Specific Aims Page

Who is the Audience?

Don’t assume too much!!

Three Key Questions

What are you going to do?	STRONG research question
Why is it important to do this?	Who cares? So what? What happens if you do this?
Why is your approach innovative?	How is your approach creative? How are you going to do it?



Specific Aims Page Structure

Carolyn Wahlby

One Example

"Image analysis for high-throughput C. elegans infection and metabolism assays"

Proposal Score: 10
Percentile: 2

Carolyn Wahlby, PhD,
Computational Biologist, PI, Imaging Platform,
Broad Institute of Harvard & MIT, Cambridge, MA, USA
Associate Professor in Quantitative Microscopy,
Centre for Image Analysis, Uppsala University, Sweden

http://www.niaid.nih.gov/researchfunding/grant/pages/appsamples.aspx

Example

- Structure
  - Background
  - Significance
  - 3 Aims
  - Impact
  - Environment
- Each Aim
  - Describes action
  - Identical organization
  - Clear and direct

Specific Aims

Microscopy has emerged as one of the most powerful and informative ways to analyze cell-based high-throughput screening (HTS) samples in experiments designed to uncover novel drugs and drug targets. 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 that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays.

We propose to develop algorithms for the analysis of high-throughput *C. elegans* images, validating them in three specific experiments to identify chemicals to cure human infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated image analysis of *C. elegans* assays will make whole-animal screening possible for a variety of biological questions not approachable by cell-based assays. Building on our expertise in developing image processing and machine learning algorithms for high-throughput screening, and on our established collaborations with leaders in *C. elegans* research, we will:

Aim 1: Develop algorithms for *C. elegans* viability assays to identify modulators of pathogen infection

Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).

Approach: We will develop algorithms that use a probabilistic shape model of *C. elegans* learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.

Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Aim 2: Develop algorithms for *C. elegans* lipid assays to identify genes that regulate fat metabolism

Challenge: To detect worms versus background, despite artifacts from sample preparation, and detect subtle phenotypes of worm populations.

Approach: We will improve well edge detection, illumination correction, and detection of artifacts (e.g. bubbles and aggregates of bacteria) and enable image segmentation in highly variable image backgrounds using level-set segmentation. We will also design feature descriptors that can capture worm population phenotypes.

Impact: These algorithms will provide detection for a variety of phenotypes in worm populations. They will also improve data quality in other assays, such as those in Aims 1 and 3.

Aim 3: Develop algorithms for gene expression pattern assays to identify regulators of the response of the *C. elegans* host to *Staphylococcus aureus* infection

Challenge: To map each worm to a reference and quantify changes in fluorescence localization patterns.

Approach: We will develop worm mapping algorithms and combine them with anatomical maps to extract atlas-based measurements of staining patterns and localization. We will then use machine learning to distinguish morphological phenotypes of interest based on the extracted features.

Impact: These algorithms will enable addressing a variety of biological questions by measuring complex morphologies within individual worms.

In addition to discovering novel anti-infectives and genes involved in metabolism and pathogen resistance, this work will provide the *C. elegans* community with (a) a versatile, modular, open-source toolbox of algorithms readily usable by biologists to quantify a wide range of important high-throughput whole-organism assays, (b) a new framework for extracting morphological features from *C. elegans* populations for quantitative analysis of this organism, and (c) the capability to discover disease-related pathways, chemical probes, and drug targets in high-throughput screens relevant to a variety of diseases.

Primary collaborators

Gary Ruvkun and **Fred Ausubel**, MGH/Harvard Medical School: Development, execution, and follow-up of large-scale *C. elegans* screens probing metabolism and infection. **Polina Golland** and **Tammy Riklin-Raviv**, MIT Computer Science and Artificial Intelligence Lab: Illumination/bias correction, model-based segmentation, and statistical image analysis. **Anne Carpenter**, Broad Imaging Platform: Software engineering and support.

Opening Paragraph

Microscopy has emerged as one of the most powerful and informative ways to analyze cell-based high-throughput screening (HTS) samples in experiments designed to uncover novel drugs and drug targets. 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 that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays.
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Novel computational tools for automated image analysis of C. elegans assays will make whole-animal screening possible for a variety of biological questions not approachable by cell-based assays. Building on our expertise in developing image processing and machine learning algorithms for high-throughput screening, and on our established collaborations with leaders in C. elegans research, we will:

Aim 1

- Simple words and statements
- Direct and explicit addressing of all points
- Scope is reasonable, not saving the world in one grant!

Aim 1: **Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection**
Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).
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Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Placing Emphasis

Actual version

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection

Alternative 1

Aim 1: Identify modulators of pathogen infection by means of C. elegans viability assays

Alternative 2

Aim 1: Carry out C. elegans viability assays to identify modulators of pathogen infection

POWER Positions!

Example Aim 2

Aim 1: **Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection**

Aim 2: Develop algorithms for *C. elegans* lipid assays to identify genes that regulate fat metabolism

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Example Aim 2

- Next level of detail in image recognition (deal with background vs. shape)
- Start to tie in the biology
- Link to, but do not depend, on other aims

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Specific Aims Bioengineering 6061 Proposals

Example Aim 3

- Next level of sophistication, integration of data and approaches.
- Highlights impact on biomedical goals.

Aim 3: Develop algorithms for gene expression pattern assays to identify regulators of the response of the *C. elegans* host to *Staphylococcus aureus* infection

Challenge: To map each worm to a reference and quantify changes in fluorescence localization patterns.

Approach: We will develop worm mapping algorithms and combine them with anatomical maps to extract atlas-based measurements of staining patterns and localization. We will then use machine learning to distinguish morphological phenotypes of interest based on the extracted features.

