Follicular Lymphoma Foundation: Therapeutic Development Initiative

November 11, 2021

This report was created by the Milken Institute Center for Strategic Philanthropy at the direction of the Follicular Lymphoma Foundation.
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EXECUTIVE SUMMARY

The Follicular Lymphoma Foundation engaged the Milken Institute Center for Strategy Philanthropy to develop a prioritized list of targets to guide its emerging Therapeutic Development Initiative. We first distinguished the Foundation’s goal of curing follicular lymphoma at first relapse. Given the high degree of relapse, we believe orienting towards this North Star maximizes the benefit for all patients – developing better treatment options for those who have yet to relapse, unlocking more options for those who may have already relapsed, and fueling our understanding for how to prevent relapse.

We then embarked on a multistage process of identifying, characterizing, and prioritizing the therapeutic areas and specific targets best positioned to leverage philanthropic capital in service of this goal. This prospectus provides the context and rationale underlying the Foundation’s programmatic objectives, details our analytical methods, and offers recommendations for ensuing philanthropic activity.

Curing FL will require a toolkit of therapies given the heterogeneity of the disease. We propose a two-track funding program directed towards CAR-T, the single most promising therapeutic modality in follicular lymphoma, and targeted therapies like epigenetic regulators. A widely supported position holds that sequencing or otherwise combining these two therapy classes could prime, amplify and/or sustain the remarkable clinical impact generated from CAR-T alone, but that outstanding questions persist before a combination approach is clinically ready.

As such, we recommend applying philanthropy’s unique risk appetite and structural flexibility to drive each track forward independently, while maintaining line of sight to this potential future strategy. We detail promising targets and funding approaches in each of these tracks to support the development of a call for proposals. Finally, we briefly summarize key considerations in the FL research ecosystem that complement a focus on therapeutic development.

Science is rapidly changing. We are embracing a learning mindset to continue to adapt this program and future funding announcements to meet the needs of and innovations in the field. We welcome partnership across all fields and disciplines to stay focused on areas where philanthropy can uniquely accelerate treatments for people living with FL.
INTRODUCTION

The Follicular Lymphoma Foundation was established in 2019 as an international effort on a mission to find new treatments and cures for follicular lymphoma (FL). The Foundation seeks to: deliver lower toxicity, precision treatments and cures direct to FL patients; close the gaps in FL research and drug development to drive quicker clinical testing; and maximize collaboration and funding in the field of FL for rapid development and prioritization. In the spring of 2021, the Foundation engaged the Milken Institute Center for Strategic Philanthropy to assess and prioritize drug targets for philanthropic development of FL therapies.

Outcomes for patients with FL have improved substantially over the last 40 years: the 5-year survival rate has increased from 65% in 1980 to 90% in 2021. While several first-in-class drug therapies have recently been marketed for FL, the 1997 introduction of the anti-CD20 monoclonal antibody Rituximab remains the defining advance in the field.

A majority of patients are diagnosed at an advanced stage, when curative radiotherapy is not an option and FL must be managed as a chronic disease. Nearly all patients experience relapse, often multiple relapses, over the course of their disease. A subset of patients experience early disease progression and face 5-year survival rates as low as 50%. Even patients with more favorable survival rates endure both the psychological toll of an incurable, relapsing disease and the increasing toxicities of therapies designated for later relapses.
In recognition of the unmet needs of people living with FL, the Foundation’s goal is to cure at first relapse. Here, cure is defined as the eradication of detectable malignant cells. Achieving this goal will require a suite of research strategies and tools, including more robust understanding of basic disease biology, well characterized registries and biobanks, and biomarkers across all contexts of use. While the Foundation will pursue programs and encourage peer organizations across this suite, this initiative focuses specifically on one critical pillar: accelerated drug development.

To date, FL has rarely been the central focus for drug development: most drugs available to treat FL are also indicated for other lymphomas. By putting FL front and center, this initiative will catalyze focused development of therapies for this still underserved patient population. While private sector companies ultimately bring these drugs to market, philanthropy is uniquely positioned to: de-risk early-stage assets, making them more attractive for investment; expand the pool of drug candidates developed specifically for FL; and accelerate the timeline to development.

