Institute for Follicular Lymphoma Innovation

Investigator Brief

2023 IFLI Moonshot Initiative

IFLI's Moonshot Initiative is focusing on unraveling the early pathogenesis of FL, with a particular focus on the common/clonal precursor cell (CPC) and the lymphoma microenvironment (LME). To launch the Moonshot Initiative, IFLI assembled a Moonshot Team with expertise in the cancer biology and clinical treatment of FL.

The following are areas that have been discussed, not only by the Moonshot Team[1] but also by other experts in hematology and oncology.[2] Key aspects of the biology of FL pathogenesis to be addressed are as follows:

Follicular Lymphoma Common Precursor Cell (CPC)

Clones and subclones – tumorigenesis could stem from one clone and/or from many subclones, which derive from trunk/founder mutations. Clonality can also be measured in terms of the epigenetic marks that are accumulated by the cell.[2]

- Deep sequencing is needed to capture spatial heterogeneity within a tumor.
- Longitudinal studies of patients (tumor and blood) will also reveal molecular changes

Driver mutations—somatic mutations are common in FL.[3] Cell-autonomous or non-cell-autonomous alterations contribute to tumor evolution at any stage – initiation, progression, metastasis and resistance to therapy—and there is a need to define how these alterations/mutations promote proliferation, survival, invasion and/or immune evasion, and thereby result in tumor heterogeneity.[2]

- ctDNA is an important marker of lymphoma detection, evolution and progression, in addition to its use for mutational genotyping, but it has been underutilized in FL research. ctDNA technology faces challenges – volume of DNA, proportion of tumor cell DNA, and the diversity of mutational profiles, and these are especially relevant in FL.[4]

Cell states

Defined by the interplay of the genome, epigenome, transcriptome and proteome. Genetic and epigenetic contributions to cell states are likely intertwined and mutually dependent. [2]

Germinal center (GC) B cells maintain epigenetic plasticity and there is an important role of memory B cell clones in seeding and re-seeding GCs, making tumors more heterogenous. [5]

Even genetically identical cells can exist in different cell states, owing to epigenetic differences and influence of the LME. Genetically distinct cells may be in a similar cell 'state' and hence may be susceptible to treatment with the same drugs. Epigenetic marks are dynamic and represent the history of the cancer – once a cell has passed through a particular cell state, some of these epigenetic marks remain and can provide information about the previous, present, and potential future states of the cell.[2]

- Better identification of relevant cell states and how and when cells pass through these particular states is needed.

Lymphoma Microenvironment (LME)

The FL LME is highly variable across patients, influenced by tumor cell-intrinsic characteristics and associated with patient outcome. Large cohorts are required to study the relationship between somatic mutations, tumor B cell expression profiles, LME cellular subsets, and other changes in the LME.[3]

- Understanding the LME requires the integration of multi-latyered data from single cell analyses, DNA sequences, Epigenome, Transcriptome, Protein, Metabolites, Infiltrating immune cells in both tumor and stroma.
- A focus on the modification of the LME and/or the generation of mutations could influence the role of cytotoxic and genotoxic drugs – to maximize the effect of immunotherapy.[2]

References

1. IFLI Moonshot Team meetings: Ash Alizadeh, Wendy Béguelin, Todd Fehniger, Michael Green, Ari Melnick, Bertrand Nadel, Laura Pasqualucci, Gilles Salles, Christian Steidl (2022/23)

2. Alizadeh, et al. Toward understanding and exploiting tumor heterogeneity. Nature Medicine, 21: 846-852, (2015)

3. Han, et al. Follicular Lymphoma Microenvironment Characteristics Associated with Tumor Cell Mutations and MHC Class II Expression. Blood Cancer Discovery 3: 428-43 (2022)

4. Roschewski, et al . Circulating tumor DNA in lymphoma: principles and future directions. Blood Cancer Discovery 3: 5-15 (2022)

5.Milpied, et al. Follicular Lymphoma Dynamics. Advances in Immunology 150: 43-85 (2021)

About IFLI

The Institute for Follicular Lymphoma Innovation (IFLI) is dedicated to supporting advances in understanding the biology of follicular lymphoma (FL) and transformed FL (tFL) to accelerate the development of innovative treatment options, extend the life expectancy of people with follicular lymphoma and ultimately develop a cure.

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IFLI aims to promote data sharing among researchers and institutions working on different aspects of FL research, fostering collaboration and enabling the exchange of knowledge and expertise.

The objectives of IFLI are:

1. **Improve the understanding of the pathogenesis of FL:** Identify the molecular mechanisms and pathways that drive the development and progression of FL, including the genetic and epigenetic changes that occur in FL cells and elucidate how these complex factors work together within the lymphoma microenvironment (LME).
2. **Develop new diagnostic and prognostic biomarkers**: Accurately identify FL patients who are at risk of early disease progression, histological transformation, or relapse.
3. **Identify new therapeutic targets**: Develop more effective treatment options for patients at higher risk of progression.
4. **Accelerate clinical trials**: Advance clinical research for FL by facilitating collaboration between researchers, KOLs, and industry partners.

IFLI is supporting a variety of initiatives through awards and partnerships to accomplish these objectives over the next ten years. Moonshot is one of these initiatives, launched in June 2023.