



**CrownBio**  
CONNECTING SCIENCE TO PATIENTS

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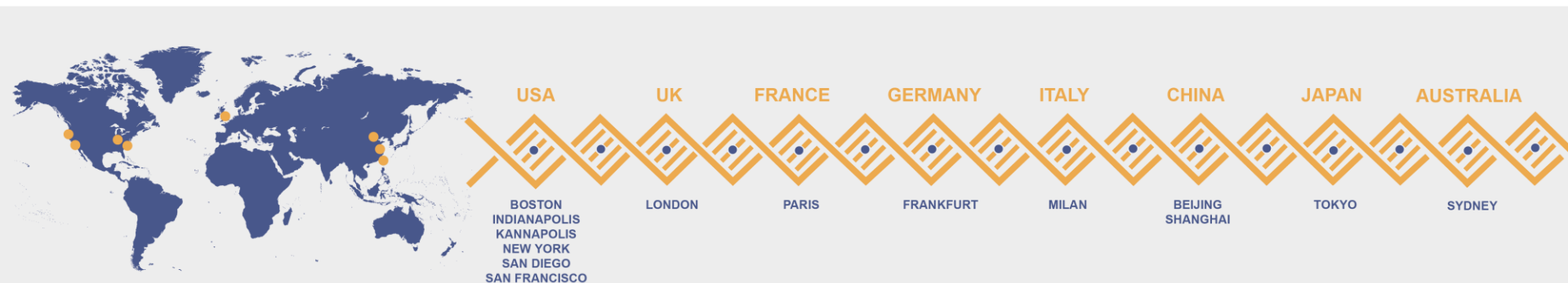
# Clinically Relevant Models to Validate Efficacy and Improve Patient Selection

**Laurie Heilmann**  
SVP of Business Development

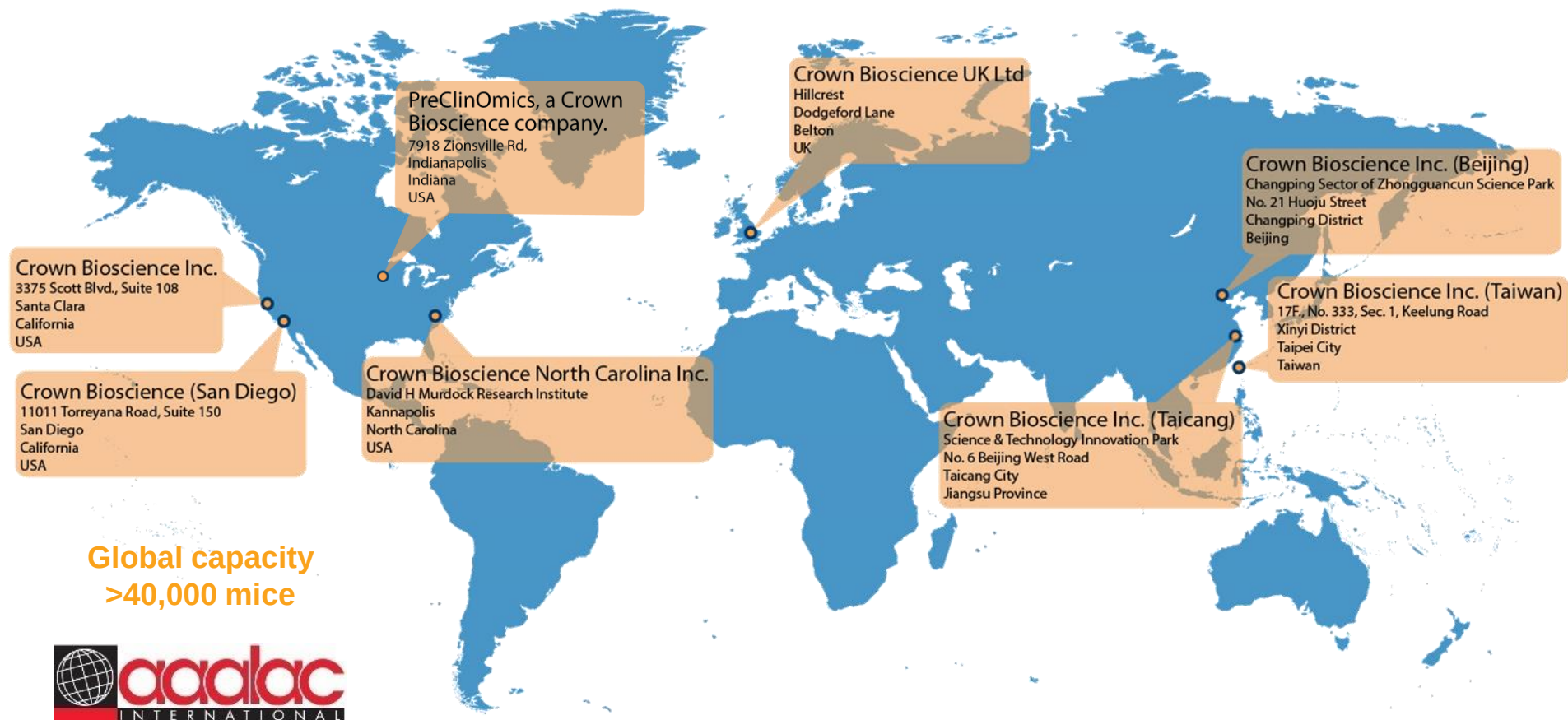
**Michelle Mack**  
Senior Manager of Business Development

