The Avner Pancreatic Cancer Foundation Funding Agreement

This Funding Agreement incorporates Avner Pancreatic Cancer Foundation Standard Grant Terms and Conditions (referred to in this document as the "**Standard Terms**"). Please read this document and the Standard Terms together carefully before signing where indicated. On signing, you agree to be bound by the terms of this Funding Agreement and the Standard Terms.

The left-most column of the below table guides you to those clauses of the Standard Terms that are most applicable to the subject matter being described in the other columns. Please note however that the clause references are a guide only and that any clause should be read in the context of the full set of Standard Terms and this Funding Agreement.

Most applicable clauses from the Standard Terms	**Matter**	**Details**
1.1,1.2 and 20.4	**Avner Pancreatic Cancer Foundation (referred to as "Foundation")**	**AVNER PANCREATIC CANCER FOUNDATION LIMITED** ABN: 22 145 513 060 PO Box 1216 Manly NSW 1655 Our Relationship Manager: **Caroline Kelly** **M** 0415 503 971 **E** info@avnersfoundation.org.au Notices: Service of notices under the Standard Terms and this Funding Agreement are to be directed to: **Caroline Kelly** **M:** 0415 503 971 **E:** info@avnersfoundation.org.au
1.1, 1.2 and 20.4	**Curtin University of Technology (referred to as "Grant Recipient")**	**CURTIN UNIVERSITY OF TECHNOLOGY** ABN: 99 143 842 569 Kent Street, Bentley, Perth, WA 6102 Your Relationship Manager: Paula Haslehurst Position: Research Support P: (08) 9266 3456 | E: ORD-Support-HTH@curtin.edu.au Notices: Service of notices under the Standard Terms and this Funding Agreement are to be

		directed to: **Mr Charlie Thorn**, Director, Office of Research and Development P: (08) 9266 9062 | E: Director.Research@Curtin.edu.au
2.1	**Standard Terms apply**	Foundation Standard Grant Terms and Conditions apply to and are part of this Funding Agreement. Capitalised terms used in the Standard Terms have the same meaning within this Funding Agreement.
1.2	**Project**	***A novel therapeutic target in pancreatic cancer: Implications for therapy and diagnosis*** Project details are in accordance with the APCF00170616 Curtin University Grant Application (Appendix A)
2.2 and 17.2	**Project start date**	This Funding Agreement starts on the date this Funding Agreement is signed by both parties
2.3 and 17.3	**Project end date**	The Project to which this Funding Agreement relates will be completed by 31 December 2019
3.3	**Objectives and outcomes**	As described in Appendix A and outlined below AIMS (Specific) 1. To validate the ABCC3-GPR55 axis as a potential target for PDAC therapies. 2. To reveal the mechanisms that govern the expression of ABCC3 and GPR55 3. To study the mechanisms by which GPR55 and ABCC3-related pathways induce pancreatic cancer progression. AIM (Overall) 1. To investigate the effect of different inhibitors of ABCC3 and GPR55 on PDAC cell proliferation and progression, both in vitro and in vivo
3, 5.2 and 8.2	**Grant Recipient obligations**	The Grant Recipient will meet the activities outlined in rows 1 to 17 in Schedule 1 within the timelines specified in column C and no later than the dates outlined in column E. An extension beyond the deadlines outlined in column E can only be undertaken with agreement by the Foundation. The Grant Recipient will work with the Foundation from time to time to promote the initiative being supported by the Foundation. This will include, but is not limited to the provision of a speaker for events and editorial content for communication purposes. The Grant Recipient agrees that funding is dependent on appropriate approvals being in place as outlined in Appendix A. The Foundation is to be notified when approvals are granted, cease

		or require amendment.
6	**Funding provided by the Grant Recipient**	Not applicable
7	**Other resources provided by the Grant Recipient**	The Grant Recipient must provide the resources required to properly deliver and manage the Project to a high professional standard including as described by the Grant Recipient in the Grant Funding Application form.
6 and 10	**Funding provided by the Foundation**	The Foundation will provide a total of **$674,251.79** (excl GST) for the Project, split over a number of tranches. Unless otherwise agreed by the parties, on receipt of a valid tax invoice the Foundation will transfer the amount specified in Column F of the table in schedule 1 to the Grant Recipient provided that the activity described in the corresponding Column B and all preceding activities have been completed by no later than the date specified in Column E. Grant Recipient bank account details: Account name: Curtin University of Technology BSB: 306 065 Account number: 4643333
7	**Other resources provided by the Foundation**	Not applicable
5.3 and 10	Fees	Not applicable
6.7	Duty to account	The Grant recipient is to provide an acquittal statement to the Foundation with each end of year report detailing the expenditure of grant funds for the delivery of the Project.
8	**Working with children and vulnerable people**	Standard Terms apply
9	**Review and evaluation**	Standard Terms apply
4.1	**Reports**	The reports described in schedule 1, Column B, Rows 6, 9, 10, 11 and 17 must be provided to the Foundation in a readily readable format using widely accepted word processing and spreadsheet software. The Grant Recipient must use all reasonable endeavours to provide the Foundation with information in the report format provided by the Foundation from time to time. The Grant Recipient is to report against the achievement of and progress towards activities outlined in column B of schedule 1.

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>4.2</td><td>Meetings</td><td>Standard Terms apply</td></tr>
<tr><td>12.1</td><td>Intellectual property provided by the Foundation</td><td>Standard Terms apply</td></tr>
<tr><td>12.2</td><td>Intellectual property provided by the Grant Recipient</td><td>Standard Terms apply</td></tr>
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<tr><td>14</td><td>Collection and use of information</td><td>Standard Terms apply</td></tr>
<tr><td>14</td><td>Confidentiality and Personal information</td><td>Standard Terms apply</td></tr>
<tr><td>11.1</td><td>Acknowledgement of support and use of branding etc by the Grant Recipient</td><td>The Grant Recipient must acknowledge the financial assistance provided by the Foundation. By acknowledging this support, the Grant Recipient is informing the community appropriately about how Foundation funding is being used.

The Grant Recipient must acknowledge the Foundation in all publicity relating to funded activities/operations directly related to the Project. This includes word acknowledgment and logo acknowledgment.

Word acknowledgement should be:
This project is made possible by an Avner Pancreatic Cancer Foundation grant
www.avnersfoundation.org.au

Logo acknowledgement will be in line with the 2015 Foundation brand guidelines as per Clause 11.1. Grant recipients are to have read and acknowledged the brand guidelines as part of this agreement.

Foundation funding for the Project is to be acknowledged in:

<table>
<tr><td>Activities/operations directly related to the Project</td><td>Word acknowledgement</td><td>Logo acknowledgement</td></tr>
<tr><td>Publications</td><td>✓</td><td></td></tr>
<tr><td>Media releases</td><td>✓</td><td>✓</td></tr>
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		<table><tr><td>Speeches /public announcements</td><td>✓</td><td>✓</td></tr><tr><td>Annual Reports</td><td></td><td></td></tr><tr><td>Promotional videos</td><td></td><td>✓</td></tr><tr><td>Television and newspaper advertisements</td><td>✓</td><td>✓</td></tr><tr><td>Newsletters</td><td>✓</td><td>✓</td></tr><tr><td>Print and electronic promotional materials (such as brochures, posters, conference programs, performance programs and invitations)</td><td>✓</td><td>✓</td></tr><tr><td>Signage at promotional events</td><td></td><td>✓</td></tr><tr><td>Websites</td><td>✓</td><td>✓</td></tr><tr><td>Correspondence (such as email signatures)</td><td>✓</td><td></td></tr></table>
11.2	**Acknowledgement of support and use of branding etc by the Foundation**	Standard Terms apply **Summary for public release:** The following descriptor of the purpose and expected outcome of the project will be used in media or other publicity material. *We have discovered that a protein named GPR55 promotes pancreatic cancer growth. Our preliminary data demonstrates that a GPR55 inhibitor, in combination with a drug used in therapy, is able to increase survival in mice that develop pancreatic cancer. Our plan is to identify more potent drug combinations to treat pancreatic cancer and also identify new marker that will enable the earlier diagnosis of pancreatic cancer.* The summary can be adjusted with the prior written agreement of the parties
3.2, 6.4, 17.4 and 17.5	**Timeline and deadlines**	The Grant Recipient must comply with the timelines set out in Column C, schedule 1 and the corresponding deadlines in Column E, schedule 1 to this Funding Agreement. Any departure from the above timelines and deadlines as outlined in schedule 1 must be agreed upon between the Foundation and the Grant Recipient.
17.5	**Termination of a funding agreement with notice**	Standard Terms apply
16.1	**Loss suffered**	Standard Terms apply
16.2	**Liability limit**	Standard Terms apply

16.3	**Required Insurance**	In addition to the standard terms the Grant Recipient must hold the following insurance to at least the level of cover listed: • Public Liability $10,000,000 • Professional Indemnity $10,000,000 • Workers compensation as required by law
14.2, 20.2	**Subcontracting**	Standard Terms apply
20.1	**Nominated Governing Law State**	New South Wales
2.4	**Special Conditions**	The Grant Recipient must not expend any of the funding on the following without the prior consent of the Foundation: • Institutional overhead costs, including ongoing operating costs of the organisation, in excess of 10% of the grant funds • Attendance at events or conferences, prizes or award ceremonies • Feasibility studies for the project • Marketing and communication costs • Central administrative support • Travel of investigators on activities that are not inherent in the project • Website development unless this is inherent in the project The Grant Recipient agrees that the Principal Investigator of this project is: Dr Marco Falasca Professor Curtin University, School of Biomedical Sciences P 08 9266 9712 E marco.falasca@curtin.edu.au The Foundation may terminate this Funding Agreement immediately if the Grant Recipient: fails to give the Foundation reasonable notice of any change in Principal Investigator in writing, or fails to find a suitable replacement Principal Investigator within the timeframe agreed between the parties in writing.

