ASSOCIATE PRINCIPAL SCIENTIST

Summary

Significant experience in early target validation space driving program to LID, LO, PCC, and clinic. *Past program expertise includes targeting GPCRs, cytokines, kinases, Sphingosine-1-phosphate receptors, oxidative stress, and phenotypic screens. *Experienced manager and mentor for associate level scientists. Mentor and project coordinator for colleague working on a Master's thesis. *Areas of expertise: 1) Human translation target validation and mechanism of action (MOA) studies using human primary cells from peripheral blood and tissues 2) In vivo mouse and rat pre-clinical MOA and PK/PD studies 3) Flow Cytometry

Experience

Merck & Co., Inc. January 2009 to Current Associate Principal Scientist
Fairfield , CT

Bristol Myers Squibb January 1994 to January 2009 Principal Scientist
Washington , DC

- Leveraging my breadth of Immunology knowledge to drive key studies and decision making for autoimmune and oncology target discovery.
- Instrumental in establishing/designing key in-vitro/ex-vivo human and rodent assays (target engagement (TE), functional, MOA assays, and biomarker) to support target validation, LID/LO, preclinical in-vivo PK/PD, efficacy, and clinical studies.
- Biology lead on multiple collaborations with CROs and academic researchers to successfully drive program decisions for target validation, SAR, or program development of autoimmune diseases targets.
- Led academic collaboration to evaluate genetically modified mice lacking CXCR3 in a severe relapsing-remitting asthma pre-clinical mode.
- Led academic collaboration to provide in-vitro human pDC translational data for advancing a Lupus program.
- Led biotech collaboration for the evaluation of a GPCR target for inflammatory bowel disease.
- Lead the advancement of a biomarker assay to clinic for a chemokine receptor program; trained clinical lab scientists on the implementation of the assay; guided clinical colleagues on the interpretation of data.
- Established key functional cell trafficking assays in rodents which facilitated progression of a chemokine receptor program to PhI for psoriasis.
- Co-lead of an in-vivo non-GLP safety study that determined that observed alterations in PB leukocyte number or activation state were not attributable to the intended biological activity of a pre-clinical candidate and correlated with the clinical pathology report.
- Optimized an in vitro target engagement and functional assay for the CRTh2 program that advanced to PhII for respiratory disease (MK-1029).
- Designed and established primary immune cell and immune-cell line co-culture assays to use as phenotypic screens for new target discovery.
- Key leader in human translational studies: implemented human translation assays utilizing various cell and tissue sources.
- Assays included 1) cell proliferation, killing, activation, and trafficking and mediator production 2) cellular infiltrate phenotypes in pre-clinical models and human samples Assays supported multiple programs including CXCR2, CXCR3, CRTh2, and GPR43, TNF*, TACE (ADAM17), cyclooxygenase, IL-23, Syk, and Btk Whole blood (WB) assays to support kinase and GPCR biomarker identification.
- WB, Primary PBMC, and monocyte assays supported the TACE (ADAM17) program for SAR and confirmed various substrates of ADAM17 related to efficacy and AEs.
- Various PBMC cell assays supporting multiple kinase and GPCR programs forte and functional studies.
- Peripheral blood (PB) B cell assays were used to drive Syk and Btk programs for biology validation.
- PB-derived T-effector cell assays in combination with Treg and/or MDSCs to support phenotypic screens, and validation of proposed T cell or MDSC targets.
- PB-derived pDC assays were evaluated in collaboration with an academic researcher and provided support for a kinase program for a Lupus indication.
- PB derived Treg-Teff suppression assays have supported both immunology and oncology programs by validating small molecule or biologic modulation of the Treg function; anti-GITR reversed the Treg suppressive function.
- Implemented multiple pre-clinical in-vivo models of psoriasis, inflammatory bowel disease (IBD) and T cell dependent diseases to evaluate small molecule inhibitors.
- Project leader for transgenic mouse models that utilized GFP to study cell trafficking and Flt3-ligand to study the role of DC subsets.
- Led immunology efforts with the diabetes-metabolic syndrome group to understand the impact of diet on chronic inflammation related to obesity.
- Organizer and participant in multiple Scientific Input Engagement meetings with external scientific experts.
- Established working groups to align efforts, resources and cross-communication across therapeutic areas, which lead to shared enhanced technical skills for associates and progression of various programs.

