BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Maciejewski, Jaroslaw P.

eRA COMMONS USER NAME (credential, e.g., agency login): jaroslawmaciejewski

POSITION TITLE: Professor and Chairman

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Humboldt University Berlin, Medical School (Charite)	M.D.	1990	Medicine
Humboldt University Berlin, Medical School (Charite)	Ph.D.	1990-91	Immunology
University of Nevada, School of Medicine, Reno, NV	Residency	1991-93	Internal Medicine
Hematology Branch, NHLBI, NIH, Bethesda MD	Fellowship	1997-00	Hematology

A. Personal Statement

My specific interests have evolved from molecular and immune mechanisms of bone marrow failure syndromes, including myelodysplastic syndrome (MDS) and related diseases, aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), large granular lymphocyte leukemia (LGL) and pure red cell aplasia (PRCA) to drug discovery for these conditions. My research in leukemia genetics is highly translational and directed towards identification of molecular lesions to be applied in diagnostics or serving as targets for rational drug discovery and clinical trial applications. My original research training, followed by clinical training, was at the Hematology Branch of NHLBI. My career path as a physician-scientist began during my fellowship at the NIH where I investigated dysfunction of hematopoietic stem cells under the mentorship of Dr. Neal Young. This research contributed to the better understanding of immune-mediated attack and the resultant hematopoietic stem cell (HSC) damage in AA and PNH. In this application I have also studied HSC biology, including HSC compartment damage and changes in disease and aging, respectively and HSC regeneration and expansion.

I started my independent career at Cleveland Clinic where I built a research program in molecular pathogenesis of bone marrow failure. I received my first NHLBI R01 in 2003, and have had concurrent NHLBI funding, including subsequent R01's, U54, LLS TRP, DOD and Midcareer K24 award which enabled me to create an Experimental and Clinical Hematology training program which has trained numerous young scientists/physician-scientists. Most recently my research has been funded through NIH R35 Distinguished NIH Investigator Award. Initially, our studies focused on investigation of T cell repertoire using molecular analysis of TCR and later clonal analyses by deep TCR sequencing. This is a productive line of investigation led to discovery of clonotype sharing and switch leading to major brake thoughts in understanding of LGL and discovery STAT3 mutations. Since that time my research has included various aspects of leukemia genetics including discovery of new somatic and germ line mutations and study of clonal architecture.

My laboratory has made several important contributions to the understanding of hematologic disease documented by publications in Cancer Cell, Nature Genetics, Nature Medicine, NEJM, Nature, JCO, and Blood illustrating major achievements, including introduction of SNP arrays as a clinical karyotyping platform in MDS diagnostics and various applications of next generation sequencing in bone marrow failure. These studies led to discovery of various somatic and germ line mutations and their implications for the understating of the disease mechanisms as a consequence of these molecular lesions and clinical implications. In sum, my research career has achieved high scientific productivity, with over 450 publications, many in high impact journals and 2 presented in plenary sessions at ASH meetings. As a physician-scientist, I consider my utmost goal to be the translation of scientific advances into improvement of patient care and cures. Below are provided recent examples of clinical and discovery manuscripts.

a. Saunthararajah Y, Sekeres M, Advani A, Mahfouz R, Durkin L, Radivoyevitch T, Englehaupt R, Juersivich J, Cooper K, Husseinzadeh H, Przychodzen B, Hobson S, Earl M, Sobecks R, Dean R, Reu F, Tiu R, Hamilton B, Copelan E, Lichtin A, Hsi E, Kalaycio M, **Maciejewski J.** Evaluation of noncytotoxic DNMT1depleting therapy in patients with myelodysplastic syndromes. ***J Clin Invest.*** (2015) 125:1043-55.

b. Makishima H, Yoshida K, Ruffalo R, Przychodzen B, LaFramboise T, Hosono H, Gómez- Seguí I, Husseinzadeh HD, Thota S, Clemente MJ, Sanada M, Nagata Y, Okuno Y, Sato Y, Saunthararajah Y, Sekeres MA, Shih L-Y, Ogawa S, **Maciejewski JP**. Landscape of somatic mutations in whole exomes of myelodysplastic and related myeloid neoplasms. ***Nat Med.*** 2017 Feb; 49(2):204-212.

