Research Development

Beverly Collins
Amber Nestor
Erin Schubert

Protocol Development

Erin Schubert
Administrative Director, PET Center

Protocol Development

- Idea → Grant/Pilot Funding → Protocol
- Plan your protocol from the beginning
- Several protocol sections overlap required grant sections for NIH or foundation grants
- IRB submission & review takes ≥ 6-8 weeks from submission to approval
- IND submission can add ≥ 30 days

Planning Human Research

- Planning the human subjects research early will help take an idea to the next stage
  - Preliminary data may be needed before a grant is submitted
  - Can fine tune ideas into grant aims
  - Develop budget and budget justifications
  - Identify key personnel and resources
  - Human subjects required for some grants

Regulatory Requirements

- Navigating Penn regulatory committees (IRB, RRSC, CTSRMC) will take time
- NIH or other grants may require IRB approval as part of JIT submissions
- Avoid unnecessary start up delays
- Minimal risk studies may allow for retrospective reviews that can provide pilot data

Human Research Requirements

- Background and Scientific Rationale
  - Motivating issue(s)? Impact(s) on field?
- Objectives
- Study Design

Study Building Blocks

- Participant selection
  - What population do you plan to study?
  - Prospective vs Retrospective or Quality Control
- Recruitment
  - How to access your subject population? Does this require additional collaborators?
- Investigational agent?
  - Does the study require an IND?

Study Building Blocks

- Procedures
  - Who will perform the procedures? Identify potential writers of letters of support
  - Are there prospective procedures or retrospective data collection/analysis
- Risks
  - Minimal risk vs More than minimal risk
- Statistical Plan
  - Would statistician consultation be helpful?

Investigational Drugs or Devices

- Does your study involve an investigational drug or device
- Is the drug or device currently made at Penn or does it need to be developed?
- Will your study require a new IND or IDE or does Penn already have an active IND or IDE?

Key Regulatory Contacts

- Erin Schubert – Protocol, IND, Regulatory document development and submission
- Kathleen Thomas and Patty Atkinson- Radiology IND support office for all IND submissions and monitoring
- Sharon Lee – Cyclotron contact for development of drug synthesis, validation testing and CMC creation

Key Links - Research at Penn

- IRB : https://hsera.apps.upenn.edu
- RRSC: https://ehrs.upenn.edu/radiation-safety/topics/research
- CTSRMC: http://www.ctsrmc.org/
- CAMRIS: https://www.med.upenn.edu/camris/
- OCR: https://www.med.upenn.edu/ocr/

Key Links - Research at Penn

- PennERA: https://www.pennera.upenn.edu/
- RSNA grants: https://www.rsna.org/en/research/funding-opportunities/research-grants
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People in department

- Beverly Collins: grant funding, proposal development
- Amber Nestor: budget development
- Erin Schubert: protocol development, IND and IDE , regulatory submissions
- Kathleen Thomas: Regulatory support and resources, clinical trial support
- Bill D'Arcy : Business Administrator for grants, pre- and post-award

Proposal Development

Beverly Collins

Grant Coordinator for Radiology

Submitting a Proposal

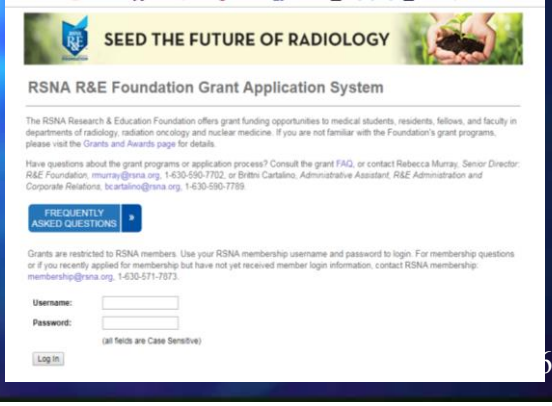
- 2 ways a grant may be submitted
  1. P.I. (Principal Investigator) submits the grant directly to the funding agency.
  2. A representative of Penn submits the grant to the funding agency.

  - Funding agency designates which

Submitting a Proposal

- RSNA's application is submitted by the P.I. online through their website.

- But....



Penn's review process

- EVERY externally-funding proposal must be entered into Penn's online grant application system (PennERA/PD)

In-house review process

- This is all to protect you and the institution from legal issues
- The grant, and the responsibility, falls on the institution.
- You're a sharecropper!

- They will basically review the budget, not the science
- This record will also be used in administering the grant post-award

Penn's review process

- For non-NIH proposals, use the application provided by the funding agency and upload to PD for institution review and approval.
- The funding agency will indicate whether the application is to be submitted by an institutional official.
- (NIH proposals are created from the PD record; you do not use the NIH application package.)

