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**SUMMARY STATEMENT**  
( Privileged Communication )

**Release Date:** 11/17/2015

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**Application Number:** 1 F30 CA199947-01A1

Beckwitt, Colin Henry  
University of Pittsburgh  
3550 Terrace Street  
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**Review Group:** ZRG1 F09B-B (20)  
Center for Scientific Review Special Emphasis Panel  
Fellowships: Oncological Sciences

**Meeting Date:** 11/02/2015

**Council:** JAN 2016

**PCC:** 6OTR

**Requested Start:**

**Dual IC(s):** EB

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**Project Title:** Oxygen impact on tumor metastasis dormancy and therapy

**Requested:** 5 years

**Sponsor:** Wells, Alan

**Department:** Pathology

**Organization:** UNIVERSITY OF PITTSBURGH AT PITTSBURGH

**City, State:** PITTSBURGH PENNSYLVANIA

**SRG Action:** Impact Score: 13 Percentile: 2

**Next Steps:** Visit [http://grants.nih.gov/grants/next\\_steps.htm](http://grants.nih.gov/grants/next_steps.htm)

**Human Subjects:** E4-Human subjects involved - Exemption #4 designated

**Animal Subjects:** 10-No live vertebrate animals involved for competing appl.  
Clinical Research - not NIH-defined Phase III Trial

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**BUDGET MODIFICATIONS**

## 1F30CA199947-01A1 Beckwitt, Colin

### COMMITTEE BUDGET RECOMMENDATIONS

**RESUME AND SUMMARY OF DISCUSSION:** This fully responsive dual degree fellowship application submitted by Colin Beckwitt, proposes to investigate the role of oxygen tension levels in the switch from oxidative phosphorylation to glycolytic metabolism when micrometastases leave quiescence by using a microphysiological system (MPS). The applicant was considered excellent being supported by good academics and strong letters of support. The sponsor, Dr. Wells, is a member of a multidisciplinary team working in this area of three dimensional organ modeling, who has a long record of publication, mentorship and funding and therefore was considered by the panel to be a strong positive aspect of this application. The research training plan was successfully revised including appropriate biostatistics which lead the panel to conclude that this application possesses exceptional training potential. Negative score driving concerns were Mr. Beckwitt's limited publication record and the range of oxygen tension being tested. Discussion around the oxygen range suggested that a wider range should be considered. Overall the panel concluded that, if funded, this application would have a high positive impact on the future career of Mr. Beckwitt.

**DESCRIPTION** (provided by applicant): Following dissemination from a primary lesion, a few surviving carcinoma cells establish residency in distant sites (micrometastases). Many micrometastases assume a dormant (quiescent) cellular phenotype, characterized by a G0/G1 arrest that may persist years to decades before outgrowth to form clinically evident metastases; these emergent tumors almost inexorably lead to death. Unfortunately, micrometastases often appear to be refractory to therapeutic agents, even ones that show success against the primary tumors from which they derive. This situation is particularly daunting in breast cancer that can lie dormant for a decade or more before recurring. Signals from the tumor microenvironment have been shown to play a critical role in maintaining this dormant phenotype on the one hand or facilitating emergence from cellular quiescence on the other. Culture of breast cancer cell lines in a novel all human liver microphysiological system (MPS) our lab employs has been shown to reliably induce cancer cell dormancy. Traditionally, rapidly proliferating cancer cells resort to glycolysis in order to accumulate the massive amounts of metabolic intermediates required for cell division ("Warburg Effect"). However, the phenotypically dormant cancer cells may exhibit a different metabolic profile, which may be essential to both maintaining quiescence and successful novel treatment approaches. Our foundational model is that dormant micrometastases adapt a low metabolic and proliferative state concordant with chemoresistance and reduced glycolytic flux. We hypothesize that oxygen tension levels will dictate the switch between oxidative phosphorylation and glycolytic metabolism, and thereby impinge on dormancy. This model will be tested by measuring the basal glycolytic and oxidative phosphorylation fluxes of dormant cancer cells by quantifying glucose uptake, glycolytic enzyme expression, and intracellular ATP concentration through cell culture experiments and immunofluorescence. A novel hemoglobin-based oxygen carrier (HBOC) will be introduced to the system to modulate the oxygen tension to which the cancer cells and liver tissue are exposed. Sensitive ruthenium oxygen sensors will be used to determine the oxygen tension to which the cells are exposed and the trans-tissue oxygen gradient to elucidate the impacts of oxygen tension on tumor dormancy phenotype and cell metabolism. Finally, select anti-tumor agents, including the chemo-therapeutics doxorubicin and cisplatin, will be incorporated into the liver MPS to determine whether therapeutic efficacy is dependent on cancer cell metabolic state and concurrently monitor toxicities to the liver tissue. Understanding the influence of oxygen tension on dormant micrometastasis phenotype, metabolism, and treatment susceptibility is expected to yield insights into basic tumor biology and promote translational studies into improving the efficacy of current treatments (drug rescue) and the discovery of novel therapies.

