Innovations in Cancer & Blood Disorders

Rady Children's Hospital San Diego

Rady Children's - A comprehensive system focused solely on children.

PEOPLE

New physician brings expertise in tumor immunology

A. Preethi Ganesan, M.D., Ph.D., recently joined the Division of Hematology/Oncology at Rady Children's Hospital-San Diego. She will be providing inpatient care to patients with leukemia and lymphoma, which are her clinical interests.

Dr. Ganesan's research is focused on studying the dynamic interaction between the tumor immune-microenvironment and cancer stem cells that drive relapse. She seeks to investigate immune responses in pediatric tumors, with the ultimate goal of finding a novel immunotherapy.

During her fellowship at Rady Children's and UC San Diego, Dr. Ganesan evaluated the molecular profile of tumor-infiltrating lymphocytes isolated from patients with cancer and discovered that a distinct subset of T cells predict improved patient survival (in press, *Nature Immunology*). In her doctoral work, using patient tumor samples and a transgenic mouse model of cancer, she demonstrated the role of T regulatory cells in propelling tumor growth and mechanistically demonstrated that this was mediated by inhibition of anti-tumor CD8 cytotoxic T lymphocyte recruitment and function within tumors.

Dr. Ganesan completed her pediatric residency and doctoral program in tumor immunology, both in the United Kingdom. Among her honors and accomplishments, she received the Ray Owen Award for Outstanding Postdoctoral Scholar in 2017, a Hyundai Hope on Wheels Research Scholar grant in 2016 and a Berkeley Fellowship, awarded by University College London and Gonville & Caius College Cambridge, in 2013.

PROGRAMS

Solid Tumor Program tailored to patient population

The Division has launched

a Solid Tumor Program to better meet the challenges and complex needs of this patient population.

Program director Janet Yoon, M.D., will lead an interdisciplinary team of physicians, a nurse practitioner (Nathalie LeFloch, R.N., M.S.N., CPNP) and nurse case manager (Lynn Schubert, B.S.N., R.N.C., CPON). The physicians are Hyunah Ahn M.D., Sun Choo M.D., Jennifer Elster M.D., Victor Wong, M.D., and Peter Zage M.D., Ph.D. Dr. Choo has particular expertise in Ewing sarcoma; Dr. Elster specializes in both neuro-oncology and pediatric solid tumors; and Dr. Zage has particular expertise in neuroblastoma. About 100 children a month are expected to be treated. For various tumors, the team is increasingly utilizing the personalized medicine approach.

The team will work closely with the Pediatric Surgery program, specifically Nicholas Saenz, M.D., who attends the weekly Solid Tumor team meetings and twice a month tumor board conferences. Additionally, the team will work collaboratively with and rely on the expertise of the Acute Pain Service and the Hematology/Oncology Supportive Care Program, specifically JoAnne Auger, R.N., CHPPN, supportive care nurse for the Peckham Center for Cancer & Blood Disorders, and Kimberly Bower, M.D., division chief of Palliative Medicine, to assist with symptom management and provide multidisciplinary psychosocial support to patients and their families.

The program's research component will involve therapeutic clinical trials, many of which utilize novel agents, as well as quality improvement projects specifically targeting the solid tumor patient population.

RESEARCH

Understanding low clinical trial enrollment for Hispanic patients

A research project by Paula Aristizabal, M.D., M.A.S., aims to understand the reasons why Hispanic parents are less likely than non-Hispanic white parents to enroll their children in clinical trials. Preliminary results point to disparities in obtaining informed consent.

Dr. Aristizabal is an assistant professor of pediatrics at UC San Diego and a member of the UC San Diego Moores Cancer Center Reducing Cancer Disparities Program. Her primary research area is addressing disparities in access to care in Hispanic pediatric

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cancer patients, with a particular focus on clinical trial participation as well as patient-provider communication. She has received grant funding for her research from the National Cancer Institute, American Cancer Society, Alex Lemonade Stand Foundation, American Society of Hematology and Hyundai Hope on Wheels. At her clinic at the Peckham Center for Cancer and Blood Disorders at Rady Children's Hospital, she treats a patient population that is approximately 90 percent Hispanic and 65 percent Spanish-speaking.

