Innovative Bioincubator and Pre-Clinical Contract Research Organization

Offering
Discovery Research Products and Services

September 2023
• SBH Sciences is an innovative Bioincubator and a Contract Research Organization (CRO) which has been operating for over 26 years, providing over 300 companies with quality products and services.

• SBH Sciences has supported many start-up companies. We have collaborated with three companies through all stages of drug development, bringing seven NCE’s to clinical trials. One of the seven drugs – Xpovio was granted FDA approval (07/2019).
SBH Sciences has produced and commercialized 30 recombinant cytokines, 8 enzymes, and 40 MAb

<table>
<thead>
<tr>
<th>Activin-A</th>
<th>Soluble receptors (s-IL-6R)</th>
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<tbody>
<tr>
<td>Bone Morphogenic Proteins</td>
<td>TGF-Beta (TGF-b2)</td>
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<tr>
<td>(BMP-2, BMP-7)</td>
<td>TNF Receptor (HVEM-Fc)</td>
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<td>CD22</td>
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<tr>
<td>Growth Factors (HGF)</td>
<td>Enzymes (8 Glycosyltransferases)</td>
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<td>GDF-15/MIC-1 *</td>
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<tr>
<td>IGF-BPs (IGF-BP-6)</td>
<td>Monoclonal Antibodies:</td>
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<td>Interferon (IFN-b)</td>
<td>Anti-TNFα; Anti-VEGF, Anti-Galectin-3</td>
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<tr>
<td>Interleukins (IL-12, IL-23) **</td>
<td>Anti-T, Anti-Tn, Anti-STn</td>
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* Only company that produces GDF-15/MIC-1 naturally from human cells

** Licensed human IL-12 process technology to Neumedicines, a California based company, and collaborated with them to develop IL-12 for Acute Radiation Syndrome. The project was supported by BARDA and DoD and is in Phase II / III clinical trials.
Extensive Services Offered to Support and Accelerate Your Research Programs

- Biomarker Analysis [11-platform]
- Cell-Based Assays
  - [cytokine, chemokine, oncology, inflammation, TLRs]
- T-Cell Activation
- Development of Biologics
  - Cell Culture
  - Protein Purification
  - Cell-based assays
  - Analytical HPLC
  - ELISA / RBA [e.g., PD1/2 binding assay]
  - FACS
  - Formulation
  - Stability
  - Anti-Drug Antibody (ADA) assay
- Molecular Biology
- Gene and Cell Therapy
Comprehensive Biomarker Analysis Services

• We offer 11 innovative platforms for the analysis of biomarkers including SMCxPRO and Isolight.
• First CRO to offer automated simple western blot services on “Peggy Sue”, “WES” and “Jess” [ProteinSimple].
• First CRO to offer Simple Plex assays on “ELLA”.
• SBH Diagnostics, our strategic partner company, is a contract research organization providing biomarker analysis under CLIA certification and GLP.
• We assist companies and enable translation from non-regulated to regulated environment [clinical trials].
Eleven Platforms to Assist with Biomarker Analysis

- AlphaScreen® and AlphaLISA®
- MultiPlex: ProteinSimple ELLA
- ELISA [Tecan]
- Flow Cytometry – FACS Analysis
- HTRF®/ TR-FRET
- Luminex®200 [Multiplex Analysis]
- MSD QuickPlex SQ 120
- Automated Western Blot
  [ Peggy Sue / Wes / Jess ]
- Isolight [IsoPlexis]
- qRT-PCR
- SMCxPRO [MilliporeSigma]
Bioanalytical Services

- ELISA-Based Assays
- Receptor/ Ligand - Binding Assay
- Anti-Drug Antibodies [ADA]
- Analytical HPLC
- Chromatography
- Pharmacokinetics (PK) and Pharmacodynamic (PD)
- Multiplex Services (Luminex, ELLA, MSD, Isolight)
- Automatic Western Blot [Jess / WES]
- Endotoxin
- Cell-Based Potency Assays
- Flow-Cytometer Based Assays
Comprehensive Pathway Analysis
(Companion Biomarkers)

Pathways
- MAP Kinases
- JAK/STAT
- Apoptosis
- Stress Response
- NFkB
- Cell Cycle
Cell Culture Services (Mammalian & Insect Cells)

- Production of recombinant proteins, monoclonal antibodies, and vaccines.
- Optimization of growth conditions (media optimization and serum-free adaptation).
- Multi-liter supply of any mammalian cell line, before or after cytokine stimulation.
- Customized services (10 human primary cells and > 500 mammalian cell lines are currently available).
- Creation of new stable cell lines.
- Commercial production of cell culture spent media [8 years; 18 lots; > 150 L each lot].
- 2D and 3D assay capabilities.
- Irradiation experiments (combination of anti-cancer therapy).
- Preparation and isolation of Exosomes.

