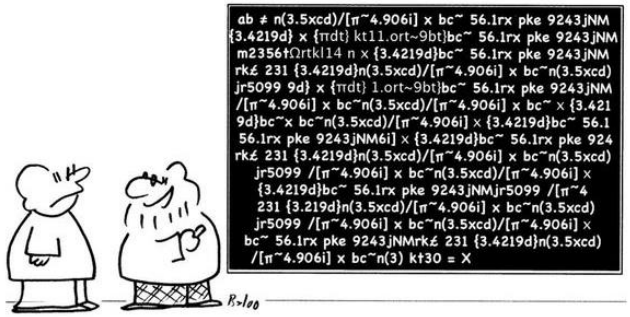
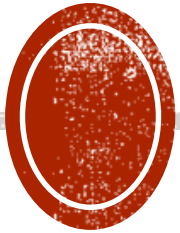
WRITING WINNING GRANTS



"It's a foolproof formula for writing grant applications."



OUTLINE:

1. Overview of funding sources
2. How to conceive a research proposal
3. How to structure a research proposal
4. Principles of grantsmanship
5. Brief overview of other, important grant components
6. Responding to a summary statement

WHERE DO RESEARCH GRANTS COME FROM?

Government:

National Institutes of Health (NIH) - $37B

National Science Foundation (NSF) - $7B

Department of Defense (DoD) - $500M

Philanthropic organizations:

Bill and Melinda Gates Foundation - $10B

American Cancer Society - $145M

Susan Komen Foundation - $100M

For a full list of current opportunities contact your Grant Support Office!

PHILANTHROPIC FOUNDATIONS

Funding Projects

Bill and Melinda Gates Foundation

American Cancer Society

Susan Komen Foundation

American Diabetes Association

American Heart Association

Funding Investigators

Burroughs Welcome Fund

Howard Hughes Foundation

https://www.nih.gov/institutes-nih/

TYPES OF GRANTS

https://grants.nih.gov/grants-funding

Research Grants (R)

R01, R21, R35, R43/R44 (SBIR)

Career Development Awards (K)

K01, K02, K07, K12

Training Grants and Fellowships (T & F)

T32, T34, D43, F31

Program Project/Center Grants (P)

P01, P30 (Center Core), P50 (Specialized Center)

Resource Grants (various series)

