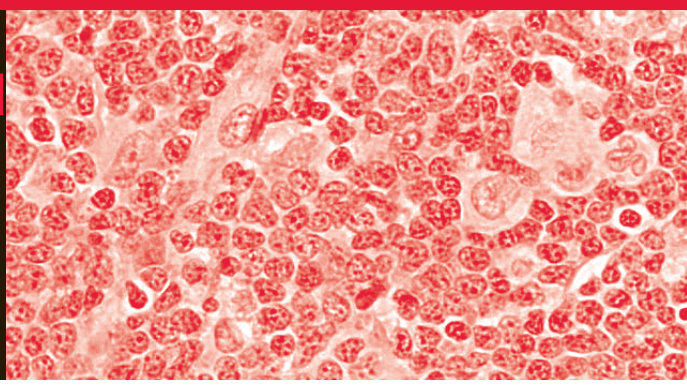
LYMPHOMA RESEARCH • FOUNDATION

Fall 2019

RESEARCH Report



Foundation Scientific Advisory Board Welcomes New Leadership, Members

Scientific Advisory Board Chair Andrew D. Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center at the 2017 North American Educational Forum on Lymphoma

In July 2019, the Lymphoma Research Foundation (LRF) announced the election of a Chair, Chair-Elect, and two new members to its Scientific Advisory Board (SAB). The SAB is comprised of world-renowned lymphoma experts who lend their perspectives and expertise to evaluating the Foundation's research grants portfolio, providing guidance to scientific, professional, and patient programming and supporting advocacy efforts to strengthen lymphoma research and patient care.

LRF's new SAB Chair is Andrew D. Zelenetz, MD, PhD of Memorial Sloan Kettering Cancer Center, where he is the Medical Director of Quality Informatics. Dr. Zelenetz has been a member of the SAB since its inception, as well as an active participant in LRF patient programs, including the New York Lymphoma Workshop and North American Educational Forum on Lymphoma, and has lent his scientific expertise on a wide variety of topics, including the development of LRF's research grants portfolio, scientific workshops, educational materials and digitial programming. He will serve a two-year term as Chair.

"We thank all members of our Scientific Advisory Board for their enduring commitment to our mission of eradicating lymphoma and serving those impacted by this blood cancer," said Meghan Gutierrez, LRF Chief Executive Officer. "We are confident that Dr. Zelenetz' guidance will help to usher in a new era in research supported by LRF, and innovative scientific programing."

Joining Dr. Zelenetz in leadership of SAB is the incoming Chair-Elect, Sonali Smith, MD of The University of

[CONTINUED ON PAGE 2]

"I look forward to the opportunity to lead this extraordinary group of individuals in our shared pursuit of improving outcomes for lymphoma patients and moving the national research agenda forward."

FEATURED IN THIS ISSUE: Profiles of LRF's New Scientific Advisory Board Members Page 4

The Foundation's newly elected Scientific Advisory Board members, including James Cerhan, MD, PhD of Mayo Clinic, Rochester (pictured, left), discuss their research interests and goals for their SAB tenure.

LETTER FROM THE CEO

Dear LRF Friends and Supporters,

This issue of Research Report introduces our new Chair Andrew D. Zelenetz of Memorial Sloan Kettering Cancer Center and Chair-Elect Sonali M. Smith of The University of Chicago of our Scientific Advisory Board (SAB), as well as our new members. Those of you familiar with LRF patient and scientific programs will know Dr. Zelenetz and Dr. Smith have been active participants in LRF initiatives for many years, and we are thrilled to have their leadership supporting our research portfolio and education programming.

In April 2019, LRF hosted a first-of-its-kind international scientific workshop solely focused on marginal zone lymphomas (MZL). This complex group of lymphomas presents a unique set of challenges to research and patient care; LRF's MZL Scientific Workshop assembled experts from around the globe to identify those challenges and establish a roadmap to potential solutions. You can find a summary of the workshop on page 8.

Recently, LRF completed an analysis of academic publications featuring LRF-funded research. Among their findings, they discovered that grantee publications have been cited more than 50,000 times by other academic papers. You can read more about this intriguing analysis and the impact the Foundation is making on the field of lymphoma research on page 6.

As always, the work of the Foundation would not be possible without your continued support. Thank you for all you do in support of lymphoma research and our efforts to aid those impacted by this disease.

Sincerely,

Meghan Gutierrez
Chief Executive Officer

New SAB

[CONTINUED FROM PAGE 1]

Chicago, where she is the Interim Chief of the Section of Hematology/Oncology and Director of the Adult Lymphoma Program. She is also Vice-Chair of the Southwest Oncology Group (SWOG) Lymphoma Committee, Chair of the Career Development and Engagement Subcommittee for the American Society of Oncology (ASCO), and Chair of the Women's Networking Center for ASCO's annual meeting. Dr. Smith will serve a two-year term as Chair-Elect, assuming the role as Chair at the conclusion of Dr. Zelenetz' term in 2021.

In addition to the new leadership team, the SAB welcomed two new members: James Cerhan, MD of Mayo Clinic, Rochester and Peter Martin, MD of Weill Cornell Medicine. Drs. Cerhan and Martin bring expertise in research ranging from epidemiology to investigating new therapies for indolent lymphomas.

Dr. Zelenetz assumes the Chair from Thomas Habermann, MD of Mayo Clinic, Rochester, who concludes a successful two-year term that oversaw key scientific meetings convening the world's leading experts on marginal zone lymphoma (MZL) and adolescent and young adult lymphoma (AYA). Dr. Habermann will remain on the SAB as a general member.