**PUBLIC HEALTH RELEVANCE:** Tumor metastasis to the liver, one of the most common manifestations of advanced cancers, commonly establishes dormant, treatment refractory micrometastases that herald mortality from the disease. The metabolic activity of these dormant tumor cells will be studied along with the impact of altering the oxygen tension of the tumor microenvironment on cancer cell metabolism, dormancy phenotype, and treatment potentiation. Understanding these processes will provide novel insights into the basic tumor biology of metastases, promote translational studies into improving the efficacy of existing agents (drug rescue), and motivate the development of new adjuvant therapies for this mortal stage of cancer progression.

## Critique 1

Fellowship Applicant: 2  
Sponsors, Collaborators, and Consultants: 1  
Research Training Plan: 2  
Training Potential: 2  
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** The model is that dormant micro-metastases adapt to a low metabolic and proliferative state concordant with chemoresistance and reduced glycolytic flux. Oxygen tension levels will dictate the switch between oxidative phosphorylation and glycolytic metabolism, and thereby impinge on dormancy. The response to review was strong with direct changes implemented to include addition of statistical support and consideration of both tumor changes as well as host tissue changes in the design. The strengths of the application include the high quality of the applicant (letters, background, undergraduate publication and strong statement), outstanding mentoring team and achievable realistic goals in the research training plan.

## 1. Fellowship Applicant

### Strengths

- Outstanding letters of reference indicating his research passion and creativity
- Outstanding personal statement indicating his career plan and how research fits into the plan and has been incorporated thus far
- Colin is currently undertaking his third summer rotation in Dr. Wells' laboratory in July and August 2015 prior to starting graduate school.
- Continue his work studying hypoxia in micrometastasis, building on his success incorporating and validating oxygen sensors in a continuous-perfusion primary liver culture device modeling micrometastases.
- Established relationships with two clinical mentors. Dr. Wallis Marsh is a nationally known hepatobiliary surgeon with experience in liver transplantation. Dr. Gary Gruen is an orthopedic trauma surgeon who focuses mostly on fracture repair and bone healing.

### Weaknesses

- Peer reviewed publication record during MSTP program (2013-2015) is one paper.

## 2. Sponsors, Collaborators, and Consultants:

### Strengths

- Outstanding career mentor in Dr. Wells with an established track record in research training, his own outstanding peer reviewed research and his dedication to training for two decades MD PhD students.
- Building on a model that involved other collaborators (Organotypic Bioreactor).
- Multi-disciplinary program includes bioengineers, pharmacology and surgery colleagues.

#### **Weaknesses**

- None detected.

### **3. Research Training Plan:**

#### **Strengths**

- Research plan is achievable given the timeline and the scope
- Organotypic model is in place and the tools are in hand
- Research fits with his stated career goals

#### **Weaknesses**

- None identified.

### **4. Training Potential:**

#### **Strengths**

- Clearly motivated and enthusiastic applicant
- Added the statistical considerations to a revised plan
- Redesigned the research plan according to reviewer concerns

#### **Weaknesses**

- None identified.

### **5. Institutional Environment & Commitment to Training:**

#### **Strengths**

- Outstanding environment, no concerns
- Commitment to training in evidence by description of the program and functions

#### **Weaknesses**

- No concerns

#### **Protections for Human Subjects:**

Not Applicable (No Human Subjects)

- Human samples not subjects

#### **Vertebrate Animals:**

Not Applicable

**Biohazards:**

Not Applicable (No Biohazards)

**Resubmission:**

- Responded positively to reviewer concerns
- added statistical considerations to the plan
- Redesigned the plan according to the reviewer points

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- No concerns

Comments on Subject Matter (Required):

- No concerns

Comments on Faculty Participation (Required):

- No concerns

Comments on Duration (Required):

- No concerns

Comments on Frequency (Required):

- No concerns

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Acceptable

- No concerns

**Budget and Period of Support:**

Recommended budget modifications or possible overlap identified:

- 5 years of support requested whereas applicant says done by 2020.

