Modeling drug response in solid and hematologic PDX tumors using humanized mice and ex vivo models
Champions End to End Pharmacology Solutions

- Syngeneic & CLX
- Clinical Flow Cytometry
- Solid & Heme PDX
- Bioinformatics
- Humanized Models
- Ex Vivo Assays

Discovery → Preclinical → Translational → Clinical
TumorGrafts®: faithfully conserving human tumor biology

- Retain histological/pathological micro-architecture and cyto-structure of parental tumor
- Retain expression of important tumor antigens; e.g. surface receptors, immune antigens
- Retain primary driver mutations, gene expression patterns, and copy number variations
- Heterogeneous tumor biology representing cancer patient populations

DeRose, Y.S. et al, Nat Med, 2011
Izumchenko, E. et al, Ann of Oncol, 2017
Gao, H. et al, Nature Medicine, 2015
TumorGrafts®: a robust low passage platform for modeling cancer

Solid Tumor

Tissue from biopsy or surgery

Hematological Tumor

Leukapheresis
Champions national and international presence

Champions corporate headquarters
Hackensack, NJ

Champions laboratory operations
Rockville, MD

Champions TumorGraft® implantation sites & clinical collaborators
Large cohorts of clinically-relevant TumorGraft® models

Nearly 1200 models established across multiple tumor types

Other tumor types:

- Adrenocortical carcinoma
- Liposarcoma
- Ampullary
- Merkel cell
- Bladder
- Myxofibrosarcoma
- Cervical
- Myxoma
- Chondrosarcoma
- Osteosarcoma
- DSRCT
- PEComa
- Duodenal
- Rhabdomyosarcoma
- Endometrial
- Small bowel
- ETANTR
- Small cell ureter
- Ewing sarcoma
- Small intestinal
- Fallopian tube
- Sialoblastoma
- Gallbladder
- Synovial sarcoma
- GBM
- Testicular
- Hepatoblastoma
- Thymoma
- Histiocytoma
- Uterine
- Leiomyosarcoma
- Transitional cell carcinoma
Champions TumorGrafts® reflect clinical trial populations

**Tumor status**
- Metastatic: 49%
- Primary: 43%
- Local metastatic: 7%

**Clinical stage**
- IV: 56%
- III: 21%
- II: 16%
- I: 7%

**Treatment status**
- Naïve: 39%
- Pretreated: 61%

**Ethnicity**
- Caucasian: 76%
- Asian: 11%
- Hispanic/Latino: 4%
- Black/African American: 8%
- Other: 1%
Champions TumorGraft® Characterization Data

<table>
<thead>
<tr>
<th>Tumor profile</th>
<th>Patient demographics</th>
<th>Patient medical history</th>
<th>Genetic and molecular profile</th>
<th>In vivo drug sensitivity</th>
<th>Growth characteristics</th>
</tr>
</thead>
</table>
| • Cancer type and subtype  
• Stage, grade, histology  
• Harvest site | • Gender, age  
• Ethnicity  
• Smoking history | • Clinical diagnosis  
• Pre-treatments  
• Post-treatments  
• Treatment responses | • Mutations (SNVs and indels)  
• Copy number variations  
• Novel fusions/rearrangements  
• Gene expression levels | • Standard of Care response (%TGI, dT/dC) | • Doubling time  
• Time to 150mm$^3$  
• Time to 1000mm$^3$ |
### Champions TumorGraft® predictive power – nearly 90% clinical correlation

<table>
<thead>
<tr>
<th>Clinical accuracy measures</th>
<th>Result</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td>85% (80/94)</td>
<td>76% - 91%</td>
</tr>
<tr>
<td>(Mouse Response = Patient Response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative Predictive Value</strong></td>
<td>91% (32/35)</td>
<td>76% - 98%</td>
</tr>
<tr>
<td>(Mouse Progression = Patient Progression)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

129 clinical response correlations from 92 patients

Champions TumorBank is comprised of clinically-relevant models with demonstrated correlations to patient outcomes

Izumchenko, E. et al, Ann of Oncol, 2017
AML model cytarabine response: survival curves

**CTG-2229**

![Graph showing survival curves for CTG-2229.](image)

*no. huCD33+ cells/μl (day 14)*

*\( p = 0.0003 \) (logrank)

**CTG-2238**

![Graph showing survival curves for CTG-2238.](image)

*no. huCD33+ cells/μl (day 14)*

*\( p = 0.6 \) (logrank)
Designing A System to Assess Pharmacodynamics

- HSC
- Common Myeloid Progenitor
- Myeloblast
- Basophil
- Neutrophil
- Eosinophil
- Monocyte
- NK Cell
- T Lymphocyte
- TNK Progenitor
- B Lymphocyte
- Common Lymphoid Progenitor

