RxCelerate

Oncology Models

info@rxcelerate.com rxcelerate.com

RxCelerate approach to oncology drug discovery and development

We can provide a range of models to align with stage of discovery and development, from proof-of-concept through to multiple indication efficacy.

Efficacy studies may need a combination of models to predict successful progression to clinic. Based on fundamental understanding of target and primary and subsequent indications, we can build a programme that obtains the key data in the most effective way possible.

Typical oncology pipeline

Target validation

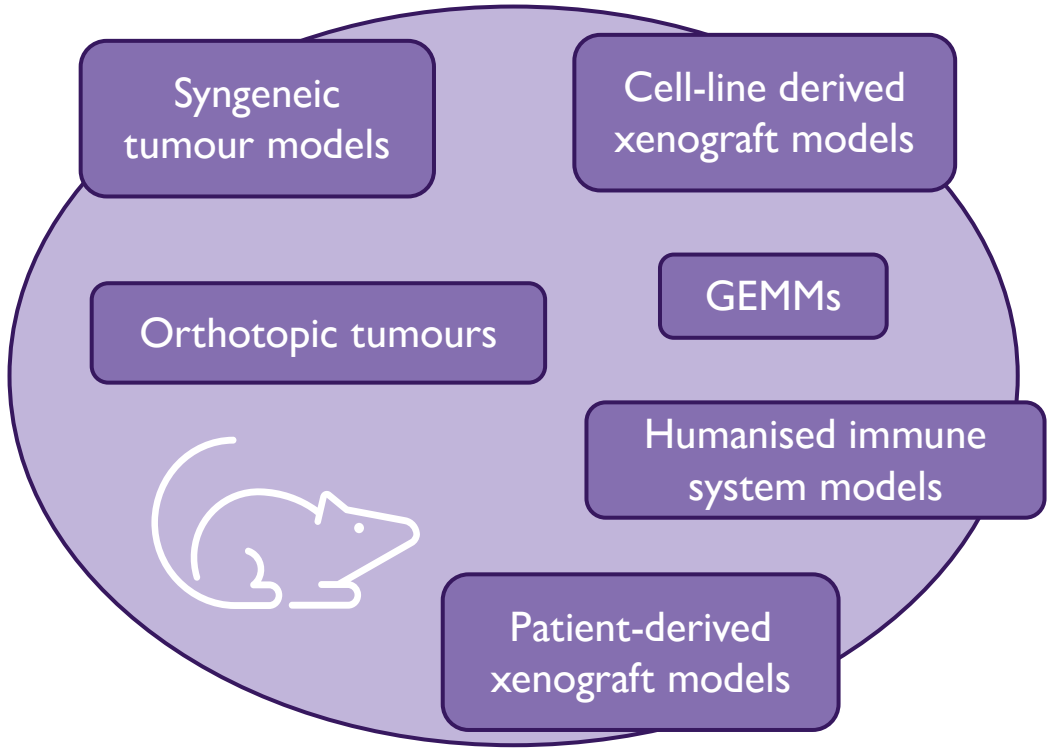
e.g. subcutaneous (xenograft or syngeneic depending on target)

- Growth characterisation (inhibition or stasis)
- Comparator evaluation
- Potential combination therapies

Model and candidate selection

(e.g. orthotopic, humanised, PDX)

- Desired PD endpoints
- Efficacy demonstration in simple and complex models
- Establish dosing regimen
- Investigate combination therapies



Model capabilities – which model is right for you?

We have extensive experience in model development and disease induction, ensuring our models represent translatable tools as close to the human disease as possible.

The ethos of all of our animal model use is: "BACK TO FIRST PRINCIPLES"

Our *in vivo* work is embedded within cutting-edge high health and welfare status animal units across the Cambridge area, with access to a wide range of state-of-the-art in-life monitoring equipment and surgical facilities.

Subcutaneous

- Quick to establish.
- Easy to measure and monitor.
- Xenograft:
  - Initial screening of novel therapeutics on tumour growth.
- Syngeneic:
  - Ideal for screening of cancer immunotherapies.

