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## REVIEW

# Follicular lymphoma research: an open dialogue for a collaborative roadmap

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## Follicular lymphoma research: an open dialogue for a collaborative roadmap

Follicular lymphoma (FL) is the second most common type of lymphoma (20% of all non-Hodgkin lymphomas), derived from germinal centre (GC) B cells, and is characterised by its significant clinical, prognostic and biological heterogeneity, leading to complexity in management. Despite significant biological investigation and indisputable clinical progress since the advent of the immunotherapy era more than 20 years ago, much remains to be done to understand and cure this lymphoma. Today, FL is metaphorically a giant puzzle on the table with patches of sky, landscape and foliage clearly appearing. However, many of the remaining pieces are held by various stakeholders (e.g. clinicians,

pathologists, researchers, drug developers) without global agreement on what the gaps are, or any clear blueprint on how to solve the puzzle of understanding the heterogeneity of this disease and create curative and tailored therapies. With the advent of new investigation and drug technologies, together with recent advances in our capacity to manage big data, the time seems ripe for a change of scale. More than ever, this will require collaboration between and within all stakeholders to overcome the current bottlenecks in the field. As for every investigator, we acknowledge that this first draft is necessarily biased, incomplete and some FL expert readers might recognise some

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**Abbreviations:** Ag, antigen; AI, artificial intelligence; BCL, B cell lymphoma; BCR, B cell receptor; BM, bone marrow; CAR-T, chimeric antigen receptor T; COO, cell of origin; cFL, constrained FL; CMG, chromatin modifying genes; CPC, cancer progenitor cells; CRR, complete response rate; ctDNA, circulating cell-free tumour DNA; DZ, dark zone; dFL, DLBCL-like FL; DLBCL, diffuselarge B cell lymphoma; FFPE, Formalin-fixedparaffin-embedded; FL, follicularlymphoma; FLIPI, FL international prognosticindex; GC, germinalcenters; GOF, gain-of-function; ICT, immunochemotherapy; Ig, immunoglobulin; LOF, loss of function; LZ, light zone; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24months of treatment; PRC2, polycomb repressive complex 2; RISC, relapse-initiating subclones; RT-PCR, reversetranscription–polymerase chain reaction; RR, relapse/refractory; SHM, somatic hypermutation; SLO, secondary lymphoid organs; SOC, standard of care; TFH, T follicular helper cell; tFL, transformed FL; TME, tumour microenvironment; TNF, tumour necrosis factor; WHO, World Health Organisation; ZO, zanubrutinib in combinationwith obinutuzumab.

remaining gaps not addressed. We hope they will reply to make this effort a collaborative one to assemble all the pieces in the most ideal fashion. As such, this

review intends to be a first step and an interactive platform to a collaborative roadmap towards better understanding and care of FL.

## Introduction: unmet clinical needs as a starting point

The management of follicular lymphoma (FL) begins with histological diagnosis by a surgical pathologist, which is relatively straightforward, and based on the presence of centrocytes and admixed centroblasts with an immunophenotype consistent with a GC cell of origin (COO). FL is, at least partly, usually associated with a follicular pattern and the presence of BCL2 and/or BCL6 gene rearrangements, although subtypes that deviate from this have been recently characterised.<sup>1</sup> The majority of FL patients present with lymphadenopathy in multiple sites with variable systemic distribution, tumour burden and association with symptoms (e.g. localised or systemic lymphadenopathy with no symptoms versus extensive lymphadenopathy with B symptoms or symptoms related to site of involvement). FL is characterised by a clinical heterogeneity at time of diagnosis that relies upon biological heterogeneity, which is still challenging to capture fully. This heterogeneity results in the application of a variety of first-line treatment strategies, including 'watch and wait' for patients without symptoms to immunochemotherapy (ICT) with rituximab maintenance for patients with a clinically symptomatic disease, associated with a median progression-free survival (PFS) of 10.5 years, with a 10-year overall survival (OS) estimate of 80%.<sup>2,3</sup> However, the absence of a plateau on all progression-free survival curves after this and other available first- and second-line therapies reflects the frequent occurrence of relapses, leading to FL being considered as a mainly incurable disease. Each sequential relapse tends to occur more quickly and with increased aggressivity and refractoriness to subsequent therapeutic options.

The clinical prognosis of FL patients after therapy is also heterogeneous and relatively unpredictable. A significant subset of treated FL patients (15–20%) harbour a chemo refractory disease from the outset or experience an early relapse within 24 months of first-line chemotherapy (POD24), associated with an increased risk of death from lymphoma.<sup>3,4</sup> Transformation to an aggressive lymphoma (tFL) is responsible for this poor outcome in most of these cases.<sup>5,6</sup> Conversely, 50% of treated FL patients will be

long-term responders without relapses after 10 years of follow-up and for whom the leading cause of death will not be lymphoma, but rather independent malignancies, cardiovascular disease or other unrelated causes. This has led to the evolution of the definition of 'cure' in FL, and the emergence of the concept of 'functional cure'.<sup>3</sup>

There are three critical unmet clinical needs in FL: (1) lack of useful prognostic tools at the time of diagnosis and prior to therapy, to guide clinical management; (2) the need for novel and more effective therapeutic targets derived from a comprehensive understanding of FL biology and tailored for defined subsets of FL patients; and (3) the lack of effective biomarkers to effectively follow therapeutic responses. In this review we will discuss the issues underlying these bottlenecks, highlight evidence gaps and propositions to overcome them.