January 1989 to January 1994 Junior Scientist

- Contributed technical expertise to the advancement of multiple target using techniques such as cloning, Q-PCR, western blotting, sequencing, bacterial culture systems, protein expression and purification amongst others.
- A highlight was the optimization of a technique to obtain soluble protein expression from an over-expression system that led to inclusion body formation.

Care New England Health System January 1985 to January 1989 Research Assistant
Redding , RI

- Responsible for the for the cloning, expression, and evaluation of heat-shock proteins in Ecoli.
- Responsible for the teaching of electron and scanning microscopy labs.

Education and Training

Rutgers University 1993 PH.D : Molecular Biology/Microbiology City , State Molecular Biology/Microbiology Advisor: Dr. Ann St. John Employed a reporter system to shotgun clone and identified carbon starvation inducible genes in E.coli as a potential for targeting pathogens Publication: Characterization of the carbon starvation-inducible and stationary phase-inducible gene slp encoding an outer membrane lipoprotein in Escherichia coli,

Rutgers University 1989 M.Sc : Microbiology/Molecular Biology City , State Microbiology/Molecular Biology

Bucknell University 1984 B.A : Biochemistry City , State Biochemistry President's Award: Schering Plough research Institute, 2001 Societies American Academy for the Advancement of Science

Publications

Sukumar S, Wilson DC, Yu Y, Wong J, Naravula S, Ermakov G, Riener R, Bhagwat B, Necheva AS, Grein J, Churakova T, Mangadu R, Georgiev P, Manfra D, Pinheiro EM, Sriram V, Bailey WJ, Herzyk D, McClanahan TK, Willingham A, Beebe AM, Sadekova S. Characterization of MK-4166, a clinical agonistic antibody that targets human GITR and inhibits the generation and suppressive effects of T regulatory cells. Cancer Res. 2017 Jun 13. pii: canres.1439.2016. doi: 10.1158/0008-5472.CAN-16-1439. Shin YS, Takeda K, Ohnishi H, Jia Y, Shiraishi Y, Cox ML, Fine JS, Rosenblum S, Lundel D, Jenh CH, Manfra DJ, Gelfand EW. (2011) Targeting CXCR3 reduces ligand-induced T-cell activation but not development of lung allergic responses. Ann Allergy Asthma Immunol. 2011 Aug;107(2):145-53. doi: 10.1016/j.anai.2011.04.013. Epub 2011 Jun 12. Poulet FM, Penraat K, Collins N, Evans E, Thackaberry E, Manfra D, Engstrom L, Geissler R, Geraci-Erck M, Frugone C, Abutarif M, Fine JS, Peterson BL, Cummings BS, Johnson RC (2010) Drug-induced hemolytic anemia and thrombocytopenia associated with alterations of cell membrane lipids and acanthocyte formation. Toxicol Pathol. 2010 Oct;38(6):907-22. doi: 10.1177/0192623310378865. Epub 2010 Aug 30. Engstrom LW, Bober L, Chen SC, Fine JS, Li Y, Stanton MC, Kinsley D, Cui L, Jackson JV, Rojas-Triana A, Lundell D, Laverty M, Gustafson EL, Jenh CH, Kowalski TJ, Manfra DJ. (2010) Kinetic assessment and therapeutic modulation of metabolic and inflammatory profiles in mice on a high-fat and cholesterol diet. PPAR Res. 2010;2010:970164. Epub 2010 Apr 22. Engstrom L, Pinzon-Ortiz MC, Li Y, Chen SC, Kinsley D, Nelissen R, Fine JS, Mihara K, Manfra D. (2009) Characterization of a murine keyhole limpet hemocyanin (KLH)-delayed-type hypersensitivity (DTH) model: role for p38 kinase. Int Immunopharmacol. Sep;9(10):1218-27. Epub 2009 Jul 16 Abbondanzo SJ, Manfra DJ, Chen SC, Pinzon-Ortiz M, Sun Y, Phillips JE, Laverty M, Vassileva G, Hu W, Yang S, Gustafson EL, Fine JS, Hedrick JA. (2009) Nmur1-/- mice are not protected from cutaneous inflammation. Biochem Biophys Res Commun. Jan 23;378(4):777-82. Epub 2008 Dec 12. Fan X, Patera AC, Pong-Kennedy A, Deno G, Gonsiorek W, Manfra DJ, Vassileva G, Zeng M, Jackson C, Sullivan L, Sharif-Rodriguez W, Opdenakker G, Van Damme J, Hedrick JA, Lundell D, Lira SA, Hipkin RW. (2007) Murine CXCR1 is a functional receptor for GCP-2/CXCL6 and interleukin-8/CXCL8. J. Biol Chem. Apr 20 282(16):11658-66. Hyde LA, McHugh NA, Chen J, Zhang Q, Manfra DJ, Nomeir AA, Josien H, Bara T, Clader JW, Zhang L, Parker EM, Higgins GA (2006) Studies to investigate the in-vivo therapeutic