Cutaneous Lymphoma Foundation

Research Report: The Impact

Cutaneous Lymphoma Foundation: Staying Focused on Research to Serve Our Community

In 2018, the Cutaneous Lymphoma Foundation (CLF) was able to make great strides in funding young investigators, planning for future research programs, and bringing patients' voices to researchers around the world!

CLF awarded three Young Investigator Awards this year – one more than usual. These travel grants allow researchers the ability to attend an annual meeting of the Society for Investigative Dermatology, the Society for Hematology or the European Organization for Research and Treatment of Cancer – Cutaneous Lymphoma Task Force where their work has been selected to be presented. You can read more about the great work being completed by our three Young Investigator Award recipients in this publication. To learn more about our current Young Investigator Awards, visit the CLF website at www.clfoundation.org/young-investigator-award.

Additionally, in August of 2018, the Research Advisory Council members gathered in Philadelphia, PA, to discuss the Cutaneous Lymphoma Foundation's place in research, and where we, as a community, can make the greatest impact on the world of cutaneous lymphoma research. As a short-term outcome of the meeting, we are excited to be launching our all new **Cutaneous Lymphoma Catalyst Research Grant**. This grant will provide researchers with the funding needed to continue and/or complete their work being done in cutaneous lymphoma. Depending on funding, the CLF will be offering two (possibly more) $50,000 grants per year for the next two years.

Research Advisory Council pictured from left to right: (Front Row) Stuart Lessin, MD; Christine Eischen, PhD, Co-chair; Susan Thornton, CEO; Pierluigi Porcu, MD, Co-chair; Rick Winneker, PhD, Consultant. (Back Row) Bradley Haverkos, MD, MPH; Laura McGirt, MD; Christopher Shipp, Patient; Alison Moskowitz, MD; Alejandro Gru, MD; Jaehyuk Choi, MD, PhD; and Anjali Mishra, PhD. (Not pictured: Steven Jones, MD, Patient; and Michael Khodadoust, MD, PhD.)

Traveling the globe on behalf of our community bringing the patients' voices to the research community has also been a big part of our 2018-19 efforts. We have attended medical meetings and met with researchers to discuss the needs that continue to surface among our population. As part of advocating on your behalf, this year we were also proud to participate with Drs. Michi Shinohara and Erica Shantha to continue the Quality of Life research initially complete by Dr. Marie-France Demierre and funded by CLF. Helping research(ers) understand your needs is a vital part of addressing the challenges patients face with diagnosis, treatments and the search for a cure for cutaneous lymphomas. Thank you for trusting the Cutaneous Lymphoma Foundation to do this important work on your behalf!

People pay attention to you when you get this funding. In my experience the CLF chooses the right people for their grants.

- Larisa Geskin, MD – YIA Recipient

2018 American Society of Hematology (ASH) Award Recipient

Evaluation of maintenance therapy in cutaneous T-cell lymphoma patients receiving total skin electron beam radiation therapy

Pamela Blair Allen, MD, MS
Assistant Professor of Medicine,
Division of Hematology and Oncology
Emory University and Winship Cancer Institute

Introduction: Total skin electron beam (TSEB) therapy is a well-established treatment modality for patients suffering from cutaneous T-cell lymphoma (CTCL). It is often augmented with maintenance therapy, including skin directed and systemic therapies. However, the utility of maintenance therapy remains controversial. We performed a retrospective analysis in patients with CTCL to assess whether maintenance therapy following TSEB improved outcomes.

