Columbia U, Life Raft Use Pathway Approach to Find New Therapies for Resistant GI Tumors

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Premium

NEW YORK (GenomeWeb) – A recent partnership between Columbia University Medical Center, New York-Presbyterian Health System, and the Life Raft Group (LRG) aims to explore the value of a Columbia-developed systems biology approach to identify more effective treatment options for patients with advanced cases of gastrointestinal stromal tumors (GIST).

The approach uses software developed in the laboratory of Andrea Califano, a professor of chemical and systems biology at Columbia. Specifically, the researches will use the so-called Virtual Inference of Protein-activity by Enriched Regulon (VIPER) analysis software to study molecular networks of GIST patients whose tumors have become resistant to approved tyrosine kinase inhibitors. They hope to identify new therapeutic agents that target so-called master regulators or tumor checkpoints in GIST cells.

GISTs are a subtype of sarcomas, rare cancers that grow in connective tissues. According to Gary Schwartz, a sarcoma oncologist and chief of New York-Presbyterian/Columbia University Medical Center's division of hematology and oncology, there are currently 3,000 to 4,000 newly-diagnosed patients with GIST in the United States. Currently patients are treated with Novartis' Gleevec, (imatinib), an oral medication that targets the c-KIT gene which is responsible for tumor growth in 90 percent of GIST patients. The drug is used to treat patients with advanced forms of the cancer that have metastasized as well as to prevent cancer recurrence post-surgery.

However, some patients ultimately become resistant to the therapy due to the rise of new mutations in other exons of the C-KIT gene, Schwartz explained in an interview. Such patients move on to second- and third-line therapies — Pfizer's Sutent (sunitinib) and Bayer's Stivarga (regorafenib), respectively. However, the problem with those drugs is that "though responses can be seen, they are often not very durable and patients will progress on these therapies," he said. And once they progress, "there really aren't any other drugs available to treat this patient population."

The current study aims to address this dearth of drugs by looking at the system of interactions within the cancer cell rather than a single gene. That means analyzing not just DNA mutations but also RNA and protein data to identify points of convergence or "bottlenecks" between pathways in the cell. Existing research has shown that these convergence points can be targeted with approved drugs or drugs currently

in late-stage development. With VIPER's help, "we can drug that point and kill the cancer cell effectively and maybe even cure cancerin a way that has not been done before," Schwartz said.

Since GIST cases are few in number, Schwartz's team is partnering with the LRG, a patient advocacy group that represents patients with these tumors in the US and abroad. The group is active in over 50 countries worldwide. Other partners on the project include Fox Chase Cancer Center, Oregon Health & Science University, University of California, San Diego, University of Miami, Washington University, and Stanford University. By partnering with the LRG, the institutions will have access to enough samples for their study. "It's an unbelievable resource," Schwartz said. "It's an untapped mine of data" that has "never been utilized."

Under the terms of the agreement, CUMC researchers and their partners will store clinical and molecular data from study participants in the LRG's patient registry, a data-management tool developed by the patient advocacy organization to track GIST patients' histories. Since it was developed 16 years ago, "we have been gathering and updating medical histories for patients with GIST," LRG Executive Director Norman Scherzer said in an interview.

"What's unique about that is that most registries that are based in hospitals often remove the patients from their registry after they leave the hospital. But they go on to other treatments. The advantage of our registry is that we are able to track people over time." In addition, "we are often able to get information from patients that kind of escape mainstream medicine," Scherzer said. "For example, patients are much more likely to tell us that they are not taking their medication than they are to tell the doctor."

Each patient's history is linked to a companion record of tissue and mutational data from their tumors which are housed in a tissue bank established by LRG at Stanford. After surgery, GIST patients can have their tumor tissue shipped to the LRG where its tagged with a code and recorded in the registry. The tissue sample is then sent to a team at OHSU which does mutational testing on the sample and then sends copies of the results to the patient's physician and to the LRG. The physical tissue sample is then sent on to Stanford. All of the data is deidentified before its logged in the registry. In total, the LRG registry contains data from 1,800 patients. 30 percent of that data comes from patients outside the US.

