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# Spherical Nucleic Acids: Adding a New Dimension to Nucleic Acids and Clinical Chemistry

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Spherical nucleic acids, or SNAs (1), were first introduced in our 1996 paper in *Nature* featured here. The original nanoconstructs were composed of gold nanoparticles modified with a layer of DNA at a density high enough to force the strands upright, forming a shell that adopted the spherical shape of the nanoparticle template. Since then, many other core and nucleic acid compositions have been synthesized and explored. SNAs were born from an idea I had after attending a seminar on colloidal crystallization. Researchers were exploring ways of engineering such crystals on the basis of electrostatic and simple small-molecule interactions between particles. I imagined a new type of chemistry in which the interactions between nanoparticles could be programed using sequence-specific DNA interactions—a system in which the particles could be viewed as atoms and the DNA as programmable bonds between them, offering an almost limitless number of possibilities for controlling the assembly of particles into hierarchical materials, crystals in particular. To test this concept, I asked then-Northwestern graduate students Bobby Mucic and James Storhoff to seek out Bob Letsinger, the pioneer of oligonucleotide synthesis, and learn how to make strands of DNA that could be chemically immobilized on gold. Soon after, Bobby and James synthesized two sets of gold particles, each approximately 13 nm in diameter, with DNA strands linked to their surfaces via thiol adsorption on gold; they observed a reversible red-to-blue color change when these particles were mixed with the appropriate complementary linker, which we now know indicates the assembly of these particles via programmable hybridization. These nanostructures have since ushered in whole new areas of materials and clinical chemistry.

Initial discoveries involving the color change associated with SNA assembly led to my group's development of simple biosensing schemes based mainly upon visualization or ultraviolet-visible spectroscopy; but as we learned more, we devised ones with increased complexity and sophistication. For example, we found that SNAs displayed sharp, highly cooperative melting transitions and enhanced binding properties (compared to the same sequence of linear nucleic acids). Not long after we synthesized the first SNA, we

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introduced the SNA-based scanometric and biobarcode assays in 2000 and 2003 papers in *Science*, respectively (2, 3). These papers and subsequent related ones showed the power of utilizing well-characterized nanomaterials as probes for the detection of biomolecules at analytical sensitivities rivaling and, in some cases, even surpassing PCR and ELISA. Taking what we had learned from a decade of using SNAs in extracellular biological environments, we then envisioned how SNAs could be used for monitoring and ultimately regulating what goes on inside living cells. Both SNAs and cell walls are highly negatively charged, yet we made the surprising observation that SNAs naturally entered many cell types in high quantities without the use of positively charged transfection agents. We tracked their mode of entry and determined that it was based upon scavenger receptor and caveolin-mediated endocytosis. This understanding made the development of SNAs as highly potent, nontoxic, and nonimmunogenic classes of intracellular gene regulatory (antisense (4) and small interfering RNA (5)) and immunomodulatory materials (6) possible.

By 2012, it had become clear that SNAs constituted a new form of matter (1)—spherical forms of nucleic acids with no known natural equivalent and with properties vastly different from those of their linear counterparts that would make them exceedingly useful in clinical medicine. Many different classes of SNAs, defined by core and nucleic acid shell composition, now exist and are the basis for commercial clinical products and systems that are improving and, in certain cases, saving the lives of patients. The FDA-cleared Verigene™ system, now a part of Luminex's product portfolio, represents the first commercialized molecular medical diagnostic system in the modern era of nanotechnology, and it is used in over half of the nation's top hospitals with capabilities in rapid point-of-care ultrasensitive nucleic acid analysis. SNA-based SmartFlares™, which have been commercialized by AuraSense with Merck Millipore, can be used intracellularly to identify and quantify genetic content at the level of a single *live* cell. The SNA™ therapeutic platform for gene regulation and immunomodulation is being commercialized by Exicure via several key partnerships. SNAs are useful therapeutic modalities because they can be delivered to almost any tissue, including topically to the skin and systemically to the brain. Promising results from first-of-their-kind human clinical trials have pointed to the suitability of a SNA-based lead compound, AST-005, for the topical treatment of psoriasis and proved SNAs to be a class of nucleic acids with privileged access to tissues and organ systems that linear nucleic acids normally do not enter, major milestones in nucleic acid drug development (7). In addition to being heavily used within the field of medicine, SNAs illustrate a very important point—structure matters. In this case, when arguably one of the most important classes of molecules chemists have learned to synthesize and mass produce—nucleic acids—is restructured on the nanoscale, a new material with previously unobserved and enabling properties in biology and medicine emerges.

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## References

1. Cutler JI, Auyeung E, Mirkin CA. Spherical nucleic acids. J Am Chem Soc 2012;134:1376–91. [PubMed: 22229439]
2. Taton TA, Mirkin CA, Letsinger RL. Scanometric DNA array detection with nanoparticle probes. Science 2000;289:1757–60. [PubMed: 10976070]
3. Nam JM, Thaxton CS, Mirkin CA. Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins. Science 2003;301:1884–6. [PubMed: 14512622]
4. Rosi NL, Giljohann DA, Thaxton CS, Lytton-Jean AKR, Han MS, Mirkin CA. Oligonucleotide-modified gold nanoparticles for intracellular gene regulation. Science 2006;312:1027–30. [PubMed: 16709779]
5. Giljohann DA, Seferos DS, Prigodich AE, Patel PC, Mirkin CA. Gene regulation with polyvalent siRNA-nanoparticle conjugates. J Am Chem Soc 2009;131:2072–3. [PubMed: 19170493]
6. Radovic-Moreno AF, Chernyak N, Mader CC, Nallagatla S, Kang R, Hao L, et al. Immunomodulatory spherical nucleic acids. Proc Natl Acad Sci USA 2015;112:3892–7. [PubMed: 25775582]

7. American Association for the Advancement of Science. Science Magazine News. http://www.sciencemag.org/news/2016/08/spherical-rna-therapy-shows-promise-against-psoriasis-first-human-trial (Accessed May 2017).