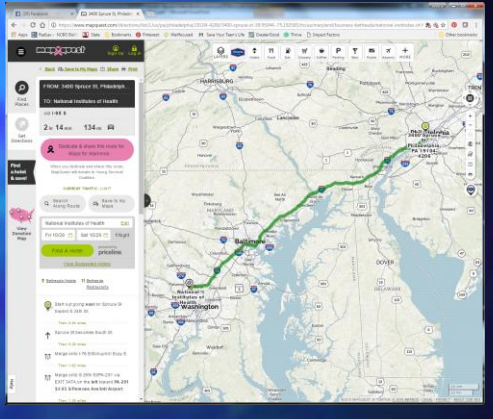
Penn's review process

- I can help you set up the proposal in PD
- You don't need to enter the budget info into PD. We have people to do that for you.
- Amber Nestor handles all RSNA grants and most resident proposals.

On to the proposal itself

2 different views

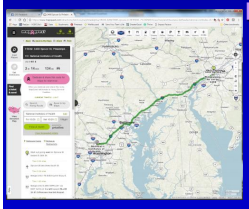
Big picture



Roadmap

Your reviewers need to understand both:

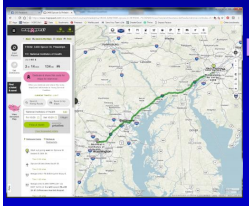
- The BIG PICTURE
  - WHY?
  - What is the point of your research?
  - How does it relate to bigger topics?
  - How is it relevant?



- The ROADMAP
  - HOW?
  - What are the turn-by-turn directions?
  - Could someone else get there from your description?

Also in working on your proposal, you need both:

- The BIG PICTURE
  - Goals
  - Deadlines
  - List of all elements needed



- The NITTY GRITTY
  - Completing of all the individual elements

ELEMENTS OF A GRANT

- Abstract/Summary (overview)
- Specific Aims (goals)
- Research Plan (why and how)
- Bibliography
- CV/biosketch
- Budget and justification
- Resources description
- Letters of support

Grant Sections

- Abstract/Summary

  "State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals…."

Grant Sections

- Abstract/Summary
  - One of most important parts of proposal
  - Write this last.
  - Follow the instructions.
  - "Movie review"

Grant Sections
Abstract/Summary

Abstract·of·Proposed·Plan:¶
Mortality·from·cardiovascular·disease·is·improving·in·the·US.··Yet·the·rate·of·decline·is·less·for·women·than·it·is·for·men.··Women·have·an·increased·rate·of·stroke·risk·with·age·and·more·severe·debilitating·outcomes.··This·difference·can·be·partly·attributed·to·the·various·reproductive·stages·of·a·woman's·life·leading·to·differences·in·vascular·biology·and·ultimately·clinical·outcomes.··However,·most·prevention·and·treatment·strategies·do·not·distinguish·between·gender.··Current·clinical·practice·guidelines·extrapolate·evidence·from·studies·using·a·mixed-gender·or·male·dominant·cohort,·resulting·in·a·gap·in·knowledge·about·women.··Moreover,·although·it·is·universally·accepted·that·intracranial·atherosclerotic·disease·is·a·leading·cause·of·stroke,·only·recently·have·imaging·techniques·for·visualizing·vessel·wall·changes·gained·recognition.··Given·that·injury·first·occurs·within·the·vessel·walls,·studying·the·site·of·an·injury·itself·may·improve·screening·and·diagnostic·accuracy.··Studies·have·shown·gender·differences·in·vascular·biology,·plaque·composition·and·stroke·mechanisms.··However,·how·intracranial·atherogenesis·and·stroke·outcomes·differ·between·genders·have·not·been·addressed.··The·short-term·aim·of·this·proposal·is·to·use·3T·multicontrast·vessel·wall·MRI·to·identify·gender·differences·in·intracranial·vessel·wall·lesion·burden·and·contrast·risk·factor·profiles·in·stroke·patients.··The·translation·aim·compares·clinical·3T·and·ultra-high·field·7T·MR·imaging·with·quantitative·susceptibility·mapping·to·characterize·gender·differences·in·plaque·composition.··The·long-term·aim·is·to·investigate·how·women's·reproductive·stages·(e.g.·pre-·peri-·and·post-menopausal·stages)·influence·risk·factors,·intracranial·atherosclerosis·and·stroke·outcomes.··By·recognizing·gender·disparities·in·stroke·outcomes·and·the·unique·physiology·of·a·women's·life,·the·overarching·objective·of·this·investigation·is·to·help·establish·gender-specific·screening·and·therapy·guidelines.¶

