LEUKEMIA & LYMPHOMA SOCIETY®

Chronic Myelomonocytic Leukemia

A Road Map to Cures

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Executive Summary

The Leukemia & Lymphoma Society (LLS) is dedicated to promoting research to realize cures for chronic myelomonocytic leukemia (CMML). Our current research portfolio contains numerous projects devoted to investigating drug targets found in CMML patients (>$15 M), but much of this work is focused on studying the same targets in other diseases--acute myeloid leukemia (AML), myelodysplastic syndrome (MDS)--or in relation to prevention of blood cancer. The reason for the emphasis on AML and MDS is that these diseases are approximately 10-fold more prevalent than CMML (approximately 1,100 new patients/year in the US). The discovery of novel therapeutics for CMML patients, some of which may be unique to CMML, could be dramatically accelerated through a program specifically focused on CMML. This Road Map to Cures provides a review of the research and treatment landscape of CMML and details a $17 M investment dedicated to CMML, which will enable the focused, comprehensive research effort needed to make significant progress toward cures for patients battling this disease.

For most patients, CMML is an incurable cancer with a poor prognosis. There are only three FDA-approved therapies, all with a similar mechanism of action, to attempt to control CMML. However, none of them enhance overall survival. The only curative option for CMML patients with advanced disease is a bone marrow transplant (BMT), which carries its own risks, especially since BMT in an elderly population (average age of a CMML patient is 72) has significant safety concerns.

Our understanding of the molecular basis for CMML has advanced considerably in the past 10 years. This is coupled by the realization that many of the mutations associated with CMML are also found in precursor conditions, in healthy individuals (that put people at higher risk of developing leukemia) as well as in AML and MDS patients. Therefore, there is an intense interest in the research community to identify and develop inhibitors for these new targets. LLS has the capability and desire to bring the learnings from all leukemias to accelerate research and development for CMML patients. **A concentrated research and development program in CMML will not only build on our existing efforts but, importantly, place a concentrated effort on understanding the unique features of CMML.**

The new program describes an investment of $17 M to support new research and development specifically focused on CMML. $13 M will fund two, large, collaborative research teams, as well as four targeted investigations ($0.75 M each). This research will be complemented by $2 M deployed through the LLS venture philanthropy program, called Therapy Acceleration Program (TAP), to fund and advise biotech companies for the exploration of novel first-in-class assets in clinical trials with CMML patients.

The research program will produce a deeper understanding of the molecular basis of the disease, define new targets for drug discovery, and fund clinical trials with novel therapeutics

for CMML. LLS will closely monitor the progress of all these efforts with quarterly updates, and semi-annual reviews.

Since discovering new targets and generating new therapeutics are a major goal, a dedicated effort to speed enrollment of CMML patients into new clinical trials is critical to success, especially because CMML is a rare cancer. To this end, $2 M will be focused on supporting CMML patients by LLS' existing Information Resource Center (IRC) and Clinical Trial Service Center (CTSC) as well as administrative and legal expenses. The IRC and CTSC are staffed with social workers and oncology nurses with a broad knowledge of blood cancer and an advanced skill set to assist with patients, caregivers, and physicians. These services will be expanded to include CMML experts who provide individual consultation with CMML patients, especially those for whom a clinical trial is the best chance of obtaining control of their disease. **Our goal is to become the key resource center for CMML patients.**

LLS has seen miraculous progress in certain leukemias, lymphomas, and myelomas in the past 2 decades that have markedly extended the lifespan of patients with excellent quality of life. While progress in CMML lags, we believe cures for CMML are possible. The road to cures for CMML patients requires a focused, intense effort as outlined in this document.

Disease Classification

CMML is characterized by the presence of a high monocyte count (>1 x 10^9/L peripheral monocytes with monocytes ≥10% of white blood cell count) along with dysplastic features in the bone marrow (Patnaik and Tefferi, 2022). There are two types of CMML classifications: the MDS or MPN type based on peripheral cytopenias, recurrent infections, and transfusion dependance versus those with leukocytosis, hepatomegaly, and splenomegaly, respectively.

The disease can be further classified into three categories based on peripheral blasts (PB) and bone marrow (BM) blast count:

- CMML-0: < 2% PB blasts and <5% BM blasts,
- CMML-1: 2-4% PB blasts and 5-9% BM blasts, or
- CMML-2: > 5% PB blasts and 10-19% BM blasts

Patients with BM blast counts exceeding 20% are considered to have AML.

Epidemiology

Approximately 1100 new cases of CMML are reported every year in the United States (Patnaik and Tefferi, 2022). The median age of diagnosis is, on average, 72 years with approximately a 2-fold male predominance. Approximately 10% of CMML is due to prior therapy (t-CMML). Clinical outcomes are poor for CMML patients. The estimated 5-year survival is 10-20% in patients with CMML-2 or CMML-1 (American Cancer Society, 2017). Overall, 15-30% of CMML patients progress to AML in 3-5 years; 18% and 63% of CMML-1 and CMML-2 patients develop AML within 5 years of their diagnosis, respectively (American Cancer Society, 2017). AML, particularly in elderly patients, is difficult to control and cure.