METHODS

To inform target prioritization, we first assessed the current state of FL therapeutic development. Through a literature review (references provided in appendix), and queries of ClinicalTrials.gov and BioCentury’s BCIQ industry pipeline, we assembled a database of nearly 200 assets in development either specifically for FL, or more broadly for non-Hodgkin’s lymphoma with a possible use in FL. Using research themes extracted from the literature, we then developed a taxonomy of these assets organized by both therapeutic class (e.g., B-cell signal pathway inhibition) and therapeutic modality or drug platform (e.g., antibody). We also developed a pipeline visualization of FL-specific assets, organized by drug target and phase of development.

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METHODS

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We tested the taxonomy and accompanying pipeline in a series of targeted interviews with experts in the field (individuals listed in appendix), asking: which therapeutic classes and/or modalities should we prioritize in service of the Foundation's goal of curing FL at first relapse? Which should we deprioritize, and why? How well is the current pipeline positioned to meet this goal?

These interviews, together with insights from the literature, converged on select areas within the taxonomy prioritized for further study. For this more detailed assessment, we profiled the strengths and weaknesses of each drug development area, catalogued all active and potential drug targets, and enumerated assets in development with their respective sponsors. We used additional interviews with topic experts to validate this material and assess the feasibility and potential clinical utility of these targets.

Finally, we convened key Foundation staff, their advisors, and a small, curated group of experts for a prioritization retreat designed to cull the long list of evaluated targets down to a short list of high priority targets. Participants provided detailed target assessments through a pre-retreat workbook exercise where they were invited to rate and comment on individual targets, and select high, medium, or low on the following parameters: clinical impact (potential for curative effect, alone or in combination, per Foundation's goal); probability of success (likelihood of a viable clinical development pathway); and philanthropy role (potential for philanthropy to accelerate timeline to market). We then dedicated the half day retreat to discussions of the most promising paths forward, key unanswered questions, and suggested focus areas for philanthropic attention.

**PRIORITY DIRECTIONS**

**Overview**

Our findings converged on two priority directions: immunotherapeutic modalities, including CAR-T cell therapy and bispecific antibodies, and targeted therapies, including epigenetic regulators.
Immunotherapy – most notably CAR-T cell therapy – emerged as holding the greatest promise for curative effect of any modality or class evaluated. To date, CD19 CAR-T has demonstrated a 95% overall response rate and 81% complete response in relapsed/refractory (r/r) FL patients treated with axi-cel (Yescarta, ZUMA-5 study), and limited but compelling follow up data: a response maintenance at 15 months in ZUMA-5, and 2+ years in smaller trials. The FDA has approved 4 CAR-T therapies; three of the four are indicated or in NDA for r/r or transformed FL. New CAR technologies are advancing this modality, including the optimization of costimulatory domains. Efforts to improve the tolerability and manufacturing process could also allow these modalities to reach a wider patient population. However, CAR-T therapies are limited by a small menu of known tumor antigens presented on the cell surface and are not effective in all patients for reasons that remain unknown.

A second prong within an immunotherapy focus is the bispecific antibody, which has demonstrated a 60-90% overall response rate and 40-60% complete response in r/r indolent and FL patients (mosunetuzumab, glofitamab, odronextamab). Three bispecific antibody therapies are currently FDA approved, though only one of the three is marketed for lymphoma (blinatumomab for lymphocytic leukemia). Notably, these drugs have shown to be effective in patients who failed on CAR-T therapy. Newer formats have lower toxicity profiles than blinatumomab, and design advances could allow a wider range of antigen specificities.

While targeted drugs administered as monotherapies are unlikely to achieve the same curative impact, they still can play an important role in the FL armament. Given the high frequency of FL epimutations, and evidence for their role in tumor evasion of immune surveillance, epigenetic reprogramming could potentially prime, amplify or sustain an immunotherapeutic effect. This class may also be capable of targeting the underlying CPC population. Tazemetostat, FDA approved in 2020 for r/r FL, has shown a 68-82% overall response rate in r/r FL patients with an EZH2 mutation. HDAC inhibitors have induced overall response rates of 47% - 64%. However, complete response rates have been low in both classes, and expansion of the epigenetic toolkit has been hampered in part by the difficult in targeting loss of function mutations.

