Postdoctoral Individual National Research Award (F32)

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Outline

- Brief description of F32 proposal and training objectives
- Strengths and weaknesses of proposal as outlined in study section
- F32 resubmission and responses to reviewers

F32 Application (first submission)

- *RAS* genes are frequently mutated in cancer.
- *KRAS* is mutated most often compared to other RAS isoforms.
- *KRAS* is enriched in rare codons that slow translation, resulting in a weakly expressed oncogene.

"The role of KRAS codon bias in tumorigenesis"

Aims

Aim 1. Determine the role of *Kras* codon bias on early tumorigenesis *in vivo*.

- Novel mouse models in which the codon bias of an oncogenic version of the *Kras* gene has been altered (to all common or all rare)

Aim 2. Elucidate the mechanism by which cancer cells overcome poor translation of KRAS.

- Examine *Kras* gene amplification in lung tumors driven by aforementioned alleles.
- Genome-wide shRNA screen in cancer cell lines to identify modifiers of KRAS translation.

Aims

Aim 1. Determine the role of *Kras* codon bias on early tumorigenesis *in vivo*.

- Novel mouse models in which the codon bias of an oncogenic version of the Kras gene has been altered (to all common or all rare)
  - ✓Successful homologous recombination in ES cells of 1 of 2 new alleles.
  - ✓Biological effect of expressing cDNA versions in cells.

Aim 2. Elucidate the mechanism by which cancer cells overcome poor translation of KRAS.

- Examine *Kras* gene amplification in lung tumors driven by aforementioned alleles.
- Genome-wide shRNA screen in cancer cell lines to identify modifiers of KRAS translation.
  - ✓Evidence in one cancer cell line that KRAS expression is amplified independently of gene amplification (NO proof of principle or pilot study of screen design).

Training Objectives

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- Sponsor and Training Environment

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✓Ph.D. acquired at UNC (strong molecular biology background in cellular and animal models)

✓2 first author primary papers and a review

✓Successful at acquiring funding in grad school

✓Training objectives focused on attaining skills to address biological questions surrounding tumorigenesis

✓Selection of a sponsor that is well established in molecular cancer biology field and with a strong training background

Training Objectives

- Applicant and Training Potential
- Sponsor and Training Environment

✓Training Plan (written by Sponsor):

1. Attendance at variety of institutional seminar series, lab meetings, journal club, and scientific conferences.
2. Mentoring grad students
3. Weekly meetings with sponsor
4. Biannual meetings with a mentorship committee

✓Environment (written by Sponsor)

1. Well-funded lab with productive publication record
2. Strong training background, as evidenced by success of previous trainees.

Application Review

- Not Discussed (bottom 50% of all grants)

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Strengths:

- ✓Training potential of applicant
- ✓Strong letters
- ✓Training environment
- ✓Training plan and sponsor's training record
- ✓"Interesting and relevant hypothesis"
- ✓Complementary *in vivo* and *in vitro* approaches

Application Review

- Not Discussed (bottom 50% of all grants)

Weaknesses:

- ✓Proposal is overly ambitious, lacks rational and depth, and translational impact not clearly presented.

"The hypotheses and approaches proposed reflect that she has not fully grasped the recent literature yet."

- ✓Aim 1: Mouse models have not been generated.
- ✓Aim 2: No pilot study demonstrating feasibility of screen and no plan for mechanistic follow-up of screen results.
- ✓Co-dependency of two aims (use of mouse models in both aims)

F32 Resubmission

"Proposal is overly ambitious, lacks rational and depth, and translational impact not clearly presented."

1. Expanded discussion of background and rational
   (34 vs. 75 references)
2. Publication of paper on codon bias in intervening year (intermediate author)
3. MORE DETAIL in experimental design
4. Outlined ALL POSSIBLE outcomes of experiments and what I would do in each case
5. End each Aim with some "Big Picture" directions (less specific)

More specifically..

Aim 1.

- Established a collaboration (with accompanying letter of support) to assist with Aim 1
- Demonstrated evidence that mouse models are now available

Aim 2.

- Removed the unbiased screen (except as an alternative approach)
- Removed any use of mouse models to avoid dependency on Aim 1
- Replaced with focused approaches to test specific hypotheses

Resubmission Review

- Impact Score: 18
- Percentile: 4%

"There was consensus among reviewers that the major strength of this revised application is the focused, well-written, and innovative research plan addressing an important and clinically relevant problem."

Take Home Messages

- The scientific rational of the proposal should be sound and very well supported by the literature and/or preliminary data.
- DETAILED and FOCUSED methodology
- Know where you are going, in the short and long term
- Don’t underestimate the importance of the Training Plan and Environment