

NIH R01 New Submission, *DRAFT SPECIFIC AIMS*

**Prospective Study to Establish a Prognostic Index Model and Impact of Major Therapies in
Advanced Mycosis Fungoides and Sézary Syndrome**

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Specific Aims

Cutaneous T cell lymphoma (CTCL) is recognized not only as a rare/orphan disease, but also a heterogeneous entity in clinical presentation, histopathology, and molecular features. This project brings together an international community of CTCL experts with the shared goal of generating large-scale meaningful data to improve patient management and outcome. Mycosis fungoides (MF) and Sézary syndrome (SS) represent 70% of CTCL and is the subject of this proposal. Clinical management is primarily stage-based; however, there is wide range of outcomes within a clinical stage. Advanced stage MF and SS have unfavorable outcome with survivals that range 1-5+ years. Currently, we lack prospectively validated prognostic models that augment clinical staging and can be utilized for risk stratification in clinical management or therapeutic trials. Published prognostic studies in MF/SS have been largely retrospective and data have been pooled across institutions, resulting in selection bias, inconsistency in data capture and criteria. Thus, the impact of these previous studies is limited, and underscores the importance and need of large, prospective prognostic studies with well-defined parameters to build useful prognostic models. The newly established prognostic model can then be applied to assess the differential outcome of major treatments according to risk groups. Furthermore, there is huge geographic variability in availability of treatments in the US vs. non-US countries and potential differential impact of major therapies in clinical outcome has not been studied. Towards this end, the international community of experts in cutaneous lymphoma has formed an unprecedented large-scale collaborative alliance, the Cutaneous Lymphoma International Consortium (CLIC), to establish an efficient conduit where well-defined, prospective data are captured, tissue/blood clinical samples are collected and processed using a standard protocol, to allow us to pool data and resources to support research which will have global impact. The CLIC investigators have demonstrated the feasibility of a large-scale collaboration by successfully completing a retrospective study that screened for candidate prognostic parameters, and highlighted the intrinsic flaws of a retrospective analysis, thus further supporting the need for a prospective approach. Moreover, the CLIC partners have worked collectively to establish the consensus criteria for data collection and the process to optimize data quality including central review of pathology. This project will consolidate our CLIC alliance and provide widely applicable prognostic tools that will serve as a foundation for future collaborative translational research.

Specific Aim 1. Determination of prognostic factors in advanced MF and SS in a prospective design

The pilot study, described in Research Approach, guided the optimal design of a prospective project. CLIC collaborators have established well-defined selection criteria and protocols that will be used in a prospectively collection of clinical, laboratory/pathology, and biomarker data which will be used to determine meaningful prognostic factors. **Hypothesis:** *Large-scale prospective study propelled by CLIC will allow highest quality controlled meaningful data that will be used to build our CL prognostic index model (CLIPi).*

- A. Prospective data capture with established protocols and data quality management.
- B. Assurance of pathology quality control with central review and interim evaluations of prognostic variables.

Specific Aim 2. Development of Cutaneous Lymphoma International Prognostic Index (CLIPi) towards improved prognostication and stratification for management in advanced MF and SS

The current TNMB and clinical staging system in MF/SS has failed to reliably distinguish outcome in advanced stage patients with MF and SS. **Hypothesis:** *Adverse prognostic factors established with prospective data analysis can be combined to build a prognostic index model (CLIPi) that will improve our prognosticating power beyond the current staging system.*

- A. Derivation of meaningful CLIPi risk groups in advanced MF and SS.
- B. Validation of derived CLIPi in prospective cohort subset.

Specific Aim 3. Characterization of geographic pattern of treatment utilization and CLIPi-based differential clinical outcome of major systemic treatments in advanced MF and SS

Treatment options and utilization patterns vary widely in the US and non-US regions; however, it is unknown if such variability impacts clinical outcome. Validated CLIPi can provide meaningful risk-stratified guide for treatment selection. **Hypothesis:** *Application of CLIPi to parallel treatment data will establish risk-stratified differential clinical outcome.*

- A. Assessment of geographic variability in treatment utilization and impact on outcome.
- B. Determination of CLIPi-based impact on survival outcomes in major systemic treatment cohorts.