SOLICITED GRANTS

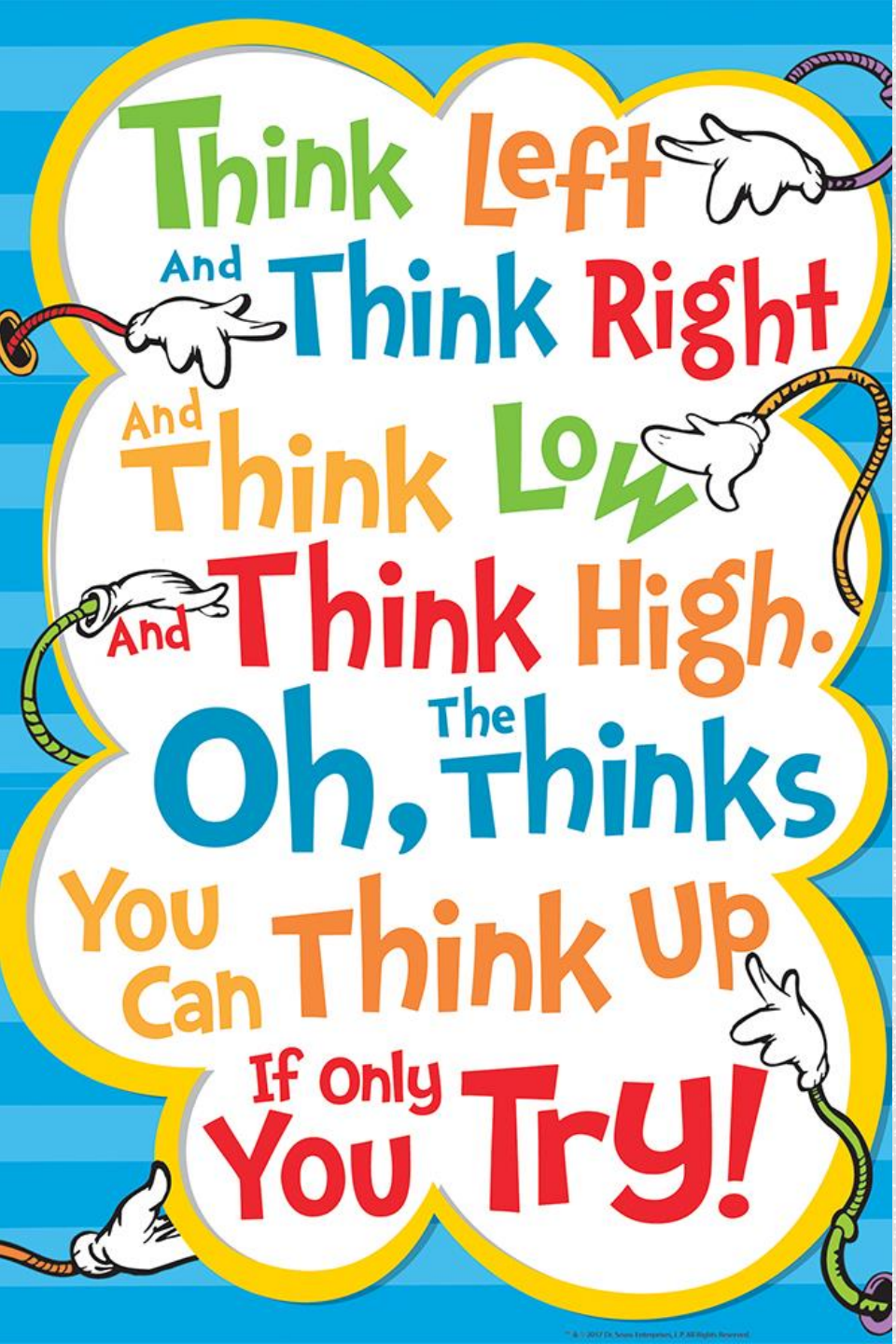
https://grants.nih.gov/grants-funding

Program Announcement (PA)

- Invites grant applications in a given research area
- Generally has no funds set aside
- Applications reviewed in CSR along with unsolicited grant applications

Request for Applications and Proposals (RFA and RFP)

- Invitation to submit applications or contract proposals for a one-time competition in a well-defined scientific area
- Funds are set-aside of for a certain number of awards
- Applications generally reviewed within the issuing institute by special CSR



BEFORE YOU BEGIN…

Be aware of trends and funding initiatives ("translational" vs "basic" studies, RFAs, PAs).

Talk to mentors, colleagues and collaborators about your ideas.

Be familiar with the literature in your field.

Define your strengths and weaknesses in terms of publications, preliminary data, collaborators.

Think how you will combine this into a convincing ***STORY…***

Don't forget your ***AUDIENCE…***

BASIC ELEMENTS OF YOUR "STORY"

Who are you?
Bio-sketch (personal statement)

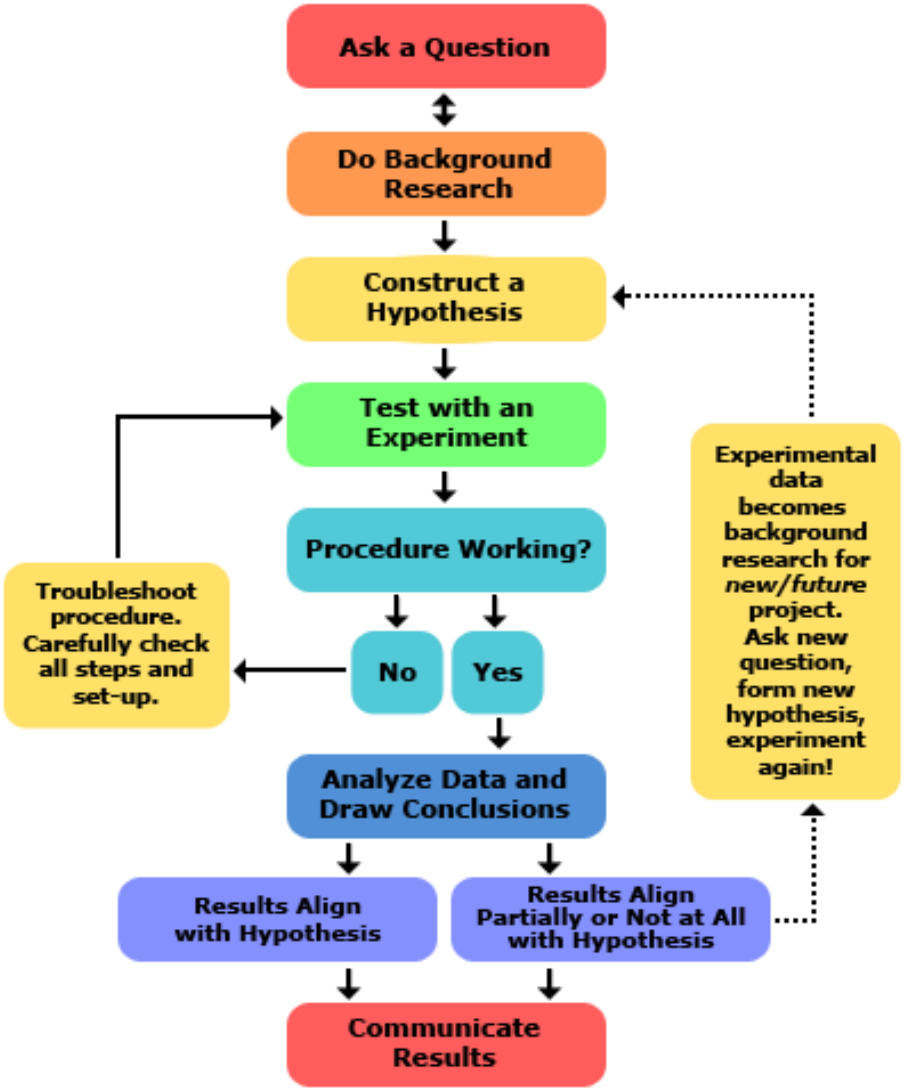
Where are you?
Institution and resources

