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Tailored organoid may help unravel immune response mystery

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What if you could design an adaptable, biomaterials-based model of an organ to track its immune response to any number of maladies, including cancer, transplant rejection and the Zika virus?

The lab of Ankur Singh, assistant professor in the Sibley School of Mechanical and Aerospace Engineering, has asked – and begun to answer – that very question.

Singh and a team of researchers from the Meinig School of Biomedical Engineering and Weill Cornell Medicine have developed a modular immune organoid that can replicate the anatomical structures found within lymph nodes. The organoid mimics the early stages of a germinal center, where B cell differentiation and initiation of immunological responses take place during infection.

By manipulating the components of the organoid, the researchers are able to dictate the action of the immune-cell response and demonstrate, for the first time in a controlled manner, the role of the lymph node's environment in immune cell activation. And as opposed to two-dimensional models, the 3-D organoid enables much quicker and more plentiful replication of B cells, which are antibody-producing lymphocytes.

"This method presents the first lab-made 3-D immune tissue that allows you to change things found in immune organs once you get infected – the altered extracellular matrix, cell-cell interactions – and control the

pace at which immune cell respond," Singh said.

Their paper, "Modular immune organoids with integrin ligand specificity differentially regulate ex vivo B cell activation," was published Dec. 13 in the American Chemical Society journal *Biomaterials Science & Engineering*.

Co-lead authors were doctoral students Alberto Purwada and Shivem B. Shah of the Meinig School. Also contributing were Dr. Ari Melnick, the Gebroe Family Professor of Hematology/Oncology at Weill Cornell Medicine, and Wendy Beguelin, an instructor in the Melnick Lab.

A related paper, "Immuno-engineered organoids for regulating the kinetics of B-cell development and antibody production," was published Dec. 22 in *Nature Protocols*, a journal geared to bench researchers. Singh and Purwada authored that work.

Germinal centers (GCs) are dynamic structures within lymphoid tissues that develop once B cells receive activation signals from surrounding immune cells in the presence of infection. During the GC process, naïve B cells (unexposed to antigens) differentiate into a specific immune marker (GL7) and then rearrange into high-affinity B cell receptors, but the underlying mechanisms of this progression aren't understood.

Gaining a full understanding of those mechanisms, through the use of a "plug-and-play" system like the organoid that can be tailored to a specific disease, could provide better understanding of B cell biology and responses to a wide range of maladies, including cancer, asthma, arthritis and transplant rejection, along with faster responses to emerging infections such as H1N1 and Zika.

"Up to now, we have not been able to study the earliest steps of malignant transformation of cells in the immune system," said Melnick,

who is also a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. "Now we can design experiments that will give us unprecedented understanding of how these tumors form, which will in turn provide critical insights into how to treat these diseases."

Singh says the organoid – in either a synthetic polyethylene glycol or semi-synthetic gelatin-based platform – offers a quick and robust method for mimicking the GC microenvironment. That eliminates the need to implant the model inside a living creature.

"It's living tissue that allows you to model certain parameters that you cannot do in vivo," said Singh, who last week was selected to receive the top young investigator award from the Society for Biomaterials.

Singh said his group published its findings in *Nature Protocols* because they want the greater scientific community to know about it.

"Our goal was to make this technology available to scientists who can use this to understand immunology in a much better way," he said. "I have a role and responsibility in advancing the science by putting this forward."

More work in this area is ongoing, said Singh, who earlier this year was one of five Cornell recipients of a National Science Foundation CAREER award, which helped support this work. But he noted that the ability to drive immune reactions through the use of organoids will "grant us the ability to reproduce immunological events … for more rapid development and better understanding of B cells."

More information: Alberto Purwada et al. Modular Immune Organoids with Integrin Ligand Specificity Differentially Regulate Ex Vivo B Cell Activation, *ACS Biomaterials Science & Engineering* (2017). DOI: 10.1021/acsbiomaterials.6b00474

Alberto Purwada et al. Immuno-engineered organoids for regulating the kinetics of B-cell development and antibody production, *Nature Protocols* (2016). DOI: 10.1038/nprot.2016.157