**Crown Bioscience Inc.**

**Rational Combinations 360°**  
**June 23, 2016**



# CrownBio: Your Global Partner



# Oncology Expertise: *In Vivo* Pharmacology

## CDX

XenoBase

- ValidatedXeno™: **Large CDX collection** (>200) including metastatic and bioluminescent models
- 28 validated syngeneic models (GEMM, MuPrime™, HuGEMM™)
- PrimeXeno™: A **unique CDX collection derived from our PDX models**

## PDX: HuPrime®

HuBase2®

- **A large PDX collection** (>2,500)
- A large cohort of **live PDX models**
- **Asian and Caucasian** models; **pretreated and treatment naïve; primary and metastatic** models
- **PDX in Humanized mice**

## HuKemia®

HuBase2®

- A **unique collection of patient-derived blood cancer models**
- **18 ALL, 6 AML, 24 Lymphoma** models

# Oncology: *In Vivo* Pharmacology

## PDX - HuPrime

| Cancer Type         | Established |
|---------------------|-------------|
| ALL                 | 16          |
| AML                 | 4           |
| Adrenal             | 2           |
| Bladder             | 18          |
| Brain Tumor         | 9           |
| Breast              | 87          |
| Cervical            | 24          |
| Cholangio-carcinoma | 23          |
| Colorectal          | 319         |
| Esophageal          | 41          |
| Fallopian           | 2           |
| Gallbladder         | 12          |

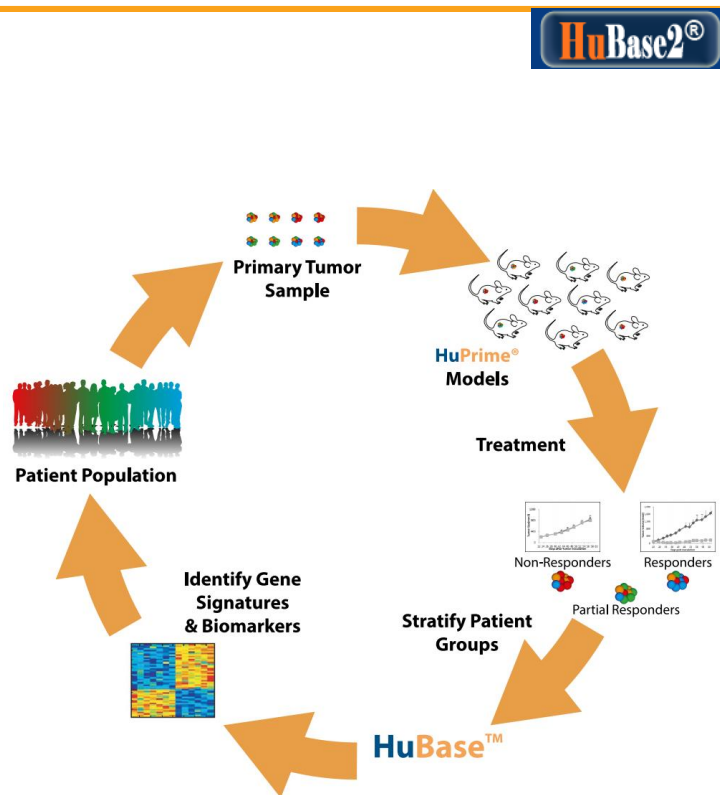
| Cancer Type      | Established |
|------------------|-------------|
| Gastric          | 172         |
| GIST             | 5           |
| Head & Neck      | 90          |
| Kidney           | 16          |
| Liver - HCC      | 105         |
| Liver - Other    | 54          |
| Lung - NSCLC     | 259         |
| Lung - SCLC      | 72          |
| Lung - Other     | 45          |
| Lymphoma - HL    | 2           |
| Lymphoma - NHL   | 10          |
| Lymphoma - Other | 12          |
| Melanoma         | 26          |

| Cancer Type              | Established |
|--------------------------|-------------|
| Neuroendocrine Tumor     | 20          |
| Ovarian                  | 84          |
| Pancreatic               | 146         |
| Parotid Carcinoma        | 1           |
| Peritoneal Cancer        | 1           |
| Sarcoma                  | 15          |
| Salivary Gland Carcinoma | 4           |
| Testis                   | 1           |
| Thyroid                  | 6           |
| Unclear Primary Site     | 21          |
| Uterine Cancer           | 23          |

