

SUMMARY STATEMENT
(Privileged Communication)

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Application Number: 1 F31 CA206236-01

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Review Group: ZRG1 F09A-D (20)
Center for Scientific Review Special Emphasis Panel
Fellowships: Oncology

Meeting Date: 11/05/2015

Council: JAN 2016

PCC: O6TR

Requested Start:

Project Title: Computational Analysis of Subclonal Evolution in Chronic Lymphocytic Leukemia

Requested: 3 years

Sponsor: Kharchenko, Peter V

Department: Division of Medical Sciences

Organization: HARVARD MEDICAL SCHOOL

City, State: BOSTON MASSACHUSETTS

SRG Action: Impact Score: 26 Percentile: 19

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.

1F31CA206236-01 Fan, Jean

RESUME AND SUMMARY OF DISCUSSION: This F31 fellowship proposal is submitted by a very promising student Jean Fan, who proposes to develop statistical methods and computational software to analyze single cell RNA-seq data derived from CLL patient samples. The exceptional and highly motivated applicant is recipient of many awards, has stellar academic and excellent publication records. The reference letters are extremely laudable, emphasizing high level of her creativity, research commitment and strong leadership drive. Strong computational training environment and resources at Harvard were the additional score-driving strengths. The sponsor is an expert in computational analysis of genomic and epigenetic data sets and has solid funding. Very limited sponsor's training record is mitigated by the addition of a highly accomplished co-sponsor on the mentoring team. The proposed research plan leverages sponsors' and collaborators' funded work and extends it to an important new area. One of the assigned reviewers raised concerns that the proposed aims are entirely phenomenological and do not put the specific hypothesis to any experimental validation test, and that there is only incremental benefit from training perspective for the applicant who already possesses very strong computational skills. During the thorough discussion the panel remained divided and enthusiasm for the proposal ranged from very good to exceptional. The committee voted and concluded that a fellowship award will likely have a high impact on the future scientific career of Ms. Fan as an independent investigator.

DESCRIPTION (provided by applicant): Intratumor genetic and transcriptional heterogeneity is a common feature across diverse cancer types, including. CLL is a particular cancer that exhibits genetic and transcriptional heterogeneity along with a highly variable disease course among patients that remains poorly understood. Previous research has established that the presence of particular subclonal mutations in CLL can be linked with adverse clinical outcomes and that these subclonal mutations change over time in response to therapy. Therefore, genetic and transcriptional characterization of these subclonal populations will be paramount to enabling precision medicine and synergistic treatment combinations that target subclonal drivers and eliminate aggressive subpopulations thereby improving clinical outcome. While bulk measurements and analysis has provided key insights into cancer biology, etiology, and prognosis in the past, this approach does not provide the resolution that is critical for understanding the interactions between different genetic events within the same environmental and genetic backgrounds to drive metastatic disease, drug resistance and disease progression. Single cell measurements are uniquely able to definitively unravel and connect these relationships. However, simultaneous extraction of DNA and RNA from the same single cells is currently not reliable. Therefore, new statistical methods and computational approaches are needed to identify and resolve genetic subpopulations using single cell transcriptional data alone. In this proposed research, I will develop statistical methods and computational software to analyze single cell RNA-seq data derived from CLL patient samples. Specifically, I will develop methods to identify aspects of genetic heterogeneity, such as the presence of small single nucleotide mutations and regions of copy number variation, in single cells. I will then reconstruct the genetic subclonal architecture and characterize the gene expression profiles of identified subclonal populations. The proposed work will yield innovative statistical methods to enable the identification and characterization of subclonal populations in cancer and yield opensource software that can be tailored and applied to diverse cancer types. Ultimately, application of these developed methods to CLL will provide a better understanding of CLL development and progression.

PUBLIC HEALTH RELEVANCE: Intratumor genetic and transcriptional heterogeneity is a common feature across diverse cancer types, including, chronic lymphocytic leukemia (CLL). Understanding how this heterogeneity impacts clinical outcome and shapes therapeutic resistance is paramount to improving treatment strategies and enabling more personalized cancer treatments. This research

proposal will develop statistical methods and computational software to analyze and connect these different aspects of heterogeneity to provide a better understanding of cancer development and progression, using CLL as a primary focus.

CRITIQUE 1:

Fellowship Applicant: 1

Sponsors, Collaborators, and Consultants: 1

Research Training Plan: 2

Training Potential: 2

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: This is an exciting proposal to develop new statistical and computational approaches to analyze single cell RNA-seq data. The methods developed by the applicant will be used to determine the presence of SNVs and CNAs, and with those data to reconstruct subclonal architectures for CLL. The proposed research, the applicant's previous training and prior research experience, and the training environment that are afforded by the host institution, sponsors and collaborators will position Ms. Fan for a career as an independent investigator. The applicant's commitment to research and the collaborations already established by the applicant and her sponsors afford a superb training opportunity. The overall impact is high.

