Patent highlights April–May 2020

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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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Keywords: brain injuries • chronic • epigenomics • heart failure • hyperalgesia • neoplasms • renal insufficiency • traumatic

WO/2020/064597

Use of Epac1 activators for the treatment of chronic kidney diseases

Inventors: Lezoualc'h F, Chatziantoniou C, Kavvadas P

Assignee: Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France; Université Paul Sabatier Toulouse III, Toulouse, France; Sorbonne Université, Paris, France

While the effects of the universal 'second messenger' cAMP have traditionally been attributed to phosphorylation events catalyzed by PKA, the Epac family of proteins are directly activated by cAMP. These are Rap-specific guanine-nucleotide exchange factors that are activated by the binding of cAMP to a cyclic nucleotide monophosphate-binding domain [1]; both isoforms are strongly but differentially expressed in kidney tissue [2], where their role in pathophysiology has received only limited attention. Here, the inventors show that glomerular expression of Epac1 is decreased in wild-type mice injected with nephrotoxic serum, and that its genetic ablation additionally accelerates the decline of renal function in this model of glomerulonephritis. A known activator of Epac1, 8-(4-chlorophenylthio)-2'-O-methyladenosine-3',5'-cyclic monophosphate (8-pCPT) improved structural and functional renal parameters after nephrotoxic serum injection. The inventors suggest that gene therapy with a vector expressing Epac1, or small molecules modelled after 8-pCPT, could be a disease-modifying therapy for chronic kidney disease. This is not surprising; the beneficial effect of 8-pCPT in acute ischemic kidney failure was reported a decade ago [3,4], and is probably due to reduced oxidative stress [5].

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MeSH Keywords: guanine nucleotide exchange factors/RAPGEF3 protein, human/renal insufficiency, chronic

WO/2020/067485

Inducer of cardiac ability to synthesize acetylcholine

Inventors: Kakinuma Y, Nakamura S

Assignee: Nippon Medical School Foundation, Tokyo, Japan

That acetylcholine is not only tightly regulating heart function but can also be produced and released by cardiomyocytes even when vagus nerves are not active, has been known since the mid-1950s [6], but the issue was not followed up until the millennium. Non-neuronal cardiac acetylcholine does not only help maintain the balance between parasympathetic and sympathetic control of heart function [7]; it also reduces oxygen demand of cardiomyocytes during ischemia and limits their hypertrophy during mechanical overload while cardiac parasympathetic activity is disrupted (a common hallmark of a variety of cardiovascular diseases including acute myocardial infarction) [8]. Controlled stimulation of the cardiac non-neuronal cholinergic system could therefore offer important cardiotherapeutic perspectives [9]. The inventors have found that derivatives of S-nitroso-N-acetyl-DL-penicillamine (SNAP), in particular S-nitroso-N-pivaloyl-D-penicillamine (SNPiP) are such an inducers of acetylcholine synthesis which elevate the intracellular cGMP levels and nitric oxide levels in H9C2 rat cardiomyoblasts and HEK293 human

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embryonic kidney cells, resulting in the gradual transactivation and translation of the choline acetyltransferase gene. The increased expression was maintained for at least 32 h. Cardiac production of acetylcholine was stimulated 3.5-fold 72 h after intraperitoneal administration of SNPiP to wild-type mice, significantly boosting end-diastolic volume, stroke volume, cardiac output and ejection fraction but not the heart rate. In the db/db diabetic mouse model functional improvement was seen when 1 nmol of SNPiP was administered once daily for 5 days. Several related nitrosothiols are also claimed. For the peer review companion papers see Oikawa *et al.* [10,11]

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MeSH Keywords: acetylcholine/choline o-acetyltransferase/heart/nitric oxide/s-nitroso-n-acetylpenicillamine

WO/2020/072580

Matriptase 2 inhibitors & uses thereof

Inventors: Venkatraman S, Mukherjee S, Goswami R, Gummadi VR, Raja AB, Hadianawalla M

