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Potential Future Cough Therapies: What's in the Research Pipeline

Announcer:
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Dr. Dicpinigaitis:
Hello, my name is Dr. Peter Dicpinigaitis. I'm a professor of medicine at the Albert Einstein College of Medicine, and I'm the director of the Cough Center at Montefiore Medical Center, in New York. Our presentation today is on the topic of potential future cough therapies. What's in the research pipeline?

The last decade has been a very exciting one in the field of cough because we've learned a lot about the underlying pharmacology, and physiology of cough. And that has translated into multiple drug development programs currently in process, looking at potential safe, and effective cough-suppressing drugs. Of all the programs, currently ongoing, the most advanced of those is looking at the so-called P2X3 antagonists; P standing for purinergic. There are a number of other development programs earlier on that we'll discuss at the end of the presentation.

So, as I mentioned, we've learned a lot about pharmacology and physiology of cough, and the various receptors and ion channels, that are relevant in the induction of the afferent signal from lung to brain, to induce cough. One particular area of intense interest is with the P2X3 receptor antagonists; These are receptors; the P2X3 receptors line the airway epithelium, and they are stimulated when there is an increase of ATP within the airway, which can occur with inflammation, or with other organ injury. ATP then stimulates the P2X3 receptor, to cause cough. So, there have been a number of P2X3 antagonists developed, as potential antitussives. Now, the P2X3 ion channel exists as a P2X3 homotrimer, but also a P2X2 slash three heterotrimer. This is relevant because the P2X3 homotrimer is related to the induction of cough, but the P2X2 slash three heterotrimer is also relevant to the sensation of taste. So, an interesting side effect of the P2X3 receptor antagonist has been that some patients notice a diminution or an alteration of the sensation of taste. We'll talk more about that in a moment. So, the first P2X3 receptor antagonist in development was Gefapixant, and the first phase two proof of concept study of Gefapixant was published back in 2015, in the Lancet. Since then, multiple subsequent phase two studies showed the drug's effect, and that led to the first-ever phase three study of any antitussive drug; this was Gefapixant. And, this phase three trial was published just this past March 2022, in the Lancet. These were parallel phase three studies called Cough-1, and Cough-2, looking at Gefapixant in refractory chronic cough.

There were two doses of Gefapixant evaluated; 15 milligrams and 45 milligrams, twice daily. And, the larger 45-milligram dose were shown to be statistically, significantly more effective than placebo against chronic cough. As has been the case with most cough studies recently, there was a very large placebo effect; however, the drug did show statistically significant cough suppression activity beyond the placebo effect. As I mentioned, Gefapixant is the first of the P2X3 antagonists in development, just finishing phase three. But there are several other companies developing other P2X3 antagonists that are currently in phase two, and these drugs are felt to be more P2X3 specific than Gefapixant. That being relevant, because the theory then is that these drugs will have less of a taste effect, as did the less specific P2X3 receptor antagonist. So, there are multiple phase two studies, and phase three studies being planned with these

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molecules.

As I mentioned, the P2X3 antagonists are furthest along the research pipeline. But there are a number of other programs that hopefully we'll be hearing about in the years to come, as some of these programs are in phase two and hopefully heading towards phase three. And those include the neurokinin antagonists, the TRPM8 agonists, which are menthol-like agents. There's a lot of excitement with voltage-gated sodium-channel blockers. There are at least two programs in early phase two there. And one program of an opioid-type drug that is, in fact, a new opioid antagonist, but a CAPA agonist. So, hopefully, we have interesting times ahead, with multiple drugs in the pipeline that, hopefully, the clinicians will soon be able to use for our very difficult, and challenging group of patients with refractory chronic cough. Thank you very much for your attention.

Announcer:
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