## Tools to predict clinical behaviour

For decades, haematopathologists, clinicians and translational researchers have dedicated much effort towards identifying clinical, histological, molecular and/or imaging features of FL that may risk-stratify FL patients into groups with different survival outcomes.

### CLASSIC MORPHOLOGICAL APPROACH

Traditionally, cases of FL with higher numbers of large lymphoma cells (centroblasts) were thought to be more clinically aggressive. Pathologists have applied variations of the original Mann and Berard approach<sup>7</sup> of histological grading based on the number of centroblasts counted upon microscopic review. Over the years, the reproducibility and prognostic significance of grading in FL has been increasingly debated among pathologists.<sup>8,9</sup> Several clinical trials performed for targeted therapies have shown identical outcome for grades 1, 2 and 3a FL.<sup>2,10,11</sup> In addition, it has been shown that histological transformation of FL is not correlated with histological grade.<sup>8</sup> For these reasons, grading has been removed from the fifth edition of the World Health Organisation (WHO) classification (WHO-HAEM5) (Box 1).<sup>1</sup>

**BOX 1. Key opportunities for advancing prognostic biomarkers**

Identifying high-risk individuals remains a challenge. Current strategies, including histological grading and prognostic scoring systems are imperfect, requiring improvement. Furthermore, focusing solely upon this group overlooks the chance to enhance the quality of life and outcomes for the largest fraction of follicular lymphoma (FL) patients. We need to:

- Prioritise defining the large population of low-risk FL patients with indolent behaviour to identify those who can safely reduce or avoid therapy
- Evolve the biomarker strategies from being primarily prognostic-based to also encompass identification of predictive and dynamic biomarkers for more precise therapy individualisation
- Leverage advanced machine learning and artificial intelligence (AI) technologies, combined with large-scale, readily accessible FL biopsies, to drive the development of tissue-based biomarkers

**CLINICAL AND CLINICO-MOLECULAR APPROACHES**

Several clinical prognostic scoring systems have been developed with the primary goal of identifying high-risk patients in daily practice and for clinical trial inclusion selection. Most of these systems focus on 'at diagnosis' or pretreatment tools based on clinical parameters (e.g. FLIPI, FLIPI-2, FLEX) to stratify patients at diagnosis into groups with different survival outcomes. Some scoring systems, such as PRIMA-PI, are easier to compute, relying upon factors such as bone marrow (BM) involvement and blood  $\beta$ 2M levels. However, BM biopsies are not universally performed in all patients at baseline.<sup>12–15</sup> As clinical tools are essentially surrogates for FL biology, more biologically derived prognostic tools have been developed. One of the first was the m7-FLIPI, computed using the gene mutation status of seven genes (*ARID1A*, *CREBBP*, *EP300*, *EZH2*, *CARD11*, *FOXO1*, *MEF2B*) with the patient's performance status and FLIPI score to segregate patients into low- and high-risk groups.<sup>16</sup> Later, gene-expression-based

prognostic tools (*PRIMA* 23-gene) were developed using several clinical trials and population-based cohorts.<sup>17</sup> While these tools can identify high-risk groups, they exhibit variable prognostic accuracy, particularly in identifying specific high-risk groups posing the greatest clinical challenge, such as patients with POD24 or transformation. The 'high-risk' groups defined by these scoring systems remain heterogeneous, encompassing a range of clinical phenotypes. Additionally, the disease trajectory of patients within any given group is often differentially influenced by the type of treatment regimen they receive (Box 1).

**THE EMERGENCE OF ARTIFICIAL INTELLIGENCE (AI) FOR PREDICTING CLINICAL BEHAVIOUR**

During the last decade there have been major advances in artificial intelligence (AI)-based deep learning to increase clinical-grade accuracy in histopathological image-based cancer classification.<sup>18–20</sup> Pathologists and AI experts are currently developing strategies to harness this technology to assist and optimise lymphoma diagnostics,<sup>21</sup> including FL grading. Moreover, machine learning also holds great promise for enabling the discovery of tissue-based prognostic biomarkers.<sup>19</sup> Additionally, multimodal data fusion methods<sup>22,23</sup> that integrate radiological, pathological, laboratory and clinical data will probably be even more powerful in enabling the accurate prediction of these clinical groups at diagnosis. Further progress requires inter-institutional collaboration between pathologists for the analysis of large numbers of heterogeneous FL cases and to harness overfitting issues (Box 1).

**How to approach therapeutic innovation in FL****MAJOR PITFALLS**

Two major pitfalls in the approach to therapeutic innovation in FL are related to (1) the targeted population and (2) the drugs considered. Most immune or targeted agents are classically tested in the relapse/refractory (RR) setting, aiming to achieve an overall response rate (ORR) in Phase II to justify investments in Phase III trials against standard of care (SOC) therapies. The 'winners' are then subsequently approved for all FL patients. However, RR FL represents a heterogeneous minority of FL cases and cannot be generalised to the majority of FL patients. Furthermore, the discrepancy between the 'discovery (RR)' and the

**BOX 2. Key challenges and opportunities towards therapeutic innovation**

The current drug market remains mostly follicular lymphoma (FL)-biology agnostic. We need to:

- Change the way the drug market is approached and align the development of drugs in FL with its key biological characteristics/mechanism of action rather than repositioning drugs showing efficacy in other indications (or even other lymphoma subtypes). Together with this, drug repurposing based on biological and testable rationales should become more frequent and used in parallel to our progress on FL biology
- Advocate for a personalised approach with theragnostic information as part of pathology reporting
- Provide the community with a routinely available biomarker of response, or a theragnostic classification, for each novel agent in development

extension cohorts may lead to limited improvements when therapies are applied in the first-line setting.

