Putting the Clinical and Biological Heterogeneity of Non-Hodgkin Lymphoma into Context

Owen A. O’Connor1 and Kensei Tobinai2

Abstract

The lymphomas represent one of the most heterogeneous groups of malignancies in all of cancer medicine. Whether one attempts to understand these diseases in the context of their complicated ontogeny, unique biologic features, or clinical presentation, this heterogeneity has been a mixed blessing. On the one hand, it has created an ever-changing way to classify these diseases, as classification schemes have been compelled to reflect the rapidly emerging information that seems to split the disease into smaller and smaller subtypes. On the other hand, the biologic and clinical dissection of these diseases has allowed for the identification of unique biologic features—features that have led to novel targets and generated a plethora of new drugs. Virtually every subtype of non-Hodgkin lymphoma has benefited from these efforts to understand the biology of the different subtypes. This paradigm has led to new clinical trials that tailor novel drug regimens to specific biologic disease subtypes. As a prelude to this CCR Focus section, we attempt to put this evolving heterogeneity into context, bridging historical and modern-day views of classification of these diseases. Then, some of the world’s leading lymphoma researchers share their perspectives on how to formulate new concepts of care in this era of biologic discovery. Over a relatively short time, the advances in lymphoma research have been nothing short of stunning. There now seems to be little doubt that these recent breakthroughs will redound favorably on the majority of patients diagnosed with a lymphoproliferative malignancy.

See all articles in this CCR Focus section, "Paradigm Shifts in Lymphoma."

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Introduction

Anyone who has tried to keep abreast of the literature, or attended any national or international meetings in the field, knows we are living in the midst of an era where data and information are being revealed at a dizzying pace. Information, now measured in terabytes, has created new fields of study and employment in bioinformatics, a relatively new interdisciplinary scientific field dedicated to the formulation of software for storing, retrieving, organizing, and analyzing biologic data. It is interdisciplinary as it relies on the principles of mathematics, statistics, and computer science to study and process biologic data. It is no longer possible to comprehensively analyze by hand the large datasets on disease biology, or the treatment-related predictors of response or toxicity. With the terabytes of data available, the question now becomes, have we become more knowledgeable? If information provides answers to questions of "what," "where," and "when," knowledge answers the question of "how." How does one translate the seemingly infinite amount of information into practical guidelines? How can we optimally leverage the terabytes of data to improve the outcome of a disease, or to help a patient navigate a challenging diagnosis of cancer? Although astounding progress has been made in generating data and information around the sphere of cancer biology, it is clear that the rate-limiting step hindering the realization of real progress in treating neoplastic disease comes down to answering the question "how." Translating the basic science into practice is often the rate-limiting step.

So, have we become more knowledgeable? I believe the answer is yes, absolutely. Although we have just begun to visualize the possibilities for translational medicine emerging across all of cancer medicine, I believe the lymphoid neoplasms offer a useful paradigm for thinking about innovative ways to tailor new and existing therapies to discrete biologic entities of disease. This CCR Focus has brought together some of the world’s leading authorities focused on trying to make sense of the biologic heterogeneity that defines the lymphoproliferative malignancies. As information and data emerge about the biologic origins of lymphoma, we have learned that this disease is characterized by remarkable heterogeneity, heterogeneity that has compelled us to continuously rebuild a "knowledge" base for each of the ever-expanding number of subtypes. Every subtype of these complex diseases is being

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reclassified and recategorized on the basis of an array of cellular and molecular descriptors. The authors have tried to present a framework for how to interpret the heterogeneity of their disease, and how the field is thinking about using this information to generate new concepts around treatment.

The degree of biologic heterogeneity seen in any biologic system is highly dependent on the tools available to probe its details. How one sees that heterogeneity also depends on the lens through which one views the complexity. At a practical level, clinicians confront the heterogeneity of lymphoma every day in the clinic, without a clear understanding of its basis. Why do some patients with diffuse large B-cell lymphoma (DLBCL) do better than others? Why are some patients with gastric MALT cured with antibiotics, and others not? Why can some patients with mantle cell lymphoma (MCL) be watched, while others need a stem cell transplant? Hematopathologists may describe it in terms of cellular morphology, tissue architecture, patterns of IHC staining, or presence of translocations or chromosomal additions or deletion. Basic scientists may see it in the strict context of any of the emerging –omics (genomics, proteomics, epigenomics, metabolomics). Clinicians see it in the context of a patient’s experience, with some being cured, while others not.

