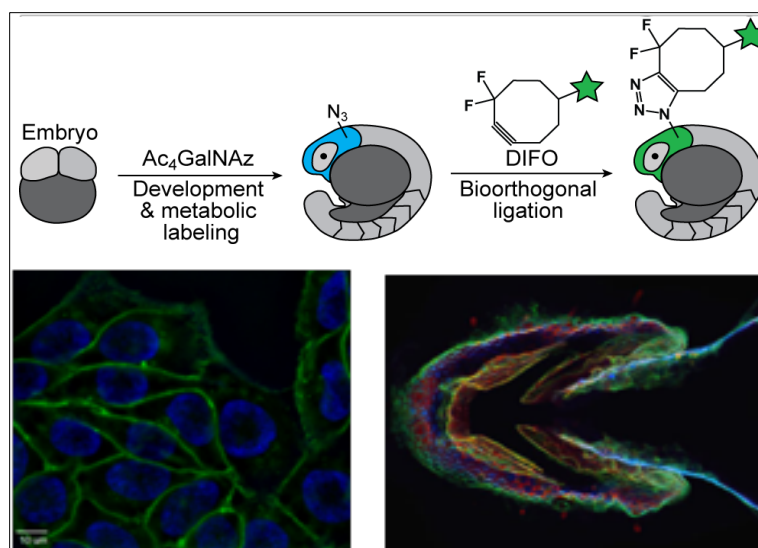


**2010 Winner of the \$500,000 Lemelson-MIT Prize**  
**Dr. Carolyn Bertozzi**

**Bioorthogonal chemical reactions**

Dr. Carolyn Bertozzi invented the concept of bioorthogonal chemical reactions, a term she coined to describe reactions among chemical functionalities that neither interact nor interfere with biological molecules. These reactions are so selective and biocompatible that they can be used to label molecules including proteins, sugars, nucleic acids, and lipids within live cells and organisms, with no harmful consequences. Researchers are now using these bioorthogonal reactions for a myriad of applications, such as the covalent labeling of biological molecules with imaging probes or with small molecule tags for their purification and characterization.



*Figure 1. Imaging glycans using bioorthogonal chemistry. Top: Cells, embryos or adult animals are administered a modified sugar, which is incorporated into cell surface glycans; Bottom left: glycans imaged on cancer cell surfaces; Bottom right: glycans imaged in developing zebrafish*

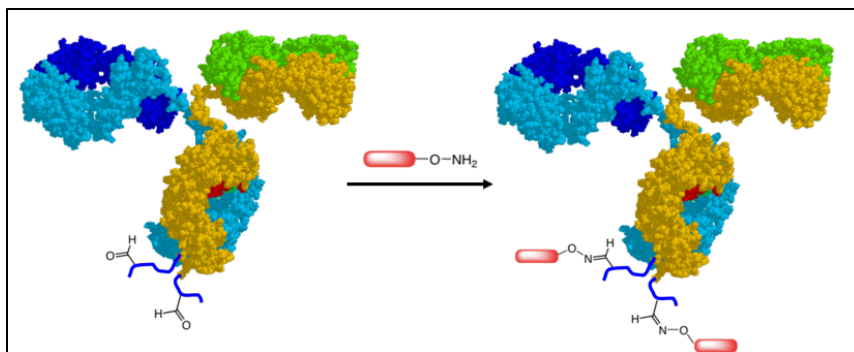
**Glycobiology innovations-imaging glycans**

In her own lab, Bertozzi uses bioorthogonal chemical reactions to label cell surface sugars with imaging probes. She targets the sugars for labeling by feeding cells simple sugar precursors bearing a bioorthogonal functional group. Their metabolism by cells leads to incorporation of the modified sugars into more complex cell surface sugars. A bioorthogonal reaction with an imaging probe bearing complementary functionality allows specific labeling of the sugars amidst the complex sea of cell surface molecules. The extent of labeling reflects the cell's metabolic state, which often differs between diseased cells and their healthy relatives.

Bertozzi has utilized bioorthogonal chemical reactions for non-invasive imaging of sugar molecules in live animals, which can potentially lead to applications for cancer detection. Prior to her work, sugars were invisible during the imaging process, making it hard to recognize glycan structures that can report on diseases such as cancer. Bertozzi studies the relationship between glycosylation, the addition of sugar groups to a molecule, and disease – specifically how glycans contribute to bacterial infections and the changes in glycosylation that accompany cancer onset and progression. Using zebrafish as a model organism, Bertozzi was able to show that sugars can be imaged during the process of embryogenesis, a major breakthrough that might facilitate studies of stem cell differentiation in live animals.

## Genetically-encoded aldehyde tags

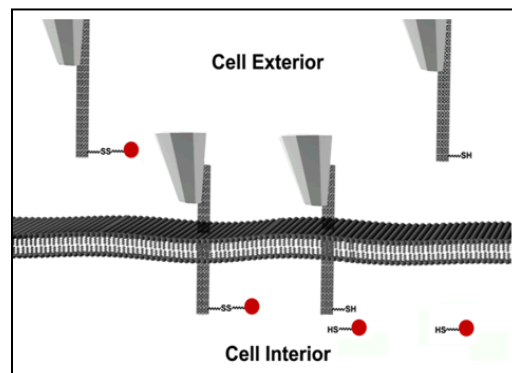
Building from her work on bioorthogonal chemical reactions, Bertozzi developed a genetically-encoded aldehyde tag technology to expand the chemical space of protein therapeutics, making it possible to augment protein structures with cytotoxins or moieties that extend serum half-life. The technology provides a general method for site-specific chemical modifications of proteins expressed in any cell type and involves simply engineering three amino acids into a protein's primary sequence. Examples of protein targets include monoclonal antibodies, the fastest growing class of drugs, as well as enzymes, growth factors and hormones.



*Figure 2. The genetically-encoded aldehyde tag technology enables site-specific chemical modification of recombinant proteins. Shown is an example of a therapeutic monoclonal antibody that is chemically modified with a small molecule drug. Such antibody-drug conjugates are major targets of the biopharmaceutical industry.*

## Cell nanoinjector

Bertozzi developed an instrument that delivers cargo to a cell's interior with spatial control and minimal damage to the membrane. An individual carbon nanotube (CNT) is mounted on the tip of an atomic force (AFM) microscope, and the cargo is attached to the nanotube via a disulfide linker – or chemical bond. After the “nanoneedle” penetrates the cell membrane, a disulfide reduction within the cell releases the cargo. The injector is then retracted by AFM control, leaving the cargo inside the cell. Unlike the classic microinjection, which can damage cells, Bertozzi's technique causes no visible harm to the cell. The cell nanoinjector is now the subject of a patent application and a number of companies are interested in turning this technology into a commercial device.



*Figure 3. Carbon nanotube-based cell nanoinjector; a collaborative effort with Professor Alex Zettl of the UC Berkeley physics department. Injection of nanotube into cells results in reductive cleavage of the disulfide bond in cell cytosol and subsequent cargo release.*