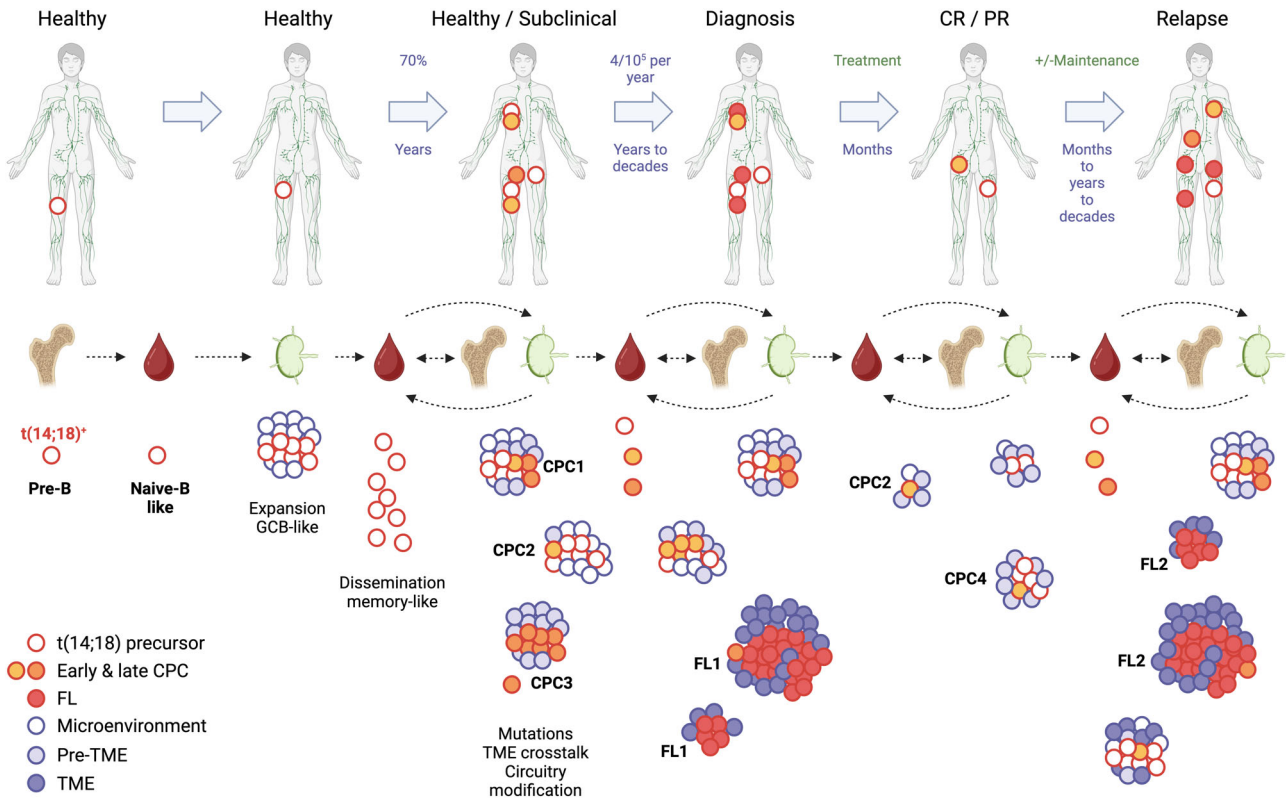
Secondly, given the diversity of the mechanism of action of the different drugs in the various drug developer pipelines worldwide, one would think that the challenges of FL heterogeneity could easily be addressed with novel drugs targeting different intracellular pathways, modulating epigenetic hallmarks or the immune and tumour cell cross-talk. However, very few novel FL therapeutics in development represent new drug classes, and virtually none of these drugs (to the notable exception of tazemetostat;<sup>24</sup> see below) are driven by or specifically tailored to new discoveries in FL biology. Furthermore, most, if not all of the most recently approved therapeutic agents in FL do not target a specific vulnerability present in subpopulations of FL, but rather are applied to all patients without a reliable biomarker of response (Box 2).

Going forward, we should keep in mind that one size does not fit all in FL and that a personalised strategy should be the goal. We need to define effective therapeutic targets that consider the heterogeneity observed for decades in FL (clinical and biological) and the complex layers of biology that underlie this heterogeneity. This probably means defining different therapeutic targets for different subpopulations of FL driven by the unique biological features of that

subpopulation. As part of this effort, it is critical that specific and reliable biomarkers of response are developed for each therapeutic agent. This will require the collaboration of pathologists and clinicians in the performance of clinical trials (including Phase III) that are carefully designed with paired clinical and biological endpoints integrated as part of the trial design. Naturally, the identification of novel high-yield targets in subsets of FL will depend upon significant advances in our understanding of the complex layers of FL biology (Box 2).

