



2024 Application Guidelines for the Crazy 8 Initiative Program on Childhood Cancer Predisposition

Letter of Intent Due: January 8, 2024

Full Application Due: May 6, 2024

Finalist Virtual Presentations: To Be Announced



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About Alex's Lemonade Stand Foundation (ALSF)

Alex's Lemonade Stand Foundation (ALSF) emerged from the front yard lemonade stand of 4-year-old Alexandra "Alex" Scott, who was fighting cancer and wanted to raise money to find cures for all children with cancer. Her spirit and determination inspired others to support her cause, and when she passed away at the age of 8, she had raised \$1 million. Since then, the Foundation bearing her name has evolved into a national fundraising movement. Today, ALSF is one of the leading funders of pediatric cancer research in the U.S. and Canada, funding more than 1,000 research projects and providing programs to families affected by childhood cancer. ALSF is also the only childhood cancer research organization that has been given the NCI peer-reviewed funder designation for rigorous selection of research grants. The mission of ALSF is to change the lives of children with cancer through funding impactful research, raising awareness, supporting families, and empowering everyone to help cure childhood cancer.

The Crazy 8 Initiative Award Program

Childhood cancer is the leading cause of death in children in the United States and Canada and the Crazy 8 initiative's aim is to change the trajectory of pediatric oncology. With this goal, the Crazy 8 initiative kicked off in the Fall of 2018 with a meeting that brought together more than 90 scientists from around the world to help define the research landscape in eight key areas of need to tackle major obstacles impeding progress toward cures for childhood cancer, ALSF has awarded 6 research teams across 21 institutions, a total of \$26 million, funding innovative research that addresses topics of drugging the undruggable and the developmental origins of cancer. To see the scope of projects funded in the previous round of Crazy 8 Award funding, [navigate here](#).

In 2024, ALSF Crazy 8 Initiative will focus on Childhood Cancer Predisposition and Prevention.

It is now estimated that at least 15-20% of children with cancer harbor a germline cancer predisposition gene. Although currently about 100 cancer predisposition syndromes are known, there are clearly more syndromes and more genes to be discovered. There is a need to identify cancers in these individuals early to establish surveillance protocols for effective treatment. In addition, there is a need to develop effective approaches to prevent or delay tumor onset in children determined to be genetically at risk. The focus of this award will be on multiple aspects of a single cancer predisposition syndrome, or on a broader area (e.g. surveillance) across a number of different syndromes. Five major areas of focus have been identified for this Crazy 8 RFA:

- **New Gene Discovery**
- **Genotype-phenotype correlations**



- **Surveillance optimization**
- **Predisposition Models**
- **Cancer Prevention**

Program Description

This ALSF Crazy 8 RFA focuses on understanding childhood cancer predisposition and prevention. The focus must be on pediatric/adolescent cancer predisposition and should be a consortium of two or more institutions with different areas of research collaborating to integrate their expertise. **It is strongly encouraged to have a patient advocate on the team.** The proposal should address a topic that is responsive to at least one of the five areas of focus listed above.

The proposals will be judged on innovation, scientific soundness, significance, and the potential for impact on improving the lives of children with cancer. The award selection process involves three stages: (1) a **letter of intent** to narrow the pool to the projects most in line with the scope of the Crazy 8 Initiative; (2) a **full proposal** to select finalists; and (3) a **virtual presentation** to ALSF leadership and the Crazy 8 Scientific Advisory Board to choose the award recipient(s).

Application Timeline and Review

- A letter of intent (LOI) must be submitted, and all eligibility criteria met to be considered for the full proposal stage.
- Full proposals must meet all guideline criteria and all eligibility criteria; otherwise, applications will be administratively rejected.
- LOIs and full proposals will be reviewed by an independent panel of experts according to the NIH recognized peer-review process overseen by the Crazy 8 Initiative Scientific Review Board.
- Please hold the dates for the Finalist Presentations listed below. If invited, teams are expected to be available at this time.

Crazy 8 Initiative Award application timeline	
Letter of Intent Due	January 8 th , 2024 by 8:00PM ET
Invitation to Submit Full Proposal	March 2024
Full Proposals Due	May 6 th , 2024 by 8:00PM ET
Invitation to Present	July 2024
Finalist Presentations (Virtual)	To Be Announced
Award Notification	October/November 2024

Eligibility

- PIs, Co-PIs, and Co-Is must have an MD, PhD, or MD/PhD or equivalent and be appointed as faculty (or equivalent) at an academic institution.

