Report on the 1st International Conference

Organized by the Global Cancer Consortium

The 1st Annual Global Cancer Conference organized by the Global Cancer Consortium was held virtually *via* Zoom on December 2th-4th, 2021. The conference was organized by faculty of the Mayo Clinic, Manipal Academy of Higher Education, Tata Memorial Centre, Markey Cancer Center, and Saroj Gupta Cancer Centre and Research Institute. The program's panellists were Drs. Keith Knutson, PhD, Professor, Mayo Clinic, Jill Kolesar, PharmD, Professor, University of Kentucky Markey Cancer Center, Derek Radisky, PhD, Professor and Chair of the Department of Cell Biology, Mayo Clinic, and consortium founding members Drs. Mahadev Rao, Vivek M Rangnekar, Dev Mukhopadhyay and Erin Oakley**.** Over 280 attendees from 15 different countries participated in the three-day conference. A total of 15 speakers from 15 different institutions across the world participated in the three sessions, that is Cancer Immunology and Immunotherapy, Precision Medicine and Cancer Stem Cells, of the conference. In addition to the support from the organizing institutions, the conference was sponsored by Torrent Pharmaceuticals and Alkem Laboratories. A few selective highlights of the conference are indicated below.

Day 1 of the conference (December 2nd, 2021). The session theme for Day 1 was Cancer Immunology and Immunotherapy. The conference commenced at 8.00 am US EST with a “welcome address” delivered by the consortium chair Dr. Vivek M. Rangnekar, PhD, Professor and Alfred Cohen Chair, University of Kentucky Markey Cancer Center, Lexington, Kentucky, USA. The chair of the Cancer Immunology and Immunotherapy session, Dr. Keith Knutson, PhD, Professor, Mayo Clinic, Jacksonville, USA, then made the opening comments pertaining to the session. The

first speaker Dr. Dirk Jäger, MD, Medical Director of German Cancer Research Center, Heidelberg, Germany, spoke on "Individualization of Immunotherapy Strategies in CRC". Dr. Jager provided an overview of the results of immunotherapy trials in colorectal cancer. His talk focused on reasons for successes and failures, with a particular emphasis on developing a better understanding of the immune microenvironment and how that can inform future development of combination approaches to individualize treatment. Next, Dr Peter Schmid, FRCP, MD, PhD, Chair of Cancer Medicine at the Barts Cancer Institute, Queen Mary University of London, United Kingdom, spoke on "Immunotherapy for Breast Cancer". Dr. Schmid spoke about the role of immune checkpoint blockade in the management of breast cancer, particularly focusing on triple negative breast cancer. He emphasized the use of immune checkpoint therapy along with chemotherapy prior to surgery in order to improve cure rates. Dr. Subbarao Bondada, PhD, Professor at University of Kentucky Markey Cancer Center, Lexington, KY, USA, then expounded on the "Role of IL-10 in Anti-tumor Responses to Chronic Lymphocytic Leukemia (CLL)". Dr. Bondada presented studies that his team has conducted over the last two decades demonstrating that IL-10 is produced at high levels by CLL tumor cells and is a primary mediator of immune suppression. His more recent work demonstrated that therapeutic blockade of IL-10 improved natural immune responses to CLL and bolstered the activity of immune checkpoint blockade. The next speaker, Dr Paulina Velasquez, MD, Assistant Professor at St Jude Children's Research Hospital, Memphis, TN, USA, expatiated the topic of "CAR T Cell Therapy for Hematological Malignancies: A Pediatric Perspective". Dr. Paulina provided the attendees with an overview of CAR T cell therapy and how her group is applying CAR T cells to treat pediatric acute lymphoblastic leukemia and acute myeloid leukemia. She focused on

the need for identifying additional CAR T cells targets given the propensity of these diseases to evade treatment. The session chair Dr. Knutson then spoke about on “New Development in Cancer Vaccination”. Dr. Knutson spoke on the development of a novel Th17 T cell inducing vaccine, its effectiveness in preventing relapse following first line treatment in ovarian cancer, and the potential utility of the vaccine in combination with immune checkpoint blockade. The last talk in this session was presented by Dr. Andrew D. Weinberg, PhD, Professor and Judith A. Hartman Endowed Chair for the Laboratory of Basic Immunology at the Earle A. Chiles Research Institute Providence Cancer Institute, Portland, Oregon, USA, on "OX40 Agonists Enhance Tumor Ag-specific T Cell Responses in Cancer Patients". Dr. Weinberg discussed his pioneering work on the biology of the immune activating protein, OX40, and the development of agonistic OX40 antibodies that could be used to treat human diseases such as cancer. He discussed the results of clinical trials conducted with OX40 agonistic antibodies and the potential for improving outcomes in other immunotherapy settings including vaccines (both infectious disease and cancer) and immune checkpoint blockade therapy for cancer. The day ended with the closing remarks by Dr. Keith Knutson summarizing the highpoints of the session.

