## Pediatrics 2017 Annual Report – Division Highlights

# Hematology, Oncology and Bone Marrow Transplant

#### **DIVISION DESCRIPTION**

The Division of Hematology, Oncology and Bone Marrow Transplant provides state-of-the-art integrated care, utilizing conventional treatments (such as chemotherapy, radiation and surgery), cellular therapies, molecular- and radioisotope-targeted therapies and stem cell transplant, aimed at curing malignancies and treating hematological disorders in children.

Research interests include ways to recognize and destroy cancer cells using immunologic, cellular and molecular biologic pathways, bone marrow transplantation as immunotherapy, CAR T-cell therapy, systemic targeted radiotherapy, cancer survivorship, neuro-oncology and palliative care.

#### **2017 HIGHLIGHTS**

- The Midwest Athletes Against Childhood Cancer (MACC) Fund has funded nine separate two-year, \$100,000 grants in the Departments of Pediatrics and Human Oncology:
  - Christian Capitini, MD: "Improving Graft-Versus-Leukemia Effects of Ex Vivo Activated NK Cells through JAK/STAT Blockade"
  - Ken DeSantes, MD: "Support for Clinical Research Infrastructure"
  - Ken DeSantes, MD: "Treatment of Relapsed or Refractory Neuroblastoma with Ex-Vivo Activated and Expanded Haploindentical NK Cells and Hu14.18-IL2"
  - Jacquelyn Hank, PhD: "Monitoring of Immune Network Responses in Pediatric Neuroblastoma Patients Treated with Anti-GD2 Immunotherapy"
  - Inga Hofmann, MD (with Emery Bresnick, PhD): "Prognostic Markers and Therapeutic Targets in GATA2-Related Myelodysplastic Syndromes and Leukemia"
  - Mario Otto, MD, PhD: "Targeted Molecular Radiotherapy to Improve the Outcomes in Children with Malignant Brain Tumors"
  - Mario Otto, MD, PhD (with Dana Baiu PhD): "Strategies for Improving Recovery of Immune Function following TCRab-depleted Hematopoietic Stem Cell Transplantation"
  - Alexander Rakhmilevich, MD, PhD: "Combining Innate and Adaptive Immune Activation for Treatment of Experimental Neuroblastoma"
  - Paul Sondel, MD, PhD (with Amy Erbe Gurel, PhD): "Determining the Influence of KIR/KIR-ligand Genotypes in the Outcome of High-Risk Neuroblastoma Patients Following Anti-GD2 Based Immunotherapy"
- Inga Hofmann, MD, was chosen as the first medical director of the Program for Advanced Cell Therapy (PACT) (link to YIR story on faculty leadership), a collaboration of the University of Wisconsin School of Medicine and Public Health and UW Carbone Cancer Center.
  - Dr. Hofmann also received a \$50,000 infrastructure grant from the St. Baldrick's Foundation to support her work in advanced cellular therapies for pediatric cancer and cancer predisposition syndromes.
- Fellow Miriam Kim, DO, received a two-year St. Baldrick's Fellowship Award that, with her mentor
   Christian Capitini, MD, will support her project, "Developing MSC-derived exosomes to enhance HSCT for pediatric leukemia."

- Neha Patel, MD, organized and hosted UW Health's first Neurofibromatosis Type 1 (NF1) symposium
  to help children and families learn more about the disease, meet other NF1 patients and families and
  learn about resources and support available for NF1 patients.
- Paul Sondel, MD, PhD, received the Richard V. Smalley, MD, Memorial Lectureship Award from the Society for Immunotherapy of Cancer (SITC); he was the first pediatric oncologist to receive this recognition.

In addition, Kayla Rasmussen, an undergraduate student mentored by Dr. Sondel, received a 2017-2018 University of Wisconsin Hilldale Undergraduate/Faculty Research Fellowship.

- In 2017, U.S. News and World Report ranked American Family Children's Hospital (AFCH) among the
  top 50 children's hospitals for pediatric oncology (<a href="https://www.uwhealthkids.org/news-and-events/american-family-childrens-hospital-ranks-among-us-news-world-report-best-hospitals/51058">https://www.uwhealthkids.org/news-and-events/american-family-childrens-hospital-ranks-among-us-news-world-report-best-hospitals/51058</a>).
- The AFCH pediatric oncology program was chosen as a member of the newly formed Pediatric Cancer Immunotherapy Trials Network (Pediatric CITN).

