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SUMMARY STATEMENT
(Privileged Communication)

Release Date: 11/12/2019
Revised Date:

Application Number: 1 F31 NS116981-01

HOLLAND,RUBY
University of Pittsburgh
M250 Scaife Hall
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Review Group: ZRG1 F03B-R (20)
Center for Scientific Review Special Emphasis Panel
Fellowships: Biophysical, Physiological, Pharmacological and
Bioengineering Neuroscience

Meeting Date: 10/24/2019

Council: JAN 2020

PCC: OSHIMLCN

Requested Start: 04/01/2020

Project Title: Descending facilitation of pain by mu-opioid receptor-expressing
neurons in the rostral ventromedial medulla

Requested: 3 Years

Sponsor: Ross, Sarah E

Department: Neurobiology

Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

City, State: PITTSBURGH PENNSYLVANIA

SRG Action: Impact Score:20 Percentile:8 +

Next Steps: Visit https://grants.nih.gov/grants/next_steps.htm

Human Subjects: 10-No human subjects involved

Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

1F31NS116981-01 HOLLAND, RUBY

RESUME AND SUMMARY OF DISCUSSION: In this submission of a pre-doctoral fellowship application, the candidate proposes to elucidate the specific circuitry through which MOR (mu-opioid receptor)+ RVM (rostral ventromedial medulla) spinal projection neurons facilitate pain. The applicant, Ruby Holland is an outstanding MD-PhD graduate student with extensive research background, superb letters of reference, and excellent history of productivity with one first author and 4 co-author publications. She has a remarkable writing skill as demonstrated by her well-written proposal. The sponsor has an outstanding history of productivity and successful track record of mentoring MD-PhD students. The co-sponsor is a leader in the field with excellent expertise in electrophysiology. Together, they have established collaboration and have an excellent history of productivity, mentoring, and funding. The research training plan is to test the hypothesis that MOR+ RVM neurons facilitate pain by inhibiting interneurons in the superficial dorsal horn. The knowledge gained thru these studies can have significant impact on the field of RVM-Spinal cord neural circuitry. The aims are independent with clear description of potential pitfalls and alternative strategies. Minority of reviewers raised concerns regarding the research training plan (i.e. absence of appropriate controls). They also thought that the applicant will be spreading too thin across multiple areas, limiting her ability to learn some of methodologies in depth. They voiced concern regarding the overambitious nature of the experiments given the proposed timeline and the fact that the applicant has to carry on with clinical rotations. However, all of these concerns were considered minor and were offset by an outstanding training potential. The training plan is highly individualized with clear plans and professional goals. The applicant will be given excellent opportunities to acquire combination of cutting edge genetic, electrophysiological, and behavioral methodologies. Overall, despite some concerns regarding the research training plan, the panel members were unanimously enthusiastic about this outstanding applicant and exceptional mentoring team and felt that there is an excellent likelihood that the fellowship will enhance the candidate's potential for a productive independent scientific research career in neuroscience research.

DESCRIPTION (provided by applicant): Pain is a debilitating and prevalent condition which severely impacts quality of life. Unfortunately, our current treatment options are limited by adverse effects, and the pathways modulating pain signaling are not fully understood. The rostral ventromedial medulla (RVM) is a brainstem site which plays a critical role in pain modulation, primarily by sending descending projections to the spinal cord. While non-specific electrical stimulation of the RVM produces analgesia, RVM neurons can either facilitate or inhibit pain. RVM spinal projections can be characterized as ON-cells, OFF-cells, or NEUTRAL-cells based on their response to, and effect on, nocifensive reflexes, but many details remain unclear. Morphine acts at the mu-opioid receptor (MOR) to inhibit neuronal activity and produces analgesia in part by activating OFF-cells and inhibiting ON-cells. Thus, it follows that ON-cells express MOR. Numerous studies support the assertion that ON-cell circuitry is implicated in chronic pain and opioid-induced hyperalgesia. However, until recently we lacked the genetic tools necessary to dissect the circuitry of MOR-expressing neurons, including ON-cells, in the RVM. With the recent development of the Oprm1-Cre knock-in mouse, we now have the genetic tool necessary to study these circuits in better detail. The goal of this proposal is to therefore test the hypothesis that MOR+ RVM neurons facilitate pain by inhibiting interneurons in the superficial dorsal horn. I will test this hypothesis using a combination of genetic, molecular, electrophysiological, and behavioral approaches. Aim 1 will investigate which cell types in the RVM express MOR through viral tracing, fluorescent in situ hybridization (FISH), and immunohistochemistry (IHC). Aim 2A will identify the MOR+ RVM inputs received by interneurons in the dorsal horn through optogenetics and slice electrophysiology. Aim 2B will explore the electrophysiological, neurochemical, and morphological phenotype of dorsal horn interneurons receiving input from MOR+ RVM neurons using a combined electrophysiology and anatomical approach. Aim 3 will test the hypothesis that MOR+ RVM neurons facilitate mechanical, chemical, and thermal pain through the use of chemogenetics and behavioral assays of acute and chronic neuropathic pain. The work detailed in this proposal is critically important

