Ronald M. Evans
Professor
Gene Expression Laboratory

Salk Institute for Biological Studies
10010 N Torrey Pines Rd
La Jolla, California 92037

PH (858) 453-4100 x1302
FX (858) 455-1349

www.salk.edu

To: John Reynolds and Tanya Sharpee, ApCom

From: Ron Evans and Tony Hunter

Date: June 8, 2023

Re: Adjunct Professor David Brenner – re-appointment

Dear John and Tanya,

On behalf of Tony Hunter and myself, we would like to request the renewal of Dr. David Brenner's Adjunct Professor appointment.

David is the current President and CEO of Sanford Burnham Prebys, and was most recently the Vice Chancellor for Health Sciences and Dean of the UCSD School of Medicine. David runs an active research program on metabolic syndrome and liver disease, and we are long-standing collaborators on the molecular biology of liver inflammation, fatty liver disease and hepatic fibrosis. Many of us at the Salk have regular opportunities to interact with David.

With his previous role as UCSD Vice Chancellor and current role at Sanford Burnham, David plays an important role on the Mesa, and is a valuable contact at both SBP and the UCSD medical school and cancer center.

David received his BS, MD and conducted his residency at Yale (1975, '79 and '82 respectively), and has an excellent track record in both leadership and research. Dr. Brenner's CV and completed adjunct service questionnaire are attached for your reference.

Ronald M. Evans
Professor, March of Dimes Chair in Molecular and Developmental Biology
Head, Salk Gene Expression Lab

Tony Hunter
Renato Dulbecco Chair
American Cancer Society Professor
Molecular and Cell Biology Laboratory

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: DAVID A. BRENNER,MD

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

POSITION TITLE: President and CEO, Sanford Burnham Prebys

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
Yale University, New Haven, CT	BS	06/1975	Biology
Yale University, New Haven, CT	MD	06/1979	Medicine
Yale University, New Haven, CT	Resident	06/1982	Internal Medicine
NIH/NIDDK, Bethesda, MD	Fellowship	06/1985	Genetics & Biochem
UC San Diego, La Jolla, CA	Fellowship	06/1986	Gastroenterology

A. Personal Statement

I received extensive training in clinical and experimental hepatology at Yale, National Institute of Health, and UC San Diego. I have developed a research program to study the molecular pathophysiology of chronic liver diseases. My research program's general approach is to start with mouse models of chronic liver injury that reflect the different type of human diseases; common bile duct ligation (cholestatic liver disease), carbon tetrachloride administration (toxicant liver injury, (TASH)), intragastric alcohol feeding (alcoholic liver disease, (ASH)), and diet induced obesity, choline deficient amino acid supplemented diet, or mup-UPA with high fat diet (non-alcoholic steatohepatitis (NASH)). By utilizing mouse genetics, my program has compared the severity of liver diseases between different transgenic mice and their wild-type litter mates to determine genes that are protective or are causative in chronic liver injury of different etiologies and to identify the step in which each gene exerts its influence. This approach has identified key steps in chronic liver injury starting with the gut microbiome and intestinal permeability, the injury to parenchymal cells by the etiological agent, the generation of reactive oxygen species, hepatic inflammation, the activation of myofibroblasts, and the accumulation of a fibrous scar. Furthermore, I have developed techniques to purify and culture primary hepatic cells from mouse and human livers: hepatocytes, sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells/macrophages. These primary cultures are used to study cellular activation and intracellular signaling and to model the direct effects of toxicants such as CCl_4 and the metabolic syndrome on hepatic cell populations. My studies have also used lethal irradiation, clodronate in liposomes, and bone marrow transplantation to replace bone marrow derived cells with donor cells to generate chimeric mice to identify the cell source of key gene products. Finally, I have translated some of the observation in mouse models of liver disease to patients by utilizing biopsies of patients in order to study gene expression and cellular constituents in chronic liver diseases and studying primary cultures of human liver cell populations.

