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To the editor:

A roadmap for discovery and translation in lymphoma

Non-Hodgkin lymphomas, Hodgkin lymphoma, and chronic lymphocytic leukemia comprise more than 80 unique subtypes[1] that can be further divided based on histology, immunophenotype, genetics, and other aspects of biology. Despite this diversity, advances in the treatment of lymphoma have served as models for curative cancer therapy.[2-5] To review the state of science in lymphoma biology, the American Society of Hematology (ASH) organized the inaugural ASH Meeting on Lymphoma Biology in August 2014. The Steering Committee for the meeting was asked to develop a roadmap for future discovery in lymphoma biology that could inform funding allocations (eg, requests for applications at the National Institutes of Health) and direct advocacy by ASH and other organizations. This roadmap is outlined in Table 1 and consists of both infrastructure and research priorities.

The investigation of individual lymphoma subtypes is largely limited by the same considerations that affect many other tumors, including:

- inadequate numbers of representative cell lines and in vivo models, including patient-derived xenografts and genetically engineered mouse models;
- inadequate characterization of the genetic, epigenetic, transcriptional, proteomic, and metabolomic landscape of each subtype;
- limited interest from pharma in rare subtypes with poorly understood pathobiology; and
- insufficient collaboration across centers, which limits both expertise and resource availability.

These inadequacies are compounded by the biologic heterogeneity within each lymphoma subtype. Preclinical studies that capture this heterogeneity will require large numbers of samples and/or models to facilitate patient stratification and biomarker validation. For most lymphoma subtypes, the necessary reagents to perform these studies either do not exist or are scattered across multiple institutions. As a result, many patients with lymphoma continue to experience poor outcomes. These include patients with mantle cell lymphoma, subtypes of peripheral T-cell lymphoma, and lymphomas that harbor specific genetic markers [eg, del(17p) in chronic lymphocytic leukemia, concurrent *MYC* and *BCL2* translocations in diffuse large B-cell lymphoma].

The biological consequences of most genetic aberrations observed in human lymphomas remain unclear. Therefore, functional approaches are needed to distinguish driver events and to define critical dependencies that can be exploited therapeutically. Another high priority is to develop new prognostic models that incorporate biologically informative predictive factors along with clinical factors to enable patient selection for clinical trials and to highlight the biological pathways and mechanisms that influence therapeutic response. Comprehensive investigations of larger collections of clinically annotated patient samples are needed to identify additional determinants of treatment response, and these predictive features will inevitably shift with new therapies.

Advances in the targeting of lymphoma depend on an improved understanding of the fundamental biology of lymphoid development. Because the majority of B-cell lymphomas arise from cells undergoing the germinal center reaction, insights into this process shed light directly on lymphomagenesis. Lymphomas highjack other aspects of lymphocyte biology, including mechanisms that regulate proliferation, differentiation, interaction with immune and stromal cells in the microenvironment, motility, dissemination, and response to antigens. An important goal of future research will be to define genetic and nongenetic mechanisms that perturb these processes.

Interactions between lymphoma cells and nonmalignant cells within the bone marrow, lymph node, and other tumor microenvironments may represent additional targetable dependencies. Strategies to identify and therapeutically modulate these interactions are a priority, and include interventions to disrupt tumor angiogenesis, block critical adhesion molecules, and abrogate the nurturing effect

Table 1. Priority areas for lymphoma discovery and translation, divided into infrastructure and research areas

