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: Sam Lee

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

POSITION TITLE: Research Scientist, Yale University School Medicine

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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California	PhD	1988	Molecular Genetics
University of California, San Francisco	Post-doc.	1988	Molecular Genetics
DFCI/Harvard Medical School, Boston, MA	Post-doc.	1992	Cancer Genetics

A. Personal Statement

I was a faculty member in Harvard Medical School since 1994 and recently moved to Yale due to family reason in 2019. My 3 NIH RO1 grants ended in 2018. I had a health issue for a while, but I completely recovered and have returned to Science. We have submitted our recent study to one of the major journal, but still working on the revision since early 2020. I would like to continue on an exciting project related to novel immune checkpoint regulator, DD1alpha/VISTA that is an important target in cancer immunotherapeutic. The inefficient clearance of dying cells has been coupled to abnormal immune responses such as unresolved inflammation and autoimmune conditions. We found that tumor suppressor p53 controls “eat-me” signaling-mediated phagocytosis of apoptotic cells through its novel target DD1α, suggesting that p53 executes not only the pro-apoptotic pathway but also post-apoptotic events. Cancer cells take advantage of this nature ability by exploiting various immune escape mechanisms to persist despite anticancer treatment. We identified a post-apoptotic target gene, DD1α that is highly responsive to genotoxic stresses, induced in apoptotic cells, and expressed in immune cells. DD1α has similarity with several members of the immunoglobulin superfamily with the IgV domain, including TIM family proteins and immune-checkpoint modulators PD-1 and PD-L1. We have investigated that activation of such immune checkpoint regulators in response to genotoxic stress contributes to tumor cell survival, thus limiting the full potential of anti-tumor immunity and facilitating relapse.

Yoon, K.W., Byun, S., Hwang, S.-Y., Kwon, E., Chu, K., Hiraki, M., Weins, A., Hakroush, S., Cebulla, A., Greka, A., Mundel, P., Sykes, D.B., Fisher, D.E., Mandinova, A. & **Lee, S.W.** Control of signaling-mediated clearance of apoptotic cells by the tumor suppressor p53. Science 349 (6247): 1261669 (*Research Article*), 2015 PMID: 26228159 (Perspectives in *Science* 349, 2015; Highlighted *Nat Rev Immunol* 15, 2015; highlighted in *Cancer Discovery* 5, 2015).

Munoz-Fontela, C., Mandinova, A., Aaronson, S.A. & **Lee, S.W.** The emerging roles of tumor suppressor genes in immune responses. Nat. Rev. Immunol. 16: 741-750, 2016 PMID: 27667712

ElTanbouly, M., Yanding, Z., Nowak, E., Jiannan, Li., Schaafsma, E., Le Mercier, I., Peng, C., Carriere, C., Huang X., Day M., Koehn, B., **Lee, S.W.**, Morales M., Hogquist K.A., Jameson, S.C., Mueller, D., Rothstein, J., Blazar, B., Cheng, C. & Noelle, R. VISTA, a checkpoint regulator of naïve T cell

quiescence and tolerance in the periphery. Science 367 (6475) (Research Article), 2020 PMID: 31949051

B. Positions and Honors

Positions and Employment

1983 - 1988 Ph.D. thesis, Univ. of California, Mentor: Dr. N. Agabian, Univ. of Calif,
1988 - 1988 Post-doctoral Follow, University of California, San Francisco
1989 - 1991 Post-doc. Fellow, Dana Farber Cancer Institute, Mentor: Dr. Ruth Sager
1992 - 1993 Assistant Professor, Division of Cancer Biology, Univ. of Michigan Medical School
1994 - 2002 Assistant Professor, Cancer Biology Program, Harvard Medical School
2002 - 2018 Associate Professor, Harvard Medical School, and Massachusetts General Hospital
2006 - 2018 Associate Director, Cutaneous Biology Research Center, Massachusetts General Hospital
2009 - 2018 Associate member of Broad Institute of MIT and Harvard
2015 - 2018 Member of ImmunoOncology Program, Dana Farber Cancer Institute
2019- Research Scientist, Yale University School of Medicine

