



2021 Application Guidelines for the Crazy 8 Initiative Award Program

Letter of Intent Due: April 26, 2021

Full Application Due: August 5, 2021

Finalist Virtual Presentations: December 8-10, 2021



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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

Background

Alex's Lemonade Stand Foundation (ALSF) has focused on enhancing collaborations that develop cures since its beginning. As ALSF continues to distinguish itself as a leader in funding childhood cancer research and accelerating cures, the Foundation's grants have facilitated unprecedented collaborations between the brightest minds in childhood cancer research from around the globe. ALSF launched the Crazy 8 Initiative with the purpose of harnessing that collaborative spirit to detail roadmaps to cures for specific high-risk childhood cancers and to identify and solve critical challenges facing the childhood cancer community.

The Crazy 8 Initiative kicked off in 2018 with a meeting that brought together more than 90 top scientists from around the world to contribute their expertise in eight key pediatric oncology disciplines.

Crazy 8 Disciplines

1. Embryonal brain cancers
2. High-grade gliomas
3. Fusion-positive sarcomas
4. Fusion-negative sarcomas
5. Leukemias
6. Neuroblastoma

7. Big data
8. Catalyzing clinical trials

The group aimed to undertake the big question: How can we tackle major obstacles impeding progress towards cures for childhood cancer through multidisciplinary collaborative research? The outcomes of the meeting included a list of addressable problems and proposed pathways forward to overcome these obstacles to make cures a reality. The group identified four cross-cutting research themes that form the basis of this RFA, with the overarching goal of making a major impact on the field of childhood cancer.

Crazy 8 Research Themes

1. Developmental Origins of Pediatric Cancers
2. Drugging Currently Undruggable Pediatric Cancer Drivers
3. Developing Novel Immunotherapies
4. Discovery and Development of Novel Pediatric Cancer Drug Targets

The Crazy 8 Commitment

In addition to its current grant opportunities, the Crazy 8 Initiative creates a new funding pillar for ALSF, allowing the foundation to tackle specific challenges in pediatric cancer research that require substantial support for collaborative teams. ALSF has committed \$25 million to support the Crazy 8 Initiative.

Program Description

The Crazy 8 Initiative Award will fund research into innovative and rigorous approaches that directly address the most intractable issues in pediatric cancer research today. This award is designed to coalesce cross-disciplinary cores of scientists working collaboratively in order to accelerate the pace of new cure discovery.

Investigations may involve the exploration of a novel scientific hypothesis or the development of new model systems, tools or technologies that have the potential for significant impact on the field of childhood cancer. Collaboration and resource sharing are a priority for this research program. We expect successful applications to propose multidisciplinary teams with a very clear plan for collaboration that would empower the study of big ideas that would not be easily addressable otherwise. Childhood cancer research applicants are encouraged to bring new, necessary expertise into the field.



The proposal should address a topic that is responsive to at least one of the four pediatric cancer research themes listed above. It is expected that successful applications will address one or more of the eight disciplines that formed the basis of the Crazy 8 Initiative. For 2021, *priority will be given to projects involving innovative studies of high-grade gliomas, nonmedulloblastoma embryonal brain tumors, non-Ewing Sarcoma fusion-positive sarcomas, fusion-negative sarcomas, big data and/or catalyzing clinical trials.* Investigators with proposals focusing on leukemias, neuroblastoma, Ewing sarcoma and medulloblastoma are welcome to apply, but ALSF has set areas of prioritization for this round of funding in order to fund a broadly representative community of investigators working across many different cancer types. To see the scope of projects funded in the previous round of Crazy 8 Award funding, [navigate here](#).

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 award finalists; and (3) a **virtual presentation** to ALSF leadership and the Crazy 8 Scientific Advisory Board to choose the award recipient(s).

ALSF has committed \$25 million USD to the Crazy 8 Initiative. Approximately \$18.5 million was allocated in the first round of funding in 2020, and this RFA is issued as the second round of funding for this Initiative. ALSF anticipates funding one to two awards in this round of funding to bring the total commitment to \$25 million.

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 Advisory Board.

CRAZY 8 INITIATIVE AWARD APPLICATION TIMELINE

LETTER OF INTENT DUE	April 26, 2021 by 8:00PM ET
INVITATION TO SUBMIT FULL PROPOSAL	By June 11, 2021
FULL PROPOSALS DUE	August 5, 2021 by 8:00PM ET
INVITATION TO PRESENT	By November 5, 2021
FINALIST PRESENTATIONS	December 8-10, 2021
GRANT START DATE	Q1 2022

Eligibility

- Applicants must have an MD, PhD, or MD/PhD or equivalent and be appointed as faculty (or equivalent) at an academic institution.
- Applicants must have a track record of publication and funding productivity that demonstrates that the project can be accomplished by the investigators.
- Applicant 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.