B. Positions, Scientific Appointments, and Honors

Positions

1986 -1990	Assistant Professor of Medicine in Residence, UC San Diego, CA
1988 -1989	Acting Assistant Chief of Medicine, Veteran's Administration Medical Center, San Diego, CA
1987- 1992	Staff Physician, Veteran's Administration Medical Center, San Diego, CA
1990 -1992	Associate Professor of Medicine, UC San Diego, CA
1992 - 2003	Professor of Medicine & Biochemistry & Biophysics, & Chief, Division of Digestive Diseases and Nutrition, University of North Carolina, Chapel Hill, NC
2000- 2003	Nina C. and John T. Sessions Distinguished Professor of Digestive Diseases and Nutrition
2003 - 2007	Chairman, Department of Medicine and Samuel Bard Professor, Columbia University College of Physicians and Surgeons, Director, Medical Service, NYPH-CUMC.
2007-2018	Dean, School of Medicine, UC San Diego, CA.
2007-2022	Vice Chancellor for Health Sciences & Distinguished Professor of Medicine, UC San Diego, CA.
2022-Present	President and CEO, Sanford Burnham Prebys
2013-Present	Adjunct Professor of Biology, Salk Institute for Biological Studies

Honors (selected)

1989-1992	National Counselor, American Federation for Clinical Research
1991-1995	Research Committee, American Association for the Study of Liver Diseases
1992-1995	Research Committee, American Gastroenterological Association
1992-Present	American Society of Clinical Investigation
1994-2003	Co-Director, Center for Gastrointestinal Biology and Disease, University of North Carolina at Chapel Hill and North Carolina State University
1994-2007	Glaxo Institute for Digestive Health Scientific Advisory Board, President (2004-2007)
1995-1998	Teaching and Education Committee, American Gastroenterological Association
1996-1999	Public Policy Committee, American Association for the Study of Liver Diseases
1997-2000	Chair, Manpower and Training Committee, American Gastroenterological Association
1997-1998	Kenan Fellow in support of sabbatical
2001-2006	Editor-in-Chief, *Gastroenterology*
2003-2014	AlphaOne Foundation Board of Directors
2009-2014	BioCom Board of Directors
2005-Present	Association of American Physicians, Councilor, Secretary, President (various years)
2007-Present	Rady Children's Hospital and Health Center Board of Trustees
2007-Present	California Institute for Regenerative Medicine, Citizens Oversight Committee
2007-Present	CONNECT Board of Directors
2013-2018	NIDDK Advisory Council
2013-Present	National Academy of Medicine
2018-Present	La Jolla Institute of Immunology, Board of Directors
2018-Present	America's Essential Hospitals, Board of Directors
2019	American Liver Foundation Distinguished Scientific Career Award
2019	AGA Section Council Research Mentor Award

C. Contributions to Science

1. My original research was on the enzymatic and molecular defects in the porphyrias. This required me setting up a new enzymatic assay for a protoporphyrinogen oxidase that was adapted from bacteria to mammalian cells. Subsequently, I used the newly described skin fibroblast cultures from patients to compare enzymatic and genetic mutations in culture skin fibroblasts that I had obtained from normal controls and from patients with porphyria. This lead to my identification of the enzymatic defect in variegate porphyria to my identification of the genetic mutations in protoporphyria. My research group subsequently studied the regulation of expression of the ferrochelatase gene in multiple tissues and

generated a mouse model of protoporphyria by knocking into the mouse genome one of the mutations that we had identified in our patients.

a) Brenner DA, Bloomer JR. The enzymatic defect in variegate porphyria. Studies with human cultured skin fibroblasts. N Engl J Med. 1980 Apr 3;302(14):765-9. PMID: 7354807
b) Brenner DA, Frasier F. Cloning of murine ferrochelatase. Proc Natl Acad Sci U S A. 1991 Feb 1;88(3):849-53. PMID: 1704134
c) Brenner DA, Didier JM, Frasier F, Christensen SR, Evans GA, Dailey HA. A molecular defect in human protoporphyria. Am J Hum Genet. 1992 Jun;50(6):1203-10. PMID: 1376018
d) Tugores A, Magness ST, Brenner DA. A single promoter directs both housekeeping and erythroid preferential expression of the human ferrochelatase gene. J Biol Chem. 1994 Dec 9;269(49):30789-97. PMID: 7983009

