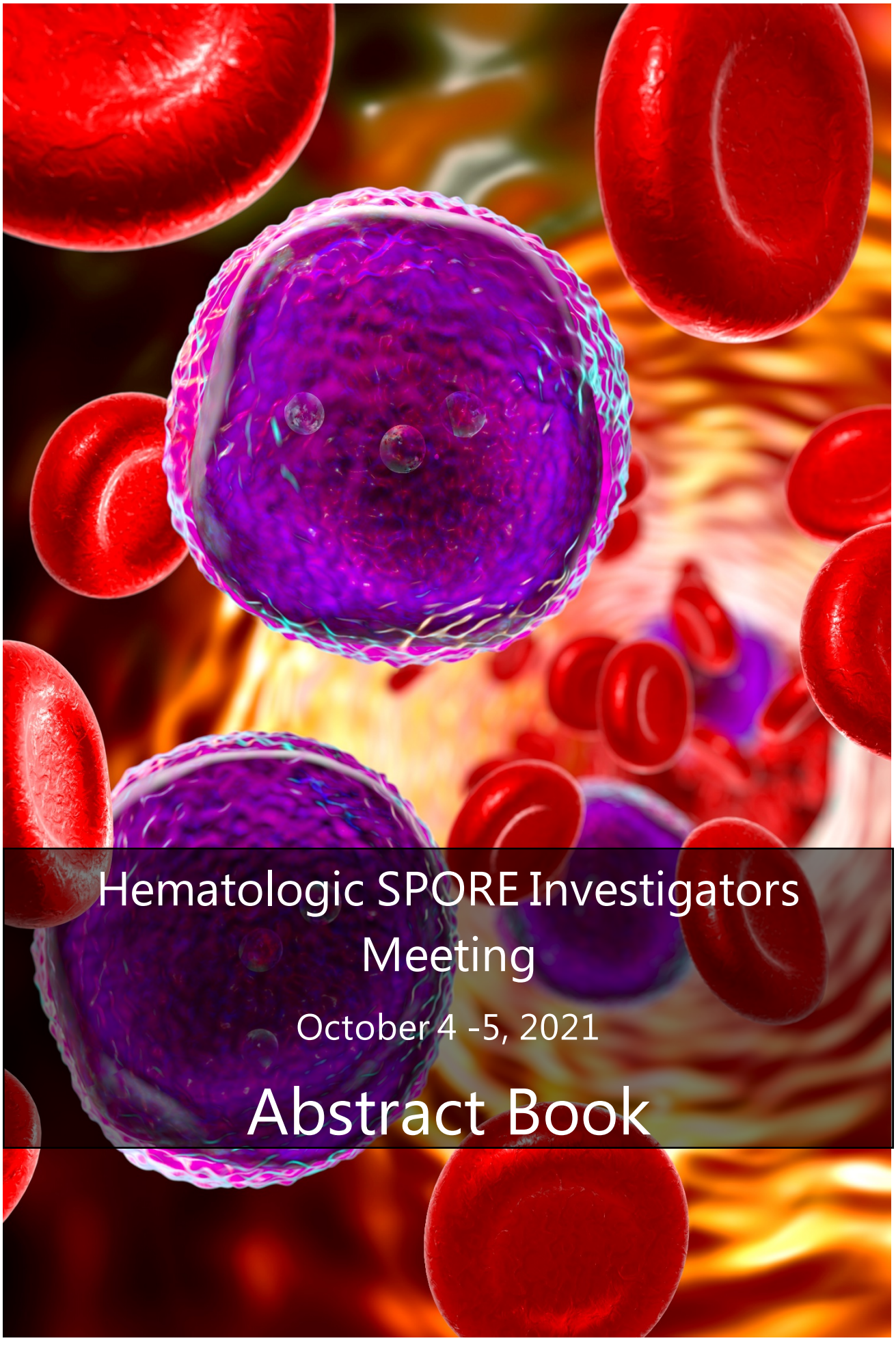

Hematologic SPORE Investigators Meeting

October 4 -5, 2021

Abstract Book

Hematologic SPOREs Investigator Meeting

October 4-5th, 2021

Meeting Agenda

Virtual Meeting via Zoom
Hosted by: University of Iowa Holden Comprehensive Cancer Center

Zoom Link/Information:
https://uiowa.zoom.us/j/97150240629?pwd=QXozUVR4cDFTenFUaWQ5bEpoeC8vUT09
Password: **SPORE**

If joining by phone:
1-301-715-8592 Meeting ID: 971 5024 0629
All Times are Eastern Time

Monday – October 4, 2021

Session I – Immunotherapy

Chair: Ken Anderson, Dana Farber Cancer Institute

12:00 – 12:10 PM ET	Orientation and Opening Remarks
12:10 – 12:30 PM ET	Presentation: "Activating Phagocytic Macrophages in non-Hodgkin Lymphoma (NHL)" – Stephen Ansell (University of Iowa/Mayo Clinic Lymphoma SPORE)
12:30 – 12:50 PM	Presentation: ""Off-the-Shelf" Allogeneic CAR-Expressing Immune Effectors for Treatment of CD19+ or CD30+ Lymphomas" – Carlos Ramos (Baylor Lymphoma SPORE)
12:50 – 1:10 PM	Presentation: "Immune Compatible Donor Memory Natural Killer Cells Functionally Persist for Months following Adoptive Transfer into Leukemia Patients" – Todd Fehniger (Washington University Leukemia SPORE)
1:10 – 1:30 PM	Presentation: "Preclinical Optimization of T Cell Directed Therapy in Multiple Myeloma" – Marta Chesi (Mayo Clinic Multiple Myeloma SPORE)
1:30 – 1:50 PM	Presentation: "Targeting AML Using Novel Bispecific and Antibody-Drug Conjugates" – Michael Rettig (Washington University Leukemia SPORE)
1:50 – 2:10 PM	Presentation: "Successful Execution and Translational Relevance of a Dedicated Pediatric Lymphoma Tissue Bank" – Rayne Rouce (Baylor Lymphoma SPORE)
2:10 – 2:30 PM	**Break**

Session II – Immunotherapy
Chair: John DiPersio, Washington University

2:30 – 2:50 PM	Presentation: "Personalized Cancer Vaccine for Acute Myeloid Leukemia" – David Avigan (DFCI/Harvard SPORE in Myeloid Leukemia)
2:50 – 3:10 PM	Presentation: "Response-adapted Anti-PD1 Based Salvage Therapy for Hodgkin Lymphoma with Nivolumab +/- ICE (NICE)" – Alex Herrera (City of Hope Lymphoma SPORE)
3:10 – 3:30 PM	Presentation: "Viroimmunotherapy for Multiple Myeloma (Systemic Oncolytic VSV Virotherapy for Hematologic Malignancies)" – Martha Lacy (Mayo Clinic Multiple Myeloma SPORE)
3:30 – 3:50 PM	Presentation: "Off-the-shelf Engineered Cord Blood-Derived Natural Killer Cells for the Treatment Acute Lymphoblastic Leukemia" – Katy Rezvani (MDACC Leukemia SPORE)
3:50 – 4:10 PM	Presentation: "In situ Immunization of Lymphoma with a Virus Like Particle Containing a TLR9 Agonist Combined with Anti-PD1 Therapy" – George Weiner (University of Iowa/Mayo Clinic Lymphoma SPORE)
4:10 – 4:30 PM	Presentation: "Chimeric Antigen Receptor T Cells for Acute Myeloid Leukemia" – Anthony Daniyan (MSKCC Leukemia SPORE)
4:30 – 4:50 PM	**Panel Discussion hosted by Session Chair**

Tuesday, October 5,2021

Session I – Molecular Diagnostics
Chair: Smita Bhatia, University of Alabama at Birmingham

12:00 – 12:20 PM	Presentation: "Molecular Markers of Therapy-related Myeloid Neoplasms After Autologous Transplant for Lymphoma" – Smita Bhatia (City of Hope Lymphoma SPORE)
12:20 – 12:40 PM	Presentation: "The Iowa/Mayo Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER) Cohort Study" – James Cerhan (University of Iowa/Mayo Clinic Lymphoma SPORE)
12:40 – 1:00 PM	Presentation: "Use of Clinical Whole-Genome Sequencing for Fast, Accurate, and Accessible Genomic Profiling of Acute Myeloid Leukemia Patients" – Dave Spencer (Washington University Leukemia SPORE)

Session II – Targeted Therapies

Chair: Scott Armstrong, Dana Farber Cancer Institute

1:00 – 1:20 PM	Presentation: "Biologic and Therapeutic Studies in Juvenile Myelomonocytic Leukemia (JMML)" – Elliot Stieglitz (Developmental and Hyperactive RAS SPORE, Indiana University/UCSF)
1:20 – 1:40 PM	Presentation: "Co-targeting BET Bromodomain Proteins and Aberrant Signaling in Acute Myeloid Leukemia (AML)" – Benjamin Huang (Developmental and Hyperactive RAS SPORE, Indiana University/UCSF)
1:40 – 2:00 PM	Presentation: "Targeting the Palmitoylation/Depalmitoylation Cycle in NRAS Mutant Hematologic Cancers" – Kevin Shannon (Developmental and Hyperactive RAS SPORE, Indiana University/UCSF)
2:00 – 2:20 PM	Presentation: "Targeting Menin in Leukemia" – Scott Armstrong (DFCI/Harvard Myeloid Leukemia SPORE)
2:20 – 2:40 PM	Presentation: "Increasing Therapeutic Efficacy In IDH-Mutant AML" – Ross Levine (MSKCC Leukemia SPORE)
2:40 – 3:00 PM	Presentation: "New Epigenetic Therapy Targets" – Jean-Pierre Issa (MDACC Leukemia SPORE - Coriell Institute)
3:00 – 3:20 PM	**Panel Discussion hosted by Session Chairs**
3:20 – 3:30 PM	**Break**

