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TITLE:
Dual Epithelial and Stromal Targeting in Breast Cancer Using the Phase II ROCK2 Inhibitor KD025 Guided by Intravital Imaging Technology

PRINCIPAL INVESTIGATOR: Professor Paul Timpson

CONTRACTING ORGANIZATION: University of New South Wales

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Fort Detrick, Maryland 21702-5012

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Dr David Herrmann

5d. PROJECT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

A key factor that limits the efficacy of drug treatment for breast cancer is extensive deposition of extracellular matrix (ECM) or fibrosis, which (i) hinders drug delivery and (ii) provides positive biomechanical feedback signaling to tumors to enhance tumor progression and treatment resistance. We have access to the clinically relevant ROCK2 inhibitor KD025 and have confirmed here that pharmacological ROCK2 inhibition can significantly reduce fibrosis in our breast cancer models. Using cell-derived matrix assays and collagen contraction assays, we have shown that ROCK2 inhibition significantly reduces ECM production and remodeling resulting in a 'softer' ECM. Organotypic invasion assays showed that this inhibition of ECM remodeling (stromal targeting) in combination with ROCK2 inhibition during breast cancer cell invasion (epithelial targeting) significantly reduces breast cancer cell invasiveness.

15. SUBJECT TERMS
Breast cancer, fibrosis, extracellular matrix (ECM), Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2)

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

   Breast cancer (BC) initiation and progression is accompanied by extensive extracellular matrix (ECM) deposition and remodeling, known as fibrosis. Tissue fibrosis is commonly found in aggressive cancers, such as the triple negative breast cancer (TNBC) subtype, and can limit drug delivery as well as fuel treatment resistance. In this project we assess the efficacy of the novel 'anti-fibrotic' phase II ROCK2 inhibitor KD025 to improve standard-of-care chemotherapy performance and extend survival in *in vitro* and *in vivo* models of TNBC.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

   Breast cancer, fibrosis, extracellular matrix (ECM), Rho Associated Coiled-Coil Containing Protein Kinase 2 (ROCK2)

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

   What were the major goals of the project?
   List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

   Major Task 1: Optimize KD025 'priming' therapy in 3D *in vitro* assays.
   Months 1-12. 90% completed.

   Major Task 2: Optimizing *in vivo* KD025 'priming' therapy using optical imaging windows in primary and secondary sites.
   Months 1-12. 80% completed.

   Major Task 3: KD025 priming in CDK1/RhoA-biosensor models of BC
   Months 7-18. 33% completed.

   Major Task 4: Long-term survival studies
   Months 19-36. This task will be initiated during the next reporting period.

   Major Task 5: Personalized therapy
   Months 1-36. 16% completed.

   What was accomplished under these goals?
   For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the

emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: Optimize KD025 'priming' therapy in 3D *in vitro* assays.

The anti-fibrotic efficacy of ROCK2 inhibition (ROCK2i) in breast cancer was initially assessed in cell-derived matrix (CDM) assays. CDM assays can allow for the assessment of extracellular matrix (ECM) deposition of breast cancer-associated fibroblasts (CAFs) upon anti-fibrotic therapy (*Figure 1A*). Following 7 days of incubation with ascorbic acid to stimulate ECM deposition/secretion in the

