**SUMMARY STATEMENT**

**PROGRAM CONTACT:**
**SONIA JAKOWLEW**
**301-496-8580**
**jakowles@mail.nih.gov**

**( Privileged Communication )**

***Release Date:*** **04/05/2013**

***Application Number:*** **1 F32 CA180655-01**

**Boehm, Frederick J MD**
**The Board of Regents of the University of Wisconsi**
**5730 Medical Sciences Center**
**1300 University Ave**
**Madison, WI 53706-1510**

***Review Group:*** **ZRG1 F09A-L (20)**
**Center for Scientific Review Special Emphasis Panel**
**Fellowship: Oncology**

***Meeting Date:*** **03/14/2013**
***Council:*** **MAY 2013** ***PCC:*** **1STR**
***Requested Start:***

***Project Title:*** **Sample size planning methods in post-GWAS breast cancer eQTL studies**

***Requested:*** **1 year 7 months**

***Sponsor:*** **NEWTON, MICHAEL A**
***Department:*** **Biostatistics/Med Info**
***Organization:*** **UNIVERSITY OF WISCONSIN-MADISON**
***City, State:*** **MADISON WISCONSIN**

***SRG Action:*** **Impact Score: 33 Percentile: 37**
***Next Steps:*** **Visit http://grants.nih.gov/grants/next_steps.htm**
***Human Subjects:*** **10-No human subjects involved**
***Animal Subjects:*** **10-No live vertebrate animals involved for competing appl.**

**1F32CA180655-01 Boehm, Frederick**

**RESUME AND SUMMARY OF DISCUSSION:** The research project will explore sample size planning for eQTL studies in post-GWAS SNP characterization, where high dimensionality of genomic data complicates the eQTL study design. The training plan is comprehensive and includes regular meetings with the mentor and co-mentor. The applicant is strong; however, he has no first author research publications. The research strategy showed a number of weaknesses, which reduces enthusiasm for the fellowship. The proposal is written from a biostatistics viewpoint and validation of the initial results is not considered and the translational impact is not discussed. The research plan lacks details, which makes it difficult to evaluate. Overall, reviewers agree that the fellowship would have a moderate impact on the research career of the applicant.

**DESCRIPTION (provided by applicant):** Frederick Boehm, M.D. seeks to translate genome-wide association study (GWAS) results into clinical applications and to become an independent biomedical investigator. To achieve these goals, he will undertake a rigorous postdoctoral training program in biostatistical genomics under the mentorship of Michael Newton and Michael Gould. The research component of Boehm's program requires him to: 1) develop methods for expression quantitative trait locus (eQTL) study sample size planning with false discovery rate control in the setting of post-GWAS SNP characterization, and 2) develop sample size planning methods for pathway-based inference in eQTL studies. Boehm's approach uses hierarchical mixture modeling of variations in gene expression levels. To assess the statistical models, Boehm will apply his methods both in simulation studies and in analysis of pilot genomics data from 62 breast tissue samples. The proposed research will enable post-GWAS SNP characterization studies. Such studies are a critical intermediate step between GWAS results and their clinical application. These post-GWAS studies have the potential for major public health impacts by enabling personalized genomic medicine. Boehm's training plan includes courses in statistical theory and methods. Course topics include Bayesian methods, high-dimensional inference, survival analysis, and statistical consulting. These courses also will fulfill a requirement for the statistics Ph.D. program in which Boehm is a student. Boehm will supplement formal coursework with independent study of key texts and journal articles in multivariate and high-dimensional statistics. Professor Newton will meet regularly with Boehm to discuss questions that arise from his readings. To facilitate professional development throughout the fellowship period, Boehm will enroll in courses that address skills such as grant proposal writing, manuscript writing, research team management, and research mentoring. To refine mentoring skills, he will train a summer undergraduate researcher during his second year. Boehm also will undertake an ambitious program for training in responsible conduct of research that includes a capstone research ethics presentation to the university community.

**PUBLIC HEALTH RELEVANCE:** Our project will develop biostatistical tools to advance public health by enabling 1) discovery of novel biological targets for drugs to treat breast cancer and 2) development of markers for early detection of breast cancer. In this manner, our research is a translational bridge between recent advances in genetics technology and improvements in breast cancer diagnosis and treatment.

