BIOGRAPHICAL SKETCH

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NAME: Ravi Jasuja

eRA COMMONS USER NAME (credential, e.g., agency login): ravijasuja

POSITION TITLE: Director, Translational Research and Discovery, Mens Health: Muscle and Metabolism, Brigham and Women's Hospital, Harvard Medical School

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
Indian Institute of Technology, Delhi, India	B. Tech.	05/1992	Engineering
University of Hawaii, Manoa, Honolulu, HI	PhD	05/1997	Biophysics/Phys. Chem.
Albert Einstein College of Medicine	Fellow	03/1999	Biophysics/Physiology

A. Personal Statement

I am a translational investigator with expertise in androgen biology, androgen signaling, and mechanisms of testosterone's effects on the skeletal muscle. My scientific contributions reflect seamless integration of my expertise in modern biophysical techniques to our studies of signal amplification and cellular reprogramming after androgen binding to its cognate receptor. As the Director of the Preclinical Discovery Core of the Boston Pepper Center, I have optimized state-of-the art assays for the non-invasive functional and metabolic phenotyping in preclinical animal models.

By combining mesenchymal multipotent cell signaling with animal models of androgen deprivation, we were the first to establish a quantitative framework for characterization of androgenic ligands. The data from these mechanism-based assays were subsequently utilized by the Drug Enforcement Agency to justify the placement on several novel anabolic steroids (e.g. tetrahydrogestrinone) and steroid precursors (e.g. Δ-4 androstenedione) on the list of controlled substances.

My laboratory has applied a comprehensive set of computational and biophysical techniques to elucidate the non-linear dynamics in testosterone's binding to its binding partner sex hormone binding globulin (SHBG). Our studies have shown that testosterone's binding to SHBG is a multi-step dynamic process that involves an allosteric interaction between the two binding sites on the SHBG dimer. These groundbreaking findings have stimulated renewed interest by international governing bodies including CDC and ReproUnion (European consortia) in redefining population reference ranges across lifespans including pubertal dynamics.

Our recent research on tissue specific signaling that mediates testosterone action in prostate and muscle has revealed novel mechanistic insights involving polyamine biosynthesis. While selective androgen receptor modulators have been under development for decades at several academic centers and commercial entities, these findings provide a novel, mechanisms-based approach to attain tissues specificity.

With my background in Biophysical Spectroscopy, algorithms development, data sciences, and noninvasive imaging and animal models of aging, I have particular expertise in novel technologies for the assessment of body composition, muscle performance, and physical function, and in optical and magnetic resonance spectroscopies. As the PDC Leader, Dr. Jasuja will continue to serve as a member of the OAIC Executive Committee and will report to the OAIC Director and Executive Committee.

B. Positions and Honors

Professional Experience

03/00 - 05/02	Director, Worldwide Business Development, ArsDigita, Cambridge, MA
05/02- 01/04	DevLogics; e.Solve, Sharon, MA
01/04 – 08/07	Assistant Professor, Charles Drew University and Hospital, Los Angeles, CA.
05/2007-11/2011	Assistant Professor of Medicine, Boston University, Boston, MA
01/2013- present	Director, Preclinical Discovery Core; Translational Research and Discovery, Boston Claude D. Pepper Older Americans Independence Center; Research Program in Men's Health: Aging and Metabolism, Brigham and Women's Hospital, Harvard Medical School

Honors and Awards

- 10/09: Evans Junior Faculty Merit Award for translational research
- 12/03: Glaxo Smithkline Scholar
- 06/03: NSF Fellowship for "Molecular Modeling of Biomolecules", Univ. of Georgia, Atlanta GA.
- 05/03: NIH fellowhip award for "Mathematics of Biological Complexity", Georgia Institute of Tech., Atlanta.
- 09/99: Young scientist fellowship by the International Union of Pure and Applied Biophysics, XIII International Biophysics Congress.
- 05/97-03/99: Belfer followship for Postdoctoral research.
- 08/88: Awarded Council for Scientific and Industrial Research (C.S.I.R.) of India fellowship for four years of undergraduate study.
- 11/86: National Talent Search Award by the National Council for the Educational Research and Training for six years of college education in India.