Orthotopic

- Mimics a primary tumour in a more clinically relevant organ & tumour microenvironment (TME).
- May require surgery for implantation.

Systemic

- Injection of tumour cells into the bloodstream to model cancers stemming from blood-forming tissues.

Metastatic

- Investigate mechanism of disease, progression, and seeding.
- Some orthotopic tumour models may spontaneously metastasize.
  - Closer simulation of early to late-stage disease progression.
- Experimental metastasis models for late to end-stage of disease.
  - Intravenous or intracardiac injection seeds to bones and distant organs.
  - Direct injection into organ (e.g. through the BBB).

Humanised models

- Immunocompromised mice receive cells to "reconstitute" a functioning immune system resembling that of humans.
- Recreates the environment that drugs will encounter in humans.
- Different immune cell subtypes can be used to:
  - Test efficacy of therapeutic agents in different immune states.
  - Investigate mechanisms involved in their action on the disease.

Subcutaneous (heterotopic) tumour models

"First pass" screening tool for early discovery to ensure appropriate pharmacology and activity.

Experience with a range of xenograft and syngeneic cell line-derived breast cancer models to evaluate efficacy.

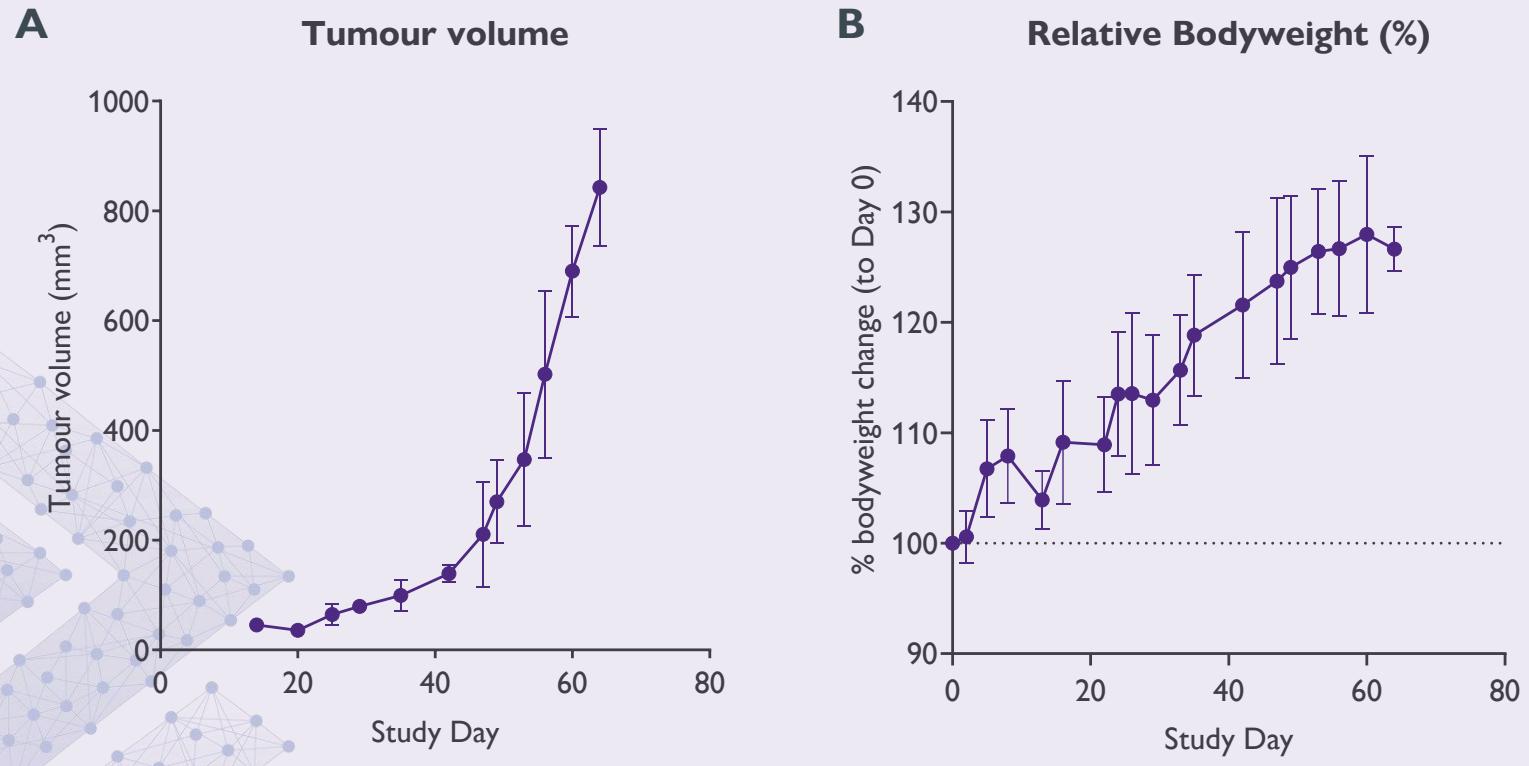


Figure 1. Mean tumour volume (n=4, ±SD) of mice implanted subcutaneously with human TNBC (A) and mean relative % bodyweight compared to Day 0(n=4, ±SD) (B).

- Subcutaneous model of human triple negative breast cancer (TNBC).
- TNBC model lacks receptors for estrogen, progesterone, and HER2.
- The model was established in female NSG mice.
- Tumour volume measured by electronic calliper measurements.
- No model-related bodyweight loss observed.

Orthotopic models – breast cancer

Murine TNBC cells injected into the mammary fat pad of female athymic nude mice.

- Growth monitored by electronic calliper measurements and bioluminescent imaging (BLI).
- Cell seeding to the lungs, liver, and long bones can be observed with *ex vivo* BLI.
- H&E images of FFPE embedded tissues were able to demonstrate pleomorphic cells in the tissue regions corresponding to the luminescence.

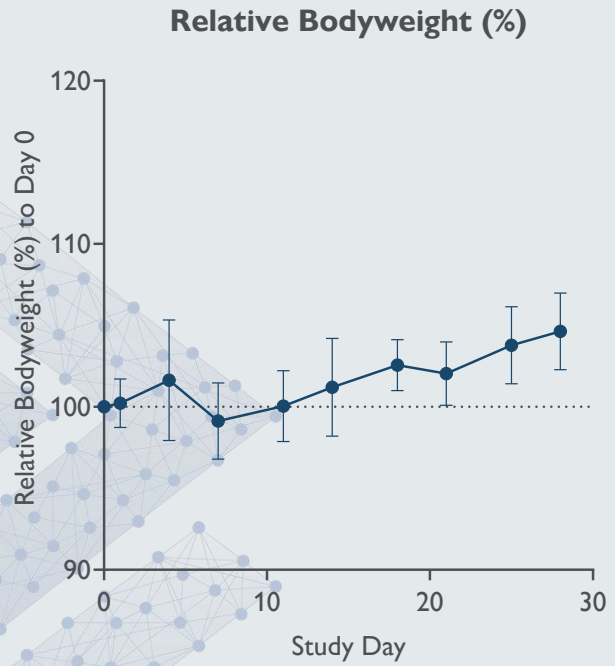
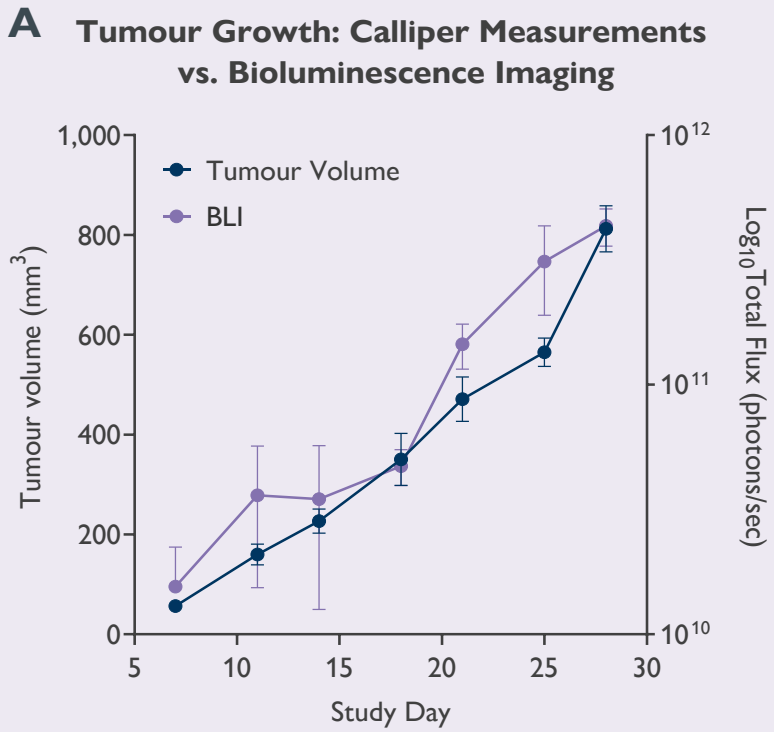


