BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
STEWART, Andrew Fyfe	Principal Investigator
eRA COMMONS USER NAME (credential, e.g., agency login) AFSTEWART	

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
Trinity College, Hartford, CT	BS	06/70	Biology
Columbia Univ., Coll. Physicians & Surgeons, NY	MD	05/74	Medicine
Yale University, New Haven, CT	Postdoc	06/77	Endocrinology

A. Personal Statement. Dr. Stewart has worked in the areas or basic and clinical research for 30+ years. He purified and sequenced PTH-related protein, the peptide growth factor that is produced by many human and animal cancers and leads to humoral hypercalcemia of malignancy (HHM). He defined the posttranslational processing of PTHrP into a family of peptides, described the binding and signaling of PTHrP to its G-protein coupled receptor in bone and kidney, developed the first two-site immunoassay for PTHrP, showed that PTHrP concentrations are elevated in humoral hypercalcemia of malignancy, reproduced the HHM syndrome in animals and humans through infusion of PTHrP, and has shown that PTHrP, administered intermittently, is a potent skeletal anabolic agent for the treatment of postmenopausal osteoporosis.

Over the past 20^{+} years, beginning with the documentation that PTHrP and its receptor are present in the pancreatic beta cell, he turned his focus to the pancreatic beta cell. He and his group demonstrated in the 1990's that PTHrP, hepatocyte growth factor and placental lactogen, delivered transgenically and/or adenovirally, are capable of stimulating increases in beta cell replication in living mammals, with resultant increases in beta cell mass and function. Most recently, he has focused on understanding the fundamental mechanisms of cell cycle control and upstream signaling in human and rodent beta cell regeneration. In this application, he serves as the Contact PI.

B. Positions and Honors

1974-75 Intern and Resident, Roosevelt Hospital, New York, NY
1980-85 Asst. Professor of Medicine, Yale University School of Medicine, New Haven, CT
1980-84 Asst. Director, Clinical Research Center, Yale-New Haven Hosp., New Haven, CT
1985-89 Assoc. Professor of Medicine (Term), Endocrinology, Yale University, New Haven, CT
1984-97 Chief, Endocrinology, West Haven VA Medical Center, West Haven, CT
1989-93 Assoc. Professor (Tenured), Yale University School of Medicine, New Haven, CT
1993-97 Professor of Medicine (Tenured), Yale University School of Medicine, New Haven, CT
1997-12 Chief, Division of Endocrinology, University of Pittsburgh, Pittsburgh, PA
1997-12 Professor of Medicine (Tenured), University of Pittsburgh, Pittsburgh, PA
2012- Scientific Director, Diabetes Obesity Metabolism Institute, Mt. Sinai School of Medicine, NY, NY
2012- Irene and Dr. Arthur Fishberg Professor of Medicine, Mt. Sinai School of Medicine, NY, NY

Honors: Program Chair, Annual Meeting of the Endocrine Society, 1996. Councilor, Endocrine Society 1999-2002. Councilor ASBMR 1994-1997. American Society for Clinical Investigation. Association of American Physicians. Columbia University Alumni Recognition Award for Excellence in Clinical Investigation 1992. Program Cte, Int'l Soc. for Endocrinology 2000. Editor for bone and mineral, *Endocrinology* 1997-2002. Sec'y-Treasurer, ASBMR 1999-02. Associate Editor, *J Bone Min Research* 2003-8. Chair, Science Policy Cte, ADA, 2003-5. Secretary-Treasurer, The Endocrine Society, 2007-2010. Chair, NIH/NIDDK Islet Cell Resource Center Users' Working Group, 2007-9; The Endocrine Society Gerald D. Aurbach Award for Outstanding Scientific Achievement, 2008; ADA Awards Cte 2009-2011; Chair, Program Committee, ADA Annual Scientific Sessions 2010, 2011; Co-Director, Keystone Conference on Beta Cell Biology, Monterey CA, 2012. Invited Speaker 2014, Keystone Meeting on Diabetes and Obesity, Vancouver. University of Uppsala Diabetes Center Ray Kroc Scientific Award, 2014.

