ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by: ICR

Project details

Project title:	AI/ML-based Characterisation of Metabolic Addictions in Pancreatic Cancer

Supervisory team

Primary Supervisor:	Anguraj Sadanandam
Associate Supervisor(s):	Yuta Ikami
Secondary Supervisor:	Maggie Cheang

Divisional affiliation

Primary Division:	Molecular Pathology
Primary Team:	Systems and Precision Cancer Medicine
Site:	Sutton

Project background

Metabolic reprogramming is pivotal in sustaining malignant characteristics, such as rapid proliferation and invasion, within hostile tumour microenvironments, collectively called metabolic phenotypes. This proposal builds upon our recent Nature publication (Nwosu and Sadanandam et al., 2023), *unveiling that pancreatic ductal adenocarcinomas (PDAs) rely on an alternative nutrient source, uridine, alongside glucose*. Additionally, we were pioneers in demonstrating the heterogeneity of PDAs, *identifying three distinct subtypes based on gene expression profiles* (Collisson, Sadanandam and Colleagues, *Nature Medicine*, 2011)

Our compelling preliminary data, derived from large-scale Phenotypic Microarrays (Biolog technology), suggest that PDAs exhibit differential nutrient dependencies akin to metabolic addictions. While our previous work identifies a specific transcription factor as a potential metabolic regulator in PDA subtypes, little is known about the impact of alterations in multiple nutrient dependencies on tumour evolution and metabolic phenotypes, mirroring our research in pancreatic neuroendocrine tumours (Sadanandam et al., Cancer Discovery 2015).

To address this gap, we aim to decipher metabolic dependencies in PDA using a comprehensive resource toolkit. This toolkit includes 20 human PDA cell lines and two non-malignant cell lines, serving as in vitro subtype models. We have meticulously generated extensive qualitative and quantitative metabolomics, proteomics, transcriptomics and phenomics (>40 drugs) data at bulk, single cell and spatial levels.

Our research endeavours to unravel how nutrient-dependent changes impact tumour evolution and metabolic phenotypes within PDA subtypes, leveraging our well-characterized cell models and multi-omics datasets.

Project aims

Specifically, we will execute the following aims:

Aim 1. To systematically characterise the metabolic dependencies, intrinsic transcriptomic, (phosphor)proteomic and drug response of PDA subtypes using integrated multiomics-phenome analysis and artificial intelligence/machine-learning (AI/ML).

Aim 2. To validate the findings from Aim 1 in patient samples (>700) and ex vivo models (organoids/explant cultures).

Aim 3. To establish the role of PDA subtype-specific critical metabolic regulators and test potential therapies.

Research Proposal

Aim 1 will provide a comprehensive understanding of the intrinsic transcriptomic and metabolic dependencies of PDA subtypes. The expected outcomes include:

- Identification of distinct functional subtypes of PDA.
- Discovery of regulatory genes/proteins influencing metabolite uptake and phenotypic changes.
- Validation of metabolic dependencies using carbon-13 flux analysis.
- Insights into how PDA subtypes utilise different carbon nutrients and adapt to the microenvironment.

Aim 2 involves the validation of findings from Aim 1 in patient samples at both bulk and single-cell levels, as well as validation in ex vivo models (explants and organoids). Here are the specific expected outcomes for each of the three components outlined in Aim 2:

- Validation of functional subtypes in bulk and single-cell data using transfer learning AI/ML methods.
- Identification of cell types associated with functional subtypes using single cell and spatial analysis.
- Validation of metabolic dependencies in ex vivo models.
- Provides robustness of the findings from Aim 1 and potential translational opportunities.

Aim 3 aims to establish the role of subtype-specific genes in metabolic regulation and test potential therapies. The expected outcomes encompass:

- Confirmation of the importance of subtype-specific genes in metabolic/phenotypic dependencies.
- Evaluation of the therapeutic potential of targeting specific pathways in PDA subtypes.
- Insights into novel therapeutic strategies tailored to PDA subtypes, potentially leading to subtype-specific treatments.

Overall, these aims aim to advance our understanding of PDAC, paving the way for personalised therapeutic approaches that target the specific molecular and metabolic characteristics of different PDA subtypes.

Literature references

COLLISSON, E. A., SADANANDAM, A., OLSON, P., GIBB, W. J., TRUITT, M., GU, S., COOC, J., WEINKLE, J., KIM, G. E., JAKKULA, L., FEILER, H. S., KO, A. H., OLSHEN, A. B., DANENBERG, K. L., TEMPERO, M. A.,

SPELLMAN, P. T., HANAHAN, D. & GRAY, J. W. 2011. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat Med,* 17**,** 500-3.

