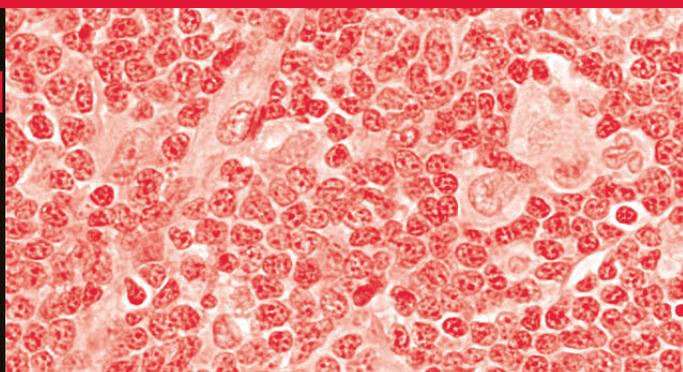
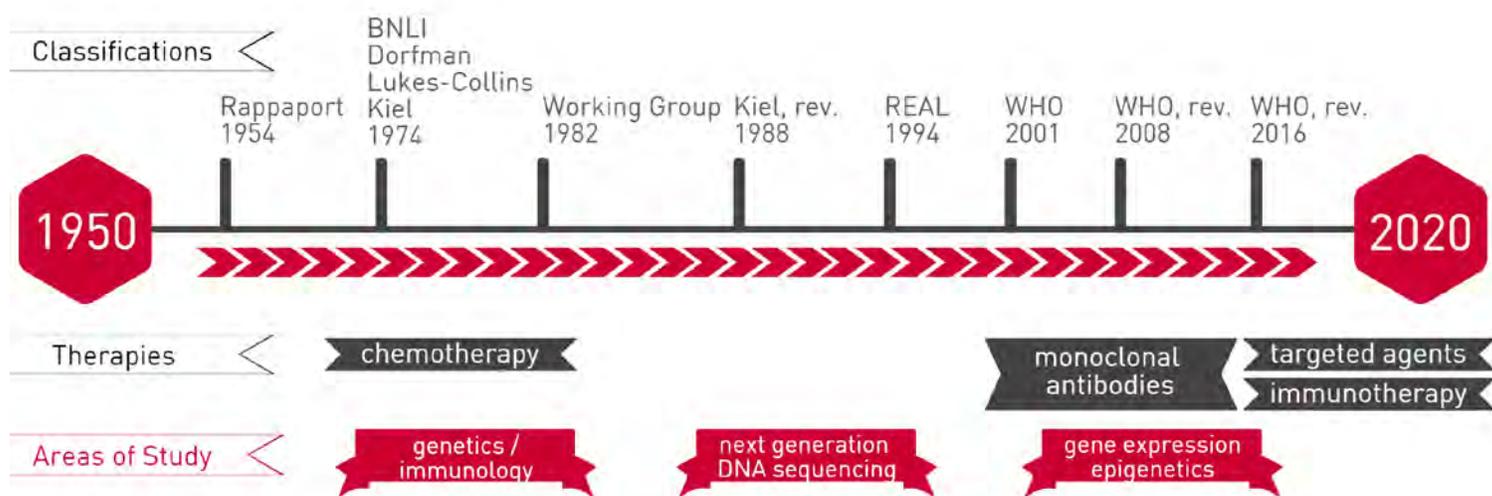


# RESEARCH Report



## Research Advances Drive Revisions to WHO Classification for Lymphoma



Classifications for lymphoma (top), have developed to keep pace with new therapies (in gray), and new ways of studying the biology of lymphoma (in red).

**B**efore diseases can be diagnosed, treated, or studied with any effectiveness, they must be named, defined, and described with definitions and terminology that are largely agreed upon by the medical community. Classifications of disease are intended to identify clearly defined and clinically distinctive forms of a general disease that together comprises all known entities of that disease. In lymphoma, this means a classification which identifies all known forms of lymphoid neoplasms, which are

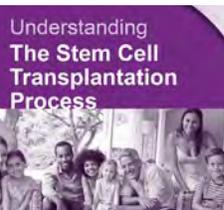
the diseases which derive from clonal expansion (production of multiple cells from a single cell) and proliferation of B- and T- lymphocytes specifically.

First published in 2001, the World Health Organization (WHO) classification of the lymphoid neoplasms have helped establish such guidelines for the diagnosis of malignant lymphomas. The WHO classification seeks to identify common clinical, pathological, and genetic characteristics of homogeneous groups

of lymphomas, or subtypes, with both common and rare groups included. Following a revision of the original classification in 2008, a second revision including recognition of new stratifications of disease, particularly in B-cell lymphomas, has been released in 2016.

A crucial tool in diagnosing lymphoma and guiding patient treatment, the WHO classification is also a testament to how advances in research contribute to further

[CONTINUED ON PAGE 2]



Understanding  
The Stem Cell  
Transplantation  
Process

**FEATURED IN THIS ISSUE: Advancing The National Conversation on Lymphoma**

**Page 4**

The Lymphoma Research Foundation has released several new publications and educational resources to promote discussion and education around key topics in lymphoma research and treatment.



