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BIOGRAPHICAL SKETCH

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NAME: Timothy A. J. Haystead

eRA COMMONS USER NAME Hayst001

POSITION TITLE: 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)*	Completion Date MM/YYYY	FIELD OF STUDY
University College Cardiff, Wales.	B.Sc. (Hons)	1983	Biochemistry
University of Dundee, Scotland	Ph.D.	1988	Biochemistry
The Howard Hughes Medical Institute, University of Washington, Seattle, WA	Postdoctoral	1991	Pharmacology

A. Personal Statement

My graduate and postgraduate training in the laboratories of Professor Grahame Hardie (Dundee University UK) and Professor Edwin Krebs (Seattle, University of Washington) focused on delineating signal transduction pathways mediating insulin action. During the 1980s to mid 1990's this was a rapidly developing and exciting field in which to gain a broad research experience. In keeping with practices of the time, rather than compete with my mentors, I began my independent career studying signaling pathways regulating smooth and striated muscle contraction and plasticity. I was drawn to this topic mostly because of the physiological models that had been established by the muscle community. I felt these models provided the perfect conduit to apply some of the molecular targeted approaches we were developing based on affinity tools. At the time we were developing affinity reagents based on phosphatase and protein kinase inhibitors to study signaling pathways regulating myosin phosphatase. This strategy blossomed for us and took us into new fields expertise to what now is called proteomics. At that time we saw technologies such as mass spectrometry as a tool to rapidly identify proteins bound to our affinity resins. This work evolved into the development of a chemoproteomic platform we called proteome mining (circa 1996). This method was originally designed to interrogate small molecule libraries to identify inhibitors for protein kinase involved in regulating Ca2+ independent muscle contraction. This also resulted in our first introduction to Hsp90 with the finding that the protein bound to our ATP resin and the finding that it could be selectively eluted with its homologs GRP94 and TRAP 1 with the inhibitor geldanamycin. Since this was novel at the time we shared these findings with Len Neckers (NCI) and David Toft (University of Michigan) who went on to publish the first paper to definitively show that Hsp90 was an ATPase. In my own work we used the technology to purify and identify Zipper interacting protein kinase (ZIPK) (a). Although my career path has diverted away from smooth and striated muscle we have maintained a strong effort on understanding the biology of ZIPK and developing it as a therapeutic target for hypertension and reperfusion injury after stroke. To this end using a variation of our proteome mining platform we recently reported the discovery of a highly selective series of inhibitors targeting the protein kinase in vivo (b). In 2000, my career took on a new direction when I came to Duke and I founded the biotechnology company Serenex Inc (Durham, NC). Serenex practiced proteome mining technology and used it to discover a novel indoline scaffold targeting Hsp90. This evolved into a clinical candidate, SNX5422, the first synthetic orally bioavailable inhibitor of Hsp90. In 2008, Serenex was acquired by Pfizer for this compound and it is currently progressing through Phase 2 trials with multiple indications in cancer. Throughout the Serenex's life I ran both a fully funded academic laboratory, started and participated in my company. This exposed me to medicinal chemistry

and drug development, from discovery to clinical trials. My academic career is now focused on applying the Serenex model in an academic setting.

a. Identification of the endogenous smooth muscle myosin phosphatase-associated kinase.MacDonald JA, Borman MA, Murányi A, Somlyo AV, Hartshorne DJ, **Haystead TA.** Proc Natl Acad Sci U S A. 2001 Feb 27;98(5):2419-24.
b. Fluorescence Linked Enzyme Chemoproteomic Strategy for Discovery of a Potent and Selective DAPK1 and ZIPK Inhibitor. Carlson DA, Franke AS, Weitzel D, Speer BL, Hughes PF, Hagerty L, Fortner CN, Veal JM, Barta TE, Zieba BJ, Somlyo AV, Sutherland C, Deng JT, Walsh MP, Macdonald JA, Haystead TA. ACS Chem Biol. 2013 Sep 26.