Figure 2. Mean relative % bodyweight compared to Day 0 (±SD) of mice injected with murine TNBC, (n=4).



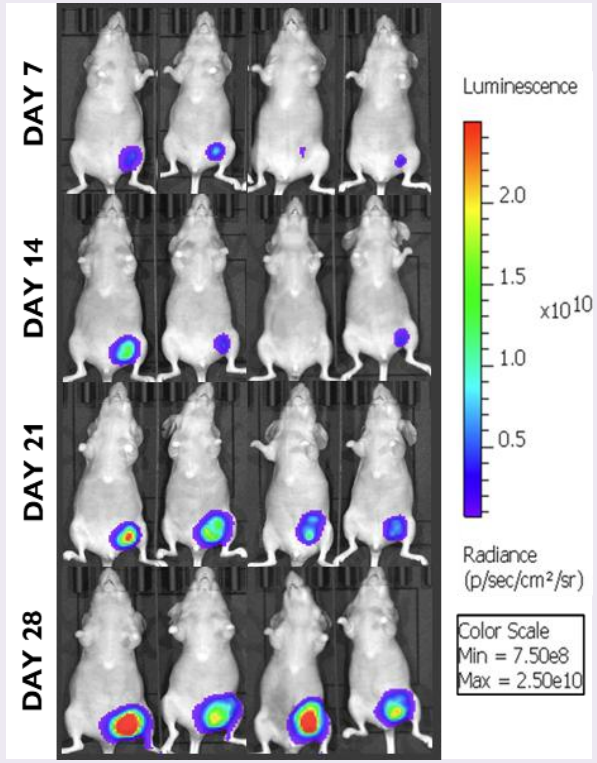
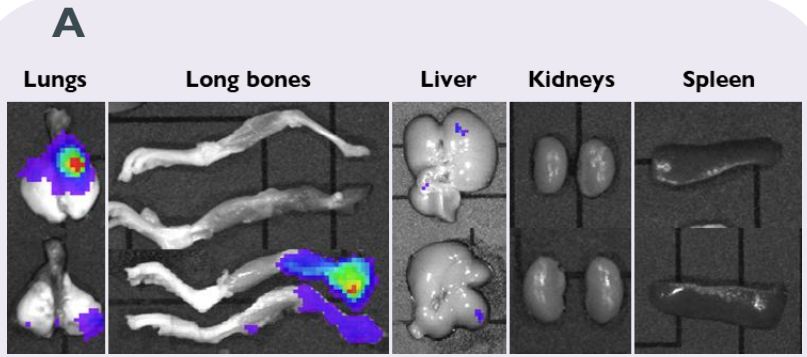


Figure 3. Mean tumour volume (electronic callipers) vs mean BLI of mice injected with murine TNBC (±SD) (A) and representative in-life BLI images at selected days throughout the study (B), (n=4).

