CHANGE OF GRANTEE ORGANIZATION

Form Approved Through 6/30/2012 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
Whole-Genome Prediction of Type-2 Diabetes Susceptibility in Various Populations

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☐ YES
(If "Yes," state number and title)
Number: PAR-09-060 Title: NIDDK Mentored Research Scientist Development Award (K01)

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Klimentidis, Yann, C.	Ph.D.	YANNKLIMENTIDIS

3c. POSITION TITLE
Assistant Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
1295 N. Martin Avenue., Buidling 202A
Tucson, Arizona 85719

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Epidemiology and Biostatistics

3f. MAJOR SUBDIVISION
Mel & Enid Zuckerman College of Public Health

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: FAX:

E-MAIL ADDRESS:

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☒ No ☐ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☒ No ☐ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes	5a. Animal Welfare Assurance No.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
8-6-12	8-5-17	137,327	$148,309	$712,081	769,047

9. APPLICANT ORGANIZATION
Name: Arizona Board of Regents, University of Arizona
Address: P.O. Box 3308
Tucson, AZ 85722-3308

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1-742652689A1
DUNS NO. 80-634-5617 Cong. District 7

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Sherry L. Esham
Title: Director, Sponsored Projects Services
Address: University of Arizona
P.O. Box 3308
Tucson, AZ 85722-3308
Tel: 520-626-6000 FAX: 520-626-4137
E-Mail: Sponsor@u.arizona.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Leslie P. Tolbert, Ph.D.
Title: Vice President for Research, Graduate Studies
Address: University of Arizona
P.O. Box 3308
Tucson, AZ 85722-3308
Tel: 520-626-6000 FAX: 520-626-4137
E-Mail: Sponsor@u.arizona.edu

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*
Kelly Sellow acting for Leslie P. Tolbert

DATE 6/28/12

PROJECT SUMMARY (See instructions):

The applicant's career goal is to become a productive independent investigator in the area of statistical genetics, particularly in the area of genomic-based prediction of type-2 diabetes (T2D) risk. To meet this goal, the applicant proposes a career development plan that includes hands-on and didactic training in statistical learning as applied to quantitative genetics, categorical and case-control data analysis, informatics as applied to high dimensional genetic data, and the biology and genetics of T2D. A highly accomplished and diverse set of investigators with proven track records of successful mentoring will oversee the applicant's career development. The research component of this project seeks to improve our ability to use genetic information to predict an individual's risk of developing T2D. Publically available genetic and phenotypic data from sources such as dbGaP (The database of Phenotypes and Genotypes) will be used to develop and test various models for prediction of T2D risk among three racial/ethnic groups. This project will capitalize on newly developed statistical methods that are able to incorporate information from tens of thousands of genetic markers at once, which represent a major advance over current methods that typically take fewer than 100 markers into account. The aims of the study are: 1) To test the hypothesis, in different populations, that individualized whole-genome prediction of T2D (along with standard covariates of sex, age, and BMI) will offer major improvements over current genetics-based prediction models, and will offer equal or greater accuracy than prediction based on family history; 2) To impute additional genetic markers to determine whether prediction can be improved, and to identify the subset of markers that is most useful in predicting T2D; 3) To develop prediction models for T2D risk given a certain body mass index (BMI), by including as predictors the interaction of BMI and genotypes. This project will greatly enhance our ability to predict an individual's susceptibility to T2D within various populations, leading to earlier and targeted prevention strategies, will increase our understanding of the genetic basis of T2D, and will provide critical training for Dr. Klimentidis' development as an independent scientist.

RELEVANCE (See instructions):

Genetic factors are known to play a major role in type-2 diabetes (T2D) risk. In this application, we propose to use novel statistical methods that enable us to build and test predictive models for T2D risk using thousands of genetic variants simultaneously, among individuals of European, Mexican, and African descent. This project has the potential to improve prediction of T2D risk, provide a better understanding of specific genetic factors involved in T2D risk, and bring us closer to the era of personalized medicine.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: ABOR, Univeristy of Arizona			
DUNS: 806345617			
Street 1: 1295 N. Martin Avenue., Building 202A		Street 2:	
City: Tucson	County: Pima		State: AZ
Province:	Country: USA		Zip/Postal Code: 85724-5210
Project/Performance Site Congressional Districts: AZ-007			

Additional Project/Performance Site Location			
Organizational Name:			
DUNS:			
Street 1:		Street 2:	
City:	County:		State:
Province:	Country:		Zip/Postal Code:
Project/Performance Site Congressional Districts:			

SENIOR/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Klimentidis, Yann	YANNKLIMENTIDIS	University of Arizona	Principal Investigator
Allison, David B.	Dallison1	U. of A. at Birmingham	Mentor
Chen, Zhao	ZHAOCHEN	University of Arizona	Mentor
Garvey, W. Timothy	GARVEYT	U. of A. at Birmingham	Co-mentor
Martinez, Fernando	fmartinez	University of Arizona	Co-mentor

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

The name of the program director/principal investigator must be provided at the top of each printed page and each continuation page.

RESEARCH GRANT
TABLE OF CONTENTS

Appendix *(Five identical CDs.)* ☐ Check if Appendix is Included

* Follow the page limits for these sections indicated in the application instructions, unless the Funding Opportunity Announcement specifies otherwise.

Program Director/Principal Investigator (Last, First, Middle): Klimentidis, Yann C.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY	FROM 8-6-2012	THROUGH 8-5-13

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Klimentidis, Yann	PD/PI	10.80			[redacted]	[redacted]	[redacted]	[redacted]
TBH	IT-Biostatistics	1.20			[redacted]	[redacted]	[redacted]	[redacted]
SUBTOTALS →						[redacted]	[redacted]	[redacted]

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)* Materials and supplies	875
TRAVEL Domestic	5,600
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* ADP - Computer Services $5,000; Computer for PI $3,000; Tuition $1,000; Software; Membership dues in professional Societies $750.	9,750
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*	$ 137,323
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	$ 137,323

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form Page 4)*	2nd ADDITIONAL YEAR OF SUPPORT REQUESTED	3rd ADDITIONAL YEAR OF SUPPORT REQUESTED	4th ADDITIONAL YEAR OF SUPPORT REQUESTED	5th ADDITIONAL YEAR OF SUPPORT REQUESTED
PERSONNEL: *Salary and fringe benefits. Applicant organization only.*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CONSULTANT COSTS					
EQUIPMENT					
SUPPLIES	875	852	513	414	155
TRAVEL	5,600	3,600	3,600	3,600	3,600
INPATIENT CARE COSTS					
OUTPATIENT CARE COSTS					
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES	9,750	9,250	10,250	9,500	8,900
DIRECT CONSORTIUM/ CONTRACTUAL COSTS					
SUBTOTAL DIRECT COSTS *(Sum = Item 8a, Face Page)*	137,323	140,730	145,131	144,664	144,233
F&A CONSORTIUM/ CONTRACTUAL COSTS					
TOTAL DIRECT COSTS	137,323	140,730	145,131	144,664	144,233

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD **$** 712,081

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

A. PERSONNEL

Yann C. Klimentidis, PhD (Investigator - 9.0 calendar mos. in Years 1-5) is currently an Instructor in the Office of Energetics at the University of Alabama at Birmingham (UAB). He will become an Assistant Professor in the Department of Epidemiology at the University of Arizona (UA), effective August 6th 2012. Based on his training and experience in human evolutionary and population genetics, and his proven record of publishable research, he brings a unique perspective to the study of the human disease genetics. His post-doctoral research has thus far resulted in nine authored publications (four first-authored) in peer-reviewed journals. He has been chosen to orally present his research at major meetings (The Obesity Society and the American Association of Physical Anthropologists), and has won an award for a poster presentation at a UAB symposium. Using this background, he plans to bring a cross-disciplinary approach to quantitative/statistical genetics and complex trait prediction. UA's faculty fringe rate of 31.20% is requested.

Budget Jusfication

A. PERSONNEL... Continued

TBH (Programmer - 1.2 calendar months) will be a staff member with experience in data analysis and experience in doing candidate gene and GWAS data analysis. This employee will have experience working with large-scale genetic data, working with the Unix system, PLINK, and doing genetic imputation. Our Programmer will be responsible for (1) assisting with large scale data storage solutions, (2) refining algorithms for speed in parallel processing, (3) assisting with execution of genomic imputation and training Dr. Yann Klimentidis in the use of imputation software, (4) *hardening* any software developed for public distribution, and (4) training Dr. Klimentidis in the effective use of HPC resources.

B. EQUIPMENT

No funding is requested.

C. TRAVEL

Funds are requested in the amount of **$20,000** for travel in all years. $5,600 for the first year, and then $3,600 for the four following years is requested for travel expenses for Dr. Klimentidis to travel to professional conferences and meetings, and short courses: including the annual American Society of Human Genetics and American Diabetes Association meetings, Gordon conference, short courses, and visits to Dr. Gianola's lab.

D. SUPPLIES

Funds for supplies totaling **$2,809**. (Yr. one- $875.) (Yr. two – $852.) (Yr. three - $513.) (Yr. four - $414.) (Yr. five - $155.). Requested for purchase of storage drives, paper, toner, thumb-drives, paper, toner, and miscellaneous office supplies such as hanging folders, envelopes, staplers, etc.

E. OTHER EXPENSES

Tuition and fees:

Funds in the amount of **$7,000.** are requested for didactic training at UA, and for registration at short courses. Yr. one - $1,000.; Yrs.four through five - $1,500. each.

High-performance computing support

Funds are requested in the amount of **$25,000.** ($5,000 per year), for utilizing the UA High Performance Computing/High Throughput Computing center (HPC/HTC). HPC/HTC is a campus resource dedicated to enhancing research computing productivity at UA. It is sponsored by UA Information Technology Services and is available to members of the UA community in need of increased computational capacity. Dr Klimentidis will use the UA HPC/HTC resources to perform parallel computing jobs using R, PLINK, and IMPUTE software in support of his data analyses and to temporarily store large data files, including all datasets downloaded from dbGaP.

E. OTHER EXPENSES.... Continued

Publication costs
Funds are requested in the amount of **$8,000.** ($2,000. per year in years two through five) for costs associated with the publication of abstracts and manuscripts.

Software
We requested a total of **$3,150.00.** We maintain an extensive library of software including "standard" applications such as SAS, SPSS, and SPlus; commercial compilers like Intel and Portland Group for programming languages such as C, C++. The cost for **purchasing** or site licensing these software products is shared among many projects and only a small portion will be charged to this grant. Specifically, we budgeted Yr 1 – through Yr. 3 at $750. Per year; Yr 4 - $500.; and Yr. 5 - $400. This is a small fraction of our respective Departments' yearly software and manual expense.

Computer for PI
In the course of the project, PC's will break and become obsolete, printers will wear out requiring replacement, and the workstations will require maintenance. **$3,000 in year one** for a computer and IT support for the PI.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Klimentidis, Yann Charles	Instructor
eRA COMMONS USER NAME (credential, e.g., agency login) YANNKLIMENTIDIS	

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
Texas A&M University, College Station, TX	B.A.	05/98	Biology
University of New Mexico, Albuquerque, NM	M.S.	05/02	Anthropology
University of New Mexico, Albuquerque, NM	Ph.D.	08/08	Anthropology
University of Alabama at Birmingham	Postdoctoral	12/12	Statistical Genetics

A. Personal Statement

I am writing this mentored career development award to facilitate my goal of becoming an independent research scientist in the fields of statistical and human disease genetics. Most of my training has been in the areas of anthropology, population genetics, and evolutionary genetics. I am making a significant career transition from these fields to statistical and disease genetics, with more direct applications to human health, and a greater focus on cutting-edge statistical and computational methodologies. In recent years I have begun to work and publish in the areas of genetics and population differences in type-2 diabetes and obesity. Most recently, I have collaborated on projects that utilize statistical learning methods for whole-genome prediction of a model polygenic trait – human height. This K award will allow me to obtain further training in quantitative and statistical genetics, cutting-edge statistical-learning methods, categorical and case-control data analysis, as well as in the genetics and biology of type-2 diabetes etiology. The field of human genetics is currently very exciting given the surge of genetic data that is being generated, and its potential use for individualizing and improving health. I plan to pursue a career in which I develop and apply tools to answer questions about how genetic variation is translated into phenotypic variation, and how that can be used to predict individualized disease susceptibility, with a focus on traits such as type-2 diabetes that appear to be variable across populations.

B. Positions and Honors

Positions and Employment

Aug. 1998 – May 2002	Research Technician - Pediatrics and Molecular and Cellular Biology Baylor College of Medicine, Houston, TX
Sep. 2000 – Dec. 2002	Research Technician - Department of Biochemistry and Molecular Biology; University of New Mexico
Jan. 2003 – Aug. 2003	Research Assistant - Tsimane Life History and Demography, Dr. Hillard Kaplan, Professor; University of New Mexico
Aug. 2003 – Dec. 2003	Course Instructor - French 102; University of New Mexico
Jan. 2003 – May 2008	Editorial Assistant - *Human Nature;* University of New Mexico
Jun. 2005 – Dec. 2008	Course Instructor - Introduction to Human Evolutionary Ecology (and laboratory section for this course), Introduction to Biological Anthropology; University of New Mexico
Jan. 2009 – Jan 2012	Postdoctoral Fellow - Section on Statistical Genetics, University of Alabama at Birmingham
Aug. 2012 – current	Assistant Professor – Department of Epidemiology, University of Arizona

Honors

2012	Second Place, Poster presentation, Alabama Public Health Association
2012	First Place, Poster presentation (Faculty category), UAB School of Public Health Research Day
2010	Second Place, Postdoctoral Presentation, UAB School of Public Health Research Day
2010	Faculty of 1000 library of the top 2% of published articles in biology and medicine: **Yann C. Klimentidis**, T. Mark Beasley, ... & David B. Allison (2010) Canaries in the Coal Mine: A Cross-Species Analysis of the Plurality of Obesity Epidemics. *Proceedings of the Royal Society, B.* 278(1712):1626-32

Professional Societies

2001 - 2003	Human Behavior and Evolution Society
2006 -	American Association of Physical Anthropologists
2009 -	American Society of Human Genetics
2009 -	The Obesity Society

C. Selected Peer-reviewed Publications

Most relevant to the current application

1. Robert Makowsky, Nicholas Pajewski, **Yann C. Klimentidis**, Ana I. Vasquez, Christine Duarte, David B. Allison, Gustavo de los Campos (2011) Beyond missing heritability: Prediction of complex traits. *PLoS Genetics 7(4): e1002051. PMCID: PMC3084207*

2. **Yann C. Klimentidis**, Marshall Abrams, Jelai Wang, Jose R. Fernandez, David B. Allison (2011) Natural selection at genomic regions associated with obesity and type-2 diabetes: East Asians and sub-Saharan Africans exhibit high levels of differentiation at type-2 diabetes regions. *Human Genetics.* 129: 407-418. PMC Journal - In Process.

3. **Yann C. Klimentidis**, Jasmin Divers, Krista Casazza, David B. Allison, Jose R. Fernandez (2010) Ancestry informative marker between THADA and BCL11A is associated with insulin-related traits in a racially diverse sample of children. *Human Genomics.* Jan 5(2):79-89. PMC Journal - In Process.

4. **Yann C. Klimentidis**, Guo-Bo Chen, Mardya Lopez-Alarcon, Jacqueline Harris, Christine Duarte, Jose Fernandez. Testing the association of GWAS-identified variants with obesity-related traits in a multi-ethnic sample of children. *Archives of Medical Research.* In press.

5. **Yann C. Klimentidis**, Akilah Dulin-Keita, Krista Casazza, Amanda Willig, David B. Allison, Jose R. Fernandez (2010) Genetic admixture, social-behavioral factors, and body composition are associated with blood pressure differently by racial-ethnic group among children. *Journal of Human Hypertension.* In press.

6. **Yann C. Klimentidis**, Miller G, Shriver MD (2009) The relationship between European genetic admixture and body composition among Hispanics and Native Americans. *American Journal of Human Biology*, 21(3):377-382.

Additional publications (in chronological order)

1. **Yann C Klimentidis**, Brahim Aissani, Mark D Shriver, David B Allison and Sadeep Shrestha (2011) Natural selection among Eurasians at genomic regions associated with HIV-1 control. *BMC Evolutionary Biology.* In press.

2. **Yann C. Klimentidis**, T. Mark Beasley, Hui-Yi Lin, Giulianna Murati, Gregory E. Glass, Marcus Guyton, Wendy Newton, Matthew Jorgensen, Steven B. Heymsfield, Joseph Kemnitz, Lynn Fairbanks, & David B.

