Interview

From traditional polymer science to nanomedicine: the interplay between disciplines to drive innovation

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Professor Joseph DeSimone speaks to Hannah Stanwix, Assistant Commissioning Editor

Professor Joseph DeSimone attended Ursinus College (PA, USA) where he received his Bachelor of Science Degree in Chemistry. He completed his PhD in Chemistry in 1990 at Virginia Polytechnic Institute and State University (VA, USA). Professor DeSimone moved to the University of North Carolina at Chapel Hill (UNC-CH; NC, USA) where he was Assistant Professor of Chemistry until 1994. He was appointed Mary Ann Smith Professor of Chemistry at UNC-CH and Professor of Chemical Engineering at North Carolina State University (NC, USA) in 1995 and subsequently became William R Kenan Jr Distinguished Professor of Chemistry at UNC-CH in 1999. He is currently the Chancellor's Eminent Professor of Chemistry at UNC-CH and the William R. Kenan Jr Distinguished Professor of Chemical Engineering at NC State. In 2004, Professor DeSimone founded Liquidia Technologies (NC, USA) which received the first ever equity investment by the Bill and Melinda Gates Foundation in a for-profit biotechnology company. He has received over 50 awards and accolades throughout his career, including the 2008 Lemelson-MIT Prize. Professor DeSimone has authored over 290 papers, as well as issuing 130 patents.

■ How did you first get involved in the field of nanomedicine & generally science at the nanoscale?

It has been an interesting road here. For my graduate PhD work, I worked in the area of lithography, which is the backbone of the microelectronics industry. I made new photoresists for making better computer chips as part of my PhD thesis. For the first 15 years of my career, my research interests were heavily focused on areas of polymer science that had nothing to do with medicine. I had an overture from a colleague in the school of medicine, at the University of North Carolina (NC, USA), Rudy Juliano, to help deliver a cargo for gene therapy. He is the one that brought me in to the field. Juliano is a world-renowned researcher in nanomedicine. The approaches we used in the collaboration were based on the traditional ways of making nanoparticles at the time, which involved emulsion polymerization techniques. When we studied the literature to see how we could help, I started to realize that people were using emulsion techniques for nanomedicine and I was struck by the fact that, to me, these emulsion techniques are really cousins to paint technology. Here, I was delivering DNA, the most exquisite and sophisticated molecule that I had ever worked with and we were going to deliver that with a cousin to paint. I thought there had to be a better approach. Given my history in graduate school with lithography, and realizing that the current research in my laboratory was starting to use soft lithography to make particles, I thought there was a great opportunity to bridge these experiences together to drive the use of precision particles for use in medicine. It was a combination between timing and history. The history of lithography, getting pulled into medicine and recognizing the gulf between paint and gene therapy and starting to make particles, all culminated in us developing particle replication in non-wetting templates (PRINT™).

■ You & your group are currently working on soft lithography & one of your breakthroughs has been the development of the PRINT method. What led you to investigate this area?

This is another interesting story. I was selected to participate in the Defence Science Study Group, a Defense Advanced Research Projects Agency (VA, USA) program, which selects approximately 20 young faculty members to immerse

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themselves into the Department of Defence research needs and culture. It was a great group of people, some of the best people in science today, for example Angie Belcher (Department of Material Science, Massachusetts Institute of Technology [MIT], MA, USA), Jennifer West (Department of Biomedical Engineering, Rice University, TX, USA, now at Duke University, NC, USA), Steve Quake (Department of Applied Physics, Caltech, CA, USA, now at Stanford, CA, USA), among others. We spent 40 days together over a 2-year period. In that environment I got to know Quake really well. Quake was a pioneer in microfluidics. That is basically an offshoot of what he did with George Whitesides (Department of Chemistry, Harvard, MA, USA), to make microchannels to do lab-on-a-chip. I asked Quake what the number one materials science issue is that he faces. I like to ask people in different fields open-ended questions to find out where we can bring our 'toolbox', the toolbox being expertise in polymer science. Quake said unequivocally that it was the solvent resistance of the microfluidic device. He was using silicones as the main materials to form the lab-on-a-chip microfluidic devices. Silicones are really wonderful materials but they are not solvent resistant, they swell in almost every organic solvent. He wanted to do some PCR-like experiments and needed a chip with the ability to use organic solvents. So within just a couple of months we came up with an alternative material, based on something we were making called 'liquid Teflon®'. It was an alternative material for microfluidics. It made a wonderful chip that looked just like a silicone chip but it was made out of a fluoroelastomer and it solved all of the solvent-swelling issues. That material has just been selected by the Jet Propulsion laboratory (CA, USA)to be on the next Mars module, for the search for life on Mars. It's not a really big market! But it is a high performance material. So then I started looking at what Whitesides was doing in the soft lithography field. I saw that they were making microfluidics and stamping and moulding and that those techniques are also riddled with solvent swelling issues. We decided to go in there with a different approach for making these structures and we published a paper in *Angewandte Chemie* about moulding patterns on surfaces. Then we realized we could actually remove something called a flash layer, so instead of just molding a film where you have a topological pattern on the top of a surface, we realized that we could fill these cavities to the brim of the cavity without interconnecting the features. This really led us to making the particles.

