Turning the Repertoire’s Most Potent Antibodies into Superior Therapeutics

Immuno-Oncology Targets and Therapeutic Antibodies

Q4 2014
Summary

• Theraclone deploys a proprietary platform technology that interrogates the human immune system to discover therapeutic mAbs

• Theraclone’s mAb technology platform – I-STAR™ is validated
  ➢ mAbs to HIV, mAb to Influenza A, and mAbs to a specific solid tumor (cancer)

• Partnerships include:
  ➢ Gilead – HIV; Zenyaku Kogyo – Flu; Pfizer - Oncology; Pfizer – Infectious Disease

• Theraclone is also uniquely positioned to discover therapeutic mAbs from cancer patients who respond to immuno-oncology therapies (cancer vaccines, checkpoint inhibitors and immuno-modulators)
Immuno-Oncology Mission

Discover novel targets and antibodies, and develop therapeutic monoclonal antibodies, by using our proprietary B-cell technology platform to mine the immune system of cancer patients who have responded to cancer immunotherapies.
Agenda

- Platform technology overview and proof of principle case study (HIV)

- I-STAR™ for cancer antibody discovery
  - Opportunities in finding antibodies from cancer immunotherapy patients who have rare robust immune responses

- Brief on leadership and other corporate assets
I-STAR™ Proven Discovery of Rare Antibodies & Subdominant Epitopes
Interrogating the Human Memory B Cell Repertoire

Access to rare human subjects
- Convalescent/vaccinated
- Elite controllers/responders
- Long term survivors
- Those with unique immune response

Rare antibodies
- Directed to less immunogenic, sub-dominant epitopes
- Inaccessible to other antibody discovery platforms

Therapeutic candidates
Antibody sequences – basis for engineering
- Effector function engineering
- ADC; Bi-specifics
- Vector delivery or CAR T cell therapy

Collect IgG⁺ Memory B cells
"Archive of immunological history"

B-cell activation of >10,000 human mAb clones per subject per run

Identify B cell clones with desired properties via rapid screens for binding and function

Deep sequencing of all hit wells to immortalize heavy and light chain sequences

Generate recombinant cell lines for therapeutic mAb candidates

THERACLONE SCIENCES
I-STAR™ – Demonstrated Track Record of Effective Productivity

• I-STAR is industrialized, miniaturized, robot-sized and high-throughput
  – Tens of thousands to hundreds of thousands of B-cell clones can be interrogated relatively quickly

• I-STAR generates consistent and reliable discovery of therapeutic mAb candidates
  – > 30 HIV mAbs from 5 donor samples
  – Phase 2 clinical candidate for influenza A from 1 donor sample
  – >100 preclinical mAbs from 10 donor samples for a gram-negative pathogen
  – > 50 preclinical mAbs from 50 donor samples for a single tumor type

• I-STAR provides timely delivery of relevant antibodies
  – Initial antibodies inform experimental strategies and provide early go/no-go
  – First recombinant antibodies in hand within 3 months of donor sample acquisition
  – Full panel of preclinical candidates in 9-12 months

• I-STAR yields therapeutic mAbs with high clinical candidacy
  – Fully human, derived from germane clinical settings
  – Fully matured by human immune system
  – Successful antibody discovery that is inaccessible to other platforms
I-STAR™ Discovery of Potent Anti-HIV Antibodies
Promising Targets for Prophylaxis and Therapy

Potent broadly neutralizing Anti-HIV mAbs (bNabs): “Finding a needle in a haystack”
- HIV highly variable and mutates rapidly
- Very few HIV infected patients make broadly neutralizing antibodies
- bNabs are rare: Only 4 discovered before I-STAR
- No effective vaccine immunogen has yet elicited bNabs

Deployment of I-STAR™ to discover broadly neutralizing Anti-HIV antibodies
> 150K mAb clones from HIV-positive subjects (Elite Neutralizers) screened

Discovery of over 30 monoclonal HIV-neutralizing Abs with rare specificities in more than 15 years:
- Broad, highly potent neutralizing activity: Neutralize over 75% of viruses across eight HIV clades
- Novel, conserved neutralizing epitopes
- Captures rare, subdominant human immune response