Assignee: Disc Medicine, Inc., Cambridge, MA, USA

Mutations in matriptase-2, a liver cell-surface serine protease, cause iron-refractory iron deficiency anemia because expression of the peptide hormone hepcidin is not downregulated by matriptase suppression of the Bmp/Smad pathway [12]. Conversely, relative overactivity of matriptase-2 – as for example, in hemochromatosis – leads to genetic or acquired diseases of iron overload [13], which is why interest in designing small-molecule matriptase inhibitors has surged recently [14]. The inventors have made a massive contribution by synthesizing 827 heavily substituted indoles (mostly indole-2-carboxamides or carboxylates), characterizing them by NMR spectroscopy, and testing them in two *in vitro* assays based on human recombinant matriptase-2. Their biological significance remains undisclosed in this document, which is the first one filed by the applicant, a hematology company focused on hepcidin biology.

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MeSH Keywords: hepcidins/iron overload/matriptase 2

WO/2020/072857

Methods & compositions related to Plod3

Inventors: Hu S, Cui L

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

Three lysyl hydroxylases (LH1, LH2 and LH3) are encoded by the three *PLOD* genes; their expression is regulated by multiple cytokines, transcription factors and microRNAs. Dysregulation of *PLODs* promotes cancer progression and metastasis [15]. This has been mainly reported for gastric, lung and primary brain cancers, but the inventors have identified the overexpression of *PLOD3* in head and neck squamous cell carcinoma (for which platinum/5-fluorouracil remains the first-line therapy) as a prominent diagnostic marker and a potential therapeutic target. Their claimed agents are interfering RNAs, a therapy modality that has almost fallen out of favor with pharmaceutical companies. That miRNAs can be used as biomarkers for head and neck cancer diagnosis has been reported before [16]. Multiple miRNA target prediction programs now showed, confirmed by luciferase reporter assays and expression data from human tumor biobanks, that miR-124-3p is a highly conserved and powerful suppressor of *PLOD3* that directly targets its 3'-UTR region. Functional analysis showed that focal adhesion and regulation of actin cytoskeleton – which are activities of FAK – were the most affected pathways following downregulation of *PLOD3* expression by miR-124-3p or its mimetics claimed in the patent application. This was confirmed in a xenograft mouse model; knockdown of *PLOD3* in SCC1 and SCC23 cell lines significantly decreased xenograft tumor volume and weight compared with the controls.

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MeSH Keywords: MIRN124-3 microRNA, human/procollagen-lysine, 2-oxoglutarate 5-dioxygenase/squamous cell carcinoma of head and neck

WO/2020/074944**Inositol phosphates for the treatment of ectopic calcification***Inventors: Perelló Bestard J, Salcedo Roca C, Canals Hamanin A-Z**Assignee: Sanifit Therapeutics S.A., Palma de Mallorca, Spain*

Calciophylaxis is a serious form of ectopic calcification, a condition characterized by abnormal deposition of calcium in small blood vessels and other tissues and thrombosis leading to necrosis of the skin and fatty tissue with a high risk of severe infection and a 50% rate of death within the first year after diagnosis; 1–4% of patients with end-stage renal disease develop it. There is no approved treatment [17]; the benefit of sodium thiosulfate is limited [18]. Sanifit is developing SNF472, an intravenous formulation of myo-inositol hexaphosphate which inhibits the formation and growth of hydroxyapatite crystals, the final common pathway in the pathophysiology of vascular calcification. It has orphan drug status for the treatment of calciophylaxis from both the EMA and US FDA. A 12-week open-label Phase II clinical trial (NCT02790073) met both its primary and secondary end points (dermal ulcer healing as measured by the Bates-Jensen Wound Assessment Tool and pain reduction, resp.) in 2018, and a Phase III trial (NCT04195906) is recruiting patients. This is the patent application underlying this drug development project, also claiming derivatives with varying numbers of phosphate groups and with heterologous moieties, such as polyethylene glycols or polyglycerols that are supposed to extend half-life. For the peer review companion papers see Brandenburg *et al.* [19] and Raggi *et al.* [20]