2. While a junior faculty member at UC San Diego, I became interested in the intracellular signaling in hepatic injury. These studies were conducted in collaboration with Dr. Michael Karin. I used the molecular techniques and assays that I learned in his laboratory to adapt to the physiological state of liver injury including liver regeneration, liver fibrosis, and toxic liver injury. This lead to a series of studies that identified a role for JNK in hepatic injury, including ischemia-reperfusion. It also lead to the identification of the protective role for NFκB in hepatic injury. We also carefully distinguished the signal transduction in hepatocytes from the signaling and activation of hepatic stellate cells in liver injury. In particular, signal transduction via NFκB that was protective of injury in hepatocytes would actually promote hepatic stellate cell activation and proliferation leading to fibrosis.

a) Brenner DA, O'Hara M, Angel P, Chojkier M, Karin M. Prolonged activation of jun and collagenase genes by tumour necrosis factor-alpha. Nature. 1989 Feb 16;337(6208):661-3. PMID: 2537468
b) Westwick JK, Cox AD, Der CJ, Cobb MH, Hibi M, Karin M, Brenner DA. Oncogenic Ras activates c-Jun via a separate pathway from the activation of extracellular signal-regulated kinases. Proc Natl Acad Sci U S A. 1994 Jun 21;91(13):6030-4. PMID: 8016110
c) Schwabe RF, Bradham CA, Uehara T, Hatano E, Bennett BL, Schoonhoven R, Brenner DA. c-Jun-N-terminal kinase drives cyclin D1 expression and proliferation during liver regeneration. Hepatology. 2003 Apr;37(4):824-32. PMID: 12668975
d) Liu X, Xu J, Rosenthal S, Zhang LJ, McCubbin R, Meshgin N, Shang L, Koyama Y, Ma HY, Sharma S, Heinz S, Glass CK, Benner C, Brenner DA, Kisseleva T. Identification of Lineage-Specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution. Gastroenterology. 2020 May;158(6):1728-1744.PMID: 31982409

3. Applying advanced techniques in signal transduction and gene transcription, we studied the regulation of Type I Collagen, the most abundant extracellular matrix protein in hepatic fibrosis. We developed a series of reporter mice in which this gene's enhancers and promoter were identified. One of our transgenic reporter mice that expresses GFP driven by the collagen a1(I) promoter/enhancer, has been used extensively by our lab and others to characterize the activation of myofibroblasts in fibrotic organs. We went on to show that a major regulatory step in fibrosis is the stabilization of the Type I Collagen mRNA. There are regulatory regions in both the 5' untranslated stem loop and the 3' untranslated RNA binding site for the RNA binding protein αCP. Furthermore, we created a knock-in mouse in which the 5-prime stem loop was disrupted so it could no longer be bound by mRNA-binding proteins. This created a transgenic mouse with unstable collagen mRNA and translational inefficiency that is phenotypically normal but resistant to liver fibrosis.

a) Stefanovic B, Hellerbrand C, Holcik M, Briendl M, Liebhaber SA, Brenner DA. Posttranscriptional regulation of collagen alpha1(I) mRNA in hepatic stellate cells. Mol Cell Biol. 1997 Sep;17(9):5201-9. PMCID: PMC232371
b) Lindquist JN, Kauschke SG, Stefanovic B, Burchardt ER, Brenner DA. Characterization of the interaction between alphaCP(2) and the 3'-untranslated region of collagen alpha1(I) mRNA. Nucleic Acids Res. 2000 Nov 1;28(21):4306-16. PMCID: PMC113122

c) Lindquist JN, Parsons CJ, Stefanovic B, Brenner DA. Regulation of alpha1(I) collagen messenger RNA decay by interactions with alphaCP at the 3'-untranslated region. J Biol Chem. 2004 May 28;279(22):23822-9. PMID: 14973140
d) Parsons CJ, Stefanovic B, Seki E, Aoyama T, Latour AM, Marzluff WF, Rippe RA, Brenner DA. Mutation of the 5'-untranslated region stem-loop structure inhibits α1(I) collagen expression in vivo. J Biol Chem. 2011 Mar 11;286(10):8609-19. PMCID: PMC3048743

