SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **06/09/2010**

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Application Number: **1 R01 GM095672-01**

Principal Investigator

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Applicant Organization: BROAD INSTITUTE, INC.

Review Group: **MI**
Microscopic Imaging Study Section

Meeting Date: **06/03/2010** ***RFA/PA:*** **PA10-067**
Council: **OCT 2010** ***PCC:*** **C104GJ**
Requested Start: **12/01/2010**

Project Title: **Image analysis for high-throughput C. elegans infection and metabolism assays**

SRG Action: **Impact/Priority Score: 10 Percentile: 2**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Project Year	Direct Costs Requested	Estimated Total Cost
1	250,000	378,505
2	250,000	378,505
3	250,000	378,505
4	250,000	378,505
5	250,000	378,505
TOTAL	1,250,000	1,892,525

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

EARLY STAGE INVESTIGATOR, NEW INVESTIGATOR

1R01GM095672-01 Wahlby, Carolina

EARLY STAGE INVESTIGATOR
NEW INVESTIGATOR

RESUME AND SUMMARY OF DISCUSSION: With this application, the Principal Investigator seeks funding to develop and implement algorithms for the high-through-put analysis of C.elegans image data, with the goal of automated phenotype classifications. Relations between morphological changes and patterns of gene expression due to perturbations such as bacterial infections are to be investigated using the proposed tools. Software implementation of the algorithms will be distributed as open source which, in this panel's opinion, adds significant value to the project. The reviewers are confident that the project will be accomplished as planned and will result in a very useful tool as C.elegans is a very important model organism. In addition, significant and timely scientific questions are posed here. The research plan includes many challenging and highly innovative components such as the development of novel segmentation methods. The applicant and her collaborators are a very strong team with complementary expertise and a record of successful collaborations. Their prior efforts resulted in widely used software tools which contributed to important biological discoveries; it is expected that the current project will bring a similar impact to the field.

DESCRIPTION (provided by applicant): High-throughput screening (HTS) is a technique for searching large libraries of chemical or genetic perturbants, to find new treatments for a disease or to better understand disease pathways. As automated image analysis for cultured cells has improved, microscopy has emerged as one of the most powerful and informative ways to analyze screening samples. However, many diseases and biological pathways can be better studied in whole animals-particularly diseases that involve organ systems and multicellular interactions, such as metabolism and infection. The worm Caenorhabditis elegans is a well-established and effective model organism, used by thousands of researchers worldwide to study complex biological processes. Samples of C. elegans can be robotically prepared and imaged by high-throughput microscopy, but existing image-analysis methods are insuf- ficient for most assays. In this project, image-analysis algorithms that are capable of scoring high-throughput assays of C. elegans will be developed. The algorithms will be tested and refined in three high-throughput screens, which will uncover chemical and genetic regulators of fat metabolism and infection: (1) A C. elegans viability assay to identify modulators of infection. The proposed algorithms use a probabilistic shape model of C. elegans in order to identify and mea- sure individual worms even when the animals touch or cross. These methods are the basis for quantifying many other phenotypes, including body morphology and subtle variations in reporter signal levels. (2) A C. elegans lipid assay to identify genes that regulate fat metabolism. The algorithms proposed for illumination correction, level-set-based foreground segmentation, well-edge detection, and artifact removal will result in improved or- business in high-throughput experiments. (3) A fluorescence gene expression assay to identify regulators of the response of the C. elegans host to Staphylococcus aureus infection. The proposed techniques for constructing anatomical maps of C. elegans will make it possible to quantify a variety of changes in fluorescent localization patterns in a biologically relevant way. In addition to discovering new metabolism- and infection-related drugs and genetic regulators through these specific screens, this work will provide the C. elegans community with (a) a new framework for extracting mor- phological features from C. elegans for quantitative analysis of this organism, and (b) a versatile, modular, open-source toolbox of algorithms enabling the discovery of genetic pathways, chemical probes, and drug can- didates in whole organism high-throughput screens relevant to a variety of diseases. This work is a close collaboration with C. elegans experts Fred Ausubel and Gary Ruvkun at Massachusetts General Hospital/Harvard Medical School, with Polina Golland and Tammy Riklin-Raviv, experts in model-based segmentation and statistical image analysis at MIT's Computer Science and Artificial Intelligence Laboratory, and with Anne Carpenter, developer of open-source image analysis software at the Broad Institute.