SIGNED by an authorised person on behalf of **Avner Pancreatic Cancer Foundation** in the presence of the witness named below:

CarolineKelly

Print Name: Caroline Kelly

Position: Chief Executive Officer

Date: 14/11/16

Witness Name: Philippa Marston

SIGNED by an authorised person on behalf of **Curtin University of Technology** in the presence of the witness named below:

Print Name:

PROFESSOR CHRIS MORAN
Deputy Vice-Chancellor, Research
Curtin University

Position:

Date: 8.11.2016

Witness Name:

JO CLEMENTS - Executive Assistant
Deputy Vice-Chancellor, Research
Curtin University

Schedule 1 - Project Activities, Milestones, Deadlines and Funding Schedule

	A	B	C	D	E	F
	Invoice ref number	Activities	Timelines* (as per Appendix A)	Milestone	Deadline^	Amount (excl GST)
1		1. Signing of agreement	-	-	14 Nov 2016	-
2	R2 MF 1.1	2. Foundation notified of animal ethics approval being granted for the project	-	Y	31 Dec 2016	$134,800
3		3. Advertise for Research Assistant (RA)	Jan 2017	-	31 Jan 2017	-
4		4. Appointment and training of RA in specialised techniques	Feb 2017	-	28 Feb 2017	-
5		5. Investigation of the effect of novel CBD combinations in vitro	Feb – Aug 2017	-	31 Aug 2017	-
6	R2 MF 1.2	6. Yr. 1 funding report to Foundation	-	Y	15 Dec 2017	$134,800
7		7. Investigation of the effect of novel CBD combinations in KPC mice	Sept 2017- Mar 2018	-	31 Mar 2018	-
8		8. Investigation of the effect of novel CBD combinations in PDX model	Jan 2018 – May 2018	-	31 May 2018	-
9	R2 MF 1.3	9. Yr. 2 interim report to Foundation	-	Y	30 June 2018	$134,800
10	R2 MF 1.4	10. Yr. 2 funding report to Foundation	-	Y	1 Nov 2017	$67,400
11	R2 MF 1.5	11. Interim Yr. 3 report to Foundation	-	Y	30 Jun 2018	$67,400
12		12. Investigation of the mechanism of action of the GEM+CBD combination	Feb 2017 – Dec 2018	-	31 Dec 2018	-
13		13. Investigation of LPI production in pancreatic cancer cell lines	Jun 2018 – Dec 2018	-	31 Dec 2018	-
14		14. Investigation of LPI production in plasma and urine samples from transgenic mouse model of PDAC	Jan 2019 – Jun 2019	-	30 Jun 2019	-
15		15. Project editorial piece for public release	-	Y	30 Sept 2019	-

16		16. Investigation of LPI production in plasma and urine samples from normal and pancreatic cancer patients	July 2019 – Dec 2019	-	**31 Dec 2019**	-
17	R2 MF 1.6	17. Final project report submitted to Foundation	-	**Y**	**31 Dec 2019**	**$135,051.79**
					TOTAL	**$674,251.79**

*As specified by the Grant Recipient in the grant application, ^ Date set by the Foundation

Avner Pancreatic Cancer Foundation Standard Grant Terms and Conditions

Please read these standard terms and conditions carefully. These standard terms and conditions incorporate and should be read together with, each of the Avner Pancreatic Cancer Foundation Funding Agreements ("**Funding Agreements**"). On execution of a separate Funding Agreement, the terms of these standard terms and conditions, will become binding on you and together with the Funding Agreement, will govern the relationship between us, and the relevant project.

1 Introduction and definitions

1.1 **Parties**: These standard terms and conditions (referred to within this document as "Standard Terms") apply to the Avner Pancreatic Cancer Foundation with ABN 22 145 513 060 (referred to in this document as "Foundation", "we", "our" or "us") and each grant recipient named in a Funding Agreement (referred to in this document as "Grant Recipient", "you" or "your"). If the context requires each Grant Recipient and the Foundation may each be referred to as a "party" or referred to together as the "parties".

1.2 **Definitions**: In these Standard Terms:

- "Confidential Information" of a party means all information of that party which is by its nature confidential, is designated by that party as confidential or which another party knows or reasonably ought to know is confidential.
- "Funding Agreement" means the document entitled "Avner Pancreatic Cancer Foundation Funding Agreement " that sets out the specific terms, conditions and details of a Project and that may include objectives, timelines, funding, obligations and other information relating to the implementation, running and evaluation of that Project.
- "Project" means a project, program, initiative or other arrangement funded or resourced by the Foundation (in whole or in part); and
- "Relationship manager" means the person identified as such in the Funding Agreement or as otherwise notified to the other party from time to time.
- "Third Party Provider" means any entity that provides funding, property, personnel or other resource in connection with a Project other than the Foundation and the Grant Recipient.

2 Special conditions and the application and duration of these Standard Terms

2.1 **Standard Terms part of Funding Agreement**: These Standard Terms are part of, and should always be read together with, each Funding Agreement.

2.2 **Start Date**: These Standard Terms commence on the date a Funding Agreement has been signed by both parties or, if the Funding Agreement specifies a different date, on that date.

2.3 **End date**: Except for those terms and conditions that, by their nature, continue after a Funding Agreement ends, these Standard Terms stop applying with respect to a particular Funding Agreement when that Funding Agreement ends.

2.4 **Special conditions**: Each party must comply with any special conditions set out in the relevant Funding Agreement.

2.5 **Differences between the Standard Terms and a Funding Agreement**: Sometimes the terms and conditions of a Funding Agreement will be different from these Standard Terms. If so, these Standard Terms will apply to the exclusion of any inconsistency, unless a Funding Agreement specifically states otherwise.

3 Performance of obligations

3.1 **Standard of performance**: Each party agrees to perform its obligations under these Standard Terms and each Funding Agreement in accordance with the law, with care and skill and to the best of its ability.

3.2 **Time**: Each party agrees to:

- Perform its obligations under these Standard Terms and each Funding Agreement in a diligent, efficient and timely manner; and
- Follow any Project timeline and meet any of its designated targets and deadlines that may be described in a Funding Agreement.

3.3 **Objectives and outcomes: You must** strive at all times and in good faith to meet any objectives or outcomes described in a Funding Agreement.

4 Reports, meetings and inspections

4.1 **Reports**: You agree to keep us informed of the progress of each Project and to provide us with any report (including any financial report) described in a Funding Agreement by the times and in the format specified.

4.2 **Meetings**: The parties will meet as specified within a Funding Agreement and at any other time as may be reasonably requested by us. Unless otherwise agreed, all meetings will be held at the address or by the method specified in the relevant Funding Agreement.

4.3 **Inspections**: You agree to allow us to inspect your premises and inspect any books, accounts and records but only:

- If the inspection is connected with these Standard Terms or a relevant Funding Agreement;
- Upon reasonable notice and within usual working hours; and
- So long as such inspection will not breach your confidentiality or privacy obligations.

5 Services and staff

5.1 **Introduction**: The development, implementation, running and evaluation of a Project may involve the provision of certain services or the commitment of certain human resources by either or both of the parties. The nature of the services to be provided and who will provide them, the number of people to be committed to the Project, the level of experience and skill required, the duties and tasks to be performed, the number of hours or days to be committed, which party is to commit the resources and where the resources are to be deployed and other details will vary depending on the Project and, if required, will be described in the relevant Funding Agreement.

5.2 **Obligations**: When receiving services or hosting one or more persons, you will ensure that each such service provider and each person is:

- Treated with respect and dignity;
- Supplied with a safe and healthy work environment;

- Not subject to any workplace discrimination, abuse, bullying or harassment; and
- Given all reasonable access, assistance, materials and co-operation needed to perform the services or to fulfil the person's agreed duties.

5.3 **Fees**: whether or not fees are to be paid in connection with the provision of services or the hosting of one or more persons and the amount of such fees will depend on each Project and will, if required, be described in a Funding Agreement.

6 Funding

6.1 **Introduction**: the amount of funding provided for or towards a Project by each party and when, where and for what purpose the funds are provided will depend on the nature of the Project. Each Funding Agreement will provide more detail.

6.2 **Payment of funds**: Subject to clause 10.2, each party agrees to pay the funds it has committed to a Project in accordance with the arrangements described in a Funding Agreement or as otherwise agreed by the parties.

6.3 **Use of funds**: You must, and must ensure that those working with and for you:

- Use any funds received in connection with a Project in accordance with these Standard Terms and any corresponding Funding Agreement which may include a specific budget, timeline and/or targets; and
- Do not lose, steal or misappropriate any funds received in connection with any Project or otherwise use such funds in a fraudulent or unlawful way.

6.4 **Withholding and stopping funding**: We may withhold or stop any or all of the funding we have agreed to commit to one or more Projects if you do not carry out your obligations in accordance with these Standard Terms or a relevant Funding Agreement. You acknowledge that some Projects may involve multiple payments, each tied to certain targets or a certain timeline, and agree that failure to follow any timeline or to meet one or more targets may result in us withholding or stopping one or more payments or withdrawing the funding altogether.

6.5 **Repaying the funding**: You agree to repay the funding (or the relevant part of it) if we overpay you or pay you an amount you are not entitled to, if you fail to use the funding provided in the way required under the corresponding Funding Agreement or if you spend an amount in a way inconsistent with or in contravention of these Standard Terms or the terms of the Funding Agreement under which the funds were provided. You agree to repay any amount within 14 days after you have been notified and that we may charge interest on any amount that is outstanding for more than 14 days calculated at 5% on a daily compound basis. We may recover the amount and any interest as a debt due to us including by deducting it from amounts we are yet to pay under a current or future Funding Agreement.

6.6 **Conflict with Third Party Provider**: You agree to promptly notify us of any conflict that arises, or could arise, between your obligations under an arrangement with any Third Party Provider and your obligations under these Standard Terms or a Funding Agreement.

6.7 **Duty to Account**: We may request that you account for any funds you receive from us in connection with one or more Projects by, for instance, providing receipts and invoices relating to the use of the Funds. If we do ask you to account, you will do so in accordance with any request.

7 Support and resources

7.1 **Introduction**: The type and amount of non-monetary support and resources each party is to contribute to a Project and whether or not a fee is payable for the contribution will depend on

the nature of the Project. The non-monetary support and resources may be provided on its own or together with funding. Each Funding Agreement will provide more detail.

7.2 **Use of resources**: You must, and must ensure that those working with and for you:

- Use any property or other resources received in connection with a Project in accordance with these Standard Terms and the corresponding Funding Agreement; and
- Do not lose, steal, damage or misuse any property or other resources received in connection with any Project or otherwise use such property or other resources in a fraudulent or unlawful way.

8 Working with children and Vulnerable People

8.1 **Vulnerable person**: For the purpose of this clause, "Vulnerable Person" means:

- An individual under the age of 18; or
- An individual aged 18 years and above who is or may be, unable to take care of themselves or is unable to protect themselves against harm or exploitation for any reason, for instance, because of that persons illness, trauma or disability.

8.2 **Obligations**: You must, and must ensure that all those working with and for you (including each of your officers, employees, contractors and volunteers) and who are involved in working with or contacting children and Vulnerable People in connection with a Project:

- Undertake all applicable checks including a criminal record check;
- Are not prohibited by any Commonwealth, State or Territory law from being engaged in a capacity where they may have contact with children or Vulnerable Persons;
- Comply with all applicable laws; and
- Comply with any specific obligations and requirements relating to working with and contacting children and vulnerable people described in the relevant Funding Agreement.

9 Review and evaluation

9.1 **Acknowledgements**: You acknowledge that:

- Projects often require, or benefit from, evaluation and review; and
- The funding provided to a Project may sometimes be subject to certain terms and conditions relating to the evaluation and review of a Project;

9.2 **Review and evaluation**: You agree that any Project may be reviewed or evaluated:

- In accordance with a Funding Agreement;
- As reasonably directed by us from time to time; and
- Even if the Project has been completed or has otherwise ended.