- PIs, Co-PIs, and Co-Is must have a track record of publication and funding productivity that demonstrates that the project can be accomplished by the investigators.
- PIs, Co-PIs, and Co-Is institutions may be based in the United States or abroad, and applicants need not be United States citizens. Funds must be granted to nonprofit institutions or organizations and will be distributed in US dollars.
- PIs, Co-PIs, and Co-Is may not be a PI, Co-PI, or Co-I on a currently funded Crazy 8 Project Team. If a Co-I with special expertise is needed to complete the team, please send your request with a brief description of why this member is critical for the team to Margaret Poore at M.Poore@AlexsLemonade.org and we will review it administratively.

Budget

The requested budget should be in proportion to the scope of the proposed project and its corresponding potential for impact. Depending on the type of project and the size of the team, the requested budget should be in the range of \$3-5 million USD over four years. Cost efficiency will be one of the major considerations in review and funding decisions. Funding through subsequent years of the grant period is contingent upon satisfactory progress as determined by a Crazy 8 Initiative Scientific Review Board.

ALSF will pay up to 10% in indirect costs; if the applicant elects to request indirect costs, the total budget including indirect costs may not exceed the range of \$3-5 million USD. The 10% indirect costs should be assessed on the Total Direct Costs. Indirect costs may be assessed on subawards' Total Direct Costs but must be excluded from the primary institution's Total Direct Costs for calculating indirect.

Restrictions:

- ALSF adheres to the NIH salary cap for principal investigator(s).
- The grant may not be renewed; one no-cost extension request is allowed with the Final Report.
- Other budget items may include fringe, travel, supplies, and small pieces of equipment. ALSF funds cannot be used for tuition remission. View ALSF's complete [budget policy](#).
- If utilizing a subcontract or subaward, you must include this expense in the budget. The PI's institution is responsible for disbursing funds for subawards and/or subcontracts.

Project Focus Areas

The aims of the research proposals must be designed to directly address the most intractable issues in pediatric cancer research today with the ultimate goal of curing pediatric malignancies.

The proposal should be responsive to at least one of the five focus areas listed above and described in more detail below.

- 1) New Gene Discovery:** Knowledge of predisposing genetic/genomic signatures in children could lead to better understanding of the etiology of tumors. Even with the widespread adoption of gene sequencing, there are predisposition syndromes and patients who present with unknown underlying genetic mutations. There is a need to gain insights of novel germline genetic drivers that can be adapted to pediatric oncology care. Topics of interest include, but are not limited to:
 - Identifying epigenetic mechanisms that lead to gene alterations and mutations in childhood cancer predisposition syndromes.
 - Identifying low-penetrance genes that drive childhood cancer predisposition syndromes.
 - Identifying uncommon moderate-penetrance variants in cancer-predisposing syndrome genes.
 - Non typical or atypical variants to known genes of cancer predisposition.
 - Identifying genetic/epigenetic modifiers that impact penetrance of phenotype associated with particular driver gene alterations.
 - Based on real-world phenotype data collection and associated genetic correlations through non-biased sequencing analysis, develop a screening panel for patients with cancer predisposition
- 2) Genotype-phenotype correlations:** Two significant challenges in the field of pediatric cancer predisposition are: 1) to determine what role(s) genes associated with adult-onset cancers may play in the pediatric context; and 2) to determine the causal relationship of mutations/variants of variable penetrance on cancer phenotype. Hence there is a need to understand and identify genes with an evidence-based causal relationship with the phenotype. This information can inform patient care and genetic counseling for high-risk families. Topics of interest can include but are not limited to:
 - New associations between genotype and phenotype that can inform on cancer susceptibility.
 - Identification/definition of the role of adult-onset tumor predisposition genes in children/adolescents.
 - Incidence of genetic alterations by germline genetic analysis to identify genetic variants.
 - Correlation between family history and germline genetic analysis data to get prognostic information.

3) Surveillance optimization: Surveillance has shown to improve outcomes in Li-Fraumeni Syndrome (LFS) patients with germline *TP53* mutations, in patients with constitutional mismatch repair deficiency (CMMRD), and other cancer predisposition disorders.