Session III – Overview

Chair: Leif Bergsagel, Mayo Clinic, Arizona

3:30 – 3:50 PM	Presentation: "The Memorial Sloan Kettering Cancer Center SPORE in Leukemia" – Omar Abdel-Wahab
3:50 – 4:10 PM	Presentation: "Washington University SPORE in Leukemia: Overview" – Daniel Link
4:10 – 4:30 PM	Presentation: "Overview of Baylor Lymphoma SPORE" – Helen Heslop
4:30 – 4:50 PM	Presentation: "M.D. Anderson Cancer Center SPORE in Leukemia Overview" – Marina Konopleva
4:50 – 5:10 PM	Presentation: "The Mayo Clinic Multiple Myeloma SPORE" – Leif Bergsagel
5:10 – 5:30 PM	Presentation: "City of Hope Lymphoma SPORE Overview" – Stephen Forman
5:30 – 5:50 PM	Presentation: "Overview of The University of Iowa/Mayo Clinic Lymphoma SPORE" – Thomas Witzig
5:50 – 6:10 PM	**Panel Discussion hosted by Session Chair**

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Tuesday, Oct. 5: Session III - Overview

Monday, October 4, 2021

Session I – Immunotherapy

12:00 PM – 2:10 PM

Activating Phagocytic Macrophages in non-Hodgkin Lymphoma (NHL)

Abstract Presenter: Stephen Ansell

Stephen Ansell, Hyo Jin Kim, ZhiZhang Yang, Xinyi Tang, Anne Novak, Andrew Feldman

University of Iowa/Mayo Clinic Lymphoma SPORE

Monocytes and macrophages represent the central components of the innate phagocytic immune system and CD68+ tumor associated macrophages (TAMs) are associated with the prognosis of patients with NHL. To determine the phenotype and function of TAMs in NHL, we measured the expression of signal-regulatory protein alpha (SIRPα), a receptor that inhibits phagocytic function and regulates macrophage-mediated removal of lymphoma cells. Based on SIRPα expression, we identified three distinct populations of TAMs – those that are CD14+SIRPα^{high} and those that were CD14-SIRPα^{low} or CD14-SIRPα^{neg}. We found that CD14+SIRPα^{high} cells express common macrophage markers; exhibit characteristic differentiation, migration, and phagocytosis; and suppress T-cell function. However, CD14-SIRPα^{low} cells express fewer typical macrophage markers; migrate less and phagocytose tumor cells less efficiently; and stimulate rather than suppresses T-cell function. Interestingly, the CD14-SIRPα^{neg} subset express distinct macrophage markers compared to the other two subsets; have limited ability to migrate and phagocytose; but stimulate T-cell function.

The induction of phagocytosis by 'eat-me' signals on tumor cells is countered by 'don't-eat-me' signals such as CD47, which binds to SIRPα on macrophages and inhibits phagocytosis. When using SIRPα-Fc to block the interaction between SIRPα and CD47, phagocytosis of tumor cells was differentially increased in the three macrophage subsets. To clinically test whether we could modulate macrophage function by blocking SIRPα signaling, we tested TTI-621 (SIRPα-Fc), an immune checkpoint inhibitor consisting of the CD47 binding domain of human SIRPα linked to the Fc region of human IgG1, to block the CD47 "do not eat" signal. In a phase 1 study, 164 patients received TTI 621: 18 in dose escalation and 146 in dose expansion (monotherapy, n=107; rituximab combination, n=35; and nivolumab combination, n=4). The ORR with single-agent TTI-621 was 29% (2/7) for DLBCL and 25% (8/32) for T-cell NHL and was 25% (6/24) for DLBCL treated with TTI-621 plus rituximab.

We conclude that blocking CD47 signaling promotes phagocytosis of malignant B cells resulting in clinical benefit. To further test whether simultaneous activation of both macrophages and T-cells improves clinical outcome, we are developing a phase II clinical trial testing the combination of SIRPα inhibition and immune checkpoint blockade.

“Off-the-Shelf" Allogeneic CAR-Expressing Immune Effectors for Treatment of CD19+ or CD30+ Lymphomas

Abstract Presenter: Carlos Ramos

Carlos Ramos, Premal Lulla, David Quach, Amy Courtney, Rayne Rouce, Huimin Zhang, Natasha Lapteva, Sachin Thakkar, Bambi Grilley, Adrian Gee, Malcom Brenner, Cliona Rooney, Leonid Metelitsa, Helen Heslop

Baylor Lymphoma SPORE

Autologous T cells engineered to express a CD19-specific chimeric antigen receptor (CAR) mediate high rates of complete response in patients with B-cell malignancies. However, autologous cell therapy products are time- and resource-intensive to manufacture and vary in potency. “Off-the-shelf” immune effector products that are banked from healthy donors would improve accessibility, allow rapid treatment, and reduce costs. Major obstacles to the success of allogeneic T cells are GVHD and graft rejection, mediated by host and recipient alloreactive T cells, respectively. We are exploring whether Epstein Barr Virus specific T cells (EBVSTs) or NKT cells represent two allogeneic platforms that overcome these limitations.

EBVSTs are virus reactive rather than alloreactive and have not produced GVHD in 300+ recipients. When EBVST express CD30.CARs, they kill both CD30+ and EBV+ lymphomas through their CAR and native TCR, respectively. Moreover, the CD30.CAR may prevent rejection of allogeneic CAR-T cells, since recipient alloreactive T cells upregulate CD30 and themselves become targets for the CD30.CAR-EBVSTs. We have treated 8 patients with multiply relapsed CD30+ lymphomas in a dose-escalation study, infusing 4-40×107 CD30.CAR EBVSTs after lymphodepletion. At 6 weeks, 2 patients had a CR and 3 a PR.

NKT cells show similar promise. Unlike T cells that are restricted by polymorphic HLA molecules, Vα24-invariant natural killer T cells (NKTs) are restricted by the CD1d molecule, which is monomorphic. These cells are therefore non-alloreactive. We have treated 5 patients (4 DLBCL and 1 ALL) in another dose-escalation trial of 1-10×107/m2 allogeneic NKTs expressing a CD19.CAR. Three of 4 DLBCL patients had a PR, and the ALL patient had a CRi at 4 weeks. Donor-derived NKT and CAR-NKT cells were present in peripheral blood and in tumor biopsies.

Both CAR-EBVSTs and CAR-NKTs were well tolerated. Commonest adverse effects were nausea and cytopenias related to lymphodepletion, but there were no dose-limiting toxicities, GvHD or greater than grade 1 CRS.

Therefore, either banked allogeneic CD30.CAR EBVSTs or CD19.CAR NKT cells can safely be given to allogeneic recipients and produce significant tumor responses, including complete remissions. Each may have value as a platform for other “off-the-shelf” CAR-T cell therapies.

Immune Compatible Donor Memory Natural Killer Cells Functionally Persist for Months following Adoptive Transfer into Leukemia Patients

Abstract Presenter: Todd Fehniger

Melissa Berrien-Elliott, Jennifer Foltz, David Russler-Germain, Carly Neal, Jennifer Tran, Margery Gang, Pamela Wong, Bryan Fisk , Celia Cubitt, Nancy Marin, Alice Zhou, Miriam Jacobs, Mark Foster, Timothy Schappe , Ethan McClain , Sweta Desai , Patrick Pence , Michelle Becker-Hapak , Jeremy Eisele , Matthew Mosior, Lynne Marsala, Obi Griffith, Malachi Griffith, Saad Khan, David Spencer, John DiPersio, Rizwan Romee, Geoffrey Uy, Camille Abboud, Armin Ghobadi, Peter Ghobadi, Peter Westervelt, Keith Stockerl-Goldstein, Mark Schroeder, Fei Wan, Patrick Soon-Shiong, Allegra Petti, Amanda Cashen, Todd Fehniger

Washington University Leukemia SPORE

Natural killer (NK) cells are innate lymphoid cells that eliminate cancer cells and produce cytokines and are being investigated as a nascent cellular immunotherapy. Impaired NK cell function, expansion, and persistence within cancer patients remain key challenges for optimal translation to the clinic. One promising strategy to overcome these challenges is cytokine-induced memory-like (ML) NK cells, whereby NK cells acquire enhanced anti-tumor function following brief stimulation with IL-12, IL-15, and IL-18. Here, reduced-intensity conditioning (RIC) HLA-haploidentical hematopoietic cell transplantation (HCT) was augmented with same-donor ML NK cells on Day+7 to treat patients with active acute myeloid leukemia (AML) in a clinical trial (NCT02782546, Fig A). In 15 patients treated, donor ML NK cells were well-tolerated with 87% of patients achieving a composite complete response at Day+28, which corresponded with clearing high-risk mutations, including TP53 (Fig B). NK cells were the major blood lymphocytes for two months post-HCT with prolific expansion (1104-fold) over 1-2 weeks. Multidimensional mass cytometry (Fig C,D) and CITE-seq (Fig E,F) specifically identified donor ML NK cells as distinct from conventional NK cells and persisting for at least two months. Trajectory analysis (pseudotime) also identified a unique ML NK cell state that changed over time within the patient (Fig G). ML NK cells expressed CD16, CD57, and high granzyme B and perforin, along with a unique transcription factor profile. Furthermore, ML NK cells differentiated in patients had enhanced ex vivo function compared to conventional NK cells from both patient and healthy donors. Thus, same-donor ML NK cell therapy augmenting RIC-HCT has an excellent safety profile, enhanced NK cell persistence and functionality, and the ability to induce remissions in high-risk AML patients.