C. Other Experience and Professional Memberships

2002 - 2006 Chemical Pathology/Cancer Etiology Study Section, Member, Grant Review, NIH
2004 - 2008 Carcinogenesis Study Section, Member, American Cancer Society
2005 - NCI/NIH Program Project, Reviews
2013 - 2017 BMCT (Regular member), CSR, NIH

2007 - 2010 Associate Editor, *Cancer Research;*
2010- 2016 Editorial Board for Cancer Research & J. Biol. Chem.
2015- 2018 Associate Editor for Cancer Medicine

2002 - 2003 Ph.D. Subcommittee - Faculty Development Advisory Board
2005 - 2018 Seminar Series Committee, Cutaneous Biology Research Center, MGH
2005 - 2018 Faculty Recruitment Committee, Cutaneous Biology Research Center, MGH
2008 - 2018 Promotion Committee, Department of Dermatology, Harvard Medical School
2011 - 2018 Red Book Committee, Harvard Medical School
2015 - 2017 Member of ImmunoOncology Program, Dana Farber Cancer Institute

D. Contribution to Science

1. I have been studying functional aspects of oncogenes and tumor suppressor genes since I was a postdoctoral fellow and early in my career when I was part of a team that developed the technology, cloned and characterized several cancer-specific genes involved in DNA damage, invasion and cancer progression.
   a. Lee, S.W., Tomasetto, C., and Sager, R. Positive selection of candidate tumor-suppressor genes by subtractive hybridization. Proc Natl Acad Sci U S A. 88: 2825-9, 1991 PMID: 1849277
   b. Lee, S.W., Tomasetto, C., Paul, D., Keyomarsi, K., and Sager, R. Transcriptional downregulation of gap-junction proteins blocks junctional communication in human mammary tumor cell lines. J Cell Biol.118: 1213-21, 1992 PMID: 1324944
   c. Lee, S.W., Tomasetto, C., Swisshelm, K., Keyomarsi, K., and Sager, R. Down-regulation of a member of the S100 gene family in mammary carcinoma cells and reexpression by azadeoxycytidine treatment. Proc Natl Acad Sci U S A. 89: 2504-8, 1992 PMID: 1372446
   d. Lee, S.W. H-cadherin, a novel cadherin with growth inhibitory functions and diminished expression in human breast cancer. Nature Med. 2: 776-82, 1996 PMID: 8673923

2. I was the first to discover that pro-survival pathway activation is directly associated with p53-dependent DNA damage/genotoxic responses and have provided a unique and significant contribution in this area. As an Assistant and then as an Associate Professor at the BIDMC and the MGH/Harvard Medical School, I pursued my major interest in how p53-mediated transcriptional regulation influences cell fate decisions: live or die. Genotoxic stress, including irradiation and DNA

damage agents, ultimately eliminate tumor cells by the induction of apoptosis, but the stress-mediated cell death is eroded by pro-survival mechanisms in cancer cells, which inhibits apoptosis. This concept led us to investigate the effects of p53 pro-survival targets in tumorigenesis/carcinogenesis.

a. Ongusaha, P., Kim, J-I., Fang, L. Wong, T.W., Yancopoulos, G.D., Aaronson, S.A., and Lee, S.W. p53 induction and activation of DDR1 kinase counteract p53-mediate apoptosis and influence p53 regulation through a positive feedback loop. EMBO J. 22: 1289-1301, 2003. PMID: 12628922
b. Ohtsuka, T., Ryu, H., Minamishima, Y.A., Aaronson, S.A., and **Lee, S.W.** ASC functions as an adaptor for Bax and regulates a p53-Bax mitochondrial pathway of apoptosis. Nature Cell Biol. 6: 121-128, 2004. PMID: 14730312
c. Das, D., Raj, L., Zhao, B., Bernstein, A., Aaronson, A.A., and Lee, S.W. Hzf, a key modulator of p53 mediated transcription, functions as a critical determinant of cell survival and death upon genotoxic stress. Cell 130: 624-637, 2007. PMID: 17719541
d. Ongusaha, P.P., Qi, H.H., Raj, L., Kim, Y.-B., Davis, R.J., Shi, Y., Liao, J.K., and Lee, S.W. Identification of ROCK1 as an upstream activator of JIP-3-JNK signaling axis in response to UVB damage. Science Signal. 1 (47): ra14, 1-11, 2008. PMID: 19036714