In addition, the AFCH pediatric neuro-oncology program joined the Nationwide Children's NEXT Consortium to conduct Head Start 4, a randomized clinical trial to treat very young children with brain tumors.

#### RECENT PUBLICATIONS

Ascierto PA, Agarwala SS, Ciliberto G, Demaria S, Dummer R, Duong CPM, Ferrone S, Formenti SC, Garbe C, Halaban R, Khleif S, Luke JJ, Mir LM, Overwijk WW, Postow M, Puzanov I, **Sondel P**, Taube JM, Thor Straten P, Stroncek DF, Wargo JA, Zarour H, Thurin M. Future perspectives in melanoma research "Melanoma Bridge", Napoli, November 30th-3rd December 2016. J Transl Med. 2017 Nov 16;15(1):236. doi: 10.1186/s12967-017-1341-2. PubMed PMID: 29145885; PubMed Central PMCID: PMC5691855.

**Baiu DC**, Marsh IR, Boruch AE, Shahi A, **Bhattacharya S**, Jeffery JJ, Zhao Q, Hall L, Weichert JP, Bednarz B, **Otto M**. Targeted molecular radiotherapy of pediatric solid tumors using a radioiodinated alkylphospholipid ether analog. J Nucl Med. 2017 Jul 26. pii: jnumed.117.193748. doi: 10.2967/jnumed.117.193748. [Epub ahead of print] PubMed PMID: 28747518. \*

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Erbe AK, Wang W, Goldberg J, Gallenberger M, Kim K, Carmichael L, Hess D, Mendonca EA, Song Y, Hank JA, Cheng SC, Signoretti S, Atkins M, Carlson A, Mier JW, Panka DJ, McDermott DF, **Sondel PM**. FCGR polymorphisms influence response to IL2 in metastatic renal cell carcinoma. Clin Cancer Res. 2017 May 1;23(9):2159-2168. doi: 10.1158/1078-0432.CCR-16-1874. Epub 2016 Oct 14. PubMed PMID: 27742794; PubMed Central PMCID: PMC5392177. \*\*

Erbe AK, Wang W, Reville PK, Carmichael L, Kim K, Mendonca EA, Song Y, Hank JA, London WB, Naranjo A, Hong F, Hogarty MD, Maris JM, Park JR, Ozkaynak MF, Miller JS, Gilman AL, Kahl B, Yu AL, **Sondel PM**. HLA-Bw4-I-80 isoform differentially influences clinical outcome as compared to HLA-Bw4-T-80 and HLA-A-Bw4 isoforms in Rituximab or Dinutuximab-based cancer immunotherapy. Front Immunol. 2017 Jun 12;8:675. doi: 10.3389/fimmu.2017.00675. eCollection 2017. PubMed PMID: 28659916; PubMed Central PMCID: PMC5466980.

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Masucci GV, Cesano A, Eggermont A, Fox BA, Wang E, Marincola FM, Ciliberto G, Dobbin K, Puzanov I, Taube J, Wargo J, Butterfield LH, Villabona L, Thurin M, Postow MA, **Sondel PM**, Demaria S, Agarwala S, Ascierto PA. The need for a network to establish and validate predictive biomarkers in cancer immunotherapy. J Transl Med. 2017 Nov 3;15(1):223. doi: 10.1186/s12967-017-1325-2. PubMed PMID: 29100546; PubMed Central PMCID: PMC5670700.

McCabe KE, Pollock AJ, Rehm JL, **DeSantes KB**. Curative potential of allogeneic hematopoietic stem cell transplant in type 1 diabetes. Pediatr Diabetes. 2017 Dec;18(8):832-834. doi: 10.1111/pedi.12430. Epub 2016 Aug 30. PubMed PMID: 27572817. \*\*

Miller JS, Morishima C, McNeel DG, Patel MR, Kohrt HE, Thompson JA, **Sondel PM**, Wakelee HA, Disis ML, Kaiser JC, Cheever MA, Streicher H, Creekmore SP, Waldmann TA, Conlon KC. A first-in-human phase 1 study of subcutaneous outpatient recombinant human IL-15 (rhIL-15) in adults with advanced solid tumors. Clin Cancer Res. 2017 Dec 4. pii: clincanres.2451.2017. doi: 10.1158/1078-0432.CCR-17-2451. [Epub ahead of print] PubMed PMID: 29203590. \*

Mody R, Naranjo A, Van Ryn C, Yu AL, London WB, Shulkin BL, Parisi MT, Servaes SE, Diccianni MB, **Sondel PM**, Bender JG, Maris JM, Park JR, Bagatell R. Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. Lancet Oncol. 2017 Jul;18(7):946-957. doi: 10.1016/S1470-2045(17)30355-8. Epub 2017 May 23. PubMed PMID: 28549783; PubMed Central PMCID: PMC5527694.

