BIOGRAPHICAL SKETCH

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NAME: Lu, Sydney

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

POSITION TITLE: Assistant Professor

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 (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Dartmouth College, Hanover, NH	BA	06/2003	Chemistry, Biology
Weill Cornell Medical College, New York, NY	PHD	06/2009	Immunology
Stanford Medical School, Palo Alto, CA	MD	06/2013	N/A
NY Presbyterian Hospital, Weill Cornell Campus, New York, NY	Resident	06/2015	Internal Medicine
Memorial Sloan-Kettering Cancer Center, New York, NY	Fellow	06/2019	Hematology & Medical Oncology

A. Personal Statement

My graduate, medical and postdoctoral training have led my interests to converge at the intersection of RNA processing, immunology, hematopoiesis, and cancer biology. I am a new independent laboratory-based investigator at Stanford Medical School in the Division of Hematology, Department of Medicine, where I am studying clinically-important questions at the interface of RNA metabolism, immunology, and cancer. This liminal domain is well-suited to my skills and interests. Moreover, I believe that understanding and controlling RNA metabolism will be an emerging and novel approach for cancer therapy.

The current focus of the laboratory builds upon two postdoctoral projects. In the first, I studied the therapeutic utility and mechanism-of-action of a novel class of “anti-cancer sulfonamides” in the context of myeloid neoplasms. These molecules, which are in active clinical trials, target and degrade a key RNA splicing gene, RBM39 to mediate anti-tumor activity. This work was published as a shared first-author manuscript in Cancer Cell in 2019. In more recent work, I combined several RNA splicing modulator compounds with immune checkpoint blockade to establish a novel therapeutic strategy to enhance the efficacy of anti-PD1 therapy. This work was published in Cell in 2021.

In my independent research career, I am now building upon these two projects to study:

1) alterations in RNA processing and their roles in anti-tumor immunity, with a focus on RNA-processing derived tumor neoantigens

2) the role of RNA processing in regulating normal and pathological immunity, including in cancer.

1. Lu SX, De Neef E, Thomas JD, Sabio E, Rousseau B, Gigoux M, Knorr DA, Greenbaum B, Elhanati Y, Hogg SJ, Chow A, Ghosh A, Xie A, Zamarin D, Cui D, Erickson C, Singer M, Cho H, Wang E, Lu B, Durham BH, Shah H, Chowell D, Gabel AM, Shen Y, Liu J, Jin J, Rhodes MC, Taylor RE, Molina H, Wolchok JD, Merghoub T, Diaz LA Jr, Abdel-Wahab O, Bradley RK. Pharmacologic modulation of RNA splicing enhances anti-tumor immunity. Cell. 2021 Jul 22;184(15):4032-4047.e31. PubMed Central PMCID: PMC8684350.
2. Wang E, Lu SX, Pastore A, Chen X, Imig J, Chun-Wei Lee S, Hockemeyer K, Ghebrechristos YE,

Yoshimi A, Inoue D, Ki M, Cho H, Bitner L, Kloetgen A, Lin KT, Uehara T, Owa T, Tibes R, Krainer AR, Abdel-Wahab O, Aifantis I. Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. Cancer Cell. 2019 Mar 18;35(3):369-384.e7. PubMed Central PMCID: PMC6424627.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2022 -	Assistant Professor, Stanford University School of Medicine, Department of Medicine, Division of Hematology, Palo Alto, CA
2022 -	Visiting Investigator, Memorial Sloan-Kettering Cancer Center, New York, NY
2019 - 2022	Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center, Department of Medicine, Myeloma Service, New York, NY
2015 - 2019	Hematology & Medical Oncology Fellow, Memorial Sloan-Kettering Cancer Center, New York, NY
2013 - 2015	Resident in Internal Medicine, Weill Cornell / NY Presbyterian Hospitals, New York, NY

