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Bioscience Wonders

Lisa Marshall

Anne Lenaerts, associate professor of microbiology, Immunology and pathology, with research staff, studies tuberculosis at Colorado State University.

Inside a 25,000-square-foot laboratory on the Colorado State University campus, an army of tuberculosis researchers clad in respirators and white biosafety suits wages war on what some are calling the return of the “White Plague.” Sixty-five miles to the south, at the University of Colorado Cancer Center, 248 scientists are collaborating to turn the historic one-size-fits-all paradigm for treating that disease on its head. Meanwhile, in the glistening new $160 million home of CU-Boulder’s BioFrontiers Institute, biologists and computer scientists are joining forces to map the inside of the human gut.

Infectious disease, cancer, and the human microbiome are just a few areas of research helping to put Colorado on the map as a hub of bioscience at a time when the industry has been waning nationwide.

According to the nonprofit Colorado Bioscience Association, the state’s bioscience industry grew 4.6 percent in employment between 2007 and 2010, while nationally bioscience declined 1.4 percent. More than 600 bioscience companies are now located here, and each year, Colorado’s research institutions spin out 20 more. With the advent of the new BioFrontiers Institute, the near completion of the 578-acre Fitzsimons Life Science District and adjacent CU Anschutz Medical Campus in Aurora, and the continued expansion of CSU’s veterinary and infectious disease programs, the future looks bright.

“Strategy was laid 10 years ago by our research institutions, the Governor’s office and industry to build Colorado into one of the top bioscience clusters in the country,” said CBA president April Giles. “We have created the ideal ecosystem to foster innovation and grow great companies here.”

Keeping the White Plague at bay

When CSU first established a five-person tuberculosis research program in a corner office on campus in the early 1980s, TB was not a high priority among global researchers.

“There was an assumption in the late ’60s and ’70s that TB was done, that we had beaten it,” said Dean Crick, one of 163 researchers who now make up CSU’s Mycobacteria Research Laboratories.

The highly contagious, airborne disease swept through Europe in the 17th and 18th centuries, earning the moniker of White Plague. By the early 20th century, TB was a leading cause of death in the United States. But by the mid-20th century, thanks to the availability of a vaccine called BCG and the advent of several new drugs, the epidemic seemed to lie down.

Later in the 20th century came the HIV epidemic, which compromised immune systems and made people more vulnerable to TB. Soon multidrug-resistant strains began to proliferate. By 1993, the World Health Organization had declared TB a global health emergency.

Today, 8.7 million are infected annually and 1.4 million die. An estimated 9 percent of cases worldwide are completely resistant to all the drugs available. These kinds of cases have now been reported in 84 countries.

“It is the revisiting of the White Plague,” said Diane Joyce Ordway, an assistant professor in the department of microbiology, immunology, and pathology at CSU. “It is a big problem.”

To address it, CSU has developed one of the largest academic TB research programs in the world, drawing roughly $12 million annually to study everything from cheaper, faster diagnostics to better vaccines and new drug targets.

In 2009, Ordway and her colleagues rocked the TB research world when they discovered that strains grown in a lab and long used in animal models did not realistically model the way new drug-resistant strains behave in humans. That meant that while therapies might have worked when tested on animals, they might not work in the real world.

“We have been setting ourselves up for failure,” she said.

Her group now uses only more realistic “clinical strains,” derived from human TB patients, for testing new treatments. “That’s why people come to us. They want to work with real strains that affect real people.”

The MRL has also become the go-to source for labs wishing to acquire TB reagents so they, too, can study the disease. Between 2006 and 2009 it served more than 600 international labs in 44 countries.

As a result, progress is being made. On Dec. 31, 2012, the Food and Drug administration approved the first new TB drug in the past 40 years — bedaquiline, which Johnson & Johnson has been testing at CSU for several years.

“This is a huge breakthrough,” said Ian Orme, who helped found the MRL in the 1980s.

Filling a gap in cancer research

If you looked at the map of National Cancer Center Network members across the country, historically you would have found a gaping hole across the middle of the United States, with the most prestigious cancer research and treatment facilities located on the East and West coasts. That is no longer the case.

This year, NCCN is expected to add the University of Colorado Cancer Center to its list.

“This is a very big coup, to become a part of this exclusive group, and something the state can be really proud of,” said Dr. Dan Theodorescu, Cancer Center director.

While it is housed on CU Anschutz Medical Campus, the Cancer Center consortium includes all National Cancer Institute-funded researchers in the state, including those from CU-Boulder and CSU. Collectively, its 248 members draw about $160 million in annual cancer research funding, pumping out more than 3,000 cancer-related publications since 2005. In 2008 alone, 22 patents were filed out of UCCC-member research, and between 2006 and 2009, 11 startup companies were formed.