Allison (2010) Canaries in the Coal Mine: A Cross-Species Analysis of the Plurality of Obesity Epidemics. *Proceedings of the Royal Society, B.* 278(1712):1626-32. PMCID: PMC3081766

3. Maria De Luca, **Yann C. Klimentidis**, Krista Casazza, Michelle Moses Chambers, Ruth Cho, Susan T. Harbison, Patricia Jumbo-Lucioni, Shaoyan Zhang, Jeff Leips, and Jose R. Fernandez. (2010) A conserved role for syndecan family members in the regulation of whole-body energy metabolism. *PLoS One 5(6): e11286.* PMCID: PMC2890571

4. Mauricio A Martins, Nancy A Wilson, Jason S Reed, Chanook D Ahn, **Yann C. Klimentidis**, David B Allison, and David I Watkins (2010) T-cell correlates of vaccine efficacy after a heterologous SIV challenge. *Journal of Virology*, 84(9):4352-65. PMCID: PMC2863752

5. Thomas C. Friedrich, Shari M. Piaskowski, Enrique J. Léon, Jessica R. Furlott, Nicholas J. Maness, Kimberly L. Weisgrau, Caitlin E. Mac Nair, Andrea M. Weiler, John T. Loffredo, Matthew R. Reynolds, K Y. Williams, **Yann C. Klimentidis**, Nancy A. Wilson, David B. Allison, and Eva G. Rakasz. (2010) High viremia is associated with high levels of *in vivo* MHC-I downregulation in rhesus macaques infected with SIVmac239. *Journal of Virology*, 84(10):5443-7. PMCID: PMC2863841

6. Laura E. Valentine, John T. Loffredo, Alex T. Bean, Enrique J. León, Caitlin E. MacNair, Dominic R. Beal, Shari M. Piaskowski, **Yann C. Klimentidis**, Simon M. Lank, Roger W. Wiseman, Jason T. Weinfurter, Gemma E. May, Eva G. Rakasz, Nancy A. Wilson, Thomas C. Friedrich, David H. O'Connor, David B. Allison, and David I. Watkins (2009) Infection with "escaped" virus variants impairs control of SIVmac239 replication in Mamu-B*08+ macaques. *Journal of Virology*, 83(22) 11514-27. PMCID: PMC2772717

7. **Yann C. Klimentidis**, Miller G, Shriver MD (2009) Genetic admixture, self-reported ethnicity, self-estimated admixture, and skin pigmentation among Hispanics and Native Americans. *American Journal of Physical Anthropology*, 138(4): 375-83.

8. **Yann C. Klimentidis**, Shriver MD (2009) Estimating genetic admixture proportions from faces. *PLoS One*, 4(2): e4460.

9. Hadsell DL, Bonnette S, George J, Torres D, **Yann Klimentidis**, Gao S, Haney PM, Summy-Long J, Soloff MS, Parlow AF, Sirito M, Sawadogo M (2003) Diminished milk synthesis in upstream stimulatory factor 2 null mice is associated with decreased circulating oxytocin and decreased mammary gland expression of eukaryotic initiation factors 4E and 4G. *Molecular Endocrinology* 17(11):2251-67.

10. Hadsell DL, Alexeenko T, **Yann Klimentidis** , Torres D, Lee AV (2001) Inability of overexpressed des(1-3) human insulin-like growth factor I (IGF-I) to inhibit forced mammary gland involution is associated with decreased expression of IGF signaling molecules. *Endocrinology* 142: 1479-88.

D. Research Support

Completed Research Support

2009 & 2010 NIH T32 HL072757 (PI: Suzanne Oparil)
2011 NIH T32 HL105346 (PI: Victor Thannickal)

Ongoing Research Support

N/A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David B. Allison	Distinguished Professor; Quetelet Endowed Professor of Public Health; Associate Dean for Science; Director, Office of Energetics; Director, Nutrition Obesity Research Center
eRA COMMONS USER NAME Dallison1	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MMYY	FIELD OF STUDY
Vassar College, Poughkeepsie, New York	B.A.	May 1985	Psychology
Hofstra University, Hempstead, New York	M.A	Aug 1987	Clinical Psychology
Hofstra University, Hempstead, New York	Ph.D.	Jul 1990	Clinical Psychology
Johns Hopkins University School of Medicine	Post-doc	Aug 1991	Behavioral Pediatrics

A. Personal Statement

I am unequivocally committed to the career development and pathway to independence of Dr. Klimentidis. My research interests include obesity, quantitative genetics, clinical trials, and statistical and research methodology. In recent years, my work has involved several major areas: (a) The relations among body weight, body composition, caloric intake, and changes thereof with longevity in animal models and humans; (b) The genetic and environmental influences on obesity and related traits; (c) Statistical methods for genetic and epidemiologic studies; (d) Design, implementation, and analysis of randomized controlled trials for weight loss; and (e) Research integrity. I have also hosted many meetings and conferences and served as principal investigator or co-principal investigator for over a half dozen successful NIH R13-funded conferences.

In terms of mentoring, I have mentored students (from high-school through masters level) starting in 1992. In addition, I have mentored at least 7 predoctoral trainees, 22 postdoctoral trainees, and many young faculty members. I have initiated many training programs: 2003 T32HL072757 UAB Statistical Genetics Post-Doctoral Training Program; 2004 T32DK062710 UAB Obesity Training program for postdoctoral fellows; 2005 T32HL079888 UAB Biostatistics Pre-doctoral Training Program; 2006 the T32NS054584 UAB Pre and Post Doctoral Training Program in Biostatistics (which I currently co-direct); 2007 UAB Doctoral Training Program in Obesity and Nutrition Research; and just awarded for 2011 T32HL105349 UAB Predoctoral Training Program in Obesity-related Research. Presently, I mentor 3 predoc trainees, 6 postdoc trainees, and several young faculty members. I also won a presidential award for my mentorship as described below, and have been nationally recognized for my mentoring (see below). I will continue to ensure that Dr. Klimentidis has access to every resource at my disposal in order to help him to achieve his career goals.

B. Positions and Selected Honors.

Post-Doctoral Fellowship - New York Obesity Research Center, St. Luke's/Roosevelt Hospital, Columbia University College of Physicians & Surgeons - 1991-1994.

September 1994 to April 1999 -- Assistant Professor of Clinical Psychology (in Psychiatry), Columbia University College of Physicians and Surgeons.

April 1999 to March 2001 -- Associate Professor of Medical Psychology (in Psychiatry), Columbia University College of Physicians and Surgeons.

June 1994 to March 2001 -- The NY Obesity Research Center, Saint Luke's/Roosevelt Hospital Center. Position: Associate Research Scientist.

March 2001 to Present -- University of Alabama at Birmingham. Professor (with Tenure) of Biostatistics; Head, Section on Statistical Genetics & Director, Nutrition Obesity Research Center, Dept of Nutrition Sciences

Appointed Distinguished Professor by the Board of Trustees of The University of Alabama at Birmingham, 2011

Appointed Quetelet Endowed Professor of Public Health by the Board of Trustees of The University of Alabama at Birmingham, 2012

Honors & Awards (Selected from ~ 30)

Appointed Quetelet Endowed Professor of Public Health by the Board of Trustees of The University of Alabama at Birmingham, 2012

Appointed Distinguished Professor by the Board of Trustees of The University of Alabama at Birmingham, 2011. Dr. Allison was on the 21st person in the history of UAB to be awarded this honor.

Selected as the 2011 Distinguished Faculty Lecturer by the University of Alabama at Birmingham. The award recognizes faculty who have advanced the frontiers of science or otherwise made a significant contribution to the health of people. This has been called the highest award a faculty member at UAB can receive.

Elected as fellow of the American Association for the Advancement of Science (AAAS), 2009.

Received the 2009 TOPS Research Achievement Award from the Obesity Society. Recognizes an individual for singular achievement or contribution to obesity research.

Recipient of the 2009 American Society of Nutrition's Centrum Center for Nutrition Science Award. Given in recognition of recent investigative contributions of significance to the basic understanding of human nutrition.

Recipient of the 2006 Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring (PAESMEM). Administered by the National Science Foundation, the award was accompanied by a Presidential certificate and a personal visit with President Bush in the Oval Office.

Recipient of 2002 Andre Mayer Award from the International Association for the Study of Obesity (IASO). International award given once every four years for outstanding achievement by an investigator under age 40.

Recipient of the 2002 Lilly Scientific Achievement Award from the North American Association for the Study of Obesity (NAASO). Annual award signifying outstanding achievement by an investigator who is within 15 years of having received their doctoral degree.

Recipient of the 1999 Award for Outstanding Achievement in Health Psychology from the Health Psychology Division of the American Psychological Association.

Recipient of the 1996 Neal Miller Early Career Award from the Academy of Behavioral Medicine.

C. Selected publications (selected from >400)

1. Allison DB, Heshka S, et al. (1993). Counting calories? - Caveat emptor. JAMA 270, 1454-56.
2. Allison DB. (1997). Transmission disequilibrium tests for quantitative traits. Am. J. Hum. Genet. 60, 676-690.
3. Comuzzie AG, Allison DB. (1998). The search for human obesity genes. Science 280, 1374-1377. PMCID PMC1712500.
4. Allison DB, Fontaine KR, Manson J, Stevens J, Van Itallie TB. (1999). Annual deaths attributable to obesity in the United States. JAMA 282, 1530-1538. http://jama.ama-assn.org/cgi/reprint/282/16/1530
5. Allen TM, ... Allison DB, ...& Watkins DI. (2000). Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viremia. Nature, 407, 386-390.
6. Allison, D. B., et al. (2000). Testing The Robustness Of The New Haseman-Elston Quantitative Trait Loci (QTL) Mapping Procedure. Am J Hum Genet, 67, 249-252. PMCID PMC1287085.
7. Fontaine, K. R., Redden, D. T., Wang, C., Westfall, A. O., & Allison, D. B. (2003). Years of Life Lost Due to Obesity. Journal of the American Medical Association, 289, 187-193.http://jama.ama-assn.org/cgi/reprint/289/2/187
8. Tschöp, M., ...Allison, D. B.... & Heiman ML. (2004). Does gut hormone PYY3-36 decrease food intake in rodents? Nature, 430, 1 p following 165; discussion 2 p following 165. http://www.nature.com/nature/journal/v430/n6996/pdf/nature02665.pdf
9. Mehta, T., Tanik, M. & Allison, D. B. (2004). Toward Sound Epistemological Foundations of Statistical Methods for High Dimensional Biology. Nature Genetics, 36, 943-947. http://www.nature.com/ng/journal/v36/n9/pdf/ng1422.pdf
10. Olshansky, S. J., ... & Allison, D. B., & Ludwig, D. S. (2005). A Life Expectancy Decline in the United States in the 21st Century? New England Journal of Medicine, 352(11), 1138-45. http://content.nejm.org/cgi/reprint/352/11/1138.pdf
11. Redden, D. T., Divers, J., Vaughan, L. K., Tiwari, H. K., Beasley, T. M., Fernandez, J. R., Kimberly, R. P., Feng, R., Padilla, M., Liu, N., Miller, M. B., Allison, D. B. (2006). Regional admixture mapping and structured association testing: conceptual unification and an extensible general linear model. PloS Genetics, Aug 25;2(8):e137. PMCID PMC1557785.
12. Allison, D. B., et al. (2006). Microarray Data Analysis: From Dis-array to Consolidation & Consensus. Nature Reviews Genetics, 7, 55-65. PMCID PMC2409977

13. Gadbury GL, ... & Allison DB. (2008) Evaluating Statistical Methods Using Plasmode Data Sets in the Age of Massive Public Databases: An Illustration Using False Discovery Rates. PLoS Genet 4(6): PMCID: PMC2409977.
14. Colman, R. J., ... Allison, D. B., ...& Weindruch, R. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. Science, 325, 201-204. PMCID: PMC2812811.
15. de los Campos, G., Gianola, D., & Allison, D. B. (2010). Predicting genetic predisposition in humans: the promise of whole-genome markers. *Nature Reviews Genetics* 11, 880-886. doi:10.1038/nrg2898

D. Research Support.

In the past three years, Dr. Allison has worked on projects in four primary areas: (a) The relations among body weight, body composition, caloric intake, and changes thereof with longevity in animal models and humans; (b) The genetic and environmental influences on obesity and related traits; (c) Statistical methods for genetic studies; and (d) Clinical trials of weight loss methods. *Some* of the grants supporting these projects are summarized below.

(a) Relations among body weight, body composition, caloric intake, and changes thereof with longevity.

NIH P30DK056336 (Allison) 06/01/00 - 06/30/12
UAB CLINICAL NUTRITION RESEARCH UNIT
This research center supports all aspects of research on nutrition with an emphasis on obesity.

NIH R01 R01AG033682 (Allison) 02/15/10 – 02/14/15
Body Composition, Energetics, and Longevity.
The goal of this study is to examine the effects of repeated weight loss and regain on longevity in mice.

NIH P01 AG11915 (Weindruch) 07/01/99 – 06/30/10
Dietary Restriction and Aging in Rhesus Monkeys
The goal of this study is to examine the effects of caloric restriction on longevity in rhesus monkeys.

NIH R01DK076771 (Allison) 08/15/07 - 06/30/10
Obesity & Mortality
To elucidate the relations between obesity indices and mortality indices in the US population.

(b) Genetic & environmental influences on obesity and related traits.

NIH R01DK52431 (Leibel/Allison/Chung – multiple PI) 8/01/03 – 11/30/13
Molecular Genetic Analysis of Human Obesity
To evaluate the association of obesity candidate genes with obesity phenotypes.

NIH R01DK074842-01A1 (Boyer) 09/13/07-08/31/12
Genetics of Obesity in Yup'ik Eskimos
Conduct linkage genome scan & exhaustive gene-based candidate gene association study related to obesity.

(c) Statistical methods for genetic studies.

NIH R01GM077490 (Allison) 9/01/07 - 08/31/11
Genome-wide Structured Association Testing & Regional Admixture Mapping
Developing, evaluating, and applying enhanced methods in the context of genome-wide association studies.

NSF 0650606 (Allison) 09/01/08 – 08/31/10
Short Course on Statistical Genetics and Statistical Genomics
This course provides introductory/advanced statistical methodologies in genetics to investigators nationwide.

(d) Clinical trials.

NIH R01DK078826 (Allison) 3/01/09-2/28/12
Design Issues in Obesity RCTs: Building an Evidence Base
To use meta-analytic and raw data pooling methods to evaluate merits of various design feature in obesity RCTs.

Jason Pharmaceuticals (Allison) 09/14/10 – 09/13/12
Medifast, Inc.
Randomized Clinical Trial of the Medifast 5&1 Plan
To conduct a randomized controlled trial of a weight loss program.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Chen, Zhao	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) ZHAOCHEN	

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
Beijing Teaching University, Beijing, China	BS	1983	Biology
Graduate School, Academic Sinica, Beijing	MS	1985	Biological Anthropology
University of Arizona, Tucson, AZ	MPH	1995	Public Health Nutrition
University of Arizona, Tucson, AZ	PhD	1996	Physical Anthropology
University of Arizona, Tucson, AZ	Postdoc	1997	Epidemiology

A. Personal Statement

I have had over 17 years experience in biomedical research and have been PI on NIH-funded studies including genetic research. I have mentored many graduate students, postdoctoral researchers and junior facutly. My research expertise, interests and experience are closely related to Yann Klimentidis' project.

