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KEVAN M. SHOKAT

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview Conducted by

William Van Benschoten

at

University of California, San Francisco San Francisco, California

on

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Selected Publications

- Van Keymeulen, A., Wong, K., Knight, Z.A., Govaerts, C., Hahn, K.M., Shokat, K.M. and Bourne, H.R. (2006) To stabilize neutrophil polarity, PIP3 and Cdc42augment RhoA activity at the back as well as signals at the front. J Cell Biol. (Epub ahead of print)
- Brodersen, P., Petersen, M., Bjorn Nielsen, H., Zhu, S., Newman, M.A., Shokat, K.M., Rietz, S., Parker, J. and Mundy, J. (2006) Arabidopsis MAP kinase 4 regulates salicylic acid-and jasmonic acid/ethylene-dependent responses via EDS1 and PAD4. Plant J [Epub ahead of print]
- Wei, F., Wang, G.D., Zhang, C., Shokat, K.M., Wang, H., Tisen, J.Z., Liauw, J. andZhuo, M. (2006) Forebrain over expression of CaMKII abolishes cingulate long term depression and reduces mechanical allodynia and thermal hyperalgesia. Mol. Pain., 15; 2(1):21.
- Fan, Q-W., Knight, Z.A., Goldenberg, D.D., Yu, W., Mostov, K.E., Stokoe, D., Shokat, K.M. and Weiss, W.A. (2006) A dual PI3 kinase/mTOR inhibitor reveals emergent efficacy in glioma. Cancer Cell, 9:341-349.
- Wohlbold, L., Larochelle, S., Liao, J.C., Livshits, G., Singer, J., Shokat, K.M. andFisher, R.P. (2006) The cyclin-dependent kinase (CDK) Family member PNQALRE/CCRK supports cell proliferation but has no intrinsic CDK-activating kinase (CAK) activity. Cell Cycle, 5(5):546-54.
- Kung, C., Kenski, D.M., Krukenberg, K., Madhani, H.D. and Shokat, K.M. (2006) Selective kinase inhibition by exploiting differential pathway sensitivity. Chem Biol. Apr; 1 3(4):399-407.
- Knight, Z.A., Gonzalez-Perez, B., Feldman, M.E., Zunder, E., Goldenberg, D., Balla, A., Balla, T., Loewith, R., Weiss W.A., Williams, R.L. and Shokat, K.M. (2006) A pharmacological map of the PI3-K family defines a role for p1 10a in insulin signaling. Cell, in press.
- Fan, Q.W., Knight, Z.A., Goldenberg, D.A., Stokoe, D., Weiss, W.A. and Shokat, K.M. (2006) A family-based chemical screen identifies cooperative inhibition of mTOR and p1 10a in glioma, Cancer Cell, submitted
- Ventura, J.J., Hubner, A., Zhang, C., Flavell, R.A., Shokat, K.M. and Davis, R.J. (2006) Chemical Genetic Analysis of the Time Course of Signal Transduction by JNK. Mol Cell. (5):701-10.
- Pinsky, B.A., Kung, C., Shokat, K.M. and Biggins, S. (2006) The Ipl1-Aurora protein kinase

activates the spindle checkpoint by creating unattached kinetochores. Nat Cell Biol., 8(1):78-83.

