System Opens Biospecimen Repository, Enhances Research Capabilities

Carolinas HealthCare System has created a biospecimen repository (BSR) to collect and process blood, tissue, DNA and other samples from patients across the System, enhancing the capabilities of dedicated Carolinas HealthCare System investigators conducting clinical and translational research. The BSR will enable the evolution of Carolinas HealthCare System into a nationally recognized clinical service provider that can leverage tissues for molecular prognostication and application to personalized medicine. This “bedside-to-bench” approach will ultimately lead to a more personalized approach to treatment of cancer patients.

Biospecimens removed from patients during a procedure are processed and stored at the BSR for future analysis at the System’s core or laboratory facilities or for use in collaboration with strategic partners. These biospecimens provide insight into the patient’s disease and enable better care by yielding information on risk of disease, prognosis and likelihood of response to a certain treatment modality. The process for this collection is complex and varies for each disease site, sample type and facility location. An important goal for the Carolinas HealthCare System BSR is to integrate into current clinical processes seamlessly, minimizing the impact on the clinic staff while ensuring collection of high-quality samples.

The construction of the BSR facility, located at Carolinas Medical Center-Mint Hill, was completed this summer and includes numerous backups and security systems to ensure quality samples. Specimen freezers are equipped with triple-backup systems and are monitored 24/7 with multiple redundancies. A state-of-the-art information system, complete with sample barcoding and scanning, was developed to track biospecimen collection at every stage.
Message from the President of Levine Cancer Institute

It is gratifying to see that the Institute’s reputation is growing. I recently was honored to moderate a session focused on science and society for the Echo Foundation at Charlotte’s McGlohan Theater alongside two Nobel Laureates in Chemistry, Peter Agre, MD, (Johns Hopkins) and Martin Chalfie, MD (Columbia University). In addition to a stimulating discussion on advances in scientific research, we also were able to host a think tank at Levine Cancer Institute, featuring Dr. Chalfie, and attended by many community business and scientific leaders. We believe that one of our roles at the Institute should be to interface with community leaders and, thus, stimulate scientific (and sociological) thinking in our community. To that end, we were also pleased to be key participants in a recent Chamber of Commerce meeting focused on “Charlotte – An Emerging National Destination Site in Health Care.”

We are honored to be adding to the fabric of Charlotte society as a medical and cancer institution, a research center, and a community-minded team – right in line with the vision we established three years ago!

Sincerely,

[Signature]

We welcome your feedback at LevineCancerInstitute@CarolinasHealthCare.org and look forward to bringing you more news in the future!

---

The Hematologic Oncology Translational (HOT) Laboratory

Belinda Avalos, MD (right)  Vice Chair of the Department of Hematology and Blood Disorders

Jonathon Gerber, MD (left)  Director of Leukemia Program

Levine Cancer Institute, part of Carolinas HealthCare System, is proud to announce the opening of the Hematologic Oncology Translational (HOT) Laboratory. Under the direction of Belinda R. Avalos, MD, and Jonathon M. Gerber, MD, the HOT Laboratory focuses on clinically relevant research in hematologic malignancies, particularly myeloid diseases, in order to develop better prognostic tools and more effective treatments for patients with these disorders. In addition, the laboratory is investigating the influence of age, race, and ethnicity on disease biology.

Dr. Avalos, the vice chair of the Institute’s Department of Hematologic Malignancies and Blood Disorders and a former professor at The Ohio State University, brings vast experience in cell signaling pathways. Dr. Gerber, the director of the leukemia program at Levine Cancer Institute and a former assistant professor at The Johns Hopkins University School of Medicine, lends expertise in leukemia stem cell biology. Additionally, the laboratory is staffed by two senior scientists: Lawrence Druhan, PhD, an accomplished molecular biologist, and Sarah Baxter, PhD, an expert in proteomics. Their efforts are further supported by three skilled, full-time technicians: Andrea Price, Amanda Patterson and Jenna Sackenheim.

The laboratory team has state-of-the-art facilities at their disposal, with extensive capability for next-generation sequencing (whole genome, exome, transcriptome, and methylome), proteomic analyses, cytokine multiplex assays, cellular immunophenotyping, fluoractivated cell sorting, cell culture, and microscopy.