Preclinical Optimization of T Cell Directed Therapy in Multiple Myeloma

Abstract Presenter: Marta Chesi

Marta Chesi, Erin Meermeier, Seth Welsh, Leif Bergsagel

Mayo Clinic Multiple Myeloma SPORE

The recent approval of CAR T cells targeting BCMA on the surface of myeloma cells has generated great excitement due to unprecedented response rates in a population of heavily pre-treated patients. However, responses are generally transient and patient eventually relapse, so combination therapies are under evaluations. Other modalities of T cell redirected therapy against BCMA are also showing impressive clinical results although associated with similar dose limiting toxicities (CRS). We believe it is of paramount importance to optimize immunotherapy efforts in a fully immunocompetent, orthotopic and clinically relevant mouse model of myeloma. Therefore, we have taken advantage of our Vk*MYC^{hCRBN} mouse model and derivative transplantable lines to dissect in vivo the determinant of response or failure to BCMA redirected T cell therapy. First, we established a inverse correlation between efficacy of anti-BCMA bispecific antibody (BsAb) and high tumor burden, which rapidly induced T cell exhaustion, at least in part mediated by high expression of PDL1 on tumor cells. The addition of an IMiD increased the short-term response to the BsAb regardless of tumor burden including in tumors that are not IMiD sensitive, but further promoted T cell exhaustion, showed acute toxicities in few cases and had no effect on the overall survival of the treated mice. Surprisingly, the combination of BsAb with cyclophosphamide was well tolerated and curative in most of the treated mice. Importantly, it was accompanied by the development of immunological memory, which prevented disease relapse. Mechanistically, cyclophosphamide reduced tumor burden through a direct anti-tumor activity, depleted regulatory T cells and reshaped the immune-microenvironment allowing newly generated cytotoxic T cells to expand in the presence of BsAb. While studies are in progress to demonstrate the development of endogenous immunity, we propose that the combination of BsAb + cyclophosphamide should be evaluated in a clinical trial.

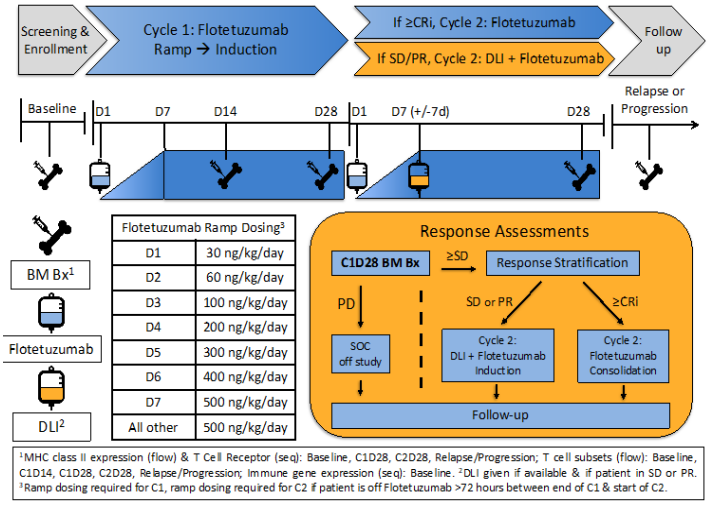
Targeting AML Using Novel Bispecific and Antibody-Drug Conjugates

Abstract Presenter: Michael Rettig

Michael Rettig, Matt Christopher, Peter Westervelt, John DiPersio

Washington University Leukemia SPORE

Background: Allogeneic hematopoietic cell transplantation (alloHCT) is the only curative therapy for patients with high-risk and refractory acute myeloid leukemia (AML). Unfortunately, roughly 40% of AML patients will relapse after alloHCT and face a dismal prognosis with a 2-year survival of approximately 20%. In this project, we are examining if flotetuzumab, a CD123 x CD3 bispecific antibody is an effective approach to treat AML relapse after alloHCT. In **Aim 1**, we are conducting a Phase II clinical trial of flotetuzumab in patients with relapsed or refractory (r/r) AML after alloHCT (NCT04582864). Patients receive flotetuzumab for the first 28 days of the study (cycle 1). Based on day 28 response assessment, patients with CR/CRi continue on flotetuzumab for another 28 days (cycle 2); patients with PR/SD receive DLI plus flotetuzumab (cycle 2); and patients with PD come off study. In **Aim 2**, we are determining the immunophenotype and transcriptional profiles of r/r AML and T cells before and after treatment with flotetuzumab. Recent research has shown that 30-50% of post-alloHCT AML relapse samples have downregulation of MHC class II (MHC-II) expression, which may promote immune effector evasion and disease relapse. In preclinical studies, we found that flotetuzumab led to both direct AML killing as well as significant upregulation of MHC-II expression on AML cells both in vitro and in vivo. In **Aim 3**, we are testing if inhibition of the CD40L/CD40 co-stimulatory and/or phosphatidylinositol-3-kinase (PI3K) signaling pathways can mitigate flotetuzumab-associated cytokine release syndrome (CRS) while maintaining anti-leukemia activity using in vitro and in vivo preclinical models. T cell engaging therapies, which include bispecific retargeting reagents like flotetuzumab, have been limited by CRS. We are testing if anti-CD40L and/or duvelisib, a PI3K-γ,δ inhibitor, reduces flotetuzumab-mediated CRS but not target cell killing in immunodeficient humanized NSG-SGM3 mice and immunocompetent humanized CD3ε-knock-in mice.



Successful Execution and Translational Relevance of a Dedicated Pediatric Lymphoma Tissue Bank

Abstract Presenter: Rayne Rouce

Rayne Rouce, Carl Allen

Baylor Lymphoma SPORE

Pediatric lymphoma represents > 70 distinct histologies. Even among the most common (e.g., mature B cell lymphomas), there are distinct mechanisms of pathogenesis reflecting unique exposures and differentiation events in developing immune systems of children. We have established a dedicated clinical lymphoma program at Texas Children's with catchment area from Louisiana to New Mexico and national and international referrals. We see approximately 200 new patients every year for analysis of pediatric lymphoma and enroll almost all to research studies where we bank tissue including viably preserved blood mononuclear cells, bone marrow aspirate, and tumor tissue, with corresponding clinical information. Beyond Texas, we are also partnering with institutions in Sub-Saharan Africa through Global HOPE that will expand epidemiological studies in pediatric lymphoma. We are able to use these tissues for short-term primary cell culture, expansion in PDX models, and are working on development of organoid models. Thus, the pediatric lymphoma program within the BCM Lymphoma SPORE represents a unique resource to support discovery research, test mechanistic hypotheses, and perform pre-clinical analysis of therapeutic strategies.

Given the broad scope of our pediatric clinical lymphoma program, corresponding tissue bank and connections to the Center for Cell and Gene Therapy and adult lymphoma programs at BCM, we are uniquely poised to conduct novel clinical trials in pediatric lymphoma. The robust tissue bank inclusive of tumor tissue and corresponding clinical information is available to SPORE researchers for use in pre-clinical aims, which often inform clinical testing of novel immunotherapeutic agents in first-in-human trials. Accordingly, the clinical projects within the BCM Lymphoma SPORE include pediatric investigators which enables simultaneous study of investigational agents in pediatric lymphoma patients, conducted under the same IND. To date, we have extended study of novel CAR T-cells targeting T-cell malignancies, CAR T-cells targeting the CD30 antigen and virus-specific T cells targeting EBV-associated malignancies to children, with plans to extend novel CAR-modified off-the-shelf strategies to children as well. Our program thus models a successful platform for safe translation of immunotherapeutic strategies targeting lymphoma to children.


Monday, October 4, 2021
Session II – Immunotherapy
2:30 PM – 4:50 PM

Personalized Cancer Vaccine for Acute Myeloid Leukemia

Abstract Presenter: David Avigan

David Avigan, Jacalyn Rosenblatt

Dana Farber Cancer Institute/Harvard SPORE in Myeloid Leukemia

We have developed a personalized cancer vaccine in which patient derived acute myeloid leukemia (AML) cells are fused with autologous dendritic cells (DCs) such that a broad array of antigens are presented in the context of DC mediated co-stimulation. In a phase II trial, vaccination of older patients following cytoreductive chemotherapy resulted in the durable expansion of leukemia specific T cells in the peripheral blood and bone marrow resulting in 71% of patients remaining without evidence of progression at a median follow up of more than 5 years. The vaccine study provides a powerful platform to interrogate the T cell repertoire with respect to the emergence of dominant clonal populations, their functional status, and correlation with clinical outcome. We have previously demonstrated the emergence of individual T cell clonal populations that persist in the context of durable clinical response. In an ongoing study, DC/AML fusion vaccination is being examined following allogeneic transplantation. In a murine model, we have shown that DC/tumor fusion exhibits synergy with checkpoint inhibition with respect to protection leukemia engraftment and the selective expansion of tumor reactive lymphocytes. We have demonstrated potent therapeutic synergy between the DC/AML fusion vaccine and HMA/venetoclax and have identified a novel mechanism underlying this interaction. Vaccine educated T cells demonstrate remarkable capacity to induce BH3 priming further augmented by venetoclax exposure. We have shown that HMA therapy similarly enhances leukemia cell immunogenicity by augmenting antigen presentation and T cell activation via upregulation of endogenous retroviral elements that induce IFN production. These findings offer a powerful rationale for combination therapy between this unique personalized cell therapy and the potent anti-leukemia platform with immunoregulatory activity.

Response-Adapted Anti-PD1 Based Salvage Therapy for Hodgkin Lymphoma with Nivolumab +/- ICE (NICE)

Abstract Presenter: Alex Herrera

Alex F. Herrera, Robert Chen, Joycelynne Palmer, Nicole Tsai, Kathryn McBride, D. Lynne Smith, Ivana Melgar, Joo Song, Saro Armenian, Jasmine Zain, Liana Nikolaenko, Leslie Popplewell, Auayporn Nademanee, Steven Rosen, Larry Kwak, Stephen J. Forman, Hun Ju Lee, Matthew Mei

City of Hope Lymphoma SPORE

Introduction: Nivolumab is tolerable and effective in patients with relapsed/refractory classical Hodgkin lymphoma and nivolumab combined with brentuximab vedotin (BV) as first salvage therapy yields a high complete response (CR) rate and favorable progression-free survival (PFS) as a bridge to autologous stem cell transplantation (ASCT). With increasing frontline use of BV, we sought to evaluate nivolumab as salvage therapy independent of BV. We performed a phase 2 trial evaluating PET-adapted nivolumab alone or nivolumab combined with ifosfamide, carboplatin, and etoposide (NICE) as first salvage therapy in RR HL.

