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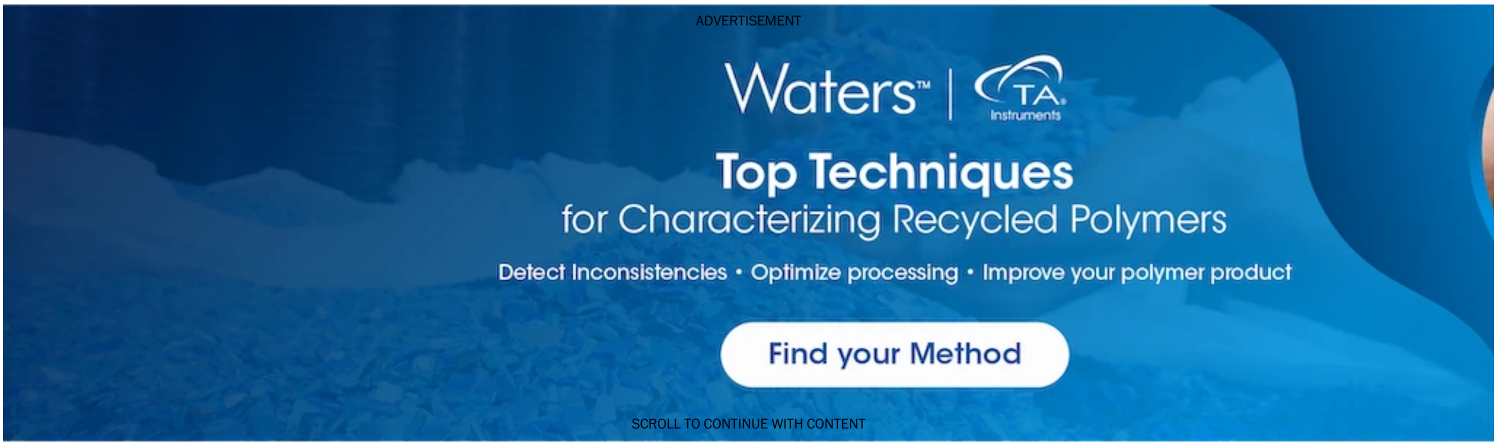

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NOBEL PRIZE

Click and bioorthogonal chemistry win 2022 Nobel Prize in Chemistry

Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless receive prize for their work on reactions that quickly link molecules and the application of the reactions in living cells

by ***Mark Peplow, special to C&EN***

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Credit: Laura Morton (Bertozzi), University of Copenhagen (Meldal), Sandy Huffaker (Sharpless)

From left: Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless

Three scientists have won the 2022 Nobel Prize in Chemistry: **Carolyn R. Bertozzi** of Stanford University, **Morten Meldal** of the University of Copenhagen, and **K. Barry Sharpless** of Scripps Research in California share the prize for their work on click chemistry and bioorthogonal reactions. Click chemistry involves reactions that unite two synthetic molecules quickly and irreversibly. Some of these reactions can be performed inside living cells without disrupting biochemical processes, making them bioorthogonal.

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This approach is used to tag biomolecules with fluorescent probes that **illuminate the inner workings** of cellular biochemistry, for example, and it also offers a way to produce **antibody-drug conjugates** that have highly targeted therapeutic action in the body. Click chemistry is even being **directly applied inside patients**, in ongoing clinical trials of a powerful cancer therapy. “I truly believe that the potential applications of click chemistry are unlimited—from materials science to life-saving drugs, click chemistry is here to stay,” said John Moses, a click chemistry researcher at Cold Spring Harbor Laboratory, in an email to C&EN.

