CHEMPARTNER
DEDICATED TO LIFESCIENCE

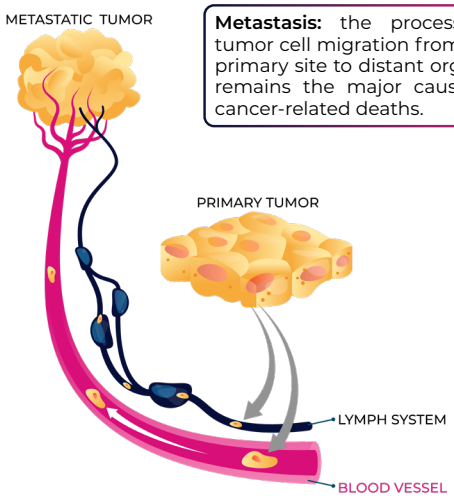
IN VIVO MODELS FOR MIMICKING METASTATIC DISEASE

Metastasis is an inefficient process, but the consequences are devastating as metastatic disease accounts for >90% of cancer-related deaths.

Spontaneous metastatic models allow the dynamics between the primary tumor, local region spread, and ultimately disseminated disease, to be mimicked. Experimental metastatic models provide critical tools for understanding the biology of metastasis and also facilitate the development of novel therapeutic approaches

- New, effective therapies need to account for:
  - The dynamic plasticity of the cancer cells as they progress through the metastatic cascade
  - The mechanisms used by dormant and growing metastases to evade immune surveillance

ChemPartner has developed and validated a number of CDX and syngeneic *in vivo* models that aim to recapitulate the biological complexity associated with late-stage disease.



Metastasis: the process of tumor cell migration from the primary site to distant organs, remains the major cause of cancer-related deaths.

MOUSE MODELS OF METASTASIS

MODEL	ADVANTAGES	DISADVANTAGES
SPONTANEOUS METASTASIS	• Development of metastases from primary site mimics human disease • Models all stages of metastatic cascade • Immunocompetent host (allograft) • Low cost	• Mouse microenvironment • Applicable to a limited number of cell lines • Poor tropism of metastasis in reference to clinical setting • Asynchronous metastatic development • Resection of primary tumor only possible for certain models • Immunocompromised host (xenograft)
EXPERIMENTAL METASTASIS	• Rapid and reproducible development of metastases • Site-specific metastases development • Wide applicability to vast number of cell lines and tumor models • Immunocompetent host (allograft) • Low cost	• Mouse microenvironment • Only models late stage of metastatic cascade • Immunocompromised host (xenograft)
GEMM	• Metastatic spread on spontaneous de novo tumors — mimics human disease • Tumors develop in natural environment • Tumors display heterogeneity and resemble molecular and histopathological features of human disease • Potential to model all stages of metastatic cascade • Immunocompetent host	• Mouse microenvironment • Genetics are often not representative of human disease • Promoters not well defined to a specific lineage • Can have low penetrance and long latency to development of metastatic disease • Poor tropism of metastasis in reference to clinical setting • Require extensive breeding programs (cost and time) • Asynchronous metastatic development

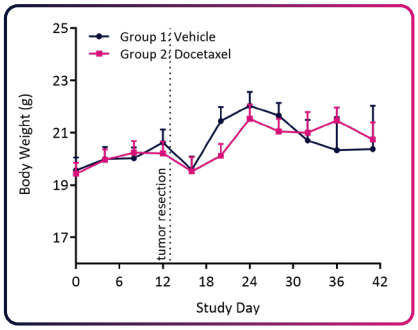
Table adapted from DOI: 10.1242/dmm.030403

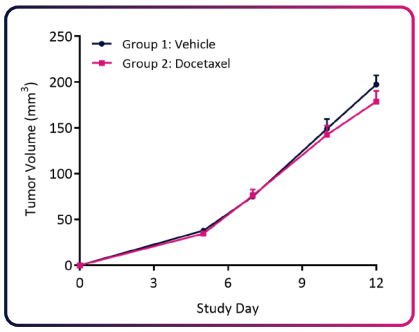
VALIDATED SYNGENEIC MODELS

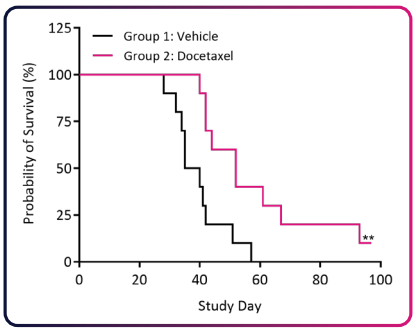
4T1 MOUSE ORTHOTOPIC SPONTANEOUS BREAST CANCER METASTASIS MODEL

