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THE NAI FELLOW PROFILE: AN INTERVIEW WITH DR. FRANCES LIGLER

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Celebrated researcher, inventor, and educator Dr. Frances Ligler recently granted an interview to *T&I,* in which she discusses her exciting new work in microfluidics and tissue-on-chip, the innovative research and educational collaborations between the University of North Carolina at Chapel Hill and North Carolina State University, and the value in leading from behind.

INTRODUCTION

Technology and Innovation (T&I) is honored to present Dr. Frances Ligler—pioneer in biosensors and microfluidics—as the subject of this issue's NAI Fellow Profile. After 28 years at the United States Naval Research Laboratory (NRL), Ligler now serves as the Lampe Distinguished Professor of Biomedical Engineering at North Carolina State University (NC State) and the University of North Carolina at Chapel Hill (UNC-Chapel Hill).

Ligler received her B.S. in biology and chemistry from Furman University and her D.Phil. in biochemistry and D.Sc. in biosensor technology from Oxford University. Her prolific career has spanned a variety of research areas, including biosensors, microfluidics, tissue-on-chip, biochemistry, immunology, and proteomics. She is the author of over 400 full-length publications, inventor on 31 issued U.S. patents, and creator of 11 commercial biosensor products. Among her many accolades, Ligler is a member of the National Academy of Engineering; a fellow of

(photo courtesy of Frances Ligler)

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the American Institute for Medical and Biomedical Engineering, the National Academy of Inventors, the American Association for the Advancement of Science, and the Society for Photooptical Instrumentation Engineering; a 2017 inductee of the National Inventors Hall of Fame; and a two-time recipient of Presidential Rank Awards.

Because her research interests have ranged widely, Ligler has had major impacts in many key areas, including bioterror defense, environmental monitoring, food safety, and drug delivery. Her early work focused heavily on biosensors. In this field, she did seminal work on the development of detection systems based on optical biosensor technology, developing portable, automated biosensors for detection of everything from pathogens to pollutants to explosives. These sophisticated biosensors provide data for high-impact decisions; for example, the military fielded Ligler's biothreat detection systems during Desert Storm for base protection. More recently, she has moved into other areas, such as microfluidics and tissue-on-chip. She and her fellow researchers are already making great strides, showing early positive results in the use of microfluidic strategies for creating materials laden with cells that can be used to mimic natural tissue and organ function, a potential game-changer in regenerative medicine. Ligler has also been an exemplar in the translation of research to commercial products and has been instrumental in stimulating important collaborative research and educational initiatives at NC State and UNC-Chapel Hill.

Dr. Ligler recently granted an interview to *T&I,* in which she discusses her exciting new work in microfluidics and tissue-on-chip, the innovative research and educational collaborations between UNC-Chapel Hill and NC State, and the value in leading from behind.

INTERVIEW

T&I: Why don't you tell me a little about some of the current projects you've been working on?

Ligler: I don't have my own lab, but I support four postdocs that I have placed in more junior professors' labs, usually assistant professors, so we can do something that's not tied to a grant—something that can be pretty innovative and follow the intersections of the interests of all of us. That's been really fun because I get to learn a lot of new science and raise awareness about areas that they don't know anything about. I get to help out wherever I'm needed, without having to push a personal agenda. In that context, I'm working with Glenn Walker on microfluidics and making disposable pumps that are programmable and can be used to drive microfluidic systems for less than a penny. We actually have a patent filed on that technology, and we're trying to get it to the point of being ready for commercialization.

A second project I'm working with several professors on is in the tissue-on-chip area. Before I came down here, Michael Daniele and I figured out how to use microfluidics to make capillaries by the meter with cells inside them. These microvessels really recapitulate new capillaries, and we're using them to make vascularized tissue on the chip. With investigator Ke Cheng, from the College of Veterinary Medicine at NC State, we have actually made tissue patches that we've used to restore function in rat hearts following a heart attack. We'll be doing pigs next because it actually works amazingly well. The patches stimulate vasculature and muscle tissue to reform in areas that would ordinarily fill with scar tissue, and that's pretty exciting.