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MeSH Keywords: HEM dysplasia/kidney failure, chronic/phytic acid/vascular calcification

WO/2020/081680**Quinone reductase 2 inhibitor compounds & uses thereof***Inventors: Lascola CD, Laskowitz DT**Assignee: Duke University, Durham, NC, USA*

Chloroquine and hydroxychloroquine are aminoquinolines with multimodal activities, not all of which are completely understood. Originally developed to treat malaria, they were subsequently found to have therapeutic efficacy for other indications, including autoimmune diseases, stroke, cancer and (in the case of hydroxychloroquine) coronavirus infection. They inhibit quinone reductase-2 [21,22], thereby reducing oxidative stress [23,24], an overarching phenomenon in most of the diseases they are used or investigated for. However, retinal and cardiac toxicity are dose limiting because these drugs accumulate preferentially in lysosomes: at lysosomal pHs between 4 and 5.5, nearly 100% of chloroquine is doubly protonated, rendering it strongly hydrophilic, membrane impermeable and thus, trapped within the acidic organelle. In designing nonlysosomotropic inhibitors of quinone reductase-2 the inventors used cLogP and LogD calculations and LiPE analysis to arrive at compounds that retained the aminoquinoline core scaffold, but have their amino group derivatized by pyridines and benzimidazoles. One compound, 7-methoxy-4-(pyridin-3-yl) methylaminoquinoline (QR2i-44) improved rotarod and Morris water maze performance in a mouse model of closed head injury for up to 4 weeks when administered 4 h after trauma, indicating lasting protection of both vestibulomotor and cognitive function; hippocampal volume loss was also mitigated. The compound was also active in a lupus mouse model. The crystal structure of the reduced enzyme in complex with FADH and QR2i-44 to 1.60 Å resolution confirmed binding in a mode resembling the natural substrate quinone; with the advantage of potential ability to penetrate the substrate binding site and achieve optimal stacking of planar aromatic functional groups with FAD isoalloxazine.

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MeSH Keywords: aminoquinolines/brain injuries, traumatic/lupus erythematosus, systemic/nrh-quinone oxidoreductase2

WO/2020/083975**Aminopyridine/pyrazine derivatives as Ctps1 inhibitors***Inventors: Quddus A, Novak A, Cousin D, Blackham E, Jones G, Wrigglesworth J et al.**Assignee: Step Pharma S.A.S., Paris, France*

Cytidine 5' triphosphate is not just a building block for nucleic acids; it is also required for the synthesis of phospholipids and the sialylation of proteins. Its sources are the salvage pathway and *de novo* synthesis by the CTP synthases 1 and 2 [25]. While the functional differences between the two isozymes are not yet fully elucidated, Ctps1

is critical for lymphocyte proliferation [26], and hence the cellular immune system which requires rapid synthesis of large amounts of DNA and RNA for an adequate response to pathogens. Conversely, Ctps1 inhibitors might represent a new class of immunosuppressive agents and also for oncology because the Ctps enzymes are upregulated in fast-growing tumors. The inhibitors presented here are (cyclopropanesulfonamido)pyridin-2-yl derivatives or the analogous pyrazines, a continuation of the compound series disclosed in Step Pharma's WO/2019/106156, WO/2019/106146, WO/2019/179652 and WO/2019/180244 and quite distinct from the 3-deazauridine prodrugs and the reactive glutamine derivatives that have been developed by others. Compounds were assayed for inhibition of human full length active C-terminal FLAG-His-tag Ctps1, some showing IC₅₀ values <100 nM and >60-fold selectivity against Ctps2. Selectivity against this isoenzyme might be important for cancer therapy: reduction of Ctps2 expression by siRNA increases the resistance of colorectal cancer cell lines to 5-fluorouracil [27].

