The Anatomy of the Specific Aims Page

Karen H. Costenbader, MD, MPH
Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital

SPECIFIC AIMS

Chronic pain affects approximately 116 million people, more than the total affected by diabetes, heart disease and cancer.[1] Pain is a hallmark symptom of rheumatoid arthritis (RA), the most common systemic inflammatory arthritis, with an overall prevalence of 1-2%.[2] Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority,[3] and approximately one-third of RA patients do not respond to DMARDs, according to the European League Against Rheumatism (EULAR) response criteria, which include both pain and inflammatory measures.[4] Studies report high rates of co-morbid fibromyalgia in RA,[5, 6] suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to alterations in central nervous system pain regulatory mechanisms. It is not known whether enhanced pain sensitivity predisposes RA patients to experience more intense pain, beyond what is expected from peripheral joint inflammation. It is also not known whether these patients respond less well to DMARDs, which act on peripheral inflammation, compared with therapies that act on central pain mechanisms. To decrease the burden of pain and improve the treatment of RA, there is an *urgent need* to understand the im[illegible] of central pain mechanisms on clinical pain intensity and DMARD non-response.

[illegible] inflam[illegible]tory pain have characterized two specific central pain mechanisms: 1) the de[illegible]ending a[illegible]ge[illegible] pathw[illegible], which dampen pain signals extending from the brain to the spinal cord, and 2) cen[illegible]l s[illegible]tion, which heightens excitability of the central nervous system neurons transmitting pain. Our res[illegible]rc[illegible]s o[illegible] few[illegible]th experience in the use of quantitative sensory testing (QST) to assess central pain regulatory mechanisms in inflammatory diseases. Our preliminary data indicate RA patients have altered central pain processing compared with healthy controls. A subgroup of RA patients with low inflammation but diffuse pain, fatigue, and sleep problems have the greatest alterations in central pain processing, demonstrated by low extra-articular pressure pain thresholds. The *overall objective* of this proposal is to understand the relationship between pain regulatory mechanisms, the clinical pain experience and DMARD response in a population of RA patients starting or switching DMARD therapy. This population is important [illegible]se[illegible]y have high clinical pain [illegible]els, [illegible] substantial medical resources and are exposed to [illegible]ncreased risk (infections, cancer) due [illegible]mm[illegible] suppression. Our *central hypothesis* is alterations in central [illegible]pain regu[illegible]on [illegible]s[illegible]soc[illegible]e[illegible]ten[illegible]su[illegible]nic[illegible]pain[illegible]y [illegible]or[illegible]in[illegible]rf[illegible]nce[illegible]nd [illegible]r D[illegible]RD [illegible]spo[illegible]. T[illegible] *rationale* [illegible] p[illegible]posal [illegible]ur[illegible]standi[illegible] rela[illegible]sh[illegible]be[illegible]cen[illegible]pain[illegible]ech[illegible]m[illegible] clinic[illegible]pa[illegible]nd D[illegible]r[illegible]por[illegible] will [illegible]ab[illegible] physicia[illegible] to [illegible]he[illegible], [illegible]p[illegible]ma[illegible]m[illegible]in [illegible]c[illegible]d[illegible]ases. Du[illegible]*im*[illegible] is to improve [illegible]fre[illegible]nt[illegible] p[illegible]pa[illegible]nts [illegible]th [illegible]te[illegible]c [illegible]mma[illegible] diseases using treatments targeted to specific pain [illegible]sms. W[illegible]pla[illegible]st o[illegible]cen[illegible]l hy[illegible]sis by pursuing the following *specific aims*:

1. To identify the associa[illegible]ns [illegible]etween [illegible]entral pain [illegible]echan[illegible]sms and measures of clinical pain experience among RA patients with active disease. In a [illegible]oss-sectional study of 272 RA patients starting or switching DMARD therapy, we will assess overall central pain regulation (via extra-articular pain thresholds), descending analgesic mechanisms (via conditioned pain modulation, assessing pain thresholds before and after a noxious conditioning stimulus) and central sensitization (via temporal summation, assessing response to repeated noxious stimuli). Adjusted linear regression models will be used to determine the independent association between these measures and measures of the clinical pain experience, including pain intensity.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with measures of clinical pain experience (e.g., high clinical pain intensity), adjusted for peripheral inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMAR[illegible] resp[illegible]se. W[illegible] fo[illegible]w th[illegible] 272 RA patients from Aim 1 and assess extra-articular pain thresholds, c[illegible] pa[illegible] mo[illegible]ati[illegible] a[illegible] temporal summation at baseline and after 12-weeks on new DMARD therapy. [illegible]he ind[illegible]p[illegible]nt ef[illegible]ct o[illegible] ea[illegible] pain mechanism on DMARD response will be examined in adjusted linear regr[illegible]sion m[illegible]dels.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

With respect to *expected outcomes*, the proposed work will determine: 1) the association between central pain mechanisms and measures of clinical pain among RA patients and 2) the effect of central pain mechanisms on DMARD response. These outcomes will have an important *positive impact* by identifying predictors of DMARD non-response and assessing appropriate targets for chronic pain treatment in systemic inflammatory diseases.

Key Points:

Write so **anyone can understand** your proposal.

Get the reviewers **excited** about your research.

Reviewers have **60-to-90 seconds** to explain your application.

SPECIFIC AIMS

Chronic pain affects approximately 116 million people, more than the total affected by diabetes, heart disease and cancer.[1] Pain is a hallmark symptom of rheumatoid arthritis (RA), the most common systemic inflammatory arthritis, with an overall prevalence of 1-2%.[2] Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority,[3] and approximately one-third of RA patients do not respond to DMARDs, according to the European League Against Rheumatism (EULAR) response criteria, which include both pain and inflammatory measures.[4] Studies report high rates of co-morbid fibromyalgia in RA,[5, 6] suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to altered central control of pain regulatory mechanisms. It is not known whether enhanced pain sensitivity predisposes RA patients to experience more intense pain, beyond what is expected from peripheral joint inflammation. It is also not known whether these patients respond less well to DMARDs, which act on peripheral inflammation, compared with therapies that act on central pain mechanisms. To decrease the burden of pain and improve the treatment of RA, there is an ***urgent need*** to understand the impact of central pain mechanisms on clinical pain intensity and DMARD non-response.

Studies of chronic, non-inflammatory pain have characterized two specific central pain mechanisms: 1) the descending analgesic pathways, which dampen pain signals extending from the brain to the spinal cord, and 2) central sensitization, which heightens excitability of the central nervous system neurons transmitting pain. Our research team is one of few with experience in the use of quantitative sensory testing (QST) to assess central pain regulatory mechanisms in inflammatory diseases. Our preliminary data indicate RA patients have altered central pain processing compared with healthy controls. A subgroup of RA patients with low inflammation but diffuse pain, fatigue, and sleep problems have the greatest alterations in central pain processing, demonstrated by low extra-articular pressure pain thresholds. The ***overall objective*** of this proposal is to understand the relationship between central pain regulatory mechanisms, clinical pain experience and DMARD response in a population of RA patients starting or switching DMARD therapy. This population is important because they have high clinical pain levels, consume substantial medical resources and are exposed to increased risk (infections, cancer) due to immunosuppression. Our ***central hypothesis*** is alterations in central pain regulatory mechanisms are associated with heightened measures of clinical pain (pain intensity, pain behavior, pain interference) and poor DMARD response. The ***rationale*** for this proposal is understanding the relationship between central pain mechanisms, clinical pain and DMARD response will enable physicians to tailor therapy, improving pain management in RA and other systemic rheumatic diseases. Our ***long-term goal*** is to improve the treatment of pain in patients with systemic inflammatory diseases using treatments targeted to specific pain mechanisms. We plan to test our central hypothesis by pursuing the following ***specific aims***:

1. To identify the associations between central pain mechanisms and measures of clinical pain experience among RA patients with active disease. In a cross-sectional study of 272 RA patients starting or switching DMARD therapy, we will assess overall central pain regulation (via extra-articular pain thresholds), descending analgesic mechanisms (via conditioned pain modulation, assessing pain thresholds before and after a noxious conditioning stimulus) and central sensitization (via temporal summation, assessing response to repeated noxious stimuli). Adjusted linear regression models will be used to determine the independent association between these measures and measures of the clinical pain experience, including pain intensity.

