Case Study

Anti-BCMA-ADC Antibody Program
AvantGen Company Overview

• Services
  – San Diego-based leader in providing antibody discovery and optimization services based on its state-of-the-art yeast display technology platform
    • Rapid discovery of human antibodies
    • Superior antibody humanization and optimization
    • Rabbit mAb generation for IHC and PK/PD studies

• Core technologies
  – Advantageous antibody yeast display platform
    • Proprietary, inducible, secretable display motif
  – Comprehensive human antibody database
  – Large collection of human antibody libraries

• Team
  – Proven expert R&D and business leaders in therapeutic antibodies
Accomplished Leadership

• **Xiaomin Fan, Ph.D. – Founder, President & CEO**
  - Founded AvantGen in 2006; Inventor of the company’s technology platforms
  - > $10M to-date from NIH SBIR grants/contracts (19 total) and service contracts
  - Previously, Scientist/Sr Scientist/Group Leader, Targeted Molecules Corp.
  - Lead antibody therapeutic programs which were licensed and subsequently partnered with Sanofi for >$600M, currently in Phase II and I clinical trials
  - Ph.D., University of Kansas; Post-doc, University of Pennsylvania

• **Tom Smart – Chief Business Officer**
  - Biopharma business leader with multiple Board and CEO appointments
  - Prior C-level and BD positions at therapeutic antibody technology pioneers AnaptysBio, Chairman & CEO (NASDAQ: $2B mkt cap); XOMA, CBO; Cell Genesys (Abgenix/Amgen), and other business roles at Genetics Institute (Pfizer) and Searle (Pfizer)
  - BS, Cornell University; MBA, University of Chicago Booth School of Business

• **Catherine Woods, Ph.D. – Vice President of Research**
  - Joined AvantGen in 2007; Broad and extensive experience (>20 years) in the pharmaceutical and biotech industry
  - Previously, Exec Director, Research, Targeted Molecules Corp; Assoc. Director, Clinical Research/Sr Director, Biological Research & Tech Transfer, Alliance Pharmaceutical Corp; Research Fellow, Merck Research Laboratories
  - Ph.D., University of California, Davis; Post-doc, California Institute of Technology
Anti-BCMA-ADC Antibody Program

• An internal project pursued to highlight the performance advantages of AvantGen’s human antibody discovery and optimization platform

• AvantGen’s anti-BCMA antibody program generated a large number of antibodies with compelling properties, including AVG-A11 which has been assessed across many property and performance parameters

• In a head-to-head comparison, AVG-A11 demonstrates the potential to outperform J6M0 (the antibody that GSK2857916, an anti-BCMA-ADC, is based on which has generated highly promising clinical data)

• AVG-A11 (for ADC), and our portfolio of anti-BCMA antibodies, represent an attractive in-licensing opportunity for existing and new entrants into the anti-BCMA field
Multiple myeloma is the second most common hematologic malignancy after non-Hodgkin’s.

The global multiple myeloma therapeutics market was valued at USD 7.5 billion in 2015 and is expected to reach a value of USD 37.5 billion by 2024.

B-cell maturation antigen (BCMA) is preferentially expressed on plasmoblasts and plasma cells but not naïve or memory B lymphocytes.

It has been shown to specifically bind BAFF and to lead to NF-kappaB and MAPK8/JNK activation – thereby transducing signals for cell survival and proliferation.

Antibodies targeting BCMA in various formats, including ADC, bispecific, and CAR-T, have been shown to effectively kill BCMA-positive MM cells in many preclinical studies.
## Competitive landscape for anti-BCMA programs (Major competitors)