Honors

2019 - 2020	Fellow Career Development Award, Leukemia and Lymphoma Society
2018 - 2020	Lymphoma Research Fellowship, American Association for Cancer Research
2018 - 2020	Research Award, Aplastic Anemia and MDS International Foundation
2017 - 2019	Loan Repayment Program, National Institutes of Health
2016 - 2018	Lacher Foundation, Memorial Sloan-Kettering Cancer Center
2011 - 2012	MacKenzie Foundation Scholarship, Stanford Medical School
2019	Portlock Challenge-Robert Hirschhorn Endowment Award, Memorial Sloan-Kettering Cancer Center
2019	Physician Scientist Fellowship (awarded & declined), Doris Duke Charitable Foundation
2019	Research Training Award for Fellows (awarded & declined), American Society of Hematology
2017	Young Investigator Award, Conquer Cancer Foundation / ASCO
2009	Travel Scholarship, ASBMT
2009	Travel Award, ASH
2006	Travel Scholarship, ASBMT
2003	Zabriski Award, Dartmouth College
2003	Merck Index Award, Dartmouth College

C. Contribution to Science

1. Pharmacologic splicing modulation for cancer immunotherapy: in recent postdoctoral studies, we began with the observation that neoantigen burden is (roughly) correlated with response to immune checkpoint blockade for many cancer histologies. Given this, I hypothesized that pharmacologic RNA splicing modulators, which promote the generation of novel mRNA species, can in turn generate novel peptides presented on MHC I to promote anti-tumor immunity. We showed that splicing modulator compounds could synergize with anti-PD1 blockade by this mechanism, thereby identifying RNA-splicing derived peptides presented on MHC I as an abundant and reversible source of neoantigens for cancer immunotherapy. In this same work, we showed that some classes of RNA splicing modulator compounds are not immunosuppressive in vivo, and do not promote off-target non-tumor inflammation when combined with anti-PD1 blockade, suggesting that this may be a novel therapeutic approach to increase the applicability and efficacy of immune checkpoint blockade.

    a. Lu SX, De Neef E, Thomas JD, Sabio E, Rousseau B, Gigoux M, Knorr DA, Greenbaum B,

Elhanati Y, Hogg SJ, Chow A, Ghosh A, Xie A, Zamarin D, Cui D, Erickson C, Singer M, Cho H, Wang E, Lu B, Durham BH, Shah H, Chowell D, Gabel AM, Shen Y, Liu J, Jin J, Rhodes MC, Taylor RE, Molina H, Wolchok JD, Merghoub T, Diaz LA Jr, Abdel-Wahab O, Bradley RK. Pharmacologic modulation of RNA splicing enhances anti-tumor immunity. Cell. 2021 Jul 22;184(15):4032-4047.e31. PubMed Central PMCID: PMC8684350.

2. My efforts in the Omar Abdel-Wahab group at Memorial Sloan-Kettering Cancer Center focused on understanding the role of mutations in RNA binding proteins (RBPs) as they drive the initiation and maintenance of malignancies and explored how exploiting endogenous or pharmacologically-generated aberrancies in RNA splicing can be used for the treatment of cancer. One major project focused on a class of small molecules in clinical trials for cancer, the so-called “anti-cancer sulfonamides.” These drugs degrade the key splicing factor RBM39 by rendering it a neosubstrate of the Ddb1/CUL4 E3 ubiquitin ligase complex via the adapter protein DCAF15. My work demonstrated the safety of these compounds in murine model systems, their anti-leukemic efficacy against myeloid cancers, and their selectivity for neoplasms harboring recurrent splicing factor mutations and high DCAF15 expression. The underlying mechanism-of-action was synthetic lethality by disrupting RNA splicing in such neoplasms. (Lu*, Wang*, et al., Cancer Cell 2019 *equal first author). With respect to other work on RBP mutations in cancer, I contributed to the development of novel models to xenograft into immunocompromised animals, previously difficult-to-study myeloid neoplasms which frequently harbor mutations in RBPs of interest to us. This has allowed for the evaluation of clinical grade targeted therapeutics in vivo in such models. In addition, I have been investigating the role of the recurrent SF3B1 K700E mutation as it relates to neoplasia. In this work we identified both redundant (convergent) signaling pathways downstream of mutated SF3B1 and SRSF2 splicing proteins as well as other gene targets whose loss is synthetic lethal when both mutations are present in a cell. These investigations elucidated mechanisms behind the notable observation that RNA splicing factor mutated cancers tend to harbor only a single splicing factor mutation, and also further validated the concept of synthetic lethality in splicing factor mutated cancers by further perturbations of RNA splicing. Most recent efforts have focused on studying Brd9, a key downstream target of the recurrent SF3B1 K700E mutation, and its role in regulating the growth of melanomas bearing splicing factor mutations.

