An analysis of 15,000 abstracts from the latest ASCO, AACR and ASH meetings by BioCentury’s machine-learning program, with commentary on the top trends in targets, indications, therapeutic modality and more.
LEADING WITH LUNG

By Emily Cukier-Meisner, Senior Writer and Meredith Durkin-Wolfe, Associate Editor, Research & Analytics

Lung cancer squeezed past breast cancer as the top indication at the American Society of Clinical Oncology meeting this year as targeted therapies duke it out within genetically defined subgroups, while immunotherapies seek their best molecular subpopulations, combination partner or both.

BioCentury analyzed the roughly 3,600 meeting abstracts related to clinical, preclinical, biomarker or basic cancer research released in advance of the meeting taking place June 2-6 in Chicago.

Analyses of the top indications and targets reflect a huge emphasis on the role of the immune system in cancer (see “Top Indications at ASCO” and “Top ASCO Targets”). This is not a surprise, as checkpoint inhibitors and other immunotherapies have been the hottest programs in industry’s cancer pipeline for the past few years, and every company with a checkpoint inhibitor is testing it with multiple combination partners and across several types of cancer.

Lung cancer was one of the first indications for which PD-1 and PD-L1 inhibitors were approved, and a great deal of work on immunotherapies in this indication continues.

PD-1 and PD-L1 were each mentioned in roughly one-sixth of the lung cancer abstracts. These include clinical studies attempting to bring Opdivo nivolumab from Bristol-Myers Squibb Co. and Keytruda pembrolizumab from Merck & Co. Inc. up the lines of therapy or into new combinations.

However, immunotherapies only partly explain lung cancer’s predominance at ASCO this year. Several abstracts concern studies that are testing when and how to use a bevy of recently approved or late-stage therapies that span a diverse set of targets.

For instance, two late-breaking abstracts to be presented on Tuesday feature head-to-head clinical studies comparing a new targeted therapy to an older member of the same class. One will discuss results from a Phase III study of Pfizer Inc.’s dacomitinib vs. AstraZeneca plc’s Iressa gefitinib for first-line treatment of EGFR-positive non-small cell lung cancer (NSCLC). Iressa inhibits EGFR, and dacomitinib inhibits EGFR, HER2 and EGFR4.

The other will present data from a Phase III study of Roche’s Alecensa alectinib vs. Pfizer’s Xalkori crizotinib in first-line anaplastic lymphoma kinase (ALK)-positive NSCLC. Xalkori is a dual inhibitor of c-Met receptor tyrosine kinase (c-MET; MET; HGFR) and ALK, and Alecensa is an ALK inhibitor.

NEXT WAVE

While PD-1 and PD-L1 had roughly the same number of mentions as the old-school targets HER2 and EGFR in...
abstracts presenting data, the checkpoint targets have a much greater presence in abstracts devoted to clinical trials coming down the pike.

PD-1 and PD-L1 were the top two targets among “trials in progress” abstracts presented at ASCO, racking up about twice as many mentions apiece as the third most popular target, HER2 (see “ASCO Trials in Progress”). The ASCO abstracts also yielded eight novel targets described in preclinical studies (see “Novel Targets at ASCO”). Some of the new targets could apply to different cancer subtypes or patient populations than current therapies, such as those described in four abstracts published online in conjunction with the meeting but not presented there.

For instance, researchers from Fukushima Medical University described a study suggesting that family with sequence similarity 83 member B (FAM83B) may promote tumor proliferation in EGFR-wild type lung adenocarcinoma. And researchers from Orlando Veterans Affairs Medical Center and the University of Central Florida related experiments that correlate overexpression of T-complex 1 (TCP1; CCT1) with progression in small cell lung cancer (SCLC), an underserved subtype of lung cancer.

While most of the new targets are proteins, two are long non-coding RNAs (lncRNAs). An electronic abstract submitted by researchers at Nanfang Hospital and Southern Medical University showed that the lncRNA EIF3J antisense RNA 1 (EIF3J-AS1) may help gastric cancer resist chemotherapy. Another team from Southern Illinois University School of Medicine contributed an abstract showing that the lncRNA p53 activating non-coding RNA (PANCR) acts as a tumor suppressor through its interaction with p53.

MODALITIES
BioCentury’s analysis of therapeutic modalities represented in the ASCO abstracts yielded few surprises. Antibodies were mentioned far more than any other approach (see “Modalities at ASCO”). Most of the newer therapeutic modalities — including protein therapies other than traditional antibodies, vaccines and oncolytic viruses, and cell or gene therapies — were distributed pretty evenly across indications.

Antibody-drug conjugates were more common in lung cancers relative to other indications, while nanoparticles were overrepresented in gastric cancers and cell therapy was most often mentioned in leukemia abstracts.

Cell therapy also stood out in the abstracts related to pediatric cancers — although just 65 abstracts at ASCO focus specifically on cancers in children. Among these, the most commonly mentioned target was CD19. All six abstracts that mentioned the target are testing chimeric antigen receptor (CAR) therapy in children with hematologic cancers (see “Pediatric Targets at ASCO”).

COMPANIES AND INSTITUTIONS MENTIONED
American Society of Clinical Oncology (ASCO), Alexandria, Va.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Fukushima Medical University, Fukushima, Japan
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Nanfang Hospital, Guangzhou, China
Orlando Veterans Affairs Medical Center, Orlando, Fla.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Southern Illinois University School of Medicine, Springfield, Ill.
Southern Medical University, Guangzhou, China
University of Central Florida, Orlando, Fla.

REFERENCES
TOP INDICATIONS AT ASCO

Lung cancer surpassed breast cancer in abstracts presented at this year’s American Society of Clinical Oncology meeting, with 616 mentions compared with 564. Last year, breast cancer was the most common indication mentioned in abstracts at the meeting.

For both indications, the proportions of abstracts for a given subtype remained consistent between 2016 and this year. In lung cancer, non-small cell lung cancer (NSCLC) had 10 times the mentions of small cell lung cancer (SCLC), a poorly served subtype. About one-fifth of the breast cancer abstracts concerned triple-negative breast cancer (TNBC) this year and last year.

Compared to ASCO 2016, skin cancer climbed in the rankings from the sixth to fourth most common indication, while prostate cancer dropped from fourth to tenth.

The analysis below shows the 19 indications that were mentioned in at least 50 abstracts. In total, the analysis included 2,921 abstracts assigned to any of ASCO’s presentation tracks focused on a particular cancer type. Abstracts in tracks related to epidemiology, survivorship and supportive care were excluded, as were abstracts assigned to tracks that concerned biomarkers and those assigned to tracks related to health services research and clinical informatics. Indications were assigned by a machine learning algorithm designed by BioCentury; double counting was allowed for abstracts that included more than one cancer subtype. Source: ASCO abstracts as of May 17.

![Graph showing the number of abstracts for each cancer type and subtype]
TOP ASCO TARGETS

The top figure shows that immunotherapy targets PD-1 and PD-L1 will once again dominate the discourse at ASCO. Combined, the two targets were mentioned in 566 abstracts, and this year PD-1 and HER2 traded places for the top spot. The presence of CD4 and CD8 among top targets shows increasing consideration of immunology in cancer treatment, such as the role of CD8 T cells in prediction or assessment of responses to immunotherapy for lung cancer, skin cancer and breast cancer.

The heat map in the bottom figure shows the most common indications for the hottest targets. Pink/red indicate the most frequently cited targets, while blue shows the lowest number of mentions. Lung and breast cancers featured the highest concentrations of the hottest targets, driven by mentions of molecules that are both therapeutic targets and biomarkers — EGFR in lung cancers, and HER2 in breast cancers.

Mentions of PD-1 and PD-L1 spanned the greatest range of indications, but they were most common by far in lung cancer and skin cancer, reflecting the indications where inhibitors of these checkpoints are approved.

For both analyses, a total of 2,921 abstracts were searched by a machine learning algorithm designed by BioCentury to identify mentions of any target in any context. The top figure shows the 22 targets that were mentioned in at least 50 abstracts; the bottom heat map shows those targets matched to indications that were mentioned in at least 150 abstracts. Abstracts in tracks related to epidemiology, survivorship and supportive care were excluded, as were abstracts assigned to tracks that concerned biomarkers and those assigned to tracks related to health services research and clinical informatics. Source: ASCO abstracts as of May 17.
ASCO TRIALS IN PROGRESS

PD-1 and PD-L1 were mentioned more than any other targets in abstracts describing ongoing clinical studies. Other immunotherapy targets that entered the top ranks include cytotoxic T-lymphocyte associated protein 4 (CTLA-4; CD152) and CD80 (B7-1), a checkpoint target that is also hit by anti-PD-L1 mAb Imfinzi durvalumab from AstraZeneca plc (LSE:AZN; NYSE:AZN).