- ***Working Hypothesis***: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with measures of clinical pain experience (e.g., high clinical pain intensity) reported by people with inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMARD response. We will follow the 272 RA patients from Aim 1 and assess extra-articular pain thresholds, conditioned pain modulation and temporal summation at baseline and after 12-weeks on new DMARD therapy. The independent effect of each pain mechanism on DMARD response will be examined in adjusted linear regression models.

- ***Working Hypothesis***: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

With respect to ***expected outcomes***, the proposed work will determine: 1) the association between central pain mechanisms and measures of clinical pain among RA patients and 2) the effect of central pain mechanisms on DMARD response. These outcomes will have ***positive impact*** by identifying predictors of DMARD non-response and assessing appropriate targeted therapies for treatment in rheumatic inflammatory diseases.

"The Hook"

"The Big Idea"

"The Finer Points"

"The Grand Finale"

“The Hook”

SPECIFIC AIMS

Chronic pain affects approximately 116 million people, more than the total affected by diabetes, heart disease and cancer.[1] Pain is a hallmark symptom of rheumatoid arthritis (RA), the most common systemic inflammatory arthritis, with an overall prevalence of 1-2%.[2] Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority,[3] and approximately one-third of RA patients do not respond to DMARDs, according to the European League Against Rheumatism (EULAR) response criteria, which include both pain and inflammatory measures.[4] Studies report high rates of co-morbid fibromyalgia in RA,[5, 6] suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to alterations in central nervous system pain regulatory mechanisms. It is not known whether enhanced pain sensitivity predisposes RA patients to experience more intense pain, beyond what is expected from peripheral joint inflammation. It is also not known whether these patients respond less well to DMARDs, which act on peripheral inflammation, compared with therapies that act on central pain mechanisms. To decrease the burden of pain and improve the treatment of RA, there is an ***urgent need*** to understand the impact of central pain mechanisms on clinical pain intensity and DMARD non-response.

Studies of chronic, non-inflammatory pain have characterized two specific central pain mechanisms: 1) the descending analgesic pathways, which dampen pain signals extending from the brain to the spinal cord, and 2)

Chronic pain affects approximately 116 million people, more than the total affected by diabetes, heart disease and cancer.[1] Pain is a hallmark symptom of rheumatoid arthritis (RA), the most common systemic inflammatory arthritis, with an overall prevalence of 1-2%.[2] Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority,[3] and approximately one-third of RA patients do not respond to DMARDs, according to the European League Against Rheumatism (EULAR) response criteria, which include both pain and inflammatory measures.[4] Studies report high rates of co-morbid fibromyalgia in RA,[5, 6] suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to alterations in central nervous system pain regulatory mechanisms. It is not known whether enhanced pain sensitivity predisposes RA patients to experience more intense pain, beyond what is expected from peripheral joint inflammation. It is also not known whether these patients respond less well to DMARDs, which act on peripheral inflammation, compared with therapies that act on central pain mechanisms. To decrease the burden of pain and improve the treatment of RA, there is an ***urgent need*** to understand the impact of central pain mechanisms on clinical pain intensity and DMARD non-response.

to repeated noxious stimuli). Adjusted linear regression models will be used to determine the independent association between these measures and measures of the clinical pain experience, including pain intensity.

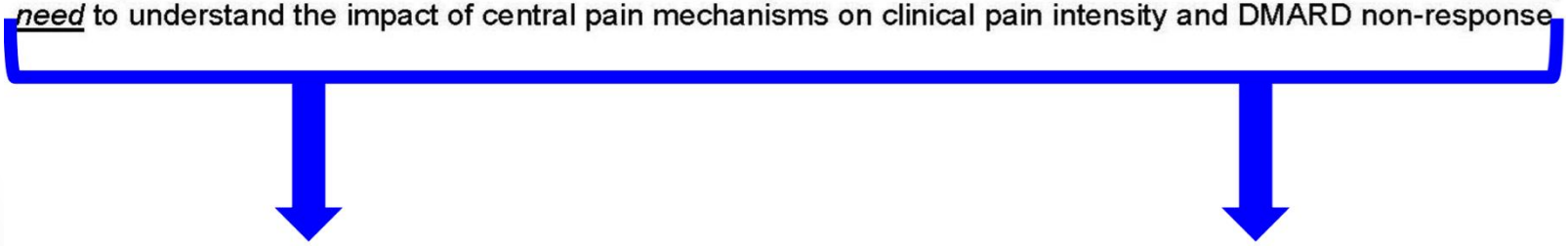
- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with measures of clinical pain experience (e.g., high clinical pain intensity), adjusted for peripheral inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMARD response. We will follow the 272 RA patients from Aim 1 and assess extra-articular pain thresholds, conditioned pain modulation and temporal summation at baseline and after 12-weeks on new DMARD therapy. The independent effect of each pain mechanism on DMARD response will be examined in adjusted linear regression models.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

With respect to *expected outcomes*, the proposed work will determine: 1) the association between central pain mechanisms and measures of clinical pain among RA patients and 2) the effect of central pain mechanisms on DMARD response. These outcomes will have an important *positive impact* by identifying predictors of DMARD non-response and assessing appropriate targets for chronic pain treatment in systemic inflammatory diseases.

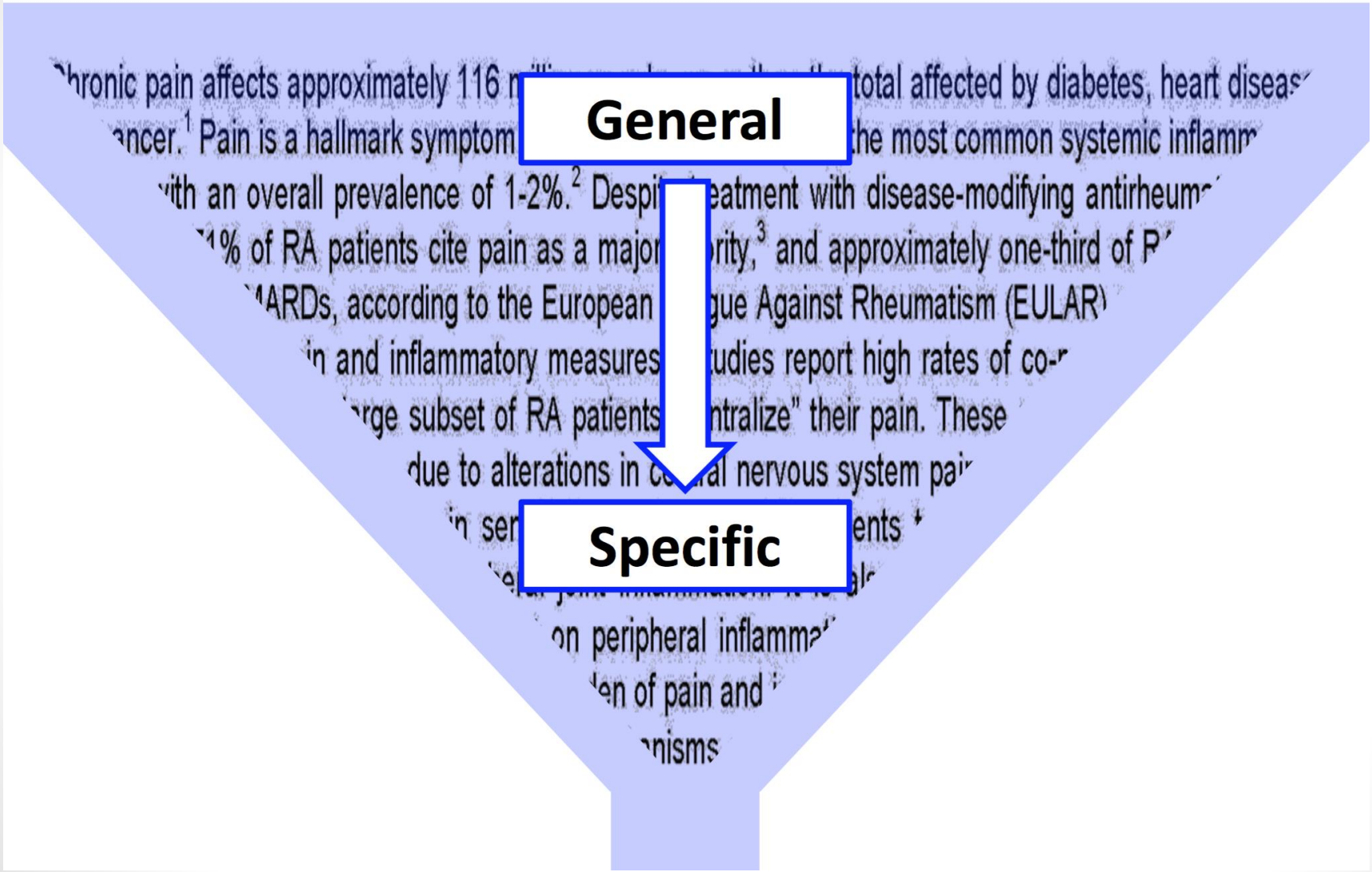
Chronic pain affects approximately 116 million people, more than the total affected by diabetes, heart disease and cancer.[1] Pain is a hallmark symptom of rheumatoid arthritis (RA), the most common systemic inflammatory arthritis, with an overall prevalence of 1-2%.[2] Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority,[3] and approximately one-third of RA patients do not respond to DMARDs, according to the European League Against Rheumatism (EULAR) response criteria, which include both pain and inflammatory measures.[4] Studies report high rates of co-morbid fibromyalgia in RA,[5, 6] suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to alterations in central nervous system pain regulatory mechanisms. It is not known whether enhanced pain sensitivity predisposes RA patients to experience more intense pain, beyond what is expected from peripheral joint inflammation. It is also not known whether these patients respond less well to DMARDs, which act on peripheral inflammation, compared with therapies that act on central pain mechanisms. To decrease the burden of pain and improve the treatment of RA, there is an ***urgent need*** to understand the impact of central pain mechanisms on clinical pain intensity and DMARD non-response

