THE NANODESIGNER

Defying all odds, Wenbin Lin made his way from a coastal village in China to a U.S. graduate school and on to the frontiers of medical nanotechnology, where his inventions promise to supercharge cancer therapy.

Within a year of Wilhelm Roentgen's discovery of X-rays, the ionizing radiation was already being deployed in the clinic to destroy tumors. In the 123 years since, technologies for the sourcing, targeting and detection of X-rays have improved dramatically. But the one thing nobody has yet done is boost the primary effects of the radiation—the generation of violently reactive ions known as free radicals that induce the destruction of tumors—without also amplifying the treatment's toxicity. This, Ludwig Chicago's Wenbin Lin will tell you, is what he and his team have accomplished.

In 2018, Lin and his colleagues reported in *Nature Biomedical Engineering* and *Nature Communications* their design and preclinical evaluation of a nanotechnology to boost the effects of radiotherapy when delivered into tumors. The studies, done in collaboration with Ludwig Chicago Co-director Ralph Weichselbaum, demonstrated that, when combined with checkpoint blockade, the treatment not only destroyed the targeted tumors but also led to the regression of untreated tumors in mouse models of breast and colorectal cancers, neither of which is typically responsive to immunotherapy.

Proletarian antecedents

Lin was born in 1966 in the Fujian Province of China, just as Mao Zedong's decade-long Great Proletarian Cultural Revolution was getting underway. But its upheavals—the suspension of education, the dismantling of the urban intelligentsia—were not much of a factor in Lin's early life. He was, after all, a peasant child, growing up in a small coastal town, where his parents subsisted off a small patch of land and fished off the coast in the Taiwan Strait to feed their growing family. "To say that I come from a humble background would be an understatement," says Lin.

He was, he recalls, expected to pull his weight on field and sea. Schooling was a secondary consideration. There was certainly no time for homework; hobbies and interests were luxuries beyond contemplation. "Surviving was my interest," Lin says, laughing. "Not dying from hunger was *really* my interest."

