Office for Faculty Mentoring
Grant Writing Programs

Path to Independence Program

**WHO:** Assistant Professors writing NIH R01, R03, R21, or DOD grants

**WHAT:** Small group workshops, full internal review, and individualized feedback sessions

**WHEN:** Three times a year to coincide with NIH review cycle

---

K Club

**WHO:** Assistant Professors and outstanding postdocs writing NIH Career Development Awards

**WHAT:** Small group workshops, full internal review, and individualized feedback sessions

**WHEN:** Three times a year to coincide with NIH review cycle

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Duke Medicine
Primer on Grant Preparation: Keys to Being Competitive

Mark W. Dewhirst, DVM, PhD
Associate Dean for Faculty Mentoring
Competition for grants is increasing at a rate that far exceeds available dollars.
Writing a grant is like a fishing expedition
Grant writing resources

http://www.grantcentral.com/index.html
The Science of Scientific Writing
George D. Gopen & Judith A. Swan

If the reader is to grasp what the writer means, the writer must understand what the reader needs.

This article was originally published in the November-December 1990 issue of American Scientist.
Before you apply for a grant

• Develop unique capabilities

• Look for opportunity - Program Announcements
  - Sign up for listserv or Twitter notifications
  - Call Program Director – establish relationship with this person

• Be prepared to encounter failure
http://grants.nih.gov/grants/guide/
Make sure that your idea is unique
Search NIH RePORTER to look for who is in your intellectual space

• Search by:
  – Subject
  – Investigator
  – Date
  – Agency
  – Funding mechanism

http://projectreporter.nih.gov/reporter.cfm
http://www.science.gov/
There are many different types of grants. You need to decide which type you want to apply for.

- **K grants (mentored)**
  - K01 (Re-entry into science – mentored)
  - K08 (Basic Science)
  - K23 (Clinical)
  - K99/R00 – research with 2 years of mentoring and then independent funding for 3 years
  - Many others

- **R grants**
  - R03
  - R21
  - R01
The R03 grant mechanism supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology.

$50k/year x 2 years
R21

• The R21 grant mechanism is intended to encourage exploratory/developmental research by providing support for the early and conceptual stages of project development.
• The combined direct cost budget may not exceed $275,000 with no more than $200,000 in any single year.
• Cannot be renewed
• No preliminary data are required but may be included if available.
• The Research Strategy may not exceed 6 pages.
The R01 grant is an award made to support a discrete, specified, circumscribed project in an area representing the investigator's specific interest and competencies, based on the mission of the NIH.

Applications for an R01 award are not limited in dollars but need to reflect the actual needs of the proposed project.

- Modular applications are most prevalent with modules of $25,000, up to the modular limit of $250,000.
How do you prepare for and complete a grant?
Know your audience

- You are trying to communicate with several audiences
  - The person(s) reviewing your grant
  - Everyone else on the study section that did not read your grant
  - The NIH program director who has to sell your grant to the division director
    - The division director has veto power over study section, depending on institute priorities

- Identify best study section and review membership
Review Criteria

- Scored individually
  - Significance
  - Investigators
  - Innovation
  - Method
  - Environment

- Considered in overall impact score
  - Protections for human subjects
  - Inclusion of women
  - Inclusion of minorities
  - Children

- Vertebrate Animals

Scores from 1-9

NOTE: 70% of score is still based on method

Duke Medicine
## Scoring System

<table>
<thead>
<tr>
<th>Impact</th>
<th>Score</th>
<th>Descriptor</th>
<th>Additional Guidance on Strengths/Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>Exceptional</td>
<td>Exceptionally strong with essentially no weaknesses</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Outstanding</td>
<td>Extremely strong with negligible weaknesses</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Excellent</td>
<td>Very strong with only some minor weaknesses</td>
</tr>
<tr>
<td>Medium</td>
<td>4</td>
<td>Very Good</td>
<td>Strong but with numerous minor weaknesses</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Good</td>
<td>Strong but with at least one moderate weakness</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Satisfactory</td>
<td>Some strengths but also some moderate weaknesses</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>Fair</td>
<td>Some strengths but with at least one major weakness</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Marginal</td>
<td>A few strengths and a few major weaknesses</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Poor</td>
<td>Very few strengths and numerous major weaknesses</td>
</tr>
</tbody>
</table>
General Guidelines

Make the grant easy to read and understand

• Formatting
  – Arial Font, 11pt
  – Embed figures in text – do not use separate pages
  – Put all relevant data in grant
  – Minimize use of jargon and abbreviations
First Principle

- Do not make the reviewer have to think!
- If you start an idea, finish it!
How NOT to finish an idea

“It is well known that lemmings follow each other blindly.”