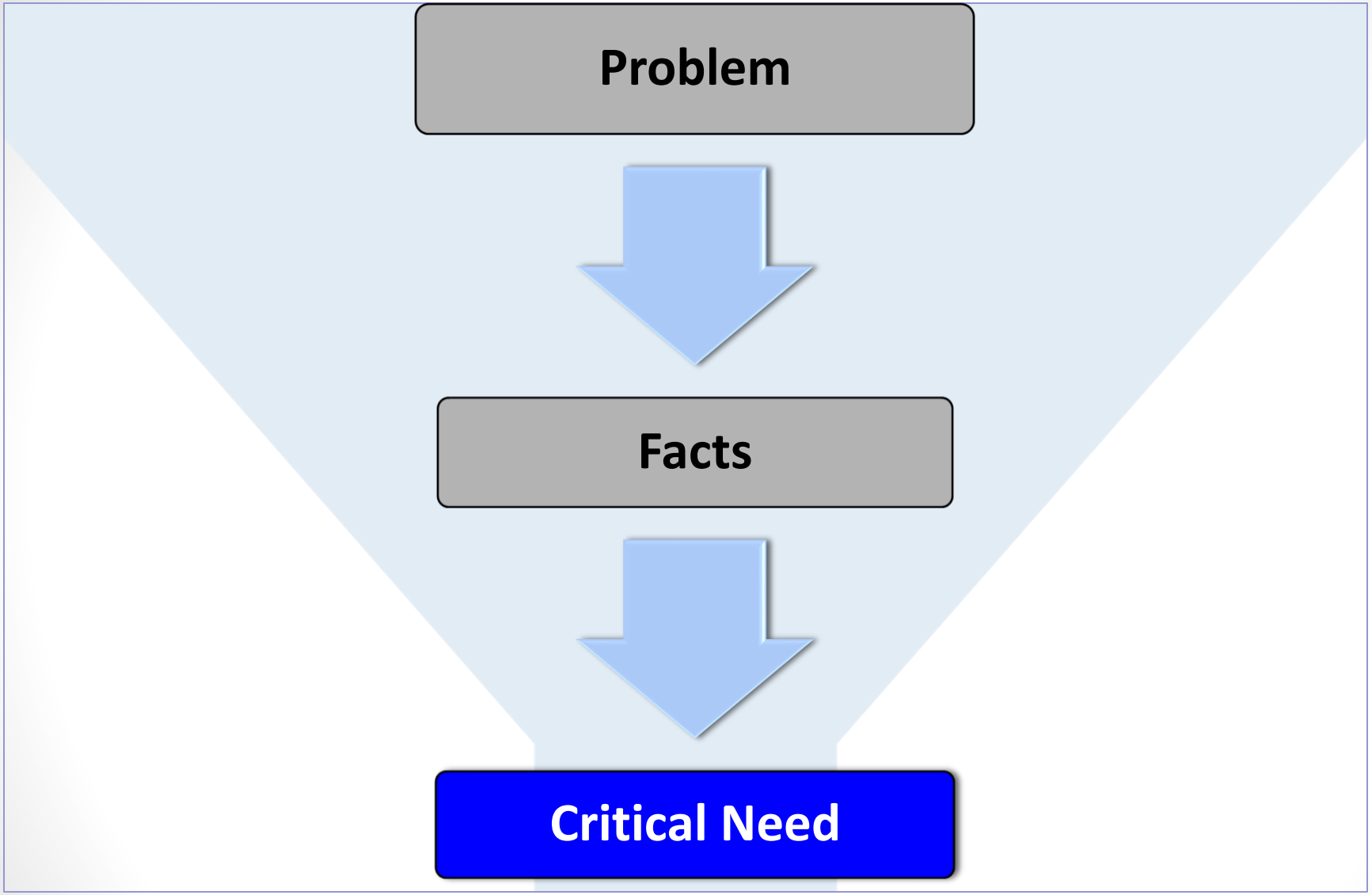


Gap in knowledge

Critical need

Consider a “funnel shape” while writing



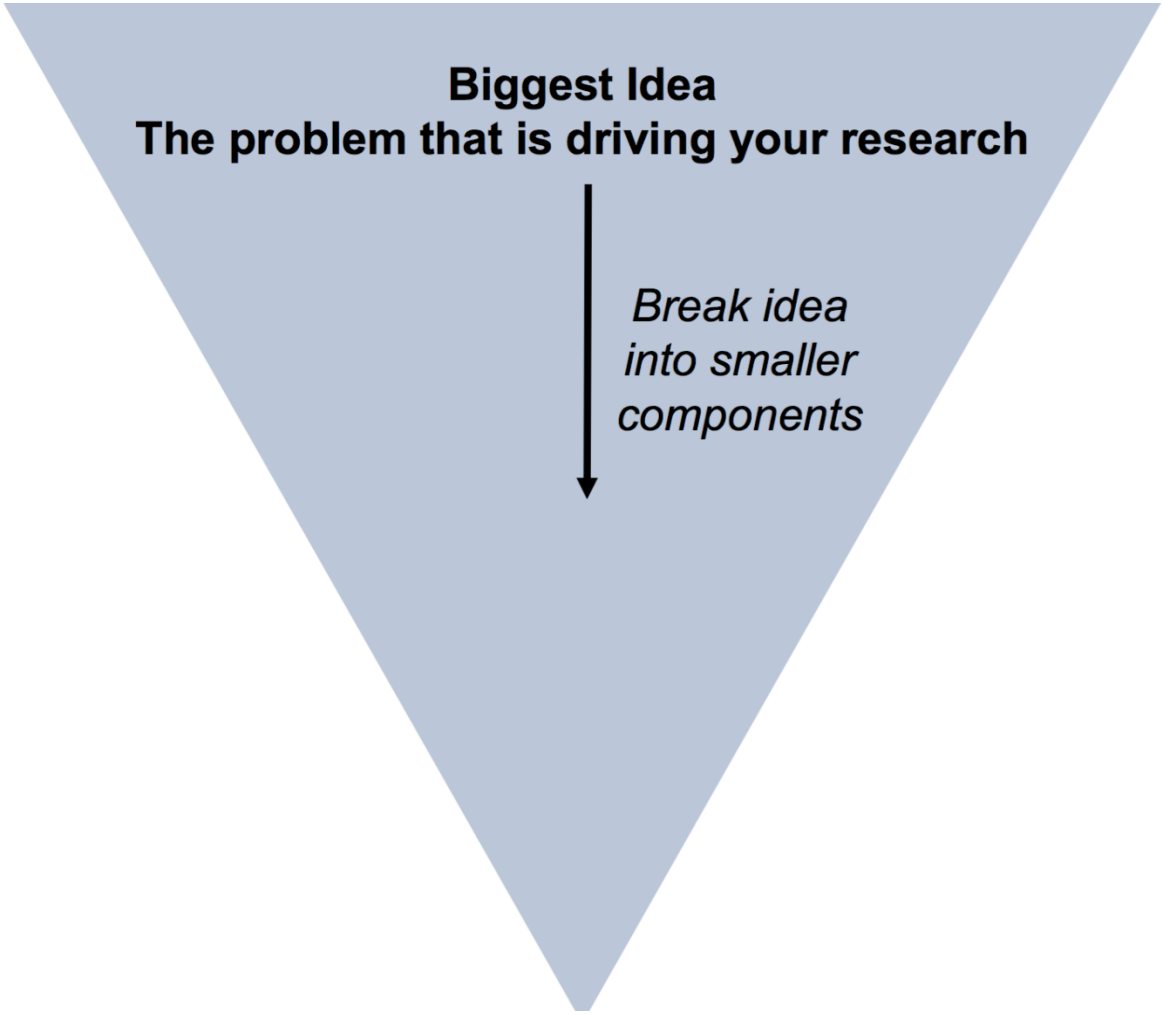

Problem
Facts
Critical Need

Critical Need

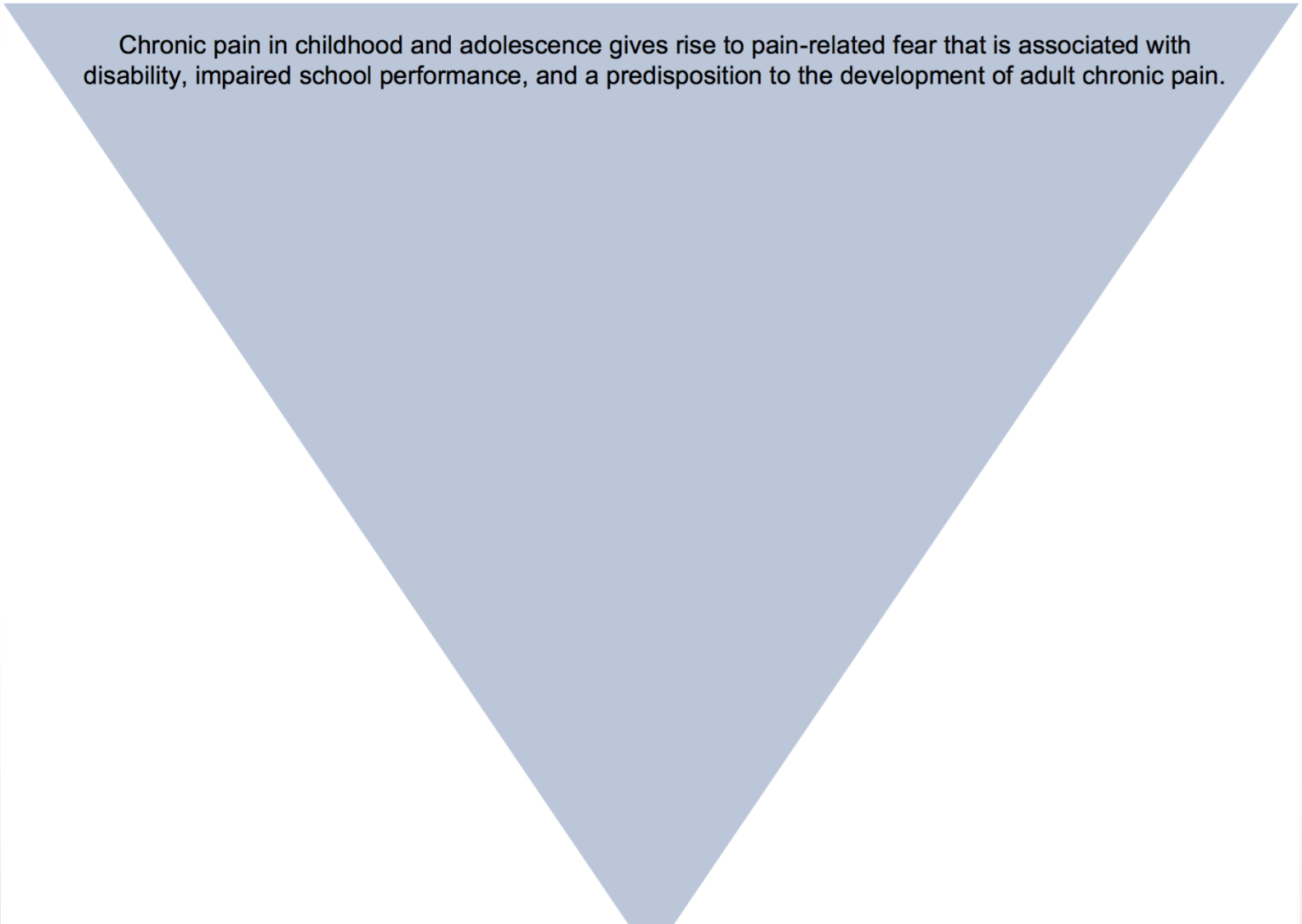
"To decrease the burden of pain and improve the treatment of RA, there is an *urgent need* to understand the impact of central pain mechanisms on clinical pain intensity and DMARD non-response."

WHY?

Specific Aim Example



Broad Topic Sentences for Each Paragraph



Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain.

Children respond to fear of pain with either avoidance or confrontation.

Detail

Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain.

Children respond to fear of pain with either avoidance or confrontation.

Detail

Avoidance (fear conditioning) leads to the exacerbation of pain though negative reinforcement; confrontation (extinction learning) allows children to confront their pain, viewing it as temporary and a condition that may be alleviated.

More detailed

Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain.

Children respond to fear of pain with either avoidance or confrontation.

Avoidance (fear conditioning) leads to the exacerbation of pain though negative reinforcement; confrontation (extinction learning) allows children to confront their pain, viewing it as temporary and a condition that may be alleviated.

However, a significant portion of children and adolescents gravitate toward the detrimental "avoidance" of pain rather than its productive counterpart, "confrontation."

Transition to adolescence

Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain.

Children respond to fear of pain with either avoidance or confrontation.

Avoidance (fear conditioning) leads to the exacerbation of pain though negative reinforcement; confrontation (extinction learning) allows children to confront their pain, viewing it as temporary and a condition that may be alleviated.

However, a significant portion of children and adolescents gravitate toward the detrimental ”avoidance” of pain rather than its productive counterpart, “confrontation.”

Given the unique critical period od neural development primed for modification by experience, adolescents may be more sensitive to avoidance of pain, less responsive to confrontation, and, therefore more treatment resistant if they develop chronic pain.

Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain.

Children respond to fear of pain with either avoidance or confrontation.

Avoidance (fear conditioning) leads to the exacerbation of pain though negative reinforcement; confrontation (extinction learning) allows children to confront their pain, viewing it as temporary and a condition that may be alleviated.

However, a significant portion of children and adolescents gravitate toward the detrimental "avoidance" of pain rather than its productive counterpart, "confrontation."

Given the unique critical period od neural development primed for modification by experience, adolescents may be more sensitive to avoidance of pain, less responsive to confrontation, and, therefore more treatment resistant if they develop chronic pain.

To identify effective targets for the treatment of chronic pain in adolescents, there is a critical need to understand the behavioral and neurological mechanisms underlying fear learning and extinction.

Most detailed describes needed research

Consider underline or italics for your statement of critical need

SPECIFIC AIMS

Chronic pain in childhood and adolescence gives rise to pain-related fear that is associated with disability, impaired school performance, and a predisposition to the development of adult chronic pain. Children respond to fear of pain with either avoidance or confrontation. Avoidance (fear conditioning) leads to the exacerbation of pain though negative reinforcement; confrontation (extinction learning) allows children to confront their pain, viewing it as temporary and a condition that may be alleviated. However, a significant portion of children and adolescents gravitate toward the detrimental ”avoidance” of pain rather than its more productive counterpart, “confrontation.” Given the unique critical period of neural development primed for modification by experience, adolescents may be more sensitive to avoidance of pain, less responsive to confrontation, and, therefore more treatment resistant if they develop chronic pain. To identify effective targets for the treatment of chronic pain in adolescents, there is a critical need to understand the behavioral and neurological mechanisms underlying fear learning and extinction.