10 Fees, Funding and GST

10.1 **Fees**: Each party agrees to pay any fees owing to the other party within 30 days after receipt of a valid tax invoice from that party.

10.2 **Funding:** Notwithstanding anything else in these Standard Terms, but subject to the terms of a Funding Agreement, We will pay you the agreed funding amounts within 14 days after the receipt of a valid tax invoice.

10.3 **GST**: Any consideration or amount payable in connection with these Standard Terms or a Funding Agreement including any non-monetary consideration (**Consideration**) is inclusive of GST.

If GST is or becomes payable on a Supply made under or in connection with these Standard Terms or a Funding Agreement, the party providing the Consideration for that Supply must pay an additional amount to the party making that Supply (**Supplier**) equal to the amount of GST payable on that Supply as calculated by the Supplier in accordance with the GST Law (**Additional Amount**). The Additional Amount is payable at the same time and in the same manner as the Consideration for the Supply.

11 Acknowledgement of support, use of brand and announcements

11.1 **Our support and branding**: If you wish to use our name, logo or other branding or acknowledge our involvement in a Project, or if we require this of you, you agree to follow the terms of the relevant Funding Agreement and any brand guidelines we may provide you from time to time. You may use our name, logo and other branding in other ways but only after first obtaining our written approval.

11.2 **Your support and branding**: If we wish to use your name, logo or other branding or acknowledge your involvement in a Project, we agree to follow the terms of the relevant Funding Agreement and any brand guidelines you may provide us from time to time. We may use your name, logo and other branding in other ways but only after first obtaining your written approval.

11.3 **Third Party Provider branding**: If a Project is supported or funded by a Third Party Provider and that Third Party Provider is known prior to the start of the Project then you must:

- provide us with details about the proposed use of that Third Party Provider's name, logo and other branding;
- work with us in good faith to agree on how that Third Party Provider's name, logo and other branding are to be used in connection with the Project and ensure that any agreement between you and that Third Party Provider properly reflects the agreed position.

If a Third Party Provider becomes involved with a Project after that Project has started, then you may not use that Third Party Provider's name, logo or other branding without first obtaining our prior written approval.

11.4 **Announcements and releases**: you must not make press or other announcements or releases relating to a Project or a Funding Agreement without our prior approval unless the announcement or release is permitted under the corresponding Funding Agreement or is required by law.

12 Intellectual Property

12.1 **Intellectual property provided by us**: We retain ownership over any pre-existing documents and other materials that we contribute to a Project (referred to as "**Foundation IP**"). You may use Foundation IP for your own internal purposes, as may be described in a Funding Agreement and as otherwise agreed by us first in writing.

12.2 **Intellectual property provided by you**: You retain ownership over any pre-existing documents or other materials you contribute to a Project (referred to as "**Grant Recipient IP**"). You agree we may use the Grant Recipient IP for our own internal purposes, as may be described in an applicable Funding Agreement and as otherwise agreed by you first in writing.

12.3 **New intellectual property**: Any intellectual property resulting from a Project (referred to as "**New IP**") will be owned by the Grant Recipient unless otherwise stated in a Funding Agreement.

12.4 **License to Foundation**: The Grant Recipient hereby grants the Foundation a worldwide, irrevocable, royalty-free, perpetual, non-exclusive license to use all New IP for its own internal purposes, including to aid it in its work by, among other things, when working with other grant recipients on other Projects, and to sublicense the New IP to another grant recipient in circumstances contemplated by clause 17.7.

12.5 **Third party intellectual property rights**: Each party agrees to reimburse the other party for any loss or damage it incurs because of a legitimate claim by a third party that the use of Foundation IP or Grant Recipient IP (as the case may be) has breached that third party's intellectual property rights.

12.6 **Consents**: Each party will, if required under a Funding Agreement, ensure that each contributor to a Project or the materials associated with a Project waives all Moral rights that person may have in the Project or the materials associated with a Project in favour of the person or entity stated in that written request.

13 Property

13.1 **Title to property**: The title to any equipment or other property we contribute to a Project, or provide to you for use in connection with any Project (referred to as "**Foundation Property**") remains with us unless otherwise specified in a Funding Agreement.

13.2 **Use of property**: You must not, and must ensure that those working with and for you do not, sell or part with possession of the Foundation Property without our prior written consent. You must, and must ensure that all those working with and for you:

- Only use the Foundation Property for the purpose of fulfilling or completing the Project for which the property was provided;
- Keep the Foundation Property free of encumbrances, separate from other goods and marked to clearly indicate that the property belongs to us; and
- Keep the Foundation Property in clean and good condition.

14 Confidentiality and Privacy

14.1 **Collection and use of confidential information**: Each party must maintain the confidentiality of the terms of each Funding Agreement and the other party's Confidential

Information and must only use such Confidential Information to perform its obligations or exercise its rights under these Standard Terms and any relevant Funding Agreement.

14.2 Disclosure of Confidential Information: A party may not disclose the Confidential Information of the other party to any person except:

- To any of its advisors, employees, volunteers, officers, directors and subcontractors requiring that information in connection with these Standard Terms, a Project or a Funding Agreement;
- With the consent of the Party who supplied the information which consent may be given or withheld in that party's absolute discretion;
- Where required by law or a stock exchange or in connection with legal proceedings but only to the extent required;
- Where the Confidential Information is in the public domain or already known by the recipient without a breach of this paragraph; or
- Where the Confidential Information has been independently created, developed or acquired by the recipient without breach of this paragraph.

14.3 Confidentiality: You must, if required under a Funding Agreement or as we may otherwise reasonably require, arrange for your officers, employees, contractors and volunteers engaged in the applicable Project to give written confidential undertakings relating to the use and non-disclosure of any confidential information. If required, you agree to use the form of confidentiality deed or other document we provide for that purpose.

14.4 Personal Information: Each party will ensure that any personal information collected, processed, used, disclosed or transferred in connection with these Standard Terms, a Funding Agreement or a Project is handled in accordance with all relevant privacy legislation.

15 Conflicts of interest

You must, and must ensure that all those working with and for you, properly identify, disclose and manage all conflicts of interest that arise in connection with, or in relation to, a Project in accordance with proper governance practices and the law. Any conflict that does, or could, directly affect the outcome or progress of the Project or that could damage our reputation must be notified to us in writing within 5 days after the date you become aware of the conflict.

16 Loss, damage and insurance

16.1 Loss suffered: Each party (referred to as the "**Offending Party**") agrees to reimburse the other party for any loss it suffers as a direct result of:

- A breach by the Offending Party of its obligations under these Standard Terms or a Funding Agreement; and
- Personal injury or death of any person caused by the Offending Party or others working with or for it in connection with a Project.

16.2 Maximum amount of reimbursement: Unless otherwise specified in a Funding Agreement, the maximum amount payable by any party to any other party for loss arising out of or in connection with a Project is the total amount of funding actually provided for that Project.

16.3 Insurance: In addition to any specific insurance requirements that may be required under a Funding Agreement, The Grant Recipient must obtain and maintain all necessary and appropriate insurances for each Project during the term of a Funding Agreement and for a period of 12 months after the expiry or termination of that Funding Agreement. The Grant

Recipient agrees to promptly provide the Foundation with evidence of the currency of that insurance upon request.

17 Term and termination

17.1 Introduction: Clause 2 of these Standard Terms provides that these Standard Terms continue to apply for so long as one or more Funding Agreements are in operation. As such it is important to understand when a Funding Agreement starts and ends.

17.2 Start date: A Funding Agreement starts on the date that Funding Agreement has been signed by both parties or, if the Funding Agreement specifies a different date, on that date.

17.3 End date: a Funding Agreement terminates on the earlier of:

- The date on which the Project to which that Funding Agreement relates has been completed and
- The date on which that Funding Agreement is terminated in accordance with clause 17.4 or 17.5.

17.4 Termination of a Funding Agreement immediately: A party may terminate a Funding Agreement immediately upon notice in writing to the other party if that other party:

- Breaches a material term of a Funding Agreement or these Standard Terms and does not remedy the breach within 14 days of receipt of a notice specifying the breach and requiring it to be remedied; or
- Becomes or resolves to become subject to any form of insolvency, administration, receivership, liquidation, bankruptcy or similar.

17.5 Termination of a Funding Agreement with notice: We may terminate a Funding Agreement by giving you at least seven days' notice if:

- you do not comply with a timeline or meet a deadline specified in that Funding Agreement;
- you do not complete the Project by the completion date specified in that Funding Agreement or such later date as agreed between the parties; or
- you damage our reputation or, in our reasonable opinion, the continuation of the Project or our continued association with you is likely to damage our reputation.

17.6 Transition and wind-down: The relationship managers agree to meet as soon as practicable after the parties become aware that a Project is to be terminated for the purpose of:

- Devising an appropriate exit strategy for the Project which may include the transition to another organisation; and
- Minimising, so far as is possible, the effect that the termination may have on each party and any end user or recipient of goods, services or funding under that Project.

17.7 Assistance with transition: If a Project is, or is to be, terminated, we may nominate another organisation to continue that Project. If we do, each party will provide reasonable assistance with the transition of the Project even if such assistance is required beyond the date on which the relevant Funding Agreement is terminated, including:

- transferring by way of assignment any New IP to that organisation; and

- providing that organisation with a worldwide, royalty-free, irrevocable, perpetual, non-exclusive license to use all Grant Recipient IP necessary for that organisation to properly continue that Project.

-

17.8 Return or destruction of Confidential Information: Upon termination or expiry of a Funding Agreement, each party must promptly return the Confidential Information of the other party relating to that Funding Agreement or, if directed to do so by the other party, destroy it.

17.9 Return of Property: As soon as practicable after a Funding Agreement has expired or been terminated you must, and must ensure that those working with and for you, return the Foundation Property to us unless we decide otherwise.

17.10 Survival: all Terms of the Standard Terms and each Funding Agreement that by their nature are intended to survive termination will survive termination.

18 Changes to Projects

18.1 Introduction: Each party understands and acknowledges that:

- Things can happen from time to time that will, or could, delay or stop a Project, result in the change to the scope or nature of a Project or result in a Project no longer being possible at all (referred to as "**Project Change**"); and

- Some Projects have been funded or resourced for a specific purpose or out of a particular funding stream and that changes to a Project may not always be possible or desirable.

18.2 Project Change: You must let us know of any circumstances that have, or could, result in a Project Change as soon as practicable, but no more than 7 days, after you become aware of such circumstances. You must meet with us as soon as practicable, but no more than 7 days, after notifying us of any circumstances that have, or could, result in a Project Change. Notification of a Project Change should consider, among other things:

- The details of, and reasons for, a Project Change;

- What effect, if any, a Project Change could have on other Projects;

- Strategies on how to remove or limit any negative effect of a Project Change;

- If relevant, a proposed new completion date for the Project or Projects; and

- Any criteria under which the funding or resources were granted.

