



BY RUTH ANN HENSLEY

## Coming to the Table for Discovery

The department of Chemical Biology and Therapeutics brings discoveries from the bench to the bedside—creating new therapies for catastrophic pediatric diseases.

**W**henever family and friends are invited to your home, chances are the evening will end with everyone lingering in the kitchen. Perhaps someone has a warm pot of coffee to share, a story or a hearty laugh. Whatever the attraction, the heart of the home beats strongest when everyone joins together. At St. Jude Children's Research Hospital, the Chemical Biology and Therapeutics (CBT) department serves a similar role. If the basic research and clinical research areas of the hospital were cousins from different sides of the family, CBT is where they would come together to break bread and, more importantly,

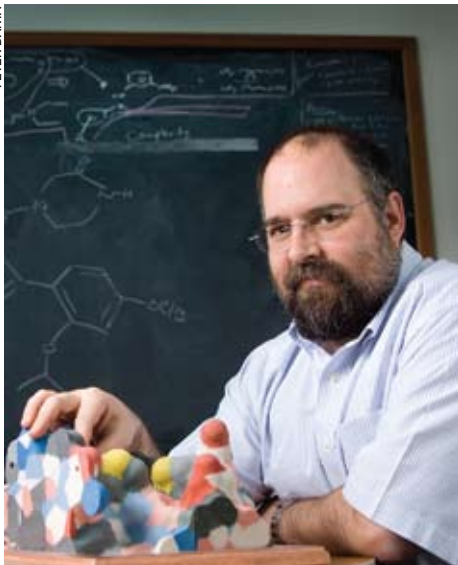
to create new recipes for more effective and less-toxic treatments for catastrophic pediatric illnesses.

The head chef of the operation is Kip Guy, PhD, department chair, and the main dish is drug discovery. But Guy is not a knife-wielding, spotlight-stealing, celebrity-type gourmand. In his arena, too many chefs don't spoil the broth—they all contribute something to the mix.

## A key ingredient

"In our department we work with numerous people across the hospital—from a basic researcher in the lab to clinicians who are interested in taking new drugs to the clinic. These are extremely complex and multidisciplinary projects," Guy says. "The only way these collaborations work functionally is when groups of highly skilled people come

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**Kip Guy, PhD, Chemical Biology and Therapeutics chair, brings clinicians and researchers together to create new drugs that may save the lives of children.**

*“Walking into our department is like finding a small, biotech company within the confines of a research hospital.”*

together, each bringing an individual expertise.”

So what does CBT bring to the table?

“We are the crucial link in the translational research process,” says Julianne Bryan, CBT director of operations. “We help bridge the gap between basic research and clinical research—from the bench to the bedside. Our department facilitates the teamwork necessary to pursue drug discovery projects and supports the process with the chemistry skills needed to ultimately deliver therapies to children in the clinic.”

This focus on therapy and treatment was one of the primary elements that drew Guy to St. Jude in the spring of 2005 to establish the department.

“Initially it was being called a department of Chemical Biology [the study of biology using chemical tools], but I said, ‘That’s not really what I’m interested in doing,’” Guy explains. “I suggested it should be called the department of Chemical Biology and

*Therapeutics* and that its goal should be to discover new treatments rather than focusing strictly on academic pursuits.”

The other magnetic force was the hospital’s mission. “That was a major difference from other research hospitals, and it’s what really brought me here,” Guy says.

## Find, make, refine

The origins of those applications begin at the molecular level. Just as the kitchen is the center of the home, small molecules are at the core of almost everything CBT does. Guy explains that the primary focus of the department is to find small molecules that share characteristics with drugs, even though they are not yet proven to have therapeutic utility, and to explore how they affect disease processes.

This is achieved through a complex, high-throughput screening process in which literally hundreds of thousands of new and existing compounds are tested

for their effect on specific molecular targets that drive disease.

In the instance of cancer, when a cell is mutated and receives a message to multiply uncontrollably, this testing enables CBT to pose the question, “Can we revert this mutation by the application of this compound in such a way that it will cause a tumor to shrink or be destroyed?”