Diagnosis and Characterization of CMML

A sustained high level of monocytes with monocytes constituting ≥ 10% of the white blood cell count differential found on a complete blood count from peripheral blood is the first possible sign of CMML. After ruling out other diagnoses (such as infectious diseases, lupus, connective tissue disorders), other malignant blood disorders such as CML (with distinct Philadelphia chromosome and BCR-ABL1 fusions), PDGFR rearranged myeloid neoplasms, and other myeloproliferative neoplasms (MPNs), further diagnostics for CMML should be considered. A bone marrow biopsy is done to assess blast count (and rule out AML) and examine the cells microscopically. Flow cytometry is done to assess the types of monocytes.

Abnormal histopathology and immunocytochemistry are detected in a BM biopsy in CMML patients. Approximately 80% of patients have micro-megakaryocytes with abnormal nuclear

contours or lobations, and 30% of patients have an increase in reticulin fibrosis (Patnaik and Tefferi, 2022). Precursors of monocytes (promonocytes) are noted. Myelomonocytic antigens can be expressed in BM samples including markers of CD13 and CD33, with variable expression of CD14, CD68 and CD64.

Cytogenetic abnormalities are found in 20-30% of CMML patients. Common genetic alterations include trisomy 8, loss of the Y chromosome, abnormalities of chromosome 7, trisomy 21 and complex karyotypes. High risk abnormal karyotypes include trisomy 8, chromosome 7 abnormalities or complex karyotypes and are generally associated with a 5-year overall survival of only 4%.

Mutations are found in 90% of CMML patients. These include mutations in the following types of genes (from Patnaik and Tefferi, 2022):

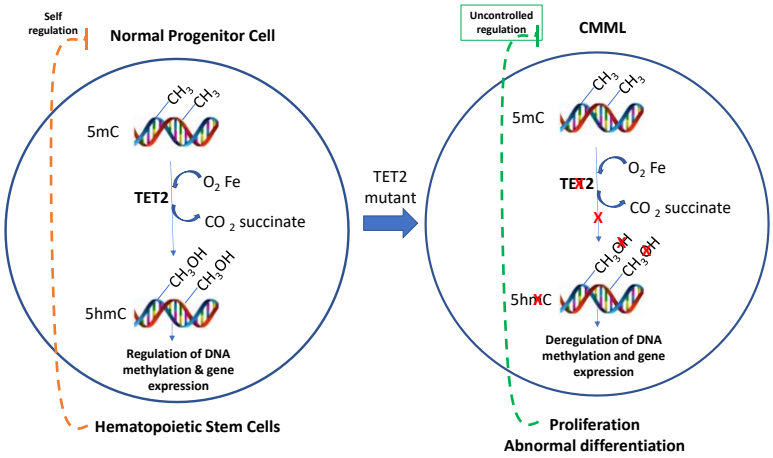
- epigenetic control of transcription (EZH2, ASXL1, UTX) and DNA methylation (TET2, DNMT3A, IDH1, and IDH2)
- spliceosome machinery that alters proteins (SRSF2, SFB31, U2AF1, ZRSR2, PRPF8)
- regulators of cell signaling (JAK2, KRAS, NRAS, CBL, PTPN11 and FLT3)
- transcription factors and nucleosome assembly regulators (RUNX1, SETBP1)
- DNA damage response genes (p53, PHF6).

Major class of genetic mutation		Gene	Frequency of mutation (%)
Epigenetic control	Histone modification	*ASXL1*[a]	40
		EZH2	5
	DNA methylation	*TET2*	60
		DNMT3A[a]	5
	Dual effect	*IDH1*	1
		IDH2	5
Cell signaling		*JAK2V617F*	10
		CBL	15
		NRAS[a]	15
		KRAS	10
		PTPN11	5
		NF1	<5
		FLT3	<5
Pre-mRNA splicing		*SRSF2*	50
		SF3B1	5–10
		U2AF1	5–10
		ZRSR2	5
Transcription and nucleosome assembly		*RUNX1*[a]	15
		SETBP1[a]	15
		GATA2	5
DNA damage		*TP53*[b]	<1
		PHF6	5

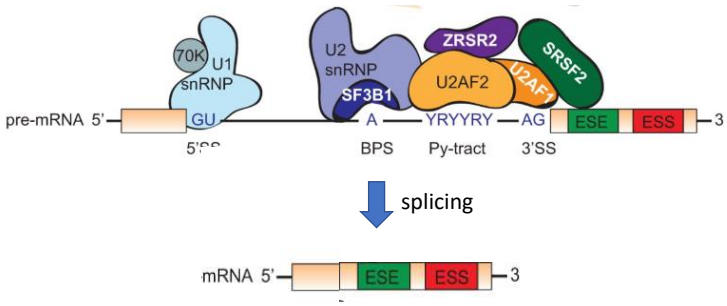
[a]Annotates genes that have been shown in various studies to have an independent and adverse prognostic impact on survival outcomes.
[b]*TP53* mutations are very infrequent In CMML and if present, usually occur in the context of therapy related CMML.

