# Functional Genomics in DLBCL

Subjects: Oncology

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Lymphoma research is a paradigm of integrating basic and applied research within the fields of molecular marker-based diagnosis and therapy. In recent years, major advances in next-generation sequencing have substantially improved the understanding of the genomics underlying diffuse large B-cell lymphoma (DLBCL), the most frequent type of B-cell lymphoma. This review addresses the various approaches that have helped unveil the biology and intricate alterations in this pathology, from cell lines to more sophisticated last-generation experimental models, such as organoids. We also provide an overview of the most recent findings in the field, their potential relevance for designing targeted therapies and the corresponding applicability to personalized medicine.

Keywords: B-cell lymphoma ; diffuse large B-cell lymphoma ; genomics ; functional model ; cell lines ; murine models ; gene editing ; organoid/spheroid ; therapy ; cancer

## 1. Unraveling Aggressive B-Cell Lymphomas: The Elusive Link between Genomics and Personalized Treatment

Lymphoma research is a paradigm of the integration of basic and applied research within the fields of molecular-marker-based diagnosis and therapy. Basic research on lymphomas has deepened our knowledge of cancer mechanisms, while helping to elucidate how aging, infection, the immune system, and other genetic and environmental factors might account for the increasing incidence of this disease in western countries. The rapid rise of high-throughput technologies in recent years has led to a growing number of genomic studies that emphasize and characterize the high degree of genomic heterogeneity in lymphomas. Genetic classification and other phenotypic and clinical data are currently used to predict which patients could benefit from standard treatment. However, new therapies that could be of use to patients at higher risk from refractoriness or relapse have yet to be applied in daily clinical practice. Indeed, the proposal of alternative treatments for diffuse large B-cell lymphoma (DLBCL) patients who do not respond to standard immunotherapeutic regimens (up to 30–40%) is mostly empirical, based on trial and error, and does not consider their genetic complexity. This is primarily due to the intricate mosaic of genetic and epigenetic alterations in lymphomas, and the unpredictable effects on their phenotype, which make it difficult to foresee which drug will work for any given patient. Epigenetic processes, such as methylation and demethylation, are responsible for the dynamic plasticity of B-cells and affect tumor behavior (for a recent review, see [1]). Interestingly, many of the genetic mutations that occur in DLBCL affect genes involved in chromatin remodeling (*EZH2*, *CREBBP*, *KMT2D*, etc.) and other epigenetics functions such as DNA methylation (*TET2*).

Patient treatment based on genomic analysis alone is not straightforward. Matching a patient's genes or a specific genetic signature to drug sensitivity by directly testing live tissues is the basis of the concept of precision medicine. However, in the case of lymphomas, we need to expand this concept beyond genomics to eventually provide better treatment options for patients in need of alternative therapeutic approaches. Functional assays could help fill this gap. Established models, such as those of tumor cell lines and mice, do not completely capture the complex genetic and epigenetic landscape that each patient presents, and, therefore, the translation of findings from these models to the clinic remains inefficient. Three-dimensional (3D) models, such as organoids, which can be generated from several cell types and reproduce the interactions of a patient's immune system with their tumor, will be a promising tool in personalized medicine in the near future.

## 2. Diffuse Large B-Cell Lymphomas: Clinically Unresolved Genomic Complexity

### 2.1. Diffuse Large B-Cell Lymphoma: A Traditional Overview

DLBCL is an aggressive and heterogeneous disease with a variable clinical outcome. It is the most common non-Hodgkin lymphoma (NHL) subtype, with 3.13 and 5.6 new cases diagnosed per 100,000 habitants per year in Europe [2] and the United States [3], respectively. DLBCL is subdivided into morphological variants, molecular subtypes and different clinical

entities (for a recent review, see [4]). The cases classified as DLBCL not otherwise specified (DLBCL-NOS) are biologically heterogeneous and the current classification for this lymphoma is based on its cell of origin (COO). Two subtypes are recognized based on the gene expression profile: activated B-cell (ABC) and germinal center B-cell (GCB) DLBCL [5][6]. Around 10–15% of cases cannot be classified as either of these subtypes and, therefore, remain unclassified. This classification is of prognostic value, with ABC-DLBCL being associated with poorer clinical outcome.