<table>
<thead>
<tr>
<th>Format</th>
<th>Company</th>
<th>Development Stage</th>
<th>Deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>AvantGen</td>
<td>Preclinical Outperforms GSK’s antibody in multiple assays</td>
<td>To be partnered</td>
</tr>
<tr>
<td></td>
<td>GSK</td>
<td>Clinical Phase I</td>
<td>Drug linker technology in-licensed from Seattle Genetics</td>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>Amgen/BI</td>
<td>Clinical Phase I</td>
<td>2016: Amgen acquired from BI (which had licensed from Micromet). Terms not disclosed</td>
</tr>
<tr>
<td></td>
<td>Celgene</td>
<td>Preclinical</td>
<td>2016: Celgene acquired EngMab for $625 M upfront and a total deal size of $3.08 billion</td>
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<tr>
<td></td>
<td>Pfizer</td>
<td>Clinical Phase I</td>
<td>Internal</td>
</tr>
<tr>
<td>CAR-T</td>
<td>Celgene/Bluebird</td>
<td>Clinical Phase I</td>
<td>2013: $10M upfront, up to $225M/product in milestones. Bluebird bio option (exercised 2018) to 50/50 co-dev and profit share in US</td>
</tr>
<tr>
<td></td>
<td>JNJ/Legend Biotech</td>
<td>Clinical Phase I</td>
<td>2017: J&amp;J paid $350M upfront and will share 50-50 cost-sharing/profit-split, except in China, where Janssen and Legend have a 30-70 split.</td>
</tr>
<tr>
<td></td>
<td>Juno/Memorial Sloan Kettering</td>
<td>Clinical Phase I</td>
<td>2016: Undisclosed upfront payment, dev, reg, sales milestones, and royalties</td>
</tr>
<tr>
<td></td>
<td>Novartis/University of Pennsylvania</td>
<td>Clinical Phase I</td>
<td>2012: $20M upfront, undisclosed milestone and royalty payments for each product</td>
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</table>
GSK2857916 shows striking efficacy

- GSK2857916 is an ADC based on the anti-BCMA antibody, JM06
- GSK ’916 has received orphan drug designation by the FDA and the EMA in addition to breakthrough and PRIME designations
- Overall response rate of 60% as a monotherapy in a small trial of 35 patients (part 2 of the DREAMM-1 study; S. Trudeau et al., ASH 2017; Abstract 741)
  - 57% of the patients had had five or more prior treatment regimens
  - 90% of the patients had previously received stem cell transplantation

AvantGen’s anti-BCMA-ADC has potential to out-perform GSK’916
AvantGen’s anti-BCMA clone A11 (AVG-A11) recognizes native BCMA on transfected and MM cells

AVG-A11 was isolated from AvantGen’s yeast display human antibody libraries and further optimized

AVG-A11 binds to 293F cells transiently transfected with the human BCMA gene, but not to non-transfected 293F cells

AVG-A11 binds to BCMA-positive MM cell lines, but not to a BCMA-negative cell line (Raji)
AVG-A11 does **NOT** bind hBAFFR or hTACI, two proteins with homology to BCMA

**ELISA**
AVG-A11 binds to both human and cyno BCMA protein, but not to homologous proteins or baculovirus coated wells

**BAFFR**
Positive control antibody: eBioscience, anti-hBAFFR, clone 8A7,Cat#14-9117-82

**FACS**
AVG-A11 does not bind to 293F cells transiently transfected with the human hBAFFR or hTACI gene

**TACI**
Positive control antibody: eBioscience, anti-hTACI, clone 11H3,Cat#13-9217-82
AVG-A11 triggers more effective BCMA internalization than J6M0

**AVG-A11**

1.85 nM

**GSK-J6M0**

**Internalization assay**

AVG-A11 or GSK-J6M0 were incubated with IncuCyte® FabFluor before adding to the cells. Fluorescent intensity was monitored and recorded for 38 hours.
AVG-A11 out-performs GSK-J6M0 in killing MM cells in an ADC format

High BCMA level cell line: H929 (3 days)

Low BCMA level cell line: MM.1S and RPMI8226 (6 days)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>H929 Cells</th>
<th>MM.1S Cells</th>
<th>RPMI8226 Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC50 (nM)</td>
<td>Fold better than GSK-J6M0</td>
<td>IC50 (nM)</td>
</tr>
<tr>
<td>AVG-A11</td>
<td>0.79</td>
<td>4.4</td>
<td>0.55</td>
</tr>
<tr>
<td>GSK-J6M0</td>
<td>3.5</td>
<td></td>
<td>1.7</td>
</tr>
</tbody>
</table>

Cell viability assay

Cells were incubated with the indicated concentration of primary antibodies, AVG-A11 or GSK-J6M0, in the presence of Fab anti-human-Fc-MMAF for 3 or 6 days.
MMAF conjugated AVG-A11 exhibits highly potent toxicity to MM cells, but not to BCMA negative cells.