19 Managing disputes

19.1 Resolution through relationship manager: Where possible, a dispute arising in relation to these Standard Terms or a Funding Agreement, should be resolved between the most relevant relationship managers of each party.

19.2 Notice of dispute: If a dispute arises in relation to these Standard Terms or a Funding Agreement, and it is not possible for the dispute to be resolved by the relationship managers, the party claiming that a dispute has arisen must give written notice to the other party indicating the nature of the dispute (referred to as a "**Dispute Notice**").

19.3 Resolving the dispute: A senior representative of each party must meet and attempt to resolve the dispute within 5 business days after receipt of the Dispute Notice. If within a

further 5 business days the parties are unable to resolve the dispute, the Chief Executive Officer of each party (or his or her nominee) must meet and attempt to resolve the dispute.

19.4 **Dispute not resolved**: If, within 15 business days after receipt of the Dispute Notice, the parties are unable to resolve the dispute, the parties may take whatever action they consider necessary to resolve the dispute.

19.5 **Injunctive relief**: Nothing in this clause prevents a party from issuing proceedings seeking urgent injunctive relief.

20 General

20.1 Each Funding Agreement, together with these Standard Terms, is governed by the laws of the state designated in the Funding Agreement and each party irrevocably and unconditionally submits to the exclusive jurisdiction of the courts of that state. These terms supersede all previous agreements about their subject matter and embody the entire agreement between the parties. Neither party will be liable for any failure to perform its obligations under these terms where that performance is delayed, prevented, restricted or interfered with for any reason outside that party's control. No rule of construction applies to the disadvantage of a party because that party was responsible for the preparation of these terms. The rights of a party under these terms are in addition to and do not exclude or limit any other rights or remedies provided by law. If any part of these terms and conditions is held to be unenforceable, the unenforceable part is to be given effect to the greatest extent possible and the remainder will remain in full force and effect. No, amendment or addition to these Standard Terms or a Funding Agreement is binding unless in writing and signed by an authorised representative of each party.

20.2 **Assignment and subcontracting**: Unless specified in a Funding Agreement, no party can assign, subcontract or novate its rights or liabilities under these Standard Terms or a Funding Agreement without the prior written consent of the other party, such consent not to be unreasonably withheld or delayed.

20.3 **Legal Relationship**: Except as expressly provided in these Standard Terms or a Funding Agreement:

- Nothing in these Standard Terms or a Funding Agreement is intended to constitute a fiduciary relationship or an agency, partnership or trust; and
- No party has authority to bind any other party.

20.4 **Notices**: Any written notice given in connection with these Standard Terms or a Funding Agreement must be given by emailing the notice to the email address of the other party set out in the Funding Agreement.

20.5 **Counterparts**: These Standard Terms and a Funding Agreement may be executed in any number of counterparts, each of which, when executed, is an original. Those counterparts together make one instrument.

20.6 **Interpretation**: Where a word or phrase is given a particular meaning, other parts of speech and grammatical forms of that word or phrase have corresponding meanings. A monetary amount is in Australian dollars. Phrases such as "for example", "for instance" and "such as" are not, and should not be interpreted to be, words of limitation unless the context otherwise requires.

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Grant Application Form

All applications for funding MUST be submitted on the following application form. Failure to do so will render your application ineligible:

Date: 22/7/2016

Type of Grant:
Please indicate the type of grant you are applying for:

Accelerator Grant ☒ **Innovation Grant** ☐

SECTION 1 – APPLICANT DETAILS			
Organisation name:	Curtin University		
Postal address:	Curtin University, School of Biomedical Sciences, CHIRI Biosciences GPO Box, Perth Western Australia 6845 Australia		
Street Address	Kent Street, Bentley Campus Perth Western Australia 6102 Australia		
Suburb:	Bentley		
State:	WA	**Post code:**	6102
GST registered	Yes ☒	No ☐	

SECTION 2 – PREFERRED CONTACT PERSON *All application correspondence will be directed to this person*				
Title:	Dr ☒	Mr ☐	Mrs ☐	Ms ☐
Name:	**Firstname:**	Marco		
	Surname:	Falasca		
Position Held:	Professor			
Business Phone:	0892669712			
Email:	marco.falasca@curtin.edu.au			
Postal Address: *If different from above*	As above			
Suburb:				
State:			**Post code:**	

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SECTION 3 – THE PROJECT

Project Title:	A novel therapeutic target in pancreatic cancer: Implications for therapy and diagnosis
Project Status:	**New** ☒ **Ongoing** ☐

Application Status:

Is this application a resubmission, renewal or revision of an existing project? Has the project or other projects with major overlaps been previously rejected by any other funding sources? (Please provide detail)

This is a new project

Submission to other funding sources for this project: *List the names of the other funding source(s) and the amount(s) requested/received in the past 5 years. Include already submitted and pending applications*	NHMRC 2016 $552,299.10 (pending application)
Amount requested: *(ex GST)*	$674,251.79

Project summary: *(limited to two A4 pages)*

Please include:

- *A summary of your research question*
- *What you hope to achieve/goals*
- *Some background to the project including references where applicable*

Summary of research question

. Following our recent discovery of a new drug combination able to increase threefold the life of mice with pancreatic cancer, is it possible to find an even better drug combination and progress to human trial?

. Can we unravel the mechanisms leading to the efficacy of our new drug combination opening the path for developing new additional treatments for Pancreatic Ductal AdenoCarcinoma (PDAC)?

. Can a specific species of lysophosphatidylinositol (LPI) be used as a biomarker and work as a predicting tool for PDAC?

Goals

We aim to validate the ABCC3-GPR55 axis as a potential target for PDAC therapies. We want to reveal the mechanisms that govern the expression of ABCC3 and GPR55, and to study the mechanisms by which GPR55 and ABCC3-related pathways induce pancreatic cancer progression. The ultimate aim is to investigate the effect of different inhibitors of ABCC3 and GPR55 on PDAC cell proliferation and progression, both in vitro and in vivo.

Background

Pancreatic ductal adenocarcinoma (PDAC) is the most common (around 90%) form of pancreatic

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cancer. PDAC prognosis is very poor and is the result of late diagnosis and high resistance to chemotherapy(1). That is why the study of molecules and signalling pathways important for PDAC progression, and the investigation of novel potent therapies is essential(2). It was indicated by our group among others that GPR55, one of many G-protein coupled receptors (GPCRs), is overexpressed in many cancer types and is responsible for regulation of cancer cell proliferation, including pancreatic cancer(3-8). It has been demonstrated that downregulation of GPR55 expression resulted in significantly decreased cell proliferation in vitro and increased survival rates in vivo. These results indicate the significant role of the GPR55 signalling pathway in PDAC progression. Chemotherapy resistance of pancreatic cancer is caused in part by overexpression of ATP binding cassette (ABC) transporters. Although so far ABC transporters have been mostly studied as multi-drug resistance proteins, there is evidence that, apart from effluxing drugs from the cells, they directly contribute to cancer progression(9). It has been demonstrated that, by releasing bioactive lipids, ABC transporters activate pathways essential for cell proliferation and migration(3,9). The preliminary data from our group suggest that, in PDAC, phospholipase A2 (PLA2)(10) produces lysophosphatidylinositol (LPI)(11) that is released by ABCC3 and, once outside the cell, LPI activates GPR55(12,13), forming an autocrine loop and enabling continuous stimulation of cancer cell proliferation (Figure 1, see supporting documentation). This fact makes ABCC and GPR55 potent targets for novel combinational therapies.

Available resources for our research.

We have different in vitro and in vivo models to study pancreatic cancer. We have already used the KRAS/p53 (KPC) transgenic mouse, which represents a valid model, to study PDAC development. KPC mice (Pdx1-Cre+/+/KRaswt/G12D/p53wt/R172H) have a mutant activated Kras and a mutation in p53. Activating mutations in KRAS are frequent in human PDAC (above 90%) and cause permanent stimulation of its downstream signalling pathways, influencing many cellular processes and resulting in increased cell proliferation, and a change in metabolism, cell environment. and metastasis. Another frequently mutated gene is p53, which is altered in around 75% of PDAC cases and confers a metastatic phenotype. In addition, we generated a new mouse model (KPCG) by crossing the KPC (Pdx1-Cre+/+/KRaswt/G12D/p53wt/R172H) transgenic mouse with a GPR55 knockout mouse, which resulted in highly increased mouse survival. Our collaborator, Prof Vincenzo De Laurenzi, has established different cell lines of patient-derived xenografts (PDX) from tissues derived from pancreatic patients. We also have tissue microarrays, a collection of more than 500 clinical annotated, prospectively collected blood and urine samples obtained from patients at Barts and The London HPB (HepatoPancreatoBiliary) Centre, patient-derived xenografts, and 15 cell lines. Furthermore, Prof Falasca is member of the Australian Pancreatic Cancer Genomic Initiative (APGI) and can apply to obtain further valuable materials.

Preliminary Results. (see Supporting Documentation)

References

1. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, Real FX, Van Laethem JL & Heinemann V. 2015, 'Addressing the challenges of pancreatic cancer: future directions for improving outcomes', Pancreatology, 15: 8-18.

2. Falasca M, Kim M & Casari I. 2016 Pancreatic cancer: Current research and future directions. Biochim Biophys Acta, 1865: 123-132.

3. Piñeiro R, Maffucci T & Falasca M. 2011, 'The putative cannabinoid receptor GPR55 defines a novel autocrine loop in cancer cell proliferation', Oncogene, 30: 142-152.

4. Andradas C, Caffarel MM, Pérez-Gómez E, Salazar M, Lorente M, Velasco G, Guzmán M & Sánchez C. 2010, 'The orphan G protein-coupled receptor GPR55 promotes cancer cell proliferation via ERK', Oncogene, 30: 245-252.

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5. Hu G, Ren G & Shi Y. 2011, 'The putative cannabinoid receptor GPR55 promotes cancer cell proliferation', Oncogene, 30: 139-141.

6. Ford LA, Roelofs AJ, Anavi-Goffer S, Mowat L, Simpson DG, Irving AJ, Rogers MJ, Rajnicek, AM & Ross RA. 2010, 'A role for L-alpha-lysophosphatidylinositol and GPR55 in the modulation of migration, orientation and polarization of human breast cancer cells', British Journal of Pharmacology, 160: 762-771.

7. Pérez-Gómez E, Andradas C, Flores JM, Quintanilla M, Paramio JM, Guzmán M & Sánchez C. 2013, 'The orphan receptor GPR55 drives skin carcinogenesis and is upregulated in human squamous cell carcinomas', Oncogene, 32: 2534-2542.