**Target Detail**

Within each of these priority directions, we assessed the attractiveness of individual targets for philanthropic development in service of the Foundation’s goal. The complete set of evaluated targets is available in the appendix; here, we consider the short list selected for additional evaluation by our invited experts.

In the CAR-T space, CD19 garnered by far the highest ratings overall and for clinical curative impact, though three assets are already marketed for this target in FL and an additional 15 are in development. While CD20 as a single input CAR-T was not particularly favored, experts noted the
advantages of combining CD20 and CD19 in a bispecific CAR-T to address antigen escape. Three assets with this approach are in early clinical development. Experts proposed the following additions to this CAR-T short list: bispecific CAR-T for CD19 and either CD79a or CD79b, TCR T-cells, and novel target identification.

Figure 5. Summarized ratings by invited experts for priority targets in CAR-T therapy.

<table>
<thead>
<tr>
<th>CAR-T Targets</th>
<th>Rating, 1-10 Mean (range)</th>
<th>Clinical Impact</th>
<th>Probability of Success</th>
<th>Philanthropy Role</th>
<th>Representative Comments</th>
</tr>
</thead>
</table>
| CD19          | 8 (5-10)                  | All High        | Mostly High            | Mostly Medium     | • Not a novel target, already on the market  
• Philanthropy could fund better understanding of best combos, and why some patients relapse |
| CD20          | 4 (2-7)                   | Mixed           | Mostly Medium          | Mostly Low        | • CD20 already primary target in first line – more of the same unlikely to overcome relapse/resistance  
• High bar for superiority to CD19 CAR, or CD20 mAb |
| CD19; CD20    | 6 (2-10)                  | Medium to High  | Medium to High         | Low to Medium     | • Significant activity in this space already with clear path to development  
• Has curative potential, but more evidence needed |

Evaluations of bispecific antibody targets were overall less enthusiastic, and when pressed, experts advised pursuing the development of CAR-T therapy ahead of this modality, which may offer less potential curative impact. There was some interest in exploring a CD47 macrophage target as part of the bispecific construct, though this is a novel area with only two assets in early development and many unanswered questions. CD20; CD3, with 11 assets in industry development, was assessed as the most attractive area, though experts were mixed on the potential for philanthropy to be catalytic in development timelines. Experts proposed the following additions to this bispecific antibody short list: NK cell engagers in combination with CD19 or CD20, TCR-mimetics, and CD79a or 79b in combination with CD19 or CD20.

Figure 6. Summarized ratings by invited experts for priority targets in bispecific antibodies.

<table>
<thead>
<tr>
<th>Bispecific Antibody Targets</th>
<th>Rating, 1-10 Mean (range)</th>
<th>Clinical Impact</th>
<th>Probability of Success</th>
<th>Philanthropy Role</th>
<th>Representative Comments</th>
</tr>
</thead>
</table>
| CD20; CD3                   | 6 (5-8)                   | Medium to High  | Medium to High         | Mixed             | • Need to understand why some patients fail on this  
• May be curative in combo, but toxicities may limit |
| CD19; CD47                  | 5 (2-9)                   | Mostly Low      | Mixed                  | Mostly Medium     | • Many unanswered questions, potential for philanthropy funding to assess opportunity |
| CD20; CD47                  | 5 (2-9)                   | Mostly Low      | Mixed                  | Mixed             | • Unclear if this will be better than CD20; CD3  
• Macrophages may play a role but likely not key |

In the targeted therapy space, experts noted that epigenetic regulators are less likely to be curative on their own but could be combined with immunotherapies to potentiate or sustain their clinical impact. EZH2-directed therapy, which is already marketed and has an additional 5 assets in development, has demonstrated moderate effectiveness regardless of mutational status. The dual (and next generation) EZH1/2, with 4 assets in development, garnered mixed reviews. KMT2D/KMD5 received the highest rating for philanthropy role of any target across these short lists. There are no assets in development for this target in FL or NHL, and experts cautioned of a challenging development pathway. Experts proposed the following additions to this epigenetics short list: CREBBP/HDAC and hypomethylating DNA.
Finally, experts were given the opportunity to suggest other targeted therapies, outside the realm of epigenetic regulators, that could be coupled with immunotherapy to potentially achieve curative impact. The 10 proposed targets are available in the appendix. Some are backed by strong biological rationale but face a difficult technical development path, while others are theoretically easier to develop but still lack underlying biological foundations. Given the breadth of targets in the open solicitation, this “other” category within the tumor targeting priority area may be an intriguing source for emerging ideas as the Foundation considers the design of its funding program.