How TO finish an idea

“It is well known that lemmings follow each other blindly. This can lead to death by drowning of all lemmings if the leader falls into the ocean.”

Do not assume that the reviewers will know your conclusion. You have to tell them.
General Guidelines

Make the grant easy to read and understand

• Use subheadings to help reader follow outline
• No more than one idea per paragraph
• Avoid full pages of text – break them up with figures and tables when possible
• Avoid a lot of **underlining, bolding and italicizing**. This is hard to read.
• Put space between paragraphs
• Avoid poorly worded compound sentences because reading them is hard for the reviewer, as they are usually doing this at night after work and they are tired and would much rather be reading a book or watching TV or playing with their kids or even mowing the lawn.
Gopen Principles -
Take his course if you have not already

• Emphasis point of sentence should come before the period, semicolon or colon.
  – Avoid putting main clause first
• Avoid separating the subject of the sentence and the verb
• Use backward link when going from sentence to sentence
• The words “and” and “that” can be ambiguous. Which part of the sentence is most important?

During the Specific Aims Workshops, we will help you see such problems in your writing.
General Guidelines

• Do not hypothesize something that you do not intend to test. This is a common mistake.

• Make liberal use of tables and diagrams to illustrate protocols, procedures, organization
  – Pictures are a lot easier to comprehend quickly than a lot of text.
  – Especially important with the new page limitations
Organizational Charts can replace many paragraphs of text

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mechanism of Action</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Control</td>
<td>10</td>
</tr>
<tr>
<td>ExTek adenovirus</td>
<td>Block Tie 2 phosphorylation</td>
<td>10</td>
</tr>
<tr>
<td>ExFlk adenovirus</td>
<td>Block Flik phosphorylation</td>
<td>10</td>
</tr>
<tr>
<td>Ang 1 adenovirus</td>
<td>Stabilize Tie 2 phosphorylation</td>
<td>10</td>
</tr>
<tr>
<td>Ang 2 adenovirus</td>
<td>Block Tie 2 phosphorylation</td>
<td>10</td>
</tr>
</tbody>
</table>
General Guidelines

• Run the spell-check!!!
• Get rid of unnecessary words and phrases
  – “a”, “the”
• Have someone else read the grant before you send it out
  – Internal or external consultants are very valuable sounding boards.
  – The more reviewers you have the better the grant will be. The trick is to satisfy many people, each with their own interpretation of what you are saying.
Significance

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?
Investigators

Are the PD/PIs, collaborators, and other researchers well suited to the project?

If Early Stage Investigators or New Investigators, do they have appropriate experience and training?

If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)?

If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?
Innovation

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?
Innovation, cont.

- Horizontal vs. Vertical
- Incremental vs. Paradigm Shifting
Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?

Are potential problems, alternative strategies, and benchmarks for success presented?

If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves clinical research, are the plans for 1) Protections for Human Subjects, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?
Environment

Will the scientific environment in which the work will be done contribute to the probability of success?

Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed?

Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?
Impact Score

The impact/priority score for an application is based on each individual reviewer’s assessment based on the five scored criteria plus additional criteria regarding the protection and inclusion of human subjects; vertebrate animal care and welfare; biohazards, and criteria specific to the application.