3. In collaboration with Broad scientists, our profound interest in therapeutics related to p53-mediated prosurvival pathways also complemented the long-term goal of the laboratory to dissect specific stress-mediated responses of the cell and to develop unique ways to modify them.

a. Mandinova, A., and **Lee, S.W.** The p53 pathway as a target in cancer therapeutics: obstacles and promise. Science Transl. Med. 3 (64), 64rv1, 2011. PMID: 21209413
b. Gurkar, A.U., Chu, K., Raj, L., Kim, Y.-B., Dunn, S.E., Mandinova, A., and Lee, S.W. Identification of ROCK1 kinase as a critical regulator of Beclin1 mediated autophagy during metabolic stress. Nature Comm. 4: 2189, 2013. PMID: 23877263
c. Hiraki, M., Hwang, S.Y., Cao, S., Ramadhar, T.R., Byun, S., Yoon, K.W., Chu, K., Gurkar, A.U., Kolev, V., Zhang, J., Namba, T., Murphy, M.E., Newman, D.J., Mandinova, A., Clardy, J., and Lee, S.W. Small molecule reactivation of mutant p53 to wt-like p53 through the p53-Hsp40 regulatory axis. Cell Chem. Biol. 22: 1206-1216, 2015. PMID: 26320861
d. Hwang, S.-Y. Deng, X., Lee, C., Lee, S.-J., Suh, H., Zhang, J., Kang, Q., Zhang, T., Westover, K.D., Mandinova, A., & Lee, S.W. Direct targeting of β-catenin by a small molecule stimulates proteosomal degradation and suppresses oncogenic Wnt/β-catenin signaling. Cell Rep. 16: 28-36, 2016. PMID:27320923

4. It has been recognized that wt-p53 can commit cancer cells to a survival path in response to stress such as genotoxic stimuli. Thus, wt-p53 can also function as a “guardian” in cancer cells containing wt-p53 to impose a proper cancer cell survival against stress, thereby raising the view that wt-p53 activity may not always be helpful in preventing tumorigenesis. There are now growing numbers of p53-induced survival genes/pathways identified and such survival p53 downstream genes or pathways in cancer cells may be used as novel targets for the development of cancer therapeutics. Thus we continued to functionally characterize p53-prosurvival targets in cancer cell signaling pathways to understand the mechanisms.

a. Mandinova A, Lee, S.W. The Guardian of the genome: inside the quest to characterize the role of p53 in cancer. Science 348: 49 (*Review*), 2015
b. Munoz-Fontela, C., Mandinova, A., Aaronson, S.A., Lee, S.W. The emerging roles of tumor suppressor genes in immune responses. Nat. Rev. Immunol. 16: 741-750, 2016 PMID: 27667712
c. Kwon, E., Todorova, K., Wang, J., Horos R, Lee KK, Neel VA, Negri GL, Sorensen PH, Lee, S.W., Hentze MW, Mandinova, A. The RNA-binding protein YBX1 regulates epidermal progenitors at a posttranscriptional level. Nature Comm. 9: 1734, 2018.
d. Shin S.H. et. al. Synthetic lethality by targeting the RUVBL1/2-TTT complex in mTORC1-hyperactive cancer cells. Science Adv.(31) 2020 PMID: 32789167