The most recent revision of lymphoid neoplasms by the WHO [7][8] recognized a more aggressive, high-grade B-cell lymphoma subtype with a worse prognosis, the 'double-hit'/'triple-hit' (DH/TH) lymphoma, which is characterized by *MYC* rearrangements that are associated with *BCL2* and/or *BCL6* rearrangements. Lymphomas that co-express the MYC and BCL2 proteins, known as double-expressor lymphomas, are relatively frequent, and have a worse prognosis than other DLBCL-NOS, although their behavior is not as aggressive as that of the DH/TH lymphomas [9].

In recent years, several studies using massive sequencing analysis have helped to define the genetic landscape of DLBCL by identifying many genetic alterations. Primarily, DLBCL has alterations in genes involved in B-cell differentiation pathways, such as chromosomal rearrangements of the *BCL6* locus and mutations/deletions in *PRDM1* [10][11][12] and *IRF8* [13][14] and BCR/NF-κB signaling, such as *CD79B*/*A*, *BCL10*, *TNFAIP3*, and *CARD11* [11][12][14][15][16][17][18][19][20]. Other relevant pathways are also affected, such as the Toll-like receptor pathway, with mutations in *MYD88* and, less frequently, in *TRAF6* [11][12][14][17][18][19][20][21]; the p53 and DNA damage pathway, with deletions/mutations in *TP53* and *UBE2A* [11][14][17][19][22], and methylation/deletions of *CDKN2A* [23]; and the PI3K/AKT pathway with mutations in *PTEN* and *PIK3CA* [24]. Other genes that are frequently or significantly altered are *MYC* (which modulates many cellular functions, such as DNA replication and cell proliferation), *BCL2* (cell apoptosis), *NOTCH1*, *NOTCH2,* and *DTX1* (cell differentiation), *GNA13* (cell migration), *CD58* and *B2M* (immune evasion), *PIM1*, *BTG1,* and *CCND3* (cell cycle), and the epigenetic regulators *EZH2*, *HIST1H1E*, *HIST1H1C*, *KMT2D*, *CREBBP,* and *EP300* [11][12][14][17][18][19][20][25][26][27][28][29][30] (Figure 1).

