl moiety which in turn is meta-substituted by an (optionally substituted) unsaturated fused bicyclic ring system containing at least one nitrogen atom. The compounds are said to be within the broadest generic scope of applications WO/2008/103351, WO/2006/065277, WO/2005/058311 (all assigned to Schering Corp. and Pharmacoepia Drug Discovery, Inc., both NJ, USA) and WO/2006/041404 (AstraZeneca AB, Södertälje, Sweden) and Astex Therapeutics (Cambridge, UK) but were not specifically disclosed in these documents. All compounds exhibit IC₅₀ values of 50 μM or better in a plasmepsin V enzyme assay, typically in the range of about 0.01 nM to about 5 μM. For competing work from an Italian group see Gambini *et al.* [3].

Published: 1 June 2017

WO/2017/093272**Furane derivatives as inhibitors of ATAD2***Inventors: Berger M, Hübner J, Ter Laak A et al.**Assignee: Bayer AG, Berlin (Germany)**MeSH Keywords: adenosine triphosphatases • DNA-Binding Proteins • histones • neoplasms*

ATAD2, also known as ANCCA or PRO2000, is a bromodomain and AAA ATPase domain containing nuclear protein which under normal circumstances is expressed only in male germ cells. However, ATAD2 is massively overexpressed in many tumors, where it functions as a co-factor of oncogenic cyclins, cyclin-dependent kinases and kinesins [4]; but only when its bromodomain is intact [5]. The present invention identifies compounds which are ATAD2 bromodomain inhibitors. In a TR-FRET assay which detects the binding of a biotinylated synthetic peptide derived from acetylated histone H4 to an N-terminally GST-tagged recombinant peptide comprising ATAD2 bromodomain amino acids 981–1108, most compounds had IC₅₀ values in the high nanomolar range. The di-acetylation marks on the histone H4 are highly relevant because they recruit ATAD2 to replication sites, tagging newly synthesized histones during replication-coupled chromatin reassembly [6]. N-[(2R)-1-[(4-aminocyclohexyl)amino]-3-(4-cyanophenyl)propan-2-yl]-2-chloro-4-methoxy-5-[5-({[(1R)-

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1-(4-methylphenyl)ethyl] amino}methyl)-2-furyl]benzamide seems to be the best, with an IC₅₀ of 166 nM and 50% growth inhibition of cultured MCF7 breast cancer cells and NCI-H526 lung cancer cells at 3.2 and 2.4 μ M, respectively. For related work, see Bamborough *et al.* [7] and (from the same group) Demont *et al.* [8].

Published: 8 June 2017

WO/2017/093363

Compound for use in the prevention and treatment of neurodegenerative diseases

Inventors: Konrat R, Sealey M.

Assignee: Universität Wien, Vienna (Austria)

MeSH Keywords: *alpha-Synuclein* • *calixarenes* • *lipocalins* • *Parkinson disease*

Progressive accumulation of the synaptic protein α -synuclein plays a critical role in the pathogenesis of Parkinson's disease, dementia with Lewy bodies and multiple system atrophy. Its interaction with neuronal cell membrane lipids has been proposed to be an important step in the process of oligomerization and resultant cytotoxicity. Reactive astrocytes secrete lipocalin 2, a potent neurotoxic mediator [9] that is increased in the substantia nigra of patients with Parkinson's disease [10]. The inventors have identified novel calixarenes that target α -synuclein in its folded state in the cellular membrane and, at higher concentrations, release it from the membrane and thereby affect its aggregation propensities. Calixarenes are oligomers that assume basket, cup or bucket shapes, are capable of self-assembly, lend themselves to host-guest chemistry, and can be efficient ionophores and even enzyme mimetics. Their potential in pharmacology is significant [11,12]. However, in contrast to prior art compounds, the molecules of the invention also bind to the N-terminal domain of the soluble, monomeric form of α -synuclein and thus affect its binding to some of its endogenous protein interaction partners, such as calmodulin and (with a K_d of 700 nM) to lipocalin 2. This makes them powerful neuroprotectants which even have some neurotrophic properties, selectively increasing the number of astrocytes in the cortex of transgenic mice but not in healthy control mice. Sulfocalixarene is most effective: it protected SH-SY5Y RA/PMA differentiated neuronal cells against toxicity exerted by MPP+, hydrogen peroxide and lipocalin 2; and it improved the performance of motor-impaired mice in the beam walking and pasta gnawing tests. Neuropathological and ultrastructural studies confirmed that the synaptic vesicles and terminals of mice were unaffected in mice not overexpressing α -synuclein.

