Cutaneous Lymphoma Foundation

2015 Research Report

Cutaneous Lymphoma Foundation and Research

We are pleased to share with you our new Research Report. The Research Report will be published annually to provide an overview and update of the clinical research supported by the Cutaneous Lymphoma Foundation. In 2012, the Cutaneous Lymphoma Foundation expanded its commitment to advancing research specific to cutaneous lymphoma with the launch of the CLARIONS (Curing Cutaneous Lymphoma by Advancing Research, Innovation and Offering New Solutions) research awards program, the first of its kind and dedicated exclusively to funding cutaneous lymphoma research. The goal of the CLARIONS research awards is to support researchers interested in conducting innovative cutaneous lymphoma studies that will help uncover causes, advance treatments and improve quality of life for patients. The first CLARIONS award winners were announced in December, 2013 for funding January - December, 2014. In addition to renewing the funding for these recipients for an additional year in December, 2014, we were privileged to name two new CLARIONS award recipients who will receive funding for January – December, 2015.

Since 2003, the Cutaneous Lymphoma Foundation has presented the Young Investigator's Awards (YIA), to physicians and scientists in the specialties of medical oncology and dermatology. These travel grants support attendance at the annual meetings of the American Society for Hematology (ASH) and the Society for Investigative Dermatology (SID), where YIA recipients present their research on cutaneous lymphoma. Over 15 recipients have received the YIA award and many continue to be actively engaged in cutaneous lymphoma research.

I would like to thank my medical professional colleagues who have volunteered to participate in the Cutaneous Lymphoma Foundation research award application review process. Their commitment and integrity creates a merit-based process that ensures the highest quality cutaneous lymphoma research. A special thanks to former CLF Board Member, Dr. Pierluigi Porcu for his vision and leadership in the development of the CLARIONS award program. The cutaneous lymphoma community appreciates your time and expertise to support this effort.

We look forward to continuing to expand our funding to support research and as always, our commitment to those affected with cutaneous lymphomas remains steadfast and unwavering.

Stuart Lessin

Stuart Lessin, MD
Member, Board of Directors
Cutaneous Lymphoma Foundation

Thank you to the physicians who have served on the CLARIONS Scientific Review Board:

Thomas Kupper, MD, Committee Chair - *Brigham and Women's Hospital*
Francine Foss, MD - *Yale Cancer Center*
Lars French, MD - *University Hospital Zurich*
Susan Geyer, MD - *Ohio State University*
Youn Kim, MD - *Stanford School of Medicine*
Stuart Lessin, MD - *KGL Skin Study Center*
Barbara Pro, MD - *Jefferson Cutaneous Lymphoma Center*
Steven Rosen, MD - *City of Hope National Medical Center*
Jonathon Said, MD - *UCLA Medical Center*

CLARIONS Research Grant

Award Recipients - January, 2015 – December, 2015

Sergei Koralov, PhD

Assistant Professor of Pathology
New York University School of Medicine

Examining the Role of Commensal Bacteria in Cutaneous T-cell Lymphoma

Dr. Koralov's study will look at skin-resident bacteria as a critical element in cutaneous T-cell lymphomas (CTCL) initiation and progression. In CTCL, transformed lymphocytes (white blood cells) accumulate at the skin – the barrier of our bodies to the outside environment. Inflammatory conditions such as psoriasis and dermatitis have long been associated with specific bacteria that live on the skin. CTCL patients often suffer from bacterial infections and the correlation between the presence of certain strains of Staphylococcus aureus (bacteria) and disease severity has been observed. Commensal and pathogenic bacteria present at the skin can influence differentiation, survival and the production of lymphocytes through expression of bacterial proteins that are in turn recognized by these cells of the immune system – thus bacteria may contribute to a microenvironment that is ideal for tumor initiation and progression.