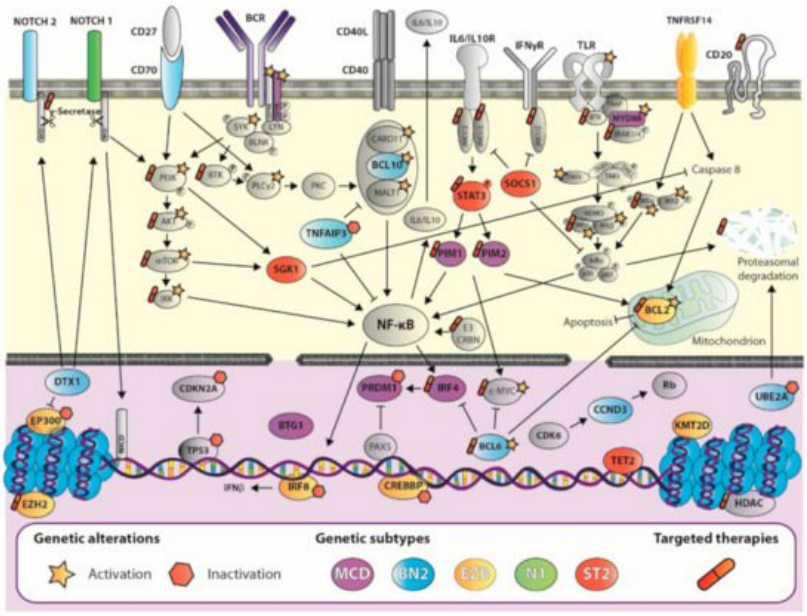


**Figure 1.** Diffuse large B-cell lymphoma complexity: untangling the networks underlying genetic subtypes. Schematic view of the most relevant genetic events in B-cell physiology pathways for each genetic subtype (GS) highlighted in purple (MCD), light blue (BN2), yellow (EZB), green (N1), or red (ST2), as described in the figure key. Mutations in CD79A and CD79B and SYK lead to chronic activation of the B-cell receptor (BCR; of special importance in the MCD GS), which triggers the activation of SYK, BTK, and PKC promoting the formation of the CARD11-BCL10-MALT1 complex. Mutations in genes that encode all the components in this complex can be identified in a subset of DLBCLs and are especially relevant for the BN2 GS. Mutations in genes that encode MYD88, IRAK1, and IRAK4 activate Toll-like receptor (TLR) signaling, which is further promoted by alterations in positive regulators downstream TLR, such as TRAF6. Alterations in Notch signaling, binding of CD27 to CD70, and BCR activation also lead to abnormal activation of PI3K-AKT-mTOR pathway, which also presents genetic alterations in this disorder. Most of these pathways converge in the activation of IKK and downstream NF-κB signaling, promoting lymphomagenesis. Tumor cell survival is boosted by alterations in the BLC2 and BCL6 axis, TP53, and imbalances in cytokine related pathways: interleukins (IL), interferon gamma (IFNγ), or tumor necrosis factor (TNF), which overall lead to increased survival and decreased apoptosis in these cells. Alterations at the nuclear level are also common in all genetic subtypes (except for the N1 subtype), and involve p53, DNA damage pathway, epigenetic regulators, and other components involved in proliferation and survival cell processes. Currently,

there are targeted therapies against several components downstream these pathways (tagged with a pill icon). Activating genetic events are highlighted with a star, while those involving inactivation are flagged with a hexagon.

For some genes, the mutation rate differs depending on the COO subtype. ABC-DLBCLs have a high frequency of alterations in *MYD88* (MYD88$^{L265P}$ occurs almost exclusively in ABC-DLBCL) *PRDM1*, *CD79B*, *BCL10*, and *BCL6* rearrangements [26][28][30]. GCB-DLBCLs have a better prognosis and frequently feature mutations in *BCL2, GNA13, TNFSR14*, *EZH2*, *CREBBP,* and *BCL2* rearrangements [26][28][30].

Around 30% of DLBCL cases show rearrangements of the 3q27 region, involving *BCL6*, most commonly in the ABC subtype. *BCL2* rearrangements (t(14;18), a hallmark of follicular lymphoma), have been detected in 20–30% of DLBCL cases, usually in those of GCB, and the *MYC* rearrangement is observed in 8–15% of cases [8]. When *MYC* translocation occurs simultaneously with *BCL2* and/or *BCL6*, the cases are classified as DH/TH high-grade B-cell lymphoma, as mentioned previously [28][30].