The analysis below includes targets mentioned in at least 10 of the 268 abstracts ASCO designated with a “TPS” to indicate trials in progress. These targets were then mapped to the 16 indications that were mentioned in at least 25 TPS abstracts. Source: ASCO abstracts as of May 17.
NOVEL TARGETS AT ASCO

Selected new targets mentioned in abstracts at ASCO are shown below. (A) T-complex 1 (TCP1; CCT1) has been proposed as a target in neurology but may be new in cancer. Sources: ASCO abstracts as of May 17; BCIQ: BioCentury Online Intelligence

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication(s)</th>
<th>Description</th>
<th>Presenting institution(s)</th>
<th>Abstract code</th>
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<tr>
<td>DLC1 Rho GTPase activating protein (DLC1); angiominolike 2 (AMOTL2)</td>
<td>Estrogen receptor-positive breast cancer</td>
<td>Phosphopeptide mapping shows absence of DLC1 and phosphorylation of AMOTL2 promote invasiveness by activating Yes-associated protein 1 (YAP1; YAP)-WW domain containing transcription regulator 1 (WWTR1; TAZ) signaling</td>
<td>Indiana University School of Medicine; Indiana University</td>
<td>11592</td>
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<td>EIF3J antisense RNA 1 (EIF3J-AS1)</td>
<td>Gastric cancer</td>
<td>In gastric cancer cells resistant to oxaliplatin or epirubicin, EIF3J-AS1 inhibition decreased autophagy and increased sensitivity to oxaliplatin and epirubicin</td>
<td>Nanfang Hospital; Southern Medical University</td>
<td>e15581</td>
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<td>Family with sequence similarity 83 member B (FAM83B)</td>
<td>Lung cancer</td>
<td>Microarray expression data and knockdown studies in cancer cell lines suggest FAM83B inhibition could reduce tumor cell proliferation in lung adenocarcinoma patients with wild-type EGFR</td>
<td>Fukushima Medical University</td>
<td>e23136</td>
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<tr>
<td>G protein-coupled receptor 87 (GPR87)</td>
<td>Lung cancer</td>
<td>An adenoviral vector expressing shRNA targeting GPR87 has antitumor effects in in vitro and in vivo studies</td>
<td>Kagawa University</td>
<td>e23152</td>
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<tr>
<td>p53 activating non-coding RNA (PANCR)</td>
<td>Breast cancer</td>
<td>PCR and RNA methods show PANCR is downregulated in breast cancer cell lines and tissues and inversely correlates with malignancy. Mimicking PANCR binding to p53 could activate p53 and suppress tumors</td>
<td>Southern Illinois University School of Medicine</td>
<td>e23016</td>
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<td>Sialophorin (SPN)</td>
<td>Acute myelogenous leukemia (AML); myelodysplastic syndrome (MDS)</td>
<td>A sialylated epitope on sialophorin is overexpressed on AML and MDS cells; an antibody to the epitope eliminated AML cells in vivo</td>
<td>Academic Medical Center; AIMM Therapeutics B.V.; Leiden University Medical Center</td>
<td>7009</td>
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<tr>
<td>T-complex 1 (TCP1; CCT1) (A)</td>
<td>Lung cancer</td>
<td>CCT gene alterations are associated with lung cancer, and CCT expression in small cell lung carcinoma cells correlates with susceptibility to a therapeutic peptide that targets CCT</td>
<td>Orlando Veterans Affairs Medical Center; University of Central Florida</td>
<td>e23163</td>
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<td>Tubulin polymerization promoting protein family member 3 (TPPPP3)</td>
<td>Colorectal cancer</td>
<td>TPPP3 is overexpressed in colorectal cancer specimens; in vitro knockdown of TPPP3 inhibited cell proliferation, migration and invasion and induced apoptosis</td>
<td>Shandong University; Shandong Cancer Hospital and Institute</td>
<td>e23006</td>
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MODALITIES AT ASCO

The top figure shows antibodies were by far the dominant therapeutic modality mentioned in the ASCO abstracts. This modality was mentioned in 244 abstracts spanning all of the top 15 indications represented at the meeting. The next most abundant were small molecules, followed by vaccines and antibody-drug conjugates (ADCs).

The bottom figure excludes antibodies and small molecules, and looks at the indications associated with the remaining therapeutic modalities. Most of these modalities were employed proportionally across top indications at the meeting. However, nanoparticles were overrepresented in gastric cancer abstracts, and cell therapy was more commonly mentioned in leukemia abstracts.

A substantial proportion of abstracts mentioning RNA-based modalities did so in the context of research tools, as did all that mentioned gene editing. Modalities were identified using a text search of 2,921 abstracts assigned to any of ASCO’s presentation tracks focused on a particular cancer type. Abstracts in tracks related to epidemiology, survivorship and supportive care were excluded, as were abstracts assigned to tracks that concerned biomarkers and those assigned to tracks related to health services research and clinical informatics. Source: ASCO abstracts as of May 17
PEDIATRIC TARGETS AT ASCO

Of the 2,921 therapeutically focused abstracts presented at ASCO this year, only 65 specifically concerned pediatric cancers. These were identified by including all abstracts in the meeting’s Pediatric Oncology track, as well as searching the remaining abstracts for the words “pediatric” or “children.”

The figure below shows targets mentioned in at least two abstracts. The most commonly cited target, CD19, was mentioned in six abstracts testing chimeric antigen receptor (CAR) therapy in children with hematologic cancers. Other targets with multiple mentions include those associated with molecular alterations likely to lead to early or aggressive cancers, such as subtypes of the neurotrophic tyrosine kinase receptor (Trk) family, and Ewing sarcoma breakpoint region 1 (EWSR1; EWS).

Several targets common in adult cancers also appeared in pediatric abstracts, such as PD-1/PD-L1, phosphoinositide 3-kinase (PI3K), MEK, PARP and protein kinase B (AKT; AKT1; PKB; PKBA).

The analysis excluded abstracts assigned to tracks related to epidemiology, survivorship and supportive care, along with abstracts assigned to tracks that concerned biomarkers and those assigned to tracks related to health services research and clinical informatics. Source: ASCO abstracts as of May 17.
This year’s meeting of the American Association for Cancer Research (AACR) will keep the spotlight on immuno-oncology, where preclinical science is continuing to expand the use of different types of innate and adaptive immune cells in a range of different cancers. Other highlights include a rising profile of ovarian cancer and at least 21 new targets covering DNA damage repair or pathways of cancer metabolism.

BioCentury’s second annual analysis of the almost 6,000 AACR abstracts recapitulates several of the themes from last year, showing a steady growth in cancer immunotherapy against a backdrop of decades-old targets that still occupy, at least numerically, a dominant position.

The meeting takes place on April 1-5 in Washington, D.C., and represents one of the biggest collections of preclinical cancer research. Its abstracts, released one month ago, provide a snapshot of the state of cancer research and trends in the field.

Across indications and targets, the bulk of the activity is in areas already well represented in clinical development. Three of the top cancers studied — breast, lung and prostate — each have dozens of compounds in clinical development, according to BioCentury’s BCIQ database. (see “Top Indications at AACR 2017”).

However, the spread largely reflects the distribution of NIH funding, which is weighted to the same top cancer indications. In the last three years, breast cancer funding far outstripped other cancers, with an annual average of $685 million — about twice the funding of any other type. Most of the other top indications received about $300 million per year (see “NIH Funding for Cancer”).

One standout is ovarian cancer, which received an average of $123 million per year from NIH, the least of the top cancers. Ovarian cancer jumped from eighth position in the 2016 AACR abstracts to sixth position this year, and seven of the new targets — identified in four abstracts — were in cell lines and animal models of ovarian cancer (see “Novel Cancer Targets at AACR 2017”).