B. Positions and Honors.

Positions and Employment

1985 - 1988 Research Associate, Section of Physical Anthropology, IVPP, Academic Sinica, Beijing China
1988 - 1996 Graduate Teaching and Research Assistant/Associate, Department of Anthropology, University of Arizona, Tucson
1996 - 1997 Research Associate, Section of Epidemiology, Arizona Prevention Center, College of Medicine, University of Arizona, Tucson
1996 – 2000 Member, Section of Osteoporosis, Arizona Arthritis Center, College of Medicine, University of Arizona, Tucson
1997 - 1999 Research Assistant Professor, Section of Epidemiology, Arizona Prevention Center, College of Medicine, University of Arizona, Tucson, AZ
1998 - present Member, Cancer Prevention and Control, Arizona Cancer Center, University of Arizona, Tucson, AZ
2000 - 2004 Assistant Professor of Public Health, Epidemiology and Biostatistics Division, the Mel and Enid Zuckerman Arizona College of Public Health, University of Arizona, Tucson, AZ
2002 - present Core faculty, Arizona Geriatric Education Center, Arizona Center on Aging, University of Arizona, Tucson, AZ
2003- 2005 Director of Epidemiology Concentration, Mater of Public Health Program, the Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ
2006 – 2007 Chair, Graduate Program of Public Health, the Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ
2004- 2009 Associate Professor of Public Health, Epidemiology and Biostatistics Division, the Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ
2006- Now Affiliate Faculty, Center for Physical Activity and Nutrition, University of Arizona 2008- Now Associate Member, Southwest Environmental Health Sciences Center, College of Pharmacy, University of Arizona
2008- Now Director, Division of Epidemiology and Biostatistics. Mel and Enid Zuckerman College of Public Health, University of Arizona
2009- Now Professor of Public Health, Epidemiology and Biostatistics Division, the Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

Honors

1990 Graduate Academic Award, University of Arizona
1991 Graduate Academic Award, University of Arizona
1992 Graduate Academic Award, University of Arizona
1997 Career Development Award, National Institution of Health

C. Selected peer-reviewed publications (in chronological order).

1. **Chen Z**, Maricic M, Lund P, Tesser J, Gluck O. How the new Hologic hip normal reference values affect the densitometric diagnosis of osteoporosis. *Osteoporosis International* 1998; 8(5):423-427. [PMID:9850349]
2. **Chen Z**, Maricic M, Nguyen P, Ahmann FR, Bruhn R, Dalkin BL. Low Bone density and high percentage of body fat among men who were treated with androgen deprivation therapy for prostate carcinoma. *Cancer* 2002;95:2136-44. [PMID:12412167]
3. **Chen Z**, Pettinger MB, Ritenbaugh C, LaCroix AZ, Robbins J, Caan BJ, Barad DH, Hakim IA. Habitual Tea Consumption and Risk of Osteoporosis -- A Prospective Study in the Women's Health Initiative Observational Cohort. *American Journal of Epidemiology* 2003, 158:772-81. [PMID:14561667]
4. **Chen Z**, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ, Lewis CE, Kipersztok S, Borne MC, Jackson RD. Validity of Self-Report for Fractures among a Postmenopausal Multiethnic Cohort. *Menopause* 2004, 11(3): 264-274. [PMID:15167305]
5. **Chen Z**, Stini WA, Marshall JR, Martinez ME, Guillén-Rodríguez JM, Roe D, Alberts DS. Wheat Bran Fiber Supplementation and Bone Loss among Participants in a Colon Cancer Prevention Trial. *Nutrition* 2004, 20:747-751. [PMID:15325680]
6. **Chen Z**, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS. Fracture Risk among Breast Cancer Survivors-Results from the Women's Health Initiative. *Archive of Internal Medicine* 2005; 165:552-228. [PMID:15767532]
7. **Chen Z**, Maricic M, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, Gass M, Leboff MS, Bassford TL. Osteoporosis and Rate of Bone Loss among Postmenopausal Survivors of Breast Cancer --- Results from a Subgroup in the Women's Health Initiative Observational Study. *Cancer* 2005;104:1520-30. [PMID:16110508]
8. **Chen Z**, Bassford T, Green SB, Cauley JA, Jackson RD, LaCroix AZ, Leboff M, Stefanick ML, Margolis KL. Postmenopausal Hormone Therapy and Body Composition --- Results from the Women's Health Initiative E & P Clinical Trial. *The American Journal of Clinical Nutrition* 2005; 82:651-6. [PMID:16155280]
9. **Chen Z**, ZiMian Wang, Tim Lohman, Steven B. Heymsfield, Eric Outwater, Jennifer S. Nicholas, Tamsen Bassford, Andrea LaCroix, Mark Punyanitya, Guanglin Wu, Duane Sherrill, Scott Going, DXA is a reliable tool for assessing skeletal muscle mass in older women. *J. Nutr.* 2007; 137 2775-2780 [PMID:18029498]
10. **Chen Z,** Beck TJ, Cauley JA, Lewis CE, LaCroix A, Bassford T, Wu G, Sherrill D, Going S. Hormone Therapy Improves Femur Geometry Among Ethnically Diverse Postmenopausal Participants in the Women's Health Initiative Hormone Intervention Trials. *Journal of Bone and Mineral Research,* 2008 23:1935-1945. [PMID:18665788]
11. **Chen Z**, Thomson CA, Aickin M, Nicholas JS, Van Wyck D, Lewis CE, Jane A. Cauley JA, Bassford T. The Relationship between Incidence of Fractures and Anemia in Older Multiethnic Women. *Journal of the American Geriatrics Society* 2010 Dec; 58(12):2337-44. [PMID: 21143442]
12. **Chen Z**, Qi L, Beck T, Robbins J, Wu G, Lewis C, Cauley J, Wright N, Seldin M. Stronger Bone Correlates with African Admixture in African American Women. *Journal of Bone and Mineral Research* 2011, 26(9):2307-3316.
13. Gomez-Rubio P, Roberge J, Arendell L, Harris RB, O'Rourke MK, **Chen Z**, Cantu-Soto E, Meza-Montenegro MM, Billheimer D, Lu Z, Klimecki WT. Association between body mass index and arsenic methylation efficiency in adult women from southwest U.S. and northwest Mexico. *Toxicol Appl Pharmacol.* 2011 Apr 15; 252(2):176-82. [PMID: 21320519]
14. Reiner AP, Lettre G, Nalls MA, Ganesh SK, Mathias R, Austin MA, Dean E, Arepalli S, Britton A, **Chen Z**, Couper D, Curb JD, Eaton CB, Fornage M, Grant SFA, Harris TB, Hernandez D, Kamatini N, Keating BJ, Kubo M, LaCroix A, Lange LA, Liu S, Lohman K, Meng Y, Mohler ER, Musani S, Nakamura Y, O'Donnell CJ, Okada Y, Palmer CD, Papanicolaou G, Patel K, Singleton AB, Takahashi A, Tang H, Taylor HA, Taylor K, Thomson C, Yanek LR, Yang L, Ziv E, Zonderman AB, Folsom AR, Evans MK, Liu Y, Becker DM, Snively BM, Wilson JG. Genome-wide association study of white blood cell count in 16,388 African Americans: the Continental Origins and Genetic Epidemiology Network. PLoS Genet 2011. 7(6): e1002108. doi:10.1371/journal.pgen.1002108.
15. Chen CTL, Ferna´ndez-Rhode L, Brzyski RG, Carlson CS, **Chen Z**, Heiss G, North KE, Woods NF, Rajkovic A, Kooperberg C and Franceschini N. Replication of loci influencing ages at menarche and menopause in Hispanic women: the Women's Health Initiative SHARe Study. Human Molecular Genetics, 2011 1–14 doi:10.1093/hmg/ddr570 (HMG Advance Access published December 13, 2011).

D. Research Support.

Ongoing Research

2P30ES006694-16A1 04/30/2012--03/31/2017 15%
NIEHS/NIH
Southwest Environmental Health Sciences Center $1,050,000($1,590,750)
(SWEHSC) $5,250,000($7,953,750)
The mission of SWEHSC is to understand the
Mechanisms behind the modulation of human disease
risk by environmental exposures unique to the Southwest
Role: Co-investigator

1R21AR060811-01 (Z CHEN & Samy Missoum) 09/01/2011 – 08/31/2013 5%
A New Hip Fracture Risk Prediction Tool $165,623 (First Year TOTAL)
Based on Common Predictors and Hip
Geometry
To develop a new prediction model for hip fractures in older women using hip geometry and other conventional predictors as innovative modeling approaches
Role: Co-PI

R01 AG027373-01A1 (Z CHEN) 09/15/07 –06/30/12
NIH/NIA
Biomarkers and Genetic Factors Related
to Sarcopenia in Older Women
To investigate genetic determinants and biological indicators for skeletal muscle loss in older Hispanic and non-Hispanic white women.
Role: PI

Completed Research Support

Cancer Prevention Small Grant Chen (PI) 2/2000-6/2002
Arizona Cancer Center
Feasibility Study
To development effective approaches for recruiting Hispanic and Non-Hispanic white women and conducting bone mineral density and mammographic density analysis among this population.
Role: PI

1 K01 AR 02060-01 Chen (PI) 10/1/97 - 6/30/2003
NIH
Ethnicity, Body Composition, Bone Density and Breast Cancer
1) Assess body composition and bone mineral density among newly diagnosed postmenopausal breast cancer patients who are either Hispanic or Non-Hispanic white; 2) compare bone mineral density and body composition between breast cancer patients and non-cancer controls.
Role: PI

BCTR 2000 538 Chen (PI) 5/2001-10/2004
The Susan G. Komen Breast Cancer Foundation
The Association between Mammographic Density and Bone Mineral Density among White and Hispanic Women.
To study the association of risk of breast cancer and risk of osteoporosis in two different ethnic groups and to identify factors that may alter risk of both breast cancer and osteoporosis.
Role: PI

NIH-2R01-AR39559-04A3 Bassford (PI) 10/1994 - 9/2005
NIH
Women's Health Initiative: Nationwide prevention trial for women addressing heart disease, cancer, and osteoporosis.
Role: Co-investigator

DAMD17-02-1-02721 Arendell (PI) 7/2002- 6/2004
Department of Defense

Relationship between Mammographic Density and IGF levels among Hispanic and Non-Hispanic White Women.

To investigate the association of hormonal factors and mammographic density among different ethnic groups of women.
Role: Mentor

Eli Lilly and Company (Z. CHEN) 12/15/05 —10/30/07
Bone Density and Breast Cancer Risk
To study bone density and Gail score as predictors for breast cancer in postmenopausal women.
Role: PI

The Susan G. Komen Breast Cancer Foundation Thomson (PI) 7/2004 – 6/2007
Green Tea Intervention for Weight Gain Prevention among Women with Breast Cancer.
To test whether a green tea intervention during and after chemotherapy for breast cancer prevent weight gain, improve quality of life, and regulate hormone factors, such as IGF-1 and IGFBP-3.
Role: Co-investigator

ES06694 SWEHSC pilot program (Z CHEN) 01/25/2008-01/24/2009
NIH
Arsenic Exposure and Women's Health
To explore the impact of arsenic exposure on multiple health outcomes, including osteoporosis, sarcopenia, and breast cancer, among older Arizona women.
Role: PI

1R01 AR049411-01 (Z. CHEN) 07/01/03 - 06/30/09
NIH/NIAMS
Longitudinal Changes in Hip Geometry and Skeletal Muscle.
To study effects of interventions and aging on skeletal macrostructure and muscle mass among multiethnic postmenopausal women in the U.S.
Role: PI

Supplement to 1R01 AR049411-01 (Z CHEN) 07/01/06 – 6/30/10
NIH/NIAMS
Longitudinal Changes in Hip Geometry and
Skeletal Muscle: Research Supplements to
Promote Diversity in Health Related Research.
PI & Mentor
To provide research training opportunity for a minority doctoral candidate to engage in arthritis research among multiethnic groups of older people.

1 R01 AG029133-01 (Z CHEN) 05/15/07 – 4/29/11
Anemia and Its Relationship with Sarcopenia,
Physical Function, and Mortality
PI
To investigate health impacts of anemia and to examine best hemoglobin cutoff points for defining anemia in different age and ethnic groups of older women.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
W. Timothy Garvey, MD	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) GARVEYT	

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
Washington University, St. Louis, MO	B.A.	1974	Biology
St. Louis University, St. Louis MO	M.D.	1978	Medicine
Washington University/Barnes Hospital	Residency	1981	Internal Medicine
U of Colorado and U of California San Diego	Fellowship	1984	Endocrinology & Metab

A. Personal Statement

Dr. Garvey is an internationally recognized expert in insulin resistance, adipocyte and muscle cell biology, obesity, Metabolic Syndrome, and Type 2 Diabetes, bringing basic technologies to the study of humans. He is well positioned to be a co-mentor for Dr. Klimentidis' career development award, as he has a body of knowledge and experience in the areas of Type-2 Diabetes physiology and genetics.

B. Positions and Honors

Positions and Employment

1984 - 1989 Instructor & Assistant Professor, Department of Medicine, University of California, San Diego
1989 - 1993 Associate Professor of Medicine, Physiology and Biophysics, Indiana University
1993 - 1994 Professor of Medicine, Physiology and Biophysics, Indiana University School of Medicine, and Chief, Section of Endocrinology, Indianapolis VAMC, Indianapolis, IN
1994 - 2003 Director, Division of Endocrinology, Diabetes, and Medical Genetics, Medical University of South Carolina, and Staff Physician at Charleston VAMC
2003 -present Chairman and Professor, Department of Nutrition Sciences, University of Alabama at Birmingham, and Staff Physician/GRECC investigator at Birmingham VAMC
2008 -present Director, UAB Diabetes Research and Training Center (DRTC)

Other Experience and Professional Memberships

Member: ADA; Endocrine Society; NAASO, FASEB, ASCI; AAP. Study Sections: ADA 1992-1995 and 2005-2008; JDRF 1994-1997; American Federation for Aging Research 2004-present; VA Merit Review Endocrine Section 1996-2000; NIH Metabolism Study Section 1998-2002; member and chairman of multiple NIH ad hoc; Chairman, DSMB for NHLBI Vascular SCCOR 2005-2010; Chair ADA Sci & Med Mtgs Oversight Com 2006-8.

Honors and Awards

Alpha Omega Alpha Honor Medical Society, 1977; Alpha Sigma Nu Jesuit Honor Society, 1978; Wendell Griffith Prize in Biochemistry, St. Louis U., 1978; Pfizer Postdoctoral Fellowship Award, 1984; Pfizer Scholars Award, 1987; 1988; American Society for Clinical Investigation, 1994; Pfizer Visiting Professor, 1999-2000, Association of American Physicians, 2002. Charles E. Butterworth, Jr.,MD, Professorship at UAB, 2006. UAB Excellence in Mentoring Award, 2011.

C. Selected Peer-reviewed Publications **Selected from total > 150**

Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in Type II diabetes mellitus. ***Diabetes*** 34:222-234, 1985.

Garvey WT, Olefsky JM, Matthaei S, Marshall S. Glucose and insulin co-regulate the glucose transport system in primary cultured adipocytes: A new mechanism of insulin resistance. ***J Biol Chem*** 262:189-197, 1987.

Garvey WT, Hueckstead TP, Birnbaum MJ. Suppression of an insulin-responsive glucose transporter gene in diabetes mellitus. ***Science*** 125-2341-2349, 1989.

Garvey WT, Maianu L, Hueckstead TP, Birnbaum MJ, Molina JM, Ciaraldi TP. Pretranslational suppression of a glucose transporter protein causes cellular insulin resistance in non-insulin-dependent diabetes mellitus and obesity. ***J Clin Invest*** 87:1072-1081, 1991. PMCID:PMC329903

Garvey WT, Maianu L, Hancock JA, Golichowski AM, Baron A. Gene expression of GLUT 4 glucose transporters in skeletal muscle from insulin-resistant patients with obesity, impaired glucose tolerance, gestational diabetes, and non-insulin-dependent diabetes mellitus. ***Diabetes*** 41:465-475, 1992.

Garvey WT, Maianu L, Zhu J-H, Brechtel-Hook G, Wallace P, Baron AD. Evidence for defects in the trafficking and translocation of GLUT4 glucose transporters in skeletal muscle as a cause of human insulin resistance. ***J Clin Invest*** 101: 2377-86, 1998. PMCID:PMC508827

Argyropoulos G, Brown AM, Willi SM, Zhu J-H, He Y, Reitman M, Gevao SM, Spruill I, **Garvey WT**. Effects of mutations in the human uncoupling protein 3 gene on the respiratory quotient and fax oxidation in severe obesity and type 2 Diabetes. ***J Clin Invest*** 102: 1345-51, 1998. PMCID:PMC508981

Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Pugh K, Jenkins AJ, Klein RL, Liao Y. The Effects of Insulin Resistance and Type 2 Diabetes Mellitus on Lipoprotein Subclass Particle Size and Concentration Determined by Nuclear Magnetic Resonance. ***Diabetes*** 52:453-462, 2003.

Klein RL, McHenry MB, Lok KH, Hunter SJ, Le N-A, Jenkins AJ, Zheng D, Semler A, Page G, Brown WV, Lyons TJ, **Garvey WT**, and the DCCT/EDIC Research Group. Apolipoprotein C-III Protein Concentrations and Gene Polymorphisms in Type 1 Diabetes: Associations with Microvascular Disease Complications in the DCCT/EDIC Cohort. ***J Diabetes Complications*** 19:18-25, 2005. PMID:15642486

McLean DC, Spruill I, Argyropoulos G, Page GP, Shriver MD, **Garvey WT**. Mitochondrial DNA (mtDNA) Haplotypes Reveal Maternal Population Affinities of Sea Island Gullah-speaking African Americans. ***Amer J Phys Anthropol,*** 127:427-438, 2005 PMID:15624208

Fu Y, Luo N, Klein RL, **Garvey WT**. Adiponectin Promotes Adipocyte Differentiation, Insulin Sensitivity, and Lipid Accumulation: Potential Role in Auto-Regulation of Adipocyte Metabolism and Adipose Mass. ***J Lipid Res*** 46:1369-1379, 2005. PMID:15834118

Lara-Castro C, Luo N, Wallace P, Klein RL, **Garvey WT**. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. ***Diabetes*** 55:249-259, 2006. PMID:16380500

Chen M, Aprahamian CJ, Celik A, Georgeson KE, **Garvey WT**, Harmon CM,Yang Y. Molecular characterize-ation of human melanocortin-3 receptor ligand-receptor interaction. ***Biochem*** 45:1128-1137, 2006.

