



Molecule Makers

A UNIQUE CHEMICAL LIBRARY OFFERS NEW HOPE FOR HARD-TO-TREAT DISEASES / BY KATE BECKER

Can a molecule be beautiful?

As director of BU's Center for Molecular Discovery (CMD), John Porco has helped to create some 7,000 new molecules that just might be able to treat diseases that today's drugs can't cure.

The molecules in the CMD's boutique library are far more complex than those found in standard off-the-shelf compounds. They are more biologically active than molecules found in nature and more likely to deliver precision treatments that aren't toxic to healthy cells.

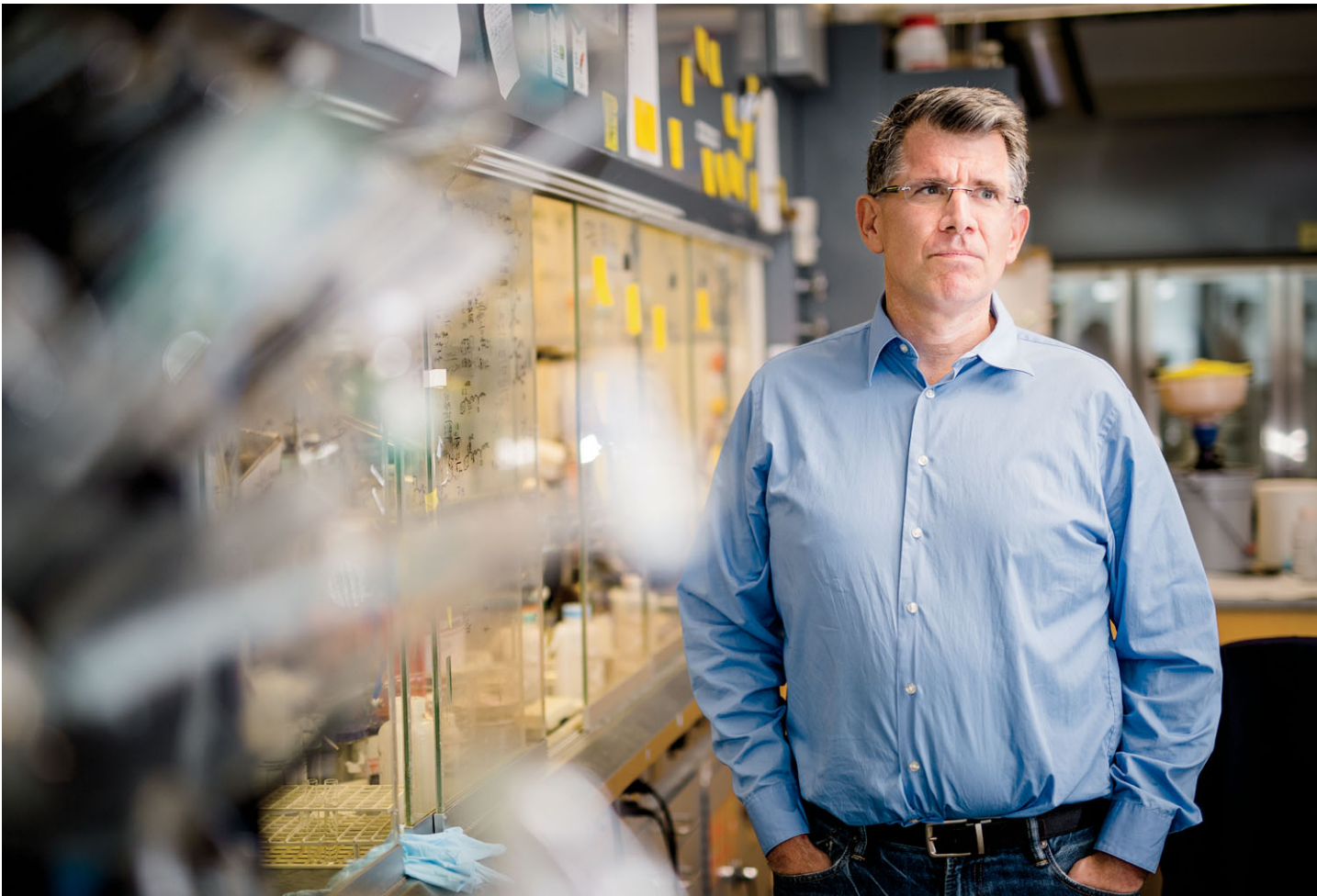
With support from a major National

Institutes of Health grant, Porco and his colleagues spent more than a decade developing what he calls novel chemistries—new ways to synthesize molecules—and learning to manage their growing library, which operated as the Center for Chemical Methodology & Library Development until it was recast as the CMD in 2014. Each new compound was built on a molecular scaffold designed using a process pioneered by Porco, a College of Arts & Sciences professor of chemistry, and Aaron Beeler, CMD co-principal investigator and a CAS assistant professor of medicinal chemistry.

It sounds like the invention of a freewheeling cook: start with chemicals that seem likely to react with one another, then see what happens

when they are dropped into different solvents, at different temperatures, and in the presence of different catalysts. Other promising scaffolds were borrowed from the labs of BU chemists specializing in synthetic organic chemistry.