LAN, L., EVAN, T., LI, H., HUSSAIN, A., RUIZ, E. J., ZAW THIN, M., FERREIRA, R. M. M., PS, H., RIISING, E. M., ZEN, Y., ALMAGRO, J., NG, K. W., SORO-BARRIO, P., NELSON, J., KOIFMAN, G., CARVALHO, J., NYE, E. L., HE, Y., ZHANG, C., SADANANDAM, A. & BEHRENS, A. 2022. GREM1 is required to maintain cellular heterogeneity in pancreatic cancer. *Nature,* 607**,** 163-168.

NWOSU, Z. C., WARD, M. H., SAJJAKULNUKIT, P., POUDEL, P., RAGULAN, C., KASPEREK, S., RADYK, M., SUTTON, D., MENJIVAR, R. E., ANDREN, A., APIZ-SAAB, J. J., TOLSTYKA, Z., BROWN, K., LEE, H. J., DZIEROZYNSKI, L. N., HE, X., PS, H., UGRAS, J., NYAMUNDANDA, G., ZHANG, L., HALBROOK, C. J., CARPENTER, E. S., SHI, J., SHRIVER, L. P., PATTI, G. J., MUIR, A., PASCA DI MAGLIANO, M., SADANANDAM, A. & LYSSIOTIS, C. A. 2023. Uridine-derived ribose fuels glucose-restricted pancreatic cancer. *Nature*.

NYAMUNDANDA, G., EASON, K., GUINNEY, J., LORD, C. J. & SADANANDAM, A. 2020. A Machine-Learning Tool Concurrently Models Single Omics and Phenome Data for Functional Subtyping and Personalized Cancer Medicine. *Cancers (Basel),* 12.

NYAMUNDANDA, G., POUDEL, P., PATIL, Y. & SADANANDAM, A. 2017. A Novel Statistical Method to Diagnose, Quantify and Correct Batch Effects in Genomic Studies. *Sci Rep,* 7**,** 10849.

SADANANDAM, A., LYSSIOTIS, C. A., HOMICSKO, K., COLLISSON, E. A., GIBB, W. J., WULLSCHLEGER, S., OSTOS, L. C., LANNON, W. A., GROTZINGER, C., DEL RIO, M., LHERMITTE, B., OLSHEN, A. B., WIEDENMANN, B., CANTLEY, L. C., GRAY, J. W. & HANAHAN, D. 2013. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nat Med,* 19**,** 619-25.

SADANANDAM, A., WULLSCHLEGER, S., LYSSIOTIS, C. A., GROTZINGER, C., BARBI, S., BERSANI, S., KORNER, J., WAFY, I., MAFFICINI, A., LAWLOR, R. T., SIMBOLO, M., ASARA, J. M., BLAKER, H., CANTLEY, L. C., WIEDENMANN, B., SCARPA, A. & HANAHAN, D. 2015. A Cross-Species Analysis in Pancreatic Neuroendocrine Tumors Reveals Molecular Subtypes with Distinctive Clinical, Metastatic, Developmental, and Metabolic Characteristics. *Cancer Discov,* 5**,** 1296-313.

YOUNG, K., LAWLOR, R. T., RAGULAN, C., PATIL, Y., MAFFICINI, A., BERSANI, S., ANTONELLO, D., MANSFIELD, D., CINGARLINI, S., LANDONI, L., PEA, A., LUCHINI, C., PIREDDA, L., KANNAN, N., NYAMUNDANDA, G., MORGANSTEIN, D., CHAU, I., WIEDENMANN, B., MILELLA, M., MELCHER, A., CUNNINGHAM, D., STARLING, N., SCARPA, A. & SADANANDAM, A. 2021. Immune landscape, evolution, hypoxia-mediated viral mimicry pathways and therapeutic potential in molecular subtypes of pancreatic neuroendocrine tumours. *Gut,* 70**,** 1904-1913.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:	M.Sc.
Intended learning outcomes:	The learning outcomes for the student are: a) understanding the basics of metabolism, cancer, machine learning and personalised medicine, b) get trained in interdisciplinary field of computational genomics to learn bioinformatics, statistics and mathematics and how to apply to above cancer project and c) learn single cell sequencing and animal experiments and handling of high-dimensional data (RNAseq/exome) from cancer field.

Advertising details

Project suitable for a student with a background in:

- ☒ Biological Sciences
- ☒ Physics or Engineering
- ☒ Chemistry
- ☒ Maths, Statistics or Epidemiology
- ☒ Computer Science