EDITORIAL

The Landscape of Blood Cancer Research Today—and Where the Field Is Headed

Nicole Haloupek

Summary: This editorial integrates the views of *Blood Cancer Discovery*'s editors-in-chief and scientific editors to explore the current and near-future landscape of the study of hematologic malignancies—from the most intriguing new developments in clinical and basic research to the greatest upcoming challenges and how they will be confronted.

This is an immensely exciting time in the study of hematologic malignancies, marked by tremendous progress in basic, translational, and clinical research. To highlight just a few major advances, engineered T-cell treatments and other immunotherapies, along with targeted therapies, represent definitive progress in the clinical realm. In basic science, greater understanding of the tumor microenvironment (TME) and cancer genomics has inspired new paradigms for understanding disease and has driven progress in the clinic. These advances have been fueled in large part by a rapid proliferation of powerful techniques such as next-generation sequencing and CRISPR–Cas9-based gene editing, among many others.

The emergence of these promising advances bodes well not only for research on hematologic malignancies but also for studies of other cancers. "Research in hematologic malignancy has been at the forefront of the understanding of the biology of cancer in general," says Riccardo Dalla-Favera, MD, co–editor-in-chief of *Blood Cancer Discovery*, Director of the Institute for Cancer Genetics and a professor at Columbia University.

Blood cancer researchers have pioneered treatments that have been widely adopted, such as targeted therapies, which "were really founded and first explored in hematologic malignancies," says Kenneth Anderson, MD, co–editor-in-chief of *Blood Cancer Discovery* and a professor at Harvard Medical School. The targeting of the BCR–ABL fusion kinase with the inhibitor imatinib in chronic myelocytic leukemia and the treatment of acute promyelocytic leukemia with all-*trans* retinoic acid and arsenic trioxide have both been hailed as great successes in targeted therapy.

Furthermore, combination therapy for cancer was spearheaded in hematologic malignancies, Anderson says, "first with conventional chemotherapy, and more recently with targeted and immune therapies, predicated upon preclinical modeling." The idea dates back to at least 1965, when the POMP regimen (methotrexate, 6-mercaptopurine, vincristine, and prednisone) was first developed to treat pediatric leukemias. Today, combination targeted and immune therapy for many cancers, including both hematologic malignancies and solid tumors, is increasingly being explored and adopted.

As a final example, engineered T cell–based treatments, most notably chimeric antigen receptor (CAR) T-cell therapies, were first developed to treat hematologic malignancies by targeting CD19. Although technical hurdles have precluded their use in solid tumors for now, expanding the use of CAR T-cell therapies to treat other malignancies is an active area of research.

CLINICAL ADVANCES IN HEMATOLOGIC MALIGNANCIES AND THE CHALLENGES AHEAD

Clinical blood cancer research has accelerated dramatically over the past several years, and perhaps no area has seen as much interest as immunotherapy, including treatment with immune-checkpoint inhibitors such as the PD-1 antibody nivolumab for classic Hodgkin lymphoma. All these novel treatments hold promise, but among the immunotherapies for hematologic malignancies, none has generated as much excitement as CAR T cell–based treatments.

Highlighting the promise of these therapies, rapid and deep responses have been achieved using CAR T cells targeting B-cell maturation antigen in multiple myeloma. Ongoing research is being dedicated to improving safety as well as efficacy, specifically as it relates to prolonging response and preventing relapse. Techniques to improve efficacy include methods such as altering CAR T-cell products to select for central memory cells and manipulating the host to try to prolong survival of the immune response to sustain clinical benefit, Anderson explains.

A major challenge facing CAR T cell–based therapies in hematologic cancers is that, although they can be very effective for certain B-cell malignancies, these treatments are lacking for myeloid malignancies due to the need to identify appropriate cell-surface targets. Adaptation of CAR T cell–based therapies for the treatment of solid tumors is also an area of intense study, once again illustrating that research in blood cancers is often at the forefront of cancer research. "I think CAR therapy is just in its infancy, because just a few targets have been used, and only T cells are being used," says

American Association for Cancer Research, Philadelphia, Pennsylvania.

Corresponding Author: Nicole Haloupek, American Association for Cancer Research, 615 Chestnut Street, 17th Floor, Philadelphia, PA 19106. E-mail: nicole.haloupek@aacr.org

Blood Cancer Discov 2020;1:1–4

doi: 10.1158/2643-3249.BCD-20-0083

Dalla-Favera, adding that the use of CAR NK cells, currently under investigation, is a clear next step.

