

Preparing an NIH Grant (Research and Ks)

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28th Annual “Aspen” NICHD Conference on Maternal-Fetal-Neonatal-Reproductive Medicine



Maroon Bells



Golden Aspen



Halam Lake from
the Given Institute



Colorado Blue
Columbine



Joe Butterfield



Duane Alexander

Reality Check _BY DAVID SIPRESS

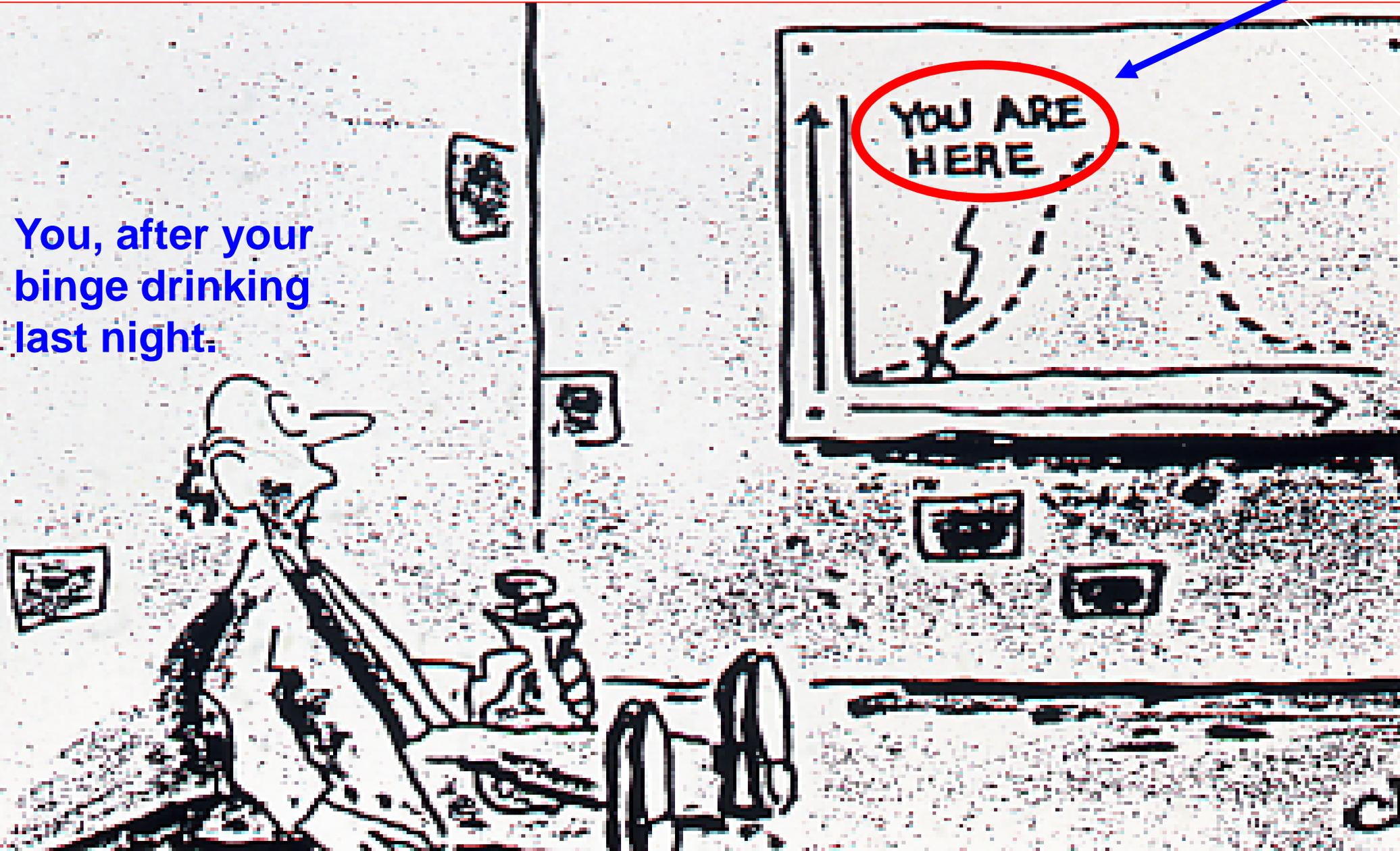


**How most of us
feel after writing
a grant.**

Hi, Honey—how's everything in the world of academia?

So, we are going to try to make it easier for you, because

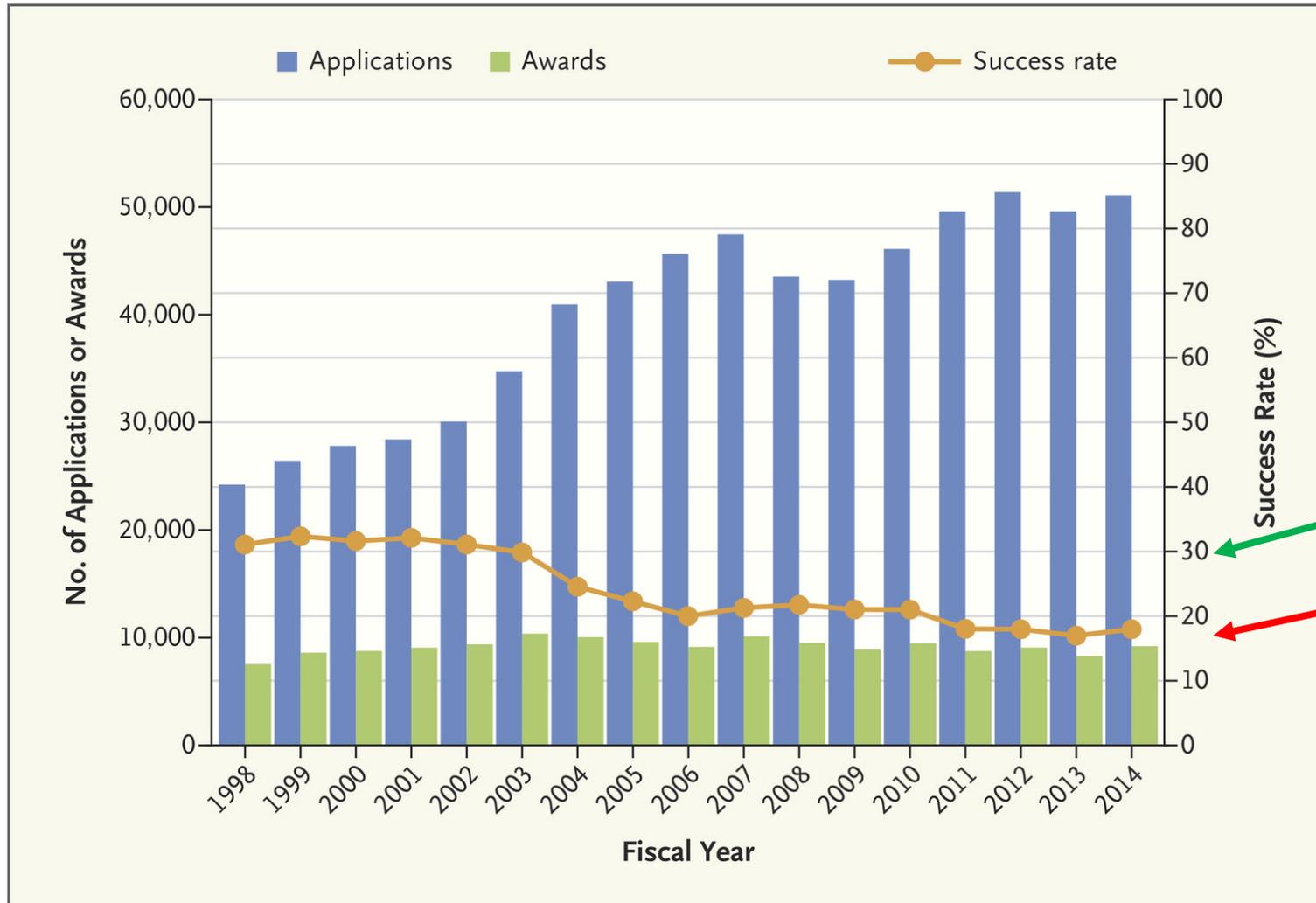
You, after your
binge drinking
last night.