The other area I'm working on is engineering drug delivery with Zhen Gu, a rather incredible faculty member. The idea is to make smart materials that control release of insulin automatically for diabetic patients. When glucose is high, insulin is released, and when glucose goes back to a normal level, the release stops. The smart material is introduced painlessly either into the skin or just below the skin. Mouse studies show that you don't have to monitor glucose levels to keep the correct amount of insulin in the bloodstream. Now we are trying to scale up to perform similar studies in larger animals prior to testing in people.

T&I: The diversity of your work strikes me. Could you talk about how working with people from different disciplines drives and promotes cutting-edge work?

Ligler: My interest is two-fold. I find the science very exciting, but I'm also interested in helping the young faculty members (as well as the postdocs) build successful careers. I'm basically there to fill in the gaps and help with whatever is necessary, whether it's project management, writing proposals, writing papers, or mentoring the postdocs or the students to do what they need to do to further their careers—basically filling in the gaps.

I also do a lot of bridging, so if a project needs a particular expertise, I help find that expertise and bring in those collaborators, both from within North Carolina and outside. Some faculty members need that help, and some of them don't.

I also try to ask the questions that a younger scientist or engineer might not have thought about yet. I have a broader perspective than most faculty members on what it takes to get things into the hands of the users or into a corporate environment, how to deal with the legal aspects of patents or contracts, or how to find the people that know how to do that. Probably the most valuable thing I do is ask questions.

T&I: Just as now, your earlier work with biosensors was very diverse, covering food safety, disease diagnosis, and pollution control, among other areas. However, I was particularly drawn, probably because of our historical moment, to the work you have done on biological terrorism defense. How did that work on biosensors respond to the increased threats of bioterrorism that we face in our modern times?

Ligler: The time period for that work spans 27 years. When we first started out, lasers were huge devices, and we were going to put one in the middle of the ship and dangle fibers out of the portholes. It was that crude. I realized that we could use antibodies to recognize toxins and biological molecules and convert the recognition event to an optical signal. So, we worked very closely with the people in the optical sciences to take advantage of the developments in the telecommunications industry and make biosensors smaller and more portable. The manually operated biosensor that went to the first Persian Gulf War weighed 150 pounds and would keep your tent warm at night. The technology advanced a long way very rapidly; by the mid-90s, we had made biosensors with increased capability that weighed less than 10 pounds, were fully automated, and could fit on a small drone. We continued to take advantage of the technology that came out of the cell phone industry and the communications industry to make biosensors increasingly user friendly. To me, it was a relief when other people started losing sleep over the threat of bioterriorism, appreciated the need for a practical detection system, and explored a variety of approaches for biothreat detection.

The current problem dominating biodefense considerations is that the biothreats themselves are moving targets. The biotech industry has moved so fast in terms of providing tools for new (and very useful) product design, and making these tools easy to use, that I don't think the security community will ever catch up with the capability of biowarfare in terms of defense. What we can do is learn a lot from pandemics and how they move through a community. If we can defend ourselves against Mother Nature, we can also defend ourselves against bioterrorists. I think that that realization has become more pervasive, and the medical community has become much more involved in biodefense than they used to be, and I think that's necessary.

The idea of trying to have a monitor that will protect you against everything a bioterrorist might produce is not very practical anymore. You really have to know what you're looking for ahead of time. If the intelligence community can tell us what we're up against, that's fine. We can build a sensor for almost anything, but we cannot build sensors against everything.

T&I: It's analogous in a lot of ways to hackers and computer viruses. We try to stay one step ahead of the ever-evolving viruses by creating systems to defend against them, but there is always another one around the corner.

Ligler: Yes, we probably have a little longer time factor than those fighting computer viruses do, but the idea is the same. But, again, we have a wonderful model in what Mother Nature does; she's a terrifying terrorist. So, if we practice defense with Ebola, SARS, and Zika and learn from those kinds of situations, those lessons will help us as much as anything.