The heterogeneity we see in lymphoma is a direct product of the natural features of lymphocyte development and differentiation (Fig. 1). B- and T- lymphocyte ontogeny is complex, and involves a multitude of genetic steps required to generate diverse and B- and T-cell populations to produce an expanded repertoire of immune cells prepared to contend with diverse antigenic exposures. These cells, at various stages of their development, undergo complex V(D)J recombination, IgV, or somatic hypermutation (SHM) and isotypic switching (refs. 1, 2; Fig. 1). SHM in fact represents a unique and intrinsic mechanism to “naturally” generate cellular diversity and heterogeneity. Through the process of affinity maturation, SHM diversifies B-cell receptors that are important in recognizing antigen, producing an armed immune system able to contend with a variety of challenges (Fig. 1). The mechanism of BCR diversification involves a process of controlled mutagenesis affecting the variable

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Figure 1. B and T lymphocytes naturally undergo “controlled” recombination SHM, leading to immunoglobulin diversity. ALL, acute lymphoblastic lymphoma; BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma.
regions of the immunoglobulin genes, a process that is restricted to the immune cells, that is, it does not produce heritable changes in the genome (2). During proliferation, the B-cell receptor undergoes the highest rate of somatic mutation seen anywhere in the body, approximately 10^5- to 10^6-fold greater than that seen across the rest of the genome (1, 2). These mutagenic events primarily involve single base substitutions, and to a lesser extent insertions and deletions, and occur at hypervariable regions of the DNA called “hot-spots.” A mistargeting of SHM during the germinal center reaction has been called “aberrant somatic hypermutation,” (ASHM) and has been invoked to explain mutations in important regulatory genes like tumor suppressor or proto-oncogenes. It has also been implicated in the pathogenesis of DLBCL (3). Thus, in lymphocyte biology, the concept of heterogeneity has many contexts. While a necessary and critical component of B- and T-lymphocyte biology, there is also the heterogeneity that comes with a desire to explain differences in behavior of similar diseases and differences in outcome. It is a process that naturally lends itself to splitting, and splitting, and more splitting. Although this process has provided deeper insights into pathogenesis (e.g., ASHM), the emergence of heterogeneity at so many different levels has created a conundrum as well. Will it ever be possible to conduct clinical studies on the increasingly smaller and smaller subsets of an already rare disease? Assuming we had all the right drugs, how long would it take to prove that treatment of one subtype differentially could make a difference?

Organized Heterogeneity: Development of Classification Systems

The evolution of classification systems is medicine’s attempt to organize heterogeneity. In the late 1960s, the tools were a microscope with dyes staining basic and acidic macromolecules, which produced a purely morphologic classification of lymphoma, based on only two descriptors: (i) cells were large or small and (ii) patterns of infiltration were either nodular or diffuse. As a result, the Rapport classification (4), in its simplest form, classified lymphoid malignancies simply as diffuse small cell, nodular small cell, and the like (Fig. 2). Not all that heterogeneous by today’s standards. Advances in immunology in the 1970s led to the recognition of cell surface proteins (in particular the clusters of differentiation, or CD markers), and the observation that with the more markers one could survey, diffuse small cell lymphoma (as an example) in fact consisted not merely of one homogenous entity, but many (5–7). The repertoire of cell surface markers vastly expanded both the number of possible diagnoses, and indirectly, the heterogeneity. Nonetheless, the standardization and routine integration of IHC staining techniques produced a quantum leap forward. IHC informed Karl Lennert (Kiel classification) and Lukes and Collins as they formulated a more sophisticated immunologic perspective of the lymphoproliferative malignancies, recognizing the importance of cell lineage (B- and T cells) in their classification system (5, 6). In the mid-1970s, the NCI convened a panel of experts to make sense of this daunting biologic heterogeneity, by focusing less on biology and more on clinical features. The NCI Working Group formulated a clinically based classification system that integrated all the original concepts, producing a more clinically oriented set of descriptors, dividing the lymphomas into low grade, intermediate grade, and high grade (8, 9). Low-grade lymphoid malignancies like diffuse small cell or nodular small cell lymphomas were recognized as very indolent, slow-growing disease (growing over months to years), whereas intermediate-grade lymphomas like nodular large cell or DLBCL were aggressive (growing over weeks to months), and if not treated promptly were fatal. Small noncleaved cell or lymphoblastic lymphomas were considered as high grade (growing over days to weeks). While not yet a biologically based classification system, the clinical behavior descriptor added yet another variable that needed to be considered as new ways to think about these diseases emerged (Fig. 2). The tools at this stage were comparatively simple: morphology, IHC, and clinical behavior. However, the insight and ability to synthesize and configure many apparently diverse lines of data were ingenious. These decades of focus by pathologists and clinicians still form the foundation upon which all future lymphoma classification systems are based (Fig. 3).

