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Interview: An interview with Chad Mirkin: nanomedicine expert

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Chad Mirkin speaks to Hannah Stanwix, Assistant Commissioning Editor

Professor Chad Mirkin received his Bachelor of Science Degree in Chemistry from Dickinson College (PA, USA) in 1986. He holds a PhD in Chemistry from Pennsylvania State University (PA, USA) and was a Postdoctoral Fellow at the Massachusetts Institute of Technology (MA, USA). He subsequently moved to Northwestern University (IL, USA) as a Professor of Chemistry in 1991. In 2004, Professor Mirkin became Director of the International Institute for Nanotechnology and holds that post currently. He is also the George B Rathmann Professor of Chemistry, Professor of Chemical and Biological Engineering, Professor of Biomedical Engineering, Professor of Materials Science and Engineering and Professor of Medicine at Northwestern University. Professor Mirkin is a member of the National Academy of Engineering, the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He is also currently a member of President Obama's Council of Advisors for Science and Technology. Professor Mirkin is best known for his work on spherical nucleic acid nanoparticle conjugates and the invention of Dip-Pen Nanolithography. He has received over 70 awards and accolades for his accomplishments. Currently, based on total citations, Professor Mirkin is one of the most cited chemists and nanomedicine researchers in the world. He has authored over 500 publications, as well as over 440 patents and applications worldwide.

What took you from a background in chemistry in to the fields of nanoscience and medicine?

It is natural if you think about it, because chemists make things. To make an impact in any technology area you have to have new materials and create new capabilities. I got very interested in miniaturization in chemical systems when I worked as a post-doc at the Massachusetts Institute of Technology (MA, USA) under the guidance of Professor Mark Wrighton, looking at the chemical consequences of highly miniaturized systems. At that time, 'highly miniaturized' referred to the microscale, not the nanoscale, size regime. Wrighton made all sorts of interesting microchemical devices that had impact in the development of chemical sensors and soft-electronic structures. When I came to

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Northwestern University (IL, USA), I became very interested in related topics. That was when scanning probe microscopy systems were becoming available commercially, and we were able to obtain an atomic force microscope at Northwestern. I taught myself how to do atomic force microscopy (AFM) and then naturally got very interested in how things behaved on that scale. Pretty soon, we became very adept at doing scanning probe microscopy and that led to a lot of interesting discoveries, including the invention and development of Dip-Pen Nanolithography (DPN).

One of your earliest & most renowned discoveries was finding that gold nanoparticles could be used to detect DNA. What led you to investigate this area?

The reason we put DNA on nanoparticles initially was to create a new way of making materials. The idea was to use DNA to transform nanoparticles into programmable atoms, and then use them to prepare well-defined lattices. Early on, we discovered that when you do that, you naturally make a new material that exhibits new properties. For example, the property changes observed as nanoparticles go from a dispersed to an assembled state can become the basis for a diagnostic event. With gold, the property change was a plasmon resonance shift, which gives rise to a spectacular color change that allows one to create the equivalent of a litmus-like test for DNA.

My research is almost always driven from fundamental curiosity. How can we do things differently? How can we make things that haven't been made before? Then, once we have made new materials, new structures, or new chemical systems, what are their properties? If we identify unusual properties, how can we use them to develop novel applications? In the case of gold nanoparticle assembly, it was obvious that we had the basis for a new and relatively simple diagnostic system. We then began to learn a lot about medical diagnostics and the commercial drivers in that field – we wanted our systems to be fast, inexpensive and simple because most of the diagnostic systems at the time, and in fact today, are large, cumbersome systems, and therefore, diagnostic screening has to be carried out at remote laboratories. But what if you had the technology and capabilities to do that closer to the point-of-care – in hospitals or in a doctor's office and maybe one day in the home? That becomes possible when you start thinking about simple colorimetric systems. Then you ask, is it possible to get analytical improvement in terms of sensitivity and selectivity? That turns out to be possible with these types of nanostructures – the ones we've developed.

I want to make the point that not all nanoparticles are created equal, and it is important not to assume all nanoparticle-based diagnostic and therapeutic systems possess the same set of advantages. Just like with chemical systems, each system has different properties; some provide advantages, while others don't. There is nothing inherently more useful about using a nanostructure for a medical application versus a traditionally-used molecular material. But there are some things that you can make with nano-technology that no molecular counterpart can compete with.