Unlike breast cancer, which according to BCIQ has 16 targeted therapies on the market, ovarian cancer has only three: the VEGF inhibitor Avastin bevacizumab; the GnRH/LHRH receptor agonist Decapeptyl triptorelin pamoate; and the recently approved PARP inhibitors Rubraca rucaparib and Lynparza olaparib. However, there are no marketed therapies against ovarian cancer-specific proteins.
TOP INDICATIONS AT AACR 2017

Breast cancer, featuring in about 1,200 abstracts for the American Association for Cancer Research (AACR) annual meeting next week, continues to be the biggest focus in preclinical cancer research, trailed distantly by lung, colorectal and prostate cancer. Abstracts mentioning brain or ovarian cancer increased significantly over 2016, while only leukemia and skin cancer saw fewer mentions than last year. Although year-on-year the proportion of most subtypes remained consistent within each cancer type, pancreatic ductal adenocarcinoma (PDAC) grew to account for 43% of all pancreatic cancer mentions. Lymphoma includes both Hodgkin’s disease and non-Hodgkin’s lymphoma (NHL), with T cell lymphoma, B cell lymphoma, follicular lymphoma and mantle cell lymphoma (MCL) categorized as NHL subtypes and cutaneous T cell lymphoma (CTCL) categorized as a subtype of T cell lymphoma. The chart depicts 13 cancer types that are mentioned in 100 abstracts or more, broken down by cancer subtype. “Unspecified subtype” includes the number of abstracts that did not fall into the selected categories. Source: AACR abstracts (as of March 2, 2017)
NIH FUNDING FOR CANCER

The number of preclinical cancer abstracts presented at the American Association for Cancer Research (AACR)’s annual meeting mostly mirrors the level of NIH funding for each cancer type. Between 2014 and 2016, breast cancer received the largest allocation from the NIH budget of all cancer types. Lung cancer, which has a lower prevalence but much greater mortality, received less than half as much, but was the second highest funded type. NIH funding for leukemia includes Hodgkin’s disease, but the prevalence and mortality figures do not incorporate the Hodgkin’s disease figures. In addition to the figures shown, NIH also allocated almost $5.5 billion to unspecified cancers annually. Source: NIH

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<thead>
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<tbody>
<tr>
<td>Breast cancer</td>
<td>$685 million</td>
<td>50,427</td>
<td>1.4% (0.08%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>$322 million</td>
<td>164,882</td>
<td>0.3% (0.03%)</td>
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<tr>
<td>Brain cancer</td>
<td>$299 million</td>
<td>16,358</td>
<td>0.3% (0.02%)</td>
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<tr>
<td>Lymphoma</td>
<td>$282 million</td>
<td>26,450</td>
<td>0.3% (0.04%)</td>
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<td>Prostate cancer</td>
<td>$280 million</td>
<td>39,624</td>
<td>2.0% (0.14%)</td>
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<td>Pancreatic cancer</td>
<td>$159 million</td>
<td>42,215</td>
<td>Unavailable</td>
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<tr>
<td>Leukemia (childhood)</td>
<td>$140 million</td>
<td>Unavailable</td>
<td>Unavailable</td>
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<tr>
<td>Ovarian cancer</td>
<td>$124 million</td>
<td>15,236</td>
<td>0.4% (0.07%)</td>
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<tr>
<td>Liver cancer</td>
<td>$83 million</td>
<td>26,794</td>
<td>0.1% (0.02%)</td>
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</table>

Brain cancer also saw more interest, rising from ninth position in 2016 to fifth in 2017. That too is an area with no targeted therapies on the market for disease-specific proteins.

Lymphoma and leukemia are among the most well-funded cancer indications, receiving an average of $282 million and $140 million in NIH funding, respectively, but were ranked lower in the AACR abstracts. Lymphoma ranked tenth, while leukemia ranked eighth.

And within each area, some researchers are increasing their focus on underserved indication subsets. For example, within breast cancer, about one third of the abstracts are in triple-negative breast cancer (TNBC), and in brain cancer, about 60% of the activity is in glioblastoma, two areas of high unmet need.

BEYOND CAR T CELLS

One of the most striking changes from last year is the increase in abstracts covering different types of immune cells, with natural killer (NK) cells showing a jump of 88% (see “Top Cell Types at AACR 2017”).

Over the past year, BioCentury has followed the surge in company interest in the NK cell space and documented at least seven biotechs developing NK-cell based therapies. Other companies are working on therapeutics that activate the cells or direct them to tumors.

That interest is reflected at AACR too, where 50% of this year’s NK cell abstracts are presented by companies, which is more than for any other cell subtype. NK cells are part of the innate immune response and detect cancer by recognizing abnormal cells, but lack the antigen specificity of T cells. Their lure for drug developers is that they can be more easily developed as off-the-shelf products than T cells, and don’t run the same risk of cytokine storm.

NKT cells, which can elicit both innate and antigen-specific immune responses against tumors, were mentioned in nine abstracts compared with four last year, two of which came from companies: the WuXi AppTec unit of New WuXi Life Science Ltd. and Berg LLC. While the WuXi abstract described a new humanized mouse model to study the effects of cancer immunotherapies on human immune cells, including NKT cells, the Berg abstract showed that the anticancer mechanism of one of its clinical candidates, BMP31510, involves triggering NKT cell proliferation. Despite the small number, this is a class to watch as these cells could offer the advantages of both innate and adaptive immune cells in treating cancer.

Among adaptive immune cells, Tregs and myeloid-derived suppressor cells (MDSCs) show notable increases over last year, while γδ T cells are still relatively under-explored.

Tregs also represent an emerging drug target because certain Tregs infiltrate tumors to suppress antitumor immunity. MDSCs contribute to the immunosuppressive tumor microenvironment and can be depleted to allow penetration of other immune cells into solid tumors, whereas γδ T cells...
TOP CELL TYPES AT AACR 2017

Cell types mentioned in abstracts for upcoming American Association for Cancer Research (AACR) meeting. Abstracts were searched using a machine learning algorithm for mentions of the selected cell types shown, and include mentions of the cells either as therapeutic agents or in the context of therapies that target, activate or recruit the cells. CD4+ cells, CD8+ cells, cytotoxic T cells, B cells and other cells were excluded from the search.

**Top panel:** Cell therapy mentions increase across the board, with natural killer (NK) cells showing the greatest jump at 88%, followed by Tregs at 49% compared with 2016. Chimeric antigen receptor (CAR) T cells showed little change from last year. The newer cell types in the field, γδ cells and NKT cells, were found in few abstracts this year, but showed comparable or greater numbers than in 2016.

**Bottom panel:** While the cell types analyzed spanned all of the major cancer types, skin cancer was by far the most common, featuring in about 60% more abstracts than breast, lung and colorectal cancer, which were the most heavily researched areas overall. Source: AACR abstracts (as of March 2, 2017)
**TOP TARGETS AT AACR 2017**

**Top panel:** While traditional long-studied cancer targets continue to dominate, interest in cancer immunotherapy targets has grown from 2016 to 2017, as shown by the increased number of mentions in abstracts for the upcoming American Association for Cancer Research (AACR) meeting. Mentions of PD-1 grew by nearly 50% and those for PD-L1 nearly doubled, while the most frequently mentioned targets — p53, AKT and EGFR — changed little year-on-year. MEK moved in the opposite direction, with 25% fewer mentions this year. Of the top 20 targets mentioned in abstracts, CTLA4, c-MET and VEGF are new to the list.

**Bottom panel:** The heatmap shows the most common indications for the 20 most abundant targets. Breast, colorectal and lung cancer feature the highest concentrations of those hottest targets (pink/red) and AKT and p53 are cited most broadly across indications.

**AKT** (AKT1; PKB; PKBA) - Protein kinase B; c-MET (MET; HGFR; c-Met proto-oncogene) - c-Met receptor tyrosine kinase; CTLA4 (CD152) - Cytotoxic T-lymphocyte associated protein 4; EGFR (ErbB1; HER1) - Epidermal growth factor receptor; PD-1 (PDCD1; CD279) - Programmed cell death 1; PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1; TCR - T cell receptor; VEGF - Vascular endothelial growth factor.

Source: AACR abstracts (as of March 2, 2017)
represent a new cell therapy class and are thought to be better at penetrating solid tumors than their αβ T cell counterparts. In both cases, the majority of abstracts were presented by academic groups rather than companies.

Only two companies, Compugen Ltd. and F-star Biotechnology Ltd., are presenting abstracts that mention γδ T cells. Compugen’s abstract covers PVRIG, a new checkpoint target expressed on NK cells and T cell subsets including γδ T cells, and shows that antibodies blocking the interaction between PVRIG and its ligand PVRL2 increase antitumor T cell activity and decrease growth of colon cancer and melanoma in mouse models. Compugen announced its preclinical program targeting PVRIG earlier this month.

According to an abstract from chimeric antigen receptor (CAR) T cell pioneer Carl June, a different myeloid cell subset, macrophages, represents an even newer cell therapy subtype that could be deployed to treat solid tumors. His group engineered macrophages, which are naturally recruited to solid tumors, to express chimeric antigen receptors (CARs) for various solid tumor antigens. The CAR-macrophages, dubbed CARMAs, phagocytosed antigen-expressing tumor cells in vitro and in mice, decreasing tumor volume and increasing survival in the animals.

