Dramatic grant writing - 201

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Ruth Ziegler Professor
City of Hope, Los Angeles, CA

Components of a R-type NIH Grant

- Abstract (paragraph)
- Specific Aims – 1 page
- Innovation/Significance – combined 1 page
- Preliminary Data – either first or merged
- Methods
- Human Subjects
- Vertebrae Animals

6 or 12 pages

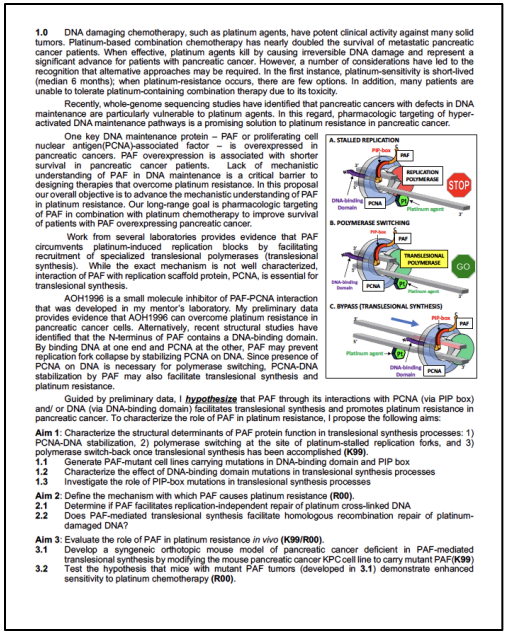
Get into the mindset of the reviewer

Reviewing grants is a poorly paid, thankless job that gives you great intimacy with cheap, moldy hotels.

The Reviewers are typically the good guys – make their lives easier.

Specific Aims Page

The Reviewer needs to feel the drama and innovation of your project in their heart.



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Recently, whole-genome sequencing studies have identified that pancreatic cancers with defects in DNA maintenance are particularly vulnerable to platinum agents. In this regard, pharmacologic targeting of hyper-activated DNA maintenance pathways is a promising solution to platinum resistance in pancreatic cancer.

One key DNA maintenance protein – PAF or proliferating cell nuclear antigen(PCNA)-associated factor – is overexpressed in pancreatic cancers. PAF overexpression is associated with shorter survival in pancreatic cancer patients. Lack of mechanistic understanding of PAF in DNA maintenance is a critical barrier to designing therapies that overcome platinum resistance. In this proposal our overall objective is to advance the mechanistic understanding of PAF in platinum resistance. Our long-range goal is pharmacologic targeting of PAF in combination with platinum chemotherapy to improve survival of patients with PAF overexpressing pancreatic cancer.

Work from several laboratories provides evidence that PAF circumvents platinum-induced replication blocks by facilitating recruitment of specialized translesional polymerases (translesional synthesis). While the exact mechanism is not well characterized, interaction of PAF with replication scaffold protein, PCNA, is essential for translesional synthesis.

AOH1996 is a small molecule inhibitor of PAF-PCNA interaction that was developed in my mentor's laboratory. My preliminary data provides evidence that AOH1996 can overcome platinum resistance in pancreatic cancer cells. Alternatively, recent structural studies have identified that the N-terminus of PAF contains a DNA-binding domain. By binding DNA at one end and PCNA at the other, PAF may prevent replication fork collapse by stabilizing PCNA on DNA. Since presence of PCNA on DNA is necessary for polymerase switching, PCNA-DNA stabilization by PAF may also facilitate translesional synthesis and platinum resistance.