- CD8+ T cells
- Treg cells
- B cells
- NK cells
- Dendritic cells

- Macrophage
- Inhibition
- Activation
- Cytotoxicity
- Anti-tumor mAbs

- NOG
- NOG-IL6
- NOG-IL15
- NOG-EK

- NOG-IL6 Hu-IL6
- NOG-IL15 Hu-IL15
- NOG-EK Hu-IL3/GM-CSF
PBMC-HIS model in immunodeficient mice strains

1x10^7 PBMC IV

Peripheral blood engraftment checks

Day 0  Week 2  Week 8

Spleen, bone marrow, peripheral blood:
Flow cytometry

NSG
NSG-B2M

Percent survival

Days post PBMC implant

NSG  NSG-B2m

% huCD3 (mean ± SEM)

Weeks (post-implant)

NSG  NSG-B2m
PDX models derived from patients receiving IO treatments

**IO-treated prior to model development**

- CTLA-4
- PD-1
- PDL-1
- CTLA-4 + PD-1

**IO-treated post model development**

- PD-1
- PDL-1
- CTLA-4 + PD-1
- Others
Evaluation of Nivolumab in a NSCLC PDX derived from patient that subsequently was treated and responded to Nivolumab

<table>
<thead>
<tr>
<th>Patient Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cisplatin/Etoposide</td>
<td>Mixed partial response, 2 months</td>
</tr>
<tr>
<td>2 Carboplatin/Pemetrexed</td>
<td>Mixed partial response, 3 months</td>
</tr>
<tr>
<td>3 Docetaxel/Ramucirumab</td>
<td>Mixed partial response, 3 months</td>
</tr>
<tr>
<td><strong>--PDX collection--</strong></td>
<td></td>
</tr>
<tr>
<td>4 Nivolumab</td>
<td>Complete response</td>
</tr>
</tbody>
</table>

Irradiated NOG-EXL CB-CD34

Periphery engraftment check

PD-L1+ NSCLC PDX implant

Dosing start Nivolumab (10mg/kg) BIW

CTG-1932
Donor-dependent Anti-tumor Efficacy in CD34-ImmunoGraft Model

**Donor 1**

- **Tumor Volume (mm$^3$)**
  - **Time (days)**: 0, 5, 10, 15, 20, 25
  - **Control**
  - **Nivolumab**

- **Percent survival**
  - **Days post study start**: 0, 10, 20, 30

**Donor 2**

- **Tumor Volume (mm$^3$)**
  - **Time (days)**: 0, 5, 10, 15, 20, 25
  - **Control**
  - **Nivolumab**

- **Percent survival**
  - **Days post study start**: 0, 10, 20, 30

Confidential
Immune cell subsets in HIS-PDX NOG-EXL mice (CTG-1932 NSCLC PDX)

G-MDSC/l,m-MDSC CD33+CD11b+HLA-DR-CD14-
M-MDSC: CD33+CD11b+HLA-DR-CD14+
Mφ = CD33+CD11b+HLA-DR+CD14+

* 2 Cord Blood Donors, 17-19 weeks post CD34 inoculation, 4-6 weeks post tumor implantation
Champions’ *Ex Vivo* Solutions

Utilizing a Superior Ex Vivo Platform for Preclinical & Translational R&D
Ex Vivo Hematologic Assay

Using Primary AML & PDX Sources

Applications

- Drug screen
- Biomarker discovery
- Mechanism of action
- In vivo model selection

Specimen input:
- Leukapheresis
- PBMC
- Bone marrow sample
- PDX explant

Study endpoints:
- Proliferation
- Tumor cytotoxicity
- Apoptosis
- Phenotyping

Drug

Enriched growth media

24-96- or 384-well format
AML Model Clinical Annotation

✓ Established proof-of-concept with primary specimen PDX modeling program
  • 42 characterized AML patient models available for PDX studies
  • Provide for up to 10,000 P1 mice on study

✓ Unfavorable prognosis
  • Deletion of part of chromosome 5 or 7 (4 models)
  • Translocation or inversion of chromosome 3 (2 models)
    ▶ Chromosome 3q/EVI1 translocation (1 model)
  • Translocation between chromosomes 6 and 9
  • Translocation between chromosomes 9 and 22 (1 model)
  • Abnormalities of chromosome 11 (at band q23)
    ▶ Chromosome 11q23/MLL translocations (1 model)
AML Model Genomics

Unfavorable prognosis

- FLT3 gene mutations - multiple targeted agents in development
  - ITD (Internal Tandem Duplication) - approximately 30% of AML (20 models)
  - D835 (mutation at aspartic acid residue 835) - approximately 7% of AML (1 model)
- IDH1 or IDH2 gene mutations - (1 model with R132C mutation)
- NPM1 gene mutations (in the context of FLT3 mutations - 10 models)
- DNMT3A gene mutations - approximately 30% of AML.
- p53 mutant - extremely poor prognosis (6 models)
Validation of Growth & Stability During Culture

