R01 Countdown: Tools for Writing Concise and Compelling Grants

8 recommended elements for writing a concise and compelling specific aims page

Adjust 'relative weight' of aims page	• Imagine reviewers only read the aims. Provide everything reviewers need to scientifically evaluate the entire proposal within the 1 page. It should be able to stand alone • Within ½ page, include (only) 1-2 sentences about clinical significance, followed by 1-2 paragraphs setting up scientific significance, and then a separate paragraph setting up innovation • In the remaining ½ page, state three aims as testable hypotheses. Under each aim, concisely provide essential, relevant details so reviewers can already begin to evaluate methodological rigor • Provide equal level of detail and space to all aims, especially the (often neglected) third aim • [Preliminary Data] Integrate preliminary data throughout the 1 page if available, including scientific significance, innovation, and each of the three individual aim paragraphs • Leave reviewers already compelled about the science and excited to read more (the 'POW factor'). Imagine the Research Strategy is designed merely to expand on details
Clearly differentiate among clinical significance, scientific significance, and innovation	• Assume proposals need to receive 1-2s on both NIH criteria (significance and innovation) for an outstanding overall impact score. Receiving any 3-4s ('Land of Mush') on either of these criteria may not be sufficient, and fixing approach details will not be enough • Within the 1 page, address both parts of the NIH significance criterion: clinical significance (addresses a clinical problem) and scientific significance (advances scientific knowledge) • Place more emphasis on scientific (not clinical) significance, including relative number of sentences • Make it easy for reviewers to assign separate and stellar scores for significance and innovation by constructing separate paragraphs for each criteria that stipulate substantively different, non-overlapping strengths. Consider the two criteria 'orthogonal' to one another • One strategy: Distinguish what new paradigm shift is being proposed (scientific significance) from how it will be accomplished (innovative methods/technologies)
Briefly address clinical significance	• [Clinical Significance] In (only) 1-2 sentences, state clinical significance. Include 2-3 convincing, evidence-based numerical details on prevalence, morbidity, mortality, and/or health care costs. Seek out details and synthesize across reference citations. Avoid vague phrases like 'increased risk'
Use contrast sentences to emphasize scientific significance	• Make it easy for fast-moving reviewers to detect scientific significance by starting a new paragraph rather than burying it deep within or at the end of a paragraph • [Paradigm Shift] In 1 concise sentence, state the paradigm shift being proposed. Bold it. Reviewers return to this single sentence for writing reviews and orally presenting to study section • [Synthesized Limitations] In 1 concise sentence, synthesize the limitations of prior paradigm(s) • Choose 1 of 2 contrast tactics to explicitly juxtapose the paradigm shift with prior paradigm(s): [1] FUNNEL DOWN] Lead with synthesized limitations (and preliminary data), then paradigm shift [2] [GO BOLD] Lead w/ paradigm shift, then limitations (and prelim data). Go Bold is riskier, but fun • To underscore the contrast between the paradigm shift and synthesized limitations, use the same dimensions and same key terms in the same order in both sentences
Use contrast sentences to highlight innovation	• [Innovation Topic Sentence] Make it easy for fast-moving reviewers to detect innovation by using 1 brief, bolded topic sentence with the key term 'innovative' and state # of innovative aspects • [Innovation] Describe each innovation in 1 sentence. Use numerical transitions (e.g., First, Second) to introduce each innovation sentence • [Innovation Contrast] Just because it's never been done before doesn't make it innovative. Instead, follow each innovation sentence with 1 succinct contrast sentence that explicitly juxtaposes the innovation's strengths with the limitations of current methods or standards in the field • To underscore the contrast between the innovation and the limitations of current methods in the field, use the same dimensions and same key terms in the same order in both sentences • Use convincing numerical details in the innovation and contrast sentences when possible
Identify team expertise	• [Team Expertise] In 1 sentence, identify the expertise areas of the multidisciplinary team • For disciplines, use the same key terms from the earlier significance and innovation paragraphs
State a hypothesis and method details for each aim	• [Hypothesis] In 1 sentence, explicitly state the direction of hypothesis for each aim (e.g., bigger, 'badder', better). Reviewers are compelled by applications that marshal evidence and take a stand • [Methods Details] Include concise, essential, and specific methodological details for each aim • Underline each innovative method from the innovation paragraph earlier
Write concisely	• Avoid scientific jargon. If it's a multidisciplinary application, particular reviewers may only have expertise in 1 discipline and little knowledge of even basic vocabulary for the other disciplines • Avoid ice-cream consumption–the pervasive academic tendency to use more complicated or highfalutin words than necessary. Instead, simply…eat more ice cream • Eliminate pink fluff–delete any repetitive or vague words, phrases, or sentences that do not explicitly add new information–or risk reviewers being distracted by their email or cell phone • To systematically condense as concisely as possible, combine Mimi Zeiger's writing techniques (Zeiger M. Essentials of Writing Biomedical Research Papers. 2nd ed. McGraw-Hill; 2000): 'repeat key terms' (p. 58), 'use a consistent point of view' (p. 84), 'put parallel ideas in parallel form' (p. 89), and then condense • To enhance 'continuity' (Zeiger, p. 58) for an easy, seamless read, use another Zeiger combination: 'repeat key terms' (p. 58) and 'use a consistent order' (p. 83), including across all tables and figures