- Larochelle, S., Batliner, J., Gamble, M.J., Barboza, N.M., Kraybill, B.C., Blethrow, J.D., Shokat, K.M. and Fisher, R.P. (2006) Dichotomous but stringent substrate selection by the dual-function Cdk7 complex revealed by chemical genetics. Nat Struct Mol Biol., 13(1):55-62.
- Dephoure, N., Howson, R.W., Blethrow, J.D., Shokat, K.M. and O'Shea, E.K. (2005) Combining chemical genetics and proteomics to identify protein kinase substrates. Proc Natl Acad Sci U S A., 102(50):17940-5.
- Juris, S.J., Shah, K., Shokat, K., Dixon, J.E. and Vacratsis, P.O.(2006) Identification of otubain 1 as a novel substrate for the Yersinia protein kinase using chemical genetics and mass spectrometry. FEBS Lett., 580(1):179-83.
- D'Aquino, K.E., Monje-Casas, F., Paulson, J., Reiser, V., Charles, G.M., Lai, L., Shokat, K.M. and Amon, A. (2005) The protein kinase Kin4 inhibits exit from mitosis in response to spindle position defects. Mol. Cell., 19(2):223-34.
- Kenski, D.M., Zhang, C., von Zastrow, M. and Shokat, K.M. (2005) Chemical genetic engineering of G protein-coupled receptor kinase 2. J. Biol. Chem., 80(41):35051-61.
- Zhang, C., Kenski, D.M., Paulson, J.L., Bonshtien, A., Sessa, G., Cross, J.V., Templeton, D.J. and Shokat, K.M. (2005) A second-site suppressor strategy for chemical genetic analysis of diverse protein kinases. Nature Methods, 2(6):435-441.
- Cohen, M.C., Zhang, C., Shokat, K.M., Taunton, J. (2005) Structural Bioinformatics-Based Design of Selective, Irreversible Kinase Inhibitors. Science, 308: 13 18-1321.
- Knight, Z.A. and Shokat, K.M. (2005) Features of selective kinase inhibitors. Chemistry & Biology, 12:621-637.
- Tanaka, M., Bateman, R., Rauh, D., Vaisberg, E., Ramachandani, S., Zhang, C., Hansen, K.C., Burlingame, A.L., Trautman, J.K., Shokat, K.M. and Adams, C.L. (2005) An Unbiased Cell Morphology Based Screen for New Biologically Active Small Molecules. PLOS Biology, 3(5):e128.
- Shokat, K.M. (2005) Chemicals Call Bacteria, and A New Membrane Protein Machine Answers. Cell, 121:163-166.
- Murattani, M., Kung, C, Shokat, K.M. and Tansey, W.P. (2005) The F box proteinDsg1/Mdm30 is a transcriptional coactivator that stimulates Gal4 turnover and cotranscriptional mRNA processing. Cell, 120(6):887-899.
- Allen, J., Lazerwith, S.E. and Shokat, K.M. (2005) Bio-orthogonal Affinity Purification of Direct Kinase Substrates. J. Amer. Chem. Soc., 127(15):5288-9.
- Chen, X., Ye, H., Kuruvilla, R., Ramanan, N., Scangos, K.W., Zhang, C., Johnson, N.M., England, P.M., Shokat, K.M. and Ginty, D.D. (2005) A chemical-genetic approach to studying neurotrophin signaling. Neuron, 46(1): 13-21.
- Alaimo, P.J., Knight, Z.A. and Shokat, K.M. (2005) Targeting the gate keeper residue in phosphoinositide 3-kinasesBioorg & Med Chem, 12:2825-2836.
- Kung, C, Kenski, D.M., Dickerson, S.H., Howson, R.W., Kuyper, L.F., Madhani, H.D. and Shokat, K.M. (2005) Chemical genomic profiling to identify intracellular targets of a multiplex kinase inhibitor. Proc. Natl. Acad. Sci., 102(10)3587-3592.
- Kung, C. and Shokat, K.M. (2005) Small-Molecule Kinase-Inhibitor Target Assessment. ChemBiochem, 6(3):523-526.

