Request for Proposals: 2025 LCRF | Bayer Research Award on Innovative Therapeutic Strategies to Treat Lung Cancers Harboring HER2 Mutations and/or Other HER2 Alterations

1. Program Summary

Lung cancer is responsible for more deaths worldwide than any other cancer accounting for an estimated 125,070 deaths annually in the United States alone.[1] The last 10-15 years have seen accelerated clinical trials and FDA approvals of targeted therapies for non-small cell lung carcinoma (NSCLC) in part due to advances in molecular profiling of tumors. Many of these targeted therapies are directed against oncogenic drivers.

The HER family of tyrosine kinases include HER1 (epidermal growth factor receptor [EGFR] or ERBB1), HER2 (HER2/neu or ERBB2), HER3, and HER4. EGFR mutations were one of the first oncogenic drivers that were successfully targeted with the use of tyrosine kinase inhibit ors. Despite substantial progress in this area, available treatments are generally not curative, and resistance invariably develops. 20 years ago, HER2 mutations have also been identified as potential oncogenic drivers in lung cancer.[2,3] HER2 does not have an endogenous ligand but rather heterodimerizes with other HER family receptors and activates downstream signaling through the PI3K/AKT and RAS/MAP/MEK pathways. HER2 mutations occur in up to 4% of NSCLC. In the past two decades, several clinical trials have investigated the use of anti-HER2 therapies in lung cancer but led to disappointing results. On August 11, 2022, the Food and Drug Administration granted accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic NSCLC whose tumors have activating HER2 mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.[4] This is a small but positive step forward for patients with NSCLC whose tumors harbor these mutations.

Immunotherapeutic strategies have not been successful in the treatment of lung cancers with EGFR or HER2 mutations. It is of vital importance that there is a better understanding of the mechanism of tumor response and resistance. Moreover, given that therapeutic options available to date are not curative, there is a need for novel approaches to treat HER2-mutant lung cancers. This grant mechanism will focus on the science behind HER2 alterations as oncogenic drivers of malignancy and/or the development of novel therapeutic approaches for patients with tumors harboring HER2 mutations and/or other HER2 alterations.

Work supported through this mechanism will address important mechanistic questions and developmental therapeutics across the care continuum and have the potential to increase survivorship. Given the specific interest in the development of novel therapies for this group of patients, it is preferred that a clinical trial be associated with or planned as a result of the

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[1] Siegel RL, Giaquinto AM, Jemal A. CA: A Cancer Journal for Clinicians, Vol 24, Issue 1, Jan/Feb 2024
[2]Stephens P et al. Intragenic ERBB2 kinase mutations in tumours. Nature 431:525, 2004.
[3]Riudavets M et al. Targeting HER2 in non-small-cell lung cancer (NSCLC): a glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations. ESMO Open 6:100260, 2021
[4]Li BT et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer, N Engl J Med 386:241, 2022.

findings of the project. It is also expected that a program of correlative, translational research will be proposed that will enhance the understanding of these oncogenic-driven lung cancers.

We encourage applications on a wide variety of topics related to HER2 alterations and lung cancer, including but not limited to the following:

- The proposal must be associated with a clinical trial, either ongoing or planned as a result of the project. The trial can investigate novel treatment approaches, new therapies (i.e. next generation drugs or agents with novel mechanisms of action), and novel combinations. Therapy can include targeted agents (TKIs), antibody-drug conjugates, immunotherapies, cell therapies etc. if there is a reasonably strong rationale supporting the investigation.
- The proposal must have a program of basic and/or translational work associated with the clinical trial. Topics of interest can include but are not limited to mechanisms of primary or secondary resistance, studies on the immune landscape and tumor microenvironment, biology and mechanisms of tumor progression, identification of biomarkers to predict sensitivity to specific therapies, methods for optimizing treatment (efficacy and/or tolerability), etc.
- The proposal must include studies in patients with lung cancer harboring HER2-mutations and /or other HER2 alterations.
- A patient/patient advocate needs to be part of the research team applying for the grant and that this individual should have a role in the design of the research.