The recognition that every cancer is fundamentally a disease of aberrant gene expression, a genetic disease, has had a profound impact on our thinking. The ability to define new subsets of lymphoma based on very particular genetic events has become an essential component of all present-day classification systems. For example, the 11:14 translocation involving the immunoglobulin heavy chain gene promoter and cyclin D1 t(11:14), leads to accumulation of cyclin D1 and in pathognomonic of MCL. Likewise, the pathognomonic (14:18) translocation leads to accumulation of Bcl-2 in follicular lymphoma. These techniques produced yet another quantum leap in our thinking, lymphoma complexity, and as a result, heterogeneity. The routine integration of new tools in cytogenetics (FISH, comparative genomic hybridization) has helped rewrite the algorithms routinely used in subclassifying many subtypes of lymphoma.

The World Health Organization (WHO) and REAL (Revised European and American Lymphoma) classifications have emerged as the most current iteration in lymphoma subtype organization (10–12). These classification systems have synthesized all the available information on cellular morphology, tissue architecture, IHC, and cytogenetic and clinical features (Fig. 2 and Table 1). The WHO classification now recognizes about 65 different subtypes of lymphoma. In the United States, there are about 70,000 cases of non-Hodgkin lymphoma (NHL) per year. If these diseases were evenly distributed, that would mean there would only be about 1,000 cases of each type per year. In fact, two subtypes, DLBCL and follicular lymphoma, comprise about half of all cases, which leaves about 60 subtypes for the remaining 35,000 cases per year—making many subtypes of lymphoma incredibly rare orphan diseases. Many subtypes of lymphoma now have an incidence
measured in 1 to 3,000 cases annually in the United States. Although the heterogeneity in the disease as a whole has increased substantially over prior classification schemes, more recently we have seen an expansion of the heterogeneity seen in individual subtypes (Table 1). For example, DLBCL is now widely recognized as not one, but many different diseases.

With the advent of new and more sophisticated tools to interrogate the genome, has come new ways to reclassify many human diseases, and new opportunities to split still further. The most recent era of lymphoma classification is clearly focused on how to interpret gene expression profiling. The seminal observations by Alizadeh and colleagues from the NCI (13), as well as Shipp and colleagues from Boston (14), have opened a new door, changing how we view lymphoproliferative malignancies. Although under the microscope, the cells from a patient with DLBCL appear large, grow in a diffuse pattern, and all express the same profile of CD markers on their surface [CD19(+); CD20(+); PAX5(+); CD3(-)], some patients with a diagnosis of DLBCL will be cured, whereas others will succumb in short order. But how could patients with the same disease have such divergent outcomes? Yielding vivid differences on a heatmap, what appears indistinguishable under the microscope, gene expression profiling now reveals as obviously different. Although these techniques are not yet routinely available for clinical practice (though they will be soon), every patient and doctor now approach every case...
of DLBCL wanting to know where they fit in the lexicon of expression profiling. In the case of DLBCL, the NCI experience has emerged as the one most commonly referenced, though it is clear there are many valid ways to sort and classify gene expression profiles. Dunleavy and colleagues (15) report on the NCI gene expression profiling (GEP) experience in DLBCL, which has provided a biologic context that nicely separates differences in outcome seen in patients with DLBCL, based on ontogeny. Their approach, defining the disease based on the cell of origin (COO), has described all cases of DLBCL as being derived from the germinal center (GC), or postgerminal center, or activated B-cell type (ABC). A third type represents a smaller fraction, now known to represent primary mediastinal large B-cell lymphoma, a highly favorable subtype of DLBCL genetically closer to Hodgkin lymphoma than DLBCL. Now, through the filter of GEP, those patients with lymphomas derived from the GC exhibit a more favorable outcome, and have disease prominently defined by enrichment of cells with dysregulated Bcl-6, and other features indicative of marked epigenetic dysregulation like EZH2 (16). Those patients with DLBCL of the ABC subtype appear to have an inferior outcome, and have disease enriched for dysregulation of NF-κB signaling. This molecular classification of DLBCL is already leading to new translational efforts, allowing us to leverage the GEP data to inform us how to treat patients differently. Drugs such as ibrutinib, proteasome inhibitors, and lenolidomide appear to be more active in the ABC phenotype, and are now being integrated into upfront R-CHOP–based chemotherapy regimens in randomized clinical studies. In contrast, other studies have optimized histone deacetylase inhibitors to target the Bcl-6–p53 axis in GC-derived DLBCL with promising results (17). In this particular example, we have become more knowledgeable, as data and information from efforts in quantitative experimentation are translated into clinical studies. Although we
Table 1. Common lymphomas and their characterization