FIRST STEPS TOWARDS THERAGNOSTIC CLASSIFICATION USING MOLECULAR SUBTYPING

Moving away from a blanket treatment approach in FL requires detailed understanding of the molecular underpinnings of different groups of FL patients to support differential therapeutic approaches. Do molecular subtypes exist in FL? Several recent studies have shed light on this. Using a targeted gene panel of 293 genes, a first study identified three genotypical subgroups identified: one associated with a high burden of aberrant somatic hypermutation (SHM), a second with frequent *STAT6* and *CREBBP* mutations, and a third group enriched for *KMT2D* mutations without the features of the prior clusters.<sup>25</sup> Although a key limitation in this study was using targeted gene sequencing to resolve these subgroups, none of these three groups were associated with patient risk or propensity to transformation. In another study, whole genome sequencing of 423 diagnostic biopsies from FL (some with or without later transformation), transformed FL and *de-novo* diffuse large B cell lymphoma (DLBCL) cases led to the proposition of two genetic FL subtypes associated with significantly different risks of transformation: constrained FL (cFL) versus DLBCL-like FL (dFL).<sup>1</sup> The cFL cohort was associated with a reduced risk of transformation and genetically harboured a lower mutational burden, less SHM but an enrichment of *CREBBP* KAT missense mutations and mutations in genes involved in mTORC1 signalling (*RRAGC*, *ATP6V1B2*, *ATP6AP1*).<sup>26,27</sup> By contrast, dFL had a much higher risk of HT and was associated with more frequent aberrant SHM and *CREBBP* nonsense mutations. A third study initially used bulk transcriptome on the FL B cells to resolve three transcriptional states referred to as inflamed, proliferative and chromatin-modifying.<sup>28</sup> Each of these states correlated with specific genetic and immune microenvironment features, although were not demonstrated to have any prognostic impact. Finally, a study by Han and colleagues



**Figure 1.** A model of FL oncogenesis: t(14;18) is occurring during pro-B cell development in the bone marrow and leads to ectopic BCL2 expression without preventing further B cell maturation. Upon cognate antigen stimulation, peripheral naïve BCL2+ cells are preferentially activated by TFH and GCs. There, ectopic BCL2 expression uncouples GC check-point selection from affinity maturation, leading to clonal expansion, differentiation and exit of BCL2+ memory-like B cells with heterogeneous, unselected, low-affinity and potentially polyreactive BCR. The propensity of such large pools of BCL2+ clones to disseminate in blood, niche in SLO and iteratively visit GC can be assumed as the second (immunological) hit, heading to the accumulation of mutations. Although most will be passengers, some will directly and recurrently impact further steps of oncogenesis either through providing competitive advantage (e.g. proliferation) or resistance to the host immunity and/or to therapy (e.g. quiescence). FL, follicular lymphoma; BCL, B cell lymphoma, TFH, T follicular helper cell; BCR, B cell receptor; GC, germinal centres; SLO, secondary lymphoid organs.

analysing the tumour microenvironment (TME) using single-cell RNA sequencing defined four FL clusters based on TME composition: a ‘naïve’ cell-rich cluster, a ‘warm’ cluster, an ‘intermediate’ cluster and a ‘depleted’ cluster, the latter being associated with poorer survival outcomes.<sup>29</sup> Although the technical approaches were different in each of these studies, they refer the underlying biological heterogeneity of FL being driven by more than just genetic aberrations (Box 2).

**Biological knowledge to build the bridge for a biology-informed treatment**

Why is FL so effective at escaping current therapies? The answer lies in the natural history of FL<sup>30</sup> (Figure 1), involving a long and complex multistep

process, starting decades before diagnosis and/or symptomatic manifestations. The process involves four key steps setting the stage for malignant transformation and recurrent relapses: early BCL2 activation, dysregulation of B cell dynamics, co-evolution of propitious TME/tumour ecosystems and genomic instability leading to epigenetic dysfunction. This indolent, Darwinian-like evolution of FL generates both the peculiar complexity and heterogeneity of this disease.

**CPC (COMMON PRECURSOR CELLS)**

The complex parallel evolution of early expanding precursor clones resulting from iterative visits to the GC of a large pool of long-lived BCL2+ memory B-like cells (Figure 1) probably constitutes the first and

### BOX 3. Key requirements towards therapeutic innovation based on biological knowledge

Will be achieved by:

- Fully characterising the common precursor cells (CPC) and relapse initiating subclones (RISC) at the genetic, phenotypical and functional levels and identify their associated niches. Large-scale efforts using deep-sequencing and single-cell technologies will be required to decipher and understand such rare cell populations. Collaborative academic and industry efforts will be needed to develop or adapt drugs to directly target CPCs aiming to delay or prevent relapses. Drug development roadmap should include mandatory efforts to minimise toxicity and optimise specificity, in order to envision a prevention/maintenance type of therapeutic scheme
- Clearer understanding of the factors underlying the dynamics and plasticity of follicular lymphoma (FL) cell populations and determining if specific transcriptional states are associated with drug resistance or sensitivity and exploit druggable vulnerabilities
- Developing innovative model systems that truly recapitulates the multiple epigenetic alterations seen in patients that will allow better dissection of the complex intrinsic and extrinsic cell circuitry and identify vulnerabilities and epigenetic targets. Current epigenetic therapies have perhaps been underwhelming because we miss this detailed understanding. We should harness such information to guide drug discovery towards novel best-in-class epigenetic drugs with increased specificity and efficacy, together with the development of appropriate biomarkers
- B cell receptor (BCR) activation and signalling are complex and varied, influenced by diverse ligands, isotypes and genetic factors. This complexity, together with patient-specific immune history, poses challenges for current FL models. Targeting receptor–ligand interactions, together with signalling pathways, requires the development of more reliable *ex-vivo/in-vivo* preclinical models.
- Exploring the long-term effects of chronic stimulation by existing bispecific T cell engagers is crucial. Advancing next-generation chimeric antigen receptor T (CAR-T) designs with more tumour-specificity, enhanced functionality and persistence with reduced toxicities
- Combining different treatment modalities based on biological rationale and potential synergy is essential. Identifying effective combinations with minimal side effects, whether targeting tumour cells, epigenetic circuitry or the tumour microenvironment (TME) is key
- Leveraging ongoing and future clinical trials of novel and existing drugs, with a focus on ancillary studies. Collaborative biobanking, suitable methodologies and strong research and development commitments from all stakeholders are essential