### 2.2. Advances in DLBCL Genomics: Genetic Signature Helps Design Tailored Therapies

In recent years, new DLBCL genetic classifications have emerged based on specific genetic alterations defining different subtypes. In 2017, Reddy et al. presented a multivariate model using gene expression data and COO classification in combination with genetic alterations to classify patients into three risk groups with different survival outcomes [29]. A year later, Schmitz et al. [28] identified four genetic profiles—MCD, BN2, N1, and EZB—based on mutational and translocation data (Table 1). These were subsequently refined by the addition of two subtypes: ST2 and A53 [31]. MCD was characterized by mutations in *MYD88*$^{L265P}$ and *CD79B*, while N1 presented mutations in *NOTCH1*. In both subtypes, most cases were ABC-DLBCL, and had a worse prognosis than BN2, based on *BCL6* fusions and *NOTCH2* mutations, and EZB, which was characterized by *BCL2* translocations and mutations in the *EZH2* gene [28]. The ST2 subtype was characterized by recurrent mutations in *SGK1* and *TET2.* Most cases were GCB-DLBCL and had a better survival. The A53 subtype comprised aneuploidy cases with mutations and deletions in *TP53*, with a worse prognosis among ABC-DLBCLs [31]. Another important study, by Chapuy et al. [32], defined five subtypes, including two ABC-DLBCL groups, one with lower risk and a possible marginal zone origin (C1, with *BCL6* translocations and mutations in *NOTCH2*), and the other a high-risk group (C5) featuring a high frequency of cases with mutations in *MYD88*, *CD79B*, and *PIM1*; they also described two distinct subsets of GCB-DLBCLs with favorable (C4) and poor outcomes (C3), and an ABC/GCB-independent group (C2) with biallelic inactivation of *TP53*, *CDKN2A* loss, and associated genomic instability [32]. Similar results from a large real-world population-based patient cohort in which MYD88 (similar to MCD) and NOTCH2 (similar to BN2) subtypes had a worse prognosis than BCL2 (EZB), SOCS1/SGK1, and TET2/SGK1 subtypes, which, together, could be considered similar to ST2 [33] (Table 1). More recently, another study by Pedrosa et al. [34] classified samples in MCD$^{2\text{-}S}$ (*MYD88*, *CD79B*, *PIM1*, *PIM2*, *PRDM1*, *BTG1,* and *CD58*), BN2$^{2\text{-}S}$ (*BCL6* fusion, *NOTCH2*, *BCL10*, *TNFAIP3*, *UBE2A*, *CD70*, *CCND3,* and *DTX1*), N1$^{2\text{-}S}$ (*NOTCH1*), EZB$^{2\text{-}S}$ (*BCL2* fusion and mutation, *EZH2*, *CREBBP*, *TNFRSF14*, *KMT2D IRF8,* and *EP300*), and ST2$^{2\text{-}S}$ (*SOCS1*, *SGK1*, *TET2,* and *STAT3*) with a two-step classifier based on the studies by Schmitz et al., Chapuy et al., and Lacy et al. [28][32][33]. Furthermore, the Lacy cohort showed a strong consensus across three classification strategies [34][35], reinforcing the high degree of reproducibility of these subtypes.

**Table 1.** DLBCL genomics: the genetic signature helps predict patient outcome. Comparison of the newly proposed genetic subtypes in DLBCL. The names of the genetic subtypes proposed by each group are highlighted in bold. COO: cell of origin; ABC: activated B-cell like; GCB: germinal center B-cell like; amp: amplification; transl: translocation.

Knowledge of these alterations may allow for the selection of better treatments than the standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), based on the patient's genetic background. Furthermore, it may prompt the development of novel agents or strategies targeting selected combinations of genes and pathways that synergistically affect the currently available drugs. These target survival pathways are driven by specific genetic and epigenetic events, such as BCR signaling, of which BTK, PI3K, and mTOR inhibitors stand out, and other agents targeting epigenetic modifiers, apoptosis, and the immune system regulator or the NF-κB pathway. To date, despite the arrival of new agents in the last decade, the actual treatment of DLBCL has changed little since the introduction of immunochemotherapy [26][36][37], and further effort is needed if precision medicine is to be successfully applied in the treatment of this pathology.

### 2.3. Friend or Foe: The DLBCL Microenvironment

Despite the intrinsic relevance of genetic aberrations within lymphoma cells, DLBCL complexity comprises more than genetic alterations in the tumoral cells. DLBCL cell survival and physiology depend on their interactions with the non-malignant cells and stromal elements, which constitute the tumor microenvironment (TME). The DLBCL TME involves the

interactions of lymphoma cells with host immune cells, including natural killer (NK) cells (±20% of total cell content), dendritic cells (DCs) (±15%), M2-type macrophages (±15%), CD4+ T cells (±10%), and CD8+ T cells (<5%) [38]. Significantly, TME composition and its highly heterogeneous interactions with neoplastic cells determine DLBCL pathogenesis and progression [39].