Guided by preliminary data, I ***hypothesize*** that PAF through its interactions with PCNA (via PIP box) and/ or DNA (via DNA-binding domain) facilitates translesional synthesis and promotes platinum resistance in pancreatic cancer. To characterize the role of PAF in platinum resistance, I propose the following aims:

Aim 1: Characterize the structural determinants of PAF protein function in translesional synthesis processes: 1) PCNA-DNA stabilization, 2) polymerase switching at the site of platinum-stalled replication forks, and 3) polymerase switch-back once translesional synthesis has been accomplished **(K99)**.
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Aim 2: Define the mechanism with which PAF causes platinum resistance **(R00)**.
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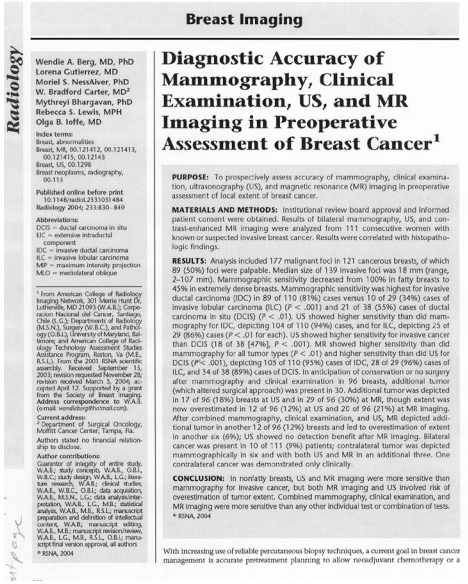
- **2.2** Does PAF-mediated translesional synthesis facilitate homologous recombination repair of platinum-damaged DNA?

Aim 3: Evaluate the role of PAF in platinum resistance *in vivo* **(K99/R00)**.
- **3.1** Develop a syngeneic orthotopic mouse model of pancreatic cancer deficient in PAF-mediated translesional synthesis by modifying the mouse pancreatic cancer KPC cell line to carry mutant PAF(**K99**)
- **3.2** Test the hypothesis that mice with mutant PAF tumors (developed in **3.1**) demonstrate enhanced sensitivity to platinum chemotherapy **(R00)**.

A. STALLED REPLICATION
PIP-box
PAF
REPLICATION POLYMERASE
STOP
DNA-binding Domain
PCNA
Platinum agent
B. POLYMERASE SWITCHING
TRANSLESIONAL POLYMERASE
GO
C. BYPASS (TRANSLESIONAL SYNTHESIS)

Specific Aims Page

Magazine Cover



Manuscript

Share the grant aims page EARLY with as many people as possible.
Many times the person who give the most criticism (within reason) is the most helpful.

Framing - tell a compelling story

In the United States, rectal cancer (RC) affected an estimated 39,610 individuals in 2015, with 68% of individuals surviving more than 5 years.[1, 2] The median age at diagnosis for RC was 65 years, which is typically younger than that for colon cancer.[3] A common long-term adverse treatment effect for RC survivors is bowel dysfunction, with symptoms that ranges from frequent and urgent bowel movements, loss of control with soiling, to constipation, gas, and bloating, with oscilliations between diarrhea and constipation. Bowel dysfunction-related symptoms may occur whether the survivor has a resection with permanent intestinal ostomy or an anastomosis with or without a temporary ostomy. Previous research by our team found that RC survivors utilized many strategies to manage bowel dysfunction and associated symptoms.[4, 5] Our findings suggested that the ability to successfully manage bowel dysfunction symptoms could result in greater perceived control in several areas for survivors, including intimacy, work, social activities, and travel. While several strategies were described (e.g., physical activity, over-the-counter and prescription medications), dietary modifications –e.g., number of daily meals, choice of foods, portion sizes, and timing of eating - were among the most consistently reported strategies for achieving bowel control.

Get into the mindset of the reviewer

Make the reviewers happy.