potentially one of the most serious barriers to effective therapy.<sup>31</sup> This sets the stage for the co-occurrence of constant new generations of evolving FL progenitor cells (called CPC) concurrently present at any time, probably in various anatomical locations and at various advanced stages of malignant transformation, waiting in line to emerge as FL.<sup>32–35</sup> As a direct consequence of CPC dissemination, spatially distinct FL involved sites (lymph node, BM, blood) exhibit genetic and transcriptional heterogeneity.<sup>36–38</sup> Concurrent CPCs might globally benefit from protumoural TME reshaping by the most advanced TME/tumour ecosystems. The early genealogical branching of this ‘CPC factory’ (i.e. before malignant transformation) is the source of intratumoural heterogeneity in FL, and is most probably the source of resistance and relapse.<sup>39–41</sup> Because CPC or daughter

relapse-initiating subclones (RISC) are rarely detectable at diagnosis, anticipating targeted therapy for relapse based on late oncogenic alterations found at diagnosis (post-CPC branching) is not a rational precision medicine option. Understanding the most frequent sequence of alterations paving FL genesis is thus mandatory to identify and target actionable early hits present in all or most subclones. Unfortunately, BCL2 has proved to be a weak functional and therapeutic target in FL.<sup>42</sup> By the time that overt disease manifests, BCL2 has gradually built a global stage for oncogenic substitutes and probably does not constitute a tumour addiction, as evidenced by disappointing clinical trials using BCL2 inhibitors. Thus, despite the emergence of new generations of more potent BCL2 inhibitors, targeting BCL2 alone is unlikely to address the relapse conundrum. Next in

line, genetic and deep-seq studies have identified mutations in CREBBP as the earliest hit following t(14;18), in some cases appearing in healthy individuals up to a decade before FL diagnosis.<sup>35,43</sup> CREBBP mutations are found in 60–70% FL patients, and CREBBP loss of function is actionable through the inhibition of the antagonist NCOR/SMRT/HDAC3/BCL6 complex.<sup>44–46</sup> This opens the first precision medicine perspectives specifically aimed at eradicating (or at least delaying) FL relapses. Several black boxes nonetheless remain, and further research efforts will be necessary to fully rationalise future targeted therapeutic approaches (Box 3).

#### FL DYNAMICS AND PLASTICITY

Normal mature B cells display inherent cell dynamics and plasticity associated with major (reversible) changes of transcriptional states [differentiation, de-differentiation and light zone to dark zone (LZ to DZ) transition].<sup>30,47</sup> The transition between states (e.g. from DZ to LZ) is a tightly regulated process, with sets of genes expressed or repressed with high synchronicity throughout a continuum of intermediate cell states.<sup>48–51</sup> This synchronicity observed for normal DZ/LZ B cells during the GC reaction is lost in FL,<sup>48</sup> partly due to chromatin-modifying gene (CMG) alterations putting the brakes on differentiation and eventually locking FL cells as GC B cells, preferentially homing in the GC.<sup>52–57</sup> The locking is, however, not absolute, as it allows egress and dissemination, but it may prevent differentiation and/or restrain transition of states. Similarly to the gradual transition from DZ to LZ in normal B cells, current single-cell data indicate that FL cells in the tumour bulk also display a continuum of expression signatures. Unlike normal B cells, however, the continuum is spanning from GC-like (centroblasts?) to Mem-like (interfollicular?) states, with intermediate states (centrocytes?) constituting most of the bulk FL cells.<sup>48,58,59</sup> Each patient displays a distinct balance of such intermediate states, some leaning to GC-like, others to Mem-like, and this constitutes one of the main components of interpatient transcriptional heterogeneity. The skewing of these states towards Mem-like could increase the propensity for tFL transformation.<sup>59</sup>

From the therapeutic standpoint, the various transcriptional states have shown various sensitivities to chemotherapy, immunotherapy and (epi)genetic inhibitors.<sup>60</sup> If components of the tumour can adapt and swiftly transit from one state to the other, this might constitute an important escape route to a given selective pressure (Box 3).

Altogether, emerging single-cell data are thus drawing a picture where FL cells remain dynamic, undergoing profound transitions of states, probably as a result of TME signalling. This plasticity may drive inter- and intratumoural heterogeneity and constitute an additional layer of complexity adding to effective therapy escape. Clearer defining of each grand category of state and their underlying dynamics might accelerate identifying new Achilles' heels and devising combined strategies to target all categories at once and/or strategies to prevent transition of states.

