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"From bench to bedside" is a phrase frequently used to explain how translational research works in science and medicine. There's a growing school of thought, however, that it's more like "from bedside to bench and back" - a circular rather than linear process.

The University of Kansas Cancer Center, which just received National Cancer Institute designation, is developing one such circular collaboration where ideas and observations cycle freely between clinicians and basic scientists. The aim: demystifying sarcomas, rare solid tumors of the body's tougher tissues such as muscles, nerves and bones. It's modeled after The Learning Collaborative (TLC), a public-private partnership between KU Cancer Center, the Leukemia and Lymphoma Society and the National Center for Advancing Translational Sciences (NCATS). In less than a year, TLC identified the rheumatoid arthritis drug Auranofin's potential activity against chronic lymphocytic leukemia, a rare blood cancer, and moved the drug into a clinical trial.

For now, this new venture is simply known as the Sarcoma Learning Collaborative. Its genesis lies in the inevitable "How can we make a difference?" question that accompanies every cancer diagnosis but is especially poignant when tackling rare forms of the disease, including sarcomas.

"From a drug development perspective, sarcomas are rare enough that pharmaceutical companies can't afford to spend much effort on them," says Scott Weir, Pharm.D., Ph.D., director of KU's Institute for Advancing Medical Innovation (IAMI) and one of TLC's founders. "By applying TLC's partnership model to sarcoma research, we've enabled multiple people to work together and address this unmet medical need."

The collaborative's leaders will evaluate projects swiftly but carefully; each will be advanced or terminated through short-term, commercially-focused "go" or "no go" decisions, Weir says. They hope to dramatically accelerate the pace at which better therapies against sarcomas are discovered and propelled to the clinic.

Unraveling sarcoma science

Sarcomas may be lesser known cancers to the lay public, but two forms that occur in bone - osteosarcoma and Ewing's sarcoma - are common culprits in children, teenagers and young adults. Ted Kennedy Jr., for instance, lost a leg to osteosarcoma as a child.

"Among childhood cancers, they're right behind leukemias and brain tumors in frequency," says Raymond Perez, M.D., medical director of KU's Clinical Research Center, "and if kids with Ewing's relapse, there are no good follow-up therapies."

Perez has treated sarcoma patients for nearly two decades and considers the subset of sarcomas with simple genetics - in the case of Ewing's, a mutation that fuses together two otherwise separate genes - a ripe area for targeted drug discovery. He plans on leveraging KU's basic science expertise in both Ewing's and osteosarcoma for this new collaborative.

"We have two unique animal models in which to test new treatments prior to clinical trials," he says. In the first, Mizuki Azuma, Ph.D., an assistant professor in Molecular Biosciences, has replicated the specific genetic mutation that causes Ewing's sarcoma - in zebrafish. "It's an early model that will require further tweaking," Perez says, "but she's seeing tumors form in these fish, including the small round blue tumor cells characteristic of this disease." Using translucent zebrafish, Azuma and fellow researchers can easily track the effects of drugs on tumor growth.

In the second model, Rama Garimella, Ph.D., a research assistant professor in Internal Medicine, has figured out how to recreate osteosarcoma in mice - by injecting human cancer cells directly into their bone marrow. These cells readily grow and spread to the lungs, behaving much like the disease in humans. Like Azuma's zebrafish, her mouse model will enable clear visualization of tumor size and spread - because the injected cancer cells glow fluorescent green and are easily seen with special cameras. Garimella is also working with Ross Stein, Ph.D., IAMI's deputy director of discovery and lead generation, to screen compounds with potential in treating osteosarcoma.

Meanwhile, Andrew Godwin, Ph.D., director of molecular oncology in Pathology and Laboratory Medicine and associate director of translational research at KU Cancer Center, is studying the basic science of gastrointestinal stromal tumors (GISTs). Relative to other sarcomas, GISTs are genetically simple: specific proteins messed up by mutations send nerve cells that normally regulate movement along the digestive tract into overdrive. Gleevec, a drug originally approved for chronic myelogenous leukemia, works well - at least for a while - in about 85 percent of metastatic GIST cases, because it

suppresses the hyperactivity of these mutant proteins.