Orthotopic models – breast cancer



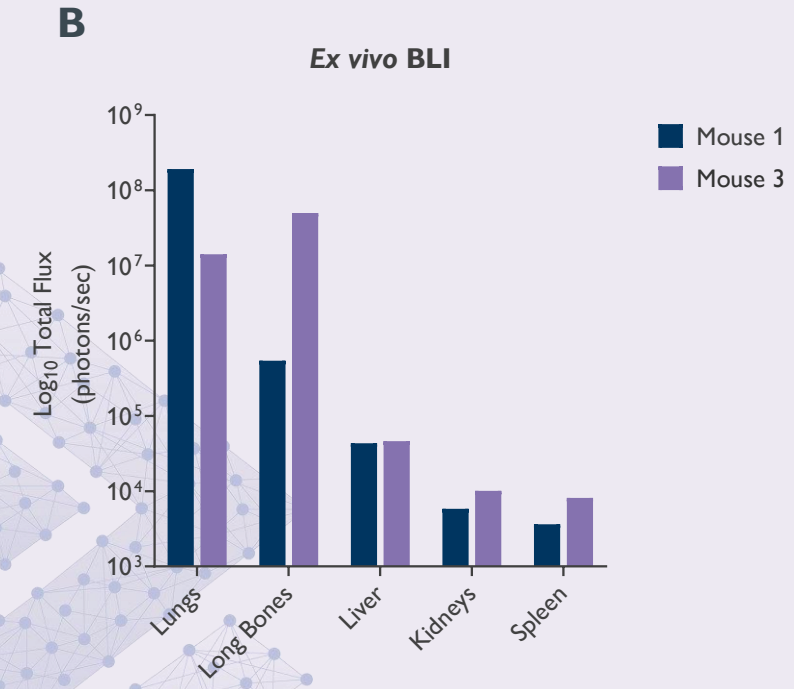


Figure 4. *Ex vivo* bioluminescence images of target organs (A). Positive signal was observed in the lungs, long bones, and liver (B).

