Leaders' Update

A message from Steven Grant, M.D.,
associate director for translational research
and Developmental Therapeutics co-leader

Massey is continuing to develop promising research concepts and to effectively translate them into clinical trials.

Some highlights of current research in the process of translation include the work of **Paul Fisher**, M.Ph., Ph.D., Cancer Molecular Genetics co-leader; **Paul Dent**, Ph.D., Developmental Therapeutics member; and **Sarah Spiegel**, Ph.D., Cancer Cell Signaling co-leader. In laboratory studies, Dent and Fisher collaborated with David Curiel (Washington University) to develop a new virus-based gene therapy for renal cell carcinoma (kidney cancer) that has been shown to kill cancer cells not only at the primary tumor site but also in distant tumors not directly infected by the virus. The therapy involves sorafenib, a drug approved by the FDA to treat kidney cancer, in conjunction with a novel adenovirus, Ad.5/3-mda-7. In mouse models, injection of the virus caused kidney cancer cells and normal cells lining the kidneys to secrete the protein MDA-7/IL-24. In the primary tumor site in which the virus was first injected, the secreted MDA-7/IL-24 protein caused the tumor to stop growing. Furthermore, once the protein entered the blood stream, it inhibited the growth of a second, separate tumor not directly infected by the adenovirus. Importantly, normal cells were unaffected by this therapy. Also, sorafenib enhanced MDA-7/IL-24 toxicity in the laboratory and significantly increased its anti-tumor effects in animal tumor models. The team is now working with the FDA to develop a tropism-modified adenovirus that could be tested in clinical trials to infect cancer cells. **Learn more about this research.**

Spiegel's team uncovered a mechanism that promotes chronic intestinal inflammation and the development of colorectal cancer, and they found that fingolimod, a drug currently approved for the treatment of multiple sclerosis, could potentially eliminate or reduce the progression of colitis-associated cancer (CAC). They discovered that increased production of an enzyme known as sphingosine kinase 1 (SphK1) causes cells lining the intestine to produce more of a signaling molecule known as sphingosine-1-phosphate (S1P), which activates a variety of biological mechanisms that lead to chronic intestinal inflammation and the development and progression of CAC. The research team also used animal models to demonstrate that the drug fingolimod decreased expression of SphK1 and S1P's receptor, S1PR1, which subsequently interfered with the development and progression of CAC, even in established tumors. As this drug is already approved for clinical use, the team is working to initiate a clinical trial to study its efficacy in patients with CAC in combination with approved therapies. **Learn more about this research.**

In addition, there are a number of exciting early phase trials in both solid tumors and hematologic malignancies at Massey. One trial uses a novel combination of chemotherapeutic agents for the treatment of advanced solid tumors, such as some forms of breast, colon and lung cancer, for which there are no current potentially curative therapies. The treatment involves pemetrexed, which was co-developed by **Rick Moran**, Ph.D., associate director for basic research and Developmental Therapeutics co-leader, and is now a leading medication for lung cancers, as well as sorafenib, which Dent found contributes to autophagy, a process that can lead to cell suicide. Working together, Moran and Dent discovered that when combined, pemetrexed and sorafenib trigger a form of autophagy called toxic autophagy, in which the system goes into overdrive and the cell consumes itself and dies. Led by

principal investigator **Andrew Poklepovic**, M.D., Developmental Therapeutics member, this clinical trial is one of the first to explore using toxic autophagy as an anti-cancer treatment. Early responses have been seen in heavily pre-treated breast cancers, including triple negative breast cancer. **Learn more about this research**.

Another trial also uses a novel combination of chemotherapeutic agents; in this case for the treatment of leukemia. Led by principal investigator **Beata Holkova**, M.D., Developmental Therapeutics member, the trial is based on pre-clinical findings from my group indicating that very low concentrations of two targeted agents, belinostat and bortezomib, were toxic to cancer cells derived from leukemia patients. In collaboration with M.D. Anderson and H. Lee Moffitt Cancer Center, the trial is designed to determine how patients tolerate various dose levels of the combination. Although still preliminary, results to date have been encouraging: six patients have achieved objective responses, including one who achieved a complete remission. **Learn more about this research**.

Finally, plans are underway to expand our translational research enterprise through key recruitments. Over the next three years, Massey hopes to add two new translational researchers in hematologic malignancies and two to four new translational researchers in solid tumors. One of those positions has already been filled by Danielle Shafer, D.O., who will join us this fall from Loyola University Medical Center, where she is an assistant professor in the Division of Hematology/Oncology. At Massey, she will assist in the translation of pre-clinical research into clinical trials, working with Massey laboratory investigators as part of our phase 1/2 program. She will also provide outpatient cancer care for patients with hematologic malignancies and lung cancer.

Please visit the **Massey news blog** for more of the cancer center's latest translational research highlights.

Regards,

Steven Grant, M.D.
Associate director for translational research and Developmental Therapeutics co-leader