Drugs targeting cancer metabolism and unmet need in HER2-positive breast cancer, as well as cytotoxic agents wrapped into novel delivery technologies, are among the top 10 unpartnered oncology drugs to be showcased at Windhover’s Therapeutic Area Partnerships meeting in Boston from Nov. 28-30.

Each year at the TAP meeting, expert consultants present their take of the hottest unpartnered assets available for licensing in a range of therapeutic areas, including oncology, cardiovascular medicine, neuroscience and infectious disease (“Therapeutic Area Partnerships, Only 1 Month Away, at the Westin Copley Place Boston on November 28-30, 2012” – “The Pink Sheet,” Oct. 29, 2012).

In charge of making selections for the meeting’s oncology track, consultants at the Cambridge, Mass.-based Campbell Alliance started with a pool of 500 candidates and whittled the list down to 10. The process was informed by a range of sources, including discussions with key opinion leaders, the consultants’ own experiences helping companies with oncology strategies, trends in licensing activity, and Campbell’s 2012 Dealmakers’ Intentions survey.

Campbell Alliance’s research suggests that in the next six years in oncology, most companies, with the notable exception of Roche, will be relying on acquisition of externally sourced candidates, which will account for about half of revenue. Considering the dearth of late-stage assets, pharmas in licensing mode are placing their bets on early stage, unproven candidates, some of which are available for a nominal up-front fee.

As part of the sweeping review, the consultants considered evidence for the mechanism of action, development risk and costs, unmet need, opportunities to expand to other indications, recent licensing trends and prospects for reimbursement in the future. At a time of exorbitant pricing in oncology and a trend toward combination of new expensive agents, payers are on guard (“Pfizer’s Xalkori Joins The Six-Figure Oncology Drug Club” – “The Pink Sheet,” Sep. 5, 2011). Campbell also considered pharmas’ need for diversification across oncology franchises.

Interviews with key opinion leaders suggest strong interest in cancer metabolism as a direction for oncology research in the future, Campbell consultants observed. This sentiment is not surprising in light of deal activity in recent years. Forma Therapeutics Inc. struck a deal with J&J subsidiary Janssen Pharmaceutical Cos. to develop and commercialize drugs for tumor metabolism in January, an agreement that included an undisclosed upfront payment and up to $700 million in development, regulatory and commercial milestones (“Janssen Teams Up With Forma On Tumor Metabolism” – “The Pink Sheet” DAILY, Jan. 9, 2012). The same month, Forma also teamed up with Boehringer Ingelheim GMBH, in a preclinical development deal that included a $65 million upfront payment and up to $750 million in pre-commercial milestones (“Boehringer, Forma Strike Discovery Deal In Oncology” – “The Pink Sheet” DAILY, Jan. 5, 2012). Previously, in 2011 Celgene Corp. extended a deal with Agios Pharmaceuticals Inc. for cancer metabolism discovery. The original agreement, signed in April 2010, garnered a whopping $130 million upfront payment and potential to earn up to $120 million for each program developed (“Celgene Expands Agios Collaboration In Cancer Metabolism” – “The Pink Sheet” DAILY, Oct. 7, 2011).

The Agios deal has provided a “halo effect” for other companies working in cancer metabolism and led biotechs to be optimistic about potential for deals on preclinical assets, said Jonathan Betts, engagement manager at Campbell Alliance. Research in cancer metabolism dates back to the 1920s, so knowledge about various pathways and targets is extensive (“Biotechs Target Cancer Metabolism” – START-UP, September 2010). This backdrop has set the scene for development of a broad new set of drugable targets.
Campbell is expecting to see more early stage deals for cancer metabolism assets, because while the technology is largely unproven, it hypothetically could have very wide application in oncology.

"More and more research is going on in this area, where you can have therapeutics that could interfere with cancer cell metabolic pathways and you can have a transformational technology in hand," said Guru Muralimohan, who is an engagement manager at Campbell Alliance.