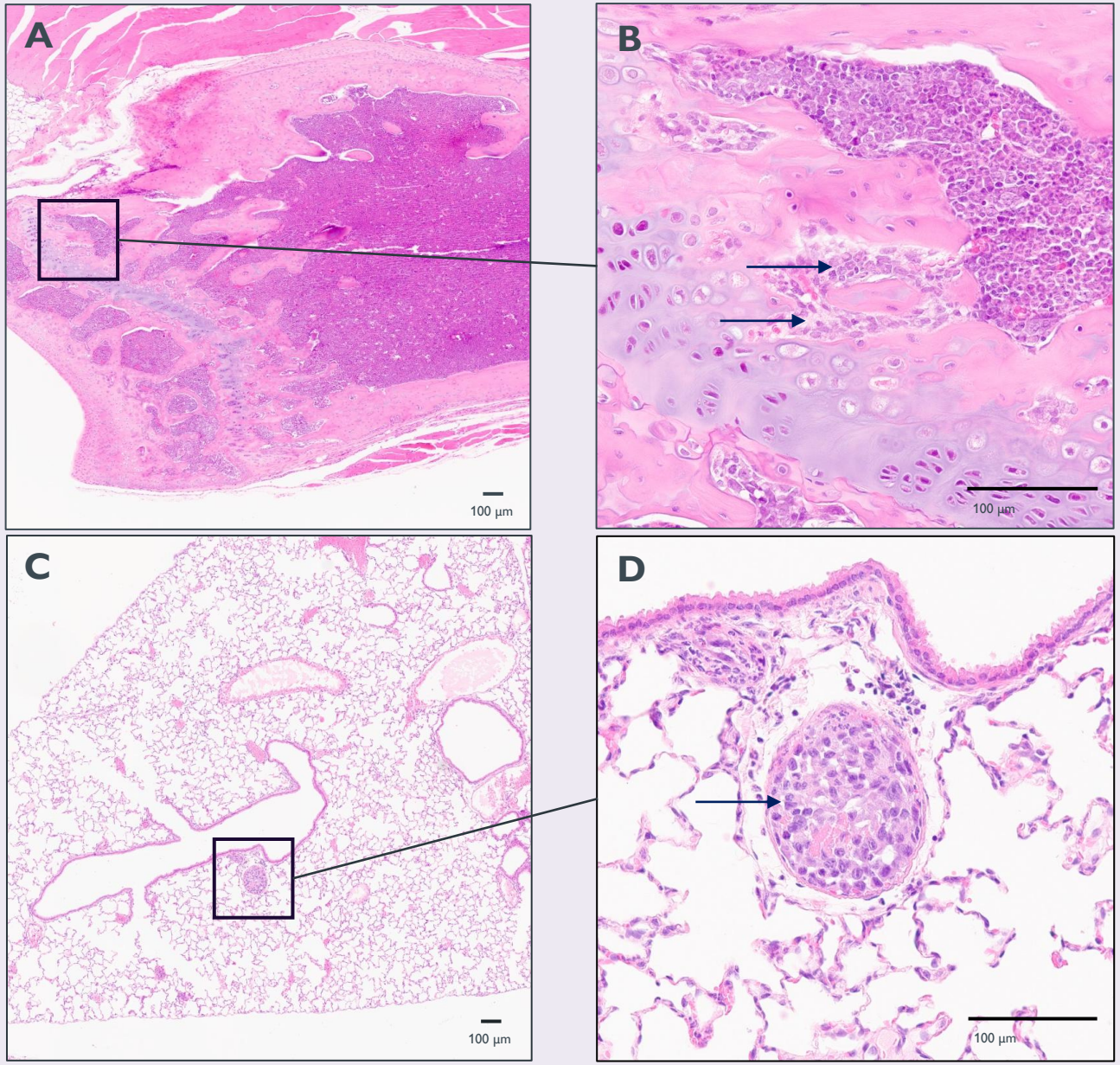
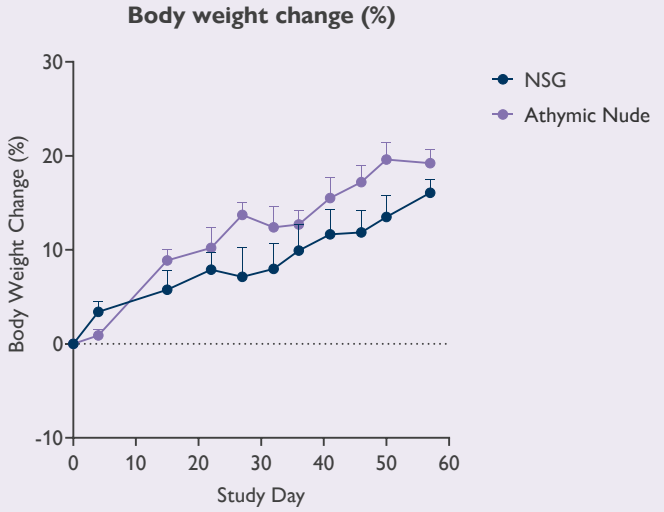


Figure 5. H&E of the femoral head where there was clear luminescent signal at 3x magnification (A) and 20x magnification (B). Arrows demonstrate pleiomorphic cells proliferating within the bone.

H&E of lungs show a small tumour mass at 3x magnification (C) and 20x magnification (D). The arrow highlights the encapsulated mass of pleiomorphic tumour cells.