**Cell viability assay**

Cells were incubated with the indicated concentration of AVG-A11-MMAF for 6 days. Total ATP amount was measured with CellTiter-Glo.

<table>
<thead>
<tr>
<th>ADC</th>
<th>H929</th>
<th>U266</th>
<th>MM.1S</th>
<th>RPMI8226</th>
<th>Raji</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVG-A11-MMAF</td>
<td>0.074</td>
<td>0.10</td>
<td>0.16</td>
<td>0.18</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>
AVG-A11 blocks the BCMA-BAFF interaction, and out-performs GSK-J6M0 in blocking BAFF induced NF-κβ activation

ELISA
AVG-A11 Fab blocks BCMA binding to BAFF-coated wells

ELISA
AVG-A11-IgG is 3.7 fold more potent than GSK-J6M0 in blocking BCMA’s binding to BAFF

Reporter Assay
AVG-A11 is 6.1 fold more potent than GSK-J6M0 in inhibiting NF-κβ activation
AVG-A11 and GSK-J6M0 exhibit similar affinity and thermostability

**Affinity analysis**

Antibody Fab binding to captured BCMA at 30°C (by Octet)

<table>
<thead>
<tr>
<th></th>
<th>AVG-A11</th>
<th>GSK-J6M0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KD(M) Kon(1/Ms) Koff(1/s)</td>
<td>KD(M) Kon(1/Ms) Koff(1/s)</td>
</tr>
<tr>
<td>Human BCMA</td>
<td>1.05E-09 5.78E+05 6.05E-04</td>
<td>1.33E-09 2.38E+05 3.15E-04</td>
</tr>
<tr>
<td>Cyno BCMA</td>
<td>4.37E-09 5.47E+05 2.39E-03</td>
<td>3.41E-09 2.39E+05 8.15E-04</td>
</tr>
</tbody>
</table>

**Thermostability analysis**

<table>
<thead>
<tr>
<th></th>
<th>AVG-A11</th>
<th>GSK-J6M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tm (°C)</td>
<td>70.76</td>
<td>71.72</td>
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</tbody>
</table>
AVG-A11 exhibits better developability than GSK-J6M0

**HPLC analysis**
Antibodies were purified using a protein A column and analyzed by HPLC (Yarra™ 3 µm SEC-3000 LC Column)

**AVG-A11**
- Column retention time (peak width): 0.152 min
- (narrower peak width, no tail correlates with better developability)

**GSK-J6M0**
- Column retention time (peak width): 0.179 min

15
AVG-A11-MMAF exhibited cytotoxicity to BMMCs isolated from MM patients, but not from a healthy individual.

Cell viability assay

About 200 K per well of BMMCs from two patients and normal BMMCs from one healthy individual were cultured in the presence of the indicated amount of AVG-A11-MMAF for 3 days. The amount of ATP was quantified with CellTiter-Glo.
### Summary of the head-to-head comparison data

<table>
<thead>
<tr>
<th></th>
<th>AVG-A11</th>
<th>GSK-J6M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody origin</td>
<td><strong>Fully human</strong></td>
<td>Humanized</td>
</tr>
<tr>
<td>Affinity</td>
<td>$K_D=1.0$ nM</td>
<td>$K_D=1.3$ nM</td>
</tr>
<tr>
<td>Thermostability</td>
<td>$T_m=70.76^\circ$C</td>
<td>$T_m=71.72^\circ$C</td>
</tr>
<tr>
<td>Cytotoxicity on cells with high BCMA level (H292)</td>
<td>$IC_{50}=0.79$ nM</td>
<td>$IC_{50}=3.5$ nM</td>
</tr>
<tr>
<td>Cytotoxicity on cells with lower BCMA level (RPMI8226)</td>
<td>$IC_{50}=0.51$ nM</td>
<td>$IC_{50}=2.7$ nM</td>
</tr>
<tr>
<td>Inhibition of BCMA-mediated NF-kB activation</td>
<td>$IC_{50}=1.8$ nM</td>
<td>$IC_{50}=11.0$ nM</td>
</tr>
<tr>
<td>Column retention time (peak width) (better developability with a shorter time)</td>
<td>0.152 min</td>
<td>0.179 min</td>
</tr>
</tbody>
</table>