"I am honored to serve as Chair of the Lymphoma Research Foundation's prestigious Scientific Advisory Board. I look forward to the opportunity to lead this extraordinary group of individuals

NEW SAB

[CONTINUED FROM PAGE 2]

in our shared pursuit of improving outcomes for lymphoma patients and moving the national research agenda forward," said Dr. Zelenetz, "I'd like to thank Dr. Habermann for his leadership and I look forward to continuing the work of Dr. Habermann and my colleagues on the board."

LRF also thanks two retiring SAB members for their work in service of the lymphoma community: Thomas Witzig, MD of Mayo Clinic, Rochester; and Anas Younes, MD of Memorial Sloan Kettering Cancer Center.

Chair-Elect Sonali Smith, MD of The University of Chicago Medicine addresses attendees at the 2016 North American Educational Forum on Lymphoma

LRF Thanks Immediate Past-Chair Thomas M. Habermann, MD

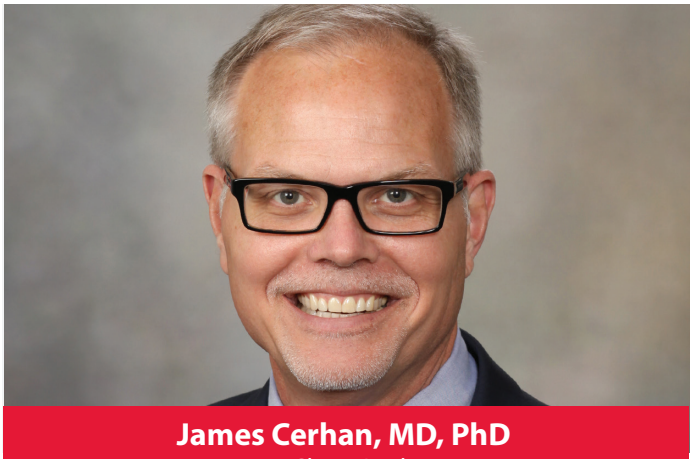
Thomas M. Habermann, MD of Mayo Clinic, Rochester addresses attendees at the 2016 North American Educational Forum on Lymphoma

The Lymphoma Research Foundation and the Scientific Advisory Board extend their thanks to outgoing SAB Chair Thomas M. Habermann, MD of Mayo Clinic, Rochester, for his outstanding leadership and service. Dr. Habermann assumed Chair of the SAB in 2017 after being elected Chair-Elect in 2015. Under his leadership, LRF has awarded 38 grants totaling more than $3.3 million.

During Dr. Habermann's tenure as Chair, the LRF SAB has initiated several scientific programs around important issues in lymphoma research including co-chairing LRF's first international scientific workshop on marginal zone lymphoma (MZL) in partnership with the International Extranodal Lymphoma Study Group, as well as the Foundation's largest -to-date scientific workshop on adolescent and young adult lymphoma (AYA). Dr. Habermann is also an active participant in LRF programs, including the Minnesota Lymphoma Workshop, one of LRF's premier regional patient education programs, which he has Chaired since its inception.

"Dr. Habermann has brought an incredible depth and breadth of knowledge of lymphoma and a unwavering commitment to patients to his work as Chair of the Scientific Advisory Board," said Meghan Gutierrez, LRF Chief Executive Officer. "We are grateful for his commitment to our mission and look forward to his continued work on the SAB and with our organization."

NEW SAB MEMBER PROFILES



James Cerhan, MD, PhD
Mayo Clinic, Rochester

Dr. Cerhan is the Professor of Epidemiology and the Ralph S. and Beverly Caulkins Professor of Cancer Research at Mayo Clinic, Rochester, where he is also Chair of the Department of Health Sciences Research. He was drawn to lymphoma research when he was a post-doctoral fellow working on the Iowa Women's Health Study cohort, where he, along with a team of researchers, identified several medical history and dietary factors associated with the risk of developing lymphoma.

Dr. Cerhan's research focus is in two major areas: identifying risk factors for developing lymphoma, including genetic, medical history and lifestyle factors, in order to both understand the causes of lymphoma as well as modifiable risk factors that could prevent the disease; and understanding factors that predict better survival (quantity of life) and survivorship (quality of life) after developing lymphoma, including genetic and lifestyle factors. He is most excited about the Mayo Clinic's national cohort of lymphoma survivors called the Lymphoma Epidemiology of Outcomes (LEO) cohort, launched in 2015. "We have enrolled over 11,000 newly diagnosed patients across eight centers, and we plan to follow this cohort over the long-term," Dr. Cerhan says. "We will use the LEO cohort to support broad and cutting-edge research that identifies clinical, epidemiologic, host genetic, tumor, and treatment factors that impact short and long-term outcomes, in order to improve both survival and survivorship of lymphoma patients."

Dr. Cerhan received his MD and a PhD in Epidemiology from the University of Iowa before a research fellowship at the Institute of Medical Research and a postdoctoral fellowship at the University of Minnesota. He is a past Chair of the InterLymph Consortium, EPIC Study Section, and the NCI Cohort Consortium, as well as chairing working groups for AACR and American Cancer Society. He is a current elected member of the Scientific Council, International Agency for Research on Cancer.

Peter Martin, MD
Weill Cornell Medicine

Dr. Martin is an Associate Professor of Medicine, the Charles, Lillian, and Better Neuwirth Clinical Scholar in Oncology, and Chief of the Lymphoma Program at Weill Cornell Medicine. His research focuses on the clinical investigation of new and promising therapies, primarily in the indolent lymphomas, as well as patient outcomes research. "I am most proud of our work in mantle cell lymphoma," Dr. Martin says. "Over the past decade we have made a strong case for the tremendous heterogeneity in mantle cell lymphoma and the people living with it. Our aim is to develop strategies - ideally curative strategies - that sees people as individuals, not as one massive identical population with the same problem."