Initially, the partners will use data from 100 patients from the LRG database to create roadmaps for identifying GIST master regulators, Schwartz said. They will then validate the roadmaps in a second cohort of around 90 consenting patients with metastatic GIST who have either failed first- or second-line therapies. In addition to medical history data, the researchers will sequence and analyze RNA from the patient samples. They plan to test the efficacy of about 100 approved drugs as well as drugs currently in early and late clinical development as part of the study, Schwartz said. They also plan to create multiple cellular maps that cover multiple GIST subtypes. "We'll then be able to take the patient's RNA and see what map they fit into," he said. "Every map will show us different bottlenecks and we'll pick the right drugs to test based on the bottlenecks."

VIPER's developers described the algorithm in a paper that was published last year in *Nature Genetics*. As explained in the paper, the software uses a probabilistic framework to infer protein activity in tumors from gene expression data. The paper also describes the developers' efforts to use VIPER to evaluate non-silent somatic mutations in just under 4,000 samples from the Cancer Genome Atlas dataset. Among other results, they found that 27 percent of non-synonymous mutations induced aberrant protein activity in the samples. They also found that many wildtype samples had aberrant protein activity comparable to and in some cases greater than samples with actionable mutations suggesting that these individuals could benefit from targeted therapies.

In addition to managing data, the LRG will act as the monitoring arm of the study, the partners said. Specifically, they'll use InterGR, a proprietary cloud-based research platform for sharing visualizing, and analyzing health data that builds and expands on the LRG's patient registry. According to its developers,

InterGR facilitates rapid export and pooling of de-identified clinical data from different academic institutions and offers statistical tools for performing collaborative research across institutions. It also features a patient tissue directory and duplicate tracker that analyzes incoming records to find commonalities in each set of data points and alert users of collaborative opportunities. The partners plan to use the tool to house the data collected by the investigators at the different academic institutions.

The partners see their collaboration as an example of the role that patient advocacy groups play in bridging the gaps between researchers and motivated patient populations who want to share their clinical histories and tissue for research studies that aim to improve patient outcomes. Recently, the Pancreatic Cancer Action Network launched Precision Promise, a large-scale clinical trial for pancreatic cancer patients starting this year that is being run in partnership with 12 academic institutions.

Both Schwartz and Scherzer believe that the current collaboration between LRG, CUMC, and their partners and their adopted methodology serves as a model for other academic medical institutions. "It's trying to do something truly innovative to a patient population that's in desperate need of therapies who've gone through all the conventional treatments," Schwartz said. "We're hopeful that this can really offer patients with GIST a whole new opportunity in drug therapy."

"In the last [several] years, you've heard more and more about the concept of personalized medicine and targeting treatments," Scherzer added. "We have built a whole framework around identifying and trying to deal with mutations and interrupt the signaling between these mutations within GIST mutations. This [study] takes it to another level and it's exciting." Furthermore, "if this system identifies an existing drug that works for a particular patient, the drug is available today," he added. "In most clinical trials we are looking for drugs that aren't even approved yet and years may pass by. It's all about shortening the time between identifying a treatment and getting that treatment to a patient."

But beyond GIST, Schwartz sees potential applications for the systems biology approach in the context of other cancer subtypes including triple negative breast cancers and tumors of the pancreas. "This new model is … the next step forward in drug therapy," he said. "If we can show [the approach] is successful in rare cancer, there's no reason it shouldn't work in larger cancers."

The partners are currently seeking additional funding to support their studies. They expect the study to run for up to five years and cost millions of dollars, Schwartz said. In addition to providing tissue, data, and infrastructure, the LRG has also provided some financial help, but the researchers are still applying for more funding. "We have actually submitted an application to the FDA Orphan Drug grant program and that's being reviewed now and we're going to submit a separate grant to the NCI," he said. "It's a five-year plan but if we have the funding, we can probably do it in three years."

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