- Jones, M.H., Huneycutt, B.J., Pearson, C.G., Zhang, C., Morgan, G., Shokat, K., Bloom, K., Winey, M. (2005) Chemical genetics reveals a role for Mps1 kinase in kinetochore attachment during mitosis. Curr Biol., 15(2):160-5.
- Wong, S., McLaughlin, J., Cheng, D., Zhang , C., Shokat, K.M., Witte, O.N. (2004) "Sole BCR-ABL inhibition is insufficient to eliminate all myeloproliferative disorder cell populations." Proc Natl Acad Sci U S A., 101(50):17456-61.
- Kunkel, E.J., Plavec, I., Nguyen, D., Melrose, J., Rosler, E.S., Kao, L.T., Wang, Y., Hytopoulos, E., Bishop, A.C., Bateman, R., Shokat, K.M., Butcher, E.C., Berg, E.L. (2004) "Rapid structure-activity and selectivity analysis of kinase inhibitors by BioMAP analysis in complex human primary cell-based models." Assay Drug Dev Technol., Aug;2(4):43 1-41.
- Simon, M.D., Sato, K., Weiss, G.A. and Shokat, K.M. (2004) A phage display selection of engrailed homeodomain mutants and the importance of residue Q50. Nucleic Acids Res., 32(12):3623-31.
- Maly, D.J., Allen, J.A. and Shokat, K.M. (2004) A Mechanism-Based Crosslinker for the Identification of Kinase-Substrate Pairs. J. Am. Chem. Soc., 126(30):9160-61. 79.
- Knight, Z.A., Chiang, G., Alaimo, P.J., Kenski, D.M., Ho, C.B., Coan, K., Abraham, R., and Shokat, K.M.* (2004) Isoform-specific phosphoinositide 3-kinase inhibitors from an arylmorpholine scaffold. Bioorg. & Med. Chem. Ltrs., 12(17)4749- 59.
- Sato, K., Simon, M.D., Levin, A.M., Gothard, C.M., Shokat, K.M. and Weiss, G.A. (2004) Dissecting the Engrailed-DNA Interaction by Phage-Displayed Alanine Shotgun Scanning. Chem. Biol., 1 1(7):1017-23.
- Simon, M.D. and Shokat, K.M.* (2004) Adaptability at a protein-DNA interface: re-engineering the engrailed homeodomain to recognize an unnatural nucleotide. J. Am. Chem. Soc., 126(26):8078-79.
- Provance, D.W., Jr., Gourley, C.R., Silan, C.M., Cameron, L.C., Shokat, K.M., Goldenring, J.R., Shah, K., Gillespie, P.G. and Mercer, J.A. (2004) From the Cover: Chemicalgenetic inhibition of a sensitized mutant myosin Vb demonstrates a rolein peripheralpericentriolar membrane traffic. Proc. Natl. Acad. Sci., 17:101(7): 1868-73.
- Liu, Y., Kung, C., Fishburn, J., Ansari, A.Z., Shokat, K.M. and Hahn, S. (2004) Two cyclindependent kinases promote RNA polymerase II transcription and formation of the scaffold complex. Mol. Cell. Biol., 24(4):1721-35.
- Hindley, A.D., Park, S., Wang, L., Shah, K., Wang, Y., Hu, X., Shokat, K.M., Kolch, W., Sedivy, J.M., Yeung, K.C. (2004) Engineering the serine/threonine protein kinase Raf-1 to utilize an orthogonal analogue of ATP substituted at the N(6) position. FEBS Lett., 556(1-3):26-34.
- Zhang, C. and Shokat, K.M. (2003) Engineering Protein Kinases with Specificity for Unnatural Nucleotides and Inhibitors. Handbook of Cell Signaling, Vol. 1 Chapter 98:583-587.
- Fan, Q., Specht, K.M., Zhang, C., Goldenberg , D.D., Shokat, K.M. and Weiss, W.A. (2003) Combinatorial Efficacy Achieved Through Two Point Blockade Within a Signaling Pathway—A Chemical Genetic Approach. Cancer Res., 63(24):8930-8.
- Papa, F.R., Zhang, C., Shokat, K., and Walter, P. (2003) Bypassing a Kinase Activity with an ATP-Competitive Drug. Science, 302(5650):1533-7.
- Wan, L., De Los Santos, T., Zhang, C., Shokat, K., Hollingsworth, N.M. (2003) Mek1 kinase activity functions downstream of RED1 in the regulation of meioticDSB repair in

budding yeast. Mol. Biol. Cell, 15(1):1 1-23.

