NCI GRANT sparks explosion of EARLY PHASE TRIALS

When Patricia LoRusso, DO, Professor of Medicine and Associate Director of Innovative Medicine came to Yale in 2014, she not only brought 25 years of experience in developing new drugs, but also a prestigious National Cancer Institute (NCI) grant that has launched more than a dozen new clinical trials at Smilow Cancer Hospital, with more coming.

The grant, called a UM1, is a 5-year grant that funds investigator-initiated clinical trials. UM1s are highly competitive—nationwide, the award is given to only 11 principal investigators and institutions, who can select other academic sites for collaborations in research and recruitment of patients. As Yale's associate sites, Dr. LoRusso chose Wayne State, Vanderbilt, and the Universities of California at San Francisco and San Diego. In North America, 44 academic sites are under the umbrella of the 11 UM1s.

The grants support the NCI's Experimental Therapeutics Clinical Trials Network (ETCTN), whose purpose is to encourage early phase clinical trials of innovative cancer therapies. Dr. LoRusso's UM1 is certainly having that effect at Yale.

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A key aspect of the UM1/ ETCTN is the NCI's collaborative agreements with

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pharmaceutical companies, whose new therapies become part of the NCI's portfolio of drugs. This allows the NCI to provide these drugs to UM1-funded researchers who need them for clinical trials. "It gives our researchers great access to drugs that otherwise can be hard to get," explains Dr. LoRusso.

For instance, if exciting lab data generates an idea that includes testing a drug against a rare tumor, and if that drug is in the NCI's pharmacopeia, the investigator can submit the idea to the NCI for review. If the NCI finds the idea is worth exploring, it requests a formal protocol. If the project is approved, the NCI gives the investigator the drug to study in a clinical trial, and the UM1 grant provides the funding.

Currently, a further benefit of the UM1 is that projects approved under this mechanism may also be eligible for supplemental NCI grants to cover expenses related to an early phase clinical trial. "For instance, you might need to use or develop a biomarker to select a certain subset of patients or help to better understand how the drug is working against the tumors," says Dr. LoRusso, "or you might need special imaging or biopsies or a special assay. You can apply for a supplement to cover that. So far we've been very successful in obtaining supplements to help us carry out the translational components of the clinical trials on the UM1."

By the end of 2016, the NCI had approved 10 supplemental grants for Yale researchers, ranging in value from $20,000 to $1.3 million for biomarker research and also to help develop later stage, or Phase 2, clinical trials.

Nearly all of the UM1 projects pair a senior investigator with a junior investigator, in keeping with the grant's objective to encourage mentorships that train the next generation of clinical investigators. "It's a great way for junior faculty and fellows to learn the intricacies of what it takes to do clinical and translational research, what it takes to get an idea from the lab into the clinic," explains Dr. LoRusso.

All the trials supported by Dr. LoRusso's UM1 have translational components. "We not only ask a pivotal question in the lab and come up with results," says Dr. LoRusso, "we're asking if that science means improved outcomes for patients in the clinic."

She reels off several examples. Joseph W. Kim, MD, Assistant Professor of Medicine, is testing two drugs in combination against prostate cancer, pancreatic cancer, triple-negative breast cancer, and small-cell lung cancer. He is looking at biomarkers of angiogenesis and alterations on vascular biomarkers, and how those relate to drug response. Both drugs came from the NCI's pharmacopeia. With support from the UM1, says Dr. LoRusso, Dr. Kim's idea is moving forward into a clinical trial.

In hematology, Amer M. Zeidan, MBBS, Assistant Professor of Medicine, and Thomas Prebet, MD, PhD, Assistant Professor of Medicine, are working on UM1-funded concepts involving leukemia and lymphoma. Another project developed by Dr. LoRusso and Joseph M. McLaughlin, MD, a former medical oncology fellow who is now in private practice, is combining a PARP inhibitor with a checkpoint inhibitor against BRCA-mutant triple-negative breast cancer, again using drugs from the NCI pharmacopeia.

Michael Cecchini, MD, a second-year Clinical Fellow, illustrates how Dr. LoRusso and the UM1 nurture ideas with the potential to ripen into early phase clinical trials. Dr. Cecchini is interested in gastrointestinal malignancies. In late 2015, during a clinic with Dr. LoRusso, the two clinical scientists batted around ideas to explore. They noticed that a recent paper had mentioned a subset of gastric cancer patients who had a mutational signature characteristic of homologous DNA repair. This signature has been linked to several cancers, including pancreatic, breast, and ovarian, and has been countered with PARP inhibitors, which kill cancer cells by hindering them from repairing their damaged DNA.

But defective DNA repair hadn't previously been associated with gastric cancer, so Dr. Cecchini and Dr. LoRusso saw an opportunity to try PARP inhibitors against it. They also speculated that adding an angiogenesis inhibitor that suppressed the development of new blood vessels in the tumor could boost the PARP inhibitor's effectiveness. This combination has shown promise against other cancers, especially ovarian.

The two submitted the idea to the NCI in spring of 2016 and were asked to submit a full protocol. The project was approved under the UM1 at the end of the year, and Dr. Cecchini says they expect to start enrolling patients in their clinical trial by mid-2017. The University of California at San Francisco will collaborate on the trial and several ETCTN sites will help to enroll patients.

Asked how important the UM1 grant has been to him as a junior investigator, Dr. Cecchini says, "It's incredible. Any type of clinical trial is really challenging, and I've learned so much. We're integrated with the NCI but also potentially working with 44 other centers, and we also have our collaborators at UCSF. As a junior investigator, I'm getting to interact with faculty across the country. Without the UM1, none of that would be possible. I haven't heard of many other fellows getting such a unique opportunity. I feel really fortunate, and also fortunate that Dr. LoRusso is available as a mentor for me."

Dr. LoRusso is in the third year of her five-year UM1, and she hopes that Yale and their UM1 consortium will be able to renew the grant again—she has successfully re-competed for the NCI's early therapeutics grants for about 20 years. She is hopeful that this explosion of investigator-initiated research at Yale sparked by the UM1 will continue for years to come.

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Images of the dedicated space for Phase 1 Trials. **Carl Kaufman** photographer