BIOGRAPHICAL SKETCH

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NAME: Grinspoon, Steven K.

eRA COMMONS USER NAME: SKGRINSPOON

POSITION TITLE: Professor of Medicine, Harvard Medical School
Director MGH Program in Nutritional Metabolism

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University, New York	B.A.	1983	Political Science
Univ. of Rochester School of Medicine & Dentistry	M.D.	1988	Medicine

A. Personal Statement

Dr. Steven Grinspoon is a Professor of Medicine at Harvard Medical School, Director of the MGH Program in Nutritional Metabolism, and Co-Director of the Nutrition Obesity Research Center at Harvard. His work investigates the neuroendocrine regulation of body composition, and physiologic consequences of fat distribution on cardiovascular disease and inflammation. He has investigated the effects of reduced growth hormone on metabolic dysregulation in obesity and was the first to propose the use of a GHRH analogue to increase endogenous GH secretion on lipodystrophy and generalized obesity, which led to the FDA approval of tesamorelin for excess visceral fat accumulation in HIV-infected patients. More recently, his research focuses on the inflammatory mechanisms by which ectopic fat and other metabolic perturbations contribute to HIV-CVD, and in this regard, he led the AHA State of the Science Conference on CVD in HIV. Additionally, he is leading the large multicenter REPRIEVE study, the first study of a primary prevention strategy for CVD in HIV. He has served on the Harvard faculty since 1995 and has been selected to the American Society for Clinical Investigation and the Association of American Physicians for his scientific contributions. He received the American Federation of Medical Research Investigator of the Year Award in 2005 and the Edward H. Ahrens Jr. Award for Patient Oriented Research in 2014. At MGH, he is PI of the Harvard Training Grant in Nutritional Metabolism and is an active mentor. Given his extensive research experience in HIV-associated CVD and successful mentorship record, he will ensure that Dr. Toribio will achieve her career goal of an independent clinical investigator in the field of HIV-associated CVD.

B. Positions and Honors

Positions and Employment

1988-1992 Resident and Chief Resident in Medicine, Columbia-Presbyterian Hospital, New York
1992-1995 Clinical and Research Fellow in Medicine, Neuroendocrine Unit, MGH
1995-1996 Instructor in Medicine, Harvard Medical School
1997-2001 Assistant Professor of Medicine, Harvard Medical School
1999- Assistant Director, General Clinical Research Center, Massachusetts Institute of Technology
2001-2007 Associate Professor of Medicine, Harvard Medical School
2002- Director, Program in Nutritional Metabolism, Massachusetts General Hospital
2007- Professor of Medicine, Harvard Medical School
2012- Co-Director, Nutrition Obesity Research Center at Harvard
2015- Director, Nutrition Obesity Research Center at Harvard

Other Experience and Professional Memberships

1999 Co-Chair, Wasting and Weight Loss Working Group, Department of Health and Human Services – Expert Panel on National HIV/AIDS Nutrition Guidelines
2000- 2008 Editorial Board, *Journal of Clinical Endocrinology and Metabolism*
2001- Member, International AIDS Society USA, Expert Panel on Metabolic Complications
2001- Director, Endocrinology and Metabolism Research and Executive Committee, MGH CFAR

2002- Executive Committees, Harvard Center for Nutrition Research and Harvard Div. of Nutrition
2002- 2006 Member, Study Section, NIH NCRR Clinical Research Review Committee
2003- 2005 Co-Chair, Research Affairs Committee, Endocrine Society
2004- 2006 Member, World Health Organization Technical Advisory Group on Nutrition in HIV Disease
2005- PI & Director, Harvard Training Grant in Nutritional Metabolism
2006- 2008 Co-Chair, American Heart Association and American Academy of HIV Medicine, State of the Science Conference on CVD in HIV

Honors

2003- Member, The American Society for Clinical Investigation
2004 Pfizer Visiting Professorship, University of California at Davis
2005 American Federation of Medical Research Outstanding Investigator Award
2011- Member, The Association of American Physicians
2014 Association for Clinical and Translational Science Ahrens Award for Translational Research
2016 Endocrine Society Gerald Aurbach Laureate Award for Translational Research
2016 MGH Endowed Chair in Neuroendocrinology and Metabolism

C. Contribution to Science

1. Effects of Augmenting Endogenous GH Pulsatility on Visceral Fat in Lipodystrophic Patients with Abdominal Fat Accumulation