And because success rates for NIH grants have declined--

Applications for NIH Research Grants, Grants Awarded, and Success Rates, 1998–2014.



From 30% in 2003 to 18% in 2014.

About the same or lower today.

Basic Components of Grant Proposals

1. Title & Abstract—the idea--what will be done, rationale– why , approach--how, long term goal--value, and **IMPACT**
2. Specific Aims (Hypotheses, Questions, Models: what)
3. Significance (rationale--why)
4. Innovation (**What is new?—ideas, methods**)
5. Convincing preliminary data (**can it be done and well?**)
6. Expertise of the Investigator (s) (**can you do it?**)
7. Approach: Methods and Statistical design (how).
8. Environment (**institutional resources and successes**)
7. Summary, restating long term value (goal) and overall **IMPACT**

First, what does an NIH grant application look like?

PHS SF424 (R&R) Adobe Forms Version C Application Guide

PHS business processes. Agency validations will be performed by the eRA Commons system after the application has been submitted.

For those forms that are more than one page, click the Next button at the top of the form or scroll down (using the scroll bar on the right hand side of the screen) to navigate to a subsequent page. Once all data have been entered scroll up using the scroll bar to return to the Grant Application Package Screen.

4.2 Cover Form

OMB Number: 4040-0001

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE: [] State Application Identifier: []

1. TYPE OF SUBMISSION
 Pre-application Application Change/Corrected Application

4. a. Federal Identifier: []
b. Agency Routing Identifier: []

2. DATE SUBMITTED: [] Applicant Identifier: []
c. Previous Grants.gov Tracking ID: []

5. APPLICANT INFORMATION
Organizational DUNS: []

Legal Name: []
Department: [] Division: []
Street1: []
Street2: []
City: [] County / Parish: []
State: [] Province: []
Country: [] (USA: UNITED STATES) ZIP / Postal Code: []

Person to be contacted on matters involving this application
Prefix: [] First Name: [] Middle Name: []
Last Name: [] Suffix: []
Position Title: []
Street1: []
Street2: []
City: [] County / Parish: []
State: [] Province: []
Country: [] (USA: UNITED STATES) ZIP / Postal Code: []
Phone Number: [] Fax Number: []
Email: []

6. EMPLOYER IDENTIFICATION (EIN) or (TIN): []

7. TYPE OF APPLICANT: [] (Please select one of the following)
Other (Specify): []
Small Business Organization Type Women Owned Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:
 New Resubmission Renewal Continuation Revision
If Revision, mark appropriate box(es):
 A. Increase Award B. Decrease Award C. Increase Duration D. Decrease Duration
 E. Other (specify): []

Is this application being submitted to other agencies? Yes No What other Agencies? []

9. NAME OF FEDERAL AGENCY: []
10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: []
TITLE: []

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
[]

12. PROPOSED PROJECT:
Start Date: [] Ending Date: []

13. CONGRESSIONAL DISTRICT OF APPLICANT: []

Cover Form

- Type of submission
- Applicant information
- Employer information
- Descriptive title of project

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: [] First Name: [] Middle Name: []
 Last Name: [] Suffix: []
 Position/Title: []
 Organization Name: []
 Department: [] Division: []
 Street1: []
 Street2: []
 City: [] County / Parish: []
 State: [] Province: []
 Country: [USA: UNITED STATES] ZIP / Postal Code: []
 Phone Number: [] Fax Number: []
 Email: []

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested []
 b. Total Non-Federal Funds []
 c. Total Federal & Non-Federal Funds []
 d. Estimated Program Income []

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE: []
 b. NO PROGRAM IS NOT COVERED BY E.O. 12372; OR PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

I agree []

*The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL (Disclosure of Lobbying Activities) or other Explanatory Documentation

[] Add Attachment [] [] []

19. Authorized Representative

Prefix: [] First Name: [] Middle Name: []
 Last Name: [] Suffix: []
 Position/Title: []
 Organization: []
 Department: [] Division: []
 Street1: []
 Street2: []
 City: [] County / Parish: []
 State: [] Province: []
 Country: [USA: UNITED STATES] ZIP / Postal Code: []
 Phone Number: [] Fax Number: []
 Email: []

Signature of Authorized Representative [] Date Signed []
Completed on submission to Grants.gov Completed on submission to Grants.gov

20. Pre-application [] Add Attachment [] [] []
21. Cover Letter Attachment [] Add Attachment [] [] []

Application Page—2

- PI name
- Estimated project funding
- Authorized Institutional official

Modular Budget

Total Budget Summary

5.4.1 Budget Period Form

PHS 398 Modular Budget OHS Number: 0925-0001

Budget Period: 1

Start Date: End Date:

A. Direct Costs		Funds Requested (\$)
Direct Cost less Consortium F&A		<input type="text"/>
Consortium F&A		<input type="text"/>
Total Direct Costs		<input type="text"/>

B. Indirect Costs		Funds Requested (\$)	
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)
1. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Co-granting Agency (Agency Name, POC Name and Phone Number):

Indirect Cost Rate Agreement Date: Total Indirect Costs:

C. Total Direct and Indirect Costs (A + B)		Funds Requested (\$)
		<input type="text"/>

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A. Total Direct Cost less Consortium F&A for Entire Project Period	\$	<input type="text"/>
Section A. Total Consortium F&A for Entire Project Period	\$	<input type="text"/>
Section A. Total Direct Costs for Entire Project Period	\$	<input type="text"/>
Section B. Total Indirect Costs for Entire Project Period	\$	<input type="text"/>
Section C. Total Direct and Indirect Costs (A+B) for Entire Project Period	\$	<input type="text"/>

2. Budget Justifications

Personnel Justification:

Consortium Justification:

Additional Narrative Justification:

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	<input type="text"/>
Section B, Other Personnel	<input type="text"/>
Total Number Other Personnel	<input type="text"/>
Total Salary, Wages and Fringe Benefits (A+B)	<input type="text"/>
Section C, Equipment	<input type="text"/>
Section D, Travel	<input type="text"/>
1. Domestic	<input type="text"/>
2. Foreign	<input type="text"/>
Section E, Participant/Trainee Support Costs	<input type="text"/>
1. Tuition/Fees/Health Insurance	<input type="text"/>
2. Stipends	<input type="text"/>
3. Travel	<input type="text"/>
4. Subsistence	<input type="text"/>
5. Other	<input type="text"/>
6. Number of Participants/Trainees	<input type="text"/>
Section F, Other Direct Costs	<input type="text"/>
1. Materials and Supplies	<input type="text"/>
2. Publication Costs	<input type="text"/>
3. Consultant Services	<input type="text"/>
4. ADP/Computer Services	<input type="text"/>
5. Subawards/Consortium/Contractual Costs	<input type="text"/>
6. Equipment or Facility Rental/User Fees	<input type="text"/>
7. Alterations and Renovations	<input type="text"/>
8. Other 1	<input type="text"/>
9. Other 2	<input type="text"/>
10. Other 3	<input type="text"/>
Section G, Direct Costs (A thru F)	<input type="text"/>
Section H, Indirect Costs	<input type="text"/>
Section I, Total Direct and Indirect Costs (G + H)	<input type="text"/>
Section J, Fee	<input type="text"/>

Biographical Sketch

FF Principal Investigator/Program Director (Last, first, middle)

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
------	----------------

EDUCATION: (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
--------------------------	--------	----------------	----------------

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Other Support

GG Principal Investigator/Program Director (Last, first, middle)

OTHER SUPPORT

(Use continuation pages if necessary)

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or possible funding of the application. If there are changes in the information after submission, notify the scientific review administrator of the initial review group before the review; if changes occur after the review, notify the appropriate scientist.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available to the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means. However, in the case of prizes and gifts, only those that support the specific project must be reported. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Reporting requirements are for each of the key personnel, describe (1) all currently active support and (2) all applications and proposals pending review or award, whether related to this application or not. If the support is part of a major project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the format as shown below. Information may be combined as long as the format remains the same. For example, all key personnel who have no other support may be listed on a single page. DO NOT SEND in a separate page for each person listed for whom "None" is checked.

Name _____ Active _____ Pending _____ None _____

a. Source and identifying no. _____ P.I. _____

Title _____

b. Your role on project _____ % Effort _____

c. Dates and costs of entire project (For renewals, include only the most recent completed award. List direct and indirect costs separately.)

d. Dates and costs of current year _____

e. Specific aims of project _____

f. Describe scientific and budgetary overlap

g. Describe acquisitions you will make if the present application is funded (budget, % effort, aims, etc.)

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEED THE SPACE PROVIDED.

The **Abstract**—the most important page in the entire application.

Description (Abstract)
WHAT you are going to do, **WHY** you are going to do it, **HOW** you are going to do it, and the **VALUE** of doing it.
Always emphasize its **IMPACT.**

PERSONNEL ENGAGED ON PROJECT, INCLUDING CONSULTANTS/COLLABORATORS. Use continuation pages as needed to provide the required information in the format shown below on all individuals participating in the scientific execution of the project.

Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____
Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____
Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____
Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____
Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____
Name _____	Degree(s) _____	Social Security No. _____
Position Title _____	Date of Birth (MM/DD/YY) _____	Role on Project _____
Organization _____		Department _____



Personnel engaged on project

Specific Aims

The objectives of the Specific Aims (in one page) are to:

- **Generate interest** Tell a compelling story
 - Why? – define the problem and your unique solutions
- **Give a concise overview of the Research**
- **Clearly state what will be learned**
(and briefly describe the experimental plan)
- **Clearly state importance/impact of results**

This is the 2nd most important page in your application.

Specific Aims

1. More than two or three Specific Aims usually are too many.
2. Each Aim should be stated in one simple sentence, saying as directly as possible what will be done.
3. Each Aim either should be, or include, a hypothesis to be tested, a question to be answered, or a model to be tested for predictability (for both experimental and observational-epidemiological studies).
4. Each Aim should include a *brief* statement of the purpose (**what**), rationale (**why**, significance), and approach (**how**).
5. Each aim should have a specific statement of what you expect to learn, and how this will be important (**value**).
6. Conclude with a summary statement that emphasizes what you will learn and the **impact** this will have on the field.

SPECIFIC AIMS

Restoration of skeletal muscle growth in the fetus with intrauterine growth restriction (IUGR) is a fundamental priority, as impaired muscle growth is a major contributor to lifelong reductions in muscle mass and metabolic disease risk. There are gaps in knowledge, however, about the basic mechanisms that regulate fetal muscle mass and when in gestation muscle growth is plastic and will respond to anabolic stimuli after exposure to placental insufficiency (PI). Our overarching aim is to determine the mechanisms that link low fetal nutrient supply to decreased muscle growth, and to test, for the first time, whether supplemental nutrients and/or anabolic hormones could restore muscle growth in the IUGR fetus. Our previous studies and preliminary data have uniquely shown that inadequate maternofetal nutrient flow from PI results in suppressed myoblast proliferation, reduced muscle amino acid (AA) uptake, and increased protein breakdown, which, together with reduced fetal insulin and AA availability, decrease muscle mass (Fig 1). We now propose to test the plasticity of these conditions and determine mechanisms that underlie the potential for 1) insulin to stimulate myoblast proliferation and 2) AA to stimulate myofiber hypertrophy during critical developmental windows of myogenesis (Fig 1). We will use our well-developed sheep model of IUGR that uniquely mimics the features of human PI-induced IUGR to determine muscle-specific metabolism in response to insulin and AA. Comprehensive investigation into the key factors that regulate fetal muscle growth at a physiological, cellular, and molecular level is a prerequisite for designing novel approaches to restore muscle growth, setting the stage for future efforts to preempt the complications of IUGR related to low muscle mass.

Aim 1: Determine the effect of insulin on cell cycle and proliferative responses in fetal myoblasts. Identifying the primary factors that stimulate myoblast proliferation in IUGR will pave the way for the development of novel strategies to promote myogenesis and preempt the risk of lifelong sarcopenia.

Hypothesis 1a. Correcting insulin concentrations in IUGR fetal sheep increases myoblast proliferation. Fetal insulin concentrations will be restored to control (CON) fetal values by direct fetal infusion during peak myoblast proliferation (70% of gestation). Proliferating myonuclei will be identified using BrdU and PCNA.

Hypothesis 1b. Insulin promotes fetal myoblast proliferation by releasing cells from G₀/G₁ arrest. The impact of insulin on cellular mechanisms that increase cell cycle progression, myoblast proliferation rates, and cell size will be determined in muscle sections and myoblasts isolated from IUGR fetuses.

Aim 2: Establish the impact of AA on fetal myofiber hypertrophy. Identifying the adaptations that develop within the myofiber to chronically-reduced AA supply, and the response to reintroduction of AA, will inform future attempts at how to deliver protein to augment muscle protein accretion.