**CRITIQUE 1:**

Fellowship Applicant: 2
Sponsors, Collaborators, and Consultants: 1
Research Training Plan: 3
Training Potential: 1
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** Proper integration of GWAS findings with other genomic data will bridge the chasm between GWAS findings and personalized medicine implementation. A natural extension of

GWAS is studies that address whether disease-associated SNPs impact gene expression in relevant tissues. We use the term “eQTL”, an abbreviation of “expression quantitative trait locus”, to refer to SNPs whose genotypic variation associates with difference in mean expression level of one or more transcripts. While many investigators have undertaken eQTL studies in post-GWAS SNP characterization, high dimensionality of genomic data complicates eQTL study design. Sample size planning for eQTL studies remains an open question.

Aim 1: Develop methods to estimate eQTL study sample size with false discovery rate control in the setting of post-GWAS SNP characterization.

Aim 2: Develop sample size planning methods for pathway-based inference in eQTL studies. Completion of these aims will bridge a gap between GWAS results and their clinical applicability through personalized genomic medicine.

This research project is timely and of broad scientific interest. The overall impact is high, both from the perspective of the research project and the likelihood that the applicant will achieve independence.

**1. Fellowship Applicant:**

**Strengths**

- The PI Frederick Boehm completed an MD in 2007 and is currently working on a PhD in biostatistics – the mix of clinical knowledge and bio-statistical methodology is desired.
- Excellent academic record with many awards and honors.
- He has 4 publications and 4 clinical book chapters.
- Four very strong reference letters: Weir, Professor Dept. Biostatistics, Univ. Washington; Zhang, Professor, Dept. Statistics, Univ. Wisconsin-Madison; Crosslin, Senior Research Scientist U. Washington; (no name provided for fourth letter).
- Letter from Newton – sponsor.

**Weaknesses**

- Only one abstract/presentation listed in 2000.
- Fourth reference letter not provided with the name of the referee.

**2. Sponsors, Collaborators, and Consultants:**

**Strengths**

- Sponsor: Michael Newton, Professor of Statistics with more than 80 publications and very good funding record.
- Co-sponsor: Michael Gould, Professor of Oncology with >190 publications.
- Both have had previous pre-and post-doctoral students who have moved onto independent research positions.
- Good mix of necessary skills – biostatistics, molecular genetics and clinical.

**Weaknesses**

- None.

**3. Research Training Plan:**

**Strengths**

- Very timely topic – investigation of post-GWAS loci.

- The sample size required for eQTL analysis is the subject of much debate.

**Weaknesses**

- Aim 2 was not well described.
- The overall proposal may benefit from access to additional databases which have both genotype and expression data.
- There was not enough description on the validation of the results.

**4. Training Potential:**

**Strengths**

- Excellent plan with good mix of coursework, seminars, collaborations with other scientists/physicians, teaching and communication skills.
- Regular meetings with mentor and co-mentor.
- Comprehensive approach.

**Weaknesses**

- None.

**5. Institutional Environment & Commitment to Training:**

**Strengths**

- Outstanding.

**Weaknesses**

- None noted.

**Protections for Human Subjects:**

- Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

- Not Applicable (No Clinical Trials)

**Vertebrate Animals:**

- Not Applicable (No Vertebrate Animals)

**Biohazards:**

- Not Applicable (No Biohazards)

**Training in the Responsible Conduct of Research:**

- Acceptable

Comments on Format (Required):

- Comprehensive well laid out plan

Comments on Subject Matter (Required):

- Adequate

Comments on Faculty Participation (Required):

- Adequate

Comments on Duration (Required):

- Adequate

Comments on Frequency (Required):

- Adequate

**Select Agents:**

- Not Applicable (No Select Agents)

**Resource Sharing Plans:**

- Acceptable
- They state they will freely share open-source code and accompanying tutorial via the Bioconductor software repository.

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 2:**

Fellowship Applicant: 4
Sponsors, Collaborators, and Consultants: 1
Research Training Plan: 3
Training Potential: 3
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** The applicant proposes to develop methods for sample size estimation in eQTL analysis and pathway based eQTL inference. The applicant has had a complicated journey to graduate school which is not 100% reassuring. Enthusiasm is lessened based on confusion of how the applicant's MD benefits the work is biostatistics

**1. Fellowship Applicant:**

**Strengths**

- Outstanding undergraduate grades.
- Very good medical school and graduate school grades.

**Weaknesses**

- Unclear why applicant is leaving medicine.
- The personal statement discusses a program to focus on personalized medicine which is not revealed in the application to determine statistical power for eQTL analyses.

**2. Sponsors, Collaborators, and Consultants:**

**Strengths**

- Outstanding advisors and track records.

**Weaknesses**

- None noted.

**3. Research Training Plan:**

**Strengths**

- Clear, achievable goals.