It is NOT a numerical average of the individually scored criteria.
NIH format for grants

• The new NIH biosketch is very important. You have a paragraph beneath your training summary to tell the reviewer why you are best suited to do the work. This should be carefully written for each participant.
• Specific Aims (1 page)
• Research Strategy (R1=12 pages; R21 = 6 pages)
  – Significance
  – Innovation
  – Approach
  – Time Table
  – Future Directions (optional)
Specific Aims

- Spend a lot of time on the Specific Aims
  - Well conceived SA will make the grant much easier to write.
Abstract and Intro to Specific Aims

• Introduction paragraph before SA is essential to getting the reviewer’s attention.
  – Objective of work
  – Working (central) Hypothesis
  – Approach
  – Rationale
Specific Aims

• No more than 3
  – Multiple experiments within one aim is acceptable
  – Hypotheses should accompany each specific aim

• There is a difference between a long term goal and testable hypotheses!
  – Goal: Eradicate hypoxia in all human tumors
  – Hypothesis: Hyperthermia treatment with \( T = 40-42^\circ\text{C} \) will improve median tumor \( \text{pO2} \)

Do not hypothesize something you cannot test
Specific Aims

• SA 1 should have strong preliminary data
  – Leave no question that it can be done- preferably a paper already published (for R01)

• SA 2 should shown to be feasible
  – Compelling preliminary results

• Do not propose to do something that you do not have expertise to do
  – Collaborations with others who have expertise

• Avoid having one SA be dependent on success of another –
  – Straw man or Achilles’ Heel
Components of Aims Page

- Introductory Paragraph
  - Opening Sentence –
    - Often a statement about disease state being studied and importance of this disease
  - Current Knowledge
  - Gap or need
  - Why gap is important

- Who, What, Why
  - Long term goal
  - Overall objective of this application
  - Central Hypothesis
  - Rationale
Components of Specific Aims, Con’t

• Specific Aims Paragraph
  – Lists aims and hypotheses for each

• Payoff Paragraph
  – Expected outcome
  – Who will benefit if grant is successful?
Cellular inflammation and the production of inflammatory cytokines occur in all forms of human pulmonary hypertension (PH). Circulating cytokine levels predict survival in human PH, suggesting that such factors play a direct causal role in PH progression. A central component of inflammation in PH is the accumulation of myeloid inflammatory cells (monocytes, macrophages, and dendritic cells) in and around pulmonary vessels. In other vascular systems, myeloid cells play a key role in vascular remodeling. Specific subsets of myeloid cells migrate to areas of hypoxia using the chemokine receptor CXCR4 and, in response to hypoxic stimuli, develop vascular remodeling activity. It remains unknown whether myeloid cells are required for the development of PH or how they may contribute to PH patho-physiology. Studies suggest that the vascular remodeling activity of myeloid cells is due to their expression of as yet unidentified morphogenic factors and their ability to induce such factors in other cell types. One family of factors known to be critical for vascular development and homeostasis is the Notch ligands. Stimulation of the Notch3 receptor on smooth muscle cells occurs in human PH and is known to be required for the development of hypoxia-induced PH in mice. Neither the Notch ligand that stimulates Notch3 during PH nor its cellular source has been identified.
Our long-term goal is to identify therapeutic targets for PH: signaling events that are required for pulmonary vascular remodeling and PH progression. The overall objective of this application is to determine the role played by myeloid inflammatory cells in PH. Our central hypothesis is that, in PH: 1) a subset of constitutive monocytes is recruited to the lung via CXCR4 and, 2) in response to hypoxic stimuli, develops into a population of myeloid cells that stimulates pulmonary vascular remodeling by 3) stimulating the expression of the Notch ligand Jag2 on endothelial cells (EC). This hypothesis was formulated based on our preliminary studies of myeloid cell accumulation and Notch ligand expression in PH, along with published studies examining the role of myeloid cells in other models of vascular remodeling. The rationale for these studies is that defining the role that myeloid cells play in PH will likely lead to the identification of new therapeutic targets for this disease.
1. To determine the role of CXCR4-mediated myeloid cell migration in PH.
To test the hypothesis that CXCR4-dependent myeloid cell accumulation is required for PH, we will examine myeloid cell-specific CXCR4 knockouts for the development of PH, endothelial cell proliferation, inflammation, and the expression of key genes in individual cell types.

2. To determine the contribution of myeloid cell hypoxic responses to PH.
To test the hypothesis that hypoxic responses in myeloid cells are required for PH, we will examine myeloid cell-specific HIF1α/HIF2α knockouts for the development of PH and the associated endpoints described in Aim1.

