CrownBio
CONNECTING SCIENCE TO PATIENTS

Corporate Headquarters:
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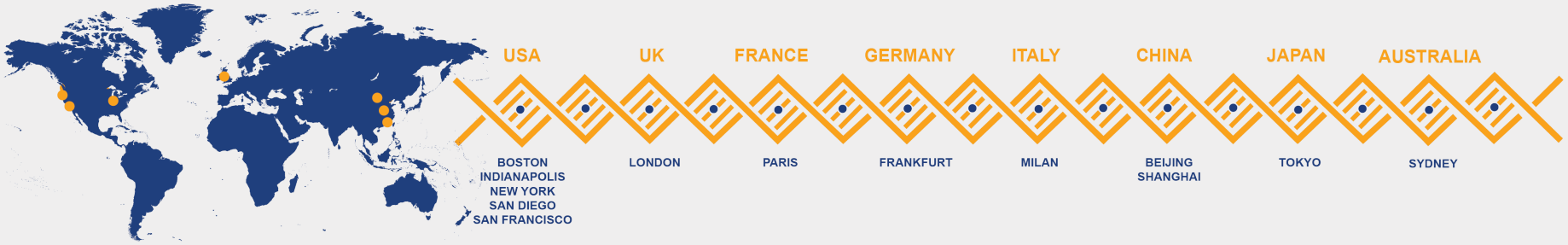
www.crownbio.com

CrownBio Resources for Breast Cancer Research

Premium Models and Services for Oncology Drug Discovery



Breast Cancer Facts and Treatment Options

- Leading cancer type diagnosed in women worldwide
- 25% of all cancer cases, >half a million deaths per year
- Treatment decisions based upon tumor histology and status of 3 main biomarkers
  - **ER+ and PR+** breast cancer (hormone driven; 2/3 of breast cancers) treated with **antihormonal agents**
  - **HER2+** cancers (15%-20% of breast cancers) early and advanced stage disease treated with **targeted agents** e.g. Herceptin®
  - **TNBC** (including BRCA1/2 deficient tumors) lacks ER, PR, and HER2, associated with **poor prognosis and limited treatment options**

Need for Preclinical Models to Test New Treatment Options

- Survival rates of patients with early breast cancer have improved steadily over the past 15 years
- However metastatic disease prognosis still poor
- Treatment options for TNBC still limited
- To accelerate treatment progress, the discovery and development of new preventative and therapeutic strategies is needed
- Development of better and more representative *in vivo* models of human breast cancer is of crucial importance for preclinical trials testing new cancer therapeutics

CrownBio Breast Cancer Translational Platform

- Rapidly progress your integrated drug and immunotherapeutic development programs for hormone dependent, independent, and TNBC with:
  - A vast array of matched models for a seamless transition from *in vitro* **cell line screening** to validated *in vivo* **cell line derived xenograft lead compound evaluation**
  - **Bioluminescent xenograft** models for **real time tracking** of disease progression and intervention analysis
  - **Patient-derived xenograft (PDX)** models, preserving the pathological and genetic characteristics of the original patient tumor, providing **robust preclinical data before moving into the clinic**
  - A comprehensive, well-characterized collection of **syngeneic**, advanced **murine allograft**, **humanized PDX and xenograft** models for **immunotherapeutic drug discovery and development**

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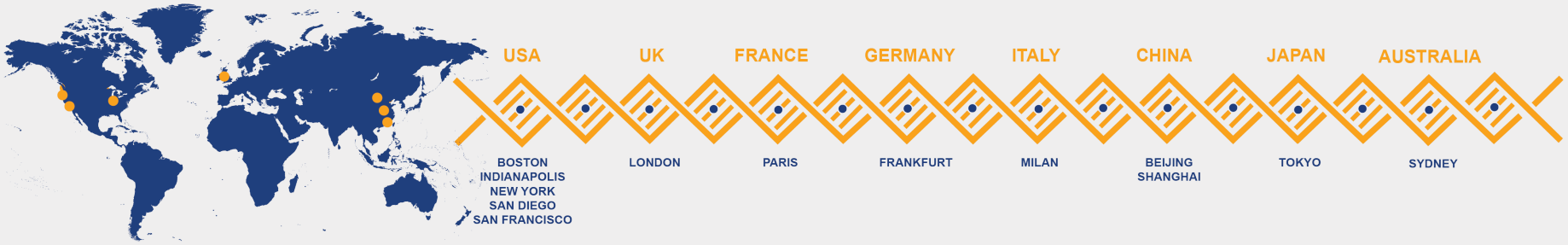
ValidatedXeno Metastatic Cell Line Derived Xenograft Models