Day 2 of the conference (December 3rd, 2021). The session theme for Day 2 was Precision Medicine. The opening comments were given by the session chair Dr. Jill Kolesar, PharmD, Professor, University of Kentucky Markey Cancer Center, Lexington, Kentucky, USA. She described the evolution in cancer treatment from chemotherapy to targeted therapy, highlighting the improvement in outcomes for individuals with cancer. Four different talks in precision medicine were delivered on this day. Dr. Shridar Ganesan, MD, PhD, Professor, Rutgers Cancer Institute of New

Jersey, New Brunswick, New Jersey, USA, gave a lecture on "Aiming Targeted Therapy: Monitoring Clonal Dynamics in the Clinic". His remarks described the clonal evolution of cancer during the course of treatment. He also outlined the remarkable treatment course of a pediatric patient with colorectal cancer who received multiple chemotherapy regimens and targeted therapies in response to the clonal evolution of her cancer. Dr. Susanne Arnold, MD, Professor, University of Kentucky Markey Cancer Center, Lexington, Kentucky, USA, further delivered a talk on "Update on Targeted Therapy for Lung Cancer in 2021". Recent advances in targeted therapies for non-small cell lung cancer were reviewed. The clinical activity, adverse effects and pharmacological principles of sotorasib, recently approved for *KRAS G12C* mutations, and capmatinib and tepotinib, recently approved for MET exon 14 skipping mutations were highlighted. Next, Dr. Mark Burkard, MD, PhD, Professor, University of Wisconsin, Madison, Wisconsin, USA, presented a talk on "Academic-Community Collaboration for Precision Oncology". Dr. Burkard implemented a state-wide Molecular Tumor Board at the University of Wisconsin with significant community participation from around the state. He described a patient with advanced disease heading for hospice who underwent genomic sequencing, Molecular Tumor Board review and received a targeted therapy, and is now alive and well several years after initiating this treatment. Dr Lorna Rodriguez, MD, PhD, Professor, City of Hope Comprehensive Cancer Center, Duarte, California, USA, then spoke on "Incorporating Tumor Molecular Profiling in Standard Gynecologic Cancer Care". This presentation featured the utility of somatic mutation testing in gynecologic cancer, and the advent of targeted therapies and novel surgical techniques, including HIPEC for the management of ovarian cancer. The closing remarks were given by session chair, Dr. Jill Kolesar, PharmD.

Day 3 of the conference (December 4th, 2021). The theme of the final day of the conference was Cancer Stem Cells. Five different speakers talked about their research in cancer stem cells and potential targets for cancer therapy. The opening comments were given by session chair Dr. Derek Radisky, PhD, Professor and Chair, Department of Cancer Biology, Mayo Clinic, Jacksonville, USA. Dr. Nai Yang Fu, PhD, Assistant Professor, Duke-NUS, Singapore, discussed the "Molecular Regulation of Quiescent Mammary Stem Cells". In his presentation, he showed that quiescent breast stem cells were identified by the expression of genetic markers Lgr5 and Tspan8. Moreover, Foxp1 was unravelled as a key transcription factor that controls the exit of breast stem cells from dormancy to orchestrate differentiation and development through supressing Tspan8 expression. His studies also revealed an unexpected degree of complexity within the adult breast stem cell compartment and a remarkable molecular link between quiescent breast stem cells and claudin-low breast cancers. This presentation was followed by Dr. Marilene Hohmuth Lopez, PhD, Assistant Professor at Institute of Biomedical Sciences, University of São Paolo, Brazil, who delivered a talk on "Signaling Hubs in Glioblastoma Biology: Prion Protein as Orchestrator". In it, she showed that prion protein (PrPc), a plasma membrane glycoprotein, acts as a promiscuous molecule that is able to interact with several partners and orchestrate many intracellular signaling pathways involved with glioblastoma stemness. Her data suggests that PrPc scaffolding property may favor protein recruitment and higher-order assemblies into a dynamic molecular platform on the plasma membrane and provide an efficient and reversible mechanism to control intercellular signaling pathways. Her more recent findings highlighted the role of PrPc as a sensor of environmental cues, functioning as a key molecule in dynamic control of multiprotein modules in glioblastoma stem cells biology. The third speaker

