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Turning Stressed Immune Cells Back Into Fierce Cancer Fighters

BY VALERIE NEFF NEWITT

Juan R. Cubillos-Ruiz, PhD, "fell in love" with immunology and has translated that passion into award-winning research. Specifically, he is trying to understand how immune cells see and attack cancer cells, and how tumors can influence the function of immune cells and suppress the action of the immune system.

His fascination all began with Dolly the Sheep. As a boy in Bogota, Colombia, Cubillos-Ruiz, now Assistant Professor of Microbiology and Immunology at Weill Cornell Medicine, New York City, he was charmed by the wooly cloned beauty who took the world by storm.

"I knew I wanted to do something related to genetic engineering, but back home that was impossible—we didn't have any programs like that specifically.

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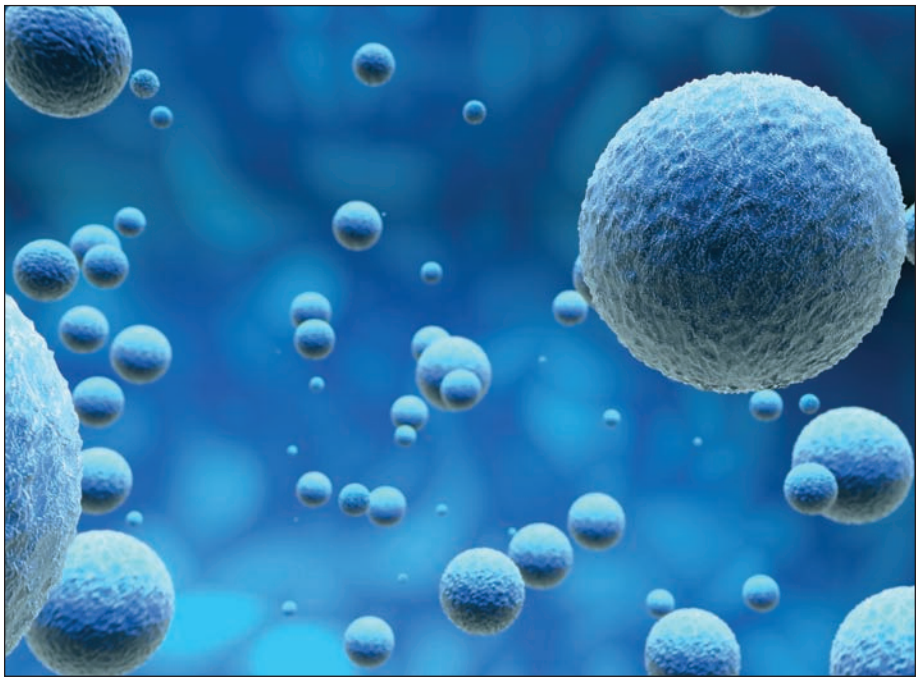

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New Report Tracks Explosive Global Growth of Immuno-Oncology

BY PEGGY EASTMAN

A new analysis of immuno-oncology (IO) by the nonprofit Cancer Research Institute (CRI) has found that the field is rapidly expanding globally—so fast that it is difficult for clinicians to keep up with progress. While cause for celebration, this rapid expansion has led to fragmentation, lack of coordination, overlap, and duplication in clinical trials, which the study authors state could be alleviated if professionals in academia, industry, regulatory agencies, and nonprofit organizations work together collaboratively toward common goals in the IO field.

Drawing on its database of 2,004 IO agents, the authors sought to track all the current IO agents in clinical development and the clinical trials in which they are being tested. The worldwide, independent analysis—believed to be the first of its kind—found that as of September

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Genomics in Chronic Lymphocytic Leukemia: Current Research & Future Implications

BY BRANDON MAY

An initially slow-growing common B-cell malignancy with a variable clinical course, chronic lymphocytic leukemia (CLL) represents the most common hematological neoplasm in the developed world (*Hematol Oncol Clin North Am* 2013;27(2):173-206). Although many patients can survive with asymptomatic disease and require no therapy, some patients with CLL experience disease that rapidly progresses in spite of aggressive therapeutic intervention (*Discov Med* 2011;11(57):115-123). According to Gwen Nichols, MD, Chief Medical Officer of The Leukemia & Lymphoma Society, recent advancements in next-generation sequencing have improved our clinical understanding of CLL, and the heterogeneity of the disease represents a key reason why research has shifted away from the one-size-fits-all approach and into a greater emphasis on targeted therapeutic agents.

