2019 Scientific Retreat
FRIDAY, APRIL 26, 2019

Together, Taking on Cancer’s Toughest Challenges

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PROGRAM OVERVIEW

William Drobyski, MD
DDT PROGRAM CO-LEADERS

William Drobyski, MD
Professor of Medicine, Pediatrics, Microbiology & Molecular Genetics
Mariette and Philip Orth/Tom Anderson Chair in Oncology
• Program Leader, 2010
• Physician, BMT Program
• Research Focus: Transplantation Immunology

Raul Urrutia, MD
Director, Human and Molecular Genetics Center
Professor, Department of Surgery
• Program Leader, 2017
• Research Focus: Cancer epigenetics, pancreatic cancer, novel cancer mouse model systems
• Former Team Leader: Mayo Center for Individualized Medicine
GOALS OF THE DDT PROGRAM

1. To identify immunotherapeutic-based approaches for the treatment of hematological malignancies and solid tumors and to develop strategies to suppress unwanted off-target effects.

2. To identify and exploit novel therapeutic targets based on new insights into structural biology, signaling pathways, advanced genomics, epigenomics, and bioinformatics, and test new therapeutic agents and combinations to treat cancer more effectively.
MAJOR THEMES OF THE DDT PROGRAM

- Immune Checkpoint Inhibition
- Adoptive Immunotherapy
- Transplant/GVHD Biology

- Novel Target Discovery
- Chemokine Biology

- Epigenetic Regulation of Leukemia
- Identification of Novel Targets in Myeloma
- Novel Agent-based Clinical Trials

- Prostate cancer
- Pancreatic cancer
- Breast Cancer

2019 Scientific Retreat: Together, Taking on Cancer’s Toughest Challenges
1. Stat5a/b is critical for viability of prostate cancer cells *in vitro* and human prostate cancer xenograft tumor growth in mice, and inhibition of Jak2-Stat5a/b induces cell death in clinical patient-derived prostate cancers *ex vivo* in 3D tumor explant cultures.

2. Stat5 inhibition blocks castrate-resistant prostate cancer growth after surgical androgen deprivation in preclinical models.
   - **Nevalainen Lab:** Gu et al., Clin Cancer Research, (AACR) 2013.

3. Stat5 gene locus undergoes amplification during prostate cancer progression to advanced metastatic castrate-resistant disease (appr. 30%), and over-expression of Stat5a/b promotes prostate cancer xenograft tumor growth in nude mice.
   - **Nevalainen Lab:** Haddad et al., Am. J. Pathol., 2013.

4. Stat5 induces epithelial-to-mesenchymal transition and metastatic progression of prostate cancer in preclinical models.
   - **Nevalainen Lab:** Gu et al., Endocrine-Related Cancer, 2010; Talati et al., Am. J Pathology, 2015.

5. Active Stat5 predicts development of advanced prostate cancer in patients after radical prostatectomy.
   - **Nevalainen Lab:** Li et al., Cancer Research, 2004; Li et al., Clin. Cancer Research, 2007; Mirtti et al., Human Pathology 2014; Erickson et al., Cancer Epidemiology, Biomarkers and Prevention, in press 2019.
NEW-GENERATION ENZALUTAMIDE INDUCES HYPERACTIVATED JAK2-STAT5 FEED-FORWARD LOOP IN PROSTATE CANCER WHICH REPRESENTS A TARGETABLE MOLECULAR VULNERABILITY

1) Phase I/II Trial for Efficacy of Jak2 Inhibitor Pacritinib for Non-Metastatic Castrate-Resistant Prostate Cancer

2) Phase II Trial for Efficacy of Pacritinib in Enzalutamide-Resistant Castrate-Resistant Prostate Cancer

Udhane et al., J. Clin Invest, In Review, 2019
CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY

Major side effect of this therapy is Cytokine Release Syndrome which can cause life threatening neurotoxicity.