Dr. Martin received his MD from the University of Alberta Faculty of Medicine and completed an MS in Clinical Investigation and Translational Research at Cornell prior to joining the faculty. As a SAB member, he hopes to advance LRF's research agenda. "Ever since I was a lymphoma clinician, LRF has been advocating for patients and setting the agenda for future research," he says. "I'm looking foward to learning from, and collaborting with, colleagues so that I, in turn, can help the next generation."

Dr. Martin was elected to the Lymphoma Research Foundation MCL Consortium Executive Committee in 2018 and has served as faculty for several LCRMP Workshops and LRF patient education programs, including Ask the Doctor, teleconferences, and the North American Educational Forum on Lymphoma; as well as aided in the development of LRF patient education publications.

LRF Grantee and SAB Member Discovers Protein Responsible for Lymphoma Cell Growth

A study partially funded by the Lymphoma Research Foundation and recently published in the *Journal of Experimental Medicine*, revealed surprising new functions for a protein called MYC—that the powerful oncogene affects the efficiency and quality of protein production in lymphoma cells, thus fueling their rapid growth and rendering immunotherapy ineffective for treatment. These functions of MYC are potentially targetable.

MYC functions as a transcription factor that controls the production or protein-encoding messenger RNAs (mRNAs) from thousands of different genes within a cell. Due to this process, MYC is known to drive the development of a range of cancers, enhancing the growth and proliferation of tumor cells. It is theorized that MYC might also control the subsequent "translation" of mRNAs into proteins, a process carried by ribosomes. A ribosome is a minute particle that bind messenger RNA and transfer RNA to synthesize polypeptides and proteins.

The researchers of the study, led by LRF Grantee and Scientific Advisory Board (SAB) member, Hans-Guido Wendel at the Memorial Sloan Kettering Cancer Center; Zhengqing Ouyang at The Jackson Laboratory for Genomic Medicine; and Gunnar Rätsch at the ETH Zürich, analyzed the mRNA translated by ribosomes in lymphoma cells containing either low or high levels of MYC. It was discovered that high levels of MYC stimulate the translation of a unique group of mRNAs, many of which encode components of the respiratory complexes that allow the cells' mitochondria to produce energy.

It was also discovered that low levels of MYC in a lymphoma cell produces a truncated version of a protein called CD19 that, unlike full-length CD19, is no longer exposed on the surface of the lymphoma cell.

This is important because lymphoma can be treated using CAR T immune cells that have been genetically engineered to recognize and kill CD19-expressing cancer cells. Loss of surface CD19 is associated with resistance

LRF Grantee and Scientific Advisory Board (SAB) member, Hans-Guido Wendel, MD (Memorial Sloan Kettering Cancer Center)

to CAR T-cell therapy, but how lymphoma cells reduce CD19 levels is unclear. It was found that CAR T-cells were less able to recognize and kill lymphoma cells that lacked surface CD19 because they expressed low levels of MYC.

"These new MYC activities depend on certain RNA binding proteins and our study makes them therapeutic targets and a new way to go after MYC-driven lymphomas," said Dr. Wendel.

The researchers plan to investigate how MYC regulates these different aspects of protein production in cancer cells.

To learn more about LRF grantees, visit the Researcher Spotlight section of LRF's website at lymphoma.org/researcherspotlight.

Lymphoma Research Foundation Grant Publications Cited More than 50,000 Times

The Lymphoma Research Foundation completed an updated analysis of academic publications proceeding from LRF research grants in August 2019. As a result of the availability of new digital tools for tracking grantee publications more accurately, the analysis revealed that the Foundation's 383 grants awarded since 1992 have resulted in 937 publications that have been cited more than 50,000 times by other academic researchers.

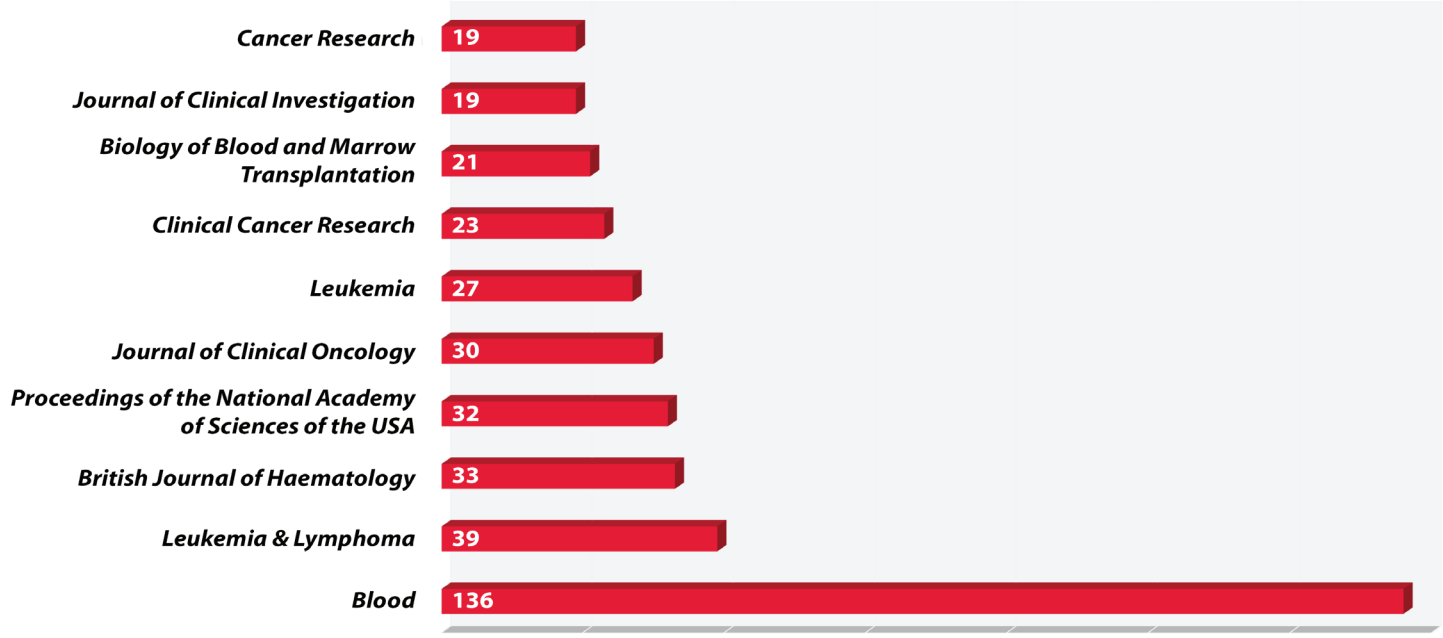
Publication of research findings in academic journals is a primary tool for researchers who wish to share their results with a wider community. Tracking grantee publications and the performance of those publications helps LRF and other nonprofit research funders measure the impact the research they fund has on the broader scientific community.

