The Stanford Multidisciplinary Cutaneous Lymphoma Program (MCLP) is an international leader in cutaneous lymphoma research offering a multidisciplinary, personalized approach to diagnostics, prognostication, and treatment for patients with the rare subset of Non-Hodgkin’s Lymphoma (NHL) with primary skin involvement. 25 years ago, departments of dermatology and radiation oncology joined forces to initiate an unprecedented collaborative clinical and research program in cutaneous lymphoma. We have since added our medical oncology and BMT members to our core program and continue to expand our collaborative network for basic discoveries and to find better therapies. Together, we have advanced the standard of care for cutaneous lymphomas worldwide, pioneering new diagnostic and prognosticating methods and breakthrough therapies and offering novel treatments that are not yet available at other institutions. Over the years, Stanford MCLP has also partnered closely with industry leaders to bring promising new therapies for FDA approval, thus allowing general use of new therapies to treat these rare lymphomas. In addition, the Stanford MCLP offers innovative, interdisciplinary clinical trials that integrates discoveries in medical therapies and/or combine new approaches of medical and radiation therapies. This ranges from utilizing new immune therapies that stimulate patients own immune system to fight against cancer cells to utilizing health donor stem cells to replace the job of the patient’s defective immune system.

Our overarching goal is to continue building our interdisciplinary collaborations, which is the basis for Stanford’s unparalleled clinical and research achievements. We have put together experts and leaders in their clinical and research focus, bringing the talent of many, to find answers in cutaneous lymphoma. There is no better institution to realize such impactful interdisciplinary goals in a rare disease such as cutaneous lymphoma. This was made possible with the exceptional generosity of the Haas Family, in particular Peter Haas, Jr. The Haas Family has fueled and catalyzed our collaborative network and enabled the integration of the Stanford’s cutting-edge research that led to the groundbreaking discoveries with Khavari and Chang groups. Our blood stem cell program built with Wen-Kai Weng has now saved lives that would have been lost. Moreover, with Haas Family support, our program has been able to stimulate the needed research in immune mechanisms and immunotherapies, allowing us to recruit Michael Khodadoust, the newest faculty member of our MCLP. In our special 25th year program update, we highlight the key areas of research and outcome led by our core program and collaborative leaders of the Stanford MCLP.
Collaborative Genomics and Epigenomics Discoveries
The Stanford MCLP established early collaborations with Paul Khavari and Howard Chang, who are world leaders in cancer genomics and epigenomics. Their research defines the basic genetic code/message and mechanisms by which the cancer cells arise, survive, and behave in the human body. Determining the alterations in the basic genetic code or message (e.g., mutations) and learning the mechanisms of how they are regulated enables us to find drugs or therapeutic approaches that can target those abnormalities and eliminate cancer cells.

Collaborative work with the Khavari laboratory involved sequencing lymphoma genomes (DNA code) from a large series of patients treated in the MCL clinic at Stanford. This work identified key genetic alterations that underlie and drive cutaneous lymphoma. **This effort led by Paul Khavari and colleagues discovered a new role for a mutation in TNFR2, a protein expressed more on the lymphoma cells, that provides cancerous cells a survival advantage by stimulation of a T-cell survival and activation pathway.** Additionally, a number of other molecular targets were identified for which available therapeutics can now address. Other groups have confirmed our findings as well. Investigations are now underway to explore targeted therapies against the TNFR2 and its related pathways in cell culture and animal models. Our findings have energized efforts by investigators and industry to translate the discovery of these actionable targets to therapeutics, and thus clinical trials with the relevant therapies are currently ongoing in patients with cutaneous and systemic T-cell lymphomas.

We will continue to collaborate with the Khavari laboratory as the samples from these patients on clinical trials will be tested for the presence of the genetic alterations, and we would need to modify the therapeutic strategy as we learn more about any mechanisms of resistance or escape from these targeted therapies.