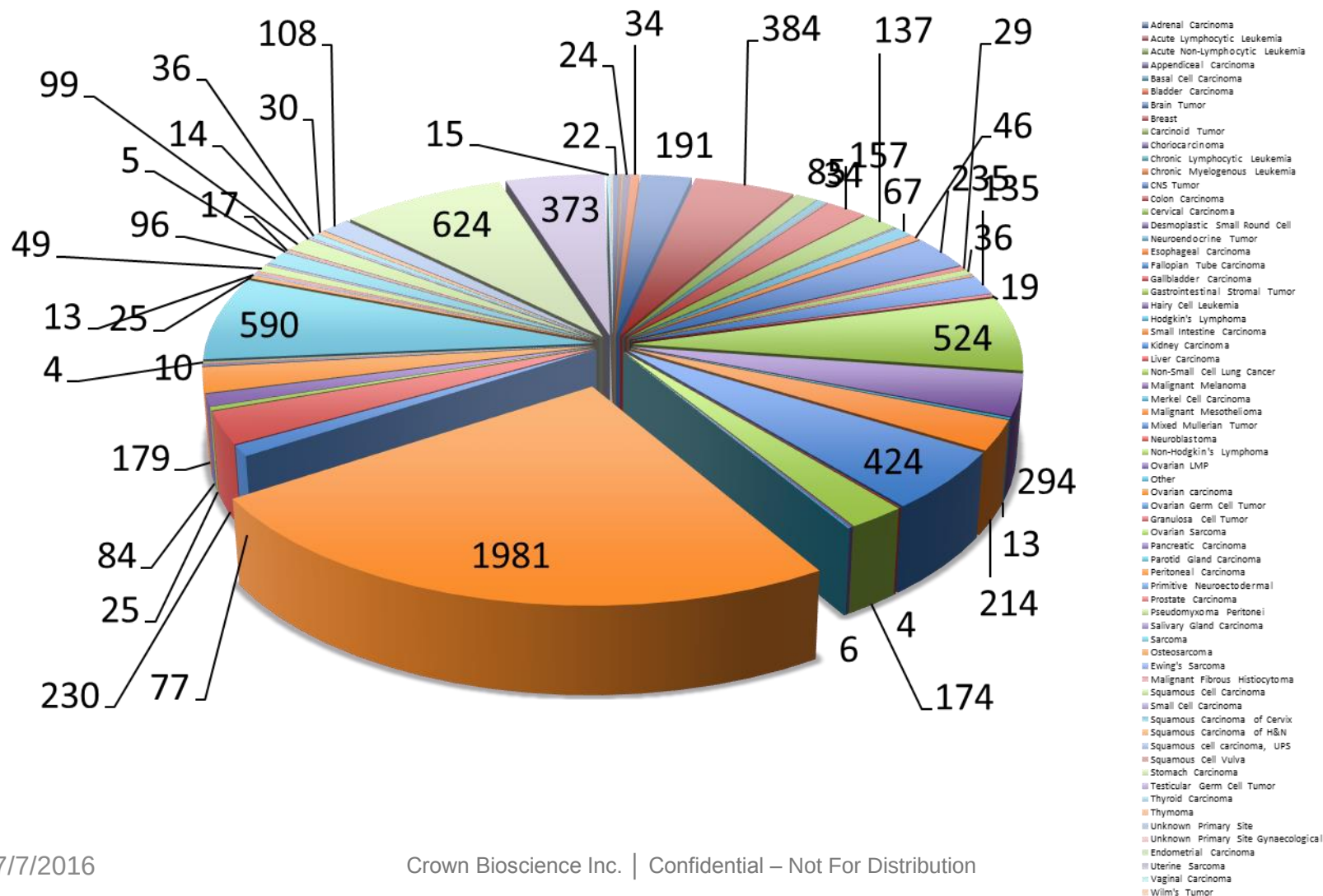
**Over 2,500 PDX Models**

- **A unique collection of patient-derived blood cancer models**
- *In vivo* ALL, NHL, and AML and *ex vivo* ALL, AML, CML, CLL, and MM patient-derived blood cancer models for efficacy testing
- **HuKemia** models are well-characterized and annotated with expression profiling (U219) and gene copy number (SNP6) data
- MicroRNA, exome sequencing, RNAseq, and hotspot analysis available
- **18 ALL, 6 AML, and 24 Lymphoma models**
- **Patient-relevant mutations e.g. IDH2 mutation, FLT3-ITD**
- **Unique models for targeted therapy**