Figure 1

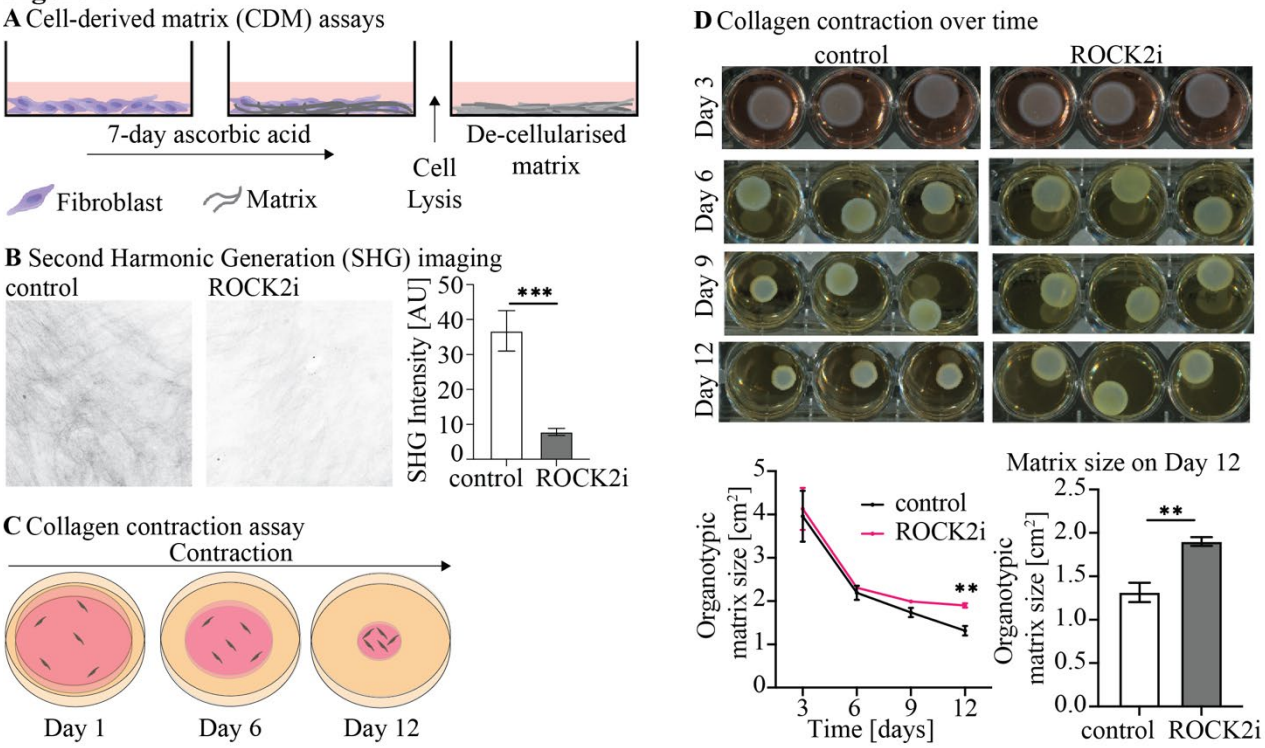

Figure 1: Cell-derived matrix (CDM) assays and collagen contraction assays to assess CAF-mediated ECM production and remodeling upon ROCK2 inhibition. *Schematics of the CDM assay consisting of incubation of CAFs with ascorbic acid to stimulate ECM production followed by CAF de-cellularisation after 7 days leaving only the native intact ECM behind (**A**). Representative SHG images of CDMs treated with vehicle (control) or ROCK2i followed by quantification of SHG signal intensity (**B**). Schematics of the collagen contraction assay where CAFs are embedded into rat tail collagen and allowed to contract the collagen matrix (**C**). Representative images of collagen matrices on Days 3, 6, 9, 12 treated with vehicle (control) or ROCK2i with quantification of matrix size (**D**). Graphs show mean ± SEM (n=3). Statistical significance determined using an un-paired t test. *P < 0.05, **P < 0.01, and ***P < 0.001.*

presence of either vehicle or ROCK2i, CDM assays were de-cellularised using a detergent-based extraction buffer to leave the native, intact ECM behind (*Figure 1A*). Second Harmonic Generation (SHG) imaging was then performed to quantify cross-linked collagen I as a readout of ECM production (*Figure 1B*). Here, ROCK2i resulted in a significant, >4-fold decrease in SHG signal

intensity demonstrating that ROCK2i can significantly reduce CAF-mediated ECM production and remodeling (*Figure 1B*).

In order to further assess ROCK2i in breast cancer fibrosis *in vitro*, three-dimensional (3D) collagen contraction assays were performed (*Figure 1C*). Here, CAFs were embedded into rat tail collagen and allowed to contract the collagen matrix in the presence of vehicle (control) or ROCK2i over 12 days (*Figure 1C*). Matrix size was quantified on Days 3, 6, 9 and 12 as a readout of CAF-mediated collagen contraction and showed a significant reduction in collagen contraction on Day 12 upon ROCK2i treatment compared to control (*Figure 1D*).