Methods: Patients with biopsy-proven RR HL after frontline therapy received 3 mg/kg nivolumab every 2 weeks for up to 6 cycles (Figure 1). PET-CT was performed after C3 and C6. After C6, patients in CR proceeded to ASCT while patients with progressive disease (PD) at any point or not in CR after C6 nivolumab received NICE for 2 cycles. The primary endpoint was CR rate according to 2014 Lugano classification. PFS and overall survival (OS) were calculated using the Kaplan Meier method.

Results: 43 patients were evaluable for toxicity; 42 were evaluable for response. Baseline characteristics are shown in Table 1. 34 patients received nivolumab alone and 9 patients received nivolumab/NICE. After nivolumab, the ORR was 83% (34/42) and the CR rate was 73% (30/42). Among the 9 patients receiving NICE, all 9 (100%) responded with 8 (89%) achieving CR. At the end of all protocol therapy (Nivo or Nivo/NICE), the ORR and CR rates were 93% (39/42) and 91% (38/42). 33 patients proceeded to ASCT directly after protocol therapy, including 25 after nivolumab alone. The 2-year PFS and overall survival in all treated patients (n=43) were 72% (95% CI: 56 - 83) and 95% (95% CI: 82 - 99), respectively. Among the 33 patients who proceeded to AHCT directly after protocol therapy (Nivo/NICE), 2-year PFS was 94% (95% CI: 78-98). There were no unexpected toxicities observed after nivolumab or NICE.

Conclusion: PET-adapted sequential salvage therapy with nivolumab followed by NICE was well-tolerated and effective, resulting in a high CR rate and allowing most patients to proceed to AHCT without chemotherapy.

Viroimmunotherapy for Multiple Myeloma (Systemic Oncolytic VSV Virotherapy for Hematologic Malignancies

Abstract Presenter: Martha Lacy

Martha Lacy, Stephen Russell, Kah Whye Peng, Joselle Cook, Nora Bennani, Thomas Witzig

Mayo Clinic Multiple Myeloma SPORE

Clinical success with intravenous oncolytic virotherapy has to date been anecdotal. For myeloma SPORE project 1 we conducted a first-in-human, phase 1 dose escalation trial of one intravenous infusion of an oncolytic Vesicular Stomatitis Virus (VSV) incorporating interferon beta and sodium iodine symporter transgenes (VSV-IFNβ-NIS) in 15 patients with relapsed refractory myeloma (7), T cell lymphoma (7) or AML (1). Viral infusions were well tolerated, with no dose limiting toxicities and no viral shedding in saliva or urine. Activity in the myeloma patients was limited to transient reduction in FLC levels. However, three of the seven T cell lymphoma (TCL) study subjects achieved objective responses, most notable at the highest dose level. Serum levels of virally encoded IFNβ provided a convenient real time biomarker to track virus infection and to elucidate the relative contributions of oncolytic and immune tumor cell killing in individual subjects. Based on preclinical studies, additional study arms are now open to accrual, combining VSV-IFNβ-NIS with (i) the Jak inhibitor ruxolitinib to enhance oncolytic potency and drug tolerability or (ii) cyclophosphamide to reboot the antitumor immune response and amplify the oncolytic phase of the therapy. Additional arms addressing B cell lymphomas and/or incorporating checkpoint inhibitor therapy, bispecific antibodies or CART cells are planned.

“Off-The-Shelf" Engineered Cord Blood-Derived Natural Killer Cells for The Treatment Acute Lymphoblastic Leukemia

Abstract Presenter: Katy Rezvani

Katy Rezvani, Elizabeth Shpall

MD Anderson Cancer Center Leukemia SPORE

Aim 1: Test the safety and antitumor activity of iC9/CAR.19/IL15-transduced CB-NK cells in patients with relapsed or refractory acute lymphoblastic leukemia. NK-cells are attractive contenders for cell therapy as they exert potent antitumor cytotoxicity and unlike T-cells, do not cause graft versus host disease (GVHD) in the allogeneic setting. Through our Good Manufacturing Practice (GMP) facility, we have successfully engineered NK cells to express a specific CAR and are currently conducting a first-in-human trial of CAR.19/IL-15 transduced CB NK-cells in lymphoid tumors. Preliminary data prove their safety and efficacy with 8 of 11 patients with NHL or CLL treated to date achieving a complete or partial remission (NCT03056339). The data from the Phase I portion of this trial was published in the New England Journal of Medicine {Liu, 2020}. One of the problems with enrolling ALL patients was that most were too refractory to wait the 14 days for CAR-NK cell manufacture. We have now optimized the CAR-NK cell cryopreservation procedure so these will be off-the shelf products that will be infused immediately after thawing. This should markedly enhance accrual.

Aim 2: Track the fate of iC9/CAR.19/IL-15+ CB-derived NK cells after adoptive transfer and correlate the findings with disease response. Correlative studies have shown the persistence of the CAR-NK cells in the blood of the patients for up to one year following infusion.

Aim 3: Determine if targeting TGF-βR2, will further improve the therapeutic potential of IC9/CAR.19/IL-15+ CB-NK cells by protecting them from the immunosuppressive tumor microenvironment. The Rezvani laboratory developed and optimized a protocol for combined C9/CAR.19/IL-15 retroviral transduction and Cas9 ribonucleoprotein (Cas9 RNP)-mediated gene editing of TGF-βR2 to protect CAR-NK cells from TGF-β-mediated suppression in the TGF-β-rich ALL microenvironment. The gene-edited NK cells efficiently killed CD19 B cell cancer targets in vitro, even in the presence of exogenous TGF-β.

In situ immunization of lymphoma with a Virus Like Particle containing a TLR9 agonist combined with anti-PD1 therapy

Abstract Presenter: George Weiner

Umar Farooq, Shakoora Sabree, Sue Blackwell, Chaobo Yin, Caitlin Lemke, George Weiner

University of Iowa/Mayo Clinic Lymphoma SPORE

Project 2 of the Iowa-Mayo Lymphoma SPORE is entitled "Microenvironment Modification and Anti-PD1 Immunotherapy of Lymphoma". The underlying hypothesis of this project is that modifying the lymphoma microenvironment to augment antigen release, uptake and presentation, will increase the lymphoma T cell response and enhance the efficacy of anti-PD1 therapy for non-Hodgkin Lymphoma (NHL). This project includes preclinical and clinical evaluation of a virus-like particle known as CMP-001 (now also known as vidutolimod). CMP-001 is composed of the Qβ bacteriophage capsid encasing a TLR9 agonist. CMP-001 is injected into an involved lymph node along with systemic anti-PD1 therapy. We found *In vitro* and in animal models that anti-Qβ antibody is required for CMP-001 to induce production of IFNα from pDCs and to induce an anti-tumor immune response. The first lymphoma patients enrolled in the SPORE-supported CMP-001 clinical trial lacked benign B cells (due to recent anti-CD20 therapy or CAR-T therapy). Consistent with preclinical results, these patients failed to develop an anti-Qβ, immunologic or therapeutic response to therapy. The third patient had benign B cells and developed an anti-Qβ antibody response. A PET scan after six CMP-001 doses suggested progression, however biopsy revealed only benign follicular hyperplasia. The repeat PET improved indicating the initial PET was pseudo-progression. Based on these results, the protocol was modified to reflect the need for benign B cells and the possibility of PET revealing pseudo-progression. A fourth patient with Anaplastic T cell Lymphoma had a clear Partial Response and a fifth patient is currently undergoing therapy. These results suggest in situ immunization with CMP-001 plus systemic anti-PD1 is a promising therapy in lymphoma. A melanoma trial of CMP-001 plus anti-PD1 antibody was recently published in Cancer Discovery and shows this approach to cancer therapy has implications beyond lymphoma. Shakoora Sabree, an MD/PhD student supported by a SPORE minority supplement, has focused on further exploration of the complexity of the immune response to CMP-001. In vitro studies, animal modeling and the clinical trial are continuing.

Chimeric Antigen Receptor T Cells for Acute Myeloid Leukemia

Abstract Presenter: Anthony Daniyan

Anthony Daniyan, Renier Brentjens

Memorial Sloan Kettering Cancer Center Leukemia SPORE

Over the last decade, chimeric antigen receptor (CAR) T cells have emerged as the most potent form of adoptive immunotherapy. CAR T cell mediated elimination of tumor cells is dependent on the surface expression of tumor-associated antigens, and is independent of the tumor cell's sensitivity to chemotherapy. Given this, CAR T cells could potentially eliminate LSCs through the targeting of tumor-associated surface antigens. Unfortunately, unlike B-cell derived leukemias and lymphomas which ubiquitously express CD19, AML lacks a single universal targetable antigen, necessitating the need for a dual-antigen targeted approach. CD33 and CD371 (CLEC12A, CLL-1 and MICL) have emerged as very promising dual targets in AML given their coexpression on bulk AML cells as well as putative LSCs. Hence, CAR T cells simultaneously targeting CD33 and CD371 have the potential for bringing about cures in AML. However, despite appropriate antigen coverage, as seen with targeting CD19, CAR T cell therapy leads to suboptimal clinical outcomes in a majority of patients. Factors responsible for these clinical failures include: (i) the utilization of non-human derived single-chain variable fragments (scFvs) to generate CAR T cells leading to immune rejection of the synthetic CAR construct, (ii) the inaptitude of CAR T cells to proliferate and persist in the presence of high antigen burden, and (iii) the inability of CAR T cells to function in the presence of low antigen density disease. Therefore, for AML-directed CAR T cells to be efficacious, there is an urgent and critical need to develop platforms that (i) simultaneously target CD33 and CD371 with human-derived scFvs, (ii) proliferate and persist in the presence of high tumor burden, and (iii) demonstrate activity in the context of low-antigen density disease.

To address this urgent and critical need, we are developing a fully-human AML-directed CAR T cell capable of simultaneously targeting CD33 and CD371, with future iterations of this platform integrating synthetic modifications allowing for enhanced proliferation in the setting of both low-antigen density and high tumor burden disease.


