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What makes us human

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Science needs a new model for testing how cells react, both to things that can cure us and things that can kill us. With her half-million-dollar grant, assistant professor Kristen Comfort '02 is developing a human model with dynamic potential.

Kristen Comfort wanted to build a city for tiny bits of life, a comfortable habitat where free-ranging cells could grow as naturally as they do tucked inside our bodies.

It was serious science — with significant promise for environmental research and a host of human health studies — but to the assistant professor in chemical and materials engineering, it felt like play: squirting a liquid gel into one-inch diameter cylinders, watching the gel cure like Jell-O in the fridge, then adding the cells to weave their way into the porous material.

And it worked. The lung and immune cells she put in the wiggly culture moved in and took up housekeeping. Then she turned on a pump to move liquid through the system to the pulsing rhythms of a beating heart.

Disaster. Her formerly tidy cylinders were ragged ruins, the cell's once happy home ready for a tiny wrecking ball. It looked like B-roll on a disaster news broadcast.

"I don't consider it lost time," she said after this and other efforts to create cell high-rises failed. Every failure is one step closer to success. This is how the science game is played.

Still, there's a great deal at stake. The National Science Foundation has awarded her more than a half-million dollars over the next five years to create a new laboratory test system, one that better predicts how our bodies and our cells react to potentially toxic compounds or potentially helpful ones. NSF called it work with potentially "deep scientific impact" across many disciplines. If the system is successful, Comfort predicts, it could reduce the need for animal studies and provide a more accurate appraisal of our body's reaction to new substances than the usual laboratory approach. It could even help treat cancer.

Her office on the fifth floor of Kettering Labs is decorated with artwork from her three daughters, Holly, 9; Megan, 8; and Caitlin, 7. Rainbow drawings. Sweet notes with childish printing, "I love you Momme." Paper hearts. Handprint flowers. Paper plate picture frames. And dead center between two long to-do lists on her office white board, a heart scrawled in green, now a few months old. It said, "I love you so much Mommy." ("I can't find it in my heart to erase it," Comfort said.)

Comfort, director of the graduate bioengineering program, came to her passion for science naturally. As an 8- or 9-year-old she corralled the family's Barbies — with three girls in the house, she had an army of them — pulled off an arm here, a leg there, and created a Barbie hospital. When she was 8, she asked for a microscope for her birthday and subjected everything she could think of to its low-power scrutiny. Before that, the whole family overslept one morning because 7-year-old Kristen had taken apart her mother's alarm clock to see how it worked, then failed to put it back together again. Somewhere along the way, her native curiosity joined forces with imagination, and the problem-solving demands of science drew her in. That led Kristen Krupa, as she was then known, to the University of Dayton, where she earned a chemical engineering degree in 2002, which eventually led to her present project: Think of it as human-in-a-box.

Her goal is to improve the way laboratories test cells. Typically, studying the biological impact of any chemical or drug involves squirting it onto a flat dish carpeted with identical, growing cells, then watching what happens. Do the cells emit chemical help signals? Do they change shape, alter structurally, stop multiplying, multiply faster? Do they use less oxygen or require fewer nutrients? Do communications between cells break down? Do they die? Or does everything tick along smoothly?

Theoretically, the way that pancake of cells responds predicts the way our bodies will respond to the same chemical. It seems a reasonable supposition. And if we were cell pancakes, it would be. But too often, laboratory studies aren't borne out when scientists take the research to the next level — usually studies in rodents. That's certainly been the case for silver nanoparticles, which is what Comfort plans to test in the experimental system she's creating. In cell pancakes, silver nanoparticles are bad actors. Cells exposed to these tiny creations of 1 to 100 nanometers — 600 times smaller than the width of a human hair — look stressed, act weird and die. But expose mice to these same tiny bits of silver and — nothing, or very little. The mice carry on their little mouse lives with their usual brio. Clearly, something isn't translating between culture dish and four-footed human stand-in.

