**Supporting Materials for “Writing and Editing for Impact”**

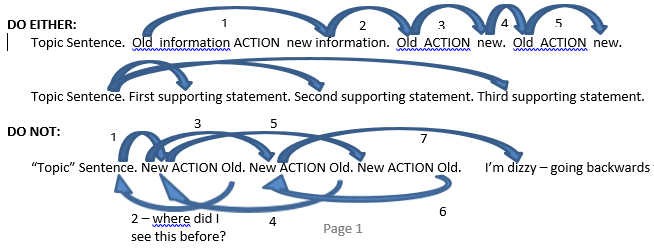
**April 29, 2019**

**NORDP 2019, Providence, RI**

Joanna Downer, Duke University School of Medicine

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**Paragraph structure/organization:**



**Writing examples**

**(Remember, every first draft is perfect, because it just has to exist!)**

**Gopen’s “Reader Expectations” – Whose story is it, action in the verb, stress positions, and backwards links.** First paragraph of Aims page for a new NIH R01 application. Underline what is in the “stress positions”, circle items that seem to be “backwards links”. Are they related to one another as they should be? (i.e., one sentence’s stress position should be reflected in the next sentence’s backwards link)

Focal and segmental glomerulosclerosis (FSGS) is a frequent cause of end-stage renal disease. The pathogenesis of FSGS has not been precisely defined with no consistently effective treatments. Recent studies identifying causal genes in rare forms of inherited FSGS have provided powerful insights into its pathogenesis that are also relevant to other forms of glomerular diseases. Genetic heterogeneity has been the precedent; mutations in at least six genes have been associated with familial FSGS.

**2. SPLAT:**

Melanoma is extremely resistant to conventional chemotherapy and radiotherapies. Although BRAF/MEK targeted therapies have produced a significant response, their efficacy is rather limited by the development of resistance within 6-12 months of treatment. It has become increasingly clear that melanoma malignancy and resistance to therapy are attributed to a divergent array of mechanisms that ultimately converge on pro-growth and pro-survival signals. The objective of this study is to explore therapeutically targetable regulators of [a particular protein] which represents a common process pivotal for signal transduction.

**3. FLUFFY AND SPLAT, A BIT CIRCULAR, AND ALSO TELLS RATHER THAN SHOWS**

(First paragraph of the overall of an NIH Center-type application):

Medical imaging involves some of the most advanced and most beneficial technologies used in medicine today. Justified by the indispensable information that it brings forth, imaging is integrated into the diagnosis and management of a wide range of human disorders. The complexity of medical imaging has continued to accelerate outpacing our ability to optimize the clinical use of its many new features and abilities. Given this rapid technological evolution, determining the optimal use of imaging technologies has proven to be a significant challenge across many and diverse objectives of scientific inquiry and clinical application.

**UNCERTAINTY/DISTRUST created by MULTIPLE NON-IDENTICAL STATEMENTS OF A DISTINCT IDEA:**

**4.** (From an NIH R01 resubmission):

Aim 1 Hypothesis: ER-localized mRNAs undergo distinct, cohort-specific modes of membrane association in vivo.

Elsewhere in Aim 1:

We hypothesize that SRP-independent mRNA localization to the [cellular subcompartment] operates by a mechanism schematically illustrated in **Fig. 1B**, where mRNAs encode intrinsic localization signals (“zip codes”) that, through the activity of *trans*-binding factors, enable the direct localization of mRNA to the [cellular subcompartment].

…we hypothesize that mRNAendo transcripts contain *cis*-localization information

In this subaim, we propose to further test the hypothesis that mRNAs undergo cohort-specific segregation into distinct ER membrane subdomains.

**5.** (From an NIH R01 submission)

(Aims page) Aim 2 Hypothesis: Cohort-specific modes of mRNA binding to the ER are mediated by distinct subsets of RNA binding proteins.

(First sentence in Aim 2 background):

We hypothesize that the distinct ER membrane binding properties of mRNAendo transcripts are mediated through RNA binding proteins that selectively associate with this mRNA cohort.

**EXCESSIVE COUCHING OR TIMIDITY:**

**Stories:**

**6.** Joanna’s favorite examples of these are when folks say they’ll “try to” or they “plan to”, or they “believe”. She always imagines Dana Carvey’s Church Lady character from *Saturday Night Live* saying “Isn’t that special?”

**7.** Other common examples include use of multiple “couching” words per sentence, such as might, may, could, potential, possible, etc., suggesting the likelihood of the described – and desired – event is vanishingly small.

**8. OVERLY BOLD** (from an NIH Center-type grant):

We will greatly expand the library to encompass all possible combinations of sex, age, height, and weight indicative of patients seen in a hospital-scale population.