PUBLIC HEALTH RELEVANCE: Large-scale screening experiments that test the effects of thousands of chemicals or genetic perturbants by microscopy and image analysis can discover new treatments

and help biomedical scientists understand dis- ease mechanisms. Microscopy screens of cultured cells are routine, but researchers wish to study complex processes like metabolism and infection in a whole animal like the tiny worm Caenorhabditis elegans, for which existing image analysis methods are insufficient. The goal of this research is to develop open-source software to automatically identify and measure C. elegans in microscopy images, thereby making it possible for researchers worldwide to screen a wide variety of complex biological processes related to human disease.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 2
Approach: 1
Environment: 1

Overall Impact:

Strengths

- This proposal has the goal of developing tools for high throughput screening of C. elegans. The tools would be capable of scoring worm assays in a high throughput environment.
- The methods will allow new phenotyping in worm models.
- The opening of high throughput to whole organism studies should make an impact on the field.
- The investigators elucidate several problems that need this technology including the identification of novel modulators, regulators and new possibilities for screening.
- Really, this proposal contains a comprehensive team, significant challenges, and well thought out solutions.

Weaknesses

- None reported

1. Significance:

Strengths

- The challenges in this research are well described and are non-trivial.
- The applicants do an excellent job of convincing the reader of significance to a broad audience.

Weaknesses

- None reported

2. Investigator(s):

Strengths

- The PI does have experience leading a large EU effort.
- The investigators contain the necessary expertise in both image analysis and biology. In addition, the software dissemination record gives good confidence that they will develop tools that will be actually deployed and used.

Weaknesses

- The PI is experienced in her field but this reviewer is not sure about related experience in leading a large effort such as the one proposed.

3. Innovation:

Strengths

- The shape descriptor is fairly innovative although it borrows from standard methods.
- The atlas of Aim 3 is innovative, as is the application to regulators to infection.

Weaknesses

- None reported

4. Approach:

Strengths

- Shape description, dimensionality reduction and pose characterization are well thought out.

Weaknesses

- It is not clear how variability in the reference model used in Aim 3 will be characterized or incorporated into the model.
- Aim 2 methods read a bit like a laundry list. It would be nice to emphasize the tough problems that require innovation.

5. Environment:

Strengths

- The facilities at Broad and the other participating institutions are more than ample.

Weaknesses

- The applicants give an interesting disclaimer regarding the value of their team vs. that of traditional PhD students.

Budget and Period of Support:

Recommend as Requested

- The PI is being supported at 8.4 months per year.

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 3
Approach: 1
Environment: 1

Overall Impact:

Strengths

- Improved high-throughput large–scale screening software will greatly facilitate experiments that test the effects of chemicals and genetic mutations in C. elegans.
- This exceptionally well designed project will advance our understanding of the complex biological processes related to human disease.

Weaknesses

- None reported

1. Significance:

Strengths

- Improvement of software for analysis of C. elegans HTS data.
- The project offers a “full package” – a very strong team in all the areas required that will ensure highly significant results.

Weaknesses

- None reported

2. Investigator(s):

Strengths

- The PI and assembled team are all well qualified for this project.

Weaknesses

- None reported

3. Innovation:

Strengths

- None reported

Weaknesses

- Innovation is moderate. The project appears to be an extension of previous algorithm development; however this reviewer does not really consider this to be a true weakness. Innovation for the sake of innovation is overrated. The project pulls together the needed resources to advance HTS analysis of C. elegans and is therefore highly significant, but not highly innovative.