“The Big Idea”

Studies of chronic, non-inflammatory pain have characterized two specific central pain mechanisms: 1) the descending analgesic pathways, which dampen pain signals extending from the brain to the spinal cord, and 2) central sensitization, which heightens excitability of the central nervous system neurons transmitting pain. Our research team is one of few with experience in the use of quantitative sensory testing (QST) to assess central pain regulatory mechanisms in inflammatory diseases. Our preliminary data indicate that RA patients have altered central pain processing compared with healthy controls. A subgroup of RA patients with low inflammation but diffuse pain, fatigue, and sleep problems have the greatest alterations in central pain processing, demonstrated by low extra-articular pressure pain thresholds. The *overall objective* of this proposal is to understand the relationship between pain regulatory mechanisms, the clinical pain experience and DMARD response in a population of RA patients starting or switching DMARD therapy. This population is important because they have high clinical pain levels, consume substantial medical resources and are exposed to increased risk (infections, cancer) due to immunosuppression. Our *central hypothesis* is that alterations in central pain regulatory mechanisms are associated with heightened measures of clinical pain (pain intensity, pain behavior, pain interference) and poor DMARD response. The *rationale* for this proposal is that understanding the relationship between central pain mechanisms, clinical pain and DMARD response will enable physicians to tailor therapy, improving pain management in RA and other systemic rheumatic diseases. Our *long-term goal* is to improve the treatment of pain in patients with systemic inflammatory diseases using treatments targeted to specific pain mechanisms. We plan to test our central hypothesis by pursuing the following *specific aims*:

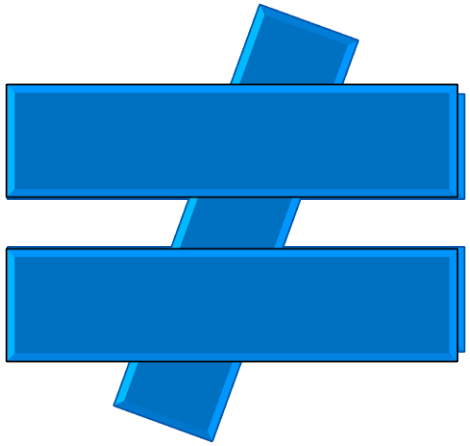
Studies of chronic, non-inflammatory pain have characterized two specific central pain mechanisms: 1) the descending analgesic pathways, which dampen pain signals extending from the brain to the spinal cord, and 2) central sensitization, which [illegible] transmitting pain. Our research team is one of few with experience in the use of quantitative sensory testing (QST) to assess central pain regulatory mechanisms in inflammatory diseases. Our preliminary data indicate that RA patients have altered central pain processing compared with healthy controls. A subgroup of RA patients with low inflammation but diffuse pain, fatigue, and sleep problems have the greatest alterations in central pain processing, demonstrated by [illegible] pressure pain thresholds. The overall objective of this proposal is to understand the relationship between pain [illegible] experience and DMARD response in a population of RA patients starting or switching DMARD therapy. This population is important because they have high clinical pain levels, consume substantial medical resources and are exposed to increased risk (infections, cancer) due to immunosuppression. Our *central hypothesis* is that alterations in central pain reg[illegible]sity, pain behavior, [illegible] that understanding t[illegible] will enable physician[illegible]ses. Our *long-term g*[illegible]sing treatments targ[illegible] the following *specific aims*:

⇨What you want to do.

⇨Why you should do it.

➡ Central Hypothesis

Long-term goal



Effect on your field

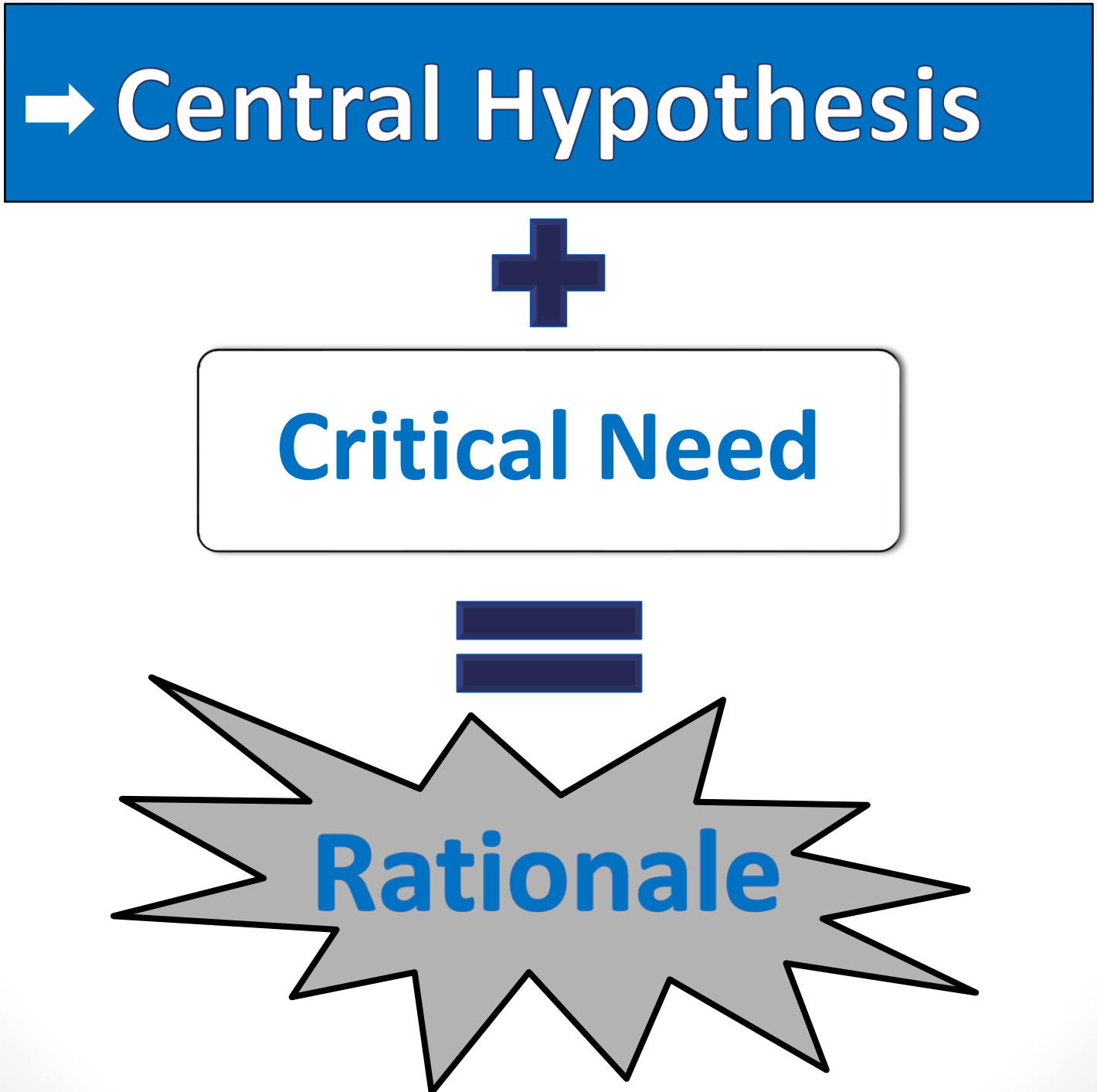
➡Central Hypothesis

- ☑ **GOAL** of your proposal
- ☑ **TESTED** by your specific aims
- ☑ One **CLEAR**, overarching idea

"Our central hypothesis is…"

"Our following aims will test our hypothesis that…"

"This application will build upon previous studies and test our central hypothesis that…"


Central Hypothesis
Critical Need
Rationale

“The Finer Points”