<table>
<thead>
<tr>
<th>Disease</th>
<th>ABC subtype</th>
<th>COO divides disease into GC, ABC subtypes, and PMLCL</th>
<th>Stromal microenvironment correlates with prognosis</th>
<th>Proliferation index (Ki67 surrogate) correlates with survival</th>
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<tr>
<td>DLBCL</td>
<td>COO</td>
<td>Molecular classification</td>
<td>Cytogenetic features</td>
<td>Diffuse effacement of nodal architecture</td>
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<td>Follicular lymphoma</td>
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<td>MCL</td>
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<td>Marginal zone lymphoma</td>
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still need the results of the randomized studies under way, in my opinion, the process is likely to represent a major step forward in our quest to cure all patients with DLBCL.

The advances in classification, while remarkable, represent only a portion of the advances in lymphoma therapy in recent years (Fig. 3). In this CCR Focus, five world-renowned groups provide insights on how our concepts in basic biology are being translated into practical treatment strategies, approaches that represent marked departures from the “one-size-fits-all” model of the past. Using the GEP profiling experiences from the NCI as a platform, Dunleavy and colleagues (15) outline a path in which the molecular classification of DLBCL based on the cell of origin (COO) model is being used to define molecular phenotypes of the disease, phenotypes that appear to exhibit a differential sensitivity to many of the newer drugs now in development. The ABC subtype of DLBCL, for example, appears to be sensitive to agents targeting the Bruton tyrosine kinase (BTK) and immunomodulatory drugs, which when combined with upfront treatment platforms like R-CHOP, produce remarkably high response and complete response rates, concepts now being vetted in international randomized phase III studies. In a similar manner, Dreyling and colleagues (18) have shown that a disease like MCL, historically thought of as one of the most challenging lymphomas, is in fact a disease that exhibits a broad spectrum of behavior. This behavior is tightly linked to its proliferation index, with patients having the higher proliferation rate exhibiting the worse outcome, whereas those with low proliferation indices exhibit a highly favorable outcome. Remarkably, patients with a low index may require nothing more than a “watch-and-wait” approach, whereas patients with a high index could require an autologous stem cell transplant. This is a perfect example of how the heterogeneity within a particular subtype is influencing treatment decision making. Patients with the same histologic subtype of the disease can be managed by two extremes in care. Zucca and colleagues (19) and Tsukasaki and Tobinai (20) introduce the notion that many subtypes of lymphoma are actually caused by infectious agents, and that controlling or eradicating the infectious etiology can be a very effective way to treat the malignant disease. Zucca and colleagues (19) underscore the casual relationship between the many known etiologic agents linked to marginal zone lymphomagenesis, and the heterogeneous nature of that disease based on the infectious agent, and the underlying genetics of the lymphoma. It is the underlying genetic nature of the disease that defines those patients likely to benefit from antibiotic therapy. In similar fashion, human T-cell lymphotropic virus type I (HTLV-1) causes adult T-cell leukemia–lymphoma (ATL). Tsukasaki and Tobinai (20) provide a detailed update on the epidemiology of HTLV-1, and share data demonstrating that measures to control HTLV-1 have led to a reduction in the malignant disease. Just as importantly, CC chemokine receptor 4 (CCR4), a protein expressed on the surface of ATL cells, can now be targeted by a newly developed defucosylated humanized anti-CCR4 monoclonal antibody (mogamulizumab), which has...
in which chemotherapy may not be required. Of course, in diseases where there is little consensus on a standard of care, it is easier to design such studies. In the case of follicular lymphoma, the second most common subtype of lymphoma, Bachy and Salles (21) provide interesting insights into how the treatment of this disease will change over the next few years. The emergence of new monoclonal antibodies, antibody drug conjugates, immunomodulatory drugs, and more pathway-targeted agents such as BTK inhibitors, PI3K inhibitors, and B13 only mimetics, could create successive lines of therapy that allow the practitioner to manage follicular lymphoma as a chronic illness, with drugs exhibiting a safety profile that might allow longer periods of administration. Although there may be important synergetic interactions with these newer agents and classic DNA-damaging drugs or topoisomerase inhibitors, new regimens with new components are moving us away from the standard CHOP backbone. Certainly, in such diseases as double-hit lymphomas and many subtypes of peripheral T-cell lymphoma, it is likely that new non–CHOP-predicated backbones will emerge here first.