**Deprioritized Directions**

To support a robust program focused on the above priority directions, we dismissed less attractive areas at two different stages during the process. The first cut was made at the level of therapeutic classes and modalities/drug platforms, when immunotherapy and targeted therapy were selected as priority areas for further study. Here, we deprioritized areas from the taxonomy that were judged as one or more of the following:

- *Unlikely to be more effective than current standard of care:* B-cell signal pathway inhibition with small molecules, B-cell surface antigen targeting with naked antibodies, radiotherapeutic antibodies
- *Subject of repeated disappointments in development:* antibody-drug conjugates, single checkpoint modulators
- *Insufficiently supported by underlying biology:* vaccines, metabolic regulators

Second, within the priority areas, we edited the long list of targets down to a short list for further expert evaluation. The logic underlying this cut, as well as the targets that were deprioritized at this stage, are available in the appendix. We recommend reassessing the prioritization on a recurring basis as the science develops and more data become available. Given the focus on translational research and curative approaches, we propose focusing on the most promising science today, rather than building a broader knowledge base for areas with less evidence.
Programmatic Recommendations

To support the development of curative therapies for FL, we recommend a two-track funding program that advances both cellular immunotherapy and targeted therapy. In the long term, rational sequencing of these two classes is likely to be the optimal path for curative impact. However, combination therapy for FL may not be an appropriate pursuit until more is known about optimal patient selection, mechanisms of resistance, and duration of effect of each distinct class. As such, programs that advance each therapeutic strategy separately with line of sight to a future combination approach will offer the greatest value to patients in both the near and long term.

Within cellular immunotherapy, we recommend focusing on CAR-T given its superior potential to achieve curative effect. To best address unmet needs, philanthropic funding should be directed towards early-stage candidates too often lost in the valley of death between initial academic publication and sponsorship by industry and other private funders. This developmental stage is particularly important for CARs with superior engineering but otherwise lacking perceived market value differentiation from similarly targeted candidates. Industry has and will continue to advance vetted technologies with validated targets, as well as develop new engineering and manufacturing processes to make these therapies more tolerable and accessible.

Specifically, within CAR-T, we recommend directing funding towards high potential IND-enabling and Phase I or I/II studies, with some allowance for promising programs in the preclinical space. Listing eligible targets may be limiting; instead, we recommend the funding call emphasize the importance of biologically validated target(s) and an engineering design that minimizes opportunities for antigen escape and other resistance pathways. The difficulty and expense of manufacturing CARs, likely a hurdle for many investigators, may be addressed through partnership with the National Cancer Institute’s Experimental Therapeutics (NExT) program, which provides cell therapy product manufacturing to select investigators who will receive or are receiving the funding necessary for a study.

In the second track of this funding program, we recommend supporting the development of both epigenetic regulators and other tumor targeting approaches that could be curative in eventual combination with immunotherapy. Given the heterogeneity of FL tumors it is probable that multiple targeted approaches will be required in addition to the available EZH2-directed therapy. KMT2D, whose loss of function mutation is present in 60-90% of FL cases, is a high value target whose development will likely require philanthropic activity given industry neglect to date. We suggest specifying KMT2D/KMD5 as an area of high interest in the funding call, which should also be open to other targets proposed by investigators.

Associated Considerations

While this initiative is focused specifically on therapeutic development, a robust biomedical research ecosystem includes much more than drug targets and their leads. In FL, perhaps the most frequently cited unmet need is for validated biomarkers across contexts of use: prognostic biomarkers to identify patients likely to progress early, predictive biomarkers that guide treatment decisions, surrogate biomarkers to verify a curative state earlier than 10 years out, and more. The deeply characterized biosample banks necessary to develop this biomarker toolkit are currently insufficient or poorly integrated into the global research landscape.
Beyond biomarkers, experts also cited a need for robust disease models that capture the breadth of FL subtypes and allow for more efficient evaluation of new therapeutic avenues. Researchers also have much to learn from patient cohorts with divergent outcomes, tracked longitudinally. Data infrastructure capable of receiving, harmonizing, and deeply analyzing these multi-omic data is a challenging but vital goal in nearly all disease states, FL included.