MDA-MB-231 and MCF7



The Need for Metastatic Disease Models

- Metastatic breast cancer currently remains incurable with a poor 5-year overall survival rate
- Unmet need for new and improved models and treatments for this patient group
- CrownBio has developed a range of breast cancer metastasis models
  - orthotopic, experimental, and bioluminescent models of lung, bone, and brain metastasis based on the MDA-MB-231 TNBC and MCF7 hormone dependent cell line derived xenograft models

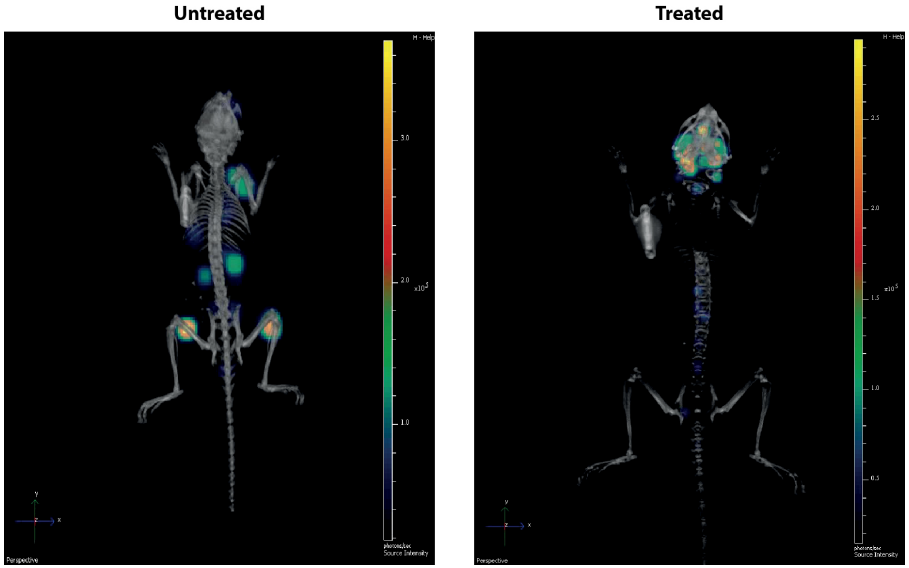
Spontaneous Lung Metastasis MDA-MB-231 Model

- MDA-MB-231 model metastasizes to the lung from orthotopic implantation or tail vein injection

Group	Mice with Lung Metastasis			Number of Metastatic Foci		
	Week 5	Week 6	Week 7	Week 5	Week 6	Week 7
Vehicle	2/4 (50%)	3/4 (75%)	3/4 (75%)	>100	>100	>100
Docetaxel	0/4	0/4	0/4	0	0	0

