Going fourth: Thurmond investigates H4.

of histamine's actions. This observation led Swedish investigators to propose, in 1948, that there are two types of receptors sensitive to histamine, and close to two decades later British researchers gave the name H1 to the receptor blocked by the known antihistamines.

Today, more than 40 antihistamines that target H1 are available around the world. Early versions of these drugs caused drowsiness, so drug companies spent years trying to design more specific H1 antagonists to avoid this side effect. They finally succeeded in the late 1980s, when Claritin was developed by Scherling-Plough. Claritin and the other next-generation H1 antihistamines, which include Allegra and Zyrtec, are now top sellers.

After the discovery of H1, the number of known histamine receptors kept multiplying. The H2 receptor was confirmed in 1972, and French researchers characterized a third histamine receptor—H3—in 1983. The discoveries of the H2 and H3 histamine receptors, though notable, did little to help allergy researchers. Whereas the H1 receptor is expressed pretty much everywhere in the body, the H2 and H3 receptors act mainly in the digestive system and brain, respectively.

Even with the knowledge of these three types of receptors, however, many forms of allergy and asthma were unaffected by the available treatments, which led some researchers to believe that there might be another type of histamine receptor still lurking. Yet it wasn't until the turn of the millennium, with the sequencing of the human genome, that at least six independent laboratories, including one at Johnson & Johnson, identified the H4 receptor.

Many scientists originally thought the H4 receptor might be functionally related to the H3 receptor, which seems to have a role in cognition and regulating sleep cycles, but that turned out not to be the case. So, at Johnson & Johnson, for example, neuroscientists handed over the project to their colleagues studying allergies.

> "Histamine is having a sort of revival right now."

"When they realized that the H4 receptor seemed to be expressed mostly in immune cells, they weren't very interested in it any more, and that's how I got involved," says Robin Thurmond, an immunologist at Johnson & Johnson's Pharmaceutical Research and Development center in San Diego, California. Thurmond jumped at the chance to take on the project. "I was excited because here was a new receptor that could explain the discrepancies between histamine and asthma," he remembers.

Breathing easy

Thurmond has hit some bumps in the road in his journey exploring H4's relation to asthma. Early animal models suggested that this histamine receptor depended on mast cells, white blood cells that spew out histamine during an asthma attack. But in the end, "it turned out, all the effects of the H4 receptor were on T cells, which was a big surprise," he says[1].

Whereas histamine may be the fuel that ignites the flames of asthma, T cells are the fans that keep the fire burning. T cells produce the cytokine molecules that promote inflammation in animals' lungs and airways, and they perpetuate asthma symptoms by signaling for other cells in the lung to release more and more histamine.

These findings could one day help asthma sufferers. Even the most selective antihistamines on the market have little effect on asthma. "Treating seasonal allergies with antihistamines can help asthma somewhat, but only in patients with allergic asthma, and only indirectly," says Linda Rogers, a pulmonologist at New York University who specializes in asthma.

Inhalers that dispense corticosteroids remain the go-to treatment for asthma. These therapies reduce airway inflammation, but they can be costly—up to $200 per month. Plus, clinicians say, they don't work for everyone. "About 20 to 30% of patients require additional treatments, but there's not a lot out there," Rogers says. A new class of drugs that targets the immune system called leukotriene inhibitors has emerged as one option, but there is certainly room for more, and an antihistamine would make a favorable candidate, given the drug class's reputation for safety.

There is hope from Thurmond's lab. When the group administered Johnson & Johnson's H4 receptor antagonist to asthmatic mice,

A timeline of histamine and its receptors

1907— Adolf Windaus and his associate W. Vogt produce histamine synthetically by removing the carboxyl group from the amino acid histidine.

1910—Henry Dale and his colleagues at the Wellcome Physiological Research Laboratories isolate histamine from mold and show that it can elicit the physiological responses associated with allergic reaction.

1927—Researchers discover histamine in vertebrate tissue, particularly in the lungs.

1942—Antergan becomes the first antihistamine tested in humans and goes on the market.

1972—James Black discovers the H2 receptor and characterizes its antagonist, burimamide.

1999—Researchers at a subsidiary of Johnson & Johnson clone the H3 receptor.

2000—Seven groups in the US, Europe and Japan clone the H4 receptor.

2006—Phase 1 clinical trials of H3 antagonists for neurological disorders begin.

2010—Spain's Palau Pharma announces favorable results from a phase 1 clinical study of its H4 antagonist for nasal allergies.

1900 1925 1950 1975 2000