because an enhanced understanding of the circuitry underlying the RVM can pave the way for the development of novel pain therapeutics and will advance the field of neuroscience. Furthermore, this proposal is heavily inspired by my clinical interest in anesthesiology, where I plan to work as a pain specialist and investigate pain signaling mechanisms to minimize patient suffering and improve quality of life. The professional, technical, and intellectual skills which will be developed over the course of this fellowship will position me for success as a physician-scientist in academic anesthesiology.

PUBLIC HEALTH RELEVANCE: Chronic pain is a debilitating condition which severely impacts quality of life for millions of people worldwide. Ascending pain signals undergo descending modulation by mu-opioid receptor (MOR)-positive neurons in the rostral ventromedial medulla (RVM) through circuits which are not completely understood. In this proposal, I will elucidate the specific circuitry through which MOR+ RVM spinal projection neurons facilitate pain using a combination of genetic, electrophysiological, and behavioral approaches.

CRITIQUE 1

Fellowship Applicant: 1

Sponsors, Collaborators, and Consultants: 1

Research Training Plan: 2

Training Potential: 1

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: This is a new F31 submission from Ruby Holland, an MD/PhD student at U Pitt. Ms. Holland is a 1st year graduate student, having completed 2 years of medical school. She is requesting 3 years of support. Ms. Holland received her BA in chemistry from U Penn. As an undergrad, she conducted research on mechanisms underlying chemotherapy-induced eating disorders. She was first author on a paper (*Physiol & Beh*) and coauthor on 4 other manuscripts. Following 2 rotations, Ms. Holland chose to conduct her PhD research in the lab of Dr. Sarah Ross, an Associate Professor in the Dept. of Neurobiology at U Pitt and a member of the Pittsburgh Center for Pain Research. She has an excellent publication record and is PI or co-PI on a number of NIH grants. She has funding available for the duration of the project. Dr. Ross has an excellent record of graduate mentorship. The co-mentor, Dr. Richard Koerber, is a Professor in the Dept. Neurobiology at U Pitt. He is a recognized expert in the pain field, is funded by two R01's, and publishes regularly with Dr. Ross. The Applicant has identified 3 primary training goals for the proposed period: expansion of technical skills, scientific experimental design, and development of scientific communication skills. These are clearly articulated with the necessary support and/or training components identified. The training goals outlined by the applicant mesh nicely with the training plan provided by Drs. Ross and Koerber. The proposed studies will examine the role of MOR+ RVM neurons in pain signaling using the newly developed Oprm1^{cre} mouse. Three aims are proposed. Aim 1 will use tract tracing and FISH to delineate the phenotype of MOR+ RVM neurons retrogradely labeled from the dorsal horn of the spinal cord in mice. Additional studies using anterograde viral tracing will confirm that RVM bulbospinal neurons terminate in the dorsal horn of the spinal cord, and in particular, Lamina I and II. Aim 2 will use optogenetics and in vitro patch clamp to characterize dorsal horn neurons receiving input from the RVM. At the end of the experiment, cells will be filled and phenotyped based on cell morphology. In Aim 3, spinally projecting MOR+ neurons will be chemogenetically activated or inhibited and the impact on acute and persistent pain measured. The experimental design is solid, and potential pitfalls/caveats recognized. Although preliminary data are lacking for most of the proposed experiments, the techniques are all feasible and the aims independent. Successful completion of these studies will address multiple gaps in our current knowledge regarding the neural circuitry of the RVM-spinal cord pathway and will provide the PI with a repertoire of advanced skills that will facilitate her development into an independent scientist.