Dear LRF Friends and Supporters,

Each autumn the Lymphoma Research Foundation turns its focus to Blood Cancer Awareness Month and the multitude of programs and new Foundation initiatives launched across the country. As part of our Blood Cancer Awareness Month campaign this September, the Foundation hosted a Twitter chat featuring representatives from the Food and Drug Administration's (FDA) Office of Hematology and Oncology Products; launched an innovative online resource for patients with diffuse large B-cell lymphoma; and published a first-of-its-kind patient guide for those considering transplantation as a treatment option. LRF's scientific and clinical meetings also continue to make an impact in the field: a number of Foundation-led scientific workshops have recently published white papers and academic articles, including a publication in the prestigious journal *Blood*. Details on these and other resources related to the Foundation's ongoing work in advancing the conversation on lymphoma research may be found on page 4.

The advent of fall also marks the end of the busy summer conference season. This year, both the Annual Meeting of the American Society of Clinical Oncology and the Congress of the European Hematology Association featured research from several Foundation Scientific Advisory Board (SAB) members and grantees. Highlights from both of these conferences can be found in News from the Field on page 6. In addition, the World Health Organization (WHO), through a committee which included many Foundation SAB members and grantees, released a revision of its classification of lymphoid neoplasms. The 2016 revision reflects recent scientific advances in the understanding of lymphoma, several of which are reflected in Foundation-funded research. Our story on the WHO classification and its implications for patient treatment begins on page 1.

As always, it is the efforts of our donors, volunteers, and scientific advisors that fuel our work to support innovative lymphoma research and bring these advancements to people with lymphoma and CLL. Thank you for all you do in support of our shared mission to eradicate lymphoma and serve those touched by this disease.

Sincerely,

A handwritten signature in black ink, appearing to read 'Meghan Gutierrez', written in a cursive style.

Meghan Gutierrez  
Chief Executive Officer

## WHO Classification

[CONTINUED FROM PAGE 1]

refinement of our understanding of lymphoma. This article offers a brief overview of the history of lymphoma classification, a look at how the 2016 revisions correlate with research funded by the Lymphoma Research Foundation, and potential implications for patients.

### Lymphoma Classification: A Complex History

The 2016 classification, though accepted in a true consensus throughout the international medical community, is the most recent result of decades of work to establish a standard definition of the various types of lymphoma and its treatment. Although

Hodgkin lymphoma (previously Hodgkin Disease) was identified in 1832 and officially named in 1865, identification and acceptance of non-Hodgkin lymphoma (NHL) was far more complicated. Prior to 1975, classifications proposed by various researchers (most significantly Rappaport's classification of NHL in 1956), relied solely on morphology, or the form and structural features, of lymphoma tumors. As researchers developed an understanding of immunology and genetics in the late 1960s and 1970s, a divide began between those who wanted to continue using morphology alone for classifications and those who advocated for moving to a functional approach that looked not at physical morphology but the cellular morphology of a given tumor and its relationship to cells of a normal peripheral lymphoid system.

## WHO Classification

[CONTINUED FROM PAGE 2]

In 1974, four different classifications divided along these two approaches were published, including the Lennert-Kiel classification, which advocated the functional approach. A meeting convened by the National Institutes of Health (NIH) with clinicians and hematopathologists who had proposed classifications reached no consensus.

In 1982, the National Cancer Institute of the NIH developed the working formulation classification (also called “working group”) as a way of translating among the different existing classification systems. This classification found a broader consensus among researchers, particularly in the United States, and was followed in 1994 by the Revised European-American Lymphoma (REAL) classification, developed by the International Lymphoma Study Group (ILSG). The REAL classification mitigated some of the controversy over lymphoma classification by noting that each listed disease was defined by a combination of morphology, immunophenotype, genetic features, and clinical features, and that the importance of these features could vary depending on the disease type. The effectiveness of the classification was backed by an international study of 1300 patients, which demonstrated that expert pathologists using the REAL classification consistently identified disease type in lymphoma patients with a better than 85 percent success rate, with 27 percent of the cases identified belonging to diseases that were not recognized in the Working Formulation, accompanied by marked improvements in survival for those cases.

Building on this success, the European Association of Pathologists (EAHP) and the Society of Hematopathology (SH)

began developing a new classification under the auspices of WHO. The first version of the WHO Classification of Lymphoid Neoplasms, released in 2001, updated the REAL classification and introduced the idea of a conceptual grouping of NHL subtypes into four categories (indolent, localized indolent, aggressive, and highly aggressive). Around this time, DNA microarrays and other new technologies allowed researchers to gain more insight into how molecular genetics distinguished one lymphoma from another. The continued advance of technology prompted both the revision of the WHO classification in 2008, and the revision released in 2016.