Complete List of Published Work in My Bibliography (133 total)**:**

http://www.ncbi.nlm.nih.gov/sites/myncbi/sam.lee.1/bibliography/40494957/public/?sort=date&direction=ascending

D. Other Support

Active:

R01 AR073607-01A1 (Lee, Francis Y.) 02/01/2019 – 01/31/2024 3.0 calendar months
NIAMS/NIH
Non-hormonal function of locally delivered PTH for rescue of impaired fracture healing
This A1 translational therapeutic research proposal seeks to enhance fracture repair with a locally delivered parathyroid hormone (hPTH1-34) as a fracture repair enhancing factor in the setting of impaired fracture healing as seen in diabetic patients, chronic smokers, and elderly people with the goal of avoiding fracture associated complications.
Role – Co-Investigator

Pending:

1 R01 CA258915-01A1 (Lee, Sam W.) 10/01/2021 – 09/30/2026 3.0 calendar months
NCI/NIH
p53-driven post-apoptotic scavenger function
This grant investigates the p53→DD1α mediated activation in response to genotoxic stress/chemo agents whether it contributes to tumor cell survival, thus limiting the full potential of anti-tumor immunity and facilitating relapse.
Role - PI

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: Randolph J. Noelle

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

POSITION TITLE: Professor of Microbiology & Immunology, Geisel School of Medicine at Dartmouth

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)*	Completion Date MM/YYYY	FIELD OF STUDY
SUNY at Stony Brook	B.S.	1974	Biochemistry
Albany Medical College	Ph.D.	1980	Microbiology/Immunology
U. of Texas Health Science Center at Dallas	Postdoc	1984	Immunology

A. Personal Statement

The scientific and translational merits of this project are significant. VISTA has been an enigmatic molecule for many years, and only now are we appreciating its profound impact in both the myeloid and T cell lineages. Our recent successes and the use of the technologies presented in this proposal have already re-defined the function of this molecule, and the proposed studies will continue to unravel its function. Anti-VISTA antibodies have entered clinical trial in cancer and soon in inflammatory disorders and the knowledge gained in this proposal will help to guide its future clinical development.

B. Positions and HonorsProfessional Experience

1984-present Member of Norris Cotton Cancer Center, Member of Microbiology/MCB Ph. D. Program
1984-1989 Assistant Professor of Microbiology
1990-1995 Associate Professor of Microbiology, Adjunct Associate Professor of Biochemistry
1995-2009 Professor of Microbiology and Immunology
2001-present Co-Director of the Immunology and Immunotherapy Program (ICIP)
2002-2003 Deputy Director of the Norris Cotton Cancer Center
2005-2009 Director of the Immunotherapy Center at Dartmouth
2008-2010 Acting Chair Department of Microbiology and Immunology
2006-Present Founder and CSO, ImmunRx Corporation
2009-present Founder and CSO of ImmuNext
2009-2014 Professor of Transplant Science and Immunotherapy, Kings College, London

Awards and Honors
2003 Eijkman Award, Ultrecht, The Netherlands
2004 MERIT NIH Award
2010 Wellcome Trust Principal Research Fellowship Award
2010 Wellcome Trust Distinction Award

2012	Fellow/member of the National Academy of Medical
2017	Sciences AAI Distinguished Investigator Award

Service and Committees

1991	Site Review, NCI Oct
1992	Immunotoxicology Study Section (Ad hoc) Feb
1993	Ad hoc NIH Toxicology Study Section
1994	NCI RFA Study Section, AIDS related Lymphoma
1994	Ad hoc, NIAID, Immunobiology
1994-1996	NIH Toxicology Study Section, Member
1995-1997	National Arthritis Foundation Study Section, Member
1996	Ad hoc NIH Immunogical Sciences Study Section,
1996-2000	Member, Immunological Sciences Study Section, NIH
2001	Special Emphasis Study Section. Primate Transplantation, NIAID,
2002	Site Visit, NCI, Tampa Fl.,
2009-2010	ALS Advisory Board
2010-2013	Cancer Research UK
2010-2014	Wellcome Trust Transitional Awards
2015	Chair, NIH ZRG1 EMNR Study Section, NIH/SREA Study Section