Orthotopic models – breast cancer



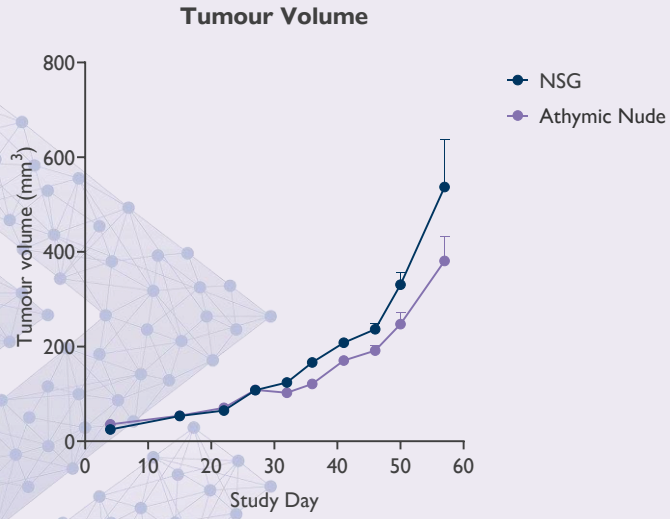
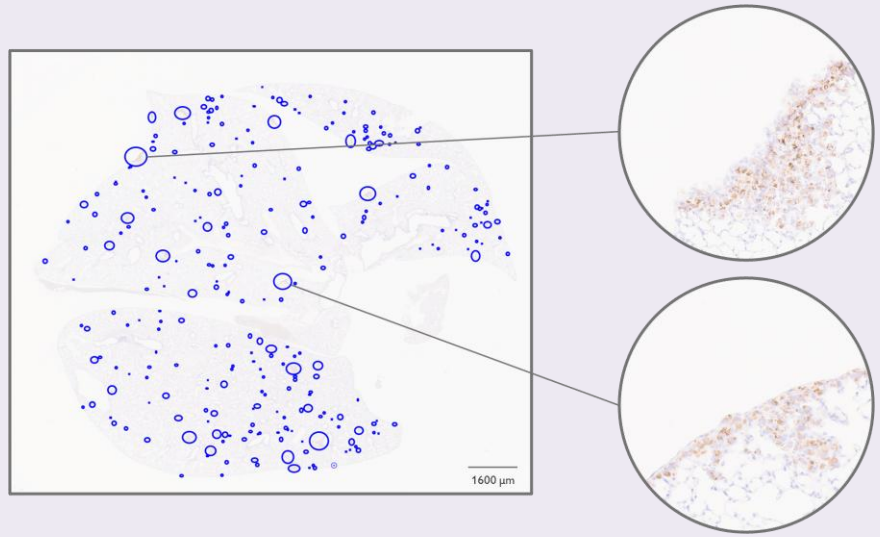


Figure 6. Mean relative % bodyweight compared to Day 0 (+SD) (A) and mean tumour volume (+SD) of mice implanted orthotopically with human TNBC (B). (n=4-6)

Human TNBC cells in mammary fat pad of female NSG and athymic nude mice.

- Primary tumour implanted into the mammary fat pad of female mice.
- Tumour growth monitored by electronic calliper measurements.
- Cell seeding to the lungs, liver, lymph nodes, and kidneys can be observed at later stages.
- Option of bioluminescent imaging using luciferase tagged cell lines to monitor tumour growth and metastasis in-life.
- Option of histology and using IHC techniques assess quantitatively spatial variation of tumour cells in the tissue.



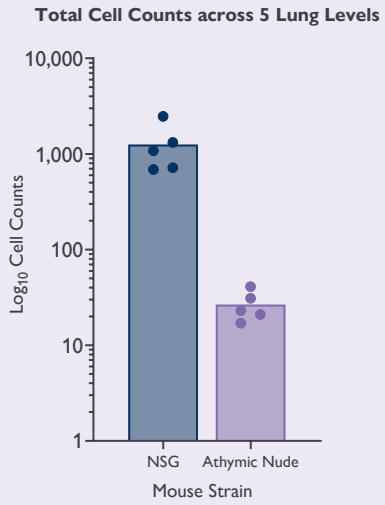


Figure 7. IHC antibody marker specific to human cells enlisted to highlight mobile tumour cells in a xenograft model. Quantitative assessment of positive single cells and clusters across 5 lung levels showed tumour cell mobility and seeding was greater in the lungs of NSG mice compared to athymic nude mice.