1. To identify the associations between central pain mechanisms and measures of clinical pain experience among RA patients with active disease. In a cross-sectional study of 272 RA patients starting or switching DMARD therapy, we will assess overall central pain regulation (via extra-articular pain thresholds), descending analgesic mechanisms (via conditioned pain modulation, assessing pain thresholds before and after a noxious conditioning stimulus) and central sensitization (via temporal summation, assessing response to repeated noxious stimuli). Adjusted linear regression models will be used to determine the independent association between these measures and measures of the clinical pain experience, including pain intensity.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with measures of clinical pain experience (e.g., high clinical pain intensity), adjusted for peripheral inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMARD response. We will follow the 272 RA patients from Aim 1 and assess extra-articular pain thresholds, conditioned pain modulation and temporal summation at baseline and after 12-weeks on new DMARD therapy. The independent effect of each pain mechanism on DMARD response will be examined in adjusted linear regression models.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

clinical pain intensity), adjusted for peripheral inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMARD response. We will follow the 272 RA patients from Aim 1 and assess extra-articular pain thresholds, conditioned pain modulation and temporal summation at baseline and after 12-weeks on new DMARD therapy. The independent effect of each pain mechanism on DMARD response will be examined in adjusted linear regression models.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

Specific Aims

- ➪ Test your central hypothesis
- ➪ Objectives or milestones
- ➪ Test your central hypothesis
- ➪ Brief description of approach, sometimes called a “working hypothesis”

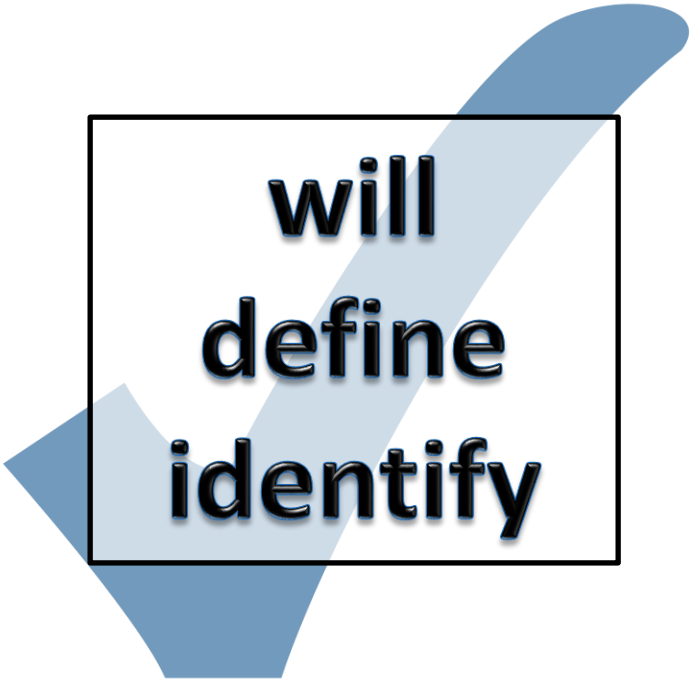
1. To identify the associations between central pain mechanisms and measures of clinical pain experience among RA patients with active disease. In a cross-sectional study of 272 RA patients starting or switching DMARD therapy, we will assess overall central pain regulation (via extra-articular pain thresholds), descending analgesic mechanisms (via conditioned pain modulation assessing pain thresholds before and after a noxious conditioning stimulus) and central sensitization (via temporal summation, assessing response to repeated noxious stimuli). Adjusted linear regression models will be used to determine the independent association between these measures and measures of clinical pain experience, including pain intensity.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with measures of clinical pain experience (e.g., high clinical pain intensity), adjusted for peripheral inflammatory disease activity.

2. To evaluate the effects of altered central pain mechanisms on DMARD response. We will follow the 272 RA patients from the cross-sectional study and re-assess extra-articular pain thresholds, conditioned pain modulation and temporal summation at baseline and after 12-weeks on new DMARD therapy. The independent effect of each pain mechanism on DMARD response will be examined in adjusted linear regression models.

- *Working Hypothesis*: Low extra-articular pain thresholds, low conditioned pain modulation and high temporal summation are independently associated with inadequate DMARD response, assessed by changes in the Disease Activity Score in 28 joints, the EULAR response criteria and changes in pain intensity.

Word choice is key!



Avoid being “too ambitious”

- ☑ No more than two-to-three aims
- ☑ Avoid sub-aims
- ☑ No individual hypotheses
- ☑ Cannot rely on success of previous aims

“The Grand Finale”

Final Impression:

Make your reviewers want to read your entire application.

- The “Grand Finale” is the last impression you will give your reviewers. Therefore, it is vital that this section leaves an impact. It should touch upon the issues stated in the first paragraph and indicate how the work you have just proposed will advance your field of research. These are the expected outcomes of your work. You should write this as though it is inevitable, demonstrating ultimate confidence in your proposed work.

- For K grant applicants, this is where you should include the statement: “These outcomes are expected to position the candidate to submit a competitive R01 application.”

Research Strategy

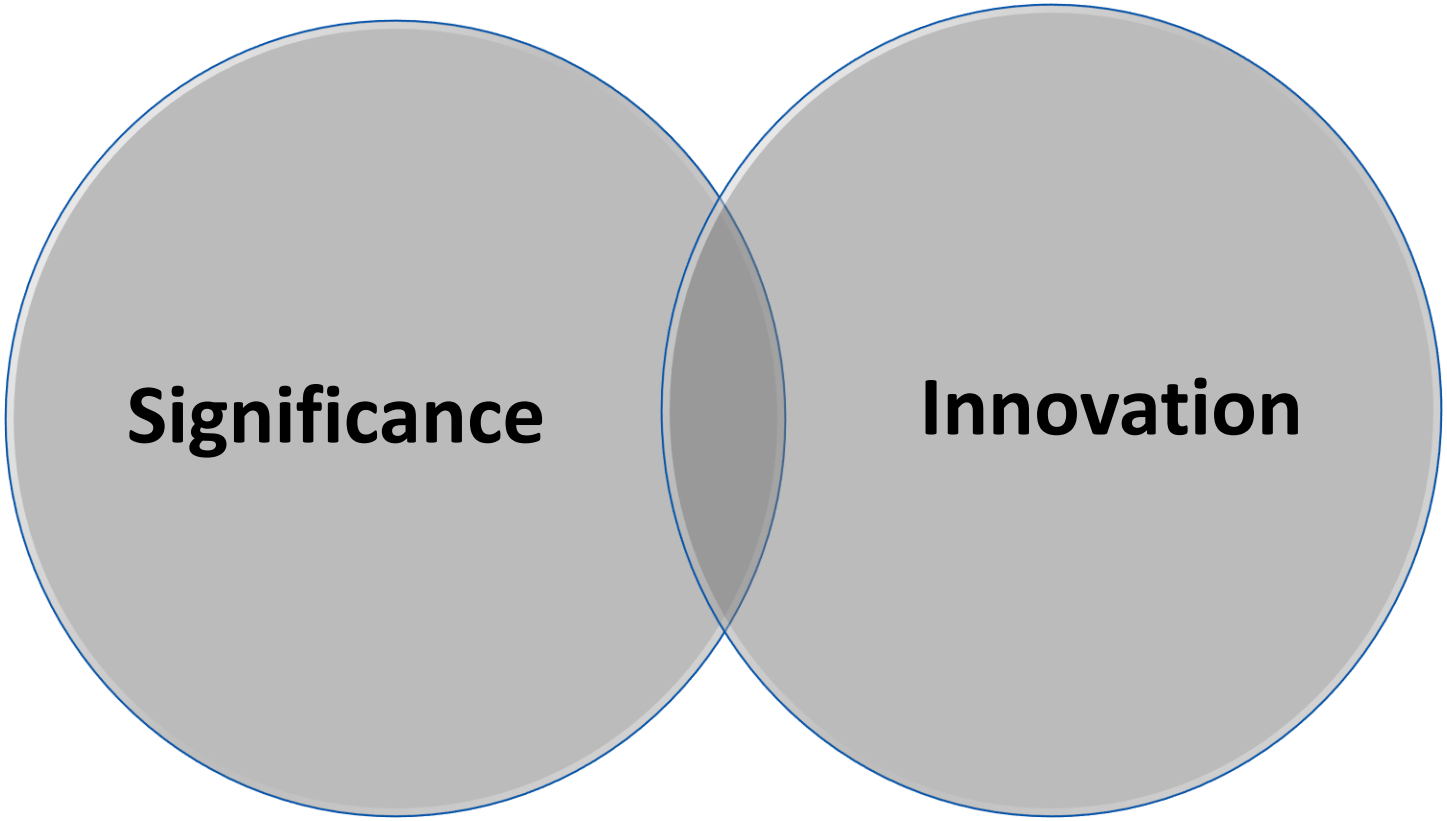
- ***Significance***
- ***Innovation***
- *Approach*

