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Nobel Prize 2022 to Sharpless, Meldal, Bertozzi Click Chemistry – molecular lego

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Editorial Note

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The concept of click chemistry, initially pioneered by Barry Sharpless 20 years ago, and aided by his colleagues V. Fokin and M.G. Finn, has been transformative in many areas of chemistry, materials science, biology, and medicine. It has given rise to new highly functional materials, has catalyzed important pharmaceutical developments, and has been influential in areas too numerous to mention, including numerous biophysical applications for studying cellular processes.

The archetypal click reaction, the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), the copper-catalyzed version of the original Huisgen reaction, was discovered simultaneously by Sharpless and Meldal. The ‘accidental’ discovery of the CuAAC reaction in Meldal’s lab is a fascinating story and a great example of Pasteur’s famous quote ‘chance only favors the prepared mind’. Unlike the uncatalyzed alkyne–azide reaction, CuAAC works under mild conditions and makes exclusively 1,4-disubstituted 1,2,3-triazoles. It is a new concept to join molecules together in a highly selective and efficient manner and can be looked upon as ‘molecular lego’. Crucially, it is orthogonal to most other chemical reactions, and can be carried out in most media including water. These properties, particularly the fact that it is ‘invisible’ to most other functional groups and molecules, make it incredibly flexible and broadly applicable. Applications are almost endless, for example, it has been of enormous value to our own research in the nucleic acids field.

The remarkable work of Carolyn Bertozzi has given rise to new types of click reactions that do not require copper catalysis, collectively termed ‘bio-orthogonal click chemistry’. This concept can be used in applications where the CuAAC reaction and related metal ion catalyzed reactions are not feasible due to the toxicity of the metals. An example of bio-orthogonal click chemistry is the SPAAC reaction (strain-promoted alkyne–azide cycloaddition) involving the reaction of an azide with a strained cyclooctyne. Importantly Bertozzi’s work enables click reactions to be done in living systems, providing spatial and temporal information. It enables the visualization of molecules in living cells and organisms, the study of disease processes, and development of new drugs including improvements in drug delivery. It has very much been used to great effect in the study of glycans (polysaccharides) that play a major role in all essential functions of the human body, including the immune system. A new age of chemical interrogation of complex biological systems has begun.

This is Sharpless’s second Nobel Prize in Chemistry, a stunning achievement. Anyone who knows him will testify that he is a unique character who is remarkably imaginative and passionate about chemistry.