Hypothesis 2a. AA supplementation to IUGR fetal sheep increases myofiber AA uptake and hypertrophy. Fetal muscle AA kinetics (including muscle protein synthesis and breakdown rates) and myofiber area will be measured in response to fetal AA infusion during peak myofiber hypertrophy (90% of gestation).

Hypothesis 2b. AA promote net protein accretion by increasing AA transport capacity and suppressing protein breakdown in isolated muscles. The impact of AA on cellular mechanisms that regulate hypertrophy will be determined in freshly isolated myofiber preparations and myotubes harvested from IUGR fetal sheep.

Aim 3: Determine the effect of restoring insulin and AA supply on muscle growth in the IUGR fetus. This aim represents a proof-of-concept study of the potential to improve fetal muscle growth, providing an important foundation for the development of novel intervention strategies in IUGR. We hypothesize that sequential fetal insulin and AA infusions during critical developmental windows will increase muscle mass.

Our studies will, for the first time, determine 1) the key regulators that promote fetal myoblast proliferation and myofiber hypertrophy and 2) the critical periods during an IUGR gestation when fetal muscle growth might be recovered. IUGR is a highly prevalent disorder affecting ~8% of all pregnancies, with no known cure and no current means of improving fetal growth *in utero*. Understanding the mechanisms responsible for reduced fetal muscle growth is the first step in preventing low muscle mass, not only for the fetus affected by IUGR, but for other conditions and disorders later in life that result from poor muscle growth.

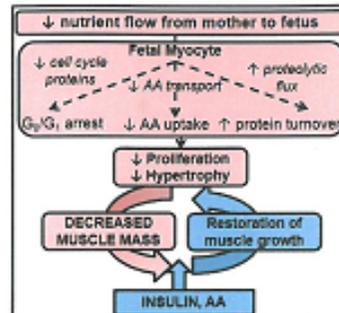


Fig 1. Mechanisms for muscle growth restriction (pink) and interventions to restore growth (blue).

Specific Aims page

Summary diagram of central concepts is helpful.

Clearly set off each SA with its overall goal, value, hypothesis, method(s), and what will be learned.

Make sure your summary & impact statement stand out separately (unlike this one!).

Hypothesis, Question, Model

Hypotheses or questions or models formulated from your “good idea” must be:

- Clear, testable, answerable, with robust science (**Rigorous**), and verifiable (**Transparent**): consult with a statistician before you write down the study design.
- Of limited scope (i.e., can be completed in a 3-5 year period)
- Important, with high potential impact, as well as interesting
- New, unique, extend knowledge, solve an important problem, fill in an essential missing link, predict/generalize to future similar situations.
- Focus the research on
 - better understanding of how mechanisms control a key biological process
 - better disease recognition, prevention, or treatment

Research Strategy (Background, Rationale)

Not just a literature review (although this must be included).
Provides the rationale for what you propose to do.

Significance

The scientific premise forming the basis of the proposed research
Puts your proposed research into perspective---what it will do and
the importance of the results.

If the aims of the application are achieved, in what specific ways
will scientific knowledge will be advanced.

What will be the effects of your studies on the concepts or
methods that drive this field.

Innovation

How the project employs novel concepts, approaches, or
methods. What is really new about your methods or outcomes.

How the project challenges existing paradigms or develops new
methodologies or technologies.

Preliminary Data

Demonstrates feasibility. Can it be done? Can you do it? Will the results be accurate? Are your methods state-of-the-art? Will the hypotheses probably be supported? Prove that assays and other technical methods in your lab are in working order.

Balance between preliminary data that show feasibility and likelihood of success vs. proof of hypothesis which guarantees success and definitive conclusion.

- Too much prior proof - no reason to fund, it's done; just filling in "n".**
- Not enough prior proof - too risky; too unlikely to succeed.**

Approach (Methods)

1. Experiments

Emphasize the essential experiments.

Refer to literature for established methods.

Identify new methods and their value and **proof that they work.**

2. State clearly what each experiment will

demonstrate or prove, why that outcome is particularly important to obtain, and what will be the overall impact on the scientific field of what you will learn.

Approach (Methods)

3. Statistical design and analyses

How will data be interpreted?

Emphasize the rigorous experimental design for robust and unbiased results that you will use.

- This should come early in your grant preparation.
- First, define the accuracy of your methods.
- Then, determine how many animals/human subjects are needed for each measurement.
- Then, choose the largest number of animals/subjects that will allow a $p < 0.01$ test of the least accurate measurement—this allows you more animals/subjects than the most accurate measurement does.

Approach (Methods)

4. Potential Problems and Alternative Strategies

- Show an awareness of the problems that may arise and of the alternative approaches that can be used if the problems occur.
- Best to show that alternative outcomes also are important and would have high impact.
 - Define the level of high-risk, high-reward
 - Demonstrate understanding of risks & plans to overcome
 - Define “go” (prove what works) / “no-go” (prove what won’t work) experiments to thoroughly test proof of concept (scientific “Rigor”)

RIGOR AND TRANSPARENCY

NIH has introduced new language and instructions intended to enhance the reproducibility of research findings through explicit attention to scientific rigor and transparency.

Updates focus on four areas:

1) The scientific premise forming the basis of the proposed research

Significance Section

2) Rigorous experimental design for robust and unbiased results

Approach Section

3) Consideration of relevant biological variables, including sex and age

4) Authentication of key biological and/or chemical resources
("Authentication plan").

Timeline: What will be done when

Example 1

NUMBER OF ANIMALS AND TIME TABLE:

Protocol	Year 1	2	3	4	5
1. Developmental changes in placental glucose and amino acid metabolism	----- 20	----- 15			
2. Effect of glucose and amino acid supply on placental amino acid metabolism	----- 5	----- 10	----- 25	----- 25	----- 25
Total # of animals	25	25	25	25	25

Example 2

Year 1	Year 2	Year 3	Year 4	Year 5
Saline infusions CON and IUGR (70% and 90% of gestation)				
Skeletal muscle collection for myoblast incubations (low oxygen), myotube experiments, fiber incubations (AA transport)				
Insulin infusion PI-IUGR (70% of gestation)				
Muscle collection for Pax7, BrdU, cell cycle marker identification, FACS analysis				
	AA infusion PI-IUGR (90% of gestation)		Insulin + AA infusion PI-IUGR	
	Fiber collection for AA transport assays, fiber morphometry, protein/RNA analysis (AA transporters, autophagy activation)			

Fig 16. Timeline for in vivo (blue) and in vitro (white) studies.

Summary

What will be learned?

How will the results support the hypotheses (answer the questions, test predictability of the models) and meet the specific aims and goals?

How will the results be new and important?

IMPACT !

Gaps in our knowledge that this project will fill:

“These studies will determine the fundamental mechanisms responsible for producing cardiorespiratory rhythms that originate in the medulla.”

Why this is important (essential) to do:

“These studies will identify which receptors and processes are altered in diseases of the cardiorespiratory system such as SIDS, allowing novel, specific, more effective therapy.”