I think what we are really known for, and what we should be known for, is the introduction of the concept of the spherical nucleic acid (SNA) construct. The idea that one can use gold and other materials, such as silver, iron oxide and even core-less structures, to arrange nucleic acids into a densely-packed, highly oriented form, creating a structure with properties completely different from those of other forms of nucleic acids, is quite powerful. Those differences, in the case of diagnostics, include the ability to bind a complementary nucleic acid 100-times more tightly than the same free oligonucleotide in solution. The incredibly sharp melting transitions, exhibited by probes based upon these SNA structures, make them much more selective than any known molecular probe. Furthermore, we have the most highly selective diagnostic systems out there. Those advances form the basis for the Verigene[®] system at Nanosphere (IL, USA), which is a US FDA-cleared, commercial diagnostic tool. It is the first point-of-care, medical diagnostic system enabled by nanotechnology, and it is beginning to be used all over the world. It allows panel assays to be performed in hospitals, rapidly – in less than 90 min – and inexpensively because it does not require PCR. That's pretty exciting!

This technology is now used in practice, in hospitals & clinics worldwide.

How does it feel to see your discovery being so widely used?

It's extremely exciting to think that real people are now routinely tested using this technology! NOVA (PBS, VA, USA) did a story in their episode called 'Making things smaller' where the host visited Nanosphere, the company that commercialized this technology, and was tested for a genetic predisposition to blood clotting and the genetic marker for an inability to metabolize warfarin, the treatment for blood coagulation. It turns out that one in eight people have this genetic predisposition to blood clotting, and one in three people have an inability to metabolize warfarin. So, in real time, they do this test on the host, and he's got both! It wasn't great news for him, but it was certainly a statement of the power of the technology!

Your research group is currently working on a wide variety of different projects, including nanoflares. How are these particles different to other nanoproboscopes?

SNAs, a class of nanoparticle – nucleic acid conjugate, are naturally taken up by cells. That's an unusual property. Cells do not naturally pick up linear DNA because the cell membrane is negatively charged. But if you take the same oligonucleotides that won't go into cells and arrange them into a densely-packed, highly oriented form on the surface of a nanoparticle, they are taken up better than anything known to man. The cell recognizes them and picks them up very rapidly.

The way it works is that the particle with this dense array of oligonucleotides can act as a scaffold to pick up scavenger proteins, which trigger endocytosis. The oligonucleotides alone are not very effective at doing that. It's really remarkable – take a cell culture and feed it enormous concentrations of DNA, and the DNA will not go into the cells. If you take that same type of DNA and put it on the surface of a particle it goes in like gangbusters and is

effective as a therapeutic even at one hundredth the concentration that is typically applied! That is a truly important observation, not just in nanoscience, but in biology and chemistry in general. Essentially, it teaches us that, if you take one of the most important molecules ever synthesized and mass produced – DNA – and you simply arrange it on the nanoscale in a high-density, highly oriented, 3D format, it behaves completely differently from any other form of matter ever studied.

The advantage, of course, is that SNA technology enables all sorts of new constructs capable of performing intracellular assays and regulating gene expression. These are the only single-entity gene-regulation components out there. Current gene-regulation schemes rely on making polymers that trick cells into picking up DNA and RNA – these polymers, however, are typically toxic. By contrast, SNAs can enter cells on their own and be used to knock down genes inside cells without eliciting a cellular immune response. If you put fluorophores in the form of NanoFlares™ (AuraSense, IL, USA) on SNAs they interact with target DNA or RNA sequences inside the cells, and through release of these fluorophores one can track and differentiate live cells based upon genetic content. There's no other way to do that! Nanoflares are commercialized, and they are going to have a big impact on the research and medical diagnostic communities.

All of these advances are based upon the idea that SNAs are extremely important, they have properties that are very different from either the nanoparticle or the nucleic acid alone, and those properties enable applications that are really quite critical in terms of solving some of the most pressing problems in biology and medicine. In the case of diagnostics, SNAs are enabling point-of-care detection; in the case of therapeutics, they are enabling a new gene regulation platform that will allow us to target all sorts of diseases that have a genetic basis including many forms of cancer, and cardiovascular, neurodegenerative and skin diseases.