- Ubersax, J.A., Woodbury, E.L., Quang, P.N., Paraz, M., Blethrow, J.D., Shah, K., Shokat, K.M. and Morgan, D.O. (2003) Targets of the Cyclin-Dependent Kinase Cdk1. Nature, 425(6960):859-64.
- Wang, H., Shimizu, E., Tang, Y.P., Cho, M., Kyin, M., Zuo, W., Robinson, D.A., Alaimo, P.J., Zhang, C., Morimoto, H., Zhuo, M., Feng, R., Shokat, K.M. and Tsien, J.Z. (2003) Inducible Protein Knockout Reveals Temporal Requirement of CaMKIIReactivation For Memory consolidation in the Brain. Proc. Natl. Acad. Sci., 1 00(7):4287-92.
- Knight, Z.A., Schilling, B., Row, R.H., Gibson, B.W. and Shokat, K.M. (2003) Phosphospecific Proteolysis: A Chemoenzymatic Approach for Mapping the Phosphoproteome, Nature Biotechnology, 21(9): 1047-54.
- Sreenivasan, A., Bishop, A.C., Shokat, K.M., Kellogg, D. (2003) "Specific Inhibition of Elm1 kinase activity in vivo reveals a G1 function. Mol. Cell. Biol., 23(17)6327-37.
- Denzel, A., Hare, K.J., Zhang, C., Shokat, K., Jenkinson, E.J., Anderson, G. and Hayday, A. (2003) Cutting edge: a chemical genetic system for the analysis of kinases regulating T cell development. J. Immunol., 171(2): 519-23.
- Shah, K. and Shokat, K.M. (2003) A chemical genetic approach for the identification of direct substrates of protein kinases. Methods Mol. Biol., 233:253-71.
- Ulrich S.M., Kenski D., and Shokat, K.M. (2003) Engineering a "methionine clamp" into Src family kinases specificity towards unnatural ATP analogs. Biochemistry, 42(26):7915-21.
- Eblen S.T., Kumar N.C., Shah K., Henderson M.J., Watts, C.K., Shokat K.M. and Weber M.J. (2003) Identification of novel ERK2 substrates through use of an engineered kinase and ATP analogs. J. Biol. Chem., 278(17):14926-35.
- Sekiya-Kawasaki M., Groen A.C., Cope M.J., Kaksonen M., Watson H.A., Zhang C., Shokat K.M., Wendland B., McDonald K.L., McCaffery J.M. and Drubin, D.G. (2002) Dynamic Phosphoregulation of Actin and Endocytosis Revealed by Real-Time Chemical-Genetic Analysis. J. Cell Biol., 162(5):765-72.
- Alaimo P.J., Shogren-Knaak, M.A., Shokat, K.M. (2002) Chemical genetic analysis of protein kinase cascades. Scientific World Journal, 2(1 Suppl 2):108-10.
- Benjamin, K.R., Zhang, C., Shokat, K.M., and Herskowitz, I. (2002) Control of Landmark Events in Meiosis by the CDK Cdc28 and the Meiosis-Specific Kinase Ime2. Genes and Dev., 17(12)1524-39.
- Abeliovich, H., Zhang, C., Dun, Jr., W.A., Shokat, K.M. and Klionsky, D.J. (2002) Chemical Genetic Analysis of Apg1 Reveals a Non-Kinase Role in the Induction of Autophagy. Mol. Biol. Cell, 14(2):477-90.
- Ulrich, S.M., Sallee, N.A., and Shokat, K.M. (2002) Conformational Restraint is a Critical Determinant of Unnatural Nucleotide Recognition by Protein Kinases. Bioorg. & Med. Chem. Ltrs., 12:3223-3227.
- Buzko, O. and Shokat, K.M. (2002) A kinase sequence database: sequence alignments and family assignment. Bioinformatics, 18(9): 1274-75.
- Kraybill, B., Blethrow, J., MorganD. & Shokat, K.M. (2002) Inhibitor scaffolds as new allele specific kinase substrates. J. Am. Chem. Soc., 124:12118-12128.
- Weiss, E.L., Kurischko, C., Zhang, C., Shokat, K., Drubin, D and Luca, F.C. (2002) The Saccharomyces cerevisiae Mob2p-Cbk1p kinase complex promotes polarized growth

and acts with the mitotic Exit Network to facilitate daughter cell-specific localization of Ace2p transcription factor. J. Cell Biol., 158(5): 885-900.

