What the Nose Knows

Humans can tell the difference between at least a trillion smells.

**EVERY DAY, WE’RE** confronted by a multitude of smells, good and bad: perfume, body odor, baking cookies, ripe garbage. But how many smells can the human nose actually distinguish? According to a recent study by HHMI Investigator Leslie Vosshall, it’s more than 1 trillion.

For decades, people believed that the human nose could discriminate between 10,000 different smells. That estimate, never empirically tested, didn’t sit right with Vosshall. “The number was from theoretical empirically tested, didn’t sit right with it’s more than 1 trillion.”

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Twenty-six volunteers were presented with three vials of these scent cocktails; two were identical, the third was different. It was the sniffer’s job to pinpoint the outlier. Each volunteer did this more than 250 times. On average, they could easily distinguish between mixtures with fewer than half their components in common; above that, discrimination became harder.

From the data, the team extrapolated how many different odors the average human can detect. Vosshall likens the process to a survey—rather than asking the entire country what presidential candidate they will vote for, you telephone a few thousand voters and use your findings to make an estimate of the entire population’s preferences based on this sampling. The number, published March 21, 2014, in Science, was 1.7 trillion—a conservative projection, as there are many more than 128 odorants in the world.

No one encounters a trillion smells in a day, so the ability to distinguish between so many odorant molecules isn’t really necessary. But being able to discriminate between similar smells, such as spoiled milk versus fresh milk, is certainly useful.”

—Nicole Kresge

IN BRIEF

implying that VRAC had been inactivated. They named that gene SWELL1 and published their findings on April 10, 2014, in the journal Cell. “When cells swell, the SWELL1 protein is activated and pumps chloride and other solutes out of the cell, which initiates the process to shrink a cell back to original volume,” says Patapoutian.

Now that the team has a molecular understanding of VRAC, they plan to investigate how the channel senses volume change and the role SWELL1 plays in physiology and disease.

**LEGO FOR THE LAB**

Synthesizing a molecule is a lot like doing a jigsaw puzzle. You start with many pieces, figure out how they fit together, and eventually, after a lot of trial and error, you’re done. HHMI Early Career Scientist Martin Burke has come up with a way to simplify the process using Lego-like building blocks that take the puzzling out of synthesis.

Burke and his team at the University of Illinois at Urbana-Champaign analyzed almost 3,000 polyenes found in nature. These molecules—commonly used as drugs, pigments, and fluorescent probes—contain chains of carbon atoms connected by alternating single and double bonds. The scientists realized that more than three-quarters of the natural products could be created with only 12 different chemical building blocks joined by a single type of coupling reaction. Like 12 pieces of Lego that can be combined to make just about anything, from a house to a dinosaur, the researchers mixed and matched the basic polyene building blocks to produce several different molecules.

The discovery, reported in the June 2014 issue of Nature Chemistry, provides chemists with a simple way to build polyenes that are challenging or too expensive to extract from their natural sources. Burke eventually hopes to expand his chemical Lego set to include more than just polyenes. “This paper covers about 1 percent of all natural products isolated to date,” he says. “We want to determine how many building blocks it takes to reach most of the remaining 99 percent, and to create a highly optimized machine that can automatically stitch those building blocks together.”

**CLIPPING CONTROL**

When a strand of DNA in a yeast cell breaks, one of the first responders is the endonuclease Sae2. The enzyme’s job is to trim a little from the damaged ends of the DNA in preparation for repair. But if Sae2 lingers around too long, it might end up clipping some perfectly good DNA as well. HHMI Investigator Tanya Paull of the University of Texas at Austin has figured out how cells keep the enzyme in check.

Paul’s team discovered that Sae2 normally forms nonfunctional, insoluble protein aggregates in the cell. But after DNA damage occurs, an enzyme called cyclin-dependent kinase adds several phosphate molecules to Sae2. This causes the protein clusters to break apart, and the now-soluble single molecules of Sae2 become active. The DNA damage also triggers the degradation of Sae2, ensuring the cellular “clipper” is only transiently available. The findings were published March 2014 in Molecular and Cellular Biology. “Sae2 is an endonuclease that is potentially very toxic to cells when unregulated,” explains Paull. “So this strategy is ideal for sequestering the protein into a form that is not toxic, yet is available for immediate activation through phosphorylation.”

Paull recently discovered that CtIP—the human version of Sae2—is an endonuclease with even more phosphorylation than Sae2. The results, published in the June 19, 2014, issue of Molecular Cell, have prompted her to investigate if CtIP is also regulated by changes in solubility.