It all started coming together very quickly. One of the key things is controlling chemical composition. In emulsion techniques you have partition coefficients and it is really difficult to get what you want in the particle versus the continuous phase in the emulsion because of partitioning. When you simply mold, it is a lot easier to control composition. So it was initially driven by composition control and the uniformity of the particles was second. The fact that one can now change shapes and look at the implications of that all came together very quickly.

■ **How quickly do you see the medical applications of PRINT developing?**

We formed a company (Liquidia, NC, USA) in 2005 and that company now has 60 employees and has raised US$60 million. We have now converted the technology to a GMP-compliant technology and that allows us to put products in the clinic. We actually have our first product in the clinic already. That went in to the clinic in 2011 and our first paper was published in 2005, so that is pretty quick.

We have a significant focus on vaccines with three different major classes of vaccine, a significant focus in respiratory inhalation products and a significant focus in oncology. We are doing proof-of-concept in about a dozen other areas.

■ **One of your earliest & most renowned discoveries was the invention of an environmentally friendly method to make fluoropolymers & high-performance plastics, such as Teflon. What prompted you to investigate this area?**

That was the first part of my career, focused on more environmentally friendly methods of making polymers. One of the polymers we happened to make in carbon

dioxide was this liquid Teflon that we made into that microfluidic device. That liquid Teflon became the first generation of our PRINT moulding technique.

■ What other areas of research are you & your group pursuing?

Approximately 10% of the laboratory is working on the materials science side of PRINT, for example nonbiofouling surfaces for marine coatings and medical devices and some work in battery applications. It is a small portion of our laboratory but it is important because it is the background for a lot of what we do.

■ Is there a particular application of PRINT that you are most excited about?

I think it is unquestionably the area of vaccines. I had the privilege of speaking with Bill Gates (Founder and fomer CEO of Microsoft) approximately 2 years ago. Gates used to talk about the magic of software, and now he talks about the magic of vaccines. When I was introduced to Gates and he asked what we do, I explained that we are using the manufacturing tools of the computer industry to make better vaccines. That was a rifle shot at Microsoft (WA, USA) and The Gates Foundation (WA, USA). That culminated in the first ever equity investment, a US$10 million equity investment by The Bill and Melinda Gates Foundation in Liquidia. Therefore, they are part owners of our company now. That is driving a commitment to not only focus on technologies, such as vaccines and medicines, for the developed world but also on global access for the developing world. It really is a nice blend for us to be able to commit to both. We are now designing vaccines for malaria, dengue fever, prostate cancer and pneumococcal bacteria. So we are working in a whole host of different areas. It is a really exciting technology and I think it is going to be very important.

We have a separate major initiative in inhalation products. Inhalation products are some of the largest products in the pharmaceutical industry and if you look at dry powder inhalers for instance, the particles have no control of size and shape and are very poyldisperse. They deposit in the airways in a very polydisperse manner. We can now mold several classes of pharmaceutical ingredients into precise sizes and shapes that range from small molecules to monoclonal antibodies and enzymes. So we are now delivering biologicals to the airway. There is no inhaled monoclonal antibody on the market today. As big as the biotechnology industry is, there is a lot of interest in getting biologicals either systemically delivered via the airway or locally delivered. That is a big focus for us.

Finally, my academic laboratory is fortunate enough to have one of the nine centers for Cancer Nanotechnology Excellence, funded by the National Cancer Institute (Washington DC, USA). We have hundreds of animals underway in preclinical trials focused on nonsmall-cell lung cancer, ovarian cancer, pancreatic cancer and breast cancer. We are working with researchers at the MD Anderson Cancer Center (FL, USA), Memorial Sloan-Kettering Cancer Center (NY, USA) and the Lineberger Comprehensive Cancer Center (NC, USA). There are a lot of different cancer applications underway.

■ Has the development of PRINT been the highlight of your career so far?

The PRINT story is unfolding in front of us. I was fortunate to be part of a team that developed a medical device, involving a bioabsorbable stent, a coronary heart stent that goes away after 18 months. We launched that company and it was bought by the Guidant Corporation (IN, USA) and is now part of Abbott Laboratories (IL, USA). There are almost 1000 people with these stents inside them. The stent technology certainly has had more traction in the clinic, but I think the implications for PRINT in vaccines, cancer and respiratory disorders will surpass that by severalfold. We are privileged to have the resources to pursue this and we have assembled a fantastic team but there is a lot of work to do.

■ Finally, where do you see your research & the nanomedicine field in general in 10 years time?

I think there are a lot of exciting things out there. I think the world's investment in nanomedicine is going to pay off. Looking around, beyond my laboratory, you see what is going at Northwestern University

(IL, USA) with Chad Mirkin and his spherical nucleic acids; I think that is going to be a major breakthrough. I think what Robert Langer (Department of Chemical Engineering, MIT) and Omid Farokhzad (Department of Anesthesia, Harvard Medical School) are doing and how they are out of the gates now with oncology therapies and in the clinic is really exciting. Samir Gambhir at Stanford University and Paula Hammond at MIT both have some really great projects going on. I think all of this work is going to have a big impact.

Financial & competing interests disclosure

J DeSimone is a founder of Liquidia Technologies. He is a member of the Board of Directors and a consultant, and also has a financial stake in Liquidia. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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