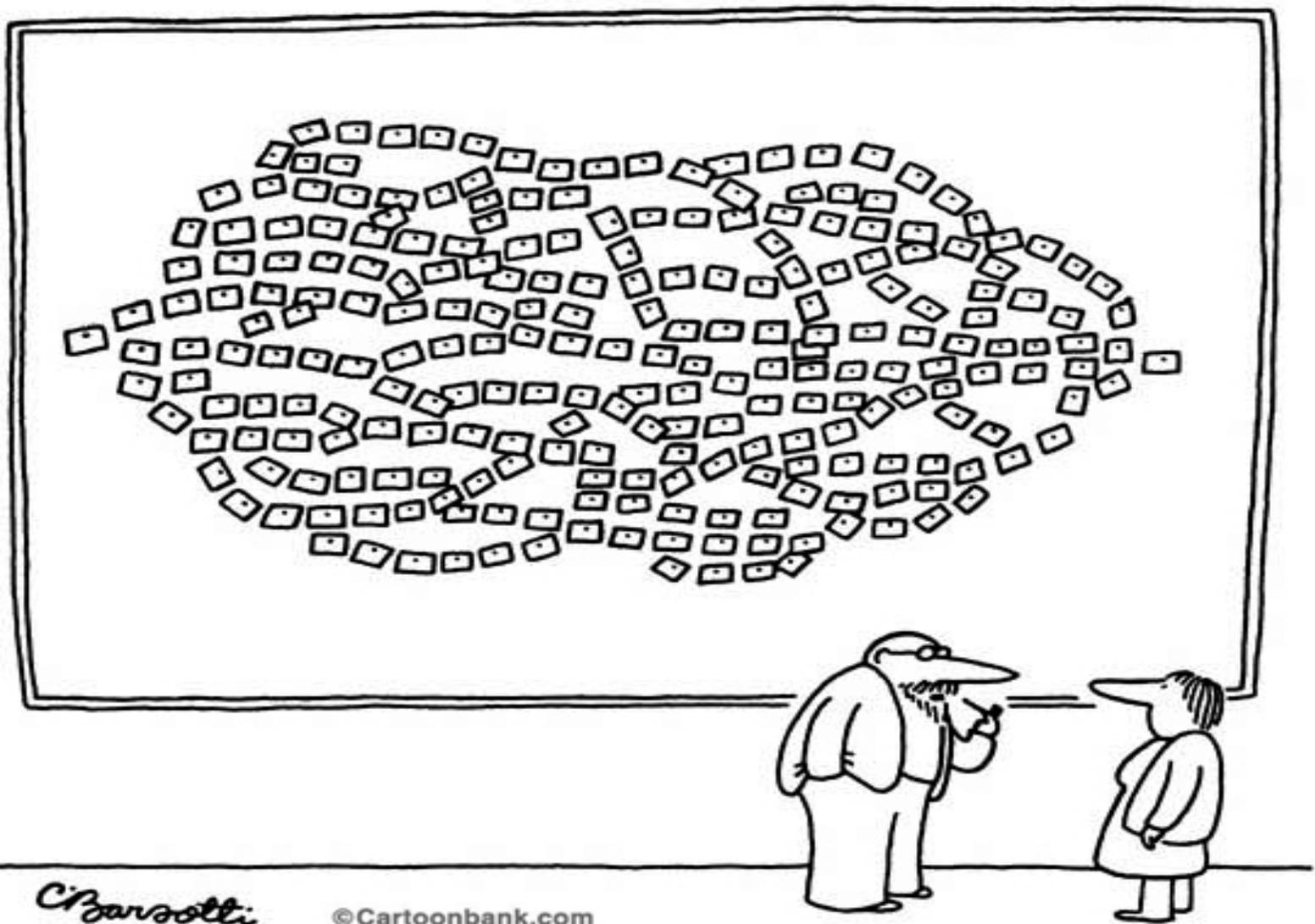
Animal Care and Use / Human Subjects

Follow the guidelines in the application exactly

Do not assume that your IACUC or IRB protocol is sufficient.

Document that this work has not been done before, that it does require an animal model or a human subject and why, and that all possible non-animal or non-human alternatives have been considered and shown to be insufficient to solve the problem(s) that the research addresses.

Above all, show that all possible discomfort of any kind to the animal or the human subject is known, anticipated, and prevented or minimized



C. Barvotti

©Cartoonbank.com

"It's plotted out. I just have to write it."



**What
commonly
happens at this
point is**

Writer's Block.

("Block Island")

Writing a Grant: General Principles

Start fresh! Don't use grants that were rejected for templates.

Organization: Outline first, write second.

Prepare the figures and tables first. Often these are already done—for abstracts and presentations.

Clarity: Appropriate syntax, clear and lucid style, plain language,
Easy conversational style, eliminate scientific jargon
unique to your field.

Short sentences. Be concise.

Keep it simple! Tell a single story—the more concepts and hypotheses and experiments included, the more difficult to understand.

A golden rule: Never submit a sloppy grant.

Assistance: Have others read it (expert and non-expert).



Key Ingredients

Technical writing:

- Clear statement of need and idea
- White space
- No silly mistakes

Proposal development:

- Explicit link to funder – NIH, Foundation
- **Potential impact**
- **Novelty and innovation**



Use Plain Language

Passive vs. active voice

- ***Passive:***

Research has been cited to demonstrate that an estimated 20% of primary school children are developing reading problems

- ***Active***

Researchers estimate that up to 20% of primary school children have reading problems.

Write it plainly

- ***Verbose:***

“Scintillate, scintillate, diminutive celestial body”

- ***Written plainly:***

“Twinkle, twinkle, little star”

Don't use words you don't absolutely need.

“Utilize” is over used (not over utilized).

“Use” is just fine.

(exception—metabolic rates are “utilization” rates)

Don't run sentences/phrases together with “however”

Confusing-- We found separate effects of glucose and insulin however the insulin effect was the stronger.

Better-- We found separate effects of glucose and insulin; insulin was the stronger.

And many more!

Strunk & White, *The Elements of Style*--still the bible
of writing English

Words NOT to use

Describe
Evaluate
Characterize
Look at
Check
Estimate
Correlate
Observe
Study
Ask / Question
Compare

And don't use “alter”
or “change”

Words OK to use

Test
Define
Determine
Measure
Quantify
Prove / Disprove

use “increase” or
or “decrease”—
or “changed from ... to ...”

Be specific!

Good Editing—The Most Essential Aspect of Good Writing

- **Why? Because bad editing preserves bad writing, which leads to misunderstanding, and all too often to confused and therefore sometimes hostile (or stupefied) reviewers.**
- **For example, you do not want these in your grant—**
- **“...causes of which include, but are not limited to, maternal malnutrition, maternal hypertension, and **idiopathic** placental insufficiency.”**
- **“These fetuses are at increased risk of hypoglycemia, hypoxia, and **academia**, as well as spontaneous preterm delivery...”**

Fortunately, I am not alone in making this mistake--

“...this report underscores the difficulty for obstetricians to identify...babies destined to develop **academia...”**

A. Fanaroff MD

2010 Year Book of Neonatal and Perinatal Medicine

Make the Application look good.

