2024 ASPIRE Award Request for Proposals:

Biomarker Discovery in Follicular Lymphoma

PURPOSE:

The past decade has seen progressive advances in our understanding of both follicular lymphoma (FL) pathogenesis and normal germinal center B cell biology, underscoring key roles for epigenetic control and complex interplay with the microenvironment. This increased understanding along with rapid improvement in technologies for multi-omic analyses such as single cell and spatial approaches make it an opportune time to re-visit biomarker development in FL, moving toward defining a cure for FL.

The Mark Foundation for Cancer Research in collaboration with the Follicular Lymphoma Foundation (FLF) held an investigators' workshop in December 2023 that brought together a diverse group of clinical and scientific experts in lymphoma and new molecular technologies to discuss the potential to develop biomarkers for FL. The FLF also surveyed patients in November 2023, to determine what benefits they would envisage from biomarkers.

To continue the momentum of the workshop and patient survey findings, The Mark Foundation and FLF present this request for proposals through the ASPIRE Award program **for projects focused on development of potential biomarkers for various stages of the FL patient experience.** This is expected to lay the foundations for translating the findings into clinical impact. Given the specific characteristics of FL, we also expect that successful efforts in FL will translate more broadly across other B-cell blood cancers, as well as other blood and even solid cancers.

BACKGROUND:

Follicular lymphoma (FL) is the 2nd most common non-Hodgkin lymphoma, with ~ 16,000 new cases/yr in the U.S, and an estimated prevalence of ~200,000. FL is a germinal center B cell derived indolent lymphoma, characterized by t(14:18) dysregulating BCL2 expression (necessary but not sufficient), at least 1 epigenetic mutation in > 90% of cases, with an important but incompletely understood role of the tumor microenvironment (TME), especially T_{FH} cells. It is a heterogeneous disease biologically and clinically:

- ~80% survive > 10 years, with ~1/3 never needing treatment and the rest requiring repeated treatment courses over years;
- ~20% progress within 2 years (POD24) with OS ~5 years (some of these have transformed to aggressive lymphoma in that time); subsequently ~ 2-3%/yr transform.

There is no current predictive method for POD24 until it happens, or to molecularly detect transformation until it has been biopsy-documented.

SCOPE OF PROBLEM:

The patient voice is central to the FLF's work and it is important to ensure that funded programs take the patient view into consideration. The FLF's recent patient survey revealed important insights, from 714 respondents representing all stages of FL, from over 40 countries globally. FL patients' **biggest concern is whether their FL will return after treatment**, followed by whether their FL will become more aggressive. FL

patients' **highest priority for biomarker development was to predict at diagnosis whether they'll need treatment straight away**, followed by predicting likelihood of relapse or transformation.

Because biomarker development for FL has lagged behind other blood cancers, the investigators' workshop was organized to identify barriers to more successful FL biomarker development and what needs to be in place to overcome such barriers. The workshop selected the following transition points in the FL patient journey as CHALLENGES that would benefit from biomarker development. The LOI must list which of the CHALLENGES below is/ are potentially addressed by the proposal or justify another CHALLENGE area as important for patients.

CHALLENGE #1: At diagnosis:

- Prognostic marker for POD24 vs not (FL cell; TME; other?)
- Detect & characterize FL clonal architecture - Detect early evidence of aggressive clone that will transform
- Characterize the progenitor cell (CPC) to permit targeted treatment
- Status of host immune system and its response to FL
- Predictive: Allow targeted therapy selection (if/when treatment indicated?)

CHALLENGE #2: Completion of a "line" of treatment:

- Response depth - prediction of duration of remission, role for maintenance (MRD)
- Characterize residual clones/CPCs to direct subsequent therapy selection

CHALLENGE #3: During observation (Watch & Wait / post-treatment)

- Quantitate pace of disease growth/doubling time
- Detect and characterize evolving clonal architecture of to direct subsequent therapy
- Detect evidence of aggressive clone and pace of its specific growth
- Immune status

GLOBAL APPLICATION PROCESS:

Applications are welcome from all geographical regions. The application process will begin with a letter of intent stage consisting of a 2-page description of the project. **The portal for the letter of intent will open March 7th, 2024, and letters are due by 5pm EDT on April 15th, 2024.**

TO APPLY:

1. Go to https://themarkfoundation.smapply.org/
2. Register on the site and verify your email address (or log in if you already have an account). Please check your spam folder if you do not see an email from noreply@mail.smapply.io.
   Select the program Biomarker Discovery in Follicular Lymphoma or click here.