Campbell’s list of top unpartnered assets includes ME-344, a mitochondrial inhibitor from MEI Pharma Inc. (formerly Marshall Edwards Inc.), which has shown activity in a Phase I study of a range of solid tumors. The candidate’s mechanism of action was discovered by chance, commented CEO Daniel Gold. As part of a research collaboration, Yale University scientists were screening MEI Pharma’s compounds. The lab of Gil Mor, in Yale’s department of gynecology and obstetrics, observed that a compound named

### Top Oncology Partnering Opportunities 2012

Every year, Windhover’s Therapeutic Area Partnerships meeting showcases licensing opportunities across a range of disease types. For 2012, Campbell Alliance consultants selected the top oncology candidates, below, out of a pool of 500 assets.

<table>
<thead>
<tr>
<th>Company/Headquarters</th>
<th>Candidate</th>
<th>Description</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apogenix/ Heidelberg, Germany</td>
<td>Apocept (APG-101)</td>
<td>CD95-Fc fusion protein therapeutic that blocks interaction between CD95 ligand and CD95 receptor, inhibiting tumor cell growth.</td>
<td>Met primary endpoints in Phase II glioblastoma multiforme trial. Phase II for myelodysplastic syndromes slated for 2013.</td>
</tr>
<tr>
<td>Bind Biosciences/ Cambridge, Mass.</td>
<td>BIND-014</td>
<td>Proprietary “Accurin” designed to deliver docetaxel chemo in target tissue.</td>
<td>Phase II in four solid tumor indications slated for late 2012.</td>
</tr>
<tr>
<td>Ceres Oncology (newly formed Circadian Technologies subsidiary)/ Victoria, Australia</td>
<td>VGX-100</td>
<td>Fully human monoclonal antibody against vascular endothelial growth factor C.</td>
<td>Phase I study of drug alone and co-administered with bevacizumab in advanced or metastatic solid tumors.</td>
</tr>
<tr>
<td>EnGeneIC/ New South Wales, Australia</td>
<td>EnGeneIC delivery vehicle (EDV)</td>
<td>Proprietary EDV technology allows packaging of a range of anti-cancer drugs. Bispecific antibody delivers payload directly to tumor cells.</td>
<td>Phase I first-in-man study completed.</td>
</tr>
<tr>
<td>KaloBios/ South San Francisco, Calif.</td>
<td>KB004</td>
<td>EphA3, receptor tyrosine kinase monoclonal antibody.</td>
<td>Phase I hematologic malignancies.</td>
</tr>
<tr>
<td>Macrogenics/ Rockville, Md</td>
<td>MGAH22</td>
<td>Next-gen Fc-optimized HER2 antibody, works in low-HER2 expressing tumors without gene amplification.</td>
<td>Phase I solid tumors.</td>
</tr>
<tr>
<td>MEI Pharma/ San Diego, Calif.</td>
<td>ME-344</td>
<td>Mitochondrial inhibitor</td>
<td>Phase I, solid refractory tumors.</td>
</tr>
<tr>
<td>Shape Pharmaceuticals/ Cambridge, Mass.</td>
<td>SHP-141</td>
<td>Topical HDAC inhibitor</td>
<td>Phase Ib CTCL and psoriasis.</td>
</tr>
</tbody>
</table>

Sources: Campbell Alliance, company websites
NV-128, ME-344's precursor, worked in a subset of cells in ovarian cancer that is resistant to chemotherapy. One of the first things that happened with exposure to the test drug was that the cells stopped producing energy in the mitochondria of normal cells, researchers discovered.

“There was no deliberate intent like with some of more modern targeted therapies to target a particular enzyme, it really was working backward from the basic discovery of an activity and then elucidating the mechanism of action,” Gold said.

Chemo and surgery are effective for getting rid of the majority of a tumor, but a small number of stem cells refractory to treatment remain and later repopulate. While the drug appears to be broadly active in cancer, the company expects that based on experience at Yale, ovarian cancer is the logical place to start for the next phase of studies, Gold said.

**Targeting Unmet Needs**

Cancers of the ovaries, pancreas and brain, among other organs, still represent areas of unmet need in oncology and as such are expected to have an easier time winning approval and reimbursement.

