Researchers look to mathematics, nature, to understand the immune system and its role in cancer

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These circular diagrams represent the T cell repertoire of two donors. In the first diagram, only the J segment is displayed, with obvious similarities. The fractal order is observed even as the donors' V and D segments are added. Credit: VCU Massey Cancer Center

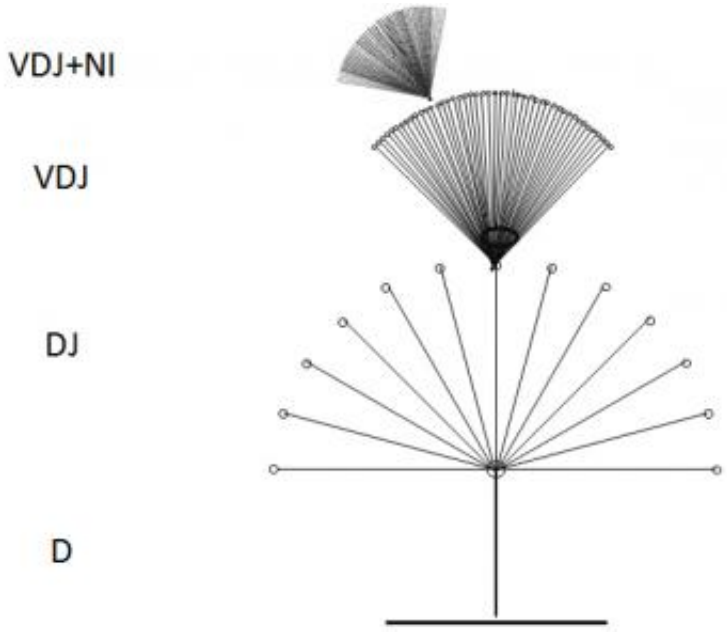
Can the patterns in tree branches or the meandering bends in a river provide clues that could lead to better cancer therapies? According to a

new study from Virginia Commonwealth University Massey Cancer Center, these self-similar, repeating patterns in nature known as fractals help scientists better understand how the immune system is organized and may one day be used to help improve stem cell transplant outcomes in leukemia patients by predicting the probability of transplant complications.

Recently published in the journal *Biology of Blood and Marrow Transplantation*, the study led by Amir Toor, M.D., found a fractal pattern in the T cell repertoire of 10 unrelated stem cell transplant donors and recipients. T cells are a family of immune system cells that keep the body healthy by identifying and launching attacks against pathogens such as bacteria, viruses or cancer. T cells have small receptors that recognize antigens, which are proteins on the surface of foreign cells. Once T cells encounter a foreign cell, the antigen fits into the T cell's receptor like a key in a lock and the T cell's deadly arsenal is unleashed on the threat. Once activated, T cells divide into many clones with receptors designed to recognize and guard against that specific pathogen. Over the course of a person's life, he will develop millions of these clonal families, which make up his T cell repertoire and protect him against the many threats that exist in his unique environment.

"The technological advancements of high throughput sequencing have only recently allowed scientists to sequence the genetic material responsible for T cell repertoire. At first glance, the data looks like a chaotic jumble of information," says Toor, a hematologist in the Bone Marrow Transplant Program and researcher in the Developmental Therapeutics program at VCU Massey Cancer Center. "However, if you study a person's T cell repertoire by analyzing the DNA segments responsible for the various types of T cell receptors, you begin to notice a fractal pattern based on segment usage." Toor and his team are hopeful that this information will give them clues that will help them better understand the recovery of immune function following stem cell

transplantation and possibly predict complications such as graft-versus-host disease in transplant recipients.



This model depicts the fractal branching pattern of the D, J and V segments that make up a person's T cell receptors. Credit: VCU Massey Cancer Center

Much like a child can assemble Lego blocks to create a range of different models, humans have evolved a highly efficient process by which a short span of the genome called the T cell receptor locus rearranges gene fragments to create a multitude of different T cell receptor families. In this process, DNA segments known as variable (V), diversity (D) and joining (J) segments are rearranged to create the millions of T cell receptor families, or clones, that the body uses to combat disease. Similar to how the branching pattern of a tree is faithfully replicated from the trunk all the way to its farthest branches, T cells have families that are created from DNA segments branching out

from one another to form a shield that provides protection from diseases.

Toor's team looked at the frequency of T cell clones bearing different V, D and J segments in stem cell transplant donors and recipients following stem cell transplantation. Using a circular diagram designed by researcher Jeremy Meier, B.S., to better visualize the arrangement of the different DNA segments, the team observed a similar fractal order in the T cell receptor families of the donors. This order was even apparent in donors of different ethnicities living on different continents. In patients who had received a stem cell transplant, Toor found that this pattern was disrupted and the patients displayed a lower level of complexity in their T cell receptor repertoire at three months after transplant, followed by a modest improvement when a full year had elapsed after transplantation.

"Attempting to restore the fractal order of a patient's T cell receptor repertoire by optimizing the stem cell transplant process could serve as a valuable therapeutic target," says Toor. "Additionally, our findings lend an insight into nature, such that even in complex biological systems bereft of physical form, mathematically determined organization is observed."

Toor and his colleagues plan to continue using high throughput sequencing of patients' T cell receptors to learn more about how the immune system recovers following stem cell transplantation. The team hopes this will give them valuable information about the effectiveness of future stem cell transplant and immunotherapy clinical trials developed in their clinic.

More information: www.sciencedirect.com/science/ … ii/S1083879112011408