**9. ARROGANT OR NAIVE** with seemingly insurmountable problem, & tell not show:

(NIH Center-type grant; part of an abstract for a Project):

Virtual trials offer a number of advantages over clinical imaging trials. However, prior work on [this problem] has led to [simulations] that are either too slow, too generic, or too coarse for the timing, accuracy, and the resolution needs of [these trials]. This project develops a rapid, accurate, and realistic simulation platform capable of generating [amazing] CT images of highly detailed anatomy under a variety of clinical protocols. The work builds on our considerable expertise in developing simulation tools for assessing image quality and dose in X-ray based technologies. We will build a new hybrid simulation platform where high spatial and temporal details are provided by [one method], precise scatter and dose estimates are provided by [another], and the entire platform is implemented in [an] environment to meet the desired speed and throughput of [these trials].

The ***specific aims*** of the project are to modelCT acquisition subcomponents in detail (**Aim 1**), to model CT acquisition schemes for estimating primary signal, scatter, and radiation dose (**Aim 2**), to implement processes for integration, image formation, and validation of the simulation platform (**Aim 3**), and to build a modular and user-friendly interface to enable effective use of the simulator (**Aim 4**). The simulation will include generic, user-defined, and scanner-specific models and reconstruction algorithms, encoded as individual modules. [We will also build] a customized user-interface with [two key kinds of] utility. The simulation will generate sinograms for the acquisition and reconstruct images using either generic, user-defined, or manufacturer-specific reconstruction algorithms. We will then perform task-based verification and validation of the simulation package and optimize its overall performance. The project further generates virtual CT image datasets from multitudes of virtual phantoms as a resource for distribution to the imaging community.

This work will provide a first-of-its-kind rapid, accurate, and CT simulator with generic, user-customizable, and scanner-specific 3D and 4D modeling capabilities. Users will be able to utilize the simulator for a variety of CT-based technology development and applications, including radiation dose optimization, task-based design and evaluation of CT technologies, and artificial intelligence (AI)-based training through generating large-scale, on-demand hyper-realistic image datasets.

**10. EXCESSIVE ADJECTIVES** (from a background section to a large institutional grant):

Investigators face decreased funding from traditional sources, and clinician-scientists are under mounting pressure to generate clinical revenue. Proliferating regulatory and compliance requirements are increasing costs and timelines [ref], and massive expansion of new technologies means that few investigators will have all the expertise or resources needed to translate a scientific finding into a potential therapy; they need improved ability to access scientific collaborators, complex technologies and expertise in key translational disciplines including regulatory science, technology transfer, biostatistics, informatics and ethics.

**MISLEADING ARGUMENTS OR SURPRISES:**

**Stories, since examples tend to be pages long:**

**11.** In the FSGS grant application whose first original paragraph is included above, the investigator had mentioned in passing but not described in detail her unique, robust cohort of families, some of them quite large. That led to reviewer concerns that wasn’t using her robust cohort for some unstated reasons, and that as a result she didn’t have enough families and wouldn’t have robust phenotype information. (This also can be identified as a “real estate” problem, where the space allocated doesn’t accurately reflect the importance of the topic to the research.)

**12.** (an experience with a Project within an NIH Center-type grant): A Project had very clearly and carefully explained a particular approach, but when you turned the page it said “However, we’re not going to use this approach” without first laying out what its weaknesses or disadvantages were or that there was a better (or any other) option.

**13.** Other useful examples of failure to foreshadow and quick/brief solutions include when the Aims page doesn’t mention use of animals or humans, or other general hints of the ways in which the questions will be answered/investigated.

**UNCERTAINTY created by multiple potential interpretations:**

**14.** (From an NIH Center-type grant Overall description):

More specifically, virtual trials offer a number of key advantages:

1. Virtual trials allow experiments to be conducted quickly and cost effectively on a computer with precise controls and known ground truth.

…

5. Patient-specific protocols can be adjusted based on size or weight, while providing radiation dose levels become personalized and accurate.

**16. SPLAT, UNCERTAINTY CREATED BY INCONSISTENT TERMINOLOGY USAGE, and OVERLY TECHNICAL** (from an NIH R01):

Glaucoma is a group of human disorders characterized by a progressive loss of retinal ganglion cells and irreversible vision loss. There are multiple types of glaucoma, depending on the etiology. Primary open angle glaucoma (POAG), the most common form, is a disease often coincident with aging and elevated intraocular pressure (IOP) resulting from excessive resistance to aqueous humor (AH) drainage through the trabecular meshwork (TM), the primary outflow tract.