To gain greater insight into the development of CTCL, Dr. Koralov has established a mouse model of the disease that faithfully recapitulates many pathological features of this cancer. His team will study the role of skin microbial communities in triggering cancer pathogenesis. Specifically, they will attempt to establish a causative link between microbial communities on the skin and CTCL initiation by comparing disease progression in mice maintained in entirely aseptic, germ-free conditions to those either colonized with single bacterial species or maintained in a normal environment where the skin of the animals is colonized with a wide spectrum of skin resident microbes. This study will examine whether specific bacterial products are responsible for promoting T-cell malignant transformation in the context of CTCL and whether bacteria and bacterial products can together with genetic predisposition, influence disease initiation and progression. Dr. Koralov and his team believe that these studies will provide significant insight into CTCL disease pathogenesis and thus impact selection of future therapies for this malignancy.

Tae Jin Kim, PhD

Postdoctoral Scholar
Stanford University School of Medicine

Capturing Radiation-Induced Light to Improve Electron Radiotherapy of Cutaneous T-Cell Lymphoma

Dr. Kim's study will develop a new method that can 'see' radiation during cutaneous T-Cell Lymphoma (CTCL) treatments. Stanford School of Medicine is historically one of the pioneers of modern electron radiotherapy for CTCL, where the renowned Stanford technique exposes the patient with two oblique electron beams while maintaining one of six poses. However, since radiation is invisible and the treatment area is large, there may be missed spots (cold spots) depending on the patient's size, shape and pose. This would result in the cancer cells residing within the cold spots not being completely eradicated. Currently, it is impossible to identify regions of the skin where this occurs.

In order to solve this problem, Dr. Kim formed a team consisting of experts in Mechanical and Electrical Engineering, Biomedical Physics and Radiation Therapy to develop a method akin to adding an 'eye' to the total skin electron therapy. To accomplish this, pictures of light that emanates from the patient's skin will be taken, the same type of light which was first observed by Pavel Cherenkov when fast electrons hitting a target emitted a faint light, and reconstruct the radiation dose in real-time 3D to highlight the cold spots. The team will also take pictures of light from the radiation beam to verify the correct functioning of the linear accelerator. This phenomenon is based on the fact that nitrogen gas molecules in the atmosphere can also emit dim light when a fast electron collides with them. In the successful completion of the project, therapists will be able to perform total skin electron therapy with higher accuracy by avoiding cold spots, thus providing the patients with an improved treatment and potentially lowering the risk of recurrence.

CLARIONS Grant

CLARIONS Award 2015 Calendar

February 20, 2015
Public Announcement of Request for Application

July 31, 2015
Application Deadline

August - October, 2015
Scientific Review Board review

November 1, 2015
Recipients notified of award

December, 2015
Grant awards announced at ASH Meeting

January, 2016
Disbursement of Award and beginning of new award cycle

This report was made possible through the support of our corporate partners:

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Clinical Trials Currently Underway

We are always excited to learn about new clinical trials underway which are specific to cutaneous t-cell lymphoma. Below are a few that we are following closely and hope will offer new treatment options down the road:

Angimmune – Resimmune® or A-dmDT390-bisFv(UCHT1), contains an immunotoxin, which is a type of protein that targets and depletes a high percentage of T-cells in the body, both malignant and normal. After the normal T-cells are depleted, they are able to grow back faster than malignant cells. Clinicaltrials.gov Identifier: NCT00611208

Oncosec Medical – A Phase II safety and efficacy trial using ImmunoPulse to deliver DNA IL-12 (a gene that triggers cells to attack and eliminate cancerous cells) in patients with early and late stage cutaneous T-cell lymphoma. Clinicaltrials.gov Identifier: NCT01579318

Tetralogic Pharmaceuticals - SHAPE, a second clinical-stage product candidate, is an HDAC inhibitor being developed for topical use for the treatment of CTCL. SHAPE is a novel therapeutic intentionally designed to maximize HDAC inhibition locally in the skin with limited systemic exposure. As a result, SHAPE has characteristics that could allow it to be used topically over large body surface areas with minimal systemic absorption. By potentially avoiding toxicities typical of orally-administered HDACi, SHAPE may provide a more favorable safety profile than an HDAC inhibitor delivered systemically. Clinicaltrials.gov Identifier: NCT02213861