June’s lab spun out Tmunity Therapeutics Inc. in 2015 to develop CAR T cells and engineered Tregs to treat cancer. June is professor in immunology at the University of Pennsylvania’s Perelman School of Medicine.

The surge in other cell types reflects the research community’s response to the need to go beyond CAR T cells and engineered TCR-based cell therapies, which have produced dramatic results in clinical studies on hematological malignancies, but have yet to make an impact in solid tumors. The therapies are also hampered by high toxicity and manufacturing challenges that make it hard to generate off-the-shelf, allogeneic treatments.

The number of abstracts analyzing CAR T cells remained relatively flat between 2016 and 2017, but abstracts covering the

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### NOVEL CANCER TARGETS AT AACR 2017

Select new targets in cancer presented at the 2017 American Association for Cancer Research (AACR) annual meeting. Source: AACR Abstracts

<table>
<thead>
<tr>
<th>TARGET</th>
<th>INDICATION(S)</th>
<th>DESCRIPTION</th>
<th>INSTITUTIONS/COMPANIES</th>
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<tr>
<td>6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKFB2)</td>
<td>Ovarian cancer; breast cancer</td>
<td>Cell culture and animal studies suggest inhibiting PFKFB2 could help treat ovarian and breast cancers.</td>
<td>University of Texas MD Anderson Cancer Center</td>
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<td>Antioxidant 1 copper chaperone (ATOX1); copper chaperone for superoxide dismutase (CCS)</td>
<td>Breast cancer</td>
<td>Cell line studies suggest inhibiting ATOX1 and CCS could help treat triple-negative breast cancer (TNBC).</td>
<td>University of Chicago; Rosalind Franklin University of Medicine and Science</td>
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<td>ATPase H+ transporting accessory protein 2 (ATP6AP2)</td>
<td>Endometrial cancer</td>
<td>Cell line studies suggest inhibiting ATP6AP2 could help treat endometrial cancer.</td>
<td>University of Newcastle</td>
<td>4136</td>
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<td>Defective in cullin neddylation 1 domain containing 1 (DCUND1)</td>
<td>Lung cancer</td>
<td>Chemical library screening and cell culture studies identified DCUND1 inhibitors that could help treat squamous cell carcinoma of the lung.</td>
<td>Herbert Wertheim College of Medicine; St. Jude Children’s Research Hospital; University of Kentucky</td>
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<td>Engulfment and cell motility 1 (ELMO1)</td>
<td>Colorectal cancer</td>
<td>Cell line studies suggest inhibiting ELMO1 could help treat metastatic colorectal cancer (mCRC).</td>
<td>Sun Yat-sen University; Guangzhou Medical University</td>
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<td>Glypican 2 (GPC2)</td>
<td>Neuroendocrine tumors</td>
<td>Patient sample, cell culture and mouse studies suggest inhibiting GPC2 could help treat neuroblastoma.</td>
<td>NIH; Jilin University</td>
<td>3648</td>
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<td>Karyopherin subunit α 2 (KPNA2); low-density lipoprotein receptor-related protein 8 (LRP8)</td>
<td>Breast cancer</td>
<td>Patient sample studies suggest KPNA2 and LRP8 could help predict patient outcomes.</td>
<td>National Cancer Institute of Mexico (INCan); Nanopharmacia Diagnóstica, Universidad Autónoma de la Ciudad de México (UACM); Mexican Social Security Institute (IMSS)</td>
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<td>Karyopherin subunit β 1 (KPNB1)</td>
<td>Ovarian cancer</td>
<td>Patient sample, cell culture and mouse studies suggest inhibiting KPNB1 could help treat epithelial ovarian cancer.</td>
<td>Osaka University; Nigata University; Houston Methodist Research Institute</td>
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<td>Lysine-specific demethylase 5B (KDM5B)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Patient sample and cell culture studies suggest inhibiting KDM5B could help treat NSCLC.</td>
<td>Emory University</td>
<td>1962</td>
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<td>microRNA-450a (miR-450a)</td>
<td>Head and neck cancer</td>
<td>Cell line studies suggest inhibiting miR-450a could help treat head and neck squamous cell cancer (SCCHN).</td>
<td>National Health Research Institutes</td>
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<td>Nuclear factor I A (NFIA); NFIB; NFIC; NFIX</td>
<td>Brain cancer</td>
<td>Patient sample, cell culture and mouse studies suggest promoting expression of the nuclear factor I family of transcription factors (NFIA, NFIB, NFIC and NFIX) could help treat glioma.</td>
<td>University of Queensland</td>
<td>3536</td>
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<td>Peptidase mitochondrial processing β subunit (PMP12)</td>
<td>Liver cancer</td>
<td>Cell culture and in vivo studies suggest inhibiting PMP12 could help treat hepatocellular carcinoma (HCC).</td>
<td>Kyoto University; National Cancer Institute (NCI); Kanazawa University Hospital</td>
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<tr>
<td>Poliovirus receptor related immunoglobulin domain containing (PVRIG; CD112R); poliovirus receptor-related 2 (PVRL2)</td>
<td>Colorectal cancer; melanoma</td>
<td>Mouse studies suggest antibodies blocking the interaction between PVRIG, an immune checkpoint expressed on NK and T cells, and its ligand PVRL2 could help treat colorectal cancer and melanoma.</td>
<td>Compugen Ltd. (NASDAQ:CGEN; Tel Aviv:CGEN)</td>
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<td>Protein activator of interferon induced protein kinase EIF2AK2 (PRKRA)</td>
<td>Ovarian cancer</td>
<td>Cell line and mouse studies suggest inhibiting PRKRA could help treat mucinous ovarian cancer.</td>
<td>University of Texas MD Anderson Cancer Center: University of Southern California</td>
<td>473</td>
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<tr>
<td>Protein arginine methyltransferase 1 (PRMT1)</td>
<td>Pancreatic cancer</td>
<td>Patient sample, cell culture and animal studies suggest inhibiting PRMT1 could help treat pancreatic ductal adenocarcinoma (PDAC).</td>
<td>University of Texas MD Anderson Cancer Center</td>
<td>3016</td>
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<td>Ribonuclease H2 subunit C (RNASEH2C)</td>
<td>Breast cancer</td>
<td>Patient sample, cell culture and mouse studies suggest inhibiting RNASEH2C could help treat metastatic breast cancer.</td>
<td>NIH; Jilin University</td>
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<td>Seryl-tRNA synthetase (SARS)</td>
<td>Breast cancer</td>
<td>Cell culture and mouse studies suggest promoting SARS expression could help breast cancer.</td>
<td>Nankai University; The Scripps Research Institute</td>
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<tr>
<td>Taxt binding protein 3 (TAXIBP3)</td>
<td>Lung cancer; brain cancer</td>
<td>Cell line and mouse studies suggest antagonistic antibodies targeting TAXIBP3 could help treat lung cancer and glioblastoma.</td>
<td>Washington University in St. Louis</td>
<td>4599</td>
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<td>Tyrosinase related protein 1 (TYRPI) mRNA</td>
<td>Melanoma</td>
<td>Cell culture and in vivo studies suggest inhibiting TYRPI mRNA could help treat melanoma.</td>
<td>Free University of Brussels (ULB); Flanders Institute for Biotechnology (VIB); Institut National de la Santé et de la Recherche Médicale (INSERM)</td>
<td>3048</td>
</tr>
<tr>
<td>Ubiquitin protein ligase E3 component n-recognin 1 (UBR1); UBR2; UBR5</td>
<td>Liver cancer</td>
<td>Cell culture and mouse studies suggest inhibiting UBR1, UBR2 and UBR5 could help treat HCC.</td>
<td>Skolkovo Institute of Science and Technology; Massachusetts Institute of Technology (MIT)</td>
<td>3131</td>
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<td>Ubiquitin specific peptidase 19 (USP19)</td>
<td>Cancer</td>
<td>Cell culture studies suggest inhibiting USP19 could help treat cancer.</td>
<td>Almac Discovery Ltd. subsidiary of Almac Group Ltd.</td>
<td>1181</td>
</tr>
<tr>
<td>XPA DNA damage recognition and repair factor (XPA); replication protein A1 (RPA1); RPA2; RPA3</td>
<td>Lung, pancreatic, breast and ovarian cancers</td>
<td>Studies in cancer cell lines identified XPA and replication protein inhibitors that could help treat several cancers.</td>
<td>Indiana University; NERx BioSciences Inc.</td>
<td>1416</td>
</tr>
</tbody>
</table>
New therapeutic modalities mentioned in abstracts for upcoming American Association for Cancer Research (AACR) meeting. The charts include modalities mentioned in more than 10 abstracts, but exclude small molecules, unmodified recombinant proteins and unconjugated mAbs.