8. Falasca M & Ferro R. 2016, 'Role of the lysophosphatidylinositol/GPR55 axis in cancer'. Adv Biol Regul. 60: 88-93.

9. Falasca M & Linton KJ. 2012 'Investigational ABC transporter inhibitors'. Expert Opin Investig Drugs. 21: 657-66.

10. Burke JE & Dennis EA. 2009, 'Phospholipase A2 structure/function, mechanism, and signaling', Journal of Lipid Research, 50: 237-242.

11. Pineiro R & Falasca M. 2012, 'Lysophosphatidylinositol signalling: new wine from an old bottle', Biochimica Biophysica Acta, 1821: 694-705.

12. Oka S, Nakajima K, Yamashita A, Kishimoto S & Sugiura T. 2007, 'Identification of GPR55 as a lysophosphatidylinositol receptor', Biochemical Biophysical Research Commununication, 362: 928-934.

13. Ross RA. 2011, 'L-α-lysophosphatidylinositol meets GPR55: a deadly relationship', Trends Pharmacologica Science, 32: 265-269.

Summary for public release:

In no more than 350 characters (approx. 50 words), please provide a brief descriptor of the purpose and expected outcome of the project which is suitable for media or other publicity material. Do not duplicate or simply truncate the 'Project summary'

We have discovered that a protein named GPR55 promotes pancreatic cancer growth. Our preliminary data demonstrates that a GPR55 inhibitor, in combination with a drug used in therapy, is able to increase survival in mice that develop pancreatic cancer. Our plan is to identify more potent drug combinations to treat pancreatic cancer and also identify new marker that will enable to diagnose pancreatic cancer earlier.

Project relevance:

a) Accelerator Grant – limited to two A4 pages

b) Innovation Grant - no more than 500 words

Describe how the project will support Avner Pancreatic Cancer Foundation to work towards its Vision "To break through 40 years of no progress by doubling the number of people who survive Pancreatic cancer by 2020".

Pancreatic cancer is a very aggressive disease with an extremely high mortality rate, mainly because it does not present any symptoms in its early stages and so it is usually diagnosed too late. The overall objective of this proposal is to develop more effective and less toxic treatments for pancreatic cancer. We propose to use drugs in combination that specifically target different pathways in order to obtain a more efficacious effect on this very aggressive tumour. Our plan is to test in our animal model the most promising drug combination identified in the laboratory setting. We expect to see a significant increase in survival upon drug combination compared to both the untreated and the mice treated with single agents. Our ultimate aim is to provide strong pre-clinical data to propose a progression to clinical trials. If the extraordinary results obtained in the KPC mouse model could be translated in the human trials,

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this will certainly support Avner Pancreatic Cancer Foundaton's vision to increasing the number of patients who survive pancreatic cancer. In addition, if we validate the lysophospholipid LPI (that we recently found to be released by pancreatic cancer cells) as a pancreatic cancer biomarker, this could allow early diagnosis of pancreatic cancer and consequently save many lives. Our aim is to validate LPI as a novel marker to predict pancreatic cancer development. Since the LPI molecule can exist in different forms, we will also identify the precise chemical composition of the specific LPI released by pancreatic cancer cells.

Probability of success:

What probability (expressed as a percentage) do you associate with the project achieving its research goals?

99%

Time required to complete project: 3 years

SECTION 4 – PERSONS INVOLVED

Principal Investigator

Title:	Dr ☒	Mr ☐	Mrs ☐	Ms ☐
Name:	**Firstname:**	Marco		
	Surname:	Falasca		
Highest Qualification:	PhD			
Position Held: *Include year appointed*	Professor (2014)			
Institution:	Curtin University			
Business Phone:	08 92669712			
Email:	marco.falasca@curtin.edu.au			
Number of years work experience: a) Clinical Health practice b) Post graduate research	30 years			
Time contribution to this project: *(hours/week)*	7.5 hours/week			

In addition to the Principal Investigator please provide details of other research team members (where applicable). Please copy and paste additional tables as required.

SECTION 4 CONT – PERSONS INVOLVED

Research Team Members

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Title:	Professor	
Name:	**Firstname:**	Peter
	Surname:	Meikle
Highest Qualification:	PhD	
Position Held: *Include year appointed*	Professor	
Institution:	Baker IDI Institute	
Business Phone:	03 8532 1770	
Email:	peter.meikle@bakeridi.edu.au	
Role in project:	Lipidomic analyses	
Time contribution to this project: *(hours/week)*	3 hours/week	

SECTION 4 *CONT*– PERSONS INVOLVED
Research Team Members

Title:	Professor	
Name:	**Firstname:**	Vincenzo
	Surname:	De Laurenzi
Highest Qualification:	PhD	
Position Held: *Include year appointed*	Professor	
Institution:	University of Chieti, Adjunct Professor Curtin University	
Business Phone:	+39-0871-541580	
Email:	delaurenzi@unich.it	
Role in project:	Drug testing in Patient-derived-xenograft model of pancreatic cancer	
Time contribution to this project: *(hours/week)*	3 hours/week	

SECTION 4 *CONT*– PERSONS INVOLVED
Research Team Members

Title:	Dr	
Name:	**Firstname:**	Tatjana

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	Surname:	Crnogorac-Jurcevic
Highest Qualification:	PhD	
Position Held: *Include year appointed*	Reader	
Institution:	Queen Mary University of London	
Business Phone:	+44 (0)20 7882 3554	
Email:	t.c.jurcevic@qmul.ac.uk	
Role in project:	Biomarker analysis of samples from pancreatic cancer patients	
Time contribution to this project: *(hours/week)*	3 hours/week	

SECTION 5 – COLLABORATIONS

Does the project involve collaborations? **Yes** ☒ **No** ☐

If 'yes' please provide detail as to the nature of the collaboration/s, including the institution/s and department/s

This project is a collaboration of four uniquely specialized laboratories. Prof Falasca is a research academic employed by the Faculty of Health Sciences at Curtin University and is part of the newly funded Curtin Health Innovation Research Institute (CHIRI). He is an expert in metabolism and pharmacology and has a longstanding interest in pancreatic cancer. Prof Peter Meikle is an Associate Professor at Baker IDI Institute and is an accomplished lipid analysis expert. Dr Tatjana Crnogorac-Jurcevic is a Reader at the Barts Cancer Institute QMUL. She is an expert in molecular pathology of cancer development and progression and in developing urine biomarkers for early, non-invasive detection of pancreatic cancer. Prof Vincenzo De Laurenzi is a research academic employed by the Department of Medical sciences, Universtity of Chieti and is Adjunct Professor at Curtin University. He is a renowned cell signalling expert and has extensive portfolio in cancer research.

SECTION 6 – ETHICS

Does the project require submission to a human research ethics committee?	**Yes** ☐	**No** ☒
Does the project require submission to an animal research ethics committee?	**Yes** ☒	**No** ☐
Will the project/research require the use of human stem cells?	**Yes** ☐	**No** ☒
Will the project/research require the use of animal stem cells?	**Yes** ☐	**No** ☒

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If you answered 'yes' to any of the above questions please provide details (eg approval granted, pending, yet to be applied for)

Approval pending

SECTION 7 - INNOVATION

Describe how the project is innovative:

a) Accelerator Grant – Maximum 1 page

b) Innovation Grant – limited to two A4 pages

This project is innovative because its starting point is a recent breakthrough in pancreatic cancer research. We have discovered that a member of the G protein coupled receptor family, called GPR55, and its ligand lysophosphatidylinositol (LPI), have a critical role in pancreatic cancer. Our preliminary data show GPR55 blockade, using different strategies, is able to inhibit pancreatic cancer growth in vitro and in vivo. Mice that spontanously develop PDAC in a way similar to humans were treated for the first time with a new drug combination and showed a threefold life increase compared to mice treated with traditional therapies. This represents a considerable advancement in the pancreatic cancer field that, if reproduced in human trials, will substantially improve pancreatic cancer patients survival.

In this project we will test the hypothesis that GPR55 blockade using specific antagonists, such as cannabidiol, can render the tumour more responsive to chemotherapeutics and ultimately can block or reduce cancer growth. This is also a novel approach since, while cannabidiol is already being used to treat other diseases, it has never been tested on PDAC.

The overall objective of this proposal is to develop more effective and less toxic treatments for pancreatic cancer. We propose to use drugs in combinations that target specifically different pathways in order to obtain a more efficacious effect on this very aggressive tumour. Our plan is to test in our animal model the most promising drug combination identified in laboratory setting. We expect to see significant increase in survival upon drug combination compared to both the untreated and the mice treated with the single agents.

This study has an enormous potential to validate cannabidiol and other compouds in combination with traditional drugs as successful treatments for PDAC, and could lead to clinical trials in patients with pancreatic cancer.

Another novel hypothesis that we aim to test in this project is that lysophosphatidylinositol (LPI), the GPR55 natural ligand that we found to be released by pancreatic cancer cells, is a potential biomarker for PDAC. As there are many different species of LPI, we intend to identify a specific species that could function as a biomarker. Our ultimate aim is to provide strong pre-clinical data to propose a progress to clinical trials.

The significance and originality of our project is based on:

1. New combination therapies are imperatives in the fight againsts pancreatic cancer in order to beat its resistance to chemotherapy. We have already identified a specific target and a drug combination working effectively to slow down pancreatic cancer growth both in vitro and in vivo. In this project we will study the mechanisms of action of this combination and try to uncover other active combinations.

2. One of the main causes of Pancreatic cancer's lethality is that it is almost always diagnosed too late. This is also due to the lack of reliable biomarkers for this disease. In this project we aim to validate a molecule, that we discovered for the first time to be released by pancreatic cancer cells, as a specific

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biomarker for pancreatic cancer.

Describe what distinguishes this work from other research being carried out in this area
(maximum ½ page)

To date there are very few treatments available for pancreatic cancer patients and these provide a very limited increase in survival. Our preliminary data in our animal model, that closely resemble the human disease, shows that a combination of the GPR55 antagonist with gemcitabine induces a remarkable threefold extension in mice survival, an effect that is unique and, if reproduced in pancreatic cancer patients, would represent a breakthrough in the field. As far as we know, no other group has obtained such a massive efficacy in preclinical studies in pancreatic cancer, and particularly using the transgenic KPC model that mimics the human disease. These data are extremely important, considering that pancreatic cancer can be highly resistant to drug treatments.