Epigenetic studies in cancer leads to understanding of the gene expression and function that occur in the cancer cells without involving a change to the basic genetic code. A significant portion of genetic codes are expressed and regulated in the patient is learned from research of the epigenetics of cancer. Thus, a comprehensive understanding of cancer biology includes not only knowing the basic alterations in the genetic codes but also the mechanisms of how they are expressed and regulated, that are specific to each patient like a barcode. **Our collaboration with the Chang laboratory revealed the epigenetic landscape of cutaneous lymphoma.** Using a new technology invented at Stanford (by Howard Chang and colleague), this research showed that cutaneous lymphoma cells rely on three distinct gene expression programs. This research further provided the first predictive indicator of response to a class of drugs called histone deacetylase inhibitors that can eliminate cancer cells. Current efforts include developing cutting-edge single-cell methods to capture the mutant T-cell receptor and epigenetic states from cutaneous lymphoma cells. This type of new information, enabled only with novel, cutting-edge methods, can improve precision diagnosis, aid in tracking of disease, assist in treatment selection, and help understand how the immune system can fight lymphoma cells effectively, critical for our goal in advancing immunotherapies in cutaneous T-cell lymphoma.

Development of Immune Therapies
Immunotherapy is revolutionizing the treatment of cancer. Investigators at Stanford have led the global effort in immunotherapy in cancer including lymphoma/cutaneous lymphoma. For decades, we have been innovating new ways to target and poison cancer cells. Immune therapies work in a completely different way compared with conventional chemotherapies. The target of immunotherapy drugs is not necessarily the cancer itself, but rather the normal immune system of patients with cancer. Our immune systems protect our bodies from foreign invaders, such as bacteria and viruses. We now know that by boosting the immune system in the right way, it can also eradicate cancer. **With Dr. Michael Khodadoust at the helm, the Stanford MCLP has made it a priority to bring new immunotherapies to our patients with cutaneous lymphomas.** Dr. Khodadoust has joined our MCLP in November 2015, and since has been instrumental in advancing our immunotherapy goals. His success at Stanford has culminated in high impact papers and we are excited to have him co-direct our program. We anticipate great contributions from the Khodadoust laboratory.

As cancers develop, they sometimes acquire the ability to shut off the immune response around them, allowing them to hide from the immune system. Among the most exciting breakthroughs in immunotherapy have been the emergence of so-called immune checkpoint inhibitors that can “release the brakes” on the immune system, allowing them to return to their job of fighting cancer. Last year, we reported the results of the first trial of this exciting new class of therapy to be specifically focused on patients with cutaneous T-cell lymphoma. We found that treatment with pembrolizumab, a drug (antibody) that targets the immune checkpoint and releases the brakes, could induce very long lasting responses, even in patients with difficult to control lymphomas. We are leading an effort in collaboration with the National Cancer Institute to better predict patients who will benefit from this potentially game-changing therapy and to understand how to further exploit the immune system in the fight against cutaneous lymphomas. We hope to combine with therapies that have the effect of stepping on the gas pedal as well as releasing the brakes, allowing even more improved outcome.

One of the mysteries surrounding immunotherapy is how the immune system can distinguish a cancer cell from a normal cell. Unlike bacteria and viruses, cancer cells are genetically nearly identical to the normal cells in our bodies. It is no small feat for the immune system to separate the good cells from the bad ones. Yet, our immune systems are often
capable of picking up subtle clues genetically encoded into lymphoma cells to weed out cancer cells from their normal counterparts. Uncovering these clues would enable us to design new strategies to train the immune system to better attack cancer.

Research led by Dr. Khodadoust seeks to identify cancer immune targets, called antigens, which allow the immune system to recognize cancer. We have long known that these antigens reside on the surface of the lymphoma cell within specialized proteins that present them to the immune system. Traditional strategies to find antigens can only indirectly infer the antigens on the surface of cancer cells. In a collaboration with a team of preeminent experts across multiple disciplines at Stanford, we have developed a new system to directly purify antigens from the surface of lymphoma cells and then determine their exact identity by a powerful, mass spectrometry. Of particular interest to us are the antigens that are created by the genetic (DNA) mutations found in cancer cells. Such antigens, dubbed neoantigens, have increasingly been found to drive clinical immune responses. However, because these antigens are unique for every patient, it has been exceedingly difficult to identify them.