The TM consists of sheets of connective tissue beams lined by TM endothelial cells. Each beam is composed of a central elastic core surrounded by collagen fibers embedded in a ground substance. The glaucomatous outflow pathway is characterized by thickening of the trabecular lamellae and accumulation of long-spacing collagen bundles and elastic fiber sheaths, which is presumed to stiffen the TM and prevent the tissue to respond to mechanical cues. The exact causes underlying the deposit of extracellular material (ECM) and thickening of the beams remain unknown; but it is likely a consequence of excessive synthesis of ECM components (likely resulting from the increased TGF-β content described in the AH of glaucoma patients), decreased proteolytic degradation, or both. Matrix metalloproteinases (MMPs) have been historically believed to be the major proteases involved in ECM degradation; however, emerging evidence indicates that while MMPs play a critical role in initiating ECM degradation in the extracellular environment, other proteases or the coordinated action of several types of proteases (i.e. cysteine and serine proteases) are responsible for the bulk matrix degradation, occurring pericellular- and intracellularly in the lysosomal compartment, associated to lysosomal cathepsins. The contribution of a cathepsin-mediated pericellular and intracellular ECM degradative pathway and the effect on outflow physiology has not been studied so far.

**17. RIGHT INFORMATION IN RIGHT PLACE (STRESS POSITION):**

This study advances the field … by testing the efficacy of portable, technology-based neuromodulatory approaches to enable Veterans to manage pain in a self-directed manner outside a clinic setting.

**RIGHT MATERIAL IN THE RIGHT PLACE AND WITH THE RIGHT LABEL** (or “obey your subheadings”):

**18.**

**After modest training and support, Veterans with chronic pain and traumatic brain injury can implement neurofeedback and mindfulness treatments at home via mobile technology.** Both mobility and self-directedness address barriers that Veterans report with traditional treatments. Developing these alternative mobile treatments would also reduce dependence on pharmacological treatments, reduce the need for clinic visits, and minimize associated stigma.These self-directed approaches also allow Veterans to be actively engaged in their own treatment, a desire endorsed in our national survey by three-quarters of Veterans with traumatic brain injury: "It’s up to me to work out my own problems."{ref}

**19.**

**Objectives.** Chronic pain is a critical problem for Veterans with traumatic brain injuries. The main objective of this proposal is to conduct a randomized controlled trial to test the efficacy of using mobile technology to deliver interventions for reducing chronic pain among Veterans with complex brain injuries.

**20. RIGHT INFORMATION IN THE RIGHT PLACE** (show don’t tell):

**Duke Scholars in Molecular Medicine Program (infectious diseases track; optional).** Through this separate program, our trainees will have a unique opportunity to identify unmet challenges in clinical medicine related to their areas of basic scientific inquiry and gain first-hand knowledge of the processes related to bench to bedside translation. This program allows emerging basic scientists to build collaborative relationships with clinical colleagues early in their experimental work in a way that promotes innovation and purpose. Direct clinical experiences are complemented by case conferences in which participants are involved in patient presentations, pathological and radiographic correlates, and discussions about “missing” links: areas with knowledge gaps (mechanistic, therapeutic, and diagnostic) and how those gaps may be addressed through basic scientific investigations. Program participants also engage in clinical research focused on journal clubs in which they will learn about the transition from pre-clinical studies into clinical trials, understand the stages of clinical research, and identify challenges and barriers in the translation of ideas and knowledge from the bench into the clinics. This program also includes a guest faculty series in which world-class translational and clinical investigators meet with our program participants to discuss their careers and serve as role models. The program is 9 months long and does not impede the bench training experience or impact the length of training.

**21. RIGHT INFORMATION IN RIGHT PLACE** (with “don’t make reviewers work”, and “show, don’t tell”):

The training program faculty were selected using criteria including research interests, funding level, and diversity in terms of seniority, scientific expertise, ethnicity, and gender. By intentionally selecting faculty members at different career stages and with varying levels of experience and accomplishments, we are also creating a program in which younger mentors can learn from senior mentors, collegiality is encouraged, and trainees have a range of choices. We have 8 Assistant Professors, 11 Associate Professors and 9 Professors. In addition, 2 faculty members are current and former Department Chairs ([names were provided]), 7 are current Center or Institute Directors ([names were provided]), 8 are women, and 3 are underrepresented minorities ([names were provided]). The list of mentors is also presented in **Table 2**. Based on the information provided in **Table 4** and the biosketches, it is clear that all of the mentors have well-funded research laboratories, and most have a record of sustained grant support. All of the Assistant Professors are funded by generous start-ups and also, in most cases, external sources of funding. While our faculty are currently well-supported, should lapses arise, the Duke School of Medicine has a Bridge Funding program; thus even in a difficult research funding climate, our faculty have a safety net to help ensure stability. **Table 5** documents the extensive training experience of our faculty members. **Table 6** shows the productivity of the trainees. Taken together, these data illustrate the strength and vitality of the proposed program as well as its breadth and quality.

**CREATING UNCERTAINTY** (every word, phrase, sentence, paragraph and idea presented should have only one possible interpretation, ever):

**22.**

This training program is intended to provide ongoing support for 5 predoctoral trainees in the general field of host-microbial interactions. Participating faculty in this program are 28 faculty members in various academic departments at Duke University, working in the area of bacterial, fungal, and viral pathogenesis (see above). Overall, the broad research programs of the participating faculty include the use of a number of vertebrate and invertebrate model hosts, genetic and genomic technologies, and the study of the influence of human genetic determinants and the microbiome on susceptibility to infections, host physiology, and inflammatory disorders. This faculty trains graduate students and post-doctoral fellows who are supported by a variety of mechanisms including institutional research training programs, research grants, and individual pre- and post-doctoral fellowships. **This application requests support for** **5 predoctoral trainees during their 2nd and 3rd years**. Through this funding mechanism, our goal is to seek support for a number of students who are interested in host-pathogen interactions.