Methods: We conducted a single center retrospective analysis at the Winship Cancer Center of Emory University analyzing CTCL patients who received TSEB from 1998 – 2018. Patients who received TSEB were selected from an existing cutaneous lymphoma database, and cross referenced with a list of patients obtained from the Emory Cancer registry through the Lymphoid Malignancies Enterprise Architecture Database (LEAD). Consent was waived due to the retrospective nature of the project. The primary objective was to assess progression free survival in patients who received maintenance therapy following TSEB (PFS-TSEB) compared to those who did not. Maintenance therapy was defined as therapy started either concurrently or within 1 month of the initiation of TSEB. Secondary objectives were to assess overall survival following TSEB (OS-TSEB), and overall survival following diagnosis (OS). Additionally, we evaluated patient demographics, number of treatments, and time to TSEB from diagnosis. Equality of variances between groups was assessed with F-test. Numerical variables were analyzed with unpaired two-tailed t-tests or Welch's t-test and categorical variables were analyzed with chi-squared tests.

Results: 101 patients with a median age of diagnosis of 55 (range 10 – 89 y, 95% CI 52 – 58 y) underwent TSEB. 52% of patients were male, 48% female; 50% were black, 46% white/Hispanic, 1% other, and 3% unknown. 65% had MF, 16% SS, 16% CTCL nos, 1% CD30+, and 2% other. At diagnosis, 33% were stage 1, 39% stage 2, 10% stage 3, and 18% stage 4.

48% of patients received maintenance treatment and 52% did not. 36% of maintenance was given concurrently with TSEB, 34% after, and 30% unknown. The most common maintenance therapies were bexarotene (29%), interferon (23%), and PUVA (15%). From diagnosis, median time to first treatment was 48 d (IQR 11 – 152), time to TSEB was 429 d (IQR 136 – 1225), and median time to first treatment after TSEB was 51 D (IQR 18 – 115). A median of 2 therapies were received prior to TSEB (IQR 1 – 4; 1 skin-directed, 1 systemic, 0 RT). A median of 2 therapies occurred following TSEB (IQR 0 – 4.5; 0 skin-directed, 1 systemic, 0 RT). The most common skin directed and systemic treatments overall were topical steroids (pre, post-TSEB), PUVA (pre-TSEB), and retinoids (post-TSEB).

Overall, 80% of patients progressed after TSEB with a median time to progression of 118 d (IQR 36.5 – 231.5). OS-TSEB and OS were 642.5 d (IQR 248 – 1587.5) and 1523 (IQR 785 – 2698), respectively, with 46% of patients alive and 54% dead. In comparing outcomes of maintenance to no maintenance, PFS-TSEB was 171 d (IQR 30.25 - 333.75) versus 66.5 d (IQR 30 – 178.75) (Welch's t-test, P = .067), OS-TSEB was 1135 (IQR 476.5 – 1845.5) versus 433.5 (IQR 219 - 1309.75) (t-test, P = .046), and OS was 1871 (IQR 961 – 2698) versus 1329.5 (IQR 676.5 - 2830.75) (t-test, P = 0.74), respectively. We found no difference in gender, race, diagnosis, stage, or age at diagnosis between maintenance and no maintenance groups. However, in comparing maintenance to no maintenance, time to initiate TSEB from diagnosis was shorter in the maintenance group (322 d [109.5 – 772] versus 456 d [IQR 152 – 1784]) (t-test, P = 0.041). Median total number of treatments was 8 (IQR 4 – 10) versus 5 (IQR 3-9) (t-test, P = 0.052), respectively.

Evaluation of maintenance therapy...*continued*

Discussion: We defined demographics, diagnoses, stage, treatment number, treatment type, and outcomes in a cohort of CTCL patients undergoing TSEB. Patients receiving maintenance therapy had an increase in overall survival and a trend towards an increase in progression-free survival measured after TSEB. A possible limitation to these findings is that patients receiving maintenance therapy in our cohort received TSEB earlier than those without maintenance, with a trend towards more overall treatments. Our retrospective findings suggest a benefit of maintenance therapy in CTCL following TSEB and provide a basis for initiating prospective studies to further evaluate this approach.