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WO/2017/095237

Carbon monoxide releasing norborneone compounds

Inventors & applicants: Sammut IA, Harrison JC, Hewitt RJ *et al.* (New Zealand, Australia, United States)

MeSH Keywords: *bridged bicyclo compounds* • *carbon monoxide* • *organ preservation*

Carbon monoxide can kill by blocking hemoglobin – however, it is also an important second messenger molecule. Delivery of CO gas at low concentrations has anti-inflammatory effects, protects organs from ischemic injury while inducing a preconditioning response [13,14], and is cytoprotective even in the respiratory system [15]. CO-releasing molecules, mostly metal carbonyls but also PEGylated carboxyhemoglobin [16], are being investigated as a potential new drug class to treat a very broad range of inflammatory and ischemic conditions as well as hypertonia, especially under stress conditions. The inventors have developed norbornenone compounds that can release carbon monoxide upon pH changes, and are optimally suited for preservation of explanted organs and to prevent organ rejection. The preferred compound (oCOM-21) released 50% of its carbon monoxide within 20 min when dissolved in UW solution (a commercial cold storage solution for hypothermic flushing and storage of organs that can also be used as a machine perfusion solution). Figures show improved cardiac tissue viability following exposure to two compounds at 3 μ M, and the vasorelaxant effects on rat aortic rings. Further data concerning isolated rat hearts and kidneys are also presented. For a related (but chemically very different) invention, see WO/2011/110315 from the University of Zürich claiming Re(II) complexes with monodentate ligands that release CO with a half-life of 6 min to almost 1 h.

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WO/2017/097838**Methods & pharmaceutical compositions for the treatment of systemic sclerosis***Inventors: Naquet P, Batteaux F, Kavian N**Assignees: Institut National de la Santé et de la Recherche Médicale (INSERM), Paris (France); Université d'Aix-Marseille, Paris (France); Centre national de la recherche scientifique, Paris (France); Université Paris-Descartes, Paris (France); Assistance publique - Hôpitaux de Paris, Paris (France)**MeSH Keywords: pantetheinase • scleroderma, systemic*

Vanin-1, a 70 kDa glycosylphosphatidyl-inositol-anchored protein that shows homology only with human biotinidase, converts the vasculoprotective pantethine into profibrotic pantothenic acid and pro-oxidant cystamine [17]. Its expression is upregulated in response to free fatty acids, PPAR activation, or oxidative stress [18,19]. Systemic inflammation and oxidative stress are involved in the autoimmune disease, systemic sclerosis (SSc) [20], which led the inventors to investigate vanin-1 inhibitors as potential therapeutics. In wild-type mice with HOCl-induced SSc, the pantetheinase pathway was dysregulated with elevation of skin vanin-1 activity and high levels of serum pantothenic acid, while *VNN1* knockout mice did not develop the characteristic features of the disease upon HOCl induction, nor did they show endothelial activation. Furthermore, serum pantothenic acid was higher in 51 SSc patients than in the 30 healthy subjects tested ($97.8 \pm 11 \mu\text{g/l}$ vs $31.3 \pm 3.6 \mu\text{g/l}$, $p < 0.0001$). Patients with diffuse SSc were more affected in this respect than patients with a limited/CREST form of SSc (134.2 ± 17.59 vs 78.11 ± 14.07). SSc patients with pulmonary hypertension had the highest serum concentrations ($237.5 \pm 433.23 \mu\text{g/l}$). The vanin-1 inhibitors can be chosen from the small molecules disclosed by Jansen *et al.* [21], or in WO/2014/048547; they can also be antibodies, antisense oligonucleotides or ribozymes. However, no data showing the effect of such inhibitors are disclosed. For the companion peer review paper, see Kavian *et al.* [22].