An additional challenge facing the adoption of CAR T cell–based therapies is that they are expensive and time-consuming to generate, having to be created individually for each patient. This fact is part of the impetus to further develop bispecific antibodies, which are cheaper, off-the-shelf immunotherapies that have generated considerable enthusiasm. "We will see the use of bispecific antibodies, which may substitute or complement CAR T," says Dalla-Favera. "The trials are in the initial stages," he adds. Ultimately, combination immune approaches may be needed to achieve prolonged responses.

Notwithstanding the buzz around CARs and immune-checkpoint blockade, immunotherapies are hardly the only area in which clinical progress in hematologic malignancies is taking place: Targeted therapies have also elicited a favorable response from the hematologic-oncology research community. "We are coming out of 30 years of study on the genetics of blood cancer, and now it is the opening era of exploiting that research for therapy," says Dalla-Favera. "Targeted drugs have now entered clinical practice, and we're seeing them in blood cancer more than any other cancer."

Although targeted therapies can produce dramatic responses when used in the appropriate patients, a major roadblock is the development of resistance. One approach to quashing resistance is to employ next-generation drugs that act on the target of interest from a different angle, for example, by using an allosteric rather than a direct inhibitor. Another option to deal with resistance is to focus on treating patients when the number of cancer cells is low by detecting cancer or relapse early, limiting the probability that resistant cells already exist within the cancer-cell population. An additional obstacle facing targeted therapies is the management of side effects, which may be due to off-target effects or the direct effects of a given drug. Also, one area of active research is how to hit "undruggable" targets such as transcription factors, which are altered in large proportions of cancers.

Ultimately, despite their promise, neither immunotherapy nor targeted therapy is the sole solution to blood cancers. "My overarching feeling is that we in hematologic malignancies or cancer more generally will utilize combinations of targeted and immune treatments," Anderson says.

Furthermore, there continues to be a role for conventional chemotherapy and radiotherapy—at least for now. "I think that we will be using conventional therapies, but we will hopefully use them in a more informed way predicated upon preclinical testing," Anderson says. For example, alkylating agents act by damaging DNA, and proteasome inhibitors inhibit DNA-damage repair, among other activities. Preclinical studies demonstrated that the combination of alkylating agents and proteasome inhibitors induced DNA damage and blocked DNA-damage repair, thereby causing synergistic cytotoxicity to myeloma cells. These studies informed the use of alkylating agents, such as cyclophosphamide, plus proteasome inhibitors, such as bortezomib—a combination that is commonly used as an initial treatment for multiple myeloma today.

"I do not think targeted therapies should replace, necessarily, chemotherapy," says Dalla-Favera. "There are cancers that are cured by chemotherapy, and it will be quite difficult for targeted therapy to replace them just because it is difficult to replace something that is working." However, Dalla-Favera adds, an effort should be made to replace these older treatments, notably because the long-term toxicity of chemotherapy and radiotherapy is sometimes underestimated, and secondary malignancy is a major concern.

A final and perhaps underappreciated area that is ripe for clinical advances is drug repurposing: taking existing drugs developed for a certain disease, perhaps not even a cancer, and testing them in another disease. One advantage of repurposing is that, if a drug under investigation has already been approved or at least gone through phase I trials, it can reach patients more quickly. Another advantage of repurposing is that new therapeutic targets may be identified by testing large numbers of existing drugs in different malignancies and determining which ones work and why, Dalla-Favera notes.

One example highlighting the utility of drug repurposing comes from Dalla-Favera's group, who recently reported preclinical evidence that the chronic myelogenous leukemia drug dasatinib may be of use in diffuse large B-cell lymphoma because of shared biochemical pathways. A second recent example is the targeting of BCL2 with venetoclax, which is approved to treat leukemia and lymphoma and is now showing efficacy in acute myeloid leukemia (AML) and a subset of myelomas that overexpress BCL2.

Of course, innovative basic and translational research is still required for the development of the novel therapies of the future.

TOPICS OF SPECIAL INTEREST IN BASIC AND TRANSLATIONAL RESEARCH ON HEMATOLOGIC MALIGNANCIES

When it comes to basic and translational science, the blood cancer field abounds with exciting new areas of research that will undoubtedly lead to better understanding of disease and yield new treatments. Among these topics, few have generated as much enthusiasm as the TME, which comprises not only the tumor cells, but also the surrounding stroma and immune infiltrates. The populations of nontumor cells in the TME are not negligible—in fact, in malignancies such as T-cell/histiocyte–rich large B-cell lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, and many forms of T-cell lymphoma, cancer cells are in the minority.