**Top panel:** Abstract mentions of all but one of the modalities increased year-on-year, including a 38% increase in microRNA (miRNA) — making it the most mentioned — and a near-doubling of antibody-drug conjugates (ADCs). The only exception to the trend was a slight decrease in the mention of siRNA, last year’s most popular modality.

**Bottom panel:** Nanoparticles and most nucleic-acid based therapies mirrored the general trend of therapeutic areas, appearing in abstracts about breast cancer more often than other cancer types, with prostate, colorectal and lung cancers not far behind. Vaccines are mentioned most in skin cancer and breast cancer abstracts, while ADCs appear most frequently in lung cancer and lymphoma abstracts. Source: AACR abstracts (as of March 2, 2017)
cells in solid tumors has increased by 63%. TCR-based T cell
abstracts rose 27% this year.
The most advanced CAR T cell programs are the CD19-
targeting therapies from Novartis AG and Kite Pharma Inc.
This week, Novartis announced that FDA accepted its BLA and
granted priority review for CTL019 in pediatric B cell acute
lymphoblastic leukemia (ALL). Kite submitted a rolling BLA
for axicabtagene ciloleucel (KTE-C19) to treat non-Hodgkin’s
lymphoma (NHL) beginning in December. According to BCIQ,
no CAR T cell therapies have reached Phase II for solid tumors.
The data reflect the number of abstracts that mention each
selected cell type, including abstracts that analyzed the biology
of cells used in cancer therapy as well as cells used as therapeutic
agents.
STEADY ON TARGETS
There is little change at the top of the targets list from last year,
and most, such as top-ranked p53, AKT and EGFR have been
studied for decades. Still, the proteins are expressed in a large,
diverse set of cancers, and their biology remains relevant to new
product development (see “Top Targets at AACR 2017”).
Moreover, for p53, there is renewed interest in companies
developing compounds that directly target the molecule,
with at least five disclosing programs in preclinical or clinical
development.
The immuno-oncology wave is underscored by the checkpoint
targets, which rose in the ranks with PD-1 in the fourth spot this
year compared with the seventh last year, and its ligand PD-L1
in eighth place, whereas last year it did not make the list.
The original checkpoint target CTLA4, which likewise didn’t
make the cut last year, is ranked fifteenth this year. Renewed
interest in the target reflects the emerging trend of combining
cancer treatments with existing immuno-oncology drugs like
CTLA4 inhibitor Yervoy ipilimumab from Bristol-Myers Squibb
Co., which is marketed to treat melanoma. Many preclinical
researchers are studying the biology around those targets, and
investigating other targets that could be combined to produce
more potent and/or safer drugs.
Also, newer and less-known checkpoint targets such as TIGIT
and VISTA appear at this year’s meeting, with 15 and eight
abstracts respectively.
At least two companies have anti-TIGIT antibodies in the clinic.
The most advanced, BMS-986207, from Bristol-Myers Squibb, is
in Phase I/II testing to treat solid tumors.
There is less clinical activity for VISTA as a single target, but
Aurigene Discovery Technologies Ltd. and Curis Inc. have CA-
170, a small molecule antagonist of VISTA, PD-1 and PD-L1, in
Phase I testing for lymphoma and solid tumors.
At the conference, Hummingbird Bioscience Pte. Ltd. will
present an abstract covering a new anti-VISTA mAb, HMBD-
002, showing the antibody decreases growth of a colon cancer
xenograft in mice.
Outside of checkpoint targets, this year’s top list continues to
feature targeted, subtype-specific therapies. The list includes
established targets with broad roles across cancer subtypes such as
PI3K and PTEN as well as a handful of subtype-specific
targets like BCL-2 for lymphoma, HER2 for breast cancer, BRAF
for melanoma and androgen receptor for prostate cancer.
Despite the high drug development potential of targeted therapies,
a pathway analysis shows much research still focuses on the more
general mechanisms of DNA regulation or cell growth.
At least two new targets identified in the AACR abstracts this
year fall into those categories. XPA and RPA1 are new targets
involved in DNA repair, whereas nuclear importation protein
KPNB1 and ubiquitination proteins DCUND1 and UBR5 are
cytosolic growth mediators.
Other pathways to watch from this year’s abstracts include
regulators of apoptosis and autophagy, which account for five
relatively new targets, and the growing list of immune cell
modulators and antigens for immunotherapy that reflect the
surge in cancer immunology research (see “Seeing the Wood
for the Trees”: BioCentury Innovations (March 30, 2017)).
Top targets were identified by analysis of the top 125 targets
identified by a machine learning program and verified for
translational relevance.
MODALITIES IN MODE
New therapeutic modalities outside of small molecules,
antibodies and standard protein therapeutics are also seeing
increased relevance to cancer research, with abstract numbers
in each category higher this year than last.
Nucleic acids top the list of 13 modalities analyzed by
BioCentury, but nanoparticles and antibody-drug conjugates
(ADCs) are also heavily represented.
Nanoparticles, which are in 26% more abstracts this year
than last, are increasingly being used not only as therapeutic
modalities on their own, but also as drug delivery vehicles for
new therapeutic classes like nucleic acids, gene editing and gene
therapy.
ADCs sees an even bigger increase, almost doubling last year’s count.

Although most gene therapy products fall outside the oncology space, the number of abstracts covering the modality has also almost doubled this year, suggesting improvements in gene therapy technologies are driving greater interest in the modality for cancer.

And while interest in most of the non-standard modalities increased, DNA vaccines and macrocycles still have yet to take off, not yet making the cut (see “Top New Modalities at AACR 2017”).

Top modality counts are based on the number of abstracts that mention each modality selected, which includes the use of each modality as a research tool or for drug development. A large number of abstracts involving RNAi and siRNA included their use as research tools.

COMPANIES AND INSTITUTIONS MENTIONED

Aurigene Discovery Technologies Ltd., Bangalore, India
Berg LLC, Framingham, Mass.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Compugen Ltd. (NASDAQ:CGEN; Tel Aviv:CGEN), Tel Aviv, Israel
Curis Inc. (NASDAQ:CRIS), Lexington, Mass.
F-star Biotechnology Ltd., Cambridge, U.K.
Hummingbird Bioscience Pte. Ltd., Singapore
Kite Pharma Inc. (NASDAQ:KITE), Santa Monica, Calif.
New WuXi Life Science Ltd., Shanghai, China
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

TARGETS

AKT (AKT1; PKB; PKBA) - Protein kinase B
BCL-2 (BCL2) - B cell lymphoma 2
CTLA4 (CD152) - Cytotoxic T-lymphocyte associated protein 4
DCUND1 - Defective in cullin neddylation 1 domain containing 1
EGFR (ErbB1; HER1) - Epidermal growth factor receptor
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
KPNB1 - Karyopherin subunit β1
PARP - Poly(ADP-ribose) polymerase
PD-1 (PDCD1; CD279) - Programmed cell death 1
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1
PI3K - Phosphoinositide 3-kinase
PTEN (MMAC1; TEP1) - Phosphatase and tensin homolog deleted on chromosome ten
PVRL2 - Poliovirus receptor-related 2
RPA1 - Replication protein A1
TCR - T cell receptor
TIGIT - T cell immunoreceptor with Ig and ITIM domains
UBRS - Ubiquitin protein ligase E3 component n-recogin 5
VEGF - Vascular endothelial growth factor
VISTA - V-region immunoglobulin-containing suppressor of T cell activation
XPA - DNA damage recognition and repair factor

REFERENCES

TARGETS & MECHANISMS

SEEING THE WOOD FOR THE TREES

By Karen Tkach, Senior Writer, and Winnie Pong, Staff Writer

A survey of molecular targets mentioned in abstracts from next week's meeting of the American Association for Cancer Research (AACR) suggests the field has not abandoned its roots in cellular proliferation, growth hormone and DNA regulation, even as research on immune modulators continues to grow. And while newer areas like cancer metabolism and autophagy have been generating buzz, they have yet to gather a substantial presence at the field's biggest preclinical meeting.

BioCentury’s analysis identified about 100 translational targets that were mentioned in 10 or more AACR 2017 abstracts corresponding to seven mechanistic categories, each represented by a tree (see “The Hundred Target Wood”).

The analysis is based on the top 125 targets identified by a machine learning program run against the full list of about 5,000 targets in BioCentury’s BCIQ database. Results were manually verified for relevance and sorted according to their likely function in cancer.

For each category, the targets are ordered according to their abstract count, with those at the bottom of the tree mentioned in the largest number of abstracts, and those at the top in...

THE HUNDRED TARGET WOOD
The fewest. The target categories are further subdivided into branches according to their functions.