Epigenetic mutations. TET2 and ASXL1 regulate the epigenome. Both of these genes regulate the expression of genes by either altering the DNA itself or the processing of DNA into mRNA. Mutations in ASXL1 are associated with worse overall survival, while mutations in TET2 have no effect or even better overall survival (Zhao et al., 2022). These data suggest that targeting ASXL1 mutations, or downstream mediators of ASXL1 function could be an important therapeutic strategy. Indeed ASXL1 regulates the polycomb-group repressive complex proteins, and mutations in ASXL1 have been shown to result in loss of histone H3K27 tri-methylation. Since histones decorate the DNA and block the ability of DNA to read by RNA polymerases, loss of histone methylation can alter transcription and thereby promote oncogenesis.

TET2 is also an epigenetic regulator. It has enzymatic activity that converts 5-Me cytosine to 5-OHMe-cytosine. TET2 mutants have reduced enzymatic activity and ultimately may result in disruption of normal hematopoietic differentiation. TET2 mutations do not appear to be correlated with reduced overall survival in CMML patients (Patnaik et al., 2016, Abdel-Wahab et al., 2009).



Splicing mutations. pre-mRNA contains regions that encode mRNA (exons) and regions that do not encode mRNA (introns). Introns are spliced out during the conversion of preRNA to mRNA so proteins can be read out of the mRNA in a linear fashion. RNA splicing is conducted by a large complex called the spliceosome that contains proteins including SF3B1, U2AF2, ZRSR2, U2AF1 and SRSF2.



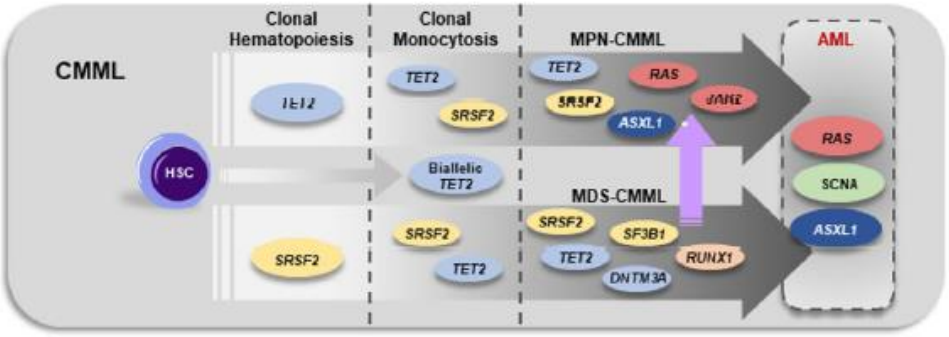
(Figure adapted from Anczukow and Krainer, 2016)

If elements of the spliceosome are mutated, dysfunctional proteins can be produced. Spliceosome mutations are very common in CMML patients. In particular, SRSF2 is the most common splicing gene mutated in CMML (in 50% of patients) compared to other splicing genes (5-10%). SRSF2 mutation has been associated with inferior overall survival (Itzykson et al., 2013). Only a few inhibitors of spliceosomes have been developed to date (Stanley and Abdel-Wahab, 2022). This is a rapidly expanding field. The development of specific SRSF2 inhibitors may be possible.

Cell Signaling Mutations. Mutations in the RAS pathway occur in 30% of CMML patients. The association between RAS mutations and outcomes for CMML patients is controversial. Inhibitors of the RAS pathway exist and may have therapeutic value for CMML patients.

Transcriptional Regulation by RUNX1. RUNX1 mutations are found in 10-15% of CMML patients. RUNX1 influences normal hematopoiesis. Disruption of RUNX1 in humans contributes to several hematopoietic disorders including AML and familial platelet disease (FPD). In the latter, germline mutations in RUNX1 lead to low platelet counts and a high likelihood of transformation to AML (Sood et al., 2017). Strategies to overcome the effects of RUNX1 mutations are beginning to be identified (Krutein et al., 2021), and gene replacement of hematopoietic stem cells with wt RUNX1 is being contemplated in FPD patients.

Sequential mutations in CMML. It is not entirely clear what is the sequence of mutations that leads to CMML or transformation of CMML to AML. However, driver mutations in TET2 are likely an initial event. Subsequent mutations in ASXL1, DNMT3A, RUNX1, SETB1, or SF3B1 are likely to induce an MDS-CMML type of disease. RAS mutations are likely to play a role in transformation to AML. The sequence of acquisition of mutations is critically important to understand since it not only has diagnostic and prognostic value but is likely needed to identify patients who will respond optimally to precision medicine therapies that target some of these mutated genes. A proposed sequence of events is depicted below (Patnaik and Tefferi, 2022).



Many of the mutations commonly found in CMML also occur in clonal hematopoiesis of undetermined potential (CHIP) in healthy, asymptomatic individuals. These mutations include DNMT3A, TET2, ASXL1. Approximately 10-30% of healthy individuals over 70 years of age have one or more of these mutations associated with CHIP and the frequency of such mutations increases with age (Jaiswal and Ebert, 2019). Beyond that, the presence of these mutations is correlated with an increased risk of developing leukemias, cardiovascular disease, gout, possibly Alzheimer's disease, and other diseases. This finding suggests that CHIP may also increase the risk of developing CMML as a result of an accumulation of mutated genes. Understanding how these mutations lead from CHIP to leukemia will likely improve our ability to improve outcomes of patients with CMML. Ultimately, the progression to CMML might be blocked with early detection of CHIP and the deployment of effective therapies at that time point. However, therapies for CHIP are just beginning to be explored.

