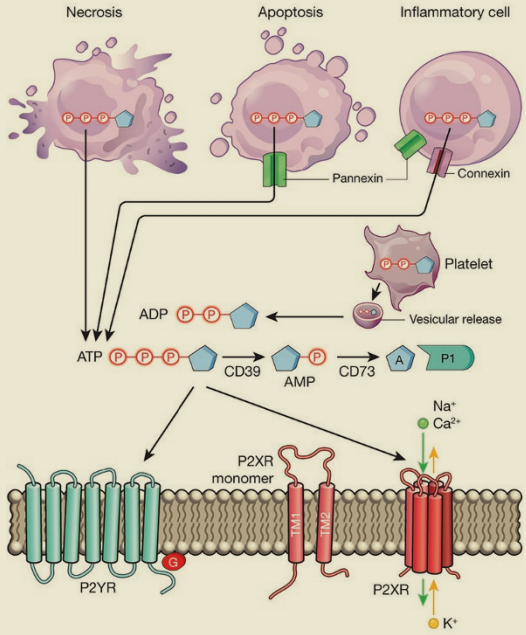
Merck stakes out 'irritable' neuron territory with $1.25 billion

Merck's acquisition of neurology specialist Afferent Pharmaceuticals for $500 million in cash—and up to $750 million more in development and commercial milestones—closed on July 27. The deal gives the big pharma access to Afferent's clinical-stage small molecule AF-219 for treating persistent coughing. Beyond this first-in-class drug candidate, Merck gains the biotech's deep expertise in the biology of a novel drug target: the P2X3 purinergic receptor. The approach pioneered by the venture-backed Afferent could broaden to tackle a variety of neurogenic conditions—from hypertension to chronic pain—where P2X3-driven nerve oversensitization leads to abnormal sensory perception.

P2X3 is a ligand-gated ion channel present on neurons that are normally silenced. Afferent's founder and CSO Anthony Ford identifies non-myelinated C-fiber afferent (sensory) neurons, which abundantly express P2X3 receptors, as the likely participants in these pathological processes. "They tend in many systems to be considered a silent population," he says. "The thinking is that inflammation, injury and distress trigger reactivation and unsilencing of the fibers, which are normally in a quiescent state." The overarching hypothesis implicates aberrant ATP signaling, which leads to chronic activation of P2X3 receptors and, depending on the physiological context, sensations of pain, itch, irritation or bladder urgency, for example.

San Mateo, California–based Afferent was formed in 2009 to take on a research initiative on the P2X3 receptor, which originated in Basel, Switzerland–based Roche. So far, in a phase 2 trial, Afferent has reported dramatic evidence of efficacy in patients with chronic cough unresponsive to other therapies. Afferent's lead drug AF-219 cut the frequency of daytime coughing by 75% compared with placebo, as measured by a digital audio recording device (*Lancet* **385**, 1198–1205, 2015). "It is unprecedented—we're very excited about this," says Maria Belvisi, professor of respiratory pharmacology at Imperial College, London. Cough is a medical problem that is not adequately served by current therapies and has not been a major focus of drug development. "Most companies have been searching for disease-modifying therapy and see cough as just a symptom of disease," says Belvisi.

A cough monitor developed through a collaboration between medical device maker Vitalograph, of Maids Morton, UK, and researchers at the University of South Manchester Wythenshawe Hospital was a key enabler in the recent trial. "Before that there was no objective measure of cough," Belvisi says, and as a result, studies were bedeviled by a high placebo effect. Merck will continue to develop AF-219 for cough. One area demanding attention will be how to manage the taste disturbances associated with high doses of the compound, which led to a 25% dropout rate in the phase 2 study. "It's not just about reduction of cough frequency—you also have to positively impact patients' perception of disease," says Stuart Green, vice president and therapeutic area head for respiratory and immunology at Kenilworth, New Jersey–based Merck. Data unveiled at the American Thoracic Society meeting in May showed that lower doses of the drug appear to retain much of the efficacy, with reduced effects on taste perception. "The taste disturbance frequency was lower, but it was still significant," Green says.



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During mechanical injury, necrosis, apoptosis or inflammation, cells release ATP or ADP. These nucleotides function as extracellular signalling molecules activating purinergic P2 receptors belonging to two groups, P2Y receptors (GPCRs) and P2X receptors (nucleotide-gated ion channels).

Afferent is also developing a second P2X3 antagonist, AF-130, which is currently in phase 1 trials, for hypertension, but Merck has just begun a wide-ranging review of the clinical potential of P2X3 antagonism—its future development plans will follow the biology. "We haven't made final decisions about where we're going to put the next investment," Green says.

Other firms are also exploring the target. The Rinat Laboratories arm of New York––based Pfizer recently reported on a panel of antibodies that modulate P2X3 receptors when present as homotrimers, or as P2X2/3 receptor heterotrimers (*J. Biol. Chem.* **291**, 12254–12270, 2016). Gedeon Richter, of Budapest, Hungary, has published data on two small-molecule classes of P2X3 inhibitors (*Bioorg. Med. Chem. Lett.* doi:10.1016/j.bmcl.2016.07.009, 2016; *Bioorg. Med. Chem. Lett.* doi:10.1016/j.bmcl.2016.07.013, 2016).

Ford credits an academic collaborator, Geoffrey Burnstock of University College London—who at 87 years is still active in research—for opening up the field of extracellular ATP signaling. In the early 1970s, when he first proposed the concept, "he was pilloried by the cognoscenti," Ford says. Cloning and molecular characterization of the receptors—once dismissed as 'imaginergic receptors'—during the 1990s has helped to reorient our understanding of ATP as an extracellular biological irritant as well as the intracellular currency for energy exchange.

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