    a. Inoue D, Chew GL, Liu B, Michel BC, Pangallo J, D'Avino AR, Hitchman T, North K, Lee SC, Bitner L, Block A, Moore AR, Yoshimi A, Escobar-Hoyos L, Cho H, Penson A, Lu SX, Taylor J, Chen Y, Kadoch C, Abdel-Wahab O, Bradley RK. Spliceosomal disruption of the non-canonical BAF complex in cancer. Nature. 2019 Oct;574(7778):432-436. PubMed Central PMCID: PMC6858563.
    b. Wang E, Lu SX, Pastore A, Chen X, Imig J, Chun-Wei Lee S, Hockemeyer K, Ghebrechristos YE, Yoshimi A, Inoue D, Ki M, Cho H, Bitner L, Kloetgen A, Lin KT, Uehara T, Owa T, Tibes R, Krainer AR, Abdel-Wahab O, Aifantis I. Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. Cancer Cell. 2019 Mar 18;35(3):369-384.e7. PubMed Central PMCID: PMC6424627.
    c. Lee SC, North K, Kim E, Jang E, Obeng E, Lu SX, Liu B, Inoue D, Yoshimi A, Ki M, Yeo M, Zhang XJ, Kim MK, Cho H, Chung YR, Taylor J, Durham BH, Kim YJ, Pastore A, Monette S, Palacino J, Seiler M, Buonamici S, Smith PG, Ebert BL, Bradley RK, Abdel-Wahab O. Synthetic Lethal and Convergent Biological Effects of Cancer-Associated Spliceosomal Gene Mutations. Cancer Cell. 2018 Aug 13;34(2):225-241.e8. PubMed Central PMCID: PMC6373472.
    d. Yoshimi A, Balasis ME, Vedder A, Feldman K, Ma Y, Zhang H, Lee SC, Letson C, Niyongere S, Lu SX, Ball M, Taylor J, Zhang Q, Zhao Y, Youssef S, Chung YR, Zhang XJ, Durham BH, Yang W, List AF, Loh ML, Klimek V, Berger MF, Stieglitz E, Padron E, Abdel-Wahab O. Robust patient-derived xenografts of MDS/MPN overlap syndromes capture the unique characteristics of CMML and JMML. Blood. 2017 Jul 27;130(4):397-407. PubMed Central PMCID: PMC5533204.

3. My graduate studies focused on clinically relevant murine models of allogeneic hematopoietic stem cell transplantation, with a special emphasis on the pathobiology of donor alloreactive T cells and their contributions to experimental graft-versus-host-disease (GVHD), as well as on the interplay between

alloreactivity and reconstitution of the immune system after ablative stem cell transplant. My studies have shown that T cell trafficking, via the proteins integrin β7 subunit, P-selectin and PSGL-1 to be crucial for mediating both GVHD and the graft-versus-tumor effect. My investigations have also shown that the Ceacam-1 protein, an important negative regulator of T cell activation, is implicated in restraining donor alloreactivity after transplant. In the area of post-transplant immune reconstitution, my studies of the thymus after hematopoietic stem cell transplantation revealed donor-derived TRAIL and Fas ligand to be critically important in impeding donor lymphoid (T cell) regeneration post-transplant.