Research that addresses surveillance approaches that will provide standardized guidelines globally is critical. Topics of interest include but are not limited to:

- Compare the effect of germline sequencing of all childhood cancer predisposition genes vs (targeted) genetic testing based on clinical selection. This will help evaluate current surveillance protocols to determine if what is being done and its frequency is effective (or necessary).
- Evaluate psychosocial impacts on families and patients on germline sequencing of all childhood cancer predisposition genes vs (targeted) genetic testing based on clinical selection to help develop surveillance optimizations that can be implemented successfully.
- Develop enhanced surveillance diagnostic modalities that include any of the following: multi-omic liquid biopsies/circulating tumor material; Microbiome profiling; volatile organic compounds (VOC) patterns in breath; enhanced imaging technology that will overcome issues of current modalities that pediatric patients face such as a need for prolonged sedation/anesthesia.

4) Predisposition Models: Development of pediatric cancer predisposition models is challenging because pediatric cancers are heterogeneous and occur during the developmental stage and in addition to molecular features the developmental lineage of the cell of origin of the cancer also needs to be taken into consideration. Topics of interest include:

- Animal models that reflect the cancer predisposition seen in humans with the same genetic change are needed to test novel surveillance approaches and to study prevention.
- Organoid and other in vitro models that can recapitulate cancer genetic changes and can be used for high throughput mutational analysis to inform on effective personalized therapies.

5) Cancer Prevention: In childhood cancer predisposition there is a need to explore novel approaches to prevent or delay cancer initiation, or cancer interception to improve patient outcomes. Topics of interest can include but are not limited to:

- Development of in vitro/ in vivo models of cancer predisposition syndromes to explore novel drug screens to delay or prevent cancer onset.
- Introduction of biomarkers to complement early phase human studies of pharmacologic prevention in cancer predisposition.

Resource and Data Sharing

Applicants should describe their track record of generating resources that are broadly re-used, the specific resources that will be generated in this proposed project, and the mechanisms by which those resources will be shared. To demonstrate a commitment to sharing that will be actualized, applicants should provide information in their sharing plan that clearly states the type of resource that will be shared, the method, characterization and timing of such sharing, and the anticipated resources (budget, personnel, etc.) required by the applicant and the resource user. Reviewers will consider the extent to which the dissemination of resources produced under the award will enhance or diminish the impact of the proposed work. For a full description and an example, see [the Resource Sharing Form](#). For the full Resource Sharing Policy visit our [Resources for Grant Applicants](#) page.

Resubmissions

One resubmission of an application previously reviewed by ALSF's Crazy 8 Review Board is permitted. Applicants should respond to the prior ALSF critique of the proposal in the Resubmission section of the application. The response to critique will be scored in the review process, and resubmissions compete with new applicants for funding.

Restrictions

- Proposals must fall within the scope of Alex's Lemonade Stand Foundation's mission, focused on childhood cancers. Proposals with a sole/primary focus on patients >19 years of age will not be considered.
- ALSF does not fund proposals for research utilizing human embryonic stem cells or non-human primates. Research with human induced pluripotent stem cells is permissible.
- Investigators may submit one LOI as PI.

Grant Reporting Requirements

- Please review ALSF's Grant Policies, including Budget Expenditures, Resource Sharing and Grant Agreement with IP, found on the [Resources for Grant Applicants](#) page
- Annual progress reports followed by an update teleconference with ALSF.
- Attendance at a yearly Crazy 8 Summit, to be held in person.
- Each year of funding is contingent upon demonstration of satisfactory progress toward the completion of proposed research objectives and appropriate budget expenditures.
- Minor carry-over of funds (25% or less) is permitted each year with justification. Each year's budget will be approved subsequent to the review of project progress. If carry-over is excessive, ALSF may elect to partially fund or hold new funds.

- A final report is required at the conclusion of funding. Report must state findings, expenditures, as well as publications and presentations which acknowledge ALSF funding. The grant may not be renewed; one no-cost extension may be requested in the final report.
- Publications, presentations, and posters featuring results of the experiments funded by this grant mechanism should acknowledge “Alex’s Lemonade Stand Foundation (Grant #)”. Copies should be sent via email to Grants@AlexsLemonade.org.