Tuesday, October 5, 2021
Session I - Molecular Diagnostics
12:00 PM – 1:00 PM

Molecular Markers of Therapy-Related Myeloid Neoplasms After Autologous Transplant for Lymphoma

Abstract Presenter: Smita Bhatia

S. Bhatia, CC Yan, C Gibson, Y Chen, A. Bosworth, J. He, L. Hagerman, D. Crossman, P. Singh, B. Ebert, Stephen J. Forman, Ravi Bhatia

City of Hope Lymphoma SPORE

Therapy-related myeloid neoplasm (t-MN) is a lethal complication of autologous hematopoietic cell transplantation (aHCT) for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma NHL). t-MN after aHCT is associated with older age at aHCT, pre-aHCT exposure to alkylators, etoposide and radiation, peripheral blood stem cell (PBSC) mobilization with etoposide, and conditioning with total body irradiation (TBI). The elevated risk of t-MN after aHCT coupled with the dismal prognosis, presents an unmet need for pre-aHCT identification of patients at risk for post-aHCT t-MN to guide use of alternative therapeutic options (other than aHCT) for HL/NHL management.

We have constructed a cohort of ~1300 HL/NHL patients undergoing aHCT at City of Hope (COH) and have followed it for development of t-MN. We observed altered gene expression in PBSC samples from patients who subsequently developed t-MN when compared with patients who did not. This information was used to develop an optimal 38-gene PBSC classifier (positive predictive value: 93.3%; specificity: 95%; sensitivity: 87.5%).

For the proposed project, we hypothesized that a clinical+genetic risk prediction model applied prior to aHCT will allow identification of HL/NHL patients at increased risk post-aHCT t-MN. The COH cohort serves as the Discovery Cohort. HL/NHL patients undergoing aHCT at the University of Nebraska [UNE] or University of Minnesota [UMN] will serve as Validation Cohorts.

Discovery Cohort: The cumulative incidence of t-MN was 6.8% at 15y. Factors associated with t-MN included older age at aHCT (HRper_year_increase_in_age=1.06; p=0.006) and exposure to TBI+Fludarabine (HR=13.4, p <0.001; reference: no TBI/Fludarabine). Targeted sequencing (depth >1000x) in PBSC samples focused on 91 genes recurrently-mutated in clonal hematopoiesis. Somatic mutations were identified in 20% of the cohort. The most commonly mutated genes included DNMT3a, PPM1D, TET2 and TP53. The prevalence of CHIP mutations increased with age at aHCT, approaching 40% among those who were >60y at aHCT. The cumulative incidence of t-MN was higher among those who presented with CHIP in the PBSC product. Further, the cumulative all-cause mortality rate was higher among those with CHIP. We are in the process of constructing the risk prediction models, with the goal to validate them in the independent Validation Cohort.

The Iowa/Mayo Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER) Cohort Study

Abstract Presenter: James Cerhan

James Cerhan, Brian Link, Thomas Habermann, Matthew Maurer, Andrew Feldman, Sergei Syrbu, Lisa Rimsza, Umar Farooq, Carrie Thompson, Allison Rosenthal, Anne Novak, Stephen Ansell, Thomas Witzig, George Weiner

University of Iowa/Mayo Clinic Lymphoma SPORE

The MER was initiated in 2002 at the University of Iowa and Mayo Clinic Rochester as a prospective cohort study of newly diagnosed lymphoma patients. It was designed as a population science resource to identify clinical, epidemiologic, host genetic, biologic, tumor, and treatment factors that impact lymphoma outcomes and long-term survivorship. At enrollment, participants complete a medical history questionnaire, provide a blood specimen (for DNA, plasma and serum), and allow access to their medical records. Clinical and treatment data are abstracted using a common protocol, and pathology is centrally reviewed and archived in tissue microarrays. Participants are contacted every 6 months for 3 years after diagnosis and annually thereafter to ascertain a variety of clinical, quality of life and other survivorship data; all disease progression/relapse, retreatment, transformation, cause of death and new cancers are validated against medical records. In 2015, the MER was expanded as the Lymphoma Epidemiology of Outcomes (LEO) cohort, adding six additional academic centers to enhance geographic and racial/ethnic diversity. In 2016 the MER was opened in Mayo Clinic Arizona. Cumulatively through 6/30/2021, 10,616 participants have been enrolled into the MER (2,198 co-enrolled in LEO). To date, 2,924 have died (1405 due to lymphoma or its treatment) and <100 have been lost to follow-up. Over 175 papers have been published using the MER cohort. Selected key contributions include finding that pretreatment vitamin D insufficiency was associated with inferior outcomes in DLBCL and T-cell lymphoma as well as CLL, findings that provided the rationale for two active intervention trials; identifying and validating the novel clinical endpoint of EFS at 24 months after diagnosis (EFS24) for R-CHOP treated DLBCL patients and immunochemotherapy-treated follicular lymphoma patients, endpoints that demonstrate the importance of reassessing prognosis after treatment and are useful for patient counseling and management, biomarker discovery and trial design; whole-exome sequencing of paired tumor-normal DNA that identified novel somatic driver mutations in DLBCL; and a genome-wide association study that identified germline predictors of prognosis in DLBCL. Access to the MER cohort for collaborative research can be requested through the Iowa/Mayo SPORE Data and Biospecimens Access Committee.

Use of Clinical Whole-Genome Sequencing for Fast, Accurate, And Accessible Genomic Profiling of Acute Myeloid Leukemia Patients

Abstract Presenter: David Spencer

Eric Duncavage, Molly Schroeder, David Spencer

Washington University Leukemia SPORE

Genome analysis is essential for the diagnosis and treatment of patients with acute myeloid leukemia (AML). For more than 30 years, metaphase karyotyping has been performed on leukemic cells to identify recurrent and patient-specific chromosomal abnormalities, which form the basis for the diagnostic classification of AML and stratification of patients into risk groups that predict relapse after initial therapy. Although other genetic assays are also used to identify clinically relevant AML mutations, including fluorescent in situ hybridization to detect specific chromosomal rearrangements and targeted DNA sequencing to identify gene mutations, conventional cytogenetic analysis is still performed for every patient.

We recently developed a streamlined whole-genome sequencing (WGS) assay, ChromoSeq, that can be used in place of conventional cytogenetics to obtain genetic profiles of AML patients for diagnostic classification and risk stratification. This approach uses rapid library preparation from bone marrow or peripheral blood, sequencing to >50x genome coverage, and a custom analysis that is optimized for speed and the detection of known, clinically relevant mutations, including translocations, copy number alterations (CNA), and gene mutations in selected targets. ChromoSeq results are summarized in a concise, one-page report with all the findings necessary for genetic risk stratification using established guidelines. Analysis of 235 patients with myeloid malignancies using this method demonstrated 100% sensitivity for the recurrent translocations (N=40) and CNAs (N=91) identified by conventional cytogenetics, and 89% sensitivity for mutations in 40 recurrently mutated genes (N=348). It also identified additional clinically significant genomic events not reported by the conventional clinical assays in 28.0% (66/235) of cases. Prospective sequencing of 117 consecutive patients showed that this WGS approach could be performed in <3 days and identified cytogenetically cryptic findings in 26.5% of cases (31/117), changing the genetic risk category for 22 patients (18.8%) in this unselected cohort. Assignment patients to standard genetic risk categories using WGS instead of conventional testing was predictive of clinical outcome and identified more patients with adverse-risk findings who had shorter overall survival.

These results demonstrate that our ChromoSeq WGS assay provides rapid, accurate, and clinically relevant genomic profiles for AML patients with increased yield and more efficient risk stratification. We have implemented this assay as a laboratory-developed test (LDT) and are using it for all newly diagnosed AML patients at our center in the context of a prospective trial that will further establish WGS as a clinically relevant diagnostic tool for AML patients.


Tuesday, October 5, 2021
Session II - Targeted Therapies
1:00 PM – 3:20 PM

Biologic and Therapeutic Studies in Juvenile Myelomonocytic Leukemia (JMML)

Abstract Presenter: Elliot Stieglitz

Elliot Stieglitz, Ben Braun, Kevin Shannon, Mignon Loh

Developmental and Hyperactive RAS SPORE, University of California San Francisco

Neurofibromatosis type 1 (NF1), the most common cancer predisposition syndrome, is caused by germ line mutations in the NF1 tumor suppressor gene, which encodes a GTPase activating protein that negatively regulates Ras signaling. In addition to its role as an initiating mutation in NF1-associated cancers, somatic NF1 mutations are prevalent in glioblastoma (GBM), acute myeloid leukemia (AML), melanoma, and lung adenocarcinoma. NF1 mutations have also emerged as significant cause of adaptive resistance in some cancers. The goal of the DHART SPORE is to implement effective mechanism-based therapies for cancers characterized by germline and somatic NF1 mutations.

Project 3 focuses on juvenile myelomonocytic leukemia (JMML), an aggressive myeloproliferative neoplasm (MPN) of infants and young children. Mutations in NF1 and other Ras pathway genes such as NRAS, KRAS, PTPN11, and CBL initiate JMML and are invariably present at high allelic frequency at both diagnosis and relapse. Progression to AML occurs in 20-30% of JMML patients. Consistent with the molecular genetics of JMML, using the Mx1-Cre transgene to inactivate a conditional mutant Nf1flox allele or to express oncogenic KrasG12D or NrasG12D induces a JMML-like MPN in mice. Preclinical trials in these models revealed remarkable efficacy of MEK inhibition, which restored a normal pattern of proliferation and differentiation in Kras and Nf1 mutant hematopoietic cells but did not eliminate them.

These data informed an ongoing national phase 2 trial of trametinib in relapsed/refractory JMML (ADVL1521; NCT03190915). Four of nine patients treated to date have experienced objective responses with two additional patients experiencing stable disease for the maximum 12 cycles permitted on study. Enrollment continues and we are performing correlative molecular analyses of serial patient specimens. We also collaborated with colleagues in Europe and Japan to identify global DNA methylation as an independent biomarker of outcome in JMML with the most hypermethylated samples portending the worst prognosis. We anticipate completing the ADVL1521 trial in 18-24 months and have designed the first interventional risk-stratified clinical trial in newly diagnosed JMML. We are also testing different mechanism-based therapies in JMML patient specimens and in GEM models of JMML and AML to inform future translation.