Once a reaction or “hit” has been identified or found in the screening process, things are just starting to cook. The CBT faculty and staff must perform their molecular magic, making the compound potent and selective enough to show promise for human use. Then these compounds must be refined even further before testing can begin at the clinical level.

## Coming to the table

“The amount of work in producing a pre-clinical candidate is incredible. It entails five to seven years of work involving groups of 15 to 20 people from all different disciplines,” Guy explains. “It’s a lot of expertise to bring together in one institution. It’s absolutely unique.”

CBT is participating in numerous collaborative studies across the hospital; however, some pursuits reach beyond the walls of St. Jude. One such project involves Richard Gilbertson, MD, PhD, co-leader of the Neurobiology and Brain Tumor Program. He is spearheading a project between the St. Jude department of Developmental Neurobiology and The University of Texas M. D. Anderson Cancer Center in Houston.

“We have formed the first, direct collaboration between pediatric and adult oncologists to tackle ependymoma, a brain tumor that affects both children and adults,” Gilbertson explains. “Before CBT came on board, we were totally dependent on large pharmaceutical companies to make a drug or compound that might target this disease. In reality, unless there was one already available, you could forget it. Thanks to CBT, we can actually do that work ourselves and be directly involved in the earliest stages of drug development.”

Guy explains that drug production for

childhood diseases is not economically feasible for large pharmaceutical companies.

“We are not trying to compete with drug manufacturers; we hope to partner with them,” Guy says. “The more we can do on our end to reduce risk of failure when we move compounds to the clinical level, the more likely the pharmaceutical companies will be interested in taking on our projects and doing the final stages of production so we can get these treatments to the children who need them.”

Similar screening is conducted in academic settings across the country, but Guy cites two factors that set the St. Jude approach apart from others: first, the tremendous efforts taken to screen the *right* materials when researching pediatric diseases, followed by the focus on creating functional, useful molecules with practical, clinical applications.

## Recipe for success

Of course, any recipe for success calls for the appropriate blend of

manpower, ingredients and utensils.

“The fact that we have this tremendous facility with the right people and the right equipment says that St. Jude is serious about drug discovery,” observes Bryan. “Walking into our department is like finding a small, biotech company within the confines of a research hospital.”

Particularly impressive is the department’s state-of-the-art, compound storage system called the REMP Mid-Sized Store®. The REMP can hold up to 11 million vials of chemical compounds at a constant, subfreezing temperature, thus protecting the delicate molecules from damaging freeze-thaw cycles while maintaining the integrity and shelf life of the other stored compounds. This unit is one of four CBT robotic devices that have helped put St. Jude on the drug discovery map.

Despite the excitement surrounding these technological marvels, Guy is quick to put the high-tech tools into perspective.

“People see the robots, and they think

they’re pretty snazzy but they don’t often grasp the idea that the robots are part of a workflow,” Guy says. “It’s the people, the materials *and* the equipment; you need all of those things working together in a coherent system in order to be successful at this work.”

## Icing on the cake

Gilbertson, who has been with St. Jude for seven years, enjoys the camaraderie and teamwork fostered by the CBT department’s approach to research.

“Kip Guy’s group brings a unique science to St. Jude with different techniques and technologies. It’s like making a cake—it’s a new ingredient that takes something that was good before and makes it truly great, an extra spice that flavors the way you approach your work,” Gilbertson says. “As a researcher, it would be difficult to envision how St. Jude could move to the next level in its mission without CBT.” ●



Alexander Arnold, PhD, of Chemical Biology and Therapeutics, and Jennifer Atkinson, PhD, of Developmental Neurobiology, discuss a research project that uses one of the hospital’s robots for drug discovery. St. Jude children named the four robots used by Chemical Biology and Therapeutics; the robot in this cubicle is named Billy the Robot; another one in the same room is named Tobor, which is “robot” spelled backwards.