### Research Advances Lead To Classification Revisions

In a monograph published in *Blood* to explain the revisions, the authors, including Lymphoma Research Foundation Scientific Advisory Board (SAB) members Ranjana Advani, MD of Stanford University and Andrew D. Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center, past SAB member Elaine S. Jaffe, MD of the National Cancer Institute, and Foundation grantee Elias Campo, MD, PhD of the August Pi I Sunyer Biomedical Research Institute (IDIBAPS), noted that the 2016 revision reflects an “explosion” of new data thanks to technological advances such as next-generation sequencing and genomic studies. This data has led to better diagnosis and biological understanding particularly in small B-cell lymphoid neoplasms, although T- and NK-cell neoplasms and Hodgkin lymphoma have also seen new research identify subgroups of common biomarkers and clinical features. “The 2016 WHO classification and associated monograph aim to provide updated diagnostic categories and criteria,

together with biological and clinical correlates, and facilitate state-of-the-art patient care, future therapeutic advances, and basic research in this field,” the *Blood* article concludes.

Among the research advances cited in the classification monograph as prompting revisions are several discoveries which correlate to research funded by the Lymphoma Research Foundation. A significant change in diffuse large B-cell lymphoma (DLBCL) is the requirement that all DLBCL diagnoses specify either germinal center B-cell like (GCB) or activated B-cell-like (ABC) subtype DLBCL. This new sub-classification is due to additional research which has explored the molecular pathogenesis of the two subgroups as well as developed better tests for the distinct mutations associated with each.

One researcher working specifically on ABC-DLBCL is 2014 Foundation Postdoctoral Fellowship grantee Joseph Dekker, PhD of the University of Texas at Austin. Dr. Dekker has been studying the FOXP1 mutation, which is specific to ABC-DLBCL, through his Foundation-funded research; results of his work to define FOXP1 pathways within DLBCL and to develop a mouse model through which potential therapies for this subtype can be tested in the lab, were published in the *Proceedings of the National Academy of Sciences* (PNAS) in February of 2016. 2013 Postdoctoral Fellowship grantee Lorena Fontan Gabas, PhD of Weill Cornell Medicine, investigated a separate pathway, MALT1, in ABC-DLBCL, and together with her mentor, Scientific Advisory Board member Ari Melnick, MD, has received NIH funding to further investigate this pathway for potential therapies.

Germinal center B-cell lymphomas,

[CONTINUED ON PAGE 8]

## Foundation-Sponsored Programs and Resources Advance National Conversation on Lymphoma

Every year, alongside the progress made by its grantees and Scientific Advisory Board (SAB) members in their research, Lymphoma Research Foundation (LRF) scientific and education programs continue to gain momentum. The communication of new research findings and knowledge about the treatment of lymphoma, as well as discussions about issues affecting both research effectiveness and patient outcomes is a vital component of the Foundation's research portfolio and programs. This year in particular has marked significant progress in the advancement of the conversation on lymphoma research, with the release of several new publications and LRF resources, ranging from academic publications to a new disease-specific website for patients and caregivers.

The Foundation's scientific workshops, though convened for an audience of primarily healthcare professionals, often result in outcomes which have an impact on patient treatment. *Blood*, one of the premier academic journals for hematologic malignancies, recently published a paper based upon the findings of a 2015 LRF workshop, Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents, which was co-hosted with the Cancer Research Institute. The workshop was convened to address a phenomenon called tumor flare or pseudo-progression, which can occur with patients on the checkpoint inhibitor class of immunotherapies, causing the appearance of progressive disease when the patient is actually responding to treatment. The paper reflects the recommendations of the workshop to modify existing response

criteria so patients aren't removed from a checkpoint inhibitor earlier than necessary due to a tumor flare. (For more on the workshop and this issue, see the ASH 2016 issue of Research Report.) "Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy" authored by Foundation Scientific Advisory Board members Bruce Cheson, MD, FACP, FAAAS of Lombardi Comprehensive Cancer Center and Georgetown University, Stephen Ansell, MD, PhD of Mayo Clinic, Leo Gordon, MD, FACP of Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Ranjana Advani, MD of Stanford University Medical Center, and Workshop committee members Larry Schwartz of Columbia University, Heather Jacene and Philippe Armand of Dana-Farber Cancer Institute, Alex Hoos of the Cancer Research Institute, and Sally F. Barrington of King's College London, is currently available in preprint on *Blood's* website.

Other scientific workshops hosted by the Foundation in the past academic year are seeing outcomes from their programs make their way into publication. "Oral Therapies in Lymphoma: Opportunities and Challenges in Research Treatment," a white paper proceeding from the 2015 Foundation workshop of the same name, was released in early 2016 and is available to download on the Foundation website. This pivotal publication draws attention to the myriad of related policy and scientific issues which face the lymphoma and CLL community. LRF is proud to be leading the way in efforts to ameliorate these challenges, such as advocacy for federal legislation which ensures parity for reimbursement of these therapies. Papers addressing the proceedings of the

LRF Adolescent/Young Adult Lymphoma Research Symposium, co-sponsored by The Paul Foundation in September 2015 and the 2016 MCL Scientific Workshop, held this past April, are also in process. Links to all papers from the Foundation's scientific programs are posted on the Foundation's website at [lymphoma.org/researchcommitment](http://lymphoma.org/researchcommitment) when they are made available to the public.