**Weaknesses**

- All method development, for a scientist rather than statistician this is surprising.
- No discussion of GETx.
- Lack of discussion on how a user of the tool would benefit.

**4. Training Potential:**

**Strengths**

- Very good training plan that show strong commitment.

**Weaknesses**

- None noted.

**5. Institutional Environment & Commitment to Training:**

**Strengths**

- Outstanding.

**Weaknesses**

- None noted.

**Protections for Human Subjects:**

- Acceptable Risks and Adequate Protections

**Inclusion of Women, Minorities and Children:**

- G2A - Only Women, Acceptable
- M4A - Minority Representation Unknown, Acceptable
- C4A - Children Representation Unknown, Acceptable

**Vertebrate Animals:**

- Not Applicable (No Vertebrate Animals)

**Biohazards:**

- Not Applicable (No Biohazards)

**Training in the Responsible Conduct of Research:**

- Acceptable

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 3:**

Fellowship Applicant: 3
Sponsors, Collaborators, and Consultants: 1
Research Training Plan: 2
Training Potential: 2
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** This F32 application is to develop biostatistical methods to apply GWAS results in clinical usage. The applicant is a Ph.D. student with an M.D. degree in population health sciences. The primary mentor is an expert in biostatistics, and the co-mentor is an established clinical oncologist. The research plan combines the strengths of both co-mentors, and is to develop biostatistical methods with strong potential in clinical usage. The training plan and career development plan are nicely laid out. This is an application with very high impact and training potential.

**1. Fellowship Applicant:**

**Strengths**

- The candidate obtained an M.D. degree in population health sciences at U Wisconsin Madison, and is now pursuing Ph.D. on Statistics at U Wisconsin Madison.
- The candidate is highly motivated to become a biostatistician.
- The applicant has a strong academic record in college, and has won numerous fellowships/awards.
- The applicant has written a number of review articles and book chapters.

**Weaknesses**

- The applicant has not published first author papers.
- The academic performance has declined in med/grad school.

**2. Sponsors, Collaborators, and Consultants:**

**Strengths**

- The sponsor, Dr. Michael Newton, is a full professor in the Department of Statistics and Biostatistics & Medical Informatics at the U Wisconsin Madison. Dr. Newton is an established investigator with expertise in biostatistics.
- Dr. Newton has a strong publication record and funding support, and has strong training experience.

- The co-sponsor, Dr. Michael Gould, is a full professor in the Department of Oncology. He is an expert in medical oncology of breast cancer, and has a strong publication and funding record.

**Weaknesses**

- Not noted.

**3. Research Training Plan:**

**Strengths**

- The research is to develop biostatistical methods to apply genome-wide association study (GWAS) results into clinical applications, with focus on breast cancer.
- The research plan combines the expertise from both co-mentors.

**Weaknesses**

- Not noted.

**4. Training Potential:**

**Strengths**

- The training plan and career development plan are very well laid out.
- The two co-mentors will make significant contributions to the applicant's growth.
- The applicant's medical background will largely facilitate his development in the field of biostatistics.

**Weaknesses**

- Not noted.

**5. Institutional Environment & Commitment to Training:**

**Strengths**

- U Wisconsin Madison provides an outstanding environment.

**Weaknesses**

- None noted.

**Budget and Period of Support:**

Recommended budget modifications or possible overlap identified:

**THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:**

**COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.**

**The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.**

**MEETING ROSTER**

**Center for Scientific Review Special Emphasis Panel**
**CENTER FOR SCIENTIFIC REVIEW**
**Fellowship: Oncology**
**ZRG1 F09A-L (20) L**
**March 14, 2013 - March 15, 2013**

## CHAIRPERSON

LOCKER, JOSEPH D, MD, PHD
PROFESSOR
DEPARTMENT OF PATHOLOGY
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PA 15261

## MEMBERS

ANDERSEN, BOGI , MD
PROFESSOR
DEPARTMENTS OF MEDICINE AND BIOLOGICAL CHEMISTRY
SCHOOL OF MEDICINE
UNIVERSITY OF CALIFORNIA, IRVINE
IRVINE, CA 92697

CHESNEY, JASON A, MD, PHD
ASSOCIATE PROFESSOR
DEPUTY DIRECTOR, JAMES BROWN CANCER CENTER
DEPARTMENT OF MEDICINE
UNIVERSITY OF LOUISVILLE
LOUISVILLE, KY 40202