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Examples of specific aims elements from awarded NIH grants[1]

Briefly address clinical significance	• [Clinical Significance] Osteoporosis affects 50% of women and 25% of men over age 50, increasing fracture risk. Hip fractures are particularly devastating as 20% of adults with a hip fracture die within 1 year and another 50% never walk independently again. [PI Wu R01 AR073773] • [Clinical Significance] Of the 500,000 adults who suffer a stroke each year, 15% die within 30 days and 30% are still not functionally independent 90 days later. [PI Govindarajan R01 HS026207]
Use contrast sentences to emphasize scientific significance	• [Synthesized Limitations] Devastating movement and seizure disorders can be dramatically alleviated via deep brain stimulation and ablation surgeries that target innervation sites of specific fiber pathways. Diffusion magnetic resonance imaging (dMRI) fiber tracking is the only imaging method available to map these fiber pathways, improve targeting accuracy, and identify new targets for these surgical treatments. Unfortunately, clinical application of dMRI for neurosurgical guidance is impeded by the lack of understanding for the influence of histological features on accurate fiber tracking. [Paradigm Shift] **To determine the influence of histological features, we will compare high-resolution postmortem dMRI fiber tracking against direct optical observation of individual neurons using CLARITY in the same intact, fixed human brain tissue specimens.** We propose that for a given voxel-size and degree of diffusion-weighting of the MRI signal, there will be detection limits regarding the histological features (minimum size, myelination, density, and distance from neighboring pathways) for any given fiber pathway to be accurately mapped with dMRI fiber tracking. [PI McNab R01 NS095985] • [Synthesized Limitations] Prior risk factor models suffered from serious limitations such as limited measurement of core risk factors in only one or two domains; little systematic examination within or between girls and boys or across age or developmental stages; and small samples with low power. [Paradigm Shift] We will test **a parsimonious and integrative model comprised of four sets of core risk factors across domains (key clinical symptoms, cognitive factors, genome-wide single nucleotide polymorphisms, and neural factors) and compares psychiatric outcomes across gender, age, and developmental stages.** We will leverage strengths of a large multimodal database (~10,000 8-21-year-old youth, 50% girls). [PI Singh R56 MH107243] • [Synthesized Limitations] We face two important challenges when improving clinical outcomes in neonatal resuscitation. First, conditions requiring resuscitation such as preterm birth are infrequent. Second, the recommended algorithm is complex, with six decision points made on a second-to-second basis. Healthcare teams lack practice implementing the technical knowledge, behavioral skills, and teamwork required for optimal resuscitation. [Paradigm Shift] **To address these two challenges and advance resuscitation science, we will use in situ simulation to train healthcare teams and improve clinical outcomes as it allows teams to practice infrequent and complex scenarios**. In situ simulation will also account for contextual factors such as equipment, personnel, policies, and hospital-specific factors influencing the complex steps of resuscitation. [PI Lee R01 HD087425]
Use contrast sentences to highlight innovation	• [Innovation Topic Sentence] **Two innovative features of our approach reduce the workload and risk compared to prior, *ex vivo* live imaging.** [Innovation #1] First, we image the midgut in situ within a living animal, [Innovation Contrast #1] which extends viability up to 8 times long than ex vivo imaging. [Innovation #2] Second, we use a 1.0 NA 20X dipping objective, which captures 4 times more cells with comparable micron resolution [Innovation Contrast #2] relative to standard 40x objectives. These features yield geometrically more data in fewer imaging sessions, which reduces workload and risk. [PI O'Brian R01 GM116000] • [Innovation Topic Sentence] **To deconstruct and target glioblastoma within the human peritumoral astrocyte microniche, we developed three innovative methods that leverage primary human tissue.