B. Positions and Honors

1991-1996	Assistant Professor, Dept of Pharmacology, University of Virginia, Charlottesville, VA
1996-1999	Associate Professor, Dept of Pharmacology, University of Virginia, Charlottesville, VA
2000- present	Professor, Dept of Pharmacology & Cancer Biology, Duke University, NC.
2000-2008	Scientific Founder, Chair Scientific Advisory Board, Serenex Inc, Durham NC.
2008- 2010	Founder, President and CSO, Institutes for Global Disease Medicines, Chapel Hill NC.
2016-	Founder, CEO and CSO, Eydisbio Inc. Durham NC.

Recent Study Sections:
DK-06-014, ZRG1 -F04B -B -(20), ZRG1 -IMM -E -(58), ZRG1 -F04B -B -(20) ZRG1 -BCMB -T -(90), ZRG1 -GGG -E -(50), ZRG1 -BCMB -T -(90), ZRG1 -GGG -E -(50), ZAI1 -LG -M -(J2), ZAI1 -LG -M -(J1), ZAI1 -NLE – M, ZRG1 -F04B -D -(20), ZAI1 -LG -M -(C1), ZRG1 F04B-D (20), ZAI1 -LG -M -(C1), ZDK1 -GRB -S -(O2) ZDK1 GRB-S (J4), ZCA1 RTRB-E (O1) S, MIST regular RO1 2016, Radiation Cancer Therapeutics 2016, ZDK1-GRB-S (J1).

Honors.
New Initiatives in Malaria Research Award 2006 Burroughs Wellcome Fund

C. Contribution to Science

My earlier career focused heavily on developing unique sets of affinity tools to study signal transduction pathways *in vivo*. These approaches took us into what now has emerged as the field of proteomics. For a brief period we were even pioneering some these approaches, but rapidly moved away to focus specifically on small molecule discovery. To date my most significant contribution to science is the discovery and development of SNX5422. The work that led to this compound came out of my smooth muscle work and our desire to develop inhibitors for ZIPK. In 1993 I developed gamma-phosphate linked ATP Sepharose which I patented in 1996. What was unique about this media was its ability to bind almost every protein in the cells that utilized purines. High throughput sequencing by mass spectrometry identified several hundred proteins bound to the media representing multiple gene families, from protein kinases, dehydrogenases, DNA and RNA binding proteins, metabolic enzymes to heat shock proteins. We called this collection the 'purinome' and have written about it extensively. Importantly, once captured the entire collection of bound proteins could be interrogated by libraries of small molecules to identify selective inhibitors, that could subsequently be developed into useful tool compounds or even drugs. I put this idea into practice when I founded Serenex in 2000. The company employed 65 scientists with expertise in medicinal chemistry, high through put screen, cancer biology and drug development. The outcome of this work was the clinical candidate SNX4522. I already know that this compound has helped several terminally ill patients that participated in phase 1 trails conducted by Serenex, Pfizer and the NCI. It continues to do so as it progresses through phase 2 studies. This I am most proud off.

a. Gamma-phosphate-linked ATP-sepharose for the affinity purification of protein kinases. Rapid purification to homogeneity of skeletal muscle mitogen-activated protein kinase kinase. Haystead CM, Gregory P, Sturgill TW, Haystead TA. Eur J Biochem. 1993 Jun 1;214(2):459-67.
b. Discovery of novel targets of quinoline drugs in the human purine binding proteome. Graves PR, Kwiek JJ, Fadden P, Ray R, Hardeman K, Coley AM, Foley M, Haystead TA. Mol Pharmacol. 2002 Dec;62(6):1364-72.
c. c. The purinome, a complex mix of drug and toxicity targets. Haystead TA.Curr Top Med Chem. 2006;6(11):1117-27. Review.

d. d. Application of chemoproteomics to drug discovery: identification of a clinical candidate targeting hsp90.Fadden P, Huang KH, Veal JM, Steed PM, Barabasz AF, Foley B, Hu M, Partridge JM, Rice J, Scott A, Dubois LG, Freed TA, Silinski MA, Barta TE, Hughes PF, Ommen A, Ma W, Smith ED, Spangenberg AW, Eaves J, Hanson GJ, Hinkley L, Jenks M, Lewis M, Otto J, Pronk GJ, Verleysen K, Haystead TA, Hall SE. Cell. Chem Biol. 2010 Jul 30;17(7):686-94