Who are your friends?
Collaborators, letters of support, recommendations

What have you accomplished?
Publications, presentations, preliminary data

What do you plan to accomplish?
Research proposal

MOST PROPOSALS ARE BASED IN THE SCIENTIFIC METHOD



WHAT IS A SIGNIFICANT QUESTION?

Your niche defines you

The questions you ask will be determined by where you are, who you work with, what you work on, what models you use.

Innovation is key

Is the work new and unique? Will the findings move your field forward?

Translational value

Do the findings have potential to improve human health?

Examples:

How does protein X bind to protein Y?

How does the interaction between X and Y transform cells?

WHAT IS A PREMISE?

All scientific findings, including yours, that are relevant to the proposal.

Consider the rigor, strengths and weaknesses of published research or preliminary data crucial to your application.

Weaknesses should be acknowledged, and the data should either be excluded or addressed by the proposal.

FORMULATING A HYPOTHESIS

A hypothesis is a **proposed explanation** for an observed phenomenon.

A scientific hypothesis must be **testable** and **falsifiable**.

Simpler hypotheses are preferable to more complex ones because they are more testable.

A **central hypothesis** focuses research around a topic/theme.

Example: Increased levels of the X/Y complex transform hepatocytes.

FORMULATING SPECIFIC AIMS

Independent
Three sets of related experiments that aim to prove your central hypothesis.

Focused
Address only the hypothesis and can be completed in 4-5 years.

Deterministic (not descriptive)
Controlled experiments that prove part of the hypothesis.

Based on preliminary data
Do not propose anything that you have no evidence for!

Example:
Show that signaling pathways associated with an epithelial-mesenchymal transition are modulated by X and Y stoichiometry

Show that hepatocytes acquire migratory and invasive properties when X or Y are overexpressed

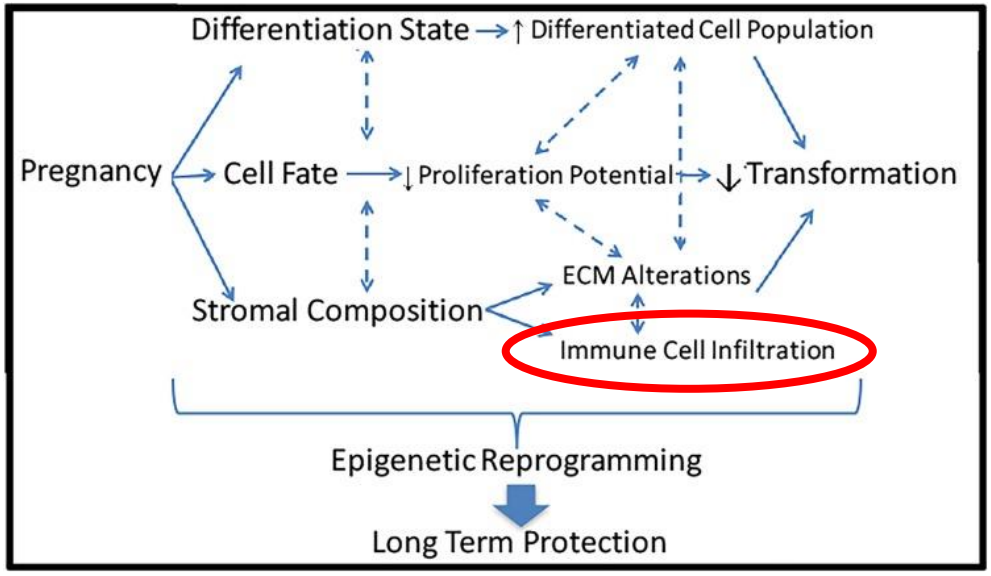
Demonstrate that mice overexpressing X or Y have a higher incidence of hepatocellular carcinoma

EXAMPLE

Observation: A full-term pregnancy before age 23 reduces the risk of developing breast cancer by 50%.

Question: How does early pregnancy protect from breast cancer?

Premise:



WHAT WILL YOU PROPOSE?