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WO/2017/100849**6-Oxopurine phosphoribosyltransferase inhibitors***Inventors: De Jersey J, Guddat LW, Hocková D, Keough DT, Pohl R, Rejman D**Assignees: The University of Queensland, Queensland (Australia); Institute of Organic Chemistry and Biochemistry ASCR, V.V.I., Prague (Czech Republic)**MeSH Keywords: hypoxanthine phosphoribosyltransferase • malaria • tuberculosis*

Complete deficiency of HGPRT, a 6-oxopurine phosphoribosyltransferase which catalyzes the reutilization of hypoxanthine and guanine to the purine nucleotides IMP and GMP, respectively, causes the rare Lesch–Nyhan syndrome, with the symptoms of gout and severe neurological impairment [23]. However, many microorganisms, including *Plasmodium* spp., and *Mycobacterium tuberculosis*, totally depend on HGPRT because they have no closely related enzymes and, unlike mammalian cells, these pathogens are auxotrophic for the purine ring while humans are capable of *de novo* synthesis in addition to the salvage pathway [24,25]. Partial inhibition of human HGPRT to treat malaria or tuberculosis should not have any serious side effects: only 3–5% of normal activity of this enzyme is required for a normal life. The inventors have developed a new series of acyclic nucleoside phosphonates (a chemical class to which several antiviral reverse transcriptase inhibitor drugs belong). The new compounds comprise a nitrogen containing heterocyclic group (pyrrolidine or piperidine) which replaces the oxygen atom in the acyclic portion of the earlier molecules, providing a branching point that enables the compounds to bind at three closely spaced subsites of the target. The heterocyclic group also provides rigidity between the purine base and the phosphonate groups which, when combined with the relative stereochemistry of the ring substituents, is believed to improve the orientation of the purine base and the phosphonate groups into the active site of the enzyme. For the most active compounds, K_i values for human, *Plasmodium* and *M. tuberculosis* HGPRT were in the low nanomolar range; growth of *Plasmodium* strains was inhibited with micromolar IC_{50} values. For peer review papers on these and related compounds, see Špaček *et al.* [26] and Kaiser *et al.* [27].

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WO/2017/103851

Quinoline-3-carboxamides as H-PGDS inhibitors

Inventors: Cadilla R, Deaton DN, Hancock AP et al.

Assignees: Astex Therapeutics Ltd., Cambridge (United Kingdom); GlaxoSmithKline Intellectual Property Development Ltd., Brentford (United Kingdom)

MeSH Keywords: intramolecular oxidoreductases • muscular dystrophy, duchenne • prostaglandin D2

Prostaglandin D₂ exerts pro-inflammatory as well as anti-inflammatory functions under various pathological conditions. The compounds presented here are inhibitors of hematopoietic prostaglandin D synthase (H-PGDS; as opposed to the lipocalin-type enzyme, L-PGDS), intended for the treatment of neurodegenerative diseases such as spinal cord injury [28] and Duchenne muscular dystrophy, where tetranor PGDM (a major prostaglandin D₂ metabolite) has been found elevated in urine [29], and where inhibition of H-PGDS can limit muscular necrosis [30]. Here, the small but growing line of H-PGDS inhibitor patent applications that have been published since 2005 is extended with quinoline-3-carboxamides. According to the inventors, they might also be useful to treat surgery-related muscle injuries from joint replacement, and anterior cruciate ligament or tendon repair. 7-(Difluoromethoxy)-N-((trans)-4-(2-hydroxypropan-2-yl)cyclohexyl)quinoline-3-carboxamide, administered to hindlimb-muscle injured mice that usually restore their muscle strength within about 5 weeks, caused significantly accelerated recovery. In dystrophin-null mice (a preclinical model of Duchenne muscular dystrophy), (S)-7-(difluoromethoxy)-6-fluoro-N-(2-oxopyrrolidin-3-yl)quinoline-3-carboxamide dosed at 30 mg/kg significantly blunted the force deficit at 24 h, and improved both the rate and extent of functional recovery in these fragile muscles.

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WO/2017/112668

Small molecule lipid II inhibitors

Inventors: De Leeuw E, MacKerell A, Fletcher S et al.

