# Abner Louissaint, Jr., MD, PhD

## Louissaint Laboratory

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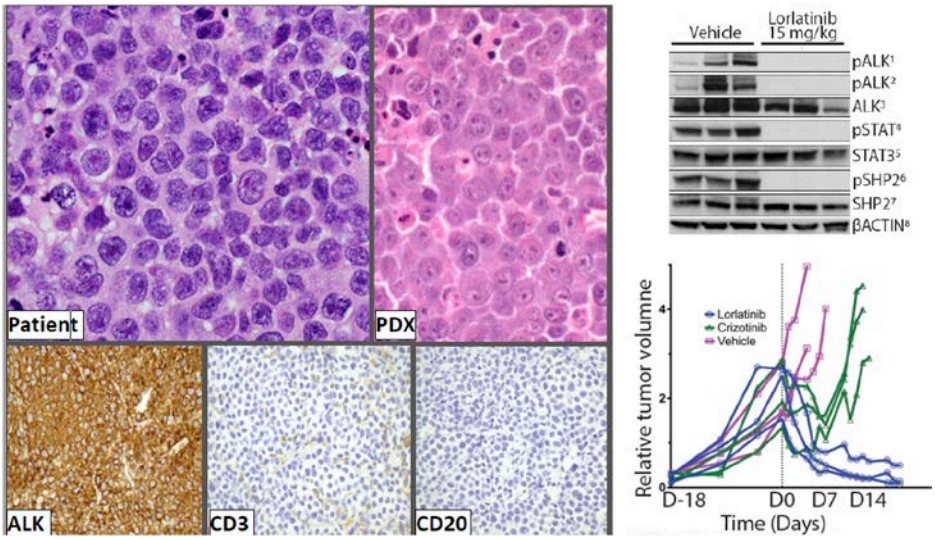
**The Louissaint laboratory** is interested in understanding how intrinsic genetic alterations and interactions of the lymphoma microenvironment drive lymphoma biology and determine the distinctive clinical behaviors of different lymphoma types. As part of our efforts, we aim to identify biomarkers of prognosis and responsiveness to therapy and to discover potential novel therapeutic targets that may be translated into improved outcomes for lymphoma patients. Traditionally, such investigation has been limited by the paucity of *in-vitro* and *in-vivo* models that faithfully capture the genetic and functional heterogeneity of human lymphomas. To overcome this challenge, our laboratory creates novel in-vivo patient-derived xenograft models and in-vitro primary cell models of lymphoma to investigate the role of genetic alterations, intratumoral heterogeneity, and microenvironment in lymphoma pathogenesis and to test the efficacy of specific therapeutic agents.

### Defining novel therapeutic vulnerabilities in aggressive subtypes of large B-cell lymphoma

There are several aggressive lymphoma subtypes of B-cell lineage for which effective therapies do not exist and for which clinical trials sometimes cannot be performed due to the rarity of the diseases and the rapidity with which patients succumb to disease. Some of these lymphomas characterized by plasmablast phenotype do not respond well to standard B-cell chemotherapies and have particularly poor prognosis. One example, anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma (ALK-LBCL), is characterized by the abnormal expression of alkaline phosphatase protein (ALK), resulting from the production of an abnormal fusion gene of CLTC with ALK. Patients who acquire this lymphoma are typically young and have a dismal prognosis — often dying within two years of diagnosis after failed attempts with standard chemotherapy regimens and preliminary efforts with first generation ALK inhibitors.

We recently created the first patient-derived xenograft (PDX) models of ALK-LBCL that recapitulates the phenotypes and molecular features of the patient lymphomas. Using these xenograft models, we showed that next-generation ALK inhibitors (ALKi) (alectinib and lorlatinib) are active in ALK-LBCL, while the first generation crizotinib inhibitors are not. In collaboration with clinical colleagues, we translated these findings to patients in a multi-institutional study in which advanced stage, chemotherapy refractory ALK-LBCL patients were treated with alectinib followed by allogeneic transplantation, resulting in the first long-term remissions reported in this disease. We have recently developed primary *in-vitro* models of ALK+ LBCL that we are currently using in functional studies to further understand the pathobiological mechanisms driven by ALK fusions in this disease and to identify novel downstream vulnerabilities to complement ALKi therapies, as well as to define the unique mechanisms underlying ALK inhibitor resistance in this disease. We are also actively working on other similarly aggressive molecular subtypes of plasmablastic-type lymphomas and poor-prognosis molecular subtypes of diffuse large B-cell lymphoma using *in-vivo* and *in-vitro* models created in our laboratory.