To help study this potentially critical class of personalized antigens, we integrate the information from DNA sequencing of the lymphoma cells to determine all the potential lymphoma-specific mutated proteins for a given patient. We can then focus our search on these critical targets, giving us an unprecedented ability to characterize all potential lymphoma targets for the immune system. Michael Khodadoust and colleagues successfully pioneered this strategy by profiling the immune targets of mantle cell lymphoma, a rare type of non-Hodgkin lymphoma. Research led by the Khodadoust laboratory is now using this strategy to crack the immunologic code for cutaneous T-cell lymphomas. Exciting early results have revealed a new class of immune targets uniquely found in T-cell lymphomas that we think may be the key to harnessing the power of the immune system to treat cutaneous lymphomas.

**Novel Donor Blood Stem Cell Therapy and New Technology to Monitor Cancer Cells**

Until the discovery of donor blood (hematopoietic) stem cell transplantation therapy, no treatment could cure patients with advanced stages of cutaneous T-cell lymphoma. This involves replacing the defective immune system of the patient with the well-functioning immune systemic of the healthy donor, otherwise called an allogeneic (from another person) blood stem cell transplantation. However, these donor stem cell transplantations have also been associated with undesirable outcomes, as the donor cells can attack the good cells (graft versus host disease, GVHD) as well as the lymphoma cells in the recipient (the patient). GVHD can lead to severe compromised body state and require drugs with significant side effects or lead to death.

Stanford investigators developed a novel transplantation regimen that reduces this unwanted GVHD but still preserves the desired graft versus lymphoma effect. **Wen-Kai Weng has led our MCLP to explore this original Stanford regimen, now tailored for our patients with cutaneous T-cell lymphoma.** This resulted in the design of a clinical trial using a novel non-myeloablative (less damage to the bone marrow) transplant regimen consisting of total skin electron beam therapy (TSEBT), total lymphoid irradiation and anti-thymocyte globulin (TSEBT-TLI-ATG). This smart regimen not only reduces GVHD but also further eliminates any residual lymphoma by irradiating the lymph nodes and removing the cancerous T-cells from the blood. The trial opened in May 2009, and currently 34 patients with advanced disease have received blood donor stem cell transplantation using our regimen. This is the largest patient experience in the world in this short time frame. Compared to other center results using different regimens, we found outstanding safety and tolerability with a very low 1-year transplant related mortality of 3% (versus >20% with other regimens) and significantly low incidences of acute and chronic GVHD. The percent of patients who have recurrence/worsening of lymphoma and who are surviving after allogeneic transplantation compared favorably to other centers’ experience. The results from our clinical trial will have significant impact on the application of the donor blood stem cell transplantation in patients with advanced stages of cutaneous T-cell lymphoma. In fact, several groups (Dr. Sean Whittaker at Guy’s and St Thomas’ NHS at London, UK; Dr. Julia Scarisbrick at University of Birmingham, Birmingham, UK) have adopted our novel, less toxic regimen in treating their patients with advanced disease. We will continue this clinical trial as our experience has revealed that this novel transplantation approach has prolonged the lives of those who otherwise would not have survived their advanced lymphoma.
Wen-Kai Weng and colleagues were also instrumental in establishing a new, highly sensitive and specific tool for tracking small amounts of lymphoma that is not measurable by existing standard methods. This method utilizes molecular sequencing of the genetic code for the patient-specific part of the T-cell receptor. This new method developed by Weng laboratory can detect one cancer cell in 1,000,000 mixed cells, whereas the older method can detect at best one cancer cell in 1,000 mixed cells. This newer detection tool enables us to determine if a patient is truly cured and helps track and predict the recurrence of their lymphoma with greater sensitivity and specificity than any currently used methods in T-cell lymphoma.