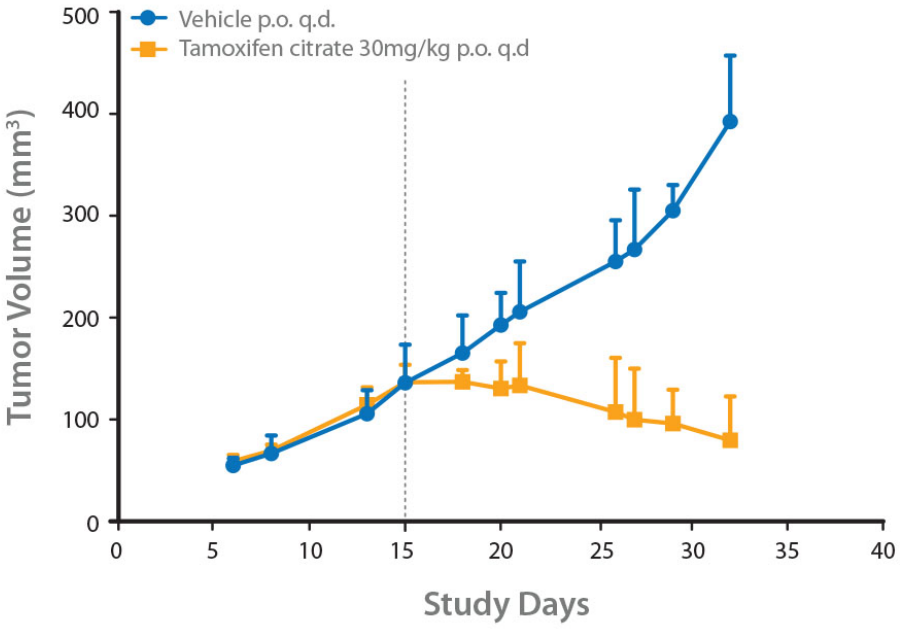
Bioluminescent MDA-MB-231 Brain Metastasis Models

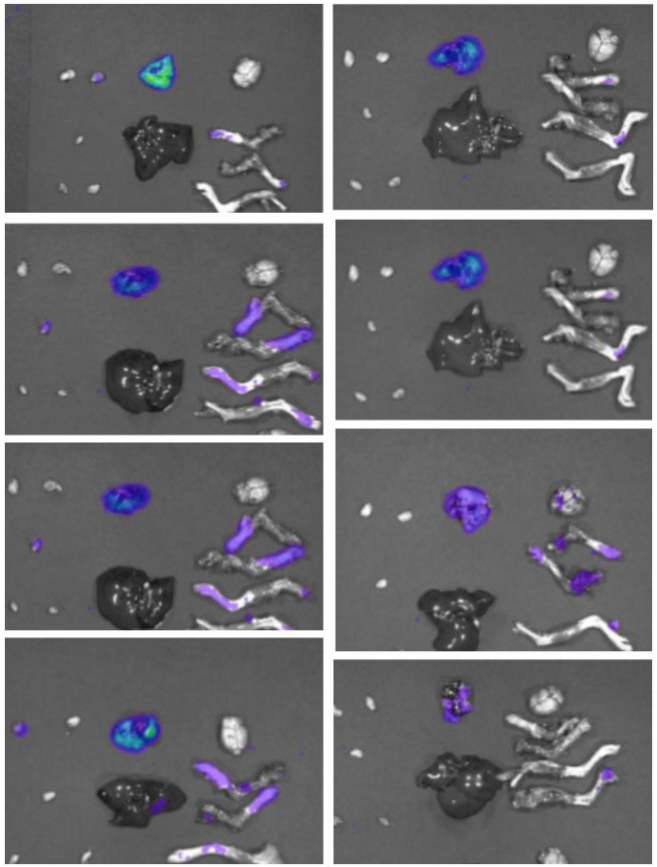
- Brain metastases especially difficult to treat due to inability of many anticancer agents to cross the blood-brain barrier (BBB)
- MDA-MB-231 bioluminescent cells implanted orthotopically in MFP, spontaneous metastases in lymph nodes, lungs, brain
- Injected intracardially to evaluate experimental bone and brain metastasis



Bioluminescent MCF7 Metastasis Model

- Primary tumor is sensitive to tamoxifen citrate
- Metastatic lesions in lung and bone detected by terminal *ex vivo* BLI