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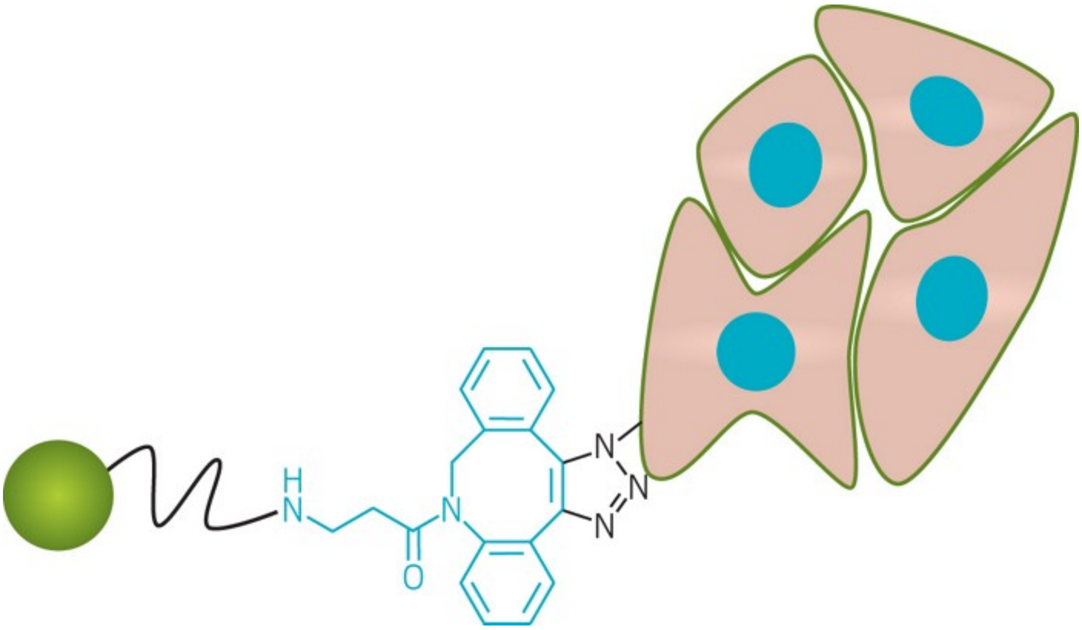
“It has led to a revolution in how chemists think about linking molecules together,” said Johan Åqvist, chair of the Nobel Committee for Chemistry, during the Stockholm press conference to announce the award. The scientists will each share one-third of the 10 million Swedish kronor (approximately $900,000) prize. “I can hardly breathe,” Bertozzi said during the press conference. “I’m still not entirely positive that it’s real, but it’s getting realer by the minute.”



Credit: ***Biomacromolecules***

A glycan modified with an azide group expressed on the surface of a cell acts as a handle for attaching functional molecules. Researchers attached a polymer containing a fluorescent group (green) to the cell via a click reaction.

“We are absolutely delighted with these awards, which recognize the enormous impact of click chemistry and bioorthogonal chemistry,” American Chemical Society president Angela K. Wilson said in a press statement. ACS publishes C&EN.

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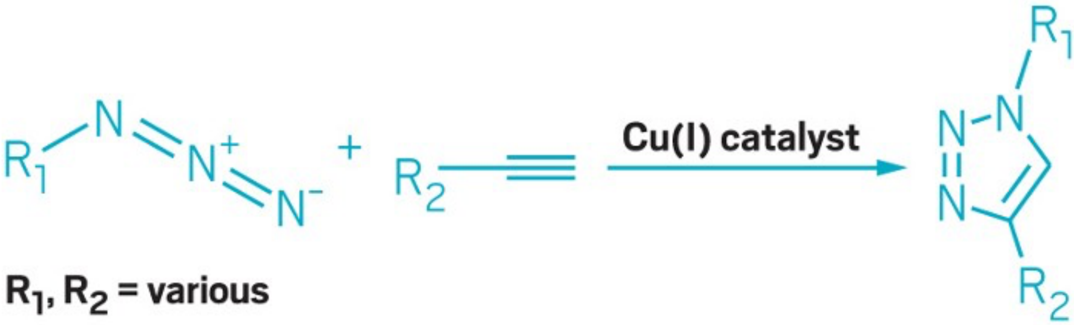
Sharpless and Meldal independently developed the first click reaction about 20 years ago. The copper-catalyzed reaction between an azide and an alkyne produces a highly stable triazole as the single product. “It's still the crown jewel of click reactions,” said Nobel committee member Olof Ramström at the press conference.

