FEATURE ARTICLE

The Role of Diversity in Commercializing Basic Science

Convergence and diversity are the keys to innovation in science.

Joseph M. DeSimone

I have spent my career as a university-based researcher. It is a privilege to be at a university because we get to choose what we want to work on. Obviously, we have to pitch our projects to generate resources, but we get a chance to work on some of the biggest problems society is faced with, including energy, food, and national security, and some of the biggest opportunities, such as electronics and 3D printing. We're focused on trying to improve the human condition, and we can take the long view. It's really a privilege to have that opportunity. Nothing captures the real value of that opportunity more for me and my students than the words of Henry Rosovsky, former dean of Arts and Sciences at Harvard University: "Research is an expression of faith in the possibility of progress. The drive that leads scholars to study a topic has to include the belief that new things can be discovered, that newer can be better, and that greater depth of understanding is achievable. Research, especially academic research, is a form of optimism about the human condition."

The challenge, and the opportunity, today is convergence, which I define as the fusion of life sciences, physical sciences, and engineering. It's challenging to pursue convergence in the university setting because we're typically trying to do 21st-century science in an 18th-century organizational structure.

It's ironic that the only place entropy does not seem to be in force is at universities: there's very little mixing between departments and there are a lot of silos. We end up working very hard to break down those silos and to facilitate internal connectivity. I would argue that today scientists need to think even beyond the sciences and engineering—convergence extends to the social sciences, the humanities, and even the performing arts.

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Nobody got this better than Steve Jobs: "It's in Apple's DNA that technology alone is not enough; it's technology married with the liberal arts, married with the humanities that yields a result that makes our heart sing." It's that sort of convergence that I think is driving a lot of industry today. One of the questions I ask myself now is, can any executive leadership team today be successful without a designer on the executive team? And yet few companies have made that commitment. Along these lines, it's interesting to look at who Apple is hiring. *Fortune Magazine* made a list that provides some insight into where Apple is going as a company. Recent hires include the former CTO of Adobe, the Former CEOs of Yves Saint Laurent and Burberry, medical device scientists, and people thinking about non-pharmaceutical methods for controlling sleep.

It's important to note that this convergence is not just about crossing disciplinary boundaries. It's also about developing cross-cultural understanding. I recently published an op-ed in *Science Translational Medicine* about this.[1] Those with different cultural backgrounds approach problems differently, and these different approaches must be respected. A student that has come from a background of poverty will think differently about solving problems than somebody who's grown up with a lot of money, for example.

Both of those perspectives are really important to have around the table. Diversity is a fundamental tenet of innovation. We learn the most from those with whom we have the least in common. To maximize learning or to catalyze innovation, we need to create the necessary chemical potential, if you will. The greater that potential—the greater the diversity around the table, and hence the potential for fruitful reactions and interactions—the more opportunity there is, for learning and for invention. I think of this a lot when we are establishing design teams: it's not just disciplinary diversity but diversity in the broadest sense that provides the secret sauce for innovation.

[1] J. M. DeSimone and C. L. Farrell, "Driving Convergence with Human Diversity," *Science Translational Medicine* vol. 6, no. 238 (2014), p. 238ed11.

That's the context for the different work that has come through my group: our diversity, in disciplinary approaches and broader life backgrounds, enables convergence and drives invention and innovation.

Entrepreneurship and Convergence

I've had the privilege to spin out a number of companies at the University of North Carolina and NC State, and every one of them has resulted from different disciplines coming together.

Of course, academics focus on publishing and on the peer review process. Entrepreneurship is peer review on steroids. I think it makes our science better when people start laying down real money to bet on the future of our ideas. It requires a level of due diligence I think is quite important. It helps academics improve their grant applications, and it certainly creates an opportunity for scale-up, which is something academia does not do. Companies are really important for translating research into practice.

Building a company is also a great validation of your work. As an academic, nothing is more reassuring than when somebody repeats your work. If you're doing things that are really different and not incremental, sometimes you feel like you're in a really tall tree and the wind is blowing, and it's nerve wracking. But nothing shakes out the truth like validating your science by scaling it up. It's an important self-check that can't be achieved any other way in the academic science world.

What we try to do in a university setting is apply things that I think a lot of you in the business world do. We frequently apply Jim Collins's hedgehog concept in deciding what to do, trying to look at opportunities through three lenses.[2] First we ask, what are we passionate about? What keeps us up at night? The second lens is, what do we think we can be best in the world at? And then, third, we seek to understand the financial implications of our subject. For some ideas, that might be a profit motive; for others, it might be how we're going to deliver a vaccine to the poorest places on the planet in a way that's affordable for those users.