1. Fellowship Applicant

Strengths

- Strong background in mathematics and remarkable productivity in ~ 2 years of PhD studies.
- Impressive GRE scores.
- Excellent undergraduate research experience.
- Involvement in STEM and specifically leadership for Harvard Graduate Women in Science and Engineering group.
- Highly laudatory letters that point to the applicant's potential for an independent research career.

Weaknesses

- No letter of support from undergraduate laboratory (Rachel Karchin) or other Johns Hopkins University faculty.

2. Sponsors, Collaborators, and Consultants

Strengths

- Outstanding co-sponsors/collaborator team.
- Dr. Church has mentored graduate students and post-docs who have risen to positions of prominence in the genetics/genomics/bioinformatics community.
- Dr. Kharchenko, although junior, has a track record in training.
- Collaboration with Wu laboratory is firmly established.

Weaknesses

- Uncertainty as to the role doctoral students play in the Kharchenko laboratory.

3. Research Training Plan:

Strengths

- CLL experimental system well-suited to proposed work to develop novel statistical and bioinformatics tools to better understand heterogeneity and clonal evolution based on single cell expression data.
- Data sets already in existence or will soon be available for methods development and hypothesis testing work proposed (Wu single cell RNA-seq data sets) and as such the proposed research will almost certainly be completed during the remaining doctoral training period.
- The proposed research leverages sponsors' and collaborators' funded work and extends it to an important new area.

Weaknesses

- At times the written proposal has the voice of a PI (mentor), and the applicant's role within the larger research group is at times difficult to discern.

4. Training Potential:

Strengths

- Goals for graduate training and beyond spelled out clearly.
- Attention to strengthening background in life sciences is recognized by applicant as a priority.
- The intention to interact collaboratively with Wu Lab (cancer data sets being investigate) and with the Wang collaboration will ensure 'life sciences' context.

Weaknesses

- It is unclear which seminar series are currently attended and what areas/topics are priority for the applicant as she attends seminars and/or joint lab meetings.

5. Institutional Environment & Commitment to Training:

Strengths

- Outstanding environment.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Acceptable

Comments on Subject Matter (Required):

- Acceptable

Comments on Faculty Participation (Required):

- Acceptable

Comments on Duration (Required):

- Acceptable

Comments on Frequency (Required):

- Acceptable

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Fellowship Applicant: 1

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 2

Training Potential: 1

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: The candidate earns the “1” reserved for truly exceptional candidates. The sponsoring team is judged to be outstanding, with proper measures taken to account for the early career stage of the primary sponsor. However, the co-sponsor’s letter and offered level of input came across as weak and distant. The project is exciting and has realistic potential to reveal important insights in CLL. More broadly, the methods established upon completion of the proposed work, when shared freely, have potential to impact our understanding of the clonal evolution of CLL and other malignancies. The training plan will expand Jean’s already impressive and respected repertoire of

statistical methods applied to understanding clonal architecture. The institutional environment and commitment to training are judged as outstanding.

1. Fellowship Applicant

Strengths

- Excellent undergraduate academic record and GRE scores.
- Contributing author on recent, high impact studies. (*Cancer Cell* and *Cancer Discovery*)
- Active in outreach for women scientists. (established a non-profit, cuSTEMized, to encourage girls to envision themselves in science, technology, engineering, and math)

Weaknesses

- None noted.

2. Sponsors, Collaborators, and Consultants

Strengths

- Sponsor and applicant have an established rapport and work style that appears to be highly mutually beneficial.
- Sponsor has NSF and NIH funding through 2020.
- Sponsor is very straight about “I’m new, with limited experience with training – this is my first grad student”.

Weaknesses

- Jean is sponsor’s first graduate student; co-sponsor selection mitigates this already minor concern; lab personnel includes several postdocs.
- Co-sponsor’s letter and offered level of input came across as weak and distant; seemed to be there to prevent criticism of a young sponsor. This is a proposal that could benefit from a co-sponsor bringing some other expertise and with a way to push this young woman’s training. Dr. Church’s credentials are spectacular; no argument there. I raise this issue as respectfully as possible and hope that I worded it non-offensively.

3. Research Training Plan

Strengths

- Cutting edge question at the interface of CLL biology and computational modeling.
- One of the clearest and most professional applications I’ve read in quite some time (clerical error in first sentence of Abstract had me worried, but it was one of the only blips: “..., including.”) Also, please see comment below in this section’s “Weaknesses”.
- Release of findings/methods as open source is a valuable deliverable.