One key finding of the new analysis: the vast majority of LRF grantee publications occur within three years of the project's start date (76 percent), indicating most grantees are publishing either while their grant is still active or shortly after its conclusion. For many grantees this may mean the publishing of preliminary data or data generated by an early phase of their project, or review articles on subjects related to their research. Once a grantee has concluded their grant however, LRF-funded work frequently leads to additional research and publications, with LRF receiving credit for contributing to a new discovery, particularly if a clinical trial is involved that later reports long-term follow up results. As a result, 19 percent of LRF grantees credited LRF funding on a publication four to six years following the start of their grant, with an additional five percent publishing seven years or more after the start of their grant.

Academic citations are an effective measure of the impact a given paper has on the broader research community, as researchers cite papers that provide important underlying conclusions for their own work.

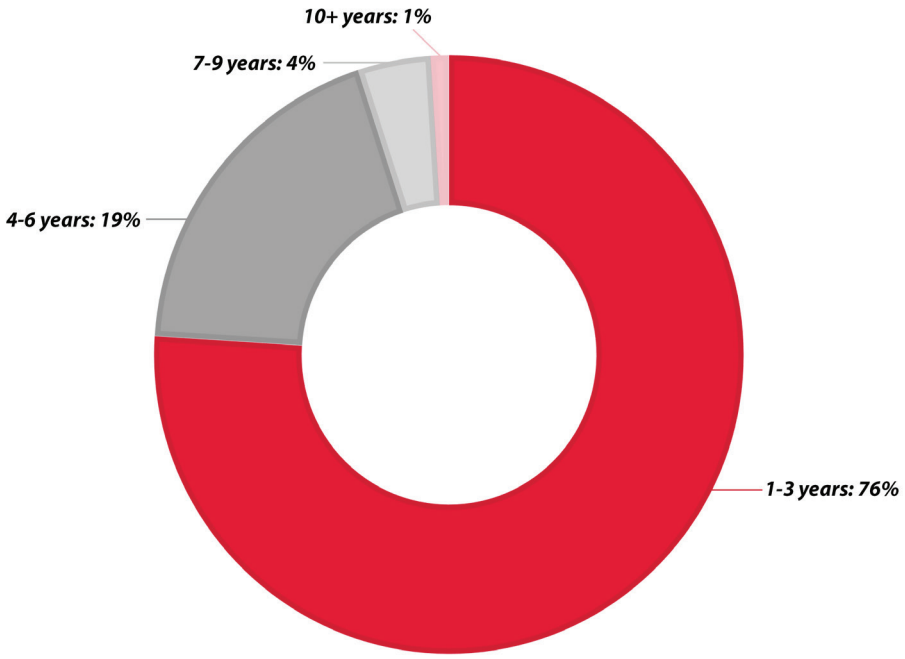
Included in the 51, 517 collective citations of all of LRF's grantee publications are an impressive 151 publications that have each been cited 100 times or more by other researchers, and an additional 465 publications cited between 10 and 99 times each, indicating that two-thirds of LRF grantee publications are cited in 10 or more other publications. Additionally, one third (302) of grantee publications occur in high-impact journals in cancer research and hematology, defined as journals

LRF Grant Publications: Top 10 Journals



[CONTINUED NEXT PAGE]

Time to Publication

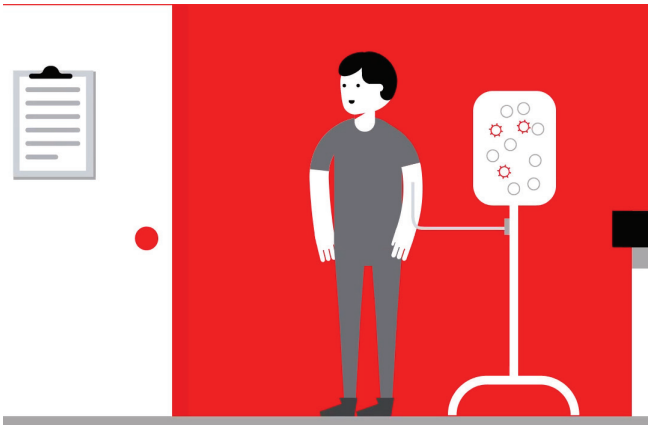


The majority of LRF grantee publications occur within three years of the projects start date (76 percent), indicating most grantees are publishing either while their grant is still active or shortly after its conclusion

in the top 15 in impact factor (a measure of the number of citations of a journal's article within the last few years). LRF grantee publications have also been cited in 37 government policy papers, 1468 patent applications, and 608 news stories, indicating that the influence of their research findings is not limited to just the lymphoma research community.

"The Lymphoma Research Foundation has always supported innovative research in lymphoma and chronic lymphocytic leukemia with the goal of advancing the scientific community's understanding of lymphoma and its treatment," said Whitney Steen, Associate Director of Research and Scientific Programs. "Now that we are able to accurately track the publications proceeding from our grant funding, we can see that the Foundation's support is translating into an impactful body of knowledge on lymphoma biology and effective therapeutic strategies."