Having an understanding of the financial constraints is really important. It's really easy to be creative if you don't have a financial constraint. You've got to be a heck of a lot more clever to be creative within financial constraints. Constraints make entrepreneurship a higher calling in a lot of ways.

Pursuing BHAGs

Jim Collins talks about BHAGs—Big Hairy Audacious Goals. He talks about good BHAGs and bad BHAGs. If you go through the proper analysis, you can make a run at a good BHAG. We've tried to do this over the years, and we've tried to do it in a number of different sectors, from bioabsorbable stents to creating clean tech, from using supercritical CO_2 to nanobiotech to medical devices to 3D printing (Figure 1). It sounds like a pretty disparate group of topics, but there are common themes: clever polymer science and convergence.

[2] Jim Collins, *Good to Great: Why Some Companies Make the Leap and Others Don't* (New York: HarperBusiness, 2001).

Entrepreneurship is peer review on steroids.

Let me walk you through a few examples and try to demonstrate the connections.

Liquid Teflon and Batteries

Early in my career, back in the early 1990s, my group spent a lot of time trying to use supercritical carbon dioxide as a solvent for polymerization reactions. We had a terrific partnership with the DuPont Company; they would provide monomer for us premixed in CO_2, and we used it to make a lot of new fluoropolymers and do a lot of polymerization kinetics.

One of things we worked on with DuPont was polymerizing tetrafluoroethylene using supercritical CO_2 and a range of copolymers. One of the polymers that we made this way was an amorphous fluoropolymer created from a perfluoropolyether generated by mixing fluoro olefins with oxygen. You do that very carefully, and it forms polymeric peroxides that photochemically degrade and kick out small molecules like difluorophosgene. These would recombine to form extremely stable perfluoropolyethers. That's a lot of chemistry, but we refer to that material as liquid Teflon. That material turned out to be really important. We decorated it with functional groups, and we treated it like silicon, but it was perfluorinated, so we could make some incredible fluoroelastomers that were extremely solvent resistant; we could make microfluidics that we could run solvents through that would make silicones swell. In 2006, DuPont built a $60 million plant in Fayetteville, North Carolina, to produce it.

A couple of other major developments came out of this work. One came from mixing polyethylene glycol with perfluorinated polyethers. Polyethylene glycol is very water soluble while perfluoropolyethers are about as water insoluble as you can get, but we found they are infinitely miscible. We could mix them and make co-networks to form crystal-clear materials that were 50 percent fluorocarbon and 50 percent water-soluble components.

Then we added lithium salts to the binary system, creating a ternary system of lithium salts, perfluoropolyethers, and PEG. We found that these lithium salts were soluble at 15 or 20 percent in a perfluoropolyether, which turns out to be a really interesting electrolyte for lithium-ion batteries. What's really important is that the mixture is completely nonflammable. We're launching a company called Blue Current to exploit this technology.

Our ability to explore and make progress in different areas based on our fundamental work comes back to the idea that diverse groups are poised to achieve innovation. Emphasizing the importance of diverse backgrounds and expertise among group members—and partners, including industry partners—has produced a convergence of perspectives from