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MeSH Keywords: aminopyridines/CTP synthetase/neoplasms

WO/2020/088575

Use of PDE10A inhibitor in preparing drugs for inhibiting fibroblast activity

Inventors: Tang H

Assignee: Zhejiang University, Zhejiang, China

The phosphodiesterase PDE10A is predominantly expressed in the striatum, and its inhibitors are in clinical development for schizophrenia by Pfizer and Takeda; they might be useful for certain subgroups of patients (see e.g., WO/2020/094591 by Lundbeck A/S). Applications in other psychiatric disorders and Huntington's disease also seem possible [28]. Very recently PDE10A was reported to be upregulated in failing murine and human hearts; one of the clinical-stage selective inhibitors (TP-10) reduces TGF- β -stimulated cardiac fibroblast activation, proliferation, migration and extracellular matrix synthesis [29]. The same line of investigation has been followed in the present patent application (which however has a much earlier priority date, November 2018), but in the mouse model of bleomycin-induced pulmonary fibrosis; notably, PDE10A had first been isolated from a human fetal lung cDNA library [30]. The old alkaloid antispasmodic papaverin at high doses, and the highly selective PDE10A inhibitor, PF-2545920 can inhibit lung fibroblast myogenesis induced by TGF- β 1 in much the same way as pirfenidone (Roche's Esbriet, approved for idiopathic pulmonary fibrosis), which is probably not a PDE10A inhibitor.

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MeSH Keywords: heart failure/PDE10A protein, human/pulmonary fibrosis

WO/2020/089263

Optionally nitrogenated isoquinolin-1(2H)-ones and 1H-isochromen-1-ones for treating pain and pain-related conditions

Inventors: Almansa-Rosales C, Rodriguez-Garrido A-D, Merce-Vidal R, Christmann U

Assignee: Esteve Pharmaceuticals S.A., Barcelona, Spain

This invention relates to new compounds that modulate the subunit $\alpha_2\delta$ -1 of voltage-gated calcium channels, the major action site for gabapentin and pregabalin [31]. Overexpression of this subunit potentiates presynaptic and postsynaptic NMDA receptor activity of spinal dorsal horn neurons to cause pain hypersensitivity [32]. The abstract of the patent application states that additional agonistic activity on μ opioid receptors is optionally present, but this is not referred to in the specification or in the results, which describe binding of 18 compounds to the $\alpha_2\delta$ -1 subunit in three categories, based on a gabapentin displacement assay with human $\alpha_2\delta$ -1-enriched membranes. Two compounds, 3-(1-[[3S,5R]-3,5-dimethylpiperazin-1-yl]butyl)-6-methoxy-2-methylisoquinolin-1(2H)-one and 3-(1-[[3S,5R]-3,5-dimethylpiperazin-1-yl]butyl)-2-ethylisoquinolin-1(2H)-one, have K_i values <500 nM. If these results translate to *in vivo* analgesic activity, it could lead to improvements in the therapy of neuropathic pain, which has not seen much progress since the millennium.

Published: 7 May 2020

MeSH Keywords: hyperalgesia/isoquinolines/voltage gated calcium channel subunit Ca alpha2delta-1, human

WO/2020/097079**Methods for treating traumatic brain injury***Inventors: Newell-Rogers MK*