- Perform a **surrogate clinical trial** in a preclinical setting, **stratifying** your patient population to **identify responders and non-responders** to your treatment regimen, and **discover and validate biomarkers** of response before you enter the clinic
- **HuPrime** models are reflective of the diversity of genetics, tumor heterogeneity, and response in a patient population
- Identify:
  - **Responsive patient populations before you enter the clinic**
  - **Optimal partner drugs for combination**
  - **Biomarkers of response** for companion diagnostic development



# Oncology: *In Vivo* Pharmacology Tumor Tissue Bank Cancer Types





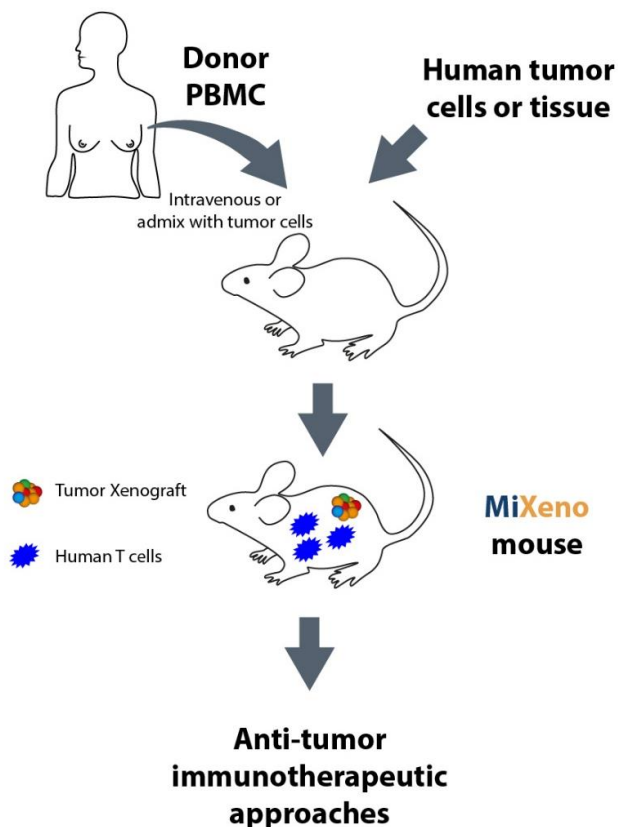
# Oncology: *In Vivo* Pharmacology Tumor Tissue Bank Curated Data

- **8,000 specimens** from a panel of 30,000 viable tumour tissues
- **Biomarker based model creation**
- Primary human tumor cell bank with *in vitro* chemo resistance data
- Mutational diversity captured