Co-targeting BET Bromodomain Proteins and Aberrant Signaling in Acute Myeloid Leukemia (AML)

Abstract Presenter: Benjamin Huang

Benjamin Huang, Kevin Shannon

Developmental and Hyperactive RAS SPORE, University of California San Francisco

Somatic alterations that deregulate epigenetic programs and signal transduction pathways frequently coexist in AML and this provides a rationale for testing drug combinations targeting both processes. We performed retroviral insertional mutagenesis in NrasG12D mice to generate genetically diverse AMLs and used the MEK inhibitor PD0325901 (PD901) to inhibit the Raf/MEK/ERK (MAPK) Ras effector pathway in congenic recipient mice harboring these primary leukemias. Here we report substantial preclinical efficacy of the BET bromodomain (BET) inhibitor PLX51107 at Plexxikon that was further enhanced by PD901. We first exposed five NRAS or KRAS mutant human AML cell lines to varying concentrations of PLX51107 and PD901. These studies revealed potent synergy based on cell proliferation and apoptosis readouts with PLX51107 + PD901 cooperating to potently downregulate MYC and its transcriptional targets. To follow-up on these promising in vitro data, we transplanted 5 primary Nras mutant AMLs into recipient mice and treated them with control vehicle, PLX51107, PD901, or both drugs. PLX5110 7 (10 mg/kg/day) showed impressive efficacy that was further enhanced by a modest dose of PD901 (1.5 mg/kg given 4 days per week).

We evaluated "near isogenic" matched pairs of drug-sensitive parental and relapsed leukemias to identify candidate resistance mechanisms. Re-transplanting relapsed AMLs into secondary recipients and re-treating them confirmed intrinsic resistance, which was also validated ex vivo. Multiple resistant leukemias down-regulated basal Myc protein expression, suggesting that transcriptional networks are "rewired". PLX51107 treatment of parental AMLs resulted in transcriptional changes consistent with myeloid maturation in a dose-dependent manner. By contrast, the corresponding resistant AMLs are relatively "immature" compared to their parental counterparts, consistently upregulated Myc transcriptional targets irrespective of Myc protein levels, and unexpectedly downregulate Ras transcriptional targets. We corroborated these findings by analyzing large pediatric AML transcriptome datasets. Our data indicate that BET + MEK inhibitor combinations may be effective in AMLs characterized by hyperactive Ras signaling. The efficacy of relatively low doses of PD901 used in combination with PLX51107 further suggests that this approach might overcome the frequent dose-limiting adverse side effects of single agent treatment with allosteric MEK inhibitors.

Targeting the Palmitoylation/Depalmitoylation Cycle in NRAS Mutant Hematologic Cancers

Abstract Presenter: Kevin Shannon

Kevin Shannon, Benjamin Cravatt, Micah Niphakis

Developmental and Hyperactive RAS SPORE, University of California San Francisco

Three human RAS and mouse Ras genes encode four highly homologous proteins (H-Ras, N-Ras, K-Ras4a, and K-Ras4b). Different RAS genes are preferentially mutated in distinct cancers with KRAS mutations prevalent in epithelial cancers and NRAS mutations predominating in melanoma and hematologic malignancies, including acute myeloid leukemia (AML). NRAS mutations have recently emerged as a major cause of resistance to FDA-approved inhibitors of FLT3 (gilteritinib), IDH2 (enasidenib), and Bcl-2 (venetoclax).

Ras proteins share identical phosphate-binding and "switch" domains and only diverge substantially in the last 24 amino acids. This C-terminal "hypervariable region" (HVR) contains signals that specify post-translational modifications required for proper subcellular localization. The HVR of all four isoforms terminate with a CAAX motif, where the cysteine is prenylated by farnesyltransferase (FTase). This irreversible lipid modification provides weak membrane binding affinity that is stabilized by a second signal motif. For K-Ras4b, this is provided by a polybasic lysine domain and this protein traffics directly to the plasma membrane (PM). By contrast, H-, N-, and K-Ras4a are palmitoylated at cysteine(s) adjacent to the CAAX motif. A cycle of palmitoylation/depalmitoylation mediated by palmitoyl acyl transferase (PAT) and serine hydrolase (SH) enzymes regulates intracellular H-and N-Ras trafficking across the Golgi, ER, and PM.

To date, our ongoing cross-disciplinary collaborative studies have: (1) generated genetic "proof of principle" in a novel strain of $Nras^{G12D,C181S}$ "knock in" mice that validated N-Ras palmitoylation as a therapeutic target; (2) identified the ABHD17 family of SH enzymes as key N-Ras depalmitoylases; (3) yielded a structurally distinct class of selective ABHD17 inhibitors that reduce the growth of NRAS mutant AML cell lines and exhibit genotype-specific activity in an isogenic model; and, (4) demonstrated that the reduced growth of NRAS mutant AML cells correlates with biochemical inhibition of Ras effector pathways. However, these ABHD17 inhibitors are less potent that earlier non-selective SH inhibitors. We are currently pursuing the following biologic and translational questions: (1) do additional SH enzymes impact N-Ras biology and the efficacy of ABHD17 inhibitors?; (2) does ABHD17 inhibition - alone and in combination with MEK inhibition – selectively reduce the growth of NRAS/Nras mutant AMLs *in vivo*?; and, (3) which of the >20 PAT enzymes modify N-Ras in hematopoietic cells? We anticipate that these studies will inform the development of mechanism-bsed chemical inhibitors of oncogenic N-Ras signaling. If successful, this line of investigation would have significant therapeutic impact for AML and number of NRAS-mutant cancers.

Targeting Menin in Leukemia

Abstract Presenter: Scott Armstrong

Scott Armstrong, Richard Stone

Dana Farber Cancer Institute/Harvard SPORE in Myeloid Leukemia

Dysregulated expression the homeotic (HOX) genes and their co-factor MEIS1 is found in up to 40% of cases of acute myeloid leukemia (AML). Two well-known genetic subsets, those with MLL-rearrangements and those with NPM1 mutations, are known to possess high-level expression of HOX/MEIS1 genes and have been shown to be dependent on their continued expression. Recent studies from this SPORE and others have identified the chromatin-associated Menin-MLL protein complex as being required for this continued aberrant gene expression. As such, multiple groups and pharma/biotech companies have developed small molecule inhibitors of the Menin-MLL interaction and demonstrated that these small molecules reverse HOX/MEIS1-driven gene expression. These molecules have entered clinical trial and demonstrate efficacy. In order to begin to define potential novel therapies that can be combined with Menin inhibitors, we have performed a genome wide CRISPR screen to identify synergistic targets and potential mechanisms of resistance. We have identified several chromatin complexes that are critical for Menin inhibitor action and targetable proteins whose inhibition/degradation leads to synergistic inhibition of cell growth. In vivo studies are ongoing to assess these potential combinations. This preclinical work should identify and characterize novel drugs that when combined with Menin inhibition will lead to even better anti-cancer activity, which will lay the foundation for new drug combinations to treat patients with AML in proposed second-generation clinical trials.

Increasing Therapeutic Efficacy In IDH-Mutant AML

Abstract Presenter: Ross Levine

Eytan Stein, Ross Levine

Memorial Sloan Kettering Cancer Center Leukemia SPORE

We and others have genetically and functionally characterized the contribution of recurrent somatic alterations to acute myeloid leukemia (AML) pathogenesis, including IDH1/IDH2 mutations. This has led to novel insights into AML pathogenesis and led to the identification and validation of IDH1/2 inhibitors as a therapeutic approach in AML; the first small molecule IDH1 (ivosidenib) and IDH2 (enasidenib) inhibitors are now approved for relapsed/refractory IDH1/2 mutant AML. However, not all patients respond to IDH1/2 inhibition and a subset of patients relapse following responses to IDH inhibition. We will use preclinical studies and analysis of primary samples from patients treated with IDH1/2 inhibitors to delineate molecular predictors of sensitivity and resistance to IDH inhibitors, and to test new combination therapeutic approaches to increase therapeutic efficacy in IDH1/2-mutant AML. This will include mechanism-based clinical trials in genetically defined subsets, including a novel, mechanism-based clinical trial combining FLT3 and IDH1/2 inhibition in patients with concurrent mutations. Our collaborative efforts will include genomic interrogation of patient samples, preclinical therapeutic and mechanistic studies, and clinical trials with extensive correlative science aimed to nominate the best combination therapeutic approaches for AML patients with IDH1/2 mutations.

New Epigenetic Therapy Targets

Abstract Presenter: Jean-Pierre Issa

Jean-Pierre Issa, Hagop Kantarjian

MD Anderson Cancer Center Leukemia SPORE - Coriell Institute

Epigenetic therapy aims to reprogram gene expression in cancer cells to achieve a therapeutic effect. To date, DNMT inhibition is the most effective form of epigenetic therapy in myeloid leukemias. We have developed and validated a live cell assay to screen for drugs that achieve the same degree of epigenetic reprogramming as DNMT inhibition. Using this screen, we discovered a new class of epigenetic drugs that activate silenced expression through inhibition of CDK9. CDK9 is a transcriptional regulator previously linked to gene activation through the pTEFb complex that phosphorylates RNAPII and promotes transcriptional elongation. Our new data now place CDK9 at the heart of a node that regulates both gene silencing and activation in proliferating cells. As such, targeting CDK9 has pleotropic effects on gene expression that appear ideal from an anti-tumor perspective: One observes simultaneous gene activation (of tumor suppressors), repression (of oncogenes), and induction of an interferon immune signature, which may be immune-sensitizing. Known CDK9 inhibitors (flavopiridol, SNS-032) have activity in leukemias but are marred by serious chemotherapy-like toxicities. Examining published data, we find that doses of these drugs in use clinically are at least an order of magnitude higher than what is needed to inhibit CDK9, and we speculate that the toxicity observed is typical of cross-target inhibition of other CDKs (e.g. CDK1/2). Thus, we hypothesize that low doses of CDK9-selective drugs may preserve activity through epigenetic effects of CDK9 inhibition, while reducing toxicity by avoiding other CDKs. In this grant, we will elucidate mechanisms of epigenetic effects of CDK9, determine the downstream effects of CDK9 inhibition on cellular function and immune responses, and conduct a clinical trial of a new CDK9-selective drug in myeloid leukemias. Successful completion of these aims will introduce a new form of epigenetic therapy in the treatment of leukemias.