Another ongoing effort led by Wen-Kai Weng is using a novel approach to target patient-specific cancer cells in T-cell lymphoma. Cancerous T-cells are characterized and distinguished from non-cancerous T-cells by their unique T-cell receptor signature, which can be identified by the same sequencing tool that is used to track patient-specific lymphoma cells. The concept proposed by Weng and colleagues is to develop a small panel of antibodies that can target the most commonly expressed cancer cell-specific T-cell receptor sequences (TCR Vβ sequences). Alternatively, enhanced drivers with more potent activity, chimeric antigen receptor (CAR-T) approach may be designed, again targeting the more cancer-specific T-cell receptor components along with anti-cancer T-cells that result in eliminating cancer cells. This research involves testing the therapy first in an animal model derived with patient samples and then move onto a safety-based early clinical trial in patients.

Innovative Radio-Immune Therapy
Radiation therapy remains the single most reliable and effective therapy in patients with cutaneous lymphoma. Stanford developed the original method of delivering electron beam radiation to the entire skin surface, called total skin electron beam therapy (TSEBT). TSEST can reduce the skin disease effectively in our patients; however, the traditional method used a lengthy course of radiation treatments (over 9-10 weeks) with frequent permanent hair loss and other radiation related side effects. Innovative approach led by Richard Hoppe of our MCLP uses significantly lower dose of TSEBT, maintains the efficient reduction in skin disease while reducing the skin related side effects significantly. Patients do not suffer permanent hair loss and can repair any skin side effects faster. Moreover, patients can receive the lower dose several more times in the course of their chronic disease. Given that the traditional more intensive regimen does cure either, this low-dose TSEBT approach was a hugely welcomed solution in our patients. After Hoppe and colleagues introduced the low-dose TSEBT, other expert centers have adopted this regimen, now utilized worldwide.

To take this further, we have combined this better tolerated yet effective radiation approach with new immune therapies, to prolong the great response attained from TSEBT. One such clinical trial led by Stanford is to combine the low-dose TSEBT with recombinant human interleukin-12 (IL-12), a very well-tolerated immune therapy given once a month to boost patients own immune system (stepping on the gas pedal) to fight their cancer cells. This immune therapy takes the protein fragments of cancer cells released with TSEBT into an immune augment machinery. Preliminary results demonstrate that IL-12 can be safely administered with low-dose TSEBT in our patients. The side effect profile was extremely benign as compared to standard systemic immune therapies including interferons. The overall response rate was very high with durable results. In collaboration with the industry sponsor that makes this agent, we are now developing the pivotal trial with the combination regimen in our patients with cutaneous T-cell lymphoma. We hope to continue exploring IL-12 and other immune therapies that can combine well with radiation therapy to improve the overall outcome of our patients.

Clinical Development of New Therapies and Approaches Based on Stanford Discoveries and/or Leadership
Stanford MLCP continues to serve as a world leader and collaborates with other institutions and industry partners to get newer therapies approved and available for patients. We also continue to infuse cutting-edge science that helps in learning how to make new therapies work better and to block resistance and/or escape routes generated by the cancer cells. Below is a partial listing of recent key clinical developmental success led by the Stanford MCLP:

- **Stanford's investigator-initiated trial of brentuximab vedotin, an anti-CD30 antibody-drug-conjugate, enabled patients to have access to this valuable drug and was instrumental in the recent (11/2017) FDA-approval in CTCL**
- **Stanford-led phase 1/2 trial of mogamulizumab (anti-CCR4 antibody therapy), which served as the basis for a pivotal phase 3 randomized trial**
  ⇒ The results of this phase 3 trial is under FDA review (the FIRST approval in the US of this new targeted therapy for any indication/diagnosis)
- **Low-dose/12 Gy TSEBT, the new standard (in NCCN guideline), used across the globe**
  ⇒ Combined with immunotherapy to prolong the great response of TSEBT
  ⇒ Pivotal randomized trial being developed with IL-12
- **Novel, less toxic, allogeneic blood stem cell transplantation with TSEBT+TLI/ATG, ↓ 1-year transplant-related mortality (<5% vs >20%) and can cure patients with advanced CTCL**
• Anti-PD-1 immunootherapy (pembrolizumab) in MF/SS-type of CTCL, Stanford-led, CITN-10 (multi-institution immunotherapy network) study
  ⇒ Comprehensive translational research underway including whole exome sequencing (collaboration with the NCI), antigen discovery platform, and exploring novel tissue characterization methods such as MIBI (new technology built at Stanford, Nolan laboratory)
  ⇒ Pembrolizumab + IFN-γ, CITN-13 being initiated, led by Stanford through CITN
• PI3K dual inhibitor + bortezomib or romidepsin, based on our genomics work with Khavari group, collaboration with Horwitz/MSKCC; targeted sequencing planned at Stanford
• Anti-KIR3DL2 (CD158k) antibody therapy, phase 1 study, Stanford/US lead, translational collaboration with Bagot/Innate-Paris.
  ⇒ New promising targeted therapy with limited side effects
• Anti-CD47 antibody therapy (novel immunotherapy), phase 1 study, CTCL translational expansion cohort, Stanford discovery platform (Weissman and Majeti laboratories)

Stanford MCLP as Global Co-Leaders of the Cutaneous Lymphoma International Consortium (CLIC), a Large-Scale Collaborative Research Platform for Greater Impact

Cutaneous T-cell lymphoma (CTCL) is recognized not only as a rare/orphan disease, but also as a very heterogeneous entity in its clinical presentation, histopathology, and cellular and molecular features. Thus, meaningful interpretation of research discoveries, their impact and applicability for the broader CTCL patient population will become profoundly greater with rigorously generated, well-defined large-scale data representing substantial number of patients. This vision brought together an international community of experts who united as a collaborative research alliance, the Cutaneous Lymphoma International Consortium, CLIC, with the shared goal of generating large-scale data for greater impact, ultimately to improve patient management and outcome.

The CLIC Steering Committee (SC) was established to optimize the global representation of leadership. Collectively, we recognized the potential challenges of building and sustaining an ambitious international platform, thus we identified initial objectives with stepwise build towards the ultimate goal to prepare the CLIC alliance for translational discoveries with large-scale testing and validation for optimal clinical applicability. As the first step, significant effort was channeled to establish the basic data dictionary and definitions for consistency of data across all international sites. Utilizing this basic language, we built the communication platform with which we developed the CTCL-tailored database that served as a solid foundation of data storage used for all CLIC-led projects. We developed training tools and standard procedures to optimize data quality and completeness. For the translational future, we initiated a parallel, federated Biobank where clinical samples remained at each institution. We have also established a process for digitizing glass slides for our pathology databank that will serve as the central pathology data source for CLIC-based projects.

With Stanford MCLP leading the CLIC machinery, our goals have been in three major parts (below figure); (A) infrastructure set-up, feasibility testing, and refinement, then (B) implementation of our first prospective study along with establishment of the linked Biobank and pathology databank, and (C) lastly development of our plans for the translational projects. This ambitious yet shared vision by the international community (CLIC) has been realized initially by the generous support of the Martin and Dorothy Spatz Foundation and the Haas Family Foundation. Since then, additional generous donors have made critical contributions to accelerate our progress. This has allowed us to be competitive for regional and federal funding resources.
Over the last 25 years, the Stanford MCLP has made transformative contributions in advancing the fundamental knowledge and improving the clinical management of patients with cutaneous lymphoma. By building our collaborative network at Stanford with partners who are leaders of cutting-edge science, we are now working tirelessly discovering and translating our basic research into the clinics, bringing new promising therapies to our patients, together.

We are immensely grateful to Peter Haas Jr. and the Haas Family Foundation for their most special support over the years. Peter Haas Jr. has been a role model of philanthropic partnership where his genuine, enthusiasm, kindness, insightful advice, and friendship has proven to be priceless. In addition to the Spatz Foundation, the notable support that provided the opportunity for matching funds included the gifts by Michael and Corie Koss, Iwan Sunito, David Gilbert, and Jennifer and Alan Varela and their family and friends.