**23.**

In the fall of the 2nd year, the program trainees will meet with the program Executive Committee for an advisory and informational lunch session about the program as well as with the aforementioned program External Advisory Committee during their annual visit to [the institution]. [lots of intervening text] During the 3rd year, predoctoral students will again meet with the Program EC for advising as well as the EAC.

**24.**

Thus, evolution has evolved to have a redundant back up for this function: two genes with overlapping functions.

**25.** (from an NIH Career Development Plan):

I will plan to take the following didactic courses: …

**26.**

In addition, guidelines will be established for the urgent management of acute complications of sickle cell disease, both inpatient and outpatient. Having an established relationship with patients and a working knowledge of their medical histories will allow for improved management of acute pain crises.

**27.** (from a dissertation):

**TGN Sorting.** Conventionally, sorting from the TGN can be characterized as three major pathways. In fibroblast cells, proteins can be sorted into one of the two conventional pathways: the constitutive secretory pathway and the endosomal-lysosomal compartments. Most cell surface proteins are transported to the PM through the constitutive pathway, but some proteins, such as Tfr and M6PR, can be targeted to the cell surface both via cells specialized in regulated secretion such as neuroendocrine cells. Proteins can also be sorted into the third pathway, the regulated secretory pathway. On the regulated secretory pathway, some TGN proteins, such as furin and M6PR, can be sorted into the ISGs but are retrieved out of the ISGs likely to some endosomal compartments. Moreover, the ISGs host the constitutive-like secretory pathway that can transport proteins from the ISGs to the cell surface. Finally, the TGN also communicates with the endocytic pathway, since the vesicles containing the TGN proteins (e.g. TGN38, furin, and M6PR, etc.) derived from the endosomal compartments can be transported to the TGN.

**28. CUES and READER EXPECTATIONS:**

The main objective of our research includes defining the roles that select metalloproteinase family members—chiefly matrix metalloproteinase 19 (MMP19) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 4, 9, and 15—play in ovulation.

**DIFFERENTIAL DIAGNOSIS EXERCISES**

**29.** (impact statement at the end of an Aims page for an NIH R01)

This work is expected to lead to a deeper mechanistic understanding of the processes by which pathogenic mycobacteria manipulate host immune cells and stroma to survive, leading eventually to the potential development of anti-angiogenic host therapies and their testing as novel adjunctive therapy for human mycobacterial disease.

**30.**

**Center for Excellence in Applied Research and Learning**

Oregon Health & Science University is pleased to announce that the Oregon Special Center for Something (OSCS) has received a 5–year X-90 award as a Center of Excellence in Some Kind of Research and Learning from the Agency for Applied Health Research (AAHR).

OSCS is the core applied research network (ARN) for VOLDEMORT (Very Obscure Learning Data for Education and Management in the Oregon Regional Trust), a consortium comprised of six ARNs. VOLDEMORT is one of eight research collaborative institutions receiving this award from AAHR.

OSCS has established itself as the core center for VOLDEMORT by successfully collaborating and networking with other ARNs. “The agreement among five strong, well established ARNs to collaborate with OSCS is evidence of our strong track record as both a successful collaborator and an effective leader of collaborative research,” said OSCS Director VOLDEMORT Principal Investigator Jane Scientist, PhD.

VOLDEMORT will accelerate the generation of knowledge and create a venue for community learning. The consortium aims to:

1. Foster the capabilities of six ARNs comprised of 6,000 scientists in 533 applied research practices through a robust collaboration designed to conduct research to improve the quality, effectiveness and safety of applied research.
2. Accelerate the conduct of ARN research through a well designed, high functioning common infrastructure that enables the efficient conduct of research.
3. Promote continuous learning and sharing across ARN networks and practices to accelerate the dissemination of knowledge and bi-directional communication.

**31.** (Concluding statement for an NIH training grant application)

Although the Program membership is fully funded through external grants and generous start-up packages, the current funding climate and the strong interest in host-pathogen interactions of our current students has limited our capacity to train students in this important and exciting area of research.

**32.** (Start of an NIH R01 Aims page)

Medulloblastoma is the most common malignant solid cancer in children with a 5 year survival of 85-60%. Adjuvant chemotherapy is toxic and adjuvant radiation is the cause of permanent neurocognitive disability. At recurrence, chemotherapy and radiation are ineffective and the median overall survival is less than 1 year. There is a significant need for novel and efficacious therapies to safely improve the quality of life and survival in patients with medulloblastoma.

