Hairy Cell Leukemia-2030 Research Initiative

Introduction

Hairy Cell Leukemia (HCL) is a rare, slow-growing hematological malignancy characterized by the proliferation of morphologically aberrant ("hairy") B-lymphocytes. Approximately 1200 and 1400 new cases of HCL are reported annually in the US and Europe, respectively, with an unusual 4:1 predominance in males vs. females compared to other hematological diseases (Falini and Tiacci, 2024). The use of purine analogs, cladribine or pentostatin, has been the standard of care for decades (cladribine was FDA-approved in 1993). These drugs can induce long-lasting disease control with a median relapse-free survival of more than 10 years. Nevertheless, relapses are common and cures for HCL have not been achieved for many patients. In addition, purine analogs kill normal B- and T-cells that can cause immunosuppression; this effect, combined with neutropenia and monocytopenia caused by the disease and treatment, can result in a 20-30% infection rate in HCL patients as well as failure to respond well to vaccinations, which can be a considerable concern in the post-COVID-19 epidemic era.

Our molecular understanding of the basis of the disease experienced a major step forward over 10 years ago when it was discovered that >95% of patients have a B-RAF mutation (classical HCL - cHCL). This stimulated the exploration of the B-RAF inhibitor, vemurafenib, to treat HCL. Vemurafenib, an oral medication, when used alone or in combination with an anti-CD20 antibody (rituximab or obinutuzumab) can control the disease in refractory/relapsed patients with cHCL, although relapses still occur at high frequency. Clinical trials are underway to determine the safety and long-term efficacy of vemurafenib plus anti-CD20 antibodies in relapse/refractory and newly diagnosed patients. Much of this work is supported by the 1st round of HCLF and LLS funding. However, the exact sequence, dose-levels, and long-term outcomes of B-RAF inhibitor-based therapies has not been defined. Beyond this, the use of surrogate endpoints, such as minimal-residual disease determined by sensitive methods, to predict outcomes still requires further study. In addition, approximately 5-10% of HCL patients do not have a B-RAF mutation but among these patients, approximately 50% have a MEK mutation (variant HCL - HCLv). These patients often have an inferior response to purine analogs, a shorter overall survival time, and frequently have TP53 mutations compared to cHCL patients (Toussard and Maitre, 2024).

During the past 5 years, since the inception of the HCL2025 initiative, multiple new therapeutics that could be used to treat HCL have been approved by the FDA to treat other blood cancers. This includes the 1st, and 2nd generation BTK covalent inhibitors (ibrutinib, acalabrutinib or zanubrutinib), a non-covalent BTK inhibitor (pirtobrutinb, approved for CLL and MCL), as well as the 3rd generation BTK degraders, which are showing promising clinical efficacy for CLL. Ibrutinib or acalabrutinib have already demonstrated efficacy in HCL patients. Other immunotherapeutics may also be useful to treat the disease. This includes multiple FDA-approved bispecific antibodies that mobilize T-cells to bind to CD20 on the surface of NHLs (epcoritimab, glofitamab, mosunetuzumab), which have been developed to treat diffuse large B cell and follicular lymphomas. In addition, trials with CD22-directed CAR T-therapy, which are enrolling HCL patients, are in progress (NCT04815356, NCT06349737). Indeed, the revolution in

immunotherapies, highlighted by the recent identification of T-cell directed therapies to neo-antigens found on pancreatic cancer, renal cell carcinomas, and leukemias holds great promise for the development of new therapies to treat many cancers. (Sethna et al., 2025; Braun et al., 2025; Kim et al, 2025). Do such unique surface targets exist in cHCL or HCLv? Furthermore, a deeper understanding of the tumor microenvironment, which surround the tumor cells, might provide insight to explain resistance mechanism to immunotherapies as it has for AML (Bhagwat et al., 2024). Therefore, a major expansion of technical advances combined with experimental new immunotherapies, as well as a deeper understanding of which patients might benefit the most from such therapies, can be applied to HCL patients.