Tuesday, October 5, 2021
Session III – Overview
3:30 PM – 6:10 PM

The Memorial Sloan Kettering Cancer Center SPORE in Leukemia

Abstract Presenter: Omar Abdel-Wahab

Omar Abdel-Wahab, Martin S. Tallman

Sloan Kettering Institute for Cancer Research

Despite recent progress, the majority of patients with acute myeloid leukemia (AML) relapse following treatment, targeted therapeutic approaches for many recurrent molecular subtypes of AML are still lacking, the development of effective immunotherapeutic approaches for AML has been challenging, and survival rates in AML patients remain low. To improve outcomes, there is an urgent need to develop mechanism-based, targeted, and immune-based therapies for AML patients and to identify novel biomarkers for risk classification and response to therapy. To this end, the Memorial Sloan Kettering Cancer Center (MSK) SPORE focuses on defining mechanisms that contribute to AML development and resistance to therapy, performing preclinical studies on novel molecular and immunologic targets in AML, and rapidly translating preclinical insights to innovative clinical trials for AML patients.

The overall translational aims of our SPORE program are to 1) interrogate genetic and molecular pathways required for AML initiation and maintenance; 2) develop novel targeted therapies and immunotherapeutic approaches for AML based on recurrent genomic alterations and leukemia stem-cell (LSC) specific markers; and 3) identify and validate the mechanism of action, therapeutic efficacy, and predictors of response/resistance of mechanism-based therapies for AML patients.

Our SPORE includes four projects, each addressing a different unmet need in the clinical management of AML: Project 1. Increasing therapeutic efficacy in isocitrate dehydrogenase (IDH)–mutant AML (led by Ross Levine, Andrew Intlekofer, and Eytan Stein); Project 2. Defining and exploiting genetic dependencies in complex karyotype AML (led by Scott Lowe and Martin Tallman); Project 3. Therapeutic inhibition of splicing through inhibition of protein arginine methylation in leukemia (led Omar Abdel-Wahab and Andrew Kung); and Project 4. Chimeric Antigen Receptor T-Cell Therapy for the Treatment of Acute Myeloid Leukemia (led by Anthony Daniyan and Renier Brentjens).

Washington University SPORE in Leukemia: Overview

Abstract Presenter: Daniel Link

Daniel Link

Washington University Leukemia SPORE

The Washington University SPORE in Leukemia is a highly dynamic translational cancer research program that focuses specifically on leukemias and myelodysplastic syndromes (MDS). We have assembled an outstanding group of investigators with complementary expertise in basic and clinical leukemia research. In this SPORE, we leverage expertise in cancer genomics, immunology, and hematopoiesis to develop innovative translational research in leukemia. Our long-term goal is to develop novel biomarkers and treatments for leukemias and myelodysplastic syndromes and to develop and promote innovative translational leukemia research. To achieve these goals, the following specific aims are proposed.

Aim 1. We will exploit institutional expertise in cancer genomics, immunology, and hematopoiesis to develop novel biomarkers and treatments for leukemias and myelodysplastic syndromes. Basic research at Washington University has led to the development of the following five translational research projects, all featuring innovative investigator-initiated therapeutic trials for leukemias or MDS.

- *Project 1. Molecular determinants of decitabine responsiveness*
- *Project 2. Targeted therapies for T cell acute lymphoblastic leukemia (T-ALL)*
- *Project 3. Novel therapies for splicesome-mutant MDS*
- *Project 5. Memory-like NK cell augmented hematopoietic cell transplantation for AML*
- *Project 6. Targeting AML using bispecific antibodies*

Aim 2. We will enhance the infrastructure that supports translational leukemia research. This SPORE will support the following Shared Research Resources: 1) Core A. Biospecimen Processing; 2) Core B. Biostatistics; and 3) Core C. Administration.

Aim 3. We will recruit and train new investigators in translational research. This SPORE will support a Career Enhancement Program (CEP) to recruit and mentor new investigators in translational leukemia research. The SPORE has established a successful minority post-baccalaureate training program. The SPORE also will support a Developmental Research Program (DRP) to support innovative translational concepts.

Aim 4. We will facilitate inter-SPORE collaboration. Three of the SPORE projects include multi-institutional clinical trials, including three at other Leukemia SPORE institutions. We have established CEP educational exchange and grant review programs with peer Leukemia SPORE institutions. We will continue to organize and participate in joint meetings with other Leukemia SPOREs.

Overview of Baylor Lymphoma SPORE

Abstract Presenter: Helen Heslop

Helen Heslop, Malcolm Brenner

Baylor Lymphoma SPORE

The lymphoma SPORE at Baylor College of Medicine focuses on developing and testing novel cellular immunotherapies mediated by immune effector cells to treat non-Hodgkin- and Hodgkin lymphoma (NHL and HL). We are testing highly specific immunotherapies that recognize target antigens expressed on tumor cells though native and/or chimeric antigen receptors (CARs). **Project 1** targeted 5 tumor antigens expressed in EBV-negative HL and NHL and showed the strategy was well-tolerated by lymphoma patients, both as adjuvant therapy and to treat chemorefractory lymphoma, and that anti-tumor activity including complete responses were achievable. The investigators are now evaluating this product in combination with 5-azacytidine, which increases tumor antigen expression and should therefore increase target cell recognition and killing. **Project 2** is a first-in-man study using a CAR to target the CD5 antigen on T-cell lymphomas and 4/9 patients (44%) who received autologous CD5.CAR-T cells achieved responses, including complete responses, enabling three to proceed to allogeneic transplant. This study is now being extending to allogeneic donor cells. **Project 3 will** devise and implement novel strategies of effective, low-toxicity EBV-specific T cell (EBVST) therapy for EBV-positive lymphomas. We are testing a constitutive interleukin 7 receptor (C7R) that provides intrinsic cytokine signaling and activates an anti-apoptotic program that provides resistance to tumor induced T-cell dysfunction. We hypothesize that C7R will enhance the expansion and persistence of EBVSTs in patients with lymphoma and provide resistance to the immunosuppressive tumor microenvironment and provide a non-toxic alternative to lymphodepletion. **Project 4** exploits the unique biological properties of invariant chain Natural Killer T cells (iNKT cells), targeting CD1d (expressed on many lymphoma cells) through the iNKT cell native receptor, while expressing a CD19 CAR to confer specificity to a second tumor associated antigen. iNKTs can also overcome the tumor inhibitory microenvironment through their CD1d-dependent recognition of tumor-associated glycolipids, which also ensures activation of NK cells and the control of inhibitory tumor-associated macrophages. In a clinical trial, 3 of 4 DLBCL patients treated so far had a PR, with donor-derived NKT and CAR-NKT cells detected in tumor biopsies. The long-term goal is to increase the potency and improve accessibility of these cellular immunotherapies for lymphoma.

M.D. Anderson Cancer Center SPORE in Leukemia Overview

Abstract Presenter: Marina Konopleva

Marina Konopleva, Elizabeth Shpall

MD Anderson Cancer Center Leukemia SPORE

The M.D. Anderson Cancer Center SPORE in Leukemia is a translational cancer research program that focuses on leukemias and myelodysplastic syndromes, with the goal of rapidly translate basic science discoveries into major changes in the standard of care for patients with leukemia. The Leukemia Spore leverages expertise of basic scientists and experienced clinical investigators, including experts in cell death, signaling, epigenetics and immunology. Research funded by this Leukemia SPORE resulted in discoveries that have helped change standards of care in several leukemias. Our goal remains to discover new therapies and actionable targets in leukemia. To achieve these goals, the following specific aims are proposed.

Aim 1. To establish successful, biomarker-driven, anti-leukemic therapies and provide leads for future clinical trials in leukemias and myelodysplastic syndromes, through combined utilization of biomarker, genomic and bench-to-bedside and back translational research approaches. Basic and pre-clinical translational discoveries in Leukemia Spore have resulted in development of the following four research projects.

- *Project 1. Epigenetic therapy targeting cyclin-dependent kinase 9 (CDK9)*
- *Project 2. Novel immune therapy targeting 8F4 in AML*
- *Project 4. Engineered cord blood-derived natural killer (NK) cell therapy*
- *Project 5. Targeting oxidative phosphorylation (OxPhos) in AML*

Aim 2. To support the Core infrastructure to facilitate leukemia research in Spore translational Projects. This SPORE supports the following Shared Research Resources: Administrative Core; Pathology and Tissue Core; Biostatistics, Data Management and Bioinformatics Core.

Aim 3. To continue the mentoring of the next generations leukemia investigators and researchers. This SPORE supports a Career Enhancement Program (CEP) to recruit and mentor new investigators in basic and translational leukemia research; and a Developmental Research Program (DRP) to develop innovative translational concepts.

Aim 4. To facilitate inter-SPORE collaboration. We will continue to support and participate joint meetings with other Leukemia and Hematologic Malignancies SPOREs. We have continued exchange of CEP awardees with other funded Leukemia SPORE institutions.

The Mayo Clinic Multiple Myeloma SPORE

Abstract Presenter: Leif Bergsagel

Leif Bergsagel

Mayo Clinic Multiple Myeloma SPORE

The Mayo Clinic Multiple Myeloma SPORE (SPORE) is a dynamic, productive, translational cancer research program based at all three Mayo Clinic sites (Rochester MN, Jacksonville FL, Phoenix AZ) and the Princess Margaret Cancer Centre in Toronto, Ontario. The myeloma program at Mayo Clinic was founded by Dr. Robert Kyle and has been continuously funded by the NCI since 1994. From 2003-2013 we participated in the joint DFCI/Mayo Clinic Multiple Myeloma SPORE, and since 2015 in the Mayo Clinic Multiple Myeloma SPORE. At the center of the ongoing success of the SPORE is the collaborative interaction between investigators throughout the Mayo Foundation, as well as SPORE basic laboratory, translational, clinical investigators and patient advocates focused on MM.