CME Article

In addition to the growth of greater treatment understanding in CLL, new research continues to accumulate on the role of CLL genetics. Primarily due to its high prevalence and the ease of access to suitable study material, CLL is at the forefront of genomics and human tumor research. Novel sequencing technologies have facilitated greater understanding into the complexity of the disease and enabled identification of putative drivers behind tumor heterogeneity that direct CLL progression and treatment resistance.

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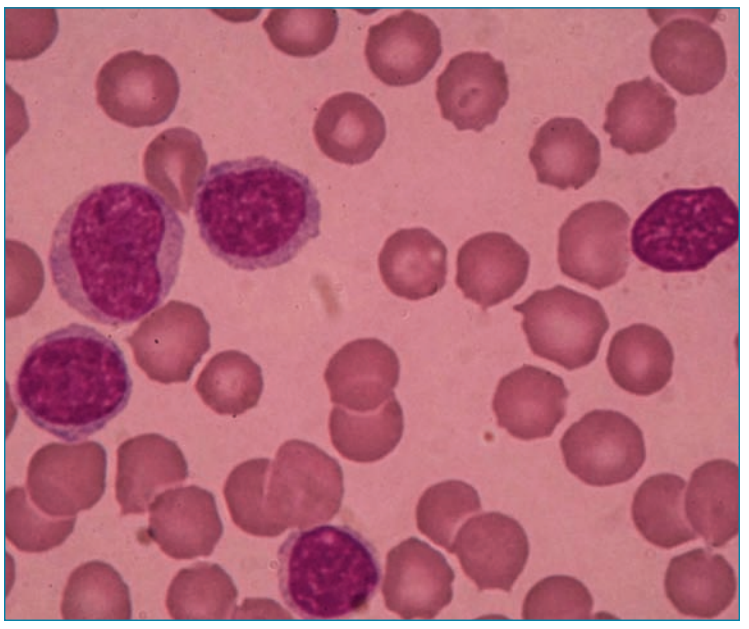
Next-Generation Sequencing

Genetic studies regarding CLL have discovered the recurrence of cytogenetic abnormalities, with the most common mutations being focal deletions on chromosomes 11q, and chromosomes 13q and 17p (*J Clin Oncol* 2017;35(9):984-993). Next-generation sequencing technology, including whole exome sequencing (WES) and whole genome sequencing (WGS), have provided a greater focus on the CLL genomic landscape.

Overall, both WGS and WES have revealed the diversity of the gene mutations that recur in CLL, as well as the genetic heterogeneity among tumor samples. Additionally, new algorithms of sequencing data have created further understanding of genetic mutations that are likely putative drivers of CLL. Recent studies on the use of WGS and WES have identified 75 mutated genes in approximately 1,000 CLL cases. In one study, the *SF3B1* represented the most frequently mutated gene, whereas the *NOTCH1* was commonly mutated in the other research report (*J Clin Oncol* 2017;35(9):984-993, *Nature* 2015;526(7574):519-524, *Nature* 2015;526(7574):525-530).

There has been a significant increase in the proportion of CLL characterization by either WGS or WES. Due to this rise in WGS and WES utilization, investigators have found it increasingly practical to study the diverse somatic mutations that work together to generate the CLL phenotype.