“It’s hard to elucidate what the payer environment will be upon approval, especially when thinking about earlier-stage assets," but it’s reasonable to expect payers will pay more attention to tumor types in which the current crop of agents are working well and treatment needs are being met, Betts said.

Despite the approval of Avastin (Roche/Genentech Inc.'s bevacizumab) for glioblastoma, the disease is still hard to treat and, therefore, represents an opportunity for the right candidate.

Campbell’s list includes a drug that has orphan status in the U.S. and Europe for this disease - Apogenix GMBH’s Apeocept (APG-101), a fully human fusion protein made up of the extracellular domain of the CD95 receptor and the Fc domain of an Ig antibody. The candidate blocks the CD95 ligand from binding to the CD95 receptor, inhibiting growth of cancer cells.

The drug met the primary endpoint for progression-free survival (PFS) in a Phase II GBM study and is gearing up for a Phase II trial in myelodysplastic syndromes in 2013. The fact that it is also in development for MDS, which is also fairly hard to treat, diversifies the development risk, Betts said.

But Campbell consultants also see some big opportunities in broad populations in which there are well-established treatment options, in terms of targeting niches with a clear value proposition or improving the delivery of standard cancer treatments.

Roche/Genentech’s Herceptin (trastuzumab) dominates human epidermal growth factor receptor type 2 (HER2) positive breast cancer, but it does not work well for the patients with lower-expressing HER2. Some HER2 genotypes are associated with poorer prognosis. Herceptin works best in those with HER2 3+, or gene amplified, tumors. MacroGenics Inc.'s MGAH22 is a next-generation Fc-optimized HER2 antibody that is aimed at patients with lower levels of HER2 expression - that is, HER2 <3+ levels without gene amplification. The company is looking to develop the candidate in Herceptin-refractory metastatic breast cancer, as well as in other tumors that have HER2 expression, such as gastric, bladder and prostate cancer.

“Here you have an asset where the mechanism is pretty well validated, and you have a patient population not being treated with targeted agents on the market," from that perspective it's an interesting asset, Muralimohan said.

Betts added that an influential advocacy effort around treatment of HER2 positive breast cancer has created a field in which patients are highly organized and physicians are informed. The infrastructure is therefore in place for new treatments of low HER2 expressing cancer. Furthermore, payers are very comfortable with covering HER2 targeted agents, and for them it would be a “clear value story as well,” Betts added.

In making their recommendations for top unpartnered opportunities, the Campbell consultants sought to balance attention to areas of unmet need with technology that has broad-based applicability. And when it comes to a broad approach, Campbell believes that EnGeneIC’s EDV technology is well-positioned as a delivery vehicle that can be used with a wide range of cancer agents. EDV allows packaging of many different kinds of established cancer therapies. A bispecific antibody delivers the payload to tumor cells - one end is attached to the EDV and the other end to the cancer cell receptor.

The rise of antibody conjugates, which link cytotoxic drugs to antibodies for direct delivery of a payload to cancer cells bodes well for EnGeneIC, in Campbell’s view. Seattle Genetics Inc.’s Ad cetris (brentuximab vedotin) was cleared for Hodgkin lymphoma in August 2011 and had sales of $102.8 million in the first three quarters of 2012. Roche’s breast cancer conjugate T-DMI (trastuzumab-DMI) is pending review, following the release of positive results at the American Society of Clinical Oncology in June.

“If T-DMI gets approved, you will see more conjugates enter the market,” Muralimohan said.

As a bispecific antibody-based platform, EnGeneIC’s EDV approach differs from ADCs, but the concept of delivering a cytotoxic payload directly to tumor cells is similar. The stability of linking technology used to be questionable, but with T-DMI coming to the market, “some of those fears are being alleviated,” Muralimohan said.

[Editor’s note: The oncology track is one of multiple therapeutic areas to be explored in Windhover-EBI’s Therapeutic Area Partnerships meeting Nov. 28-30 in Boston. For more information about registration, call 908-547-2067.]