Grant Sections
Abstract/Summary

Abstract·of·Proposed·Plan:¶
Mortality·from·cardiovascular·disease·is·improving·in·the·US.··Yet·the·rate·of·decline·is·less·for·women·than·it·is·for·men.··Women·have·an·increased·rate·of·stroke·risk·with·age·and·more·severe·debilitating·outcomes.··This·difference·can·be·partly·attributed·to·the·various·reproductive·stages·of·a·woman's·life·leading·to·differences·in·vascular·biology·and·ultimately·clinical·outcomes.··However,·most·prevention·and·treatment·strategies·do·not·distinguish·between·gender.··Current·clinical·practice·guidelines·extrapolate·evidence·from·studies·using·a·mixed-gender·or·male·dominant·cohort,·resulting·in·a·gap·in·knowledge·about·women.··Moreover,·although·it·is·universally·accepted·that·intracranial·atherosclerotic·disease·is·a·leading·cause·of·stroke,·only·recently·have·imaging·techniques·for·visualizing·vessel·wall·changes·gained·recognition.··Given·that·injury·first·occurs·within·the·vessel·walls,·studying·the·site·of·an·injury·itself·may·improve·screening·and·diagnostic·accuracy.··Studies·have·shown·gender·differences·in·vascular·biology,·plaque·composition·and·stroke·mechanisms.··However,·how·intracranial·atherogenesis·and·stroke·outcomes·differ·between·genders·have·not·been·addressed.··The·short-term·aim·of·this·proposal·is·to·use·3T·multicontrast·vessel·wall·MRI·to·identify·gender·differences·in·intracranial·vessel·wall·lesion·burden·and·contrast·risk·factor·profiles·in·stroke·patients.··The·translation·aim·compares·clinical·3T·and·ultra-high·field·7T·MR·imaging·with·quantitative·susceptibility·mapping·to·characterize·gender·differences·in·plaque·composition.··The·long-term·aim·is·to·investigate·how·women's·reproductive·stages·(e.g.·pre-·peri-·and·post-menopausal·stages)·influence·risk·factors,·intracranial·atherosclerosis·and·stroke·outcomes.··By·recognizing·gender·disparities·in·stroke·outcomes·and·the·unique·physiology·of·a·women's·life,·the·overarching·objective·of·this·investigation·is·to·help·establish·gender-specific·screening·and·therapy·guidelines.¶

Background:
Disease and conditions

Problem with current practice

Evidence that this study is needed and will be useful

Aims and goals

Grant Sections
Abstract/Summary

Abstract of Proposed Plan:¶

Recently, there have been remarkable advances in targeted cell-based immunotherapies. One of the most dramatic advances involves an FDA approved CAR T cell therapy discovered at Penn that targets CD19 on the surface of B cells and has shown dramatic efficacy in advanced acute lymphoblastic leukemia. Due to this and other recent successes, there has been an explosion of research into cell-based immunotherapies, many of which have shown limited treatment efficacy in solid tumors. For these reasons, a method of in vivo cell-tracking is needed to noninvasively monitor administered cells, enabling the determination of cell distribution, quantity, tumor penetration, and viability. Currently, there are no reliable methods to longitudinally image cell-based therapies over the long duration that they exert their therapeutic effect. Given that cell-based immunotherapies are already genetically manipulated, an attractive approach involves including a reporter gene in the genetic modification process. Here we propose an innovative approach to in vivo cell tracking using an RNA-based reporter gene system based on a well-characterized RNA aptamer that binds to tetracycline derivatives with high, sub-nanomolar affinity. An RNA aptamer-based system has numerous advantages over traditional protein-based systems including: a lack of immunogenicity, the ability to be readily engineered to bind to any molecule of interest, small size/genetic footprint, and no biological function. Furthermore, tetracycline derivatives are well characterized pharmaceutical agents with numerous attractive properties that may be readily accepted by clinicians. Overall, the goal of this proposal is to demonstrate the feasibility of an RNA aptamer as a reporter gene for cell tracking using a tetracycline based radiolabeled probe. These studies will lay the foundation for translation to human trials, and will continue building on my molecular imaging foundation as I work to transition into the role of a clinician scientist developing novel probes answering clinical diagnostic dilemmas.¶

Background: Research

Gap in current research

Proposed work and advantages of approach

Goal of project and personal goal

Grant Sections
Research Plan: RSNA

Specific Aims
Background and Significance
Preliminary Studies
Research Design and Methods
Timeline of events

Grant Sections
Specific Aims

- [RSNA] List the broad, long-term objectives and the goal of the specific research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology. One/half page is recommended.

