

# NHL DLBCL PDX Models

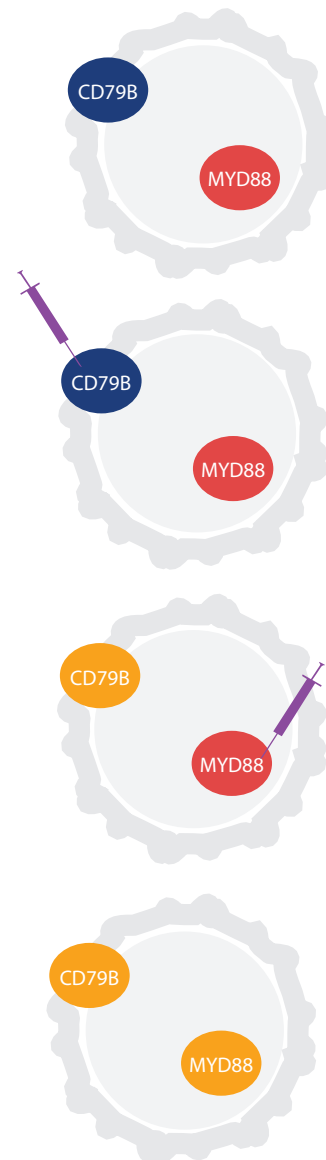
Evaluate novel therapies and combination regimens in PDX models fully characterized for DLBCL related genes

Accelerate your DLBCL targeted agent and combination therapy drug discovery programs with CrownBio's panel of well validated, clinically relevant patient-derived xenograft (PDX) models.

The ABC subtype of DLBCL develops through acquiring a range of specific mutations, either singly or in combination. Novel agents to target these mutations are under development, focused on combination therapies directed at multiple mutations within a single tumor. Their preclinical efficacy testing needs models which fully capture the complex genetic interplay seen in patients.

CrownBio provides a panel of clinically relevant DLBCL PDX models, ideal for combination therapy evaluation of agents such as BTK, IRAK4, SYK, and PI3K $\delta$  inhibitors:

- Our ABC and GCB models cover a variety of wild type and mutated genotypes, including common single or combination MYD88 and CD79B mutations, truly reflecting patient disease background.
- Models are well-characterized and fully profiled via NGS so drug response/resistance can be linked to mutational status.
- Ibrutinib benchmarking revealed a range of resistance genotypes, ready to be overcome with combination strategies using client's developing agents.





# DLBCL PDX Panel Key Facts

CrownBio provides a well-characterized panel of DLBCL PDX models, covering the main ABC and GCB subtypes:

- To progress the preclinical evaluation of novel DLBCL agents and the combination regimens required to overcome multiple mutations within a single tumor.
- PDX models from Asian and US populations, closely reflecting patient tumors for histopathological and genetic profiles and highly predictive of patient response.
- Full model background, QC, and NGS genetic profiling data searchable through CrownBio's online PDX database, [HuBase™](#).
- Panel of models includes wild type and mutated DLBCL related genes, including:
  - » common MYD88 and CD79B mutations
  - » as well as EZH2, CARD11 mutations
  - » BCL-6 and MYC translocations
  - » combination mutation genotypes.
- Ibrutinib resistance observed for a range of models/genotypes, demonstrating the need for further combination therapy evaluation.
- Standard of care and radiotherapy data also available for a selection of models.

## The Unmet Need for Novel DLBCL and ABC Treatments

DLBCL can be sorted into 2 distinct subtypes based on cell of origin and mechanism of development:

- activated B cell-like (ABC)
- germinal center B cell-like (GCB).

Despite differing genetic backgrounds and origins, both subtypes are commonly treated with the immunochemotherapeutic regimen R-CHOP. Patients with the ABC subtype have poorer treatment outcomes, highlighting the unmet need for ABC specific therapies<sup>(1)</sup>, as well as further research to fully unravel the genetic background of the disease.

ABC mutations targeting the B cell receptor (including gain of function mutations in CD79A/B in approximately 18% of ABC) and in MYD88 (around 39% of ABC) result in chronic, active or constitutive signaling, promoting tumor viability, survival, and drug resistance<sup>(2)</sup>.