- Fan, Q., Zhang, C., Shokat, K.M. and Weiss, W.A. (2002) Chemical Genetic Blockade of Transformation Reveals Dependence on Aberrant Oncogenic Signaling. Current Biology, 12:1386-94.
- Buzko, OV, Bishop, AC and Shokat, KM (2002) Modified Auto Dock for accurate docking of protein kinase inhibitors. J. Comput. Aided Mol. Des., 16(2):1 13-27.
- Shokat, K.M. and Velleca, M. (2002) Novel chemical genetic approaches to the discovery of signal transduction inhibitors. Drug Discovery Today, 7:872-879.
- Ulrich, S. and Shokat, K. (2002) Green fluorescent protein-based protein kinasebiosensor substrates. Methods Mol. Biol., 183:275-85.
- Specht, K. and Shokat, K.M. (2002) The Emerging Power of Chemical Genetics. Current Opinion in Cell Biology, 14:155-159.
- Nieswender, C.M., Ishihara, R.W., Judge, L.M., Zhang, C., Shokat, K.M. and McKnight, G.S. (2002) Protein Engineering of Protein Kinase: A Catalytic Subunits Results in the Acquisition of Novel Inhibitor Sensitivity. J. Biol. Chem., 10:107.
- Shah, K. & Shokat, K.M. (2002) A Chemical Genetic Screen for Direct v-Src Substrates Reveals Ordered Assembly of a Retrograde Signaling Pathway. Chemistry & Biology, 9:35-47.
- Holt, J.R., Gillespie, S.K., Provance, Jr., D.W., Shah, K., Shokat, K.M., Corey, D.P., Mercer, J.A., and Gillespie, P.G., (2002) A Chemical-Genetic Strategy Demonstrates Myosin 1c Mediates Adaptation by Hair Cells. Cell, 108:371-81.
- Witucki, L.A., Huang, X., Shah, K., Liu, Y., Kyin, S., Eck, M.J., Shokat, K.M. (2002) "Mutant Tyrosine Kinases with Unnatural Nucleotide Specificity Retain the Structure and Phospho-acceptor Specificity of the Wild-Type Enzyme. Chemistry & Biology, 9(1):25-33.
- Ting, A.Y., Witte, K., Shah, K., Kraybill, B., Shokat, K.M., Schultz, P.G. (2001) Phage-display evolution of tyrosine kinases with altered nucleotide specificity. Biopolymers, 60(3):220-8.
- Schauder, S., Shokat, K., Surette, M.G., Bassler, B.L. (2001) The LuxS family of bacterial autoinducers: biosynthesis of a novel quorum-sensing signal molecule. Mol. Microbiol., 41(2):463-76.
- Carroll, A.S., Bishop, A.C., DeRisi, J.L., Shokat, K.M. and O'Shea, E.K. (2001) Chemical Inhibition of the Pho85 Cyclin-Dependent Kinase Reveals a Role in the Environmental Stress Response. Proc. Natl. Acad. Sci., 98(22):12578-83.
- Shogren-Knaak , M. , Alaimo, P. J. and Shokat, K. M. (2001) Recent Advances in Chemical Approaches to the Study of Biological Systems. Ann. Rev. Cell Develop. Biol., 17:405-33.
- Alaimo, P. J., Shogren-Knaak, M. and Shokat, K. M. (2001) Chemical Genetic Approaches for the Elucidation of Signaling Pathways. Curr. Opin. Chem. Biol., 5:360-367.
- Habelhah, H., Shah, K., Huang, L., Burlingame, A.L, Shokat, K.M. and Ronai, Z. (2001) Identification of a New JNK Substrate Using ATP Pocket Mutant ADK and a Corresponding ATP Analogue. J. Biol. Chem., 276(21):18090-5.
- Habelhah, H., Shah, K., Huang, L., Ostareck-Lederer, A., Burlingame, A.L., Shokat, K.M., Hentze, M.W., and Ronai, Z. (2001) ERK Phosphorylation DrivesCytoplasmic

Accumulation of hnRNP-K and Inhibition of mRNA Translation. Nature Cell Bio., 3:325-330.