2. Budget Requirements

- The maximum award amount is $500,000 for a period of two years ($250,0000 per year). Additional budget requirements and considerations include the following:
- The LCRF grant must be the primary source of research support for the proposal. Since a clinical trial is associated with the project, it is suggested that additional funding be obtained from a funding partner to support the clinical trial costs. Additional secondary funding (e.g. for core services support) is also permitted.
- Up to 50% of the grant (i.e. $250,000 over 2 years) should be allocated to support the scientific translational work associated with the proposal.
- There is no limit on the amount of salary support that may be requested. However, appropriate justification for all budget items is required. Any salary requests more than 20% of the total budget must be explicitly justified.
- Any equipment costs must be limited and directly applicable to the research project (i.e. large, general equipment costs are not permitted).
- Direct patient care costs reimbursable by other sources may not be included.
- Travel and publication costs are permitted.
- Up to 10% of the funding from this award may be used to support institutional indirect / facilities and administrative costs.

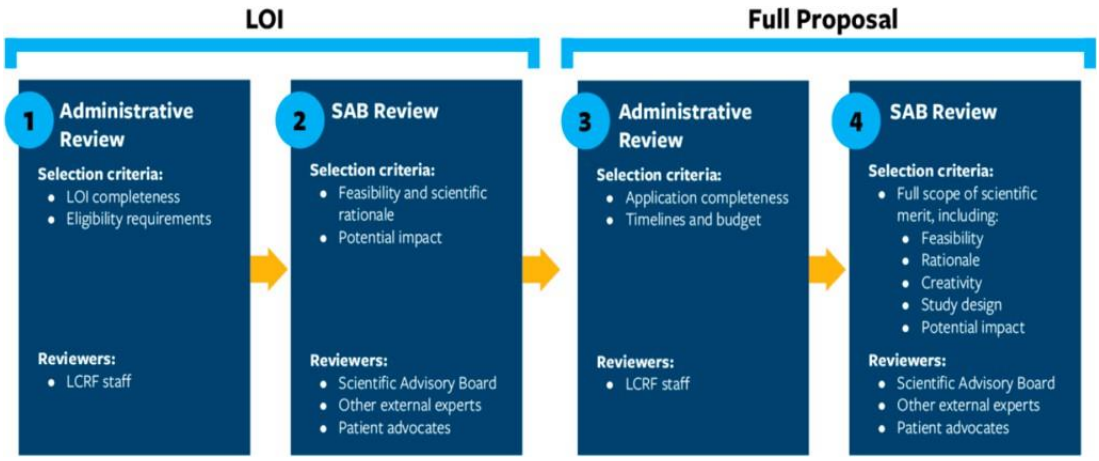
3. Applicant and Research Project Eligibility Criteria:

Investigators must be affiliated with a non-profit, academic or research institution. An applicant must have a postdoctoral or clinical research fellow appointment and/or a faculty position and may have any level of research experience. Applicants from US-based and international institutions are eligible to apply and may hold any residency/citizenship status. Applicants are prohibited from applying in more than one of LCRF's funding tracks in the same cycle. Any questions regarding eligibility should be directed to the LCRF Grants Office before the submission of an application.

4. Process of Evaluation of Applications:

Submissions will be evaluated for sound scientific rationale, study design, feasibility, and creativity/innovation. Similar to an NIH R21 award, reviewers at the full proposal will be asked to provide an impact score reflecting their assessment of the likelihood for the project to exert a sustained, powerful influence on the field of lung cancer research.

Application Review Process:



Composition of Review Committee:

- 3 LCRF Scientific Advisory Board members
- 2 LCRF Research Advocates
- LCRF's Chief Scientific Officer and/or Chair, Scientific Advisory Board
- Up to 4 Bayer representatives (non-voting members)

5. Timeline:

Request for LOIs open	January
LOIs due	March 3
Applicants notified of LOI decision	April 18
Full proposals due	June 2
Full proposal reviews	July - August
Notification of award	November

6. Application Procedures:

All applications for funding must be submitted online via Proposal Central. Applicants may only apply for one LCRF grant per grant cycle. Any applications for an extension of a previously awarded grant require resubmission as a new complete application (full proposal) and must include an update describing the progress made during the prior award period. Text should be Arial, Times New Roman, Palatino Linotype, Courier New, Georgia, or Helvetica 11-point font or higher. Margins should not be less than 0.5" on standard letter paper (8 ½" x 11"), and margins must be verified on the uploaded documents.