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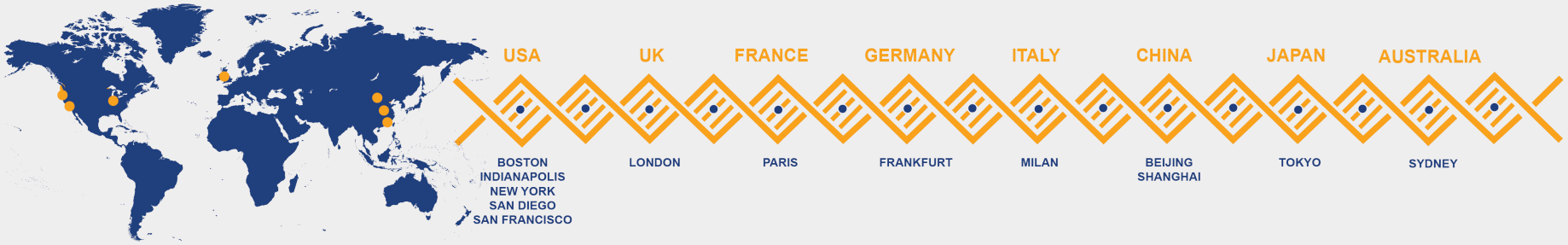
HuPrime Breast Cancer PDX Models

CrownBio

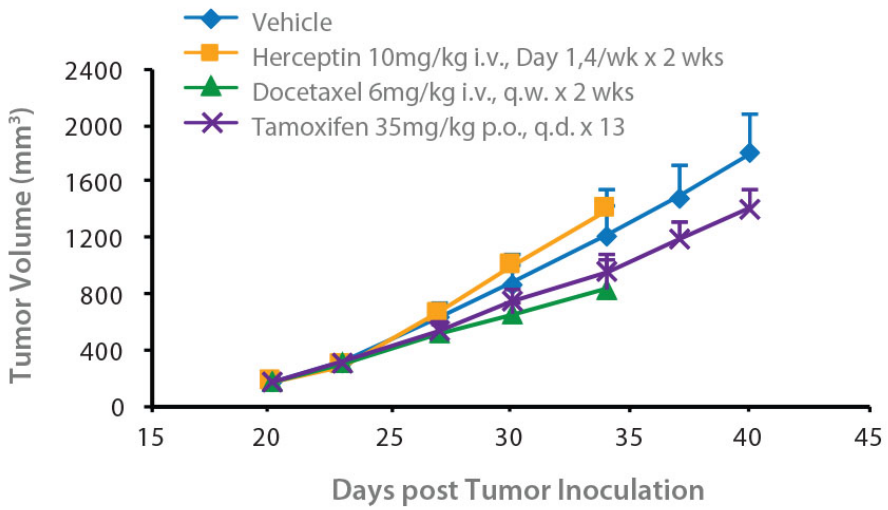


HuPrime Breast Cancer Collection

- Currently encompasses 27 different breast cancer PDX models
- Captures the diversity observed in the patient population
  - Models from US, European, and Asian populations
  - Derived from treatment naïve and pretreated patients
  - Primary and metastatic models, consistent with aggressive disease
  - Models generated from several different types of lesion
- Well-characterized and fully validated PDX
- All ER, PR, HER2 status confirmed by IHC
- Model data stored in HuBase™

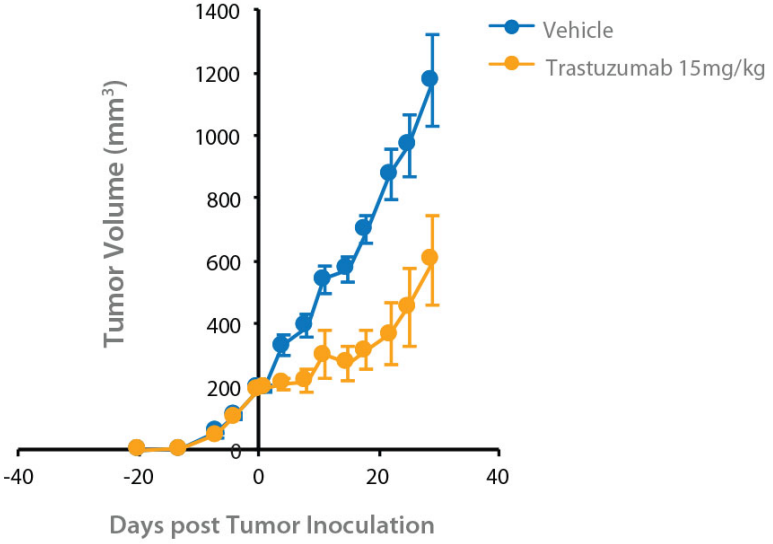
HuPrime Breast Cancer *In Vivo* Pharmacology