Leukemia Stem Cells

Despite aggressive treatments that induce complete remission in the majority of patients with acute myelogenous leukemia (AML), most will relapse and die of their disease, a phenomenon that is true of many cancers. The high rate of disease recurrence suggests that current therapies kill the bulk of partially differentiated leukemic cells but are less effective at killing the key precursor cells responsible for disease initiation and relapse—the leukemia stem cells (LSCs). Recent members of the HOT Laboratory developed a method to detect LSCs and distinguish them from normal hematopoietic stem cells. This assay has proven highly prognostic, with persistence of LSCs after therapy strongly correlating with subsequent relapse (even in those patients who achieved complete remission by all existing clinical standards).

The HOT Laboratory is one of only a handful in the world with expertise in isolating LSCs. Current research efforts are focused on further characterizing LSCs at the cellular and molecular levels through analysis of the LSC transcriptome and proteome, with the goal of identifying unique features of LSCs that can be translated into clinical biomarkers and novel therapies to target LSCs (but not the normal hematopoietic stem cells). Similar studies to identify and target the stem cell origin of other malignant hematologic disorders are also underway.

Signaling Pathways in Hematopoiesis and Leukemogenesis

Many cancers, including hematologic malignancies, are characterized by abnormalities in cell survival, proliferation, and differentiation. Knowledge regarding the signaling pathways and proteins that regulate these processes remains incomplete, and the HOT Laboratory team aims to leverage its expertise in cell signaling to better understand and target the LSCs (while sparing their normal counterparts). Members of the lab previously demonstrated important roles for numerous proteins in myeloid cell survival and differentiation. Mutations in such cell signaling pathways have been shown to play pivotal roles in leukemia, and novel targeted agents to address these aberrations are becoming an increasingly important part of the clinical armamentarium. However, better therapies are still desperately needed.

The HOT Laboratory’s research is conducted in close collaboration with clinical investigators at Levine Cancer Institute, helping to solve clinical mysteries and ensuring rapid clinical translation of any significant findings. To support this mission, the laboratory is actively banking patient samples for future research. At present, the HOT Laboratory is also critically involved in importing the LSC research assay into the clinical laboratory, so that it can be utilized in upcoming clinical trials for AML. The HOT Laboratory is also establishing collaborations with

---

[Continued on Page 3]
Recent Data From ASCO 2014

Asim Amin, MD, PhD (left)
Director of Immunotherapy

Stuart Burri, MD, PhD (right)
Director of Radiation Oncology Research

The 50th Annual Meeting of the American Society of Clinical Oncology was held in Chicago, from May 30 through June 3, 2014. The meeting was well-attended, with more than 34,000 participants from all over the world. While advances in all disciplines were presented, the emergence of immuno-oncology appeared to be a recurring theme in most therapeutic areas. Carolinas HealthCare System’s Levine Cancer Institute physicians were involved with several immuno-oncology studies, and the results are briefly summarized below.

The combination of PD-1 and CTLA-4 inhibition (nivolumab plus ipilimumab) in advanced melanoma showed an impressive 2-year overall survival of 80 percent, as reported by Sznol et al.1 Rhim et al.2 showed an overall response of 40 percent in 411 patients with advanced melanoma who were treated with PD-inhibition alone (pembrolizumab), 62 percent of the patients were alive at 18 months.

• A Phase II study of PD-1 inhibition with nivolumab monotherapy in patients with pretreated advanced renal cell carcinoma (RCC) presented by Motzer et al.3 showed a 20 percent overall response. A Phase I study of nivolumab in combination with sunitinib or pazopanib presented by Amin et al.4 showed an overall response of 52 percent and 45 percent, respectively. While the incidences of renal and hepatic adverse events were noted to be higher than observed for single agents, none of the patients treated with the combination of nivolumab and sunitinib showed an increase in tumor burden from baseline.1 A Phase I study of the combination of PD-1 and CTLA-4 inhibition (nivolumab 3mg/kg plus ipilimumab 1mg/kg) in patients with advanced RCC reported by Hammers et al.5 showed an overall response in 43 percent of the patients. This combination and dose is now being evaluated in a Phase III trial.

• An exploratory Phase I study based on PD-1 and CTLA-4 inhibition for solid tumors (including triple negative breast cancer, pancreatic cancer, gastric cancer, and small cell lung cancer) was presented by Callahan et al.6 as a trial-in-progress. Amin et al.7 shared the interim results from a Phase I study with the combination of PD-1 and CTLA-4 inhibition in non-small cell lung cancer (NSCLC). Gatterer et al.8 and Hamaishi et al.9 presented data for PD-1 inhibition in NSCLC and ovarian cancer, respectively. Continuing on the theme of immunotherapy, Amin et al.10 presented the long-term survival data from a Phase II study of the combination of AGS-003 (an autologous dendritic cell–based immunotherapy) and sunitinib in unfavorable-risk patients with advanced RCC that showed median overall survival of 30.2 months; 33 percent of the patients survived for at least 4.5 years, and 24 percent of the patients survived for more than 5 years. This combination is currently being evaluated in a Phase III trial.