Generally, in the field of nanomedicine, what do you think the most exciting developments have been?

There are many exciting developments. I think that the work that Professor Joe DeSimone (University of North Carolina – Chapel Hill, NC, USA) is doing is quite important. His group is using printing and embossing technologies to make molds that produce polymer particles that mimic almost any living entity or particle. Using it, he has made mimics of red blood cells and viruses that are very important in developing new types of therapeutics, especially in the vaccine area. This is a very clever innovation and extremely exciting.

What areas of nanomedicine are you & your group currently working on?

We are going to pursue the SNA construct to the fullest extent. When you think about what linear DNA has done for life and for the world, it's truly extraordinary. The spherical, 3D version of this incredible building block has a chance to do even more from chemical, biological and medical standpoints.

What areas of your research are you most excited about?

It's hard to say – you are asking me to pick one of my children! On the lithography side of things, we have a paper that was recently published online where we introduce a novel nanocombinatorics technique that can be used to print codes made out of biological structures on surfaces. These features can generate cues that influence how stem cells differentiate. So now, we can begin to uncover the lock and key processes that control and regulate how a stem cell chooses to become a neural, bone or muscle cell. These are pretty exciting new capabilities that are only possible when you can controllably print biological materials on the nanoscale, but over macroscale areas.

Your contributions to science are not just in the field of medicine, but also nanotechnology & chemistry, namely the development of Dip-Pen

Lithography. Why did you choose to investigate this area?

With DPN, there was a bit of serendipity. At the time, we were studying water transport. When you do an AFM experiment in air, water collects at the point of contact between tip and surface. We were the first to image this meniscus – the droplet of water that is left behind when you bring the tip into contact with the surface and then pull it away. We discovered that when you do an experiment, one of two things always happens: water is either depleted from the surface to create recessed areas or deposited on the surface to create metastable adlayers. These eventually disappear as the system equilibrates. We started thinking about this from a chemical standpoint and found that we could put molecules on the tip that could be transported through this meniscus, chemically react with the surface and allow us to create stable molecular monolayers. That was the birth of DPN. It turns out one not only can use an AFM tip to write molecular and materials features but also can use the humidity in the environment to regulate the process – if one is using water-soluble molecules such as DNA, one can increase the humidity to facilitate transport.

What has been the highlight of your career so far?

My career has been an odyssey focusing on developing chemical and surface analytical tools for controlling the architecture of molecules and materials on the sub-100-nm length scale. There have been too many highlights to count! We now have over 440 patented inventions that have come out of my laboratory, we have founded four companies and published hundreds of manuscripts. I am extremely proud of all of these accomplishments, and the brilliant students and post-docs, who have helped make these ideas a reality. I am very excited about the SNA nanostructure work, and I think it is going to be extremely important. It forms the basis for major discoveries and technologies that are being used in over 20 different countries to diagnose and treat patients on a daily basis – it is saving lives.

What would you most like to achieve in the field of nanomedicine?

I believe that the next stage of SNA development is going to be its widespread clinical validation as a fundamentally enabling platform for gene therapy for the treatment of a wide variety of diseases and disorders. Gene regulation is an incredibly powerful concept, but in

reality it has not come anywhere close to its full potential for several reasons. Traditional gene therapy approaches utilize nucleic acids, which are inherently unstable and do not enter cells on their own. This necessitates the use of highly toxic co-carriers that often stimulate an immune response. By contrast, with SNA nanostructures, co-carriers are not needed for them to enter cells, and they are also inherently more stable because their dense and highly oriented DNA shell protects them from nuclease attack. They also do not elicit an immune response; their structure allows them to bypass the enzymes that trigger it. We have recently obtained extremely powerful results showing cellular entry and gene knockdown in animals, and now our sights are set on moving the SNA construct to clinical trials in humans. If such amazing results continue to be seen, SNAs have the potential to revolutionize the medical field, offering treatment options for almost any disease with a genetic basis, including many forms of cancer!