The genetically engineered oncolytic poliovirus is a non-pathogenic poliovirus:rhinovirus chimera with a tumor-specific conditional replication phenotype. Poliovirus’ anti-neoplastic potential is due to a series of (i) direct lytic effects on tumor cells; (ii) presentation of tumor-associated antigens in a highly adjuvanted context; (iii) pro-inflammatory and danger signals stemming from tumor destruction and activation of an antiviral type 1 interferon response; (iv) infection and pro-inflammatory activation of dendritic cells and tumor associated macrophages; (v) durable anti-tumor immunity evoked by effector cytotoxic T lymphocyte responses. However, the details of these mechanisms are unknown.

Poliovirus has tropism for tumor cells by virtue of expression of CD155. CD155, an onco-fetal cell adhesion molecule ectopically upregulated in ectodermal/neuroectodermal cancers, is broadly expressed on cancerous cells, cancer ‘stem-cell-like cells’, and tumor-associated proliferating vasculature. CD155 is expressed in a variety of tumors including medulloblastoma.

To facilitate concentration of the therapeutic agent at the tumor site while minimizing systemic exposure, poliovirus is delivered directly into the tumor via convection enhanced delivery. Significant pre-clinical anti-tumor activity without neuropathogenicity of poliovirus has been observed in vitro and in several rodent solid tumor and neoplastic meningitis models by our group. The ongoing FDA approved phase I trial of poliovirus in over 30 adults with recurrent malignant glioma did not yield evidence of viral encephalomyelitis, poliomyelitis or meningitis with a proportion of patients enjoying prolonged disease survival up to 43+ months (preliminary data). Preliminary human data suggests that inflammation caused by poliovirus may be more important than tumor cell lysis for tumor response.

**33.** (full NIH Aims page)

**The main goal of the proposal is to identify targets to tame the malignancy of human Deadly Cancer (DC) by using transcription factor-mediated induced pluripotent stem cell (iPSC) methodology**. DC has a dismal prognosis, mainly because tumors are usually detected too late to be effectively treated. Although genetic mutations in key oncogenes are required for initiation of DC precursor lesions, there is now clear evidence that reversible cell factors (autonomous or non-autonomous) drive malignancy of DC. While DC has distinct subtypes that correlated with the prognosis, it is unclear how each subtype can be established and whether each subtype can be reversible. However, current models to study human DC provide only a static endpoint state of DC and are therefore less suited for studying cancer dynamics, hampering the efforts to tackle this devastating disease.

In normal embryogenesis, cellular fate is well-orchestrated through multiple layers of gene regulation by chromatin states and master transcription factors; failed regulation leads to cancer phenotypes. Defined transcription factors (DTFs) can reverse normal somatic cell fates into the iPSC throughout reverse embryogenesis, allowing studying dynamic events occurred during cell fate decision. **I previously employed this reprogramming strategy to create an iPSC-like line from advanced, recurrent human DC and demonstrated a proof-of-principle of cellular reprogramming to model the early stages of DC and utilize as a tool for the discovery of early diagnostic biomarkers.**

Common epigenetic factors can differentially elicit tumor formation or reprogramming to pluripotency. Thus, reprogramming methodology can provide a unique opportunity to disassemble and reassemble the cancer epigenome, offering a new avenue for the development of therapies. Intriguingly, while all four transcription factors (DTFS) are required for reprogramming cancer to iPS, the activation of these factors individually contributes to tumorigenesis. However, it remains unclear how and what extends the DTFS factors engage the cancer genome, begin erasing subset of cancer epigenome to reguide the cell identity to a pluripotent state. The reprogramming factors are known to suppress the original cellular identity in normal somatic cells upon induction. Our preliminary single-cell RNA-seq data show a cluster is significantly negative-correlated with master transcription factor for a subset of DC during reprogramming of DC, indicating that DTFS indeed may disrupt DC subtype cell identity. Therefore, **I hypothesize that DTFS would disrupt a subset of DC epigenomes upon reprogramming (“re-wiring of cancer epigenome”) and help the subsequent activation of master transcription factors or chromatin factors that lead to the intermediate population, which may disrupt DC identity or unmask early cancer gene signatures**. Better understanding the process of “re-wiring of the cancer epigenome” by DTFS can uncover novel targets for disrupting cancer identity and an understanding of the early stages of cancer.

Aim 1. To examine the effect of DTFS factors in DC subtype identity during reprogramming, we will examine the alteration of gene expression in each subtype tumors upon DTFS induction using single-cell RNA-seq, bulk-RNAseq, and ChIP-Seq.

Aim 2. Validate the utility of master factors rewiring DC malignancy in vitro and in vivo. To evaluate whether the top candidates are responsible for the early cancer phenotype, we will knock down them during reprogramming. Next, to determine whether the activation of these target factors can tame cancer malignancy, we will over-express the final selected candidates along with DTFS in cancer organoids derived from various DC patients.