Tumor cells account for 60–80% of the cell content in DLBCL. The acquired genetic mutations render tumor cells relatively independent of survival and proliferation signals from their microenvironment [40]. Regardless of this effaced TME composition pattern, it has an important impact on DLBCL patients' survival, therapy response and disease progression or relapse. Interestingly, a recent work has described four major DLBCL microenvironment categories associated with distinct biological aberrations and clinical behavior [41]. Indeed, TME is of predictive importance in DLBCL prognosis and has been linked to resistance to chemotherapy [24][38][42]. This prompted the development of drugs targeting TME composition and the blockade of cellular interactions with dissimilar results in clinical trials. Therapeutic blockade of CD47, in combination with rituximab, showed promising response rates in DLBCL patients, while the PD-1 blockade response fell short (for a review, see [43]). On the other hand, the immune modulator lenalidomide has shown promising results in monotherapy and in combination with R-CHOP regimens, especially in elderly ABC-DLBCL patients [40].

In conclusion, lymphomas arise within a complex microenvironment and are characterized by a considerable genetic heterogeneity. Therefore, the ideal DLBCL model should replicate both aspects, and the clinical heterogeneity of the pathology.

## 3. Functional Models for B-Cell Lymphoma Research

From its outset, lymphoma research has relied on a wide variety of models, from cell monolayers to whole-organism studies (predominantly mice). Over the years, advances in gene-editing techniques, mouse models, and the genesis of three-dimensional (3D) in vitro models have led to new approaches to the study of DLBCL biology and therapy responses in a more physiological environment. The generation of reliable models approximating human disease offers the potential to apply the obtained results in daily clinical practice.

### 3.1. Gene Editing of Lymphoma Cells

The current gene-editing techniques include DNA base editors and RNA-programmable clustered regularly interspaced short palindromic repeats (CRISPR)-associated (Cas) nucleases [44][45]. Gene editing with these systems is effective in cell lines, human samples, and murine models [46][47][48]. Both strategies allow for the generation of accurate lymphoma models that reproduce or revert the mutations identified by massive sequencing, to study their relevance to tumor behavior and drug response [46][47]. Moreover, synthetically engineered DLBCL models, generated immediately by the directed mutations in human cell lines, or by their combination with mice of a specific genetic background, have enabled co-operating genetic alterations to be studied [46][48], such as FOXP1 silencing, BCR pathway expression or silencing, the co-expression of BCL2/MYC or BCL2/BCL6, and the expression of GC-DLBCL or ABC-DLBCL-related genes [29][49][50].

Beyond the insertion of specific mutations in a certain region of interest, the CRISPR-Cas9 system was adapted for functional genomic screening in DLBCL cell lines. Unbiased high-throughput CRISPR-Cas9 knockout screenings of DLBCL cell lines prompted the study of the functional impact of potential genetic drivers of DLBCL, previously identified by integrative analysis of whole-exome and transcriptome sequencing [29][51].

Therefore, gene editing is a useful tool for investigating genetic and functional drivers, and tumor dynamics, in DLBCL. However, there are hurdles to overcome before gene editing can be applied in a therapeutic context, such as ensuring a higher base-editing efficiency with minimal off-target effects, establishing a way of delivering the gene-editing system in a target organ with a high degree of correction, and it being possible to edit 100% of the tumor cells. Cancer is not a monogenic disease, and multiple somatic genetic alterations are involved. However, CRISPR-Cas9 has shown promising results in preclinical studies involving immunotherapy with CAR T-cells, indicating its therapeutic potential [52].

### 3.2. The Rise of Drug Screening: Mission Pathways

Cancer research has largely involved cell lines and 2D cell culture (Figure 2A), as they provide a robust and reproducible model system [53][54][55]. The universalization of massive parallel sequencing has facilitated the analysis of a large number of cancer model collections, such as the Cancer Cell Line Encyclopedia (CCLE), which includes some hematological cancer-derived cell lines [56]. However, limitations of the coverage of the hematological oncology spectrum in general collections prompted the development of the LL-100 panel, which covers more than 20 human leukemia and lymphoma entities, including DLBCL (ABC- and GC-DLBCL) [57]. The association of the knowledge emerging from the cell-line panels

and the genetic studies of patient-derived lymphoma samples [31] has enabled the identification of potential therapeutic targets.