C. Contribution to Science

CD40-CD40L: basic science and into the clinic. From the late 1980's we sought to identify the T cell molecule critical for T cell help. In 1992, we identified CD40L (CD154) which was a helper T cell surface molecule critical for the development of T cell-dependent humoral immunity, and central to the development of cell mediated immunity. We produced αCD40L, that must have been used by hundreds of labs, and has proven to be an effective therapeutic in almost every model of autoimmunity and graft rejection in the mouse. In 2002, we entered clinical trials with a humanized αCD40L in multiple sclerosis that proved to have encouraging therapeutic activities. Shortly, thereafter, due to safety concerns with the antibodies to CD40L, all trials were stopped. We have developed a new, safe αCD40L and will re-enter trials in the near future.

Buhlmann, J.E., T.M. Foy, A. Aruffo, K.M. Crassi, J.A. Ledbetter, W.R. Green, J.C. Xu, L.D. Shultz, D. Roopesian, R.A. Flavell, L. Fast, F.H. Durie, and **R.J. Noelle,** *In the absence of a CD40 Signal, B Cells Are Tolerogenic.* Immunity, 1995. **2**: p. 645-653.

Foy, T.M., A. Aruffo, J.A. Ledbetter, and **R.J. Noelle,** *In vivo CD40-gp39 interactions are essential for thymus-dependent immunity. II. Prolonged in vivo suppression of primary and secondary humoral immune responses by an antibody targeted to the CD40 ligand, gp39.* J. Exp. Med., 1993. **178**: p. 1567- 1575.

Durie, F.H., R.A. Fava, T.M. Foy, A. A., J.A. Ledbetter, and **R.J. Noelle,** *Prevention of collagen-Induced arthritis with an antibody to gp39, the ligand for CD40.* Science, 1993. **261**: p. 1328- 1330.

Noelle, R.J., M. Roy, D.M. Shepherd, I. Stamenkovic, J.A. Ledbetter, and A. Aruffo, *A novel ligand on activated T helper cells binds CD40 and transduces the signal for the cognate activation of B cells.* Proc. Natl. Acad. Sci. USA, 1992. **89**: p. 6550-6554.

Long-Lived humoral immunity and BCMA. Our lab has long been committed to understanding the molecular aspects of long-lived humoral immunity**.** In 2004, we discovered that long-lived bone marrow plasma cells required two factors, BAFF and BCMA to survive. Studies showed that blocking signaling through the respective receptors would result in the rapid loss of long-lived plasma cells. these were the first insights into how to destabilize this indelible immune compartment.

O'Connor, B.P., V.S. Raman, L.D. Erickson, W.J. Cook, L.K. Weaver, C. Ahonen, L.L. Lin, G.T. Mantchev, R.J. Bram, and **R.J. Noelle,** *BCMA is essential for the survival of long-lived bone marrow plasma cells.* J Exp Med, 2004. **199**(1): p. 91-8.

O'Connor, B.P., M.W. Gleeson, **R.J. Noelle,** and L.D. Erickson**,** *The rise and fall of long-lived humoral immunity: terminal differentiation of plasma cells in health and disease.* Immunol Rev, 2003. **194**: p. 61-76.

O'Connor, B.P., M. Cascalho, and **R.J. Noelle,** *Short-lived and long-lived bone marrow plasma cells are derived from a novel precursor population.* J Exp Med, 2002. **195**(6): p. 737-45.

Retinoic metabolism and the control of T cell fate. Retinoic acid (RA) is the primary metabolite of Vitamin A. We were the first to show that RA was critical for the development and stability of adaptive regulatory Tcells. Subsequent studies established that RA was a crucial immune mediator, even in the periphery in that during any inflammatory response, high levels of RA are produced at the inflammatory site. The role of RA in controlling immunity is far more vast and important than we ever conceived, as a new study will show that RAis a master regulator of t-bet, and a master regulator of Th1 fate. We are just beginning to understand the importance of this vitamin.