Protein Purification Services for Biologics

- Development of scalable, well-validated, and reproducible purification processes.
- Liquid chromatography capabilities (Ion Exchange, HIC, Affinity, Metal, HA, SEC).
- HPLC (Preparative and Analytical methods development).
- Protein formulation and stability studies.
Cell-Based Assay Capabilities

- Inflammation, oncology, and fibrosis are the therapeutic areas where SBH Sciences is best positioned to assist you.
- 330 cell-based assays to measure cytokine activity (cytokine-induced proliferation, cytokine-induced killing, cytokine release assays, and cytokine neutralization).
- GPCR activation and determine chemokine activity (e.g., IL-8, GRO, MCP1).
- Screening of therapeutic antibodies for specific activity (includes receptor binding assays, ADCC, ADCP, ADC, CDC assays, as well as immunocytokine).
- 370 different human cancer cell lines to facilitate in-vitro lead drug optimization (cytotoxicity, invasion, and migration assays).
- T-Cell Activation (e.g., T-cell-engaging IgG-like antibody targeting FLT3 on AML cells and Activation of the 4-1BB/CD137 pathway on T cells).
- Co-Culture Experiments [e.g., RAW264.7 and ID8 cancer cells].
- Testing for the presence of anti-Adeno-Associated Virus (AAV) in pig serum.
- Immunostimulation [e.g., transfection of h-PBMC with c-di-AMP (CDN) that activate h-STING and resulted in the secretion of IFN-alpha that enhance anti-cancer activity].
- TLRs activity [e.g., cytokine induction by TLR agonists].
- Microglial Activation.
- Exosome uptake by human macrophages.
Cell-Based Assay:

h-Activin A and h-Activin B
using MPC-11 cell line

![Graph showing the relationship between relative growth and activin concentration (log scale)]
Cell-Based Assay: h-Fit 3-Ligand using AML-5 cell line
Cancer Cell Cytotoxicity

370 human cancer cell lines are ready for immediate studies
Irradiation Capability

U87MG cell line
T-Cell Activation

Human IL-2 secreted by Jurkat clone E6-1 cells after stimulation with immobilized anti-CD3 and soluble anti-CD28

- 10ug anti-CD3 + 3ug/ml anti-CD28
- 10ug anti-CD3 + 1ug/ml anti-CD28
- 10 ug/ml anti-CD3
- 5 ug/ml anti-CD3
- Cells Only
Examples of discovery projects supported by SBH Sciences

I. **Inflammation:**
   Differentiation of THP-1 cells to:
   - M1 [IFN-gamma & LPS]
   - M2 [IL-13 & IL-4]
   WES Analysis of iNOS expression by RAW 264.7 cells
   Measurement of TLR-4, TLR-5, TLR-7, TLR-8 & TLR-9 agonist activity using the SEAP reporter HEK293 or THP1 cell lines (InvivoGen)
   Screening Agonist / Antagonist compounds targeting CB1 & CB2 receptors

II. **Experiments using isolated: Neutrophil, Eosinophils, Basophils**

III. **Modulation of T-cell activation**

IV. **Isolation of Stem Cells from Human Milk**

V. **Pig, Rat and Mouse – Scale up of intestinal organoids [ileum & duodenum] and transfec**
    and create stable cells prior to in-vivo transplantation
Examples of discovery projects supported by SBH Sciences

Continue:

VI. Optimization of adeno-associated virus (AAV) vector design and function in cell lines, primary cells, ex-vivo tissues and organoids.

VII. Transfection of mouse and human pancreatic beta-cell lines. Transduction of pancreatic beta cell lines and mouse and human islets.