Letter of Intent (LOI) Instructions (Due January 8, 2024)

A Letter of Intent is required to ensure that the proposed research is within the scope of the Crazy 8 Initiative. LOIs will be reviewed by a review board prior to advancing to the full proposal stage.

Format Instructions

- **PAGE HEADER:** All pages of the LOI should be numbered; the name of the principal investigator should appear in the upper right-hand corner of each page.
- **FORMAT:** Follow NIH format guidelines: Arial, Helvetica, Palatino Linotype, or Georgia fonts with a font size of 11 points or larger with a minimum of ½ inch margins.
- **ORDER & LENGTH:** The order of the LOI should be followed, adhering to the maximum number of pages allowed for each subsection indicated in parentheses, not to exceed 2 pages.
- No appendices allowed.
- Create a **single PDF** for all sections and bio sketch(es) and upload to the ALSF online application form ([see Application Submission Instructions](#)).

LOI Section Descriptions

- **Scientific Abstract** (500 words) – Address the big problem and Crazy 8 focus areas that you will tackle. Must also include: Rationale, Hypothesis, Specific Aims, Design.
- **Investigators and Institutions** – List all key personnel, disciplines, their affiliated institutions, and any unique attributes of your team. It is understood that this may change, and the list is not considered binding.
- **Budget** (2-4 sentences) – List the total requested budget and short justification (PI and Co-I support, supplies and contracts)
- **Impact Statement** (~4 sentences) – State how this project will impact childhood cancer outcomes.

- **Innovation Statement** (~4 sentences) – State how this project is a novel approach to childhood cancer research and how specifically the innovation will help you address the big problem you are tackling.
- **Resource Sharing** (~4 sentences) – Describe how outputs from the project will be shared. State how this project’s impact will be enhanced by sharing outputs.
- **Literature References** (1 page) – Use Vancouver style: numeric references within the text.
- **Bio sketch(es)** (not included in page count) – Use the NIH 5-page bio sketch form for PI and Co-PIs.

Full Proposal Instructions (By invitation only with an approved LOI)

Application Package

- All sections described below should be combined into **one PDF** (max 20 MB) and uploaded to the ALSF online application form ([see Application Submission Instructions](#)).
- All templates mentioned can be found at ALSF’s [Information for Grant Applicants](#) page.

Format Instructions

- **PAGE HEADER:** All pages of the application should be numbered; the name of the principal investigator should appear in the upper right-hand corner of each page.
- **FORMAT:** Follow NIH format guidelines: Arial, Helvetica, Palatino Linotype, or Georgia fonts with a font size of 11 points or larger with a minimum of ½ inch margins.
- **ORDER & LENGTH:** The order of the application should be followed, adhering to the maximum number of pages allowed for each subsection indicated in parentheses.

Section Descriptions

1. Project Information

- a. **Cover Page** (1 page): Download and complete the [Cover Page Template](#).
- b. **Table of Contents** (1 page): Provide a Table of Contents with page numbers to the corresponding sections.
- c. **Scientific Abstract** (0.5 page): Summarize the research objectives and rationale.
- d. **Impact Statement** (0.5 page): How will this project impact childhood cancer?

2. Budget/Justification (3 pages):

- a. **Budget Template** (1.5 pages): Complete the [ALSF budget template](#). The signature from an institutional representative on the cover page of this grant application specifically acknowledges and accepts this budget.
 - i. The award amount is between \$3-5 million over 4 years.

