7th Annual World Bispecific Summit

September 28-30, 2016

Janine Schuurman
The Antibody Landscape

expectations and combinations

antibody format diversity and interconnections

preclinical

antibodies in cancer indications

number of antibodies in the clinic
(phase 1, 2 or 3 and approval is shown by dark to light shading)

Cut off date: March 2016
Data were made available by Janice Reichert, http://www.antibodysociety.org/
Many different bispecific formats – three major classes
Impact on bispecific discovery & development strategies

**Fragment-based bispecifics**
- BiTE - Amgen
- DART - Macrogenics
- DNLI - Immunomedics
- Flexibody/tandAb - Affimed
- Nanobody - Ablynx
- DARpins - Molecular Partners
- Adnectins - Bristol-Myers Squibb
- Alphabody - Complix

**Symmetric bispecific IgG**
- Di-diabody - Imclone/Eli Lilly
- Dual dAbs - Domantis/GSK
- DVD-Ig - AbbVie
- DART-Ig - Macrogenics
- mAB2 - F-Star
- HERCULES - Biogen Idec
- DAF - Genentech/Roche
- Scorpion - Trubion/Emergent

**Asymmetric bispecific IgG**
- Triomab - Fresenius/Trion
- CrossMab - Genentech/Roche
- Electrostatic steering - Amgen, Chugai, Merus
- SEEDbodies - Merck Serono
- κλBodies - Novimmune
- FcΔAdp - Regeneron
- pl-optimized bsAb - Xencor
- Asymmetric scaffold - Zymeworks
- Structure-based design - Lilly
- Bispecific IgG1 and IgG2 - Rina/Pfizer
- DuoBody platform - Genmab

...
Asymmetric bispecifics: regular IgG structure
Bispecific antibodies in the clinic

As of July 2016
Data were made available by Janice Reichert, http://www.antibodysociety.org/
Bispecific antibody formats in the clinic

**Symmetric**
- Tetravalent bsAb
- DVD
- DAF

**Asymmetric**
- Knob-into-hole
- BEAT
- DuoBody
- Structure-based design
- biMAb
- FcΔAdp
- Crossmab
- Biclonics
- Azymetric scaffold
- XmAb

**Other**
- Peptibody
- Nanocell

**Fragments**
- BiTE
- DART
- Nanobody
- TandAb
- Dock-and-Lock
- Adaptir

As of July 2016

Data were made available by Janice Reichert, http://www.antibodysociety.org/
## Bispecific platform & product partnering 2009-2016

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
<th>Note</th>
<th>Partner(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zymeworks</td>
<td>Azymetric Scaffold</td>
<td>Whole IgG, asymmetric</td>
<td>Merck, Lilly, Celgene, GSK</td>
</tr>
<tr>
<td>Merus</td>
<td>Biclonics</td>
<td>Whole IgG, asymmetric</td>
<td>Novartis, Ono Pharmaceutical</td>
</tr>
<tr>
<td>Macrogenics</td>
<td>DART</td>
<td>Fragment</td>
<td>Boehringer Ingelheim, Pfizer, Gilead, Servier SA, Takeda, Janssen</td>
</tr>
<tr>
<td>F-Star</td>
<td>mAB2</td>
<td>Engineered IgG, symmetric</td>
<td>Boehringer Ingelheim, Merck Serono, Denali, Abbvie</td>
</tr>
<tr>
<td>Xencor</td>
<td>Bispecific Fc domain</td>
<td>Engineered IgG, asymmetric</td>
<td>Amgen, Novartis</td>
</tr>
</tbody>
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Disclaimer: this is what I could find on the internet …. My apologies if I missed a deal or made a mistake ….
Topics – Day 1

• Discovery
  • bsAb lead selection: how to select the best targets and target pairs?
    • Abbvie, Roche, Bayer, Merus, Immunomedics, Immunomedics

  • Novel bsAb formats
    • Sanofi, Abbvie, University of Pennsylvania, Complix

• Development
  • Bispecifics: consequences for in vitro development and analytical assays
    • Pfizer, ImmTAC, Janssen

  • Translational research: testing efficacy in vivo
    • F-Star, Pieris
Innovating antibodies, improving lives

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Innovative applications of bispecific antibodies

• Crossing the blood-brain barrier (Genentech)

• Factor VIII replacement (Chugai)

• Dual targeting
  • Block macrophage-suppressive signal (CD47 X CD19 - NovImmune)
  • Co targeting resistance factors (cMet x EGFR – Genmab/Janssen)
  • Two epitopes on one target: HER2XHER2

• Induction of receptor clustering (Fap x DR5 - Roche / Genentech)

• Efficient payload delivery (Her2xCD63)

• “Trojan horse”: broadly neutralising Ebola bispecific
Innovative applications of bispecific antibodies (1): Crossing the blood-brain barrier

- Proof of principle with TfR x BACE bispecific antibody for potential treatment of Alzheimer’s disease

Innovative applications of bispecific antibodies (2): bispecific antibody mimics the cofactor function of factor VIII


Emicizumab (ACE910)

Asymmetric bispecific, Nonactive Fc (IgG4)
Innovative applications of bispecific antibodies (3): Block macrophage-suppressive signal CD47

- CD47 x CD19 BsAb (NI-1701)
  - κλ-body™ (NovImmune) - asymmetric

- Disrupts CD47-SIRPα “don’t eat me” signal
- Not tumor specific
- Low affinity

- Tumor targeting
- High affinity

- Fc-mediated effector functions
- IgG pharmacokinetics/half-life

Kosco-Vilbois, World Bispecific Summit, September 2015
Innovative applications of bispecific antibodies (4):
Dual targeting of oncogenic pathways

DuoBody cMet x EGFR (JNJ-61186372)
- Overcome acquired resistance
- Monovalent targeting of cMet prevents agonism
- Synergy: enhanced efficacy by dual targeting

Innovative applications of bispecific antibodies (5): Dual targeting of oncogenic pathways

• Crystal structures of the DARPin:target complexes reveal that bivalent binding crosslinks HER2-monomeres in a signaling-incompetent state

• Bispecific DARPin-bound state prevents HER2 kinases from forming any complex

Innovative applications of bispecific antibodies (6): Induction of receptor clustering

- DR5 x FAP bsAb (RG7386)
- Tetravalent - symmetric
- Inert Fc-domain (P329G LALA)
- Bivalent binding to both FAP and DR5 leads to avidity-driven hyperclustering of DR5
- Strong induction of apoptosis in tumor cells but not in normal cells

Brünker et al. Mol Cancer Ther 15: 946-57 (2016)
Innovative applications of bispecific antibodies (7): Efficient payload delivery by a bispecific antibody-drug conjugate

- enhancing lysosomal ADC delivery: tumor specificity combined with facilitating targeting to the lysosomal compartment
Innovative applications of bispecific antibodies (8): “Trojan horse” bispecific antibody strategy: broad protection against Ebola

DVD-Ig, not patent IgG or mixtures:
Broad neutralizing activity against Ebola viruses
Topics – Day 2

• Discovery
  • bsAb lead selection: how to select the best targets and target pairs?
    • MedImmune, OncoMed
  • Novel bsAb formats
    • BioMunex, Celgene

• Development
  • Challenges in testing the nonclinical safety and efficacy of T-cell bsAbs
    • Genentech, Pfizer, Amgen
  • Translation to the clinic and back
    • Merrimack

• Novel applications
  • Macrogenics, Bristol-Myers Squibb, KTH Royal Institute of Technology

• Perspectives on future bsAb development
  • Jounce Therapeutics, Bristol-Myers Squibb