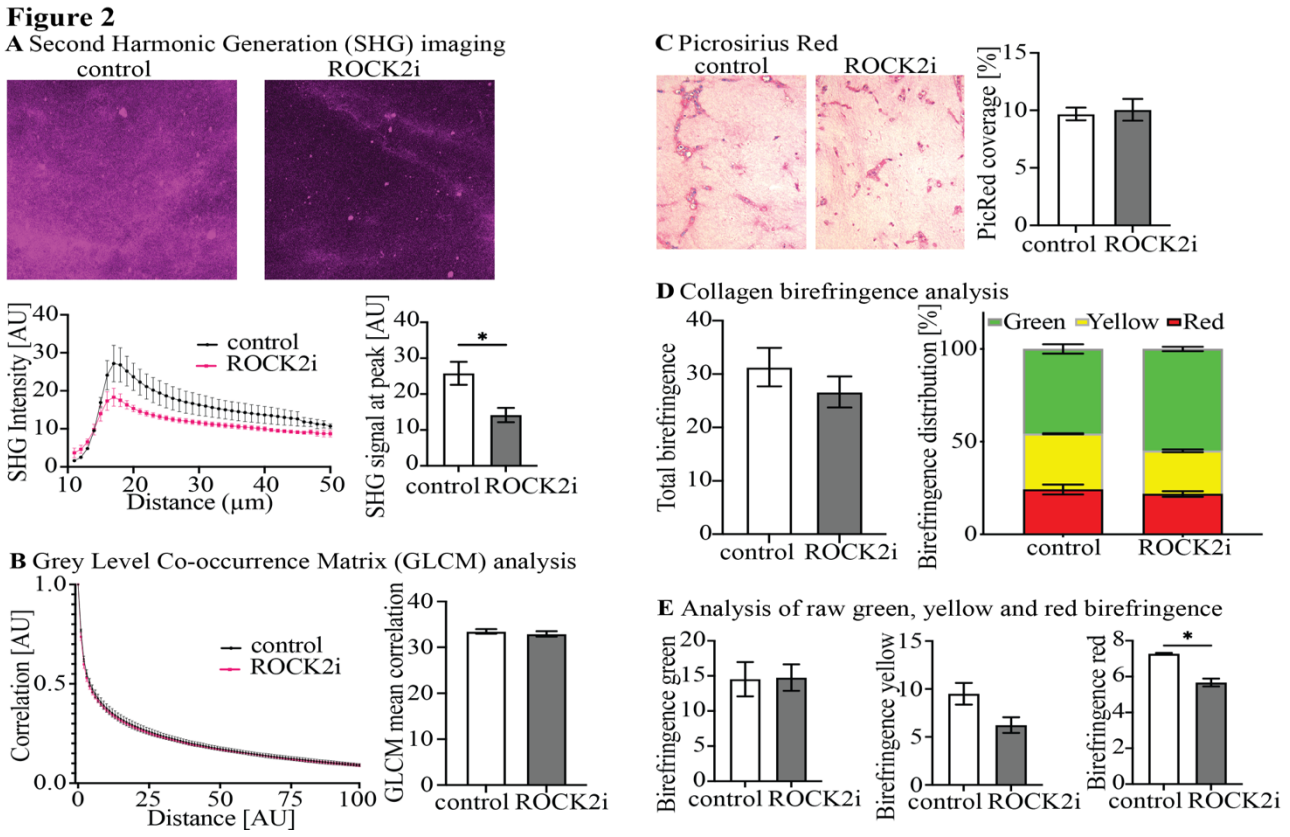

Figure 2: Imaging-based quantification of collagen remodeling upon ROCK2 inhibition. *Representative maximum projections of SHG imaging z-stacks through collagen matrices treated with vehicle (control) or ROCK2i followed by quantification of SHG signal intensity over the z-stack and graph showing SHG signal quantified at peak (**A**). Quantification of GLCM correlation across the SHG image and graph depicting mean GLCM correlation (**B**). Representative brightfield images of Picrosirius Red stained collagen matrices treated with vehicle (control) or ROCK2i followed by quantification of Picrosirius Red signal coverage (**C**). Quantification of total collagen birefringence followed by quantification of birefringence distribution (green, yellow, red indicating a range from immature over mature to highly mature fibres) upon polarized light imaging of Picrosirius Red stained collagen matrices treated with vehicle (control) or ROCK2i (**D**). Quantification of raw green, yellow and red birefringent signal upon polarized light imaging of Picrosirius Red stained collagen matrices treated with vehicle (control) or ROCK2i (**E**). Graphs show mean ± SEM (n=3). Statistical significance determined using an un-paired t test. *P < 0.05, **P < 0.01, and ***P < 0.001.*