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C. Contribution to Science

Contributions to our understanding of the mechanisms of androgen action

The studies in my lab have advanced our understanding of the molecular mechanisms that mediate the anabolic effects of testosterone on the skeletal muscle. I have developed a research program that integrates biophysical spectroscopy, computational modeling, mesenchymal stem cell signaling and in-vivo preclinical methodologies for studying mechanisms of androgen action. As the Director of Translational Research and Discovery, I have been advancing the capacity of a non-invasive metabolic phenotyping core, and development of novel optical modalities for high-throughput discovery. The studies that I led have contributed the foundational data that generated the hypotheses proposed in the current investigation. Our studies have shown that the tissue-specific regulation of polyamine signaling plays an important role in manifesting distinct effects of testosterone on prostate and skeletal muscle.

1. **Jasuja R**, Costello JC, Singh R, Gupta V, Spina CS, Toraldo G, Jang H, Li H, Serra C, Guo W, Chauhan P, Narula NS, Guarneri T, Ergun A, Travison TG, Collins JJ, Bhasin S. Combined administration of testosterone plus an ornithine decarboxylase inhibitor as a selective prostate-sparing anabolic therapy. Aging Cell. 2014 Apr;13(2):303-10.
2. Serra C, Sandor NL, Jang H, Lee D, Toraldo G, Guarneri T, Wong S, Zhang A, Guo W, **Jasuja R**, Bhasin S. The effects of testosterone deprivation and supplementation on proteasomal and autophagy activity in the skeletal muscle of the male mouse: differential effects on high-androgen responder and low-androgen responder muscle groups. Endocrinology. 2013 Dec;154(12):4594-606.
3. Zakharov MN, Pillai BK, Bhasin S, Ulloor J, Istomin AY, Guo C, Godzik A, Kumar R, **Jasuja R**. Dynamics of coregulator-induced conformational perturbations in androgen receptor ligand binding domain. Mol. Cell. Endocrinol. 2011;341(1-2):1–8.
4. **Jasuja R**, Ulloor J, Yengo CM, Choong K, Istomin AY, Livesay DR, Jacobs DJ, Swerdloff RS, Miksovská J, Larsen RW, Bhasin S. Kinetic and thermodynamic characterization of dihydrotestosterone-induced conformational perturbations in androgen receptor ligand-binding domain. Mol Endocrinol. 2009 Aug;23(8):1231-41.

5. Toraldo G, Bhasin S, Bakhit M, Guo W, Serra C, Safer JD, Bhawan J, **Jasuja R**. Topical androgen antagonism promotes cutaneous wound healing without systemic androgen deprivation by blocking β-catenin nuclear translocation and cross-talk with TGF-β signaling in keratinocytes. Wound Repair Regen. 2012 Jan-Feb;20(1):61-73.
6. Jang H, Bhasin S, Guarneri T, Serra C, Schneider M, Lee MJ, Guo W, Fried SK, Pencina K, **Jasuja R**. The Effects of a Single Developmentally Entrained Pulse of Testosterone in Female Neonatal Mice on Reproductive and Metabolic Functions in Adult Life. Endocrinology. 2015 Oct;156(10):3737-46. doi: 10.1210/EN.2015-1117.

Characterization of signaling mechanisms and testosterone's binding to its cognate binding proteins

One of my major contributions to science over the past two decades has been the integration of novel quantitative, computational and experimental techniques at the interface of engineering, biophysics and cell signaling and applying them to investigations of the dynamics of testosterone's binding to its cognate binding proteins, the intracellular signaling after testosterone's binding to the androgen receptor, and other biological processes, as reflected in some representative publications listed below. Our recent discovery of the allosteric model of testosterone's binding to sex hormone binding globulin formed the basis of the several transformative research grants and international collaborations.

1. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, **Jasuja R**. A Reappraisal of Testosterone's Binding in Circulation: Physiological and Clinical Implications. Endocr Rev. 2017 Aug 01; 38(4):302-324. PMID: 28673039.
2. Zakharov MN, Bhasin S, Travison TG, Xue R, Ulloor J, Vasan RS, Carter E, Wu F, **Jasuja R**. A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. Mol Cell Endocrinol. 2014 Sep 21;399C:190-200.
3. Zakharov MN, Ulloor J, Bhasin S, Ross JA, Narula NS, Bakhit M, Pillai BK, Kumar R, Jameson DM, **Jasuja R**. Numerical framework to model temporally-resolved multi-stage dynamic systems. Comp. Meth. and Prog. in Biomed. 2012;108(2):750-9. PMID 22727632
4. Zakharov MN, Ulloor J, Bhasin S, Ross JA, Narula NS, Bakhit M, Pillai BK, Kumar R, Jameson DM, **Jasuja R**. Guanidinium chloride-induced spectral perturbations of 4,4'-dianilino-1,1'-binaphthyl-5,5'-disulfonic acid confound interpretation of data on molten globule states. Anal Biochem. 2011; 416(1):126-8. PMID 21605623

Development and application of novel biophysical technologies to resolve difficult problems in testosterone binding to circulating binding proteins, androgen signaling, and cell signaling

Over the course of the past several years, our group has developed novel biophysical tools that have then been applied to understand mechanisms in diverse biologic systems such as testosterone's binding to SHBG, response tuning in bacterial chemotaxis, and computational tools to resolve complex, multistep molecular reactions.

1. Zakharov MN, Bhasin S, Szafran AT, Mancini MA, **Jasuja R**. Numerical framework to model temporally resolved multi-stage dynamic systems. Comput Methods Programs Biomed 2012;108(2):750–9.
2. J**asuja R**, Lin Y, Trentham DR, Khan S. Response tuning in bacterial chemotaxis. Proc Natl Acad Sci U S A. 1999 Sep 28;96(20):11346-51
3. Jayaraman S, **Jasuja R**, Zakharov MN, Gursky O. Pressure perturbation calorimetry of lipoproteins apolipoprotein to a phospholipid surface. *Biochemistry*. 2011; 17;50(19):3919-27.
4. Xue R, Zakharov MN, Xia Y, Bhasin S, Costello JC, **Jasuja R**. Research resource: EPSLiM: ensemble predictor for short linear motifs in nuclear hormone receptors. Mol Endocrinol. 2014 May;28(5):768-77.

Application of biophysical and computational tools to advance understanding of sequence-dependent electron shuttling in DNA damage and repair mechanisms

Organization of base pairs in DNA provides an interesting conduit of delocalized π electrons which could be used to shuttle electron or energy between donor and accepts pairs; conceivably a molecular wire with a photo-switch. The issue of DNA-mediated electron transfer is a critical one from fundamental biological processes in cell as well. DNA damage and repair mechanisms involve electron transport and therefore sequence specific DNA probes are being developed that rely upon electron and energy transport mechanisms. I examined the structural and thermodynamic determinants of efficiency of photo-induced electron transfer through the DNA base pairs. Using a series of computational and experimental measurements we identified the role of relative orientation along π stack, and hydrogen bonding. These studies provided seminal insights into the biophysical parameters that can govern the long-range, sequence dependent electron shuttling through DNA.