a. Lu SX, Kappel LW, Charbonneau-Allard AM, Atallah R, Holland AM, Turbide C, Hubbard VM, Rotolo JA, Smith M, Suh D, King C, Rao UK, Yim N, Bautista JL, Jenq RR, Penack O, Na IK, Liu C, Murphy G, Alpdogan O, Blumberg RS, Macian F, Holmes KV, Beauchemin N, van den Brink MR. Ceacam1 separates graft-versus-host-disease from graft-versus-tumor activity after experimental allogeneic bone marrow transplantation. PLoS One. 2011;6(7):e21611. PubMed Central PMCID: PMC3130781.
b. Lu SX, Holland AM, Na IK, Terwey TH, Alpdogan O, Bautista JL, Smith OM, Suh D, King C, Kochman A, Hubbard VM, Rao UK, Yim N, Liu C, Laga AC, Murphy G, Jenq RR, Zakrzewski JL, Penack O, Dykstra L, Bampoe K, Perez L, Furie B, Furie B, van den Brink MR. Absence of P-selectin in recipients of allogeneic bone marrow transplantation ameliorates experimental graft-versus-host disease. J Immunol. 2010 Aug 1;185(3):1912-9. PubMed Central PMCID: PMC3752704.
c. Na IK, Lu SX, Yim NL, Goldberg GL, Tsai J, Rao U, Smith OM, King CG, Suh D, Hirschhorn-Cymerman D, Palomba L, Penack O, Holland AM, Jenq RR, Ghosh A, Tran H, Merghoub T, Liu C, Sempowski GD, Ventevogel M, Beauchemin N, van den Brink MR. The cytolytic molecules Fas ligand and TRAIL are required for murine thymic graft-versus-host disease. J Clin Invest. 2010 Jan;120(1):343-56. PubMed Central PMCID: PMC2798682.
d. Waldman E, Lu SX, Hubbard VM, Kochman AA, Eng JM, Terwey TH, Muriglan SJ, Kim TD, Heller G, Murphy GF, Liu C, Alpdogan O, van den Brink MR. Absence of beta7 integrin results in less graft-versus-host disease because of decreased homing of alloreactive T cells to intestine. Blood. 2006 Feb 15;107(4):1703-11. PubMed Central PMCID: PMC1895413.

4. A final area of interest has been focused on novel techniques to understand intracellular signaling. As a graduate student, I worked with BD Pharmingen Inc., to develop novel monoclonal antibodies for the quantitative assessment of intracellular phosphorylation and other post-translational modifications in single cells via flow cytometry. These assays are significantly superior to traditional western blotting of bulk cell lysates to assess signaling pathways, in the ability for flow cytometry to provide single cell resolution information regarding the state of signaling molecules in heterogeneous populations such as primary murine tissues (via assessment of cell surface antigens), and even for the detection of multiple signaling molecules within a single cell. Using this platform I identified STAT3 phosphorylation as being critical in T cell activation in the setting GVHD model systems and showed that pharmacologic inhibition of STAT3 to be a viable strategy for attenuating disease. Subsequently, flow cytometric assessment of signaling pathways has become widely adopted and accepted in the scientific literature.

a. Lu SX, Alpdogan O, Lin J, Balderas R, Campos-Gonzalez R, Wang X, Gao GJ, Suh D, King C, Chow M, Smith OM, Hubbard VM, Bautista JL, Cabrera-Perez J, Zakrzewski JL, Kochman AA, Chow A, Altan-Bonnet G, van den Brink MR. STAT-3 and ERK 1/2 phosphorylation are critical for T-cell alloactivation and graft-versus-host disease. Blood. 2008 Dec 15;112(13):5254-8. PubMed Central PMCID: PMC2597618.