WENBIN LIN

LUDWIG CHICAGO

Photo by Anne Ryan

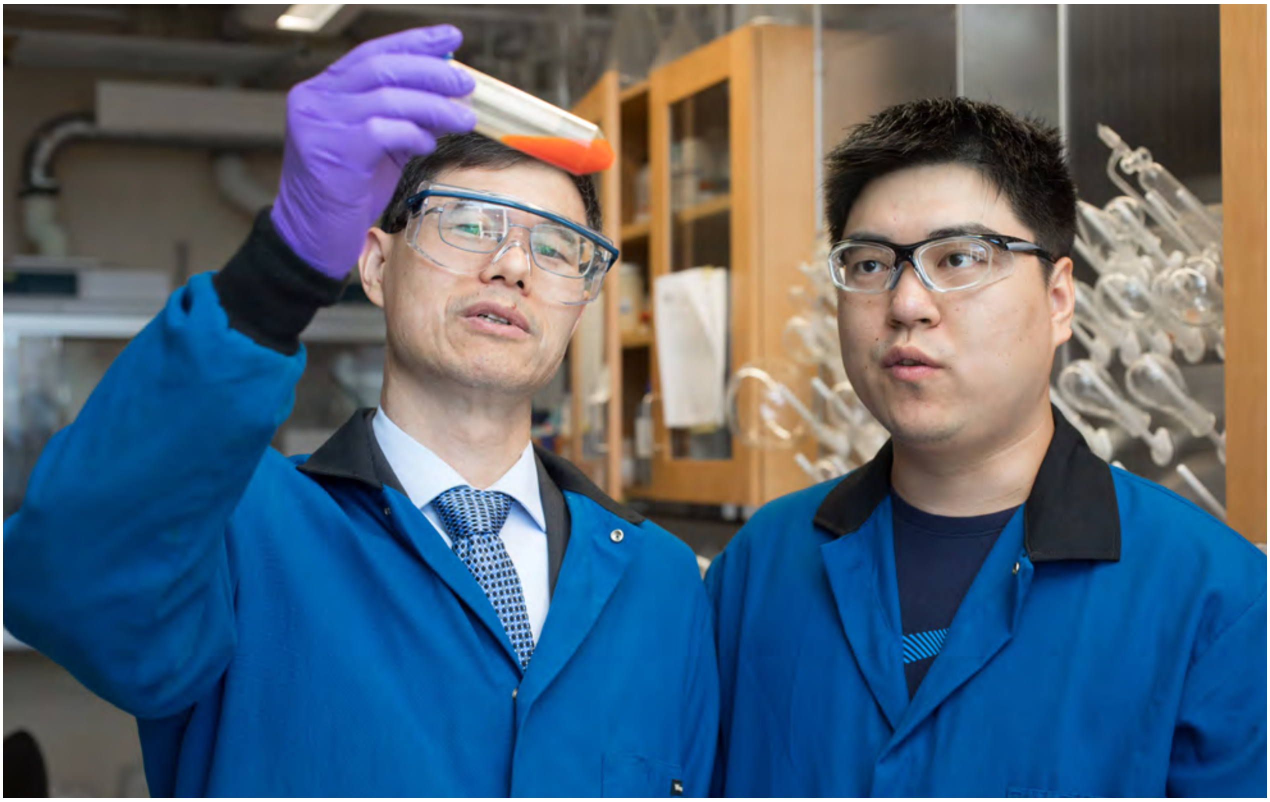

Photo by Anne Ryan

Lin in his Chicago lab with graduate student Guangxu Lan.

Still, in 1980, Lin's parents scraped together enough money to send Lin, the eldest of their four boys, to a proper school in a nearby city to complete the last three years of his secondary schooling.

Entering eighth grade, Lin became a full-time student for the first time in his life. "Even though we were dirt poor, my parents supported me," says Lin. "It wasn't much but they had to pay, and not having me working in the field was a cost as well." Lin turned out to be a gifted student and was soon dreaming about college.

After the Cultural Revolution ended in 1976, the government reopened universities and instituted national exams to select students for entry. The measure had an equalizing effect. "We knew that if you studied hard and did well, you could escape your circumstances," says Lin. "That was enough motivation for me to study hard." Lin made the cut for the University of Science and Technology of China, then the most prestigious institution of higher learning in the country. One of his younger siblings dropped out of school to help his parents make up for the lost labor. None of his brothers attended college.

Like most people in his generation, Lin says, he had no idea what he should study. The general feeling, however, was that math, physics and chemistry—in that order—would most likely help you get ahead in life. Lin decided he'd study chemical physics, a relatively theoretical take on chemistry. "We didn't know what it entailed, but the name sounded really cool," says Lin. He would eventually switch his focus to the decidedly stodgier field of inorganic chemical synthesis and enroll for an additional year, in 1988, for a master's degree. But then, halfway through that year, Lin won a fellowship to join a PhD program at the University of Illinois, Urbana-Champaign.

That he should go was beyond question. Trouble was he needed a passport, and that was going to be difficult. The rules of China's Hukou system of household registration required that Lin apply for the passport from his hometown, so he quit university and went home. "After six years of higher education," he says wryly, "I was a peasant again."

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A path forward

Obtaining the passport took time, but Lin felt lucky to have received one, even if he arrived in Urbana-Champaign three weeks late for his PhD program in 1989. But there were other problems. The professor he hoped to work with had no opening for a graduate student in his chosen area—bioinorganic chemistry. To make matters worse, his first meeting with the man was a disaster. "Instead of asking, 'what's your name?', he asked me, 'what do you want to be called?'" Lin recounts. "I had no idea what he was asking, even after he repeated it three times. It was a rough start: I had become this potential problem student because I could not speak English."

Fortunately, an organometallic and materials chemist named Gregory Girolami did have an opening in his lab—and an eye for talent that saw past the language barrier. "Working for him was the turning point of my scientific career," says Lin. "He is one the best scientists I've ever met and one of the nicest people you could ever meet."

Lin spent more than two years making and characterizing unusual molecules in Girolami's lab before venturing into chemical vapor deposition, a branch of chemistry essential to microchip design. He soon discovered an unusual reaction that permitted the exchange of metal ions after vapor deposition, and Girolami sent him over to the laboratory of his friend and colleague, Ralph Nuzzo, to figure out how it worked. "Having two advisors who were so different and focused on such different areas of chemistry was a very educational experience," says Lin.