C. Selected Peer-reviewed Publications (from a total of 239):

Most relevant to the current application

1. Vasavada R, Cavaliere C, D'Ercole AJ, Dann P, Burtis WJ, Madlener AL, Zawalich K, Zawalich W, Philbrick WM, Stewart AF. Overexpression of PTHrP in the pancreatic islets of transgenic mice causes hypoglycemia, hyperinsulinemia and islet hyperplasia. ***J Biol Chem*** 271:1200-1208, 1996. PubMed ID: 8557651
2. Garcia-Ocaña A, Takane KK, Reddy VT, Lopez-Talavera J-C, Vasavada RC, Stewart AF. Adenovirus-mediated hepatocyte growth factor transfer to murine islets improves pancreatic islet transplant performance and reduces beta cell death. ***J Biol. Chem.*** 278:343-351, 2003. PubMed ID: 12403787
3. Cozar-Castellano I, Takane KK, Bottino R, Balamurugan AN, Stewart AF. Induction of Beta Cell Proliferation and Retinoblastoma Protein Phosphorylation in Rat and Human Islets Using Adenoviral Delivery of Cyclin-Dependent Kinase-4 and Cyclin D_1. ***Diabetes*** 53:149-59, 2004. PubMed ID: 14693709
4. Cozar-Castellano I, Weinstock M, Haught M, Velázquez-Garcia S, Sipula D, Stewart AF. Comprehensive characterization of the G_1/S proteome in the islets of mice transgenic for hepatocyte growth factor, placental lactogen, or both: unique involvement of $p21^{cip}$. ***Diabetes*** 55:70-77, 2006. PubMed ID: 16380478
5. Cozar-Castellano I, Harb G, Selk K, Takane KK, Vasavada RC, Sicari B, Law B, Zhang P, Scott DK, Fiaschi-Taesch N, Stewart AF. Lessons from the Comprehensive Molecular Characterization of Cell Cycle Control in Rodent Insulinoma Cell Lines. ***Diabetes*** 57:3056-68, 2008. PubMed ID: 18650366
6. Fiaschi-Taesch NM, Bigatel TA, Sicari BM, Takane KK, Velazquez-Garcia S, Harb G, Karen Selk K, Cozar-Castellano I, Stewart AF. A Survey of the Human Pancreatic Beta Cell G1/S Proteome Reveals a Potential Therapeutic Role for Cdk-6 and Cyclin D_1 in Enhancing Human Beta Cell Replication and Function in Vivo. ***Diabetes*** 58:882-93, 2009. PubMed ID: 19136653
7. Harb G, Vasavada RC, Cobrinik D, Stewart AF. The retinoblastoma protein (pRB) and its homologue p130 regulate the G1/S transition in pancreatic ß cells. ***Diabetes*** 58:1852-62, 2009. PubMed ID: 19509021
8. Fiaschi-Taesch NM, Salim F, Kleinberger J, Cozar-Castellano I, Selk K, Cherok E, Takane KK, Stewart AF. Induction of Human Beta Cell Proliferation and Engraftment Using A Single G1/S Regulatory Molecule, Cdk6. ***Diabetes*** 59:1926-36, 2010. PMIID:20668249
9. Karslioglu E, Kleinberger J, Salim F, Cox A, Takane KK, Donald K. Scott DK, Stewart AF. cMyc is the principal upstream driver of beta cell proliferation in rat insulinoma cell lines and Is an effective mediator of human beta cell replication. ***Mol Endocrinology*** 25:1760-72, 2011. PMID: 21885567
10. Walpita D, Hasaka T, Spoonamore J, Vetere A, Takane KK, Fomina D. Fiachi-Taesch NM, Stewart AF, Schreiber SL, Wagner BK. A human islet cell culture system for high-throughput screening. ***J Biomolecular Screening*** 17:509-518, 2012. PMID: 22156222
11. Metukuri MR, Zhang P, Basantani MK, Chin C, Stamateris RE, Alonso LC, Takane KK, Gramignoli R, Strom SC, O'Doherty RM, Stewart AF, Vasavada RC, Garcia-Ocaña A, Scott DK. ChREBP mediates glucose-stimulated pancreatic beta cell proliferation. ***Diabetes*** 61:2004-15, 2012. PMID 22586588
12. Takane KK, Kleinberger J, Salim F, Fiaschi-Taesch NM, Scott DK, Stewart AF. Regulated and reversible induction of adult human beta cell replication. ***Diabetes*** 61:418-24, 2012. PMID: 22210317
13. Fiaschi-Taesch N, Kleinberger JW, Salim F, Troxell R, Cox AE, Takane KK, Scott DK, Stewart AF. Developing a human pancreatic beta cell G1/S molecule atlas. ***Diabetes*** 62:2450-59, 2013. PMID 23493571.
14. Fiaschi-Taesch NM, Kleinberger JW, Salim F, Troxell R, Cox AE, Takane KK, Srinivas H, Scott DK, Stewart AF. Cytoplasmic-nuclear trafficking of G1/S cell cycle molecules and adult human beta cell replication: a revised model of human beta cell G1/S control. ***Diabetes*** 62:2460-70, 2013. PMID 23493571.
15. Takane KK, Bender A, Scott DK, Argmann C, Kasai Y, Losic B, Ochando J, Becker T, Newgard CB, Schadt EE, Stewart AF. Efficient, specific targeting and flow cytometric sorting of purified human beta cells using an insulin promoter-mini-CMV enhancer-driven adenovirus. (submitted) 2013.