Second Harmonic Generation (SHG) can be used to quantify the abundance of crosslinked collagen I. SHG imaging of collagen matrices on Day 12 from both conditions demonstrated a significant reduction in SHG intensity (*Figure 2A*) indicating that ROCK2i treated CAFs have a significantly reduced ability to remodel collagen. Grey Level Co-Occurrence Matrix analysis of SHG images showed that ROCK2i did not significantly alter collagen organization (*Figure 2B*). Following SHG imaging, collagen matrices were formalin-fixed, dehydrated and embedded into paraffin for subsequent immunohistochemical analysis. In order to further analyse the effect of ROCK2i on CAF-mediated ECM remodeling, paraffin sections of the collagen matrices were initially stained with Picrosirius Red to visualise fibrillar collagen I/III and imaged using brightfield microscopy (Picrosirius Red signal, *Figure 2C*) and polarized light imaging (collagen birefringence, *Figure 2D,E*). Quantification of total Picrosirius Red coverage and total birefringent signal did not show significant differences between vehicle and ROCK2i treated matrices (*Figure 2C,D)*. Quantification of high, medium, and low birefringent Picrosirius Red signal (shown as green, yellow and red in *Figure 2E* indicative of a range from immature over mature to highly mature collagen fibers, respectively) demonstrated a significant reduction in red birefringent signal upon ROCK2i treatment indicating a significant reduction in highly mature fibrillar collagen (*Figure 2E*).