Although conference abstracts feature several emerging cell therapies and 21 new cancer targets, long-established pathways tower over the presentation landscape from a numbers perspective (see “Cells on the Rise.” BioCentury Innovations (March 30, 2017)).

The largest category contains cytosolic signaling mediators (A) that drive proliferation, which include five targets in the PI3K pathway and eight in the MAPK pathway. Several abstracts feature cell cycle regulators (B) or targets that control growth and differentiation (C). Proliferation-triggering endocrine growth mediators, including endocrine receptors (D) and secreted growth factors or their potentiators (E), are also highly represented, as are targets controlling DNA integrity and structure (F), and epigenetic regulators (G).

Many abstracts feature immune mediators, a comparatively new category of cancer targets dominated by immune cell modulators (H) such as the checkpoint molecule PD-1. While a few immunotherapy antigens (I) were represented — such as CD19 for chimeric antigen receptor (CAR) T cell therapies and PSA for cancer vaccines — the rise of personalized neoantigen-based immunotherapies could mean that no single molecule from this mechanistic category will become a dominant target.

The abstracts also feature targets that govern the interaction between cancer cells and their extracellular environment. A few vascularization regulators (J) such as VEGF are represented, along with cell mobility and adhesion regulators (K).

Finally, the abstracts highlight about a dozen targets that regulate intracellular homeostasis processes, including apoptosis and autophagy (L), metabolism (M) and toxin removal (N).

COMPANIES AND INSTITUTIONS MENTIONED
American Association for Cancer Research (AACR), Philadelphia, Pa.

TARGETS
MAPK (ERK) - MAP kinase
PD-1 (PDCD1; CD279) - Programmed cell death 1
PI3K - Phosphoinositide 3-kinase
PSA (KLK3) - Prostate-specific antigen
VEGF - Vascular endothelial growth factor
ASH BY THE NUMBERS

AML TAKES ASH

By Emily Cukier-Meisner, Senior Writer and Meredith Durkin, Research Consultant

An analysis of the nearly 5,000 abstracts to be presented at the American Society of Hematology meeting shows research on acute myelogenous leukemia will dominate.

BioCentury analyzed more than 2,200 abstracts concerning clinical research, including studies of therapeutics and diagnostic or prognostic biomarkers.

More than three-quarters of the clinical presentations during the Dec. 3-6 meeting in San Diego will concern hematologic cancers.

Unlike the preclinical abstracts, which were more heavily weighted toward leukemias, clinical leukemia and lymphoma abstracts each made up roughly 40% of the clinical abstract mentions, with the remaining 20% referencing multiple myeloma (MM) or myelodysplastic syndrome (MDS).

AML was most common cancer subtype, accounting for 307 (18%) of the 1,747 abstracts pertaining to cancers (see “ASH: Top Clinical Indications”).

AML also took a greater share of the preclinical cancer abstract mentions — 30% — which suggests the clinical abstracts could be at the leading edge of an incoming tide (see “Hemorrhaging Targets,” BioCentury Innovations, Nov. 17, 2016).

That would be good news, as the indication has no approved targeted therapies. The standard of care is still a four-decade-old chemotherapy regimen that many newly diagnosed patients — who tend to be elderly — cannot tolerate.

A new agent could be on the horizon. On Nov. 14, Novartis AG said FDA granted Priority Review to midostaurin to treat newly diagnosed AML with mutations in FMS-like tyrosine kinase 3 (FLT3; CD135), and to treat advanced systemic mastocytosis.

Midostaurin inhibits both FLT3 and stem cell factor (SCF) receptor tyrosine kinase (c-Kit; KIT; CD117).

More targeted therapies coming through the clinic will be on display at ASH. A further analysis of the top targets mentioned in clinical cancer abstracts again shows AML in the lead; at least seven of the top 20 cancer targets were mentioned in 10 or more abstracts pertaining to the indication (see “ASH: Top Clinical Cancer Targets”).

The approaches include both signal pathway inhibitors and immunotherapies. The targets are FLT3; Janus kinase-2 (JAK-2); c-KIT; CD3; PD-1; and isocitrate dehydrogenase 1 (IDH1) and IDH2.

“That usually says something when a lot of quality people are rushing into an area.”

Brad Loncar, Loncar Fund
Within cancer, acute myelogenous leukemia (AML) dominated the clinical data abstracts posted ahead of ASH, followed closely by B cell non-Hodgkin’s lymphoma (NHL).

In non-cancer blood disorders, although sickle cell and thrombocytopenia were most prevalent, very few of these abstracts concerned development of new drugs. Abstracts concerning anemia, hemophilia and investor favorite thalassemia were more apt to describe research on therapeutic candidates.

Out of nearly 5,000 abstracts posted in advance of the conference, BioCentury identified more than 2,000 pertaining to clinical research. BioCentury assigned abstracts to one or more indications based on mentions of the indications in the abstract text. Source: ASH abstracts as of Nov. 3
Acute myelogenous leukemia (AML) abstracts had the most mentions of distinct molecular targets that do not correspond to approved therapies. At least seven of the top cancer targets were mentioned in 10 or more clinical abstracts pertaining to AML, for which no targeted therapies are approved. The most common were FMS-like tyrosine kinase 3 (FLT3; CD135) and Janus kinase-2 (JAK-2), with 46 and 28 abstracts, respectively.

Given industry’s enthusiasm for chimeric antigen receptor (CAR) T cell therapies, it is not surprising that CD19 ranked among the top mentions. CD19 is the most common target of CAR T candidates. CD3, a costimulatory component of many of these candidates, also ranked high. However, CD3 was likely boosted by mentions in other contexts because of its role in activating cytotoxic T cells and as a T cell-specific marker. Every mention of a target in an abstract was included in the analysis, whether in a therapeutic, diagnostic/prognostic or descriptive context.

The analysis was constructed using text searches of more than 1,700 abstracts. Search terms included the top 20 cancer targets in BioCentury’s BCIQ database ranked by the number of therapeutic development programs against each target, plus additional common targets of late-stage cancer therapies. The analysis includes some double-counting of abstracts that contained multiple targets or indications. Source: ASH abstracts as of Nov. 3.
**ASH: NEW CARS**

The ASH abstracts include clinical data presentations about chimeric antigen receptor (CAR) cell therapies that incorporate up-and-coming targets beyond CD19. Among these new CAR targets are BCMA (TNF receptor superfamily member 17; TNFRSF17), CD22 and NKG2D (killer cell lectin-like receptor subfamily K member 1; KLRK1; CD314) ligands.

**bluebird bio Inc.** (NASDAQ:BLUE) has chosen a different conference to present data from a Phase I study of bb2121, a CAR T cell therapy targeting BCMA, to treat relapsed/refractory multiple myeloma (MM). The company announced on Nov. 14 that it would present interim data at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium on Dec. 1. Sources: ASH abstracts as of Nov. 3

<table>
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<tr>
<th>TARGET</th>
<th>INDICATION(S)</th>
<th>INSTITUTION</th>
<th>ABSTRACT #</th>
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<tr>
<td>BCMA (tumor necrosis factor receptor superfamily member 17; TNFRSF17)</td>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>University of Pennsylvania; Novartis AG (NYSE:NVS; SIX:NOVN)</td>
<td>1147</td>
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<td>BCMA</td>
<td>MM</td>
<td>National Cancer Institute (NCI)</td>
<td>SCI-37</td>
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<tr>
<td>CD22</td>
<td>ALL</td>
<td>National Cancer Institute (NCI); Juno Therapeutics Inc. (NASDAQ:JUNO)</td>
<td>650; 1625; 3358</td>
</tr>
<tr>
<td>NKG2D (killer cell lectin-like receptor subfamily K member 1; KLRK1; CD314) ligands</td>
<td>Acute myelogenous leukemia (AML); MM; myelodysplastic syndrome (MDS)</td>
<td>Dana-Farber Cancer Institute. Celyad S.A. (Euronext:CYAD; NASDAQ:CYAD)</td>
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</table>

*BioCentury Innovations* reported that the top preclinical targets at ASH this year are FLT3, c-KIT and B cell lymphoma 2 (BCL-2; BCL2).

B cell non-Hodgkin’s lymphoma (NHL) and MDS are also well represented in the clinical presentations at ASH.

Old standbys rubbered shoulders with young bucks among the B cell NHL targets most frequently mentioned in clinical abstracts. The most common target was CD20, a B lymphocyte antigen and the target of now-biosimilar rituximab.

It was followed closely by Bruton’s tyrosine kinase (Btk), the target of Imbruvica ibrutinib from AbbVie Inc., which was first approved in 2014 to treat chronic lymphocytic leukemia (CLL) and is still the sole approved member of its class.