Identification of new bNAbs provides path forward for alternative therapeutic approaches and vaccine design
Anti-HIV Antibody PGT-121
A Single bNAb Alone Suppresses Chronic Infection in Macaques

Rapid viral load reduction to undetectable level by day 7
- Viral decline faster than anti-retroviral therapy
  - Viral rebound once mAb waned from circulation
  - Animal 1 maintained long-term virologic control for > 100 days
- Host T-lymphocyte response exhibited improved functionality
  - Direct anti-viral effect and modulation of host immune response
- No escape mutations detected
- Reduction of pro-viral DNA in reservoir and circulating PBMCs

Gilead licensed HIV mAb program from Theraclone July 2014
PGT-121 anti-HIV mAb poised to play key role in HIV cure

Single IV bNAb administration at day 0 (10 mg/kg)

Agenda

• Platform technology overview and proof of principle case study (HIV)

• I-STAR™ for cancer antibody discovery
  ➢ Opportunities in finding antibodies from cancer immunotherapy patients who have rare robust immune responses

• Brief on leadership and other corporate assets
Human Humoral Immune Response to Cancer
Many Cancers Elicit Anti-Tumor Antibodies

- Intra-tumoral antibody response correlates with enhanced CRC patient survival
- Anti-angiogenic antibodies induced by adjuvanted immunomodulatory therapy in long-term responders
- >30% NSCLC patients anti-Muc1 positive (0% healthy)
- Rates as high as 70-90% (e.g. anti-EpCAM)

- Monoclonal auto-antibodies to cell membrane targets have been isolated from cancer patients
- Humoral immune responses against tumor associated antigens occur at low frequency

Deployment of I-STAR™
Discover rare antibodies directed to novel cell surface targets

- Confirms humoral responses to tumors
- Sero-positive patients identified in 4/4 solid tumor indications
- Two indications advanced to Discovery

- Tumor cell surface (cell line) reactive mAbs identified
- Tumor tissue specific mAbs discovered
- Internalizing mAbs discovered

Serological screening of cancer patient samples

B cell activations of sero-positive samples

>> 500,000 B cell clones interrogated

>> 200 Tumor cell line specific B cell clones identified

>100 mAbs selected for expression

Characterization of recombinant mAbs

Delivery of mAb panel

95% of mAbs have greater reactivity to tumor cell line vs normal

- 23% demonstrate single tumor cell line specificity
- 75% demonstrate multiple tumor cell line specificities
I-STAR™ – Oncology Discovery – Case Study
Large Diversity of Fully Human mAbs

Diverse mAb panel
- Specific tumor cell line binding mAbs cloned & expressed
- Reduced reactivity to normal vs tumor cell lines
- >20 different cell binding specificities observed
- > 30% of mAbs: <10nM avidity
- High & low density cell surface target expression

Potential for ADC
- Some mAbs demonstrate internalization by immunofluorescence

Select mAbs advanced to IHC studies

Tumor tissue specific mAbs
- IHC analysis
- 40 antibodies tested
- 14 mAbs demonstrate tumor tissue specificity
Human Humoral Responses to Cancer Immunotherapy
Antibodies to Relevant Antigens Observed

**Indication:** Melanoma

**Treatment:** CTLA-4 blockade after autologous tumor vaccination

**Clinical Outcome:** Durable response to metastatic disease\(^1,2\)

**Indication:** Multiple Myeloma

**Treatment:** HSCT followed by donor lymphocyte infusion

**Clinical Outcome:** Durable response \(^4\)

<table>
<thead>
<tr>
<th>Humoral Response</th>
<th>Relevance in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiopoietin 1 &amp; 2</td>
<td>Amgen, Pfizer, Medimmune in clinic targeting Ang1 &amp; 2</td>
</tr>
<tr>
<td>Macrophage Inhibitory Factor</td>
<td>Potential target for NSCLC</td>
</tr>
<tr>
<td>MHC Class I chain-related protein A</td>
<td>Innate Pharma-preclinical, overexpressed in breast, colorectal and lung tumors</td>
</tr>
</tbody>
</table>