A. Hypothesis and Specific Aims: The vast majority of breast cancers occur in women over the age of 65 with highest incidence between the ages of 65 and 80. Recent studies suggest that breast cancer incidence may be substantially reduced in postmenopausal women by tamoxifen-chemoprevention (2-4). Although these reports are encouraging, tamoxifen is associated with significant side effects especially in older women whose comorbid conditions may increase the risk of vascular, cognitive and endometrial events (5, 6). As a result, many elderly women chose to forego tamoxifen chemoprevention (7). Recently the Long Island Breast Cancer Study project reported that aspirin or non-steroid anti-inflammatory drugs (NSAIDs) significantly decreased incidence of estrogen receptor positive breast cancer, generating excitement that aspirin could have dual benefit in reducing cardiovascular risk and preventing breast cancer in older women (8). However, in order to rapidly evaluate chemoprevention in postmenopausal women, biomarkers are needed to accurately predict short-term breast cancer risk so that 1) women who are most likely to benefit from preventive therapy can be identified, and 2) response to chemoprevention can be accurately assessed. Many studies have recently established the importance of tumor suppressor hypermethylation in early mammary carcinogenesis (9-25). Random Periareolar Fine Needle Aspiration (RPFNA) is a *research* technique developed to repeatedly assess "field effects" high-risk women and is validated to test for 1) breast cancer risk and 2) response to chemoprevention (27, 28). Breast RPFNA has been successfully used by our group to 1) test for tumor suppressor hypermethylation and 2) evaluate short-term breast cancer risk. In **Preliminary Data** we observe that hypermethylation of the retinoic acid receptor-beta2 (RARβ2) P2 promoter in RPFNA obtained from pre- and early post-menopausal women predicts 1) cytological atypia (a short-term marker of breast cancer risk) and 2) alterations of breast adipose retinoid metabolites. We also observe that elimination of RARβ2 P2 methylation in RPFNA predicts a clinical response to tamoxifen chemoprevention. Here we propose to evaluate a second set of steroid-receptor/adipose-ligand markers that we ultimately will test as potential intermediate biomarkers of response to aspirin and NSAID chemoprevention in post-menopausal women. Aspirin and NSAIDs are thought to inhibit tumorigenesis through cyclooxygenease (COX)-dependent pathways. Peroxisome Proliferator-Activated Receptor-gamma 1 ($PPAR_{\gamma}1$) is thought to play an important role in mammary epithelial homeostasis and there is recent evidence that $PPAR_{\gamma}1$ may play a role mediating response to NSAIDs and aspirin. $PPAR_{\gamma}1$ is the receptor for the endogenous ligand prostaglandin15-deoxy-Δ12,14-prostagladin (15dPGJ2). 15dPGJ2 has been found to inhibit COX-2 activity and is decreased in breast cancers (35, 36). Conversely, prostaglandin-E2 reflects COX-2 activity and is increased in breast cancer (35, 36). Here we aim to **test the hypothesis that hypermethylation of the $PPAR_{\gamma}1$ A3 promoter and a decreased ratio of adipose 15dPGJ2/PGE2 may predict short-term breast cancer risk** and **evaluate the feasibility of using these markers to test response to aspirin chemoprevention in post-menopausal women**. The following **Aims** are proposed:

Specific Aim I: Test whether $PPAR_{\gamma}1$ A3 promoter methylation predicts mammary epithelial atypia in peri- and early post-menopausal women. We observe a majority of breast cancer cells, but not normal mammary epithelial cells, exhibit hypermethylation of the $PPAR_{\gamma}1$ A3 promoter. Here we will test whether hypermethylation of the $PPAR_{\gamma}1$ A1 promoter in RPFNA predicts mammary atypia in peri- and early post-menopausal women.

Specific Aim II: Evaluate the ratio of prostaglandin metabolites 15dPGJ2/PGE2 and COX-2 activity in mammary adipose tissue obtained by RPFNA performed in peri- and early post-menopausal women. The pattern of adipose prostaglandin metabolites will be evaluated and we will test for a potential correlation between the presence of mammary atypia and prostaglandin metabolite levels.

Specific Aim III: Test the frequency of $PPAR_{\gamma}1$ A3 promoter methylation, COX-2 activity, and the ratio of prostaglandin adipose metabolites 15dPDJ2/PGE2 in late post-menopausal women. Currently there is a lack of biomarkers in post-menopausal women. Promoter hypermethylation has been shown to be associated with inflammation and there is evidence anti-inflammatory agents may reduce breast cancer risk. Here we will test the frequency of $PPAR_{\gamma}1$ A3 hypermethylation and 15dPDJ2/PGE2 ratios in late post-menopausal women.

Future Goals: Data from these studies will allow us to develop pilot data in early and late post-menopausal women to then test whether 81 or 325 mg aspirin/day for 6 and 12 months 1) eliminates $PPAR_{\gamma}1$ A3 methylation and 2) increases the ratio of 15dPGJ2/PGE2 adipose prostaglandin metabolites.