window of the {gamma}-secretase inhibitor LY411,575 in the CRND8 mouse. J Pharamacol Expt Ther Dec: 319(3) 1122-1143. Jensen KK, Manfra DJ, Grisotto MG, Martin AP, Vassileva G, Kelley K, Schwartz TW, Lira SA. (2005) The human herpes virus 8-encoded chemokine receptor is required for angioproliferation in a murine model of Kaposi's sarcoma. J Immunol. Mar 15;174(6):3686-94. Wensky AK, Furtado GC, Garibaldi Marcondes MC, Chen S, Manfra D, Lira SA, Zagzag D, Lafaille JJ. (2005) IFN-gamma determines distinct clinical outcomes in autoimmune encephalomyelitis. J Immunol. Feb 1;174(3):1416-23. Pyo R, Jensen KK, Wiekowski MT, Manfra D, Alcami A, Taubman MB, Lira SA. (2004) Inhibition of intimal hyperplasia in transgenic mice conditionally expressing the chemokine-binding protein M3. Am J Pathol. Jun;164(6):2289-97. Wong GT, Manfra D, Poulet FM, Zhang Q, Josien H, Bara T, Engstrom L, Pinzon-Ortiz M, Fine JS, Lee HJ, Zhang L, Higgins GA, Parker EM. (2004) Chronic treatment with the gamma-secretase inhibitor LY-411,575 inhibits beta-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation. Manfra DJ, Chen SC, Jensen KK, Fine JS, Wiekowski MT, Lira SA. (2003) Conditional expression of murine Flt3 ligand leads to expansion of multiple dendritic cell subsets in peripheral blood and tissues of transgenic mice. J Immunol. Mar 15;170(6):2843-52 Mehrad B, Wiekowski M, Morrison BE, Chen SC, Coronel EC, Manfra DJ, Lira SA. (2002)Transient lung-specific expression of the chemokine KC improves outcome in invasive aspergillosis. Am J Respir Crit Care Med. Nov 1;166(9):1263-8. Chen SC, Vassileva G, Kinsley D, Holzmann S, Manfra D, Wiekowski MT, Romani N, Lira SA. (2002) Ectopic expression of the murine chemokines CCL21a and CCL21b induces the formation of lymph node-like structures in pancreas, but not skin, of transgenic mice. J Immunol. Feb 1;168(3):1001-8 Holst PJ, Rosenkilde MM, Manfra D, Chen SC, Wiekowski MT, Holst B, Cifire F, Lipp M, Schwartz TW, Lira SA. (2001) Tumorigenesis induced by the HHV8-encoded chemokine receptor requires ligand modulation of high constitutive activity. J Clin Invest. Dec;108(12):1789-96. Manfra, D.J. Chen, S-C., Yang, T-Y., Sullivan, L., Abbondanzo, S., Vassileva, G., Zalamea, P., Cook, D.N. and Lira, S. A. (2001) Leukocytes expressing green fluorescent protein as novel reagents for adoptive cell transfer and bone marrow transplantation studies. Am J Pathol. Jan;158(1):41-7. Wiekowski, M.T., Chen, S-C., Zalamea, P, Wilburn, B.P., Kinsley, D. J., Sharif, W.W., Jensen, K.K., Hedrick, J. A., Manfra, D.J. and Lira, S. A. (2001) Disruption of neutrophil migration in a conditional transgenic model: evidence for CXCR2 desensitization in vivo. J. Immunol. Dec 15;167 (12): 7102-7110. Holst, P.J., Rosenkilde, M.M., Manfra, D.J., Chen, S-C., Wiekowski, M.T., Holst, B., Lipp, M., Schwartz, T.W. and Lira, S. A. (2001) Modulation of the high constitutive activity of the HHV8-encoded chemokine receptor by angiogenic chemokines is essential for tumorigenesis. J. Clin. Invest Cook, D.N., Chen, S-C., Sullivan, L.M., Manfra, D.J., Wiekowski, M.T., Prosser, D.M., Vassileva, G. and Lira, S. A. (2001) Generation and analysis of mice lacking the chemokine fractalkine Mol Cell Biol. May;21(9):3159-65 Chen, S-C., Mehrad, B., Deng, J.C., Vassileva, G., Manfra, D.J., Cook, D.N., Wiekowski, M.T., Zlotnik, A., Standiford, T.J., and Lira, S. A. (2001) Impaired pulmonary host defense in mice lacking expression of the CXC chemokine Lungkine. J Immunol. Mar 1;166(5):3362-8 Cook, D.N., Prosser, D.M., Forster, R., Zhang, J., Kuklin, N.A., Abbondanzo, S.J., Niu, X-D., Chen, S-C., Manfra, D.J., Wiekowski, M.T., Sullivan, L.M., Smith, S.R., Greenberg, H.B., Narula, S.K., Lipp, M., Lira, S. A. 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(1999) Endogenous Mouse Interleukin-10 Is upregulated by exogenously administered recombinant human interleukin-10, but does not contribute to the efficacy of the human protein in mouse models of endotoxemia. Immunopharmacology, 41 (2): 119-130. Smith, S.R., Manfra, D., Davies, L., Terminelli, C., Denhardt,

