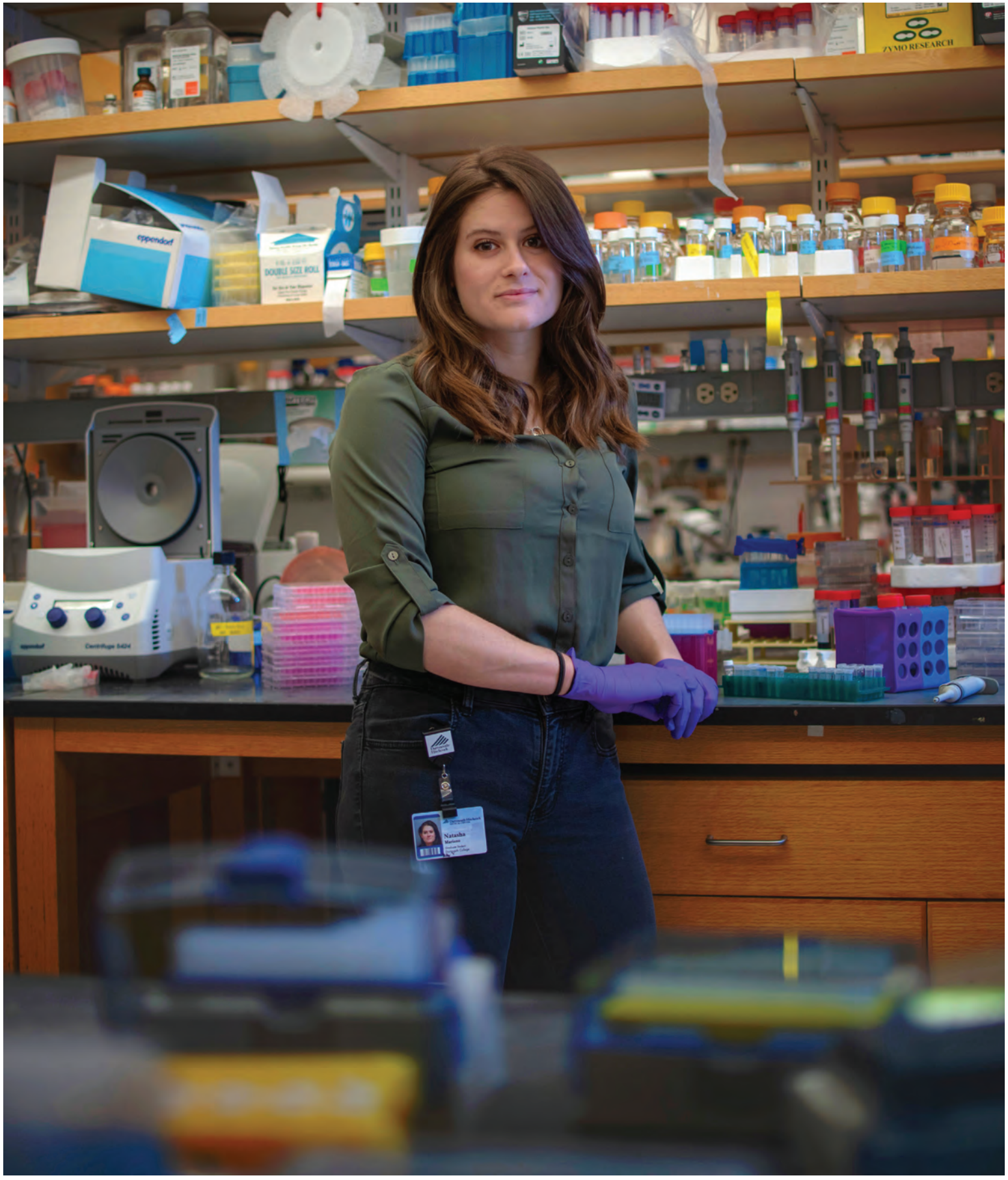
Kata Sasvari



CANCER DETECTIVE

NATASHA MARIANO, GUARINI '22, IS LOOKING FOR CLUES TO SOLVE THE MYSTERY BEHIND TRIPLE-NEGATIVE BREAST CANCER (TNBC). In this case, the clues are relative protein abundances quantified from 50 TNBC tumor specimens that revealed promising therapeutic targets specific to subtypes found within the general TNBC population.