Assignee: University of Maryland, Baltimore (USA)

MeSH Keywords: anti-bacterial agents • BAS00127538 • vancomycin resistance

Just when antibiotics developers began to become convinced that all promising mechanisms had been explored, a new target was found: lipid II, an essential cell-wall precursor required for the growth and replication of both Gram-positive and Gram-negative bacteria [31]. It is also present in bacteria without a cell wall. Vancomycin, the prototypical lipid II inhibitor peptide, was discovered over 60 years ago and remains an ‘antibiotic of last resort’ even today. Meanwhile, depsipeptides, lantibiotics, cyclic peptides and glycopeptides have been investigated, and the semisynthetic vancomycin derivatives daptomycin, oritavancin and telavancin are approved as first line treatments for Gram-positive infections; however, these also struggle with spreading resistance. BAS00127538, a di-benzene-pyrylium-indolene compound developed by one of the present patent application’s inventors [32], was the first small molecule inhibitor of lipid II; it interacts with the MurNAc moiety and the isoprenyl tail of lipid II, and is structurally different from natural or nature-derived agents. Here, the synthesis and biological evaluation of new analogs of this compound is described. (E)-2,4-bis(4-bromophenyl)-6-(4-(dimethylamino)styryl)pyrylium boron tetrafluoride salt has reduced cytotoxicity, but retains specific lipid II binding and activity against *Enterococcus* spp. *in vitro* and *in vivo*, is stable in plasma, and has a markedly improved pharmacokinetic profile, with a half-life of over 13 h upon intravenous administration. For structure–activity relationship investigations preceding work on this patent application, see Fletcher *et al.* [33]; for the peer review companion paper, see Chauhan *et al.* [34].

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WO/2017/117118

Compositions & methods for inducing conformational changes in cereblon & other E3 ubiquitin ligases

Inventors: Cathers BE, Chamberlain P, Lopez-Girona A et al.

Assignee: Celgene Corp., Summit, NJ (USA)

MeSH Keywords: CRBN protein, human • immunosuppressive agents • ubiquitin-protein ligases

Cereblon is an ion channel-interacting protein that also functions as a substrate receptor of an E3 cullin-ring ligase complex 4 (CRL4); it binds thalidomide and its related next-generation immunomodulatory drugs [35]. Lenalidomide and pomalidomide bind to cereblon, directing the cereblon–E3 ligase complex toward the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) to cause their ubiquitination and degradation [36]. The data in

this patent application underscore the pluripotent character of cereblon. The inventors believe this to be the first report that specific small molecule ‘cereblon-modifying agents’ can induce distinct conformational changes in the protein’s surface, resulting in equally distinct phenotypic responses that are dependent upon cell type and, most importantly, the agent used to interact with cereblon or its pathway. They further discovered that recruitment of a cereblon-associated protein to cereblon, as well as subsequent degradation of this binding protein by the cereblon E3 ubiquitin ligase complex, is mediated by such small molecule induced conformational changes. Exemplary compounds are 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione (‘Compound A’), 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisindolin-2-yl)piperidine-2,6-dione (‘Compound B’) and 1-(3-chloro-4-methylphenyl)-3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)methyl)urea (‘Compound C’). Compound C is capable of interacting with both cereblon and the glutathion S-transferase GSPT1, which is recruited through the recognition of a surface turn. This happens through hydrogen bonds from the backbone of GSPT1, which may indicate that the degron (i.e., the feature defining the protein degradation rate) in this instance will not be revealed by primary sequence, but instead by the geometry and sterics of a surface turn. For the peer review companion paper see Matyskiela *et al.* [37] For closely related work see Hansen *et al.* [38].

Published: 6 July 2017

WO/2017/120164**Fused quadracyclic compounds, compositions & uses thereof***Inventors: McComas CC, Serrano-Wu MH, Vacca JP**Assignee: Tabomedex Biosciences, LLC, Boxford, MA (USA)**MeSH Keywords: inflammation • p38 mitogen-activated protein kinases • MAP-kinase-activated kinase 2*

p38 MAPK is a crucial target for chronic inflammatory diseases, from rheumatoid arthritis and asthma to Alzheimer’s disease. One of its downstream targets is MK2 (MAPKAPK-2), a kinase activated protein kinase which regulates the biosynthesis of TNF- α and other cytokines [39]. In addition, MK2 is activated after DNA damage resulting in cell cycle arrest, and phosphorylates Hsp27 (a prominent biomarker of cancer progression), acting as its endogenous inhibitor [40]. MK2 inhibitors have roused some interest based on the hope that they might minimize unwanted side effects of p38 MAPK while having a similar efficacy profile; however, no advanced clinical candidate has so far emerged from any of these efforts. The 513 fused quadracyclic compounds that are presented and characterized here have IC₅₀ values in the nanomolar range, but no *in vivo* data are disclosed.