Figure 3

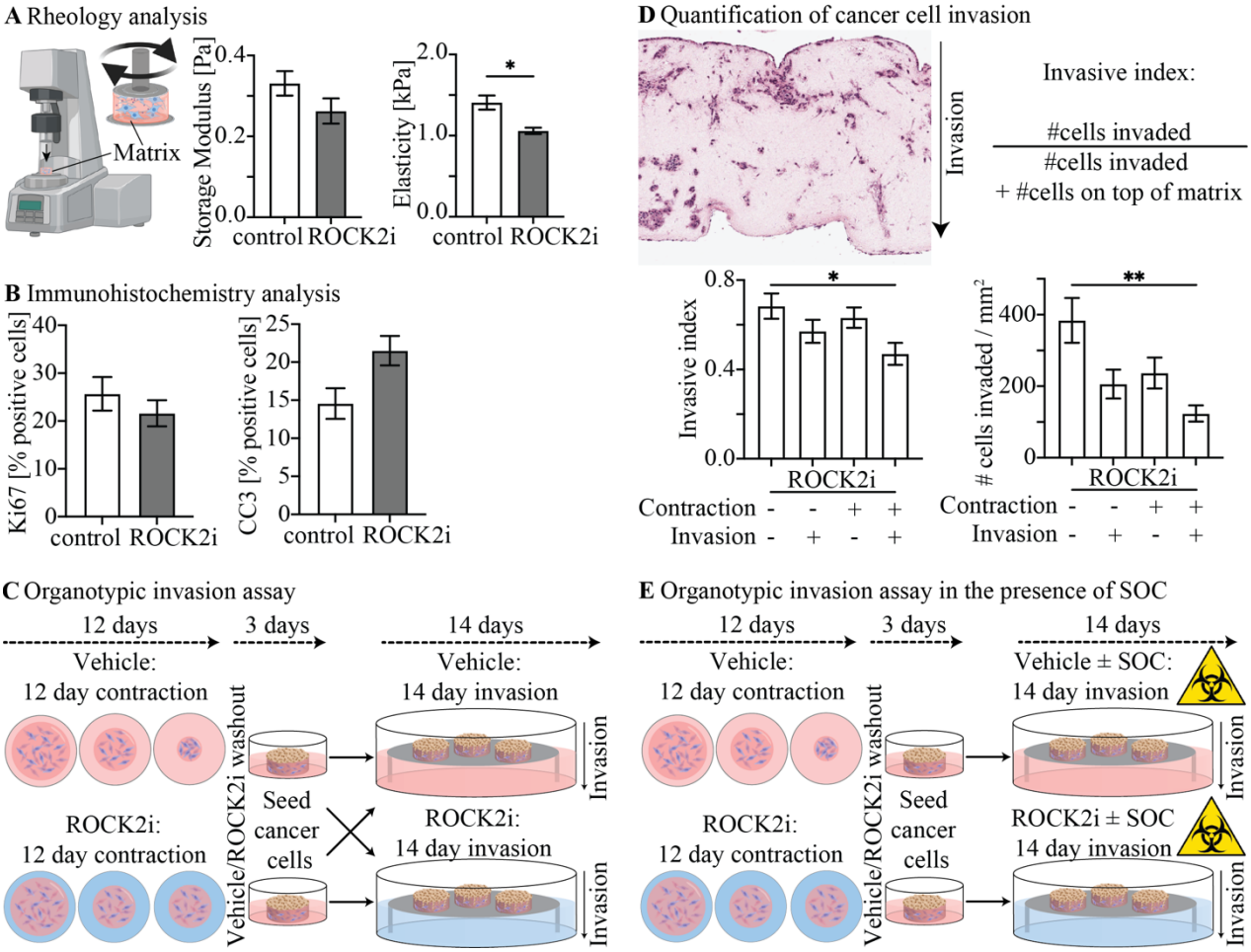

Figure 3: Biomechanical assessment of collagen matrices and cancer cell invasion assays. *Schematics of the rheometer used followed by quantification of storage modulus (shear rheology) and*

*elasticity (compression) of collagen matrices treated with vehicle (control) or ROCK2i (**A**). Quantification of Ki67 (CAF cell proliferation) and cleaved caspase 3 (CC3, CAF cell death)in collagen matrices treated with vehicle (control) or ROCK2i (**B**). Schematics of the organotypic invasion assay consisting of 12 day CAF-mediated collagen contraction followed by cancer cell seeding and growth on top of submerged matrices for 3 days and cancer cell invasion into the contracted collagen when matrices are lifted to an air-liquid interface (**C**). Vehicle (control) or ROCK2i was provided during collagen contraction only (stromal priming), during cancer cell invasion only (epithelial treatment) or during both collagen contraction and cancer cell invasion (chronic therapy, **C**). Representative image of an H&E stained section through an organotypic invasion assay followed by equation to determine the invasive index and quantification of invasive index and the number of cells invaded per mm^2 upon stromal priming, epithelial treatment or chronic therapy with vehicle (control) or ROCK2i (**D**). Schematics of the organotypic invasion assay with vehicle (control) or standard-of-care chemotherapy (Paclitaxel) was added during the last 3 days of cancer cell invasion into CAF contracted collagen matrices (**E**). Graphs show mean ± SEM (n=3). Statistical significance determined using an un-paired t test (comparison between 2 conditions) or an ordinary one-way ANOVA with multiple comparisons (>2 conditions). *P < 0.05, **P < 0.01, and ***P < 0.001.*

In order to assess whether the observed decrease in CAF-mediated collagen remodeling resulted in an alteration of the biomechanical properties of the collagen matrices, compression and shear rheology measurements were performed (*Figure 3A*). Here, a significant reduction in compression rheology (*Figure 3A*, Elasticity) was observed showing that ROCK2i reduces matrix stiffness. To identify whether the observed changes in collagen remodeling and matrix stiffness were due to changes in CAF proliferation or survival upon ROCK2i treatment, paraffin sections through matrices of both conditions were also stained for Ki-67 (*Figure 3B*, CAF proliferation) and cleaved caspase-3 (*Figure 3B*, CAF apoptosis). While a trend towards decreased CAF proliferation and increased apoptosis was observed upon ROCK2i treatment, these changes were not significant (*Figure 3B*) indicating that the changes in collagen matrix remodeling and stiffness upon ROCK2i are not predominantly driven by ROCK2i effects on CAF proliferation and survival.