Existing Treatments

There is a paucity of treatments for CMML. Hypomethylating agents, including **azacitidine, decitabine**, and more recently **oral decitabine (plus cedarzurdine)** are the only FDA approved therapies for CMML. It is thought that these agents reduce the methylation of DNA (epigenetic programming), thereby switching on genes that stop the cancer. The approvals for these agents are based on clinical trials that predominately consists of patients with MDS (about 90% of the patients). The overall response rate (complete plus partial response rate, typically defined by reduction in blast count) in CMML patients is approximately 40-50%. The complete response rate (no detectable disease; blast count normal with full blood cell recovery) is approximately 7-17%. Responses are not durable. In a large, randomized trial comparing decitabine versus hydroxyurea for high risk MPN-CMML patients, decitabine demonstrated no significant differences in overall survival (OS: 18.5 months) when compared to hydroxyurea (a cytotoxic agent – 21.9 months OS) (Itzykson et al., 2022).

Allogeneic stem cell transplant (ASCT) is the only possible curative option, although ASCT is associated with treatment related mortality (20-30%) and/or graft versus host disease (GVHD). ASCT may be contraindicated for certain CMML patients due to age, comorbidities, access to

a donor, and other limitations. It is encouraging that the 10-year OS for CMML patients that had ASCT at one institution (Fred Hutchison Cancer Center) was 40% (Eissa et al., 2016). Therapy with a hypomethylating agent prior to transplant has been examined with lower incidence of relapse in one study, although the use of an HMA may cause a cytopenia that will be further accentuated by a transplant.

Experimental Treatments in Clinical Trials

There are a number of trials that include CMML patients amongst other myeloproliferative and myelodysplastic diseases, but very few specifically designed for CMML. The results with CMML patients are summarized below. In general, while overall response rates are high with some agents (>50%), the complete response rates are low (4-38%). The sample size for most studies is low (<25 patients/trial) and therefore, the results are often considered preliminary.

Ruxolitinib is a JAK inhibitor that is FDA-approved for the treatment of primary myelofibrosis (a form of MPN). Like myelofibrosis patients, some CMML patients have enlarged spleens (splenomegaly) that contribute to morbidity. Promising results in a Phase I/II trial in patients with CMML given ruxolitinib have been recently reported (Padron et al, 2022). Of the 29 patients enrolled, 59% were considered high risk. Only a few patients had prior HMA or hydroxyurea therapy. The overall response rate was 17%. Thirty percent of patients (6/20) had > 35% spleen volume reduction. Fifty-four percent achieved a total symptom score reduction >50%. The estimated mOS was 24 months, which compares favorably to historical data among higher risk CMML patients. Ruxolitinib is indicated on the NCCN guidelines to treat CMML-2 (NCCN, 2023 guidelines). FDA-approval will require submission of an NDA from Incyte Pharmaceuticals.

Tagraxofusup is a CD123-directed antibody conjugated to diphtheria toxin. Once the drug binds to the surface of tumor cells, the diphtheria toxin is taken up and kills the tumor cell. Tagraxofusup has been approved by the FDA for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) where it is highly effective. CD123 is expressed in CMML cells. It has been shown in first line, high-risk or relapsed/refractory (R/R) CMML patients treated with tagraxofusp, that 60% of patients (9/15) had a significant reduction in spleen volume. Eleven percent (4/36) of the patients had a complete response (Patnaik et al., 2021). The safety profile was not remarkably different from what was reported for BPDCN; the most unusual toxicity related to tagraxofusup was capillary leak syndrome (which can be life-threatening) occurred in 24% of patients with grade 2-3. A phase 1/2 trials is underway with tagraxofusp and decitabine in CMML patients (NCT05038592). Interestingly, other CD123 therapies are in development for AML and other cancers including CD123 CAR T cells, CD123 bispecific antibodies, as well as CD123-directed NK cell engagers. These therapies may be safer and/or more effective than tagraxofusp in CMML patients.

Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FT). The enzyme adds a farnesyl group to RAS and enhances RAS oncogenic activity. FT inhibitors may block the RAS

pathway, which is mutated in 30% of CMML patients and can be hyperactivated. Tipifarnib produced a 22% (7/32) overall response rate (ORR) in CMML patients (Patnaik et al., 2021). Further studies by the manufacturer (Kura) are not being pursued at the present time.

Sabatolimab is an IgG4 monoclonal antibody targeting TIM-3, an inhibitory receptor that regulates the immune response. Sabatolimab was given with a hypomethylating agent to CMML patients (Brunner et al., 2020). The overall response among the eleven evaluable patients was 63.6% (4 CR, 3 marrow CR, 1 PR, and 1 SD with hematologic improvement). A large phase III trial that includes CMML-2, AML and MDS patients given sabatolimab + azacitidine is active but not recruiting (NCT04266301).