Published: 13 July 2017

WO/2017/123161**Inhibition of intracellular growth of mycobacterium species & its applications***Inventors: Singhal A, Cheng C**Assignee: Agency for Science, Technology and Research, Connexis (Singapore)**MeSH Keywords: Sirtuin 1 • tuberculosis*

M. tuberculosis can deploy a plethora of immune-evasive and suppressive mechanisms [41,42], allowing it to persist in protected niches within the body where antibiotics do not easily penetrate. Also, it is an optionally intracellular pathogen that survives in macrophages. Host-directed therapies offer promising alternatives. The present invention shows that *M. tuberculosis* downregulates the mammalian sirtuin SIRT1 (a NAD⁺-dependent deacetylase) in monocytes/macrophages, tuberculosis animal models and tuberculosis patients with active disease. Activation of SIRT1 reduced intracellular growth of drug-susceptible and drug-resistant strains of *M. tuberculosis*, and induced phagosome-lysosome fusion and autophagy in an SIRT1-dependent manner. SIRT1 activation dampened *M. tuberculosis* mediated persistent inflammatory responses via deacetylation of RelA/p65, impairing its binding to the promoter of inflammatory genes. In infected mice, use of SIRT1 activators ameliorated lung pathology, reduced chronic inflammation and enhanced efficacy of anti-tuberculosis drugs. Cytometry-based high-dimensional analysis revealed SIRT1 activation mediated modulation of lung myeloid cells in infected mice. Myeloid cell-specific SIRT1 knockout mice displayed increased inflammatory responses and susceptibility to *M. tuberculosis* infection. Many known SIRT1 activators, including resveratrol, are named as suitable drugs. Microarray and cytokine release analysis data from *M. tuberculosis* infected cultured THP-1 cells, gene expression analysis of granulomas from infected macaques, and eight publicly available clinical datasets of whole blood gene expression profiles from active and latent tuberculosis patients support the conclusions. For the peer review companion paper, see Cheng *et al.* [43].

Published: 20 July 2017

WO/2017/123633**Modulators of zinc-activated channels***Inventor: Chang Y**Assignee: Dignity Health, Phoenix, AZ (USA)**MeSH Keywords: antidepressive agents • cysteine loop ligand-gated ion channel receptors • neurotransmitter uptake inhibitors • ZACN protein, human*

The zinc-activated cation channel (ZACN), a member of the Cys-loop receptor superfamily, was discovered 15 years ago [44], and was found to be expressed in several human brain regions (primarily in hippocampal neurons), as well as in lung, liver and pancreas. It is also activated by copper ions and protons [45]. This disclosure contributes to our still very incomplete understanding of this ion channel, and identifies several known small molecules as its modulators, providing potential leads for drug development. These include Evans blue and five other blue dyes (such as nitro blue tetrazolium), heparin and its analog pentosane polysulfate, and suramin (an antiparasitic drug used to treat sleeping sickness and onchocerciasis). Several purinergic P2X receptor antagonists are agonists of the human ZACN with various potencies. Several antidepressant drugs (desipramine, doxepin, fluoxetine, mianserin, reboxetine, tomoxetine, venlafaxine) acted as antagonists on the ZACN, with no significant difference in the IC₅₀ values for the currents induced by 500 μ M and 2 mM Zn²⁺ (IC₅₀ values for desipramine, reboxetine and tomoxetine were lower than those of the four others), demonstrating that the antagonism is noncompetitive. Drug potency varied considerably within classes but the norepinephrine reuptake inhibitors appear to be most potent. The inventors also found the ZACN protein expressed in a small fraction of human thymus cells that constitute a subset of the CD4⁺ cells. The ZACN immunostaining overlaps with that of FOXP3, illustrating that this channel is specifically expressed in regulatory T cells. Whether all this indicates that ZACN is a new target for antidepressant drug development, or could help modulate Treg function in autoimmune diseases or cancer, remains to be determined. In any case, it indicates more progress in the discovery of small molecule modulators of the Cys-loop superfamily receptors [46].