VIII. qPCR assays for vector copy number and AAV titer.

IX. Investigate the potential of IL2/IL12 fusion protein to induce potent anti-tumor immunity.

X. Isolation of NK cells from human PBMC and investigate the role of NKG2D receptor - MICA interaction by FACS analysis.

XI. Screening RNA-targeting therapeutics compounds as an innovative anti-cancer drug.

Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
Promega Kit (G7010; 12.8-Fold Effector-to-Target)
Using SK-BR-3 Cells

Antibody Concentration (ug/ml) [log scale]
Human IL-6 production by THP-1 cells stimulated with LPS alone or in combination with IFNγ after Complete Media Change (CMC) to remove PMA or No Media Change.

- **CMC** (Complete Media Change)
- **No CMC** (No Media Change)

**Treatment and Concentration**

- **IFNγ + 10ng/ml LPS**
- **LPS**

**IL-6 [pg/ml]**

- 0
- 10
- 20
- 50
- 100
- 200
- 500
- 1000
- 1500
- 2000
- 2500
- 3000
- 3500
- 4000
- 4500
- 5000
- 5500
- 6000
- 6500
- 7000

**Cells Only**

**Cells + 10ng/ml LPS**
In-Vitro Model: Differentiated THP1
Positive Control: Clobetasol
Stimulation by: 1.25 ng/ml LPS + 0.5 ng/ml IFN-gamma

Reduction in cytokine secretion (%)

Clobetasol (ng/ml)

IL-1b
MCP-1
IL-6
TNF-a
h-IL-1b Production by THP-1 Cells Treated with Compound C in Combination with 10ng/ml IFNy and 2.5ng/ml LPS for 3 Days [M1]
[Pre-Treatment with PMA for 3 days prior to the experiment]

Please note: Up to 100 uM Compound C did not cause any cytotoxicity effect on the cells.
Polarization / Differentiation of THP1 Cells [M2]

- IL-1b
  - Control: 16 pg/ml
  - Plus IL-4 and IL-13: 170 pg/ml

- IL-2
  - Control: 69 pg/ml
  - Plus IL-4 and IL-13: 603 pg/ml

- IL-8
  - Control: 15 pg/ml
  - Plus IL-4 and IL-13: 8394 pg/ml

- TNF-a
  - Control: 9 pg/ml
  - Plus IL-4 and IL-13: 109 pg/ml
RAW 264.7 Cells
iNOS Peak Area
WES Analysis [Protein Simple]
HEK-Blue hTLR7 Cells
Bioassay of Residuum (R-848)
Treatment for 46 Hours
Alkaline Phosphatase Activity
In-Vitro Inflammation Model
Treatment of human PBMC by 10 ug/ml R-848
Assay Positive Control: Dexamethasone
24 Hrs. of Exposure
Bioassay STAT-3 Activity using HEK-Blue Cell Line
Anti - STAT-3 Activity (in the presence of hIL-6)

Niclosamide
BP-1-102
FLLL32
h-Pro-Collagen I Production by human Lung Fibroblast Cells Treated with 3 and 10 ng/ml TGF-b1 for 48 or 72 Hours (Diluted 1:250 or 1:500 Fold prior to ELISA)
Spheroid outgrowth over 8 days (boxes = 250 um)
No. 1 represents initial spheroid plated

Untreated GBM

The radial spread in two dimensions is reminiscent of the natural disease. Not shown here is the invasion down into the substrate as well.
Clinical Product Development - Case Study: human IL-12 a Novel Radiation Medical Countermeasure

- Proprietary human IL-12 production process was developed by SBH Sciences
- COA established for commercial release to the R&D market
- Neumedicines, Inc. (CA) licensed the technology from SBH Sciences
- In 2008, both companies collaborated to secure a Biomedical Advanced Research and Development Authority (BARDA) contract to develop IL-12 for Acute Radiation Syndrome
- In 2009, SBH Sciences optimized the process, scale-up, and transferred the technology to a GMP manufacturing
- 2011 – Submission of IND and First-In-Human for Toxicity studies
January 2014
Galectin Therapeutics and SBH Sciences, announce the formation of
Galectin Sciences, LLC,
a Collaborative Venture for Research and Development
Galectin Inhibitors
for Oral Administration

5 Provisional Patents have been submitted
2 Issued Patent
Improved specificity of Galectin-3 modulators

- In a receptor-based ELISA (A), TD139 inhibits binding of multiple galectins to integrin αMβ2 (B). An allosteric Gal-3 inhibitor (G229) shows significantly greater specificity for Gal-3 over other galectins (C).
Create Your Competitive Advantage
Advance your product from early development to pre-clinical and clinical Smoothly

SBH Sciences  ➔  SBH Diagnostics

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