Since its founding in 1987, the Cancer Center has developed a reputation as a pioneer in unraveling the molecular mechanisms behind bladder, lung, thyroid and other cancers, and several new tests and drugs have resulted.

In 2012, doctors began using a new thyroid cancer diagnostic test called Affirma, which grew out of a multiyear collaboration between CU professor Dr. Bryan Haugen and the San Francisco-based biotech company Veracyte Inc.

Typically, the 15 to 30 percent of patients with suspicious thyroid nodules that cannot be definitively diagnosed via a mild procedure called a needle aspiration must have surgery to find out whether they have cancer. Seventy percent turn out to be benign.

“It is expensive,” Haugen said. “They have to go through the risks and apprehension of having surgery, and then they have to live the rest of their lives with the potential side effects of having some of their thyroid removed.”

Haugen estimates 75,000 to 100,000 people undergo unnecessary surgery annually.

“I thought, ‘There has got to be a better way,’” he said.

In the 1990s, he started looking for a molecular marker of the disease and over time, he and colleagues found 142 associated genes. In 2007, Veracyte came to him with the idea of collaborating on a test, and ultimately they were able to develop what they call “a genomic fingerprint” of what a benign tumor looks like.

Instead of going under the knife if their first test is inconclusive, patients can now submit a second sample of thyroid fluid and have it genetically scoured for that fingerprint.

“It will improve quality of life and save money,” Haugen said.

Meanwhile at the Center, other gene sequencing technologies are being put to use to better classify human cancers into subgroups. Several kinds of lung cancer or bladder cancer may be identified, for example, and molecularly targeted drugs or existing chemotherapy agents may be identified that are best suited to treat them.

Theodorescu hopes to work more closely with CSU’s College of Veterinary Medicine and Biomedical Sciences to increasingly test such drugs on companion animals that have no other options.

“We like to break down barriers,” he said. “We want to do things together that we could not do alone.”

Gene sequencing to end hunger?

When a colleague first approached CU-Boulder BioFrontiers Institute researcher Rob Knight about a Gates Foundation grant to study childhood malnutrition in the developing world, Knight thought his friend had the wrong guy.

“I was extremely skeptical,” said Knight, who specializes in bioinformatics, the merging of computer science and biology. “I said, ‘Shouldn’t the Gates Foundation be spending its money on food, rather than DNA sequencing?’ Fascinatingly, the answer is no. It’s not that simple.”

In reality, mounting research shows that microorganisms in the human gut play a critical role in helping the body break down carbohydrates, fats and proteins efficiently. If that microbial community is damaged by malnutrition or other factors, an array of problems can ensue, including malnutrition.

“You can feed these kids as much corn or vegetable porridge as you like and it won’t reverse,” Knight said.

Armed with an $8.3 million Gates Foundation grant, along with lightning-fast computational tools developed in his own lab, Knight is collaborating with an international team of researchers over the next two years to answer two essential questions: What prompts one child’s gut bacteria to develop in a healthy way while another’s do not? And what can be given to a malnourished child, along with food, to restore nutritional health?

The Breastmilk, Gut Microbiome, and Immunity Project is the latest in a series of research endeavors that have propelled Knight, 35, to star status in the nascent field of human microbiome research, the study of the hundred trillion or so bacteria inhabiting our bodies.

Until recently, scientists interested in better understanding those microorganisms were stifled by high costs and long waits for gene sequencing. But Knight and his colleagues at CU-Boulder have helped to develop new rapid-fire “error-correcting bar-coded sequencing” techniques and software. Where it once cost $8 to analyze one gene sequence, it now costs $30,000 to analyze one billion, enabling the research to move forward at a much swifter pace.

“Knight’s work has propelled the field forward tremendously,” said microbiome research pioneer Jeffrey Gordon of Washington University in St. Louis.

Over the years, Knight has co-authored pivotal papers showing that lean and obese mice differ in their gut microbiota.

“Somehow, the altered microbial community made them want to eat more,” Knight said. Now he’s exploring the flip side of the equation — the malnutrition-microbiota link.

In June the Human Microbiome Project Consortium, a federally funded group of 200 scientists including Knight, also mapped the entire microbial makeup of a healthy human for the first time, using 4,788 specimens from 242 healthy adults.

And in November, Knight teamed up with researchers around the world to launch “American Gut,” an effort to use crowd funding and open-access data sharing to help academics and individuals learn even more about what lives within them.

People can submit a sample and a donation and get their gut microbe partially sequenced, while contributing to a larger data set for study.

Ultimately such research could lead to oral probiotics to address malnutrition and other ailments, new ways to diagnose health problems, and clues as to how people can improve their overall health by altering their guts.

“If you look at our host genome, we are all 99.9 percent the same,” Knight says. “But if you look at our gut microbiota, it can be 80 to 90 percent different between two people.”

And as he noted, it’s a lot easier to change what’s growing in your gut than it is to change your genes.

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