4. One of the areas of most intense investigation in tissue fibrosis has been the origin of the myofibroblast, the cell that produces the extracellular matrix of the fibrous scar. Our research group has used reporter mice, genetic cell fate mapping, and new FACS methods to address this issue. Our work that has been largely corroborated by others demonstrated that the epithelial-mesenchymal transition of hepatocytes or cholangiocytes does not produce any myofibroblasts in the fibrotic liver. Furthermore, bone marrow derived fibrocytes are a minor contributor to the myofibroblast population, but contribute to the inflammatory cell population that induces fibrosis. It is the endogenous mesenchymal cells that activate to become myofibroblasts. In hepatotoxic liver injury, there is direct activation of hepatic stellate cells. While in cholestatic liver injury, there is first activation of portal fibroblasts and subsequently spread of the injury to the acini with activation of hepatic stellate cells. This research program was initiated under my direction, and then advanced under the leadership of Tatiana Kisseleva with my collaboration.

a) Österreicher CH, Penz-Österreicher M, Grivennikov SI, Guma M, Koltsova EK, Datz C, Sasik R, Hardiman G, Karin M, Brenner DA. Fibroblast-specific protein 1 identifies an inflammatory subpopulation of macrophages in the liver. Proc Natl Acad Sci U S A. 2011 Jan 4;108(1):308-13. PMCID: PMC3017162
b) Kisseleva T, Cong M, Paik Y, Scholten D, Jiang C, Benner C, Iwaisako K, Moore-Morris T, Scott B, Tsukamoto H, Evans SM, Dillmann W, Glass CK, Brenner DA. Myofibroblasts revert to an inactive phenotype during regression of liver fibrosis. Proc Natl Acad Sci U S A. 2012 Jun 12;109(24):9448-53. PMCID: PMC3386114
c) Iwaisako K, Jiang C, Zhang M, Cong M, Moore-Morris TJ, Park TJ, Liu X, Xu J, Wang P, Paik YH, Meng F, Asagiri M, Murray LA, Hofmann AF, Iida T, Glass CK, Brenner DA, Kisseleva T. Origin of myofibroblasts in the fibrotic liver in mice. Proc Natl Acad Sci U S A. 2014 Aug 12;111(32):E3297-305. PMID: 25074909
d) Koyama Y, Wang P, Liang S, Iwaisako K, Liu X, Xu J, Zhang M, Sun M, Cong M, Karin D, Taura K, Benner C, Heinz S, Bera T, Brenner DA, Kisseleva T. Mesothelin/mucin 16 signaling in activated portal fibroblasts regulates cholestatic liver fibrosis. J Clin Invest. 2017 Apr 3;127(4):1254-1270. PMCID: PMC5373891

5. The mechanisms by which inflammation lead to fibrosis and HCC are largely unknown, but a possible mediator is the generation of reactive oxygen species. Rather than causing non-specific injury, we have proposed that reactive oxygen species generated by NADPH oxidases (NOXs) activate specific intracellular signaling that leads to fibrosis. We have demonstrated that NOX 1, 2, and 4 are activated in hepatic stellate cells, resulting in their activation and fibrotic gene expression. We demonstrated that the fibrotic agonists leptin, LPS, angiotensin II, insulin, TGFb and hedgehog ligands generate ROS in hepatic stellate cells via NOX. Thus, ROS via NOX is a common mediator of fibrosis and a logical target for drug discovery. We have collaborated with companies to assess NOX inhibitors and have demonstrated that a small molecule dual NOX 1 and 4 inhibitor decreases hepatic fibrosis in several mouse models and blocks ROS generation in hepatic stellate cells.