EL-ASHRY, DORRAYA , PHD
ASSOCIATE PROFESSOR
DIVISION OF HEMATOLOGY/ONCOLOGY
DEPARTMENT OF MEDICINE
UNIVERSITY OF MIAMI
MIAMI, FL 33136

GREEN, MICHAEL R, MD, PHD
PROFESSOR
HOWARD HUGHES MEDICAL INSTITUTE AND
PROGRAM IN GENE FUNCTION AND EXPRESSION
UNIVERSITY OF MASSACHUSETTS
WORCESTER, MA 01605

KOGAN, SCOTT C, MD
ASSOCIATE PROFESSOR
DEPARTMENT OF LABORATORY MEDICINE
HILEN DILLER FAMILY COMPREHENSIVE CANCER CENTER
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA 94143

MASTRO, ANDREA MARIE, PHD
PROFESSOR
DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA 16802

MELLINGHOFF, INGO K, MD
ASSISTANT MEMBER
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM
AND
DEPARTMENT OF NEUROLOGY
MEMORIAL SLOAN-KETTERING CANCER CENTER
NEW YORK, NY 10065

MILLS, ALEA A, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR AND CANCER GENETICS
COLD SPRING HARBOR LABORATORY
COLD SPRING HARBOR, NY 11724

MUKHOPADHYAY, DEBABRATA , PHD
PROFESSOR
DEPT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
DEPT OF BIOMEDICAL ENGINEERING
ASSOCIATE DIRECTOR, MAYO CLINIC CANCER CENTER
MAYO CLINIC
ROCHESTER, MN 55905

MURPHY, MAUREEN E, PHD
PROFESSOR AND PROGRAM LEADER
MOLECULAR AND CELLULAR ONCOGENESIS
THE WISTAR INSTITUTE
PHILADELPHIA, PA 19104

OLIVE, KENNETH P, PHD
ASSISTANT PROFESSOR
COLUMBIA UNIVERSITY HEALTH SCIENCES
COLUMBIA UNIVERSITY MEDICAL CENTER
NEW YORK, NY 100323702

PADGETT, RICHARD A, PHD
ASSOCIATE STAFF
DEPARTMENT OF MOLECULAR BIOLOGY
THE CLEVELAND CLINIC FOUNDATION
CLEVELAND, OH 44195

PHELAN, CATHERINE , MD, PHD
ASSOCIATE MEMBER
DEPARTMENT OF CANCER EPIDEMIOLOGY
H. LEE MOFFITT CANCER CENTER
AND RESEARCH INSTITUTE
TAMPA, FL 33612

PRUITT, KEVIN , PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR AND CELLULAR PHYSIOLOGY
LOUISIANA STATE UNIVERSITY
SHREVEPORT, LA 71130

RIEGEL, ANNA TATE PHD, PHD
PROFESSOR
DEPARTMENTS OF ONCOLOGY AND PHARMACOLOGY
GEORGETOWN UNIVERSITY
WASHINGTON, DC 20007

SPELLMAN, PAUL T, PHD
STAFF SCIENTIST
DIVISION OF LIFE SCIENCES
E.O.LAWRENCE BERKELEY
NATIONAL LABORATORY
BERKELEY, CA 94720

WALSH, MARTIN JOHN, PHD
PROFESSOR OF PEDIATRICS, STRUCTURAL AND CHEMICAL BIOLOGY, GENETICS AND GENOMIC SCIENCES
DEPARTMENT OF PEDIATRICS
MOUNT SINAI SCHOOL OF MEDICINE
NEW YORK, NY 10029

WAN, YONG WAN, PHD
ASSOCIATE PROFESSOR
ASSOCIATE PROFESSOR OF CELL BIOLOGY AND PHYSIOLOGY
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
PITTSBURGH, PA 15213

WEITZMAN, MATTHEW D, PHD
ASSOCIATE DIRECTOR FOR BASIC RESEARCH AND PROFESSOR
DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE
CENTER FOR CELLULAR AND MOLECULAR THERAPEUTICS
CENTER FOR CHILDHOOD CANCER RESEARCH
THE CHILDRENS HOSPITAL OF PHILADELPHIA
PHILADELPHIA, PA 194104

ZONG, WEI-XING , PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR GENETICS AND MICROBIOLOGY
STONY BROOK UNIVERSITY
STONY BROOK, NY 11794

## SCIENTIFIC REVIEW ADMINISTRATOR

BLOOM, MICHAEL L, PHD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

## GRANTS TECHNICAL ASSISTANT

MORRIS, DONTE
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTE OF HEALTH
BETHESDA, MD 20892

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.