Published: 20 July 2017

WO/2017/125080**Application of fullerene/metal fullerene for preparing pharmaceutical product***Inventors: Wang C, Zhen M, Zhang Y**Assignee: Beijing Fu Na Kang Biotechnology Co., Ltd., Beijing (China)**MeSH Keywords: bone marrow • free radicals • fullerenes • radiation protection*

This invention provides nanomaterials based on highly substituted fullerenes (such as water-soluble hydroxylated C₆₀ or C₇₀) that are said to quickly accumulate in the bone marrow, where they can treat myelosuppression. Optionally the fullerenes can contain metals (e.g., Gd@C₈₂(OH)_n). Such endohedral metallofullerenes are known for their broad potential in medicine and elsewhere [47]. Initial experiments were carried out with unmodified hollow fullerene spheres administered in edible oil. ICR mice were randomly divided into five groups of six, receiving either cyclophosphamide (CTX) + Olive oil-C₆₀ in gavage (60 mg/kg), CTX + Olive oil-C₆₀ i.p. (60 mg/kg), CTX + pure olive oil in gavage, CTX only, and an untreated control group. Both fullerene experimental groups had higher erythrocyte and platelet counts, higher hemoglobin levels, and regained more weight, than positive controls. The water-soluble polyhydroxylated C₆₀ with gadolinium achieved Gd concentrations of 5.84 ± 0.58 ng/mg in bone marrow 24 h after administration, while calcified bone only had 0.45 ± 0.044 ng/mg. This preparation (and hydroxy-fullerene without metal) was protective against UV-generated free hydroxyl radicals, and against a 6 Gy x-ray treatment administered as a radiation treatment of an experimental tumor induced by injecting H22 mouse hepatoma cells. These findings are particularly interesting because fulleranol in concentrations of 10 and 100 μ g/ml has been reported to have negative effects on the development of erythroid tissue [48].

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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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References