**Critique 2**

Fellowship Applicant: 4

Sponsors, Collaborators, and Consultants: 2

Research Training Plan: 3

Training Potential: 4

Institutional Environment & Commitment to Training: 2

**Overall Impact/Merit:** The purpose of this revised application is to train Collin Beckwitt to elucidate the oxygen impact on tumor metastasis dormancy and therapy. He will study the metabolic activity of dormant cells in the liver and examine the impact of altering the oxygen tension of the tumor microenvironment on cancer cell metabolism, dormancy phenotype, and treatment potentiation. Mr. Collin Beckwitt will use various research techniques that include ex vivo liver microphysiological system (MPS), tissue sectioning, immunofluorescence (IF), image analysis, and metabolic and functional analyses of dormant micrometastases and liver tissue respectively. Micrometastatic dormancy presents several clinical problems. While the primary tumor can be effectively eliminated by surgery, radiotherapy, or chemotherapy, dormant micrometastases are commonly resistant to these therapies. The outgrowth of these micrometastases is the main source of morbidity and mortality in cancer patients which demonstrates a need for the expertise this F30 proposal will provide for Mr. Collins Beckwitt. Collins Beckwitt academic course grades are excellent. Two times funded by NRSE and currently funded under the Medical Scientist Training Program, University of Pittsburgh (T32, 5T32GM008208-25, -26). If this application were funded for the requested 2 years, it would have a modest impact on Mr. Collins Beckwitt becoming a leader in American science.

## 1. Fellowship Applicant

### Strengths

- Collin Beckwitt is a second year MD/PhD student at the University of Pittsburgh with the goal to be a translational surgeon scientist. After completing BS at Massachusetts Institute of Technology, Collin is pursuing a PhD in pathology with focus on cancer biology and metabolism under the mentorship of Dr. Alan Wells as well as surgical oncology.
- During his undergraduate, Mr. Beckwitt's course grades were excellent and he was also involved in summer research with Dr. Katharina Ribbeck where he was involved in constructing films to serve as antimicrobial lubricating agents and drug delivery devices. The outcome of this experience is one publication, one poster and involved with a patent submission for the developed technology.
- During medical school and graduate work rotation period he was also involved in research that resulted in one manuscript and poster.

### Weaknesses

- Lack of productivity during undergraduate and graduate remain an issue.

## 2. Sponsors, Collaborators, and Consultants:

### Strengths

- Dr. Allen Wells is a Thomas J Gill III Professor of Pathology, Executive Vice-Chair for Laboratory Medicine, University of Pittsburgh and Staff Pathologist Pittsburgh VA Health System. Dr. Wells has very impressive training records nationally and internationally. He trained faculty, graduate students, K08 and K12. He was on 75-thesis committee.
- Dr. Wells has also been involved with the training and direction of under-represented minorities for almost two decades. He also trained five of MD-PhD students, who have subsequently launched successful careers including the establishment of independently NIH-funded laboratories

- Dr. Wells' laboratory is well funded and he has continuous funding from NIH.
- Dr. Wells' laboratory has been investigating tumor progression, focusing mainly on the hormone-responsive breast and prostate carcinomas. He investigates cell migration, tumor invasion, survival and chemoresistance signaling and ex vivo organotypic models for tumor progression and dormancy. The later match the applicant's research interest.
- Dr. Wells is very committed to training of Collins evidences with his tailored personal statement.
- Dr. Wells has two other graduate students beside Collin (MSTP student), 4 post-doctoral fellows, 2 technicians, and 2 junior faculty.

#### **Weaknesses**

- None noted.

### **3. Research Training Plan:**

#### **Strengths**

- Collin will study the metabolic activity of dormant cells in the liver and examine the impact of altering the oxygen tension of the tumor microenvironment on cancer cell metabolism, dormancy phenotype, and treatment potentiation.
- The concept of oxygen's impact on tumor dormancy is very interesting. Mr. Collin Beckwitt will use various research techniques that include imaging at the Pittsburgh Center for Biological Imaging and LiverChip model.

#### **Weaknesses**

- Clinical translatability MPS questioned by previous reviewers is still a concern.

### **4. Training Potential:**

#### **Strengths**

- The training program of Mr. Collin Beckwitt will comprise laboratory training, career development and networking, as well as a research focus on metastasis. Also Colin will spend time at MIT in the laboratory of Dr. Linda Griffith (Dept. Biological Engineering), learning the technical details of the MPS system and the nascent 3D printing of vascular conduits

#### **Weaknesses**

- The revised training potential is excellent and no weaknesses.