1. **Jasuja R**, Jameson DM, Nishijo C and Larsen RW. Singlet Excited State Dynamics of molecular Complexes of tetrakis(N-methylpyridyl)prophyrin with DNA nucleotides J. Phys. Chem.1997, 101, 8, 144-50.
2. Larsen RW, **Jasuja R**, Niu SL and Diwedi K Photo-Induced Electron Transfer within Self-Assembled Ru(L)3-Iron Porphyrin Complexes. Photochem. Photobiol., A 1997, 107, 1, 71.
3. Larsen RW, Omdal DH, S. N. Niu, **Jasuja R**, and Jameson DM,"Conformational Modulation of Electron Transfer within Electrostatic Porphyrin:Cytochrome c Complexes", J. Phys. Chem. B 1997, 101, 8012-8020.
4. **Jasuja R**, Hazlett, TL, Helms, MK, Lee, SH, Jameson, DM, and Larsen, RW" Temperature Dependence of Photoinudced Electron Transfer within Self-Associated Porphyrin:Guanine Monophosphate Complexes" Chem. Phys. Lett. (2001) 350, 515-521.

D. Research Support

Active:

1. Characterizing novel nano-formulation for sustained delivery of hormones
R33 AG068234-01
Period: 09/2020 – 5/2023
Source: NIA.
Aims: This translational project aims to characterize the biophysical/preclinical dynamis of novel nanoparticle formulation for programmable, sustained delivery of hormones.
Overalp: None

2. Assisted living communities – transforming predictive data into proactive care for COVID-19
3P30AG03167910S3
Period: 10/2020-5/2021.
Aims: The objectives of the project include implementing a comprehensive machine learning framework by integrating personalized risk profiles from preexisting conditions (EHR) with real-time physiological biosensing and ecological momentary assessment for hospitalization risk from COVID-19 infection.
Overalp: None

3. Phase II: Research and Commercialization of TruT Algorithm for Free Testosterone (Role: PI)
2R44AG045011-02
Source: NIA
Period: 09/2017 – 8/2021
Aims: To continue the development and commercialization of the TruT algorithm by validating it in common conditions characterized by altered SHBG concentrations; in healthy menstruating women and in women with hyperandrogenic disorders; and by generating population-based reference ranges for free T concentrations.
Overalp: None

4. Boston Claude D. Pepper Older Americans Independence Center; Preclinical Discovery Core (Role: Resource Core Director)
NIH/NIA 5P30AG013679
Source: NIA
Period: 06/2016 – 05/2021
Specific Aims: The aim of this P30 center grant is to provide infrastructural support and serve as a catalyst for aging research at Harvard-affiliated aging researchers
Overlap: None

Completed:

1. Novel Algorithm For Free Testosterone Detemination (Role: PI)
   10/2014-8/2016 (NIA)
   The objective of this grant is to establish the method of free testosterone determination in healthy men for submission of product FDA for approval of clinical use.

2. Mechanisms of anabolic action of testosterone (Role: Co-Investigator, PI:Bhasin)
   11/30/09-12/1/15 (NIDDK)
   The goal of this project is to examine the mechanisms of tissue-specific action of androgens.

3. Proof of Concept Preclinical study on myogenic effects of MyoT12. (Role: PI)
   8/2013-8/2016 (MyoS Corp sponsored grant.)
   The objective of this study is to examine the mechanisms of anabolic effects of MyoT12 in healthy and testosterone supplemented animal models 1. Metabolic and Inflammatory Stress and the Endothelial Cell

4. To investigate the function of the SirT1/LKB1/AMPK signaling (Role: Co-Investigator, PI:Ruderman)
   4/15/09-1/13/14 (NHLBI)
   The goal of this project is to investigate the function of the SirT1/LKB1/AMPK signaling mechanism in the vasculature. They should provide insights as to whether its dysregulation could be the cause of the endothelial cell dysfunction associate wit the metabolic syndrome.

5. To examine the role of microRNA in neonatal reprogramming by testosterone. (Role: PI)
   8/31/10-09/1/12 (Genome Science Institute)
   The goal of the project was to utilize systems biology approaches to examine the role of miRNA in mediating neonatal androgen responses

6. Develop quantitative methodologies for assessment of androgenic modulation of muscle and adipose tissue. (Role: PI)
   10/1/09- 12/1/11 (Evans Foundation Research Grant)
   The goal of the project was to develop novel translational modalities for quantifying androgenic signal amplification in muscle and adipose tissue.