Advancing the national conversation can also extend to social media, as evidenced by the return of the Foundation's successful and popular Twitter chats. As part of September's Blood Cancer Awareness Month activities, the Foundation was proud to host the first Twitter chat to include representatives from the U.S. Food and Drug Administration (FDA) Office of Hematology and Oncology Products and Health and Constituent Affairs. The hour-long chat with Drs. R. Angelo de Claro and Yvette Kasamon of the FDA provided members of the lymphoma community the opportunity to learn and ask questions about the FDA's breakthrough designation process, Patient Representative Program, patient access to clinical trials, and new lymphoma therapies. The hashtag #FDALRFChat reached more than 200,000 Twitter users and received nearly 1.5 million impressions during the chat hour. The Twitter chat is available on LRF's Storify at: <https://storify.com/lymphoma/2016-fdalrfchat>.

The next Twitter chat will take place during the North American Education Forum on Lymphoma, featuring SAB member and immediate past Chair John Leonard, MD, of Weill Cornell Medicine (see page 5 for details).

September 2016 also witnessed the launch of FocusOnDLBCL.org, the Foundation's seventh disease specific website, providing information to diffuse large B-cell lymphoma patients and their caregivers. FocusOnDLBCL.org is a part of the Foundation's Focus On Series, which includes dedicated websites for anaplastic large cell lymphoma (ALCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), Hodgkin lymphoma (HL), mantle cell lymphoma (MCL), and peripheral T-cell lymphoma (PTCL). These sites provide diagnostic information, treatment options, and free resources, including the opportunity to register for disease-specific electronic newsletters. "The Lymphoma Research Foundation's disease-specific Focus On websites enable patients and their loved ones to easily access comprehensive content based on their specific lymphoma subtype," said Peggy Ann

Torney, the Foundation's Chief Strategy, Communications and Engagement Officer. "The Foundation is proud to now offer a site dedicated to diffuse large B-cell lymphoma, the most common type of non-Hodgkin lymphoma."

As stem cell transplants become an increasingly common treatment option for several lymphoma subtypes, the Foundation has added "Understanding the Stem Cell Transplantation Process," a patient guide, to its roster of free patient education resources. Last year, the Foundation distributed nearly 100,000 of its publications, which address a wide variety of subtype and topic specific information. The publications can be ordered via [lymphoma.org/publications](http://lymphoma.org/publications) or through the patient helpline at 1-800-500-9976. Healthcare professionals wishing to make these resources available to their patients may also request the

booklets themselves or copies of the Foundation's publication order form.

"The rapid pace at which novel therapies are developed and new discoveries about lymphoma biology are being made makes it crucial for entities like the Lymphoma Research Foundation to provide resources which enable patients and professionals to remain engaged with the latest developments in the field," notes Meghan Gutierrez, the Foundation's Chief Executive Officer. "The Foundation continues to develop our portfolio of educational resources and scientific publications to provide the most accurate information and a comprehensive overview of the current research and treatment landscape."

**LYMPHOMA**  
RESEARCH • FOUNDATION

**#EdForumChat**  
**Saturday, October 29**  
**@12:45 pm CT**

Ask one of the world's leading lymphoma experts questions about the disease, treatment options and lymphoma research during the Annual North American Educational Forum on Lymphoma.

[lymphoma.org/twitterchat](http://lymphoma.org/twitterchat)

**FEATURING:**

**DR. JOHN P. LEONARD**

Meyer Cancer Center  
Weill Cornell Medical College  
New York-Presbyterian Hospital  
**@JohnPLeonardMD**

**TO JOIN THE CONVERSATION**

Use **#EdForumChat** and follow  
**@JohnPLeonardMD** and **@lymphoma**



## News from the Field: Summer 2016 Conferences

Summer 2016 saw several major medical research conferences present findings in lymphoma research. This expanded News from the Field highlights presentations from two of the largest hematology/oncology meetings: The American Society of Clinical Oncologists' (ASCO) Annual Meeting, and the European Hematology Association (EHA) 21st Annual Congress.

### ASCO

The 2016 ASCO Annual Meeting is one of the largest oncology conferences in the world, with nearly 40,000 attendees from across all cancer types. This year's meeting took place June 3-7 in Chicago, Illinois.

Foundation Scientific Advisory Board (SAB) Member Thomas E. Witzig, MD of Mayo Clinic, Rochester, presented the results of the PILLAR-2 study, a randomized, double-blind phase III study of everolimus in patients with poor-risk DLBCL. Investigators hoped to use everolimus, an mTOR inhibitor, to reduce the risk of relapse in patients with poor prognosis scores who achieved a complete remission with rituximab+chemotherapy. 742 patients enrolled in the study were randomly selected to receive either everolimus or a placebo for one year or until relapse or other adverse event. Dr. Witzig and his colleagues found that there was no overall improvement in disease free survival of the everolimus arm over the placebo, but there was a slight improvement in both overall survival and lymphoma-specific survival in the full group, as well as for disease free survival in patients with particularly poor-prognosis scores. The results suggest that particularly high-risk DLBCL patients may benefit from

everolimus; researchers recommended further investigation.