KEY DATES

7th March 2024: Letter of intent portal opens

15th April 2024, 5pm EDT: Letter of intent submission deadline

11th July 2024: Full application deadline

1st November 2024: Anticipated award start dates

The LOI can be a maximum of 2 pages, including any references, figures, or tables. The PDF must contain the following information:

- Project title.
- Brief abstract (less than 200 words).
- Problem statement describing unmet need and opportunity to enable substantial and differentiated impact for cancer research and cancer patients; the specific **CHALLENGE** area(s) that will be addressed in FL, as outlined in the "Scope of problem" section above.
- Synopsis of research plan, including key feasibility or proof-of-concept question(s) to be answered, methods overview, and list of specific aims.
- Statement of innovation, advantages of the approach over existing methods and impact on the FL field.

Full applications will be accepted by invitation only, after review of the LOI. Additional guidelines will be provided to invited applicants.

ELIGIBILITY

- Proposed projects must address follicular lymphoma, though wider impact can be delineated.
- Projects should focus on applying improving technologies to FL to develop biomarkers that will be useful for patients, and preferable point to exploitable biologic processes in the course of FL, such as: transformation, early relapse (POD24) or progression from early t(14:18) clonal B cells to FL.
- Researchers are limited to one application as principal investigator but may be co-investigators on other proposals without limitation.
- Collaborative proposals are encouraged.

TERMS OF AWARD

- Applicants may request funding to support a total budget up to $350,000 for 24 months. We can consider terms shorter than 24 months on a case-by-case basis.
- The budget and duration requested for the grant must match a realistic estimate of the cost and timeline for the proposed work.
- The budget limit includes both direct and indirect costs, with indirect costs not to exceed 10% of the direct costs.
- For more details on award terms, visit the ASPIRE Award page.

About the ASPIRE Program

The Mark Foundation for Cancer Research ASPIRE Awards are designed to enable innovative approaches to solving high-impact problems in cancer research that tend to fall outside the scope of other funding opportunities. These awards will be used to support high-risk, high-reward projects with research plans designed to answer key feasibility and proof-of-concept questions in an accelerated timeframe, typically one year. Projects that successfully demonstrate feasibility may be selected to apply for additional funding in a second phase to further develop their innovative concepts and increase the speed to impact for cancer patients.

About The Mark Foundation for Cancer Research

The Mark Foundation for Cancer Research, a charitable organization based in New York City, actively partners with scientists around the world to accelerate research that will transform the prevention, diagnosis, and treatment of cancer. Since 2017, The Mark Foundation has awarded over $220 million in grants to investigators at more than 100 academic institutions across 16 countries, with research programs focusing on early career support, team science collaboration, new technology innovation, and therapeutics discovery. Additionally, The Mark Foundation maintains a growing portfolio of investments in early-stage cancer diagnostics and therapeutics companies, including several that have transitioned from grantee projects into commercial development. To learn more please visit www.TheMarkFoundation.org.

About The Follicular Lymphoma Foundation

The Follicular Lymphoma Foundation (FLF) is a global charitable organization on a mission to find new treatments and a cure for Follicular Lymphoma (FL). We are committed to assembling the world's foremost researchers and experts. Our global presence is fortified through established legal entities in the UK, USA, and Israel. Moreover, we actively cultivate collaborative alliances on a global scale, engaging with pharmaceutical companies, charitable organizations, and the scientific community to advance our mission.
The FLF was founded in 2019 by Nicola Mendelsohn (VP Global Business Group Meta), following her FL diagnosis in 2016. Working closely with the Living with FL Facebook Group, FLF has helped grow a diverse online community of over 20,000 FL patients and increasing. Despite over 1 million Follicular Lymphoma patients globally, there has not been sufficient funding or focus on improving treatments. FL is currently an incurable cancer. We are the first charity in the world solely focusing on finding a cure for FL and finding it fast, enabling people with FL to get well and live well. To learn more please visit https://www.theflf.org/