1. Pant A, Pasupureddy R, Pande V, Seshadri S, Dixit R, Pandey KC. Proteases in mosquito borne diseases: new avenues in drug development. *Curr. Top. Med. Chem.* 17(19), 2221–2232 (2017).
2. Boddey JA, Carvalho TG, Hodder AN *et al.* Role of plasmepsin V in export of diverse protein families from the *Plasmodium falciparum* exportome. *Traffic* 14(5), 532–550 (2013).
3. Gambini L, Rizzi L, Pedretti A, Taglialatela-Scafati O *et al.* Picomolar inhibition of plasmepsin V, an essential malaria protease, achieved exploiting the prime region. *PLoS ONE* 10(11), e0142509 (2015).
4. Boussouar F, Jamshidikia M, Morozumi Y, Rousseaux S, Khochbin S. Malignant genome reprogramming by ATAD2. *Biochim. Biophys. Acta* 1829(10), 1010–1014 (2013).
5. Revenko AS, Kalashnikova EV, Gemo AT, Zou JX, Chen HW. Chromatin loading of E2F-MLL complex by cancer-associated coregulator ANCCA via reading a specific histone mark. *Mol. Cell Biol.* 30(22), 5260–5272 (2010).
6. Koo SJ, Fernández-Montalván AE, Badock V *et al.* ATAD2 is an epigenetic reader of newly synthesized histone marks during DNA replication. *Oncotarget* 7(43), 70323–70335 (2016).
7. Bamborough P, Chung CW, Furze RC *et al.* Structure-based optimization of naphthyridones into potent ATAD2 bromodomain inhibitors. *J. Med. Chem.* 58(15), 6151–6178 (2015).
8. Demont EH, Chung CW, Furze RC *et al.* Fragment-based discovery of low-micromolar ATAD2 bromodomain inhibitors. *J. Med. Chem.* 58(14), 5649–5673 (2015).
9. Bi F, Huang C, Tong J *et al.* Reactive astrocytes secrete lcn2 to promote neuron death. *Proc. Natl Acad. Sci. USA* 110(10), 4069–4074 (2013).
10. Kim BW, Jeong KH, Kim JH, Jin M *et al.* Pathogenic upregulation of glial lipocalin-2 in the Parkinsonian dopaminergic system. *J. Neurosci.* 36(20), 5608–5622 (2016).
11. Naseer MM, Ahmed M, Hameed S. Functionalized calix[4]arenes as potential therapeutic agents. *Chem. Biol. Drug Des.* 89(2), 243–256 (2017).
12. de Fátima A, Fernandes SA, Sabino AA. Calixarenes as new platforms for drug design. *Curr. Drug Discov. Technol.* 6(2), 151–170 (2009).
13. Katada K, Takagi T, Uchiyama K, Naito Y. Therapeutic roles of carbon monoxide in intestinal ischemia-reperfusion injury. *J. Gastroenterol. Hepatol.* 30(Suppl. 1), 46–52 (2015).
14. Wang P, Yao L, Zhou LL *et al.* Carbon monoxide improves neurologic outcomes by mitochondrial biogenesis after global cerebral ischemia induced by cardiac arrest in rats. *Int. J. Biol. Sci.* 12(8), 1000–1009 (2016).
15. Ryter SW, Kim HP, Nakahira K, Zuckerbraun BS, Morse D, Choi AM. Protective functions of heme oxygenase-1 and carbon monoxide in the respiratory system. *Antioxid. Redox Signal.* 9(12), 2157–2173 (2007).
16. Dhar R, Misra H, Diring MN. SANGUINATE™ (PEGylated Carboxyhemoglobin Bovine) improves cerebral blood flow to vulnerable brain regions at risk of delayed cerebral ischemia after subarachnoid hemorrhage. *Neurocrit. Care* doi:10.1007/s12028-017-0418-3 (2017) (Epub ahead of print).
17. Maras B, Barra D, Duprè S, Pitari G. Is pantetheinase the actual identity of mouse and human vanin-1 proteins? *FEBS Lett.* 461(3), 149–152 (1999).
18. Ferreira DW, Naquet P, Manautou JE. Influence of Vanin-1 and catalytic products in liver during normal and oxidative stress conditions. *Curr. Med. Chem.* 22(20), 2407–2416 (2015).
19. Kaskow BJ, Proffitt JM, Blangero J, Moses EK, Abraham LJ. Diverse biological activities of the vascular non-inflammatory molecules – the Vanin pantetheinases. *Biochem. Biophys. Res. Commun.* 417(2), 653–658 (2012).
20. Hargadóttir H, van Helvoort HA, Vonk MC, van den Hoogen FH, Dekhuijzen PN, Heijdra YF. Exercise in systemic sclerosis intensifies systemic inflammation and oxidative stress. *Scand. J. Rheumatol.* 39(1), 63–70 (2010).
21. Jansen PA, van Diepen JA, Ritzen B *et al.* Discovery of small molecule vanin inhibitors: new tools to study metabolism and disease. *ACS Chem. Biol.* 8(3), 530–534 (2013).
22. Kaviani N, Mehlal S, Marut W *et al.* Imbalance of the Vanin-1 pathway in systemic sclerosis. *J. Immunol.* 197(8), 3326–3335 (2016).
23. Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch–Nyhan syndrome. *Orphanet. J. Rare Dis.* 2, 48 (2007).
24. Keough DT, Hocková D, Krecmerová M *et al.* *Plasmodium vivax* hypoxanthine-guanine phosphoribosyltransferase: a target for anti-malarial chemotherapy. *Mol. Biochem. Parasitol.* 173(2), 165–169 (2010).
25. Ullman B, Carter D. Hypoxanthine-guanine phosphoribosyltransferase as a therapeutic target in protozoal infections. *Infect. Agents Dis.* 4(1), 29–40 (1995).
26. Špaček P, Keough DT, Chavchich *et al.* Synthesis and evaluation of symmetric acyclic nucleoside bisphosphonates as inhibitors of the *Plasmodium falciparum*, *Plasmodium vivax* and human 6-oxopurine phosphoribosyltransferases and the antimalarial activity of their prodrugs. *Bioorg. Med. Chem.* 25(15), 4008–4030 (2017).