### **5. Institutional Environment & Commitment to Training:**

#### **Strengths**

- UPMC and the Pitt School of Medicine are ranked among the best hospital systems and medical schools in the country, respectively. The University of Pittsburgh is the most common institution cited on PubMed due to its high degree of collaboration with other universities. Dr. Wells' laboratory is diverse and comprised of a many trainees at all levels with wide range of educational backgrounds.

#### **Weaknesses**

- None noted.

**Protections for Human Subjects:**

Acceptable Risks and Adequate Protections

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Resubmission:**

- Yes comments were all answered adequately

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- Online, Lectures and workshop

Comments on Subject Matter (Required):

- Adequately covered.

Comments on Faculty Participation (Required):

- Faculty from University of Pittsburgh.

Comments on Duration (Required):

- 2 hours.

Comments on Frequency (Required):

- 15 weeks.

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Acceptable

**Budget and Period of Support:**

Recommend as Requested

**Critique 3**

Fellowship Applicant: 1  
Sponsors, Collaborators, and Consultants: 1  
Research Training Plan: 3  
Training Potential: 1  
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** This is a revised dual-degree fellowship application submitted by Colin Beckwitt that proposes to investigate how oxygen tension contributes to the dormancy of metastatic breast cancer cells using a microphysiological system (MPS). This is an outstanding applicant. The mentor and the environment are superb. The applicant has attempted to answer the comments from the previous review. He has added a statistical section and a biostatistician to the application. The training plan will introduce the applicant to state-of-the-art technology which could be well suited to a physician scientist. This remains a high risk/high reward proposal which, if successful, could yield important new insights and could provide a solid foundation upon which to base his career. Based upon the mentor and the training environment, this reviewer is enthusiastic despite the risky nature of the proposed studies.

### 1. Fellowship Applicant:

#### Strengths

- Outstanding academic record and background
- Very strong letters of support
- Commitment to cancer research

#### Weaknesses

- None Noted.

### 2. Sponsors, Collaborators, and Consultants:

#### Strengths

- Sponsor is outstanding with a long track record of highly respected research, publication and mentoring.
- A biostatistician has been added to the proposal which strengthens the application.

#### Weaknesses

- None noted.

### 3. Research Training Plan:

#### Strengths

- This continues to be a very interesting proposal using state-of-the-art technologies and novel systems.
- A small statistical section has been added to the proposal as well as some other background information in response to the previous critique.
- While this proposal is high risk/high reward, if successful, important new insights will be gained regarding the regulation of micro-metastases and could in the long run lead to new therapeutic approaches.

### **Weaknesses**

- This remains a high risk, high reward proposal. – which could be challenging for a student in the event that results are not forthcoming; the lack of preliminary data poses a challenge with regard to determining the feasibility of the approach.

### **4. Training Potential:**

#### **Strengths**

- This proposal will provide a good foundation upon which to base a future career.
- Exposure to state-of-the-art novel technologies.
- Outstanding mentor.

#### **Weaknesses**

- Need to ensure that mentor carefully monitors the progress of the applicant as this is a highly complex and novel system.

### **5. Institutional Environment & Commitment to Training:**

#### **Strengths**

- Outstanding environment.

#### **Weaknesses**

- None noted.

### **Protections for Human Subjects:**

Not Applicable (No Human Subjects)

### **Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

### **Biohazards:**

Not Applicable (No Biohazards)

### **Resubmission:**

- The applicant has attempted to address many of the criticisms in the previous review

### **Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- Lecture; small group; online modules.

Comments on Subject Matter (Required):

- Extensive and appropriate.

Comments on Faculty Participation (Required):

- Faculty involved in lectures and small group.

Comments on Duration (Required):

- At least 8 hrs. per year in RCR - also took two courses.

Comments on Frequency (Required):

- Appropriate.

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Acceptable

- appropriate data sharing plan for the proposed experiment

**Budget and Period of Support:**

Recommended budget modifications or possible overlap identified:

- reduce time to four years

**THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:**

**THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:**

**PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE**

**Budget and Period of Support: Reduce years of support to match expected graduation date.**

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NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html>. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting

or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see [http://grants.nih.gov/grants/peer\\_review\\_process.htm#scoring](http://grants.nih.gov/grants/peer_review_process.htm#scoring).

## MEETING ROSTER

Center for Scientific Review Special Emphasis Panel  
**CENTER FOR SCIENTIFIC REVIEW**  
Fellowships: Oncological Sciences  
**ZRG1 F09B-B (20) L**  
November 02, 2015 - November 03, 2015

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