| Patient   |      | Clinical |                           | Histo/Path                          |                                        | Clinical |        | Pharmacology            |     |     |       |       |      |      |      |       |       |      |      |     |    |    |
|-----------|------|----------|---------------------------|-------------------------------------|----------------------------------------|----------|--------|-------------------------|-----|-----|-------|-------|------|------|------|-------|-------|------|------|-----|----|----|
| SPECNUM   | Age  | CANCER   | CLINDIAG                  | HISTOLOGY                           | PATHCOMNT                              | PRIORRX  | PREVDR | SITE                    | 4HC | 5FU | CARBO | CPLAT | DOXO | GNCB | MITC | NAVBL | TAXOL | TOPO | TXTR | VCR |    |    |
| 2.009E+09 | 60.6 | SCL      | Small cell lung carcinoma | SMALL CELL CARCINOMA                |                                        | T        |        | Chest wall              | --  | --  | E     | E     | I    | --   | E    | I     | E     | I    | --   | --  | E  |    |
| 2.003E+09 | 47.1 | SCL      | Small Cell Lung Carcinoma | METASTATIC SMALL CELL UNDIFFERENT   | C/W REFERRING DIAGNOSIS. ENTIRE TISSUE | T        |        | Cplat, VP16             | L   | --  | L     | E     | --   | L    | --   | L     | --    | I    | L    | I   | -- | E  |
| 2.002E+09 | 47.7 | SCL      | Small Cell Lung Carcinoma | SMALL CELL CARCINOMA                | C/W DIAGNOSIS. APPROXIMATELY 60% OF T  | T        |        | Etoposide, C            | I   | E   | --    | I     | I    | L    | --   | L     | I     | I    | I    | --  | -- | L  |
| 2E+09     | 58.1 | SCL      | Small Cell Lung Carcinoma | ADENOCARCINOMA                      | C/W REFERRING DIAGNOSIS. APPROXIMATE   | T        |        | Omental Nodule          | E   | --  | --    | E     | E    | --   | L    | --    | --    | --   | --   | --  | -- | L  |
| 1.995E+09 | 64.2 | SCL      | Small Cell Lung Carcinoma | SMALL CELL LUNG CARCINOMA           | TUMOR CELLS PRESENT IN CYTOSPIN PREP C | T        |        | vp16, cplat             | I   | --  | --    | L     | L    | --   | L    | --    | --    | --   | --   | --  | -- | L  |
| 2.003E+09 | 61.1 | SCL      | Small Cell Lung Carcinoma | METASTATIC SMALL-CELL CARCINOMA     | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | T        |        | Peritoneal Implant      | L   | E   | --    | I     | I    | E    | --   | L     | --    | E    | --   | E   | -- | -- |
| 2.007E+09 | 59.8 | SCL      | Small Cell Lung Carcinoma | SMALL CELL CARCINOMA (OAT CELL)     | C/W DIAGNOSIS. APPROXIMATELY 70% OF T  | T        |        | L Ovary                 | --  | --  | --    | I     | E    | --   | L    | --    | L     | L    | L    | --  | -- | I  |
| 2.008E+09 | 58.5 | SCL      | Small cell carcinoma      | METASTATIC SMALL CELL CARCINOMA (   | C/W DIAGNOSIS. APPROXIMATELY 70% OF T  | T        |        | Omentum & colon         | I   | E   | I     | --    | E    | L    | --   | I     | --    | E    | --   | --  | -- | L  |
| 2.002E+09 | 58.8 | SCL      | Small Cell Lung Carcinoma | METASTATIC SMALL CELL CARCINOMA (   | C/W DIAGNOSIS. APPROXIMATELY 90% OF T  | T        |        | R Ovary                 | --  | --  | --    | I     | L    | --   | L    | --    | L     | L    | L    | --  | -- | L  |
| 2.004E+09 | 63   | SCL      | Small Cell Lung Carcinoma | METASTATIC SMALL CELL CARCINOMA     | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | T        |        | L Breast                | --  | --  | --    | L     | I    | --   | E    | --    | L     | E    | L    | --  | -- | L  |
| 2.002E+09 | 64.6 | SCL      | Small Cell Lung Carcinoma | SMALL CELL LUNG CANCER              | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | T        |        | R Adrenal Gland         | --  | --  | --    | L     | L    | I    | --   | L     | --    | L    | E    | L   | -- | -- |
| 1.995E+09 | 54.7 | SCL      | Small Cell Lung Carcinoma | SMALL CELL CARCINOMA                | THE TISSUE CONTAINS 90% TUMOR C/W REF  | T        |        | R Ovary                 | L   | --  | --    | L     | L    | --   | I    | --    | --    | --   | --   | --  | -- | L  |
| 2.008E+09 | 72.2 | SCL      | Small cell carcinoma      | SMALL CELL CARCINOMA OF LUNG        | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | F        |        | L2                      | --  | --  | --    | L     | L    | --   | I    | --    | I     | L    | I    | --  | -- | L  |
| 2.008E+09 | 54.1 | SCL      | Small cell carcinoma      | METASTATIC SMALL CELL CARCINOMA (   | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | F        |        | Chest wall              | --  | --  | --    | I     | L    | --   | L    | --    | --    | --   | --   | --  | -- | L  |
| 1.995E+09 | 59.8 | SCL      | Small Cell Lung Cancer    | SMALL CELL CARCINOMA, METASTATIC    | C/W REFERRING DIAGNOSIS. APPROXIMATE   | F        |        | Neck Mass               | L   | --  | --    | L     | E    | --   | I    | --    | --    | --   | --   | --  | -- | E  |
| 2.009E+09 | 68.6 | SCL      | Small cell carcinoma      | SMALL CELL CARCINOMA                | C/W DIAGNOSIS. APPROXIMATELY 70% OF T  | F        |        | Right lower lobe lung   | --  | --  | --    | E     | I    | --   | L    | --    | L     | E    | L    | I   | -- | I  |
| 2.002E+09 | 65.2 | SCL      | Small Cell Lung Carcinoma | SMALL CELL UNDIFFERENTIATED CARCIN  | C/W DIAGNOSIS. APPROXIMATELY 40% OF T  | F        |        | L Neck                  | --  | --  | --    | E     | E    | --   | L    | --    | L     | I    | L    | --  | -- | L  |
| 1.996E+09 | 68.9 | SCL      | Small Cell Lung Carcinoma | SMALL CELL CARCINOMA                | THE TISSUE CONTAINS 70% TUMOR C/W REF  | F        |        | R Upper Lobe Lung       | E   | --  | --    | L     | E    | --   | E    | --    | --    | --   | --   | --  | -- | L  |
| 2.008E+09 | 59.1 | SCL      | Small cell carcinoma      | SMALL CELL NEUROENDOCRINE CARCIN    | C/W DIAGNOSIS. APPROXIMATELY 10% OF T  | F        |        | Right lower lobe lung   | I   | E   | L     | --    | E    | --   | I    | --    | L     | E    | L    | --  | -- | L  |
| 2.001E+09 | 43.9 | SCL      | Small Cell Lung Carcinoma | OAT CELL CARCINOMA                  | C/W REFERRING DIAGNOSIS. MALIGNANT TL  | F        |        | R Thoracenteris Fluid   | L   | I   | --    | --    | L    | --   | I    | --    | L     | --   | L    | --  | -- | -- |
| 2.008E+09 | 74.7 | SCL      | Small cell lung carcinoma | SMALL CELL CARCINOMA                | C/W DIAGNOSIS. APPROXIMATELY 80% OF T  | F        |        | Mediastinum             | L   | L   | --    | L     | L    | --   | --   | --    | E     | L    | --   | --  | -- | L  |
| 2.007E+09 | 67.7 | SCL      | Small Cell Lung Carcinoma | SMALL CELL (OAT CELL) CARCINOMA, UI | C/W DIAGNOSIS. APPROXIMATELY 30% OF T  | F        |        | Anterior Mediastinal LN | --  | --  | --    | L     | E    | --   | L    | --    | L     | E    | L    | --  | -- | I  |
| 1.996E+09 | 67.8 | SCL      | Small Cell Lung Carcinoma | SMALL CELL CARCINOMA                | THE TISSUE CONTAINS 80% TUMOR C/W REF  | F        |        | R Cervical LN           | L   | --  | --    | E     | --   | E    | --   | E     | --    | I    | --   | --  | -- | L  |
| 2.006E+09 | 59.1 | SCL      | Small Cell Lung Carcinoma | METASTATIC CARCINOMA                | C/W DIAGNOSIS. APPROXIMATELY 100% OF F | F        |        | Brain                   | --  | --  | --    | E     | --   | L    | --   | I     | --    | I    | E    | I   | -- | E  |
| 2.003E+09 | 74.5 | SCL      | Small Cell Lung Carcinoma | NEUROENDOCRINE CARCINOMA, PD        | C/W REFERRING DIAGNOSIS. ENTIRE TISSUE | I        |        | L Axillary Mass         | --  | --  | --    | L     | L    | --   | L    | --    | L     | L    | --   | --  | -- | -- |
| 1.996E+09 | 83.2 | SCL      | Small Cell Lung Carcinoma | ANAPLASTIC SMALL CELL CARCINOMA     | THE TISSUE CONTAINS MICROSCOPIC FOCUS  | F        |        | Pretracheal Lymph Node  | L   | --  | --    | E     | E    | --   | I    | --    | --    | --   | --   | --  | -- | L  |