Still, six of the most frequently mentioned targets in B cell NHL abstracts do not correspond to any approved therapies. MDS abstracts also had six frequently cited targets without approved therapies.

**NEW CAR LOT**

In the competitive chimeric antigen receptor (CAR) space, CD19 is still far ahead of other targets, but a new wave is on the way.

None of the new targets cracked the top 20. But the ASH abstracts include at least six presentations describing the clinical use of CAR cell therapies with novel targets.

Two describe the use of BCMA (tumor necrosis factor (TNF) receptor superfamily member 17; TNFRSF17; CD269), one of two targets that Brad Loncar of the Loncar Fund thinks could be a successor to CD19. Novartis and its partner the University of Pennsylvania, as well as the NCI, will each present abstracts (see “ASH: New CARs”).

“There’s a group of non-CAR companies using other things to target BCMA,” Loncar said. “That usually says something when a lot of quality people are rushing into an area.”

**bluebird bio Inc.** will be jumping the line by presenting clinical data on its BCMA candidate Dec. 1 at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium.

The presentation will feature interim Phase I data on bb2121, a CAR T cell therapy targeting BCMA to treat multiple myeloma (MM). bb2121 is partnered with Celgene Corp. The other target Loncar mentioned is CD7. At least four of this year’s clinical ASH abstracts describe CD47-targeted therapies, but none are CARs.

Other targets of clinical-stage CAR programs described in the abstracts include CD22 and NKG2D (killer cell lectin-like receptor subfamily K member 1; KLRK1; CD314) ligands. The abstracts also contain clinical data from next-generation CAR constructs engineered onto NK cells or that engage multiple targets simultaneously, as well as combination or
sequential regimens to increase efficacy or reduce toxicities such as cytokine release syndrome.

**BETA AND SWITCH**

Beyond cancer, clinical abstracts also describe research on therapeutic candidates for anemia, thalassemia and hemophilia. While investors have been keen on beta thalassemia and hemophilia companies, this year’s abstracts don’t reveal any obvious new targets for the indications.

Several describe the use of newer therapeutic modalities — such as gene therapy and gene editing — to increase fetal hemoglobin or beta globin production.

One field that may be ripe for emerging targets is anemia, which was the third most common non-cancer indication in BioCentury’s non-cancer analysis, and the most common among the preclinical non-cancer abstracts. In addition to the usual suspects of hepcidin and erythropoietin, the abstracts contained small clusters of newer targets such as JAK-2, GATA binding protein 1 (GATA1) and calreticulin (CALR).

**COMPANIES AND INSTITUTIONS MENTIONED**

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
American Society of Hematology (ASH), Washington, D.C.
bluebird bio Inc. (NASDAQ:BLUE), Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
National Institutes of Health (NIH), Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

**REFERENCES**

ASH BY THE NUMBERS

HEMORRHAGING TARGETS

By Mark Zipkin and Karen Tkach, Staff Writers, and Lauren Martz, Senior Writer

An analysis of the almost 5,000 abstracts set to be presented at the 2016 American Society of Hematology (ASH) meeting next month indicates this year’s hot topics in preclinical research include a spattering of new targets to watch, a growing role for nucleic acid based therapies, and a continued expansion of cell type subsets beyond the commonly used B cells and Tregs.

This year’s meeting, which takes place December 3-6 in San Diego, has a heavy emphasis on hematological malignancies, which account for more than 75% of the preclinical abstracts. Indeed, BioCentury identified eight new therapeutic targets which all fall in oncology, two of which are new chimeric antigen receptor (CAR) T cell targets in the continually growing cancer immunology space (see “Novel targets at ASH”).

Pathway analysis on cancer targets shows the bulk of attention still goes to the classical strategy of blocking uncontrolled replication. Many are old, well-trodden targets such as Src, c-Kit and tubulin. However, the list includes some emerging mediators such as PIM1 and SLAMF7, which each have only two products in the clinic or on the market (see “Pathways Forward”).

A notable number of targets involve harnessing immune cells to attack tumors, such as cytokines, cytokine receptors, checkpoint inhibitors and proteins that trigger myeloid or T cell activity.

Other pathways include targets that mark blood cells for destruction, and a small number of abstracts focus on molecules that facilitate cancer cell survival such as heat shock proteins, hypoxia inducible factors and angiogenesis agents.

For the top 25 cancer targets, the overarching take-home message is the wide spread of indications for each target. Indeed, the majority of targets are being pursued for at least six different indications, in most cases crossing into both leukemias and lymphomas.

Leukemias lead the cancer indications over lymphomas and multiple myeloma (MM), with acute myelogenous leukemia (AML) by far the most frequently researched in preclinical studies. But while BioCentury’s BCIQ: BioCentury Online Intelligence database indicates that commercial preclinical programs in MM outnumber any other hematological malignancy, the indication is relatively underrepresented in the preclinical ASH data.

Within lymphomas, B cell malignancies emerge as a top area, and many of the top molecular targets are B cell-specific, possibly reflecting the growing interest in CAR T cell therapies, which are particularly well suited to treating the cancer subset. Almost one third of the top cancer targets this year are immunology-related, supporting the trend toward increased immuno-oncology research, which aims to harness the immune system to attack tumors. However several immune targets lie outside immuno-oncology, such as Btk, which is involved in B cell receptor signaling and is up-regulated on malignant cells.

TOP CELL TYPES

In this year’s ASH abstracts, the most common type of immune cell mentioned is the B cell, which is consistent with the fact that B cell malignancies make up the bulk of hematological cancers. Interestingly, NK cells, which have only recently been appreciated for their role in antitumor immunity, were mentioned in over 60 abstracts. The less known subtypes, γδ T cells and natural killer T (NKT) cells, appear in a small number of abstracts, possibly representing the start of a trend to watch over the next few years. The chart includes select immune cell subtypes that appear in at least one ASH 2016 abstract covering preclinical research. Data were generated as described for Top Translational Cancer Targets. Source: ASH 2016 abstracts (as of Nov. 9, 2016)
PATHWAYS FORWARD

The preclinical cancer abstracts published in advance of the 58th annual meeting of the American Society of Hematology include a wide range of targets corresponding to different molecular mechanisms and pathways. The figure highlights high-level categories of cancer targets mentioned in at least three abstracts. The number of abstracts containing each target is indicated in parentheses.

The majority of targets represented in the abstracts are levers for **blocking uncontrolled replication** (left panel). From top to bottom, that includes receptors for hormones and other soluble mediators; membrane-proximal tyrosine kinases; members of the JAK/STAT, MAPK and PI3K pathways; cytosolic mediators; transcription factors; and DNA- and histone-modifying enzymes.

Other targets, which facilitate cancer cell survival in the face of stress and resource deprivation, provide routes for **cutting cancer off from its enablers** (top right). From left to right, that includes heat shock proteins, hypoxia inducible factors, and factors that help tumors boost their blood and oxygen supply.

Several lymphoid and myeloid cell surface antigens serve as handles for **marking blood cancer cells for destruction** (middle right).

In contrast, other immune cell proteins provide ways of **harnessing immune cells to attack tumors**. From left to right, that includes cytokines and cytokine receptors, proteins that trigger myeloid or T cell activity, chemokine receptors, complement factors, and checkpoint proteins.
Well-established checkpoint targets PD-1 and PD-L1 also made the top 25, suggesting research in checkpoint inhibitors is expanding from solid tumors to hematological malignancies. Although one of the approved indications for PD-1 mAb Opdivo nivolumab from Ono Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co. is Hodgkin’s disease, most clinical programs on checkpoint inhibitors are in solid tumors.

In addition to immunology targets, many well-established cancer targets such as MYC, mTOR and MEK made the cut, although the molecules may serve as markers or assay readouts rather than therapeutic targets in some studies. Most of those molecules and the other top preclinical targets are already being hit by multiple products on the market and in the clinic, which suggests little separation between the preclinical and clinical hotspots.

The standout is FLT3, which is the second most common target in preclinical cancer abstracts, and is one of the few targets in which a single indication, AML, represents the overwhelming majority of the abstracts. FLT3 is targeted by only one marketed product — Iclusig ponatinib from Ariad Pharmaceuticals Inc.