Aim 3. To investigate whether DTFS can reverse or disrupt cancer phenotype, we will re-activate Tet0-inducible DTFS expression in tumor-bearing mice injected with DC iPS-like cell I developed as well as introduce DTFS in well-established DC mouse model. Tumorigenicity will be evaluated by histology features and tumor volume (DC with DTFS vs. DC without DTFS).

Altogether, we aim to determine if the transcription factor-mediated reprogramming of cancer cells to pluripotency allows for stage-specific disassembly of the cancer transcriptome, thereby opening avenues for discovering new targets that can tame DC malignancy.

**34. IMPROVED VERSION OF EXAMPLE 1 (first graf of an NIH R01 Aims pg):**

Focal segmental glomerulosclerosis (FSGS) is a frequent cause of end-stage renal disease. The pathogenesis of FSGS has not been precisely defined and there are no consistently effective treatments. Recent studies identifying causal genes in rare, inherited FSGS, including our own studies, have associated familial FSGS with mutations in at least six genes, and each discovery has clarified molecular mechanisms of glomerular injury. To build on this productive line of inquiry, we have ascertained and carefully characterized 118 families with familial FSGS. Previously, we showed that a *TRPC6* gene mutation was the cause of autosomal dominant (AD) FSGS in one of these families, for the first time implicating dysfunction of an ion channel as a primary cause of glomerular pathology. Because channels are often amenable to small molecular antagonists, this discovery may lead to new therapeutic approaches for FSGS. We have screened the remainder of our families for mutations in genes known to cause FSGS and identified the causal mutations in an additional 6 kindreds; the genetic basis of disease in the remaining 111 families is unknown. The objective of this proposal is to use this valuable and unique family resource to systematically identify causal genes for familial FSGS.

**35. IMPROVED VERSION OF EXAMPLE 16 (first graf of an NIH R01 Aims pg),** although we don’t know yet whether trabecular lamellae = beams:

Glaucoma is a group of human disorders characterized by a progressive loss of retinal ganglion cells and irreversible vision loss. There are multiple types of glaucoma, depending on the etiology. Primary open angle glaucoma (POAG), the most common form, is often coincident with aging and elevated intraocular pressure (IOP). This IOP results from poor drainage of the aqueous humor (AH) through the eye’s primary outflow tract: the trabecular meshwork (TM). The normal TM consists of sheets of connective tissue beams – each composed of a central elastic core surrounded by collagen fibers embedded in a ground substance. These beams are also lined by TM endothelial cells. In glaucoma, the outflow pathway is characterized by thickening of the trabecular lamellae and accumulation of extracellular matrix material (ECM) – in particular long-spacing collagen bundles and elastic fiber sheaths. These changes are presumed to stiffen the TM, prevent the tissue from responding to mechanical cues, and increase drainage resistance. However, the exact causes underlying these changes to the TM remain unknown. Three main contributors are expected: excessive synthesis of ECM components, decreased proteolytic degradation, or both. Excessive ECM component synthesis likely results from increased TGF-β content described in the AH of glaucoma patients. ECM degradation is thought to be carried out in large part by matrix metalloproteinases (MMPs). However, emerging evidence indicates that while MMPs play a critical role in initiating ECM degradation in the *extracellular* environment, other proteases or the coordinated action of several types of proteases (i.e. cysteine and serine proteases) are responsible for bulk matrix degradation. This bulk degradation occurs pericellularly and intracellularly in the lysosomal compartment and is associated with lysosomal cathepsins.

While the contribution of such a cathepsin-mediated ECM degradative pathway and its effect on outflow physiology has not been studied to date, our preliminary data….

**What do you notice about these compared to the originals?**

**EXAMPLES OF EDITING vs. EDIT AND COMMENT vs. COMMENT:**

\_\_\_

**36.**

On the basis of the two criteria noted above, we hypothesize that mRNAendo transcripts contain encode *cis*-localization information.

\_\_\_

**37.**

Original:

It should be explicitly noted that the two pathways might operate simultaneously on a given mRNA; there is no *a priori* reason to assume that the two pathways are functionally autonomous.

Edit + comment:

It should be explicitly noted that SRP-dependent and -independent pathways might operate simultaneously on a given mRNA; there is no *a priori* reason to assume that the two pathways are functionally autonomous.

\_\_\_

**38.**

Original:

To gain insight into the mechanisms and pathways of mRNA localization to the ER, methods were developed for isolating highly enriched cytosolic- and ER-associated polyribosomes from tissue culture cells [[17-19](#_ENREF_17)].

Edit + Comment:

To gain insight into the mechanisms and pathways of mRNA localization to the ER, we have developed methods for isolating highly enriched cytosolic- and ER-associated polyribosomes from tissue culture cells [[17-19](#_ENREF_17)].