**A**nas Younes, MD, a Foundation SAB member from Memorial Sloan-Kettering Cancer Center, presented data from CheckMate-205, a trial of single-agent nivolumab (Opdivo) in classical Hodgkin lymphoma who had relapsed following transplant (ASCT) and brentuximab vedotin (Adcetris). Dr. Younes presented data from the relapse arm of the trial, including 80 patients who had relapsed after ASCT and brentuximab vedotin, with 54 percent of those patients not responding at all to the therapy. Overall response rate with a median follow-up of 8.9 months was 66 percent, including a complete response rate of 8.8 percent and a partial response rate of 57.5 percent. 62 percent of patients remained in response at the time of data collection, with 18 additional patients (23 percent) in stable disease. Data from this trial was cited by the FDA when nivolumab was granted an accelerated approval for relapsed cHL in May 2016.

**C**hristian Grommes, MD of Memorial Sloan-Kettering Cancer Center, presented a poster of a phase I study of ibrutinib (Imbruvica) in relapsed/refractory primary and secondary central nervous system lymphoma (PCNSL and SCNSL). Dr. Grommes, who received a Career Development Award from the Foundation in 2013 for additional research in CNS lymphomas, which occurs as an aggressive brain tumor and has poor outcomes and treatment options for patients who relapse. Of the nine patients evaluated, four achieved complete remission and three achieved partial remission, for a 78

percent overall response rate. Median progression free survival was six months. Dr. Grommes and his colleagues are continuing to enroll patients in an expansion cohort for this trial, but note that this may open targeted agents as an alternative therapeutic approach for this patient population.

### EHA

The annual Congress of the European Hematology Association (EHA), held June 9-12 in Copenhagen, Denmark, is the premier hematology conference in Europe, attracting researchers from all over the world.

**T**hree LRF Scholars, participants in the Foundation's Lymphoma Clinical Research Mentoring Program (LCRMP), presented posters at EHA. 2015 Scholar Danielle Brander, MD, of Duke University, presented a study of venetoclax (Venclexta), a BCL-2 inhibitor, in combination with rituximab for CLL/SLL. 49 patients enrolled in the study, with 47 percent achieving complete response and an overall response rate of 86 percent. Dr. Brander and her colleagues noted that seven patients who reached minimal residual disease and stopped treatment are still maintaining remission with a median follow up of 8 months. The findings suggest that venetoclax, which was approved by the FDA for relapsed CLL with 17p deletion in April 2016, may be even more effective in combination with rituximab.

**F**ellow 2015 Scholar Carla Casulo, MD, of the University of Rochester, presented preliminary results of the

[CONTINUED NEXT PAGE]

## News from the Field

[CONTINUED FROM PAGE 6]

CONTEMPO study, evaluating the safety and efficacy of duvelisib in combination with either rituximab (DR) or obinutuzumab (DO) in untreated CD20+ follicular lymphoma. The twelve patients treated in the first part of the study were evenly split between the DR and DO regimens, with no serious adverse events reported on either arm. Both arms continued to the second part of the study, which is ongoing.

**A**lex F. Herrera, MD of City of Hope, a 2016 Scholar, presented a study evaluating the prognostic impact of double-hit (DHL) and double-expression (DEL) on DLBCL patients who undergo stem cell transplant. DHL and DEL lymphomas occur when a patient's lymphoma tumors exhibit mutations on two significant genes, rather than the single mutation found in most tumors. Dr. Herrera and his colleagues looked at patients undergoing stem cell transplant between 2000 and 2013 with either relapsed/refractory DLBCL or transformed indolent lymphoma, who had DHL or DEL status due to mutations on their MYC and BCL2/BCL6 genes. They found both DEL and DHL status resulted in inferior progression free survival and overall survival particularly in autologous SCT, with 44 percent of patients achieving four-year progression free survival compared to 61 percent in the single hit group. The researchers also noted that allogeneic transplant also seemed to have a worse outcome but the sample size was not large enough for a definitive conclusion. The study highlights the need for further investigation into therapeutic options beyond current standard therapies for the DHL/DEL population.

**M**artin Dreyling, MD, PhD, of Ludwig Maximilian University of Munich and a member of the Foundation's Mantle Cell Lymphoma Consortium Executive Committee, presented a poster with the results of a study of copanlisib in relapsed/refractory NHL or CLL. Copanlisib, a PI3K-inhibitor currently being tested in both the U.S. and Europe, has shown promising activity in early clinical trials. Dr. Dreyling and his colleagues tested 20 patients with indolent NHL, 13 with CLL, and 48 with aggressive NHL, with a median of three prior therapies (80 percent of patients had received rituximab). At the time of reporting, the overall response rate was 47 percent for the full group; MCL patients reported a 64 percent response rate with two complete responses and five partial responses, while FL patients reported a 40 percent response rate with three complete responses and stable disease in 53 percent of patients. Based on the encouraging response rate and activity, researchers are conducting ongoing phase II studies of copanlisib in FL, MCL, and DLBCL.