27. Kaiser MM, Baszczyński O, Hocková D *et al.* Acyclic nucleoside phosphonates containing 9-Deazahypoxanthine and a five-membered heterocycle as selective inhibitors of plasmodial 6-Oxopurine phosphoribosyltransferases. *ChemMedChem* 12(14), 1133–1141 (2017).
28. Redensek A, Rathore K, Berard JL *et al.* Expression and detrimental role of hematopoietic prostaglandin D synthase in spinal cord contusion injury. *Glia* 59(4), 603–614 (2011).
29. Nakagawa T, Takeuchi A, Kakiuchi R *et al.* A prostaglandin D2 metabolite is elevated in the urine of Duchenne muscular dystrophy patients and increases further from 8 years old. *Clin. Chim. Acta* 423, 10–14 (2013).
30. Kamauchi S, Urade Y. Hematopoietic prostaglandin D synthase inhibitors for the treatment of duchenne muscular dystrophy. [Article in Japanese]. *Brain Nerve* 63(11), 1261–1269 (2011).
31. Ng V, Chan WC. New found hope for antibiotic discovery: lipid II inhibitors. *Chemistry* 22(36), 12606–12616 (2016).
32. de Leeuw EP. Efficacy of the small molecule inhibitor of Lipid II BAS00127538 against *Acinetobacter baumannii*. *Drug Des. Dev. Ther.* 8, 1061–1064 (2014).
33. Flercher S, Yu W, Huang J *et al.* Structure-activity exploration of a small-molecule lipid II inhibitor. *Drug Des. Dev. Ther.* 9, 2383–2394 (2015).
34. Chauhan J, Cardinale S, Fang L *et al.* Towards development of small molecule lipid II inhibitors as novel antibiotics. *PLoS ONE* 11(10), e0164515 (2016).
35. Ito T, Ando H, Handa H. Discovery of the target for immunomodulatory drugs (IMiDs). *Rinsho Ketsueki* 57(5), 556–562 (2016).
36. Ito T, Handa H. Cereblon and its downstream substrates as molecular targets of immunomodulatory drugs. *Int. J. Hematol.* 104(3), 293–299 (2016).
37. Matyskiela ME, Lu G, Ito T *et al.* A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. *Nature* 535(7611), 252–257 (2016).
38. Hansen JD, Condroski K, Correa M *et al.* Protein degradation via CRL4CRBN ubiquitin ligase: discovery and structure–activity relationships of novel glutarimide analogs that promote degradation of aiolos and/or GSPT1. *J. Med. Chem.* doi:10.1021/acs.jmedchem.6b01911 (2017) (Epub ahead of print).
39. Singh RK, Najmi AK, Dastidar SG. Biological functions and role of mitogen-activated protein kinase activated protein kinase 2 (MK2) in inflammatory diseases. *Pharmacol. Rep.* 69(4), 746–756 (2017).
40. Gurgis FM, Ziaziaris W, Munoz L. Mitogen-activated protein kinase-activated protein kinase 2 in neuroinflammation, heat shock protein 27 phosphorylation, and cell cycle: role and targeting. *Mol. Pharmacol.* 85(2), 345–356 (2014).
41. Korb VC, Chuturgoon AA, Moodley D. *Mycobacterium tuberculosis*: manipulator of protective immunity. *Int. J. Mol. Sci.* 17(3), 131 (2016).
42. Hmama Z, Peña-Díaz S, Joseph S, Av-Gay Y. Immuno-evasion and immunosuppression of the macrophage by *Mycobacterium tuberculosis*. *Immunol. Rev.* 264(1), 220–232 (2015).
43. Cheng CY, Gutierrez NM, Marzuki MB *et al.* Host sirtuin 1 regulates mycobacterial immunopathogenesis and represents a therapeutic target against tuberculosis. *Sci. Immunol.* 2(9), pii:eaaj1789 (2017).
44. Davies PA, Wang W, Hales TG, Kirkness EF. A novel class of ligand-gated ion channel is activated by Zn²⁺. *J. Biol. Chem.* 278(2), 712–717 (2003).
45. Trattinnig SM, Gasiorek A, Deeb TZ *et al.* Copper and protons directly activate the zinc-activated channel. *Biochem. Pharmacol.* 103, 109–117 (2016).
46. Sparling BA, DiMauro EF. Progress in the discovery of small molecule modulators of the Cys-loop superfamily receptors. *Bioorg. Med. Chem. Lett.* 27(15), 3207–3218 (2017).
47. Dai X, Han J, Gao Y, Wang Z. *De novo* design of an endohedral heteronuclear dimetallofullerene (U-Gd)@C60 with exceptional structural and electronic properties. *Chemphyschem* 15(17), 3871–3876 (2014).
48. Tishevskaya NV, Zakharov YM, Golubotovskii EV *et al.* Effects of fullerene C₆₀(OH)₂₄ on erythropoiesis *in vitro*. *Bull. Exp. Biol. Med.* 157(1), 49–51 (2014).