Genomic studies have demonstrated that more than one genetic driver is associated with CLL oncogenesis (*Nature* 2015;526(7574):525-530). For example, recent research has shown a consistent association between del(17p) and the *TP53* mutation in CLL (*Blood* 2014;123(21):3247-3254). Additionally, del(11q) has been associated with *ATM* and/or mutations of the *SF3B1* gene (*J Clin Oncol* 2007;25(34):5448-5457), and tri(12) has been associated



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with *NOTCH1* genetic mutations (*Blood* 2012;119(2):329-331, *Blood* 2014;123(26):4101-4110). Combination mutations consisting of *ATM*, *TP53*, and *SF3B1* have been shown to synergistically contribute to immunochemotherapy resistance (*Leukemia* 2015;29(5):1133-1142).

A subset of patients with CLL feature complex genomic profiles, as verified by array-based genomic profiling (*Genes Chromosom Cancer* 2008;47(8):697-711, *Leukemia* 2010;24(1):211-215, *Blood* 2012;120(24):4783-4794). Studies within the past 10 years have shown that genomic complexity is associated with reduced overall survival (OS) in CLL (*Leukemia* 2007;21(12):2442-2451) and may act as an independent predictor for OS (*Genes Chromosom Cancer* 2012;51(12):1125-1132).

Relatively recent technological advancements in genetic sequencing have offered investigators the ability to search the cancer genome in its entirety for sequence abnormalities or alterations. Extended patient series offer entire genome and exome sequencing data, comprising approximately 300 published CLL genomes and/or exomes (*Nature* 2011;475(7354):101-105, *Nat Genet* 2011;44(1):47-52, *N Engl J Med* 2011;365(26):2497-2506, *J Exp Med* 2011;208(7):1389-1401). The majority of these data have offered insight into recurrent genetic mutations at lower frequencies. Evidence from 2011 has demonstrated that the CLL genome contains a small proportion of somatic mutations, possibly similar in number as that of other leukemia types (*N Engl J Med* 2011;365(26):2497-2506, *Nat Genet* 2011;44(1):47-52).

> "Researchers are learning more about the role various genetic mutations in CLL, including *TP53*, *SF3B1*, and *ATM*, play in resistance to therapy."

Promising Treatment Strategies

Phase Ib/II trials have demonstrated the efficacy of ibrutinib in inducing remission of CLL and improving survival among CLL patients with adverse genomic profiles (*N Engl J Med* 2013;369(1):32-42). In addition to its potential survival benefit, ibrutinib appears to be well-tolerated in elderly patients (*Lancet Oncol* 2014;15(1):48-58). In the multicenter, randomized phase III RESONATE trial, ibrutinib demonstrated a clear significant overall survival benefit over ofatumumab in patients with CLL (P=0.005) (*N Engl J Med* 2014;371(3):213-223). The RESONATE-2 trial, which compared ibrutinib and chlorambucil, also showed a significantly greater overall response rate (86% vs. 35%, P<0.001) and a longer progression-free survival (P<0.001) with ibrutinib (*N Engl J Med* 2015;373(25):2425-2437). Additional research is also demonstrating the effectiveness of idelalisib, a phosphoinositide 3-kinase (PI3K) inhibitor that targets the BCR pathway (*N Engl J Med* 2014;370(11):997-1007).

According to a paper written by Jonathan C. Strefford, PhD, Professor in Cancer Molecular Genetics within Medicine at the University of Southampton in the U.K., "We are now undergoing a paradigm shift in the clinical management of CLL patients, from traditional cytotoxic treatments to state-of-the-art small molecular therapeutics (*Br J Haematol* 2015;169(1):14-31)." He added that this shift is occurring "as a consequence of greater insight into B-cell receptor signaling, and without reference to advances in genetics, a detailed understanding of the genomic landscape of CLL is very likely to maximize the potential of these new therapeutics." According to Strefford, this knowledge may provide greater accuracy in the early prediction of disease course, as well as in the identification of the "underlying genomic lesions that have utility as therapeutic targets."

"Researchers are learning more about the role various genetic mutations in CLL, including *TP53*, *SF3B1*, and *ATM*, play in resistance to therapy," added Nichols. "One of the most significant findings regarding genomics in CLL has been insights gained from a deeper understanding of the role that 17p deletion, and associated mutation of the tumor suppressor gene *TP53*, play in very poor prognosis and relapse for certain CLL patients." Additionally, discoveries regarding the effect of inhibiting the BCL2 protein to block apoptosis and allow the proliferation and growth of cancer cells "can enable patients to overcome resistance to therapy caused by the *TP53* mutation [and] has led to important new therapeutic approaches."

