ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	ICR

Project details

Project title: Developing novel cancer therapeutics using human patient-derived cancer organoids

Supervisory team

Primary Supervisor:	Axel Behrens
Associate Supervisor(s):	Jessica Nelson
Secondary Supervisor:	Chris Lord

Divisional affiliation

Primary Division:	Breast
Primary Team:	Cancer Stem Cell
Site:	Chelsea

Project background

Our laboratory studies the molecular mechanisms underlying the cellular heterogeneity of tumours, in particular breast and pancreatic cancer. Notable recent contributions include the identification of cancer stem cell populations in both tumour types, and elucidation of key mechanisms of cellular regulation and communication (Blaas et al., 2016, Wang et al., 2019, Lan et al., 2022).

3D tumour organoids derived from patient biopsies closely recapitulate several properties of the original tumour (Boj et al., 2015). We have established an organoid biobank derived from human pancreatic cancer tissue obtained from patients undergoing curative resection for PDAC. We have and extensively characterised the PDAC biobank by exome sequencing, RNA sequencing, and proteomics. PDAC tumour organoids maintain PDAC cellular heterogeneity and is thus an excellent experimental system to better characterize human PDAC.

Project aims

- Molecular characterization of pathways governing human pancreatic cancer biology
- Identification and validation of novel therapeutic targets for PDAC treatment

Research proposal

To identify novel therapeutic vulnerabilities, we performed a pharmacological screen using 10.000 characterise chemical small molecule compounds on PDAC organoids. This work identified pathways required for PDAC biology and novel therapeutic targets. The function of relevant genes and pathways will be assayed using Crispr/Cas9-mediated genetic modification in human PDAC organoids, a technique that is well established in the laboratory, coupled with biochemical and in vivo analysis. The ultimate aim of this PhD project is the molecular characterization of pathways governing the biology of human pancreatic cancer, and validate novel therapeutic targets for PDAC treatment.

Literature references

BLAAS, L., PUCCI, F., MESSAL, H. A., ANDERSSON, A. B., JOSUE RUIZ, E., GERLING, M., DOUAGI, I., SPENCER-DENE, B., MUSCH, A., MITTER, R., BHAW, L., STONE, R., BORNHORST, D., SESAY, A. K., JONKERS, J., STAMP, G., MALANCHI, I., TOFTGARD, R. & BEHRENS, A. 2016. Lgr6 labels a rare population of mammary gland progenitor cells that are able to originate luminal mammary tumours. *Nat Cell Biol,* 18**,** 1346-1356.

BOJ, S. F., HWANG, C. I., BAKER, L. A., CHIO, II, ENGLE, D. D., CORBO, V., JAGER, M., PONZ-SARVISE, M., TIRIAC, H., SPECTOR, M. S., GRACANIN, A., ONI, T., YU, K. H., VAN BOXTEL, R., HUCH, M., RIVERA, K. D., WILSON, J. P., FEIGIN, M. E., OHLUND, D., HANDLY-SANTANA, A., ARDITO-ABRAHAM, C. M., LUDWIG, M., ELYADA, E., ALAGESAN, B., BIFFI, G., YORDANOV, G. N., DELCUZE, B., CREIGHTON, B., WRIGHT, K., PARK, Y., MORSINK, F. H., MOLENAAR, I. Q., BOREL RINKES, I. H., CUPPEN, E., HAO, Y., JIN, Y., NIJMAN, I. J., IACOBUZIO-DONAHUE, C., LEACH, S. D., PAPPIN, D. J., HAMMELL, M., KLIMSTRA, D. S., BASTURK, O., HRUBAN, R. H., OFFERHAUS, G. J., VRIES, R. G., CLEVERS, H. & TUVESON, D. A. 2015. Organoid models of human and mouse ductal pancreatic cancer. *Cell,* 160**,** 324-38.

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.

WANG, V. M., FERREIRA, R. M. M., ALMAGRO, J., EVAN, T., LEGRAVE, N., ZAW THIN, M., FRITH, D., CARVALHO, J., BARRY, D. J., SNIJDERS, A. P., HERBERT, E., NYE, E. L., MACRAE, J. I. & BEHRENS, A. 2019. CD9 identifies pancreatic cancer stem cells and modulates glutamine metabolism to fuel tumour growth. *Nat Cell Biol,* 21**,** 1425-1435.

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:
Experience with cell-based tissue cultures systems, and molecular laboratory techniques (i.e. cloning, DNA/RNA purification, Western blotting, etc).

Intended learning outcomes:

- To work independently on a defined project and to consult when appropriate.

- To take an interest in the relevant scientific literature.
- To present work at conferences and participate regularly in group meetings.
- To publish work in the scientific press.
- To generate insight and leads to further our understanding of cancer vulnerabilities, and how this could be exploited to improve cancer therapy

Advertising details

Project suitable for a student with a background in:

- [x] Biological Sciences
- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] Maths, Statistics or Epidemiology
- [ ] Computer Science

References