Garvey WT. UCP3 and Human Metabolism. Invited Editorial, ***J Clin Endocrinol Metab*** 91:1226-1228, 2006.

Lyons TJ, Jenkins AJ, Zheng D, Klein RL, Otvos JD, Yu Y, Lackland DT, McGee D, McHenry MB, Lopes-Virella MF, **Garvey WT**, and DCCT/EDIC Research Group. Nuclear magnetic resonance-determined lipoprotein subclass profile in the DCCT/EDIC cohort: associations with carotid intima-medial thickness. ***Diabetic Medicine*** 23:955-966, 2006. PMID:16922701

Fu Y, Luo L, Luo N, **Garvey WT**. Lipid Metabolism Mediated by Adipocyte Lipid Binding Protein (ALBP/aP2) Gene Expression in Human THP-1 Macrophages. ***Atherosclerosis*** 188:102-111, 2006. PMID:16313911

Fu Y, Luo L, Luo N, **Garvey WT**. Proinflammatory cytokine production and insulin sensitivity regulated by overexpression of resistin in 3T3-L1 cells. ***Nutrition and Metabolism*** 3:28, 2006. PMCID:PMC1550232

Munoz J, Lok KH, Gower BA, Fernandez JR, Hunter GR, Lara-Castro C, De Luca M, **Garvey WT**. A polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with reduced insulin secretion in non-diabetic women. ***Diabetes*** 55:3630-3634, 2006. PMID:17130514

Vestri HS, Maianu L, Moellering DR, **Garvey WT**. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, anti-lipolysis. ***Neuropsychopharmacol*** 32:765-2, 2007

Lara-Castro C, Fu Y, Chung BH, **Garvey WT**. Adiponectin and the metabolic syndrome: mechanisms mediating the risk of metabolic and cardiovascular disease. ***Curr Opinion Lipidology*** 18:263-270, 2007 PMID:17495599; PMCID pending

Wu X, Page GP, Wang J, Maianu L, Rhees B, Rosinski J, So V, Willi SM, Osier MV, Hill HS, Allison DB, Martin M, **Garvey WT.** The Effect of Insulin on Expression of Genes and Biochemical Pathways in Human Skeletal Muscle. ***Endocrine*** 31:5-17, 2007 PMID:17709892; PMCID pending

Fu Y, Luo L, Luo N, Zhu X, **Garvey WT**. NR4A Orphan Nuclear Receptors Modulate Insulin Action and the Glucose Transport System: Potential Role in Insulin Resistance. ***J Biol Chem*** 282:31525-31533, 2007. PMID:17785466; PMCID pending

Lara-Castro C, Newcomer BR, Rowell J, Wallace P, Shaughnessy SM, Munoz AJ, Shiflett AM, Rigsby DY, Lawrence JC, Bohning DE, Buchthal S, **Garvey WT**. Effects of short-term very low calorie diet on intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetics. ***Metabolism*** 57:1-8, 2008 PMCID:PMC2271155

Lopes-Virella MF, Carter RE, Gilbert GE, Klein RL, Jaffa M, Jenkins AJ, Lyons TJ, **Garvey WT**, Virella G, and the DCCT/EDIC Study Group. Risk Factors related to Inflammation and Endothelial Dysfunction in the DCCT/EDIC Cohort and their Relationship with Nephropathy and Macrovascular Complications. ***Diabetes Care***, 31:2006-2012, 2008 PMCID:PMC2551645

Lara-Castro C, Doud EC, Tapia PC, Munoz AJ, Fernandez JR, Hunter GR, Gower BA, **Garvey WT**. Adiponectin Multimers and Metabolic Syndrome Traits: Relative Ad Resistance in African-Americans. ***Obesity*** In Press, Epub Sept 25, 2008 PMCID:PMC2721223

Ader M, **Garvey WT**, Phillips LS, Nemeroff CB, Gharabawi G, Mahmoud R, Greenspan A, Berry SA, Musselman DL, Morein J, Zhu Y, Mao L, Bergman RN. Ethnic heterogeneity in glucoregulatory function during treatment with atypical antipsychotics in patients with schizophrenia. ***Journal of Psychiatric Research***, 42:1076-1085, 2008 PMID:18295798; PMCID pending

Jenkins AJ, Rothen M, Klein RL, Moller K, Eldridge L, Zheng D, Durazo-Arvizu R, McGee D, Lackland D, Thorpe SR, **Garvey WT**, Lyons TJ, and the EDIC/DCCT Study Group. Cross-sectional associations of C-reactive protein with vascular risk factors and vascular complications in the DCCT/EDIC cohort. ***Journal of Diabetes and Its Complications***, 22:153-163, 2008 PMID:18413218; PMCID pending

Lara-Castro C, **Garvey WT**. Intracellular Lipid Accumulation in Liver and Muscle and the Insulin Resistance Syndrome. ***Endocrinol and Metab Clinics of North America*** 37:841-856, 2008 PMCID:PMC2621269

Tian L, Luo N, Klein RL, Chung BH, **Garvey WT**, Fu Y. Adiponectin Reduces Lipid Accumulation by in Macrophage Foam Cells. ***Atherosclerosis***, 202:152-161, 2009. PMCID:PMC2630479

Sale MM, Lu L, Spruill I, Fernandes J, Lok KH, Divers J, Langefeld CD, **Garvey WT**. A genome-wide linkage scan in Gullah-speaking African American families with type 2 diabetes: The Sea Islands Genetic African American Registry. ***Diabetes***, 58:260-267, 2009 PMCID:PMC2606883

Adams SH, Hoppel CL, Lok KH, Zhao L, Wong SW, Minkler PE, Hwang DH, Newman JW, **Garvey WT**. Plasma Acylcarnitine Profiles Suggest Incomplete Long-Chain Fatty Acid {beta}-Oxidation and Altered Tricarboxylic Acid Cycle Activity in Type 2 Diabetic African-American Women. ***Journal of Nutrition*** 139:1073-1081, 2009 PMCID PMC2714383

Liu J*, Wu X*, Franklin JL, Messina JL, Martin M, **Garvey WT**. Mammalian *Tribbles* Homolog TRB3 Impairs Insulin Action in Skeletal Muscle: Possible Role in Glucose-Induced Insulin Resistance. ***American Journal of Physiology***, 298:E565-E576, 2010 * = co-first authors PMCID:PMC2838520

Divers J, Sale MM, Lu L, Chen WM[3,6], Lok KH, Spruill IJ[8], Fernandes JK, Langefeld CD, **Garvey WT**. The genetic architecture of lipoprotein subclasses in Gullah-speaking African American families enriched for type 2 diabetes: The sea islands genetic African American registry (project SuGAR). ***Journal of Lipid Research***, 51:586-597, 2010 PMCID:PMC2817588

Luo N, Liu J, Chung BH, Yang Q, Klein RL, **Garvey WT**, Fu Y. Macrophage adiponectin expression improves insulin sensitivity and protects against inflammation and atherosclerosis. ***Diabetes*** 59:791-799, 2010 PMCID:PMC2844826

Wu X, Patki A, Lara-Castro C, Cui X, Zhang K, Walton RG, Osier MV, Gadbury GL, Allison DB, Martin M, **Garvey WT**. Genes and Biochemical Pathways in Human Skeletal Muscle Affecting Resting Energy Expenditure and Fuel Partitioning. ***Journal of Applied Physiology*** In Press, 2010. Epub Nov 25, 2010.

Fiehn O, **Garvey WT**, Newman JW, Lok KH, Hoppel CL, Adams SH. Plasma metabolomic profiles reflective of glucose homeostasis in non-diabetic and type 2 obese African American women. ***PLoS One*** 5(12):e15234, Dec 10, 2010

Ingram KH, Lara-Castro C, Gower BA, Makowski R, Newcomer BR, Munoz AJ, Lawrence JC, Lopez-Ben R, Rigsby D, **Garvey WT**. Intramyocellular Lipid and Insulin Resistance: Differential Relationships in European and African Americans. ***Obesity***, In Press, 2011

D. Research Support

ACTIVE

R01 DK38765, Garvey (PI) 07/01/06-06/30/11
NIH/NIDDK "Mechanisms of Human Insulin Resistance"

This porposal studies the functional and molecular defects in mitochondria from skeletal muscle that contribute to defects in lipid metabolism and insulin resistance in the Metabolic Syndrome, obesity, and Type 2 Diabetes.

Merit Review Research Grant, Garvey (PI) 10/01/10-09/30/14
Department of Veterans Affairs "Pathogenesis of Metabolic Syndrome"
This proposal assesses molecular mechanisms contributing to the metabolic syndrome trait cluster as a consequence of interactions among adipose, muscle, and liver tissues.

RO1 DK083562, Garvey (PI). 08/01/09 – 07/31/13
NIH/NIDDK "NR4A Orphan Receptors and Insulin Resistance"
This proposal will examine the role of NR4A orphan nuclear receptors in modulating insulin sensitivity in cultured cells, transgenic mice, and humans, and will develop rationale for NR4A3 as a novel target for treatment of insulin resistance, Metabolic Syndrome, and Type 2 Diabetes.

P60 DK-079626, Garvey (PI) 4/1/08 – 2/28/13
NIH/NIDDK "UAB Diabetes Research and Training Center"
This center grant enhances infrastructure for diabetes related research by funding core facilities and pilot projects, through programs in community based research and disease prevention and control, and by promoting enrichment activities and training programs relevant to diabetes.

RO1 DK-078328, NIH/NIDDK. S. Adams (PI). 8/4/09 - 9/30/2011
NIH/NIDDK "Identification of Muscle Specific Biomarkers of Fatty Acid Beta Oxidation".
This project examines metabolomic profiles of lipids to better understand mechanisms responsible for insulin resistance and abnormal metabolism in humans after exercise and subjects carrying a slice donor polymorphism for the UCP3 gene.
Role in Project: Garvey is co-investigator and PI of the subcontract from USDA.

RO1 DK- NIH/NIDDK M. Sale (PI). 7/1/09-6/30/13
NIH/NIDDK "Genetic Contributions to Diabetes and Dyslipidemia in African Americans".
This proposal involves a genome-wide association study for diabetes and obesity genes, and genes affecting lipid and lipoprotein phenotypes, in Gullah-speaking African Americans.
Role in Project: Garvey is co-investigator and PI of the subcontract from U. of Virginia.

P30 DK-56336, Allison (PI) 9/1/07 to 5/31/12
NIH/NIDDK "Nutrition Obesity Research Center"
This center grant enhances infrastructure for nutrition related research by funding core facilities and pilot projects. Dr. Garvey does not receive funds that directly support his individual research from this center grant.
Role: Dr. Garvey is co-Principal Investigator/Associate Center Director, and Interim Core Leader for "Core C: Genetics Core".

DCRI/Merck & Company, Inc., Garvey (PI). 5/27/09 to 5/26/11
MERCK 082-00. TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Mono- or Dual Combination Oral Antihyperglycemic Therapy.
This is an industry-initiated clinical trial. Role: Garvey is PI at the UAB site.

DCRI/Amylin Pharmaceuticals , Garvey (PI). 4/26/10 to 4/23/14
BCB109. A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus.
This is an industry-initiated clinical trial. Role: Garvey is PI at the UAB site.

PENDING

1R01- Fu (contact PD/PI), Garvey (PD/PI) 9/1/11 to 8/31/16
NIH "Role of the Adiponectin-Macrophage Axis in Cardiometabolic Disease"
This multiple PD/PI application examines adiponectin action in macrophage as a central locus of pathophysiology regarding both metabolic and vascular components of cardiometabolic disease.

COMPLETED

Merit Review Research Grant, Garvey (PI) 10/01/06-09/30/10
Department of Veterans Affairs "Pathogenesis of Metabolic Syndrome"
This proposal assesses molecular mechanisms contributing to the metabolic syndrome trait cluster as a consequence of interactions among adipose, muscle, and liver tissues.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Fernando D. Martinez, MD	Regents' Professor Director, Arizona Respiratory Center Director, BIO5 Institute & CTSI Swift-McNear Professor of Pediatrics
eRA COMMONS USER NAME (credential, e.g., agency login) fmartinez	

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
University of Chile, Santiago	MD	1971	Medicine
University of Chile, Santiago	Residency	1972-1973	Medicine
University of Rome, Italy	MD	1973-1975	Medicine
University of Rome, Italy	Fellowship	1976-1981	Pediatrics
University of Rome, Italy	Specialization	1976-1981	Pediatric Pulmonology

PERSONAL STATEMENT: I am a pediatric pulmonologist with special research interest in the natural history of childhood asthma, and the role of genetic, physiological, immunological and environmental factors as determinants of the risk for asthma. In addition to serving as Principle Investigator on numerous NHLBI-funded research grants, I have been a member of the Board of Extramural Advisors of the National Heart, Lung and Blood Institute (NHLBI), and of the Pulmonary and Allergy Drug Advisory Committee of the Food and Drug Administration. I was also a member of the National Asthma Education and Prevention Program's Expert Panel, which developed the last two versions of the NHLBI Guidelines for the Treatment of Asthma.

A. POSITIONS AND HONORS:

Clinical Appointments:

Attending at the Pediatric Pulmonary Ward University of Rome Pulmonary Section Department of Pediatrics	1981-1982
Pediatrician in charge of Outpatient Clinic	1983-1984
University of Rome Children's Respiratory Clinic	1985-1987
General Pediatric Practitioner, Viterbo, Italy	1981-1987
Attending Physician, Department of Pediatrics, University of Arizona	1991-present
Consulting Physician, Whiteriver Hospital, Whiteriver, Arizona	1992-present

Academic Appointments:

University of Chile Research Associate	
Department of Epidemiology & Social Medicine Area Oriente: School of Medicine, Santiago, Chile	1969-1971
University of Rome	
Lecturer at the Department of Pediatrics	1981-1986
University of Arizona	
Visiting Research Associate	1984-1985
Research Scientist (Pediatrics)	1987-1990
Research Scientist (Respiratory Sciences Center)	1987-1996
Research Assistant Professor	1990-1991
Assistant Professor	1991-1994
Associate Professor	1994-1997
Director, Arizona Respiratory Center	1996-present
Swift-McNear Professor of Pediatrics	1997-present
Co-Director, Institute for Biomedical Science and Biotechnology	2002-2005

Faculty Member, BIO5 Institute	2005-present
Director, BIO5 Institute	2009-present
Regents' Professor	2009-present

Honors and Awards (Last 5 Years)

2006

- 2005 Pfizer Visiting Professorship in Allergic Disease and Asthma, Vanderbilt University (received 2006)

2007

- 2006 Pfizer Visiting Professorship in Pulmonary Medicine, Stanford University (received 2007)

2008

- The J. Burns Amberson Lectureship, American Thoracic Society (ATS) Annual Meeting (*Unopposed)* ***A once-yearly lecture awarded to only one (out of over 20,000) ATS member for "lifetime accomplishment" in the field of respiratory medicine and science.***

2009

- The Donald K. Buffmire Visting Lectureship in Medicine, University of Arizona

Service

National

Member, Expert Panel charged with writing the NIH Guidelines for the Treatment of Asthma, National Asthma Education and Prevention Program (NAEPP)	1995-present
Member, Board of Extramural Advisors, NHLBI	1999-2006
Co-Chair, Asthma Subcommittee, National Children's Study, NIH	2002-2005
Parker B. Francis Fellowship Program Council of Scientific Advisors	2003-2005
Member, Pulmonary-Allergy Drugs Advisory Committee, FDA	2003-2011
National Heart, Lung and Blood Institute Program Project Grant Review Committee	2010-present