Hormone dependent BR1115
(ER 2+, PR 3+, HER2 0.5+)



Subcutaneous model

Hormone independent
BR5009
(ER-, PR-, HER2+)



Subcutaneous model

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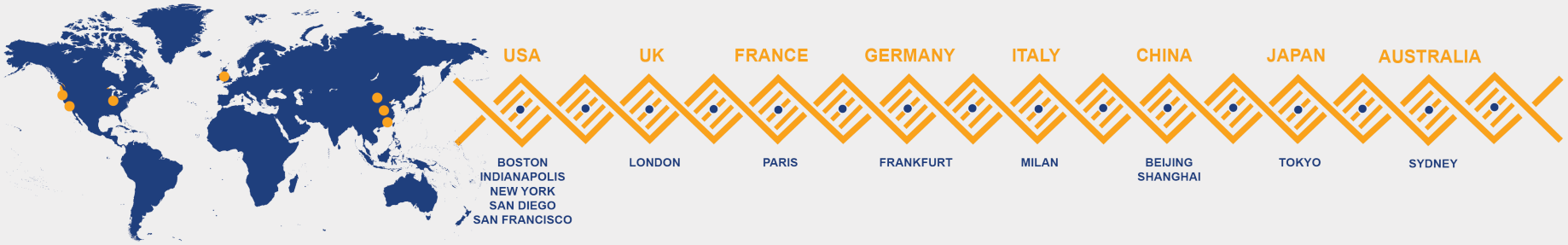
Breast Cancer Models in Immunotherapy Research

Platforms of Murine and Human Immunity



CrownBio's Translational Platforms for Immunotherapy

- Comprehensive, well-characterized collection
- Research platforms of murine immunity
  - Syngeneics
  - GEMM
  - MuPrime (murine allograft models)
- Humanized PDX and cell lined derived xenograft models

MuPrime Breast Cancer Models

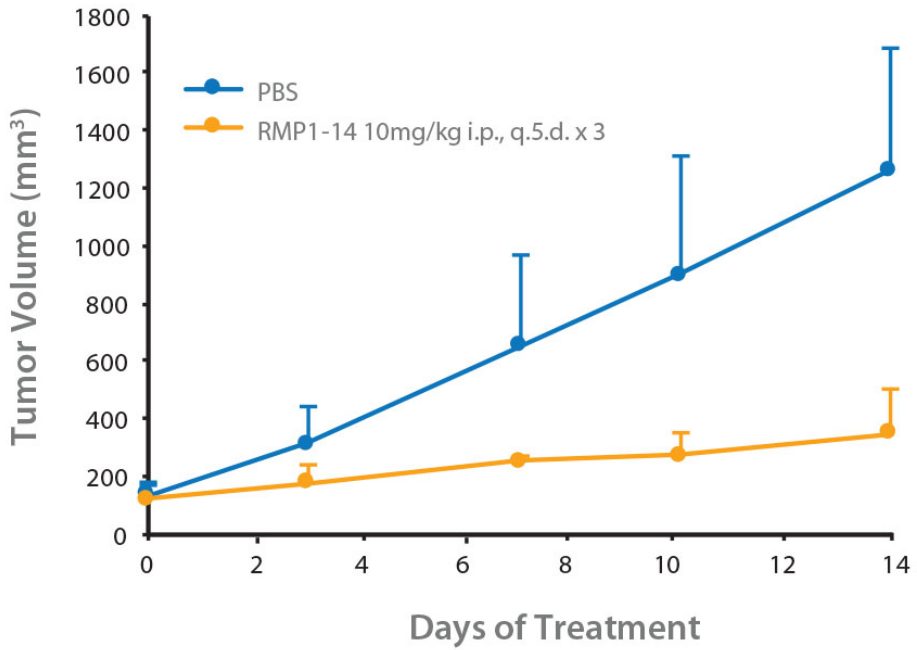
- Allografts of spontaneous murine tumors derived from GEMM or carcinogen-induced models, studied in mice with complete immunocompetency