Additional recent publications of importance to the field (in chronological order)

16. Kulkarni RN, Bernal-Mizrachi E, Garcia-Ocaña A, Stewart AF. Human ß-cell proliferation and intracellular signaling: driving in the dark without a roadmap. ***Diabetes*** 61:2205-2213, 2012. PMID: 22751699.
17. Bender A, Stewart AF. Good news for the aging beta cell. ***Diabetologia*** 57:265-9, 2014. PMID 24257895.

18. Bernal-Mizrachi E, Kulkarni RN, Stewart AF, Garcia-Ocaña A. Human β-cell proliferation and intracellular signaling, part 2: still driving in the dark without a roadmap ***Diabetes*** 63:819-31, 2014. PMID 24556859

D. Research Support

Active:

1) "Multidisciplinary Approaches to Driving Human Beta Cell Replication"
Principal Investigator: Andrew F. Stewart
Agency: NIH/NIDDK U-01 089538
Period: 7/01/10 - 6/30/14

This is a Beta Cell Biology Consortium multicenter grant focusing on the biology and therapeutic opportunities for expanding human beta cell mass for diabetes. The centers include Mount Sinai with subcontracts to Vanderbilt and Duke. The applicant's component explores several specific aspects of cdk6 biology and development of adenoviral vectors for beta cell-specific targeting. Other projects relate to islet vascularization (with the Vanderbilt group). The Duke component focuses on Pdx1 and Nkx6.1 and downstream targets.

2) "Pancreatic Islet Growth Factors: Transgenic and Viral Modeling"
Principal Investigator: Andrew F. Stewart
Agency: NIH/NIDDK R-01 55023
Period: 5/1/12 - 4/30/16

This grant was originally focused on the development and characterization of RIP-PL and RIP-HGF mice. It later evolved to focusing on p21, p27, pRb, p107 and p130 in the molecular control of cell cycle progression in the pancreatic beta cell. Its most recent renewal focuses on p107, p57 and cMyc upstream regulation in insulinoma cell lines.

3) "Defining and Removing the Blockades to Human Beta Cell Replication"
Principal Investigator: Andrew F. Stewart
Agency: Juvenile Diabetes Research Foundation, 1-2011-603
Period: 08/01/11 - 7/31/14

In this proposal, we define the stability and regulation of cyclins D2 and D3, as well as cdk6. We also explore upstream signaling that controls their expression.