Additional Research Credits:
Matthew R. Kudelka, Mary Jo Lechowicz Mohammad Khan, Natia Esiashvili, Christopher Flowers, Pamela B. Allen; *presenting and corresponding author*

2018 International Investigative Dermatology (IID) Award Recipient

Skin Commensals as Instigators of Cutaneous T Cell Lymphoma

Carina A. Dehner, MD, PhD
Physician Scientist Track Resident in Pathology
Washington University St. Louis

Cutaneous T cell lymphoma (CTCL) is a debilitating malignancy of skin-homing lymphocytes, which is thought to arise from a combination of genetic, epigenetic and environmental factors, but specific triggers remain unknown. We propose a model in which adaptive immune responses to particular skin commensals evolve into clonal proliferation of T cells in genetically predisposed individuals.

The skin and blood of 10 CTCL patients were sampled three times for V1-3 and V4 16S rRNA sequencing, skin cultures, and T cell isolations for interaction studies with candidate commensals. First, we characterized the CTCL skin microbiome and compared it to lupus and healthy skin microbiota, which revealed dysbiosis compared to controls. In CTCL skin cultures, we isolated unique bacterial strains in lesions compared to adjacent non-lesional skin, one prominent being Bacillus safensis. We extracted cutaneous T cells from malignant lesions of three patients for molecular characterization and in vitro studies with candidate commensals. STAT3 phosphorylation was significantly increased in lesional vs non-lesional skin of one patient examined, supporting features of CTCL cells in addition to clinical TCR phenotyping. Lesional T cells and CCR4+ CLA+ T cells from peripheral blood were co-cultured with autologous CD14+ monocytes and commensals. Heat-killed bacterial candidates identified in the culture-dependent skin microbiome studies were used for in vitro antigenic challenge. Cutaneous T cells from three CTCL patients examined thus far with exclusively lesional enrichment of B.safensis showed proliferation to a lesional isolate of B. safensis compared to proliferation to non-lesional bacteria.

Dissecting cancer cell-microbiota interactions revealed skin commensal candidates involved in the pathogenesis of CTCL. Pathobionts enriched in lesional skin might act as antigenic drivers for progression to clonality similar to processes involved in H. pylori-induced MALT lymphoma, a paradigm that may be applicable to skin lymphomagenesis.

Additional Research Credits: Carina A. Dehner[1], William E. Ruff[1], Francine Foss[2], Michael Girardi[3], Martin A. Kriegel[1,2]

[1]Department of Immunobiology, [2]Department of Medicine, [3]Department of Dermatology, Yale School of Medicine

2018 European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Award Recipient

For ORAL PRESENTATION

Single-cell variability drives phenotypic heterogeneity and intrinsic drug-resistance in cutaneous T-cell lymphoma

Stefan M. Schieke, MD
Assistant Professor of Dermatology
University of Wisconsin-Madison

Aims: Phenotypic heterogeneity allows individual cells to behave different from the bulk. This non-genetic variability provides a critical route to therapeutic resistance and relapse of cancer. Herein, we characterize phenotypic dynamics that generate an intrinsic and pre-existent, drug-tolerant state and identify a resistance biomarker profile to detect these "persister" cells in skin lesions of CTCL.

Methods: Various malignant T-cell lines were subjected to in vitro and in vivo tracing experiments, drug screens, transcriptome, and biomarker analyses. Human CTCL tumors were analyzed using multispectral immunohistochemistry to assess persister cell profiles.

Results: Single-cell drug screening reveals a small fraction of cells tolerant to various drugs such as doxorubicin, vorinostat, and methotrexate. In cell fate analyses, we observed selective survival of label-retaining, slow-cycling cells leading to re-growth of xenograft tumors after treatment. Slow-cycling cells are in an intrinsic and transient, drug-resistant state that precedes treatment. Reversible transition dynamics maintain an equilibrium between the drug-resistant subset and bulk cells. Single cells show a strong inherent drive to program daughter cells to occupy the slow-cycling state creating a high level of population robustness. This treatment-resistant state displays a reprogrammed transcriptional profile allowing definition of resistance biomarkers. In particular, early growth response proteins 1- 3 (Egr1-3) show increased expression levels in label-retaining cells before and after treatment. In tumor-stage lesions of cutaneous T-cell lymphoma, we identified rare individual cells with the slow-cycling, Egr2highphenotype consistent with the identified profile of the drug-resistant state.