MuPrime ID	Cancer Type	Mutations/ Carcinogen	Strain Background	Tumor Progression	MuPrime Setup	MuPrime Validation	Efficacy Ready?
Traditional GEMM-Derived MuPrime							
mBR6004	Breast	MMTV-PyVT TG	FVB/N				Ready
MuPrime Derived from Non-Germline GEMM using CRISPR-Cas9 *In Vivo* Gene Editing[§]							
	Breast	P53 cKO; BRCA1 cKO; MMTV-Cre	C57BL/6	Ongoing			
	Breast	P53 cKO; SMAD4 cKO; CDH1 cKO; MMTV-Cre	C57BL/6	Ongoing			

[§] The models have completed AAV-sgRNA-Cre vector construction and virus production. Following viral injection (which is currently being optimized) tumors will develop in two to six months

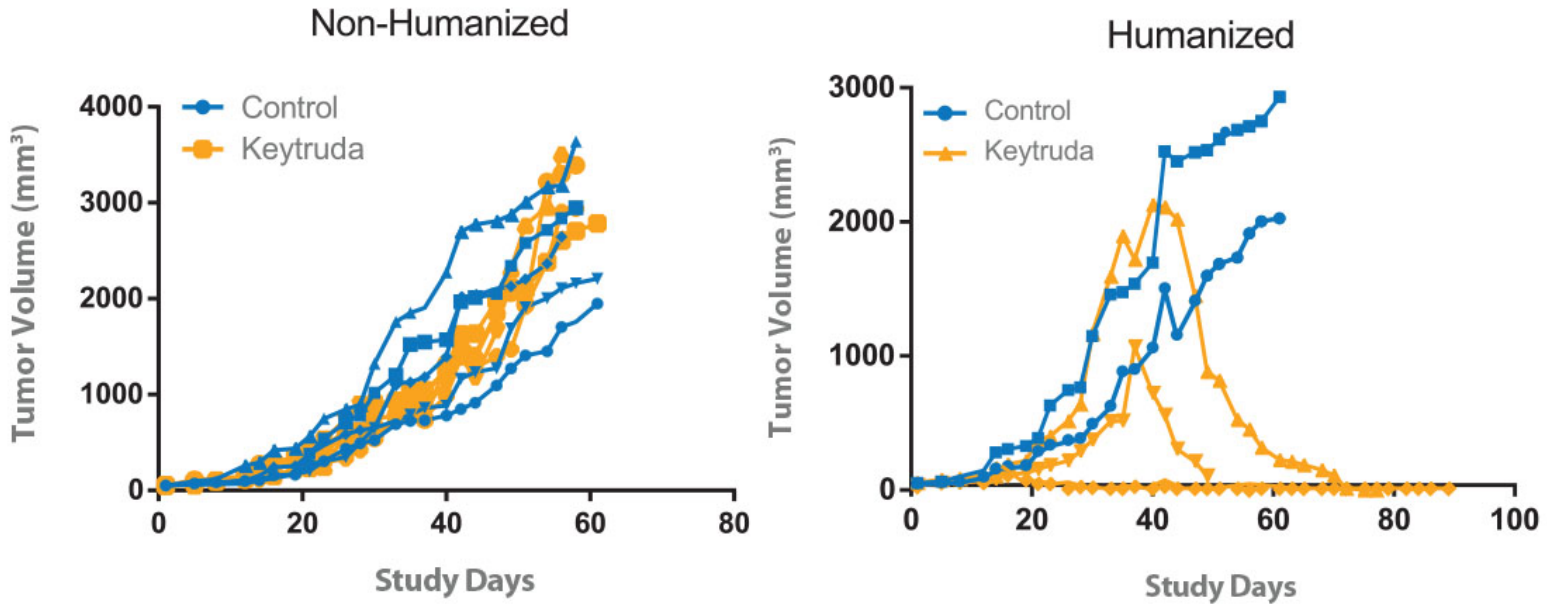
mBR6004 MuPrime Model

- Improved response to anti-PD-1 antibodies observed following model pre-immunization