For a comprehensive list of ongoing clinical trials visit: *www.clfoundation.org/research/clinical-trials/usa.*

Award Recipients - January, 2014 – December, 2015

Leandro Cerchietti, MD

Assistant Professor of Medicine
Weill Cornell Medical College

Integrin avb3 Acting as Membrane Receptor for Thyroid Hormones Mediates Angiogenesis in Malignant T-Cells

In previous studies, Dr. Cerchietti's team discovered that cutaneous T-Cell Lymphoma (CTCL) depends upon the function of a hormone for survival. They also determined that this hormone, called thyroid hormone, feeds CTCL cells by two different mechanisms. One of these mechanisms is located in the nucleus of every cell and the other is located at the outer surface of CTCL cells. Since thyroid hormone is necessary for normal life, it can't be simply removed from the body. The team discovered that it is possible to inhibit the outer surface mechanism in CTCL cells without affecting the nuclear mechanism present in every cell. By doing so, CTCL cells are destroyed without affecting other cells necessary for the body's normal function.

One of the most useful drug treatments for CTCL, generically called "rexinoids", decrease the amount of thyroid hormone in the body, forcing physicians to prescribe thyroid hormone replacement therapy to avoid serious side effects. It is believed that thyroid hormone replacement therapy could decrease the anti-lymphoma effect of "rexinoids". Dr. Cerchietti's study will determine if thyroid hormone interferes with the anti-lymphoma effect of "rexinoids" and also if, by inhibiting the thyroid hormone effect at the surface of CTCL cells that were discovered, they can increase the anti-lymphoma effect of "rexinoids". If successful, the study may offer doctors an improved treatment for CTCL.

Rachael Clark, MD, PhD

Associate Professor - Department of Dermatology
Harvard Medical School

Low Dose XRT as a Cure for Skin Resident T-Cell Lymphomas

Dr. Clark's study will examine low-dose irradiation therapy as a therapy and as a potential cure for Mycosis fungoides (MF). MF is a type of cutaneous T-cell lymphoma (CTCL) characterized by long-standing inflamed skin lesions containing a population of malignant T-cells. Although several topical therapies can suppress the disease, none are curative. Clinically, it has been found that two very low doses (4Gray) of irradiation therapy (XRT) can induce long standing improvement and a perhaps a cure of the skin lesions. Because malignant T-cells are only present within inflamed skin lesions in MF patients, a treatment that kills malignant T-cells in skin has the potential to be a true cure for this otherwise lifelong disease.

Identification of the malignant T-cells in MF is difficult and this has made it difficult to evaluate if a particular therapy actually kills malignant T cells or simply suppresses their activation. Using a new cutting edge technology called deep TCR gene sequencing, Dr. Clark's team can now identify and quantify both the malignant and healthy T-cells in MF skin lesions.

Dr. Clark will biopsy MF skin lesions before and after low-dose XRT to determine if the malignant T-cells are killed by this therapy. If so, low-dose XRT may be a true cure for MF. Also, they will study if the healthy T-cells, which have been shown to fight off infection and protect against cancer recurrence, survive in these areas of treated skin. If the initial clinical observations hold true, low-dose XRT may represent a true cure for MF that selectively kills malignant T-cells while sparing normal immunity.

Young Investigator Award

2014 SID Award Recipient

Filberto Cedeno Laurent, MD, PhD
Cutaneous Oncology Fellowship
Dermatology Department
University of Pennsylvania

Reduction of IL-31 Expression During Therapy of CTCL Correlates with Improved Pruritus*