Second, how do we move toward a more personalized or precision focused model of lymphoma care? Irrespective of the incremental improvement that may result when the data from the randomized studies reported, not everyone in the more favorable treatment cohort will be cured, and not everyone in the unfavorable treatment cohort will succumb. Not every patient with GC-derived DLBCL does well, nor does every patient with ABC-derived DLBCL do poorly. Not every patient with low Ki-67 MCL has indolent disease. About 20% of patients with follicular lymphoma do not have indolent disease, and exhibit patterns of continued rapid relapse and succumb within a couple of years of diagnosis. The exceptions to the treatment outcome or natural history reflect what we do not know about the signaling networks, what we do not appreciate when we try to resolve the heterogeneity by creating "cleaner" subgroups. To solve the exception, one approach would be to continue the splitting, refining at smaller and smaller levels the subset of the subset, until we figure it out for every patient. This would be a time-consuming endeavor. Alternatively, we can try alternative views of complex data, by distilling out irrelevant heterogeneity in an effort to identify unifying concepts.

So, finally, what unifying concepts might allow us to move forward without addressing every pathogenetic event separately? Just how does the tumor cell respond to the imposed therapy, and how do the responses of the cell to the new stressor differ between favorable-risk and unfavorable-risk patients? The notion of “one disease (or phenotype of)–one target–one drug” ignores the idea that the cell is a dynamic complex system of many interacting pathways, pathways that may respond differently to new stressors, depending on the intrinsic genetic subtleties of that particular cell. Inhibiting BTK does not produce an effect on the cell in a vacuum; it stimulates changes in a host of pathways that interface with the targeted pathway, responses that can vary in different cells from the same tumor. In some cases,
those responses may mediate the emergence of a drug-resistant clone, whereas in others, it may result in cell death. These types of descriptors (BTK level, PI3K activity, etc.) that we are now targeting in a therapeutic fashion are all diagnostic; they represent characterizations of the disease before we treat. They importantly do not reflect the phenotype of disease left after initial treatment, nor does it provide insight into the biologic response of the disease to the imposed treatment. Obtaining serial biopsies shortly after treatment and interrogating the cellular responses in the context of the larger cellular interactome are likely to shed light on the mechanisms of resistance or sensitivity, and are likely to refine our ability to more precisely ascribe the most appropriate therapy to the right patient population.