"Gleevec was a rare home run for GISTs," Godwin says, "but even so, half of the patients who take it relapse within two years - possibly because they've acquired secondary mutations or because the tumor cells have figured out how to circumvent the drug. And there's the 15 percent who don't respond at all to Gleevec; they need other options."

Godwin's work is paving the way for the Sarcoma Learning Collaborative to open its first clinical trial later in 2012. He has identified a compound that looks promising against GISTs, through screening a slew of drugs already approved for other purposes. "It targets a different molecular pathway, so it should help not only patients who never benefited from Gleevec, but also those who've become resistant to that drug," he says.

"Considering that we only began fleshing out the concept of this collaborative in February and we're getting ready to open our first clinical trial by the end of the year, I think it's safe to say that this partnership is enabling us to move really, really fast," Weir adds.

It takes a village

As ideas go, the Sarcoma Learning Collaborative is ripe for harvest because many of the building blocks - from illuminating the basic science of sarcomas to discovering and bringing new drugs into early clinical trials - can be found here at KU and in the Kansas City metropolitan area.

Besides Perez's clinical interest in these rare cancers, Midwest Cancer Alliance medical director Gary Doolittle, M.D., has a longstanding adult sarcoma practice at KU Medical Center. With children and teenagers representing another vulnerable patient population, the collaborative's leaders have also reached out to colleagues at Children's Mercy Hospital, including clinical pharmacologists Kathleen Neville, M.D., and Steven Leeder, Pharm.D., Ph.D., as well as Joy Fulbright, M.D., a pediatric sarcoma specialist.

At NCATS in Washington, D.C., director of preclinical innovation Christopher Austin, M.D., is lending a hand by testing assorted sarcoma cells grown in laboratory dishes against an extensive set of compounds - including the world's largest collection of already-approved drugs (over 3,000 in all) - to discover new candidate treatments. Prior to the Sarcoma Learning Collaborative, Austin's group was already pursuing better therapies for chordoma, another rare sarcoma that occurs along the spine, in concert with other academic researchers and the Chordoma Foundation.

"While we have considerable strengths at KU, adding NCATS really synergizes the collaborative's efforts in drug discovery and development," Weir says.

There's partnership potential with the animal health industry too: osteosarcoma is among the more common cancers that afflict dogs, Perez says. Cancer centers are beginning to create relationships

with veterinary practices - for this new collaborative, it's another building block that's already in place, Weir adds, given the proximity and excellence of the KC Animal Health Corridor.

No large-scale effort in translational science can succeed without financial support. The Sarcoma Learning Collaborative is currently buoyed by several philanthropists with a vested interest in sarcoma research. These include commercial developer Scott Rehorn and his wife Susan; their teenage son Coleman was recently successfully treated for synovial sarcoma, a malignant disease that sometimes affects the joints.

"I think it would be great if we could coalesce the philanthropy that exists here around a dedicated sarcoma research foundation in Kansas," Godwin says, "but first, we need more people to champion an awareness of sarcomas and get corporate sponsors energized."

"Doing the first human studies of new therapies costs so much more than any laboratory screen; the difference is at least half a million dollars," Perez adds. "Ultimately, we want to prove that this collaborative works. Then it should be easier to secure the funding needed for clinical trials."

Things may already be headed that way. During a recent visit to the National Institutes of Health in Bethesda, Md., Weir and several invited guests highlighted the importance of ventures like TLC - especially in discovering drugs for rare and neglected diseases - to NIH director Francis Collins, M.D., and U.S. Senator Jerry Moran (R-Kan.).

"The final take-home point on our last slide simply said *Next: The Sarcoma Learning Collaborative* ," Weir says. "So watch this space; with the expertise we're developing at KU and Children's Mercy Hospital, and national-level collaborations through our partnership model, Kansas will be the place to come for sarcoma treatment."

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