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Wang W, Erbe AK, **DeSantes KB**, **Sondel PM**. Donor selection for ex vivo-expanded natural killer cells as adoptive cancer immunotherapy. Future Oncol. 2017 May;13(12):1043-1047. doi: 10.2217/fon-2017-0039. Epub 2017 May 11. PubMed PMID: 28492088.

Wolfe AD, **Capitini CM**, Salamat SM, **DeSantes K**, Bradley KA, Kennedy T, Dehner LP, Patel NJ. Neck rhabdoid tumors: Clinical features and consideration of autologous stem cell transplant. J Pediatr Hematol Oncol. 2017 Apr 3. doi: 10.1097/MPH.000000000000829. [Epub ahead of print] PubMed PMID: 28375943. \*

### **GRANT SUPPORT**

Faculty/Role	Funding Agency	Title
Capitini, Christian Matthew (PI)	American Association of Immunologists	Travel award
Capitini, Christian Matthew (PI)	DHHS, PHS, National Institutes of Health	Inhibiting STAT1 as a novel graft-versus-host/graft-versus-leukemia therapy (K08)
Capitini, Christian Matthew (PI)	Hyundai Hope On Wheels	Anti-GD2 immunocytokine and NK cell infusions for neuroblastoma
Capitini, Christian Matthew (PI)	Midwest Athletes Against Childhood Cancer	Exploitation of the STAT1-BCL2 axis to dissect GVL from GVHD
Capitini, Christian Matthew (PI)	Novartis Pharmaceuticals KK	CTL019B2202 - A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

<sup>\*</sup>ePub only; no print citation available when report was compiled

<sup>\*\*</sup> Publication had previously appeared in 2016 report as an ePub

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Capitini, Christian	Novartis	Long term follow-up of patients exposed to lentiviral-
Matthew (PI)	Pharmaceuticals KK	based CD19 directed CART cell therapy
Capitini, Christian	Novartis	Phase II study of redirected autologous T cells
Matthew (PI)	Pharmaceuticals KK	engineered to contain anti-CD19 attached to TCR and
		4-1BB signaling domains in patients with
		chemotherapy resistant or refractory acute
	0. 5 1111	lymphoblastic leukemia
Capitini, Christian	St Baldricks	Developing MSC-derived exosomes to enhance HSCT
Matthew (PI)	Foundation	for pediatric leukemia
Capitini, Christian	Wisconsin Alumni	Travel award
Matthew (PI)	Research	
Canitini Chuistian	Foundation	Tabagaina tha agait wagaya tugang affact against
Capitini, Christian Matthew (PI)	Wisconsin Alumni Research	Enhancing the graft-versus-tumor effect against neuroblastoma
Matthew (PI)	Foundation	Tieurobiastoriia
Capitini, Christian	National Science	EAGER BIOMANUFACTURING:A Microscale Testbed to
Matthew (co-MPI) with	Foundation	Assay and Manufacture CAR T-Cell Immunotherapies
Saha, Krishanu and	Touridation	Assay and Mandiacture CAN 1-Cell Illimidiotherapies
Beebe, David (co-MPIs)		
Capitini, Christian	NIH/Office of the	CCR5-mutant monkey model to facilitate the
Matthew (co-I) with	Director	development of novel stem cell-based therapies
Slukvin, Igor (PI)	Director	for AIDS
	Children's Hospital	PIDTC protocol #6901: A prospective natural history
Desantes, Kenneth B (PI)	of Los Angeles	study of diagnosis, treatment and outcomes for
	of Los Affgeles	children with SCID disorders
Desantes, Kenneth B (PI)	Children's Hospital	PIDTC protocol #6902: A retrospective and cross-
Desantes, Renneth B (11)	of Los Angeles	sectional analysis of patients treated for SCID
Desantes, Kenneth B (PI)	Children's Hospital	PIDTC protocol #6903: Analysis of patients treated for
Desantes, Refinedi B (FI)	of Los Angeles	chronic granulomatous disease
Desantes, Kenneth B (PI)	Children's Hospital	A phase 2 multi-center, historically-controlled study of
Desantes) Remietri B (11)	of Philadelphia	dasatinib added to standard chemotherapy in pediatric
		patients with newly diagnosed Philadelphia
		chromosome positive acute lymphoblastic leukemia
Desantes, Kenneth B (PI)	Children's Hospital	A phase III randomized trial for patients with de novo
	of Philadelphia	AML using bortezomib and sorafenib for patients with
	·	high allelic ratio FLT2/ITD - AAML1031
Desantes, Kenneth B (PI)	Children's Hospital	A randomized phase III study of brentuximab vedotin
, , ,	of Philadelphia	for newly diagnosed classical hodgkin lymphoma (cHL)
	·	in children and adolescents (AHOD1331)
Desantes, Kenneth B (PI)	Children's Hospital	AALL1131 - A phase III randomized trial for newly
	of Philadelphia	diagnosed high risk B-precursor acute lymphoblastic
		leukemia testing clofarabine in the very high risk
		stratum
Desantes, Kenneth B (PI)	Children's Hospital	AAML1031: A phase III randomized trial for patients
	of Philadelphia	with de novo AML using bortezomib and sorafenib for
		patients with high allelic ratio FLT3/ITD
Desantes, Kenneth B (PI)	Children's Hospital	ANHL1131 - Intergroup trial for children or adolescents
	of Philadelphia	with B-Cell NHL or B-AL: Evaluation of rituximab
<b>D</b>	0.11.	efficacy and safety in high risk patients
Desantes, Kenneth B (PI)	Children's Hospital	APEC14B1 - Everychild protocol: a registry, eligibility
	of Philadelphia	screening, biology and outcome study

Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	COG CTSU phase II supplement
Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	COG NCORP research base, per case reimbursement
Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	COG workload intensity
Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	COG/NCTN per case reimbursement
Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	Risk-stratified randomized phase III testing of blinatumomab in first relapse of childhood B-lymphoblastic leukemia (B-ALL). AALL1331
Desantes, Kenneth B (PI)	Children's Hospital of Philadelphia	St. Baldrick's supplemental per case reimbursement (COG)
Desantes, Kenneth B (PI)	Macrogenics	A phase I, open-label, dose escalation study of MGA271 in pediatric patients with B7-H3-expressing relapsed or refractory solid tumors
Desantes, Kenneth B (PI)	Mesoblast	A single-arm, prospective study of remestemcel-L, exvivo cultured adult human mesenchymal stromal cells, for the treatment of pediatric patients who have failed to respond to steroid treatment for acute GVHD
Desantes, Kenneth B (PI)	Midwest Athletes Against Childhood Cancer	Reduced intensity haploidentical transplantation with NK cell infusions for pediatric acute leukemia and high risk solid tumors
Desantes, Kenneth B (PI) with Sondel, Paul M (co-I)	Midwest Athletes Against Childhood Cancer	Support for research data management
Desantes, Kenneth B (PI) with Sondel, Paul M (collaborator)	Midwest Athletes Against Childhood Cancer	Treatment of relapsed or refractory neuroblastoma with ex-vivo activated and expanded haploidentical NK cells and continuous infusion Hu14.18-IL2
Desantes, Kenneth B (PI)	Solving Kids Cancer	Phase I trial of ex-vivo expanded haploidentical NK cells and Hu14.18-IL2 for children with relapsed/refractory neuroblastoma
Hematti, Peiman (PI)	Novartis Pharmaceuticals KK	A multicenter study of apheresis collection of peripheral blood mononuclear cells (PBMC) in patients with CD19 expressing malignancies who could be eligible for a CTL019
Hofmann, Inga (PI)	EvansMDS	Prognostic markers and therapeutic targets in GATA2- related myelodysplastic syndromes and leukemia
Hofmann, Inga (PI)	Midwest Athletes Against Childhood Cancer	Prognostic markers and therapeutic targets in GATA2- related myelodysplastic syndromes and leukemia
Otto, Mario (PI)	American Association of Immunologists	A novel phospholipid ether analog to combine targeted molecular radiotherapy and immunotherapy in pediatric solid tumors
Otto, Mario (PI)	Cannonball Kids Cancer Foundation	TCR-α/β+ and CD19+ depleted KIR/KIR ligand- mismatched haploidentical hematopoietic stem cell transplant and Zoledronate for pediatric relapsed/refractory hematologic malignancies and high risk solid tumors

