BIOBUSINESS BRIEFS

PATENT WATCH

The evolving intellectual property landscape for pruritus therapies

Pruritus, or itching, is the unpleasant sensation that causes a desire to scratch. Chronic pruritus can be a debilitating manifestation of varied pathologies such as cholestasis, renal failure, and certain forms of cancer (*Expert Opin. Pharmacother.* **11**, 1673–1682; 2010).There is a significant unmet need for pruritus treatment, as the standard treatment of antihistamines and/or corticosteroids has limited effectiveness.

To better understand the intellectual property (IP) surrounding pruritus therapies, we analysed English-language US, European, and international (that is, covered by the Patent Cooperation Treaty (PCT)) patents and applications published from January 1978 to May 2017. To identify treatments for systemic pruritus rather than topical dermatological therapies, we limited our search to oral therapeutics and antibodies. We used a combination of keywords and Cooperative Patent Classification classes with pruritus keyword terms to identify relevant documents. Documents were indexed according to the number of indications and, if possible, molecular target. We were able to classify 70% of the 367 unique patent families (each of which describes a single invention) into 1 of 61 distinct molecular pathways.

To obtain a more precise view of the assignees actively pursuing pruritus therapies, we narrowed our analysis to the 47 families that contained claims restricted to pruritus, rather than a broad swath of indications, to identify key molecular pathways. Among the 24 assignees (FIG. 1a), 50% (12) are publicly traded companies, 25% (6) are private companies, and 25% (6) are research institutions. The largest assignee is Neurogen, with patents covering 19 families. Neurogen's portfolio, which is exclusively focused on small-molecule modulators of transient receptor potential (TRP) ion channels, does not seem to be being actively pursued, as the latest patent document was filed in 2009, the same year Neurogen was acquired by Ligand Pharmaceuticals.

In the focused pruritus IP set, 19 different molecular pathways are represented, of which the majority (14) are being pursued by a single assignee (FIG. 1b). Although most of the pathways in the list do not have approved therapeutics for pruritus, many have either approvals or drug development programmes in clinical trials for other indications, potentially lowering the competitive barriers to entering the pruritus therapeutic space. Four of the five pathways that have multiple assignees — the opioid, cannabinoid, serotonin, and neurokinin-1 receptor (NK1R; also known as substance P receptor) pathways — have been actively pursued for nervous system indications, including pain. Pain and itch share some mechanistic parallels, and clinical trials have investigated the use of opioid antagonists in uraemic pruritus. CR845 from Cara Therapeutics is a κ-opioid antagonist in clinical trials for both pain (NCT02542384) and uraemic pruritus (NCT02858726). A κ-opioid agonist, nalfurafine hydrochloride, is approved for treatment of uraemic pruritus in Japan and is being evaluated in the USA for cholestatic pruritus (NCT02659696).

Antibodies account for approximately 10% of both the pruritus-specific and the larger multi-indication set. Although only Bristol-Myers Squibb (BMS) appears in the list for specific pruritus treatment claims using IL-31 therapeutics, Chugai Pharma also developed a therapeutic antibody, nemolizumab, that targets the IL-31 receptor and was licensed to Galderma in 2016. The BMS anti-IL-31 antibody, BMS-981164, has completed phase I clinical trials in patients with atopic dermatitis, and nemolizmab improved pruritus in patients with moderate-to-severe atopic dermatitis in a recently published phase II trial

