Regenerating Battle Wounds, Together

How many laboratories does it take to heal the wounded warrior?

In 2008, the U.S. Department of Defense (DOD) launched the Armed Forces Institute for Regenerative Medicine, or AFIRM, a 5 year initiative modeled on the assumption that bringing together a multi-institutional throng of talent is a far better approach than adhering to the isolating, competitive status quo of team versus team. AFIRM's mission is to accelerate the development of therapies for those who have served, especially those injured in Iraq and Afghanistan, and since the DOD was already backing a few ventures into regenerative medicine—Defense Advanced Research Projects Agency (DARPA)'s Restorative Injury Repair Program, for instance—that became the new project's signature mark as well.

AFIRM's research areas were chosen in light of a hard truth about modern warfare. Even though new and improved life-saving strategies have reduced the number of fatalities, more soldiers are returning from combat with devastating wounds that once would have killed them. AFIRM is less about regenerating entire parts, and more about using adult stem cells and progenitors to restore tissue torn apart by lethal, modern-day explosives: blast-induced burns and nerve damage; loss of bone, muscle, tendons, fingers, ears, and noses; and deep wounds to the head and abdomen.

Today, 4 years down the line, AFIRM's multidisciplinary strengths are more appreciable than ever, notably its scientists' quicker than usual strides toward clinical trials, and while the initiative has experienced some rockiness—"When you put 200 to 300 scientists in one boat, what do you expect?" one researcher remarked—the DOD plans to renew AFIRM for another 5 years. An announcement to that effect is imminent, said Terry Irgens, AFIRM's director since October 2010.

Ship in the Making

Something unique about AFIRM, other than its sheer size, is its structure. Researchers at Rutgers University and the Cleveland Clinic head one network of 15 institutions, while Wake Forest and the University of Pittsburgh's McGowan Institute for Regenerative Medicine head a second group of 16. Both consortia also collaborate with scientists at the U.S. Army Institute of Surgical Research, and connect with industrial partners who help open the way to clinical trials. The U.S. Army Medical Research and Material Command (MRMC), meanwhile, is responsible for overseeing the whole ocean liner and managing funds. The original DOD funding came to roughly $100 million, with funds coming from the MRMC in conjunction with the Office of Naval Research, the NIH, the Air Force Office of the Surgeon General, and the Department of Veterans Affairs. In addition, laboratories themselves brought in over $100 million, monies that their projects had attracted from the NIH, the state, universities, and other sources.

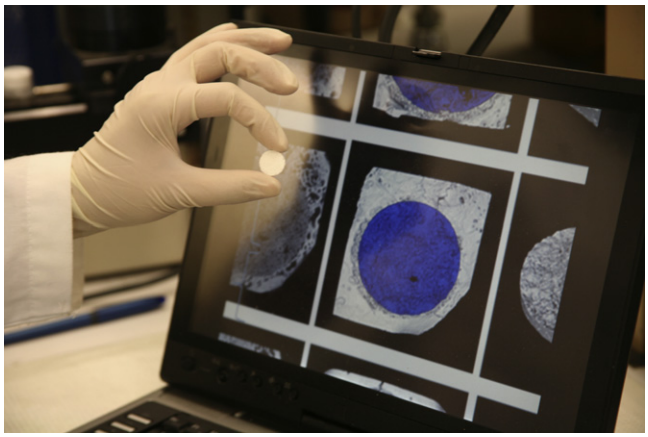
When the initiative was first announced, seven proposers representing dozens of institutions went head-to-head for the grant, the competitive spirit still apparent at AFIRM's first meeting. "I've been told that all the Wake Forest-Pittsburgh scientists sat on one side of the room and the Rutgers-Cleveland group sat on the other," Irgens recounted. The two-prowed vessel "posed a bit of a dilemma, as we had to figure out a way for the separate groups to work together." Ever since, the emphasis has been on shedding a competitive mentality and thinking collaboratively. The approximately 75 projects currently in progress are a testament to AFIRM's success.

Collaborative Sailing

The workload is divided into five research areas—burn repair, scarless wound healing, craniofacial reconstruction, limb-digit salvage, and compartment syndrome repair—which creates plenty of opportunity for investigators to interact. Working on seven burn-repair projects, for instance, are ten investigators from the Wake Forest-Pittsburgh consortium, seven from the Rutgers-Cleveland group, and four from the Army Institute of Surgical Research. Each research project is conducted by either an academic or a physician scientist, and all projects within each area of focus are overseen by a Program Leader.

"What the government model originally overlooked was the tremendous amount of synergy that is unleashed when you change the culture of our scientists from a competitive nature into a collaborative nature," said Joachim Kohn, director of the Rutgers-Cleveland group. "To our great delight, that synergy is creating many successes."