"There is an increasing understanding of the biological and functional sequelae resulting from the interaction between tumor cells and their microenvironment," Anderson says. The TME can influence immunosuppression through cell- and cytokine-mediated mechanisms, and knowledge of these mechanisms may contribute to the discovery of new therapeutic targets and strategies. For example, in multiple myeloma, the tumor microenvironment consists of accessory cells such as plasmacytoid dendritic cells, myeloid-derived suppressor cells, regulatory T cells, and others, and these cells not only confer increased tumor-cell growth, survival gains, and drug resistance, but also lead to immunosuppression. Targeting these cells may therefore represent a novel treatment paradigm.

In addition, fully characterizing the TME is necessary to understand disease pathogenesis. For example, in multiple myeloma, there exists a precursor condition called monoclonal

gammopathy of undetermined significance (MGUS). It has been shown that, even at this precursor stage, the majority of genomic aberrations found in multiple myeloma is already present. Some further genomic alterations are acquired upon progression to multiple myeloma, but the microenvironment also becomes much more immunosuppressive. If a way to circumvent this could be determined, it may be possible to prevent progression from MGUS to multiple myeloma.

Still, research on the TME remains largely in the basic-science category. "There's no question that many tumors, if not all, are dependent on a supportive microenvironment that feeds them and that the tumor educates to be useful for its own interests," Dalla-Favera says. "I am not aware, though, of many successes yet in targeting the microenvironment directly," he adds, concluding that the TME remains a valid target but that more basic research is needed.

One area of basic science that has already proved clinically fruitful is tumor-cell genomics. Many driver mutations, some of which have been successfully targeted, are now known, although more certainly remain to be discovered. Going forward, though, focusing on individual genes may not always be the most efficient path to developing new therapies. "We know a lot of mutations, but we still have a very incomplete picture of how to organize them in pathways to target them well," says Dalla-Favera. When affected pathways, rather than solely the individual genes, are identified and characterized, many entry points into the pathway can be identified for targeting. But to elucidate those pathways, Dalla-Favera says, "you are going to basically have to understand more of the biology."

"The importance of not only understanding genes and proteins, but understanding pathways and their role in biology, normal and abnormal, is paramount," Anderson concurs, adding that the interactions among pathways should also be considered. "The importance is not only to define the targets in a particular pathway, but to understand the interactions between pathways that may be additive or synergistic in promoting tumor-cell growth or that could be redundant and confer drug resistance," Anderson says.

Notably, findings about pathways affected in one malignancy sometimes provide the basis for discoveries in other cancers. For example, once the RAS–RAF–MAPK pathway was characterized, leading to the development and FDA approval of the $BRAF^{V600E}$ inhibitor vemurafenib for melanoma, it was apparent that this drug might also work for a subset of multiple myelomas, in which the same pathway is implicated in tumor-cell growth.

Although the TME and cancer cell genomics are just two of a multitude of basic-science topics identified by our editors as being of special importance, it is clear that these fields have generated more interest across subdisciplines in hematologic oncology than most. Crucially, though—regardless of the scientific questions being addressed—the potential impact of developing novel methods cannot be overemphasized.

TECHNIQUES THAT HAVE TRANSFORMED AND WILL CONTINUE TO SHAPE BLOOD CANCER RESEARCH

To make further progress and address the remaining challenges in basic, translational, and clinical blood cancer research, powerful methods are needed. Fortunately, we are in an era of rapid growth in techniques that can be used in research on hematologic malignancies.

Many changes in the way blood cancer researchers conduct science can be attributed to advances in technology and computing, leading to the ability to perform high-throughput assays, multiplexed imaging, big-data sharing, and more. Next-generation sequencing is an exemplary development that has enabled the pinpointing of cancer-driving mutations and proved clinically useful in subclassification of disease. For example, experiments using next-generation sequencing revealed that some patients with AMLs that would have been characterized as having AML with normal karyotype, for which allogeneic bone marrow transplantation is indicated, do not require such treatments if they harbor *NPM1* mutations but not specific other genetic aberrations.

Another technical advance with clearly recognizable utility is CRISPR–Cas9-based gene editing. "The big CRISPR revolution is having a tremendous impact on research," Dalla-Favera says, although he's skeptical that gene editing could be used therapeutically, as some have suggested. "Hitting every cell in cancer is difficult—correcting the genetics of every single cell. If you leave a few cells behind, that will grow the tumor back," he says. But gene-editing methods have substantially increased the pace of research, with CRISPR–Cas9-based genetic screens allowing the identification of cancer-associated mutations and CRISPR–Cas9-based gene editing enabling much more rapid creation of animal models, just to name two examples.