Pruritus (itching) is one of the most common and debilitating symptoms in patients with cutaneous T-cell lymphoma (CTCL). This symptom does not typically respond well to conventional treatments with anti-histamines and neuroleptic drugs, and only improves when the lymphoma is treated. A recently discovered molecule, IL-31, has been shown to be produced by the malignant T-cells. For the first time, Dr. Laurent's team showed that the levels of this molecule are reduced when the condition is treated with different modalities. They hypothesized that treating patients with CTCL may reduce the expression of IL-31 and concomitantly help to suppress their pruritus as lower levels of IL-31 parallel diminished itching in the treated patients. They showed that in vitro treatment of primary malignant T-cells with corticosteroids or the histone deacetylast (HDAC) inhibitor Vorinostat, significantly reduces the level of IL-31 at the protein level. Similarly, they compared IL-31 expression from malignant and non-malignant T-cell populations and after in vivo treatment with another HDAC inhibitor (Romidepsin), currently in phase III clinical trial. The data revealed that both treatments effectively mitigate pruritus in patients and that response directly correlates with lower levels of IL-31. Therefore, the blocking the IL-31 pathway is a key factor for symptomatic relief of patients with intractable pruritus in CTCL.

**Abstract Co-Authored by, E. M. Singer, University of Pennsylvania Dermatology, B. M. Benoit, University of Pennsylvania Dermatology, M. Wysocka, University of Pennsylvania Dermatology, G. Yosipovitch, Temple University Dermatology, K. J. Ellen, University of Pennsylvania Dermatology, A. H. Rook, University of Pennsylvania Dermatology*

Past YIA Award Winners

2003: Karen McGinnus, MD, University of Pennsylvania (SID)

2004: Narin Apisanthanarax, MD, Case Western (SID)

2005: Larisa Geskin, MD, University of Pittsburgh (SID)

2006: Christiane Querfeld, MD, Northwestern University (SID)

2007: Rachael Clark, MD, PhD, Harvard Medical School (SID)

2008: Xiao Ni, M.D., PhD, MD Anderson (SID)

2009: Chunlei Zhang, MD, PhD, MD Anderson (SID)

2010: Makato Sugaya, MD, University of Tokyo, Japan (SID)

2011: Oleg E. Akilov, MD, PhD, University of Pittsburgh (SID); Salvia Jain, MD, NYU (ASH)

2012: Rei Watanabe, MD, PhD, Harvard Skin Disease and Research Center (SID); Georgia Saporiti, MD, University of Milan, Italy (ASH)

2013: Sima Rozati, MD, University Hospital Zurich (IID*); María Florencia Cayrol, PhD, University of Buenos Aires, Argentine (ASH)
**International Investigative Dermatology Meeting*

2014: Filiberto Cendeno Laurent, MD, PhD, University of Pennsylvania (SID); Tianjiao Wang, PhD, University of Michigan (ASH)

We wish to thank the members of the Cutaneous Lymphoma Foundation's Medical Affairs Committee for their service in selecting the Young Investigator Award recipients.

2014 ASH Award Recipient

Tianjiao Wang, Ph.D.
Department of Internal Medicine
Division of Hematology and Oncology
University of Michigan

T-Cell Receptor Engagement Confers Resistance to Chemotherapy in T-Cell Lymphoproliferative Disorders*

T-cell lymphomas (TCL) are a group of heterogeneous T-cell lympho-proliferative disorders. The first-line treatment for the aggressive/advanced TCL is chemotherapy (e.g. CHOP), however, frequent occurrence of chemo-resistance among the TCL patients results in dismal outcome with median overall survival of approximately 2 years for patients with aggressive TCL. It is thus important to understand the mechanism of chemo-resistance in TCL for improving its therapeutics.

T-cell receptor (TCR), a molecule on the T-cell surface, is widely expressed in TCL, approximately 95% of the time. However, its role in TCL pathogenesis is unknown. To elucidate the role of TCR in TCL pathogenesis, Dr Wang's team studied in vitro TCL cell lines, TCL xenografts in mouse and clinical patient specimens using molecular, cellular and genomic approaches. They found that macrophages were abundant in TCL microenvironment and macrophages could trigger TCR signaling and TCL proliferation, which resulted in chemo-resistance in TCL. Agents targeting TCR signaling pathway significantly inhibited chemo-resistance in TCL. Their finding indicates that TCR signaling plays a role in TCL pathogenesis and chemo-resistance and may serve as rational therapeutic targets in TCL.

**Additional contributors to this abstract include Avery Polk, BS, Ye Lu, MD and Ryan A. Wilcox, MD, PhD*

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