We next assessed whether ROCK2i alone can significantly affect breast cancer cell invasion using 3D organotypic invasion assays (*Figure 3C*). Here, cancer cells were seeded onto CAF contracted collagen matrices and allowed to grow for 3 days on top of the matrix followed by cancer cell invasion for 14 days (*Figure 3C*). ROCK2i was added to the assay during collagen contraction only (stromal priming), during cancer cell invasion only (epithelial treatment) or during both matrix contraction and cancer cell invasion (chronic therapy). Following 14 days of cancer cell invasion, organotypic matrices were paraffin-embedded and cancer cell invasion was assessed on histological sections by determining the invasive index (number of cells invaded/number of cells on top of the matrix) and the number of cells invaded per mm^2 (*Figure 3D*). Here, quantification of cancer cell invasion showed a non-significant trend towards decreased cancer cell invasion upon ROCK2i priming or ROCK2i epithelial treatment with significant reduction in cancer cell invasion only upon chronic ROCK2i therapy (stromal priming and epithelial treatment) demonstrating that both stromal priming of the CAF-mediated ECM remodeling and epithelial treatment during cancer cell invasion are required to affect breast cancer cell invasiveness (*Figure 3D*).

We subsequently assessed whether chronic ROCK2i treatment would significantly affect standard-of-care (SOC) Paclitaxel chemotherapy performance in 3D organotypic invasion assays (*Figure 3E*). Here, chemotherapy vehicle (control) or Paclitaxel chemotherapy was added to 3D organotypic invasion assays under chronic treatment with ROCK2i vehicle (control) or ROCK2i during the last

72 hours of the invasion stage (*Figure 3E*). Quantification of immunohistochemical markers of chemotherapy efficacy (Ki-67 and cleaved caspase 3) is still ongoing.

Major Task 2: Optimizing *in vivo* KD025 'priming' therapy using optical imaging windows in primary and secondary sites.

We have obtained local IACUC approval and DoD ACURO approval to optimize our novel combination therapy *in vivo*. Following *in vitro* assessment of the anti-fibrotic efficacy of ROCK2i, we have also performed intravital imaging studies by implanting mammary imaging windows above primary mammary tumours (*Figure 4A*) and lung imaging windows above the lung upon tail vein injection of breast cancer cells (*Figure 4B*) to assess treatment efficacy of ROCK2i in combination with Paclitaxel SOC in both primary and secondary breast cancer sites, respectively. In particular, we used intravital imaging to assess whether ROCK2i can decrease fibrosis (assessed by SHG imaging of cross-linked collagen I), improve vascularity (Quantum Dot imaging of blood vessel structure and patency) and augment chemotherapy performance (fluorescent biosensor imaging) in live tissue (*Figure 4C)*. Quantification of the intravital imaging data and post-imaging immunohistochemical data is still ongoing.

Figure 4

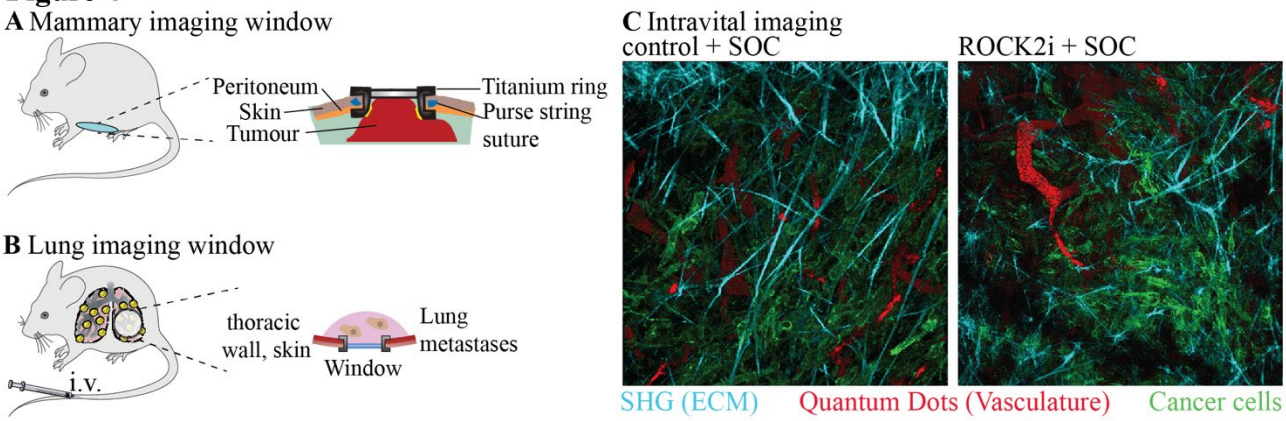

Figure 4: Intravital imaging to assess treatment efficacy in live primary and secondary breast cancer sites. *Mammary imaging windows were implanted above primary mammary tumours to assess the efficacy of ROCK2i priming on Paclitaxel SOC performance in vivo in live primary tumours (**A**). Lung imaging windows were implanted above the lung upon tail vein injection of breast cancer cells to assess the efficacy of ROCK2i priming on Paclitaxel SOC performance in vivo in live secondary sites (lung metastases, **B**). Representative images of fluorescent biosensor expressing breast cancer cells (green) in the context of SHG-derived ECM signal (cyan) and the vasculature, red, **C**).*