Flexible and comprehensive tumour analysis

Bioluminescent imaging (BLI):

- Visual confirmation of cell placement and viability.
- Non-invasive, real-time measurement of tumour establishment, growth, and seeding.
- *Ex vivo* imaging can be used to detect metastatic lesions.

Wide range of downstream tumour analysis methods:

- Histological and genetic profiling.
- Analysis of tumour-infiltrating immune cells via flow cytometry.
- Tumour gene and protein expression (RNAseq, proteomic analysis).
- Presence of test agents in excised tumours, including detection of in vivo modifications and/ or cleavage with our ProQuant™ MS platform.

Histological profiling:

- Tinctorial stains for specific tissue changes.
- Tailored immunohistochemistry to interrogate key in vivo changes including cell turnover, cell populations, and drug target distribution.
- Pathologist interpretation of slides, including morphometric analysis.
- Perform qualitatively or quantitatively assessment of tissues and assess spatial variation.

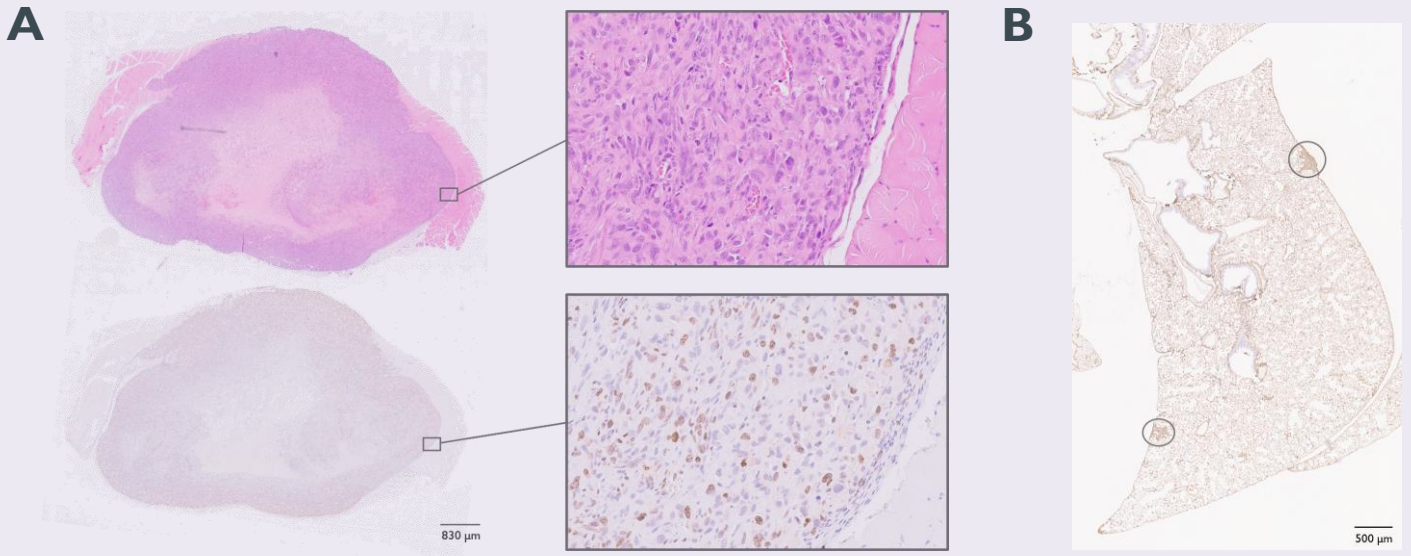


Figure 2. H&E and Ki67 IHC of tumours from an orthotopic TNBC model highlighting sites of necrosis and active cell proliferation (A). IHC of human specific marker in the lungs shows tumour cell seeding and early formation of a niche within the pleura (B).

RxCelerate

Architects of Drug Discovery and Development

RxCelerate
The Dorothy Hodgkin Building
Babraham Research Campus
Babraham, Cambridge CB22 3FH

T: +44 (0)1223 839 557

info@rxcelerate.com

rxcelerate.com

rxcelerate-limited