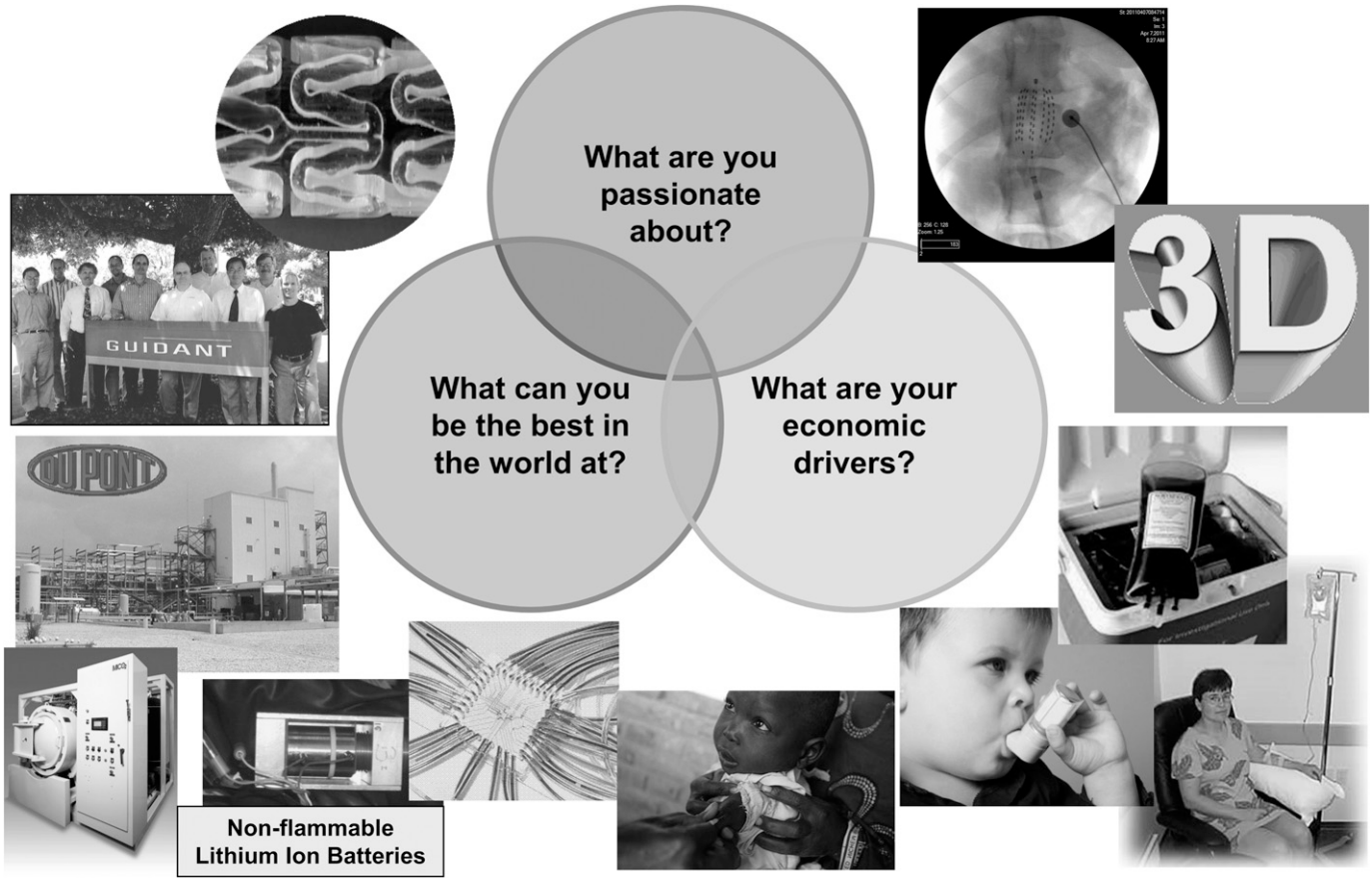

FIGURE 1. Identifying BHAGs by analyzing problems through three lenses

chemistry, engineering, and other areas that has yielded significant progress on multiple fronts.

3D Printing

Another material has opened up a new horizon for us in 3D printing. We've launched a really cool new company in this space backed by Sequoia Capital. We have a 3D printer that works from fundamentally different physics than every other printer, and it allows the printer to go between a hundred and a thousand times faster than any other printer out there.

This printer is going to compete with injection molding for precision and speed, and it's going to do it at room temperature. It will allow a degree of flexibility that will make it possible to throw out the old design rules. Complexity is free with 3D printing. This printer will allow you to print at the speed of manufacturing, and that's going to be a big, big driver going forward.

What will enable this is a convergence of multiple technologies.

3D printing represents opportunity on an awesome scale. With cost barriers to the fabrication of complex things dropping to near zero, a lot of people will be empowered to do exciting things. Today, computation is essentially free; that's happened in our lifetimes. What 3D printing is going to do is make complexity free. If you can achieve that complexity and flexibility at manufacturing-like speeds, it's going to be as transformative as the plummeting costs of computation.

What will enable this is a convergence of multiple technologies. The physics of the printer we've invented is fundamentally different, enabled by breakthroughs in materials and processes. I can't tell you how excited we are about the things we're fabricating this way. It's a big, big breakthrough. And it was enabled by a diverse set of people thinking about something differently, looking at what everyone else had looked at, but thinking about it differently. This also highlights the importance of leveraging diverse expertise and perspectives to accelerate innovation.