Grant Sections
Specific Aims

1. Specific Aims

Intracranial atherosclerosis (ICAD) is a leading cause of stroke. Although men have a higher life-time risk for stroke, women account for a larger proportion of stroke events in the older age group. Compared to men, older women may be predisposed to poorer risk factor profiles leading to less favorable functional outcomes due to the hormonal changes during the reproductive stages.1 Although gender-differences in physiology and vascular biology are recognized, how gender affects ICAD and stroke outcomes remains unexplored. ¶

Conventional vessel imaging modalities such as time-of-flight magnetic resonance angiography (TOF-MRA) and computed tomography angiography (CTA) show changes in lumen diameters. However, information about the vessel wall (the site of original injury) is absent.2-4 For instance, ICAD initially develops with deposition of an intimal "fatty streak" causing inflammation and intimal thickening with stenosis occurring later.5 Vessel wall MR imaging (VWI) may be able to detect these pre-stenotic pathologic changes by showing wall thickening and enhancement.6,7 Multicontrast VWI also allows us to study plaque composition and characterize high risk plaque features.8 Gender-differences in symptomatic plaque composition in the more accessible extracranial carotid and coronary arteries have been reported and has implications in reducing risk of stroke recurrence.9,10 Yet, whether the pathophysiology of ICAD parallels atherogenesis in the extracranial arteries has not been addressed. We **hypothesize** that total intracranial vessel wall lesion burden will be significantly different between men and women with stroke. To test this hypothesis, the **short-term objectives** of this proposal are to compare intracranial vessel wall lesion burden between age-matched men and women with stroke using VWI and to contrast their cardiovascular risk factors and plaque composition. The **long-term objectives** are to develop gender-specific screening and therapeutic interventions to target women early when prevention strategies can be individualized and optimized. ¶

Specific Aim 1: Measure gender-differences in the burden of intracranial vessel wall lesions in stroke patients by vessel wall MR imaging on 3T MR. ¶

Specific Aim 2: Compare cardiovascular risk factors of age-matched women and men with degree of intracranial arterial lesion burden. ¶

Specific Aim 3: Characterize gender-differences in symptomatic plaque components *in vivo* using 3T MR and ultra-high field 7T MR and quantitative susceptibility mapping. ¶

Background

Technical details: physiology and imaging

Hypothesis, objectives, Specific Aims

Grant Sections

SPECIFIC AIMS

T cells re-engineered with chimeric antigen receptors (CARs) that target tumor-associated antigens have shown dramatic activity in a variety of cancers. However, a major obstacle in the development of CAR T cell therapy and other methods of adoptive immunotherapy for solid tumors is the difficulty in assessing treatment efficacy. Thus, in vivo cell-tracking methods are needed to noninvasively monitor the presence, distribution, quantity, and viability of the administered cells. Currently, there are no imaging agents to reliably image cell-based therapies over the long period of time by which they exert their therapeutic effect. Given that CAR T cells are already genetically engineered, an attractive approach would be to include a reporter gene as part of the genetic modification process. Currently, the three most common reporter genes available for molecular nuclear imaging include the herpes simplex virus-1 thymidine kinase (HSV1-tk), the sodium iodide symporter (NIS), and the dopamine 2 receptor (D2R). However, all of these reporter genes have limitations including immunogenicity, undesirable reporter probe properties, and concern that the reporter gene alters cell physiology.

An innovative approach to in vivo cell tracking, which overcomes many limitations of the currently available reporter genes, involves the use of an RNA aptamer as a reporter gene. Although RNA aptamers have been used as therapeutic agents, directly labeled molecular imaging agents (i.e. the aptamer itself is radiolabeled ex-vivo and administered to the patient), and as the signaling component for in vitro assays, they have not yet been used as a reporter gene. **The advantages of an RNA aptamer-based reporter gene over more traditional protein-based systems include a lack of immunogenicity, the ability to be engineered to bind to any molecule of interest, small size/genetic footprint, no biological function, the ability to link multiple serial aptamers to boost effective expression, and the potential to couple ligand-binding aptamers to ribozyme elements to modulate gene expression.** The goal of this project is to provide a proof of concept for a reporter gene that encodes an RNA aptamer, by demonstrating that cells that contain the RNA aptamer are capable of binding the corresponding radiolabeled probe. A well characterized, high affinity tetracycline-binding RNA aptamer (KD <~1nM) will be used in this study.