Hypothesis:

Early pregnancy protects against breast cancer by allowing patrolling immune cells to set up residence in the mammary gland before the accumulation of carcinogenic insults.

Specific Aims:

Show that mammary glands are populated by NK and CD8 cells after pregnancy.

Demonstrate that pregnancy upregulates epithelial markers and extracellular matrix proteins that promote adhesion of patrolling immune cells.

Demonstrate that inhibiting the migration of patrolling cells into mammary glands of mice during early pregnancy increases the incidence of breast cancer.

WHAT'S IN A TITLE?

General and Reusable

Include important information about the research area, the research problem and your goals.

Show that early pregnancy increases the presence of NK and T cells in the mammary gland

Identify immune mechanisms induced by pregnancy in the mammary gland

++++

The role of X and Y overexpression in the EMT transition in hepatocytes

The effect of X/Y stoichiometry on cellular transformation

++++

STRUCTURE OF AN "R" GRANT

Specific Aims Page (1 page)

Research Strategy (12 pages for R01)

- **Significance** (<1 page)
- **Innovation** (<1 page)
- **Approach** (11 pages)
  - 3-4 pages:
    - **Background**
    - **Preliminary Results**
  - 7-8 pages:
    - **Specific Aims 1-3**
      - experimental design
      - rigor & reproducibility

Bibliography (~100 references)

PHS 398 Forms:

- Face Page (Title)
- Summary (30 lines)
- Project Narrative (3 sentences)
- Bio-sketches
- Personnel Justification
- Budget Justification
- Other Support
- Resources
- Key bio and chem resources
- Data sharing plan
- Animal protocols
- Human Subjects
- *Letters of support

SPECIFIC AIMS PAGE

<u>This is a SUMMARY of your entire proposal</u>

- Introduce the field and its importance to human health
- State the problem/question you are studying

- Provide a synopsis of the **premise** (state of knowledge)
- State your **hypothesis**
- Briefly describe your **preliminary data** in support of the hypothesis

- INDEPENDENT Specific Aims

- How will your work advance the field
- Why your proposal is significant to human health

SPECIFIC AIMS TITLES

To define the mechanism by which KDM5 affects Foxo recruitment to oxidative stress target genes and to determine the functional defects of the intellectual disability-associated allele kdm5L854F.

Determine the functional deficit of a KDM5 mutant associated with intellectual disability.

Examine the role of oligomerization and higher-order self-association in the ability of MXB to bind the HIV-1 core.

Determine the role of MXB oligomerization in binding to the HIV-1 core.

Study the regulatory network that governs segmentation and rostrocaudal polarity of somites by integrating quantitative data and computational modeling.

Integrate experimental findings and computational modeling to determine how segmentation and polarity are acquired in somites.

SPECIFIC AIMS FORMATS

Specific Aim 1. Establishing Imaging Tools and a Specific Timeline. We will first perform baseline μPET/CT images in 20 Sprague Dawley Rats (10 for each radiotracer, 20 total) using [^{18}F]AER-001 (CB2 specific) and [^{18}F]RPS-534 (CXCR4 specific) imaging agents. Each animal will serve as its own control. After inducing an MI in the rats (a reperfusion model clamping the left LAD artery for 45 minutes) we will daily μPET/CT images for a week. Three images per week will be performed for an extra 2 weeks. At 3 weeks post-MI and under isoflurane anesthesia the chest will be reopened, and Evan's Blue will be injected into the heart. Then, 1 ml of saturated potassium chloride solution will be injected. The heart will be excised and sectioned. Sections will be stained with 2% triphenyl tetrazolium chloride (TTC). Pictures of the slides will be used to create a 3D stack, and compared to the μPET/CT imaging findings. No clinical intervention will be performed in this aim, and the induced infarctions will be allowed to undergo natural ventricular remodeling. We will establish a timeline for each tracer and determine the time of maximum uptake and the optimal imaging time post-MI.

Specific Aim 1. Establish an imaging protocol using inflammation markers. PET/CT images using CB2-specific and CXCR4-specific agents will be acquire at baseline and following myocardial infarction in rats. No clinical intervention will be performed, allowing for natural ventricular remodeling. After three weeks, rat hearts will be analyzed by histochemistry. This will allow us to determine the time of maximum uptake and optimal imaging for each inflammation marker.

SIGNIFICANCE & INNOVATION

Significance (1/2 page):

1) introduce field and important question
2) summarize the **premise**, including your work
3) state your **hypothesis** and supporting preliminary data
5) how will your proposal advance the field (and improve human health)?

Innovation (1/2 page):

Conceptual

1) explores new and unique scientific questions
2) has a novel hypothesis
3) will create new knowledge

Technical

4) relies on novel techniques and analytical tools

APPROACH

Background (1 page):

A summary of the relevant literature in the field, from "dogma" to controversial. Provide basics here, and more details on a need-to-know basis throughout the grant. Address rigor & reproducibility.