1. Fellowship Applicant:

Strengths

- Conducted extensive research as an undergrad and is first author on 1 paper and co-author on 4 others. She has also presented work from her graduate rotations at internal conferences.
- Assumed a leadership position in a number of societies/organizations/committees.
- Letters of recommendation attest to her skills, intellect and drive.
- Proposal is well developed and well written.

Weaknesses

- None noted.

2. Sponsors, Collaborators, and Consultants:

Strengths

- Dr. Sarah Ross is the primary mentor. She has an excellent record of training PhD and MSTP students, is well funded, and publishes on a regular basis. She is well suited to provide excellent mentorship for the proposed studies.
- Dr. Richard Koerber is a co-mentor. He is a recognized leader in the field of pain physiology. He will provide guidance on the electrophysiology experiments proposed in Aim 2.
- Drs. Ross and Koerber have a strong record of collaboration and are co-PI on grants and a number of co-authored papers.

Weaknesses

- None noted.

3. Research Training Plan:

Strengths

- Co-mentors have a clear and well-delineated role on the project, with Dr. Ross overseeing Aims 1 and 3 and Dr. Koerber Aim 2. Together with the faculty of the PCPR, and in particular Dr. Gold, these studies have a high likelihood of success.
- Experimental design is sound; figures help emphasize flow of experiments.
- Successful completion of these studies will significantly advance our knowledge of the neural circuitry of the RVM-spinal cord descending circuit.

Weaknesses

- Lack of preliminary data supporting the aims. However, this is viewed as a minor weakness as the critical foundation for these experiments have been established beginning with the pioneering anatomical studies of Basbaum and Fields (1979).
- Although sex as a biological factor is mentioned, it is not clear in terms of animal numbers how females will be incorporated into the Aims.

4. Training Potential:

Strengths

- Outstanding. The applicant has consistently demonstrated a commitment to research, has the intellect and drive necessary to see these experiments through to completion. In addition, she has assembled a strong team to facilitate her advancement through the CNUP.

- Professional goals are clearly articulated, and a plan of action provided.
- Both mentors have developed a strong training plan for the PI.

Weaknesses

- None noted.

5. Institutional Environment & Commitment to Training:

Strengths

- Outstanding. The Center for Pain Research at Pitt provides an outstanding training environment. It has a strong history of successfully training MSTPs.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all criteria addressed

- All criteria are adequately addressed.

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Applicant will complete course on Ethics for Medical Students. Consists of 5 two-hour long group sessions.

Comments on Subject Matter (Required):

- Subjects covered include reproducibility and rigor, falsification/fabrication of data, and data documentation and ownership.

Comments on Faculty Participation (Required):

- Course is taught by Drs. Steinman and Schmidt, faculty directors of the Responsible Conduct of Research Center.

Comments on Duration (Required):

- 10 hours formal course plus 1:1 with advisor.

Comments on Frequency (Required):

- 1x during graduate training.

Budget and Period of Support:

Recommend as Requested.

CRITIQUE 2

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 5

Training Potential: 2

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit: This is an F31 application from an MD-PhD applicant, Ruby Holland, designed to test the hypothesis that MOR+ RVM neurons facilitate pain by inhibiting interneurons in the superficial dorsal horn. Hypothesis testing will utilize a combination of genetic, molecular, electrophysiological, and behavioral approaches. Inclusion of this wide spectrum of very state-of-the-art sophisticated methodologies is considered to be both a positive (serving as a wonderful training experience, demonstrating the use of multiple different methodologies to explore different but related dimensions of a problem,) as well as a negative (possibly spreading the learning experience too thin and preventing in depth consideration of the limitations and confounds of each level of analysis, which were in many cases not adequately addressed). This notwithstanding, the proposed research itself is deemed to be potentially consequential, the mentoring team assembled superb, and the applicant herself to be highly motivated, directed and very likely to achieve a productive career as an independent researcher. Primary mentor, Sarah Ross has committed on hand funding for the duration of the requested training period.