c. Makishima H, Yoshida K, Nguyen N, Przychodzen B, Sanada M, Okuno Y, Ng KP, Gudmundsson KO, Vishwakarma BA, Jerez A, Gomez-Segui I, Takahashi M, Shiraishi Y, Nagata Y, Guinta K, Mori H, Sekeres MA, Chiba K, Tanaka H, Muramatsu H, Sakaguchi H, Paquette RL, McDevitt MA, Kojima S, Saunthararajah Y, Miyano S, Shih LY, Du Y, Ogawa S, **Maciejewski JP.** Somatic SETBP1 mutations in myeloid malignancies. ***Nat Genet.*** (2013) 45:942-6.

d. Polprasert C, Schulze I, Sekeres MA, Makishima H, Przychodzen B, Hosono N, Singh J, Padgett RA, Gu X, Phillips JG, Clemente M, Parker Y, Lindner D, Dienes B, Jankowsky E, Saunthararajah Y, Du Y, Oakley K, Nguyen N, Mukherjee S, Pabst C, Godley LA, Churpek JE, Pollyea DA, Krug U, Berdel WE, Klein HU, Dugas M, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Yoshida K, Ogawa S, Müller-Tidow C, **Maciejewski JP**. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. ***Cancer Cell.*** (2015) 27:658-70.

B. Positions and Honors

2000-01	Staff Scientist, Hematology Branch, NHLBI, NIH, Bethesda MD
2001-08	Section Head, Experimental Hematology, Cleveland Clinic, Cleveland, OH
2001-	Staff, Hematologic Oncology and Blood Disorders, Cleveland Clinic, Cleveland, OH
2003-07	Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (CCLCM)
2002-04	Chair, Medical Advisory Board of International Aplastic Anemia and Myelodysplastic Foundation
2004-	Reviewer, various NIH study sections
2006	Elected member of the American Society of Clinical Investigation
2008	Elected Fellow of American College of Physicians
2008-12	Member of Editorial Board of Blood Journal
2007-	Professor of Medicine, CCLCM
2009	Young Investigator Award for Achievements in Clinical Hematology Research
2009-13	Member ASH Scientific Subcommittee on Myeloid malignancies
2009-	Chairman, Department of Translational Hematology and Oncology Research, Cleveland Clinic
2011-16	Associate Director Case Comprehensive Cancer Center for Lerner Research Institute
2011-	Program Leader, Hematologic Malignancies and Stem Cell Transplantation Program, Case Comprehensive Cancer Center
2014	Chair, ASH Scientific Subcommittee on Myeloid malignancies
2014	Member of Editorial leukemia Journal
2016-	Associate Director for Translational Research, Case Comprehensive Cancer Center
2017-	Elected Member of American Association of Physicians
2018-	Permanent Member, Molecular and Cellular Hematology Study Section
2018-	Member American Association for Advancement of Science
2019-	Named Eminent Polish American Scientist, Kosciuszko Foundation, New York

C. Contribution to Science

1. **Contribution to the understanding of immune mediated and idiopathic bone marrow failure syndromes including pathogenesis of aplastic anemia, paroxysmal nocturnal hemoglobinuria and large granular lymphocyte anemia.** These studies led to identification of the role of Fas and/FasL pathways in regulation of hematopoietic stem and progenitor cells and the pathogenic role of these mechanisms in immune-mediated bone marrow failure. The results of these investigations also clarified the mechanism of the action of interferon-gamma in normal and aplastic bone marrow. Investigation on immune

pathogenesis of AA also involved the study of clonal and oligoclonal T cell expansions using molecular T cell receptor clonotyping, most recently performed by applying targeted deep TCR sequencing as a means of a comprehensive assessment of TCR repertoire. Investigation into the nature of cytopenia and the mechanisms of clonal expansions led to the investigation of large granular lymphocyte leukemia culminating in discovery of somatic STAT3 and STAT5 mutations and establishment of the concept of clonal drift discovered through analysis of clonal dynamics. Selected recent publications:

a. Koskela HL, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmäki H, Andersson EI, Lagström S, Clemente MJ, Olson T, Jalkanen SE, Majumder MM, Almusa H, Edgren H, Lepistö M, Mattila P, Guinta K, Koistinen P, Kuittinen T, Penttinen K, Parsons A, Knowles J, Saarela J, Wennerberg K, Kallioniemi O, Porkka K, Loughran TP Jr, Heckman CA, **Maciejewski JP**, Mustjoki S. Somatic STAT3 mutations in large granular lymphocytic leukemia. ***N Engl J Med.*** (2012) 366:1905-13.