a) Bataller R, Schwabe RF, Choi YH, Yang L, Paik YH, Lindquist J, Qian T, Schoonhoven R, Hagedorn CH, Lemasters JJ, Brenner DA. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. J Clin Invest. 2003 Nov;112(9):1383-94. PMCID: PMC228420
b) De Minicis S, Seki E, Paik YH, Osterreicher CH, Kodama Y, Kluwe J, Torozzi L, Miyai K, Benedetti A, Schwabe RF, Brenner DA. Role and cellular source of nicotinamide adenine dinucleotide phosphate oxidase in hepatic fibrosis. Hepatology. 2010 Oct;52(4):1420-30. PMCID: PMC2947612

c) Aoyama T, Paik YH, Watanabe S, Laleu B, Gaggini F, Fioraso-Cartier L, Molango S, Heitz F, Merlot C, Szyndralewiez C, Page P, Brenner DA. Nicotinamide adenine dinucleotide phosphate oxidase in experimental liver fibrosis: GKT137831 as a novel potential therapeutic agent. Hepatology. 2012 Dec;56(6):2316-27. PMCID: PMC3493679
d) Liang S, Ma HY, Zhong Z, Dhar D, Liu X, Xu J, Koyama Y, Nishio T, Karin D, Karin G, Mccubbin R, Zhang C, Hu R, Yang G, Chen L, Ganguly S, Lan T, Karin M, Kisseleva T, Brenner DA. NADPH Oxidase 1 in Liver Macrophages Promotes Inflammation and Tumor Development in Mice. Gastroenterology. 2019 Mar;156(4):1156-1172. PMID: 30445007.

Salk Adjunct Service/Contributions Form

Name: David A. Brenner **Appointment Start Date:** 7/1/23
Sponsors: Ron Evans

To be eligible for appointment and reappointment in the Adjunct series, appointees are expected to be engaged in **at least two** Institute-related activities outlined below. If you are being considered for your first Adjunct Professor appointment, provide information about your plans to engage in the Salk community and select any of the activities you would be interested in below. If you are being considered for reappointment, select your ongoing activities and give a brief summary of your engagement in each activity during the past appointment period. Also provide a summary of your plans to engage in the Salk activities during the next appointment period.

Salk Activities (list the course/seminar titles, committees, and student names if known)
** Please note research collaborations with a Salk Faculty sponsor(s) do not qualify as Institute-related activities expected for an Adjunct position*

- ■ Giving Seminars, such as those hosted by Sponsors or by the Institute
- ☐ Teaching in Salk-organized courses
- ☐ Serving on UCSD Student Review committees and/or Thesis Committees in Salk Labs
- ☐ Reviewing Postdoctoral and other Internal Grants
- ☐ Participating in Salk's outreach and educational efforts to recruit underrepresented minority student applicants
- ■ Consulting on Salk scientific initiatives or multi-PI grants
- ■ Serving on Faculty Review Committees
- ☐ Promoting award and nomination opportunities for Salk Faculty
- ☐ Organizing or participating on Salk Meetings or Conferences
- ☐ Other

Salk Service Summary & Plans: Describe your plans to engage in the activities marked above during the next appointment period (i.e.: Salk Course or Seminar Titles, names of Student or Faculty review committee, description of contributions to grants, etc. if unable to fit above). If you are being considered for reappointment, also describe your engagement in the Salk activities during the last appointment period. You may attach a supplemental letter with these activities as needed.

I have had a long term relationship with Salk. In the past, I have collaborated with Salk Investigators resulting in grants and publications. I have coordinated interactions between Salk investigators, UCSD investigators, and biotech. Going forward, Ron Evans will sponsor me as a seminar speaker at Salk. I am also working on a joint Salk, Sanford Burnham Prebys, UCSD metabolism program to share resources and promote translational research. I have a lot of experience reviewing grant applications and academic promotions and can help Salk in these areas.