We've launched a company, EIPI Systems, to develop and market this technology. The name EIPI comes from Euler's Theorem, which says e**iPi = –1. In wave theory, –1 = 180 degrees; we think this technology is a 180-degree shift in how people will think about 3D printing. Very geeky, but it led to some really good investments, and we're excited about it.

Drug Delivery

Let me walk you through what we've been focused on in the nanoparticle world. What my group is doing is taking some of the advanced lithographic techniques used to make computer chips and adapting them to make new medicines and new vaccines. It's back to convergence: we're bridging semiconductor electronics fabrication with the medical world.

Many of you are familiar with Moore's Law, which posits a doubling of the number of transistors in a given area every 18 months. Back in the early 1970s, the minimum feature size of a transistor was fairly large—a little bit bigger than a red blood cell, or about ten microns. At that size, only about 2,000 transistors could fit on a chip. Today, the minimum feature size is down around the size of a virus particle, around 20 nanometers. At that size, you can fit billions of transistors in the same area.

We're now in a size regime that's very similar to micelles and liposomes, colloidal particles, inkjet-like structures, and it's now appropriate to think about using top-down manufacturing techniques to fabricate dispersed systems.

We developed a technology we refer to as PRINT—particle replication in non-wetting templates. We lithographically define wafers, then we wet them with that liquid Teflon material I spoke about above. We light cure it so it's decorated with acrylic groups, and once we do that, we have a membrane that takes on the desired relief patterns; for instance, we can produce a series of regularly spaced cavities, like a micron-scale ice cube tray.

We use an intrinsically dry roll-to-roll process, which allows us to use a lot of hydrolytically unstable chemistries. This is a scalable process that allows us to control particle size and shape and chemistry, which is a landmark development in itself. We make particles in a lot of different chemistries with a lot of different applications, though we've focused mainly on organics, from organic polymers to particles of enzymes.

The key is that this is a GMP-compliant process—it conforms to the FDA's standards for the manufacture of drugs and pharmaceutical products. The ability to control size and shape and ensure homogeneous products is a key criterion for GMP standards. The FDA hates heterogeneity. The idea of bringing the precision and uniformity of the microelectronics industry to bear on the manufacture of particles has received a lot of support from the agency. I don't know of another platform nanotechnology that has this kind of capability at scale. There are certainly nano products that might be GMP-compliant for one-off batches, but as far I am aware, this is the only platform capability.

We've been working on this process since 2005. We've had particles in a clinical trial; we've scaled up and moved products into the clinic. Via our company, Liquidia, we've invested tens of millions of dollars and made particles that actually go into the clinic to support various clinical trials.

I want to give you a flavor of the kinds of things that my students and the company are trying to address using this platform technology. We are asking all sorts of crazy questions related to the roles particle size and shape play in biological systems. For instance, our airways internalize particles of different sizes and different shapes differently. We are asking about the kinetics, the fate of particles of different sizes and shapes, the different biological mechanisms through which these particles are internalized.

We're doing all sorts of interesting *in vitro* work. For example, we're working with cancer cells to explore how to get particles into cells, so we can take advantage of the cell environment to make Trojan horse–like particles. The idea is to trap drugs in the particles so that they can be delivered directly to the cells where they are needed. The cells gobble up the particles and then the particles fall apart. This offers a really potent way to deliver known drugs, in a way that might evade some of the drug-resistant mechanisms that are on the surface of cells.

It's all *in vitro* work now, meaning cells in a Petri dish. The next step is to go *in vivo*, and for that I'm really fortunate to be at the University of North Carolina at Chapel Hill. It's a biomedical powerhouse, an $800 million research organization that's seventh in the country in NIH funding. UNC's research labs have mouse models of just about every disease known, and we get to work with physician scientists there.

One of the great opportunities for nanotechnology is in the treatment of cancer. The reason is that a lot of tumors—those that are rapidly proliferating—need a nutrient supply and a recruitment of blood vessels. When blood vessels grow quickly, they grow immaturely, and they often have leaks, gaps that are typically 100 to 200 nanometers in size. These gaps are too small for a red blood cell, which is 8,000 nanometers in size, to pass through, but drug molecules can be engineered to be small enough to enter these vessels.