#### BCR ACTIVATION AND SIGNALLING PATHWAYS

The B cell receptor (BCR) constitutes a key oncogenic pathway that has been shown to promote cancer cell growth and survival in various types of non-Hodgkin lymphomas (NHL).<sup>61</sup> The targeting of BCR signalling pathways has proved very successful in several indications, such as chronic lymphocytic leukaemia, and thus constitutes an important area of drug development for tailored therapy in B-NHL. In FL, the BCR (rarely lost despite an active SHM process) is assumed to represent one of the tumour's addictions and has therefore also been the target of several trials using kinase inhibitors. As antigen-independent tonic BCR signalling involving the PI3K/AKT/mTOR pathway has been proposed to be essential for FL cells survival,<sup>62</sup> PI3Ki held great promise and gained approval in RR patients.<sup>63–65</sup> However, poor response rates and the absence of biomarkers to enable identification of patients who most benefit, together with a challenging safety profile, led to withdrawal of these molecules. Next, despite the absence of strong evidence of FL's dependency towards the BTK/NFκB pathway, the success of BTKi in other lymphomas drove the development of several trials in FL. Although initial BTKi monotherapies (ibrutinib, acalabrutinib) failed to produce durable responses in FL, the Phase II randomised study of zanubrutinib (a new generation and more selective BTKi) in combination with obinutuzumab (ZO) met its primary endpoint by greatly increasing ORR compared to monotherapy,<sup>66</sup> and a Phase III trial is now ongoing (NCT05100862).<sup>67</sup>

Most importantly, the unanticipated outcomes of the various kinase inhibitors so far illustrate the important gaps in the current knowledge regarding FL signalling pathways highlighting the disconnection between biology rationale and drug development. A clearer understanding of FL's BCR signalling is urgently needed to avoid future random achievements and disappointments, but also to consolidate success. Indeed, even if positive and approved, the ZO will ideally require a



companion biomarker for patient selection, given that only a fraction of the patients is likely to benefit from this strategy.

Another area of great interest lies in upstream BCR activation. During the decades of preclinical FL development with a GC check-point selection invalidated for BCR/antigen (Ag) fitness, an 'Ag switch' probably operates from the initial cognate Ag towards other BCR stimuli, probably with great interpatient variabilities in an opportunistic fashion. Among these, the acquisition of N-glycosylation sites in immunoglobulin (Ig) variable regions might provide a recurrent (~80% FL cases), continuous and low-intensity Ag-independent BCR activation pathway via interaction with lectins in the TME (e.g. DC-SIGN on macrophages).<sup>68</sup> Notably, this peculiar activation would drive better signalling through an IgM than an IgG. As most patients with early relapses express IgM,<sup>69</sup> disrupting this signalling<sup>70,71</sup> might open important new targeting avenues.

Altogether, BCR activation and signalling circuitry are complex and more varied than initially anticipated. Many knowledge gaps remain to reliably guide tailored drug development of signalling pathway inhibitors in FL (Box 3).

#### EPIGENETICS AND CELL INTRINSIC CIRCUITRY

Epigenetic regulators play a prominent role in the clonal evolution of FL, as 90% of FL cases harbour at least one somatic mutation in histone modifiers including *KMT2D*, *CREBBP*, *EP300* and *EZH2*.<sup>39,40,72</sup> Mutations in *KMT2D*, a histone methyltransferase specific to H3K4, and *CREBBP*, a histone acetyltransferase specific to H3K27, commonly lead to a loss of function (LOF), while mutations in *EZH2*, a histone methyltransferase that forms the catalytic component of the polycomb repressive complex 2 (PRC2) responsible for laying repressive methylation marks on H3K27, are gain-of-function (GOF). Consequently, all CMG mutations in FL lead to repression. A cell-intrinsic circuitry model accounting for the prominent role of epigenetic repression in FL lymphomagenesis suggests that such circuitry prevents further differentiation of GCB-like cells, in line with FL's COO.<sup>52-57</sup> Mutations in epigenetic regulators may also contribute strongly to inducing an immune evasive TME by dampening down different components of the immune synapse. For example, *EZH2* mutations reprogramme T follicular helper cell (TFH) signalling and their cross-talk with FL cells, while *CREBBP* aberrations down-regulate the antigen presentation machinery.<sup>57,73,74</sup>

The key pathogenic role played by these epigenetic regulators combined with their high frequency makes them interesting targets. The discovery of GOF *EZH2* mutations in ~25% of FL<sup>75</sup> led to the only example of drug development issued from specific FL discovery. The first-in-class *EZH2* inhibitor, tazemetostat, demonstrated a greater ORR in *EZH2*-mutated (69%) compared to *EZH2*-unmutated patients (35%). The presence of responses in the *EZH2*-unmutated patients is consistent with the fact that, as normal GC-B cells, FL cells express *EZH2*, with the mutant form increasing PRC2 repression activity through the enhancement of H3K27me2 to H3K27me3. The activity and equivalent duration of response in both groups led to approval of tazemetostat for both mutated and unmutated patients.<sup>24</sup> Eventually, this questions whether *EZH2*, the sole actionable mutation in FL, represents a truly predictive biomarker for tazemetostat, given that it is found in merely a quarter of FL patients and that its inhibition does not provide a curative answer, particularly in monotherapy. Combination treatment approaches are currently being evaluated. *EZH2*'s role in TME reprogramming is also being investigated to determine how it may enhance the efficacy of immunotherapies such as chimeric antigen receptor T (CAR)-T.<sup>76</sup> Finally, as *EZH2* LOF are oncogenic in leukaemia, secondary cancer concerns ought to be monitored in the long term, with potential restriction of *EZH2* inhibitors usage in later lines of the therapeutic sequence (> 3L).

