BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Hauschka, Stephen D.	Professor of Biochemistry
eRA COMMONS USER NAME (credential, e.g., agency login) HAUSCHKA	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Amherst College, Amherst MA	BA	1962	Biology (O. Schotte)
Johns Hopkins & Carnegie Institution, Balt. MD	PhD	1966	Biology (I. Konigsberg)
University of Washington, Seattle, WA	Post Doc	1966-1967	Biochemistry (W. Rutter)

A. Personal Statement

I have been carrying out basic research in the field of skeletal muscle development and gene regulation since 1962, and since 1989 have also been studying the regulation of cardiac muscle gene transcription. Major advances that have come from my lab are as follows: (1.) discovery of collagen as the unknown component of the conditioned medium that was required for the optimal growth and differentiation of primary skeletal muscle myoblasts; (2.) discovery of a non-collagen conditioned medium component required for the differentiation of early embryonic myoblast types; (3.) the first application of *in vitro* clonal analysis to developmental changes within *in vivo* myoblast populations during skeletal muscle development (4.) the first clonal analysis of human skeletal muscle development; (5.) identification of the collagen polypeptide regions to which skeletal muscle cells bind; (6.) discovery that myoblast binding to collagen occurs via interactions with fibronectin; (7.) development of a quantitative *in vitro* cell adhesion assay for the analysis of cell – biomaterial interactions; (8.) discovery of hyaluronate and chontroitin sulfate synthesis by myoblasts and interactions of these proteoglycans with muscle cells: (9.) production of the first antibody with specificity for skeletal alpha-actin; (10.) a complete clonal analysis comparison of chick and human embryonic and fetal myoblasts; (11.) discovery of proximal distal gradients of muscle colony-forming cells in the developing limb; (12.) discovery that distinct muscle colony phenotypes are heritable through successive subclonal passages until the onset of proliferative senescence; (13.) discovery of the first reproducible technique for deriving permanent clonally derived lines of mouse myoblasts; (14.) discovery that mouse myoblasts bind to laminin and exhibit distinct morphologies on laminin vs. collagen substrates; (15.) discovery that the commitment process of terminal muscle differentiation is dominant to proliferation signals in myocyte-G1 myoblast heterokaryons; (16.) discovery of fibroblast growth factor as the first known mitogen for muscle cell growth; (17.) first purification and biochemical characterization of purified fibroblast growth factor receptor; (18.) discovery that both EGF receptor and FGF receptor synthesis is repressed during terminal muscle differentiation; (19.) discovery of multiple alternative splice forms of FGF receptor; (20.) discovery of two muscle colony-forming cell types in mouse and human muscle that are FGF-dependent and FGF-independent for clonal differentiation; (21.) first published quantitative analysis of changing FGF levels during embryonic development; (22.) discovery of the MAP kinase pathway for FGF receptor signal transduction in skeletal muscle; (23.) cloning of the mouse Muscle creatine kinase (MCK) gene; (24.) discovery of the first proven skeletal muscle gene enhancer; (25.) discovery of the key enhancer control element as an E-box; (26.) discovery of the first muscle–specific transcription factor (MEF1); (27.) discovery that MEF1 is MyoD and that the MyoD binding site is an E-box control element; (28) discovery of multiple control elements in the MCK enhancer and promoter; (29.) discovery of shared and unique differences between the functions of MCK enhancer control elements in skeletal and cardiac muscle; (30.) the first demonstration of muscle gene regulatory region function using transgenic mouse technology; (31.) first proof of concept study demonstrating that MCK gene regulatory components could be used in conjunction with a dystrophin cDNA to prevent muscular dystrophy in the DMD mdx mouse; (32.) derivation of an atrial cardiomyocyte cell line and characterization of its muscarinic AChRs;