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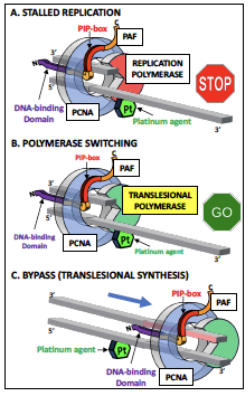

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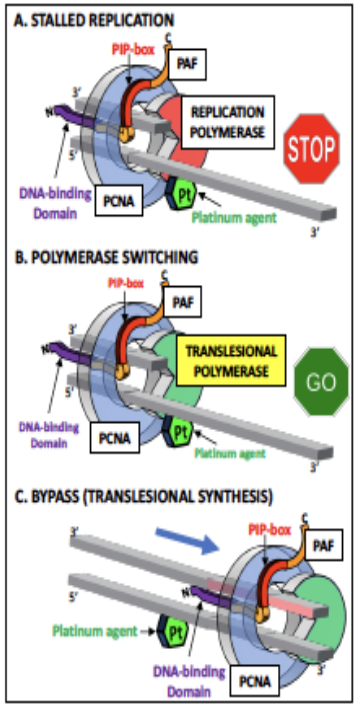

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What is the problem?
Where is the grant going?

Background

Specific background

Preliminary data from the literature

Preliminary data generated by the PI

Hypothesis

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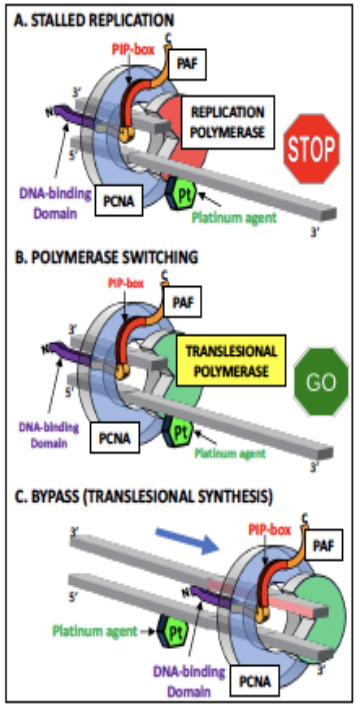

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Platinum agents have efficacy but resistance develops.
Defects in DNA repair are associated with PR.

Introduction to the DNA repair gene (PAF) that will be targeted

Preliminary data from the literature showing that PAF is a promising target

Preliminary data generated by the PI that supports targeting PAF

Hypothesis

Get into the mindset of the reviewer

Aim 1: Characterize the structural determinants of PAF protein function in translesional synthesis **(K99)**
This aim will test the hypothesis that PAF facilitates translesional synthesis at platinum-stalled replication forks by stabilizing PCNA-DNA interaction and preventing replication fork collapse rather than unmasking translesional polymerase binding site. By introducing mutations in PIP box and DNA-binding domain through a gene-editing approach will provide new insights into the function of PAF and the structural basis for its function.
Aim 2: Define the mechanism with which PAF causes platinum resistance **(R00)**
Translesional synthesis is a key process not only in DNA replication but also in DNA repair. This aim will test the hypothesis that PAF facilitates DNA damage repair **in addition to** DNA damage tolerance through translesional synthesis. By using DNA repair- deficient and intact pancreatic cancer cells, we will determine the role of wild-type and mutant PAF protein in platinum resistance.
Aim 3: Evaluate the role of PAF in platinum resistance *in vivo* **(K99/R00)**
We will develop a transgenic mouse model of pancreatic cancer deficient in PAF-mediated translesional synthesis **(K99)** by modifying an existing and robust KPC mouse model (LSL-$Kras^{G12D}$/+;LSL-$Trp53^{R172H}$/+;Pdx-1-Cre) of pancreatic cancer to additionally carry a mutant PAF protein. This aim will then test the hypothesis that mice with mutant PAF (developed in **3.1**) demonstrate enhanced sensitivity to platinum chemotherapy. **(R00)**

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3.2 Test the hypothesis that mice with mutant PAF tumors (developed in **3.1**) demonstrate enhanced sensitivity to platinum chemotherapy **(R00)**

Unveiling the mysteries of the PINK Sheet

How do I know if my NIH reviewer loves me?