Conclusion: Transcriptomic reprogramming controls a rare, drug-resistant state in cutaneous T-cell lymphoma that provides a non-mutational, pre-existing path to relapse after various treatments. Characterization of this subset of lymphoma cells will help to identify therapeutic targets in the resistance programming of "persister" cells to prevent relapsing disease.

Additional Research Credits (CoAuthors):
Khan, Hamidullah; Roy, Sushmita; Xiao, Tony; Anshu, Ashish: University of Wisconsin, Madison, United States of America

For POSTER PRESENTATION

Metabolic dynamics control invasion and dissemination of cutaneous T-cell lymphoma

Aims: The goal of our work is to identify mechanisms determining dissemination of cutaneous lymphoma. Emerging evidence indicates that cellular metabolism is a critical factor in cancer progression. Here, we demonstrate that lymphoma invasion and spread depends on metabolic dynamics that can be modulated by environmental factors such as dietary nutrient supply.

Methods: Malignant T and B cell lines and isolated Sézary cells were used in vitro and in mouse xenograft studies to assess invasive and disseminative properties and metabolic phenotypes through genetic, pharmacologic, and dietary modulations.

Metabolic dynamics...*continued*

Results: We find that malignant T and B cells oscillate between non-invasive and highly invasive states providing a rationale for novel treatment approaches "locking" cells into a non-invasive state. This oscillation follows variations in mitochondrial reactive oxygen species (mROS) which we identify as a critical link between cellular metabolism and invasive properties. The highly invasive state shows a reprogrammed metabolic profile with increased glycolysis and reduced oxidative phosphorylation (OXPHOS) indicating a critical role of bioenergetic wiring in disease dissemination. Furthermore, the highly invasive state shows redoxmediated activation of HIF-1a which is necessary for in vitro migration and in vivo dissemination of malignant cells. Interestingly, the metabolic reprogramming is independent of HIF-1a placing it in between metabolic dynamics and dissemination potential of leukemia/lymphoma cells. Importantly, we find that altering the metabolic environment through high-fat and ketogenic diets markedly decrease disease dissemination in xenograft studies. These low-carbohydrate diets induce a shift away from the glycolytic, highly invasive state towards OXPHOS and limited disease dissemination in xenograft models.

Given the relatively small research community in (cutaneous lymphoma), CLARIONS-funded research can make a big impact in the field...(F)unding is hard to get in general and for a rare disease even harder due to competition with other hematologic malignancies.

Stefan M. Schieke, MD,
CLARIONS Recipient, YIA Recipient

Conclusion: We have identified a process whereby bioenergetic rewiring promotes dissemination of leukemia and lymphoma cells through mROS and HIF-1a. Our findings highlight the critical role of metabolic dynamics and nutrient environment in regulating disease dissemination and help to develop novel therapeutic strategies to prevent progression of T cell lymphoma.

Additional Research Credits (CoAuthors):
Roy, Sushmita; Khan, Hamidullah; Nihal, Aman; Buethe, Patrick: University of Wisconsin, Madison, United States of America

Thank you to the physicians who served on this year's Scientific Review Council:

Stuart Lessin, MD, Committee Chair
KGL Skin Study Center

Steven Horwitz, MD
Memorial Sloan Kettering Cancer Center

Youn Kim, MD
Stanford Cancer Institute

Lauren Pinter-Brown, MD
Chao Family Comprehensive Cancer Center

Pierluigi Porcu, MD
Thomas Jefferson University

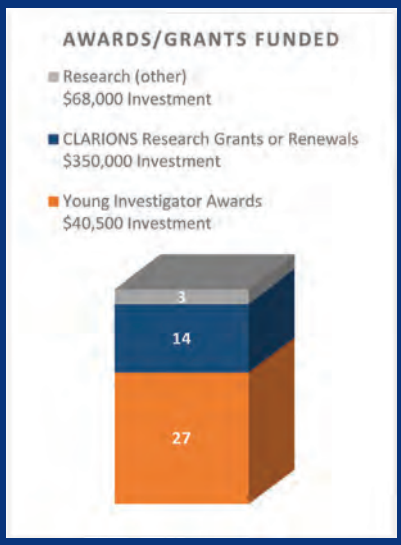
Thank you to all of our generous donors, including the

DRS Martin & Dorothy Spatz Foundation

for making our involvement in cutaneous lymphoma research possible.

Why Fund Research? The Impact of Funded Research

As a patient organization formed with the primary purpose of providing education and support, while raising awareness around the world regarding cutaneous lymphomas, it was not always clear the role the Cutaneous Lymphoma Foundation (CLF) would have in research. In short time, both the scientific and patient community expressed the need and their desire for CLF to include "facilitating research" as part of its Strategic Plan. CLF listened and, since 2005, has provided a combined total of 44 awards and grants to support research(ers) around the world.



With nearly $500,000 spent directly on cutaneous lymphoma research(ers) - can you imagine the impact this investment has made in the world of cutaneous lymphomas?

For a rare disease, such as cutaneous lymphoma, it is significant that the vast majority of both the Young Investigators and CLARIONS recipients remain working in the area of cutaneous lymphoma. Their areas of focus spread from disease understanding, diagnostic methods, treatments, quality of life impact, in addition to others. Several researchers have expressed that receiving funding from CLF gave added visibility and validation to their work when applying for, and being awarded, additional funding. Not only does funding research advance care, treatment options and hopefully lead us toward a cure, but each paper published as an outcome from CLF-funded research also raises awareness about cutaneous lymphomas throughout the larger clinical community.

CLARIONS Funded Research Updates:

- Research to identify patient-specific dysfunctions that could be addressed efficiently with personalized therapeutic approaches. This could greatly speed progress to finding therapies for patients. - Patrizia Fuschiotti, PhD
- Work led to advances in patient risk stratification by identifying markers that predict CTCL disease progression. Improved ability to predict disease progression from early stage MF by quantifying the frequency of malignant T cell clones and CD8+ T cell density in the skin. - John O'Malley, MD
- Developing biomarkers to identify rare treatment resistant CTCL cells that are likely responsible for eventual disease relapse. - Stefan M. Schieke, MD
- Study provided a better understanding of the mechanisms by which thyroid hormones sustain CTCL cell survival and the role of the thyroid hormone membrane receptor, integrin αvβ3, in sending prosurvival signals to CTCL and as a potential target for CTCL. It also examined how the drug cilengitide targets this receptor and allows rexinoids to work better. Targeting this mechanism could constitute an effective and potentially low-toxicity chemotherapy-free treatment of CTCL patients. - Leandro Cerchietti, MD

Bringing the Patient Voice to Research

It is an exciting time in cutaneous lymphoma research as research for improving diagnostic methods and treatments is occurring globally. There is also a growing understanding that what directs the course of research, should include the patient perspective, such as the recent request for your participation in the Quality of Life survey by researchers from the University of Washington/Seattle Cancer Care Alliance and the University of Pennsylvania . While clinicians and researchers are the experts on the science, it is patients who are the experts on how cutaneous lymphoma's unique set of symptoms (such as intolerable itching, negative impact on sleep, and frequent infections) and non-clinical issues (like treatment travel time and costs, depression and anxiety due to appearance) impacts their daily life.

Ensuring that the "patient voice" is heard within the research arena is integral to the Cutaneous Lymphoma Foundation's mission. As the cutaneous lymphoma research community increasingly becomes a globally collaborative community, the Foundation is committed to participating both within the U.S. and abroad to make certain patients are represented.