Clinically, breast cancer type is categorized by the positive or negative staining of three proteins: estrogen receptor, progesterone receptor, and the human epidermal growth factor receptor 2, which act as the primary drivers of growth and progression for the tumors that express them. Doctors use the amount of each biomarker present within a tumor to inform treatment decisions, which consist of targeted therapies that are effective and well tolerated by patients.

But nearly 20 percent of breast cancers stain negative for all three biomarkers and, by default, are classified as triple-negative. TNBC is characterized by severe heterogeneity, making the identification of any targeted therapy very difficult, limiting treatment options to nonspecific cytotoxic chemotherapy. In turn, this makes TNBC an aggressive disease with a "last resort" therapy option—often resulting in a poor prognosis.

Mariano believes the ultimate goal for patient care and disease management is to move toward personalized medicine, which aims to tailor all clinical decisions made in response to knowledge and understanding of an individual patient's disease and biological variability, and away from the one-size-fits-all approach.

"My goal is to predict the most promising therapeutic strategy for a patient based on the proteomic profile of their tumors," she says. "It is a clinical imperative to identify drug targets and treatment strategies for the distinct subsets of TNBC patients most likely to benefit from them."

As a PhD candidate in the Molecular and Cellular Biology Program, she works in the lab of Arminja Kettenbach, PhD, an associate professor of biochemistry and cell biology at Geisel, one of the few Dartmouth labs that run and maintain their own mass spectrometer—an instrument capable of detecting all proteins present in a sample. Mariano and Kettenbach successfully quantified the relative expression of thousands of proteins within each tumor, creating unique protein signatures for each one.

Mariano also investigates the molecular mechanisms and underpinnings of basic cell biology, which helps to gain insight and understanding into the origins of disease.

"We in the lab, along with our collaborators, cover the spectrum of scientific research," she says. "Many seemingly unrelated diseases are the consequence of similar driving events, which means the broad application of our findings has the potential to change many lives."

Aligned with the lab's focus to study how a specific class of phosphatases regulates major biological processes through the phosphorylation state of the proteins present in a living system, Mariano received a National Science Foundation Graduate Research Fellowship to uncover previously unrecognized roles of phosphoprotein phosphatase 6 (PP6) in the context of the DNA damage response pathway—a signaling network activated when a cell senses impairment to its DNA.

The fellowship is awarded to promising early-career graduate students based on their demonstrated potential for significant research achievements in science, technology, engineering, or mathematics (STEM).

Communicating the beauty and importance of scientific research to a wider audience is important to Mariano. "I believe that all people can, and should, be inspired by scientific exploration and discovery," she says. "Yet we are failing to properly inform the general public of the impact and overall benefit that it has on our quality of life." Future plans for Mariano include engaging the public and advocating support for science through advising lawmakers on scientific literacy initiatives and healthcare policy.

She is equally enthusiastic about outreach and education. "In every stage of my scientific career, the mentoring I received has proven instrumental to my success," she says. To that end, she co-organized the 2018 Science Olympiad at Dartmouth, which welcomed over 250 dedicated high school students from around New England to compete in a tournament of events rooted within the STEM fields.

"I love what I do—every day I design and execute experiments to help answer crucial biological or medical questions," she says. "While analyzing the TNBC proteomic results, I spent weeks mapping all of the hits to their known pathways—connecting the dots until a clear picture emerged. I felt rather like a cancer detective, piecing together the clues I was given to ultimately solve the puzzle of each patient's tumor profile. It was incredible.

"Honestly, I couldn't ask for a better job."

SUSAN GREEN

"My goal is to predict the most promising therapeutic strategy for a patient based on the proteomic profile of their tumors."