C. C. Brown, D. Esterhazy, A. Sarde, M. London, V. Pullabhatla, I. Osma-Garcia, R. Al-Bader, C. Ortiz, R. Elgueta, M. Arno, E. de Rinaldis, D. Mucida, G. M. Lord, **R. J. Noelle**, Retinoic acid is essential for Th1 cell lineage stability and prevents transition to a Th17 cell program. *Immunity* **42,** 499, 2015.

Pino-Lagos, K., Y. Guo, C. Brown, M.P. Alexander, R. Elgueta, K.A. Bennett, V. De Vries, E. Nowak, R. Blomhoff, S. Sockanathan, R.A. Chandraratna, E. Dmitrovsky, and **R.J. Noelle,** *A retinoic acid-dependent checkpoint in the development of CD4+ T cell-mediated immunity.* J Exp Med, 2011. **208**(9): p. 1767-75.

Mucida, D., K. Pino-Lagos, G. Kim, E. Nowak, M.J. Benson, M. Kronenberg, **R.J. Noelle,** and H. Cheroutre, *Retinoic acid can directly promote TGF-beta-mediated Foxp3(+) Treg cell conversion of naive T cells.* Immunity, 2009. **30**(4): p. 471-2; author reply 472-3.

Benson, M.J., K. Pino-Lagos, M. Rosemblatt, and **R.J. Noelle,** *All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation.* J Exp Med, 2007. **204**(8): p. 1765-74.

VISTA: basic science and into the clinic. We were the first to report on VISTA in 2011 and defined it as a negative checkpoint regulator similar to PD-L1. We have shown it as an important negative regulator of immunity that controls the development of autoimmunity and therapeutic immunity to cancer. We showed that an antibody to VISTA can enhance the immune response to autologous tumors in mice. Continuing studies have now shown VISTA as an important mediator of myeloid function and the induction of T cell tolerance. In 2012, we began the development of fully human αhuman VISTA antibodies for the treatment of human malignancies. We will be entering the clinic in the near future.

M.A. ElTanbouly, E. Schaafsma, **R.J. Noelle**, J. L. Lines, VISTA: Coming of age as a multi-lineage immunecheckpoint. *Clin Exp Immunol*, (Jan 13, 2020).

M. ElTanbouly, Y. Zhao, E. Nowak, J. Li, E. Schaafsma, I. LeMercier, C. Carriere, X. Huang, B. H. Koehn, S.W. Lee, M. Morales, D. L. Mueller, J. Rothstein, B. Blazar, C. Cheng, **R. Noelle**, VISTA, a checkpointregulator of naive T cell quiescence and tolerance in the periphery. *Science* 367, (2020).

M.A. ElTanbouly, W. Croteau, **R.J. Noelle**, J.L. Lines, VISTA: a novel immunotherapy target for normalizing innate and adaptive immunity. *Semin Immunol* 42, 101308 (Apr, 2019).

Noelle, R. Immunoregulatory functions of VISTA. *Immunol Rev* 276, 66 (Mar, 2017).

J. L. Lines, L. F. Sempere, T. Broughton, L. Wang, **R. Noelle**, VISTA is a novel broad-spectrum negativecheckpoint regulator for cancer immunotherapy. *Cancer Immunol Res* **2**, 510 (Jun, 2014).

http://www.ncbi.nlm.nih.gov/sites/myncbi/randolph.noelle.1/bibliography/41152920/public/?sort=date& direction=ascending

D. Research Support

Active

NIH R01CA214062-A1(Noelle, MPI) Period: 04/01/17-03/30/22 1.2 calendar months
"Targeting VISTA eradicates large, established PD-1/CTLA-4 resistant tumors"

Targeting VISTA (V-region Immunoglobulin-containing Suppressor of T cell Activation) can eradicate large, established tumors that are resistant to PD-1/CTLA-4 blockade ("checkpoint-resistant" tumors). We propose this isbecause anti-VISTA can relieve T cell suppression and also reduce the myeloid-derived suppressor cell (MDSC) composition and function within the tumor microenvironment (TME). To our knowledge, there is no other antibody-based therapy that results in this outcome. Furthermore, data in human tumors are showing thathigh levels of VISTA expression

in the TME is correlated with poor survival. The mission of this proposal is to define the mechanisms underlying the anti-VISTA pro-survival impact in established tumors.