The molecule makers used a technique called combinatorial library synthesis, a mix-and-match approach in which experimental combinations of molecular building blocks yield original molecules. Now, the center's work is entering a new phase, as an international network of biomedical researchers begins tapping the library for compounds that could lead to new drug discoveries. More than 40 scientists are already testing samples from the CMD, and together they have identified some 300 molecules



as biologically active, meaning that they can interact with living cells and so potentially lead to therapies for maladies such as cancer, Alzheimer's, and infectious diseases. "It's very

CMD molecules may be able to shut down processes that keep pediatric tumors alive.

exciting to see the molecules having efficacy against an important biological target," says Porco.

TARGETING CANCER AND ORPHAN DISEASES

At St. Jude Children's Research Hospital in Memphis, Tenn., chemical biologist Kip Guy has screened a

collection of some 2,500 CMD compounds in search of new ways to treat pediatric brain tumors. More than 10,000 children are diagnosed with cancer each year in the United

States, says Guy, but for decades, the five-year survival rate for many of these cancers has plateaued at or below 60 percent. The key to changing that may

be finding therapies that specifically target pediatric cancers, he says.

"Typically, kids are treated with the same drugs as adults, and in many cases this works well," Guy says. "However, some pediatric cancers are very distinct from adult disease and probably will require novel targeted therapies."



JOHN PORCO AND COLLEAGUES

have created 7,000 molecules that are more biologically active than molecules found in nature.

Guy began tapping the CMD library six years ago. "The compounds from the CMD have unique chemical structures that for the most part have not been previously studied for pediatric oncology," he says. "There is a strong potential to find molecules that shut down the processes pediatric tumors need to survive, and that may provide starting points for developing targeted therapies."

In Tres Cantos, Spain, CMD research fellow John Kavouris (CAS'11) is testing more than 100 new compounds against a dreaded disease called leishmaniasis. The parasitic



← **ANALYTICAL CORE MANAGER**
Madeline Weber places vials of CMD compounds into a liquid handler.

infection, carried by sand flies, causes disfiguring skin sores; in its most serious form, the parasite migrates to organs like the spleen and liver, where it is deadly if not treated. The World Health Organization estimates that more than a million people will be infected, and as many as 30,000 will die of the disease, each year. Among parasitic diseases, only malaria is more deadly.

The vast majority of people with leishmaniasis are very poor, and infections often spread among people displaced from their homes by war and conflict. In Syria, where leishmaniasis is surging, it is called the Aleppo evil, and it ravages refugees. But despite this burden of misery, drugmakers have little economic incentive to develop new therapies for leishmaniasis and other orphan diseases, so-called because they are rare and affect a small percentage of the population, whose victims are too poor to pay for treatment. Indeed, CMD assistant director Lauren Brown points out, the first-line treatment against leishmaniasis is the same today as it was in the 1940s, and involves painful injections directly into the skin lesions.

Brown, a CAS research assistant professor of chemistry, and Porco see fighting neglected diseases as part of the mission of university libraries like the CMD. “Our focus on orphan diseases comes largely from a ‘how can I help’ mentality,” says Brown. “We certainly lack the manpower of a major pharmaceutical company, so we want to focus on the areas of drug discovery

in which we can be the most useful.”

That mentality led Scott Schaus (CAS’95), the center’s other principal investigator, to reach out to James McKerrow, a parasitology expert now at UC San Diego, to see if he would be willing to screen CMD compounds against the diseases he studies, including many—like leishmaniasis, African sleeping sickness, and Chagas disease—that are largely neglected by most drugmakers. In 2012, the CMD team got the call they were waiting for: McKerrow had a hit. Two of their compounds were

New compounds may offer hope in the fight against Alzheimer’s disease.

active against the leishmania parasite in cells. More good news arrived eight months later. McKerrow’s team had tested the compounds in mice infected with leishmaniasis and found that they significantly reduced the number of parasites colonizing their organs.

“We were thrilled the day that we learned these specific compounds reduced leishmania parasite counts in infected mice,” says Brown. “Going from a hit to an effective compound in a live animal model is a big leap, and it is tremendously exciting.”

In 2013, the research got another boost, when Brown, Schaus, and McKerrow won GlaxoSmithKline’s Discovery Fast Track Challenge for

their work. A few months later, Glaxo-SmithKline’s Discovery Partnerships with Academia program funded an 18-month collaboration between the CMD and the drug company’s Tres Cantos Open Lab Foundation research site. That grant supports Kavouris’ current work.

PROMISE FOR ALZHEIMER’S

At BU’s School of Medicine, the CMD also brings new hope in the fight against Alzheimer’s disease. Carmela Abraham, a MED professor of medicine and biochemistry, who has been studying Alzheimer’s for 35 years, is preparing to screen the center’s library for compounds that can stop cells from making amyloid beta, a protein that has been found to build up in the brains of Alzheimer’s patients.

One way to stop the formation of amyloid beta is to turn off the enzymes that carve it out from its parent protein, Abraham says. However, those enzymes have other essential functions in the body, so they can’t be shut down without serious side effects.

She and her colleagues have discovered a new way to keep amyloid beta in check and are searching for compounds that can exploit this pathway to provide safe and effective treatments for Alzheimer’s. Once her team identifies

molecules that are potent against amyloid beta, that are small enough to enter the brain, and that won’t be broken down too quickly by the liver, they will test them in animal models in preparation for clinical trials in humans.

“Our collaboration has just started and we have a long way ahead of us,” says Abraham. “I hope the way is paved with compounds that will become the much-needed drugs for Alzheimer’s.”

“The front-end interest is the chemistry,” says Porco. “But to see the molecules having efficacy against a certain biological target—to have the whole package—that is really awesome.”