Treatments are under development to target these mutations - ibrutinib (Imbruvica®) inhibits BTK signaling downstream of aberrant CD79A/B, with IRAK4 inhibitors similarly blocking mutated MYD88. However, multiple mutations can occur within one tumor. Therefore, combinations of these agents (as well as other drugs in development such as SYK and PI3Kδ inhibitors) may be required to fully inhibit tumor growth.

Robust preclinical models are now needed for single agent and combination therapy evaluation, which mimic the complex signaling and mutational interplay seen in patients (i.e. the combinations of wild type and mutated genes across different subtypes). These models will provide predictive efficacy data for personalized medicine development and next step decision making.

## The CrownBio NHL DLBCL PDX Panel

Xenografts derived directly from primary tumor tissue (which have never been in contact with plastic) are known to be the most predictive preclinical models available for drug evaluation<sup>(3)</sup>, closely reflecting patient tumors for both their histopathological and genetic profile. CrownBio provides the world's largest commercial collection of PDX models, [HuPrime®](#), for translational research programs.

Establishing hematopoietic malignancy PDX (including NHL models) brings specific challenges and difficulties. However, through the evolution of our PDX development techniques, we now provide a well-characterized NHL DLBCL panel for preclinical agent evaluation.

## DLBCL PDX Panel Full Background and Genomic Profiling Available

PDX model characterization information can be found within [HuBase](#), CrownBio's easily searchable PDX database, and [OncoExpress™](#) our comprehensive oncology search engine. These resources are accessed from our website at [www.crownbio.com](#) or directly from [hubase.crownbio.com](#) and [oncoexpress.crownbio.com](#).

**Table 1** summarizes a selection of our available model data, including patient background, clinical diagnosis, and treatment history. All CrownBio models undergo in house pathology QC to confirm disease type and subtype; QC information and pathology images can be found in [HuBase](#).

**Table 1** also confirms the genomic profiling information available for our models within [HuBase](#), allowing detailed searching, comparison, and selection of appropriate models based on their genetic background.



# DLBCL PDX Panel Factsheet

**Table 1: HuPrime NHL DLBCL PDX Panel of Well-Characterized Models**

HuPrime ID	Disease Subtype	Patient Background	Patient Pathology Diagnosis	PDX Genomic Profiling Available
LY0257	NHL DLBCL ABC	Asian female, treatment naive	NHL (large B-cell) IHC: CD20(+), CD45RO(-), CD3(-), CD15(-), CD79a(+), CD30(-), CK(-), CD56(-)	P5: Affy U219, SNP 6.0, RNAseq P9: WES
LY2214	NHL DLBCL GCB	Asian female, aged 54. Treatment naive	NHL (large B cell) IHC: CD3(-), CD45RO(-), CD20(+), CD79a(+), Ki-67(80%), CD10(-), CD30(-), ALK(-), BCL-6(-), MUM1(-)	P0: Affy SNP 6.0 P4: WES P5: RNAseq
LY2264	NHL DLBCL ABC	Asian male, aged 61. Treatment naive	NHL (DLBCL) IHC: CD3(-), CK(-), CD20(+), Vim(+/-), CD79a(+/-), CD45RO(-), Ki-67(80%), CD30(-), HMB45(-), Mart-1(-), Pax-5(+), Bc1-6(+), EMA(-), CK7(-), P63(-), ALK(-), CD10(-)	P3: WES P4: Affy SNP 6.0, RNAseq
LY2266	NHL B cell ABC/GCB	Asian male, aged 67. Treatment naive	NHL (B cell lymphoma with plasma cell differentiation) IHC: CK(-), CD20(+), CD3(-), CD79a(+), Ki-67(40%), CD5(-), CyclinD1(-), CD138(+/-), CD56(-), CD10(-), Bc1-6(-), Pax-5(+), MUM1(+/-), CD45RO(-)	P1: Affy U219, SNP 6.0 P3: WES P4: RNAseq
LY2298	B cell lymphoma ABC	Asian female, aged 60. Treatment naive	B cell lymphoma of right forehead IHC: CD20(++), CD79a(+), Ki-67(+80%), CD56(-), CD3(-), CD45RO(-), NSE(-), GFAP(-), Syn(-), S-100(-)	P2: Affy U219, SNP 6.0, WES P4: RNAseq
LY2318	NHL DLBCL GCB	Asian male, treatment naive	NHL, DLBCL	P4: RNAseq
LY2345	NHL DLBCL ABC/GCB	Asian female, aged 56. Treatment naive	NHL (consider large B cell lymphoma) IHC: CD3(-), CD45RO(-), CD20(+), CD79a(+), Pax-5(+), CD5(+/-), CD10(+), BCL-6(-), CyclinD1(-), MUM1(+)	P1: Affy SNP 6.0 P3: RNAseq, WES
LY3604	NHL DLBCL ABC	Asian female, aged 82. Treatment naive	DLBCL	P5: RNAseq
LY14019	NHL DLBCL	Caucasian male, aged 74. Pretreated. Biopsy site: right side brain tumor	NHL, DLBCL	Ongoing