4. Approach:

Strengths

- Excellent plan for algorithm validation - the algorithms developed will be tested in three high-throughput screens, which investigate genetic regulators of fat metabolism and infection mechanisms.
- A strong group has been assembled - the project is a well engineered collaboration with C. elegans experts Drs. Ausubel and Ruvkun at MGH, Drs. Golland and Riklin-Raviv at MIT’s Computer Science and Artificial Intelligence Laboratory and Dr. Carpenter at the Broad Institute, the developer of CellProfiler an open source HTS software suite.
- Excellent plans for dissemination.

Weaknesses

- (Minor) Although the new 12 page limit makes it difficult, it would be nice to have seen a comparison of these developments to other available software tools.

5. Environment:

Strengths

- The environment at the Broad Institute and MGH is excellent.

Weaknesses

- None reported

Resource Sharing Plans:

Acceptable

CRITIQUE 3:

Overall Impact:

Strengths

- Will have strong impact in at least two areas: (1) Establishing whole organism high throughput screening methods, exemplified on widely used model organism (C. elegans) (2) Identification of infection by phenotypic abnormalities of the host organism.
- Addresses the important issue of automated assessment of drug efficacy and large scale drug screening based on response of whole host organism.

Weaknesses

- None reported

1. Significance:

Strengths

- Development of high throughput screening methods for whole organisms that are a widely used model system (C. elegans).
- Identification of infection by whole organism response.

Weaknesses

- None reported

2. Investigator(s):

Strengths

- Established collaboration between highly productive groups that have required expertise in C. elegans biology (Ausubel and Ruvkun) and in image algorithms and software development (Wahlby, Golland and Carpenter.)

Weaknesses

- None reported

3. Innovation:

Strengths

- Image based, high throughput screening for whole organisms (C. elegans)

Weaknesses

- None reported

4. Approach:

Strengths

- Well developed plan, presented in a well written and arranged proposal.
- Three aims that interlock clear biological aims with the development of software tools.
- C. elegans is consistent biological model system.
- Aim 1: Microsporidia infection; identifying straight (dead) versus curvy (live) worm, segment worm clusters.
- Aim 2: fat metabolism; segregate worms from background (which has more artifacts due to sample prep); extraction of phenotype features.
- Aim 3: organism response to infection; machine learning to identify phenotypical infection response.
- Includes metrics for success, determining accuracy and speed goals.
- Includes potential problems and alternative strategies.

Weaknesses

- None reported

5. Environment:

Strengths

- Outstanding. Established Screening Center for C. elegans and for automated analysis of high throughput screening. Home of the CellProfiler.

Weaknesses

- None reported

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.

SCIENTIFIC REVIEW OFFICER'S NOTES: The NIH special practice for new investigator R01 applications reviewed in the Center for Scientific Review study sections applies to this application. Resubmission (amended -A1) R01 applications from new investigators may be submitted on a special receipt date for review in the very next review cycle. See this notice in the NIH Guide for Grants and Contracts for more details: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-07-083.html.

You should contact the NIH program officer whose name is shown in the upper left hand corner of page one of this Summary Statement for information about whether this application may be fundable or whether you will need to submit an amended application. The program officer can also help you decide whether the changes and improvements necessary to address the weaknesses noted in the reviewers' critiques could be accomplished in the relatively short time available. You are also strongly advised to seek input from mentors, your Department chair, etc.

You may, of course, choose to take more time to resubmit your application. If so, you should prepare the resubmission for the normal dates for amended applications as specified in this table: http://grants1.nih.gov/grants/funding/submissionschedule.htm.

If you choose to submit a resubmission application for the next review cycle under this policy for new investigators, your amended application must be received at NIH no later than Tuesday, July 20, 2010.

NOTICE: In 2008 NIH modified its policy regarding the receipt of resubmission (formerly termed amended) applications. Detailed information can be found by accessing the following URL address: http://grants.nih.gov/grants/policy/amendedapps.htm

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

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.