T&I: Branching out from the science, I was wondering if you could talk about this joint appointment you have with NC State and UNC-Chapel Hill and the role you play in stimulating translational research by linking those two institutions.

Figure 1. Frances Ligler in the lab with postdoctoral fellow Edikan Ogunnaike and Professor Zhen Gu.

Ligler: My role is basically as a bridge. When I came to North Carolina, I expected to help our new faculty get incorporated with contacts at both the UNC School of Medicine and the NC State College of Engineering and to create a seamless culture between the two. That role has expanded. I've actually gotten very extensively involved with the UNC Eshelman School of Pharmacy and the College of Veterinary Medicine at NC State. These interactions, from a research point of view, are very productive. People really want to work together, and in biomedical engineering, everybody is used to doing interdisciplinary work. They know they need clinicians for both animals and people. They know that relationships are essential for engineering solutions that make a difference—so that part of my job is really easy. The challenge is identifying the opportunities.

This bridge building actually includes more than research. The Joint Department of Biomedical Engineering started out with a graduate program in the medical school at Chapel Hill and the college of engineering at NC State, and that's pretty much where we were when I joined the department. We went through a very extensive strategic planning initiative and, as a result, ended up with the undergraduate program in arts and sciences at Chapel Hill to combine with the undergraduate program at NC State, which was very engineering oriented. Due to the newly defined joint program, the undergraduate programs on both campuses are now formally accredited engineering programs.

The changes in the undergraduate program have been startling. Because of the resources of both institutions, we've really been able to establish a whole new curriculum structure that teaches undergraduates both the breadth of hardcore engineering across bioengineering and the depth in the subsets of bioengineering that personally intrigue them. We've also built interactions with the very entrepreneurial business community in Research Triangle Park, so students have the option to work both in labs or do internships in industry. The students also have opportunities through some of our very generous donors to develop potential products, patent them, and take them to market.

We have a tremendous service culture among our undergraduate students. They have started an organization called Helping Hands and make fingers for any kid in North Carolina who is missing fingers. The students will update these prosthetic hands on a yearly basis as the kid grows, which most parents can't afford. This is only one of many service activities that our students lead or to which they contribute their time and talents. They're a very socially conscious group.

In addition to professional development and leadership opportunities, we are rescheduling courses to make it more possible for undergraduates to study abroad, which is very hard for engineering students. Our graduates will operate in a global community, so they need to appreciate other cultures. What's going on in the undergraduate program is groundbreaking on both a national and international level. We have visitors over next week from one of the universities of Japan because they're interested in what's going on and how we've created such a unique enterprise so early on in the educational experience. A lot of this development is actually led by our students. They tell us what they want to do, and we try to help them figure out what kinds of skills they need to follow a particular pathway. For example, based on a plan for going to industry vs. medical school vs. graduate school, we help them understand what kinds of skills they need to build. I never expected to get involved with the undergraduates when I got here, and now I'm spending a lot of time with them and enjoying every minute of it.

T&I: Everyone talks in entrepreneurial culture about collisions. It sounds like you have really found a way to guide these collisions.

Ligler: Yes, we are actually engineering the collisions. We even have an office now in Research Triangle Park. We have a nexus there halfway between both colleges where students and faculty meet and participate in the entrepreneurial networking activities that go on there. Some students even have gotten involved in the ethics initiative that the Rotary Club has started. There is no shortage of interesting activities for a motivated student.

T&I: You have said in regards to your leadership of research groups that your role is that of a motivator. What makes that an effective strategy for leading innovation in particular? Have you experienced other leadership styles that stifle innovation?