Stuart Burri, MD, PhD, and co-investigators from the Levine Cancer Institute neuro-oncology section11 presented data from a retrospective analysis that showed a doubling in overall survival (15.9 months versus 7.9 months; p<0.108) in patients with unrespectable glioblastoma that were treated with initial standard radiation therapy and temozolomide plus bevacizumab compared to those treated with standard therapy. The potentially practice-changing studies discussed at the plenary session included data that showed exenatide and ovarian suppression to be more effective than tamoxifen and ovarian suppression for premenopausal, hormone receptor-positive women with early stage breast cancer,12 and that the addition of docetaxel to initial hormone therapy in high-risk, hormone-sensitive prostate cancer patients improves survival over androgen deprivation therapy alone.13

The Hematologic Oncology Translational (HOT) Laboratory continued from page 3

physicians at Carolinas HealthCare System’s Levine Cancer Institute focusing on pediatric leukemia and hematopoietic stem cell transplantation.

SELECTED REFERENCES FROM THE MEMBERS OF THE HOT LABORATORY:


New Physicians at Levine Cancer Institute

Carolinas HealthCare System’s Levine Cancer Institute continues to grow, and nine new physicians have joined our team.

Manisha Bhutani, MD
Medical Oncology

Dr. Bhutani has done extensive clinical research on multiple myeloma. Dr. Bhutani did her postdoctoral fellowship at MD Anderson Cancer Center and completed her fellowship in medical oncology at the National Institutes of Health. Her translational research and clinical interests include novel therapeutics, imaging, and immunologic manipulation in smoldering myeloma, multiple myeloma and other plasma cell disorders.

Hassan M. Ebrahim, MD
Medical Oncology

Dr. Ebrahim’s clinical interests include breast, gastrointestinal and gynecological cancers, and blood disorders. He completed his fellowship in hematology and medical oncology at Howard University and came to Levine Cancer Institute from East Carolina University, Brody School of Medicine, where he was an attending physician. His previous research has included work in breast cancer and lymphomas.

Mary Ann Knoovich, MD
Director of Bleeding Disorders, Department of Hematologic Oncology and Blood Disorders

Dr. Knoovich is a board-certified hematologist who focuses on non-malignant and consultative hematology. She specializes in the care of patients with bleeding and coagulation disorders, particularly hemophilia and von Willebrand disease, thrombosis, and platelet disorders, such as thrombotic thrombocytopenic purpura. She came to Levine Cancer Institute from Wake Forest School of Medicine, where she was the medical director of the Comprehensive Hemophilia Diagnostic & Treatment Center and the adult sickle cell program for many years.

Brinda Koya, MD
Medical Oncology

Dr. Koya’s clinical interests include lung, breast and gastrointestinal cancers, as well as chronic leukemias. Prior to joining Levine Cancer Institute, she was a fellow in hematology and oncology at Kansas University Medical Center. She is an associate member of the American College of Physicians, American Society of Hematology and American Society of Clinical Oncology.

Laura Young McGirt, MD
Director of Dermatologic Oncology

Dr. McGirt earned her medical degree at Duke University School of Medicine and completed her dermatology residency and a fellowship in immunology research at The Johns Hopkins University School of Medicine. Prior to joining the Institute, Dr. McGirt worked as an assistant professor of dermatology at Vanderbilt University School of Medicine. Dr. McGirt is a member of Alpha Omega Alpha, the American Academy of Dermatology, the United States Cutaneous Lymphoma Consortium, the Dermatology Foundation and the Society for Investigative Dermatology. Her clinical and research interests include cutaneous oncology (with a special focus on cutaneous lymphoma), as well as cutaneous reactions to chemotherapy and cutaneous graft-versus-host disease.

Ala’a Muslimani, MD
Medical Oncology

Dr. Muslimani completed his fellowship in hematology and oncology at the Oakland University Beaumont Medical School in Royal Oak, MI, and came to Levine Cancer Institute from the Billings Clinic in Billings, Montana. Dr. Muslimani is a member of the American College of Physicians, the American Association of Clinical Oncology and the American Society of Hematology.