“Appearance is everything”

“Clothes maketh the man (or woman).”

Not quite true, but never, ever underestimate the **“power of presentation”**

Bad research page, difficult to read, poorly organized.

water content to hematocrit⁴⁶. Blood ¹⁴C-glucose is measured using ion exchange chromatography according to Hay et al.⁴⁷.

Calculations: Umbilical and uterine blood flow rates are calculated using Tritiated water (³H₂O) by the transplacental steady state diffusion technique.²⁸

Net uterine or umbilical uptake rates by the fetus from the placenta of amino acids (including leucine), KIC, glucose, and oxygen are determined by application of the Fick principle:

Uterine or umbilical uptake rate = Uterine or umbilical blood flow (mL/min) x (C_v-C_a) or (C_a-C_v) where C_A and C_V, and C_v and C_a are the concentrations (μmol/mL) of the metabolite measured in the Uterine arterial and venous, or umbilical venous and fetal arterial blood, respectively. Similarly, net fluxes of ¹⁴C-leucine, ¹³C-leucine, and ¹³C-KIC across the umbilical (or Uterine) circulation are measured by the Fick principle as umbilical (or uterine) blood flow times the umbilical (or Uterine) tracer arteriovenous concentration difference.

Tracer fluxes: Maternal plasma leucine disposal rate (DR_M) is calculated as:

$$DR_M = Inf \cdot ([MPE_{Mv}]/MPE_{Ma}) - 1$$

where Inf is the infusion rate of L-[1-¹³C] leucine into the mother and MPE_{Mv} and MPE_{Ma} are the leucine enrichments in the maternal infusate and maternal arterial plasma, respectively. This equation does not account for the disposal rate of the naturally occurring ¹³C-labelled leucine which is about 1.1% of the ¹³C-leucine.⁴⁸⁻⁴⁹ This equation assumes 100% enrichment of the infused isotope. Plasma [1-¹³C leucine] is calculated as the product of the leucine concentration and the molar percent excess for ¹³C leucine in each vessel.

Tracer fluxes between the placenta and the fetal plasma, and between the fetal plasma and fetal tissues, are calculated according to Carver, et al.⁵ Loy, et al.⁴⁵ and Ross, et al.⁴³

The fraction of fetal leucine tracer infusion taken up by the placenta (¹⁴f_{plac}) is calculated as:

$$({}^{14}f_{plac}) = ([1-{}^{14}C \text{ leucine}]_{Mv} \times \text{umbilical blood flow}) / [1-{}^{14}C] \text{ leucine infusion rate.}$$

The fraction of L-[1-¹⁴C] leucine infusion rate excreted as ¹⁴CO₂ via the umbilical circulation (¹⁴f_{CO₂}) is calculated as:

$$({}^{14}f_{CO_2}) = ([{}^{14}CO_2]_{Mv} \times \text{umbilical blood flow}) / [1-{}^{14}C] \text{ leucine infusion rate}$$

The net ¹⁴CO₂ flux from the fetus to the placenta is calculated as:

$$r^{14}CO_{2plac} \text{ dpm/min} = \text{umbilical blood flow} \cdot ([{}^{14}CO_2]_a - [{}^{14}CO_2]_v)$$

where [¹⁴CO₂]_a and [¹⁴CO₂]_v are the concentrations of ¹⁴CO₂ (dpm/mL) in the umbilical arterial and venous blood, respectively.

Tracer model: The model (Carver, et al., Appen. II, Pub. Man. 8) is adapted from Loy, et al.,⁴⁵ van Veen, et al.,³⁴ and Ross, et al.⁴³ In steady state, the fetal plasma leucine pool is constant in amount, balanced by equal rates of entry (from placenta and fetal tissues) and disposal (into placenta and into fetal tissues). These fluxes of leucine into and out of the fetal plasma, fetal tissues, and the placenta, which apply to the two tracers as well, are shown in the figures below; each flux is labelled with a Roman numeral after Carver, et al.⁵

A Good Research Plan Page

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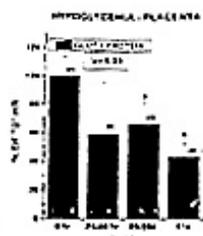
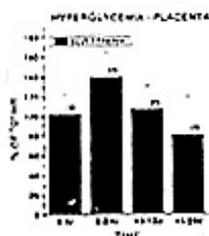
The net ¹⁴CO₂ flux from the fetus to the placenta is calculated as:

$${}^{14}\text{CO}_{2,net} \text{ dpm/min} = \text{umbilical blood flow} \cdot ([{}^{14}\text{CO}_2]_a - [{}^{14}\text{CO}_2]_v)$$

where [¹⁴CO₂]_a and [¹⁴CO₂]_v are the concentrations of ¹⁴CO₂ (dpm/mL) in the umbilical arterial and venous blood, respectively.

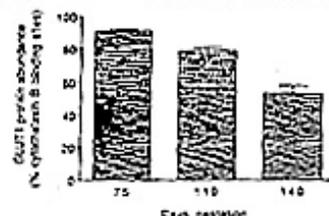
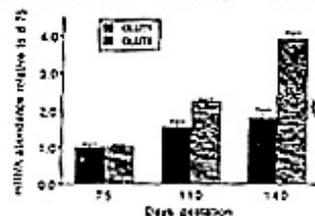
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Another Bad Page
 Figures and table too small to see



CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

We also have engaged the assistance of Dr. Alan Bell and his doctoral student, Richard Erhardt, to measure GLUT-3 and GLUT-1 mRNA using their ovine-specific cDNA probes. They have nearly completed development of ovine-specific GLUT-3 and GLUT-1 antibodies that will allow us to measure protein abundances for more direct correlation with glucose uptake and transport studies in vivo. Data below show a relative increase in GLUT-3 vs 1 mRNA (left) over the second half of gestation, with a corresponding decrease in the fraction of total cytosolic binding capacity (representing "functional" protein abundance) accounted for by GLUT-1 (right).



13. Effect of IGF-1 infusion on maternal, placental, and fetal insulin, glucose, and amino acid concentrations. Recombinant human IGF-1 from Eli Lilly Co. was infused at constant rate (30 µg/hour/kg) into 5 near-term pregnant sheep, increasing mat. [IGF-1] 3.2-fold (comparable to Gluckman's study¹¹), decreasing mat. [insulin] from 23 to 3 µU/mL, and decreasing mat. [glucose] from 3.7 to 3.2 mM; on balance, maternal glucose turnover, uptake and utilization of glucose by the placenta and fetus, and placental lactate production were not significantly altered. Most maternal amino acid concentrations were decreased (* p < 0.05 in table below).