### NOVEL TARGETS AT ASH

Select new targets for hematological malignancies and other cancers presented at the 2016 American Society of Hematology (ASH) conference. Source: ASH Abstracts

<table>
<thead>
<tr>
<th>TARGET</th>
<th>STANDARD INDICATION</th>
<th>RESEARCH SUMMARY</th>
<th>INSTITUTION(S)</th>
<th>ABSTRACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankyrin repeat and sterile α motif domain containing 1B (ANKS1B)</td>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>ANKS1B was confirmed as a target upregulated by the transcription factor 3 (TCF3; E2A)-PBX homeobox 1 (PBX1) fusion found in a subset of B cell ALL patients.</td>
<td>Tampere University Hospital; University of California San Francisco; University of Eastern Finland; University of Helsinki; University of Tampere</td>
<td>4077</td>
</tr>
<tr>
<td>B-cell receptor-associated protein 31 (BCAP31; BAP31)</td>
<td>Leukemia</td>
<td>BCAP31 was discovered as an additional target of the protein disulfide isomerase (PDI) inhibitor PS89, and its engagement is required for the inhibitor’s pro-apoptotic effect when combined with a cell growth inhibitor.</td>
<td>Helmholtz Center Munich; Ludwig Maximilian University of Munich; Saarland University; Technical University of Munich</td>
<td>2319</td>
</tr>
<tr>
<td>C-type lectin domain family 11 member A (CLEC11A)</td>
<td>Multiple myeloma (MM)</td>
<td>In MM cell lines, CLEC11A knockdown increased apoptosis.</td>
<td>Icahn School of Medicine at Mount Sinai; Multiple Myeloma Research Foundation (MMRF)</td>
<td>802</td>
</tr>
<tr>
<td>CDC42 binding protein kinase α (CDC42BPA)</td>
<td>MM</td>
<td>In MM cell lines, CDC42BPA knockdown increased apoptosis.</td>
<td>Icahn School of Medicine at Mount Sinai; Multiple Myeloma Research Foundation (MMRF)</td>
<td>802</td>
</tr>
<tr>
<td>CD7 molecule (CD7)</td>
<td>ALL; acute myelogenous leukemia (AML)</td>
<td>In AML and T cell ALL cell lines, T cells designed to express chimeric antigen receptors (CARs) targeting CD7 decreased the number of leukemia colonies.</td>
<td>Baylor College of Medicine</td>
<td>4555</td>
</tr>
<tr>
<td>Early B-cell factor 3 (EBF3)</td>
<td>ALL</td>
<td>EBF3 was identified as a tumor suppressor gene regulated by the TCF3-PBX1 fusion in B cell ALL patients.</td>
<td>Tampere University Hospital; University of California San Francisco; University of Eastern Finland; University of Helsinki; University of Tampere</td>
<td>4077</td>
</tr>
<tr>
<td>Lysosomal associated membrane protein family member 5 (LAMP5)</td>
<td>Leukemia</td>
<td>LAMP5 expression was up-regulated in mixed-lineage leukemia (MLL) fusion-positive leukemias, and LAMP5 knockdown decreased cell growth.</td>
<td>Cincinnati Children's Hospital Medical Center</td>
<td>1512</td>
</tr>
<tr>
<td>Natural cytotoxicity triggering receptor (NCR2; NKp44)</td>
<td>Cancer</td>
<td>T cells and natural killer (NK) cells expressing CARs designed based on NCR2, which is naturally expressed on NK cells and targets damage-associated molecular pattern molecules (DAMPs) found on various cancers, were cytotoxic towards various solid and hematological tumor cell lines.</td>
<td>Niigata University Graduate School of Medical and Dental Sciences</td>
<td>3517</td>
</tr>
</tbody>
</table>
— and represents a poorly served subset of cancers. The high level of FLT3 coverage suggests it could be a target to watch. Notably absent in the top cancer targets list is the emerging oncology target CD47. Commercial clinical and preclinical CD47 activity is growing, with at least six companies pursuing it for hematological malignancies and other cancers, but it appears in fewer than 20 preclinical abstracts.

While B cells and Tregs are the major cell types used in the growing field of cell therapy, other cell types are starting to attract attention in preclinical research. NK cells, which were identified by BioCentury Innovations earlier this year as an

TOP TRANSLATIONAL CANCER TARGETS

The growing trend of cancer immunology in hematological malignancy research remains evident in this year’s top preclinical targets from ASH abstracts. CD19, the leading target among preclinical abstracts, is a B cell marker that is used to help direct therapeutic antibodies and cell therapies, such as chimeric antigen receptor (CAR) T cells, to B cell malignancies. Three other B cell-specific targets — B cell lymphoma 2 (BCL-2; BCL2), BCR-ABL tyrosine kinase (BCR-ABL) and CD20 — also made the top list, as did a handful of well-established cancer targets like v-myc myelocytomatosis viral oncogene homolog (MYC; c-Myc) and mammalian target of rapamycin (mTOR; FRAP; RAFT1). The chart includes the top 25 targets, broken down by indication, from a list of top targets identified by BioCentury.

The analysis was performed by searching preclinical abstracts to be presented at the 2016 American Society of Hematology meeting for mentions of the top translational targets identified as translationally relevant based on information in BioCentury’s BCIQ: BioCentury Online Intelligence database and the Distillery section of BioCentury Innovations. All target mentions were included, whether in a therapeutic, diagnostic or descriptive context. The analysis includes some double-counting as some abstracts contain multiple targets or indications. Source: ASH abstracts (as of Nov. 9, 2016)
important cell type to watch, appears in over 60 abstracts — more than the subset of Tregs. And the less known subsets, γδ T cells and natural killer T (NKT) cells, which have also begun to attract commercial interest, show up in two preclinical abstracts each.

Non-cancer indications make up a smaller percentage of the preclinical abstracts at this year’s meeting, with anemia taking the top spot. Interestingly, monogenic blood disorders such as sickle cell disease and thalassemia — usually very big topics at ASH — are represented in a relatively small number of presentations. Despite that, gene therapy and nucleic acid therapies such as miRNA, which are often applied to monogenic disorders, still emerge as top therapeutic modalities.

Gene therapies are just beginning to appear on the market and the most advanced miRNA therapeutic in the clinic is in Phase II. The high volume of ASH abstract suggests these two modalities might be growing in hematology. In contrast, macrocycles are still a difficult class to drug, and only appear in a handful of abstracts this year.

There are few surprises in the top targets for hematology, with many falling into the categories of clotting factors or proteins involved in red blood cell formation. In contrast to the cancer

**TOP TRANSLATIONAL HEMATOLOGY TARGETS**

There are few surprises in the top hematology targets in ASH 2016 abstracts. As expected, the top two targets appearing in the most preclinical hematology abstracts this year, hepcidin and erythropoietin (EPO), were most commonly mentioned in connection with anemia. Also unsurprising are the various clotting factors in the list, which are predominantly being targeted for hemophilia. Although thalassemia and sickle cell disease are usually hot topics at the meeting, it is surprising that only three of the top targets clustered in those indications. The chart includes select hematology targets that appear in at least one ASH 2016 abstract covering preclinical science, broken down by hematology indication. Data were generated as described for Top Translational Cancer Targets. Source: ASH abstracts (as of Nov. 9, 2016)
TOP PRECLINICAL INDICATIONS

At this year’s ASH meeting, there were over three times as many preclinical abstracts in cancer as in non-oncology indications. Leukemias dominated the cancer abstracts, and acute myelogenous leukemia (AML) was by far the most commonly studied indication. Although there were fewer abstracts on lymphomas, those within the subset were primarily related to B cell malignancies including mantle cell lymphoma (MCL) and follicular lymphoma. Anemia was the top indication among the hematology abstracts, but the monogenic blood disorders sickle cell disease and thalassemia were in the top four indications. The charts include select hematological malignancies and hematological indications that appear in at least one ASH 2016 abstract covering preclinical research. Data were generated as described for Top Translational Cancer Targets. Source: ASH 2016 abstracts (as of Nov. 9, 2016)
TOP TRANSLATIONAL MODALITIES

Cell and gene therapies are among the top five therapeutic modalities covered in the 2016 preclinical ASH abstracts. Hematological malignancies account for the majority of the abstracts, and cell therapy is one of the biggest trends in oncology research this year. Other top diseases include monogenic hematology indications such as thalassemia and sickle cell disease, which account for the high numbers of abstracts mentioning the gene therapy and nucleic acid modalities. The small numbers for vaccines are expected, given the top therapeutic areas discussed in the abstracts. The chart includes select therapeutic modalities that appear in at least one ASH 2016 abstract covering preclinical research and excludes the standard small molecule and biologic therapeutic modalities. Data were generated as described for Top Translational Cancer Targets. Source: ASH 2016 abstracts (as of Nov. 9, 2016)

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Hematology (ASH), Washington, D.C.
Ariad Pharmaceuticals Inc. (NASDAQ:ARIA), Cambridge, Mass.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Ono Pharmaceutical Co. Ltd. (Tokyo:4528), Osaka, Japan

TARGETS

BCL-2 (BCL2) - B cell lymphoma 2

REFERENCES