There is still a fundamental gap in our molecular understanding of the basis of HCL. For example, the origin of the disease (e.g., HCL stem cells) remains ill defined (Chung et al., 2014). The basis of resistance to therapy is not well understood. The role of epigenetic regulation, which has become increasingly important in B-cell lymphomas and other leukemias, has just begun to be explored for HCL (Eton et al, 2024; Yamaguchi et al, 2023). In addition, the molecular basis of HCLv needs further study and could form the underpinnings for new therapies for patients with HCLv.

In sum, there is an opportunity to improve our understanding of HCL as well as develop new therapies for HCL that will prolong the life of patients, increase the chances for a cure, and provide excellent quality of life. The HCL2030 initiative invites the research and clinical community to meet these challenges.

Goals

The goals of the HCL2030 grant program are focused on four major efforts:

I. Uncovering novel features of cHCL biology,
II. Understanding the distinguishing features of HCLv and apply that knowledge in the clinic
III. Translating new medical knowledge to clinical application and testing novel treatments in patients through clinical trials
IV. Applying the HCL registry created by HCLF to examine long-term outcomes and quality of life

These activities should be driven ultimately by the overarching goal to improved patient outcomes and cure the disease.

Examples of projects of potential interest include:

- Studies of cellular activities that underlie the behavior and vulnerabilities of HCL cells including the role of novel signaling pathways, epigenetic alterations, metabolic vulnerabilities, cellular interaction with the microenvironment, and regulation of aberrant cell morphology

- Development of novel immunotherapies targeting unique or abundant HCL cell surface markers
- Exploration of novel combination therapies with the potential to provide improved efficacy and extended relapse-free survival
- Studies into the molecular basis of HCLv and alternative therapies to treat the disease
- Investigations into resistance mechanisms including immune evasion, resistant clone evolution, failure of B-RAF or RAS pathway inhibitors, and cellular changes underlying disease relapse
- Development and use of *in vitro* or *in vivo* systems to model HCL, including novel cell culture systems, patient-derived xenographs (PDX) and other animal models
- Development and evaluation of reliable surrogate blood-borne markers to predict progression-free survival, detect early relapses, or justify early interception in the 10-20% of "watch and wait" patients with HCL or those previously treated for HCL

Funding Mechanisms

We will support research advances via an investigator-initiated and peer-reviewed granting mechanism.

Two grant types will be awarded:

1. Laboratory to Clinical Research Grants (LCRG)
   - Projects focused on translational research, including basic research if justified, that has relevance to therapeutic development
   - Project led by a single Principal Investigator (PI) but may have one co-PI
   - 3 years of support, with the third-year funding dependent on progress assessment at end of year 2
   - Cost not to exceed $250,000/year ($750,000 total), including indirect costs
   - Indirect costs (institutional overhead) capped at 10% of the total grant award
   - Funds intended for flexible use that may include salaries (capped at 40%), equipment, supplies, or personnel

2. Collaborative Team Grants (CTG)
   - Projects focused on the development and implementation of novel clinical trials
   - Program activities can include pre-clinical development and correlative studies
   - Either one trial with supporting correlative work or multiple projects with related but distinct approaches that contribute to a transformational advance in the treatment of HCL
   - Up to 4 investigators (Project Leaders) led by a Program Director (PD)
   - Funding for core facilities (e.g., chemistry, genomics, animal models, computation) may be included but not exceed 20% of the total cost
   - Up to 4 years of support

- Cost not to exceed $625,000/yr ($2,500,000 total), including indirect costs; more focused applications may not require the maximum amount of funding
- Indirect costs (institutional overhead) capped at 10% of the total grant award
- Funds intended for flexible use may include salaries (capped at 40%), equipment, supplies, or personnel
- Demonstration of other financial support for the proposed work (from industry or other NFPs, which leverages funding provided by HCLF and LLS is encouraged
- A Patient Involvement Plan (PIP) is **required** for CTG grants

Applicant Eligibility

- Qualifications of the Applicant(s)
  - Degree: Applicants must hold an MD, PhD or equivalent degree.
  - Leadership:
    One PI who will be responsible for the preparation and submission of the proposal including the budget, oversight of the research projects, and adherence to all stipulations made within the HCLF and LLS contract.