Preliminary Results (no more than 6-8 figures for R01):

Summarize your published findings in the field, and provide details of your most recent, original and unpublished data that show:

-you can do what you propose to do

-your hypothesis may be provable

Title: Short and deterministic

elucidate, study, explore, understand

identify, show, determine, demonstrate

Rationale: Why, how, significance

believe, hope, speculate, seem

indicate, propose, evidence-based

Preliminary Results: Unpublished

here and/or before specific aims

Experimental Design:

what you will do and why

how you will do it (experiments)

what you will learn

Data interpretation:

statistics, rigor and reproducibility

Pitfalls and alternative approaches:

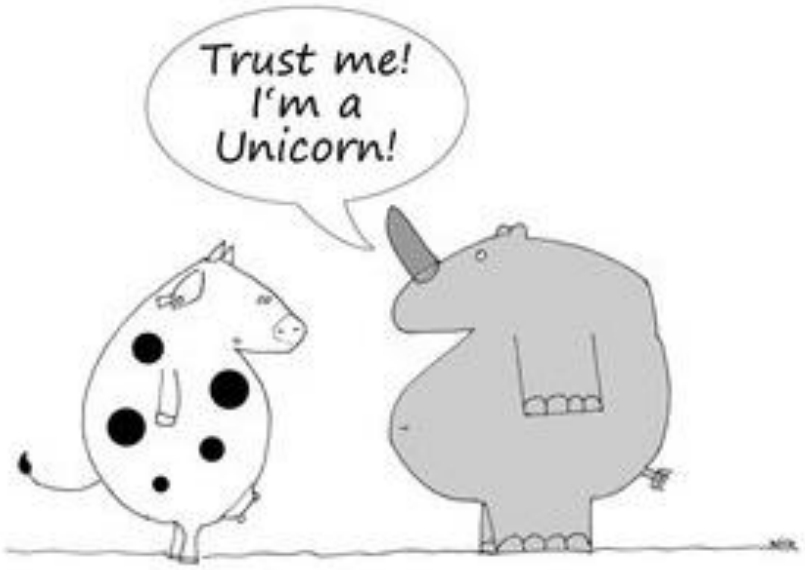
which problems you anticipate

what you will do if experiments fail

SPECIFIC AIMS

(8-10 PAGES)

BUILDING TRUST



Rigor and Reproducibility

Consistent structure

Strong, clear data

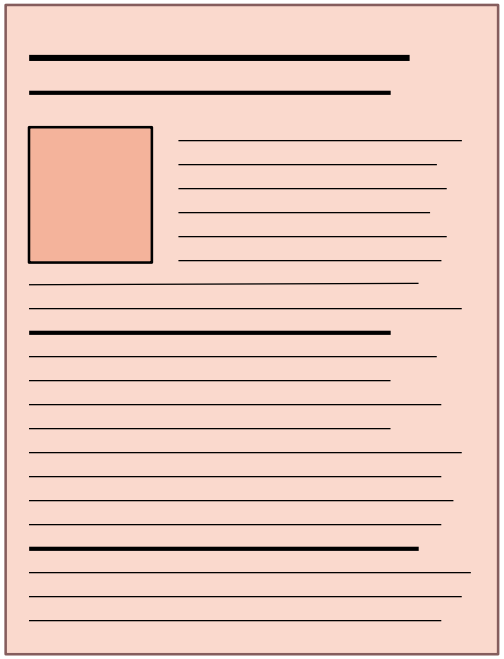
Simple language

Circular narrative

RIGOR & REPRO-DUCIBILITY

4 AREAS OF FOCUS	WHAT DOES IT MEAN?	WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?
Rigor of the Prior Research	A careful assessment of the **rigor of the prior research** that serves as the key support for a proposed project will help applicants identify any weaknesses or gaps in the line of research. Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. Describe plans to address weaknesses in the rigor of the prior research that serves as the key support for the proposed project *See related FAQs, blog post	**Research Strategy** ➢ Significance ➢ Approach
Scientific Rigor (Design)	**Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog post, examples from pilots	**Research Strategy** ➢ Approach
Biological Variables	**Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response. Explain how relevant biological variables, such as the ones noted above, are factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data or other relevant considerations must be provided for applications proposing to study only one sex. *See related FAQs, blog posts, article	**Research Strategy** ➢ Approach
Authentication	**Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not have been generated with NIH funds and: • may differ from laboratory to laboratory or over time; • may have qualities and/or qualifications that could influence the research data; • are integral to the proposed research. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post, examples	**Other Research Plan Section** ➢ Include as an attachment ➢ Do not include in the Research Strategy.