1. Fellowship Applicant:

Strengths

- Excellent background and record of research productivity.
- Excellent writing skills.
- Very purposeful, directed.
- Able to express how this mentored experience fits into career objectives, which are already well defined.
- Strong academic skill set.
- Understands importance of communication skills (writing and speaking) and ability to conceptualize in addition to mastering spectrum of methodologies.

Weaknesses

- Exclusive focuses on pitfalls and confounds in terms of technical difficulties, not in terms of limitations of particular methodology or possible ambiguities of data interpretation.
- Seemingly unaware of essential controls.

2. Sponsors, Collaborators, and Consultants:

Strengths

- Very experienced and dedicated to mentoring.
- Well defined expressed mode of interacting with applicant.
- Required expertise in methodologies proposed.
- Excellent track record of successful mentoring.

Weaknesses

- Notwithstanding strengths outlined above, the lack of attention to interpretational ambiguities highlighted under Research Training Plan below, raises concern about depth of mentoring and preoccupation with novelty of methodology.

3. Research Training Plan:

Strengths

- Proposed research is timely, substantial and likely to be impactful.
- Integrates multiple state of the art methodologies that are appropriate to problem at hand.
- Aims are interrelated.
- Research clearly delineated with learning objectives of each Aim clearly defined.

Weaknesses

- Spectrum of proposed methodologies, FISH, IHC, electrophysiology, confocal microscopy behavioral analyses using multiple pain modalities raises concerns for finishing within 3-year timeline, not to mention learning each in appropriate depth.
- Pitfalls and confounds for each Aim are inadequate.
- Some essential controls and ambiguities are not addressed, e.g., demonstration of specificity of FISH probes, the fact that presence of mRNA does not always predict protein expression.
- Inadequate description of method of quantifying co-expression, e.g., using Mander's coefficients? Will stereological unbiased methods be used for counting? If so, how will they be integrated with the use of Mander's coefficients? Conceptually, quantifying co-expression is easy but in practice much more challenging. The applicant does not seem to appreciate difficulties.
- Morphine is not MOR-specific but stimulates kappa-opioid receptor as well. Thus, the ability of morphine to inhibit 'ON' cells does not necessarily indicate that they express MOR, as is stated.
- Applicant does not consider that the increase in percentage of RVM neurons expressing MOR following persistent inflammatory pain could be compensatory to reduce inflammatory pain, and therefore not necessarily be pain facilitatory.
- Applicant does not consider the possibility that sustained activation RVM DREADD receptor by CNO for hours might result in desensitization, confounding data interpretation.
- There is no control for or discussion of possibility that retrograde transport of DREADD receptors to RVM will not uniformly label all RVM MOR+ neurons. Thus, effect of RVM CNO on nociceptive behaviors might not reflect all RVM spinal inputs. In fact, there is no independent confirmation of the magnitude or uniformity of distribution of DREADD in the RVM.

4. Training Potential:

Strengths

- Highly motivated and focused.
- Build on a very strong research background.
- Mentoring will be incorporate into an already defined career trajectory.
- Rigorous didactic training.

Weaknesses

- None noted.

5. Institutional Environment & Commitment to Training:

Strengths

- Highly dedicated team of mentors.
- Plethora of relevant expertise.
- Excellent described mentoring structure.

Weaknesses

- None noted.

Protections for Human Subjects:

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

Vertebrate Animals:

YES, all criteria addressed.

Biohazards:

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Appropriate

Comments on Subject Matter (Required):

- Appropriate

Comments on Faculty Participation (Required):

- Appropriate

Comments on Duration (Required):

- Appropriate

Comments on Frequency (Required):

- Appropriate

Resource Sharing Plans:

Acceptable

- Appropriate.