Failure to respond, in some cases, is due to loss of antigen expression on the tumor ("antigen loss variants")
MCW PHASE 1 TRIAL: FIRST-IN-HUMAN **BISP**ECIFIC, TANDEM CAR-T CELL AGAINST TWO B-CELL ANTIGENS **CD19** AND **CD20** USING A LENTIVIRAL CD3ζ AND 4-1BB CAR-T CONSTRUCT

(Nirav Shah, Bryon Johnson and Parameswaran Hari) (Collaboration between MCW and Miltenyi)

**Clinical Efficacy Data (current):**

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<th>Subject #</th>
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<th>002</th>
<th>003</th>
<th>004</th>
<th>005</th>
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**Results Highlights:**

- 8/13 patients had a complete response (CR) 28 days after CAR-T cell infusion.
- 6/7 patients at the highest dose had complete responses
- As shown on the right, none of the patients who had a complete response have had a relapse of their disease.
- No Grade 3-4 Cytokine Release Syndrome or Grade 3-4 Neurotoxicity

**Clinical Efficacy Data (current):**

Non-Hodgkin’s Lymphoma Patients

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FUTURE PLANS FOR IN-HOUSE CAR-T CELLS AT MCW

• Completion of current Phase 1 clinical trial in adult patients with treatment-resistant lymphoma by mid 2019.

• Develop a new Phase 1 CD19/CD20 CAR-T cell clinical trial in pediatric and young adult patients with treatment-resistant B cell leukemias (aged 1-40 years). Joint protocol between CHW & FH; hopefully open by mid 2019.

• Start a Phase 2 trial (focus on clinical response at the highest dose) to further evaluate efficacy of CD19/CD20 CAR-T cells in adults with treatment-resistant B cell lymphoma. Goal open by mid 2019.

• Ultimately, MCW hopes to partner with Lentigen Technologies (Miltenyi) to test CAR-T cells that go after 3 cancer targets.
BLOCKADE IL-6 SIGNALING AS A STRATEGY TO PREVENT ACUTE GVHD

Humanized anti-IL-6 receptor antibody that blocks IL-6 signaling and is FDA-approved for the treatment of severe active rheumatoid arthritis

- Pilot clinical trial using Tocilizumab for the therapy of steroid resistant acute graft versus host disease, majority had lower GI GVHD.
- Responses observed in 8/11 of patients (6 complete and 2 partial responses), BBMT, 2011
- Responses also observed 9/10 patients with lower tract GI GVHD; Ganetsky et al, ASH Meeting, 2016
## PHASE 2 TRIAL USING TOCILIZUMAB TO PREVENT ACUTE GVHD

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<tr>
<th>Day</th>
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### Conditioning Regimen

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<td>Bu/CY</td>
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<tr>
<td>Flu/BU4</td>
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### Donor Type

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### Graft Source

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<td>PBSC (83)</td>
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### Median Follow Up Surviving Patients (range)

<table>
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<th>Condition</th>
<th>Toc/Tac/MTX (n=35)</th>
<th>Tac/MTX (n=130)</th>
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<tbody>
<tr>
<td>Surviving</td>
<td>15 (9-20 months)</td>
<td>13 (3-72 months)</td>
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<tr>
<td>Patients</td>
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Demographically matched (4:1) patient cohort obtained from CIBMTR data base.
OUTCOMES—ACUTE GVHD

Acute GVHD
Grades II-IV

- Tac/MTX 41% @3mo
- Toc/MTX/Tac 12% @3mo

Grades III-IV

- Tac/MTX 15% @3mo
- Toc/MTX/Tac 3% @3mo

Acute GVHD-free Survival
Grades II-IV

- Tac/MTX/Toc 74% @1y
- Tac/MTX 42% @1y

Day +100:
Grade 2: Skin (2 patients); Upper GI Tract (3 patients)
Grade 4: Skin (1 patient)

No Lower GI Tract GVHD
“NEXT GENERATION” IL-6 DIRECTED CLINICAL TRIALS (CURRENTLY OPEN)

• Phase II single center open label study for prevention of **acute** and **chronic** GVHD using “extended” Tocilizumab administration in combination with standard GVHD prophylaxis after allogeneic transplantation
  • PI: Saurabh Chhabra, MD

• Phase 1 study of **Nivolumab** in combination with **Tocilizumab** for treatment of patients with relapsed hematological malignancies post allogeneic transplant
  • PI: Nirav Shah, MD

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DDT PROGRAM SPEAKERS

Sigfried Janz, MD
“Myeloma-Transforming the Approach to an Incurable Disease”

Gwen Lomberk, PhD
“Cell Cycle-Dependent Epigenomic Therapeutics in Pancreatic Cancer”

Brian Volkman, PhD
“Turning Cancer Discoveries into Treatments”