LRF Adds Animated CAR T-Cell Therapy Video to Library of Educational Materials



*Visit LRF's Learning Center at **lymphoma.org/cart** to watch the video and learn about CAR T-Cell therapy.*

The Lymphoma Research Foundation (LRF) is committed to providing those impacted by lymphoma and CLL with the resources they need to better understand their disease and make the most informed decisions about their treatment and long-term care.

Due to the advancement and tremendous progress made in the study of the use of chimeric antigen receptor (CAR) T-cell therapy for the treatment of certain types of lymphoma, LRF has developed a CAR T-Cell Therapy animation video which illustrates this therapy and how it can be used to treat certain types of lymphoma. The new ideo is featured in the CAR T-Cell Therapy Learning Center on the Foundation's website, which offers information to patients and caregivers seeking to better understand this groundbreaking new therapy.

Foundation's Inaugural International Scientific Workshop Addresses Current State of Marginal Zone Lymphoma Treatment and Research

Marginal Zone Lymphoma Scientific Workshop Co-Chair and SAB member Thomas M. Habermann, MD (Mayo Clinic, Rochester) addresses attendees

Marginal zone lymphoma (MZL) has been a long-neglected area of lymphoma research – particularly within the United States; and although there has been recent success in the development of novel agents, such as BTK inhibitors, the international community of MZL researchers have been largely divided over issues on how to treat the disease, and how to define treatment success and disease progression.

To bring much-needed focus on this very rare type of lymphoma and to bridge the gap between North American and European researchers, the Lymphoma Research Foundation, together with its program partner the International Extranodal Lymphoma Study Group (IELSG) hosted the first-ever U.S. based international scientific workshop on MZL in April 2019.

Co-chaired by LRF Scientific Advisory Board (SAB) members Morton Coleman, MD (Weill Cornell Medicine) and Thomas M. Habermann, MD (Mayo Clinic), the two-day workshop focused on current unmet needs in the field of MZL, with an emphasis on identifying opportunities for large-scale study designs that leverage the opportunities for collaboration that can be facilitated by LRF. These unmet needs were focused in four key thematic areas, summarized below:

Pathophysiology, Etiology, and Natural History of MZL

One of the major unresolved questions in MZL natural history concerns the source of the marginal zone lymphoma cell. During the workshop discussion, the participants agreed that further work to characterize the etiology of MZL lymphoma, as well as the molecular pathology that drives development of the disease, could open the door to disease prevention, detection of the disease at an earlier stage, and earlier disease management.

As described at the MZL Workshop, marginal zone lymphomas are frequently associated with chronic infections, chronic inflammation, and dysregulation of normal immune responses. However, aside from the localized regions where inflammation occurs, it remains unclear why MZL B-cells appear at the distinct sites where they can occur, such as the spleen, lymph nodes and extranodal sites.

To address this question, *Biology and Pathology of Marginal Zone Lymphomas: Pathogenesis of Extranodal MZLs* panelist and MZL Scientific Workshop steering committee member, Ming-Qing Du, PhD (University of Cambridge) proposed "a collective effort to tackle the biology and the genetics of these marginal zone lymphomas at different anatomic sites." Dr. Du also suggested that MZL investigators should pay more attention to the normal biology of the marginal zone B-cell in order to gain further insight into MZL pathophysiology and etiology, as well as the processes of transformation and expansion of transformed cells.

A further unresolved question in MZL natural history is related to the observation that marginal zone lymphoma

[CONTINUED NEXT PAGE]

B-cells can have different cellular fates and produce different pathology with the same underlying genetic background. Ultimately, MZL investigators must address the question of which genes (and which genetic variants) are controlling differences in the cellular and clinical manifestations of marginal zone B-cell neoplasms.

Although the biology of common genetic variants has been worked out in relation to MZL, in part owing to contributions from a group led by *Biology and Pathology of Marginal Zone Lymphomas: Pathogenesis of Splenic and Nodal MZL* panelist Davide Rossi, MD (Institute of Oncology Research), the biology of rare variants has yet to be worked out in such careful detail, and additional validation studies are required to ensure consistency across analysis pipelines and study sites.

"I think that one of the ways we can address that is looking at the transcriptomic data, where you really are taking a group of mutations together that read out at a given pathway, versus reading out a single mutation level," said *Biology and Pathology of Marginal Zone Lymphomas: MZL Microenvironment* panelist Anne Novak, PhD (Mayo Clinic). "I think integrating some of the genomics and getting more of a readout of what that impact is biologically will be important to lend insight into really potential therapeutic targets and pathways that are important."

In addition to rare genetic variants, the local microenvironment likely plays a key role in determining the trajectory of a particular MZL. Infiltrating T-cells and neutrophils, among other types of cells, are known to interact with marginal zone B-cells and to shape their cellular fates.

In light of these facts, *Epidemiology, Transformation and MZL Signature in DLBCL: MZL in DLBCL* panelist, MZL Scientific Workshop steering committee member, and SAB member Margaret Shipp, MD (Dana-Farber Cancer Institute) suggested "beginning to use some of the emerging technologies to actually image the intact microenvironment and to understand the interplay between different cell types at different stages in the disease."

"I think that may turn out to be particularly informative too, given the nature of this disease and the clear emerging story about the interplay between the malignant cells and the other cells in the microenvironment," Dr. Shipp added.

Also at issue in the natural history of MZL is the definition and characterization of MZL subtypes. Although it is well appreciated in the MZL research community that splenic MZL, nodal MZL and extranodal MZL often behave quite differently from one another, and can respond differently to treatment, at present, MZL is usually lumped together when studied in clinical trials. During the workshop, the panelists agreed these are in fact three different lymphomas that should be studied separately when possible, allowing for the development of specific diagnostic, therapeutic, and response criteria for each form of the disease.