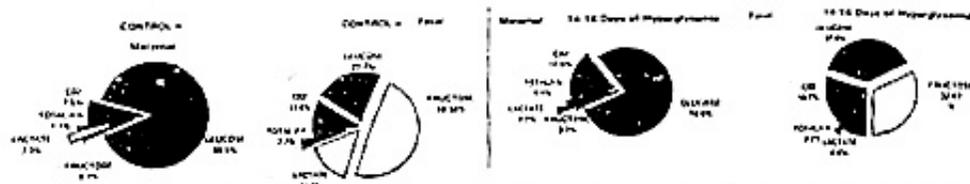
Sample	Infusion	N	Ins	Glucose	IGF-1													
Maternal	Pre	5	23.0	3.7	100	320	100	100	100	100	100	100	100	100	100	100	100	100
Maternal	During	5	3.0	3.2	320	320	320	320	320	320	320	320	320	320	320	320	320	320
Placental	Pre	5	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Placental	During	5	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

14. Statistical methods: We have developed unique statistical methods, including two and three dimensional generalized Michaelis-Menten response surface methods (Hirst et al) and curve fitting methods (Young et al), to interpret and develop models from our complex data that involve multiple measurements within an animal, at different times, of different parameters that may or may not have separate and/or joint effects, and among groups with different numbers of subjects (Appendix II, Pub. Man. 6,7). For the first time, these important advances in statistical modeling will be applied to placental metabolism to address the separate and/or joint effects of substrate supply on selected substrate metabolism in the placenta.

A BAD Page

Figures too small to see

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED



7. Placental metabolism: We also measured with $[U-^{14}C]$ glucose net uteroplacental glucose consumption rate (UPGC), lactate and fructose production rates, and glucose oxidation in late gestation pregnant sheep after 18 hours each of low and high maternal and fetal glucose concentrations. A major fraction of UPGC went to non-oxidative metabolism; UP oxygen consumption was not affected; UP lactate production was a major product of UPGC (69% during low glucose, 53% during high glucose); UP fructose production was 5% under low and 3% under high glucose, and tracer-derived umbilical vein lactate uptake from the placenta was accounted for completely by net fetal lactate uptake from the placenta, i.e., there was no substrate source of UP lactate production into the fetus other than UPGC (Appen. Abst. 4).

8. Maternal low protein diet: Although we have had considerable experience manipulating maternal diet (fasted states, several week periods of glucose and insulin clamps), for the specific purpose of developing a low protein diet in the mother that will lead to reductions in maternal amino acid concentrations, we have engaged the assistance of Dr. Alan Bell (Cornell Univ.), an expert in maternal and fetal effects of maternal dietary changes who has developed and studied maternal low protein diets in pregnant sheep that have produced fetal growth restriction (Appendix IV). Dr. Bell will help to determine the necessary diet formulation to produce an energy complete, low protein diet (see Methods).

9. Leucine infusion into normal and growth restricted fetuses or their mothers. Leucine infusion into ewes with placental insufficiency showed markedly increased uterine leucine uptake but only slight increase in fetal leucine uptake. Leucine infusion into normal fetuses produced increased leucine oxidation (accounting for increased disposal) and decreased umbilical leucine uptake. Other amino acids were affected by this infusion. Thus, although the placenta actively transports amino acids from the maternal to the fetal circulation, such transport can be affected by the relative maternal and fetal amino acid concentrations.



A "GOOD" Background/Preliminary Data Page

3. Maternal insulin infusion chronic hypoglycemia model: These studies showed that we can maintain maternal glucose concentrations at different levels over several weeks (as well as more acutely [11,41]), by glucose/insulin clamp technique, to produce sustained decrease in fetal glucose uptake and utilization, an increase in the placental/fetal glucose utilization rate ratio, fetal hypoinsulinemia, and decreased placental and fetal growth (Appen. Pub. 3).

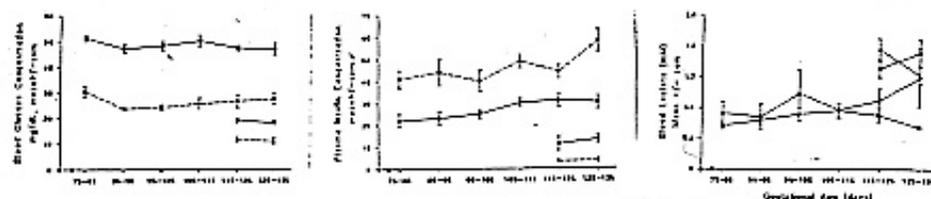


Fig. Stability of maternal and fetal [glucose] and [insulin] over gestation in the maternal hypoglycemia model.

4. Fetal amino acid metabolism: we have published before our methods for measuring maternal and fetal amino acid concentrations and the transfer of amino acids into the fetus (42,43), including details about how to measure fetal amino acid metabolism for several amino acids, and for glucose (11,38,45). These studies have been modified recently for leucine (see details below, in Methods, and Appen., Pub. Man. 8) and for glutamine, and glutamate (); more recent pilot studies with arginine are reviewed below.

5. Leucine metabolism model: Leucine metabolism in the chronically (6 weeks) hypoglycemic/hypoinsulinemic sheep model, produced by infusing insulin into the mother, was studied by infusing 1-[¹³C] and 1-[¹⁴C] leucine tracers into the fetus. In contrast to acute increased leucine oxidation with short term hypoglycemia (42), long term hypoglycemia produced an adaptation of lower energy expenditure for protein accretion and thus a slower rate of growth in the fetus, allowing the fetus to maintain normal weight-specific rates of nitrogen uptake as amino acids, oxygen consumption, fetal plasma leucine disposal rate, and leucine incorporation into protein synthesis. The umbilical uptakes of some amino acids, particularly leucine, were decreased; leucine consumption by the uteroplacenta was increased. The decreased umbilical leucine uptake and decreased leucine incorporation into protein accretion in these fetuses were accounted for by increased leucine release from fetal protein breakdown. These studies demonstrated important mechanisms by which chronic glucose deprivation regulates placental and fetal amino acid metabolism and fetal growth, and defined new tracer approaches to quantifying placental and fetal leucine metabolism. (Appendix II Pub. Man. 8).

Flux rates (mean±sem) (**P<0.01)	Control	Hypoglycemia
[1- ¹³ C] Ieu fetal plasma disposal rate	8.7±0.9	8.2±0.9
[1- ¹⁴ C] Ieu fetal plasma disposal rate	8.5±0.9	8.4±0.8
net fetal leucine uptake from placenta	4.2±0.6	2.1±0.4**
leucine into blood from fetal proteins	2.0±0.1	3.8±0.2**
CO ₂ produced by fetus from Ieu 1-C	2.1±0.1	1.9±0.3
leucine into fetal protein accretion	2.6±0.2	0.8±0.1**
leucine into fetal protein synthesis	4.6±0.3	4.6±0.2

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Critique Oriented Application

NIH now requires that your grant application is formatted to address each of the major review criteria.

In other words, NIH asks you to tell the reviewers what they are supposed to learn in your application.

Well, duh!”