University Of Arizona

Interviewer for Pediatric Pulmonary Fellowship Training Program	1988-present
Space and Facilities Committee; Steele Memorial Children's Research Center	1992-present
Professional Evaluation Committee	1992-present
Director, Arizona Respiratory Center	1996-present
Co-Director, Institute for Biomedical Science & Biotechnology	2002-2005
Member, Search Committee for Vice President for health Sciences	2000
Chair of Search Committee for Dean of College of Medicine	2003
Member, Search Committee for Vice Dean College of Medicine, Phoenix Campus	2006
Chair of Clinical and Translational Science Executive Board, UofA	2006-present
Chair of ACTREC Executive Board	2006-present
Chair of Clinical Scholars Circle	2007-present
Co-Chair of the Integrated Health Sciences Facility Core of the NIEHS-funded Southwest Environmental Health Sciences Center (SWEHSC)	2007-present
Provost's Advisory Council on Strategic Advancement	2009-present
North Central Accreditation Working Team 2	2009-present
BioScience Research Laboratories (BSRL) Selection Committee	2012

B. SELECTED PEER-REVIEW PUBLICATIONS (Most recent out of 217):

1. Simpson A, Custovic A, Tepper R, Graves P, Stern DA, Jones M, Hankinson J, Surtin JA, Wu J, Blekic M, Bukvic BK, Aberle N, Marinho S, Belgrave D, Morgan WJ, **Martinez FD**. Genetic Variation in Vascular Endothelial Growth Factor-A and Lung Function. Am J Respir Crit Care Med. 2012 Mar 29. [Epub ahead of print] *PMID: 22461367* [PubMed – as supplied by publisher].
2. Domínguez-Cortinas G, Cifuentes E, Escobar ER, **Martinez FD**. Assessment of Environmental Health Children's Population Living in Environmental Injustice Scenarios. J Community Health. 2012 Mar 15. [Epub ahead of print] *PMID: 22418761* [PubMed-as supplied by publisher].
3. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, Heymann PW, **Martinez FD**, Mauger D, Teague WG, Blaisdell C. Asthma outcomes:exacerbations. J Allergy Clin Immunol. 2012 Mar;

129(3 Suppl): S34-48. *PMID: 22386508* [PubMed – in process].
4. Antó JM, Pinart M, Akdis M, Auffray C, Bachert C, Basagaña X, Carlsen KH, Guerra S, von Hertzen L, Illi S, Kauffman F, Keil T, Kiley JP, Koppelman GH, Lupinek C, **Martinez FD...** Yaman G, Zuberbier T, Bousquet J; Understanting the complexity of IgE-related phenotypes fron childhood to young adulthood: A Mechanisms of the Development of Allery (MeDALL) Seminar. WHO Collaborating Centre on Asthma and Rhinitis (Montpellier). J Allergy Clin Immunol. 2012 Apr;129(4): 943-954.e4. Epub 2012 Mar 3. *PMID: 22386796* [PubMed – in process].
5. Torgerson DG, Capurso D, Mathias RA, Graves PE, Hernandez RD, Beaty TH, Bleecker ER, Raby BA, Meyers DA, Barnes KC, Weiss ST, **Martinez FD**, Nicolae DL, Ober C. Resequencing candidate genes implicates rare variants in asthma susceptibility. Am J Hum Genet. 2012 Feb 10;90(2):273-81. *PMID: 22325360* [PubMed – in process].
6. **Martinez FD**. Children, asthma, and proton pump inhibitors: costs and perils of therapeutic creep. JAMA. 2012 Jan 25: 307(4): 406-7. No abstract available. *PMID: 22274689* [PubMed – indexed for MEDLINE].
7. Bosco A, Ehteshanu S, Panyalal S, **Martinez FD**. Interferon regulatory factor 7 is a major hub connecting interferon-mediated responses in virus-induced asthma exacerbations in vivo. J Allergy Clin Immunol. 2012 Jan; 129(1): 88-94. Epub 2011 Nov 23. *PMID: 221112518* [PubMed – in process].
8. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, **Martinez FD**, Lemanske RF Jr, Strunk RC, Covar R, Szefler SJ, Boehmer S, Jackson DJ, Sorkness CA, Gern JE, Kelly HW, Friedman NJ, Mellon MH, Schatz M, Morgan WJ, Chinchilli VM, Raissy HH, Bade E, Malka-Rais J, Beigelman A, Taussig LM; CARE Network of the National Heart, Lung and Blood Institute. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med. 2011 Nov 24; 365(21): 1990-2001. *PMID: 22111718* [PubMed – indexed for MEDLINE].
9. **Martinez FD**. New insights into the natural history of asthma: primary prevention on the horizon. J Allergy Clin Immunol. 2011 Nov; 128(5): 939-45. Review. *PMID: 22036094* [PubMed – indexed for MEDLINE].
10. Kurzius-Spencer M, Guerra S, Sherrill DL, Halonen M, Elston RC, **Martinez FD.** Familial aggregation of allergen-specific sensitization and asthma. Pediatr Allergy Immunol. 2012 Feb; 23(1): 21-7. doi: 10.1111/j.1399-3038.2011.01220.x.Epub 2011 Oct 21. *PMID: 22017397* [PubMed – in process]..
11. Tantisira KG, Lasky-Su J, Harada M, Murphy A, Litonjua AA, Himes BE, Lange C, Lazarus R, Sylvia J, Klanderman B, Duan QL, Qiu W, Hirota T, **Martinez FD**, Mauger D, Sorksness C, Szefler S, Lazarus SC, Lemanske RF Jr, Peters SP, Lima JJ, Nakamura Y, Tamari M, Weiss ST. N Engle J Med. 2011 Sep 20;365(13):1173-83. Epub 2011 Sep 26. PMID: 21991891 [PubMed – indexed for MEDLINE].
12. Guerra S, **Martinez FD**. Is allergy an asthmatic disease? Arch Bronconeumol.2011 Oct; 47(10): 479-81. doi:10.1016/j.arbres.2011.05.016. Epub 2011 Sep 16. Eng, Spanish. No abstract available. *PMID: 21925784* [PubMed – in process].
13. **Martinez FD**, Trejo-Acevedo A, Betanzos AF, Espinosa-Reyes G, Alegria-Torres JA, Maldonado IN. Assessment of DDT and DDe levels in soil, dust, and blood samples of Chihuahua, Mexico. Arch Environ Contam Toxicol. 2012 Feb; 62(2): 351-8. Epub 2011 Aug 7. *PMID: 21822982* [PubMed – in process].
14. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux Cr. Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB, Baurley JW, Eng C, Stern DA, Celedón JC, Rafaels N, Capurso D, Conti DV, Roth LA, Soto-Quiros M, Togias A, Li X, Myers RA, Romieu I, Van Den Berg DJ, Hu D, Hansel NN, Hernandez RD, Israel E, Salam MT, Galanter J, Avila PC, Avila L, Rodriguez-Santana JR, Chapela R, Rodriguez-Cintron W, Diette GB, Adkinson NF, Abel RA, Ross KD, Shi M, Faruque MU, Dunston GM, Watson HR, Mantese VJ, Ezurum SC, Liang L, Ruczinski I, Ford JG, Huntsman S, Chung KF, Vora H, Li X, Calhoun WJ, Castro M, Sienra-Monge JJ, del Rio-Navarro B, Deichman KA, Heinzmann A, Wenzel SE, Busse WW, Gern JE, Lemanske RF Jr, Beaty TH, Bleecker ER, Raby BA, Meyers DA, London SJ; Mexico City Childhood Asthma Study (MCAAS), Gilliland Fd Children's Health Study (CHS) and HARBORS study, Burchard EG; Genetics of Asthma in Latino Americans (GALA) Study, Study of Genes-Environment and Admixture in Latino Americans (GALA2) and African Americans, Asthma, Genes & Environments (SAGE) **Martinez FD**; Childhood Asthma Research and Education (CARE) Network, Weiss St; Childhood Asthma Management Program (CAMP), Williams LK; Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE) Barnes KC; Genetic Research on Asthma in African Diaspora (GRAAD) Study, Ober C, Nicolae DL. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet. 2011 Jul 31;43(9):887-92. doi:10.1038/ng.888. *PMID: 21804549* [PubMed – indexed for MEDLINE].

Active Support

- **U10 HL64307 (Martinez, PI)** 09/01/04 – 12/31/11

NIH/NHLBI
CARE – Tucson Clinical Center
The CARE network has established a successful infrastructure to conduct clinical research in pediatric asthma.
Role: PI

- **R01 HL56177 (Martinez, PI)** 08/01/07 – 07/31/11

NIH/NHLBI
Natural History of Asthma from Birth to Early Adult Life
The major goals of this program are to assess longitudinally the roles of lower respiratory tract illnesses (LRIs) during the first three years of life, early and late allergic sensitization, persistent respiratory symptoms during childhood, and persistent bronchial responsiveness (BHR) in relation to onset, persistence, remission, and relapse of asthma and asthma-like symptoms during childhood and into adolescence.
Role: PI

- **HHSN275200800034C (Martinez)** 09/26/08-09/25/13

NIH/NICHD (National Institute for Children's Health and Development)
Arizona National Children's Study
To identify preventable environmental risk factors along the causal pathways for a number of adverse health outcomes, providing strategies that will reduce prevalence and improve health.
Role: PI

- **U10 HL098112 (Martinez)** 09/30/09 – 09/29/16

NIH
Arizona/Duke Clinical Center for AsthmaNet
This is a double-armed clinical Management trial covering adult asthma management at Duke University and pediatric asthma management at the University of Arizona. The proposal also includes a clinical research skills development core which will provide training opportunities for pulmonary and allergy fellows and other trainees in the design and implementation of clinical trials in a network setting.
Role: PI

- **RC2 HL101543 (Raby)** 10/01/09 – 09/30/11

Harvard University subcontract (NIH RC2 application)
The Asthma BioRepository for Integrative Genomics Research
The purpose of this proposal is to perform and coordinate the participation of the Childhood Asthma Research and Education (CARE) Network in the Grand Opportunity application "The Asthma BioRepository for Integrative Genomics Research".
Role: sub-PI

- **RC2 HL101651 (Ober)** 10/01/09 – 09/30/11

University of Chicago subcontract (NIH RC2 application)
The EVE Asthma Genetics Consortium: Building upon GWAS
The purpose of this proposal is to perform and provide analyses of the SHARP data (CARE and ACRN) in the Grand Opportunity application "*The EVE Asthma Genetics Consortium: Building upon GWAS*".
Role: sub-PI

Completed Support

- **R01 HL80083 (Martinez, PI)** 06/01/05-05/31/09

NIH/NHLBI
IL8- and GATA3-mediated Pathways in Asthma Exacerbations
This project studied two pathways involved in triggering AE: one centered on IL-8 and neutrophils, the other mediated by GATA3 and eosinophils. The novel mechanisms used allowed us to define the role played by these pathways and may lead to the identification of new therapeutic targets for the prevention and treatment of AEs.
Role: PI

RESOURCES

Follow the 398 application instructions in Part I, 4.7 Resources.

The PI, Dr. Klimentidis has full access to all facilities and equipment in Dr. Zhao's research program. Dr. Zhao is head of UA's Division of Epidemiology and Biostatistics. Dr. Zhao's lab contains Windows-compatible PCs for word processing data management, and statistical analyses that are available for all personnel. All computers are networked to provide internet access.

Both standard (e.g. SAS) and custom software for high-level statistical analysis is available to Dr. Klimentidis and very high level computer support is available from the programmers in the UA High Performance Computing/High Throughput Computing center and the Division of Epidemiology and Biostatistics.

Program Director/Principal Investigator (Last, First, Middle): Klimentidis, Yann C.

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☐ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ RESUBMISSION of application number:
(This application replaces a prior unfunded version of a new, renewal, or revision application.)

☐ RENEWAL of grant number:
(This application is to extend a funded grant beyond its current project period.)

☐ REVISION to grant number:
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of program director/principal investigator.

Name of former program director/principal investigator:

☒ CHANGE of Grantee Institution. Name of former institution: University of Alabama at Birmingham (UAB)

☐ FOREIGN application ☐ Domestic Grant with foreign involvement List Country(ies) Involved:

INVENTIONS AND PATENTS *(Renewal appl. only)* ☒ No ☐ Yes

If "Yes," ☐ Previously reported ☐ Not previously reported

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is request. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
NA		

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS. See specific instructions.

☒ DHHS Agreement dated: 6-8-11 ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with Regional Office.

☐ No DHHS Agreement, but rate established with Date

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

a. Initial budget period:	Amount of base $	137,323	x Rate applied	8.00	% = F&A costs	$	10,986
b. 02 year	Amount of base $	140,730	x Rate applied	8.00	% = F&A costs	$	11,258
c. 03 year	Amount of base $	145,131	x Rate applied	8.00	% = F&A costs	$	11,610
d. 04 year	Amount of base $	144,664	x Rate applied	8.00	% = F&A costs	$	11,573
e. 05 year	Amount of base $	144,233	x Rate applied	8.00	% = F&A costs	$	11,539
					TOTAL F&A Costs	$	56,966

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)? ☒ Yes ☐ No

SPECIFIC AIMS

Individualized prediction of disease risk, a greater understanding of the genetic basis of complex traits, and increased research on under-represented populations are three important goals in current biomedical research. Type-2 diabetes (T2D) is a quickly growing health challenge facing both developed and developing countries. Genetic factors have been found to play a substantial role in its etiology [1-3]. Genome-wide association studies (GWAS) have made a major contribution to our understanding of the specific genetic loci that may be involved [4]. However, the identified variants collectively explain a very small proportion of the variation that we expect genetic factors to explain, and therefore offer limited prediction utility, compared to clinical or other known risk factors [5]. This may be due to several factors, and has been the subject of much debate [6]. We have recently suggested and shown that the use of statistical methods recently developed in the animal breeding field that can simultaneously incorporate information from thousands of single nucleotide polymorphisms (SNPs) across the genome concurrently can offer substantial improvements in prediction of human traits such as height, longevity, and cancer [7,8]. Based on our published and preliminary results, **we hypothesize that such whole-genome prediction (WGP) models as applied to T2D will offer greater prediction accuracy than current 'genetic risk score' models, or models based on family history of T2D.** We aim to apply WGP to individuals of different ethnic/racial groups, and thoroughly examine the factors that may affect and enhance the accuracy of prediction. Major strengths of this proposal include the fact that much of the data are either already in hand, or can be obtained relatively easily through sources such as The Database of Genotypes and Phenotypes (dbGaP), and that we have already applied these methods to several datasets (that we obtained from dbGaP) and various traits. If this K01 is funded, I plan to apply for a R01 grant in which I explore some of the other potential uses and extensions of WGP, such as prediction of glycemic traits and health complications from T2D, and examining gene-gene and gene-environment interactions. Opportunities will also exist to use emerging sequence data to develop and utilize related and new methods for understanding the genetic basis of T2D, and improving prediction models. This project will have a major impact on our ability to use genomic information for individualized T2D risk prediction in several racial/ethnic groups, thus leading to earlier prevention and treatment. It will also provide me with training that I have yet to obtain in the areas of quantitative genetics and statistical learning, categorical and case-control data analysis, informatics, and the biology and genetics of T2D. The specific research aims are:

(1) To test the hypothesis that whole-genome prediction offers greater prediction accuracy for T2D risk than current 'genetic risk score' methods, and prediction based on reported family history. Using publically available genotypic and phenotypic data, we will develop separate models for T2D risk among individuals of European descent, and African-, and Mexican-Americans. We will compare our prediction models to current genetic risk score methods, and in some datasets, we will able to directly compare WGP to prediction based on reported family history.

(2) To test the hypothesis that prediction accuracy can be improved by using a denser SNP coverage (via imputation), including rarer SNPs, and preferentially using SNPs in genomic regions identified by GWAS. We will impute millions of SNPs using the latest data from HapMap3 and 1000 Genomes, including low-frequency SNPs, and compare prediction accuracy based on evenly spaced SNPs across the genome to prediction based on a localized, yet dense, coverage of SNPs in genomic regions identified by GWAS meta-analyses. In addition to greater prediction accuracy, this aim will afford us a better understanding of the genetic architecture of T2D (i.e. the degree to which it is largely controlled by a specific set of genomic regions, or by a very large number of loci across the genome with very small individual effects, thus resembling a so-called 'infinitesimal' trait)

(3) To test the hypothesis that WGP can be used to predict an individual's risk of T2D given a certain body mass index (BMI). There is between-individual variation in the extent to which excess weight contributes to the development of T2D. To capture this individualized risk, and extend the usefulness of WGP, we will incorporate the interaction of BMI and genotype into the WGP model.