## Applications of MiXeno



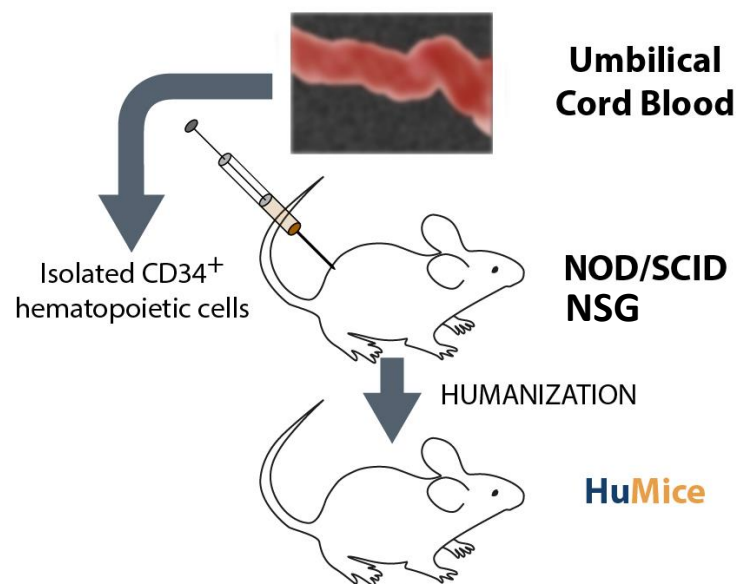
| Immune Function Involved | Test Substance                        | CrownBio Experience    |
|--------------------------|---------------------------------------|------------------------|
| T cell function          | BiTE                                  | CD19, HER2, EGFR BiTEs |
|                          | Immune checkpoint inhibitors/agonists | PD-1, PD-L1 inhibitors |
|                          | CAR-T                                 | CD19                   |
| NK cell function         | ADCC                                  | Cetuximab              |
|                          | NK modulating agents                  | N/A                    |