Pevonedistat is an inhibitor of NEDD-activating enzyme (NAE) that blocks the ubiquitin pathway leading to cancer cell death. In high risk CMML patients who were given the drug in combination with azacitidine (N=9) versus azacitidine (N=8), the overall response rate was 75% and 78%, respectively (Ades et al., 2021). The median OS was 21.7 months vs. not evaluable in the two arms of the study (HR=7.51, P=0.01), although the authors concluded the study was too small to determine if the results were meaningful. In 2021, Takeda reported that pevonedistat failed to meet its primary endpoint (event-free survival) for use in high risk MDS, low-blast count AML, or CMML.

Cobimetinib is a MEK inhibitor that is part of the signal transduction pathway stimulated by RAS. The drug is FDA approved for the treatment of multiple cancers, including a rare blood cancer (Erdheim Chester Disease). Cobimetinib is being explored in newly diagnosed or HMA-treated CMML patients (NCT04409639).

Ceralasertib (AZD6738) is a selective, potent, and oral inhibitor of Ataxia Telangiectasis and Rad3 related (ATR kinase). Since mutant spliceosome genes induce R-loops (DNA:RNA hybrids) and ATR is a critical mediator of R-loop resolution, inhibition of ATR may induce apoptosis in cells with excess R-loops. A study is being conducted in MDS and CMML patients with splicing mutations (Brunner et al, 2021). The drug has been well tolerated. It is too early to determine the efficacy in CMML patients.

Other trials include the use of **APR-246 (eprenetapopt**) + azacitidine (frontline) and **guadecitabine** vs. best therapeutic option (HMA failure). APR-246 induces apoptosis in cells with mutant p53. Guadecitabine is a next-generation HMA designed to be resistant to metabolic deactivation. Guadecitabine failed to improve overall survival in MDS and CMML patients (Garcia-Manero et al., 2022).

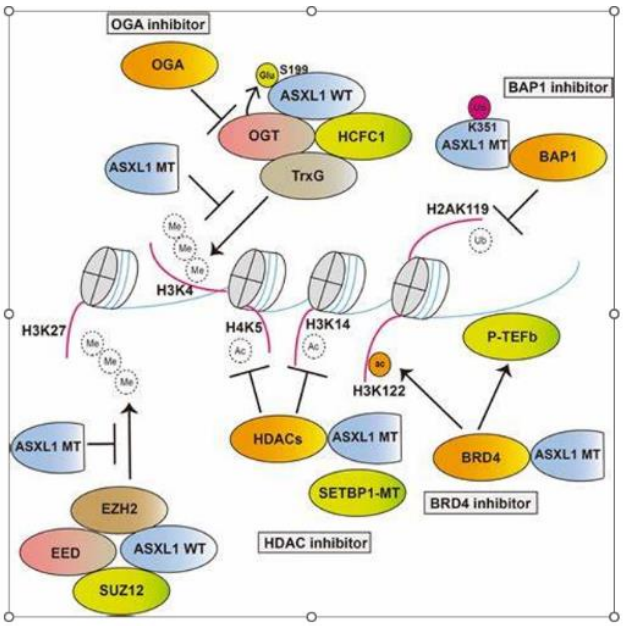
Novel Therapeutic Strategies for CMML

Novel therapeutic approaches for CMML patients should: 1) kill CMML cells, 2) avoid the development of resistance against the therapy, 3) induce long-term remissions, 4) reduce or eliminate the need for harsher drugs that kill healthy cells as well as cancer cells (e.g., cytotoxic drugs), and 5) be accessible to all patients at a reasonable cost. This includes combinations of approved therapeutic agents, as well as the development of first-in-class novel experimental therapies. Unfortunately, unlike other hematologic malignancies that occur with a higher incidence, specific treatments for CMML and studies with large numbers of CMML patients are lacking. A better molecular understanding of the disease, as well as more trials (with higher enrollment) are needed to identify better therapies for CMML patients.

The key potential areas of focus proposed below are based on the molecular driving mutations thought to promote CMML and /or the presence of targetable markers on the surface of CMML cells.

Epigenetic regulation / Chromatin remodeling

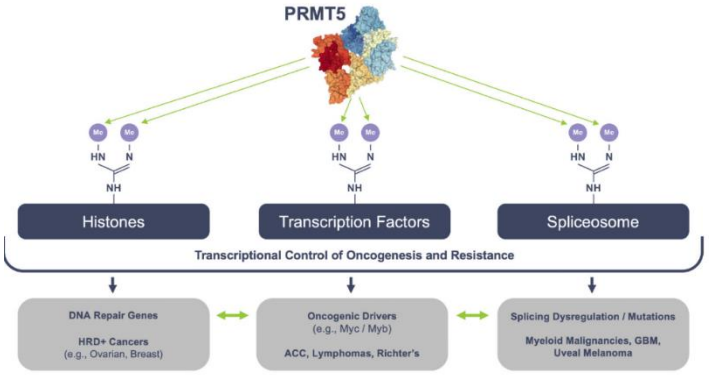
ASXL1 is an epigenetic regulator, as stated above. While direct targeting of ASXL1 may be difficult, there are many downstream pathways that interact with ASXL1 that may be amenable to inhibition. The inhibitors would alter the ability of ASXL1 to control gene transcription (summarized in the figure below). Some of these inhibitors have already been identified, are in clinical trials, or approved for other indications (e.g.,EZH2). Recent studies in animal models of CMML suggest that ASXL1 mutations cooperate with RAS mutations to accelerate CMML transformation to AML and are associated with a suppressive immune environment surrounding the tumor cells (You et al., 2022). These data suggest that RAS inhibitors (see above) or agents that activate the immune system may be useful in treating secondary AML as a result of CMML progression.