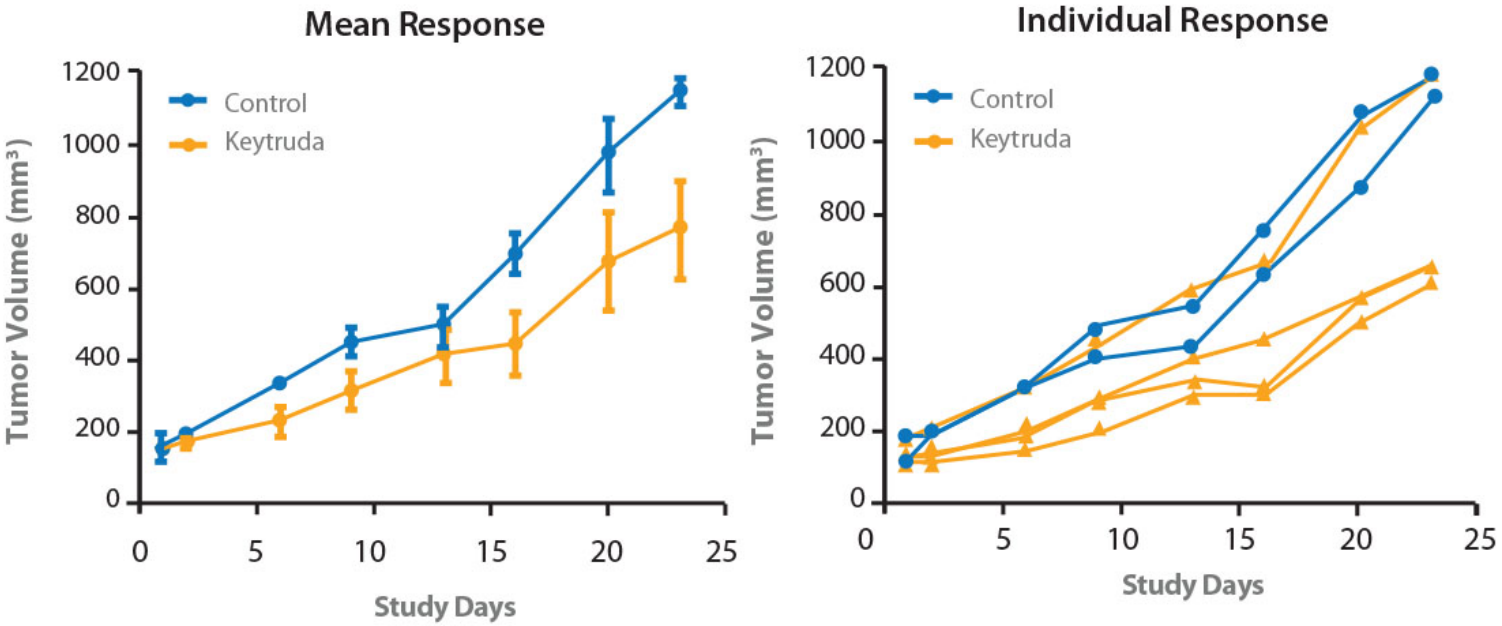
Humanization of NSG™ Mouse Required for Keytruda® Effect: MDA-MB-231

- Humanized mice display disease remission compared to non-humanized counterparts