Kohn recounted with great relish one such instance: how, through AFIRM's burn program, he met Richard Clark, a Stony Brook dermatologist who had developed a compound that prevents a burn from progressing from a second-degree to a third-degree burn. Kohn, impressed with Clark's product, then developed a custom-designed wound dressing



An unidentified AFIRM researcher at Rutgers University demonstrates a bone regeneration scaffold (round white object in foreground). The images on the computer screen represent magnified CT scans of newly regenerated bone (highlighted in blue) when the bone regeneration scaffold was used to heal a large circular defect in the skull of a rabbit in a preclinical model study. Photo by Don Lindorfer.

that releases the compound right onto the wound. Kohn then encountered Thomas Mustoe, a plastic surgeon from Northwestern University, in the same program, who applied the wound dressing to his lab's rabbit model and showed that indeed it alleviated scaring.

"No one had a clue such an outcome was possible," said Kohn. "Clark, Mustoe, and I didn't know each other, and now we are three peas in a pod."

George Muschler of the Cleveland Clinic noted that a 3 year comparison of scaffolds for bone defects had "a significant benefit" for the four laboratories involved. "Labs traditionally work on their own and don't aggressively compare their biomaterials. Each of these labs learned something important about their scaffold—what could work better and what wasn't working."

In a separate project, one related to craniofacial research, Joseph Vacanti of Harvard Medical School and Robert Langer of MIT have been trying to beat two major problems that have kept tissue-engineered ears from the clinic: scaffolding that cannot withstand the contractile force of growing tissue, and cartilage cell sources that get resorbed by the body. "I would say that over the past 4 years, it appears we have solved both of these problems," said Vacanti, thanks to funding and resources from AFIRM, and the team's collaboration with ear surgeons at the Massachusetts Eye and Ear Infirmary as well as scientists at Kensey Nash who have applied their expertise in cartilage repair devices to the ear for the very first time.

The white objects in the picture are bone regeneration scaffolds in various sizes developed at Rutgers University under AFIRM funding. In this photograph, an unidentified researcher attempts to fit one of the bone regeneration scaffolds into a defect created in the skull of a rabbit for training purposes. Photo by Don Lindorfer.

Just how quickly some products reached clinical trials surprised everyone. Eleven trials are underway, according to Terry Irgens, who expects three more products to enter Phase 1 trials later this year. One of the burn-repair technologies, a sprayable cell treatment, is likely to be the first product to reach the market as a direct result of AFIRM.

Ahoy, Clinical Trials

AFIRM has "far exceeded the very conservative goal initially set" of having one patient enrolled in a clinical trial after 5 years, noted Irgens. Already as many as 100 patients are enrolled in several. Because no one had imagined clinical trials would happen so soon, the DOD's original funding for AFIRM, roughly $100 million, had been earmarked solely for science and technology, said Irgens.

Then synergy made for shortcuts: getting rid of duplicate therapies and inferior approaches, and sharing knowledge and resources whenever possible. Resources put in place by the DOD further accelerated projects toward clinical-trial status. "We hired an FDA consultant who was available to all groups within our consortium," described Kohn. "We hired a consultant for final-stage commercialization. We established a central clinical trial coordinating group under Dr. Stanton Gerson at Case Western Reserve to help every group write appropriate proposals. Not a single group by itself could assemble these resources. If you want to hire a commercialization expert on your NIH grant, you're in trouble."

Once it became clear that some products were ready for human trials, the government contributed an extra $20 million for early Phase 1 funding. Clinical-trial coffers continue to be added to by newly arriving commercial partners, with AFIRM's total funding approaching $300 million. That cost can be seen as a bargain in that each developed technology, as required by the DOD, must meet a civilian as well as a military need.

While AFIRM's assemblage of people and technologies has bestowed the potential of fast sailing to clinical trials, the voyage hasn't been without occasional clashes between captains. "When you bring people together who on their own merit are very successful, they're used to leading projects and not necessarily used to responding quickly to other people's ideas," said Stephen Badylak of the McGowan Institute for Regenerative Medicine, a project leader in the limb salvage program for the Wake Forest-Pittsburgh consortium. Moreover, "issues related to intellectual property are always present."

A few investigators have opted out of their leadership roles or left the project entirely. "In any large organization," said Muschler, "where there are this many highly skilled investigators, where there's this much national imperative and this much money concentrated in one place, there are going to be disagreements."

Heeling Forward

For AFIRM's next 5 year term, the DOD will accept new applicants. "Although undoubtedly the existing consortia would like to carry over, we need to do a recompete out of a need for fairness," observed Irgens. "There may be other universities out there that might have technologies that are even more advanced than those currently worked on." Some scientists in the current round voiced concern that, because the project has lacked long-term vision vis-à-vis seeing technologies all the way through the pipeline, some technologies will lose financial footing and wither on the vine.

Whether or not his lab is chosen for the next round, Badylak is prepared to do whatever it takes to continue developing

his lab's approach to regenerating either missing digits or skeletal muscle, a novel technique that prompts an accumulation of cells and tissue at the site of injury. Is he confident that this technique will reach patients?

"Oh yes, absolutely. No question about it," Badylak said. "I'd be extremely disappointed if it didn't."

Ann Parson*
South Dartmouth, MA, USA
*Correspondence: parson-a@verizon.net
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