This work was initiated by an observation of reduced GH secretion in HIV patients with lipodystrophy. Subsequent studies examined the mechanisms and demonstrated reduced area under the curve per peak, but maintenance of the GH pulse generator in such patients, reasoning that augmentation of GH pulsatility might reduce visceral fat, because of its potent effects to oxidize adipose tissue, a series of studies were performed culminating in a NEJM paper demonstrating that tesamorelin and GHRH1-44 secretagogue reduced visceral fat by 20% and reduced triglyceride, while improving adiponectin. This work led to FDA approval of tesmaorelin as the only such approved drug for HIV lipodystrophy and first in class molecule. Subsequent studies, published in JAMA, demonstrated that tesamorelin significantly reduced hepatic steatosis as well, the first drug to demonstrate a significant effect among patients with HIV lipodystrophy. Most recently the drug was investigated in generalized obesity and showed significant effects to reduce cIMT, inflammatory markers, lipids and visceral adiposity.

1. Koutkia P, Meininger G, Canavan B, Breu J, **Grinspoon S.** Metabolic Regulation of Growth Hormone by Free Fatty Acids, Somatostatin and Ghrelin in HIV Lipodystrophy. Am J Physiol Endocrinol Metab. 2004; 286: E296 - 303. PMID: 14559725.
2. Koutkia P, Canavan B, Breu J, Torriani M, Kissko J, **Grinspoon S.** Growth Hormone Releasing Hormone (GHRH) in HIV-infected Men with Lipodystrophy: A Randomized Controlled Trial.JAMA.2004; 292:210-218.
3. Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, Berger B, Brown S, Richmond G, Fessel J, Turner R, **Grinspoon S.** Metabolic Effects of a Growth Hormone-Releasing Factor in HIV Patients. N Engl J Med 2007;357:2359-70. PMID: 18057338.
4. Stanley TL, Feldpausch M, Oh J, Branch K, Lee H, Torriani M, **Grinspoon SK.** Effects of Tesamorelin on Visceral Fat and Liver Fat in HIV-infected Patients with Abdominal Fat Accumulation: A Randomized Clinical Trial. JAMA. 2014 Jul 23-30;312(4):380-9. PMCID: PMC4363137

2. Mechanisms and Strategies for CVD in HIV

In 2008 I was asked to lead an AHA sponsored State of the Science Symposium on CVD in HIV. The conclusions from this conference called for a better understanding and treatment strategies of CVD in HIV. In this regard, our work began with epidemiologic studies demonstrating increased myocardial infarction rates in HIV patients. This data was followed by a series of mechanistic studies demonstrating increased prevalence of plaque, particularly noncalcified, lipid rich, plaque. We used FDG PET to demonstrate for the first time significant arterial inflammation in asymptomatic low traditional risk HIV patients, compared to Framingham risk matched control subjects, as well as non HIV patients with known CVD. Of note increased arterial inflammation was most significantly associated with increased markers of immune activation. This work was followed by studies in which we phenotyped the morphological characteristics of coronary plaque in HIV patients, demonstrating an increased prevalence of high risk plaque with low attenuation and positive remodeling, more vulnerable to rupture. Our studies suggested that treatment with a statin, might uniquely target both traditional risk factors including LDL but also increased immune activation indices driving atypical noncalcified high risk plaque in this population. This work culminated in a recent paper in Lancet HIV, in which we showed for the

first time that a statin can significantly reduce high risk plaque volume as well as improve the high risk morphological features in coronary lesions in HIV. In part due to my work in this field, I helped develop and am now a lead investigator on the large multicenter REPRIEVE trial as the first primary CHD prevention trial in HIV and recently gave the plenary lecture at CROI 2015 on this topic.

1. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, Nasir K, **Grinspoon SK**. Increased Prevalence of Subclinical Coronary Atherosclerosis Detected by Coronary Computed CT angiography in HIV- Infected Men. AIDS 2010; Jan 16;24(2):243-53. PMCID: PMC3154841
2. Subramanian S*, Tawakol A*, Burdo T, Abbara S, Wei, J, Vijayakumar J, Corsini E, Abdelbarky A, Zanni M, Hoffman U, Williams K, Lo J†, **Grinspoon S**†. Arterial Inflammation in HIV-Infected Patients. JAMA 2012. Jul 25;308(4):379-86. PMCID: PMC3724172.
3. Zanni M, Abbara S, Lo J, Wai B, Hark D, Marmarelis E, **Grinspoon S**. Increased Coronary Atherosclerotic Plaque Vulnerability by Coronary Computed Tomography Angiography in HIV-Infected Men. AIDS. 2013 May 15;27(8):1263-72. PMCID:PMC3740057
4. Lo J, Lu M, Ihenachor EJ, Wei J, Looby S, Oh J, Fitch K, Zimmerman C, Hwang J, Abbara A, Plutzky J, Robbins G, Tawakol A, Hoffman U, **Grinspoon S**. Effects of Statin Therapy on Coronary Artery Plaque Volume and High Risk Plaque Morphology in HIV-Infected Patients with Subclinical Atherosclerosis: A randomized, Double Blind Placebo-Controlled Trial. Lancet HIV Lancet HIV 2015;2:e52-e63. PMCID: PMC4820828