Future genomic and transcriptomic studies will provide greater resolution to the molecular clustering subsets that help to define MZL subtypes on the level of molecular pathology.

MZL Therapeutic Approaches

Taken together, the MZL community is moving toward utilization of more selective targeted therapies in the management of MZL, including therapies that offer patients shorter treatment and longer, higher-quality lives. However, at present, treatment patterns for MZL are neither well standardized nor well defined, which presents a major avenue for advancement of the field.

One of the most difficult questions for a clinician treating a patient with MZL to answer is when and how aggressively to treat the disease, given that it is generally indolent and slow to progress. The question of patient eligibility for treatment might be resolved by defining treatment criteria in a subset-specific manner, as proposed by Dr. Davide Rossi during the workshop discussion. However, for such criteria to be developed, there would need to be large, registry-based dataset that captures current treatment paradigms in MZL, and such data are presently lacking.

Complicating the question of *Who is eligible for treatment?* is an even larger question: *Is cure ultimately the treatment objective in MZL?* Given that MZL is usually slow to progress, it has been proposed that treatment objectives for MZL may differ based on patient age, meaning the older patients with indolent disease might be managed less aggressively to no ill effect.

"As we develop targeted therapies and understand the biology better, I think we need to be really careful in a disease where even the worst patients have a very long survival, to build quality of life, and really make sure that we're not doing more harm than good," said SAB member Ranjana Advani, MD (Stanford University School of Medicine) during the workshop discussion.

Dr. Advani added that it would be highly

[CONTINUED NEXT PAGE]

inadvisable to create a new standard of care that results in overtreating patients with otherwise indolent disease.

"The question is how to improve the outcome of those 20 to 30 percent of cases that are not living like the general population, and quite shortly, because of this disease," said Dr. Rossi, who added that recent data indicate certain abnormalities in the NOTCH signaling pathway may function as biomarkers for those patients who typically can expect a worse prognosis.

However, multiple workshop discussants cautioned that the histology and natural history of MZL does not always reflect the underlying biology, making it difficult to select patients for therapy given a specific genetic background.

A further unresolved question in MZL therapeutic approaches concerns the type and dosage of radiotherapy that is most appropriate for establishing local control. The workshop panelists suggested that a collaborative clinical trial is needed to establish the best practices for when and how radiotherapy should be employed in the treatment of MZL.

An additional area of concern relates to how special MZL patient populations are treated and described in MZL literature. One particularly vulnerable MZL patient population consists of those patients with comorbid Sjoren's disease. Although current recommendations suggest first-line radiotherapy in the context of localized Sjoren's disease-associated MALT lymphoma, when such patients are irradiated, they face extremely uncomfortable treatment-related adverse effects, such as persistent dry mouth. For these patients, it has been suggested that first-line systemic therapy with rituximab may be appropriate even for localized disease.

Even for patients without special considerations like Sjoren's, there is a need to establish an optimal dosing schedule for MZL radiotherapy and local control at different anatomic sites. Currently, there is no widespread agreement in the MZL research community about when to give a patient radiotherapy, or how much radiotherapy to give. The MZL workshop panelists suggested that a collaborative academic study may be required in order to settle the radiotherapy dosing issue.

Clinical Trial and Study Design in MZL

One of the chief unmet needs the MZL research community identified during the workshop is the need for large-scale, collaborative registry studies and studies that involve biobanking of patient samples. Such studies would provide a detailed understanding of the frequency and combination of mutations that underly MZL molecular pathology and would enable more intelligent clinical trial design. Such studies would also allow for finer-grain understanding of the association between MZL and inflammation and dysregulated immune responses. Additionally, such studies would enable MZL investigators to understand MZL on the epidemiologic level and to dissect patterns of MZL heritability within families, perhaps even identifying MZL risk factors. Because such studies require collaboration between investigators, MZL research sponsors may find opportunities to create seed grants that support the initiation of these registry-based studies.

A second and pressing unmet need in the MZL research community is the need for clinical trials that are specifically dedicated to MZL and its subtypes, rather than trials that are designed to test a given agent in a wide range of B-cell lymphomas, leaving MZL as the "stepchild." A consensus was reached during the workshop discussion session that there is a need both for clinical trials that are predominately focused on MZL and a need for trials that are structured to enable investigation of individual MZL subtypes, rather than all MZL cases collectively as a monolithic group. When there are few MZL cases included in clinical trials, it becomes difficult to draw conclusions, leaving trials perpetually hobbled as mere hypothesis generators in MZL.

One potential solution to the problem of there being few dedicated MZL studies would be the development of an omnibus adaptive trial design, a proposal that was suggested by multiple panelists during the workshop. Rather than wastefully reduplicating trial design and regulatory approval, as is currently done with many phase 2 trials, an adaptive trial design would create efficiencies by allowing new drugs to be dropped in to an existing protocol. Because industry has traditionally been reticent to participate in adaptive trial designs, academic and other types of funding may be required to advance such trials in the future.

A further challenge specific to research involving splenic MZL has to do with how regulatory criteria have defined the progression and staging of the disease. Current criteria such as the Lugano criteria require splenic MZL patients to have a 1.5 cm measurable lesion, which is rare to occur, resulting in splenic MZL patients being excluded from many MZL clinical trials. During the discussion SAB Chair

[CONTINUED ON NEXT PAGE]

Marginal Zone Lymphoma Scientific Workshop Co-Chair and SAB member Morton Coleman, MD (Weill Cornell Medicine) provides opening remarks

Andrew D. Zelenetz, MD, PhD (Memorial Sloan Kettering Cancer Center) proposed adopting a response measure for splenic MZL based on spleen size, which would avoid the unreliability of PET-based response measure and the lesion requirements of the Lugano criteria.