OR

If they hated my grant that much – why couldn't they just say so

Lesson #1: The Reviewer is not the enemy

Lesson #2 - getting angry at the Reviewer does not help your cause.

Lesson #3 Before getting started - deal with your feelings – yes - easier said than done.

It is important to talk with NIH Program

This is your new BFF

Percentile is everthing

SUMMARY STATEMENT

PROGRAM CONTACT: RICHARD MAZURCHUK
(Privileged Communication)
Release Date: 04/11/2014

Application Number: 1 R01 CA189283-01

Principal Investigators (Listed Alphabetically):
DOLA, SHERYL G. A. MD
BONI, GUSTAVO ADOLFO PHD
CTORIA L. MD (Contact)
LEE, LISA J MD

Applicant Organization: DUKE UNIVERSITY

Review Group: ZRG1 SBIB-Z (59)
Center for Scientific Review Special Emphasis Panel
PAR Panel: Awards for Research on Imaging and Biomarkers for Early Cancer Detection (R01)
Meeting Date: 03/27/2014 ***RFA/PA:*** PAR13-189
Council: MAY 2014 ***PCC:*** 3GED
Requested Start: 07/01/2014

Project Title: Combined breast MRI/biomarker strategies to identify aggressive biology

SRG Action: Impact Score: 42 Percentile: 35 #
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 2A-Only women, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 3A-No children included, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	477,109	746,385
2	479,018	749,371
3	480,400	751,533
4	481,811	753,741
5	483,246	755,986
TOTAL	2,401,584	3,757,016

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

NIH Pink Sheet Anatomy

Strengths

Weaknesses

RESUME AND SUMMARY OF DISCUSSION: This project aims to combine breast MRI with Wnt-based biomarkers to differentiate non-cancerous lesions with benign biology from those with aggressive biological potential. The significance is based on the premise that, if successful, insights gained could have significant implications in laying the foundation for future diagnostic, monitoring and therapeutic interventions in triple-negative breast cancer (TNBC). The review panel members agreed that collectively, principal investigator (PI) and investigative team are well positioned and are fully capable of successfully performing these experiments. The project in itself is quite interesting and has scientific and technical merit with well written study design but the gains appear to be only incremental. The experiments are focused and the experimental plans to achieve their goal are optimum. Institutional support, equipment and other physical resources are adequate for the proposed project. However, its successful development would meet an unmet need in only a minority of the overall number of patients with this disease which undermines the significance of this proposal. Moreover, the limitation/rationale for low numbers of total population affected in the proposed studies does not seem to be particularly strong, and might not lead to statistically defensible outcomes and/or publishable interim results. There was wide diversity in the preliminary scores for this application; discussion did not result in narrowing of the score range. The discussion was elaborated and in the end the encountered issues became the predominant score driving factors that reduced the overall level of enthusiasm for this otherwise interesting proposal. In view of the overall strengths and weaknesses, the review panel final scores reflect that as presented, the likelihood for the project to exert a sustained, powerful influence on the related research field is moderate.

Bottom line

If there was a difference of opinion

What does the reviewer really mean?

Score

- Triage
  - Scored less than 50%
  - Will need major reviews.
  - Can be fixed but will require major effort.
    - Methods and approach – might be fixable
    - Significance and Innovation – hard to fix
- Scored
  - Scored better than 50%
  - How close to the payline?
  - Most grants need re-submission need to figure out level of enthusiasm the reviewers had for the grant.

What does the reviewer really mean?

- Innovation
  - Good words
    - Innovative or potentially innovative (fix up the rest of the problems)
    - Intriguing
  - Bad words
    - “Modest innovation”
    - “Routine methods and models”
- Significance
  - Good words
    - “Likely to increase knowledge”, “highly significant”
  - Bad words
    - “has the potential to address an important area ***BUT***”
    - “the area of study is highly significant ***BUT***”

What does the reviewer really mean?