\_\_\_

**RIGHT INFORMATION IN THE RIGHT PLACE,** prevent reviewers’ defensiveness and “obey your subheadings”:

**39.**

**Potential challenges and alternative strategies.** Before submitting this application, we evaluated different options for the study design regarding the control group. With our current design, we considered that our study population might derive therapeutic benefit from routinely taking time out to relax and listen to soothing sounds for 12 weeks. Further, individuals participating in a treatment study may produce a placebo effect, and observing individuals on the study may produce a Hawthorne effect, both of which could lead to benefits in our control group. Despite these issues, we considered other options, but each had significant drawbacks. We considered having a "no treatment at all" control group, but using this approach we would be unable to discern whether differences between the control and experimental groups were attributable to the interventions themselves or merely to taking time out to engage in the interventions. We also considered a four-arm randomized clinical trial with a usual care condition as well as an unstructured relaxation condition, but this approach would lead to an expensive, complicated research design. In the end, we were persuaded by the strength of the current design's permitting us to compare conditions to determine whether mindfulness or neurofeedback add benefit above and beyond merely taking a certain amount of time to relax. If we do not find differences, our findings might at least determine that regularly scheduling relaxation time may be enough for this study population. If we do find differences, our findings would determine that interventions beyond simple relaxation time is necessary. Finally, we will develop a statistical analysis plan to include strict tests comparing different improvement trajectories if we see improvements in all three study arms.

**RIGHT INFORMATION IN RIGHT PLACE** (and not where it is prohibited!):

**40.**

Attendance at our Work in Progress meetings, our scientific events, and our sponsored seminars in host-microbial interactions (part of [the program’s] departmental seminar series) will be required for all program trainees. In the Appendix, we have attached the flyer for the upcoming symposium and the work-in-progress meeting schedule.

**41.**

Website: [included for each training program faculty member in their respective descriptions]

**CREATING UNCERTAINTY:**

**42.**

This training program is intended to provide ongoing support for 5 predoctoral trainees in the general field of host-microbial interactions. [lots of intervening text] This application requests support for 5 predoctoral trainees during their 2nd and 3rd years.

**43.** (DOD application, requests single statement of Aims)

(initially suggested alternative) Aims: To assess the efficacy of mobile interventions that provide neurofeedback and mindfulness training on reducing pain symptoms in Veterans with complex brain injuries; and to explore the interventions’ impact on risk behaviors and a predictor of cardiovascular health.

**44.** (DOD application)

(Original, suggestion in comment) If the research is successful, it will fundamentally shift clinical practice of pain management for Veterans, service members and civilians.

**45.** (comment used on writing example #**16** and edited version #**35**)

…These beams are also lined by TM endothelial cells. In glaucoma, the outflow pathway is characterized by thickening of the trabecular lamellae and accumulation of extracellular matrix material (ECM) – in particular long-spacing collagen bundles and elastic fiber sheaths. …

**Example of highly valuable comments that should also be reiterated in email text:**

[**CONTEXT**: a young investigator applying to the DOD sent his draft for review]

**46.**

I’ve adjusted the formatting to meet DOD’s very specific requirements of only Times New Roman, 12 pt (not condensed), single spacing, with half-inch margins. Be sure all of the application documents are formatted in this way.

**47.**

Some edits on this page were to allow separation of the Relevance from the Aims, as requested in the format. Doing so also revealed weaknesses in the statement of the Aims that have been addressed/called out below.

**48.**

BE SURE TO DELETE PAGE NUMBERS BEFORE PDFing TO SUBMIT

**KEYS OF AN EASY TO FOLLOW STORY –**

There’s a beginning [set the stage], middle [what happens sequentially], and end [the stage clears]

Parallel construction lets the reader start to predict what’s coming [too hot, too cold, just right; always Papa Bear, then Mama Bear, then Baby Bear]

Cues regarding time and place [bolded below]

Addresses the “who, what, when, where, why, how” at each step

Gives the bottom line [underlined below]

No surprises [dragons enter the house while Goldilocks sleeps!]

No “red herrings” [i.e., the narrator spends paragraphs and paragraphs describing the little bushes around the Bears’ house, but the bushes never reappear in the story – she doesn’t hide in them, the bears aren’t hiding in them, Prince Charming isn’t hiding in them, they didn’t attract her attention…; time isn’t spent describing how she’s raised by her grandmother, or where she got her coat, etc.]

It starts in just the right place [the story would start “too early” if it began with what she did earlier that morning, and it would start “too late” if she was already in the bears’ house]

**Goldilocks and the Three Bears**

Beginning: Once upon a time, there was a young girl named Goldilocks. One day Goldilocks was skipping through the forest when she came upon a cottage that belongs to the Three Bears. She knocked, but upon receiving no answer, she went right in.

Middle: **Once inside,** she discovered bowls of porridge and realized she’s hungry. She tried one bowl – this porridge is too hot. She tried another bowl – this porridge is too cold. She tried the third bowl – this porridge is just right – and she ate it all up.