Assignee: Bcell Solutions, Inc., Colorado Springs, CO, USA

Even relatively mild traumatic brain injury can have long-term psychiatric effects, such as cognitive impairments and behavioral changes that persist long after the inflammatory reaction in the brain has subsided. CD74, a nonpolymorphic Type II transmembrane glycoprotein with many immunological functions including high affinity for Mif [33], is one of these inflammatory determinants [34]. Mif acts in an autocrine and paracrine manner by activating the chemokine receptors Cxcr2, Cxcr4 and Cxcr7. It is this CD74-Mif interaction that the inventors propose to disrupt by administering a CD74 cleavage inhibitor that reduces the release of its cytosolic domain; a humanized anti-MIF antibody (imalumab [35]) or small-molecule antagonist (see e.g., the benzimidazolones disclosed in WO/2007/070961); or a peptide or an siRNA that antagonizes binding of the CLIP region of CD74 to MHC class II structures [36]. The inventors demonstrated a significant decrease in full-length cell surface CD74 on splenic B cells 24 h after traumatic brain injury in a mouse model (a time point where diffuse axonal injury was demonstrable by MRI), indicating either that CD74 had been internalized and/or had been cleaved into CLIP peptides. The proteasome inhibitor, bortezomib (0.1 mg/kg i.p.) was most efficacious at reducing cell-surface CLIPs on B cells, almost matched by cystatin S. For the peer-review companion paper see Tobin *et al.* [37]

Published: 14 May 2020

MeSH Keywords: bortezomib/brain injuries, traumatic/CD74 antigen/CLIP peptide/macrophage migration inhibitory factors

WO/2020/099777**Use of an organometallic compound as a DNA-demethylating agent***Inventors: Grandemange S, Monari A, Gros P, Cartron P-F*

Assignee: Universite de Lorraine, Nancy, France; Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

DNA hypomethylating agents attempt indirect demethylation by inhibiting the activity or expression of DNA methyltransferases such as Dnmt1 or Dnmt3, which reverses epigenetic repression of the methylated genes. Their primary intended application is in oncology. The inventors have developed organometallic compounds comprising an iron atom linked to two terpyridine groups [38] that are capable of causing direct demethylation of DNA in cell-free and cellular systems. These compounds cause cell cycle arrest in the G2/M or G0/G1 phase, and can be used to reduce tumor proliferation; they are primarily cytostatic, with cell death setting in only after a minimum of 96 h of incubation. The energy profile linked to the demethylation reaction was estimated using quantum chemistry calculations based on a model system comprising methylated cytosine and one of the compounds (AIM3); water effects were taken into account using a polarized continuum model. The results confirmed that direct demethylation of the DNA by AIM3 is thermodynamically favorable. Extensive cell-free and cell culture data show that DNA demethylation actually occurs. It would be extremely important if such agents would not lead to global DNA demethylation, which is also deleterious [39]. For other iron-terpyridine complexes useful for cellular imaging and phototherapy see Basu *et al.* [40].

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MeSH Keywords: epigenomics/ferrous compounds/organometallic compounds

WO/2020/099885**Heterocyclic spiro-compounds as AM2 receptor inhibitors***Inventors: Richards G, Skerry TM, Harrity JPA, Zirimwabagabo J-O, Tozer ML, Gibson KR et al.*

Assignee: The University of Sheffield, Sheffield, UK

The peptide hormone, adrenomedullin has several important physiological functions, including the regulation of blood pressure through the AM1 receptor. In contrast, the AM2 receptor is involved in numerous pro-tumorigenic actions including stimulating cancer cell proliferation, protection from stress-induced apoptosis, promoting angiogenesis and increasing invasiveness [41]. Adrenomedullin secreted by tumors leads to upregulation of the AM2 receptor in surrounding host tissues. Targeting of adrenomedullin and its receptors has been efficacious in animal models, mostly through suppression of angiogenesis [42]. Most of the reported AM2 receptor blockers are antibodies

or peptides, making the inventors' complex small molecules highly interesting. Invention compound SHF-1036 was tested in a mouse model using xenografted CFPAC-1 cells (derived from a ductal adenocarcinoma). Once-daily doses of 5 and 10 mg/kg for 21 days inhibited tumor volume growth by 43 and 57%, respectively. Another compound, SHF-1038 reduced viability of HUT-78 Sézary lymphoma cells by 68% after 9 days of *in vitro* exposure at 3 mM, a concentration that might be locally attainable in the cutaneous manifestations of this disease. Obviously, selectivity against AM1 receptors would be extremely important to avoid blood pressure effects.