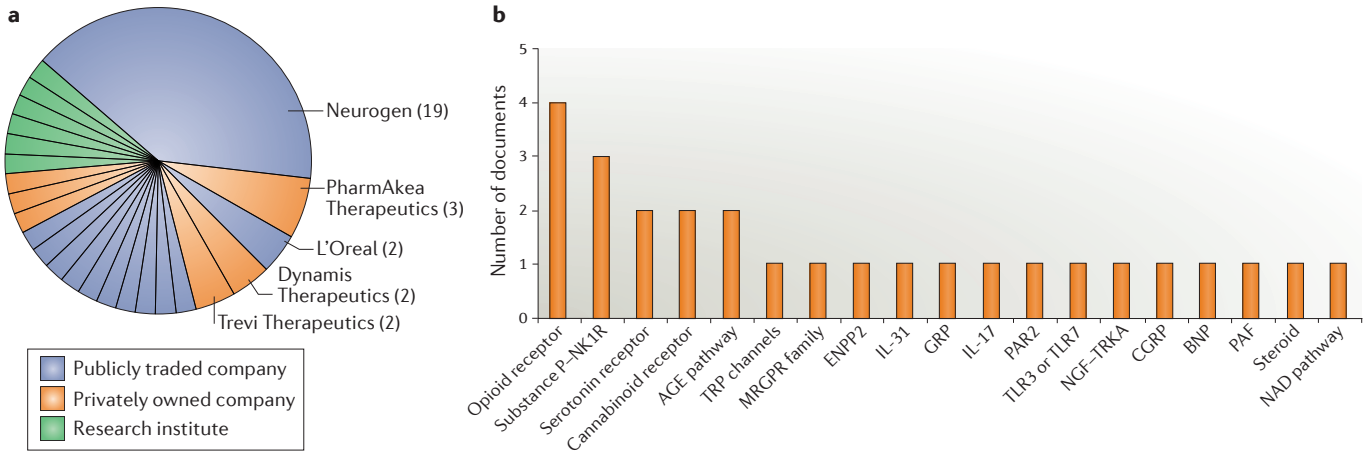

Figure 1 | **The pruritus intellectual property landscape. a** | Assignees with documents containing claims restricted to pruritus; the number of documents is indicated for assignees with two or more documents. The publicly traded companies with one document each are Allergan, BRAIN (Biotechnology Research and Information Network), Bristol-Myers Squibb, Eli Lilly, Euro-Celtique (a patent holding company), Ironwood Pharmaceuticals, Merck Sharp & Dohme, Nexvet, Shionogi and Zalicus. The privately owned companies with one document each are Green Bios, Menlo Therapeutics and NeRRe Therapeutics. Research institutes with one document each are Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital, National Institutes of Health, University of Chicago and University of California. **b** | Molecular pathways and targets for pruritus-specific therapies. AGE, advanced glycation end products; BNP, brain natriuretic peptide; CGRP, calcitonin gene-related peptide; ENPP2, ectonucleotide pyrophosphatase/phosphodiesterase family member 2; GRP, gastrin-releasing peptide; IL-17, interleukin-17; MRGPR, MAS-related G protein-coupled receptor; NGF, β-nerve growth factor; NK1R, neurokinin-1 receptor; PAF, platelet-activating factor; PAR2, proteinase-activated receptor 2; TLR, Toll-like receptor; TRKA, tropomyosin-related kinase A; TRP, transient receptor potential.

(*N. Engl. J. Med.* **376**, 826–835; 2017). Eli Lilly has claims for the inhibition of IL-17 in pruritus using their antibody ixekizumab. Currently, ixekizumab is approved for psoriasis, as are two additional IL-17 pathway-targeting antibodies, brodalumab (Valeant Pharmaceuticals) and secukinumab (Novartis).

The MAS-related G protein-coupled receptors (MRGPRs) have recently become attractive targets for pruritus therapies. MRGPRs are a large family of orphan GPCRs, the presence of which seems to define subsets of sensory neurons, including itch-specific neurons. In animal models, MRGPRs are directly activated by pruritogens, and genetic ablation of MRGPRA3-expressing neurons has been shown to substantially reduce itch responses in mice (*Nat. Neurosci.* **16**, 174–182; 2013). A recent PCT application (WO2016118632A1) from the Massachusetts General Hospital in Boston, USA, highlighted a previously unknown commonality between MRGPRs and another target for anti-pruritus therapy, NK1R. The inventors show that substance P can activate human MRGPRX2 and its mouse homologues, MRGPRB2 and MRGPRA1, in cell culture. In a related publication (*JCI Insight* **1**, e89362; 2016), they unexpectedly found the structurally similar NK1R antagonists aprepitant and L733060 inhibited substance P activation of MRGPRB2, but not MRGPRX2 or MRGPRA1 *in vitro*. The differential sensitivities of mouse and human MRGPRs to NK1R antagonists could result in re-evaluation of the translational relevance of some preclinical mouse models as well as new assays to develop more specific NK1R and MRGPR antagonists.

The modest size of the pruritus-specific IP space reflects a field that is only beginning to elucidate the pathologies underlying the disease. Compared with more mature indications such as pain management, large biotechnology and pharmaceutical companies are relatively under-represented. Given the size of the potential market, it is only a matter of time before the space experiences substantial growth.

Benjamin Leung and Drew Lowery are at Global Prior Art, Inc., 21 Milk Street, Boston, Massachusetts 02109, USA.

Correspondence to D.L.
dlowery@globalpriorart.com

doi:10.1038/nrd.2017.161
Published online 8 Sep 2017

Competing interests statement
The authors declare no competing interests.