**Indication:** Multiple Myeloma

**Treatment:** HSCT followed by donor lymphocyte infusion

**Clinical Outcome:** Durable response \(^4\)

<table>
<thead>
<tr>
<th>Humoral Response</th>
<th>Relevance in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 B cell maturation antigen (BCMA)</td>
<td>(^4) Target for CAR-T therapy (in vivo efficacy demonstrated in mouse model for mAb &amp; CAR-T)</td>
</tr>
</tbody>
</table>

\(1\) Schoenfeld et al. Cancer Res 2010, 70, pp10150
\(2\) Jinushi et al. 2006, PNAS, 103, pp9190
\(3\) Bellucci et. al Blood. 2005;105:3945-3950
\(4\) Carpenter et al Clin Cancer Res, 2013, 19, pp2048
**Immunotherapy in Oncology Leads to Objective Response**

**Enhanced Adaptive Immune Responses**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rationale</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-CTLA-4</strong></td>
<td>• CTLA-4 blockade induces CD4+ and CD8+ T cell responses</td>
<td>Melanoma, prostate, breast, others</td>
</tr>
<tr>
<td></td>
<td>• B cell responses observed in human clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α-PD-1/α-PD-L1</strong></td>
<td>• PD-1/PD-L1 blockade produces objective response to multiple tumor types**[^2]<strong>[^[^3]</strong></td>
<td>NSCLC, melanoma, renal, lung</td>
</tr>
<tr>
<td></td>
<td>• PD-1/PD-L1 blockade enhances humoral response**[^4]<strong>[^[^8]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HSCT</strong></td>
<td>• Hematopoietic stem-cell transplant produces durable clinical response**[^5]**</td>
<td>Multiple myeloma, leukemia, solid tumors</td>
</tr>
<tr>
<td></td>
<td>• Graft versus tumor effects include humoral component**[^6]**</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Infiltrating Lymphocytes</strong></td>
<td>• Durable clinical responses upon <em>ex vivo</em> expansion and subsequent infusion of TILs derived from autologous tumors**[^7]**</td>
<td>Melanoma, solid tumors</td>
</tr>
<tr>
<td><strong>Cancer vaccine</strong></td>
<td>• Humoral responses induced by cancer vaccines**[^9]**</td>
<td>Breast, ovarian, others</td>
</tr>
<tr>
<td><strong>Cytokines, IL2, IL15, GM-CSF</strong></td>
<td>• IL-2 results in durable clinical responses effects humoral responses through Th2 cell differentiation**[^11]**</td>
<td>Melanoma, others</td>
</tr>
<tr>
<td></td>
<td>• Induces expansion and differentiation of NK, B and T cells, survival of CD8+ memory T cells**[^10]**</td>
<td></td>
</tr>
</tbody>
</table>

---

[^1]: Yuan et. al. PNAS Vol. 105, pg 20410-20415
[^7]: Besser, et. al. Clin Cancer Res; 16(9); 2646–55
[^8]: Hams, et. al. J of Immunol, 2011, 186
[^9]: Julien, et. al. Biomolecules 2012, 2, 435-466
[^10]: Waldmann Nat. Rev. Immunology. 2006, Vol. 6 595
Immuno-Oncology: Humoral Response to Immunotherapy

I-STAR™ Profiling of a Vaccinated Breast Cancer Patient

7.5 year survivor of metastatic ER+/PR+/Her2- breast cancer Theratope vaccine recipient

Robust serology & durable clinical response

Over 50 tumor cell line reactive IgG+ memory B cells identified

> 10 unique binding specificities observed

Vaccinated donor demonstrates diversity in humoral response
Immuno – Oncology
Strategic Focus and Priorities

• Cancer indications
  – Melanoma
  – NSCLC
  – Triple negative Breast Cancer
  – RCC
  – Gastric Cancer
  – Prostate and Ovarian
  – Head & Neck/Oropharyngeal

• Melanoma, NSCLC, RCC have increasing number of IO treated patients
  – Other cancer types also beginning to see more experimental IO treatment
  – Includes cytokine and cancer vaccine therapy

• Bias patient selection towards therapies driving humoral response
  – Prioritize combination therapies (e.g. checkpoint inhibitors/cancer vaccines)
  – Early POP through easy access to samples from Yervoy responders
  – Pembro/Keytruda now approved

• Antibodies from IO patients may play key role in therapeutic regimens
  – Therapeutic IO-mAbs may address unmet medical need in non responders
  – Combination therapy with IO-mAbs may enhance efficacy of SOC
Agenda