## Full Mutational and Fusion Analysis Available Including DLBCL Related Genes

Part of CrownBio's PDX characterization package involves mutation analysis. As standard this covers hotspot mutations in 12 common oncogenes and tumor suppressor genes e.g. TP53, PTEN, MET, MAPK1, etc.

Using genomic profiling data we can further investigate specific genes of interest on a cancer type by type basis. For NHL DLBCL models this covers mutations in MYD88 and CD79B, as well as other relevant genes in ABC and GCB development (**Table 2**). All supporting information is found within [HuBase](#), where any other genes can be searched for further mutational status information.

**Table 2: A Range of Disease Relevant Mutations and Translocations Found in the NHL DLBCL PDX Panel**

HuPrime ID	Subtype	MYD88	CD79A	CD79B	EZH2	CARD11	TNFAIP3 (A20)	PTEN	Translocations
LY0257	ABC	L273P	WT	WT	WT	WT	WT	WT	BCL-6
LY2214	GCB	WT	WT	WT	WT	WT	WT	WT	MYC
LY2264	ABC	L273P	WT	E192A Y197S	D185H	WT	WT	WT	NA
LY2266	ABC/GCB	WT	WT	WT	WT	F596V (low quality)	WT	WT	NA
LY2298	ABC	L273P	WT	Y197N	WT	F596V (low quality)	WT	WT	NA
LY2318	GCB	WT	WT	WT	WT	WT	WT	WT	NA
LY2345	ABC/GCB	WT	WT	WT	D185H	A687V	F127C I194T	WT	NA
LY3604	ABC	WT	WT	WT	WT	WT	WT	WT	NA



# DLBCL PDX Panel Factsheet

## Ibrutinib Resistance Observed for Many Models with Both WT and Mutated CD79B and MYD88

Ibrutinib is in late stage clinical trials for DLBCL treatment, having previously been approved to treat CLL, mantle cell lymphoma, and Waldenström macroglobulinemia (a NHL subtype)<sup>(4)</sup>. We have benchmarked our models with ibrutinib, with the majority of models proving to be resistant to treatment. This demonstrates the need for combination therapy evaluation in DLBCL, to simultaneously target the multiple mutated signaling pathways active within a single tumor.