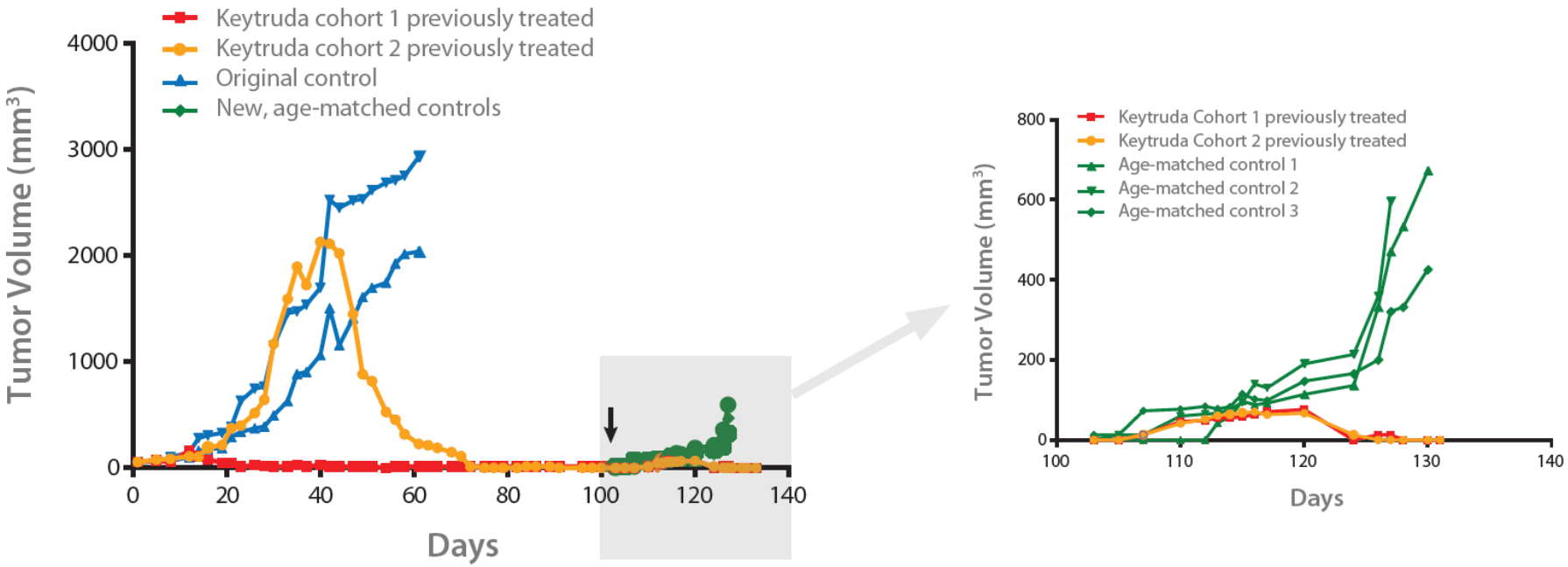
Humanization of NSG Mouse Required for Keytruda Effect: TNBC PDX

- Humanization required for Keytruda effect; response varies with differing effects observed for different HSC donors



Immune Memory Response in Treated Animals

- MDA-MB-231 rechallenge of Keytruda responder animals demonstrates an immune memory response



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Summary

- Emergence of drug resistance in metastatic breast cancer remains a survival limiting factor
- Treatment options for TNBC still inadequate
- Better and more representative *in vivo* models of human breast cancer crucial for development of new therapeutics
- CrownBio provides a comprehensive Breast Cancer Translational Platform for seamless transition from *in vitro* to *in vivo* testing of your new compound or immunotherapeutic agent
  - Matched **cell lines** and validated **cell line derived xenograft models**
  - **Bioluminescent xenograft** models
  - Clinically relevant **patient-derived xenograft (PDX)** models
  - Well-characterized **syngeneic**, advanced **murine allograft**, **humanized PDX and xenografts** models
  - FACS and additional **assay services** for immunotherapeutic drug discovery and development

Connect with CrownBio

- Contact us at **busdev@crownbio.com** for full details on our breast cancer resources and other AppNotes
- Explore CrownBio models through our online databases
- One stop search for PDX, cell line derived xenografts, and syngeneics with Onco*Express*™ at **oncoexpress.crownbio.com**
- Or investigate PDX models in HuBase, xenograft models via XenoBase, and mouse cancer cell lines (including syngeneics) in MuBase®, accessible from **www.crownbio.com**