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Editorial

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Delivery of Proteins and Nucleic Acids: Achievements and Challenges

■ THERESA M. REINEKE

I am delighted and honored to work with Ron and Vince on this *Bioconjugate Chemistry* special issue entitled "Delivery of Proteins and Nucleic Acids: Achievements and Challenges". It has been almost 20 years since I first began work in this field as a bright-eyed postdoc. It was an exciting time; recombinant biologic drugs were being approved by the FDA, the human genome was sequenced, and RNA interference discovered. Soon after, I began my first academic position and while setting up my independent lab and mentoring my first students, the importance of therapeutic innovation hit home. My mother, Gail Sobaski, was diagnosed with stage IIIB diffuse large cell lymphoma. During her 18-month treatment regime, I witnessed first-hand how nonselective chemotherapies, radiation treatments, and bone marrow transplant can wreak havoc on the human body. While her treatments were ultimately successful and her cancer no longer detectable, she faced further life-threatening illness from treatment side effects including a depressed immune system. To combat this, the doctors administered filgrastim (a recombinant protein drug that stimulates white blood cell production) and eventually a new PEGylated variant that had just been FDA approved (pegfilgrastim), which promoted longer-term biological activity of the protein. Her immune system recovered, and since that time, she has remained in remission.

In just under two decades, the field of biologics and nucleic acid drugs has witnessed many ups and downs. The field is now experiencing a renaissance, where biologic drugs have a higher FDA approval rate than small molecules. Moreover, several cell and gene therapies have now been FDA approved, with many more in the pipeline yielding promising clinical results to save lives. I recently had the pleasure of meeting the first pediatric CAR-T cell therapy recipient in the US, Emily Whitehead, and her parents, Kari and Tom. Emily's life was saved by a lentiviral gene therapy that engineered her immune cells to expresses a chimeric T cell receptor that selectively destroyed her relapsed lymphoblastic leukemia. Her family and the Emily Whitehead Foundation are now dedicated to obtaining funding and increasing awareness for innovative treatments that are less toxic and more targeted. These and many other personal experiences have continued to humanize the power of therapeutic innovation to decrease side effects and improve treatment efficacy.

In this special issue, we move a step closer to this goal by highlighting a series of innovative synthetic systems that show many promising attributes for safe, affordable, scalable, stable, and effective biologic and nucleic acid therapeutic advancement. As Ron and Vince point out below, getting large biomolecules through the cellular barrier is not an easy task. As highlighted herein, many innovative delivery approaches are described involving use of synthetic conjugates, polymer carriers, peptides, and scaffolds with responsive chemistry to overcome the many biological barriers that exist. While many clinical successes have paved the way, including FDA approval of the first nonviral siRNA drug, several hurdles remain. The high level of cross-disciplinary collaboration exemplified by this field will ultimately enable more synthetic bioconjugates to reach their final goal: to improve and prolong quality of life for patients and their families.

■ RONALD T. RAINES

The plasma membrane has evolved to keep the outside out, and the inside in. This barrier is not, however, impenetrable. Small molecules with the proper attributes can burrow through the lipid bilayer that encases human cells. Even some proteins and nucleic acids can be taken up into the cytosol by specific transporters. Macromolecules that are cationic (or made to be so) can enter endosomes readily by availing Coulomb's law and the anionic character of the plasma membrane and its glycocalyx. The interior of an endosome is, however, topologically equivalent to the outside of the cell—no membrane need be crossed to enter, and little utility is gained

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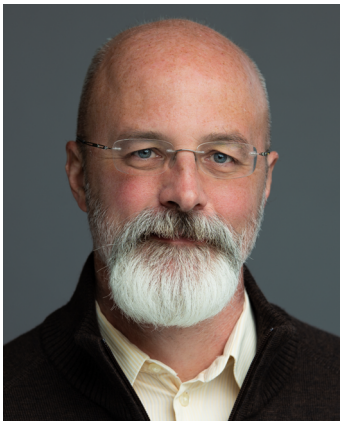
by entry. For most macromolecules, the cytosol and nucleus are out of reach.

The inability of macromolecules to gain access to the cytosol and nucleus has consequences. For example, about 80% of extant drugs are small molecules, half of which act on extracellular targets (e.g., GPCRs) and half of which act on intracellular targets (e.g., protein kinases and nuclear hormone receptors). In marked contrast, virtually all macromolecular drugs act on extracellular targets (e.g., tumor antigens). Clearly, their barrier to entry is leaving much on the table.

This special issue of *Bioconjugate Chemistry* highlights the enormous progress that is being made in the cellular delivery of macromolecules. An ideal delivery method is agnostic—applicable to a large ensemble of proteins or nucleic acids or nanoparticles. Any ensuing conjugate should not impose perturbations that are deleterious to macromolecular structure or function within the cell. And, a method should be efficient in delivering its cargo to the cytosol without incurring cytotoxicity. As described by Vince below, the authors of the articles in this issue report on extraordinary successes achieved by employing clever conjugations and packages, some inspired by Nature, others benefiting from an ever-growing toolbox of chemoselective chemical reactions.

In 1959, the Luna 3 probe delivered the first glimpse of the "dark" side of the moon. Sixty years later, we have a choice of methods for delivering macromolecules to another erstwhile inaccessible terrain—the cytosol. Some ramifications are obvious, others not yet imaginable. As Theresa conveys so compellingly, the ultimate beneficiary will be the human condition.

VINCENT M. ROTELLO



When people think of therapeutic delivery, the first thing that usually springs to mind are barriers. As Ron points out, getting things into cells is relatively easy—endosomal uptake is readily achieved through use of (generally) cationic tags (e.g., cell-penetrating peptides) or carriers. Having this as the final outcome can be quite good, for example, in vaccine delivery or lysosomal storage diseases. For most applications, however, you want to get the biologic into the cytosol and often into the nucleus. What many people do not realize is how little of the endosomally uptaken nucleic acids or proteins actually make it into the cytosol. "Success" is often a few percent (or even less) of the payload making it to the cytosol. With these numbers, it is clear that there is room for improvement.

In this issue we have many of the researchers leading the charge to make biologics delivery a viable therapeutic and imaging tool. Mastrobattista, Segura, Wei, and Narain present new strategies for nucleic acid delivery, with Reineke demonstrating the role of additives in enhancing delivery of large plasmids. The equally challenging goal of protein delivery is addressed by new results from Sullivan, Cheng, and Hackenberger, with Futaki presenting an intriguing approach that uses metal complexes to enhance cellular uptake of octaarginine tags.

Biologics delivery is a fast-moving field, so we are fortunate to have Reviews from Such, Pei, and Pellois taking a hard look at endosomal escape, including characterization of pathways and affinities. We also have Reviews from You, Gao, Pun, Grinstaff, and Tian on synthetic vectors for nucleic acid delivery, while Ghandehari focuses on matrix-mediated viral delivery. Protein/peptide delivery is likewise an important area, ably covered by Yin.

In my mind, intracellular biologics is the next "big deal" in therapeutics, as can be witnessed by the diversity of researchers and start-up companies focusing their efforts in this field. I greatly enjoyed working with Theresa and Ron on putting this issue together, and we all hope you find it stimulating and helpful.

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