R Grant Scoring Criteria

- Significance
- Investigator(s)
- Innovation
- Approach
- Environment

K Grant Scoring Criteria

- Candidate
- Career Development Plan/Career Goals & Objectives
- Research Plan (includes Significance, Innovation &Approach)
- Mentor(s), Co-Mentor(s), Consultant(s) & Collaborator(s)
- Environment & Institutional Commitment to Candidate


Significance
Innovation

Significance Criterion

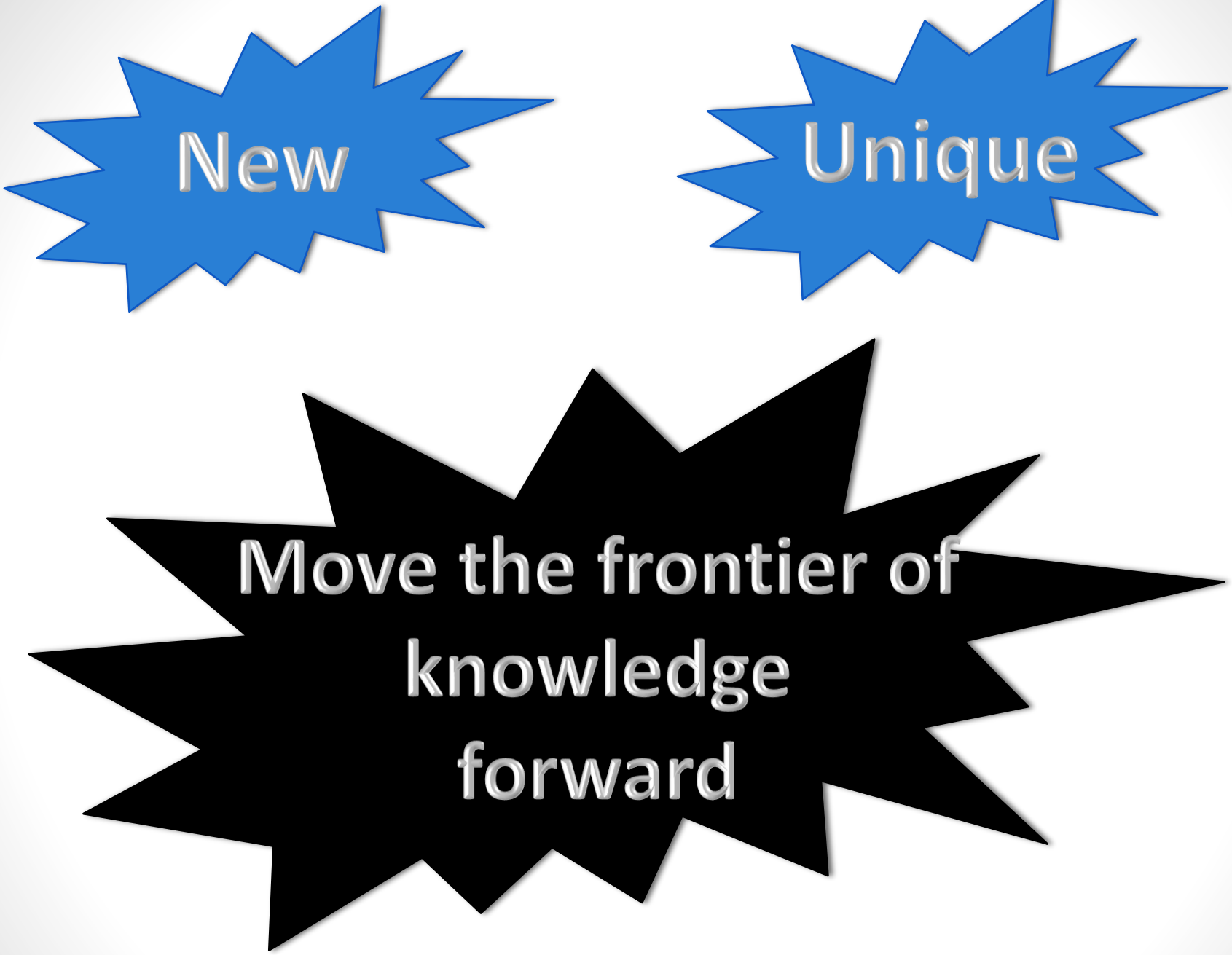
- Does the project address an important problem or a critical barrier to progress in the field?
- If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Innovation Criterion

- Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Address:

- ✓How your research will advance your field.
- ✓How it will fill knowledge gaps or address opportunities or roadblocks in the field, and how it relates to research underway.
- ✓How the work is new and unique.
- ✓How it meets the NIH mission to improve health through science, by leading to cures, treatments, or preventions for human disease.


New
Unique
Move the frontier of knowledge forward

*Respectfully discuss the **status quo**…*

*And how you will **advance** it.*

Significance is the problem and the impact your research is likely to have.

Innovation is the new way of addressing or solving this problem that could affect the field of research for the better.

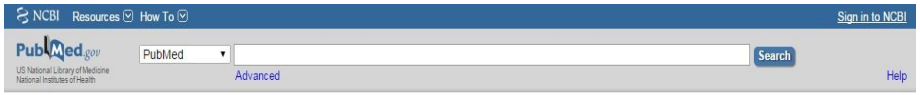
The End Result

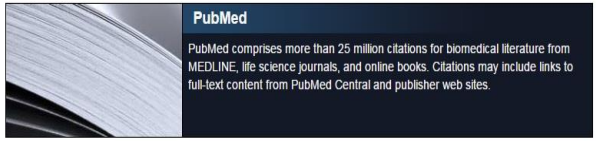
Make your reviewer want to continue reading

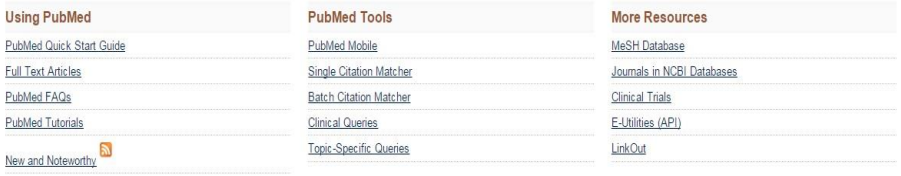
Consider your funder's priorities

Review of Literature

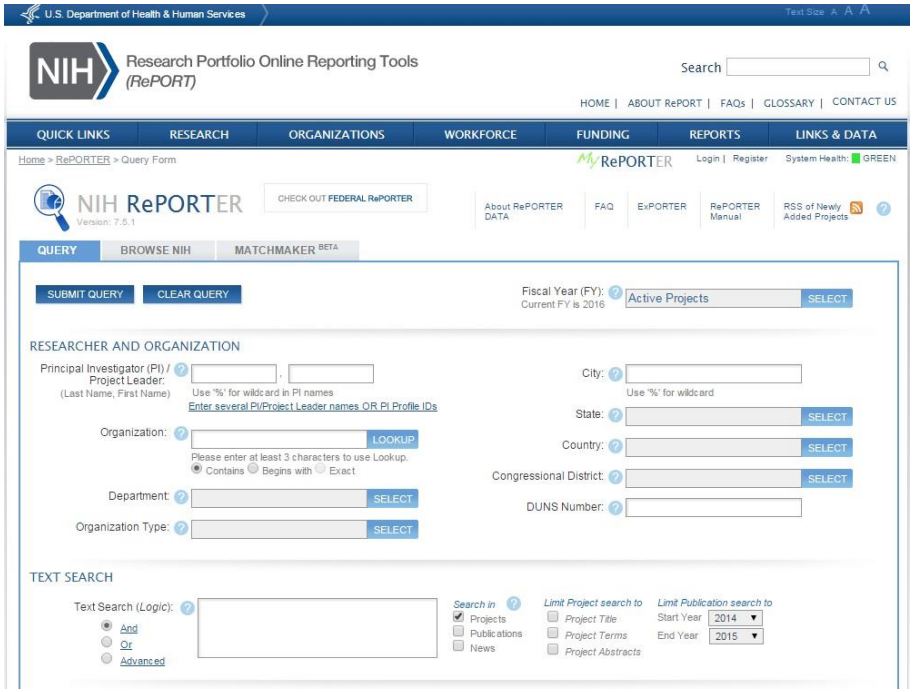
- ✓ Avoid cataloguing of publications.
- ✓ Cite relevant publications justifying each aim.
- ✓ Incorporate publications from reviewers.
- ✓ Cite any gaps reinforcing the need for your proposal.
- ✓ Include data.







