CANCER & BIOLOGICALS MARKET ANALYSIS AND OVERVIEW

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www.pharmacircle.com
CANCER

- Large segment of global products and pipeline
- **Products & Pipeline:** 16% (research to marketed phase)
- **Pipeline:** 21% (all but marketed)
MOLECULE TYPE
Biologics; half of all cancer programs

Biologics
- 40% of all therapeutic categories
- 52% of cancer
- Antibodies the largest segment in cancer biologics
CANCER TYPES VS. MOLECULE TYPE
n=3653

- Small Mol. dominates all cancer categories
- Antibodies in haematological, GI, Genito urinary cancers
- Peptides in prostate cancer
ANTIBODIES MARKETED FOR CANCER

- First diagnostic antibodies approved in 1996 for imaging; CEA SCAN, ProstaScint and Verluma
- Rituxan: First Therapeutic antibody approved in 1997 for NH-Lymphoma
- Arzerra is the latest for Cancer CLL
ANTIBODIES, CANCER

n=641

- Across all cancers; Haematological, GI, genito urinary, breast, solid, lung cancers, etc.
ANTIBODY AND CANCER

Fully Human and Humanized

Anti-CD20/-EGFr/-CD22, etc.
PROTEIN, CANCER

n=432

• Genito Urinary, haematological and skin cancers

• Proteins classes
  Interferons > Interleukins > TNFα > asparaginase analogs
PEPTIDE, CANCER

n=256

- Majority for Prostate cancer; Lupron Depot, Zoladex, etc.
- Majority of Gonadotropin Releasing Hormone Agonists
VACCINE, CANCER
N=169

- Genito urinary >GI, Breast, Skin and lung cancers
- Cell and DNA based vaccines dominate pipeline
- Cervarix (2007) and Gardasil (2006) latest approvals
siRNA & CANCER (n=40)

- Early programs across cancer categories
- Targets; VEGF, interferon, kinases, RRM2, ApoB, etc.
OLIGOS/ANTISENSE, CANCER

n=102

- Genasense (oligonucleotide, blocks Bcl-2 protein) / Genta, Cancer CLL and other cancers
- AP12009 (antisense blocks TGF-beta2), for brain cancer Antisense Pharma GMBH
GENE, CANCER
n=98

- GI, genito urinary, breast, skin and lung cancer programs
- Various targets, p53 etc.
DELIVERY VS. CANCER (n=2400)

- Small molecules delivered by injectable & oral routes
- All biologicals by injectable routes
- A few inhalation and skin delivery programs for lung and skin cancers
MOLECULE TYPE VS. INJECTION SITE

n=448

- Biologics are delivered by Injectables
- Antibodies by IV, Peptides/Proteins by SC
- A few intradermal for peptide and proteins
- Genes by intratumoral injection
PROVEN DRUG DELIVERY TECHNOLOGIES FOR CANCER DRUGS

• **Increase t1/2 in plasma;** encapsulation (liposome) or prodrug(PEG); increases chance of uptake by cancerous tissue—*for all molecule types*

• **Protect normal tissues;** target selectively through leaky vessels of cancer as bound or encapsulated; liposomes, dendrimers, nanoparticles, prodrugs, etc. - *chemo drugs/toxins*

• **Improve uptake into cancer cells;** carrier/receptor facilitated uptake by cancer cells – *all molecule types*

• **Enable escape from lysosomes;** special linking technologies for acidic environment—*all molecule types*

• **Provide long term drug release for low dose drugs;** Injectable depot, for low dose drugs
TARGETED DELIVERY VS CANCER

n=440

- Variety of targeted delivery techs for small molecules
- Prodrugs for protein and antibodies
- Receptor/carrier transport (antibody toxin conjugates) for – antibodies
- Cationic lipids for siRNA/Oligos
ANTIBODY DRUG CONJUGATES

From http://www.seagen.com
# USE OF ANTIBODIES FOR TARGETING

<table>
<thead>
<tr>
<th>Pipeline Name/Target</th>
<th>Indications/Phase</th>
<th>Technology/Owner</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mylotarg</strong> -gemtuzumab ozogamicin-Ant-CD33 Wyeth/PDL</td>
<td>Cancer AML, Marketed</td>
<td>anti-CD33 antibody linked to calicheamicin</td>
</tr>
<tr>
<td><strong>Neuradiab</strong>-Anti-tenascin Bradmer Pharmaceuticals</td>
<td>Cancer, Glioma/Glioblastoma Multiform, Phase 3</td>
<td>Anti-tenascin 81C6 monoclonal antibody labeled with I-131</td>
</tr>
<tr>
<td><strong>Trastuzumab</strong>-DM1, Anti-Her2 Roche/Genentech</td>
<td>Breast cancer, Phase 3</td>
<td>Anti-Her2 linked to DM1, a maytansinoid. Immunogen</td>
</tr>
<tr>
<td><strong>CR, 011-vcMMAE</strong>, Anti-GPNMB Curagen</td>
<td>Breast Cancer and Metastatic Melanoma, Phase 2</td>
<td>Fully human Anti-GPNMB conjugated to auristatin E (MMAE), Seattle Genetics</td>
</tr>
<tr>
<td><strong>HuM195-Bi-213</strong>, PDL Biopharma</td>
<td>Cancer AML, Phase 2</td>
<td>anti-CD33 mAb (HuM195) for use with Bi-213 Actinium Pharmaceuticals</td>
</tr>
<tr>
<td><strong>IMMU-110, Anti-hCD74</strong> Immunomedics</td>
<td>Cancer NHL and Multiple Myeloma, Phase I</td>
<td>hCD74 doxorubicin drug conjugate, Immunomedics</td>
</tr>
</tbody>
</table>
Injectable biodegradable depot techs are used for peptides in prostate cancer to provide for up to 6 months of drug release.
DELIVERY: ANTIBODY & CANCER
Injectables, produgs/antibody conjugates
DELIVERY: GENE & CANCER