RESEARCH STRATEGY

1. Significance

1.1. Specific Aim 1: In the United States, the prevalence of T2D has been rapidly increasing and now affects 11% of adults, and is even more prevalent among African-Americans (12.6%) and Hispanic-Americans (11.8%) [12]. Genetic factors have been shown to play an important role in T2D susceptibility [1-3], and may therefore be especially useful for early prediction and prevention. However, a critical barrier to accurate genetics-based prediction lies in the fact that the collection of genetic loci identified thus far through genome-wide association studies (GWAS) explains a small proportion (<10%) of the expected heritability of the trait [13]. Several groups have examined the utility of these markers for the prediction of T2D, and have generally concluded that they add very little to current risk prediction models based on other known risk factors such as age, sex, body mass index (BMI), and family history [14-18]. As this has become a major barrier for many traits and diseases, there has been considerable debate regarding how and where we might find this so-called 'missing heritability' [6,19].

The second major barrier to progress in the field has been the disproportionate allocation of research effort to populations of European descent. Although several T2D loci identified among individuals of European descent have been replicated in other populations [20-22], many have also failed to replicate [23,24]. It is likely that the effects of these loci will be different across populations due to differing allele frequencies, and it is highly plausible that the set of loci will differ altogether [25]. Furthermore, differences in genetic background and environmental exposures among groups may modify whether or how loci are implicated in T2D development. Finally, previous research, some of which has been done at UAB, has suggested that the pathophysiology of T2D differs among groups [26-28], implying that the genes and pathways involved are different. The pattern of disparities in T2D, and the fact that the genetic basis of T2D likely differs among groups, implies that research effort should be devoted equally across populations, to ensure that potential benefits such as those promised by personalized medicine will be available to all.

The scientific community has greatly invested in generating large datasets of genotypic and phenotypic information. **We propose a novel and powerful way to analyze these datasets in order to improve our ability to predict type-2 diabetes (T2D) risk in individuals of different ethnic/racial groups, and to better understand the genetic basis of T2D.** Successful achievement of this aim will result in individualized prediction of T2D risk for several populations that is substantially greater than that achieved through current genetic risk score methods, or through reported family history. Improved prediction of T2D risk will be most useful early in life, and could lead to the early identification of at-risk individuals, and targeted preventive measures. There is evidence that patients provided with their genetic risk score for T2D are motivated towards behavior change by results that show them to be at high-risk [29], and that both patients and physicians have "high expectations that genetic testing would improve patient motivation to adopt key behaviours for the prevention or control of T2D" [30]. Finally, achievement of this aim will result in the identification of additional genetic variants associated with T2D, adding to our understanding of the genetic basis of T2D.

1.2. Specific Aim 2: A major success from GWAS has been the identification of a collection of previously unknown loci associated with T2D, resulting in new insight into the etiology of T2D [4,13,31,32]. For example, many of the genes at or near these loci are associated with insulin secretion or processing, suggesting that beta-cell function plays a greater role than insulin resistance in the genetics of T2D [13]. However, given the 'missing heritability', there has been a growing realization that common single nucleotides polymorphisms (SNP) may inadequately capture all relevant genetic variation. Notably, since only common SNPs (frequency > 5%) are assayed in GWAS, it may be that rarer variants explain much of the unexplained variation. This barrier would likely also apply to whole-genome prediction (WGP).

Another critical barrier to progress in the field of T2D genetics has been our lack of understanding regarding the genetic architecture (i.e. number of causal variants, and distribution of effect sizes) of T2D. In fact, this barrier applies to many complex traits. A better understanding of the genetic architecture of T2D will provide us with a better understanding of the molecular and genetic basis of T2D. The possibility of allelic heterogeneity (the presence of several causal variants in the same genomic region) has been noted in many GWAS (e.g. [13,33]). Our approach will investigate this possibility for T2D by incorporating as much information in the regions identified by GWAS, thus testing the hypothesis that some of the missing heritability lies in multiple additional and independent variants surrounding the GWAS 'top hits'. Additionally (or alternatively), it may be that much of the missing heritability lies in the collection of loci that have p-value between, 0.05 and the

genome-wide significance threshold of 5×10^{-8}. In fact, the approach of considering the entire collection of SNPs with p-value lower than 0.05 has been used with some success for other traits [34,35].

Successful achievement of this aim would result in an improvement in prediction ability beyond that achieved in specific aim 1, and a better understanding of the genetic basis of T2D in different populations.

1.3. Specific Aim 3: Although obesity is associated with T2D, there is considerable individual variation in this association [36-38]. **For some individuals, being obese does not lead to T2D, while in others T2D can develop in the absence of obesity.** This variation is likely to have a genetic basis [39-41] and has been identified by experts in the field as a very important line of inquiry [42]. Importantly, as we progress towards more personalized medicine it may be possible to use genetic information to predict this level of variation, and thereby prioritize intervention and prevention resources.

Successful achievement of this aim will result in an increased ability to deliver highly personalized health advice, and prevention strategies, most critically for individuals who do not appear to be at risk for T2D since they are not overweight, however would be at a very high risk of T2D if they were to become so. These individuals would therefore be targeted for obesity prevention. Such risk scores would enable clinicians to provide patient tailored, genome-specific, BMI reference ranges.

2. Innovation

2.1. Specific Aim 1.

A superior approach for prediction of T2D: The traditional approach of genetic association performed one marker at a time has been very informative for some traits, but is highly limited for traits that are under the control of a large number of genetic variants that interact in complex ways. In 2001, Meuwissen et al. [43] proposed that a model that simultaneously incorporates information from all SNPs on a genotyping chip could reliably predict breeding value in livestock. As in most genetic association studies, the markers are assumed to be in linkage disequilibrium with the causal variant. The innovative aspect of these WGP models developed in the animal breeding field is that they consider thousands of markers simultaneously, and therefore more realistically reflect the underlying genetic architecture of polygenic traits as one in which a large number of genetic variants, each with small effect, contribute to phenotypic variation.

WGP typically uses thousands of SNPs across the genome to fit a model along with other covariates (eg. age, sex, BMI) to a continuous or categorical outcome. Unlike traditional genotype-phenotype associations that consider one marker at a time, this method considers all markers at once. Fundamentally, regression on a large number of genome-wide markers allows for exploiting multi-locus linkage disequilibrium between markers and causal loci, yielding higher prediction accuracy of genetic risk. Since the number of predictors (i.e. markers) greatly exceeds the number of subjects, it is necessary to use shrinkage estimation procedures such as penalized or Bayesian regression techniques [44-46]. These techniques overcome infeasibility of ordinary least squares regression when the number of predictors exceeds the number of subjects, reduce the mean squared error of estimates, and can be used to control overfitting [47].

Preliminary work: Our group has recently suggested [47] (see appendix) and demonstrated that WGP is a superior method to other statistical approaches for predicting an array of traits such as height [8] (see appendix), lifespan (manuscript submitted), and risk to several cancers (manuscript in preparation). For height, we were able to achieve an R^2 between actual and predicted height that varied between 15-36%, depending on factors such as number of markers in the model and number of direct relatives used to train the model. This is much higher than what has been previously achieved using a subset of markers showing significant associations in GWAS ($R^2 < 10\%$) [33]. More extensive work among livestock and plants has demonstrated even greater promise for these methods. For example, using 32 thousand SNPs, members of our group were able to achieve a predictive correlation of 0.68 between actual and predicted US-Holstein Net Merit Index (an estimate of the sire's ability to produce valuable offspring). This was 65% greater than the predictive correlation of pedigree-based prediction, illustrating that **WGP can achieve levels of prediction accuracy that go above and beyond of prediction based on family history [48].** Here we propose the novel approach of employing WGP analysis in predicting T2D risk. In sum, this represents a paradigm shift regarding how we conceive of polygenic traits, how we identify causative loci, and how we use genetic information to predict traits.

Uniquely positioned to predict T2D in different populations: The novel and powerful analytical tools proposed here, coupled with our access to large, diverse, and comprehensive datasets will have broad implications for predicting T2D risk in diverse populations, with group-specific prediction models.

Bringing Personalized Medicine for T2D closer to reality: It is anticipated that these methods will get us one step closer to employing a personalized medicine approach to T2D prediction and prevention in different populations, which could not be achieved by other approaches. It also has the potential to give us greater insights into the pathways and gene networks responsible for T2D susceptibility in specific populations.

2.2. Specific Aim 2:

Do rarer genetic variants explain some of the 'missing heritability'? This aim seeks to test the hypothesis that the genetic architecture of T2D is one in which common variants explain much of the genetic variation, representing the first time that WGP has been used with a panel of millions of imputed SNPs, which include many low-frequency SNPs. We plan to determine whether the addition of more low–frequency SNPs increases prediction accuracy, also thereby giving us insight into the genetic basis and natural history of T2D.

What is the genetic architecture of T2D? This project affords us the unique opportunity to test whether more variation in T2D risk is accounted for by a dense coverage of SNPs in 40 genomic regions identified as the 'top hits' in GWAS, or by all genomic regions containing at least one SNP with p-value <0.05 in GWAS, or by SNPs spaced evenly across the genome (i.e., the 'infinitesimal' model which hypothesizes that traits such as T2D are under the control of a very large number of genomic loci spread across the entire genome).

2.3. Specific Aim 3:

In a recent consensus report on obesity and type-2 diabetes based on an international working group of 32 experts in obesity and type-2 diabetes, a major question linking obesity to type-2 diabetes that needs to be addressed is ***"1) Why do not all patients with obesity develop type-2 diabetes?"*** [42] Towards the goal of personalized medicine, this aim represents a shift in how we conceive of heritable risk, and how it may hinge on realized phenotypes. While the predictions in Specific Aims 1 and 2 would be most beneficial to assess overall risk early in life, this one will result in more highly personalized and detailed health advice.

3. Approach.

3.1. Specific Aim 1: To test the hypothesis that whole-genome prediction offers greater prediction accuracy for T2D risk than current 'genetic risk score' methods, and prediction based on reported family history.

Genome-wide SNP, phenotypic and other data will be obtained via dbGaP (database of Genotypes and Phenotypes) or from WTCCC. Table 1 lists the available datasets, some of which we already have access to, and have already used in other whole-genome prediction projects. Datasets will be stored on the High-Performance Computing/High Throughput Computing (HPC/HTC) cluster at the University of Arizona (UA). Data will be stored, organized, managed, and analyzed in such a way as to ensure transparency and reproducibility under the guidance of consultant Dr. Almeida. We will perform standard quality control procedures for the genotypic data, such as checking allele frequencies, and imputing missing genotypes as previously described [8].

Table 1: Datasets in hand (Framingham & GENEVA), and publically available through dbGaP, or other means.

Dataset	Design	Population	n	SNP Chip	# of SNPs
Starr County Health Studies' Genetics of Diabetes Study [49]	T2D case-control	Mexican Americans	1,980	Affymetrix 6.0	1 million
A Whole Genome Association Search for T2D Genes in African Americans [50]	T2D case-control	African Americans	2,004	Affymetrix 6.0	1 million
Framingham Heart Study [51]	Pop. based	European Americans	~9,200	Affymetrix 500K	500K
GENEVA (NHS, HPFS) [52]	T2D case-control	European Americans	~6,000	Affymetrix 6.0	1 million
Finland-United States Investigation of NIDDM Genetics [53]	T2D case-control	Europeans	~1,700	Illumina Human HapMap	300K
Wellcome Trust Case Control Consortium [54]	T2D case-control	Europeans	~5,000	Affymetrix 500K	500K

Model fitting: For each dataset, after standard quality control procedures, we will divide the sample into a training set and testing set (an example is shown in Figure 1). Then, as shown in Fig. 1, we will fit models to the training set. A baseline model will first be fit using standard covariates such as sex, age, and BMI. Then, we will add to the baseline model subsets of SNPs, starting with approximately 5,000, and increasing up to approximately 100,000 SNPs. We will model the probability of T2D using the threshold model, or probit link. Here, the probability of developing T2D, y_i, in individual i is equal to 1 if liability to disease, l_i, exceeds zero. Otherwise, y_i=0. In a second stage of the model, l_i is modeled using a linear model of the form:

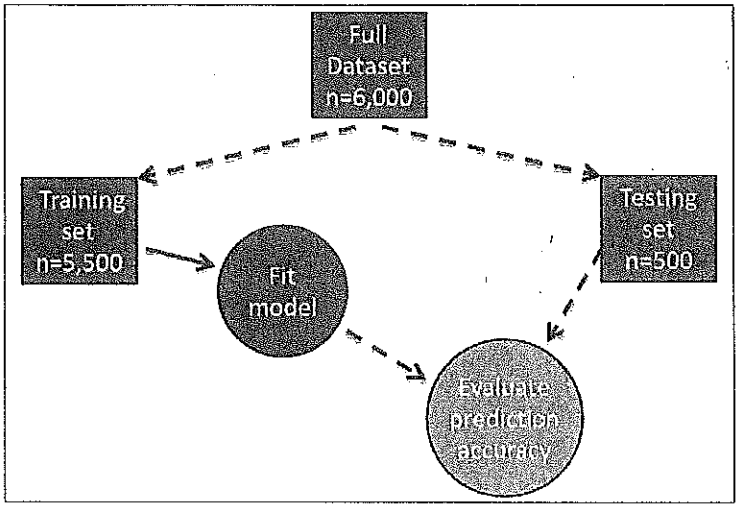

Figure 1: Procedure for evaluating prediction accuracy.

$$l_i = u + \sum_{j=1}^{p} x_{ij}\beta_j + \varepsilon_i \ ,$$

where x_{ij} represents the number of copies of SNP j, β_j represents the additive effect of the jth marker, ε_i represents the model residual, and u is the intercept. All standard covariates (age, sex, BMI, etc.) can be added to this model. In the Framingham sample, T2D will be defined as previously described [13]. Accounting for population stratification will be especially important in the African- and Mexican-American samples. This will be achieved by incorporating the first five principal components as covariates in each model. From this model it is possible to derive estimates of the effects of specific SNPs or regions of SNPs. We will therefore be able to identify regions of the genome that are contributing the most to explaining variation in T2D risk.

Internal validation: After fitting the model in the training set, we will apply the model to the individuals in the testing set to determine prediction accuracy, as shown in Fig. 1. The training-testing design shown in Fig. 1 will be replicated 20 times. Prediction accuracy will be determined by measuring the true and false positive rate and the area under the receiver operating characteristic curve (AUC). For datasets consisting of nominally un-related individuals, training and testing datasets will be chosen at random. For familial data, the testing set will be chosen from the most recent generation, and the training dataset will consist of ancestors and individuals nominally unrelated to those in the testing dataset. We will compare prediction accuracy of the model with age, sex, BMI, and no genetic markers to models in which we add the following, separately and in sequence: reported family history (available for some studies), a genetic risk score compiled by adding the number of T2D risk alleles from the 40 SNPs identified from large-scale GWAS, and increasing numbers of SNPs (from 1,000 up to 150,000). Our previous studies have shown that there are diminishing returns after approximately 150,000 markers [8]. In the Framingham dataset, we will also be able to compare prediction ability of WGP for future T2D to the prediction ability of models based on clinical risk factors (sex age, BMI, family history of T2D, systolic blood pressure, HDL, fasting plasma glucose, and triglycerides) as previously described [55]. We will place confidence intervals around the AUCs using resampling methods, for each of the nested models, and test for significant improvements in prediction ability using methods described by He et al. [56], and the net reclassification improvement method described by Pencina et al. [57]. We will also test models derived with and without the presence of individuals in the testing set that are related to individuals in the training set.

External validation: We will determine the prediction accuracy of models generated in one dataset tested in another dataset. This will require that datasets be merged so that SNP alleles in one dataset correspond to same alleles in the other datasets. Some basic imputation may be needed for cases in which the SNP chips differ between datasets. First, we will determine prediction accuracy of models developed in one dataset tested on individuals of the same ancestry in a different dataset, then on individuals of other ancestries in a different dataset. Next, assuming that models will not be transferable across groups, we will develop prediction models in each group and determine prediction accuracy in each group, and as above, compare prediction accuracy across the baseline model, the model with current genetic risk score, and if possible, to a model based on family history. Among European-descent individuals, we will be able to combine datasets so as to generate a large training set, and thereby improve prediction accuracy. Previous studies have shown that prediction accuracy improves with larger training sets [48,58].

Software: We will use R software (BLR package) developed by Dr. de los Campos (Assistant Professor in the Section on Statistical Genetics, and collaborator on this K01) which allows for different types of shrinkage estimation procedures [10]. We will use Bayesian Gaussian Regression (with a prior distribution of marker effects that is Gaussian) and Bayesian LASSO (with a double exponential prior distribution of marker effects). The version currently available through the R repository allows regression on continuous traits only. However, it has recently been extended to allow for modeling and prediction of binary and censored traits.