- ii. ALSF adheres to the NIH salary cap for principal investigator(s).
 - iii. Indirect costs are allowed up to 10% and should be assessed on the Total Direct Costs.
 - iv. If utilizing a subaward, you must include their budget. Indirect costs may be assessed on subawards' Total Direct Costs but must be excluded from the primary institution's Total Direct Costs for calculating indirect. The contact PI's institution is responsible for disbursing funds for subawards/subcontracts.
 - v. Reasonable travel expenses to national/international research meetings to disseminate findings may be budgeted. Travel to the ALSF annual Crazy 8 Summit will be at no cost to the grant recipient.
- b. **Budget Justification** (1.5 pages): Include a narrative for the following. Use N/A in sections as needed:
- i. Personnel
 - ii. Subcontractors/Subawards/Consultants
 - iii. Equipment (for equipment costs above \$5000)
 - iv. Travel
 - v. Computer and Software
 - vi. Other
3. **Biographical Sketch(es)**: Use the NIH five-page biographical sketch (SF424) format for the principal investigator and all key personnel.
4. **Research Plan**
- a. **Specific Aims** (1 page): List the goals, long-term objectives and what the specific research proposed in this application is intended to accomplish. State the hypothesis to be tested and relevance to childhood cancer research.
 - b. **Significance** (1 page): Describe the relevant background for the current research plan. State the significance and importance of your proposed project with respect to childhood cancer research. Relate the specific aims to the goals and long-term objectives.
 - c. **Innovation** (0.5-1 page): Describe how the proposed research challenges and shifts paradigms or introduces a novel concept, approach, or technology.
 - d. **Approach** (10 pages): Describe the experimental approach to the research question and how the research will be realistically accomplished within the proposed funding period. This section should include *but is not limited to*:
 - i. Feasibility of the approach to reach project goals; include preliminary studies pertinent to the project.
 - ii. Anticipated potential problems and plans to address these issues.

iii. Timeline and deliverables

5. **Resource Sharing (1-2 pages):** Use the [Resource Sharing Form](#) to complete this section of the application to describe the outputs from the proposed project and how they will be shared. Reviewers will be asked to consider the manner in which outputs from this project will be shared and the extent to which this plan will increase or decrease the impact of the proposed project.
6. **Literature Cited:** Use Vancouver or NIH style (numbered citations within text) format.
7. **Human Subjects (1 page):** If approved, include the IRB approval letter or equivalent. If approval is pending, indicate the expected approval date. If IRB approval is not applicable, include a note in this section.
8. **Vertebrate Animals (1 page):** If approved, include the IACUC approval letter or equivalent. If approval is pending indicate the expected approval date. If IACUC approval is not applicable, include a note in this section.
9. **Letters of Support:** Include any appropriate letters from individuals confirming their roles in the project. Institutional letters of support are not required, but can be included, especially if there are issues of feasibility that can be addressed.
10. **Appendix:** A brief appendix is allowed for Crazy 8 Grants. Appendices should be included only if essential to the understanding of the application. Appendices are limited to one accepted but not yet published manuscript OR two pages of additional information such as a summary of the protocol and supplementary figures. (Reminder: tables and figures noted in the text should be embedded in the body of the proposal.)
Reviewers are not required to read the appendix.

Application Submission Instructions

ALSF has migrated to Proposal Central for submitting and accessing awarded research grant applications! Please read carefully as our submission instructions have changed.

1. To start an application, navigate to [Proposal Central](#) and select "I am an Applicant."
 - a. **Returning applicants (with an existing Proposal Central):** log in with your Proposal Central ID.
 - i. *A password reset request can be sent using the following link:*
<https://proposalcentral.com/ForgotPassword.asp>
 - b. **First time applicants (using Proposal Central):** click "Need an Account?" under the "Login" Button or use the following link:
<https://proposalcentral.com/register.asp>. Enter all the required fields and click "Submit."

- c. **ORCID Registrants:** you can login using your ORCID. If you don't have one, you can obtain one by registering through the link <https://orcid.org/register>.
2. The Crazy 8 Full Application is by invitation only. To access the application, login to your Proposal Central account and navigate to the Proposal Tab. There you will see the Crazy 8 application from ALSF for you to complete.
3. The application document must be uploaded as **one PDF** (maximum of 20 MB), in the Attachments tab. Please see the guidelines for specific format and section instructions.
4. You may save your application to finish later. Just click "Save".
 - a. When you return to Proposal Central, click the "Proposals" tab at the top to navigate to your applications. You can filter your application based on Proposal Status in the upper right-hand corner. Click "In Progress" to return to your existing applications.
5. Once completed, click "Submit". Within 10 minutes you will receive a confirmation email. As long as the deadline has not passed, you may unsubmit your application to make changes by clicking the "Unsubmit" button on the "Proposals" tab.
6. If you have any questions regarding your Proposal Central account, please contact pcsupport@altum.com.

Contact

- If you have any questions regarding this grant mechanism, reach out to Margaret Poore, Grant Coordinator by email at M.Poore@AlexsLemonade.org.