Assay Design
- Equal cell number input
- IMDM-based SFEM media + supplement cocktail
- 96-well format

Stability Analysis

<table>
<thead>
<tr>
<th>CTG-2236</th>
<th>Day</th>
<th>CD33</th>
<th>CD14</th>
<th>CD117</th>
<th>HLA-DR</th>
<th>CD16</th>
<th>CD34</th>
<th>CD64</th>
<th>CD13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>+</td>
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<td>6</td>
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<td>+</td>
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</table>

<table>
<thead>
<tr>
<th>CTG-2240</th>
<th>Day</th>
<th>CD33</th>
<th>CD14</th>
<th>CD117</th>
<th>HLA-DR</th>
<th>CD16</th>
<th>CD34</th>
<th>CD64</th>
<th>CD13</th>
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</thead>
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</tr>
</tbody>
</table>
Validation of Growth & Stability During Culture

Fold expansion comparison

Fold-expansion (6 days)

Enriched

Non enriched

CTG-2225
CTG-2232
CTG-2233
CTG-2236
CTG-2240
CTG-2451
CTG-2700
Ex Vivo AML Models Exhibit Dose-dependent Responses to Ara-C
Ex Vivo Solid Tumor Assay
Using PDX Bank as Source Material

Applications
- Drug screen
- Biomarker discovery
- Mechanism of action
- *In vivo* model selection

Study endpoints:
- Proliferation
- Tumor cytotoxicity
- Apoptosis
- Phenotyping

Specimen input:
Cypre Symphony

Drug

24/96- well format
Champions’ Solid Tumor *Ex Vivo Platform*

**Symphony™ + VersaGel™**

A faster, more consistent, light-activated 3D cell model platform that builds coculture systems with:
- physiological relevance
- optical clarity
- user-friendly workflows

**Key Benefits:**
- Tunable to many tissue types
- Fast gelation time (60 seconds)
- Batch consistency
- Growth-factor free
- Optically clear
- Enzymatically digestible

**Technology**

Symphony™ uses light and a photo-masking approach to cure VersaGel™ in microtiter plates and build 3D cell models.

- **VersaGel Solution**
- **Symphony Light**
- **HIGH CROSSLINKED GEL** e.g. 10% VersaGel
- **LOW CROSSLINKED GEL** e.g. 4% VersaGel
Cytotoxicity Observed in Solid Tumor PDX

Gemcitabine

CTG-1106  CTG-1167  CTG-1883  CTG-2010  CTG-0670  CTG-1941

Paclitaxel

CTG-1106  CTG-1167  CTG-1883  CTG-2010  CTG-0670  CTG-1941
Evaluating Clinical, *In Vivo* and *Ex Vivo* Sensitivity to SOC.

<table>
<thead>
<tr>
<th>Model</th>
<th>Patient Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG-0670</td>
<td>Paclitaxel</td>
<td>Responded</td>
</tr>
<tr>
<td>CTG-1941</td>
<td>Carboplatin/Gemcitabine</td>
<td>Responded</td>
</tr>
</tbody>
</table>
Evaluating The Synergy of Drugs *Ex Vivo*.
3D co-culture Assays

Co-Culture assays provide a high through option assess activity.

The use of any PDX model is available as a haplotype matched or autologous study.

In vivo Syngeneic Studies

Syngeneic studies provide a quick and inexpensive solution to assess in vivo efficacy.

Studies can be customized or run through our quarterly SynScreen.

Humanized PDX Studies

Humanized PDX studies provide a framework to assess in vivo pharmacodynamics with a human immune system.

Different mouse backgrounds provide specialized engraftment of different immune subtypes.
Champions Oncology – your preferred model provider

<table>
<thead>
<tr>
<th>Broad bank of TumorGraft® models</th>
<th>Operational excellence</th>
<th>Customer-centric</th>
<th>Leading products and services</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large cohorts of TumorGraft® models</td>
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<tr>
<td>• Well-annotated with standard of care screens, genomics, patient history</td>
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<tr>
<td>• Bioinformatics expertise</td>
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<td>• Superior study execution</td>
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<td>• Frequent communication and access to study data</td>
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<td>• Quick identification and resolution of issues</td>
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<td>• Accessible</td>
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<td>• Responsive</td>
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<td>• Knowledgeable</td>
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<td>• Consultative</td>
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<tr>
<td>• Translational platforms</td>
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<td>• Clinical platforms</td>
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<tr>
<td>• ImmunoGraft™ platform</td>
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<tr>
<td>• AML platform</td>
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<td></td>
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<tr>
<td>• Defined molecular cohorts</td>
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<tr>
<td>• R&amp;D investment</td>
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