After receiving his PhD in 1994, Lin moved to Evanston, Illinois, to work with the prominent organometallic and materials chemist Tobin Marks at Northwestern University. His luck kicked in again: He managed to obtain permanent residency in the U.S. With green card in hand, he qualified for a postdoctoral fellowship from the National Science Foundation. Lin used the funding to explore nonlinear optical materials, which are useful for creating lasers in the blue light range—a capability of some interest to the U.S. Department of Defense.

With a strong suite of publications from that work, Lin was hired as an assistant professor at Brandeis University in 1997. But the startup funding at Brandeis was relatively small, so he began looking for ways to continue his research on the cheap. Coordination polymer chemistry fit the bill.

A class of large molecular structures that

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include the better known metal-organic frameworks (MOFs), coordination polymers are built by linking a variety of metal atoms to complex organic molecules. The resulting molecular frameworks have geometries and chemical properties that are endlessly tunable and of dizzying diversity and utility. Lin initially applied the chemistry to grow crystals for nonlinear optics but was soon exploring them as useful materials in their own right. “Coordination polymer chemistry was something that could be done in a small place with modest resources. I got into the field because of my upbringing,” he says, laughing. “You’ve got to be practical, you’ve got to survive!”

Into the nanosphere

In 2001, Lin moved his operation over to the University of North Carolina, Chapel Hill, where he was appointed professor of chemistry and quickly broadened his exploration of MOFs. Their frameworks served as exceptional platforms for fundamental research into such things as the mechanisms by which catalysts accelerate chemical reactions, and Lin continues to pursue such studies. But it was their practical utility that fascinated Lin most. “Sometimes I think I should be a CEO, not a professor,” he says. “I have a very practical mind. I want to solve problems. I give myself a hard time, asking, ‘Ok, what can this do?’ ”

Applying an acute chemical intuition, Lin has mixed, matched and fiddled with the molecular constituents of MOFs, generating multifariously structured frameworks to perform tasks ranging from capturing toxic gases to collecting uranium from seawater to stably storing hydrogen to harvesting solar energy. “It’s like building a puzzle,” he says. “You get the different pieces of the MOF to work cooperatively to give you the best effect you’re after.”

Work on the energy and environmental applications of MOFs continue in the lab today. But Lin has in recent years increasingly favored their use in medical nanotechnology. “I’m very critical about what we do because, with my background, I feel we cannot afford to waste any resource,” says Lin. “If you want to make an impact in the energy landscape, you need to invest billions of dollars to make a difference. That’s a difficult thing for an academic entrepreneur to do. But in the biomedical sciences, there’s an established, stepwise approach to translate your discoveries into products for clinical trials.”

Lin took the first of those steps a few years after he arrived at Chapel Hill. The National Cancer Institute launched its Alliance for Nanotechnology in Cancer in 2004, and Lin applied for a grant to develop an iron oxide nanoparticle for theranostic applications, which combine diagnostic and therapeutic functions in a single agent. But he never started that project. Instead, he convinced the program director to allow him to pioneer nanoscale versions of MOFs for similar purposes.

Initially, Lin and his team focused on developing nanoscale MOFs (or nMOFs) to improve the images generated by magnetic resonance imaging and computed

Photo by Anne Ryan

Lin and postdoc Tasha Drake.

tomography, publishing several papers that put the lab on the map as a pioneer in the field. Within a few years, they were designing nMOFs as vehicles for drug delivery—packaging chemotherapies, RNA therapies and other drugs into their capacious interiors to treat cancer. By 2011, his team had reported the development of coated nMOFs that could be preferentially delivered to tumors to minimize toxicity.

A year after moving to the University of Chicago in 2013, Lin and his colleagues published another paper describing a self-assembling nanoscale coordination polymer (NCP) that could carry two types of chemotherapy (for example, cisplatin and paclitaxel)—one water soluble, the other hydrophobic—at once to a tumor. Once inside, the NCP was triggered to release both drugs at the same time. The researchers also showed in mouse models of pancreatic, lung and colon cancers that their NCP system was likely to be not only less toxic but far more efficacious. In 2015, Lin established a company named Coordination Pharmaceuticals to commercialize the drug delivery system. Two NCP formulations are currently in a Phase 1 clinical trial to assess their safety and most effective dosage.