It is quite something to take ones esoteric idea (of proteome mining) and have people practice it every day and produce a drug like SNX5422. This experience changes ones perspective of ones science, wanting to repeat the experiment. With that aim in mind I have brought the technology that underpinned Serenex back into my academic laboratory. Most excitingly we have extended its utility into the development of novel imaging agents. Although I have been connected to Hsp90 since our early work in the 1990's with Len Neckers and David Toft, and then through Serenex, it is only recently that our more significant contributions to this field have been published. Recently we reported the development of a series of fluor-tethered and radio-iodinated Hsp90 inhibitors that discriminate malignant tumor cells from benign or normal cells. These inhibitors were synthesized in my laboratory and to date we have created over 100 analogs that can be imaged by multiple methods including, optical near infrared, MRI and PET. To derive the inhibitors we developed an affinity-based platform to optimize each component of the molecules such that they retain specificity towards Hsp90. This platform was reported in Hughes et al. 2012. Having established the specificity of our molecules we replaced the Sepharose beads with the imaging agents. In Barrott et al 2013 (a,b) and more recently (c) we demonstrate the utility of these molecules for the detection of malignant tumors *in vivo*. Most of our work with these inhibitors has focused on breast cancer, but it is almost certain that they will have utility in many other cancers including prostate, melanoma, colorectal, non-small lung, pancreatic cancer. Recently we successfully obtained funding from the DOD to take one or more of our tethered inhibitors into the clinic for early detection of aggressive forms of breast cancer. We have had an initial meeting with the FDA and plan to begin our trial in earlier 2016. The discovery that our probes are only internalized cells exhibiting malignant behavior led us to discover eHsp90 pathway and 90-bodies. Our future goals are to use our probes to fully define this pathway and believe that it may be exploited as an Achilles heel to develop a curative strategy for metastatic breast cancer.

a. Optical and radioiodinated tethered Hsp90 inhibitors reveal selective internalization of ectopic Hsp90 in malignant breast tumor cells. Barrott JJ, Hughes PF, Osada T, Yang XY, Hartman ZC, Loiselle DR, Spector NL, Neckers L, Rajaram N, Hu F, Ramanujam N, Vaidyanathan G, Zalutsky MR, Lyerly HK, Haystead TA. Cell. Chem Biol. 2013 Sep 19;20(9):1187-97.
b. A highly selective Hsp90 affinity chromatography resin with a cleavable linker. Hughes PF, Barrott JJ, Carlson DA, Loiselle DR, Speer BL, Bodoor K, Rund LA, Haystead TA. Bioorg Med Chem. 2012 May 15;20(10):3298-305.
c. Crowe LB, Hughes PF, Alcorta DA, Osada T, Smith AP, Totzke J, Loiselle DR, Lutz ID, Gargesha M, Roy D, Roques J, Darr D, Lyerly HK, Spector NL, Haystead TA. A fluorescent Hsp90 probe demonstrates the unique association between extracellular Hsp90 and malignancy in vivo. ACS Chem Biol. 2017. doi: 10.1021/acschembio.7b00006. PubMed PMID: 28103010

Over the last two decades the research and development efforts in pharmaceutical industry have almost collapsed, with endless mergers and program closures. The biotech industry also has become risk adverse and is not supporting basic drug discovery. Therefore, the gauntlet for finding new drug entities has been passed to the academic community. My own experiences with Serenex has enabled me to pick up this challenge and I have developed an active medicinal chemistry group at Duke. Our goal is to demonstrate that a small academic group can discovery and fully develop novel compounds and drive them to the clinic (IND stage). To this end we have embarked on a screening campaign using targets of interest that we feel could have therapeutic benefit as well as derived novel tool compounds for hypothesis testing. Targets we are actively pursuing are ZIPK, acetyl CoA carboxylase, Fatty acid synthase and the inducible form of Hsp70 (Hsp70i). The proteome mining platform has again served to enable us to screen an internal library comprising several thousands of small molecules. From these screens we have identified the HS-38 scaffold targeting ZIPK, HS-106 a highly active inhibitor of fatty acid synthase and HS-72, an allosteric inhibitor of Hsp72. Our work with HS-72 was recently reported in Howe et al. 2014, which describes the molecules discovery, synthesis and efficacy in cell and mouse models of breast cancer. Our plan is to mature this molecule to the clinic for multiple indications in cancer including breast.