b. Yoshizato T, Dumitriu B, Hosokawa K, Makishima H, Yoshida K, Townsley D, Sato-Otsubo A, Sato Y, Liu D, Suzuki H, Wu CO, Shiraishi Y, Clemente MJ, Kataoka K, Shiozawa Y, Okuno Y, Chiba K, Tanaka H, Nagata Y, Katagiri T, Kon A, Sanada M, Scheinberg P, Miyano S, **Maciejewski JP**, Nakao S, Young NS, Ogawa S. Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia. ***N Engl J Med.*** 2015 Jul 2; 373(1):35-47.

c. Shen W, Clemente MJ, Hosono N, Yoshida K, Przychodzen B, Yoshizato T, Shiraishi Y, Miyano S, Ogawa S, **Maciejewski JP**, Makishima H (2014). Deep sequencing reveals stepwise mutation acquisition in paroxysmal nocturnal hemoglobinuria. ***J Clin Invest.*** Oct; 124(10):4529-38.

d. Negoro E, Nagata Y, Clemente MJ, Hosono N, Shen W, Nazha A, Yoshizato T, Hirsch C, Przychodzen B, Mahfouz RZ, Kuzmanovic T, Sekeres MA, Makishima H, Ogawa S, **Maciejewski JP**. (2017) Origins of myelodysplastic syndromes after aplastic anemia. ***Blood.*** Blood. 2017 Oct 26; 130(17):1953-1957.

2. **Discovery and investigations of TET2 mutations.** This line of research resulted in discovery of Tet2 mutations and description of their mechanistic consequences and clinical implications.

a. Jankowska A, Afable E, McDevid M, **Maciejewski JP** (2009). TET2 Gene Harbors Mutations Associated with Myeloid Malignancies ***Blood*** 113:6403-10.

b. Ko M, Huang Y, Jankowska AM, Pape UJ, Tahiliani M, Bandukwala HS, An J, Lamperti ED, Koh KP, Ganetzky R, Liu XS, Aravind L, Agarwal S, **Maciejewski JP**, Rao A (2010). Impaired hydroxylation of 5methylcytosine in myeloid cancers with mutant TET2. ***Nature.*** 468(7325):839-43.

c. Jankowska AM, Makishima H, Tiu RV, Szpurka H, Huang Y, Traina F, Visconte V, Sugimoto Y, Prince C, O'Keefe C, Hsi ED, List A, Sekeres MA, Rao A, McDevitt MA, **Maciejewski JP** (2011). Mutational spectrum analysis of CMML includes genes associated with epigenetic regulation: UTX, EZH2 and DNMT3A. ***Blood.*** Oct; 118:3932- 41.

d. Hirsch CM, Nazha A, Kneen K, Abazeed ME, Meggendorfer M, Przychodzen BP, Nadarajah N, Adema V, Nagata Y, Goyal A, Awada H, Asad MF, Visconte V, Guan Y, Sekeres MA, Olinski R, Jha BK, LaFramboise T, Radivoyevitch T, Haferlach T, **Maciejewski JP**. Consequences of mutant TET2 on clonality and subclonal hierarchy. ***Leukemia. 2018 May 24.*** doi: 10.1038/s41375-018-0150-9.

3. **Discovery of somatic and germline mutations in MDS and other disease and their clinical and mechanistic implications.** We have discovered or contributed to discovery of UTX, CBL, EZH2, DDX41, SETPB1 and TET2 gene mutations. In particular, the discovery of TET2 microdeletions and mutations and the subsequent link of the mutations to defective methylcytosine hydroxylation, the physiologic function of TET2 gene product. Subsequent systematic application of next generation sequencing has led to discovery of somatic mutations in various spliceosomal genes, RIT2, SETBP1, including somatic and inherited mutations in DDX41, a member of RNA helicase gene family as new group of tumor suppressor genes in MDS and AML. Selected publications are:

a. Makishima H, Yoshida K, Nguyen N, Przychodzen B, Sanada M, Okuno Y, Ng KP, Gudmundsson KO, Vishwakarma BA, Jerez A, Gomez-Segui I, Takahashi M, Shiraishi Y, Nagata Y, Guinta K, Mori H, Sekeres MA, Chiba K, Tanaka H, Muramatsu H, Sakaguchi H, Paquette RL, McDevitt MA, Kojima S, Sauntharajah Y, Miyano S, Shih LY, Du Y, Ogawa S, **Maciejewski JP**. Somatic SETBP1 mutations in myeloid malignancies. ***Nat Genet.*** (2013) 45:942-6. PMCID: PMC3729750.

