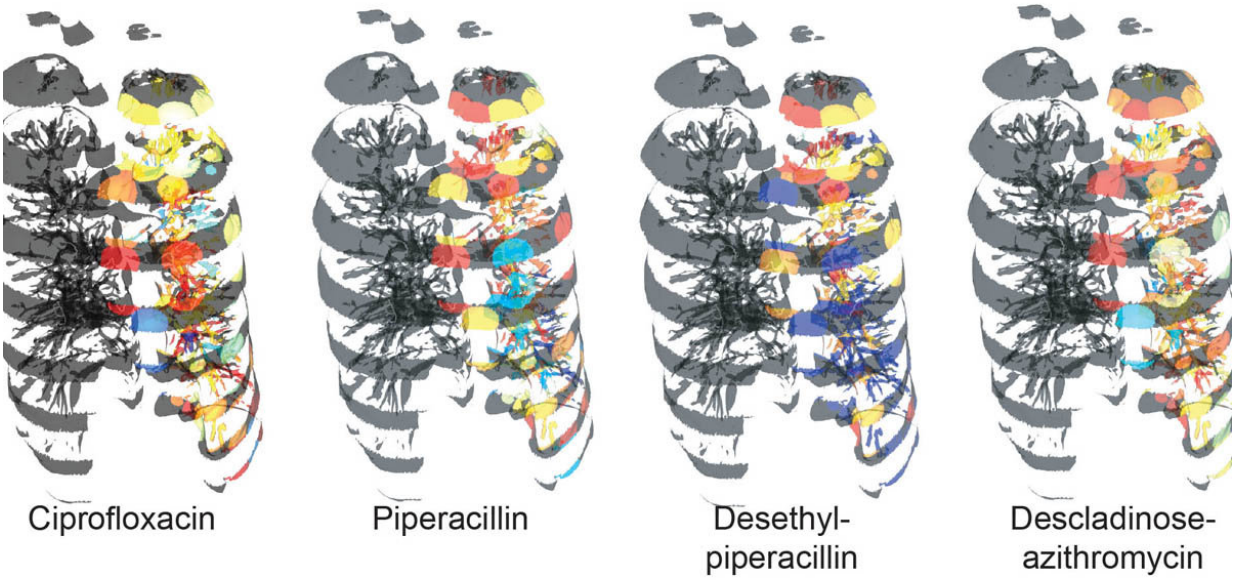
New 3-D visualization tool could enable targeted drug delivery for cystic fibrosis and other conditions

October 20 2017



The distributions of antibiotics and their breakdown products throughout the lung. Red represents the highest abundance and blue represents the lowest abundance. The mapping has been performed on the left lung. Credit: UC San Diego Health

University of California San Diego researchers have developed the first 3D spatial visualization tool for mapping "'omics" data onto whole organs. The tool helps researchers and clinicians understand the effects of chemicals, such as microbial metabolites and medications, on a diseased organ in the context of microbes that also inhabit the region. The work could advance targeted drug delivery for cystic fibrosis and other conditions where medications are unable to penetrate.

A team led by Pieter Dorrestein, PhD, professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences at University of California San Diego and a leadership team member in the UC San Diego Center for Microbiome Innovation, published the study October 19 in *Cell Host & Microbe*.

Every nook and cranny of a human organ has its own microbiome—the microorganisms and their genes that are present in a particular environment. The anatomy of the organ and its environment (temperature, pH level, nutrient availability, etc.) determine which microorganisms are present. In turn, the microorganisms respond to and affect the presence of therapeutics.

"Our understanding of the spatial variation of the chemical and microbial make-up of a human organ remains limited," said Dorrestein. "This is in part due to the size and variability of human organs, and the sheer amount of data we get from metabolomics and genomics studies."

To address this challenge, Dorrestein's team developed an open-source workflow for mapping metabolomics and microbiome data onto a 3D organ reconstruction built from radiological images.

First, the researchers obtained a lung from a patient afflicted with cystic fibrosis and sectioned it. They analyzed the samples for the presence of bacteria, their metabolites and virulence factors (molecules that add to

bacterial effectiveness and enable them to colonize a niche in the host), and any medications given to the patient during treatment.

Next, Neha Garg, PhD, a postdoctoral researcher in Dorrestein's lab at the time, and Mingxun Wang, a graduate student in the UC San Diego lab of Nuno Bandeira, PhD, modified an existing Google Chrome extension called "ili" to visualize microbiome and metabolome distributions on an entire organ.

"The application enables the user to map data onto a 2D or 3D surface, so we modified the code to allow us to map the abundance data not only onto surfaces, but also within the model," said Garg, who is now an assistant professor at Georgia Tech.

In order to visualize the spatial localization of the bacteria and molecules, the team procured CT scan images of a human lung and processed them to generate a 3D model.

With the "omics" data from the cystic fibrosis lung superimposed on the 3D lung in the modified version of "ili," the researchers were able to make important observations.

"We could see that one of the antibiotics administered to the patient prior to collecting the tissue did not penetrate the bottom of the lung—a phenomenon that has not been observed before," said Garg. "This correlated with a higher abundance of the cystic fibrosis-associated pathogen Achromobacter. Thus, different drugs may differentially penetrate the lung, limiting exposure to effective dosage. Our tool allows researchers and clinicians to visualize this significant clinical concern within a human organ for the first time. This has implications for treatment of CF and other diseases."

The researchers created open-source maps of 16,379 molecules and 56

microbes that will now serve as a resource for scientists researching cystic fibrosis and other lung-associated diseases.

"As future studies unravel more about the microbiome and metabolome, their spatial visualization will provide a means to infer their biological significance," said Dorrestein. "Furthermore, the methodology developed can be extended to any human organ—notably those with tumors, which are known to be associated with their own unique microbiomes."

The team hopes that the work will help enable improved targeted drug delivery, which could be used to rectify poor penetration of antibiotics.

More information: Neha Garg et al. Three-Dimensional Microbiome and Metabolome Cartography of a Diseased Human Lung, *Cell Host & Microbe* (2017). DOI: 10.1016/j.chom.2017.10.001

Provided by University of California - San Diego