Viral vectors for gene

Viral and nonviral vectors
N=130

Many AAV (adeno associated viral vectors), n=53
DELIVERY: OLIGOS & CANCER

Most Injectable, 1 inhalation, 1 nasal and 1 rectal, n=66

Liposomes and Cationic lipids, n=12
DELIVERY: siRNA & CANCER

n=53

Cationic lipid/liposomes, n=28
DELIBERY: VACCINE & CANCER

Injectables and a few skin delivery

Across targeted delivery platforms
WORLD SALES OF TOP 25 DRUGS
Biologicals rapidly growing in sales
# ANTIBODY BASED SALES-WORLD-2008

## (25 Products)

<table>
<thead>
<tr>
<th>Region</th>
<th>Sales (M$)</th>
<th>% of Total</th>
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<tbody>
<tr>
<td>World</td>
<td>31110</td>
<td>100</td>
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<tr>
<td>Ex_us</td>
<td>15195</td>
<td>48.84</td>
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<tr>
<td>Japan</td>
<td>1235</td>
<td>3.97</td>
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<tr>
<td>Europe</td>
<td>5008</td>
<td>16.1</td>
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<tr>
<td>Usa</td>
<td>15430</td>
<td>49.6</td>
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## (6 Products)

<table>
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<tr>
<th>Region</th>
<th>Sales (M$)</th>
<th>% of Total</th>
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<tbody>
<tr>
<td>World</td>
<td>16474</td>
<td>100</td>
</tr>
<tr>
<td>Ex_us</td>
<td>8468</td>
<td>51.4</td>
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<tr>
<td>Japan</td>
<td>608</td>
<td>3.69</td>
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<tr>
<td>Europe</td>
<td>4683</td>
<td>28.43</td>
</tr>
<tr>
<td>Usa</td>
<td>7520</td>
<td>45.65</td>
</tr>
</tbody>
</table>

6 CANCER & ANTIBODY (Bottom); 50% OF TOTAL ANTIBODY (Top) PRODUCT SALES
PRODUCT DEALS SINCE 2000
n=3338
ANTIBODY PRODUCT DEALS-SINCE 2000

More Product Deals since 2002 across all cancer categories (n=201)
## SAMPLE OF ANTIBODY DEALS

<table>
<thead>
<tr>
<th>Licensor</th>
<th>Licensee</th>
<th>Product</th>
<th>Phase</th>
<th>Current Phase</th>
<th>Total Deal/Territories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medarex Dec 2006</td>
<td>GSK</td>
<td>Arzerra</td>
<td>Phase 3</td>
<td>Marketed/US (Cancer CLL), Phase 2/3 Various cancers and others</td>
<td>$1600M ($102/$357/1200mil), USA, EU, Japan</td>
</tr>
<tr>
<td>Amgen Feb 08</td>
<td>Takeda</td>
<td>Vectibix</td>
<td>Marketed</td>
<td>Marketed, Various Cancers</td>
<td>$902 ($200/$702) Japan</td>
</tr>
<tr>
<td>PDL Pharma Aug 08</td>
<td>BMS</td>
<td>HuLuc63</td>
<td>Phase I</td>
<td>Phase I, Cancer MM</td>
<td>$860 ($60/$800) World</td>
</tr>
<tr>
<td>Seattle Genetic Dec 09</td>
<td>Takeda/Millenium</td>
<td>SGN-35</td>
<td>Phase 2</td>
<td>Phase 2/3 Haematological cancers</td>
<td>$260 (60/230), ex-US</td>
</tr>
<tr>
<td>Merrimack Oct. 09</td>
<td>Sanofi Aventis</td>
<td>MM-121</td>
<td>Phase I</td>
<td>Solid Cancers</td>
<td>$530 (60/470)-World</td>
</tr>
<tr>
<td>Oxford Biother May 09</td>
<td>GSK</td>
<td>New Antibodies</td>
<td>Research</td>
<td>Cancer</td>
<td>$370 (?)/370)-Exclusive option to license/World</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• Cancer has been the largest therapeutic target
• Biologics nearly half of all cancer programs and antibodies is the most rapidly growing segment of the biologics
• Dual role of antibodies; as a killer for cancer cells and delivery vehicle in drug conjugates
• Applications of prodrugs (PEG, etc.) for proteins & antibodies, depot techs for peptides, cationic lipids for siRNA and oligos, viral vectors for gene molecules