Major Task 3: KD025 priming in CDK1/RhoA-biosensor models of BC

As planned, we have expanded upon our genetically engineered mouse colony of MMTV-Cre; MMTV-PYMT crossed with lox-stop-lox inducible RhoA-FRET and CDK1-FRET biosensor mice to generate experimental animals for Major Task 3, which will be assessed in Year 2 of the grant.

Major Task 5: Personalized therapy.

We have obtained local IRB exemption as well as DoD HPRO exemption from human ethics for assessing our novel combination therapy in patient-derived xenografts (PDXs) of human breast cancer, which we will initiate in Year 2 of the grant.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report as the project is too early in its progress.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We aim to finish analysis of Major Tasks 1 and 2, while also initiating experiments on Major Tasks 3-5.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report as the project is too early in its progress.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report as the project is too early in its progress.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report as the project is too early in its progress.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report as the project is too early in its progress.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention,

diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

NAME: **PROF PAUL TIMPSON**
No change.

NAME: **DR DAVID HERRMANN**
No change.

NAME: **PROF MICHAEL SAMUEL**
No change.

NAME: **PROF SANDRA O'TOOLE**
No change.

NAME: **PROF ELGENE LIM**
No change.

NAME: **MS VANESSA KILLEN**
No change.

NAME: **MS JAN MUMFORD**
No change.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

NAME: ***PROF PAUL TIMPSON***

Change to inactive support:

National Health & Medical Research Council 1st Jan 2019 – 31st Dec 2022
NHMRC Project Grant
Title: "Tailored priming of pancreatic cancer progression and metastatic targeting using KD025, a phase II (ROCK2) inhibitor: fine-tuning treatment via single cell intravital imaging"
Timpson: PI
Level of effort: 20%

National Health & Medical Research Council 1st Jan 2018 – 31st Dec 2022
NHMRC Senior Research Fellowship
Title: "Biosensor imaging in preclinical pancreatic cancer targeting: taking cancer targeting to new dimensions"
Timpson: PI
Level of effort: Fellowship

Change to active support:

Avner Pancreatic Cancer Foundation 1st Jan 2022 – 31st Dec 2023
Accelerator Grant
Title: "Repurposing FDA/TGA-approved PCSK9 inhibitor evolocumab to enhance immunotherapy outcomes in pancreatic cancer"
Timpson: PI
Level of effort: 20%

US Department of Defense 1st July 2022-30th June 2025
FY21 MRP Idea Award (Direct Costs)
Title: Microenvironmental regulation of melanoma brain metastasis
Timpson: Co-I
Level of effort: 10%

National Health & Medical Research Council 1st Jan 2023 – 31st Dec 2026
NHMRC Investigator Grant
Title: "Anti-fibrotic targeting and biosensor imaging in pancreatic cancer (PC): taking cancer targeting to new dimensions"

Timpson: PI
Level of effort: Fellowship

NAME: ***DR DAVID HERRMANN***

Change to inactive support:

St Vincent's Clinic Foundation 1st Jan 2021 – 31st Dec 2021
SVCF Annual Grant
Title: "Pinpointing and targeting novel drivers of pancreatic cancer progression, invasion and metastasis"
Herrmann: PI
Level of effort: 20%

NAME: ***PROF ELGENE LIM***

Change to inactive support:

2020-2022 MRFF Genomics Grant (CIA Lakhani), "Whole Genome Sequencing in high-risk breast cancer patients". Role: CI.

2020-2022 National Health and Medical Research Council Project Grant (CIA Tilley), "A combinatorial drug strategy to target lethal forms of breast cancer" Role: CIB.

2020-2022 Cancer Council NSW Project Grant (CIA Achinger-Kawecka), "Using epigenetic therapies to overcome endocrine resistance in breast cancer". Role: CIC.

2019-2021 Love Your Sister Grant, "The establishment of clinically relevant breast cancer preclinical models to identify therapeutic vulnerabilities in cancer",. Role: CIA.