Although it is well appreciated in the MZL research community that basic research into the molecular pathology is useful in identifying new drug targets, studies of the biochemical mechanisms involved in MZL pathogenesis are presently hindered by the unavailability of pre-clinical models of MZL, and the fact that cell lines that behave like marginal zone lymphoma do not exist. During the MZL workshop, panelists discussed the feasibility of developing a bank of primary cells for use in pre-clinical research after concluding that developing a model cell line may not be possible due to the unique dependence of MZL (and particularly extranodal MZL) on its local microenvironment. Because creating a primary bank of cells would likely be a collaborative initiative, the MZL workshop panelists described such an initiative as an opportunity to build the collaborations required for larger clinical trials and registry-based studies.

MZL Diagnosis, Assessment, and Response

Clinical studies of MZL are presently confounded by the lack of a clear, uniform definition for what counts as a successful treatment. Contributing to this problem is a lack of specific assessment criteria for the evaluation of response in MZL; instead, assessment and response criteria for MZL are typically the same as those used for follicular lymphoma (FL). Thus, the MZL workshop discussants called for the definition of specific assessment and response criteria, with a greater emphasis on MZL anatomical site specificity.

The anatomic site of specificity is important, because MZL is a heterogenous disease in terms of its clinical presentation, which hinders assessing all MZL cases in the same way. However, because few existing studies have used site-specific response criteria, there are regulatory barriers to adopting the use of such criteria in clinical trials. The discussants also highlighted the need to broaden the definition of clinical response to include minor responses, because patients who experience minor responses often have outcomes similar to those of patients who experience a partial or complete response. At present, however, there is no agreed upon threshold to define what constitute a minor response.

Also suffering from an unclear definition is transformation within the context of MZL, which involves the switch from antigen-dependent cell proliferation to fully malignant, self-sufficient proliferation. Notably, clinical transformation and histologic transformation are not precisely congruent, meaning that the same histologic presentation can produce different clinical outcomes. The workshop discussants highlighted the need for a clinical definition of MZL transformation that can be correlated with histologic findings and resistance to particular therapeutic approaches, and suggested that an evidence-based, consensus definition be developed in the future, one that identifies the molecular correlates of fundamental changes in the behavior of MZL. Supporting the development of such molecular definition of MZL transformation are registry-based studies that incorporate biobanking of patient samples;

[CONTINUED ON PAGE 14]

LRF Raises Public Awareness of Lymphoma During BCAM

Long-time Lighting Partner Weylin (Brooklyn, NY) joined LRF to Light it Red for Lymphoma in September 2019

The Lymphoma Research Foundation reached millions in the lymphoma community worldwide during Blood Cancer Awareness Month (BCAM) in September through its visible awareness initiative *Light it Red for Lymphoma*.

Culminating on World Lymphoma Awareness Day (WLAD) on Sept. 15, *Light it Red for Lymphoma* is designed to garner awareness and provide hope to those impacted by this blood cancer by partnering with buildings, landmarks and businesses to light red, and encouraging individuals to dress in red and support BCAM on social media during September. In direct partnership with LRF, national and international buildings and landmarks participated in *Light it Red for Lymphoma* including CN Tower in Ontario, Canada; Bell Tower in Perth, Australia; National Concert Hall in Dublin, Ireland; Pier 17 in New York, NY; Wrigley Building in Chicago, IL; Los Angeles International Airport (LAX) in Los Angeles, CA; and many more.

"The first step in eradicating a rare disease like lymphoma is raising awareness on behalf of all those affected by this type of blood cancer," said Meghan Gutierrez, LRF Chief Executive Officer. "Each year, we at the Lymphoma Research Foundation are honored to convene so many wonderful and committed lighting partners from around the world in this truly global show of support for the lymphoma community, with the hope of raising awareness for all those touched by this disease."

In addition to the *Light it Red for Lymphoma* initiative, the Foundation raised funds and awareness during Blood Cancer Awareness Month by hosting a series of patient education events, Team LRF events including the 12th Annual Lymphoma Research Ride in Barnesville, MD on Sept. 22; and ticketed events such as the 2019 Annual Gala on Sept. 26 in New York City.

➤*Read more about the 12th Annual Lymphoma Research Ride and 2019 Annual Gala on page 13.*

Fueling Our Imact: Foundation Events Raise $1.8 Million

During the summer and early fall 2019, thousands of supporters joined the Lymphoma Research Foundation at various LRF-hosted fundraising events to raise funds and awareness for lymphoma research, education programs and support services.

TEAM LRF

Team LRF is the Foundation's community fundraising program where survivors, caregivers, friends, and supporters raise awareness and critical funds to support those affected by this blood cancer. Over the summer, the Foundation hosted several of its Team LRF Lymphoma Walk events in Minneapolis, New York City, and Chicago, bringing together more than 2,500 supporters and raising more than $450,000. The Foundation also held its 12th Annual Lymphoma Research Ride on September 22 at the Barnesville School in Barnesville, MD. The Ride, founded by past-SAB Chair, Bruce Cheson, MD, FACP, FAAS, FASCO (Georgetown University Hospital/ Lombardi Comprehensive Cancer Center) and Christine Cheson, raised more than $250,000 to support lymphoma research programs. "Now with more than a decade of momentum behind the Lymphoma Research Ride, excitement for the Ride continues to grow every year," said Dr. Cheson. "We look forward to more Lymphoma Research Rides and the Critical dollars it raises to help individuals and their loved ones."

The Foundation is looking forward to rallying with supporters at the Arizona Lymphoma Walk on October 20 at the Phoenix Zoo *(visit lymphoma.org/ArizonaWalk for more information or to register)*.