**O**wen O'Connor, MD, PhD of Columbia University Medical Center and an SAB member, presented a poster integrating the results of two recent studies of TGR-1202, a PI3K inhibitor that has exhibited lower toxicity than other therapies in its class. It is currently being studied in hematologic malignancies both as a single therapy and in combination with a CD20 monoclonal antibody, ublituximab. Dr. O'Connor and his colleagues analyzed the data of 112 lymphoma patients across the single agent and combination



*Martin Dreyling, MD PhD of Ludwig Maximilian University of Munich, at the May 2016 MCL Scientific Workshop*

studies for adverse events and found a markedly lower rate of serious side effects, with only eight percent of patients discontinuing treatment due to high grade adverse events. Of the 74 NHL patients that could be evaluated for efficacy, the overall response rate was 48 percent for indolent NHL, with 11 percent complete responses and 24 percent for aggressive NHL with 8 percent complete responses; the researchers further noted that the combination therapy was notably more effective, with a 71 percent overall response/24 percent complete response in indolent NHL and 32 percent overall response/ 16 percent complete response in aggressive NHL. Dr. O'Connor noted that a phase 3 trial for the combination therapy is ongoing in patients with CLL and studies in DLBCL and indolent NHL are planned.

*For more research news, visit [lymphoma.org/researchnews](http://lymphoma.org/researchnews).*

## WHO Classification

[CONTINUED FROM PAGE 3]

including GCB-DLBCL, have also been investigated by a number of Postdoctoral Fellowship grantees, including 2015 awardee Martin Rivas, PhD and 2016 awardee Pilar Dominguez Rodriguez, PhD both of Weill Cornell Medicine, as well as 2014 awardee Feilong Meng, PhD of Shanghai Institutes for Biological Sciences, who received his award while at Children's Hospital Boston and Harvard University. While Dr. Rivas and Dr. Dominguez Rodriguez's projects are ongoing, Dr. Meng was first author on a paper revealing the early results of his research in the journal *Cell* in December 2014. Dr. Meng's project investigated the Activation-Induced cytidine Deaminase (AID) protein, which ordinarily initiates immune response, and its role in causing the mutations that lead to germinal center B-cell lymphomas. Representing just a portion of the research being done in this area, the Foundation's Postdoctoral Fellows working in DLBCL illustrate how the growing body of knowledge on the specific biology of both ABC- and GCB- DLBCL led the WHO committee to advocate for further specification in DLBCL diagnoses.

The WHO revisions also cite several biomarkers and genetic mutations that can now be considered prognostic markers in specific lymphomas, several of which have been studied by Foundation-funded researchers. The mutation CCND1, or cyclin D1, mentioned as a frequent mutation in MCL, was studied by 2010 MCL Planning Grant awardee Jose Angel Martinez-Climent, PhD, of the Center for Applied Medical Research in Navarra, Spain. The mutation EZH2, cited as common to follicular lymphoma, was central to the Foundation-funded project of 2014 Postdoctoral Fellowship awardee Rui Lu, PhD, of the University of North Carolina at Chapel Hill. SAB

member John Chan, MD, of City of Hope Medical Center, received two Follicular Lymphoma Pathways grants, in 2009 and 2011, to investigate the common genetic abnormalities in follicular and transformed follicular lymphoma; his findings correlate closely with the most common genes cited by the WHO Classification, including CREBBP, EZH2, BCL2, and MEF2B.

The 2016 revisions also reflect what the *Blood* monograph authors call "the growing conservatism in lymphoma diagnosis," particularly as it involves the less aggressive forms of the disease. Both in situ mantle cell lymphoma (MCL) and in situ follicular lymphoma (FL), indolent forms of their respective diseases, have been renamed in situ follicular neoplasia (ISFN) and in situ mantle cell neoplasia (ISMCN). Though ISFN is more common than ISMCN, the renaming is an attempt to truly distinguish these low-grade diseases, which most commonly are observed rather than receive immediate treatment (also known as "watch and wait"), from the more aggressive FL and MCLs. The revisions also recognize that MCL has two indolent varieties: classical MCL, which develops in the lymph nodes and expresses the protein SOX11, and leukemic nonnodal MCL, which develops in extranodal sites such as the spleen and bone marrow, and generally develops from mutated cells that do not express SOX11.