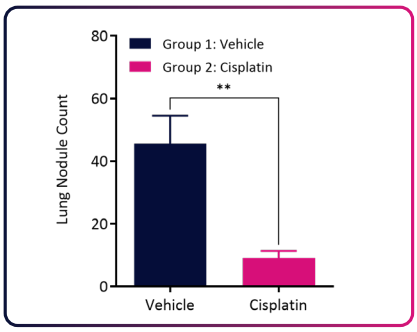
(WITH RESECTION OF PRIMARY TUMOR)

- Mouse 4T1 breast cancer cell line sourced from ATCC (CRL-2539™)
- Spontaneous metastases established following injection of 4T1 cells into the mammary fat pad of female BALB/c mice
- Primary tumor surgically resected on day 13
- Survival used as endpoint (can be tailored to use humane endpoints if required)
  - Treatment: Docetaxel significantly increases the survival of mice (p=0.0034)
- Lung weight and number of lung nodules recorded on termination
  - Treatment: Cisplatin significantly reduces the number of lung nodules (p=0.0029)



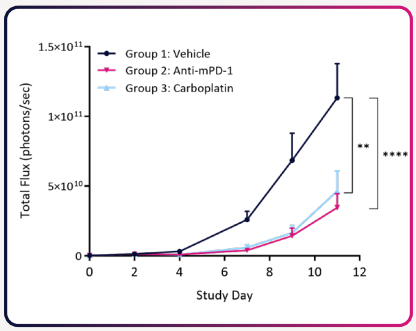


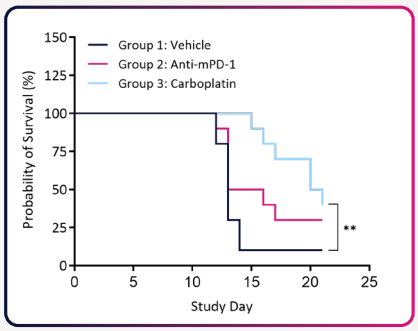


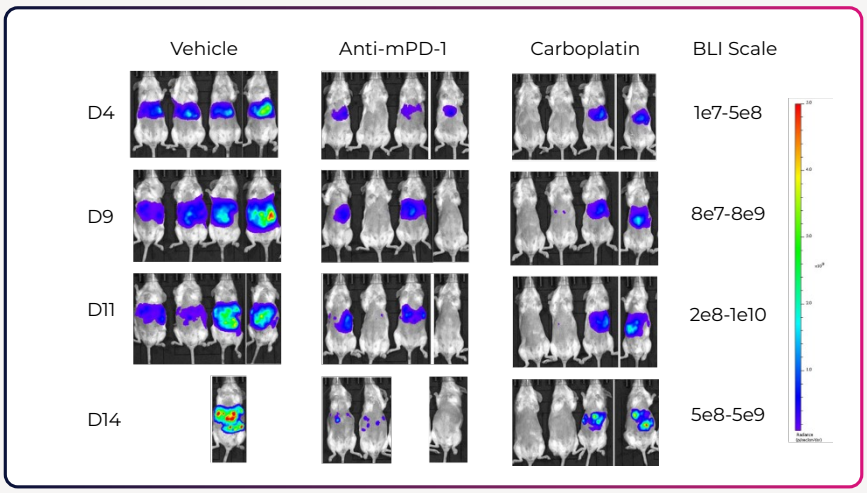


CT26-LUC MOUSE HEMI SPLENECTOMY LIVER METASTASIS MODEL

- Mouse CT26-Luc colon cancer cell line sourced from ATCC (CRL-2638™, Luc-transduced in house)
- Liver metastases modelled following hemi-splenectomy after injection of CT26-Luc cells into the spleen of female BALB/c mice
- Injected half of spleen was resected, other half of the spleen preserved
- Treatment: Significant decrease in tumor-associated bioluminescence was observed following treatment with anti-mPD-1 (p<0.0001) and Carboplatin (p=0.0010)
- Survival can be used as endpoint:
  - Treatment: Carboplatin significantly increases the survival of mice (p=0.0027)
- Evidence of lesions in the liver of mice