1. Significance

- **State how this study addresses an important problem (the scientific premise forming the basis of the proposed research).**
- **State how, if the aims of the application are achieved, scientific knowledge will be advanced.**
- **State what the effect of these studies will be on the concepts or methods that drive this field.**

2. Investigator

- **State (and document) how the investigator is appropriately trained and well suited to carry out the proposed work.**
- **State how the proposed research is appropriate to the experience level of the principal investigator and other researchers (if any).**

3. Innovation

- **State how the project employs novel concepts, approaches or methods.**
- **State how aims are original and innovative.**
- **State how the project challenges existing paradigms or develops new methodologies or technologies.**

4. Approach

Methods: State how the conceptual framework, design, methods, and analyses are adequately developed, well integrated, and appropriate to the aims of the project.

Alternative outcomes and tactics:
State/Acknowledge (with specific examples) potential problem areas and alternative tactics to resolve the problems, but also to still gain advantage through different approaches and new knowledge.

4. Approach

- **Rigorous experimental design for robust and unbiased results (strong statistical approach)**
- **Consideration of relevant biological variables, including sex and age (for both clinical and animal studies!).**
- **Authentication of key biological and/or chemical resources**

5. Environment

State how the scientific environment in which the work will be done will contribute to the probability of success.

State how the proposed experiments will take advantage of unique features of the scientific environment or employ useful collaborative arrangements.

Show evidence of institutional support.

6. Overall Impact

- Summarize the important strengths of the application.
- Tell the reviewer what you will learn and why this is essential and important.
- Tell the reviewer how the results of your proposed research—what you will learn—will produce a major **impact** on your scientific field and the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved.

What is a K Award? See NIH Website.

<http://grants.nih.gov/training/careerdevelopmentawards.html>

1. Purpose of NIH Career Development Awards is to help the promising new investigator achieve research independence (i.e. to compete successfully for R01 funding).
2. Key to Ks is a plan for receiving new or specialized training integrated with the research project that will allow you to become an independent investigator.
3. The organizing principle of your K grant application should be preparing for the R01 grant you will submit at the end of the K award.
4. Research, training, and mentoring all must be linked.

Scored Review Criteria for K Grants

- 1. Candidate—YOU.**
- 2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring**
- 3. Research Plan**
- 4. Mentor(s), Co-Mentor(s), Collaborator(s)**
- 5. Environment & Institutional Commitment to the Candidate—YOU.**

What you need to put in your Candidate Statement



Make a compelling argument why you need a K award.

- **State (and document) how you are appropriately trained and well suited to carry out the proposed work.**
- **State how the proposed research is appropriate to your level of experience and that of your collaborators.**
- **Explain exactly how additional training and mentored research experience will enable you to compete successfully for an R01.**
- **Be specific: give concrete examples of areas where you need additional training or experience in order to conduct the proposed research or areas where you are deficient that are directly related to your research career goals.**
- **State clearly, strongly, that you are committed to a scientific career in the discipline your research involves.**

What you need to state about your Career Development Plan / Career Goals & Objectives / Plan to Provide Mentoring



- State and describe your career development plan, goals, and objectives and how these will be developed and promoted specifically for you.
- State how your mentor(s) will be (or have been) selected and how you will work with your mentor(s) to most effectively guide you in your research, education, and training.
- Describe how mentors, consultants, and collaborators will contribute to your education and training, including how they will evaluate your progress and your responses to evaluations.

Describe your systematic Career Development plan

with specific goals and objectives

1. Show a logical progression from prior research and training experiences to the research and career development experiences that will occur during the career award period and then to independent investigator status.

2. Justify your need for further career development to become an independent investigator.

3. Identify specific sources of training and how they will be used.

- Your institution: university, faculty development, research resources
- NIH courses and seminars
- 2014 NIMHD Translational Health Disparities Course
- External institutions
- Hands-on skills experiences
- Mentorship meetings
- Readings

What you write in your Research Plan



Same as for a research project award, except also—

- State how your research project and research program are specifically relevant to **your** career objectives.
- State how your research project and research program are appropriate to **your** stage of research development and as a vehicle for developing **your** research skills as described in the career development plan.



What you need to state about your Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s)

- **State (and document) how your mentor(s) are appropriately experienced and well suited to help guide you in your training (and help you carry out the proposed research).**
- **The Mentors' statements must specify their commitment to you and how they will effect this commitment.**

Mentors' letters are the most important letters in your application.



What you need to state about your Environment & Institutional Commitment to Candidate

- State how the scientific environment in which the work will be done will contribute to the probability of success.
- State how the proposed experiments will take advantage of unique features of the scientific environment or employ useful collaborative arrangements.
- Show evidence of institutional support, including documentation of your formal appointment and rank, time provided, freedom from other commitments, and financial support for doing the research.

Letters of Support



1. Chair, Division Director, Dean—anyone in a position to verify you, your credentials, and the institution's support of you and your work.
2. Letters of support should be personalized to what will be done by your mentor, your Department, your institution for you, leaving off the usual flowery “heck of a guy/gal” stuff.
3. Such letters should focus on how the training will fill gaps in your education, training, and research development and how this will specifically make you competitive for R grants.
4. The enthusiasm for you in these letters should be **HIGH**.

What you should state in your Summary about Overall Impact



- Summarize the important strengths of the application—focus on you, your career development plan, your mentors, and your mentoring plan.
- Tell the reviewers what you will learn in your research and training and why this is essential and important for your career development.
- Tell the reviewer how the results of your proposed research—what you will learn—will produce a major **impact** on your scientific field and the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved.

What you should state about your proposed Training in the Responsible Conduct of Research



- Document any prior participation in RCR training and/or propose plans to receive additional instruction.
- Document your specific training in the five components outlined in the NIH Policy:
Format, Subject Matter, Faculty Participation, Duration, Frequency
- Discuss how the plan is appropriate for your career stage and how it will enhance your understanding of ethical issues related to research.
- Include content to be acquired in proposed activities.

Pitfalls to avoid

- The training does not include the five NIH component requirements.
- The training is vaguely defined and lacks specific details.

Overall--



1. Prove to us why NIH should invest time and money in—YOU.
2. Prove how **your** Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring will make **YOU** qualified and ready for independent research.
3. Prove that **your** Research Plan will teach **YOU** how to do the best research, and also lead **you** to the forefront of your field.
4. Prove that **your** Mentor(s), Co-Mentor(s), Collaborator(s) are invested in **YOU** and have the capacity and commitment to make **YOU** capable of independent research.
5. Prove that your research and training Environment & Institutional Commitment to **YOU** will make you capable of independent research.

Submit the Grant—Study Section Review

Study sections will continue to give each application a single overall score to reflect “the study section’s notion of **what the likely impact of the proposal will be on our understanding of biology and behavior and on the practice of medicine.**”

Study sections are supposed to **pay more attention to the potential impact of a grant application and less to its feasibility.**

“Study Sections and NIH should be looking for **the stuff that is truly distinguished.”**

Harold Varmus, J. NIH Research 9:31-32, 1997

What happens?

Either —

Your grant scores well and gets funded,

Now get to work, and come back and tell the next group of young investigators how you did it.

Or—

Your grant is not so well scored and does not get funded.

What do you do now?

**For resubmission—
follow the AccentureTM line—**

What it takes to be successful—

What you did—10%

What you do next—90%