Pending:

1) "Leveraging Human Insulinoma Genomics for Beta Cell Regeneration"
Principal Investigator: Andrew F. Stewart Contact PI
Agency: NIH/NIDDK HIRN UC4 DK104138
Period: 12/01/14 - 11/30/19

This is a Multi-PI Human Islet Research Consortium (HIRN) application with three PIs: Erich Schadt PhD, Jorge Ferrer MD and Andrew Stewart MD as contact PI. The goal is to examine DNA and RNA sequence data from our Human Insulinoma Biorepository to identify genomic pathways and druggable targets for human beta cell regeneration.

2) "Molecular Mechanisms of Physiologic Beta Cell Growth in Juvenile Human Pancreas"
Principal Investigator: Andrew F. Stewart PI (Al Powers Contact PI)
Agency: NIH/NIDDK HIRN UC4 DK104211 Pending
Period: 12/01/14 - 11/30/19

This is a Multi-PI Human Islet Research Consortium (HIRN) application with three PIs: Alvin C. Powers MD (Contact PI), Seung K. Kim MD and Andrew Stewart MD. The goal is to understand why PDGF and PRLR are absent in adult islets, but present in juvenile islets, and why GLP1R is able to signal to both mitogenic and incretin pathways in juvenile beta cells, but only via incretin pathways in adult beta cells. The Stewart lab will determine whether Ad.PRLR is able to restore mitogenic capability to adult human beta cells.

Completed:

1) "Exploiting Normal cMyc Biology for Human Beta Cell Expansion"

Principal Investigator: Andrew F. Stewart
Agency: Juvenile Diabetes Research Foundation, 17-2011-598
Period: 9/01/11 - 12/31/13

This was a joint application with three PIs, Matthias Hebrok at UCSF, Donald Scott at Mount Sinai, and the PI. It focuses on three goals: 1) defining the role of cMyc in driving rodent beta cell replication and function in transgenic mice (Hebrok); 2) the regulation of cMyc in beta cells by glucose via ChREBP (Scott); and, 3) the possible therapeutic use of cMyc to drive human beta cell expansion. Despite superficial similarities with the cMyc studies in DK55023 (both study some aspect of cMyc), there is no scientific or budgetary overlap: this JDRF grant will employ stable cMyc expression in a lentiviral system to create a human beta cell line, and DK55023 proposes to explore cMyc upstream regulation in the Ins1 cell line.

2) "Pathophysiology of PTH-related protein (1-36) in humans"
Principal Investigator: Andrew F. Stewart
Agency: NIH/NIDDK R-01 51081
Period: 12/01/09 -10/31/12

This grant explores the potential of daily subcutaneous injections of PTHrP as a purely anabolic skeletal agent for the treatment of postmenopausal osteoporosis.

3) "Research Training in Diabetes and Endocrinology"
Principal Investigator: Andrew F. Stewart
Agency: NIH/NIDDK T-32 DK07052-38
Period: 7/1/05 - 6/30/15

This is an NIH Training Grant for Postdoctoral Fellows. It was relinquished when Dr. Stewart left the University of Pittsburgh.

4) "Relief of Cell Cycle Inhibition for Human Beta Cell Proliferation"
Principal Investigator: Andrew F. Stewart
Agency: Juvenile Diabetes Research Foundation, 34-2008-630
Period: 09/01/08 - 8/30/11

This proposal attempted to knock down cell cycle inhibitors in an attempt to relieve the repression that prevents human beta cell cycle progression in an effort to enhance beta cell replication and function both in vitro as well as in vivo in STZ-diabetic NOD-SCID mice.

5) "Activation of Human Beta Cell Replication"
Principal Investigator: Andrew F. Stewart
Agency: Juvenile Diabetes Research Foundation 1-2008-39
Period: 03/01/08 – 2/28/11

This grant sought to catalogue by immunoblot and immunohistochemistry all of the G1/S cell cycle control molecules, and to overexpress the cyclins and cdks in an effort to enhance beta cell replication and function both in vitro as well as in vivo in STZ-diabetic NOD-SCID mice