Do your research!



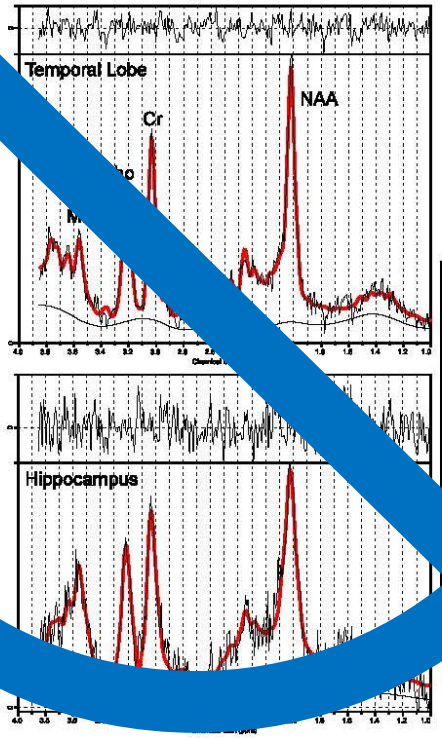
Ensure you have sufficient preliminary data to prove you are well positioned to do the work.

Preliminary Studies

- ✓ Demonstrate feasibility.
- ✓ Include primarily unpublished data.
- ✓ Discuss novel methods.
- ✓ Acknowledge potential pitfalls.
- ✓ State how your proposal will advance previous work.

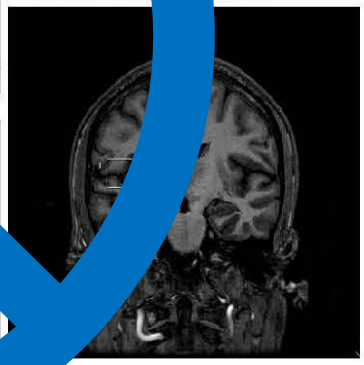
Readability Is Key!

1. Carry out an automate… order shim on this region
2. Employ the autom… CS to optimize the t… well as the solv… ppressi…
3. A solvent sup… ed spectrum… acquisition … meters as bandwidth … Hz, TR 2000 complex p… 8 step phase acquisition… This will take acquisition…



…ion sequence rec… settings as

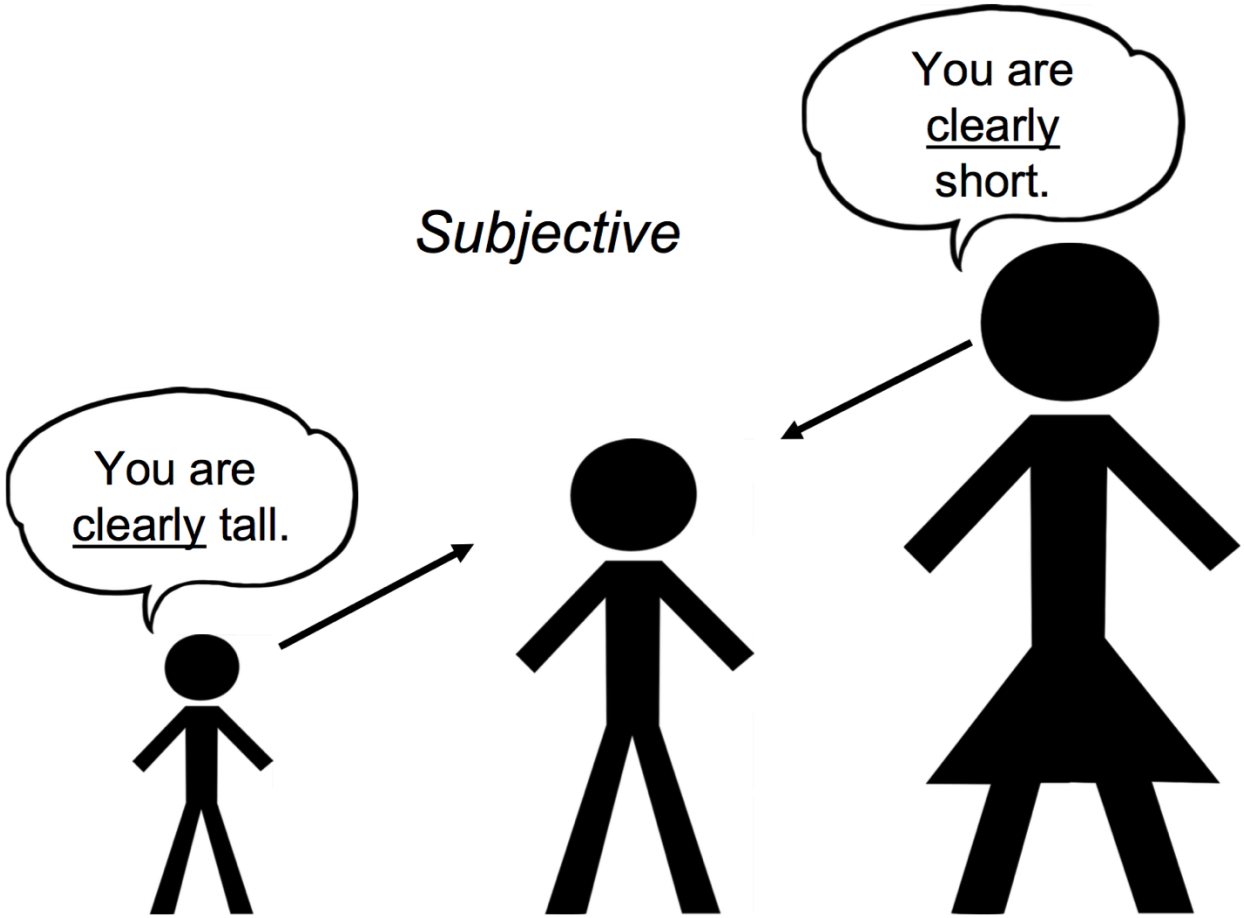
will be … ned with follows; … spectral ms, TE 3… 2048 cycle, … 128 about 4:20… tes of



Write clearly


Myocardial infarction is a medical event that results in higher mortality rates in the male geriatric population.
Heart attacks kill older men.

Avoid Subjective Statements



Academic Paper	Grant Writing
Lengthy sentences	Shorter sentences
Detailed technical terms	Avoid technical terms
Write for reviewers in your field	Write for the individuals outside your field
Impress colleagues with knowledge	Sell reviewers on merits of future work
Work already done	Future work

https://catalyst.harvard.edu/services/elementsofgrantwriting/

People & Collaboration | Consulting & Advice | Education & Training | Funding | Research Resources | Programs

Tips and work plans for the grant writing process.

Elements of Grant Writing

Login to parts of the Harvard Catalyst website will be unavailable due to system maintenance Sunday, April 9, 8am-12pm.

Overview

Contacts

At a glance

Key Features
- Tools to guide investigators in the grant application process

Useful for
- Investigators seeking grant funding from federal, foundation, and corporate sources

Available to
- All members of the Harvard Catalyst community

Access guide

Login via HMS eCommons ID, HUID, or HarvardKey required.
Need Help?

The Elements of Grant Writing guide is a compilation of tips, timelines, and templates from a variety of grant-writing experts and funders designed to aid investigators in successfully applying for grants from federal, foundation, and corporate sources. The guide is also a key component of the Grant Review and Support Program (GRASP).

Tools
A collection of templates, timelines, and checklists to help you project manage your grant application.

Writing Tips
The information investigators need for every step of the grant writing process:
- Prewriting
- Writing
- Rewriting

Samples
A repository of successful and unsuccessful grant submissions.

Spotlight

Elements of Grant Writing
Write a fundable grant: The Elements of Grant Writing has the tips and tools you need.

Sponsoring Program

Postgraduate Education in C/T Science Program

See Also
- Advanced Curriculum Compendium
- Consulting & Advice
- Grant Review and Support Program
- Pathfinder

What does a good grant look like?

Good Luck!