Through its other emerging programmatic areas, as well as the work of its mission-aligned peer organizations, the Foundation expects that this therapeutic development initiative will be complemented by advances in these other critical ecosystem needs.

**CONCLUSION**

In a disease like FL characterized by relapse, a 90% 5-year survival rate masks the psychological burden endured by patients who never know when their tumors will return or if they will transform. After multiple relapses, the therapeutic armament becomes limited and often toxic. A cure at first relapse is the paradigm shift this patient population needs, and this is the north star of the Follicular Lymphoma Foundation's emerging program in therapeutic development.

After a rigorous process of profiling the therapeutic landscape, interviewing over a dozen experts, and evaluating key opportunities for philanthropic impact, we are pleased to offer the recommended priority directions detailed in this prospectus. By putting these recommendations into action through a well-informed funding call, the Foundation is positioned to drive the field closer to its goal of a cure for follicular lymphoma.
# APPENDIX

## Detailed Target Review

### Orientation to Detailed Target Review

<table>
<thead>
<tr>
<th>Targets</th>
<th>Asset Information</th>
<th>Stakeholders &amp; funding factors</th>
<th>Warrants further exploration for FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant targets for each therapeutic class/ modality are listed in this column in descending order of number of assets in development</td>
<td>Number of marketed drugs with an FL indication (includes registration status)</td>
<td>Based on a dozen interviews and the literature, classifies target fit with FL goal to cure at first relapse: <strong>High:</strong> curative potential, alone or in combination; <strong>Mixed:</strong> evidence is mixed for potential to be curative in FL; <strong>Low:</strong> unlikely to be part of a curative approach, even in combination; <strong>Unknown:</strong> not enough evidence to determine</td>
<td>Filter function for targets that move on for closer examination and prioritization via expert workbooks and retreats</td>
</tr>
<tr>
<td>CAR-T Target Review</td>
<td>Examples of drugs on the market for non-FL indications</td>
<td>Summarizes level of enthusiasm expressed about target from a dozen interviewed experts: <strong>High:</strong> strong support; <strong>Mixed:</strong> some support, some skepticism; <strong>Low:</strong> not supported</td>
<td>Yes: Alignment is high or mixed and&lt;br&gt;- Support is high or mixed and&lt;br&gt;- Funding is any status, but if saturated, included with restrictions</td>
</tr>
<tr>
<td>CAR-T Targets</td>
<td>Number of assets in development, preclinical - Ph III, from database queries for NHL and B-Cell lymphoma. Not necessarily FL specific</td>
<td>Rates funding landscape based on number and stage of open clinical trials and types of trial sponsors: <strong>Sparse:</strong> one or zero biotech sponsors and/or preclinical only; <strong>Emerging:</strong> multiple biotech sponsors; <strong>Saturated:</strong> assets already on market and/or multiple pharma involved in Ph II+ trials</td>
<td>No: all others. There is an opportunity to “vote” these targets back into consideration in the workbook</td>
</tr>
</tbody>
</table>

### CAR-T Target Review

<table>
<thead>
<tr>
<th>CAR-T Targets</th>
<th>Asset Information</th>
<th>Stakeholders &amp; funding factors</th>
<th>Warrants further exploration for FL (if yes, detail on next slide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19 Yescarta, Breyalys, Kymriah</td>
<td>Tescovir (MCL)</td>
<td>15</td>
<td><strong>High:</strong> greatest curative potential, high CR rate</td>
</tr>
<tr>
<td>CD20</td>
<td>-</td>
<td>4</td>
<td><strong>High:</strong> most validated target for FL</td>
</tr>
<tr>
<td>CD22</td>
<td>-</td>
<td>1</td>
<td><strong>High:</strong> B cell surface antigen target</td>
</tr>
<tr>
<td>CD19; CD20</td>
<td>-</td>
<td>3</td>
<td><strong>High:</strong> could improve CD19 curative potential</td>
</tr>
<tr>
<td>CD19; CD22</td>
<td>-</td>
<td>5</td>
<td><strong>High:</strong> two promising targets on powerful CAR platform</td>
</tr>
<tr>
<td>CD19; PD-1</td>
<td>-</td>
<td>2</td>
<td><strong>Mixed:</strong> PD-1 historically underdelivers in FL</td>
</tr>
<tr>
<td>CD19; BCMA</td>
<td>-</td>
<td>1</td>
<td>Unknown: BCMA proven in MM, potential in FL</td>
</tr>
<tr>
<td>CD19; CD30</td>
<td>-</td>
<td>1</td>
<td><strong>High:</strong> combining 3 individual great targets for FL</td>
</tr>
<tr>
<td>BCMA (TNFRSF17, HM4)</td>
<td>-</td>
<td>None in FL</td>
<td>Unknown: BCMA proven in MM, potential in FL</td>
</tr>
</tbody>
</table>