From Asada and Kitamura. Progress in Hematology 2018

Regulation of TET2 mutations. TET2 is a known driver of myeloid malignances and is frequently mutated in CMML cells. While mutant TET2 may not be associated with a worse outcome in CMML (see above), it still is possible that TET2 inhibition will have therapeutic value in CMML and is therefore worth investigating. This could be explored in the laboratory both in vitro and in vivo (animal models) and possibly in the clinic. Laboratory studies demonstrate that ascorbic acid (vitamin C), which is a co-factor for TET, can restore TET2 function (Cimmino et al., 2017), although it may not be possible to achieve therapeutic levels of ascorbic acid in patients. Recently it was reported that eltrombopag, a FDA- approved non-peptidyl thrombopoietin receptor agonist, which is used to treat aplastic anemia, binds the TET2 catalytic domain and inhibits its dioxygenase activity (Guan et al., 2022). While eltrombopag mimicked the loss of TET2, it prevented neoplastic clonal evolution in vitro and in vivo in TET2 mutant myeloid cells possibly by compensatory activity of TET1 and TET3. More work is needed to understand the mechanism of action of eltrombopag in TET2 mutant tumor cells. Clinical trials are feasible because eltrombopag is FDA approved with a well-understood safety profile.

PRMT5 inhibitors. Protein arginine methyltransferase 5 (PRMT5) is the primary enzyme responsible for the symmetric arginine dimethylation of multiple proteins that can control cell proliferation.



One of the functions of PRMT5 is to methylate arginine residues on proteins that control splicing in AML (Radzisheuskaya et al., 2019). It has been proposed that the inhibition of splicing by a PRMT5 inhibitor, GSK-3326595, may lead to synthetic lethality in CMML patients with splicing mutations. A phase 2 study was performed with GSK-3326595 in AML patients (Watts et al., 2019, NCT03614728). However, the trial was terminated by GSK in February 2022 and no results have been reported. Other PRMT-5 inhibitors (Prelude Therapeutics, Jubilant Therapeutics) have also advanced to clinical trials. The performance of PRMT5 inhibitors in CMML needs further investigation. LLS is funding work to examine the mechanism of action and resistance to PRMT-5 inhibitors.

Immunotherapy

Immunotherapy has been highly effective in treating B-cell acute lymphoblastic leukemia. B-cell derived lymphomas, and multiple myeloma. In particular, bispecific antibodies, which engage T-cells, and genetically engineered T-cells (CAR T) have yielded long term disease control (some cures) in patients that failed existing and experimental therapies. The use of CAR T or using immune-targeting of cell surface markers for AML or MDS have met with far less impressive results and have produced no FDA approvals to date. However, antibody drug conjugates (ADCs) have been approved for AML and ALL, so it may be possible to find a marker on the surface of CMML cells that will kill CMML cells but avoid killing normal cells (i.e. monocytes). Even if the marker is present on normal hematopoietic stem cells (which constantly produce normal blood cells), it still may be possible to clear the disease with such a therapy, discontinue the immunotherapy, and then follow the immunotherapy with a bone marrow transplant.

Leukocyte immunoglobulin-like receptor subfamily B member 4 (LILRB4 aka ILT3) is a cell surface marker that is overexpressed in CMML cells compared to healthy cells (Chien et al, 2022). It is also highly expressed in monocytic type of AML (M4 and M5 subtypes). An antibody to LILRB4 has been developed (funded by an LLS grant) and is now being explored in CMML and R/R AML patients by Immune-Onc Therapeutics (LLS TAP investment; IO-202: NCT04372433). Merck is also evaluating the safety and efficacy of a LILRB4 antibody (MK-

0482) in R/R AML or CMML patients (NCT05038800).The development of LILRB4-directed CAR T is also being explored in AML patients (Carbiiogene Therapeutics,NCT04803929;, Hebel Yanda Ludapie Hospital, NCT05518357; Peking University Hospital, NCT05548088). The outcome of the CAR T trials in AML may provide encouraging results to stimulate the exploration of these therapeutics in CMML patients. LILRB4-directed CAR T therapy may be more potent and specific than the naked antibody.

Neoantigen Therapy. A novel approach might target a neoantigen in CMML. Since genes that control splicing are frequently mutated in CMML cells, resulting neoantigens might be expressed on CMML cells. If neoantigens can be identified, it is possible that the cognate T cell receptor could be identified, cloned, and made into an autologous cellular therapy specific for CMML cells with the neoantigen. A similar approach was recently reported to control pancreatic cancer using engineered T-cells that recognize a mutant KRAS G12D neoantigen (Leidner et al., 2022).

