Assistant Professor Ivana Bozic's research on chronic lymphocytic leukemia published in Nature

Submitted by Tony I Garcia on May 29, 2019 - 12:30pm

Originally featured in UW News, article can be found here.

In patients with chronic lymphocytic leukemia (CLL), the rate of disease growth varies widely. In a new study from the Dana-Farber Cancer Institute, the Broad Institute of MIT and Harvard, Massachusetts General Hospital and the University of Washington, scientists report that CLL growth is apt to follow one of three trajectories: relentlessly upward, steadily level or something in between. The particular course the disease takes is tightly linked to the genetic makeup of the cancer cells, particularly the number of growth-spurring “driver” mutations they contain.

The study, published online May 29 in the journal Nature, contains a further insight: Genetic changes that occur very early in CLL development exert a powerful influence on the growth pattern the CLL cells will ultimately take. This raises the possibility that physicians may one day be able to predict the course of the disease by its molecular features at the time of diagnosis.

“Our findings provide a framework not only for understanding the differing patterns of CLL growth in patients but also for exploring the basic biological mechanisms that underlie these differences,” said Dr. Catherine J. Wu of Dana-Farber, the Broad Institute and Brigham and Women’s Hospital, who is co-corresponding author with Gad Getz of the Broad Institute and Massachusetts General Hospital. “Ultimately, we'd like to be able to tie the genotype of the disease — the particular genetic abnormalities in a patient's cancer cells — to its phenotype, or how the cancer actually behaves.”

CLL is a useful model for studying the pace of cancer growth because it progresses at widely different rates from one patient to another, said Wu. In many patients, it persists at a low level for many years before advancing to the point where treatment is necessary. In others, it progresses so rapidly that treatment is required shortly after diagnosis.

To see if there were different patterns of CLL growth among patients, researchers drew on data from 107 patients diagnosed with the
disease. Beginning at diagnosis, each patient underwent periodic blood tests to track disease progress over the succeeding months and years, and continued until the disease reached a stage where treatment would begin. Each test consisted of a white blood cell count, which served as a proxy measure of CLL: the greater the number of white cells within a blood sample, the greater the burden of the disease. The tests were conducted over a period ranging from two years in one patient to 19 years in another.

The serial testing allowed researchers to calculate growth rates over time for CLL in each patient. They used a statistical model to determine if the rates were consistent with various patterns of cancer growth.

“We found that some cases of CLL show exponential growth, in which it expands without any apparent limit, while other cases show ‘logistic’ growth, in which it plateaus at a fairly consistent level,” said co-lead author Ivana Bozic, a UW assistant professor of applied mathematics.

Cases that didn’t fit either category were classified as indeterminate.

To explore whether genetic differences were at the root of these divergent growth patterns, the researchers performed whole-exome sequencing on several CLL samples collected from each patient prior to receiving therapy. Whole-exome sequencing provides a letter-by-letter readout of the regions of DNA that encode for cellular proteins.

They found that exponentially growing CLL typically carried a large number of driver mutations — those that confer a competitive advantage in growth — and quickly reached the stage where treatment was called for. In contrast, logistically growing CLL had fewer genetic alterations and fewer types of alterations and progressed relatively slowly toward the level that requires treatment. Seventy-five percent of patients with exponential growth eventually warranted treatment; by comparison, 21% of those with logistic growth and 67% of those with indeterminate growth eventually required treatment.

By analyzing patients’ serial blood samples collected over a period of time, researchers found that exponential CLL not only grows faster but also evolves faster, spinning off new subtypes of cancer cells, each with a particular set of genetic abnormalities. Whole-exome sequencing revealed that exponential CLL is marked by a great variety of tumor cell types and subtypes, while logistic CLL is marked by a relatively less diverse collection of tumor cells.

The information from whole-exome sequencing further enabled researchers to discover the growth rates of those subpopulations of cells within each patient’s leukemia that could be identified on the basis of a subset of mutations, some of them putative driver mutations. These measurements clearly revealed that many of the mutations, which were suspected to be centrally involved in CLL growth, did in fact provide subpopulations with preferential growth acceleration compared to populations lacking these putative drivers. Their results further indicate that the eventual course of CLL growth is inscribed in the genes of tumor cells early in the disease’s development.

“If the course of the disease isn’t altered by therapeutic treatment, the rate and pattern of CLL growth over time seems to ‘play out’ according to a predetermined set of genetic instructions,” said Wu.

“The discovery that CLL growth accelerates in the presence of large numbers of driver mutations is compelling evidence that these mutations do, in fact, confer a growth advantage to cells — that they truly do ‘drive’ the disease,” said co-lead author Dr. Michaela Gruber of Dana-Farber, the Broad Institute and the Medical University of Vienna.

Bozic and co-lead authors Ignaty Leshchiner and Dimitri Livitz at the Broad Institute developed methods to jointly model possible phylogenetic relationships of cancer cell subpopulations — which are a description of each subpopulation's history and relationships.
to each other during the evolution of the cancer — as well as integrate growth rates with subclone-specific genetic information.

“Combining clinical data with computational and mathematical modeling, we show that the growth of many CLLs seems to follow specific mathematical equations — exponential and logistic — each associated with distinct underlying genetics and clinical outcomes,” said Bozic. “Integrating tumor burden and whole-exome sequencing data allowed us to quantify the growth rates of different tumor subpopulations in individual CLLs, methodology that could potentially inform personalized therapy in the future.”

Co-authors of the study are: Kristen Stevenson, Oriol Olive, Reaha Goyetche, Stacey M. Fernandes, Jing Sun, Wandi Zhang and Donna Neuberg of Dana-Farber; Dr. Jennifer R. Brown of Dana-Farber and Brigham and Women’s Hospital; Laura Rassenti and Dr. Thomas J. Kipps of the Moores Cancer Center at the University of California, San Diego; Daniel Rosebrock, Amaro Taylor-Weiner, Chip Stewart, Alicia Wong and Carrie Cibulskis of the Broad Institute; Johannes G. Reiter, Jeffrey M. Gerold and Martin A. Nowak of Harvard University; Dr. John G. Gribben of the Barts Cancer Institute at the University of London; Dr. Kanti R. Rai of Hofstra North Shore-LIJ School of Medicine; and Michael J. Keating of the MD Anderson Cancer Center.

The study funded by the National Cancer Institute; the CLL Global Research Foundation; the National Heart, Lung, and Blood Institute; the European Union; and the Leukemia and Lymphoma Society.

###

For more information, contact Bozic at ibozic@uw.edu.

Grant numbers: SP01CA081534-14, 1R01CA155010-01A1, P01CA206978, U10CA180861, 1RO1HL103532-0, PIOF-2013-624924

Adapted from a release by the Dana-Farber Cancer Institute.

---

People Involved: **Ivana Bozic**

News Category:
- [Faculty and Staff](#)
- [In the Press](#)
- [Research](#)

Department of Applied Mathematics
University of Washington
Lewis Hall 201
Box 353925
Seattle, WA 98195-3925

Phone: (206) 543-5493
Fax: (206) 685-1440
[info@amath.washington.edu](mailto:info@amath.washington.edu)

**Source URL:** https://amath.washington.edu/news/2019/05/29/assistant-professor-ivana-bozics-research-chronic-lymphocytic-leukemia-published