Ligler: I think micromanagement certainly stifles innovation, although attention to detail is certainly important and gets more and more important as you get further down the development pathway. Let me give you an example. Let's say you have a vision for something you want to create, like a biosensor, and you need to bring people with different skills together to actually bring this vision to the point of being a product. You have to get everybody on the same page in terms of what the vision is and rely on them to help you identify the critical problems that have to be solved to make it work. You rely on them to have the expertise to come up with solutions in concert with other people in the group. Sometimes solutions come from places where you don't expect them. So you're basically motivating people to solve the problems to get a vision into reality. During this process, I do what I call my "sheepdog thing": repeatedly remind everyone what the vision is and keep them going in the same direction while providing the freedom to modify the vision into something that really works. They may come up with six things this creation could do instead of the four that you had thought of originally. You have to allow them to add their own interpretation of what they want the outcome to be as long as it makes sense to solve the problems that need to be solved. In that case, you're continually motivating people and continually reminding them of what the vision is and where we're trying to go but letting them create their own winding path as long as it's going in the right direction. And you motivate them to care—to care about the final outcome and care about the views of other people because other people can be helpful to them in solving their problems—and to communicate respectfully with colleagues, not wasting time and not going off on tangents. So, there's a lot of motivation involved, and the final product is usually better than the original vision. I lead best from behind.

T&I: One thing I loved was reading about your passion for reading about explorers growing up. What role did that reading, and your other childhood experiences, play in your choice of science as a career?

Ligler: I think my interest in explorers was very natural because Daniel Boone was a relative and Abraham Lincoln was a relative, and I grew up in Kentucky hearing about life in their time. My aunt had an antique shop that still had bullet holes in it from the war with the Native Americans. I grew up running around the woods with my coonskin cap and my hound dog. I grew up racing my horse around stumps, pretending that I was "counting coup" on the teepees of an enemy tribe. I spent a lot of time in the woods: My mother was an avid fisherman, my father and brother hunted, and my grandmother would take us out to identify the wildflowers every spring. I grew up with a closeness to nature. My dad used to cut up fish and say, "Look. This is a female fish, and these are the eggs and this is what she ate for lunch. This is the liver, and these are the lungs." I was always amazed and interested in how organized everything was inside an animal. My fascination with biology developed naturally and in a very immediate way. My first research project was at Oak Ridge Labs, and I was isolating a factor that controls growth in fish. I spent a lot of time out on the TVA lakes water skiing home, and I thought, "If this is science, this is for me." It didn't quite work out that way, but it was such a completely natural segue from my childhood experiences.

I also had a very good high school science teacher that got me involved in doing research to figure out how things worked from a biology point of view. As I got more and more into biology, I got more fascinated with what's going on at the molecular level, so that's why I went into biochemistry.

T&I: Thinking about those childhood influences, I wanted to take that idea full circle to your induction into the National Inventors Hall of Fame. At the time, you seemed really excited about their educational activities and the opportunities those activities offered to impact young inventors, especially females. What kinds of things do you have in mind?

Ligler: The National Inventors Hall of Fame invited me to participate in Camp Invention for elementary school students this summer. My husband and I both got involved, and it was a blast. I had so much fun. We're already signed up for two camps next summer. The excitement of the kids is amazing, and I got so many hugs! What those kids are doing is wonderful, and it's also a very mixed crowd at those camps, so I want to get more involved with that. We'd like for them to find us a camp where there are more underserved kids, and we don't mind if we have to go a ways to get there.

I also have started working with Kelly Sexton, who is the assistant vice chancellor for technology commercialization and new ventures at NC State. She and I want to start to do more to educate women faculty locally and show them that invention and patenting is a good way to get your ideas into the hands of the people who need them. It's about more than making money; it's also about social benefit. And they don't have to give their lives away to do this. They can license their patents if they get them to the point a company would be interested in the invention. There's a lot of opportunity awareness we are trying to create and ideas we're trying to push. Hopefully, if we are successful in attracting more female and minority inventors here, then our strategy will catch on at other places. Dr. Sexton made the observation that NC State has a lot more female inventors who are students and staff than faculty. So, that creates the optimistic possibility that the younger people coming up are not as inhibited as the older ones in terms of pursuing patentable intellectual property.