- Bishop, A.C., Buzko, O. & Shokat, K.M. (2001) Magic Bullets for Protein Kinases. Trends in Cell Biology, 11:167-72.
- Weiss, E.L., Bishop, A.C., Shokat, K.M., and Drubin, D.G. (2000) Chemical genetic analysis of the budding yeast p21-activated kinaseCla4p. Nature Cell Bio., 5:677-685.
- Liu, Y., Witucki, L., Shah, K., Bishop, A.C., and Shokat, K.M. (2000) Src-Abl Tyrosine Kinase Chimeras: Replacement of the Adenine Binding Pocket of c-Abl with v-Src to Swap Nucleotide and Inhibitor Specificities. Biochemistry, 3 9(47): 14400- 14408.
- Ulrich, S., Buzko, O., ShahK, and Shokat, K.M. (2000) Towards Engineering of an Orthogonal Protein Kinase/Nucleotide Triphosphate Pair. Tetrahedron Seminars-inPrint, 56:9495-9502.
- Armstrong, J.I., Portley, A.R., Chang, Y.T., Nierengarten, D.M., Cook, B.N., Bowman, K.G., Bishop, A., Gray, N.S., Shokat, K.M., SchultzP.G., Bertozzi, C.R. (2000) Discovery of Carbohydrate Sulfotransferase Inhibitors from a Kinase-Directed Library. Agnew. Chem. Int. Ed. Engl., 39:1303-1306.
- Bishop, A,C., Ubersax, J.A, Petsch, D.C., Matheos, D., Blethrow, J.A., Gray, N.S, Schultz, P.G, Shimizu, E., Tsien, J.Z., Rose, M.D., Wood, J.L., MorganD.O., & Kevan M. Shokat. (2000) A Chemical Switch for Inhibitor Sensitive Alleles of any Protein Kinase. Nature, 407:395-401.
- Bishop, A.,Buzko, O., Heyeck-Dumas, S., Jung, I., Kraybill, B., Liu, Y., Shah, K., Ulrich, S., Witucki, L., Yang, F., Zhang, C., and Shokat, K.M. (2000) Unnatural Ligands for Engineered Proteins: New Tools for Chemical Genetics. Ann. Rev. Biophys. Biomolec. Struct., 29:577-606.
- Weintraub, B.C., Jun, J.E., Bishop, A., Shokat, K.M., Goodnow, C.C. (2000) Entry of B Cell Receptor into Signaling Domains is Inhibited in Tolerant B Cells. J. Exp. Med., 191(8):1443-8.
- Buzko, O. V. & Shokat, K.M.(1999) Blocking HIVEntry. Nature Structural Biology, 6:906-908.
- Liu, Y, Bishop, A., Witucki, L., Shimizu, E., Tsien, J., Ubersax, J., Blethrow, J., MorganD.A., Shokat, K.M. (1999) "Structural Basis for Selective Inhibition of Src Family Kinases by PP1. Chemistry & Biology, 6:671-678.
- Gillespie, P.G., Gillespie, S.K.H., Mercer, J.A., Shah, K., and Shokat, K.M. (1999) Engineering of the Myosin-Ib Nucleotide-Binding Pocket to Create Selective Sensitivity to N6-Modified ADP Analogs. J. Biol. Chem., 274(44):31373-81.
- Bishop, A.C., Kung, C-Y., Shah, K., Witucki, L., Shokat, K.M., and Liu, Y. (1999) Generation of Monospecific Nanomolar Tyrosine Kinase Inhibitors via a Chemical Genetic Approach. J. Amer. Chem. Soc., 121(4)627-63 1.
- Bishop, A.C. & Shokat, K.M. (1999) Acquisition of Inhibitor-Sensitive Protein Kinases Through Protein Design. Pharm. and Therap., 82:337-346.
- Yang, F., Liu, Y., Bixby, S., Friedman, J., ShahK., & Shokat, K.M. (1999) Highly Efficient Green Fluorescent Protein Based Kinase Substrates. Anal. Biochem., 266: 167-173.
- Liu, Y., Shah, K., Yang, F., Witucki, L., & Shokat, K.M. (1998) A Molecular Gate Which Controls Unnatural ATP Analog Recognition by the Tyrosine Kinase v-Src. Bioorganic & Medicinal Chemistry, 6:1219-1226.
- Liu, Y., Shah, K., Yang, F., Witucki, L., Shokat, K.M. (1998) Engineering Src Family Protein

Kinases With Unnatural Nucleotide Specificity. Chemistry & Biology, 5(2):91-102.