was Dr Verline Justilien, PhD, Assistant Professor at Mayo Clinic, Jacksonville, Florida, USA, who delivered a talk on "Cancer Stem Cells in Lung Cancer Tumorigenesis and Treatment". She summarized data showing how lung cancer stem-like cells play critical roles lung tumor initiation, maintenance, progression and chemoresistance, and therefore must be eliminated to effectively treat lung cancer. She presented new research findings showing that PKCiota and SOX2 are genetically, biochemically and functionally linked in lung squamous cell carcinoma (LSCC), and together drive transformation of LSCC cells of origin and maintain a stem-like phenotype in LSCC. PKCiota and SOX2 also were shown to activate a Hedgehog (Hh) signaling axis in LSCC stem-like cells that drive tumorigenesis and vertical blockade of PKCiota-SOX2-Hh signaling inhibits growth of LSCC stem-like cells. Her findings suggest that inhibition of PKCiota-SOX2-Hh signaling could be developed as an effective therapeutic approach for LSCC treatment. Dr Sanjeev Waghmare, PhD, Scientist at the Tata Memorial Centre, Navi Mumbai, India, then spoke on "Sfrp1 in Tumor Initiation and Cancer Stem Cells Regulation in Squamous Cell Carcinoma". His work with Sfrp1 knockout mice revealed increased skin tumor initiation and CSC formation and consequent elevated tumorigenic potential. Further evaluation of Sfrp1 and Sox2 showed an inverse co-relation of Sfrp1 low and Sox2 high in both oral and breast cancers. He demonstrated that these differential expression patterns were linked through Sfrpl loss leading to upregulation of the non-canonical Wnt signaling mediated through Rac1 and JNK1, and consequent induction of Sox2 expression in skin squamous cell carcinoma. The last speaker of the event was Dr. Tianyan Gao, PhD, Professor and Interim Chair of the Department of Molecular and Cellular Biochemistry, University of Kentucky, Lexington, Kentucky, USA, who spoke on "Uncovering the Role of Mitochondria in Regulating Colon

Cancer Stem Cells." She described how colon tumors grow in an adipose tissue-enriched microenvironment. In the course of defining the functional consequences of increased fatty acid availability in colon cancer, she recently uncovered a novel role of mitochondria in facilitating the metabolic crosstalk between fatty acids and colon cancer cells. She showed that abundant adipocytes are in direct contact with colon cancer cells in patient specimens and uptake of fatty acids allows cancer cells to survive energy stress conditions by upregulating CPT1A-dependent mitochondrial fatty acid oxidation (FAO). Importantly, fatty acid exposure was shown to enhance the expression of genes associated with colon cancer stem cells by promoting beta-catenin acetylation and nuclear translocation; and the inhibition of FAO by silencing CPT1A blocks the tumor promoting effect of fatty acids in xenograft models. Taken together, her findings identify CPT1A-depedent FAO as an essential metabolic pathway that sustains cancer stem cell functions in colon cancer. Question and answer sessions were conducted after the completion of every talk.

Finally, the "Vote of Thanks" was delivered by Vivek M. Rangnekar, PhD, on behalf of the conference organizers, the Global Cancer Consortium. The organizers thanked the session chairs for their effective leadership, generating meaningful discussions, and keeping everyone on schedule; all the speakers of the three sessions for the high quality of their presentations and discussing some of their most recent findings; the leadership at the Mayo Clinic, Markey Cancer Center, Manipal Academy of Higher Education, Tata Memorial Centre, and Saroj Gupta Cancer Centre and Research Institute, for their enthusiastic support for the conference; Dr. Erin Oakley, Markey Cancer Center, for overseeing the logistics of the conference; and the Research Communications Office of the Markey Cancer Center for preparing the flyers and other promotional material for the global conference.