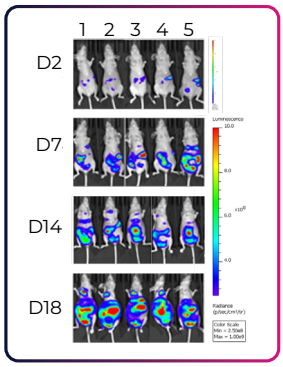


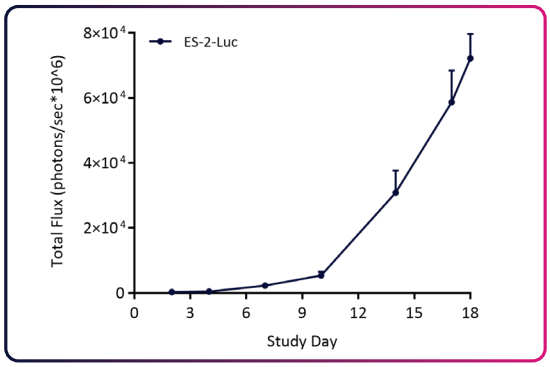


VALIDATED CDX MODELS

ES-2-LUC HUMAN OVARIAN CANCER INTRAPERITONEAL METASTASIS MODEL

- Human ovarian cancer cell line ES-2 (ATCC) was transduced to express firefly luciferase (100% STR profile match)
- Intraperitoneal growth established in female BALB/c nude mice
- Evidence of peritoneal ascites – attributed to increase in body weight after day 14
- *Ex vivo* BLI signal detected in liver, spleen, lung, kidney, pancreas, and intestines

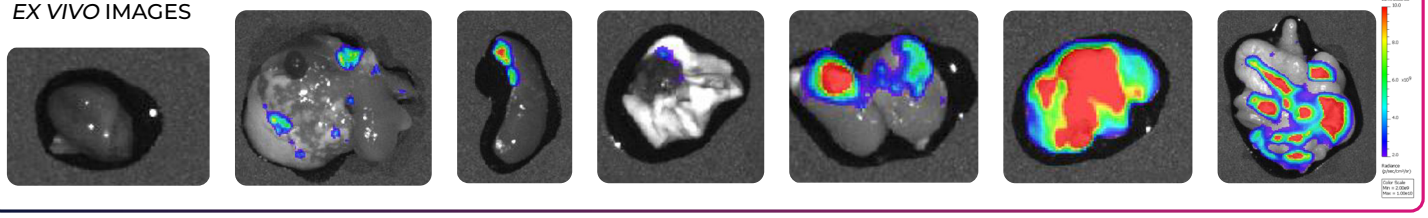




EX VIVO BIOLUMINESCENCE MEASUREMENT (PHOTONS/SEC)

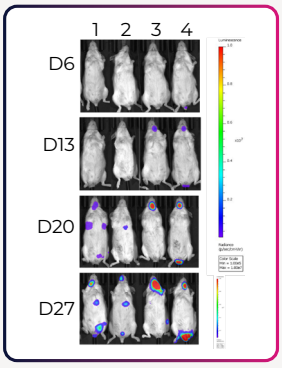
ANIMAL ID	HEART	LIVER	SPLEEN	LUNG	KIDNEY	PANCREAS	INTESTINES	ASCITES (ML)
1	1.08E+09	2.07E+10	1.95E+10	2.55E+10	6.00E+10	9.82E+10	4.29E+11	3.0
2	4.44E+08	8.60E+09	1.13E+10	2.73E+09	1.94E+10	1.84E+11	2.04E+11	3.6
3	1.81E+08	3.84E+09	5.88E+08	4.19E+09	3.10E+09	9.39E+10	2.64E+11	4.0
4	2.24E+09	4.92E+10	2.23E+10	1.26E+10	1.22E+10	2.87E+11	3.07E+11	2.8
5	3.90E+08	1.37E+10	3.58E+09	9.81E+08	1.26E+10	9.26E+10	2.42E+11	2.0