Sample size and power considerations: Sample size is known to affect prediction accuracy, and restrictions due to sample size may not allow detection differences between methods, even when these exist. Studies developed in our group with human lifespan using 5,117 individuals with a censoring rate of 60% were able to detect significant differences in prediction accuracy between methods. Similarly, in a recent (unpublished) study on skin cancer involving 718 cases and 4,414 controls, we were able to detect significant differences in cross-validation AUC. The sample size of the proposed datasets varies from 1,700 to 9,200, and the number of cases ranges from 700 to 3,000. Previous studies with similar sample sizes examining improvement in AUC with genetic-based prediction models of T2D are typically able to detect significant differences even with small improvements in AUC [14,17,33,59]. We performed calculations to determine the power to detect various differences in AUC in our smallest datasets using estimates from these previous studies as guides. Power varies with case and control sample size, and expected difference in AUC. We have 85% power to detect a statistically significant (alpha=0.05) difference of 0.03 AUC units (0.66 - 0.69), with 700 cases and 8,000 controls (similar to Framingham dataset), and 82% power to detect a statistically significant difference of 0.04 AUC units (0.66 to 0.7) with 900 cases and 800 controls. For the datasets with larger sample size, and for those that we will be able to combine, we will be powered to detect even smaller differences.

Expected outcomes: A benchmark for success is the achievement of prediction accuracy (i.e. AUC) for all groups that is greater than that achieved by current genetic risk scores. Further benchmarks for success are greater prediction accuracy than that based on reported family history, and the identification of previously unidentified regions of the genome that may be involved in T2D risk. We will make prediction equations and updated software publically available online at the PI's website, and/or will submit it through the appropriate channels such that they can easily be used for clinical purposes, and will publish our results in high-quality journals, using published recommendations, as applicable, for the reporting of 'Genetic Risk Prediction Studies' [60].

Potential pitfalls and limitations: We realize that some basic imputation may be needed for some of the GWAS-identified SNPs since these will not always appear in all datasets that we utilize (depending on SNP platform). Finding a proxy SNP is a relatively straightforward process that we have experience with. The riskiest part of our approach is that WGP fails to offer any improvement in prediction accuracy over current genetic risk scores. However, based on our previous studies, we have good reason to believe that this is unlikely. In the event that it is, there are many other alternative strategies that can be pursued such as those proposed in specific aim 2, or applying WGP to glycemic traits. Problems such as computing power, and the validity of statistical methods can be dealt with effectively since we have budgeted for computing assistance from the UA HPC/HTC center, and both the Division of Epidemiology and Biostatistics and the BIO5 Institute possess extensive statistical and computational expertise, and experience in detecting and addressing potential problems.

3.2. Specific Aim 2: To test the hypothesis that prediction accuracy can be improved by using a denser SNP coverage (via imputation), including rarer SNPs, and preferentially using SNPs in genomic regions identified by GWAS.

We will use IMPUTE v2 software [61] to impute at least 2.5 million SNPs, using all reference population samples as suggested by Jostins et al. [62], and the most up-to-date catalogs of genetic variation from HapMap3 and the 1000 Genomes Project. The PI and programmers in the Division of Epidemiology and Biostatistics and the BIO5 have experience with this and other imputation software. They will me help complete this aim, and contribute to hands-on training (see budget justification). Although memory requirements limit the number of markers that can be included in WGP models, we can use this as an opportunity to selectively include a dense coverage of SNPs that are in candidate regions as determined from GWAS (in windows of up to 2 Mb) [13,31,32]. Imputation will result in more variants overall, but also an increased number of low frequency variants.

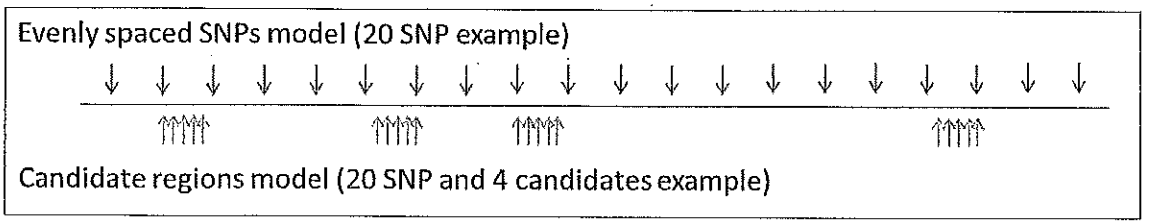

Figure 2: Comparing the candidate region WGP model to the evenly spaced WGP model. The horizontal line represents the genome, and the arrows represent SNP locations.

We will first compare prediction accuracy achieved in specific aim 1 to that achieved with the same number of SNPs in the imputed dataset. We will compare prediction accuracy across SNP selection schemes that vary according to the proportion of common (e.g., > 2%) vs. rare (e.g., <2%) SNPs. We will then compare the prediction accuracy achieved by the candidate approach to that achieved by evenly spaced SNPs across the genome (using the same number of total SNPs; see Figure 2). We will perform these analyses in all ethnic/racial groups, anticipating the possibility that the genetic architecture of T2D differs among groups, and the inclusion of candidate regions may or may not increase prediction accuracy. As in Specific Aim 1 it will also be possible to identify the regions of the genome that are contributing most heavily to explaining variation.

Preliminary work: A preliminary analysis that I have performed for height in the Framingham dataset shows that prediction accuracy (correlation between observed and predicted height) is aided by including SNPs in 180 candidate regions identified by GWAS [33] only when fewer than 5,000 SNPs are included in the model (Fig. 3). When more SNPs are included in the model, evenly spaced ones across the genome perform better in prediction, suggesting that there are many additional regions, beyond the 180 top hits from GWAS that explain variation in height.

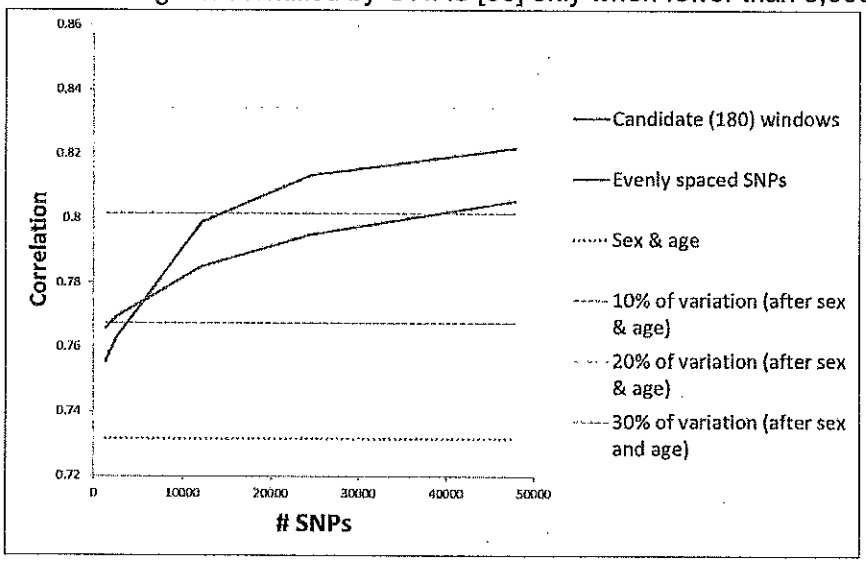

Figure 3: A comparison of prediction accuracy (correlation between actual and predicted) for height of evenly spaced SNPs vs. SNPs in 180 candidate regions (50kb to 2Mb windows).

Expected outcome *(in addition to those listed for Specific Aim 1)* **:** We expect that prediction accuracy will be significantly improved either by adding a higher proportion of low-frequency SNPs in the model, or by using targeted subsets of high-density SNPs in T2D candidate regions of the genome.

Potential pitfalls and limitations *(in addition to those listed for Specific Aim 1)*: Difficulties that we may encounter include the fact that the error associated with imputed SNPs may be high. We will set a threshold on the imputation quality score so as to minimize error, while still adding as many imputed variants as possible. Imputation can be a complicated process. The PI has experience using IMPUTE software, and the computing resources at the UA HPC/HTC will allow for computationally intensive jobs.

3.3. Specific Aim 3: To test the hypothesis that WGP can be used to predict an individual's risk of T2D given a certain body mass index (BMI).

Our approach and sample size considerations for this aim will be similar to that of the first two aims, except that we will extend the method to incorporate the interaction of BMI and genotypes in the model. The contribution of markers to prediction accuracy for this interaction is expected to be different than the contribution of markers to predicting T2D risk. The optimal level of shrinkage may be different for the coefficients modeling the main effect of markers and for those modeling the interactions between markers and BMI. Therefore, we propose to assign separate shrinkage parameters to these two sets of effects. We plan to examine this interaction for all datasets, and also plan to identify genomic regions that contribute most to

explaining variation. Specifically, we will test whether prediction accuracy of T2D risk is improved with the addition of the interactions between SNPs and BMI.

Expected outcome *(in addition to those listed for Specific Aims 1 & 2)*: This aim will result in our ability to use an individual's genetic information to predict whether he/she is particularly susceptible to the negative effects of high BMI on T2D, or conversely, whether they are at high risk of T2D even with a low BMI.

In conclusion, I am absolutely committed to a career using cutting-edge statistical methods to improve our ability to predict disease outcomes. Our current understanding of the genotype-phenotype map has improved somewhat, but is still very limited, partially owing to the absence of statistical methods that can simultaneously use information from tens of thousands of genetic markers. Another major challenge is to extend findings in disease genetics to non-European populations. For an R01 or equivalent submission, I plan to apply the training and research experience obtained during this award to apply for one or more R01 grants to investigate areas such as the genetic basis of glycemic traits, susceptibility to complications from T2D, response to T2D medication, or to examine the contribution of SNP-SNP interactions.

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Inclusion of Women and Minorities

Multiple study samples will be used and they will include roughly 50% women. Given our research aims, we have sought out datasets comprised of African-Americans and Mexican-Americans.

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Mel and Enid Zuckerman College of Public Health

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June 4, 2012

Dear Review Committee Members:

I write in full support of Dr. Yann Klimentidis' K-01 application for a Career Development Award on research of "Whole-Genome Prediction of Type-2 Diabetes Susceptibility in Various Populations." Dr. Klimentidis has had strong training in human genetics during his postdoctoral research. In this proposed training and research plan for his career development, he will complete a number of courses, seminars and dialectic research trainings which will complement his previous training and research experience and enable him to become an independent scientist in the field of genetic epidemiology.

The University of Arizona (UA) is dedicated to advancing research that enhances education and addresses social, cultural and economic needs. We have identified nine central strategic areas to target future investment and research programs. We are committed to supporting Dr. Klimentidis' career as his research interests and goals target Biomedical and Behavioral Health and Translational Medicine, both are important strategic areas of the University. We are especially excited by Dr. Klimentidis' research experience, since diabetes and human genetics are our College's focal points for research development. The University is located in a region where Type-2 diabetes rates are extremely high, particularly in minority populations. Understanding genetic attributes to the development of Type-2 diabetes has significant public health implications. Based on his curriculum vitae and the letters of recommendation, we believe that Dr. Klimentidis is an exceptional young scientist who can bring in vigor, innovation and valuable ideas to the existing interdisciplinary team at our University. We, in turn, recognize that our College and the University could provide him with the ideal intellectual community for additional training to develop his research career.

The Mel and Enid Zuckerman College of Public Health (MEZCOPH) was established in 2000 by the Arizona Board of Regents. Epidemiology is one of the few sections with a long history and a strong faculty team within the College. Recently, the PhD program in Epidemiology has ranked #8 among its national peers. In addition, our graduate program in Epidemiology has also included a Masters of Public Health and a Masters of Science degree. Epidemiology faculty are also responsible for providing core courses to graduate students from other public health concentration areas and from the public health undergraduate program in our College. Hence, we are very excited by faculty, like Dr. Klimentidis who has great enthusiasm for both research and mentoring students.

We have committed many resources to Dr. Klimentidis to help develop his career. We provided him with $114,000 for start-up expenses. Dr. Klimentidis will have an office in the new Medical Research Building. The Medical Research Building, completed in 2006, is a unique laboratory facility designed to foster interdisciplinary collaboration.

Dr. Klimentidis has received support from not only MEZCOPH but also the University. The University-wide Bio5 Institute and the Southwest Environmental Health Sciences Center (SWEHSC) have committed research resources and pilot project opportunities to Dr. Klimentidis.

I am very excited by the research and training proposal that Dr. Klimentidis has developed with his mentoring team for this K-01 application. Dr. Klimentidis has assembled a strong mentor team that will provide comprehensive guidance and support to his research career development. His proposal takes full advantage of the outstanding academic and research resources of MEZCOPH and the Bio5 Institute; both are located within the Arizona Health Sciences Center, and the spatial proximity will make communication among these resources convenient. The training program presented in the K-01 application will allow Dr.

Klimentidis to expand his existing knowledge base and skill set in anthropology and genetics, and to receive formal training in additional biomedical methods including epidemiology and biostatistics. Dr. Klimentidis will not only further develop but also fully utilize these skills in biomedical research to address a highly relevant public health question. This career development award will provide a foundation for him to develop future research proposals.

Institutional Commitment

In support of the K-01 Research Career Development Award application, the Mel and Enid Zuckerman College of Public Health at the University of Arizona is committed to provide strong support to Dr. Klimentidis as stated below.

1. Dr. Klimentidis will have an academic appointment as an Assistant Professor of Public Health within the Division of Epidemiology and Biostatistics, MEZCOPH. The appointment, the rights and privileges pertaining to full-faculty status, and the continuation of the salary are not dependent on this award.

2. We are committed to ensuring that Dr. Klimentidis maintain at least 85% research effort throughout the K award funding period to devote towards his proposed research and educational activities.

3. We will assign teaching and service duties only if they are related to Dr. Klimentidis' career development, help increase Dr. Klimentidis' potential for a research career in academia, and not interfere with his protected research and training time. Dr. Klimentidis will not teach any course in the first year of his K award and will teach one course in the second and third year of his K award. This will allow him to use the remaining of his time for attendance at seminars, conferences, and preparation of grant applications, presentations, and publications.

4. The College will provide Dr. Klimentidis with his computational resources and office space and administrative support staff.

5. The College will allocate the time and resources to Dr. Zhao Chen, Professor and Director of the Division of Epidemiology and Biostatistics to allow her to participate as a co-mentor in the research and career development plan outlined in this application.

MEZCOPH is committed to developing, educating, retaining and advancing young faculty members who show promise of making important contributions to the research program and MEZCOPH mission. I am enthusiastic in my support of Dr. Klimentidis' application, and hope this letter documents our strong institutional commitment to helping him become an independent researcher. Successful completion of this K-01 training and research would provide Dr. Klimentidis with a unique set of skills from additional training in the biomedical sciences to complement his genetic background, and allow him to build collaborations between epidemiology, biostatistics, genetics and basic medical research.

I will be happy to provide any additional information for your review. Thank you for your consideration.

Regards,

Iman Hakim, MD, PhD, MPH
Dean and Professor
Mel and Enid Zuckerman Endowed Chair in Public Health

THE UNIVERSITY OF ARIZONA.

Mel and Enid Zuckerman College of Public Health

DATE: June 6, 2012

TO: NIH/NIDDK

FROM: Zhao Chen, PhD, MPH
Professor and Director
Division of Epidemiology and Biostatistics
Mel and Enid Zuckerman College of Public Health
University of Arizona

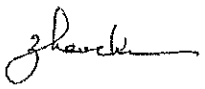
I am writing to state my strong commitment to being a local mentor to Dr. Yann Klimentidis during his K01 career development award. I have known Yann for about a year. First we worked on a manuscript together as co-authors and later I recruited him into our division faculty through a special hire mechanism supported by the Mel and Enid Zuckerman College of Public Health and University of Arizona Bio5 institute as well as the Provost's Office.

Yann strikes me as a young scientist with a strong drive for innovative ideas and diligent research work. He has demonstrated great potential for becoming an independent researcher. His research interests are closely in line with the work that I am doing. In fact, Yann's postdoctoral mentor, Dr. David Allison has served as a consultant to my "Biomarkers and Genetic Factors Related to Sarcopenia in Older Women" grant (NIA) for a number of years. Given the University of Arizona's strategic plan for developing research on diabetes and increasing our capacity in genetic studies, Yann is now in an environment that provides strong support and great opportunities for his research. As his direct supervisor, I will ensure Yann has protective time to develop his research career and adequate resources to carry out his research. I have been working closely with Yann to make a smooth transition to the epidemiology faculty position at the University of Arizona. I helped Yann redesign his training plan by adding more epidemiology and biostatistics education activities, since they are fundamental to Yann's research work and career development. I am planning to meet with Yann twice a month to review his research and to provide dialectic epidemiological training on

study design, execution and data analysis. I will help Yann connect with different research teams both within and outside of the University of Arizona to facilitate his research work and career development.