CONSISTENT STRUCTURE



Specific Aim 1:

A. Rationale

B. Preliminary Data

1. Finding
2. Finding

C. Experimental Design

1. Experiments
   a) *section*
   b) *section*
2. Experiments
3. Experiments

D. Statistics and Data Interpretation

E. Pitfalls and Alternative Approaches

STRONG & CLEAR DATA

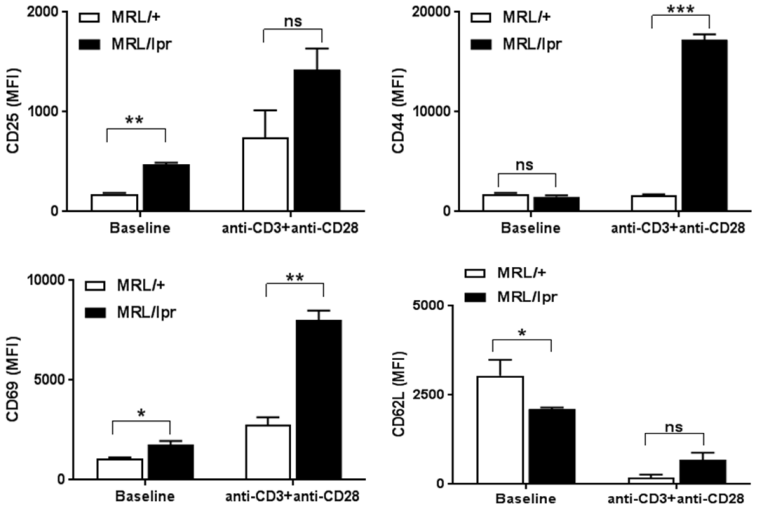


Figure 4: **Choroid plexus-infiltrating T cells in MRL/lpr mice are activated.** Choroid plexus derived cells from 16 week old MRL/lpr mice (n=4) were cultured *in vitro* (in the presence or absence of anti-CD3 and anti-CD28) for 48 hours and analyzed by flow cytometry for the expression of T cell activation markers. Shown here are the mean fluorescence intensities (MFI) of the different activation markers.

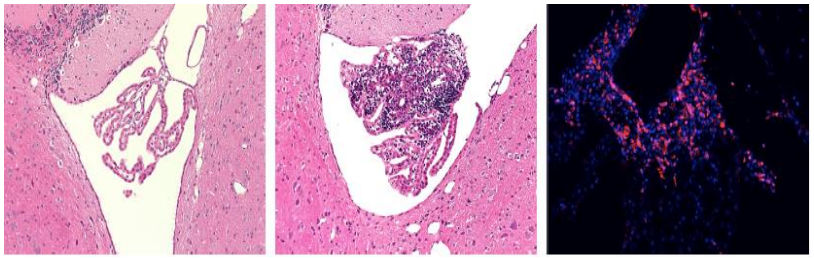


Figure 1: **MRL/lpr mice show marked infiltration of CD4+ T cells in the brain choroid plexus.** Representative H&E staining of brain sections from 16 week old control MRL/+ (left) and MRL/lpr (middle) mice are shown. The right panel demonstrates prominent immunofluorescent staining for CD4 in the choroid plexus of MRL/lpr mice. Magnification: 10X