TICKETED EVENTS

More than 300 guests attended the Foundation's third *Swirl: A Wine Tasting Event* series in Chicago on May 30. Held at the exclusive Casino, the event raised more than $130,000 and featured award-winning wines and craft whiskey presented by Founding Partner Southern Glazer's Wine & Spirits (SGWS). LRF Ambassador and acclaimed jazz singer, Rose Colella, provided a live performance with her band, the Rose Colella Jazz Quartet. Due to *Swirl: Chicago*'s success, the Foundation achieved $1.1 million raised through the *Swirl* series. During the event, LRF celebrated this milestone and honored Southern Glazer's Wine & Spirits with the coveted Hope Award in recognition of their partnership and commitment to LRF's mission.

The Foundation will round out 2019 *Swirl* on October 24 at *Swirl: Orange County* in Laguna Beach, CA *(visit lymphoma.org/swirloc for more information or to purchase tickets)*.

LRF celebrated its 2019 Annual Gala at the historic Plaza Hotel in New York City on September 26 raising nearly $1 million to advance research and patient support services. More than 450 guests came together to celebrate the Foundation's many accomplishments over the past year and recognize the evening's honorees: Distinguised Leadership Award recipient, Anas Younes, MD (Memorial Sloan Kettering Cancer Center) and Corporate Leadership Award recipient, Genentech, Inc. "I am truly honored to be recognized with the Distinguished Leadership Award," said Dr. Younes. "The Foundation is critical to helping advance research and improve therapies for lymphoma patients, and empowering patients through education."

[CONTINUED FROM PAGE 11]

when such studies follow patients over time, they allow for comparison of paired patient samples collected before and after clinical transformation has occurred.

Conclusions

The MZL 2019 Scientific Workshop provided a collegial, collaborative environment for international experts in the field of MZL to discuss the current state of knowledge, and to define what will be necessary to move the field forward in the coming years.

Although recent advances have provided more treatment options for MZL than ever before, it remains unclear when patients with MZL should receive treatment, and how much treatment they should receive, particularly given the heterogenous clinical presentation of MZL at different anatomic sites, and given the relatively indolent clinical course of the disease. To ensure that MZL treatments do not cause more harm than they resolve, MZL researchers must form collaborations to better understand the core biology and natural history of MZL, to identify biomarkers correlative of disease progression and response, and to compare the efficacy of various treatment options in particular anatomical sites and subtypes of MZL, which will allow clinicians to stratify patients according to which treatments are most likely to benefit them.

➤*The 2019 Marginal Zone Lymphoma Scientific Workshop Committee includes Morton Coleman, MD (Co-Chair), Weill Cornell Medicine; Thomas M. Habermann, MD (Co-Chair), Mayo Clinic, Rochester; Ming-Qing Du, MD, PhD, University of Cambrige; Eric D. Hsi, MD, Cleveland Clinic; Izidore Lossos, MD, University of Miami; Margaret Shipp, MD, Dana-Farber Cancer Institute; Catherine Thieblemont, MD, PhD, Hôpital Saint-Louis (Hôpitaux Universitaires Saint-Louis, Laboisière, Fernand-Widal); Anas Younes, MD, Memorial Sloan Kettering Cancer Center; and Emanuele Zucca, MD, Oncology Institute of Southern Switzerland (University of Bern and International Extranodal Lymphoma Study Group).*

SCIENTIFIC ADVISORY BOARD

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

LYMPHOMA RESEARCH • FOUNDATION

National Headquarters

Wall Street Plaza
88 Pine Street, Suite 2400
New York, NY 10005
(212) 349-2910
(212) 349-2886 fax

Helpline: (800) 500-9976
helpline@lymphoma.org
Website: lymphoma.org

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.

Planned Giving

The Lymphoma Research Foundation is committed to funding the most promising lymphoma-specific research and supporting lymphoma researchers who have the greatest potential to improve patient care and, ultimately, to improve patient outcomes. The Foundation's unique commitment to early career investigators ensures that we are not only advancing our understanding of the disease, today, but we are also accelerating new therapies for lymphoma for generations to come.

By including LRF in your estate planning, you will help to ensure the future success of the organization in its efforts to eradicate lymphoma and serve those touched by this disease.

Visit **lymphoma.org/plannedgiving** to learn more.

LYMPHOMA RESEARCH • FOUNDATION

Lymphoma Research Foundation
Wall Street Plaza
88 Pine Street, Suite 2400
New York, NY 10005

IN THIS ISSUE:

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

Breakthrough Discovery by LRF SAB member and Grantee

LRF-funded study revealed surprising new functions for a protein called MYC.
Details on Page 5

DONOR SPOTLIGHT: Maxa Berid

A long-time supporter of the Foundation and chronic lymphocytic leukemia survivor, Maxa Berid is a self-described "give it forward" supporter. Once a pioneer in the legal field, she now is helping to pioneer lymphoma research.

In 2018, LRF invited Maxa to tour the research facility at Dana-Farber Cancer Institute. That tour sparked Maxa's passion for helping others and giving back—starting with a chance to sponsor an LRF Lymphoma Clinical Research Mentoring Program (LCRMP) grantee.

She was highly impressed by the rigorous structure and focus of the LCRMP and found it to be "a donor program that produces results." She is particularly excited to "take a chance to help fund a breakthrough."

Maxa hopes her contribution to LRF continues her commitment to public service and solidifies a legacy of helping others and giving back. By sharing her story as a donor, Maxa wants to encourage others to follow her lead and demonstrate their support to LRF, noting, "This is a doable amount," and a gift that can have a lasting impact.

Named Giving and Sponsorship Opportunities

Help fund cutting-edge science and foster the careers of the next generation of lymphoma researchers while honoring a loved one, healthcare provider or caregiver.

Learn more at lymphoma.org/namedgiving.