Scripps Research Institute awarded patent for remarkable chemical technology

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The patent's diverse potential applications include the development of new drugs, bioactive nanomaterials, anti-bacterial and non-immunogenic coatings for medical implants, coatings for semiconductors, coatings and adhesives for ships' hulls, self-healing materials, microelectronics and responsive nanomaterials, and surface-sensitive adhesives, to name a few.

The patented technology stems from the discovery that, under proper conditions, copper can quickly and reliably catalyze members of two large chemical groups, azides and alkynes. These reactions enable the controlled formation of an almost endless array of new molecules.

"Because this technology is so revolutionary, it has broad applicability that is very exciting," says Polly Murphy, senior vice president of Business and Scientific Services at Scripps Research. "We believe it has the potential to be used in every branch of industry that uses chemistry."

The patented reactions are a commercially promising development within the broader domain of "click chemistry," pioneered by Nobel Prize-winning chemist Barry Sharpless, a professor at Scripps Research. Click chemistry refers to classes of reactions in which the chemical components used "click" together to bind as easily and reliably as the two pieces of a seatbelt buckle. The buckle works no matter what is attached to it as long as the two pieces can reach one another.

Click chemistry research by Sharpless and his colleagues was initially met with skepticism by a chemistry community that was more accustomed to research focused on increasingly complex chemical reactions.

"It was plain laughed at in the beginning," says Valery Fokin, an associate professor and Sharpless' colleague.

But, over time, the utility of the chemistry involved became clear, and there are now more than 1,000 citations for the work in academic publications. The new patent is further confirmation of click chemistry's importance.

Click chemistry focuses mainly on reactions involving azides, a class of nitrogen-containing molecules, and alkynes, a group of hydrocarbons such as acetylene. These groups have an extreme chemical fondness for "clicking" with each other to form stable molecules known as triazoles. As importantly, these two groups are extremely reticent to bond with any other types of molecules. Among other benefits, this means reactions involving these groups can be done almost anywhere—including in water and blood where many other reactions are impossible—without forming unwanted byproducts.

At the beginning of the work, one limiting factor with the azides and alkynes was that reactions between them usually proceeded slowly. But in 2001, Fokin and Luke Green (then a postdoc in the lab and a co-inventor) made a surprising discovery that copper salts dramatically accelerated azide-alkyne cycloaddition, and led to the new patent in the process. The scientists found that when copper was present along with azides and alkynes, the reaction between them could proceed millions of times faster and with almost 100 percent reliability—an almost unheard of concept in chemistry. "The copper acts as a sort of universal connector," says Fokin. No matter what kind of azide and alkyne—one could be attached to another molecule and one could be attached to a car—you will make the link between the two."

Though some questions about the mechanisms involved remain open, in general copper interacts with both azides and alkynes to slightly alter them, making them more reactive with each other, dramatically facilitating formation of triazoles. But despite this hyperactive reactivity, the two groups remain inert to other types of molecules.

"It was pure serendipity," says Sharpless of the discovery of the copper effect. "I just couldn't believe that reaction. It sounds like magic, but nothing can stop it. It's like a black hole." Remarkably, though, the copper has almost no effect on either an azide or an alkyne alone; the reactivity only occurs if at least one of each is present.

Of many areas where the patented technology can be used, potential applications include the production of new pharmaceutical candidates and new polymeric materials, such as glues and coatings, for use in high-tech electronics applications. Triazoles are exceptionally stable at high temperatures, which makes them ideal for use in electronics, where computers and other devices must heat up and cool down countless times for years on end without the glues in their chips (or electronic components) breaking down. Certain triazoles are also exceedingly sticky, bonding strongly to metals and other materials including glass and certain plastics, another critical factor for electronics. "Together with our colleague M.G. Finn, we've already shown that we can make adhesives that are better at ‘welding’ metal components together than anything else on the market," says Fokin.

Another advantage in developing adhesives is that the remarkable reactivity involved ensures that any two azides and alkynes can be bound together. That means designers can simply choose molecules from those groups that have needed properties, such as repelling water or absorbing certain chemicals, and bind them to form a single, web-like molecule, or polymer.

In drug discovery work, the copper-catalyzed reactions display another side of their benefits. To identify potential pharmaceuticals, researchers often test libraries of thousands or even millions of molecules to identify those that might kill a particular virus or type of cancer cell. Because the azides and alkynes are so reactive when copper is around, large groups of both types of molecules can be combined, allowing bonding to form molecule libraries that can then be run through these disease tests. Using copper-catalyzed azide-alkyne cycloaddition, Scripps Research scientists have already identified molecules with potential for fighting AIDS, nicotine addiction, and other conditions. The reactions' gluing powers have also proven extremely effective at binding fluorescent alkyne dyes to proteins and other biological components, which allows researchers to observe how they behave in cells and what roles they may play in diseases.

With the technology now patented and available for licensing, Fokin looks forward to seeing how the chemistry is applied. "A new technology is worth something only if people use it and it actually enables new and useful discoveries," he says.

Sharpless says that's all but inevitable. Within and beyond those areas already identified as ripe for use of the chemistry, he says, "People are going to be coming up with things we can't even imagine right now."

Source: Scripps Research Institute