2019-2021 Balnaves Foundation Grant, "A comprehensive approach to identifying and evaluating new therapies for patients with treatment-resistant breast cancer", Role: CIA.

2019-2021 National Breast Cancer Foundation Investigator initiated research scheme (CIA Swarbrick), "The Breast Cancer Cell Atlas". Role: CIC.

2019-2021 National Breast Cancer Foundation Project Grant (CIA Caldon), "Therapeutic targeting of dual CDK4/6 inhibitor and endocrine resistant breast cancer". Role: CIB.

2018-2022 National Health and Medical Research Council Centre of Research Excellence. (CIA Lindeman), "Centre for Translational Breast Cancer Research (TransBCR): delivering laboratory discoveries to the clinic". Role: CIG.

2018-2021 MNBCF Collaborative Research Initiative (CIA Tilley), "Transforming endocrine therapy for breast and prostate cancer. Role: CID.

2018-2021 National Health and Medical Research Council Project Grant (CIA Tilley), "Pushing AR toward better outcomes in breast and prostate cancers". Role: CIE.

Change to active support:

2022-2024 National Breast Cancer Foundation Investigator Initiated Research grant (CIA Caldon) "Reactivating cell death pathways to overcome combination therapy resistance in metastatic ER+ breast cancer" . Role: co-I

2022-2024 National Breast Cancer Foundation Investigator Initiated Research grant (CIA Stirzaker) "Novel epigenetic blood test for breast cancer detection and monitoring" Role: co-I

2022-2023 Pfizer Australia Investigator Sponsored Research Pre-clinical grant "Understanding Estrogen Receptor Signalling in CDK4/6i Resistant, Luminal Breast Cancers". Role: CIA

2022-2023 National Breast Cancer Foundation Investigator Initiated Research grant (CIA Roden) "Unravelling cellular and spatial heterogeneity in human breast cancers" . Role: co-I

NAME: ***PROF SANDRA O'TOOLE***

Change to inactive support:

2019-2021 Swarbrick A, Powell J, **O'Toole S** and Lim E, National Breast Cancer Foundation Investigator initiated research scheme, "The Breast Cancer Cell Atlas" ***Change to***

active support:

2023–2025 Swarbrick A, **O'Toole S**, Grimmond S, Perou C, Reddell R, Lundeberg J. National Breast Cancer Foundation Investigator Initiated Research grant "Genomic and proteomic mapping of breast cancer ecosystems".

2022–2024 Swarbrick A, Janes K, **O'Toole S.** National Breast Cancer Foundation Investigator Initiated Research grant "Targeting B cells for breast cancer immunotherapy" .

2022-2024 Herrmann D, Zanin-Zhorov A, **O'Toole S**. National Health and Medical Research Council Ideas grant "Single-cell intravital imaging guides anti-fibrotic therapy to improve standard-of-care treatment in triple negative breast cancer"

2022-2023 Roden D, Swarbrick A, Lim E, **O'Toole S**. National Breast Cancer Foundation Investigator Initiated Research grant "Unravelling cellular and spatial heterogeneity in human breast cancers" .

2022–2023 Parker B, Loi S, **O'Toole S**, Mann GB. National Breast Cancer Foundation Investigator Initiated Research grant. "Development of microenvironment-based biomarkers for predicting early breast cancer recurrence" .

NAME: ***PROF MICHAEL SAMUEL***

Change to inactive support:
VONBRI & The Hospital Research Foundations
1st Jan 2018 – 31st Dec 2021
Title: "Targeting ROCK-mediated microenvironment changes as a novel colorectal cancer therapy"

Change to active support:
Vonbri Foundation
1st Jan 2023-31st December 2024
Title: Targeting the microenvironment to optimise colorectal cancer therapy

AusHealth
1st July 2022 – 30th June 2023
Title:

Cancer Council SA
1st Jan 2023- 31st December 2023
Title: Exploiting the tumour secretome: does functional relevance yield predictive power?

NAME: ***MS VANESSA KILLEN***

No change.

NAME: ***MS JAN MUMFORD***

No change.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: University of South Australia
Location of Organization: Adelaide, Australia
Partner's contribution to the project: Collaboration (exchange of protocols to assess ROCK2 downstream signaling)

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

None.