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 is contingent upon satisfactory progress as determined by a Crazy 8 Initiative Scientific Advisory 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 indirects.

Project Mission Relevance

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 four research themes listed above and described in more detail below. The proposals must also address one or more of the eight Crazy 8 disciplines, and for 2021, *priority will be given to projects involving **innovative** studies of high-grade gliomas, nonmedulloblastoma embryonal brain tumors, non-Ewing Sarcoma fusion-positive sarcomas, fusion-negative sarcomas, big data and/or catalyzing clinical trials.*

Developmental Origins of Pediatric Cancers

Childhood cancers show developmental specificity based on age and tumor location at diagnosis, which suggests that there are particular vulnerabilities as cells progress through developmental programs. Enhanced understanding of the cellular origins and usurped developmental pathways essential in childhood cancers is needed to address why certain cells are predisposed to tumorigenesis in distinct developmental contexts. Discerning how these cells go through

malignant transformation may provide novel, druggable pathways. Areas of interest include, but are not limited to:

- Identifying cell of origin in childhood cancers
- Understanding how genetic alterations impart tumorigenesis during specific timepoints of development
- Discovering how epigenetic modifications influence cancer predisposition in a developmental context and how these modifications influence cancer progression
- Understanding the tissue-specific microenvironmental influence on pediatric cancer progression
- Identifying cell-specific vulnerabilities that may be targeted while minimizing harm to the normal development of tissues
- Using cell-of-origin identity to develop appropriate preclinical models
- Uncovering the effects of sex, race or ethnicity on cellular development and disease predisposition

Drugging Currently Undruggable Pediatric Cancer Drivers

Chromosomal translocations that lead to fusion oncoproteins, such as EWS-FLI in Ewing sarcoma and PAX3/7-FOXO1 in alveolar rhabdomyosarcoma, are commonly found in childhood cancers and are difficult to target. More broadly, oncoproteins critical to childhood cancers, such as transcription factors like MYCN, are notoriously challenging to target due to nuclear localization and the lack of an obvious binding pocket. More understanding of the biological mechanism and structural basis of these oncoproteins is needed as well as model systems in which to study them in order to identify potential therapeutic targets. Areas of interest include, but are not limited to:

- Understanding the underlying molecular mechanism of these difficult to drug oncoproteins
- Developing models (e.g. cell lines, iPSC models, animal models) that recapitulate the disease
- Small molecule and/or functional genomic screening for hits and subsequent validation
- Understanding the structural biology of the oncoprotein and the key protein members of the oncoprotein complex to discover unique vulnerabilities
- Identifying targetable proteins that have enhanced effects in the presence of an undruggable oncoprotein
- Developing novel therapies based on any of the areas above, including protein degraders and immunotherapies

Developing Novel Immunotherapies

Immunotherapies hold great promise in the treatment of childhood cancer, but there are challenges to their broad implementation including few known tumor-specific targets on the surface of cancer cells or presented on the MHC complex, the immunosuppressive tumor microenvironment, immune evasion and treatment resistance, and the need for better model systems for testing. Areas of interest include, but are not limited to:

- Characterizing the tumor microenvironment and its role in the response to therapy
- Identifying the molecules found on the surface of cancer cells and/or presented in the context of MHC to inform new target development
- Studying the mechanisms of immune system evasion
- Designing improved model systems to inform mechanistic understanding and preclinical testing of immunotherapies
- Developing novel immunotherapeutic approaches including multi-specific targeting and re-educating the adaptive immune response

Discovery and Development of Novel Pediatric Cancer Drug Targets

Childhood cancers exhibit a low mutational burden compared to adult cancers which makes finding targets challenging. Additionally, targets may evolve as cancers become resistant to standard therapies or relapse. The mechanisms of resistance and relapse in pediatric cancers are not well understood and a greater understanding of the underlying molecular evolution of the tumor and its microenvironment is needed. Areas of interest include, but are not limited to:

- Studying the molecular mechanisms of tumor resistance in response to therapy
- Understanding the biological processes that lead to metastasis
- Developing clinically relevant models to study resistance and relapse to prioritize drug discovery
- Characterizing tumor specimens before treatment, during, and upon relapse
- Using new technologies such as a single-cell RNA sequencing and single-nucleus sequencing to better understand tumor heterogeneity within and in the surrounding microenvironment
- Developing computational methods and workflows to analyze the large scale data
- Developing clinically relevant models for high-throughput and/or functional genomic screening
- Developing and validating new biomarkers
- Understanding cell-based dependencies and communication within the tumor microenvironment

Resource and Data Sharing

Grant recipients are expected to share unique resources developed under this funding award, and as part of the application, applicants are required to submit a Resource Sharing Plan. 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 see the [Resource Sharing Form](#).