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MeSH Keywords: adrenomedullin receptors/angiogenesis inhibitors/cutaneous T-cell lymphoma/neoplasms

WO/2020/104540

Relaxin receptor 1 for use in treatment & prevention of heart failure

Inventors: Katus H, Raake PWJ, Schlegel P, Sasipond N

Assignee: Universität Heidelberg, Heidelberg, Germany

The vasoactive peptide hormone relaxin is upregulated in heart failure patients, correlating with the severity of the disease [43]; however, this adaptive response is ultimately insufficient. In the Phase III clinical trial RELAX-AHF-2, serelaxin (a recombinant relaxin derivative) in addition to standard therapy did not improve the incidence of death from cardiovascular causes or rehospitalization for heart failure or renal failure at 180 days, or the length of the index hospital stay [44]. The inventors propose an additional supportive approach: administration of a polynucleotide mediating expression of a relaxin family receptor (RXFP) in heart tissue, in particular in the ventricles. In a transverse aortic constriction murine heart failure model, an attenuated but nonsignificant decrease in ejection fraction and fractional shortening was observed in animals receiving RXFP1 AAV9 viral gene therapy and treated with NaCl; with additional relaxin these two parameters improved significantly although left ventricular internal diameter, left ventricular mass corrected and heart rate showed no significant difference. This adjunct gene therapy could be of particular interest for heart failure with preserved ejection fraction (HFpEF; formerly diastolic heart failure) for which no effective therapy exists yet.

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MeSH Keywords: genetic therapy/heart failure/relaxin receptors

Financial & competing interests disclosure

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References

- Kraemer A, Rehmann HR, Cool RH *et al.* Dynamic interaction of cAMP with the Rap guanine-nucleotide exchange factor Epac1. *J. Mol. Biol.* 306(5), 1167–1177 (2001).
- Li Y, Konings IB, Zhao J, Price LS, de Heer E, Deen PM. Renal expression of exchange protein directly activated by cAMP (Epac) 1 and 2. *Am. J. Physiol. Renal Physiol.* 295(2), F525–F533 (2008).
- Patschan D, Patschan S, Wessels JT *et al.* Epac-1 activator 8-O-cAMP augments renoprotective effects of syngeneic murine EPCs in acute ischemic kidney injury. *Am. J. Physiol. Renal Physiol.* 298(1), F78–F85 (2010).
- Stokman G, Qin Y, Genieser HG *et al.* Epac-Rap signaling reduces cellular stress and ischemia-induced kidney failure. *J. Am. Soc. Nephrol.* 22(5), 859–872 (2011).
- Stokman G, Qin Y, Booi TH *et al.* Epac-Rap signaling reduces oxidative stress in the tubular epithelium. *J. Am. Soc. Nephrol.* 25(7), 1474–1485 (2014).
- Burn JH, Vaughan Williams EM, Walker JM. The formation of acetylcholine in the heart: its effect on the systemic output and its importance for auricular fibrillation caused by aconitine. *J. Physiol.* 131, 317–328 (1956).
- Roy A, Fields WC, Rocha-Resende C *et al.* Cardiomyocyte-secreted acetylcholine is required for maintenance of homeostasis in the heart. *FASEB J.* 27(12), 5072–5082 (2013).
- Rocha-Resende C, Roy A, Resende R *et al.* Non-neuronal cholinergic machinery present in cardiomyocytes offsets hypertrophic signals. *J. Mol. Cell. Cardiol.* 53(2), 206–216 (2012).
- Kakinuma Y. Future perspectives of a cardiac non-neuronal acetylcholine system targeting cardiovascular diseases as an adjunctive tool for metabolic intervention. *Int. Immunopharmacol.* 29(1), 185–188 (2015).