In addition to the massively impactful developments of next-generation sequencing and CRISPR–Cas9-based methods, several new trends have emerged, and it is important to mention the explosion of single-cell techniques such as single-cell RNA sequencing. "The ability to analyze single-cell sequencing and function represents an extraordinary opportunity to look at subsets of cells at particular stages of disease in hematologic malignancies," says Anderson. Data from single-cell studies can be used to generate hypotheses that can then be further examined and validated in disease model systems and may ultimately lead to novel understanding and therapeutic strategies, Anderson explains.

Despite unprecedented technological leaps, such as the ability to analyze data at the level of single cells, the impact of basic-science findings on patients will be limited without concurrent advances in translational science. Some of *Blood Cancer Discovery*'s scientific editors cited the need for new *in vivo* and *ex vivo* models of hematologic malignancies to aid in translating basic-science insights into clinically actionable knowledge. Furthermore, the way clinical trials are designed and carried out is of utmost importance—and the proposed methods to improve research in this domain are myriad.

"The historical problem is that new drugs have to be tested in very advanced patients as single agents, and measured for their ability to do better than established therapies, often combination regimen involving multiple drugs Dalla-Favera says. "That is an issue—that very high threshold for adopting them." However, some scientists have also made the criticism that standards for cancer trials are at times too lax. For example, as Dalla-Favera says, "The culture is still pervasive of running trials with new drugs without adequate in-depth genetic and biological stratification of patients." In addition, some of *Blood*

Cancer Discovery's scientific editors noted a lack of rigor in some trials and a dearth of scientifically validated endpoints.

That not all trials in hematologic malignancies are conducted based on well-established basic and translational information highlights the complex interplay between clinical and preclinical research and the need for collaboration among scientists representing both groups—an issue that may be ameliorated by providing a platform such as *Blood Cancer Discovery* for both groups of researchers to share their results. "Our goal is to define combination targeted and immune therapies in preclinical studies and then treat subsets of patients likely to respond using biomarker-driven regimens. Our scientific advances can then move more rapidly to benefit our patients," Anderson says.

LOOKING FORWARD: THE ROLE OF *BLOOD CANCER DISCOVERY*

The information presented in this editorial, including advances and challenges in research ranging from basic to clinical along with the methods that will drive further progress, emphasizes the impetus for launching *Blood Cancer Discovery*. "In our journal, we want to have clinical advances in the area of hematologic malignancies that go all the way from basic science to translational science to clinical science," Anderson says.

The journal aims to publish research that uncovers mechanisms behind all types of hematologic malignancy (including leukemias, lymphomas, myelomas, and associated diseases) at biological scales ranging from single molecules to human populations, provides novel diagnostic and therapeutic insights, and translates this information into clinical studies.

Specifically, the journal will showcase therapeutic advances at all stages of development, from experimental treatments in animal models to clinical trials. The journal is broadly interested in approaches targeting cancer cell signaling pathways and harnessing the patient's anticancer immunity or supplementing it through adoptive cell transfer. The journal's scope also includes biotechnological advances in cell engineering and manufacturing to make biological and cell-based therapies more universally applicable, affordable, and effective. These advances include synthetic biology, iPSC-derived cell therapeutics, bone marrow transplantation, off-the-shelf stem cell therapies, and CAR T- and NK-cell therapies. Because the number of new therapies and their synergistic combinations creates an urgent need for accurate and affordable disease models for preclinical testing, the journal is calling for new approaches to rational therapeutic design, high-throughput screening, organoids, and systems biology modeling.

Blood Cancer Discovery encourages submissions in precision medicine. The journal is eager to publish genomic landscape studies mapping clonal heterogeneity of preneoplastic and neoplastic states from which oncogenic trajectories of clonal evolution under different selective pressures can be reconstructed. The journal values high-dimensional studies identifying features of neoplastic states relevant to health outcomes in molecular, cellular, physiologic, and real-world datasets that advance the field clinically (by determining biomarkers that can guide medical decisions) or conceptually (by identifying patterns suggesting mechanisms of pathogenesis).

Whether it's a single-cell RNA-sequencing study of the TME or a clinical trial applying findings from such a study, *Blood Cancer Discovery* welcomes all high-impact submissions in the field of hematologic oncology.

"There is an unprecedented opportunity now because of the advances in science to make science count for patients and to improve our understanding of diagnosis, prognosis, and treatment," Anderson says. Blood cancer researchers have the potential to continue to be trailblazers in the field of cancer research as a whole, driving progress that will have a positive impact on patients—the ultimate goal of *Blood Cancer Discovery*.