Impact: These algorithms will enable addressing a variety of biological questions by measuring complex morphologies within individual worms.

Summary Paragraphs

Impact

- In addition to discovering novel anti-infectives and genes involved in metabolism and pathogen resistance, this work will provide the C. elegans community with (a) a versatile, modular, open-source toolbox of algorithms readily usable by biologists to quantify a wide range of important high-throughput whole-organism assays, (b) a new framework for extracting morphological features from C. elegans populations for quantitative analysis of this organism, and (c) the capability to discover disease-related pathways, chemical probes, and drug targets in high-throughput screens relevant to a variety of diseases.

Environment

- **Primary collaborators**

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Specific Aims Page Tips

- It is important to create a need for what they are doing in the first few sentences of the document. The reader has to get invested in why this is important.
- The documents should have a similar organizational structure in which the paper flows generally like this:
  - 1. Get the readers attention,
  - 2. Convince the reader there is a problem,
  - 3. Offer a broad solution to the problem,
  - 4. Give the specifics on how they will solve the problem
  - 5. Conclusion
- Stay away from extremely technical words and jargon

Fishing Expeditions

Vs.

Fishing Expedition

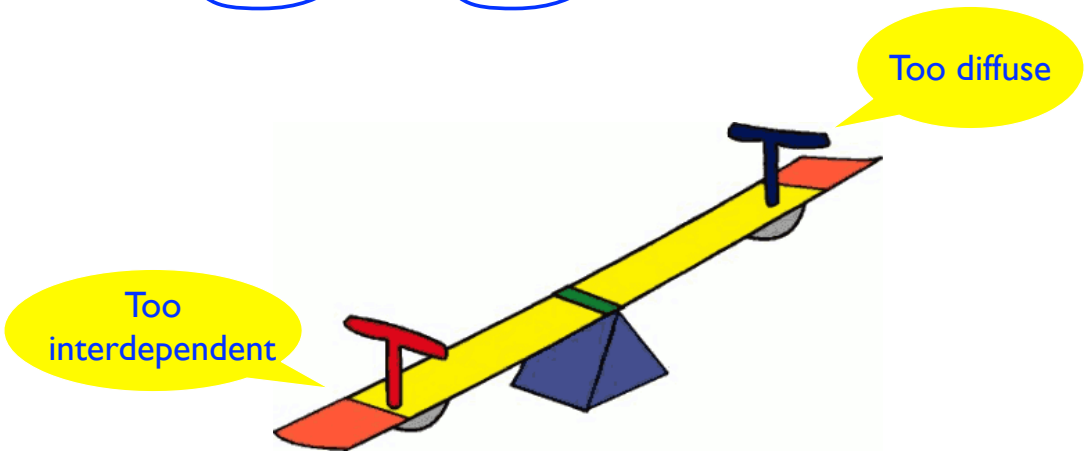
Focused Journey

It's all about FOCUS

Interdependency of Aims

Aim 1 → Aim 2 → Aim 3 → Grand Prize!

Aim 1 → Aim 2 → Aim 3 → Grand Prize!



Hypothesis Driven Research

Hypotheses avoid fishing expeditions

A hypothesis must be testable.

A hypothesis is not a restatement of your goals.

> "We propose to use such and such method to determine whether such and such substance is present in such and such part of the anatomy. Our hypothesis is that by using such and such method we can detect such and such substance in such and such part of the anatomy."

Hypothesis vs. Technical Goal

"A BRG application may propose hypothesis-driven, discovery-driven, developmental, or design-directed research"

"Bioengineering Research Grants (BRG)[R01]"
http://grants.nih.gov/grants/guide/pa-files/PA-06-419.html

Q. "Will technology development be allowed or just hypothesis-driven research?
A. Applications proposing hypothesis-driven research and those proposing the development of new tools and technologies are both encouraged. The focus is on impact and innovation."

"NIH Director's Pioneer Award Program"
https://commonfund.nih.gov/pioneer/faq.aspx#general10

"Specifically, this aspect of NIH focuses on supporting innovation through the development of high-risk technologies that have the potential to empower research."

"Thinking outside the box: fostering innovation and non-hypothesis-driven research at NIH." by R. Aragon, Sci Transl Med. 2011 Feb 16;3(70):70cm5.

Writing Specific Aims

Writing Specific Aims

- Direct, clear, active statement
- Challenge or significance
- Approach: rationale, or preliminary results
- Expected outcomes

Hofmann, pg 413

Make Sure To...

- Strive for clean, clear layout-try not to cram the suitcase.
- Define all terms not clearly known by readers
- Exclude any references to other parts of the proposal or literature citations

Information

Rob's Grant Information Page

A list of granting sources and links to grant applications. The choices reflect my biomedical bias and is in no way comprehensive.

Granting Agency Policy and Program Information

Other good grants sites

- University of Utah Health Science Resources for Basic Scientists including Research grant information
- College of Engineering grant information

NIH General Information

http://www.sci.utah.edu/~macleod/grants/

Grant Writing Tips

Some of these are specific to grants, others simply useful for any writing project.

- Rob's Writing page
- Rob's Latex Page.
- NIH Insider Guide. A set of tips from former NIH study section chairs.
- Proposal Writing: The Business of Science (pdf) by Wendy Sanders. Great advice for any grant writer.
- NIH Giudlines (also for review)
  - Grant writing tips from NIH
  - General reviewer guidlines
  - Reviewer guidance on the shortened applications
  - FAQ for review of short grants.
- RO1 Grant writing tips
- AHA Grant Writing Tips
- Proposal Writer's Guide by Don Thackrey
- The SCI text markup scheme