Budget and Period of Support:

Recommend as Requested.

Recommended budget modifications or possible overlap identified:

- Sarah Ross, the primary mentor, has committed on hand funding for the duration of the requested training period

CRITIQUE 3

Fellowship Applicant: 2

Sponsors, Collaborators, and Consultants: 1

Research Training Plan: 1

Training Potential: 2

Institutional Environment & Commitment to Training: 2

Overall Impact/Merit: The applicant is an MD/PhD candidate at the University of Pittsburgh School of Medicine and Carnegie Mellon University MSTP with the goal to become a physician scientist. Motivated by the impact of basic science research on patient quality of life, the applicant has already published as a first-author in articles and posters. The research application is centered on the

investigation of the rostral ventromedial medulla via IN-cells which facilitate pain and OFF-cells which inhibit pain with a recent developed the OPRM1cre mouse. The studies will explore how MOR+ RVM spinal projection neurons can be selectively targeted and modulated both in vitro and in vivo, to uncover the anatomy and physiology of these neurons and determine their role in acute pain behaviors and persistent pain states. Anticipated outcomes, pitfalls, alternative strategies are carefully discussed showing a level of rigor in the approaches and conceptualization of this research. The sponsor has an outstanding publication record and a diverse array of methodologies to study fundamental questions, including mouse genetics, imaging techniques, anatomical studies, behavior, and electrophysiology exposing the applicant to a vibrant scientific environment. Richard Koerber and Sarah Ross are both committed to mentor the applicant. It is likely that the applicant will succeed as an independent physician scientist investigator.

1. Fellowship Applicant:

Strengths

- Highly motivated applicant who shows rigor and structured organization of the research plan.
- Clever choice in selecting the sponsor.

Weaknesses

- Potential challenges in combining the PhD and MD training.

2. Sponsors, Collaborators, and Consultants:

Strengths

- Richard Koerber and Sarah Ross are both committed to mentor the applicant.
- Both mentors are well-funded.
- Additional Letters of support have been included that sound all positive.

Weaknesses

- None noted.

3. Research Training Plan:

Strengths

- Along with specific techniques - pain and molecular genetic approaches to study neural circuit function, including the use of Cre alleles and viruses to target and manipulate specific neuronal populations – the applicant plans to be exposed to neuroscience in general and other professional development activities.
- Courses attendance includes: statistics, ethics, and two pain-specific classes

Weaknesses

- None noted.

4. Training Potential:

Strengths

- Great balance among the training goals with potentials to nurture an outstanding future physician scientist.

Weaknesses

- None noted.

5. Institutional Environment & Commitment to Training:

Strengths

- The Pittsburgh Center for Pain Research (PCPR) provides a great environment to get trained in basic and translational pain research.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Inclusion Plans:

- Sex/Gender: Distribution justified scientifically.
- Race/Ethnicity: Distribution justified scientifically.
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Scientifically acceptable.
- Inclusion/Exclusion Based on Age: Distribution justified scientifically.
- Race and age do not apply to this proposal.

Vertebrate Animals:

YES, all criteria addressed.

Biohazards:

Acceptable

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Courses, seminars, and professional development workshops.

Comments on subject matter (required):

- Rigor and reproducibility, falsification/fabrication of data, data documentation and ownership, and mentor/mentee relationships.
- Laboratory safety, research integrity, and environmental health and safety.
- Methods and principles in ethics that translate conceptual methodologies into practical skills for evaluating ethical dilemmas.

Comments on faculty participation (required):

- Unclear how faculty will participate into the rcr training.

Comments on duration (required):

- Over 100 hours of ethics training.

Select Agents:

Acceptable

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:

VERTEBRATE ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 F31 NS116981-01; PI Name: HOLLAND, RUBY

+ Derived from the range of percentile values calculated for the study section that reviewed this application.

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

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Fellowships: Biophysical, Physiological, Pharmacological and Bioengineering Neuroscience
ZRG1 F03B-R (20)
10/24/2019 - 10/25/2019

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html> and NOT-OD-15-106 at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html>, including removal of the application from immediate review.

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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.