SECTION 8 – PROJECT PLAN

Provide detail about the project methodology *(maximum two pages)*

AIM 1. Investigation of the effect of CBD combinations in vitro and in vivo. The survival extension of the combination of CBD+GEM is unprecedented and clinical trials are currently under discussion. Our focus will now be on investigating better combinations, focusing on novel drugs such as Abraxane. Using in vivo models of GPR55 genetic ablation and a mouse model of PDAC (KRas/p53, KPC), we have observed increased survival in animal models of PDAC in the absence of GPR55 (Figure 6). Our data indicate that small molecule inhibitors of GPR55 can be safely delivered, are able to reach tumour sites, and can block enzymes that are critical for cancer progression. We proposed to use CBD, alone or in combination with chemotherapeutic drugs on pancreatic cancer progression in vitro (2D growth and 3D agarose colonization of pancreatic cancer cell lines), in vivo (KPC mice), and in patient-derived xenografts (PDX). We will focus our attention on drugs currently in use for pancreatic cancer patients such as 5-fluorouracil, oxaliplatin, FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin), and gemcitabine/nab-paclitaxel. CBD is ideal for drug development as it has appeared to be safe for use in animal studies and in humans. We will also test additional molecular targets that can be inhibited in combination with GPR55 inhibitors to more efficiently block pancreatic cancer progression. In this regard, we have now performed an extensive investigation using cell lines, animal models, and human tissues, that have successfully identified the enzyme 3-phosphoinositide dependent protein kinase 1 (PDK1) as a key player in pancreatic cancer. We have found that: a) the phosphorylated form of PDK1 is not detected in normal pancreatic tissue, whereas it progressively accumulates from PanIN1-2 to PanIN3 and it is very strongly detected in PDAC. b) Pharmacological inhibition of PDK1 and downregulation of the enzyme inhibit pancreatic cancer cell proliferation in vitro. c) PDK1 blockage dramatically reduces 3D agarose colonization of pancreatic cancer cells. d) PDK1 and GPR55 inhibitors act synergistically to reduce 2D growth and 3D agarose colonization of pancreatic cancer cells. Therefore, we not only have identified PDK1 as a novel critical player in pancreatic cancer progression but we have also found, in in vitro studies, that a combination of PDK1 and GPR55 inhibitors may represent a more efficient and very important strategy to block pancreatic cancer progression. Our collaborator, Prof Vincenzo De Laurenzi, has established different cell lines of patient-derived xenografts (PDX) from tissues derived from pancreatic patients. Therefore, the ongoing collaboration is focused on testing different drug combinations and single agents on this model. PDX are usually implanted as fragments of tumours directly from patients to immunodeficient mice, and generally retain the histological characteristics of the parental patient tumours. In addition, numerous

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studies showed that PDX models preserve mutation profiles, as well as the response patterns to targeted therapies. Since tumour heterogeneity represents one of the major challenges for cancer drug development, PDX are considered the most effective system to investigate the efficacy of anti-cancer agents. In parallel, we have developed a tetracycline-controlled transcriptional inactivation method of inducible ABCC3 expression, where transcription is reversibly turned on or off in the presence of the antibiotic tetracycline. This will allow us to investigate the effect of ABCC3 inactivation in vivo in different PDAC cell lines.

AIM 2. Investigation of the mechanism of action of the GEM+CBD combination. Our preliminary data show that the combination of GEM+CBD has an additive effect in our in vivo transgenic model, raising the question about which mechanism is responsible for this activity. Answering this question could provide the basis for more effective anti-cancer strategies and potent drug combinations. GEM is a nucleoside analogue (similar to cytosine) able to generate instability in the DNA chain during the replication process, and ultimately inducing tumour growth arrest. GEM is taken up by cancer cells by human equilibrative nucleoside transporter 1 (hENT1) and has, as its main target, the human ribonucleotide reductase (RRM1), a key enzyme in nucleotide homeostasis. Cytidine deaminase (CDA) catalyses the degradation of GEM and is involved in resistance in PDAC cells. Therefore, the levels of hENT1 and CDA will be assessed. GEM at a low concentration induces an increase of dNTP levels to compensate for toxicity mediated in the S-phase due to replication stress and fork collapse. The combination of GEM+CBD prevents dTTP pool increase and could favour cell death through dTTP depletion. We have set up a system for the accurate measurement of deoxyribonucleotide pools, and initiated the investigation of the mechanisms underlying alteration of deoxyribonucleotide pools and their relevance in human diseases. We have already started on measuring deoxyribonucleotide pools in response to GEM+CBD in pancreatic cancer cells. We will test the effects of GEM and CDB alone or in combination on hENT1, CDA, and RRM1 levels, and on deoxyribonucleotide pools. The effect of the combination will be tested on functional assays (metabolism, autophagy etc.) described in aim 2. Recent work suggested that epithelial to mesenchymal transition (EMT) could be involved in GEM resistance. Therefore, we will assess the levels of EMT markers such as Twist, Snail, and Zeb1. As an alternative plan, we will investigate the potential effect of CBD on stromal cells, which may favour the delivery of GEM to the tumour. Results from these studies will validate strategies targeting GPR55 and ABCC3 in combination with other key targets as a means to directly inhibit pancreatic tumour growth.

AIM 3. Identification of the specific LPI species released by pancreatic cancer cells and the pathway responsible for LPI synthesis and release. As discussed in the background section, different LPI species exist, according to the specific acyl chain and whether this is linked to the sn-1 or sn-2 position. Evidence in the literature suggests that the different LPI species may have distinct biological activities. In our preliminary experiments, we have performed thin layer chromatography analysis that detected an enrichment of LPI in the supernatants of pancreatic cancer cells, specifically upon EGF stimulation. This assay, although able to quantitatively assess the amount of LPI released, did not discriminate between the different LPI species. Therefore, in this part of the project, we will perform a more extensive investigation of the specific LPI species released by pancreatic cancer cell lines HPAF II and ASPC1. We will test both 1-acyl and 2-acyl LPI containing either saturated or unsaturated fatty acid, analysed by our collaborator Prof Peter Meikle (Baker IDI Heart and Diabetes Institute, Melbourne). These results will establish which LPI species are released by pancreatic cancer cells. It is important to identify the specific LPI species in order to determine if this is pancreatic cancer-specific. We will also determine the signalling pathway involved in synthesis and release of LPI. Results from this part of Aim 3 will identify the specific LPI species released by pancreatic cancer cell lines.

AIM 3A. Investigation of LPI production in transgenic mouse models of PDAC. Recent work in mice has demonstrated that the performance of a novel biomarker-development pipeline, using targeted mass spectrometry, is robust enough to support the use of an analogous approach in humans. Therefore, we will analyse the levels of LPI and PLA in plasma and urine samples from a transgenic mouse model of

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pancreatic cancer, which is already available in the laboratory. Specifically, we will use the KPC mice that generate the full PanIN lineage and also develop PDAC with 100% penetrance and with similar pathology to that seen in human PDAC. It is challenging to get enough plasma, and in particular urine, from mice, but recent data demonstrated that this is feasible. To validate the hypothesis that pancreatic tumours release LPI, and to further determine whether LPI is released early or late in the progression of the disease, we will collect plasma and urine from three groups of mice (n=10) at different stages of disease progression: a control group with no pancreatic tumours, a second group with pancreatic tumours induced by expression of oncogenic K-ras (K-rasG12D), and a third group with pancreatic tumours driven by both oncogenic K-ras and mutant p53 (KPC). Results from this part of the aim 3 will identify the specific LPI species released by KPC mice and will validate the in vitro observations.

AIM 3B. Investigation of LPI production in plasma and urine samples from normal and pancreatic cancer patients. We propose to assess whether LPI is a biomarker associated with tumorigenicity and aggressiveness in pancreatic cancer patients. Our collaborator Dr Tatjana Crnogorac-Jurcevic has a large collection (>500) of clinical annotated, prospectively collected blood and urine samples obtained from patients at Barts and The London HPB (HepatoPancreaticoBiliary) Centre. (REC number 05/Q0408/65, Study title: Biomarkers for diagnosis of pancreatic diseases). A good representation of both operable and unresectable pancreatic cancer specimens and samples from various other pancreaticobiliary tumours and pathologies is an invaluable resource that will be made available to us to investigate whether LPI can be detected by mass spectrometry and whether its presence correlates with tumour histology, age, or other adverse prognostic indicators. Other lysophospholipid species such as lysoPC, lysoPE lysoPA etc. will be investigated. Approximately 50 blood and urine samples from pancreatic cancer patients will be analysed by mass spectrometry under the supervision of our collaborator Professor Peter Meikle at the Baker IDI Heart and Diabetes Institute. A healthy control cohort will be analysed. If this initial round of analysis is successful, more samples will be processed in order to obtain a meaningful association with prognostic markers. Results from this part of the aim 3 will validate he results obtained in vitro and in KPC mice in human samples.

List all approvals that will be required before the project can go ahead. Eg ethics, intellectual property, administrative, governance

We have submitted the Animal ethics to our Animal ethics Committee (Curtin University) and few amendaments have been requested. We have the required approval from QMUL human ethics Committee (Dr Crnogorac-Jurcevic) to work with humn samples.

SECTION 8 *CONT* – MILESTONES AND TIMELINES

Outline the proposed milestones against timelines, taking into account the creation of any positions, report writing, purchase of equipment etc *(insert further rows as required)*

Milestone	Detail	Timeline
1.	Advertise for Research Assistant (RA)	January 2017
2.	Appointment and training of RA in specialized techniques	February 2017
3.	Investigation of the effect of novel CBD combinations in vitro	February 2017-August 2017

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4.	**Investigation of the effect of novel CBD combinations in KPC mice**	**September 2017-March 2018**
5.	**Investigation of the effect of novel CBD combinations in PDX models**	**January 2018-May 2018**
6.	**Investigation of the mechanism of action of the GEM+CBD combination**	**February 2017-December 2018**
7.	**Investigation of LPI production in pancreatic cancer cell lines**	**June 2018-December 2018**
8.	**Investigation of LPI production in plasma and urine samples from transgenic mouse model of PDAC**	**January 2019-June 2019**
9.	**Investigation of LPI production in plasma and urine samples from normal and pancreatic cancer patients**	**July 2019-December 2019**
10.	**Final report submitted to the Avner Pancreatic Cancer Foundation**	**TBC**

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Please complete the following table, inserting additional rows as required.

SECTION 9 - BUDGET

BUDGET ITEM	Jan 2017 – Jun 2017 ($)	Jul 2017 - Dec 2017 ($)	Jan 2018 - Jun 2018 ($)	Jul 2018 – Dec 2018 ($)	Jan 2019 – Jun 2019 ($)	Jul 2019 – Dec 2019 ($)	TOTAL ($)
POSITION HELD *specify for each position*	60129.20	60129.20	64338.24	64338.24	68841.92	68841.92	386618.69
Position 1. **(PRP) Research Fellow (PSP4) ALA-6 (1.0 FTE)** Personal Support Package 4 *new*	15438.85	15438.85	15438.85	15438.85	15438.85	15438.85	92633.10
Position 2. **(PRP) PI Research Associate (0.35 FTE)** Personal Support Package 4 *new*							
CONSUMABLES *Supplies and materials needed to complete the project*	32500.00	32500.00	32500.00	32500.00	32500.00	32500.00	195000.00
EQUIPMENT *Quotations must be attached*							

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TRAVEL	
PROFESSIONAL SERVICES	
OTHER	
TOTAL	674251.79

Where applicable, in-kind support and other source funding should be indicated against the project's costs. Detail to be provided in section 10 below.