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12
## Epigenetic Regulators Target Review

<table>
<thead>
<tr>
<th>Epigenetic Regulator Targets</th>
<th>Asset Information</th>
<th>Stakeholders &amp; funding factors</th>
<th>Warrants further exploration for FL* (if yes, detail on next slide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marked, FL</td>
<td></td>
<td>High, effective regardless of mutational status, strong potential priming immuno</td>
</tr>
<tr>
<td></td>
<td>Marked, other</td>
<td></td>
<td>High, most impactful in its class, gain of function mutation easier to work with</td>
</tr>
<tr>
<td></td>
<td>Assets in development</td>
<td></td>
<td>SATURATED: asset on market, others in early stages with biotech &amp; pharma</td>
</tr>
<tr>
<td>EZH2</td>
<td>Tazverik</td>
<td>5</td>
<td>Mixed: activity in T cells, may not be specific enough to B cells; Genetic evidence.</td>
</tr>
<tr>
<td>HDAC (CREBBP/EP300)</td>
<td>-</td>
<td>5</td>
<td>Mixed: potential, especially if tested earlier in disease, but toxicity, risk adaptation</td>
</tr>
<tr>
<td>EZH1/2</td>
<td>-</td>
<td>4</td>
<td>Emerging: 2x biotechs in early stage trials</td>
</tr>
<tr>
<td>SWI/SNF</td>
<td>-</td>
<td>1</td>
<td>Unknown: not enough evidence to determine potential for FL</td>
</tr>
<tr>
<td>HIST1H1E</td>
<td>-</td>
<td>None (in NHL)</td>
<td>Low: not relevant for mature FL, infrequent mutation</td>
</tr>
<tr>
<td>KMT2D2/ KMD5</td>
<td>-</td>
<td>None (in NHL)</td>
<td>High, mutated in 60-90% of FL cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mixed: strong biological link, but will not restore lost function, non specific effects</td>
</tr>
</tbody>
</table>

### Targeted Therapy Targets Proposed by Experts

<table>
<thead>
<tr>
<th>Targets</th>
<th>Rating 1-10</th>
<th>Clinical Impact</th>
<th>Probability of Success</th>
<th>Philanthropy Role</th>
<th>Representative Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD79b ADC (&amp; CD19 CAR-T)</td>
<td>6 (5-7)</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>• Need to understand if residual cells are CD79b+ and sensitive to payload&lt;br&gt;• Recent approval by Roche in DLBCL, FL opportunity</td>
</tr>
<tr>
<td>CD37 ADC (&amp; CD19 CAR-T)</td>
<td>5 (single rating)</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>• Need to understand if residual cells are CD37+ and sensitive to payload</td>
</tr>
<tr>
<td>CD47 (&amp; CD20, Len)</td>
<td>8 (single rating)</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>• Intriguing as a triplet therapy in R/R</td>
</tr>
<tr>
<td>PI3K (CAR-T)</td>
<td>9 (single rating)</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>• Could be more impactful in combo with CAR than as single agent</td>
</tr>
<tr>
<td>Cathepsin S (CAR-T or Len)</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTLA/HVEM</td>
<td>10 (single rating)</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>• HVEM mutations are key to FL&lt;br&gt;• BTLA engaging antibodies more difficult than blocking&lt;br&gt;• Limited commercial interest (blocking Abs is focus)</td>
</tr>
<tr>
<td>TIGIT (anti-PD1)</td>
<td>7 (single rating)</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>• Expressed in FL, though limited data, unclear value&lt;br&gt;• Could enhance disappointing single agent anti-PD1</td>
</tr>
<tr>
<td>IL-15 (&amp; CD20, Len)</td>
<td>8 (single rating)</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>• Intriguing as a triplet therapy in R/R</td>
</tr>
<tr>
<td>Adenosine axis</td>
<td>5 (single rating)</td>
<td>Medium</td>
<td>High</td>
<td></td>
<td>• Too early to say value in FL, but interest in target is high in solid tumors (AZ data on CD73)&lt;br&gt;• Philanthropy potential to explore combo for FL</td>
</tr>
<tr>
<td>Enhance T cell function: e.g., checkpoint inhibitors, BTK</td>
<td>9 (single rating)</td>
<td>High</td>
<td>Medium</td>
<td></td>
<td>• May be key to rapidly Improving CAR-T outcomes&lt;br&gt;• Moderate role for philanthropy – companies already aware of these possibilities</td>
</tr>
</tbody>
</table>