*Efficacy of ALK inhibitors (ALKi) in patient derived xenograph (PDX) models of ALK+ Large B-cell lymphoma. The image on the left shows the histology and immunophenotype of the PDX. The Western (upper right) show activity of ALKi (Lorlatinib) on ALK phosphorylation and signaling in the PDX tumor. The figure (lower right) shows efficacy of third-generation ALKi Lorlatinib on PDX ALK+ LBCL tumor (in contrast to transient partial response to first-generation ALKi Crizotinib).*

## Unraveling the role of the tumor microenvironment in follicular lymphoma

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma, accounting for approximately one quarter of new cases worldwide. As the quintessential indolent B-cell lymphoma, FL is an incurable disease characterized by multiple relapses and frequent transformation (t-FL) to more aggressive lymphomas. Approximately 20% of patients requiring chemotherapy at diagnosis show early progression, usually associated with poor outcomes.

FL, like other indolent B-cell lymphomas, is comprised of heterogeneous population of malignant B cells within a prominent tumor microenvironment including various T cell populations, follicular dendritic cell and other stromal cell populations and some myeloid populations. Interactions between these malignant B cells and elements of tumor microenvironment are critical for FL to thrive. We aim to understand the role of these interactions in lymphoma pathogenesis, and in driving early progression of disease, with the goal of possibly targeting these mechanisms therapeutically.

A major impediment to answering these questions has been the lack of *in-vivo* and *in-vitro* models of human disease that can recapitulate the complexity of genetic alterations and cellular interactions between FL clones and microenvironment that define these lymphomas. We are creating patient-derived xenograft models and *in-vitro* primary models of follicular lymphoma for the purpose of studying these critical cellular interactions within the tumor microenvironment. To unravel and dissect these critical interactions, we are applying single cell sequencing technologies, together with powerful new single cell resolution multi-modal spatial genomics technologies in collaboration with colleagues Vignesh Shanmugam, Fei Chen and Todd Golub. These efforts will accelerate our understanding of the interplay of genetic alterations and microenvironment in driving the biology of indolent lymphomas and drive the discovery of novel targets of these diseases.

## Selected Publications:


Soumerai J, Rosenthal A, Harkins S, Duffy D, Mecca C, Wang Y, Grewal R, El-Jawahri A, Liu H, Menard C, Dogan A, Yang L, Rimza L, Bantilan K, Martin H, Lei M, Mohr S, Kurilovich A, Kudryshova O, Postovalova E, Nardi V, Abramson A, Chiarle R, Zelenetz A, **Louissaint A Jr**. Next-generation ALK inhibitors are highly active in ALK-positive large B-cell lymphoma. *Blood*. 2022 140(16):1822-1826.

Zhou XA, Yang J, Ringbloom KG, Martinez-Escala ME, Stevenson KE, Wenzel AT, Fantini D, Martin HK, Moy AP, Morgan EA, Harkins S, Paxton CN, Hong B, Andersen EF, Guitart J, Weinstock DM, Cerroni L, Choi J, **Louissaint A Jr**. Genomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features. *Blood Advances*. 2021 5(3):649-661.

Crotty R, Hu K, Stevenson K, Pontius MY, Sohani A, Ryan R, Rueckert E, Brauer H, Hudson B, Berlin A, Rodenbaugh M, Licon A, Haimes J, Iafrate AJ, Nardi V, **Louissaint A Jr.*** Simultaneous Identification of Cell of Origin, Translocations, and Hotspot Mutations in Dif-fuse Large B-Cell Lymphoma Using a Single RNA-Sequencing Assay. *Am J Clin Pathol.* 2021 155(5): 748-754.

Hellmuth J*, **Louissaint A Jr.**, A*,Szczepanowski M, Haebe S, Pastore A, Staiger A, Hartmann S, Kridel R, Ducar M, Poch P, Dreyling M, Hansman M, Ott G, Rosenwald A, Gascoyne R, Weinstock D, Hiddemann W, Klapper W, Weiget O. Duodenal-type Follicular Lymphoma is Distinct by an Inflammatory Microoenvironment Rather than its Mutational Profile. *Blood.* 2018 132 (16): 1695-1702.

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*Equal contribution