Summary Statement – Impact 15 - LOVE

…The studies will likely exert a strong and sustained impact on the field due to high clinical relevance of the work, the applicant's outstanding track records, feasibility of the approach and the investigative team's access to a unique resource of triple-negative breast cancer biopsies from minority women. The applicant is a productive clinician-scientist and has assembled a strong investigative team. Other strengths include novelty of the hypothesis, feasibility of the studies, and access to a unique resource of triple negative breast cancer biopsies from minority women. Since these minority women have high frequency of triple-negative breast cancer, the studies could lead to pathological explanation of racial disparity. In addition, the tools, reagents and models are available; hence, the studies are expected to yield novel data that will advance the field. Although few minor concerns were identified regarding the deficiencies in the mechanistic aspects of the studies; however, the review panel uniformly recognized the clinical value of the studies and expressed high enthusiasm for bringing the studies to fruition.

What does the reviewer really mean?

Summary Statement – Unscored – Not loved

…While this hypothesis is reasonable and could have a substantial impact on directly relating the signal transduction pathway of leptin to Stat3 and increased tumorigenesis, it fails at providing the needed preliminary data and writing a grant whose aims are interdependent. Additionally, the PI is a Research Assistant Professor, who does not seem to be independent. She has been an Assistant Professor since 2006 with moderate productivity. No senior author papers to show independence and her mentor, Dr. XXX, appears as senior author on all her papers. There is no letters of commitment from her chair or from Dr. XXX. Such lack of commitment along with lack of preliminary data and the interdependency of the aims deterred enthusiasm for this grant.

What does the reviewer really mean?

Summary Statement – Impact 41

…The discussion revealed that, while the reviewers were quite impressed with the applicant's track record and the valuable patient cohort, they were uniformly troubled by the organization of the application, the lack of detail, and the lack of consideration of interpretation of data, alternative approaches and hypotheses. They agreed that the result was a diffuse application which was more of an extensive catalog of possible experiments than it was a focused approach to either the testing of a specific hypothesis or the development of biomarkers. Despite the application's strong points, this severely diminished the reviewers' enthusiasm for it in its current form.

What does the reviewer really mean?

Summary Statement – Impact 39

….A focus on signaling networks instead of select molecules is likely to increase our knowledge of changes in the breast that are associated with pathological states and with preventive strategies. The project is highly innovative with regard to new methodologies for studying protein expression in breast epithelial cells. The investigators and environment are excellent. Weaknesses include some of the technologies proposed for use in this project cannot measure networks at the present time and this diffuses the focus of the project. A biostatistician with experience in analysis of networks would add to the scientific environment. There are concerns regarding the approach, particularly involving the clinical study. Overall this the research could lead to new methods for evaluating treatment response, however some concerns with the design of the clinical study diminish the potential impact.

What does the reviewer really mean?

Summary Statement – Impact 38

…the proposed work has outstanding potential scientific significance and clinical relevance. The panel acknowledged that the innovation and transformative nature of the proposed studies lie in the potential to demonstrate that tissue tension could prime tissue at the molecular levels towards malignancy. Other strengths comprise elegant and cutting edge approaches, ranging from in vitro analyses to epidemiological studies. The highly qualified investigative team has the required expertise to perform the proposed work. The considerable preliminary data are supportive of the hypothesis. The research plan was deemed somewhat ambitious, but feasible and well-justified. There were only some minor concerns noted by the panel that did not detract considerably from the high enthusiasm for the translational significance and merits of the project. Thus, some reviewers thought that one mouse may not recapitulate aspects of the inflammatory response associated with TNBC; it was also noted that the application was densely written with small figures and figure captions, which made the data difficult to evaluate. Nevertheless, the strengths of the application outweighed the weaknesses; and following the discussion, the application was deemed excellent. The panel unanimously agreed that if successfully accomplished, impact of this work is likely to be high; and potentially transformative findings could significantly advance the TNBC field.