The phenotypes of cancer cell behavior we see in patients do not arise from single genes or isolated molecular events. The phenotypes we see in patients arise from the function of hundreds or thousands of macromolecules like proteins, DNA, RNA, microRNA, carbohydrates, which themselves all interact in complex regulatory networks, some of which undergo complex and critical posttranslational modifications. It is the cascade of biologic functions mediated by interacting networks that produces the behavior of cancer in any given patient. The identification of a singular gene influence or impact of the latest mutation, albeit contributing factors, obviously should not be viewed in isolation. It may seem an insurmountable enterprise, but how does one understand the impact of all these interactions at the level of the protein:protein or protein:nucleic acid level, at the genomic level, or at the epigenetic level? The answer is to take a broader “systems” level view of the biology (22–24). Systems biologists provide a holistic view of cancer by integrating genetics, signaling networks, epigenetics, proteomics, metabolomics and the like, they attempt to synthesize all the information, which to the naked eye might seem to be disjointed information. They attempt to reduce the heterogeneity, or perhaps reconfigure it, by trying to find the similarities. Systems biology provides us with the unique ability to integrate detailed data stemming from quantitative experimental analysis through the use of mathematical models and computational analysis. These holistic approaches leverage many seemingly divergent lines of data and reorganize the information in a fashion that places an emphasis on defining larger regulatory networks, reducing the heterogeneity, and defining the principles of the cells’ larger interactome. An approach that may take us full circle.

It is a remarkable accomplishment to be able to say that we have changed the natural history of not just one, but several malignant diseases in such a short period of time. In some corners, our community continues to struggle with persistent challenges in lung, colorectal, and pancreas cancer, as well as acute myeloid leukemia, looking to demonstrate even modest improvements in progression-free or overall survival. Some drugs in these settings have been approved based on survival benefits measured in weeks to months. What has occurred in the lymphoid malignancies over this period has been extraordinary (Fig. 3). Over the past 20 years, we have watched MCL move from a disease with a life expectancy measured in 3 to 4 years, to one that might in fact be curable in 2014. Through appropriate patient selection, many of these patients may be able to avoid intense cytotoxic therapy and their cancer may be manageable as a chronic disease. We have seen some forms of marginal zone lymphoma cured with antibiotic therapy, and now we recognize the molecular phenotypes associated with eradication of a malignant disease by treating an underlying infectious etiology. We have watched a disease like follicular lymphoma, a disease with a median life expectancy of 7 or so years when the original Stanford data were released by Dr. Horning, become a disease where we do not know, with over 15 years plus of follow-up, where the median life expectancy might end up in our new era of treatment. A disease changed by essentially one drug, a CD20-targeted monoclonal antibody. And now, most discussions around future management of follicular lymphoma do not include conventional chemotherapy components.

We have watched as gene expression profiling has distilled the heterogeneity seen in a disease like DLBCL. Clinical trials exploring the merits of adding new targeted drugs to standard backbones are reporting overall response rates between 90% and 100%, and appear to be more active in the prognostically worse phenotypes of the disease. Randomized studies exploring R-CHOP ± ibrutinib, new monoclonal antibodies with improved ADC, immunomodulatory drugs such as lenalidomide, and NF-κB–targeted drugs such as bortezomib, are appearing at a rapid rate. Even in a forgotten disease like PTCL, four new drugs have been approved over the past 4 to 5 years, where none had been approved over the previous 50 years (Fig. 3; refs. 25–27). Despite its rarity, four new randomized studies are under way in PTCL for the upfront setting. We are more knowledgeable, and new scientific concepts are being translated at a remarkably efficient pace. Yes, there are still important areas for improvement. We can do better by trying to identify biomarkers of response, so that we can carefully select our patients for a given therapy. We can do better in understanding the network responses of a cancer cell to a drug therapy, and use that information to prevent the emergence of drug resistance. And, of course, we can do better by collaborating with colleagues across the disciplines of biology, chemistry, mathematics, and statistics, identifying fresh new ways to interpret the diverse lines of information. Although the progress has been no less than stunning, our job is done only when each and every patient we see can be rest assured that every lymphoma is a good lymphoma.

Conclusions

Clearly, dissecting the similarities and differences in “lymphoma” behavior both among patients and between discrete entities has led to a natural splitting of subtypes. This splitting has allowed us to see more clearly those factors driving the misbehavior of these malignant cells, and how best to target its molecular roots. Our succeeding articles will share the latest perspectives on how biologic discovery in particular subtypes of lymphoma is being translated into novel concepts in care, paradigms that are changing the long-standing natural history of many lymphoma entities.
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No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: O.A. O'Connor, K. Tobinai
Development of methodology: O.A. O'Connor
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O.A. O'Connor
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.A. O'Connor, K. Tobinai
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