If you deliver a normal small-molecule drug, a drug like Gemcitabine or Paclitaxel, via IV, that drug will go into the circulatory system and diffuse throughout the whole body; its volume of distribution will be the volume of the body. But when you put a small drug molecule into a gargantuan nanoparticle, the drug stays in circulation for the most part: the drug is in the particle and the particle can't get out of circulation except by entering the tumor through the gaps in the blood vessels supplying it. These "big" particles—they're 50 nanometers or 100 nanometers in size—can slip through the leaky vasculature around a tumor, and thus into the tumor, even where red blood cells can't, but they stay in circulation otherwise. In that way, you get a preferential accumulation of chemotherapeutic in the tumor. This is called the EPR effect, or enhanced permeability and retention effect, and this is why nanotechnology is playing such a big role in cancer therapeutics. There is a significant increase in

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survivability when you use nanoparticles to deliver chemotherapeutics.

We're beginning to push the limits of this technology. Research to date has focused on particles that were 80 nanometers in size, whereas my group is now molding particles that are 50 nanometers in size. If you had asked me five or six years ago whether we'd be able to mold 50 nanometer particles using a roll-to-roll process, I don't think I would have said that we could, but we're doing it now.

We are able to use particles of different sizes for different applications, and we're starting to use our particles as a measuring stick to characterize the vascularity of different tumors. Take three different tumor types: ovarian, lung, and epithelial cancers. The particle partition is different for each tumor type because the vascularity of each one of these tumors is different. That's opening up new insights into what kinds of treatments might work and what might not.

So far, we've chosen tumors that permit our nanoparticles to get in: these are tumors that have a rich blood supply, although the vascularity and the pore size are a little bit different for each type. But there are some tumors that are not very porous; one of these is pancreatic cancer. These tumors are as white as your eyeball; they don't have much of a blood supply. Typically, to treat these cancers, people are given small-molecule chemotherapeutics by IV. We would never rely on delivery through nanoparticles because they would never be able to get into the tumor. But unfortunately, when you deliver a small molecule, the drug goes everywhere but the tumor.

We wanted to address this, and we found a solution through convergence. Let me explain. In an earlier life, back in 2001, I was approached by a scientist at Duke, an interventional cardiologist named Richard Stack. He and I cofounded a company called Biostent that developed a fully bioabsorbable drug-eluting stent. It is a plastic-based stent that dissolves after 18 months. The company was bought by Guidant, and it's now part of Abbott. There are about 10,000 people with these stents in them today and we expect FDA approval next year. It's going to be the most important advance in the stent marketplace. I learned a lot about interventional cardiology working with Richard Stack. He could put devices anywhere in the body.

At the same time, at Liquidia, we had begun working with a company called iGATE, where we were using ionospheres to create a mild electric current to drive drugs and particles into the eye, another poorly vascularized organ. We combined catheter-based technologies and ionospheres, and we developed a medical device that sets up an electric field and uses the gradient to drive a charged molecule into a poorly vascularized organ or tumor.

The devices are fairly simple. They're surgically implanted. I have an incredible collaborator, Jen Jen Yeh, who's a physician. She and her students do surgery on mice as well as humans. Mice look really complicated: they're really small. We make these miniaturized devices and we place them on human pancreatic cancer tumors in a mouse model that recapitulates the tumor vascularity of a human.

We have also used this technique to get therapeutic drugs transdermally into inflammatory breast cancer and cancers of the skin, but let me just focus on pancreatic cancer. If you take the standard small-molecule drug Gemcitabine and deliver it via an IV, it's cleared from the blood very quickly: essentially none of the drug makes it into the tumor. But when the same drug is delivered by the new device, essentially all of the drug goes into the tumor. We are able to provide local delivery of the drug to the tumor. We physically drive the drug into the tumor using the electric field, and this yields huge dividends. We have seen tumor regression achieved simply by infusing known drugs directly into the tumor using the device.

We're very excited about thinking about this problem from an engineering point of view. The idea is to use engineering technologies to make a difference in biological systems. We just launched a new company, Interventional Oncology, to move the concept forward. We think there are opportunities in a whole host of other cancers as well, which we're beginning to move forward.

Conclusion

Each of these examples illustrates the potential for different fields to come together to tackle difficult problems. It really takes a talented group of individuals with a diverse set of experiences and perspectives to come up with innovative solutions. It's a real privilege for me to represent such a talented group. It's also a privilege to receive federal funding for this kind of work. Vision without resources is just a hallucination. The US government is making big investments in technologies and in science, and I hope this continues, because this is where a lot of disruptive innovations are happening.

I think about diversity both collectively and individually. If you go to my webpage, you will find a diversity section because I think it's important to talk about your values.[3] It's the values that encourage people to work with us because they know it's an open and inclusive culture.

[3] See http://desimone-group.chem.unc.edu/?cat=10.