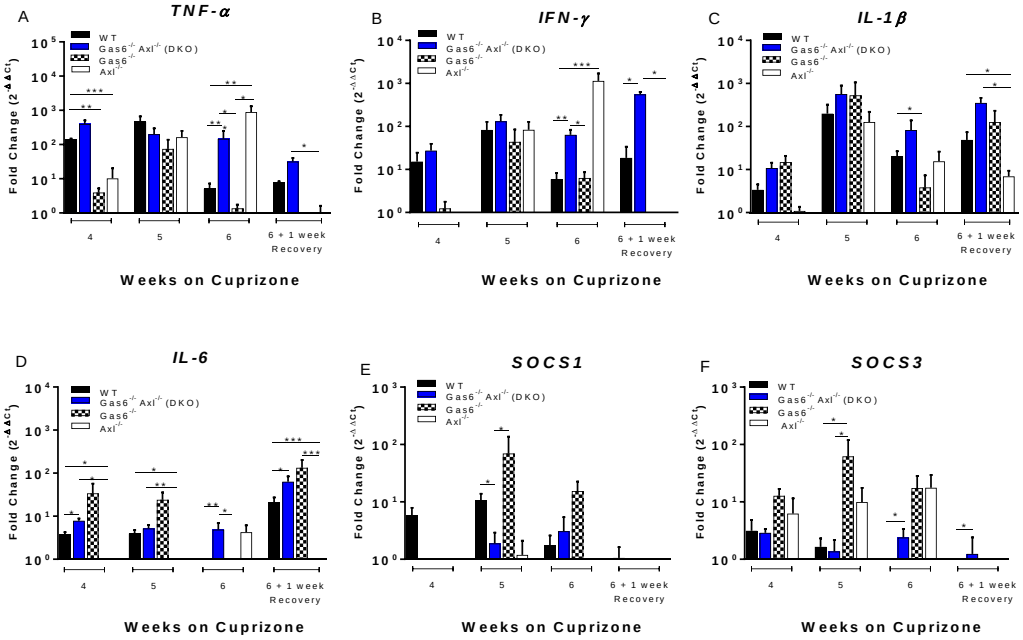
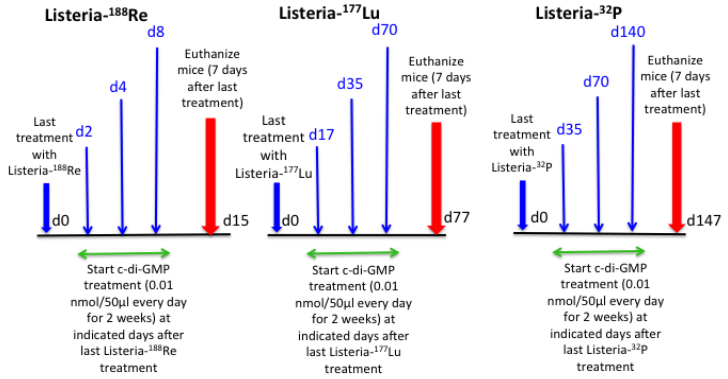
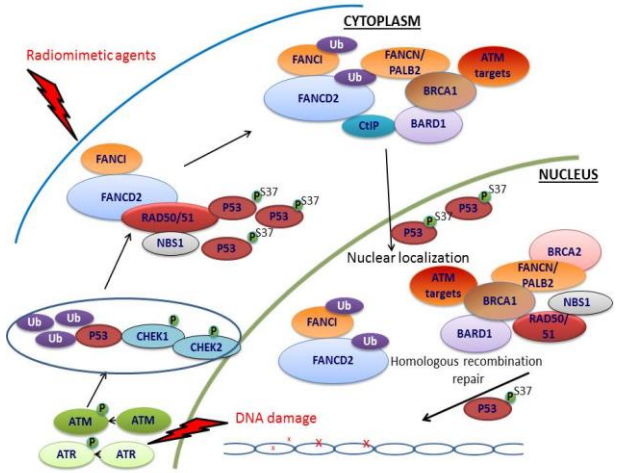
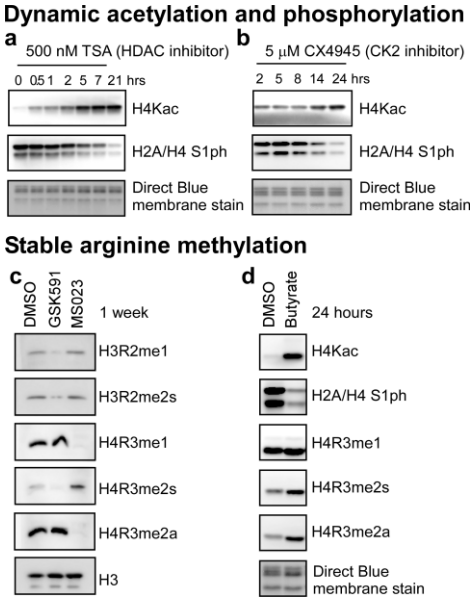


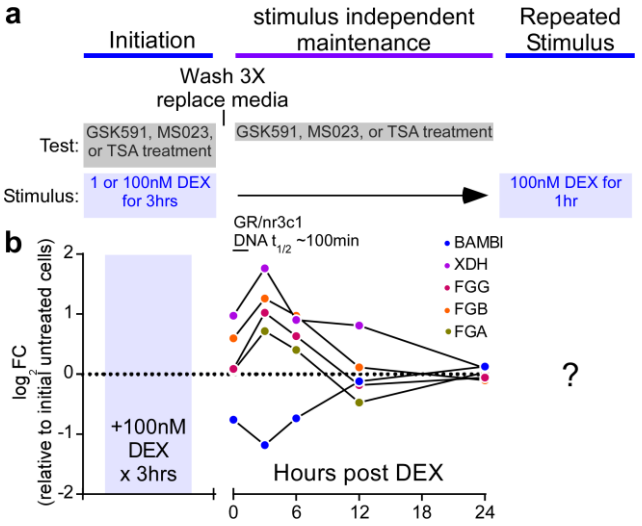
Figure 12: Schematic view of c-di-GMP treatments after RL treatment



Groups: I. Saline, II. RL, III. RL+c-di-GMP, IV. C-di-GMP. n=6 mice per group. Experiment 2x repeated. Of note is that the c-di-GMP treatments depicted in this figure will be administered after the RL treatments as outlined in Figure 10







SIMPLE LANGUAGE & WYSSAFA

S1ph is inhibitory to all PRMTs; H4K5ac stimulates PRMT1 and PRMT5 to catalyze activating H4R3me1 and PRMT1 to H4R3me2a.