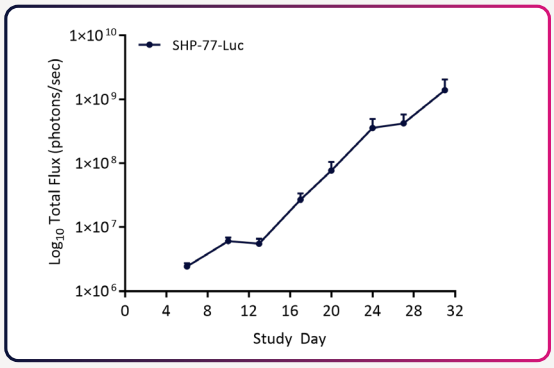
EX VIVO IMAGES



SHP-77-LUC HUMAN LUNG CANCER - SYSTEMIC METASTASIS MODEL

- Human lung cancer cell line SHP-77 (ATCC), engineered to express firefly luciferase (100% STR profile match)
- Disseminated metastases established following intravenous (tail vein) injection of SHP-77-Luc cells using female NCG mice
- Body weight maintained for the duration of the study
- Evidence of disseminated metastatic lesions

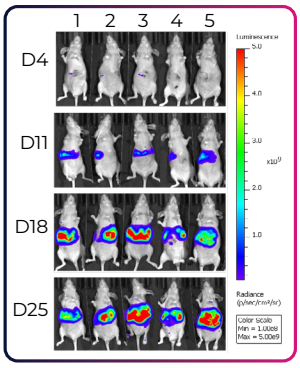


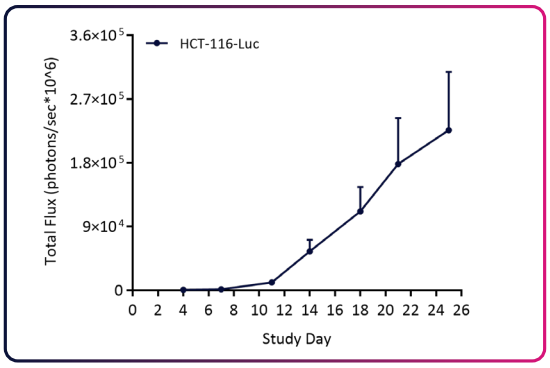


VALIDATED CDX MODELS

HCT-116-LUC HUMAN COLON CANCER – HEPATIC PORTAL VEIN METASTASIS MODEL

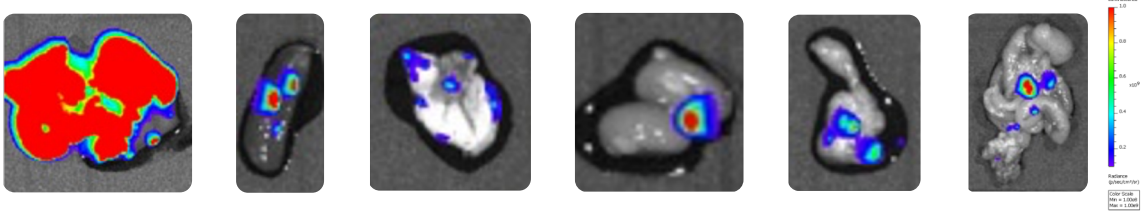
- Human colon cancer cell line HCT-116 (ATCC) transduced to express firefly luciferase (100% STR profile match)
- Metastasis established following hepatic portal vein injection of HCT-116-Luc cells using female BALB/c nude mice
- Evidence of metastatic lesions in the liver
- *Ex vivo* BLI signal detected in liver, spleen, lung, kidney, pancreas, and intestines





EX VIVO BIOLUMINESCENCE MEASUREMENT (PHOTONS/SEC)						
ANIMAL ID	LIVER	SPLEEN	LUNG	KIDNEY	PANCREAS	INTESTINES
2	3.43E+11	2.70E+07	1.23E+09	3.49E+07	7.31E+07	1.48E+10
3	1.72E+11	1.53E+07	5.62E+08	4.01E+07	1.52E+07	1.16E+08
4	4.78E+11	2.51E+06	2.32E+08	4.21E+06	2.28E+07	6.72E+08
5	2.40E+11	1.99E+09	1.14E+09	1.20E+09	1.25E+09	2.91E+09
6	1.54E+11	4.84E+06	2.34E+09	7.42E+06	2.08E+06	4.39E+08

EX VIVO IMAGES



SUMMARY

In vivo experimental and spontaneous metastatic mouse models are important preclinical tools for unraveling the complex interactions involved in the metastatic cascade.

ChemPartner's models allow for the evaluation of disease progression (invasion and migration) as well as targeting metastasis, in a range of robust and well-validated models.

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