Similar drug development efforts are ongoing for *KMT2D* (KDM5 inhibitors) and *CREBBP* mutations (HDAC3 inhibitors), although with more challenging specificity/toxicity issues due partly to the lack of direct targeting of LOF mutations and structural hurdles of the targeted proteins (Box 3).<sup>46,77</sup>

#### TME ADDICTION AND IMMUNE-BASED THERAPIES

The tumour microenvironment (TME) plays a key role in clonal evolution, tumour cell survival and clinical evolution of FL patients.<sup>78-80</sup> This cell-extrinsic circuit is crucially implicated in FL lymphomagenesis. FL TME mainly consists of immune T cells,<sup>29,81</sup> including Tfh cells, BCL6+, inducible costimulatory (ICOS+), C-X-C chemokine receptor type 5 (CXCR5+) and programmed cell death ligand 1 (PDL1+), involved in lymphomagenesis through secretion of cytokines such as interleukin (IL)-6, IL-21, IL-4 and CD40-L.<sup>82-84</sup> Regulatory T cells (Treg) CD4+, forkhead box protein 3 (FOXP3) and CD25+ are involved through immunosuppressive activity related to inhibition of cytotoxic cells infiltrating the tumour.<sup>85</sup> Additionally, other T cell populations have

been identified, such as Tfr cells FOXP3+CXCR5+ sharing characteristics of Tfh and Treg cells,<sup>86</sup> cytotoxic CD4<sup>+</sup> T cells and cytotoxic CD8<sup>+</sup> T cells. Composition of FL TME is linked to clinical outcomes of patients; a low abundance of intrafollicular memory CD4<sup>+</sup> T cells is associated with poorer progression-free survival,<sup>87</sup> whereas a rich infiltrate of cytotoxic CD8<sup>+</sup> T cells is associated with a better prognosis.<sup>88</sup>

Insights into the role of TME in FL clinical behaviour has stimulated novel immune-based approaches, including immune check-point inhibitors (ICI), bispecific T cell engagers (anti-CD3/CD20) and CAR-T cells (targeting CD19). In RR, ICI assessed in combination with rituximab led to conflicting data,<sup>89–91</sup> and biomarkers are required to evaluate whether some (even if few) patients could benefit from this strategy. Regarding T cell engager, several molecules showed impressive ORR,<sup>92,93</sup> and combinations with lenalidomide are being developed<sup>94,95</sup> with exciting preliminary results. However, so far there are no data to justify the choice of a combination versus a single agent use. Keeping in mind that the leading cause of death in these trials is infection, limiting combinations and duration of treatment appears required. The field of FL is also moving towards CAR-T cells, as lisocabtagene maraleucel, axicabtagene ciloleucel and tisagenlecleucel were recently approved [complete response rate (CRR) of 94, 79 and 68%, respectively].<sup>96–98</sup> While extremely successful and potentially curative, the financial toxicity and specific side effects suggest this should be reserved for high-risk patients. Available translational data report on the correlation of CAR-T expansion,<sup>97</sup> tumour immune contexture or pretreatment levels of Treg-related chemokines and inflammatory markers IL-2R $\alpha$  and tumour necrosis factor (TNF)- $\alpha$  with outcome.<sup>99,100</sup> These data are only preliminary, and more needs to be done to have a reliable biomarker for a risk-stratified approach for CAR-T selection. Last, but not least, we need targets that are not universal on immune cells (i.e. other than CD20, CD19 for example), but rather FL-specific, to avoid long-term side effects, and more particularly infection complications (Box 3).

#### SPATIAL TECHNOLOGIES CAN ENABLE DEEPER TME CHARACTERISATION AND BIOMARKER DISCOVERY

The past decade has seen explosive growth in the development of spatial technologies that enable the systematic dissection of the tumour microenvironment at ever-increasing spatial and molecular resolution.<sup>101,102</sup> There are two broad classes of

emerging spatial technologies; first, image-based spatial proteomic and transcriptomic technologies offer excellent spatial resolution but are limited in their multiplexing capacity. Conversely, sequencing-based technologies provide the advantage of high multiplexing capacity, including transcriptome-wide measurements, but suffer in their spatial resolution. Some newer technologies, such as Slide-tags,<sup>103</sup> attempt to bridge this important gap between multiplexing capacity and spatial resolution, where one can obtain single-cell genome-scale measurements at truly single-cell resolution. This technology also enables multimodal measurements, a notable limitation of current spatial genomic methods. High cost and lack of FFPE tissue compatibility are important limitations and active focus areas for technology development.

Recent studies<sup>69,104</sup> have applied single-cell and spatial (multiplexed immunophenotyping) technologies on clinically annotated cohorts of FL and have led to intriguing initial insights into the cellular and architectural features of the microenvironment, including exhausted T cell subsets, stromal desmoplasia and changes to the follicular growth pattern, that are associated with outcomes. These studies highlight the power of these technologies and underscore the need for additional studies in larger well-defined clinical cohorts (Box 3).

The application of these technologies to FL samples across space (different anatomical sites) and time (diagnostic and progression/transformation specimens), and computational methods for inference of paracrine and niche-specific ligand–receptor interactions by integrative analysis of single cell and spatially resolved data,<sup>105–107</sup> offer great promise in achieving the goal of developing a holistic understanding of interactions within the tumour microenvironment that drive tumour growth. Specifically, these tools and data sets should enable the discovery of novel microenvironment-derived tumour cell trophic factors and mechanisms of immune evasion. These discoveries can lay the groundwork for developing the next generation of immunomodulatory therapies, next-generation model systems and biomarkers, which are much needed in the field (Box 3).