**Value proposition:** A fast and economic way to evaluate I/O therapies alone or in combination

# MiXeno Model Summary

| Cancer Type | Model Name | PBMC Injection Rt. | Treatment             |            |        | T Cell Reconstitution | NK Cell Reconstitution | DC Reconstitution | Macrophage Reconstitution |
|-------------|------------|--------------------|-----------------------|------------|--------|-----------------------|------------------------|-------------------|---------------------------|
|             |            |                    | Checkpoint Inhibitor  | BiTE       | Others |                       |                        |                   |                           |
| Breast      | BT-474     | s.c.               | N/A                   | HER2 BiTE  | N/A    | Y                     | ND                     | ND                | N/A                       |
| Colon       | Colo205    | s.c.               | N/A                   | N/A        | ADCC   | Y                     | N/A                    | N/A               | N/A                       |
|             | HCT-116    | s.c., i.v.         | N/A                   | EGFR BiTE  | N/A    | N/A                   | N/A                    | N/A               | N/A                       |
|             | SW480      |                    | N/A                   | EpCAM BiTE | N/A    |                       |                        |                   |                           |
| Lung        | HCC827     | i.p., i.v.         | Anti-PD-1, Anti-PD-L1 | N/A        | N/A    | Y                     | ND                     | ND                | ND                        |
| Lymphoma    | Karpas299  | i.v.               | Anti-PD-L1            | N/A        | N/A    | Y                     | Low in LN              | Y                 | ND                        |
|             | Jeco-1     | i.p.               | N/A                   | CD19 BiTE  | N/A    | Y                     | N/A                    | N/A               | N/A                       |
|             | Raji       | i.v.               | N/A                   | N/A        | CAR-T  | N/A                   | N/A                    | N/A               | N/A                       |
| Melanoma    | A375       | i.v.               | Anti-PD-1, Anti-PD-L1 | N/A        | N/A    | Y                     | Y                      | ND                | Y                         |