As the representative of the Foundation and the community we serve, Susan Thornton, CEO, regularly attends and contributes to the annual meetings organizations listed in the column on the right. Each plays an important role in cutaneous lymphoma research and care.

In addition to the one-on-one interactions that Susan is able to have with clinicians, researchers, and pharmaceutical representatives at these meetings, she has also had opportunities to present during the meetings' general sessions as a guest speaker or panelist. Some of these opportunities have included:

- As a patient's voice among a physician panel on quality-of-life at last year's EORTC meeting, Susan shared valuable cutaneous lymphoma-related data collected in the Lymphoma Coalition's patient survey. She has been asked to be a panelist at this year's meeting in Athens, Greece, where she will also host a corresponding patient program.
- Susan was invited to present on the patient experience at the USCLC Workshop; her presentation included patients sharing in their own words via video the impact cutaneous lymphoma has on their daily life. The aim of the USCLC Workshop is to review the current state and future direction of research in cutaneous lymphomas and other lymphoproliferative disorders.
- Being a panelist with pharma representatives and patient organization leaders at Eye for Pharma meetings to talk about the power of incorporating the patient perspective into the drug development process.
- As a presenter at the Global Skin annual meeting, Susan brought the patient perspective to the plenary session with two dermatologists who spoke about the clinical development pipeline.

The Cutaneous Lymphoma Foundation recognizes the vital importance of the patient experience in informing the direction of cutaneous lymphoma research and is committed to making sure your voice is heard.

Meetings Attended Annually:

- T-Cell Forum
- United States Cutaneous Lymphoma Consortium (USCLC) Workshop
- American Academy of Dermatology (AAD)
- Dermatology Nurses Association (DNA)
- International Society for Cutaneous Lymphomas (ISCL)
- Society of Investigative Dermatology (SID)
- American Society of Clinical Oncology (ASCO)
- European Organization for Research and Treatment of Cancer (EORTC) - Cutaneous Lymphoma Taskforce
- American Society of Hematology (ASH)
- European Academy of Dermatology and Venereology (EADV) - when pertinent to cutaneous lymphoma
- International Alliance of Dermatology Patient Organizations - Global Skin Patient Leader Summit
- Lymphoma Coalition Patient Leader Summit

Other Attended Meetings Include:

- World Congress for Cutaneous Lymphomas - occurs every 5 years
- World Congress of Dermatology - occurs every 4 years
- International Society of Investigative Dermatology - occurs every 5 years
- UK Cutaneous Lymphoma Group - by invitation as a presenter
- World Orphan Drug Conference - by invitation
- PhARMA - by invitation
- Eye for Pharma - patient summit, value summit - by invitation as a speaker
- Rare Disease Day at the National Institutes of Health (NIH)
- U.S. Food and Drug Administration (FDA) meetings - throughout the year
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) meetings - throughout the year (NIH institute)

CUTANEOUS LYMPHOMA FOUNDATION
PO Box 374
Birmingham, MI 48012

TIME SENSITIVE MATERIALS ENCLOSED

Help us Fund Research Now to Change the Future of Cutaneous Lymphoma

As we reflect on the impact we've made through funding cutaneous lymphoma research, we are driven by what can, and will be done, with an even greater investment!

We want to continue to fund pathways that can lead to a cure. In the days ahead, we will be launching the all-new Cutaneous Lymphoma Catalyst Research Grant, in addition to our continued support of researchers through our Young Investigator Awards.

Stay tuned...with your support, there are more plans to be unveiled soon!

We are grateful for your trust, generosity and commitment to our community.

Support the Cutaneous Lymphoma Foundation

Online: www.clfoundation.org/giving-online

Phone: 248.644.9014, ext. 5

Mail: P.O. Box 374 Birmingham, MI 48012
(A remittance envelope has been enclosed for your convenience)