Comfort looked at the cell cultures, and the problem seemed obvious: “It’s just sitting there,” she said. “Nothing is moving. And you’re trying to correlate the results from a cell culture to the three-dimensional, dynamic, multicellular system of a living thing? No wonder it falls apart. Especially when you’re talking about nanoparticles."

> “Because they’re so small, any little influence changes how they interact with cells.” — Kristen Comfort

Yet it’s not practical to go straight to testing in mice. Such a solution would be both costly and involve an awful lot of mice.

Comfort hopes to create a bridge, a span to carry her from the oversimplified world of cells in a dish to the complexity of a mouse by adding in the cellular interactions that make our human bodies run.

Comfort grew interested in the problems of cell culture during her post-doctoral research year at Wright-Patterson Air Force Base while working in the laboratory of another UD alumna, Laura K. Braydich-Stolle ’01, a biologist in the Molecular Bioeffects Branch at Wright-Patterson Air Force Base.

Comfort and her husband, Donald, had arrived in the Dayton area in 2008. Donald was further along in his professional life than Kristen, having completed both his doctorate and post-graduate research, and was beginning at UD in a tenure-track position. When her husband’s job offer came through, Kristen had a freshly minted doctorate from North Carolina State University. When she moved to Dayton, she took what was on offer: part-time teaching at the University of Dayton. She had zero teaching experience and zero teacher training.

“They threw me into thermodynamics — which is not the easiest,” she said. “I loved it, loved it, loved it!”

She had never intended to teach, always dreaming of working in industry, but at UD she realized her extrovert tendencies — not exactly common among engineers, she said — were a perfect fit.

“My husband says I can talk to a blank wall,” she said. “Teaching is a way I get my words out. I love that interaction. I feed off that energy.”

After completing her post-doc with Braydich-Stolle in 2012, Comfort was hired at UD. This year, she’s preparing for tenure review.

Braydich-Stolle said Wright-Patterson had hoped to keep Comfort. Comfort’s research colleague called her “very high energy, and extremely focused … a very meticulous scientist.” But Braydich-Stolle saw her deep love for teaching, and that’s how Wright-Patterson lost out to UD. Comfort wanted to get her words out.

She and Braydich-Stolle continue to collaborate. On the NSF grant project, they create cell cultures that live, not as cell pancakes, but in three dimensions. To add to the authenticity of their experimental system, they will employ several cell types in a single test, including immune cells known as macrophages.

Picture a six-cup muffin tin made of clear plastic, but with slots between each cup so that batter can flow between them, and you have a fairly good idea what this pilot system looks like. Two of the cups are needed to cycle liquid in and out of the system. The other four could each become home to particular cell types. For instance, to test silver nanoparticles, chamber No. 1 will hold three-dimensional lung cell cultures, chamber No. 2 will feature liver cells growing on 3-D structures, and chamber No. 3 will be home to 3-D skin cell cities. (The fourth chamber won't be used.) The pulsatile pump will push liquid through the system. Finally, macrophages will travel in the liquid, cycling through each cell chamber. Then the nanoparticles will cycle through.

The tissue arrangement isn't a whim. The nanoparticles will travel to lung, liver, then skin — the same order human tissues experience inhaled nanoparticles. Adding macrophages to the mix may challenge all assumptions: Do they gobble up invading particles or ignore them completely?

Although "nanoparticles" sound exotic, they've become increasingly common in consumer products during the last 10 years as the tools to image them — things like high-powered microscopes — developed. As we got better at seeing them, we began to understand their properties, such as strength, durability and low weight, and engineer them more precisely to meet our needs.

Thus, they've made their way into hundreds of applications, including cell phone cases, toothbrush bristles and even the fur of some stuffed animals, according to a study by the Woodrow Wilson International Center for Scholars. Between 2006 and 2014 — the most recent data available — the number of products with nanomaterials increased 521 percent to encompass 1,317 items. About a quarter of those use silver nanoparticles.

“It’s used for coatings, cosmetics, anything designed to kill bacteria,” Comfort said. “It’s something we’re in contact with on a daily basis.”