The Leukemia & Lymphoma Society supported the development of venetoclax, a BCL2 targeting agent, for patients with CLL who present with the 17p deletion. According to Nichols, BTK inhibitors (e.g., ibrutinib and acalabrutinib) as well as BCL2 inhibitors provide a greater efficacy rate than that of standard of care in CLL patients with the 17p deletion.

"Now researchers are testing various combinations, including combining venetoclax with BTK inhibitors, such as ibrutinib," Nichols noted. "Research presented at the 2017 American Society of Hematology (ASH) conference showed very promising results for this combination. Peter Hillmen, MBChB, PhD, Professor of Experimental Hematology at Leeds Institute of Cancer and Pathology in the U.K., presented findings from a study that

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combined the two drugs and said that, after 6 months, 36 patients—one-third of those in the study—had achieved a deep remission with no detectable disease."

Prithviraj Bose, MD, Associate Professor from the University of Texas MD Anderson Cancer Center, Department of Leukemia in Houston, echoes Nichols' statements on the promise of BTK inhibitor. "The CLL community also has been following with great interest the development of acalabrutinib, a more specific BTK inhibitor than ibrutinib," he noted. A research group led by Bose presented promising early data on two trials at ASH 2017: ibrutinib with venetoclax in both newly diagnosed and previously treated patients as well as ibrutinib plus FC with obinutuzumab (iFCG) in treatment-naïve patients without adverse genetic features.

"Both regimens were highly effective," commented Bose, "and iFCG may facilitate limiting cytotoxic chemotherapy in a significant subset of patients with CLL, while still obtaining long-term remission with a finite duration of therapy. Ibrutinib and venetoclax complement each other, enabling MRD eradication not observed with ibrutinib alone."

Currently, challenges exist to incorporate genetic testing at the clinical level. In his research paper, Strefford suggested, "The choice of an appropriate assay will be based on the number of genes or genomic regions that have clinical value and will have ramifications on the choice of sequencing technology and downstream analytical processing." In addition, Strefford commented on the the early predictive value of gene mutations in CLL: "At disease presentation, the identification of deletions of 13q, 11q, 17p, and trisomy 12, with mutations in *NOTCH1*, *SF3B1*, *TP53*, *ATM*, and *BIRC3* are likely to aid risk-adapted stratification. At a requirement for treatment, deletions and/or mutations of *ATM* and *TP53*, *NOTCH1* mutations, and genomic lesions in genes and pathways targeted by specific therapies will help guide treatment and monitor response."

Future Directions

Due to the tremendous growth in genetic research for CLL as well as other cancer subtypes, several organizations have hit the ground running by initiating research trials aimed at identifying the importance of sequencing in improving treatment and treatment-related outcomes. Approximately 1 year ago, The Leukemia & Lymphoma Society initiated the Beat AML Master Clinical Trial, a multi-center, multi-arm research study to research a precision medicine approach for the treatment of patients with acute myeloid leukemia (NCT03013998). "The study is now open in seven cancer centers with more joining soon," said Nichols.

For this study, the Society is using Foundation Medicine, a central genomics provider, to evaluate the genetic profile of newly diagnosed patients enrolled. "Based on the success of this genomically driven trial," stated Nichols, "we are clear on the need to educate...we are planning several educational programs geared to both patients and physicians to help them gain an understanding of why it's so important for both patients and their physicians to understand their genomic profile in order to make better treatment decisions and to find better treatments or more appropriate clinical trials for their specific subtype." OT

Brandon May is a contributing writer.

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be able to identify promising treatment strategies targeting specific genomic profiles for CLL.

More 2017 ASH Research

Read additional articles highlighting the newest research unveiled at the 2017 American Society of Hematology Annual Meeting, starting on page 28.