Applicants should note that:

- It is important to calculate budgets accurately, as requests for additional funding will not be approved.
- Costs must be verified by the administering institution's Finance Officer or Business Manager at Section 12.
- Figures are to be GST exclusive

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SECTION 10 – JUSTIFICATION OF BUDGET

Each budget claim must be adequately justified. Contributions of in-kind support and other sources of funding should be outlined here *(maximum of TWO pages)*

(PRP) Research Fellow (PSP4) ALA-6 (1.0 FTE). The Postdoctoral Research Fellow (PRF) will be involved full time in all 3 aims. His/her expected level of intellectual involvement in the integration of experimental approaches and in data collation and interpretation is consistent with the appointment at Academic level. Specifically, the proposal requires expertise in in vitro (cell culturing and manipulation), ex-vivo and in in vivo experiments.

(PRP) PI Research Associate (0.35 FTE). To perform the complex and technically demanding lipidomic analyses in Aim 3 we will require a postdoctoral scientist with extensive experience in lipid chemistry, HPLC and mass spectrometry. Although the team at Baker IDI has established methodology for PI and LPI lipids (in addition to many other lipid classes) these methods were established for human plasma samples and will need to be validated in the sample types in this study.

Animal Maintenance. The proposed studies cannot be undertaken routinely using tissue from human subjects, but animal use is minimised by carrying out studies in cells. However, these in vitro investigations require a complementary in vivo model. The study will therefore involve the use of mice already available in the laboratory. Mice strains: Kraswt/LSLG12D, p53wt/LSL-R172H, Pdx1-cre+/+. The strains are interbred to obtain: Pdx1-cre+/+/Kraswt/LSLG12D/p53wt/LSL-R172H Pdx1-cre+/+/Kraswt/LSLG12D.

CellCulture. The project investigates biochemical mechanisms at a cellular level and so relies on the ability to manipulate signal transduction proteins and events and to make observations made in cell cultural systems. Budget includes: expenditure for cell culture (including media, serum, antibiotics for cell culturing, Matrigel for plate coating etc.). Our current experience indicates that $10K per year is required to support the project of this scale and complexity.

Disposable Plasticware. For all samples prepared and analysed throughout this project, we require the use of standard disposable plasticware, including pipette tips, 15 ml and 50 ml Falcon tubes. Based on our current expenditure we estimate a cost of $5K per year.

Mass Spectrometry Analysis. This work will be performed by the postdoctoral scientist under the supervision of Prof Peter Meikle. Consumables typically cost $15.00 per sample which included solvents (current standards but not PI and LPI), HPLC columns and plastic ware. In addition we will require both PI and LPI standards and calibrators. These typically cost ~$1,000/mg (Avanti Polar Lipids Inc.). Based on current analysis we estimate these costs to reach $12K per year.

Molecular Biology Reagents. Essential reagents include materials required for analysis of proteins of interest downregulation (reagents for SDS/PAGE, membranes, primary and secondary antibodies, qPCR etc), material for immunohistochemistry. A significant part of the budget will be used to purchase bulk amount of drugs for in vivo studies. Based on current use, we estimate these costs to reach $15K per year.

Salary of PI will be in kind as follows: Marco Falasca $119,754.91 (20%)

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SECTION 11 – CERTIFICATION BY PROJECT APPLICANT

a) I declare that I have agreed to take part in the research proposed in this application

b) I declare that the information supplied by me on this form is complete, true and correct in every particular

c) I understand and agree that research carried out by me will be in accordance with the relevant codes of practice and guidelines of the National Health & Medical Research Council (NHMRC) and other relevant agencies

d) I have discussed the likely impact of the project on other relevant departments and support services and this project has been approved and is acceptable to them

e) I declare that this application will be submitted to the Institution's Research Administration Office or equivalent, and I agree to obtain the relevant research governance approvals and agreements before commencement of the project.

f) I understand and agree that no further claim will be made on the Avner Pancreatic Cancer Foundation to cover any over-expenditure of budget or any costs beyond the research project.

Principal Investigator

Full name and title:	Prof Marco Falasca		
Signature:		**Date:**	22/7/2016

SECTION 12 – CERTIFICATION BY FINANCE OFFICER

I certify that:

(a) The budget costs on this application form for Prof Marco Falasca (Principal Investigator) are true and correct and reflect the latest costing information available to me; and

(b) Amounts claimed are exclusive of GST.

Full name and title:	Ian Seymour		
Position:	Accountant		
Organisation:	Curtin University		
Business Phone:	92663456		
Email:	ORD-Support-HTH@curtin.edu.au		
Signature:		**Date:**	26/7/16

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SUPPORTING DOCUMENTATION

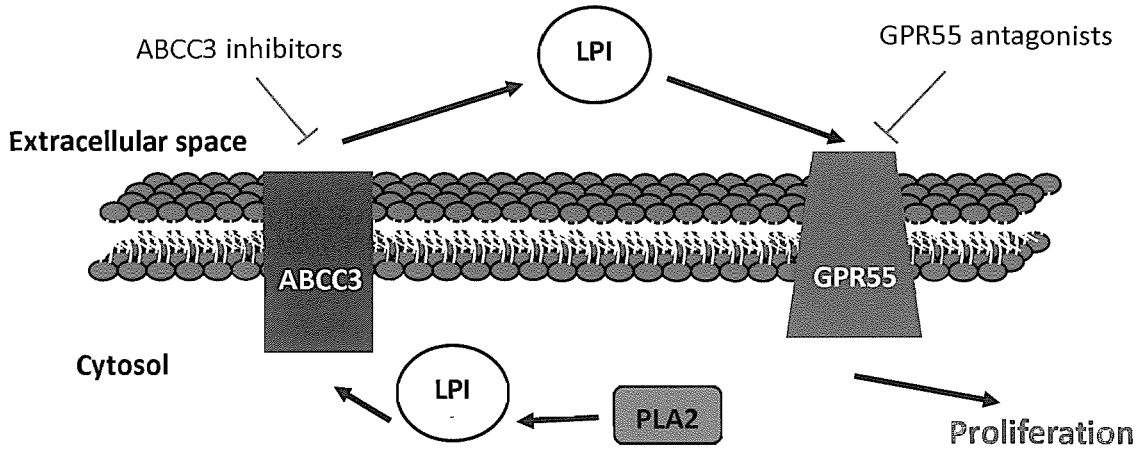

Figure 1: Autocrine loop involved in pancreatic cancer and potential drug targets

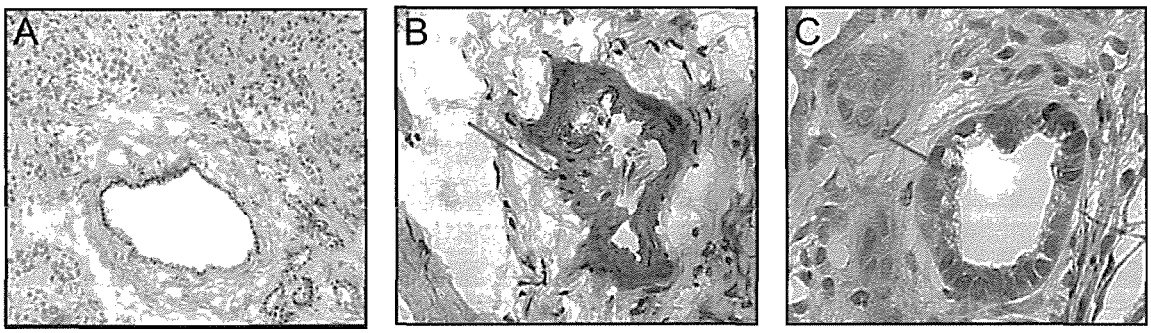

Figure 2: Immunohistochemistry analysis of GPR55 levels in pancreatic tissues

Immunohistochemistry analysis in normal human pancreatic tissue (Figure 2A) and human PDAC tissue (2B) confirmed overexpression of GPR55 in cancer, with a specific ductal localisation. Indeed, in these experiments we could only detect GPR55 in normal human (A) and murine (not shown) pancreatic tissues in islets but not in pancreatic ducts. Elevated levels of GPR55 were also observed in KPC mouse pancreatic tissues (2C) and in in tissues from patient-derived xenografts (PDX), specifically in ducts. In addition GPR55 silencing, using several siRNA sequences specifically targeting GPR55, significantly reduced anchorage dependent and independent cell growth of several pancreatic cancer cell lines (example of 3D growth in Figure 3). To assess the role of GPR55 in PDAC, mice that harbour homozygous deletion of the GPR55 gene (GPR55-/- mice) were crossed with KPC mice, which closely mimics human PDAC, to obtain Kras+/-/p53+/-/GPR55-/-/Pdx1-Cre+/+(KPCG) mice. GPR55-/- mice grow normally, and are viable and fertile. Data in Figure 4 clearly indicate that loss of GPR55 significantly improved survival of KPC mice (N=18) with a median survival of 35 days more than control KPC mice (N=21). Immunohistochemical analysis of pancreatic tumours revealed that GPR55 absence reduced expression of the proliferative index ki67 specifically in PanIN 2 and PanIN 3 progression stage.

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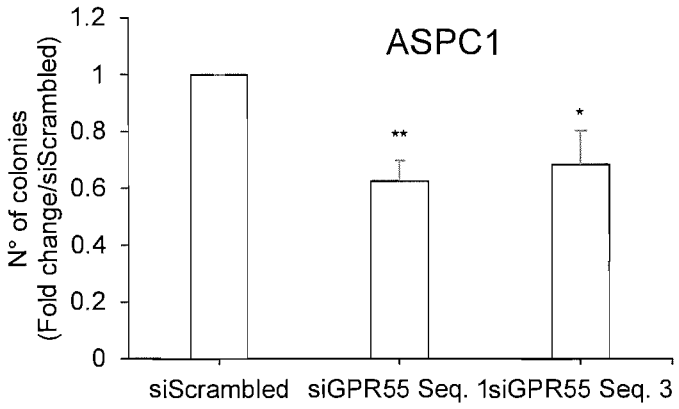