# HuMice™ Concept

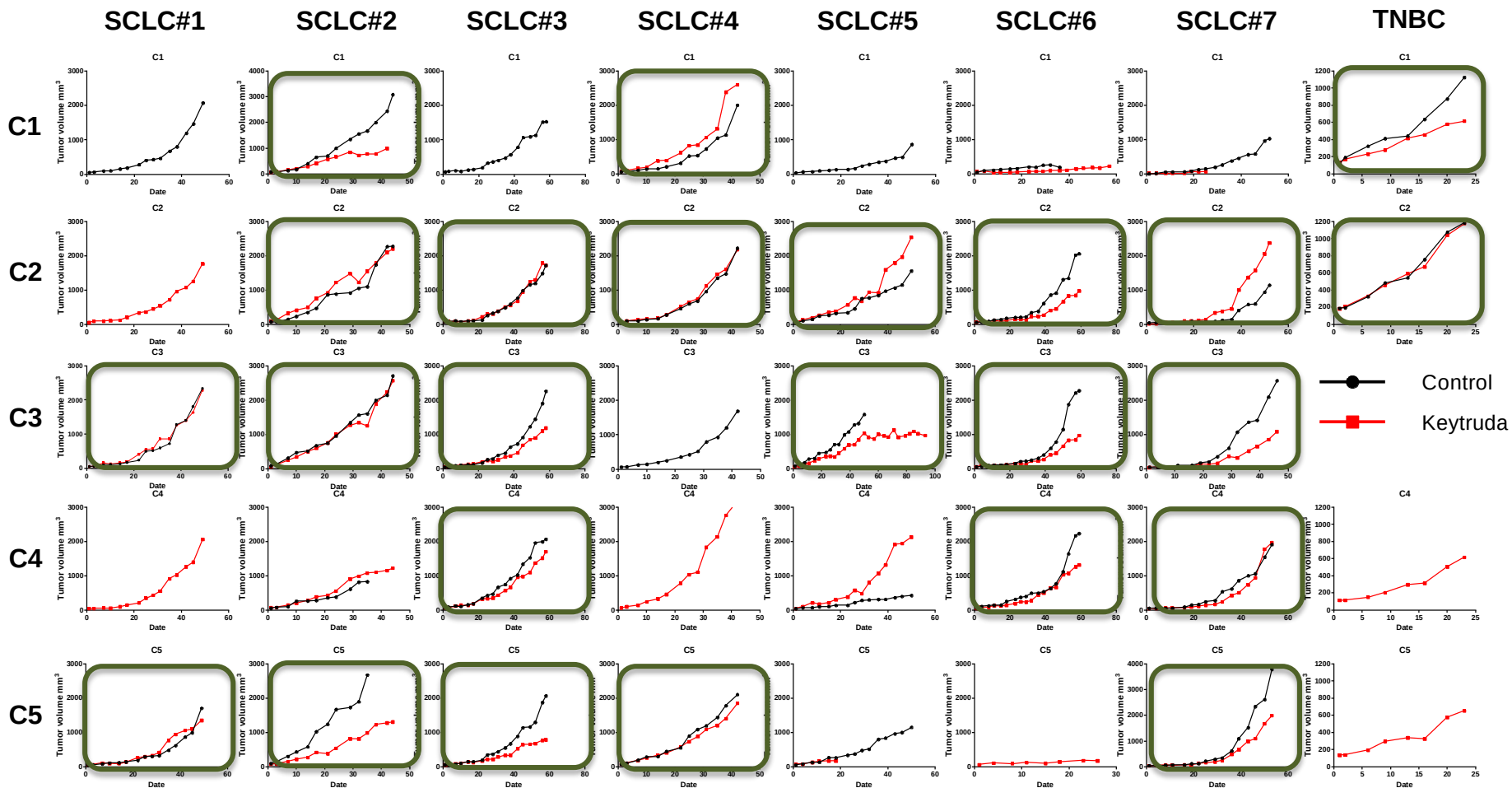


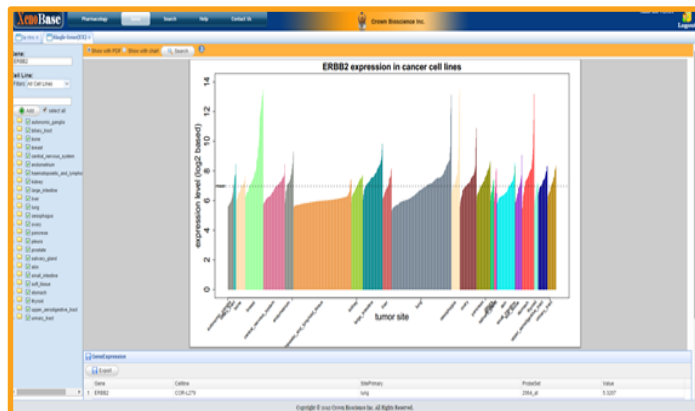
- Lymphopoiesis
  - T (CD3, CD4, CD8)
  - B (CD19, CD20)
- Myeloid (CD33, 12, 123)
- NK (CD56, CD69)
- Monocytes (CD14, CD16)
- Mø (CSF-1R, CD68)
- Neutrophil (CD11b)
- DC (CD11c, HLA-DR)
- Progenitors/stem cells (CD34)

- 1 TNBC model and 7 SCLC models (PD-L1 positive)
  - n=1 checkerboard assay using humanized mice (from The Jackson Laboratory) from 5 HSC donors
  - Treatment initiated when tumor volume reached 50-70mm<sup>3</sup>
  - Each model is run with 2 mice:
    - Vehicle: 1 animal; i.p., q5d
    - Keytruda®: 1 animal; 10 mg/kg, i.p., q5d
- Readouts:
  - TGI
  - TIL analysis
  - Histology

# SCLC & TNBC PDX Models

## CBSD





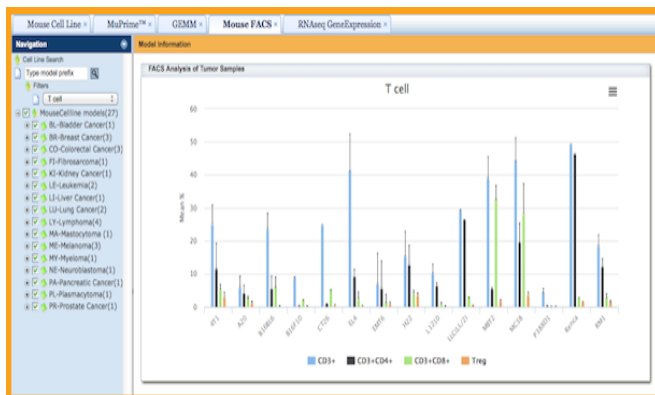
**XenoBase<sup>®</sup>**

- **Free online database for curated CDX models**
- **Over 2,000 cell lines** available
- Combining public **profiling data** (gene expression, copy number and mutation) and proprietary ***in vivo* pharmacology data**
- Make an informed decision by searching based on gene mutation, amplification and expression, tumor growth *in vivo* and response to SoC treatments



- **Free online database to access our curated PDX models**
- **Complete genomic annotation** (gene expression, copy number and mutation), **clinical and pharmacology data**
- Select models that match your criteria using: clinical information, diagnosis and pathology, whole genome gene expression profiling and copy number variation, Hotspot sequence mutation, key biomarker IHC information, tumor growth and SoC response curve





**MuBase®**

- **The world's first commercial database dedicated to mouse cancer models**
- Free online access to search **Syngeneics**, **GEMM**, **MDX (MuPrime)**, **HuGEMM**
- Make an informed decision by searching models based on gene expression, mutational status, gene fusions, etc. across our unique collection of mouse cancer models
- Wide variety of data compiled including model background, mouse strain, histopathology, genomic profiling (RNAseq), SoC, and immuno-profiling (infiltrate immune cells, cytokine profile, response to checkpoint inhibitors, etc.)

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