Radical improvements

From his early days developing contrast agents for CT imaging, Lin had been intrigued by the interactions between nMOFs and X-rays. After moving to Chicago and meeting Ralph Weichselbaum—an authority on radiotherapy—he began exploring how those interactions might be harnessed for therapy. “Ralph is big on research, and he has accumulated technology, facilities and resources at the Ludwig Center that are very valuable and accessible to researchers,” says Lin. Most significantly, Weichselbaum provided Lin with access to X-ray irradiators and a wellspring of clinical and immunologic insight.

In 2014, Lin and his colleagues published a paper in which they examined how the energy of X-rays is transferred within the framework of one of their MOFs. Their nMOF—clusters of the metals hafnium or zirconium linked by an organic molecule known as anthracene—was an X-ray scintillator. The metal clusters at the corners of the pyramidal structure served as antennae for the X-rays, capturing and transferring that energy to multiple anthracene bridges, which then emitted a flash of visible light.

It didn’t take long for Lin to realize that this system of energy transfer could be adapted to enhance radiotherapy. Lin and his group soon came up with an nMOF made of hafnium clusters linked by the organic molecule porphyrin—schematically resembling a cage bejeweled with metallic flowers—that amplified the effects of radiation in tissues. “We didn’t realize it at the time, but we had discovered an entirely new mechanism for enhancing radiotherapy,” says Lin. They named it radiotherapy-radiodynamic therapy, or RT-RDT.

When X-rays hit tissues, they break apart water molecules to generate free radicals. The damage free radicals cause prompts cells to commit suicide, which in turn induces immune responses that dismantle the targeted tumor. But X-rays interact with water molecules only rarely, limiting the generation of free radicals. The hafnium clusters in Lin’s nMOFs, on the other hand, sponge up the X-rays. So energized, they not only split water to generate hydroxyl free radicals, but transfer excess energy to the nMOF’s porphyrin linkers as well. The excited linkers then shoot off energized oxygen (also called singlet oxygen) to cause even more cellular mayhem. This explosion of reactive oxygen species makes RT-RDT about ten times more efficient than ordinary irradiation.

A platinum-based chemotherapy, cisplatin, is already used with X-rays to enhance the destruction of some head and neck tumors. But its effects are merely additive, and the combination of the two therapies can be highly toxic; Lin’s nMOFs are, on the other hand, synergistic in effect and appear to be biodegradable and nontoxic.

In 2015, Lin started another company named RiMO Therapeutics to commercialize the nMOFs as radio-enhancers. That year, Lin and Weichselbaum obtained a grant from the National Cancer Institute to develop nMOFs for radiotherapy and for photodynamic therapy, in which near-infrared light is used on superficial tumors to generate free radicals and kill cancerous cells. Over the next couple of years, the pair led studies establishing the proof of these concepts in animal models. They also showed that the cell-killing accomplished by RT-RDT and nMOF-boosted photodynamic therapy created an environment highly conducive to anti-tumor immune responses.

In the 2018 study reported in *Nature Biomedical Engineering*, Lin, Weichselbaum and their colleagues filled the cage-like nMOF with an IDO inhibitor—an apparent booster of immune responses in animal studies and early clinical trials that recently failed in larger trials—and injected it into a single tumor in a mouse. The tumor was then irradiated, and the mouse bearing it given a round of checkpoint blockade.