It is known that pediatric cancer patients enrolled in clinical trials have better survival rates, but for some racial/ethnic subgroups, such as Hispanics, clinical trial accrual rates remain low. This is despite the National Cancer Institute's efforts to improve the inclusion of minorities in cancer research. As Hispanic children have significantly higher incidences of certain cancers, and the five-year survival rates for these are worse for Hispanic than non-Hispanic white children (74 percent vs. 81 percent; $p<0.001$), improving enrollment for these patients is critical to improving their survival. Moreover, this accrual is necessary to determine if the same protocols used in non-Hispanic white children will work in Hispanic children.

Dr. Aristizabal's research program to date, in addition to providing a framework to inform future research, shows the importance of developing strategies to obtain adequate informed consent. Based on her previous research, such strategies involve surmounting language and cultural barriers. Among the barriers Dr. Aristizabal has identified are the heterogeneity in the use of interpretation services, cultural barriers regarding research participation and parental difficulties in understanding medical terms. Dr. Aristizabal's research program is focused on the development of tailored interventions to overcome these barriers.

Learn more about Dr. Aristizabal's research.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4482802/

https://www.forbes.com/sites/northwesternmutual/2016/09/15/one-doctors-quest-to-help-hispanics-fight-childhood-cancer/#73cd029d3020

INNOVATIONS

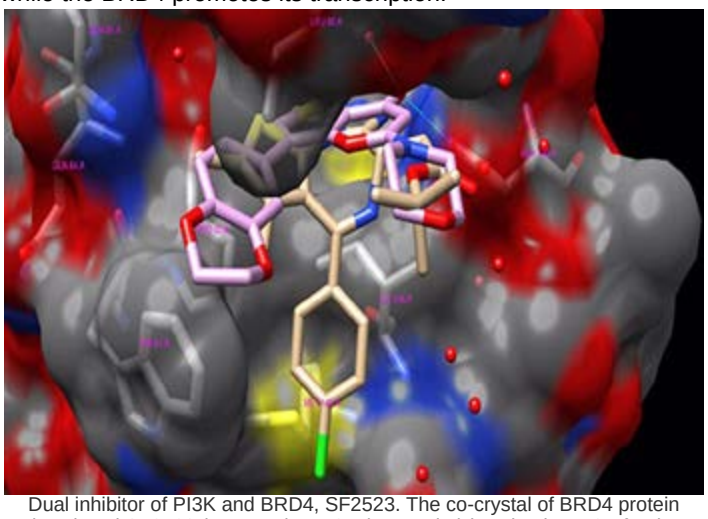
Development of *in silico* platform for small molecule dual inhibitors

SignalRx Pharmaceuticals, founded by Donald Durden, M.D.,

Ph.D., has developed an *in silico* platform for designing small molecule dual inhibitors, an advancement that could expedite the discovery of more targeted cancer agents.

The platform is being used to create compounds that inhibit the PI3K signaling pathway as well as another cancer target. Among these agents is SF2523, a dual inhibitor of PI3Ka (a critical regulator of cell growth) and BRD4 (an epigenetic regulator). Preclinical models have shown that SF2523 produces less toxicity than separate inhibitors of the two targets.

Dr. Durden, who is associate director of pediatric hematology/oncology at the UC San Diego Moores Cancer Center and a professor in the Department of Pediatrics at UC San Diego School of Medicine, says the company's strategy is to attack tumors expressing MYC by using two mechanisms that can work together to prevent development of drug resistance. With the dual inhibitor of PI3Ka and BRD4, PI3Ka prevents degradation of MYC while the BRD4 promotes its transcription.



Dual inhibitor of PI3K and BRD4, SF2523. The co-crystal of BRD4 protein (BD1) and SF2523 (magenta) or JQ1 (grey color) is solved at 1.8A for the binding of SF2523 to the BRD4 binding domain 1 (BD1). Grey regions are hydrophobic, red regions are negatively charged and blue areas are positively charged domains of BRD4/BD1.

Typically, the development of small molecule dual inhibitors requires screening numerous compounds to find the ones with the right specificities. With the *in silico* platform, one inhibitor can be designed that effectively attacks multiple targets at the same time, within the same cell. This approach not only has a better chance of being an effective treatment, Dr. Durden explains, but also avoids the possibility of overlapping toxicity that can result from using two or more agents. He adds that one drug that can hit multiple targets helps to surmount issues such as differential PK/PD, volume of distribution, half-life and elimination.

Other dual-inhibitory chemotypes developed *in silico* to date include PI3K/MEK, PI3K/PARP, PI3K/HDAC and PI3K/CDK4/6. Many more are in the pipeline.