b. A, Adelmant G, Tamburini J, Chapuy B, Shindoh N, Yoda Y, Weigert O, Kopp N, Wu SC, Kim SS, Liu H, Tivey T, Christie AL, Elpek KG, Card J, Gritsman K, Gotlib J, Deininger MW, Makishima H, Turley SJ, Javidi-Sharifi N, **Maciejewski JP**, Jaiswal S, Ebert BL, Rodig SJ, Tyner JW, Marto JA, Weinstock DM, Lane AA (2015). Mutations in G protein β subunits promote transformation and kinase inhibitor resistance. ***Nat Med.*** Jan; 21(1):71-5.

c. Makishima H, Cazzolli H, Szpurka H, Dunbar A, Tiu R, Huh J, Muramatsu H, O'Keefe C, Hsi E, Paquette RL, Kojima S, List AF, Sekeres MA, McDevitt MA, **Maciejewski JP**. Mutations of e3 ubiquitin ligase cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. ***J Clin Oncol.*** (2009) 27:6109-16. PMCID: PMC3040009.

d. Nagata Y, Narumi S, Guan Y, Przychodzen BP, Hirsch CM, Makishima H, Shima H, Aly M, Pastor V, Kuzmanovic T, Radivoyevitch T, Adema V, Awada H, Yoshida K, Li S, Sole F, Hanna R, Jha BK, LaFramboise T, Ogawa S, Sekeres MA, Wlodarski MW, Cammenga J, **Maciejewski JP**. Germline lossof-function SAMD9 and SAMD9L alterations in adult myelodysplastic syndromes. ***Blood. 2018*** Nov 22; 132(21):2309-2313.

4. **Pathogenesis of spliceosomal mutations.** Building on systematic application of NGS and exome sequencing we have developed a discovery pipeline to identify and detect and clarify the role in mis-splicing of novel spliceosomal mutation. We co-discovered U2AF1 mutations and were first to describe the splice site recognition motive allowing for prediction of genes whose splicing may be affected by U2AF1 mutations. We have also discovered new somatic mutations including those in PRPF8, LUC7L and DDX41.

   a. Polprasert C, Schulze I, Sekeres MA, Makishima H, Przychodzen B, Hosono N, Singh J, Padgett RA, Gu X, Phillips JG, Clemente M, Parker Y, Lindner D, Dienes B, Jankowsky E, Sauntharajah Y, Du Y, Oakley K, Nguyen N, Mukherjee S, Pabst C, Godley LA, Churpek JE, Pollyea DA, Krug U, Berdel WE, Klein HU, Dugas M, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Yoshida K, Ogawa S, Müller-Tidow C, **Maciejewski JP**. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. ***Cancer Cell.*** (2015) 27:658-70.

   b. Kurtovic-Kozaric A, Przychodzen B, Singh J, Konarska MM, Clemente MJ, Otrock ZK, Nakashima M, Hsi ED, Yoshida K, Ogawa S, Boultwood J, **Maciejewski JP**, Padgett RA, Makishima H. PRPF8 defects cause missplicing in myeloid malignancies. ***Leukemia.*** (2014) 29:126-36. PMCID: PMC4214909.

   c. Przychodzen B, Jerez A, Guinta K, Sekeres MA, Padgett R, **Maciejewski JP**, Makishima H. Patterns of missplicing due to somatic U2AF1 mutations in myeloid neoplasms. ***Blood.*** (2013) 122:999-1006. PMCID: PMC3739042.

   d. Makishima H, Visconte V, Sakaguchi H, Jankowska AM, Abu Kar S, Jerez A, Przychodzen B, Bupathi M, Guinta K, Afable MG, Sekeres MA, Padgett RA, Tiu RV, **Maciejewski JP**. Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. ***Blood.*** (2012) 119:3203-10. PMCID: PMC3321850.