The following application components are required for a complete submission:

Letter of Intent	**Full Proposal**

• General Information / Demographics
• Specific Aims (one page in length)
• NIH Biosketch (NIH Biosketch Instructions)
	• General Information
	• Demographics
	• Eligibility Statement from the Institution
	• NIH Biosketch
	• Lay Summary
	• Specific Aims (one-page in length)
	• Narrative (six-page maximum) including:
	  ○ Background and Significance
	  ○ Preliminary Data
	  ○ Experimental Approach
	  ○ References (not included in page-limit)
	  ○ Clinical Trial Protocol (if applicable)
	  ○ Patient Consent Form
	  ○ Patient Impact Summary (half-page in length)
	  ○ Patient Advocate Involvement Summary (half-page in length)
	• Success Factors (half-page in length)
	• Timeline
	• Future plans (half-page in length)
	• Budget

	• Mentoring plan (if less than five years of experience – one-page in length)
	• Letter(s) of Support
	  ○ Cancer Center Director or Chief of Hematology/Oncology
	  ○ Co-PI(s)
	  ○ Funding Source for Clinical Trial (if applicable)
	  ○ Mentor (if applicable)

Additional Considerations:

- All LOIs must include the NIH biosketch (five pages maximum length) of the primary investigator and any key personnel involved in the project.
- Funding will only be awarded to one PI, not to a team.
- At the full proposal stage, applications must include at least one letter of support from the principal investigator's program director/advisor affirming the following statements:
    - The applicant will be officially affiliated with or employed by the institution during the grant period.
    - There is adequate institutional space and equipment to accomplish the proposed project.
    - The program director/advisor confirms his/her commitment to and provision of institutional space and equipment for the grantee.

7. Funding Disbursement Schedule:

Funding will be disbursed to grantee(s)' institutions as described in the schedule below:

Milestone(s)	**Description**	**Amount ($)**
Initial Installment	To be paid upon receipt, following approval by LCRF's Board of Directors (expected December 2025)	$250,000 per award
Final Installment	To be paid upon receipt, following approval by LCRF of the annual status update report (expected December 2026).	$250,000 per award

8. Post-award Reporting Requirements

During the funding period, all investigators are required to submit at least two scientific progress reports and at least four lay audience update reports including the following:

Report Type	Due Date
Interim Report	At conclusion of year one of the grant term
Final Report (includes financial summary report)	Within sixty days of conclusion of the grant term
Lay audience update	Every six months after project start date

All reporting is required to be done in Proposal Central, and additional reports may be assigned when project terms are amended (e.g. in the case of a no-cost extension or institutional transfer). Receipt of the second year of funding is contingent upon submission and approval of the interim progress report at the conclusion of the first year of the grant term.

9. Data Sharing and Open Access Policy

LCRF is committed to promoting open science by helping to increase access to investigators' findings and improving collaboration and data sharing among the lung cancer research community. Accordingly, it is a condition of LCRF funding that all peer-reviewed articles supported in whole or in part by LCRF funds must be made available in the PubMed Central online archive no later than twelve months after publication. In addition, LCRF grantees must indicate explicitly in all reports, publications, and other research communications whether the data, methods used in the analysis, and materials used to conduct the research will be made available to any researcher for purposes of reproducing the results or replicating the procedure. At the time of submission of the full proposal, all investigators must indicate if they will or will not make their data, analytic methods, and study materials available to other researchers.

10. Inquiries

For questions, please contact the LCRF office at grants@lcrf.org OR

If you have any difficulties registering, logging in, or creating your application, contact Proposal Central Customer Support at: 800-875-2562 (Toll-free U.S. and Canada), +1-703-964-5840 (Direct Dial International). 875-2562 (Toll-free U.S. and Canada), +1-703-964-5840 (Direct Dial International).