3. To identify the Notch ligand required for PH and determine its cellular source.
To test the hypothesis that Notch ligand expression on EC is required for PH, we will examine mice that lack all Notch ligand expression in EC using endpoints described above. To determine if the required Notch ligand is Jag2, we will examine EC-specific Jag2 knockouts.
Expected Outcome: We anticipate that the proposed studies will determine the role myeloid inflammatory cells play in the development of PH and identify mechanisms by which these cells mediate vascular remodeling. Confirmation of our hypotheses would significantly advance our understanding of PH pathophysiology and would suggest a new class of therapeutic targets, immune mediators, for the treatment of this disease.
Significance

- The literature review does not need to be exhaustive
  - Should be directed toward the grant –
- Point out where gaps in knowledge exist
- Discussion should be tied back to the specific aims of the grant
  - How will SA of grant address these gaps in knowledge?
Bladder cancer is the 4th most common cancer in men and 7th most common in women, affecting over 70,000 patients annually in the US (NIH statistics). Non-muscle-invasive bladder cancer (NMIBC). NMIBC represents 75% of bladder cancers. First-line therapy involves tumor excision and intravesical BCG (5). Most patients experience local recurrence and are at 60% risk for having further recurrences and at 15-35% risk to progress to muscle-invasive bladder cancer (MIBC), which has a much worse prognosis (6, 7). Guidelines for this more aggressive disease include neoadjuvant chemotherapy (11, 12), but approximately 50% of patients still die from this cancer (13). We hypothesize that the addition of HT+LTSL-drugs to standard-of-care, neoadjuvant cisplatin + gemcitabine, will yield superior anti-tumor effects. MIBC is hypoxic (14, 15), providing strong rationale for specifically targeting hypoxic cells in this tumor. Positive results from pre-clinical studies in Aims 1&2 will establish a basis for adding HT+LTSL-drugs and/or hypoxic cell killing in combination with standard-of-care therapy in future human trials.
Significance

• Know your reviewers
  – You should accurately quote prominent figures in the field – they may be your reviewer
  • Know who is on study section
  • http://www.csr.nih.gov/Roster_proto/sectionI.asp
  – Make sure you quote literature accurately!
• Make liberal use of ISI science citation index (web of Science) or other similar search engines
  – Look for most often quoted papers – these should be quoted. It shows that you know the relevant literature
  – Look for the most recent papers also. These need to be quoted, if relevant to your subject
Search Engines for publications

• DUMC Library
  – http://www.mclibrary.duke.edu/
  – Look under “Popular Resources” for
    • “Web of Science”
    – This search engine will allow you to use key words, author names, etc. to search for papers. You can rank by # citations
    – You can search for study section member publications
    – You can easily upload selected refs to End Note, etc.

• Another good website is
  – http://highwire.stanford.edu/
  – Similar to Library, but can be set to allow email alerts on subjects, authors, journals, etc.
Provide hyperlinks

You can provide hyperlinks on your reference page to help the reviewers find what they are looking for.

To learn how, check the Faculty Mentoring Resource webpage.

Grant Themes

Aim 1

- Baseline expression of:
  - HIF-1
  - Abl/Arg
  - FGFR Splice Variants
  - Free Radicals

- Treatment Resistance
- Angiogenesis
- Metastasis

Aim 2

- Vascular invasion
- MET

- Free Radicals
  - Drive EMT

- Radiotherapy
- Chemotherapy

- HIF-1
- Abl/Arg
- FGFR Splice Variants

- Dead cell
- Free Radicals (ROS/RNS)
- Mesenchymal

- Macrophage/myeloid progenitor
- Microvessel
- Epithelial
- Tumor Cell
SPECIFIC AIM 1
- Radioprotection (normal tissue)
- Radiosensitization (tumor tissue)
- Imaging (normal vs tumor tissue)
- Chemosensitization (temozolomide, dexamethasone, bortezomib, cyclophosphamide)
- Anticancer (glioma, skin cancer, prostate cancer, 4T1 breast cancer)

GMP synthesis completed. Safety/Tox is planned for 2012-2013

SPECIFIC AIM 2 (MECHANISMS)
- Transcription Factors: AP-1, HIF-1α, SP-1, NF-κB
- Reactive Species: \( \text{O}_2^* \), \( \text{NOO}^* \), \( \text{ClO}^- \), \( \text{CO}_2^- \)
- Transport across blood brain barrier (BBB)
- Accumulation in mitochondria, mimicking MnSOD

SPECIFIC AIM 3 – CLINICAL TRIALS

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Strategically invest in professionals

Med Media Solutions– Stan Coffman

MedMedia Solutions Provides Medical Illustration, Poster Printing, and Design Services to the Medical and Scientific Community.