- Bishop, A.C., Shah K., Liu, Y., Witucki, L., Kung, C.-Y., Shokat, K.M. (1998) Design of allele specific inhibitors to probe protein kinase signaling. Current Biology, 8:257-266.
- Surrey, T., Elowitz, M., Wolf, P.E., Yang, F., Nedelec, F., Shokat, K.M., and Leibler, S. (1998) Chromophore-assisted light inactivation and self-organization of microtubules and motors. Proc. Natl. Acad. Sci., 95(8):4293-4298.
- Bishop, A.C., Moore, D., Scanlan, T.S., & Shokat, K.M. (1997) Screening aHydroxystilbene Library for Selective Inhibition of the B Cell Antigen Receptor Kinase Cascade. Tetrahedron Symposia-in-Print, 53(35):1 1995-12004.
- Shah, K., Liu, Y., Diermengian, C. & Shokat, K.M. (1997) Engineering unnatural nucleotide specificity for Rous sarcoma virus tyrosine kinase to uniquely label its direct substrates. Proc. Natl. Acad. Sci., 94:3565-3570.
- Liblau, R.S., Tisch, R., Shokat, K., Yang, X.-D., Dumont, N., Goodnow, C.C. & McDevitt, H.O. (1996) Inravenous Injection of High Dose Soluble Antigen Induces Thymic and Peripheral Cell Apoptosis. Proc. Natl. Acad. Sci., 93:3031-3036.
- Shokat, K.M. (1995) Tyrosine Kinases: Modular Signaling Enzymes With Tunable Specificities. Chemistry & Biology, 2:509-5 13.
- Shokat, K.M. & Goodnow, C.C. (1995) Antigen-Induced B Cell Death and Elimination During Germinal Center Immune Responses. Nature (London), 375:3 34- 338.
- Goodnow, C.C., Cyster, J.G., Hartley, S.B., Bell, S.E., Cooke, M.P., Healy, J.L., Akkaraju, S., Rathmell, J.C., Pogue, S.L. and Shokat, K.M. (1995) Self-Tolerance Checkpoints in B Lymphocyte Development. Adv. in Immunol., 59:279-345.
- Liblau, R., Pearson, C., Shokat, K.M., & McDevitt, H.O. (1995) Apoptosis in T Cell Development. Imm. Rev., 15:75-90.
- Shokat, K.M., Uno, T., & Schultz, P.G. (1994) Mechanistic Studies of An Antibody-Catalyzed Elimination Reaction. J. Am. Chem. Soc., 116:2261-2270.
- CookeM. P., Heath, A. W., Shokat, K. M., Yongjun, Z., Finkelman, F. D., Linsley, P. S., Howard, M. & GoodnowC. C. (1994) Immunoglobulin Signal Transduction Guides The Specificity of B Cell-T Cell Interactions and is Blocked in Tolerant Self-Reactive B Cells. J. Exp. Med., 179:425-438.
- Shokat, K. M. & Schultz, P. G. (1994) "Catalytic Antibodies" in Cell and Molecular Biology ed. Stephen J. Wolfe Wadworth Publishing, Belmont, CA.
- Shokat, K. M. & Schultz, P. G. (1991) Catalytic Antibodies: An Overview of Design Strategies and Their Applications. Welsch Foundation Symposium XXXV "Chemistry at the Frontiers of Medicine" 19-42.
- Shokat, K. M. & Schultz, P. G. (1991) Redirecting the Immune Response: LigandMediated Immunogenicity. J. Am. Chem. Soc., 113:1861-1862.
- Shokat, K. M. & Schultz, P. G. (1991) Catalytic Antibodies. Meth. in Enzymology, 203 :327-35 1.
- Shokat, K. M. & Schultz, P. G. (1990) The Generation of Catalytic Antibodies Containing Catalytic Residues. Ciba Foundation Symposium No. 159:118-135.
- Shokat, K. M., Ko, M. K., Scanlan, T. S., Kochersperger, L., Yonkovich, S., Thaisrivongs, S. & Schultz, P. G. (1990) Catalytic Antibodies: A New Class of Transition State Analogues Used to Elicit Hydrolytic Antibodies. Angew. Chem. Int. Ed. Engl., 29:1296-13 10.
- Shokat, K. M. & Schultz, P. G. (1990) Catalytic Antibodies. Ann. Rev. Immun., 8:335-355.