Clever-1 inhibition. Bexmarilimab is a monoclonal antibody that binds to Clever-1. Clever-1 is expressed on the surface of CMML cells (Padron, personal communication) as well as monocytes where it acts as an immune checkpoint. The antibody is being explored in patients with AML, high-risk MDS or high-risk CMML. The study is being conducted by Faron Pharmaceuticals (NCT05428969) and is supported by an investment via the LLS' Therapy Acceleration Program.

Kinase Inhibition

Small molecule kinase inhibitor. NMS-035292088 is a FLT-3, KIT-and CSF1R kinase inhibitor. The drug is being explored in an open-label Phase I/II study in R/R CMML and AML patients (NCT03922100).

DNA damage repair/p53

Restoration of mutant p53. Although p53 mutations are not common in CMML, p53 is mutated in approximately 50% of all cancers. In normal cells, p53 functions as a tumor suppressor. Mutated p53 has lost tumor suppressor activity. Since murine double minute-2 (MDM2) is a negative regulator of p53, inhibition of MDM2 may restore p53 function (perhaps only to the remaining wildtype p53 protein). To that end, milademetan (RAIN-52) is a small molecule inhibitor of MDM2-p53 interaction and activated p53. A first in human study with milademetan was recently shown to have efficacy in solid tumors and lymphomas (Gounder et al., 2023). Other inhibitors of MDM2 are in development.

Inflammation in CMML

Recently, the Padron laboratory has identified a granulocytic macrophage progenitor (GMP)-like inflammatory population of cells in CMML patients that is associated with aggressive disease and poor clinical outcomes (Ferrall-Fairbanks et al., 2023). In addition, experimental

induced stress (via lipopolysaccharide injection) promoted the expansion of GMP-like cells in a patient-derived animal model of CMML. These data are consistent with previous studies which show that CMML monocytes exhibit a proinflammatory transcriptional profile and is associated with increased cardiovascular risk (Franzini et al., 2019). Therefore, these data suggest that limiting the inflammatory state might have therapeutic value for the treatment of CMML even in asymptomatic cases. Consistent with this, three case reports from CMML patients undergoing surgery (a stress-inducing event) developed life-threatening post-operative expansion of blast cells (leukostasis) (Patel et al., 2019). A prospective trial to further examine the link between acute inflammatory events and CMML progression will get underway in March 2023 at the Moffitt Cancer Center and the Mayo Clinic.

Current Research Portfolio at LLS

LLS's research portfolio contains seven grants and two venture philanthropy programs (TAP) that either focus on CMML or more commonly include studies on CMML where the primary focus is MDS or AML. The total commitment is > $15 M. The TAP program is supporting phase I/II trials that include CMML patients. Many of the academic grants focus on drug targets that are altered in CMML but also found in AML or MDS. LLS is also supporting many grants examining the role of TET2, DNMT3A, ASXL1 and other mutated genes found in CHIP, but this work is not shown here.

Name	Institution	Project Title	Start Date	End Date	Amount
Brian Dalton	Johns Hopkins	Therapeutic modulation of serine availability for SF3B1-mutant myeloid malignancies	1-Oct-2021	30-Sept-2024	$600,000
John Pimanda	U South Wales	Optimising azacitidine responsiveness in myelodysplasia and acute myeloid leukaemia	1-Jan-2021	31-Dec-2023	$600,000
Steven Nimer, Maria Figueroa, Omar Abdel-Wahab, Ross Levine, L. Cimmino, J. Watts, P. Cole, R. Sciekhattar	U Miami, MSKCC	Targeting Epigenetics in Myeloid Malignancies: Project 3 The role of the bone marrow microenvironment in therapeutic resistance in CMML and MDS/AML	1-Oct-2022	30-Sept-2027	$1,500,000

Peter Klein	U Pennsylvania	Targeting splicing factor mutant myelodysplastic syndromes through GSK-3	1-Oct-2022	30-Sept-2025	$750,000
Timothy Graubert, Matt Walters, Omar Abdel-Wahab, Zhongsheng You	Mass General Hospital, Washington U	Exploiting Vulnerabilities in RNA Splicing to Treat Hematologic Malignancies: Project 2 (animal models) and 3 (small molecule degradation of splicing targets)	1-Oct-2023	30-Sept-2028	$3,330,000
Dan Landau	Cornell	Defining the role of DNA methylation modifier mutations in reshaping blood differentiation topology	1-Jul-2021	30-June-2026	$600,000
Tak Mak, Ross Levine, Ari Melnick	U Health Network (Canada), MSKCC, Cornell	The Immune Niche in the Development of Hematological Malignancies and Implications for Novel Therapy: Projects 1-3 on TET2, DNMT3A, and IDH	1-Oct-2022	30-Sept-2027	$3,750,000
Immune-Onc Therapeutics	Palo Alto, CA	A phase 1 study of IO-202, an antibody targeting LILRB4, in patients with monocytic differentiation AML and CMML	5-March-2021	Undetermined	undisclosed
Faron Pharmaceuticals	Finland	A phase 1/2 study of Bexmarilimab, an anti-Clever1 monoclonal antibody, in combination with azacitidine or azacitidine/venetoclax in patients with AML, MDS or CMML	30-June-2022	Undetermined	undisclosed

Dedicated Research and Development for CMML

Although a few therapeutics are approved for CMML, the disease remains incurable with a high probability of progression in a brief period of time after diagnosis and no therapeutics improve overall survival. Because CMML is a rare blood cancer (1100 new cases/year) and is overshadowed by a much higher number of AML patients (approximately 20,000 new cases/year), the lack of attention to CMML needs to be addressed to accelerate progress in this field. The proposed solution is to have a coordinated research and drug development effort focused on CMML that will seek out the best ideas from academic researchers and biopharma companies.