The [ALSF Childhood Cancer Data Lab](#) (CCDL) is available for consultations regarding the management and sharing of your research data and source code which is a required element of this award. The use of the CCDL is not required and is meant to serve as a benefit to investigators. Reach out to the CCDL Director, [Jaclyn Taroni, PhD](#), for more information.

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 >21 years of age will not be considered.
- Grant proposals must be focused on pediatric oncology, from understanding basic biologic underpinnings to new therapies, in response to the four Crazy 8 research themes.
- Funds may not be used for research utilizing human embryonic stem cells or non-human primates. Research with human induced pluripotent stem cells is permissible.

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.

Grant Reporting Requirements

- Annual progress reports followed by an update teleconference with ALSF.
- Attendance at a yearly Crazy 8 Summit, to be held in person or virtually.
- 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; no-cost extensions 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 4/26/21)

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 biosketch(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 theme(s)/discipline(s) 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.
- **Resubmission** (100 words) – Has a full application for this project been reviewed by ALSF before and not been funded? If so, describe what has changed (data, design, aims etc) in response to the prior critique. If not, skip this section.
- **Literature References** (not included in page count) – Use Vancouver style: numeric references within the text.
- **Biosketch(es)** (not included in page count) – Use the NIH 5-page biosketch form for PI and Co-PIs.

Full Proposal Instructions (By invitation only with an approved LOI, due 8/5/21)

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 indirects. 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)
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. **Resubmissions** (1 page, if applicable): If this proposal was previously submitted to ALSF and did not receive funding, describe any changes in response to the reviewer critiques (e.g. changes in experimental design, scope, new data).
 - b. **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.
 - c. **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.
 - d. **Innovation** (0.5-1 page): Describe how the proposed research challenges and shifts paradigms or introduces a novel concept, approach or technology.
 - e. **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. Timeline and deliverables

- ii. Feasibility of the approach to reach project goals; include preliminary studies pertinent to the project
 - iii. Anticipated potential problems and plans to address these issues
 - f. **Resource Sharing** (1-2 pages): Describe the outputs from the proposed project and how they will be shared. Reviewers will be asked to consider the manner in which resources will be shared and the extent to which this plan will increase or decrease the impact of the proposed project. Download and use the [Resource Sharing Form](#) to complete this section of the application.
 - g. **Literature Cited**: Use Vancouver or NIH style (numbered citations within text) format.
5. **Human Subjects** (1 page): If approved, include the IRB approval letter or equivalent. If approval is pending, indicate the expected approval date. Any funds awarded will be held until the letter is received. If IRB approval is not applicable, include a note in this section.
 6. **Vertebrate Animals** (1 page): If approved, include the IACUC approval letter or equivalent. If approval is pending indicate the expected approval date. Any funds awarded will be held until the letter is received. If IACUC approval is not applicable, include a note in this section.
 7. **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.
 8. **Appendix**: A brief appendix is allowed with the following limitations.
 - a. Appendices should be included only if they are essential to the understanding of the application, including one accepted but not yet published manuscript or two pages of additional information such as a summary of the protocol if applicable and/or supplementary figures.
 - b. Excessive appendices will result in the application being rejected administratively.

Application Submission Instructions

- ! **Applicants must not use the IE browser as it is not compatible with the online portal. Chrome and Firefox browsers are recommended.**
- 1. To start an application, navigate to the portal at ALSfapps.force.com.
 - a. Returning applicants: login with your username and password.
 - b. First time applicants: click the “New User?” link and complete your one-time registration and then login.

2. After you've logged in, follow the directions on the dashboard to submit your application. Complete the online form with applicant contact and project information.
 - a. Enter the Project Title first, even if tentative. Then Save.
 - b. Applicant will be asked for basic contact information for themselves, co-PI(s) if applicable, grant manager and institution. If someone other than the PI is entering information into the portal, the "Contact Person" name entered **must** be the PI's name.
 - c. In the respective sections enter the budget request amount, type of childhood cancer the project focuses on, as well as a 250-word summary of the research project in lay terms (this will only be requested at the full application stage), and other requested information. The applicant will be asked to release the lay summary for use at ALSF's discretion should the proposal be funded. The applicant may copy and paste information from other documents into these sections.
3. The application document must be uploaded as **one PDF** (maximum of 20 MB).
4. You may save your application to finish later. Go to ALSFapps.force.com and login again. You will land on your dashboard. Click "Applications" to edit your application in progress.
5. Once completed, **you must submit the application** by clicking Review & Submit. You will see error messages for any required fields that need to be completed.
6. After your application has been successfully submitted, an email confirmation will be sent. You will not be able to amend the application after submission. If you do not receive a confirmation email, please contact Grants@AlexsLemonade.org.

Contact

- If you have any questions regarding this grant mechanism, reach out to Anna Greene, Director of Science, by email at A.Greene@AlexsLemonade.org.