The *Blood* monograph cites multiple publications authored by Elias Campo, MD, PhD of the August Pi I Sunyer Biomedical Research Institute (IDIBAPS) in Barcelona, Spain, a Foundation MCL grantee in 2005 and 2011 as well as a MCL Consortium (MCLC) member, as examples of the studies supporting both the ISMCN renaming and recognition of two indolent varieties. The citations include a 2012 *Journal of Clinical Investigation*

[CONTINUED PAGE 10]

## Advances in Lymphoma Classification



**Kiel** NHL (Europe)  
First to recognize B- and T-cell subtypes



**Working Group** NHL (U.S.)  
Attempt to translate between systems (incl. Kiel)  
Groups identified by letters (A-J)



**REAL** Hodgkin and NHL  
First international consensus classification system



**WHO** Update of REAL system  
First classification under World Health Organization



**WHO (rev.)** Recognized certain diseases associated with particular age groups  
Integrated classification for cutaneous lymphoma  
Distinguished WM from LBL  
Refined diagnostic criteria for CLL



**WHO (2rev.)** Refined definitions of in situ B-cell neoplasia  
Required DLBCL diagnosis specify ABC- or GCB- type  
Recognition of additional T-cell entities  
Refinement of nodular lymphocyte-predominant Hodgkin

## Can We Reach A Chemotherapy-Free Future?

As part of Blood Cancer Awareness Month in September 2016, USA Today distributed a special national supplement on blood cancer in their September 25, 2016 edition. Included in that supplement, and reprinted due to popular interest, was the following piece from Foundation Scientific Advisory Board member Andrew M. Evens, DO, MSc, FACP, Director Tufts Cancer Center, and Michael E. Werner, Chairman of the Foundation's Board of Directors.

**V**ice President Biden announced the development of the National Cancer Moonshot in February, 2016. The national cancer research community responded by intensifying its commitment to improved prevention strategies, development of new tools, increased data sharing and discovery of new therapies to treat cancer.

### Creating new solutions

Organizations and community oncology practices took part in New England's Cancer Moonshot Summit earlier this year at the Museum of Science in Boston, Massachusetts, to discuss the ways in which the initiative could positively impact the lives of people with lymphoma, the most common form of blood cancer.

The last decade has seen researchers develop a better understanding of the biological mechanisms contributing to the development of cancer and a corresponding rise in new therapies to treat the disease. Some of these novel treatments include immunotherapy and other targeted agents.

The National Cancer Moonshot seeks to build upon these discoveries and hasten the development of new cancer detection and treatment options for the benefit of all. With the advent of such targeted therapies, the need for more general – and toxic – treatment options like chemotherapy are increasingly being scrutinized. While effective in treating and curing many types of cancer, including lymphoma, chemotherapy often takes a serious toll on patients, in addition to their disease.

Today with the commitment of even greater investment in cancer care in the United States, researchers, are able to ask themselves: could the end of chemotherapy be a reality in our lifetime?

### Breaking down lymphoma

The answer to that question lies in our understanding of lymphoma. With more than 70 different subtypes of lymphoma recognized, personalized treatment and decision-making has long been a part of the treatment paradigm for this complex



Andrew M. Evens, DO, MSc (left) and Michael E. Werner

disease. From the early days of combination chemotherapy to monoclonal antibodies to checkpoint inhibitors and chimeric antigen receptor T-cell and other innovative immunotherapies, finding the right treatment for the right lymphoma subtype – and for the right patient at the right time – has always been central to treating lymphoma patients.

These concepts have helped pave the way to what today is known as precision medicine. And while researchers are continually improving our understanding of the disease and developing new, more refined therapies to more effectively treat the many subtypes of lymphoma, they also seek to reduce toxicities for patients and the long term side effects of treatment.

### Looking for biomarkers

As a result of this auspicious goal, there are already several types of lymphoma being effectively treated without chemotherapy. Specific markers in protein typing and genetic coding of the tumor as well as analysis of the patient's own DNA, may enable doctors and patients to make informed decisions for predicting the most effective and least toxic therapy in order to develop highly individualized cancer care plans.

With significant and sustained federal support for the National Cancer Moonshot, coupled with innovative partnerships between the public and private sectors and with improved cooperation across academic centers and in patient-centered alliances with community oncology, the key to a chemotherapy-free future lies in our continued biologic understanding of disease, such as lymphoma. With a better understanding of these complex cancers in combination with increased funding and enhanced collaborations, the moon may very well be within reach.

*Reprinted from USA Today Blood Cancer special supplement, September 2016, pg 23.*

## WHO Classification

[CONTINUED FROM PAGE 8]

article by Dr. Campo and fellow MCLC members at IDIBAPS Dolores Colomer, PhD and Pedro Jares, PhD, himself a 2007 Foundation MCL grantee and past MCLC Executive Committee member, which acknowledged the Lymphoma Research Foundation and the MCLC for their support of their studies on the genetics of MCL.

“The Lymphoma Research Foundation seeks to support the most innovative lymphoma research in searching for a cure for this disease,” noted Meghan Gutierrez, the Foundation’s Chief Executive Officer. “The WHO Classification’s correlation to a number of Foundation funded projects demonstrates that Foundation grantees are actively pursuing research that advance our understanding of the biology of lymphoma, as well as how it can be diagnosed and treated even more effectively.”