3. Visceral Fat Accumulation, Subcutaneous Fat Loss and Metabolic Perturbation in Acquired Lipodystrophy

My initial work focused on the lipodystrophy syndrome in HIV patients as a model of acquired visceral fat accumulation and subcutaneous fat loss. This work highlighted a significant degree of insulin resistance and was the first to show the effects of an insulin sensitizing agent, metformin in this population. Subsequent work investigated the thiazolidinediones as a class to increase subcutaneous fat via PPAR agonism. This work was highly successful and les to the recognition of insulin resistance and diabetes in this population. Subsequent work was aimed at investigating the mechanisms of ectopic fat gain in this group. One such paper demonstrated increased deiodenase 2 in dorsocerivcal fat deposits in HIV-infected patients, suggesting a compensatory recrudescence of brown fat in this population. More recently, the effects of lifestyle were examined on key metabolic hormones irisin and FGF-21. The data demonstrated for the first time that FGF21 decreases with exercise suggesting a compensatory not primary increase among such patients.

1. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, **Grinspoon S.** Metformin use in the HIV lipodystrophy syndrome: A randomized, controlled trial. JAMA. 2000; 284:472-7.
2. Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, **Grinspoon S**. Effects of Rosiglitazone on Metabolic Indices and Fat in HIV Lipodystrophy: A Randomized Controlled Trial. Ann Intern Med. 2004; 140: 786-794.
3. Torriani M, Fitch K, Stavrou E, Bredella M, Lim R, Sass C, Cypess A, **Grinspoon S**. Deiodinase 2 Expression is Increased in Dorsocervical Fat of Patients with HIV-Associated Lipohypetrophy Syndrome. J Clin Endocrinol Metab. 2012 Apr;97(4):E602-7 PMCID:PMC3319185
4. Srinivasa S, Wong K, Fitch KV, Wei J, Petrow E, Cypess AM, Torriani M, **Grinspoon SK**. Effects of Lifestyle Modification and Metformin on Irisin and FGF21 among HIV-infected Subjects with the Metabolic Syndrome. Clin Endocrinol. 2014. PMCID: PMC4475409

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/steven.grinspoon.1/bibliography/40509103/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1U01HL123336-02 (Grinspoon, Douglas) 08/08/2014-04/30/2020
NIH/NHLBI
A Randomized Trial to Prevent Vascular Events in HIV-infected Patients (REPRIEVE-CCC Lead)
This study will assess the utility of statins as a novel primary prevention strategy for cardiovascular disease in HIV patients, a group at increased risk for heart attacks and strokes. The study will also determine the unique mechanisms of statins to prevent CVD in HIV, assessing effects on coronary plaque and specific inflammatory pathways in an embedded mechanistic study. The study will be performed across multiple sites in the United States, in collaboration with an established AIDS research network.

1R01AI123001 (Zanni, Looby) 09/01/2015-08/31/2020
NIH/NIAID
Cardiovascular Disease Risk in HIV-infected Women: Sex-Specific Mechanisms of Risk and Risk Reduction among REPRIEVE Trial Participants
The major goals of this project are to determine whether immune activation contributes uniquely to cardiovascular disease risk among HIV-infected women across the reproductive aging spectrum. A key component of the methodology entails launching an evidence-based education/awareness campaign to augment female recruitment to the REPRIEVE trial.

5R01DK049302-20A1 NIH/NIDDK 09/01/2016-08/31/2021
(Grinspoon/Adler)
Effect of Mineralocorticoid Receptor Blockade on Coronary Vasculature and Myocardial Structure in HIV
This study is being conducted to test the efficacy of a selective mineralocorticoid blocker, eplerenone, on improving coronary flow, myocardial fibrosis, and atherosclerotic plaque in HIV patients with excess visceral adiposity.

2P30 DK040561-19 (Grinspoon) 08/01/2012-07/31/2017
NIH/NIDDK
Nutrition Obesity Research Center at Harvard (NORCH)
The goal of this Center are to provide research in basic areas of biology relevant to problems in clinical nutrition, to promote the study of clinical nutrition and application of knowledge derived there from within the HMS, MGH and HSHP community, to promote interactions among scientists and clinical investigators to show relevance to advancing the science of clinical nutrition; and to attract "basic" investigators into the domain of clinical nutrition to promote an environment and mechanism to develop new investigator-initiated research.