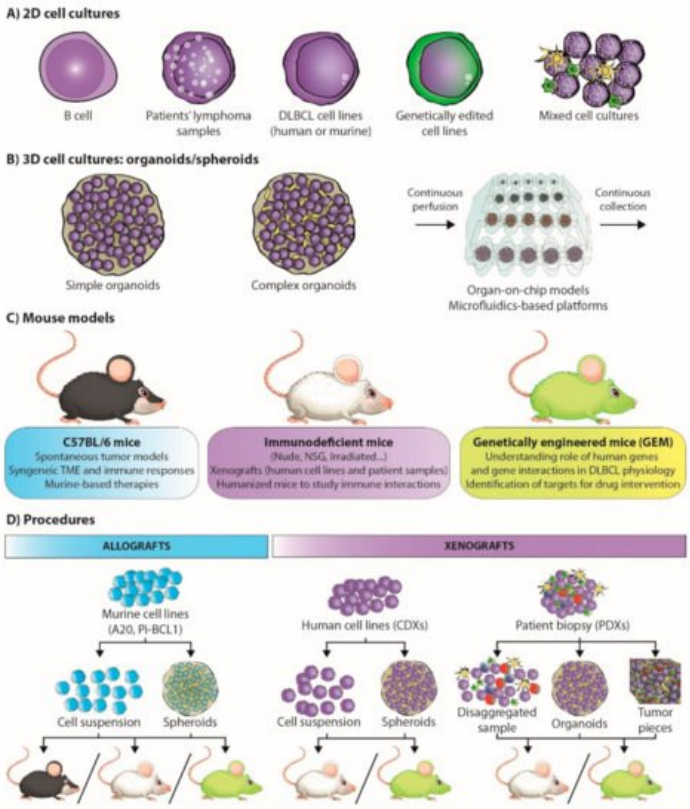


**Figure 2.** Preclinical models in lymphoma research and procedures. Research models in B-cell lymphomas include: (**A**) two-dimensional (2D) cell cultures comprising B-cells, patient lymphoma samples, DLBCL cell lines, gene edited cell lines, or mixed-cell cultures; (**B**) three-dimensional (3D) cell cultures, such as simple organoids involving a single cell type, complex organoids involving several cell types, and more complex systems, such as organ-on-chip models and microfluidics-based platforms; (**C**) mouse models, with CD57BL/6, immunodeficient, or genetically engineered mice (GEM). Their uses are summarized in the boxes below the mice. (**D**) All these elements can be combined and used to develop a variety of procedures involving cells from the same species (syngeneic allografts, left) or from different species (xenografts, right).

### 3.3. Of Mice and Men: Understanding Lymphoma Biology

In the field of lymphoma research, the mouse has been the model organism due to its genetic and physiological similarity to humans (Table 1) [58][59]. Various spontaneous tumor models (such as the Eμ-Myc, Eμ-BRD2, or Bcl6 mouse models) have been developed to study how B-cell lymphomas arise and mature in different tumor environments [60][61][62]. However, genetically engineered mouse (GEM) models (Figure 2C) have enabled the recapitulation of DLBCL genomic complexity, and have been very useful for defining the genetic causes of lymphoma [63]. Indeed, these models have clarified the understanding of the role of BCR signaling, germinal center differentiation status (by the identification of factors such as BCL6, SPIB, PAX5, and EZH2, among others), B-cell development regulators (such as PI3K) in lymphomagenesis, the study of malignant transformation drivers (such as MEF2B) and tumor suppressors (such as TET2 or CREBBP), functional cooperation between B-cell pathways (such as BCR and TLR signaling), and the identification of potential targets for drug intervention [64][65][66][67][68][69].