Otto, Mario (PI)	DHHS, PHS, National Institutes Of Health	A cancer-targeted phospholipid ether analog for molecular radiotherapy of pediatric solid tumors
Otto, Mario (PI)	DHHS, PHS, National Institutes of Health	TCR-α/β+ and CD19+ depleted KIR/KIR ligand- mismatched haploidentical hematopoietic stem cell transplant and Zoledronate for pediatric relapsed/refractory hematologic malignancies and high risk solid tumors
Otto, Mario (PI)	Hyundai Hope On Wheels	A novel phospholipid ether analog to combine targeted molecular radiotherapy and immunotherapy in pediatric solid tumors
Otto, Mario (PI)	Midwest Athletes Against Childhood Cancer	CLR1404 – A tumor-selective alkyl phospholipid analog for the treatment of pediatric solid malignancies
Otto, Mario (PI)	Midwest Athletes Against Childhood Cancer	Effect of zoledronate on engraftment and T-cell development after TCRαβ/CD19-depleted hematopoietic stem cell transplantation
Otto, Mario (PI)	Wisconsin Alumni Research Foundation	Travel award
Patel, Neha (PI)	Ann & Robert H Lurie Childrens Hospital	LGG-14C03: A phase III study comparing two carboplatin containing regimens for children and young adults with previously untreated low grade glioma
Patel, Neha (PI)	Boehringer Ingelheim Ltd	Phase I open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged 2 years to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours
Patel, Neha (PI)	Multiple Donors	Neurocutaneous disorders - NCD
Patel, Neha (PI)	Nationwide Children's Hospital	The "head start 4" protocol: Newly diagnosed children (less than 10 years old) with medulloblastoma and other central nervous system embryonal tumors, phase IV
Puccetti, Diane M (co-Pl with Ikonomidou, Hrissanthi)	DHHS, PHS, National Institutes of Health	Methods to Study Chemotherapy-Related Neurotoxicity in Children
Sondel, Paul M (PI)	Alex's Lemonade Stand Foundation	Flow hood
Sondel, Paul M (PI)	Alex's Lemonade Stand Foundation	Identifying how pre-existing anti-therapeutic antibodies are associated with better outcome in a clinical trial of ADCC-inducing anti-GD2 mAb
Sondel, Paul M (PI) with DeSantes, Kenneth B (investigator) and Capitini, Christian M and Otto, Mario (young investigators)	AACR/St. Baldrick's/Stand Up 2 Cancer Foundations	Immunogenomics to create new therapies for high-risk childhood cancers ("dream team")

Sondel, Paul M (PI)	DHHS, PHS, National Institutes of Health	Enhancing antibody-directed innate immunity to improve cancer outcome
Sondel, Paul M (PI)	Hughes (Howard) Medical Institute	Description and characterization of endogenous antibodies found in some cancer patients that are capable of recognizing various monoclonal antibodies used in cancer immunotherapy
Sondel, Paul M (PI)	Midwest Athletes Against Childhood Cancer	Enhancing immunocytokine efficacy in neuroblastoma: Synergy with radiation therapy and development of a 2nd generation immunocytokines
Sondel, Paul M (PI)	St Baldricks Foundation	Finding the target of beneficial pre-existing anti- therapeutic antibodies
Sondel, Paul M (PI)	St Jude Medical	A phase I trial of the humanized anti-GD2 antibody (HU14.18K322A) in children and adolescents with neuroblastoma or melanoma
Sondel, Paul M (PI)	St Jude Medical	Neuroblastoma protocol 2012: Therapy for children with advanced stage high-risk neuroblastoma
Sondel, Paul M (PI)	WISCONA	Murine cancer models for testing in situ vaccination strategies
Sondel, Paul M (PI) with Otto, Mario (co-I)	Wisconsin Alumni Research Foundation	Combining radiotherapeutic with antitumor antibody and IL2 to create a potent in situ cancer vaccine
Sondel, Paul M (Chair, Scientific Review Committee) and Hoover-Regan, Margo (Research Subject Advocate [RSA] for the Clinical Research Unit) with Drezner, Marc (PI)	NIH/NCATS	UW-ICTR
Sondel, Paul M (co-I) with Ponik, Suzanne (PI)	NIH/NCI & Morgridge Institute for Research, Inc.	Quantitative in Vivo Optical Imaging of Tumor Heterogeneity
Sondel, Paul M (co-I) with Asimakopoulos, Fotios (PI)	American Cancer Society, Inc	The Role of TPL2 in Regulating Macrophage-Myeloma Tumor Cell Interactions