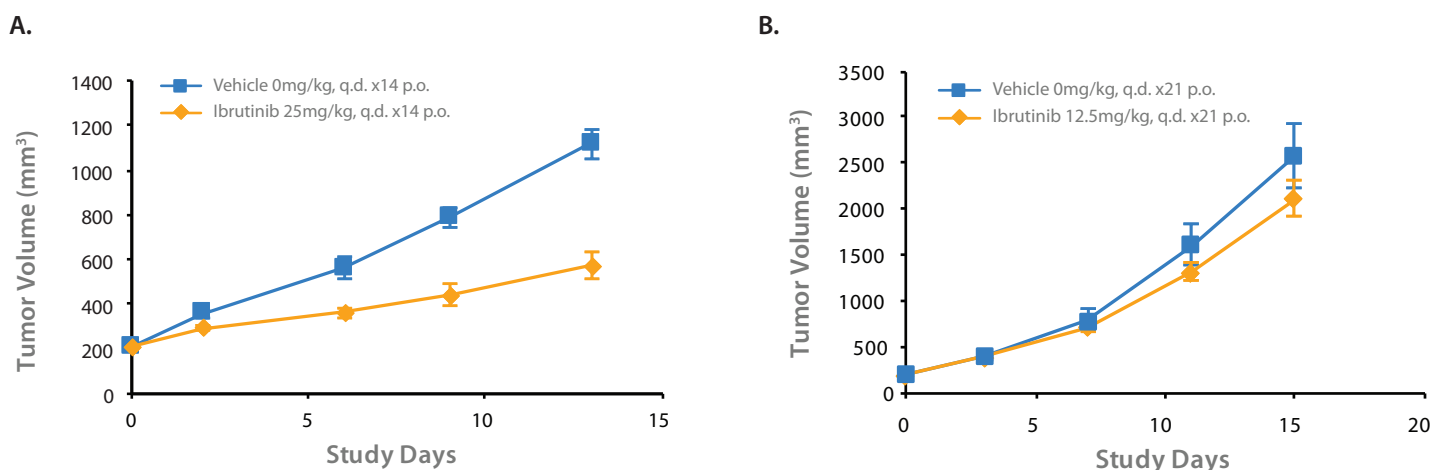
**Table 3** compares response to ibrutinib with subtype and MYD88 and CD79B mutations. Resistance occurs for ABC and GCB subtype models carrying both wild type and mutated genes. **Figure 1** displays representative response and resistance *in vivo* data.

**Table 3: NHL DLBCL PDX Panel Broadly Resistant to Ibrutinib Treatment**

HuPrime ID	Subtype	MYD88	CD79B	Ibrutinib Response
LY0257	ABC	L273P	WT	Resistant
LY2214	GCB	WT	WT	Resistant
LY2264	ABC	L273P	E192A/Y197S	Partial response
LY2266	ABC/GCB	WT	WT	Resistant
LY2298	ABC	L273P	Y197N	Resistant
LY2318	GCB	WT	WT	Ongoing
LY2345	ABC/GCB	WT	WT	Resistant
LY3604	ABC	WT	WT	Resistant

**Figure 1: NHL DLBCL PDX Models Partially Responsive and Resistant to Ibrutinib**

A: LY2264 MYD88 L273P and CD79B E192A, Y197S. B: LY0257 MYD88 L273P and CD79B WT.



Standard of care treatment data for our models is available within [HuBase](#), with models with varying degrees of sensitivity to the individual components of R-CHOP, as well as radiotherapy treatment.



# DLBCL PDX Panel Factsheet

## Summary

CrownBio has developed a panel of DLBCL PDX models, which offer well-characterized, highly predictive xenografts for preclinical single agent and combination therapy evaluation.

As next generation NHL treatments may provide a personalized medicine approach based on disease subtype and background, our models have been fully profiled for the main gene mutations and translocations associated with DLBCL development including MYD88 and CD79B. The CrownBio DLBCL PDX panel covers both ABC and GCB subtypes and a variety of wild type and mutated phenotypes, providing a comprehensive collection to evaluate novel combination strategies.

The DLBCL PDX panel has been benchmarked with ibrutinib treatment, allowing comparison and selection of models based upon response versus genetic profile. Standard of care treatment data is also available for a variety of our models, as required to fit research needs.

## References

<sup>1</sup>Wilson WH, Young RM, Schmitz R *et al.* Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nature Medicine* 2015;21: 922-926.

<sup>2</sup>Zhang SQ, Smith SM, Zhang SY *et al.* Mechanisms of ibrutinib resistance in chronic lymphocytic leukaemia and non-Hodgkin lymphoma. *British Journal of Haematology* 2015;170(4): 445-456.

<sup>3</sup>Hidalgo M, Amant F, Biankin AV *et al.* Patient-derived xenograft models: an emerging platform for translational cancer research. *Cancer Discovery* 2014;4: 998-1013.

<sup>4</sup>NIH National Cancer Institute website. A to Z list of Cancer Drugs Ibrutinib <https://www.cancer.gov/about-cancer/treatment/drugs/ibrutinib> Accessed 01 November 2016.



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### Explore Scientific Data

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