**Table 1.** Currently available DLBCL mouse models (overview). DLBCL: Diffuse large B-cell lymphoma; GC: germinal center B-cell like; ABC: activated B-cell like; (m): murine origin; (h): human origin; iv: intravenous; ip: intraperitoneal; sc: subcutaneous; PDX: patient derived xenograft; PDO: patient derived organoid.

| | Strategy | Phenotype/Incidence | Prospective Uses |
|---|---|---|---|
| **Genetically engineered mice** | Eμ-Myc | DLBCL (time dependent) [70] | |
| | Eμ-BRD2 | DLBCL [61] | |
| | Bcl6 Knock in | GC-DLBCL [62] | |
| | Bcl6/Myc | ABC-DLBCL [62] | |
| | Iμ:HA.BCL6 | 36–62% lymphoma incidence [62] | Combination with conditional *Spen* and *Tnfaip3* knockout or oncogenic *Notch2* alleles to model Cluster BN2 |
| | *Mb1:Cre;Eμ:Bcl2;Crebbp*$^{fl/fl}$ | GC-DLBCL [71] | |
| | *Cγ1*$^{Cre/wt}$*;Kmt2d*$^{fl/fl}$*;VavP:Bcl2* | 21% incidence<br>GC-DLBCL [72] | Combination of the different alleles to generate a sophisticated EZB mouse model |
| | Ezh2$^{cond.p.Y641F/wt}$;VavP:Bcl2; Cγ1$^{Cre/wt}$ | DLBCL-like lymphoma [73] | |
| | Cd19$^{Cre/wt}$;Myd88$^{cond.p.L252P/wt}$;Rosa26$^{LSL.BCL2-IRES-GFP/wt}$ | 85% incidence<br>ABC-DLBCL [74] | Modeling of the MCD cluster by combination of both alleles and a newly generated *CD79B*$^{cond.p.Y196H/wt}$ allele, or with the already existing *Prdm1*$^{fl/fl}$ |
| | *Cγ1*$^{Cre}$*;Prdm1*$^{fl/fl}$*;Rosa26*$^{LSL.IKK2ca}$ | 50% incidence IRF4, post-GC DLBCL [75] | |
| **Syngeneic models** | Pi-BCL1 (m) iv or ip in BALB/c immunocompetent mice | DLBCL [76][77] | Gene editing<br>Generation of complex organoids prior to inoculation of the cell line |
| | A20 (m) iv, intrasplenic, or sc injection in BALB/c immunocompetent mice | DLBCL [78][79][80] | |

| | Strategy | Phenotype/Incidence | Prospective Uses |
|---|---|---|---|
| **Xenograft models** | SU-DHL-4 (h) iv or sc in SCID immunodeficient mice | DLBCL [81][82] | Gene editing<br>Generation of organoids<br>Inoculation in humanized NOD/SCID mice |
| | Transduced HPCs in irradiated mice | GC- and ABC-DLBCL [71][83] | Generation of a-la-carte HPCs reproducing the genetic signatures<br>Inoculation in humanized NOD/SCID mice |
| | PDX iv or sc in immunodeficient mice | 20–30% successful engraftment | Use of humanized mice to study lymphoma physiology and drug responses<br>Personalized medicine |
| | PDO iv or sc in immunodeficient mice | 20–30% successful engraftment | Genetic modification<br>Use of humanized mice to study lymphoma physiology and drug responses<br>Personalized medicine. |

The headings of each mouse model subtype are highlighted in bold.

### 3.4. Back to the Bench: À La Carte-Engineered Spheroids

As previously mentioned, the interaction of malignant B-cells with stromal fibroblasts, endothelial cells, and other immune cells is key to the survival and progression of DLBCL [84][85][86]. 2D cultures lack the complexity, intercellular interactions, hypoxic conditions, and metabolic alterations found in the primary tumor [87][88]. This has led to 3D models being increasingly used in recent years [89]. These provide promising means of overcoming this limitation by recapitulating the organ structure, microenvironment, and physiological function, reliably mimicking disease states [90].

In vitro 3D models can be generated from cell lines or directly from the primary tumor (Figure 2C). However, unlike solid tumors, which can spontaneously self-organize into tissue-like structures (organoids), lymphoma organoids (also referred to as spheroids) are artificially engaged in 3D structures and enriched in the cell types present in the primary tumor [91][92].

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