(33.) design of an *in vitro* assay system for testing neural tube & notochord skeletal muscle inductive effects on single somites; (34.) discovery of Wnt1 as an inducer of skeletal muscle myogenesis; (35.) discovery of synergistic interactions between FGF & TGF in neural tube inductive signals for somite myogenesis; (36.) discovery of synergistic SHH, IGF1 and IGF2 induction of somite myogenesis; (37.) discovery of Myf5 activation in pre-somitic mesoderm; (38.) discovery of fast-to-slow muscle conversion in skeletal muscle transplants into adult rat heart infarcts; (39.) development of MCK-based regulatory gene cassettes for use in adenovirus-mediated gene therapy; (40.) development of miniaturized high activity MCK-based regulatory gene cassettes for use in AAV-mediated gene therapy; (41.) development of patterned surfaces for skeletal and cardiac muscle cell growth and differentiation; (42.) first application of quantitative proteomic technology for the identification of unknown sequence-specific DNA-binding factors and discovery of Six4/Six5 as important transcription factors for skeletal and cardiac muscle gene regulation; (43.) demonstration that hematopoietic stem cells do not have the "claimed capacity" to restore skeletal muscle to dystrophic dogs; (44.) modification of MCK regulatory gene cassettes for use in lentiviral vectors; (45.) discovery that nuclear lamin and emerin play roles in skeletal muscle gene expression during terminal differentiation; (46.) design of double enhancer regulatory cassettes for optimized expression in skeletal and cardiac muscle; (47.) application of improved muscle regulatory cassettes to the treatment of Pompe's Disease; (48.) application of improved muscle regulatory cassettes for the treatment of growth hormone deficiency; (49.) application of improved muscle regulatory cassettes for the treatment of insulin-resistance; (50.) use of quantitative proteomics to discover MAZ as a previously unknown transcription factor involved in skeletal muscle gene expression; (51.) use of quantitative proteomics to discover KLF3 as a previously unknown transcription factor involved in skeletal muscle gene expression; (52.) discovery of KLF3-SRF synergistic interactions; (53.) modification of MyoD transcriptional activation domain for high efficiency conversion of mesenchymal stem cells to skeletal muscle; (54.) discovery and characterization of an intronic enhancer sequence and its associated transcription factors that differentially regulate MCK gene expression in fast and slow skeletal muscle fibers; (55.) discovery of transcription rate differences between human & rodent regulatory cassettes in striated muscle cultures from each species.

B. Positions and Honors:

Positions and Employment:

1962 **B.A. Biology, Amherst College: Honors Thesis: "Endocrine Control of Amphibian Limb Regeneration" (Oscar Schotte, Advisor)**

1963-64 **Woods Hole MBL NIH Trainee: "Fertilization & Gamete Physiology" (C. Metz & A. Monroy, Advisors). "Immunological Characterization of Outer Egg Membranes & Sperm-Derived Membrane Lytic Factor.**

1966 **Ph.D. Biology, Johns Hopkins University: Ph.D. Thesis: "Collagen & the Differentiation of Skeletal Muscle In Vitro" Irwin Konigsberg, Advisor).**

1966-67 **Postdoctoral Research, Dept. of Biochemistry, University of Washington: "Genetic Regulation of Pancreatic Enzymes" (William Rutter, Advisor).**

1967-Present **Faculty Member, Dept. of Biochemistry, University of Washington**

Other Experience and Professional Memberships

1975-1976: **NIH Cell Biology Study Section.**
1977-1978: **NSF Developmental Biology Study Section.**
1982-1988: **NIH Molecular Cytology Ad Hoc Member (every other panel mtg.).**
1989-2000: **MDA Scientific Advisory Committee Study Section member.**
2005→: **Am. Society of Gene Therapy Ethics Committee.**

Member: **American Society of Cell Biology, Society for Developmental Biology, American Society for Gene Therapy.**
Editorial Boards: **Growth Factors; Molecular Therapy.**

Honors:

1981: University of Washington: "Outstanding Undergraduate Professor."
1992-2002: NIH Merit Award.
2011: University of Washington: "Outstanding Undergraduate Research Mentor."