Gilead Sciences, Inc (Grinspoon) 07/31/2012-05/31/2017
Study # IN-US-236-0133
Effects of Newly-Initiated Quad Therapy on Aortic/Coronary Inflammation in HIV-Infected Patients
The major goals of this project are to investigate ways in which systemic immune dysregulation may mediate CVD risk in HIV-infected patients and the potential of newly-initiated ARV therapy to actually reduce such risk.

Theratechnologies, EMR 200147-501 (Grinspoon) 05/07/2013-05/06/2023
A phase 4, observational, multicenter, 10-year prospective cohort safety study comparing subjects with HIV-associated abdominal lipohypertrophy exposed to EGRIFTA (tesamorelin for injection) to a similar group of subjects not exposed to EGRIFTA
The major goals of this project are to determine the safety and tolerability of long term EGRIFTA use, and compare safety endpoints and adverse events in HIV patients with lipodystrophy receiving EGRIFTA to those electing not to receive EGRIFTA.

5T32HD052961-09 (Grinspoon) 09/27/2005-04/30/2017
NIH/NICHD
Training Program in Nutrition and Metabolism
The major goal of this project is to train fellows and postdoctoral trainees in the techniques of nutrition and metabolism research.

1R01HL123351-02 (Lo) 05/07/2014-04/30/2019
NIH/NHLBI
Targeting GI Epithelial Integrity to Improve Arterial Inflammation in HIV
In this grant application, we will examine whether abnormalities in the intestinal mucosal barrier can affect inflammation downstream in the blood vessels of the heart. We will also perform a randomized double-blind placebo-controlled trial to study whether treatment to improve the integrity of the mucosal barrier can help to decrease inflammation in the blood vessels of the heart and thus affect the development of atherosclerosis.

1R01HL122177-02(Tawakol) 08/15/2014-05/31/2018
NIH/NHLBI

Effect of Low Dose Methotrexate on Arterial Inflammation in HIV
The goal of this study is to evaluate the effect of low dose methotrexate (LDMTX) on arterial inflammation. Arterial inflammation will be examined using PET/CT.

1U01AI115711-02(Grinspoon) 12/15/2014-11/30/2017
NIH/NIAID
Tesamorelin Effects on Liver Fat and Histology in HIV: A Collaborative U01 Grant
This proposal investigates the effects of a new treatment, a growth hormone releasing hormone analogue, to reduce liver fat and improve inflammation and cellular damage in HIV-infected individuals with NAFLD.

Kowa Pharmaceuticals, Inc. 12/29/2014-12/28/2017
(Stanley &Grinspoon)
CTA: Effects of Pitavastatin on Insulin Sensitivity and Liver Fat
The major goals of this project are to determine the effects of pitavastatin as compared to placebo on insulin sensitivity using euglycemic hyperinsulinemic clamp and liver fat using ^{1}H-magnetic resonance spectroscopy.

Navidea Biopharmaceuticals, Inc. 06/11/2015-06/10/2018
(Grinspoon)
CTA: Use of 99mTc Tilmanocept for Imaging Arterial Inflammation
The major goals of this project are to assess the ability of tilmanocept to image atherosclerotic plaque in HIV-infected patients.

Completed
1R21 HL122138-02 (Triant) 01/03/2014-12/31/2016
NIH/NHLBI
Statin Use and Efficacy Among HIV-Infected Patients

5R01DK049302-19 (Grinspoon) 09/21/2011-08/31/2016
NIH/NIDDK
Aldosterone Effects and Targeted Inhibition on Metabolic Indices in HIV-Infection

1R01 HL112661-04 (Fitzgerald) 09/27/2012-06/30/2016
NIH/NHLBI
HDL prevention of cholesterol crystal inflammation in HIV disease

Immunex Corporation (Grinspoon) 12/22/2011-09/30/2016
Protocol No. 20109893
Monitoring and Modifying Atherosclerotic Plaque Inflammation in Psoriasis Study (MMAPPS)

American Diabetes Association (Grinspoon) 01/01/2012-12/31/2015
The Effects Of Short Term Acipimox Treatment On Skeletal Muscle Phosphocreatine Recovery In Obesity

5 R01 HL095123-05 (Grinspoon) 08/15/2009-09/30/2015 (NCE)
NIH/NHLBI - Inflammatory Mechanisms and Treatment Strategies for Atherosclerosis in HIV