Obiageli Ogbona, MD
Medical Oncology

Dr. Ogbona’s clinical interests in gastrointestinal malignancies and breast, head, and neck cancers. She came to Levine Cancer Institute from the University of Tennessee, where she completed her fellowship. She is the recipient of a National Merit Award from the American Society of Clinical Oncology for her research in lung cancer and is a member of the International Association for the Study of Lung Cancer, among other organizations.

Gregory Pennock, MD
Medical Oncology

Dr. Pennock joined Levine Cancer Institute in May 2014. He previously served as the section leader for melanoma and sarcoma oncology at UF Health Cancer Center at Orlando Health. Additionally, he was medical director in the Office of Clinical Trials. At the Institute, he will continue to focus on the care of patients with advanced melanoma and sarcoma. He is a graduate of the University of Texas Medical Branch and completed hematology/oncology training at the University of Pittsburgh School of Medicine.

Antoinette R. Tan, MD, MHSc
Chief of Breast Medical Oncology, Chief of Medical Oncology, Pineville, Co-Director, Phase I Program

Dr. Tan most recently served as director of Phase I and Investigational Therapeutics and as an associate professor of medicine at Rutgers Cancer Institute of New Jersey. Her research is focused on the development of novel therapeutics for breast cancer. She has extensive experience in the conduct of early phase clinical trials and breast cancer studies. She was a 2012 recipient of the National Cancer Institute Cancer Clinical Investigator Team Leadership Award. Dr. Tan also has served on several American Society of Clinical Oncology (ASCO) committees, including as chair of the ASCO Cancer Education Committee from 2012-2013.

Dr. Tan earned her medical degree from Robert Wood Johnson Medical School. She completed an internal medicine residency at North Shore University Hospital-New York University School of Medicine. She completed her fellowship in medical oncology at the National Cancer Institute. She also obtained a master of arts degree from Duke University School of Medicine.

Expansion of Pharmacy Care

In this same timeframe, Levine Cancer Institute facilities that deliver infusion services will be undergoing renovations. In order to make each site meet the requirements of both the USP 797 and USP 800, the Institute is leading the way in meeting these standards and providing exceptional pharmaceutical care—right where our patients live.

Donna Feld, RPh, MBA
Director of Pharmacy

By June of 2015, Carolinas HealthCare System’s Levine Cancer Institute plans to add additional staff to its care teams at all locations. Pharmacists will be available to perform a variety of duties, including provision of drug information, patient counseling, and dose and product checking. They will also be managing drug protocols and developing order sets that will be used in the upcoming computerized physician order entry implementation. Pharmacists will routinely screen patients’ drug profiles to check for potential drug interactions. Pharmacy technicians will be available to order drugs, mix intravenous drugs, help with patient assistance programs, help manage inventory, and help manage drug shortages.

In this same timeframe, Levine Cancer Institute facilities that deliver infusion services will be undergoing renovations. In order to make each site meet the requirements of both the USP 797 and USP 800, the Institute is leading the way in meeting these standards and providing exceptional pharmaceutical care—right where our patients live.
Carolina HealthCare System’s Levine Cancer Institute recently received a Top Performance award by Forte Research Systems for the organization’s excellence in clinical research. The award was given to three sites that demonstrated exceptional research operations as measured through Forte’s Research Resonance Network (RRN). Members of RRN report metrics and benchmark these against anonymized data provided by other RRN organizations.

To determine the award winners, Forte combined metrics across all categories—including IRB Cycle Time, PRMC Cycle Time, and Open-to-Accrual-to-First-Patient-In Cycle Time—and scored each facility by comparing its percentile rankings to similar organizations. The two other Top Performance winners were Indiana University Simon Cancer Center and Iowa University Holden Comprehensive Cancer Center. A Most Improved award was given to Karmanos Cancer Institute.

According to Levine Cancer Institute’s Assistant Vice President of Clinical Trials, Mark King, the Top Performance award is particularly exciting given the vast Institute network. “Because our unique approach to decentralizing cancer care requires us to implement trials across multiple locations and across a large region, to be recognized for our efficient clinical research operations is a special accomplishment,” he said. “Our ability to rapidly review, implement, benchmark and adjust our processes is particularly valuable in our clinical trial initiation process, which is among the swiftest in the nation and helps us deliver care of the highest quality.”

Recent Data From ASCO 2014

continued from page 4

REFERENCES