10. Oikawa S, Kai Y, Mano A, Nakamura S, Kakinuma Y. A novel nitric oxide donor, S-Nitroso-N-Pivaloyl-D-Penicillamine, activates a non-neuronal cardiac cholinergic system to synthesize acetylcholine and augments cardiac function. *Cell. Physiol. Biochem.* 52(4), 922–934 (2019).
11. Oikawa S, Kai Y, Mano A, Nakamura S, Kakinuma Y. S-Nitroso-N-Pivaloyl-D-Penicillamine, a novel non-neuronal ACh system activator, modulates cardiac diastolic function to increase cardiac performance under pathophysiological conditions. *Int. Immunopharmacol.* 84, 106459 (2020).
12. Nai A, Rubio A, Campanella A *et al.* Limiting hepatic Bmp-Smad signaling by matriptase-2 is required for erythropoietin-mediated hepcidin suppression in mice. *Blood* 127(19), 2327–2336 (2016).
13. Ramsay AJ, Hooper JD, Folgueras AR, Velasco G, López-Otín C. Matriptase-2 (TMPRSS6): a proteolytic regulator of iron homeostasis. *Haematologica* 94(6), 840–849 (2009).
14. Damalanka VC, Janetka JW. Recent progress on inhibitors of the type II transmembrane serine proteases, hepsin, matriptase and matriptase-2. *Future Med. Chem.* 11(7), 743–769 (2019).
15. Qi Y, Xu R. Roles of PLODs in collagen synthesis and cancer progression. *Front. Cell Dev. Biol.* 6, 66 (2018).
16. Salazar C, Nagadia R, Pandit P *et al.* A novel saliva-based microRNA biomarker panel to detect head and neck cancers. *Cell. Oncol (Dordr)*. 37(5), 331–338 (2014).
17. Seethapathy H, Nigwekar SU. Revisiting therapeutic options for calciphylaxis. *Curr. Opin. Nephrol. Hypertens.* 28(5), 448–454 (2019).
18. Peng T, Zhuo L, Wang Y *et al.* Systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. *Nephrology (Carlton)*. 23(7), 669–675 (2018).
19. Brandenburg VM, Sinha S, Torregrosa JV *et al.* Improvement in wound healing, pain, and quality of life after 12 weeks of SNF472 treatment: a Phase II open-label study of patients with calciphylaxis. *J. Nephrol.* 32(5), 811–821 (2019).
20. Raggi P, Bellasi A, Bushinsky D *et al.* Slowing progression of cardiovascular calcification with SNF472 in patients on hemodialysis: results of a randomized Phase IIb study. *Circulation* 141(9), 728–739 (2020).
21. Graves PR, Kwiek JJ, Fadden P *et al.* Discovery of novel targets of quinoline drugs in the human purine binding proteome. *Mol. Pharmacol.* 62(6), 1364–1372 (2002).
22. Fu Y, Buryanovskyy L, Zhang Z. Quinone reductase 2 is a catechol quinone reductase. *J. Biol. Chem.* 283(35), 23829–23835 (2008).
23. Cassagnes LE, Chhour M, Pério P *et al.* Oxidative stress and neurodegeneration: the possible contribution of quinone reductase 2. *Free Radic. Biol. Med.* 120, 56–61 (2018).
24. Reybier K, Perio P, Ferry G *et al.* Insights into the redox cycle of human quinone reductase 2. *Free Radic. Res.* 45(10), 1184–1195 (2011).
25. Evans DR, Guy HI. Mammalian pyrimidine biosynthesis: fresh insights into an ancient pathway. *J. Biol. Chem.* 279, 33035–33038 (2004).
26. Martin E, Minet N, Boschat AC *et al.* Impaired lymphocyte function and differentiation in CTPS1-deficient patients result from a hypomorphic homozygous mutation. *JCI Insight* 5(5), e133880 (2020).
27. Tan WL, Bhattacharya B, Loh M *et al.* Low cytosine triphosphate synthase 2 expression renders resistance to 5-fluorouracil in colorectal cancer. *Cancer Biol. Ther.* 11(6), 599–608 (2011).
28. Wilson LS, Brandon NJ. Emerging biology of PDE10A. *Curr. Pharm. Des.* 21(3), 378–388 (2015).
29. Chen S, Zhang Y, Lighthouse JK *et al.* A novel role of cyclic nucleotide phosphodiesterase 10A in pathological cardiac remodeling and dysfunction. *Circulation* 141(3), 217–233 (2020).
30. Fujishige K, Kotera J, Michibata H *et al.* Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). *J. Biol. Chem.* 274(26), 18438–18445 (1999).
31. Offord J, Isom LL. Drugging the undruggable: gabapentin, pregabalin and the calcium channel $\alpha 2\delta$ subunit. *Crit. Rev. Biochem. Mol. Biol.* 51(4), 246–256 (2015).
32. Chen J, Li L, Chen SR *et al.* The $\alpha 2\delta$ -1-NMDA receptor complex is critically involved in neuropathic pain development and gabapentin therapeutic actions. *Cell Rep.* 22(9), 2307–2321 (2018).
33. Su H, Na N, Zhang X, Zhao Y. The biological function and significance of CD74 in immune diseases. *Inflamm. Res.* 66(3), 209–216 (2017).
34. Almeida-Suhett CP, Li Z, Marini AM, Braga MF, Eiden LE. Temporal course of changes in gene expression suggests a cytokine-related mechanism for long-term hippocampal alteration after controlled cortical impact. *J. Neurotrauma* 31(7), 683–690 (2014).
35. Mahalingam D, Patel MR, Sachdev JC *et al.* Phase I study of imalumab (BAX69), a fully human recombinant antioxidantized macrophage migration inhibitory factor antibody in advanced solid tumours. *Br. J. Clin. Pharmacol.* doi:10.1111/bcp.14289 (2020) (Epub ahead of print).
36. Wu S, Gorski J. The MHC class II-associated invariant chain-derived peptide clip binds to the peptide-binding groove of class II molecules. *Mol. Immunol.* 33(4–5), 371–377 (1996).