She **then** decided to rest her tired feet and she sat down in a chair – this chair is too big. She tried another chair – this chair is too small. She tried the third chair – this chair is just right. But no sooner had she settled into the chair than it splintered into a thousand pieces.

**Now very tired,** Goldilocks went into the next room, where she saw three beds. She tried one bed – this bed is too hard. She tried another bed – this bed is too soft. She tried the third bed – this bed is just right. Goldilocks snuggled into the bed and fell asleep.

**While she slept,** the Three Bears returned. “Someone’s been eating my porridge,” said the Papa Bear. “Someone’s been eating my porridge,” said the Mama Bear. “Someone’s been eating my porridge,” said the baby bear, “and it’s all gone!” In the next room, Papa Bear said, “Someone’s been sitting in my chair.” And Mama Bear said, “Someone’s been sitting in my chair.” And Baby Bear said, “Someone’s been sitting in my chair, and they’ve broken it all to pieces!” They entered the sleeping room, and Papa Bear said, “Someone’s been lying in my bed.” And Mama Bear said, “Someone’s been lying in my bed.” And Baby Bear said, “Someone’s been lying in my bed, and they’re still there!”

End: **At this,** Goldilocks awoke with a start, leapt out of bed, and ran out of the house, never to return again.

**OTHER RESOURCES**

**Heilmeier catechism:** George H. Heilmeier, a former DARPA director (1975-1977), crafted a set of questions known as the "Heilmeier Catechism" to help Agency officials think through and evaluate proposed research programs. Full Heilmeier catechism from DARPA (<https://www.darpa.mil/work-with-us/heilmeier-catechism> ):

* What are you trying to do? Articulate your objectives using absolutely no jargon.
* How is it done today, and what are the limits of current practice?
* What is new in your approach and why do you think it will be successful?
* Who cares? If you are successful, what difference will it make?
* What are the risks?
* How much will it cost?
* How long will it take?
* What are the mid-term and final “exams” to check for success?

**Joanna’s and Rachel’s favorite grant writing, effective communications, and editing resources (as of March 14, 2019)**

* + Grant Writers Seminars and Workshops (aka “Russell & Morrison”) Grant Writer’s Handbook for NIH <http://www.grantcentral.com> to purchase handbook
  + George Gopen & Judith Swan, “The Science of Scientific Writing” https://www.americanscientist.org/blog/the-long-view/the-science-of-scientific-writing
  + Strunk & White, Elements of Style (any edition)
  + William Zinsser, On Writing Well: The classic guide to writing nonfiction (any edition)
  + R. Day & N. Sakaduski, Scientific English: A guide for scientists and other professionals, 3rd ed. Santa Barbara: Greenwood, 2011.
  + Matthews, Bowen, & Matthews, Successful Scientific Writing: A step-by-step guide for the biological and medical sciences (any edition). New York: Cambridge University Press, 1996, 2000, and 2008.
  + NIAID’s All About Grants website and resources:

<https://www.niaid.nih.gov/grants-contracts/apply-grant> (a treasure trove so good that no other NIH institute bothers to make their own; organization isn’t as transparent as it was previously, but great information is there!)

* Common Errors in English: [http://public.wsu.edu/~brians/errors/](https://urldefense.proofpoint.com/v2/url?u=http-3A__public.wsu.edu_-7Ebrians_errors_&d=DwMGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=nM89o_vHoy5hUhdMC8OwWJRf4_o6libqmJfyyPcOtLk&m=8XZqbpJC5vQCHpXBTowo83KHotcGfjaeRCtxoc13mKs&s=UEznSIykGf00pJrtuFqnmgvDeQqEAFuq_SBjaBvWcp0&e=)
* Garner, Bryan. The Oxford Dictionary of American Usage and Style. New York: Oxford University Press, 2000.
* Lang, Thomas. How to Write, Publish & Present in the Health Sciences: A Guide for Clinicians and Laboratory Researchers. Philadelphia: American College of Physicians, 2010.
* Silvia, Paul. How to Write a Lot: A Practical Guide to Productive Academic Writing. Washington, DC: American Psychological Association. 2nd edition, 2018.
* Williams, Joseph: Style: Lessons in Clarity & Grace. (any edition! There are 9 of them, spanning numerous years and publishers, and a 10th edition edited by Williams’s colleague Gregory Colomb. Rachel got her editions at the Goodwill!)
* Fun internet tool for improving technical/scientific writing style: [http://www.sfu.ca/~whitmore/style/](https://urldefense.proofpoint.com/v2/url?u=http-3A__www.sfu.ca_-7Ewhitmore_style_&d=DwMGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=nM89o_vHoy5hUhdMC8OwWJRf4_o6libqmJfyyPcOtLk&m=8XZqbpJC5vQCHpXBTowo83KHotcGfjaeRCtxoc13mKs&s=ip-XF8iAwz4PSIpYMCqk30Ev1PPJyt1oHnWGH_VDtdg&e=)