### Implications for Patients

Although the 2016 revisions were released too recently for their effects on patient diagnosis and outcomes to have been directly studied, past research suggests that the revisions will continue the trajectory of previous classifications in providing patients with more specific diagnoses and, consequently, more appropriate therapies for their disease. In 2008, a group of researchers including SAB members Ann LaCasce, MD of Dana-Farber Cancer Institute, Jonathan W. Friedberg, MD, MMSc of the University of Rochester, and Andrew D. Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center, as well as past SAB member Myron Czuczman, MD, then at Roswell Park Cancer Institute, reviewed 731 patients referred to one of five National Comprehensive Cancer Network (NCCN) centers with

a non-Hodgkin lymphoma diagnosis between 2000 and 2004, or the first four years after the initial publication of what would become the original WHO classification. They found only six percent, or 43 patients, received a diagnosis at the NCCN center that differed from their original diagnosis at a community center, suggesting that the more WHO classification system was largely successful for this group of predominately B-cell lymphoma patients.

Though progress has been made in reaching a consistent and correct diagnosis for lymphoma patients, there is still room for improvement, particularly in less common lymphomas. In 2014, researchers – again including Drs. LaCasce, Friedberg, Zelenetz, and Czuczman, as well as SAB Chair Leo I. Gordon, MD, FACP of Northwestern University, and first author and 2016 LRF Scholar Alex F. Herrera, MD then at Dana-Farber (now at City of Hope), performed a similar study looking specifically at T-cell lymphomas in light of the updates to those diseases in the 2008 revisions. The results for that study were not as definitive, with only 44 percent of 131 eligible cases receiving an initial diagnosis that was concordant with their final diagnosis, and with one in ten patients receiving a reclassification in their final diagnosis that may have impacted their treatment. “Prognosis and therapeutic options, as well as clinical trial eligibility, are dependent on the specific subtype of T-cell lymphoma,” notes Dr. LaCasce, first author on the 2008 paper and senior author on the 2016 paper. “Given that T-cell lymphomas are rare and difficult to diagnose, I would continue to advocate for expert hematopathology review even in the setting of the new 2016 update.”

Researchers interested in epidemiology (which looks at the patterns, causes, and effects of disease conditions in defined populations) will also be using the 2016 revisions. A September 2016 publication in *CA: A Cancer Journal for Clinicians* recently examined 2016 US lymphoid malignancy statistics using the 2008 classifications; as diagnosis data becomes available based on the 2016 criteria, they will transition to those statistics. The authors of the paper, including Foundation SAB members Christopher Flowers, MD of Emory University and Lindsay Morton, PhD of the National Cancer Institute, note that “incidence and survival statistics are useful for developing management strategies for these cancers and can offer clues regarding their etiology (causes).” The further refinements to lymphoma diagnosis in the 2016 classifications should lead to even more accurate statistics, which may help pinpoint new clues as to the causes of lymphoma and why subtypes may have differing survival rates.

The 2016 revisions to the WHO Classification for Lymphoid Neoplasms, like earlier systems before them, are not only a crucial tool in diagnosing and treating lymphoma patients, but serve as a marker of how our understanding of lymphoma biology and treatment has advanced in the last eight years. Researchers, including several funded by the Lymphoma Research Foundation, continue to identify the genetic markers and other commonalities that distinguish one subtype from another. In the era of precision medicine, this knowledge will be vital in identifying treatment plans that target a patient’s specific lymphoma, developing potential new therapies, and improving outcomes for this disease.

The Lymphoma Research Foundation's volunteer Scientific Advisory Board, comprised of 45 world-renowned lymphoma experts, guides the Foundation's research activities, seeking out the most innovative and promising lymphoma research projects for support.

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**About the Research Report**

Research Report is a publication of the Lymphoma Research Foundation, providing the latest updates on our grantees and their progress, as well as on the work of the Foundation. The Lymphoma Research Foundation is the nation's largest non-profit organization devoted to funding innovative lymphoma research and serving the lymphoma community through a comprehensive series of education programs, outreach initiatives, and patient services.

**Donor Spotlight**

**Carol Deets of Saint James, North Carolina** organized a kitchen and tasting tour to raise money for lymphoma research and education in honor of her son Dan, a Hodgkin lymphoma survivor. She chose the Lymphoma Research Foundation over other organizations because of its exclusive focus on lymphoma. "We were impressed with the percentage of Foundation monies that go to either research or helping families affected by lymphoma," she says. Using the Team LRF platform, which helps donors raise money for the Foundation through their own events, the September 26, 2016 event raised nearly \$40,000, far exceeding the original \$10,000 goal. Carol credits the "fantastic committee" that helped her organize the event with this achievement. "It is our hope that our small donation when combined with other gifts will have the potential to help discover ways to cure diseases like lymphoma."

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◀ Scan using your smartphone to read our Research Reports online.

## New Publications

The Foundation has published several new scientific and educational resources on lymphoma.

Details on Page 4.

# FOCUS ON

DIFFUSE LARGE B-CELL LYMPHOMA

The Lymphoma Research Foundation's newest disease-specific website provides information to diffuse large B-cell lymphoma patients and their caregivers.

Visit [FocusOnDLBCL.org](http://FocusOnDLBCL.org) or any of the other Focus On website series, including ALCL, CLL, FL, HL, MCL, and PTCL, for diagnostic information, treatment options, and other free disease-specific resources.



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