Weaknesses

- Please re-visit your use of the word “metastatic” when referring to leukemia; I presume you mean “relapsed” or “advanced”. This set off a bit of a firestorm that had to be extinguished.

4. Training Potential

Strengths

- The candidate is already publishing her work in Nature Methods and other very high-tier journals; the best move seems to be to let her and her advisor decide on what they consider the best further training, and this project suits the bill.
- Opportunity for applicant to train and involve junior colleagues and summer students is in line with her passion and advocacy for women in science.

Weaknesses

- I found myself wanting to suggest linking the computational work to a greater investment by Jean in “wet lab” based study. That may be asking too much, but if the applicant wants to run her own lab and be as broadly prepared as possible (and can make the time), I do think this would be worth her time. Of course, the counter argument is “Why don’t all of the experimentalists learn to do computational analysis?”. I think they should, at least to a level that helps drive project and career.
- Relatedly, I worry a little that Jean could be viewed as being trained toward almost a super data analyst – great team member - rather than a principal investigator. Her “plans” are a bit vague. I suggest that she and sponsor keep an open dialogue on this issue. The analogy that comes to mind is x-ray crystallographers – some do great work but wait for projects to come, while the very best (Eric Gouaux, for example) drive their fields and even pioneer new fields. Maybe you have that kind of talent...

5. Institutional Environment & Commitment to Training

Strengths

- Appropriate, supportive institutional environment and demonstrated commitment to training.
- Clear plan for Jean’s training within the program elaborated in application.
- Detailed (highly positive) comments regarding Jean’s preliminary qualifying exam demonstrate a deep commitment by the faculty.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- adequate

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

Budget and Period of Support:

Recommend as Requested

Additional Comments to Applicant (Optional):

- You are doing really impressive things at an early career stage.

CRITIQUE 3:

Fellowship Applicant: 2

Sponsors, Collaborators, and Consultants: 4

Research Training Plan: 4

Training Potential: 2

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: Strong applicant with an expert mentor. Lack of training history and questions about the role of co-mentors and independence of primary sponsor reduce enthusiasm. The proposal tackles significant technical data analysis problems, but the clinical importance and potential impact of the proposed studies is questioned.

1. Fellowship Applicant

Strengths

- Top notch student.
- Track record of publishing productivity.

- STEM outreach and other activities show evidence of balance and potential leadership.

Weaknesses

- None noted.

2. Sponsors, Collaborators, and Consultants

Strengths

- Dr. Kharchenko is an expert in computational analysis of genomic, expression, and epigenetic data sets.
- The sponsor was trained in world leading laboratories.
- Assuming that adequate, dedicated time is spent with the applicant, the involvement of Dr. Church is a significant strength.
- Numerous opportunities for mentorship or training are noted, many of which are informal and attest to a collaborative environment.

Weaknesses

- Unclear as to the specific role for the co-mentor. One stated rationale is that the applicant finds Dr. Church “to be an inspiring visionary with ethical character”.
- Given that Dr. Kharchenko was trained in the Church lab, this raises some concern about independence of the primary sponsor.
- Primary sponsor has a very limited training record.

3. Research Training Plan

Strengths

- Hypothesis regarding roles of Wnt and Notch signaling is potentially important.
- Leverages existing data sets.
- Development of new computational methods could have a significant enabling effect on the research community.

Weaknesses

- The proposed aims are entirely phenomenological and do not put the specific hypothesis to any critical experimental test.
- Although intratumor heterogeneity is an interesting general question, it is not at all clear that intracolon heterogeneity is a clinically significant feature in CLL, and thus the overall impact of this proposal is questionable.
- From a clinical perspective, it is not obvious that there is a pressing clinical need given the recent success of BTK inhibitors (e.g. ibrutinib) in treating CLL subsets.

4. Training Potential

Strengths

- Strong computational training environment and program.

Weaknesses

- Experimental context and specific mentorship is lacking.

5. Institutional Environment & Commitment to Training Strengths

- Excellent training programs, resources, and environment.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- structured courses

Comments on Subject Matter (Required):

- broad, standard

Comments on Faculty Participation (Required):

- widespread (23 professors)

Comments on Duration (Required):

- multiple 1.25- 1.5 hour sessions in structured or small group format

Comments on Frequency (Required):

- throughout 6 yr program of study

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html>. 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

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CENTER FOR SCIENTIFIC REVIEW
Fellowships: Oncology
ZRG1 F09A-D (20) L
November 05, 2015 - November 06, 2015

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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.