*FL: Flemington*
Milken Institute Team

This report was created by the Milken Institute Center for Strategic Philanthropy (CSP) at the direction of the Follicular Lymphoma Foundation. CSP advises individuals and foundations seeking to develop and implement transformational giving strategies, and offers leadership to make the philanthropic landscape more effective. We conduct deep due diligence across a range of issue areas, with particularly expertise in health and medical research, and identify the areas where philanthropic capital can make the biggest impact and create a better world. For more information, visit philanthropy.milkeninstitute.org.

Our core project team includes:

Melissa Stevens, Executive Director, CSP - Melissa has led CSP since its inception and has overseen the development of all programmatic activities. She previously served as Deputy Executive Director of FasterCures. She began her career in the health sciences practice of PricewaterhouseCoopers, advising commercial and federal clients across the healthcare continuum, and designing and building research enterprises. Stevens received a B.Sc. in biochemistry and an M.B.A from the Pennsylvania State University.

Cara Altimus, Senior Director, CSP – Cara leads CSP’s Biomedical Research portfolio and brings more than 15 years of scientific expertise to this project. She has worked with a wide range of philanthropists focused on developing scientific strategy for new initiatives totaling more than $215 million in deployed funding. Previously, Cara led the Neural Interfaces Laboratory and provided scientific expertise for neural device applications at FDA. She holds a B.S. in genetics from the University of Georgia and a Ph.D. in biology from Johns Hopkins University.

Liza Shoenfeld, Advisor, CSP – Liza specializes in research, strategy, and program development for mission-driven organizations in health and life sciences. Prior, she worked for Gates Ventures, the private office of Bill Gates, where she developed Mr. Gates’s personal learning, strategy, and funding programs in Alzheimer’s Disease. There, she led the creation of the Diagnostics Accelerator, a $50M venture philanthropy program designed to accelerate biomarker development for Alzheimer’s. Liza has an M.S. in neuroscience from the University of Washington and a B.A. in neuroscience from Bowdoin College.
Consulted Experts

Anas Younes (AstraZeneca) and Jonathan Simons (The Marcus Foundation) served as principal advisors to the development of this work. In addition, the following individuals were engaged over the course of the work (*denotes attended retreat in addition to interview).

Ash Alizadeh (Stanford University)
Weiwei Chen (National Cancer Institute)
Yvonne Chen (University of California Los Angeles) *
Stephen Curtis (MPM Capital) *
Narendranath Epperla (Ohio State University) *
Marc Ernstoff (National Cancer Institute)
Hans Guido-Wendell (Memorial Sloan Kettering Cancer Center)
Morgan O’Hayre (National Cancer Institute)
Jessica Okosun (Barts Cancer Institute) *
Elisa Oricchio (École Polytechnique Fédérale de Lausanne) *
Krish Patel (Swedish Cancer Center)
Patricia Perez-Galan (Institut d'Investigacions Biomèdiques August Pi i Sunyer)
Sandrine Roulland (Centre d'Immunologie Marseille-Luminy)
Patrick Trojer (Constellation Pharmaceuticals)
Pin Wang (University of Southern California)
David Weinstock (Dana-Farber / Harvard Cancer Center) *
References