- Shokat, K. M., Leumann, C. L., Sugasawara, R. & Schultz, P. G. (1989) A New Strategy for the Generation of Catalytic Antibodies. Nature, 338:269-272.
- Shokat, K. M., Leumann, C. H., Sugasawara, R. & Schultz, P. G. (1988) An Antibody-Mediated Redox Reaction. Angew. Chem. Int. Ed. Engl., 27:1172-1174.
- McClard, R. W. & Shokat, K. M, (1987) Does the Bifunctional Uridylate Synthase Channel Orotidine 5'-Phosphate? Biochemistry, 26:3378-3385.

ABSTRACT

Kevan M. Shokat was born in Boulder City, Nevada, but raised (mostly) in the San Francisco Bay Area in Albany, California (except for a year in Iran), the older—by twelve years—of two brothers. His parents were both active politically, participating in anti-war movements and in anti-shah movements during the 1970s that culminated in the Iranian Revolution of 1979; they started their own copying and commercial printing business, but after some time moved into print brokering, his mother taking a position at Charles Schwab. As a child Shokat enjoyed playing sports, especially baseball and track; he excelled in high school and worked with his parents in the family business.

While his high school was vocationally-minded, a guidance counselor suggested that Shokat apply to Reed College in Portland, Oregon, which he did and subsequently attended. He majored in chemistry and enjoyed lectures offered by Thomas G. Dunne, Phyllis Cozen, and Nick G. Galaktos; he completed his thesis with Ronald W. McClard on phosphorous chemistry, making inhibitors of enzymes, and doing enzyme kinetics and nucleotide metabolism. He was unsure of the kind of graduate program that he wanted to attend so he sent applications both to PhD programs and MD/PhD programs, settling on pursuing his PhD at the University of California, Berkeley. At Berkeley he worked with Peter G. Schultz in biological chemistry in antibody catalysis, and from there went on to a postdoctoral fellowship in immunology with Christopher C. Goodnow at StanfordUniversity. He then accepted a position at Princeton University, during which time he received the Pew Scholars Program in the Biomedical Sciences award and he worked on biochemistry and immunology research in kinase-mediated cell signaling pathways. He left Princeton for a position at the University of California, San Francisco, undertaking chemical genetic research on kinases and their substrates.

At the end of the interview Shokat talks about his future research on chemical genetics and protein kinases in cell signaling pathways; the practical applications of his research; collaboration and competition in science; and his laboratory management style. He also discusses the process of writing journal articles; the issue of patents; the national scientific agenda; the grant-writing process; the privatization of scientific research; educating the public about science; and the importance of students and family in doing science.

UCLA INTERVIEW HISTORY

INTERVIEWER:

William Van Benschoten, Interviewer, UCLA Oral History Program. B.A., History, University of California, Riverside; M.A., History, University of California, Riverside; C. Phil., History, UCLA

TIME AND SETTING OF INTERVIEW:

Place: Shokat's office, University of California, San Francisco.

Dates, length of sessions: January 24, 2005; January 25, 2005; and January 26, 2005.

Total number of recorded hours: 5.0

Persons present during interview: Shokat and Van Benschoten.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew Scholars in the Biomedical Sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts's Pew Scholars in the Biomedical Sciences Oral History and Archives Project. The project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships since 1988.

To provide an overall framework for project interviews, the director of the UCLA Oral History Program and three UCLA faculty project consultants developed a topic outline. In preparing for this interview, Van Benschoten held a telephone preinterview conversation with Shokat to obtain written background information (curriculum vitae, copies of published articles, etc.) and agree on an interviewing schedule. He also reviewed documentation in Shokat's file at the Pew Scholars Program office in San Francisco, including Shokat's proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members.

ORIGINAL EDITING:

Carol Squires edited the interview. She checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

Shokat did not review the transcript, and therefore some names remain unverified.

Carol Squires prepared the table of contents and TechniType Transcripts compiled the guide to proper names.

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and competition in science.

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