Priority area	Examples for specific targets
Infrastructure	
Model development Develop disease models, including cell lines, patient-derived xenografts, and genetically engineered mouse and zebrafish models. Reliable models are essential tools for interrogating disease biology as well as experimental therapeutics.	• Establish ≥5 cell lines for each lymphoma subtype and for each common genetic aberration, with characterization by RNA and exome sequencing. • Establish ≥5 in vivo models for each lymphoma subtype and for each common genetic aberration, with characterization by RNA and exome sequencing.
Collaborative biorepositories Create repositories of biospecimens and disease models to organize, validate, and distribute well-annotated reagents. Broad access expands the impact of specimens and models, whereas collaborative banking allows for adequate numbers to capture disease heterogeneity.	• Establish a central repository of biospecimens, cell lines, and in vivo models with open access. • Establish a central portal for genomic, proteomic, metabolomic, compound sensitivity, and other data from lymphoma cell lines, building on the Cancer Cell Line Encyclopedia (www.broadinstitute.org/ccle/home) and other repositories.
Advocacy and development Organize patient advocacy to support research. Advocacy promotes fundraising, sample collection, government lobbying and disease visibility, while aligning research priorities with community goals.	• Establish educational and interactive websites for each lymphoma subtype. • Establish lymphoma advocacy groups through existing organizations (eg, ASH, Leukemia & Lymphoma Society, Lymphoma Research Foundation).
Research	
Molecular characterization Comprehensively catalog genetic, transcriptional, epigenetic, proteomic, and metabolomic alterations across lymphoma subtypes. This characterization will provide the critical foundation to understand disease pathobiology, including intratumoral heterogeneity, and to identify targets for new treatments.	• Perform whole genome sequencing, RNA sequencing, and phosphoproteome analysis on ≥500 primary specimens (with paired germ line sequencing) from each common lymphoma subtype and ≥50 from each less common subtype.
Genetic dependences Define genetic dependences using genome-wide libraries for knockdown/knockout. Loss-of-function screening can establish novel targets and elucidate lymphoma biology.	• Perform genome-wide screens using Cas9/guide RNA and/or shRNA libraries in all relevant lymphoma cell lines. • Define synthetic lethal interactions that overcome resistance to current therapies or target “undruggable” genetic alterations.
Experimental therapeutics Identify novel compound activities in lymphoma using cell line and in vivo models. As with genetic screens, compound screening can establish novel targets as well as mechanisms of action.	• Screen existing bioactive libraries against all relevant lymphoma cell lines. • Establish biomarkers for de novo sensitivity and resistance using genomic and other data. • Identify mechanisms of in vivo resistance to therapeutics.
Patient stratification Develop strategies to identify and target high-risk subsets of patients. Patient stratification can expedite clinical trials by targeting patients with specific biology.	• Establish next-generation prognostic indices that incorporate genomics and other data for individual lymphoma subtypes. • Develop a therapeutic strategy to target MYC in DLBCL. • Develop approaches to predict de novo resistance to BTK inhibitors.
Immune therapies Turn the power of the immune system against lymphoma. This includes the identification of synergistic combinations of immune therapies, targeted therapies, and chemotherapy.	• Enhance the effectiveness of therapeutic monoclonal antibodies. • Combine therapeutic antibodies and small molecules with agents that block immune checkpoints. • Perform high-throughput screening for synergy between checkpoint inhibitors and small molecule–targeted drugs. • Develop strategies for therapeutic vaccination to eradicate minimal residual disease. • Develop off-the-shelf engineered therapeutic T cells. • Engineered therapeutic T cells that target novel epitopes created by recurrent driver mutations.
Microenvironment Understand the protumoral crosstalk between neoplastic lymphoma cells and tissue-specific microenvironments.	• Develop strategies to disrupt angiogenesis within lymphomas. • Target critical adhesion molecules to disrupt lymphoma survival signals. • Abrogate the nurturing effects of cytokines and chemokines released by tumor-associated stromal and immune cells.
Normal lymphocyte development Define the common features and unique traits of specific lymphoid malignancies in comparison with their developmentally related normal lymphoid counterparts.	• Define all molecules necessary to initiate and sustain the germinal center response. • Define all key protein–protein interactions and posttranslational modifications that regulate B-cell receptor signaling. • Define critical survival signals in each T- and NK-cell subset and distinct precursor.
Clinical translation Develop robust biomarkers that can be translated into the clinical laboratory using platforms suitable to routinely available formalin-fixed, paraffin-embedded biopsy material.	• Perform clinical studies that integrate the mutational landscape and are powered to identify/validate molecular correlates of survival. • Develop transcriptional, epigenetic, and/or metabolomic signatures downstream of genetic aberrations that can be tested using large patient cohorts that received uniform therapy.

Examples of specific targets in each priority area are outlined to guide funding and advocacy. The table is not intended to be comprehensive across all aspects of lymphoma-related research, but instead to serve as a focused catalog of high-priority areas.

DLBCL, diffuse large B-cell lymphoma; NK, natural killer; shRNA, short hairpin RNA.

of cytokines and chemokines released by tumor-associated stromal and immune cells. There is a pressing need for model systems that faithfully recapitulate interactions between human lymphoma cells and the microenvironment to facilitate the preclinical testing of novel therapeutics.

Efforts to augment immune-mediated clearance of lymphoma cells have shown tremendous promise.[6-8] Specific areas for research include the targeting of immune checkpoints, improving the efficacy of adoptive cellular therapies, modulating T regulatory cells, developing novel lymphoma vaccines, and enhancing tumor-specific innate immune responses.

In summary, we outline a roadmap for discovery and translation in lymphoma that focuses on improving the understanding of disease biology across the broad diversity of subtypes. The roadmap is based on the fundamental goal of extending effective treatment to all patients with lymphoma. Achieving that goal with maximum efficiency and expedience will require a broad and collaborative effort between researchers, patients, funding agencies, pharma, and advocacy groups. Comments on the roadmap are welcome and can be posted at http://www.hematology.org/lymphoma-roadmap.

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