• Platform technology overview and proof of principle case study (HIV)

• I-STAR™ for cancer antibody discovery
  ➢ Opportunities in finding antibodies from cancer immunotherapy patients who have rare robust immune responses

• Brief on leadership and other corporate assets
# Experienced Management Team and Board

## Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Companies/Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifford J. Stocks (board member)</td>
<td>Chief Executive Officer</td>
<td>Calistoga Pharmaceuticals, Inc., ICOS Corporation, Booz Allen Hamilton</td>
</tr>
<tr>
<td>Russ Hawkinson</td>
<td>Chief Financial Officer</td>
<td>Corixa Corporation, Ernst &amp; Young</td>
</tr>
<tr>
<td>Kristine Swiderek, Ph.D.</td>
<td>Chief Scientific Officer</td>
<td>ZymoGenetics, City of Hope</td>
</tr>
</tbody>
</table>

## Board of Directors

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Companies/Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steve Gillis, Ph.D. (Chairman)</td>
<td></td>
<td>ARCH Venture Partners, Immunex, Corixa</td>
</tr>
<tr>
<td>Wende Hutton</td>
<td></td>
<td>Canaan Partners, Mayfield Fund, GenPharm International</td>
</tr>
<tr>
<td>Chris Mirabelli, Ph.D.</td>
<td></td>
<td>Healthcare Ventures, Leukocyte, Isis, SmithKline French</td>
</tr>
<tr>
<td>Wendye Robbins, MD</td>
<td></td>
<td>Stanford University SoM Clinical Associate Professor, Limerick</td>
</tr>
</tbody>
</table>
# Strategic Collaboration and Licensing Opportunities

<table>
<thead>
<tr>
<th>Asset</th>
<th>Stage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td></td>
<td>Available for collaboration</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Discovery</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td>Available for collaboration</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCN-032 Influenza mAbs</td>
<td>Phase 2</td>
<td>Available for world-wide license (excl. Japan)</td>
</tr>
</tbody>
</table>

**GILEAD**

Worldwide license to broadly neutralizing HIV mAbs discovered using I-STAR™

I-STAR™ collaboration to discover antibodies against up to four undisclosed targets in the areas of cancer and infectious disease

**ZYENYAKU KOGYO CO., LTD.**

I-STAR™ collaboration to discover and develop broadly protective antibodies for the treatment of severe seasonal and pandemic influenza

I-STAR™ collaboration to discover HIV-neutralizing antibodies
Seasonal and Pandemic Flu Opportunity
Development of Efficacious Influenza Therapy

Severe Seasonal Flu
(Hospital Market)

- 5-20% of the U.S. population infected p/year\(^1\): Young and elderly particularly at risk
- Initial market: treat hospitalized patients with severe influenza A
- Estimated total hospital cost for patients with principal influenza diagnosis: $2.1B\(^2\)
- Treatment goal: reduce infection severity/hospital costs
- Data suggest TCN-032 may lessen infection severity/symptom duration

Pandemic Flu
(Government Market)

- U.S. government funding for pandemic flu: > $6B since 2005
- Focus on development of new broad spectrum therapeutics
  - Monoclonal antibodies
  - Small molecules

\(^1\) Centers for Disease Control; \(^2\) Department of Health and Human Services 2009 report
Anti-Influenza Monoclonal Antibody TCN-032
Demonstrated POC in Phase 2a Human Viral Challenge Study

A Clinical First: Non-neutralizing antibody given parenterally may provide immediate immunity and therapeutic benefit in influenza A infection

Results

• Demonstrated reductions in total clinical symptom scores and viral load
• Safe and well-tolerated
  – No increase in adverse events compared to placebo, including lower respiratory tract symptoms
• Pharmacokinetics consistent with Phase 1 study
  – Half-life ~16 days; no evidence of immunogenicity
• No apparent emergence of resistant virus

Next Steps

• Clinical studies in natural infection including the target population of patients hospitalized with serious influenza infection
• Seeking licensing partner
Anti-Influenza mAb TCN-032
Reduces & Shortens Clinical Symptoms; Lowers Viral Shedding

Statistically significant and clinically meaningful results