    The PI must be an independent investigator who either has dedicated laboratory space, directly hires, and supervises laboratory personnel (technicians, graduate students, postdocs and staff scientists) or clinical oversight and takes responsibility for all decisions concerning use of the grant funds.

    The PI must be able to demonstrate a significant track record in the area of hematology and/or blood cancer research, preferably with experience with HCL. If the scientific achievements and expertise of the PI are in another scientific area, he or she must have a Co-PI who has the required significant track record in the area of hematology and/or blood cancer research.

  - Citizenship: Applications from appropriate institutions in any nation and investigators of any nationality will be considered.
  - Applicants based at the NIH or another government entity may apply if permission is provided by such institutions.

- Institutional qualifications: Applicants must be independent investigators affiliated with an academic or non-profit sponsoring institution expected for the duration of the award. Applications from for-profit organizations are not eligible, although a collaboration between academic institutions and biotechnology companies is encouraged. **Post-doctoral students may not apply for the awards**. The principal investigator and appropriate representative of the institution must sign off on the contract for the awarded work.

- Resources: Investigators must show that they have resources fully equipped for all aspects of the work. Applications for projects that depend on clinical samples and/or

access to patients must provide documentation confirming sample availability. Applications may involve multiple institutions; however, the Applicant's principal investigator will be responsible for signing off on all terms of the grant agreement and administering the grant within the collaboration.

– Application Limitations: An Applicant may submit only one application to each type of program.

Application Evaluation Factors:

Applications will be evaluated based on clearly stated hypotheses, scientific rationale, innovation, feasibility, preliminary data, track-record of the investigators, and potential benefit to HCL patients.

Application Process

There are two phases of the application process. In the first phase, the letter of intent (LOI) will be evaluated for eligibility, and all eligible applicants will be invited to submit a Full Application. Applications will be reviewed by a committee composed of experts in HCL or blood cancer biology and therapeutics. Final funding decisions will be based on the committee evaluation, priorities of HCLF and LLS, and the availability of funds. We may request further clarification of the application prior to making a final decision.

Key References

Andritsos LA, Anghelina M, Neal J, et al. Development of a distributed international patient data registry for hairy cell leukemia. Leuk Lymphoma. 2022. 63:3021-3031.

Bhagwat AS, Torres L, Shestova O, et al. Cytokine-mediated CAR T therapy resistance in AML. Nat Med. 2024. 30:3697-3708.

Braun DA, Moranzoni G, Chea V, et al. A neoantigen vaccine generates antitumour immunity in renal cell carcinoma. Nature. 2025. 639:474-482.

Chung SS, Kim E, Park JH, et al. Hematopoietic stem cell origin of BRAFV600E mutations in hairy cell leukemia. Sci Transl Med. 2014. 6:238ra71.

Eton EO, Ganesan S, Murray RM et al. Transcriptomic and Epigenomic Landscape of Hairy Cell Leukemia at Single-Cell Resolution. Blood 2024. 144 (supplement 1): 1604.

Falini B and Tiacci E. Hairy-Cell Leukemia. N Engl J Med. 2024. 391:1328-1341.

Kim WJ, Crosse EI, de Neef E et al. Cell Mis-splicing-derived neoantigens and cognate TCRs in splicing factor mutant leukemias. Cell. 2025. in the press.

Sethna Z, Guasp P, Reiche C et al. RNA neoantigen vaccines prime long-lived $CD8^+$ T cells in pancreatic cancer. Nature. 2025. 639:1042-1051.

Troussard X and Maitre E. Untangling hairy cell leukaemia (HCL) variant and other HCL-like disorders: Diagnosis and treatment. J Cell Mol Med. 2024. 28:e18060.

Yamaguchi, K, Abdelbaky S, Arons E. et al. DNA Methylation-Based Classification of Hairy Cell Leukemia and Splenic B Cell Lymphoma. Blood. 2023. 142 (Supplement 1): 174.