5. **Application of molecular discoveries to refine diagnosis and prognostication in myeloid neoplasms and marrow failure.** Translational application of molecular discoveries have prompted a number of translational projects designed to determine the clinical/prognostic role of mutational patterns in various bone marrow failure syndromes and myeloid neoplasms including definition of mutational patterns associated with chromosomal abnormalities, mutational hierarchy and dynamics. Most recently these studies led to discovery of more complex clonal architecture in PNH, a stem cell disease thought to be a monogenic. Similar studies followed in aplastic anemia showing that subclopnal somatic mutations can be found in immune-mediated non-malignant hematopoietic disease.

   a. Sauntharajah Y, Sekeres M, Advani A, Mahfouz R, Durkin L, Radivoyevitch T, Englehaupt R, Juersivich J, Cooper K, Husseinzadeh H, Przychodzen B, Rump M, Hobson S, Earl M, Sobecks R, Dean R, Reu F, Tiu R, Hamilton B, Copelan E, Lichtin A, Hsi E, Kalaycio M, **Maciejewski J.** Evaluation of noncytotoxic DNMT1-depleting therapy in patients with myelodysplastic syndromes. ***J Clin Invest.*** (2015) 125:104355.

   b. Negoro E, Nagata Y, Clemente MJ, Hosono N, Shen W, Nazha A, Yoshizato T, Hirsch C, Przychodzen B, Mahfouz RZ, Kuzmanovic T, Sekeres MA, Makishima H, Ogawa S, **Maciejewski JP**. (2017) Origins of myelodysplastic syndromes after aplastic anemia. ***Blood.*** Blood. 2017 Oct 26; 130(17):1953-1957.

c. Makishima H, Yoshida K, Ruffalo R, Przychodzen B, LaFramboise T, Hosono H, Gómez- Seguí I, Husseinzadeh HD, Thota S, Clemente MJ, Shiraishi M, Sanada M, Nagata Y, Okuno Y, Sato Y, Sauntharajah Y, Sekeres MA, Shih L-Y, Ogawa S, **Maciejewski JP**. Landscape of somatic mutations in whole exomes of myelodysplastic and related myeloid neoplasms. ***Nat Med.*** Nat Genet. 2017; 49:204-212.

d. Invariant patterns of clonal succession determine specific clinical features of myelodysplastic syndromes. Nagata Y, Makishima H, Kerr CM, Przychodzen BP, Aly M, Goyal A, Awada H, Asad MF, Kuzmanovic T, Suzuki H, Yoshizato T, Yoshida K, Chiba K, Tanaka H, Shiraishi Y, Miyano S, Mukherjee S, LaFramboise T, Nazha A, Sekeres MA, Radivoyevitch T, Haferlach T, Ogawa S, Maciejewski JP. Nat Commun. 2019 Nov 26;10:5386.

Complete List of Published (n=435)

http://www.ncbi.nlm.nih.gov/sites/myncbi/jaroslaw.maciejewski.1/collections/48104484/public/

D. Additional Information: Research Support and/or Scholastic Performance

R35 HL135795-01 (Maciejewski) 01/01/2017 - 11/30/2023
NIH/NHLBI
Therapeutic Implications of Molecular Defects in Bone Marrow Failure
Using integrative approaches identify disease subgroups by the presence of convergent pathways rational for selection of most suitable targets for development of new treatment strategies for bone marrow failure.

TAUB1905JM (Maciejewski) 07/01/2019 – 06/30/2022
Henry and Marilyn Taub Foundation
Induction of Synthetic Lethality by DNA Dioxygenase Inhibition as a Targeted Therapy in MDS
This project has the potential of development of a new class of agents affecting previously non-targeted biologic activity useful in a large fraction patients with myeloid neoplasia.

P30CA043703-30 (Gerson) 08/01/1997 – 03/31/2023
CWRU (Prime: NIH/NCI)
Case Comprehensive Cancer Center Support Grant
Support innovative, coordinated interdisciplinary clinical research on cancer diagnosis, treatment, and control.
Role: Co-Leader, Pathogenesis and Treatment of Hematopoietic Disorders Program