Aim 1: Measure [3H]-tetracycline uptake in cells transformed with the tetracycline-binding RNA aptamer, and compare [3H]-tetracycline uptake in cells that contain multiple sequential grouped RNA aptamers (8 and 16aptamer repeats).

Aim 2: Synthesize [125I]-7-iodotetracycline, characterize its affinity for the tetracycline-binding RNA aptamer, and measure its uptake in cells transformed with the RNA aptamer.

Aim 3: Determine the biodistribution of [125I]-7-iodotetracycline in mice, and utilize in vivo SPECT/CT imaging to measure the uptake of [125I]-7-iodotetracycline in a mouse xenograft model expressing the tetracycline binding RNA aptamer.

Background

Possible solution

Problem with current options

Proposed new option

Goal

Specific Aims

Grant Sections

- Background and Significance
- Briefly sketch the background leading to the present application, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. State concisely the importance and health relevance of the research described in this application by relating the specific aims to the broad, long-term objectives. If the aims of the application are achieved state how scientific knowledge or clinical practice will be advanced. Describe the effect of these studies on the concepts, methods, technologies, treatments, services or preventative interventions that drive this field.

Grant Sections

- Preliminary Studies
- For new applications, use this section to provide an account of the PI's preliminary studies pertinent to this application. This information will also help to establish the experience and competence of the investigator to pursue the proposed project. Preliminary data is welcome but not required for Resident, Fellow, Scholar and Seed Grant applications. If there is no preliminary data, provide supporting evidence in the existing literature.

Grant Sections

- Research Design and Methods (RSNA)
- Describe the research design conceptual or clinical framework, procedures, and analyses to be used to accomplish the specific aims of the project. Include how the data will be collected, analyzed, and interpreted. **Describe the applicant's specific roles in each phase of the project.** Describe any new methodology and its advantage over existing methodologies. Describe any novel concepts, approaches, tools, or technologies for the proposed studies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

NIH grant sections

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)¶

BIOGRAPHICAL SKETCH¶

Provide the following information for the Senior/key personnel and other significant contributors.↵
Follow this format for each person. DO NOT EXCEED FIVE PAGES.¶

NAME:¶

eRA COMMONS USER NAME (credential, e.g., agency login):¶

POSITION TITLE:¶

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*¶

INSTITUTION AND LOCATION¤	DEGREE¶ *(if applicable)*¶	Completion Date¶ MM/YYYY¶	FIELD OF STUDY¶
¤	¤	¤	¤
¤	¤	¤	¤
¤	¤	¤	¤
¤	¤	¤	¤
¤	¤	¤	¤

¶

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.¶

A. Personal Statement¶

Briefly describe why you are well-suited for your role in the project described in this application. The relevant factors may include aspects of your training; your previous experimental work on this specific topic or related topics; your technical expertise; your collaborators or scientific environment; and your past performance in this or related fields (you may mention specific contributions to science that are not included in Section C). ···Also, you may identify up to four peer reviewed publications that specifically highlight your experience and qualifications for this project. ···If you wish to explain impediments to your past productivity, you may include a description of factors such as family care responsibilities, illness, disability, and active duty military service.¶

B. Positions and Honors¶

List in chronological order previous positions, concluding with the present position. List any honors. Include present membership on any Federal Government public advisory committee.¶

C. Contribution to Science¶

Briefly describe up to five of your most significant contributions to science. For each contribution, indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in

1 of 5 | Words: 1,813 | 100%

RSNA elements

- C. Priority Statement: Describe your area of professional/scientific interest(s) and long-term career goals and objectives. Briefly describe how the proposed plan relates to the applicant's priorities and how these priorities are served at the host institution. Not to exceed 1000 words.

RSNA elements

- Scientific Advisor: brief description of the advisor's role as mentor for the applicant; describe the role of the resident/fellow in the overall project and how their **independence** will be established from previous or existing efforts). Not to exceed 1000 words.

RSNA proposals

- Process:
  - You start your application on RSNA site
  - I will give you info on who to list for institutional representatives
  - You will download the signature page, sign it, and give it to me.
  - I will get mentor & chair signatures and post to PennERA
  - When approved, we will send you the completed page w/institutional signature

RSNA proposals

- Timeframe
  - Deadline to RSNA: January 15, 2020
  - Tell Beverly by Dec 2:
    - Title
    - Whether any human or animal subjects
  - Budget deadline to Amber: December 13, 2019 finalized

Update on Larry the Lemon Tree

Update on Larry the Lemon Tree

Be like Larry!