** [Innovation #1] First, we developed a single brain cell isolation technique and RNA sequencing (RNA-seq) analysis to define the transcriptomes of individual migrating glioblastoma and their peritumoral neighbors. [Innovation Contrast #1] Prior studies in the field relied on bulk glioblastoma and peritumoral samples in which more numerous non-tumor or bystander cells drown out the migrating glioblastoma gene signature. [Innovation #2] Second, we developed novel immunopanning separation methods to isolate and culture mature human brain cell subtypes to be able to conduct multiple studies on live, pure, mature, human normal, peritumoral, and glioblastoma astrocytes. [Innovation Contrast #2] Previous cell sorting techniques (e.g. FACS) kill the primary brain cells quickly, lead to reactive states, are contaminated with other cell types, or can only be done on fetal rodent cells. [Innovation #3] Third, we have adapted primary human glioblastoma models (cell and slice culture, human-in-mouse intracranial xenograft), and CLARITY imaging to validate our genes of interest. [Innovation Contrast #3] Prior studies relied upon multiple passaged, murine, or non-infiltrating glioblastoma cell lines, which do not faithfully recapitulate human disease, and thin sectioning of tissue for imaging, which disassembles the glioblastoma-peritumoral astrocyte interactions. [PI Gephart R01 CA216054] • [Innovation Topic Sentence] **We will leverage two innovative methods to comprehensively assess the effects of PTH1R and Wnt signaling on bone formation.** [Innovation #1] First, we will use mass cytometry to analyze >40 protein parameters, allowing us to distinguish mesenchymal stem cells, osteoprogenitors and osteoblasts, and to simultaneously assess PTH1R and Wnt-activated signaling cascades in each population. [Innovation Contrast #1] Past studies relied on fluorescence which is limited to <18 parameters and therefore unable to simultaneously distinguish cell populations and assess signaling cascades. [Innovation #2] Second, we will use single-cell RNA-sequencing of osteoprogenitors to assess the individual and combined effects of PTH1R and Wnt signaling on the osteoblast gene network. [Innovation Contrast #2] Prior bulk RNA-sequencing methods were unable to examine gene expression in rare osteoprogenitors. [PI Wu R01 AR073773]
Identify team expertise	• [Team Expertise] Our research team includes experts and inventors of high-resolution postmortem dMRI and CLARITY 3D histology. We have established a strong collaboration across the disparate fields of MRI physics, neuroradiology, neuropathology, neurosurgery, neurology, and bioengineering (tissue cleaning and optical imaging). [PI McNab R01 NS095985]
State a hypothesis and method details for each aim	• **Aim 1: To test the association of multi-level risk factors with neonatal intensive care unit (NICU) quality of care.** [Hypothesis] We hypothesize sociodemographic and neighborhood factors are independently and jointly associated with quality of care within NICUs as vulnerable infants may receive worse care (Aim 1a) and across NICUs as vulnerable populations may have to seek care in low-quality hospitals (Aim 1b), over and above standard maternal and infant clinical and hospital factors. [Method Details] We will capitalize on the existing infrastructure of the California Perinatal Quality Care Collaborative to study a population-scale sample of >30,000 very low-birth-weight infants (<1500 grams) in 130+ NICUs. NICU quality of care will be assessed using the nationally recommended composite Baby-MONITOR measure (primary outcome). [PI Profit R01 HD084667] • **Aim 2:** [Hypothesis] **Determine if ferrous (Fe^{2+}) iron content is higher in hippocampal specimens with high and low Alzheimer's disease pathology than those with no pathology.** [Method Details] Fresh frozen sections be scanned with X-ray microscopy (via microfluorescence) and electron microscopy (via energy loss spectroscopy) at larger and smaller fields of view, respectively. [Preliminary Data] In our pilot data, these methods visualize the same iron seen by MR-histology in human Alzheimer's disease and discern oxidation state (Fe^{2+} vs. Fe^{3+}). [PI Zeineh R01 AG061120]

[1]Examples included with permission of Principal Investigators, see NIH RePORTER for grant details.

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