37. Tobin RP, Mukherjee S, Kain JM *et al.* Traumatic brain injury causes selective, CD74-dependent peripheral lymphocyte activation that exacerbates neurodegeneration. *Acta Neuropathol. Commun.* 2, 143 (2014).
38. Hofmeier H, Schubert US. Recent developments in the supramolecular chemistry of terpyridine-metal complexes. *Chem. Soc. Rev.* 33(6), 373–399 (2004).
39. Wilson AS, Power BE, Molloy PL. DNA hypomethylation and human diseases. *Biochim. Biophys. Acta* 1775(1), 138–162 (2007).
40. Basu U, Khan I, Koley D, Saha S, Kondaiah P, Chakravarty AR. Nuclear targeting terpyridine iron(II) complexes for cellular imaging and remarkable photocytotoxicity. *J. Inorg. Biochem.* 116, 77–87 (2012).
41. Hay DL, Conner AC, Howitt SG, Smith DM, Poyner DR. The pharmacology of adrenomedullin receptors and their relationship to CGRP receptors. *J. Mol. Neurosci.* 22(1–2), 105–113 (2004).
42. Hay DL, Walker CS, Poyner DR. Adrenomedullin and calcitonin gene-related peptide receptors in endocrine-related cancers: opportunities and challenges. *Endocr. Relat. Cancer* 18(1), C1–C14 (2010).
43. Dschietzig T, Richter C, Bartsch C *et al.* The pregnancy hormone relaxin is a player in human heart failure. *FASEB J.* 15(12), 2187–2195 (2001).
44. Metra M, Teerlink JR, Cotter G *et al.* Effects of serelaxin in patients with acute heart failure. *N. Engl. J. Med.* 381(8), 716–726 (2019).