G., and Donkin, J. (1997) Elevated levels of NO in both unchallenged and LPS-challenged C. parvum-primed mice are attributable to the activity of a cytokine-inducible isoform of iNOS. J. of Leukoc Biol., 61: 24-32. Feder, L.S., Stelts, D., Chapman, R.W., Manfra, D., Crawley, Y., Jones, H., Minnicozzi, M., Fernandez, X., Paster, T., Egan, R.W., Kreutner, W., Kung, T.T. (1997) Role of nitric oxide on eosinophilic lung inflammation in allergic mice. Amer. J. of Resp Cell and Molec. Biol. (AJRCMB) 17: 436-442. Manfra, D.J., Baum, C.L., Reschley, E., Lundell, D., Zavodny, P., and Dalie, B. (1995) Expression and Purification of two recombinant sterol-carrier proteins: SCPX and SCP2. Protein Expression and Purification, 6: 196-205. Salisbury, B.G., Weig, B.C., Shanahan, M.F., Manfra, D.J., and Dalie, B.L. (1995) Cholesterol esterification is enhanced in CaCo-2 cells transfected with sterol carrier protein-2 (SCP2). FASEB Journal, 9(4): 703. Alexander, D.M.(Manfra), and St. John, A.C. (1994) Characterization of the carbon-starvation-inducible and stationary phase-inducible gene slp encoding an outer membrane lipoprotein in Escherichia coli, Molecular Microbiol. 11(6): 1059-1071. Alexander, D.M. (Manfra), Damerau, K., and St. John, A.C., (1993) Carbohydrate uptake genes in Escherichia coli are induced by carbon starvation, Current Microbiology 27:335-340 Alexander, D.M. (Manfra), Hesson, T., Mannarino, A., Cable, M., Dalie, B.L. (1992) Isolation and purification of a biologically active human platelet-derived growth factor BB expressed in Escherichia coli. Protein Expression and Purification, 3: 204-211. REVIEWS Lira SA, Mehrad B, Chen SC, Zalamea P, Kinsley DJ, Wiekowski MT, Coronel E, Vassileva G, Manfra D, Jensen KK. (2004) Conditional transgenic models to study chemokine biology. Methods Mol Biol. 239:105-22.

Skills

academic, Biology, C, DC, decision making, designing, diabetes, forte, functional, GLP, Immunology, interpretation, mediator, meetings, oncology, optimization, Organizer, pathology, PCR, program development, Project leader, Publication, reporter, researcher, safety, scanning, Scientific, teaching, translation, validation, western blotting