T&I: This interview is going to be in the conference issue, and this year's conference theme was "Pillars of Innovation." As a master innovator yourself, what do you think are the key pillars on which innovation rests?

Ligler: I was talking with my husband about this, and we came up with three pillars for innovation. Using a takeoff from Thomas Edison's quote (Edison was the first inventor from NRL elected to the National Inventors Hall of Fame and I was the third), I would say the three pillars of innovation are focus, inspiration, and perspiration. In terms of focus, it's understanding what the capability is that you really need to solve a problem. It's not thinking in terms of technologies but asking what capabilities a user needs to solve his problems, and then, with that real understanding of the user, it's trying to think very broadly on what might be ways to get that capability, in the very broadest sense. Then you have inspiration, where you think of one or two, maybe three, ways in which to create the capability. You think of which option is practicable—not practical, but practicable from a commercialization perspective, from a marketing perspective, from a user operational perspective.

The third pillar is perspiration. It takes a lot of hard work to make something happen.

CONCLUSION

Despite her legion honors and accolades, Ligler is disarmingly humble, quick to credit others, and more than comfortable leading others from behind. She clearly understands that the work takes precedence over ego or any territorialism a researcher might have. As she notes, "One of the reasons I'm so focused on people now is that I realized to get a new technology into the hands of the user in a manufactured phase takes ten years if you're lucky. I don't know if I have ten years left, so I'm trying to teach other people how to do it." Through her amazing contributions and inspiring presence, Ligler is doing just that: teaching those around her about the value of research, the necessity to translate technology, and the imperative to bring people and institutions together to spur innovation and hopefully change the future for the better.

FURTHER READING

1. The Frances Ligler Story [video]. National Inventors Hall of Fame. 2017 May 5, 2:57 minutes. https://www.youtube.com/watch?v=-LXDx5OOfTE.
2. Chen Z, Wang J, Sun W, Archibong E, Kahkoska AR, Zhang X, Lu Y, Ligler FS, Buse JB, Gu Z. Synthetic beta cells for fusion-mediated dynamic insulin secretion. Nat Chem Biol. 2017. https://www.ncbi.nlm.nih.gov/pubmed/29083418. doi: 10.1038/nchembio.2511.
3. DiVito KA, Daniele MA, Roberts SA, Ligler FS, Adams AA. Microfabricated blood vessels undergo neoangiogenesis. Biomaterials. 2017;138:142-152.
4. Cummins BM, Chinthapatla R, Lenin B, Ligler FS, Walker GM. Modular pumps as programmable hydraulic batteries for microfluidic devices. Technology. 2017;5(1): 21-30.
5. Bhatia SK, Shriver-Lake LC, Prior KJ, Georger JH, Calvert JM, Bredehorst R, Ligler FS. Use of thiol-terminal silanes and heterobifunctional crosslinkers for immobilization of antibodies on silica surfaces. Anal biochem. 1989;178(2):408-413.
6. Rowe CA, Tender LM, Feldstein MJ, Golden JP, Scruggs SB, MacCraith BD, Cras JJ, Ligler FS. Array biosensor for simultaneous identification of bacterial, viral, and protein analytes. Anal Chem. 1999;71(17):3846-3852.
7. Delehanty JB, Ligler FS. A microarray immunoassay for simultaneous detection of proteins and bacteria. Anal Chem. 2002;74(21):5681-5687
8. Taitt CR, Anderson GP, Ligler FS. Evanescent wave fluorescence biosensors. Biosens Bioelectron. 2016;20(12):2470-2487.
9. Ligler FS, Taitt CAR. Optical biosensors: present and future. Amsterdam: Elsevier Science; 2002.
10. Ateya DA, Erickson JS, Howell PB Jr, HIlliard LR, Golden JP, Ligler FS. The good, the bad, and the tiny: a review of microflow cytometry. Anal Bioanal Chem. 2008;391(5):1485-1498.
11. Ligler FS. Perspective on optical biosensors and integrated sensor systems. Anal Chem. 2009;81(2):519-526.