MEDICAL ILLUSTRATION

With 28 years of experience as a Medical Illustrator, Stan Coffman of MedMedia Solutions can bring your ideas to life with vibrant, medically accurate images geared to your target audience.

LEARN MORE >>
Approach

• Format for each specific aim
  – Introductory paragraph
  – Justification and feasibility
    • Review of relevant literature
    • Your preliminary data
  – Research Design
  – Stats (nearly always required)
  – Expected Outcomes
  – Potential Problems and Alternative Strategies
Approach

• Organized by Specific Aim
  – Re-state the SA and hypotheses
• Discuss how you will test the hypotheses of each aim
  – Describe each experiment and literature and preliminary data that support it
  – Subheading labeled “Testing of hypothesis” is helpful
• Section(s) entitled “Anticipated problems and alternative plans” is essential
  – The reviewer needs to know how well you have thought through the study and what you might do if things do not work out
Example Introductory paragraph

S.A.1 Quantify effect of native tumor perfusion on temperature distribution

*Introduction*  The temperature elevation resulting from power deposition in a tumor, and thus the effectiveness of tumor heating, is affected by tumor perfusion. What is not known is the global relationship between tumor perfusion and the resultant volumetric temperature distribution. The *objective* of this aim is to quantify that relationship. To attain the objective we will test the *working hypothesis* that the volumetric tumor perfusion will strongly influence the volumetric temperatures obtained and thus impact the ultimate success of a hyperthermia treatment. Our *approach* will be to quantify native tumor perfusion using noninvasive imaging. Tumor heating will then be quantified, also noninvasively, using MR thermometry. Results from imaging and thermometry can be correlated precisely on a voxel by voxel basis. The *rationale* for this aim is that its successful completion will allow the character of tumor heatability to be predicted. This prediction could be the basis of redirecting patients to other therapy, or of selecting methods to improve heatability such as power steering or biologic modification of hyperthermia injury.

Note the use of italicized key words – the reviewers are looking for these
Preliminary Data

Hypothesis: Left shifted hemoglobin from spot fish will improve tumor oxygenation

• Preliminary results should convince the reviewer that you can do the work
• Provocative preliminary data will convince the reviewer that this is worth doing
Materials and Methods

• With the new guidelines, there is not room for specific methodological details

• Emphasize experimental design – Add details IF essential to the success of the experiment and it is likely that the reviewer will know that
Materials and Methods

- Statistical Design
- Statistical Design
- Statistical Design
  - Get statistical help with experimental design

Biostatistical consultation through DTMI:
https://www.dtmi.duke.edu/for-researchers/quantitative-resources/biostatistics-core
Through DCI:
http://www.cancer.duke.edu/modules/biostatistics15/index.php?id=1
Teamwork leads to success
Biosketch

• Refine biosketch for each application
• Express passion for your research in your personal statement
• Explain why you are the right person for this research
• Indicate productivity
  – 15 out of total publications
• Highlight collaborations with co-investigators in publication list
Budget

• Work cost backward from experimental plan
• Take care with justifications
  – Personnel and equipment, particularly
• A formal budget is not required for R01 grants less than $250k in direct costs per year
  – Read instructions for each type of grant carefully
Dewhirst Maxim

- A well-organized grant IS appreciated by reviewers
  - This implies that the applicant is well-organized
  - Applicant that is well organized is more likely to complete the research plan
Have a good attitude!
APPEAR FRIENDLY
BE FLEXIBLE
LOOK AT ALL POSSIBILITIES
Acknowledgements

• Joseph Bonaventura
• Hal Swartz