C. Publications most relevant to the current application:

1. Himeda C.L., Tai, P.W., Hauschka, S. D. (2012). Analysis of muscle gene transcription in cultured skeletal muscle cells. *Methods in Mol Biol.* 798: 425-443.
2. Tai, P.W., Smith, C.L., Himeda, C.L., Hauschka, S.D. (2012). Analysis of fiber-type differences in reporter gene expression of b-Gal transgenic muscle. *Methods in Mol Biol.* 798: 445-459.
3. Tai, W.L., Fischer, K., Himeda, C.L., Smith, C.L., MacKenzie, A.P., Angello, J.C., Welikson, R.E., Wold, B.J., and Hauschka, S.D. (2011). Differentiation and fiber type-specific activity of a muscle creatine kinase intronic enhancer. *Skeletal Muscle* (July Issue): 1:25; 1-19.
4. Himeda, C.L., Chen, X., and Hauschka, S.D. (2011). Design and Testing of Regulatory Cassettes for Optimal Activity in Skeletal and Cardiac Muscle. *Methods in Mol Biol.* 709: 3-19.
5. Goncalves, M.A.F.V., Janssen, J.M., Nguyen, Q.G., Athanasopoulos, T., Hauschka, S.D., Dickson G., and A.A.F. de Vries. (2011). Transcription Factor Rational Design Improves Directed Differentiation of Human Mesenchymal Stem Cells into Skeletal Myocytes. *Mol. Therapy* 19: 1331-1341.
6. Himeda, C.L., and Hauschka, S.D. (2010). Proteomic Strategies for Cardiac Transcription Factor Identification. In. "Heart Development and Regeneration" Rosenthal & Harvey, eds.
7. Himeda, C.L., Ranish, J.A., Czolij, R., Crossley, M., and Hauschka, S.D. (2010). KLF3 regulates muscle-specific gene expression and synergizes with serum response factor on KLF binding sites. *Mol. Cell. Biol.* 30: 3430-3443.
8. Himeda, C.L., Ranish, J.A., and Hauschka, S.D. (2008). Quantitative proteomics and ChIP identify MAZ as a positive transcriptional regulator of muscle-specific genes in skeletal and cardiac muscle. *Mol. Cell. Biol.* 28: 6521-6535.
9. Himeda, C.L., Ranish, J.A., Angello, J.C., Maire, P., Aebersold, R., and Hauschka, S.D. (2004). Quantitative proetomic identification of six4 as the trex-binding factor in the muscle creatine kinase enhancer. Mol. Cell. Biol. 24: 2132-2143.
10. Salva, M.Z., Himeda, C.L., Tai, P., Nishiuchi, E., Gregorevic, P., Allen, J.M., Finn, E.E., Nguyen, Q.G., Blankinship, M.J., Meuse, L., Chamberlain, J.S., and Hauschka, S.D. (2007). Design of novel tissue-specific regulatory cassettes for high-level rAAV-mediated expression is skeletal and cardiac muscle. *Molecular Therapy* 15: 320-329.
11. Hong, E.G., Ko, H.J., … Hauschka, S.D., …, and Kim, J.K. (2009). Interleukin-10 prevents insulin resistance by attenuating macrophage and cytokine response in skeletal muscle. Diabetes 58: 2525-2535.
12. Martari, M., Sagazio, A., Mohamadi, A., Nguyen, Q, Hauschka, S.D., Kim, E., and Salvatori, R. (2009). Effects of a single injection of adeno associated-viral vector expressing growth hormone (GH) driven by a muscle-specific regulatory cassette. *Human Gene Therapy*. 20: 759-766.
13. Sun, B., Young, S.P., Ping, L., Di, C., Brown, T., Li, S., Bird, A., Yan, Z., Auten, R., Salva, M.Z., Hauschka, S.D., Koeberl, D.D. (2008). Systemic correction of Pompe disease with adeno-associated virus-mediated muscle-specific transgene expression. *Molecular Therapy* 16: 1366-1371.
14. Li, S., Kimura, E., Fall, B.M., Reyes, M., Angello, J.C., Welikson, R., Hauschka, S.D., and Chamberlain, J.S. (2005). Stable transduction of myogenic cells with lentiviral vectors expressing a mini-dystrophin. *Gene Therapy*. 12: 1099-1108.
15. Moyes, K.W., Sip, C.G., Obenza, W., Yang, E., Horst, C., Welikson, R.E., Hauschka, S.D., Folch A., Laflamme, M.A. (2013). Human embryonic stem cell-derived cardiomyocytes migrate in response to gradients of Fibronectin and wnt5a. *Stem Cells Dev.* 22(16): 2315-2325.

D. Research Support

Ongoing Research Support

2 RO1 AR 18860-27 (P.I. Hauschka) 07/08/2008 – 05/31/2013 *NIH has approved continued use of unexpended funds for the period 06/01/2013 – 05/31/2014.*
NIH/NIAMS "Regulation of Skeletal Muscle Differentiation"
The long-range goals of this project are to understand how skeletal muscle differentiation is regulated. Most studies involve identification of control regions/elements and the associated transcription factors for expression of the M-creatine kinase (MCK) gene during skeletal muscle development, and during adult steady-state maintenance. Studies involve the application of quantitative proteomics to identify novel muscle transcription factors, followed by ChIP analysis to investigate transcription factor binding to the MCK gene's native chromatin. Skeletal muscle culture co-transfection studies are done to identify interacting transcription factors and to identify protein regions involved in the interactions. Transgenic mouse studies are done to identify skeletal muscle fiber type-specific regulatory regions and control elements. Basic information from these studies can then be used to design regulatory gene cassettes for treating different muscle diseases. **Role: P.I.**

1PO1 NS046788-01 (P.I. S. Froehner) 06/01//09 - 3/31/2014
NIH/NINDS Project 3: "Molecular and Cellular Therapies for Muscular Dystrophy"
The original aims of this grant have been progressively modified over the past several years. The major focus is on identifying skeletal muscle fiber type-specific regulatory regions and control elements in the MCK and other muscle genes. Analogous studies are also carried out to identify cardiac muscle regulatory regions and control elements. Skeletal muscle and cardiac muscle reporter and expression cassettes are then used in collaborative studies aimed toward creating more efficient *in vitro* systems for transforming human non-muscle cells into skeletal and cardiac muscle. Muscle gene expression is then compared in normal vs reprogrammed cells to determine whether the reprogrammed cells exhibit the same transcriptional controls associated with normal cells. This information is critical for evaluating the functional capacity of reprogrammed cells to replace defective muscle tissues. **Role: Co-investigator**

Completed Research Support: **Continuous NIH grant support since 1967.**