Figure 3

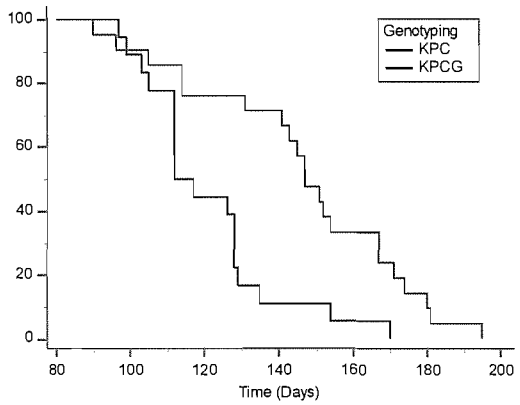

Figure 4

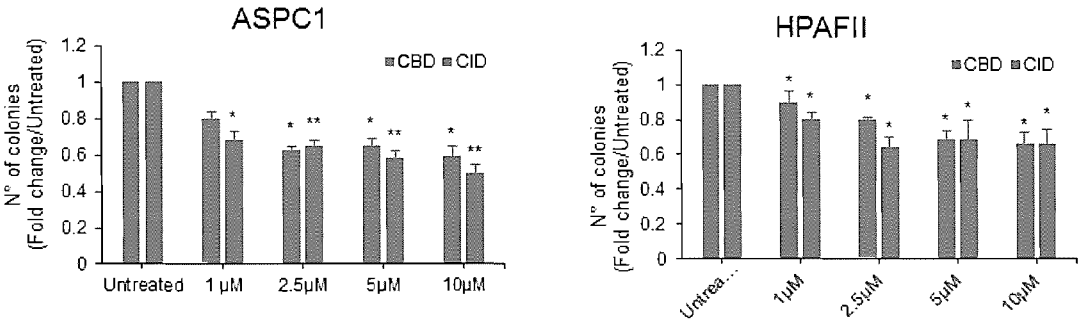

Figure 5. Pharmacological blockade of GPR55 inhibits pancreatic cancer cell growth

To investigate the effect of GPR55 pharmacological inhibition in PDAC, two GPR55 antagonists cannabidiol (CBD) and CID16020046 (CID) were used. As shown in Figure 5, CBD is able to inhibit the 3D cell growth of ASPC1 and HPAFII cell lines. Furthermore, when CBD was used in combination with Gemcitabine, we observed an almost additive effect (not shown).

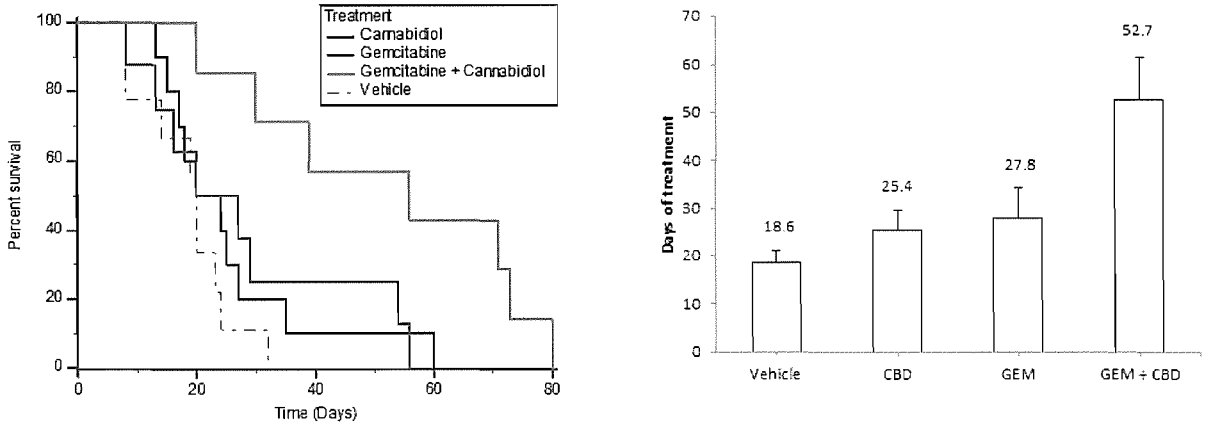

Figure 6. CBD+Gemcitabine combination caused a dramatic increase in KPC mice survival

KPC mice were treated with CBD alone or in combination with gemcitabine (Figure 6). CBD alone extended the lifespan of mice around 7 days (25.4 days vs 18.6), even though the effect was not statistically significant as was the effect of gemcitabine (27.8 days vs 18.6). Strikingly, when CBD was

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used in combination with gemcitabine, a remarkable nearly three time extension of mice survival (52.7 days vs 18.6) was observed (Figure 6). These data suggest that GPR55 blockade may represent a novel strategy to counteract PDAC progression.

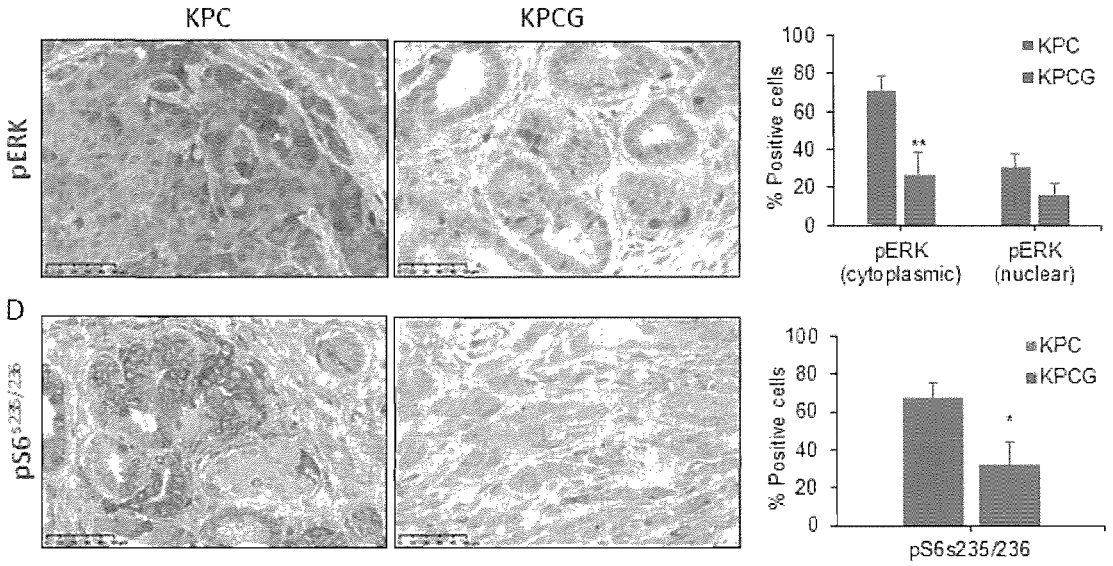

Figure 7: Representative image and quantitative analysis of pERK and pS6 expression in KPC and KPCG mice assessed by immunohistochemistry

To gain further insight into the mechanism involved in cell growth and cell cycle regulation, the signalling pathways downstream GPR55 in PDAC were investigated. Results demonstrated that, in HPAFII cells, transient down regulation using two siGPR55 sequences resulted in reduced phosphorylation of ERK1/2 at its residues Threonine 202 and Tyrosine 204, compared to control cells (not shown). As a complementary approach, the effect of GPR55 pharmacological blockage on the ERK1/2 activation was determined, and we observed a significant decrease of the ERK1/2 phosphorylation state in HPAFII cells treated with 5μM and 10μM CBD. In addition, to further investigate the role of GPR55 in the activation of MAPK/ERK-dependent signalling pathways, the activation of the ribosomal protein S6, one of its downstream effectors, was investigated. Both GPR55 silencing and pharmacological blockage reduced S6 phosphorylation at its residues Serine 235/236 compared to control cells. Consistently, immunohistochemistry analysis revealed a decrease in both ERK1/2 and S6 phosphorylation in KPCG mice compared to KPC mice (Figure 7).

ABCC3 downregulation inhibits pancreatic cancer cell growth

The expression of ABCC3 mRNA has been found upregulated in pancreatic carcinoma samples, and was correlated with tumour grading. Our data confirmed that ABCC3 is overexpressed in PDAC cell lines compared to immortalised pancreatic cell lines as well as in human and mouse PDAC tissues compared to their corresponding normal control tissues. Therefore, we investigated the effect of ABCC3 specific down regulation on cell. To this end, HPAFII and ASPC1 (not shown) cells were transiently transfected using two distinct siRNAs specifically targeting ABCC3, and an in-vitro growth assay was performed. The number of cells was determined by cell counting after 72 hours in the presence of 10% FBS. A significant reduction in cell number was detected in cells transfected with both siABCC3 sequences (47 and 53% inhibition) compared to cells transfected with non-targeting siScrambled. To investigate the existence of an auto/exocrine loop in PDAC cells, an assay to quantify the release of LPI out of the cells was optimised. In order to determine whether an auto/exocrine loop is present in PDAC cells, as previously reported in ovarian and prostate cancer cells3, several preliminary

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experiments were performed and we found that epidermal growth factor (EGF) induces LPI release to the extracellular medium in PDAC cells. To determine whether the release of LPI involves an auto/exocrine loop as observed in other cell types, HPAFII cells were transiently transfected using specific siRNAs targeting ABCC3 and cPLA2. 24 hours after transfection, cells were labelled in FBS free M199 containing [^{3}H]myo-Inositol (5µCi/ml). 48 hours after labelling, cells were incubated in HBSS in the presence or absence of EGF (20ng/ml) for 1 hour. The corresponding supernatants were collected and LPI was measured by liquid scintillation. Our data indicated that down regulation of either ABCC3 or cPLA2 totally blocked the release of LPI upon EGF stimulation (Figure 8).

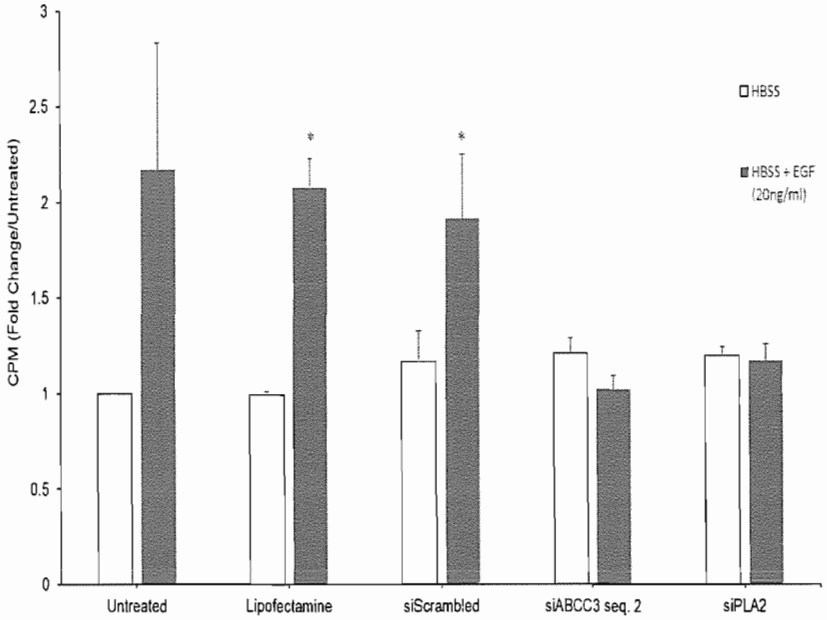

Figure 8: ABCC3 and cPLA downregulation impairs LPI release upon EGF stimulation in HPAFII.