Remarkably, this treatment completely eliminated untreated tumors in models of

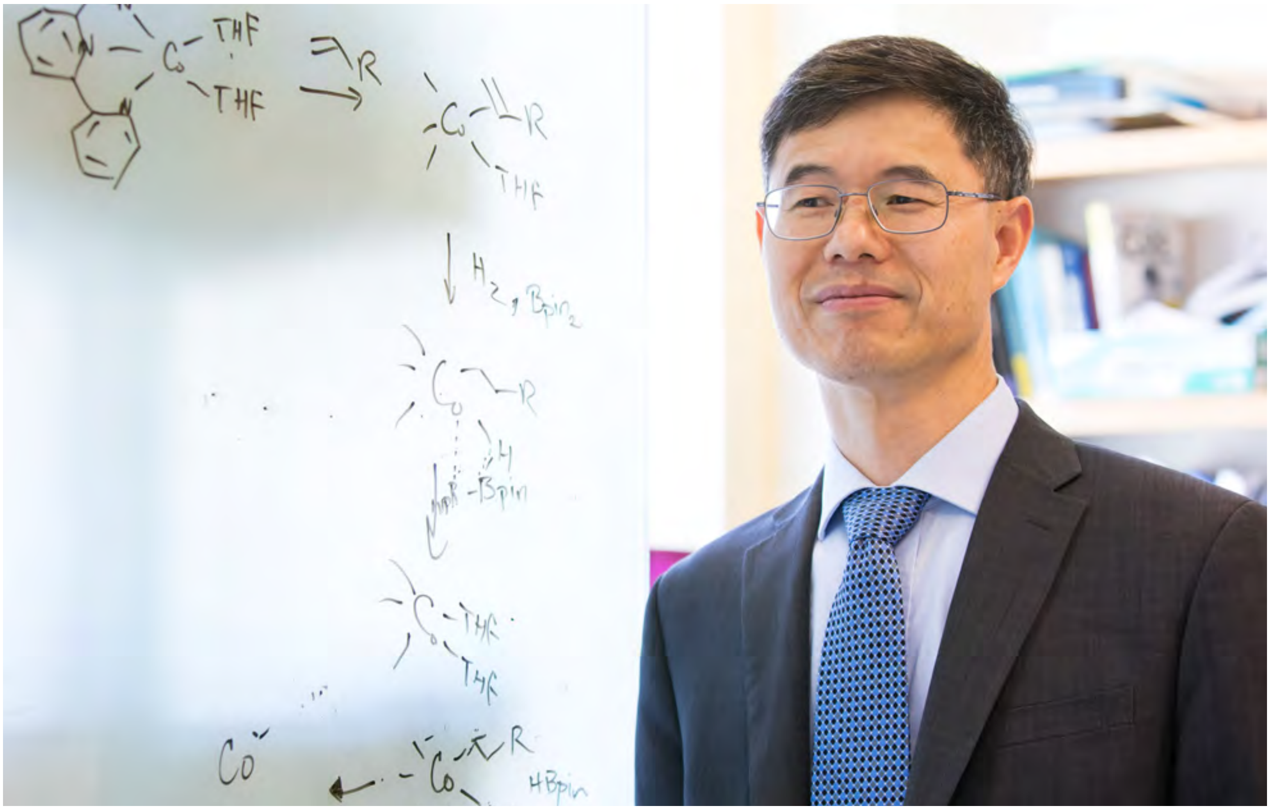

Photo by Anne Ryan

breast and colorectal cancer, both of which are typically resistant to immunotherapy. It also served as proof of concept that the drug delivery capacity of Lin's nMOFs might be combined with RT-RDT to more efficiently conquer tumors.

Their subsequent study in *Nature Communications* dispensed with the IDO inhibitor. But it too showed that the nMOF-enabled combination of radiotherapy and checkpoint blockade caused impressively broad regressions of untreated tumors—or abscopal effects—in a mouse model of colorectal cancer. The results suggest nMOFs might ultimately help expand the variety of cancers amenable to immunotherapy. But, for now, Lin is testing his nMOF only as a booster of radiotherapy: RiMO Therapeutics is already enrolling patients into a clinical trial to establish a safe and effective dosage of nMOFs for RT-RDT in head and neck cancers.

Meanwhile, Lin—who folded RiMO Therapeutics into Coordination Pharmaceuticals in 2018 to streamline operations—continues to innovate. His team separately reported in 2018 in the *Journal of the American Chemical Society* an iron-based nanoparticle that similarly drives abscopal effects in mice with colorectal cancer when combined with checkpoint blockade and photodynamic therapy. Most notably, it overcomes the limitations imposed on such therapies by the oxygen-poor environment at the heart of tumors. In another 2018 *Nature Communications* publication, his lab described an nMOF that could be targeted to mitochondria—the power stations of cells—to more efficiently induce cell death by RT-RDT.

“We hope that these technology platforms lead to things that are so new and so different that we'll really help patients in the clinic,” says Lin.

It's odds-on that something he invents ultimately will.