a. Identification of an allosteric small-molecule inhibitor selective for the inducible form of heat shock protein 70. Howe MK, Bodoor K, Carlson DA, Hughes PF, Alwarawrah Y, Loiselle DR, Jaeger AM, Darr DB, Jordan JL, Hunter LM, Molzberger ET, Gobillot TA, Thiele DJ, Brodsky JL, Spector NL, **Haystead TA.** Chem Biol. 2014 Dec 18;21(12):1648-59.
b. An inducible heat shock protein 70 small molecule inhibitor demonstrates anti-dengue virus activity, validating Hsp70 as a host antiviral target. Howe MK, Speer BL, Hughes PF, Loiselle DR, Vasudevan S, **Haystead** TA Antiviral Res. 2016 Jun;130:81-92. doi: 10.1016/j.antiviral.2016.03.01
c. Yazan Alwarawrah PH, David Loiselle, David A. Carlson, David B. Darr, Jamie L. Jordan, Jessie Xiong Lucas M. Hunter, Laura G. Dubois, J. Will Thompson, Manjusha M. Kulkarni, Annette N. Ratcliff , Jesse J. Kwiek, **Timothy A. J. Haystead**. HS-106, a selective FASN inhibitor shows potent anti-tumor activity in the MMTV Neu model of HER2+ breast cancer. Cell Chem Biol. 2016 May 27. pii: S2451-9456(16)30157-X. doi: 10.1016/j.chembiol.2016.04.011.
d.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Haystead+T

D. Research Support

Title: **Detection and Elimination of Oncogenic Signaling Networks in Premalignant and Malignant Cells with Magnetic Resonance Imaging**

Effort: 3.0 Calendar
Supporting Agency: Department of Defense
Funding Agency Grants Officer: Elaine Seiler, 301-619-7358, elayne.seiler@amedd.army.mil
Performance Period; 09/30/12 – 09/29/17
Level of Funding (Haystead): $1,611,291
Project Goals: To establish an experimental therapeutics group for the discovery and development of novel drugs targeting oncogenic signaling nodes.
Title: Development of tethered Hsp90 Inhibitors Carrying Radiolabeled Probes to Specifically Discriminate and Kill Malignant
Effort: 1.2 Calendar
Supporting Agency: Department of Defense
Funding Agency Grants Officer: TBD
Performance Period; 02/01/15 – 01/31/18
Level of Funding (Haystead and Zalutsky): $750,000
Project Goals: To develop Hsp90 inhibitors carrying therapeutic radionuclides ^{131}I or ^{211}At to achieve tumor ablation with minimal normal tissue toxicity.

Recently Completed.
Title: Discovery and Development of Broad Spectrum Anti-Flaviviral Drugs R01-AI089526
Effort: 2.40 Calendar
Supporting Agency: NIH/NIAID
MPI contact PI T. Haystead.
Funding Agency Grants Officer: Leslie Boggs, boggsl@mail.nih.gov
Performance Period; 06/01/10-05/31/15
Level of Funding (Haystead): $630,906
Project Goals: To discover novel drug targets and develop new antiviral therapies that can be used broadly to treat a variety of flaviviral infections.
1R01AI090644 - 01 MPI (PI: Haystead) 07/01/10-06/30/14
Title: A Novel Method to Stop HIV Replication: Inhibition of the Human Purinome
Specific Aim: To use purinome-capture technology to identify purine-binding proteins that are regulated in response to HIV-infection.