Chemists had long used this kind of cycloaddition reaction, but the copper catalyst was the key to making it rapid and selective. “You can take molecules that are highly functionalized and click them together in a very selective, very specific way,” Bertozzi told C&EN. “That's a rare quality in a reaction.”



Credit: C&EN

The copper-catalyzed azide-alkyne cycloaddition is click chemistry's premier reaction.

The sheer simplicity of the reaction meant that chemists embraced it enthusiastically. By incorporating clickable azides into polymers, for example, researchers can subsequently decorate the polymer with chemical groups that give the material useful properties, such as electrical conductivity or protection from ultraviolet degradation.

When Sharpless and Meldal unveiled their click reactions, Bertozzi had already been developing bioorthogonal chemistry to help image biomolecules in living cells. Her team was using a reaction called the Staudinger ligation, which reacts **an azide** with a phosphine ester, to add fluorescent tags to sugar molecules called glycans that are found on cell surfaces. But the reaction was too slow for some of the imaging experiments the researchers wanted to do.

Related: 2019 Priestley Medalist K. Barry Sharpless works magic in the world of molecules

Bertozzi wondered if click chemistry could offer a faster alternative. However, the copper ions used in the classic click reaction are toxic to living cells, limiting the application of this particular reaction in biology.

In 2004, Bertozzi came up with a solution: a click reaction between an azide and a strained cyclooctyne that did not need a catalyst and therefore did not interfere with the biochemistry of a living cell. She and her colleagues **tagged glycans** on the surfaces of cells with azide groups and then used their click reaction to couple fluorescent molecules onto those glycans so that they could be tracked using microscopy techniques.

Collectively, these click chemistry reactions marked “the start of a completely new chemical discipline,” Marc Robillard, CEO of Tagworks, a company that uses click chemistry in drug delivery and radioimaging applications, told C&EN in an email.

Since these pioneering discoveries, chemists have developed a range of click reactions suitable for bioorthogonal chemistry. “Bioorthogonal chemistry is baked into the fabric of chemical biology research now," Bertozzi says.

Researchers in the biopharmaceutical industry also use bioorthogonal chemistry to determine the biological targets of new drug molecules and to link drugs to antibodies that can seek out particular types of cell receptors. "These are robust, efficient reactions that always work, regardless the environment, even in living systems," says Petr Beier of the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, who uses click chemistry in his research. "These reactions are key tools in our efforts to understand life."

"Click chemistry and bioorthogonal chemistry have truly exploded in the last couple of decades," says José M. Mejía Oneto, founder and CEO of Shasqi, a company conducting clinical trials of a cancer therapy that uses click chemistry inside human patients (Bertozzi is an advisor to the company). "The elegant simplicity and functionality of the concept has enabled countless scientists around the world and fundamentally strengthened research, manufacturing and drug development."

Earlier this year, Bertozzi **shared the Wolf Prize** for her work on bioorthogonal chemistry. And for Sharpless, this is the second time he has been awarded the Nobel Prize in Chemistry. The first was in 2001, for his work on chirally catalyzed oxidation reactions. C&EN reached his wife, Jan, shortly after the announcement. His reaction to the news? "I guess I have to take a shower."

Later, Sharpless told C&EN that he was still trying to wrap his head around the idea that he had won a second Nobel Prize. Nevertheless, he says, it was gratifying to see that click chemistry "really had a huge reach and usefulness."

When asked how he'd celebrate, Sharpless says he is "a little bit crotchety" but adds, "I can still go to the lab and work hard on chemistry." He also conceded that the department at Scripps would probably have a party, and "we're gonna get some champagne for sure."

Additional reporting from **Bethany Halford**

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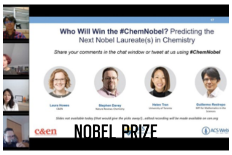

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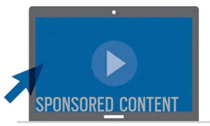

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