#### Development of dynamic biomarkers for the evaluation of therapeutic response

In order to effectively triage novel targeted therapies to the appropriate subsets of FL patients, it will be critical to develop therapy-specific biomarkers that

**BOX 4. Key requirements for MRD detection and response-driven strategies**

We need to:

- Determine which liquid biopsy-based assays have sufficiently high sensitivity for minimal residual disease (MRD) detection. This will require the creation of biobanking efforts for sequential biopsy collection from cohorts of patients with detailed clinical history to facilitate multiple assay evaluation and subsequent validation
- Identify the best time-point for MRD assessment and outcome prediction, which will probably depend upon baseline clinical/biological characteristics. Multimodal integration will be required to develop the most cost-effective MRD model
- Leverage knowledge obtained from dynamic response monitoring to design response-adapted trials with retreatment and/or escalation strategies to minimise toxicity while improving outcome for slow responders

can be used to effectively and reliably evaluate therapeutic responses.

***BCL2-IGH* REARRANGEMENT DETECTION BY RT-PCR**

Post-induction treatment biomarker evaluation has historically centred on minimal residual disease (MRD) measurement of a key molecular hallmark, the t(14;18), *BCL2-IGH* rearrangement<sup>108</sup> by reverse transcription–polymerase chain reaction (RT-PCR). Multiple studies in FL demonstrate that the presence of conventional MRD in either the peripheral blood or BM following treatment is an important predictor of relapse.<sup>109–112</sup> However, this method has limitations. First, not all FL patients have this molecular marker, as up to 40% of patients lack a *BCL2-IGH* target that can be tracked and are ineligible for monitoring.<sup>110</sup> Secondly, detection of very low MRD levels requires very high input DNA and, in turn, difficulty in distinguishing low-level signals that reflect true residual lymphoma cells from non-specific amplification of normal DNA. Thirdly, MRD negativity following chemoimmunotherapy is very high (e.g. nearly 90% of assessable patients were MRD-negative on the GALLIUM and FOLL12 trials<sup>110–112</sup>), many patients still relapse, indicating that clinical relapse cannot be accurately

predicted by this approach. Lastly, healthy individuals who do not develop FL have been shown to harbour the *BCL2-IGH* rearrangement, and therefore cells bearing this rearrangement may not all represent cells with the potential to induce relapse (Box 4).

**THE PROMISE OF CIRCULATING CELL-FREE TUMOUR DNA (CTDNA)**

The remarkable breadth and evolution of intratumoural heterogeneity that occurs in time and space (before and after treatment) in FL patients suggests that this will require dynamic biomarkers that can be easily and repeatedly monitored over time. Given the logistical impossibility of performing multiple serial or longitudinal biopsies, analysis of ctDNA fragments released into the blood—a means of liquid biopsy—may represent the best opportunity to capture and provide a better representation of therapeutic responses. In DLBCL, ctDNA has been shown to capture both the mutational landscape and clonal evolution, while demonstrating prognostic relevance at various time-points.<sup>113,114</sup> Studies evaluating ctDNA as a dynamic biomarker in FL are emerging. The pre-treatment ctDNA levels in FL patients correlated with prognosis and tumour burden as quantified by imaging.<sup>115</sup> Due to the much lower ctDNA levels in FL compared to aggressive lymphomas such as DLBCL, higher precision assays are needed for disease monitoring. Approaches ranging from clonotypical analyses to individual patient-defined amplicon mini-gene panels to broader non-individualised targeted gene sequencing have been investigated in pilot cohorts, demonstrating feasibility and varying prognostic accuracy.<sup>116–118</sup> Of added interest is the possibility of utilising ctDNA to predict FL transformation, especially as some genetic events associated with transformation can be detected several months earlier.<sup>119</sup> This minimally invasive modality might offer the opportunity to capture heterogeneity while dynamically monitoring disease response to treatment and the ability to forecast progression, but this still requires validation in larger cohorts and continued refinement of the assay precision (Box 4).

**Concluding remarks****EVOLVE OUR INFRASTRUCTURE**

- The need for multicentre collaboration to create large, collaborative biorepositories with well-annotated clinical data spanning the full spectrum of disease phenotypes from real-world cohorts. This

approach will enable the generation of multi-modal data, including various omics, imaging, and pathology, on large patient cohorts. Such comprehensive datasets will be invaluable for meaningfully addressing outcome-driven questions at scale, such as AI-based algorithms for prognosis and response prediction.

- Collaboration is essential from a wide range of stakeholders, including clinicians, researchers, administrators, pharma, funders, patients and advocacy groups. Addressing the regulatory and logistical challenges—such as governance, data sharing and harmonisation—will be critical to making this collaboration effective.

#### EVOLVE OUR RESEARCH APPROACH

- Identify key research priority areas (as highlighted in this review) and adopt a reverse translational mind-set by rapidly taking observations learnt from prior research and clinical challenges back to the laboratory to model the complexities seen in patients.

- Rather than have siloed research teams competing in parallel, which can lead to redundancies, incentivise team science and multidisciplinary initiatives to pool expertise, resources and increase efficiency of research spending.

#### EVOLVE OUR CLINICAL TRANSLATION

- Biological discovery and rationale should be at the heart of future clinical trial innovation—moving towards biology-driven platform trials. To achieve this, we must include translational research from the trial conception, dynamic specimen biobanking during the trial and funding to support these ancillary initiatives. This will allow all manner of biomarkers (prognostic, predictive and dynamic) to be evaluated in addition to ones associated with drug toxicities. Ultimately, these need to be translated into clinically accessible, affordable and tractable biomarkers.

- Prioritise existing dynamic biomarkers of response to support development of response-adapted trials that would curtail treatment in patients who are poor responders and spare toxicity in those that have already achieved a good response.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Data availability statement

Data sharing is not applicable as no new data were created or analysed in this study.

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