The overall goal of the SPORE is to support innovative, interactive, rigorous translational myeloma research that leverages exceptional laboratory, translational and clinical expertise. The unifying theme and overall goal of the SPORE since its inception is to conduct research exploring the translational implications of host factors, tumor biology and their relationship with the tumor microenvironment. Indeed, we are applying our steadily improving genetic characterization of MM to allow the early detection of MM requiring treatment, essentially developing a new genetic definition of the earliest form of "malignant" MM requiring treatment, in contrast to a "benign" condition that does not. At the opposite end of the spectrum, we are characterizing the genetic features which contribute to ultra-high-risk MM, which does not benefit from current therapy. These studies are complemented by efforts aimed to identify novel ways of modulating the host immune response using virotherapy and bispecific antibodies. In addition to a Career Enhancement Program, a Developmental Research Program, Biospecimen and Biostatistic Cores, there are 3 projects:

- Project 1: Optimizing a VSV-based virotherapy-based regimen for advanced MM
- Project 2: Multi-Omics of high-risk MM
- Project 3: Early detection and prevention of MM progression

City of Hope Lymphoma SPORE Overview

Abstract Presenter: Stephen J. Forman

Stephen J. Forman, Larry Kwak

City of Hope Lymphoma SPORE

The overall goal of the City of Hope (COH) Lymphoma SPORE is to develop powerful new therapeutics based on basic and preclinical observations in molecular and cellular immunology at COH laboratories. In addition, 5 clinical trials are proposed, 4 of which utilize agents (cells, small molecules, radiolabeled antibodies) that are being produced at COH GMP facilities (**Core D**). In **Project 1**, we engineered T cells that respond to both lymphoma and cytomegalovirus (CMV) antigen. A CMV vaccine that was developed at COH will be used to boost T cell expansion persistence and allow in vivo control of CMV-CD19 CAR T cells as a post-transplant immunotherapy for non-Hodgkin lymphoma. In **Project 2**, we build on our previously published prospective longitudinal study of lymphoma patients undergoing autologous hematopoietic cell transplantation (autoHCT), and their susceptibility to therapy-related myeloid neoplasm (t-MN). COH patients from this longitudinal study now serve as the discovery cohort, along with an external multi-institutional cohort to validate a new risk-prediction model that incorporates clonal hematopoiesis of indeterminate potential (CHIP) and other patient clinical and genetic features to estimate the likelihood of developing t-MN after autoHCT. **Project 3** addresses the poor outcomes for patients with relapsed Hodgkin lymphoma with two phase 2 clinical trials. A PET-adapted strategy using PD-1 inhibitor nivolumab ± ICE chemotherapy as a bridge to autoHCT has shown that many patients can to proceed to autoHCT without salvage chemotherapy. The aTac-BEAM trial (recently activated) is an anti-CD25 radioimmunotherapy-based augmented autoHCT regimen. **Project 4**, will utilize two unique agents produced by our own cGMP production facility to target the intracellular transcription factor STAT3 in patients with lymphoma. Specifically, we will test a modified oligonucleotide that silences STAT3 in a clinical trial (recently activated) in Specific Aim 1 (SA1) , and in SA2 we will test a modified high-affinity STAT3-DNA binding sequence that effectively competes with STAT3 DNA binding. We have thus far funded 3 CEP and 4 DRP awards which include 2 women, 1 African and 3 Asian recipients. These awards have thus far yielded one NIH R01 and an R03 grant, 2 patent applications, and an IND submission.

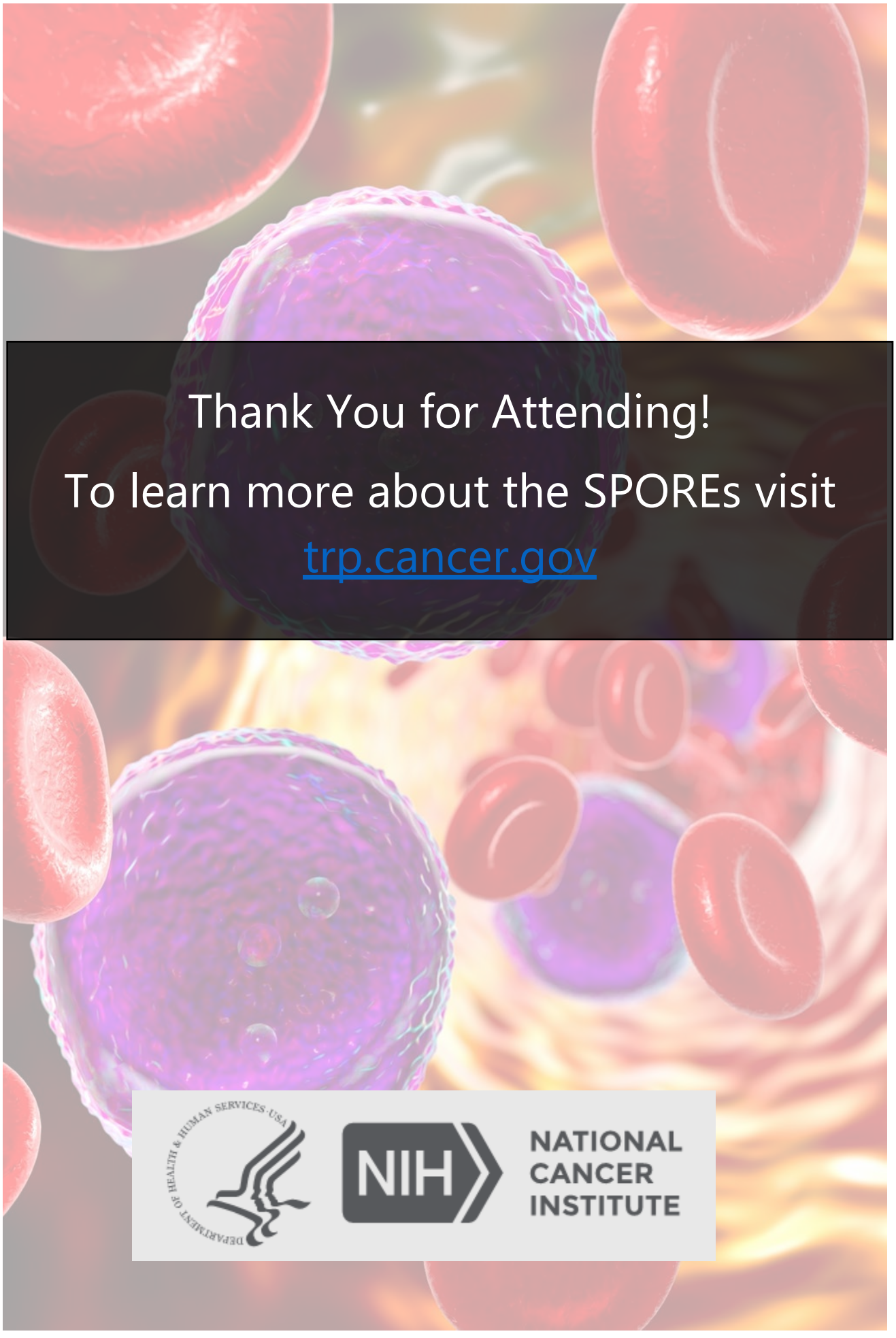
Overview of The University of Iowa/Mayo Clinic Lymphoma SPORE

Abstract Presenter: Thomas Witzig

Thomas Witzig, George Weiner

University of Iowa/Mayo Clinic Lymphoma SPORE

The University of Iowa/Mayo Clinic Lymphoma SPORE (SPORE) is a dynamic, productive, translational cancer research program based at two comprehensive cancer centers that serves as the lymphoma research hub for Iowa and Mayo through its four Projects, Cores (Administrative, Biostatistics, Biospecimens, and Clinical Research), Career Enhancement Program (CEP) and Developmental Research Program (DRP). The overall goal of the SPORE is to address critical, relevant, translational questions in lymphoma biology and therapy ranging from the epidemiology of lymphoma that impacts lymphoma risk assessment, prognostication, and survivorship, to the discovery of new biologic concepts and therapeutics that are then tested in patients through novel clinical trials with robust correlative science. It is served by both external and internal advisory boards, patient advocates and a recently formed Diversity Council. These advisors serve to ensure rigor and relevance of the research in the SPORE. The Clinical Core manages not only trials but the Molecular Epidemiology Resource (MER) that links robust, prospectively collected clinical data and outcomes with biospecimens. The MER now has a cumulative enrollment with continuous follow-up of 10,616 patients over 19 years that is linked to a large Biospecimens resource that contains blood, tumor, CSF, and stool samples. These resources are used not only by our team but also collaborators in SPOREs and other groups around the globe. The SPORE is centered in the US Midwest which has the some of the highest incidence of lymphoma in the US. To add environmental, location, urban and racial/ethnic diversity we are a member of the 8-member Lymphoma Epidemiology of Outcomes (LEO) cohort (U01 CA195568). The current SPORE (year 20) has 4 Projects - Project 1: Activating Phagocytic Macrophages in non-Hodgkin Lymphoma (Ansell/Feldman); Project 2: Microenvironment Modification and Anti-PD1 Immunotherapy of Lymphoma (Weiner/Lin); Project 3: Targeting Tumor Metabolism in Lymphoma (Bishop/Witzig); Project 4: Genomic Predictors of Early Relapse in Immunochemotherapy-Treated Follicular Lymphoma (Cerhan/Novak/Link). Project 4 is an early detection, prevention, or population science (EPPS) project. SPORE productivity over the past funding period includes six new therapeutic trials with accrual of 414 patients, 152 peer-reviewed publications, and enrollment of 2,727 new participants to the MER.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