NIH R01AR070760-01 Period: 09/01/2016-08/31/2021 1.8 calendar months “Negative regulation of Lupus by the VISTA Pathway”

VISTA (V-region Immunoglobulin-containing Suppressor of T cell Activation) is a member of the B7 negative checkpoint regulator (**NCR**) family that controls normal immunity and prevents autoimmunity. Unlike other NCRs.), many of the unique immunologic activities of VISTA would predict an important role in preventing SLE. VISTA has bi-directional functionality, acting as both a ligand and a receptor. As a ligand expressed on myeloidcells, we have shown that it suppresses the earliest events in T cell activation through a putative VISTA counter-receptor, V-set and immunoglobulin domain containing 8 (VSIG8). VISTA can also act as a receptor on T cells and myeloid cells that regulates their biology. The unique engineered tools and genetic models we have created in our lab will allow us to define the critical mechanisms by which the VISTA-VSIG8 pathway impacts on SLE. Finally, these studies will facilitate the design of therapeutic strategies to intervene in human SLE, a disease with a large unmet therapeutic need.

There is no overlap of this application with any other applications.

Past Support

NIH 1R01 AI114059-01 (Noelle, R.J. MPI) Period: 07/01/14-12/30/2019 1.2 cal. mos. Retinoic acid in gut immune homeostasis

The importance of vitamin A (VA) for host defense is undeniable and the study of its mechanisms is paramount. However, we know little of the network of RA production and signaling in the gut that that regulates immunity. The unique in vivo genetic approaches presented in this proposal will address the paradoxical impact of RA on immunity and tolerance and map the network of RA signaling and synthesis critical to the maintenance of mucosal immunity. This is critical information to develop novel vaccine approaches to enhance immunity to pathogens that infect via the gut and to understand VAD.

NIH/NIAID 1R01AI098007-01 (PI: Noelle, R.J.) Period: 12/01/11-11/30/2016 2.4 cal. mos. VISTA, a novel regulator of immunity and autoimmunity

We have defined a new checkpoint regulator, V-region Immunoglobulin-containing Suppressor of T cell Activation (VISTA), whose activity has been shown to impact on the development of immunity, autoimmunity and cancer. The Specific Aims of this proposal are to: 1. Determine how VISTA suppresses the development of pathogenic encephalitogenic T cells. 2. Delineate the function of VISTA expressed on CD4+ T cells, Treg, DCs and myeloid cells in EAE. 3. Employ structural studies to define the molecular determinants that impact onVISTA function. 4. Target the VISTA pathway for immune intervention in autoimmunity.

NIH 1R41AI00418 (Mackey, ImmuNext) 05/01/14-04/30/16 1.2 cal. mos. Validation of a negative regulator as a novel therapy for autoimmune disease

VISTA is a recently identified negative checkpoint regulator of immune function. Functional studies will determine the effects of VISTA dependent signals on T cell proliferation, effector function and differentiation. The studies also will evaluate whether VISTA may regulate the function of other immune cells providing valuable insights on where therapies modulating the VISTA pathway may have the greatest therapeutic potential. Agonists targeted to the VISTA pathway could be used to treat a variety of human autoimmune diseases, including systemic lupus erythematosus and multiple sclerosis. We believe engagement of the VISTA pathway has the potential to be harnessed as a novel treatment for a wide range of autoimmune diseases, including Multiple Sclerosis.