I have had years of experience mentoring postdoctoral fellows and junior faculty through formal mentorship or my role as the division director. Being a recipient of a K-award myself many years ago, I have first-hand experience on how to achieve a successful career development with the K-award support. Because of our shared research interests in body composition and genetics, I am confident that Yann and I will have a very productive mentee-mentor relationship. Thank you.

Sincerely,



Zhao Chen, PhD, MPH
Professor and Division Director

SCHOOL OF
PUBLIC HEALTH

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Center for Scientific Review, NIH

June 15, 2012

Dear Review Committee members,

It gives me great pleasure to write this letter in support of Dr. Yann Klimentidis' application for a K01 career development grant to be carried out at the University of Arizona. I have had the pleasure of knowing Dr. Klimentidis since he began a post-doctoral fellowship in the Section on Statistical Genetics (SSG) at UAB under my co-mentorship (with Dr. Jose Fernandez) over three years ago. Since that time, I have found him to be an enthusiastic and hard-working postdoctoral trainee, who is eager to increase his knowledge of statistics, genetics, and epidemiology, and who has been interested in how we may apply genomic information to improve risk prediction across different groups.

As a graduate student, Dr. Klimentidis realized the importance of adding genetics to his work in anthropology and human evolution. I have been most impressed by his courage and dedication to expanding his horizons. Throughout his time with us, I consistently found Dr. Klimentidis to be a team player, an eminently pleasant and collegial person to work with, and a responsible, ethical, diligent, and productive investigator who has worked to develop his skill set in this discipline. He is an intelligent person and communicates well. I believe his ability to bridge across many disciplines, and his general ability to engage and relate to others will be a great asset throughout his career.

Dr. Klimentidis impressively showed considerable initiative in the preparation of this proposal. Though his other mentors, collaborators, and I offered him guidance, it was he who identified the main thrust of the research topic, thought the issues through, built on his existing knowledge, and prepared the proposal. Our input has been limited to guidance and I am impressed by his determination and self-reliance.

It is important to stress that the research proposed by Dr. Klimentidis for this K01 award is very much at the cutting edge of our field. Given this, and the fact that Dr. Klimentidis' PhD training was in a significantly different field (Anthropology), he requires additional specialized training beyond the relatively basic training he has obtained thus far in his postdoctoral fellowship, such that he may complete his transition to becoming an independent investigator. His postdoctoral training has consisted of basic genetic epidemiological and population genetic analyses, as well as some basic statistical and computational experience. However, he has yet to work directly with analyses of categorical outcomes or with case-control studies, has yet to use Bayesian techniques, and has limited knowledge and background in quantitative genetics and the physiology of type-2 diabetes. Finally, he also requires more computational and programming experience, especially given the fact that these types of skills are quickly evolving, and becoming increasingly crucial.

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Given Dr. Klimentidis' limited training in quantitative genetics, statistical modeling of discrete traits, and case-control study analysis, these will be the main areas in which I will be able to provide guidance and mentoring. Through my recruitment of Dr. Gustavo de los Campos (Assistant Professor in SSG) and Dr. Ana Vazquez (Postdoctoral Fellow in SSG), both of whom have excellent theoretical and methodological backgrounds in whole-genome prediction (WGP) from the animal breeding field, along with my own expertise in human quantitative genetics, and research methodology and design, we will form a highly complementary team in which we are confident Dr. Klimentidis will thrive. Through his mentors at the University of Arizona, Dr. Klimentidis will benefit from training and mentoring in epidemiological theory and methods as well as in career/professional development. He will be in an environment that will enable him to expand his collaborative network, and to fully mature into an independent scientist. Importantly, I am confident that he will be able to carve out his own niche, not only by examining type-2 diabetes, but also through his interests in using imputation and examining genomic windows of interest, his interest in applying WGP to different populations, his interest in better understanding the genetic architecture of disease traits, incorporating GWAS information into WGP, and developing methods to use WGP to identify novel candidate loci. He will benefit from the expertise in type-2 diabetes physiology and genetics, and mentoring experience of Dr. Tim Garvey with whom I regularly collaborate. In addition, the expertise brought by Dr. Daniel Gianola in quantitative genetics and statistical learning methods, and the expertise in informatics from Dr. Jonas Almeida will give Dr. Klimentidis an extra layer of guidance from well-established leaders in the field of WGP and informatics. Throughout his career, Dr. Klimentidis has demonstrated an ability to incorporate new techniques into his research, so I have no doubt that through this award, he will be able to learn and successfully apply WGP, and make major contributions to the field of disease genetics.

Supervision and mentoring will come through several venues. As Dr. Klimentidis' primary UAB-based mentor, I commit to speaking on the phone with Yann on a monthly basis and communicating by email on a much more frequent basis to discuss ongoing research activities (including data analysis and manuscript preparation), as well as development activities (meetings, short courses, and other educational opportunities). I will also provide mentoring to him in extra-scientific issues, such as networking, ethics, balancing career and personal life, and the choice of future institutions. Throughout this project, Dr. Klimentidis will also benefit from a combination of hands-on training in a team environment, didactic training, intensive short courses and workshops, attendance at professional meetings, and visits to Dr. Gianola's lab. It is anticipated that he will submit an R01 by the 3rd year of this award, and explore the many other potential funding opportunities. There are many potential directions that could be taken for such a grant, many of which Dr. Klimentidis has outlined in his career goals section. Through formal semi-annual review phone meetings, I will monitor his progress towards publishing at least 5 peer-reviewed manuscripts per year, and completing all proposed training activities.

The proposed research project belongs to Dr. Klimentidis. I have not, and will not put any restrictions on him with respect to aspects of the project that he will be allowed to take with him to start his own research program. Throughout my career, I have mentored at least 7 predoctoral trainees, 22 postdoctoral trainees, and many young faculty members, many of whom have gone on to become successful independent investigators.

In conclusion, Dr. Yann Klimentidis is intellectually curious, driven to succeed, collegial, and a pleasure to work with. I am committed to doing all in my power to ensure that his training will help him reach his goal of becoming an independent researcher. We have enjoyed having him as a trainee, and now look forward to having him as a colleague.

Sincerely,

David B. Allison, PhD

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

June 17, 2012

Dear Review Committee Members,

I am writing this letter to express my full support for Dr. Klimentidis's relocation to the University of Arizona, and the plans for continuity regarding mentorship, career development, and conduct of research which remain consistent with goals outlined in the K01 application. My role in Dr. Klimentidis' career development remain constant, namely, to provide mentorship and support in achieving the proposed research and training aims, and to assist him in his efforts to subsequently obtain R01 or similar funding. Dr. Klimentidis is proposing to use state-of-the-art statistical methods to make use of information across the genome in order to predict and understand Type 2 Diabetes risk across several different racial/ethnic groups. He is in a position to become a leader in the genetics of Type 2 Diabetes by integrating his past and continued training in population genetics, genetic epidemiology, and statistical genetics.

I am an endocrinologist with nationally-recognized expertise in the metabolic, molecular, and genetic basis of insulin resistance, Metabolic Syndrome, and Type 2 Diabetes. I have mentored 9 junior faculty with K01, K23, RWJF, Fogarty, and COBRE awards; 13 post-doctoral fellows on T32 and other training grants; 9 clinical fellows pursuing research careers; 15 graduate students as primary mentor in PhD Degree programs; 19 medical students during summer research rotations; and 24 undergraduate research experiences. All of the junior faculty members and many of the pre-doctoral and postdoctoral fellows have gone on to become successful independent researchers. My clinical and research expertise in Type 2 Diabetes will complement that of Dr. Allison's and the other collaborators in providing mentorship and advice to Dr. Klimentidis in the context of the K01 career development plan. I will assure that Dr. Klimentidis will become well versed in the pathophysiology, epidemiology and genetics of Type 2 Diabetes, and assist him in the progress of his studies and in the generation and interpretation of data. This includes rationale for inclusion/exclusion criteria for research subjects, the building of statistical models for Type 2 Diabetes and related traits, and informed consideration of the molecular and genetic basis of Type 2 Diabetes.

As chair of the Department of Nutrition Sciences (DNS) and director of the Diabetes Research and Training Center (DRTC; P60 DK079626) at UAB, I can assure that he will have the opportunity to collaborate with other researchers at UAB. In fact, he has already collaborated effectively with faculty members in DNS including Drs. Jose Fernandez and Maria de Luca, leading to several peer-reviewed publications. In addition, Dr. Klimentidis will have the opportunity to collaborate with my colleague Michele Sale at the University of Virginia, with whom I am conducting an NIDDK R01 –funded genome-wide association study to investigate the genetic basis of Type 2 Diabetes among Gullah-speaking African Americans.

I am committed to continue serving as an active co-mentor for Dr. Klimentidis via regular phone conversations and frequent email communication to evaluate and discuss progress on his research and training, transition to research independence, and preparation of R01 applications and other mechanisms of extramural support. Dr. Klimentidis is pursuing new and creative statistical applications that could advance our current capacity for identifying causal genes in complex diseases. I am confident that he will succeed as an independent investigator with his proposed multidisciplinary training and research program. Dr. Klimentidis has proven himself to be among out most outstanding postdoctoral trainees, and we are committed to his transition to independent investigator status. I look forward to fulfilling my role as co-Mentor for his K01.

Sincerely,

W. Timothy Garvey MD

W. Timothy Garvey, MD
Professor and Chair, Department of Nutrition Sciences
Director, UAB Diabetes Research and Training Center

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June 7, 2012

Dear Review Committee Members:

It is my pleasure to write this letter in support of Yann Klimentidis' K01 Career Development Grant. I actively and enthusiastically participated in the process of recruiting Dr. Klimentidis to The University of Arizona. I am confident that the environment at our university will provide him with the resources and support he needs to fulfill the research and training objectives of the grant, to help him obtain R01 and other extramural funding, and to develop into a successful independent investigator in the area of genetic epidemiology.

I am a genetic epidemiologist focused mainly on childhood asthma. I have mentored 15 junior faculty and more than 20 postdoctoral fellows, many of whom have gone on to become successful independent researchers. I am the Director of the BIO5 Institute at The University of Arizona. BIO5's role is to integrate researchers from across five disciplines (Basic Science, Agriculture, Medicine, Pharmacy and Engineering) to find solutions to the complex biological-based problems faced by humanity.

I am happy to serve as a co-mentor for Dr. Klimentidis. In this role, I will meet with him on a monthly basis to monitor his progress in the research and training objectives of his career development grant. In my role as Director of the BIO5 Institute, I will be able to connect Dr. Klimentidis with other researchers across The University of Arizona who are working in similar or complementary areas. This will be especially valuable to Dr. Klimentidis as a young faculty member at a new institution. As co-mentor I will also be able to mentor Dr. Klimentidis in the area of genetic epidemiological methods, as this will be one of the main foci of his career development. I will also provide guidance as he begins to seek R01 or other funding.

I am delighted to have Dr. Klimentidis join The University of Arizona and look forward to having him as a colleague.

Sincerely,

Fernando D. Martinez, MD
Regents' Professor
Director, BIO5 Institute
Director, Arizona Respiratory Center
Director, Arizona Clinical Translational Science Institute (CTSI)
Swift-McNear Professor Pediatrics

BIO5 Institute

UAB SCHOOL OF PUBLIC HEALTH

Section on Statistical Genetics,
Department of Biostatistics

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June 10, 2012

To whom it may concern:

I am very pleased to serve as a collaborator/consultant on Yann Klimentidis' application for a career development award to be carried out at the University of Arizona. I have known Dr. Klimentidis since I arrived at UAB approximately 2.5 years ago. He has shown a commitment to learning, applying, and exploring whole-genome prediction methods, and is poised for a productive career in the areas of genetic prediction modeling as applied to human traits and diseases, such as type-2 diabetes. I believe that through this application Dr. Klimentidis, will be making major contributions to the field of disease genetics and personalized medicine in general, and type-2 diabetes specifically, by applying whole-genome prediction to different populations, by imputing more low-frequency variants and examining different SNP selection strategies, and by examining prediction accuracy of disease risk with a phenotype-by-genotype interaction as predictor.

During my PhD, I worked on the methodology of whole-genome prediction as applied to traits of agricultural interest. During this time, I developed statistical software for whole genome prediction (the BLR package of R, http://cran.r-project.org/web/packages/BLR/index.html, and R software for semi-parametric WGP). These packages have been used recently by our UAB group, as well as many other groups, having been cited over ten times. I will therefore be able to help Dr. Klimentidis with using this and similar programs.

My primary role as consultant/collaborator for Dr. Klimentidis' K01 will be to support and provide help with the computational, statistical, and quantitative genetics issues needed to achieve his research aims. We have already collaborated on several projects and I am happy to continue these collaborations. We will communicate regularly through email and phone conversations.

I believe that Dr. Klimentidis' proposed training is appropriately timed in his career. He will have the opportunity to get first-hand training from experts in the field of whole-genome prediction, quantitative genetics, type-2 diabetes, and informatics, setting him up for a promising career as an independent researcher. I'm also very excited by the proposed research, as it will make a substantial and important contribution to the field of human genetics in general, and, specifically, to the field of whole-genome prediction.

Sincerely,

Gustavo de los Campos, PhD
Assistant Professor

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May 26, 2011

Dear Review Committee Members,

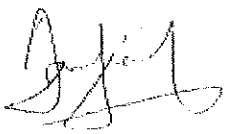
This letter is to express my willingness and pleasure to serve as a consultant for Dr. Klimentidis on his K01 career development award. I believe that the training and research that he proposes is very timely and vital to the field of complex trait genetics in humans, and will afford Dr. Klimentidis the opportunity to obtain the necessary skills, knowledge, and experience to fully transition to a position in Statistical Genetics.

As a quantitative geneticist in the field of animal breeding, I have extensive experience in prediction modeling of complex traits using genetic information, and am excited to see the methods that we have been using in this field being applied to humans and health-related traits. These applications will greatly advance our field, and will bring us nearer to personalized medicine in humans.

As Dr. Klimentidis progresses through his research and training plan, my role will be to provide feedback and advice on issues related to completing his set of specific research aims, thereby also contributing to his training. For example, we will discuss potential ways of estimating effects of single markers or single genomic regions, which will allow for the identification of biologically important genes and molecular pathways involved in type-2 diabetes.

I have already collaborated with Dr. Klimentidis' primary mentor Dr. David Allison, and this summer I have been a Visiting Professor in the SSG at UAB. I have invited Dr. Klimentidis to make at least 2 trips to visit me at the University of Wisconsin-Madison. The purpose of these visits will be for us to exchange ideas, and for him to network and develop new collaborations and avenues of future study with faculty and staff in my laboratory, and others at the University of Wisconsin-Madison. Furthermore, these exchanges will foster enduring partnerships with Dr. Klimentidis' mentor Dr Allison, and Dr. de los Campos, who is another consultant on this application, and my former PhD student.

In conclusion, I want to reiterate my support for Dr. Klimentidis' K01. I am very enthusiastic about his training and research plans, and believe that they hold great promise for him to become an independent and effective researcher.



Daniel Gianola, PhD, Dr. Sc. H. C. (Valencia, Goettingen, Århus, Montevideo)
Sewall Wright Professor of Animal Breeding and Genetics
Department of Animal Sciences
Department of Biostatistics and Medical Informatics
Department of Dairy Science

THE UNIVERSITY OF
ALABAMA AT BIRMINGHAM

Department of Pathology

June 4, 2012

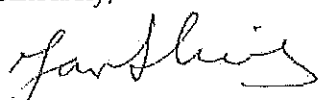
To whom it may concern:

I am delighted to write this letter in support of Dr. Yann Klimentidis' application for a K01 Career Development Award, to be completed at the University of Arizona. I recently arrived at UAB as the inaugural director of the Division of Informatics in the Department of Pathology. I believe that Dr. Klimentidis' focus on personalized medicine and his use of several large genomic datasets is very exciting. The application of informatics-based tools and approaches towards personalized medicine is one of my main research interests, so I will be happy to help him to achieve his career goals.

My primary role as consultant will be to support and guide Dr. Klimentidis in how to best obtain, organize, manage, and execute his analyses on the several large datasets that he proposes to analyze. Reproducible and transparent data and analyses are becoming increasingly important, and Dr. Klimentidis will have the opportunity to obtain training in this area.

I believe that Dr. Klimentidis' proposed training and research plans hold great promise for him to become an independent and successful researcher in the field of statistical genetics, armed with the cutting-edge skills that are increasingly becoming vital to conducting research in this field. It is anticipated that future collaborations will spring from my service as a consultant on this project.

Sincerely,



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