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B.Sc., California Institute of Technology; Ph.D., Massachusetts Institute of Technology (1986); Postdoctoral Fellow, Stanford University (1986-88); Faculty, University of Virginia Department of Chemistry (1988-1998); The Scripps Research Institute Department of Chemistry and The Skaggs Institute for Chemical Biology (1999-2012); Georgia Institute of Technology Department of Chemistry and Biochemistry, Department of Biology (2013-)

Research

Our research program rests on the twin foundations of molecular and virus particle synthesis. The former encompasses specializations in click chemistry, transition metal catalysis, and bioconjugation; the latter engages expertise in molecular biology and protein production, analysis, and purification.

Virus-Based Chemical Biology

Virus-like particles (VLPs) have four outstanding qualities as scaffolds for biomedical research: they are the largest objects with structures known to atomic resolution, are easily produced in quantity, are highly stable, and are highly immunogenic.

We take advantage of the ability of virus scaffolds to project multiple functional molecules on a surface large enough to engage multiple receptors on cell surfaces. Control of the attachment chemistry to VLP surfaces is required, and for this reason we have developed the copper-catalyzed azide-alkyne cycloaddition (CuAAC) click reaction as a superior bioconjugation technique. In addition, we can address the interior space of VLP capsules by interaction with interior surface protein residues or packaged polynucleotide. Multifunctional nanoscale objects are created with atomic resolution control over structure, by combining molecular cloning and protein expression with powerful chemical conjugation methodology.

Our current targets include the induction of strong and focused immune responses to carbohydrates and other antigens, the targeting of desired cells *in vivo*, the delivery of noncoding RNA for transcriptional gene silencing or activation, and the development of catalytic particles for chemical synthesis and biomedical applications. We are also interested in the power of evolutionary tools to solve important problems, and will be exploring new methods to evolve enzymes for desired functions.

Synthetic Chemistry

Our current small-molecule research includes the discovery of biologically active compounds, the development and understanding of click reactions, and the application of click chemistry to materials science. The first of these programs has several specific targets, including HIV protease, nicotinic and GABA receptors, hepatitis B virus, PI3 kinase, and the asialoglycoprotein receptor. Each of these projects is undertaken with a different biological collaborator, our role being to prepare candidate compounds using traditional methods of organic synthesis as well as click chemistry approaches that assemble compounds conveniently in combinatorial fashion or in the binding pockets of the enzyme targets themselves.

Click chemistry – the development and use of highly reliable methods of chemical connectivity – remains a focus for our laboratory in fundamental terms as well. We are currently developing the chemistry of 2,6-dihalo thia- and azabicyclo[3.3.1]nonane and oxanorbornadiene derivatives as reliable and reversible connectors, and retain a strong interest in the further development and understanding of the CuAAC reaction.

Lastly, we are committed to translating advances in click chemistry to materials science. Highly reliable reactions are required for the preparation of polymers, and so any new reaction introduced into the fields of polymer synthesis or modification opens up whole new worlds of potential chemical function. We have focused for several years on the CuAAC process in the synthesis of adhesives, coatings, and crosslinked gel materials. Our future work will target responsive materials that have properties of self-healing, electrical conductivity, and biocompatibility.