Phosphorylation of the first H4 serine inhibits all subsequent methylation of this histone. In contrast, acetylation of lysine 5 activates methylation of arginine 3 by protein methylases (PRMT) 1 and 5. It also activates di-methylation of arginine 3 by PRMT1.

We will establish whether central regulation of EGP can be restored by lowering FFA levels in T2D.

We will establish if lowering free fatty acid levels in type 2 diabetes can restore regulation of endogenous glucose production by the central nervous system.

CIRCULAR NARRATIVE

SUMMARY & PROJECT NARRATIVE (PHRS)

COMMUNICATE THE VALUE AND INTENT OF YOUR PROJECT TO A WIDE AUDIENCE

PHRS (2-3 lines)

Example: Over 40,000 women die every year from breast cancer. Pregnancy before age 23 offers the strongest protection against this disease. Our study aims to understand the reasons for this protective effect, and to identify novel targets for the treatment and prevention of breast cancer.

SUMMARY (30 lines)

- The project's broad, long-term objectives and specific aims
- A description of the research design and methods for achieving the stated goals

PERSONAL STATEMENT

- Tailor the Personal Statement to the application.
- In the first sentence, mention the name of the grant application and speak directly to the purpose of the funding mechanism.
- Briefly describe why you are well-suited for your role in this application. Include your: training, previous work on this or related topics, technical expertise, collaborators or scientific environment.
- Use the Personal Statement to discuss your future research direction if you are a new investigator.
- If someone is sponsoring/mentoring/collaborating with you, include this in the Personal Statement.

SUMMARY STATEMENT

(WRITTEN BY THREE REVIEWERS)

RESUME AND SUMMARY OF DISCUSSION

DESCRIPTION (provided by applicant)

PUBLIC HEALTH RELEVANCE

CRITIQUE

Overall Impact

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

} Strengths and weaknesses
Each category scored 1-9

Protections for Human Subjects, Vertebrate Animals, Biohazards, Applications from Foreign Organizations, Select Agents, Resource Sharing Plans, Authentication of Key Biological and/or Chemical Resources, Budget and Period of Support

RESPONDING TO YOUR SUMMARY STATEMENT

- Be polite and non-confrontational
- Acknowledge mistakes, oversights and problems
- Group "weaknesses" by category, and again by theme
- Focus on issues raised by more than one reviewer
- Add any new publications or preliminary data to address critiques

PARTING WORDS OF WISDOM

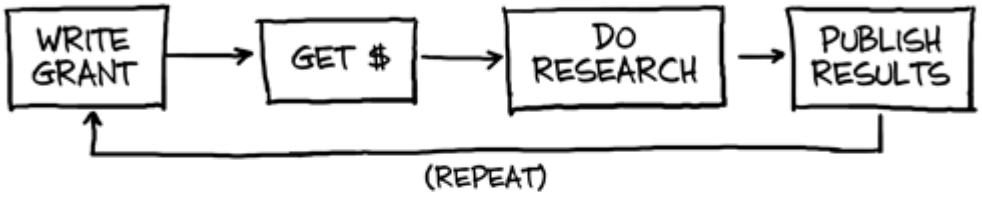
Sometimes, less is more.

~ William Shakespeare

AZ QUOTES

THE GRANT CYCLE

HOW IT'S SUPPOSED TO WORK:



HOW IT REALLY WORKS:

THE NIH REVIEW PROCESS

The Center for Scientific Review (CSR)
portal for NIH grant applications and their review for scientific merit.

Integrated Review Groups (IRG)
study sections grouped around a general scientific area
Example: Molecular, Cellular and Developmental Neuroscience (MDCN)

Scientific Review Group (Study Sections)
group of experts in the field (temporary and regular) who review grants
Special Emphasis Panels (SEPs) review applications on special topics (RFAs).
Example: MDCN includes 11 study sections:
Biophysics of Neural Systems Study Section (BPNS), Neurotransporters, Receptors, Channels and Calcium Signaling Study Section (NTRC), Cellular and Molecular Biology of Neurodegeneration Study Section (CMND)

https://public.csr.nih.gov/

NIH OFFICERS

Program Officer

Advises applicants and grantees, makes funding recommendations, oversees grantees' progress, facilitates scientific opportunities in specific areas of program responsibility, and shapes NIH policy.

Scientific Review Officer

Works with the scientific community to ensure that the study section identifies the most meritorious science for funding by the institutes and centers.

Grant Management Specialist

Works on all the administrative and organizational aspects of funded grants to ensure progress and compliance.