Program

The CMML initiative describes an investment of $17 M to support new research and development specifically focused on CMML.

A $13 M research and development effort will fund a research and patient-facing effort exclusively focused on CMML. The grant program will seek out outstanding research proposals from academic investigators world-wide. The request for proposal calls for two coordinated synergistic teams for $5 M each over 5 years, supplemented by four translational grants for $750,000 over 3 years.

$2 M will be deployed by LLS to fund biopharma companies running trials in CMML patients (see list above) and seek new companies with first-in-class promising opportunities. Funding will be deployed through opportunistic investments ($500,000) or strategic investments ($3-5 M) for a clinical asset where commercially reasonable efforts are made to enroll CMML patients.

To enhance CMML trial enrollment where appropriate, LLS will use its Information Resource Center (IRC) and its Clinical Trial Support Center (CTSC). The plan will provide an additional $1 M to support two new employees over the next 5 years: one for each function, to focus on CMML patients. The goal of each program is described below.

IRC. The IRC is a call-center led by social workers, nurses, and health educators. It provides educational material (see LLS' CMML patient booklet, 2020), help finding second opinions and treatment centers with CMML specialists, travel and financial assistance, guidance through insurance issues and other services. The most common calls from CMML patients that are either newly diagnosed and need information or those patients who have been treated with hypomethylating agents and are now looking for additional options including clinical trials.

CTSC. The CTSC works on an individual basis to assist blood cancer patients who may consider clinical trials. The advanced practice nurse navigators utilize a specialized database to provide patients and providers with an annotated list of potential trials and trial availability specifically tailored to the patient's clinical situation, individual preferences, and travel needs/restrictions. The nurses continue to work with the patient through and after enrollment for any support and information required. We intend to make LLS' CTSC a central hub that would identify CMML patients for clinical trials, thereby speeding enrollment, expediting the evaluation of new therapeutics, reducing the cost of lengthy trials, and ultimately expediting FDA approval.

$1 M will support administrative and legal expenses necessary to implement, monitor, and guide progress of the program.

Method of program evaluation

Grants. After a request for proposal is issued (March 2023), LLS will accept grant applications world-wide. Applications are reviewed by two experts and a third reader who present their evaluations to a group of ten or more researchers/clinicians with expertise in leukemia. Grants are scored using an NIH scoring system (1 = best, 9 = worst). LLS typically considers funding grants that score 4 or better, although most of our funded grants score 3.5 or better (very few achieve a perfect score of 1.00). The evaluations are presented to LLS's Medical/Science Committee composed of blood cancer experts. If endorsed by the Medical/Science Committee, the funding is approved by LLS's Mission Oversight Committee, an LLS Board of Directors Committee. Contracts are prepared by our legal group, negotiated if needed, and fully executed before funding is started.

Therapy Acceleration Program (TAP) proposals are evaluated by an internal diligence team of scientists within LLS. The team is highly qualified to examine the asset because we have 1) extensive knowledge of blood cancer, 2) previous expertise developing oncology drugs in biopharma, and 3) we evaluate approximately 50 assets per year (where only 3-5 are selected for funding by LLS). If the opportunity is of sufficient interest to the team within LLS, expert advice from key opinion leaders (KOLs) is sought. Detailed diligence reports are prepared and presented to the TAP Committee requesting approval for funding.

Outcomes

The ultimate goal of the CMML program is to generate new FDA-approved therapies for CMML that cure the disease. The 5 -year scope of this plan is the road map to this ultimate goal. The goals of the program are:

- Develop a deep understanding of the molecular basis of CMML using new state-of-the-art techniques
- Identify new molecular targets (disease drivers or cell surface markers) that could be stimulus for new therapeutics for CMML
- Support the discovery of innovative new therapeutics for CMML
- Understand the basis for resistance of approved or experimental therapies
- Explore existing novel experimental therapies (used for other diseases) for CMML in the laboratory, including in vitro and in vivo animal models
- Enable early-stage clinical trials demonstrating safety and preliminary efficacy based on 1) reduction in monocytosis, 2) reduction in blast count, and/or 3) relief of symptoms (e.g. spleen size reduction or transfusion dependance)
- Bring heightened awareness to CMML that might enable further philanthropic investments

Progress will be monitored by LLS using the following methods:

- Annual meeting bringing together all CMML grantees including those with interest in CMML in our existing grant portfolio as described above

- Annual progress reports (6-month offset from annual meeting) stating research progress, publications, and new intellectual property generated
- Quarterly progress meetings for TAP programs
- Periodic reports to the donor summarizing progress in all CMML programs

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