

Stem cells serve as new platform for biodefense preparedness

COLLEGE STATION, TEXAS—In the middle of campus at Texas A&M University, the Interdisciplinary Life Sciences Building (ILSB) sits within easy view of Kyle Field, home to the Aggies football team. On the sports ground, players practice their defensive maneuvers, while inside the newly opened \$100 million structure researchers are hard at work blitzing diseases and toxins.

On the second floor of the year-old facility, James Sacchetti, an infectious disease researcher and principle investigator of a \$12.25 million contract announced last month from the US Department of Defense, walks beside empty vent hoods that will soon be used for tissue culture. He stops at the back of the room, where Kim Loesch, a research scientist, places a 24-well plate onto an inverted microscope and focuses on a pinkish cluster of cells—mouse embryonic stem cells in the early stages of differentiation.

“That’s one of our first embryoid bodies,” beams molecular geneticist Deeann Wallis like a proud mother.

Soon, the researchers will screen mouse embryonic stem cells from 350,000 cell lines, each with a different gene missing, in search of which genes offer protection from an onslaught of deadly bacteria, chemicals and viruses. Through this novel approach—the first application of high-throughput stem cell diagnostics to biodefense research—the Texas team hopes to find new drugs and vaccines that protect against biological and chemical weapons or diseases.

As Sacchetti continues to describe the research project in his first-floor lab, he motions toward an open space that will eventually be used for high-content screening of cell lines. The necessary equipment—robotics for handling 96-well plates, an automated microscope and so on—is expected to cost more than \$600,000. To make the microscope automatically find any resistant cells, computer scientist Thomas Ioerger will be working on an artificial-intelligence solution.

The lab is designed to meet biosafety level 2 standards—stringent enough to handle moderately dangerous pathogens such as dengue fever and methicillin-resistant *Staphylococcus aureus*. With those safety measures in place, Sacchetti and Wallis plan to develop a string of tests to monitor the effects of various biological toxins on specific cell types.

Take the *Clostridium botulinum* toxin, for example. This toxin, also known as Botox, enters neurons and induces paralysis. To find a mutation that provides Botox resistance, the researchers plan to coax the mutated stem cells to form neurons and then look for cell lines that resist the typical consequences of Botox poisoning, such as the cleavage of neuronal surface receptors. They then intend to make knockout mice harboring any such resistant mutations to verify whether living animals can resist the attacker, too. One day, this information might be used to make drugs or vaccines—say, through a compound that upregulates the gene that provides resistance to a particular select agent.



Mike May

Cool science: Deeann Wallis.

neutral,” says Richard Ebricht, a molecular biologist and biodefense expert at Rutgers University in Piscataway, New Jersey. “It’s the intentions of persons using research results—not the research results *per se*—that determine whether they are used for defensive purposes or offensive purposes.”

Before the Texas A&M lab gets off the ground, however, the researchers might still face new safety regulations. On 2 July, US President Barack Obama issued an executive order that will spawn new safety rules—including increased physical security—for the deadliest toxins.

Even though the Texas A&M lab will probably never contain such high-risk select agents, Wallis explains that the facility already meets very stringent safety regulations. To access the vast collection of embryonic cell lines, she walks across campus to a separate building, just a few long football passes from the new research facility. Wallis swipes a security card to enter the building and another to access a room filled with locked freezers. Pulling a stack of cell lines from a liquid-nitrogen cloud, she remarks: “There’s a fabulous byproduct of this work. If a cell line doesn’t yield neurons, for example, then the mutated gene in that line is really important to neuronal development.”

Consequently, this work could produce even more results than expected.

Mike May

New battleground

The lab is much more than a high-throughput stem cell screening facility, the researchers maintain. “While we’re looking at targets from bacteria, viruses and toxins, the bigger picture is setting up a platform for battling emerging diseases,” Wallis says.

Although this work does not take on the scariest toxins, such as the Ebola or smallpox viruses, Sacchetti plans to be careful. For example, he would only use vaccine versions of rabies, which are safe enough even to be injected without giving someone the disease. Plus, he contends, “We’re not studying the agent but the body’s response to the agent.” That is, rather than studying how a bacterium or toxin makes its attack, Sacchetti and Wallis are looking for how a human might defend against it. “This is defensive, not offensive,” Sacchetti says.

Not everyone sees such research in the same light. “Research results are inherently



Jean Wallison, Texas A&M

Foyer request: Inside Texas A&M’s ILSB.