But what happens when we inhale these infinitesimal particles isn’t certain. They’re so small, there’s hardly anything they can’t get into. A silver nanoparticle sized 10 nanometers or smaller is half the size of most virus particles, and it can pass into a cell like a needle through fabric, like a ghost through a wall. It doesn’t even need a door.

Yet with their small size comes giant opportunities. Gold nanoparticles, for instance, could serve as drug delivery mechanisms. In traditional cell cultures, Comfort said, they work like a charm. “But put them in an animal model and the particles disappear. The macrophages eat them.” With her laboratory system, Comfort said, she could see what percentage of gold nanoparticles the macrophages leave behind. That would help determine how many particles would be required to still sneak some past the macrophages and to the targeted tissue.

Comfort is also working with a group of UD chemistry researchers on the creation and testing of compounds to treat non-small-cell lung cancer, a very aggressive, treatment-resistant disease. They are using specially engineered inorganic chemistry compounds. Once in the airways, these compounds are engineered to behave like smart bombs, adhering to lung cancer cells. Finally, laser light tuned to a specific wavelength triggers the kill signal. Comfort said her system will help determine the ideal compound dose to evade destruction by the immune system.

It’s one of the many ways Comfort’s system can be adapted to meet multiple research needs.

For instance, the system isn’t limited to nanomaterials. In a study led by Braydich-Stolle, they will use their cupcake pan-like assembly to follow the biological path of the toxic heavy metals. Metal ions leach from airplane parts, elevating metal exposures in airmen to much higher levels than experienced in the general population. To test for metal toxicity, Stolle will use liver, kidney, spleen and immune cells — the critical pathway for metal toxicity.

“There are innumerable ways we can use this system,” Comfort said. “That’s the thing I love about this project.” And, there’s potential to expand to even more types of cells. “We could focus on an airway model. We have a detox model. We could focus on tumor models. Any cell type you want to put together, you can create a focused, individualized system,” Comfort said.

Still, several challenges remain. While the problem of the cell gelatin high-rises has, for the moment, been solved with off-the-shelf materials, Comfort would rather create her own. Describing silver nanoparticle behavior in the new system will take up much of the final few years of the project. Ultimately, she hopes to compare her results with results in mice exposed to silver nanoparticles. This will tell her just how close her human-in-a-box comes to emulating life.

From watching her own children, Comfort knows that an interest in science has to start early. Her oldest daughter, Holly, nicknamed “the lawyer” for her ability to argue, wants to be a marine biologist and an artist. Megan, the middle child, is “the engineer,” undoing baby locks when she was a toddler, and taking apart an expensive toy using her plastic Black & Decker tools.

“I was angry and proud at the same time,” Comfort said. Even youngest sister Caitlin, officially “the troublemaker,” has a knack for experimentation. She discovered that if she pushed the toilet seat up, she could get daddy, the only male in the house, in trouble. How fun is that?

If a child isn’t turned on to science by second grade, research shows, it’s too late, Comfort said. So she makes outreach to children a goal, visiting her children’s day care in summer and their schools in the school year with quick, fun experiments, such as demonstrating the engineering perfection of an egg by standing on a grid of them, or piling up books atop an eggshell.

She’s also helping train today the next generation of researchers. Comfort is active in UD’s Minority Leaders Program that pairs minority students with research mentors. And the NSF grant is helping fund positions for an additional graduate student and two undergraduate students in her lab.

Katie Burns, who is completing her master’s degree in bioengineering in Comfort’s lab, feels like she lucked out when she began working with Comfort.

“To see the things she’s doing, and being successful, and at the same time having a family, it’s just pretty great to have somebody like that as my mentor,” Burns said. “I found a mentor who embodies so much of what I hope to be in the future.”

In budding researchers and precocious children, Comfort also sees the future. Each July, Comfort is part of the annual University of Dayton Women in Engineering camp. Young women from at least 20 states attend the program, living in dorms for the week while they complete experiments and learn from professional engineers. It’s one of her favorite weeks in the summer.

“You see these 16-year-olds who are, ‘I’m gonna go and I’m gonna cure cancer,’” she said.

And when they’re ready, Comfort plans to have the cell model ready for them to test their cures.

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