# Metagenomics Consortium Wins €8.8M European Grant to Devise Next-Gen Screening Platform

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***Premium***

NEW YORK (GenomeWeb) – The European Commission has awarded a new consortium €8.8 million ($9.8 million) to develop a next-generation microfluidics-based platform for the functional screening of metagenomic libraries.

The aim of the group, dubbed Metafluidics, is to replace the "cumbersome" technologies currently used to study genetic material obtained from environmental samples with a new approach that is "cheaper, faster, and higher throughput," according to project participants.

Titled, "Advanced toolbox for rapid and cost-effective functional metagenomic screening — microbiology meets microfluidics," the Metafluidics grant commenced last month and will run through May 2021. Horizon 2020, the European Framework Programme for Research and Innovation, is funding the effort.

Aurelio Hidalgo, a molecular biologist at the Autonomous University of Madrid (UAM) and principal investigator of Metafluidics, told GenomeWeb that the group wants to make microfluidics the "new standard for screening fractional libraries for metagenomics."

The consortium aims to accomplish this by implementing functional screening of metagenomic libraries in microfluidic droplets, replacing conventional approaches that rely on *in vivo* assays, often calorimetric assays on petri dishes.

"With this we can increase the throughput by two to three orders of magnitude compared to what is out there," Hidalgo noted. "This will, of course, reduce the assay volume and therefore the cost by orders of magnitude compared to what is available."

In addition to UAM, a dozen other commercial and research entities are taking part in Metafluidics. These include Qiagen Bioinformatics in Aarhus, Denmark; Drop-Tech, a Cambridge, UK-based microfluidics technology company; Danish enzyme provider Novozymes; and Prozomix, a UK firm that specializes in genome- and metagenome-mining technologies.

Researchers at INSA Toulouse in France; the Spanish National Research Council (CSIS); the University of Cambridge; the University of Alicante in Spain; the University of Coimbra in Portugal; and the Norwegian University of Science and Technology are also taking part, as are two independent research companies: Bio-Iliberis R&D in Granada, Spain, and SINTEF in Trondheim, Norway.

"The functional screening of metagenomic libraries is either very expensive or cumbersome," said

Pepa Anton, an associate professor of microbiology at the University of Alicante and Metafluidics participant. "The combined used of metagenomics and microfluidics — cheaper, faster and with higher throughput — will enable an expansion of functional metagenomic analyses of different natural environments," she told GenomeWeb.

According to Hidalgo, using current methods, researchers can typically screen about 1,000 clones per plate, limiting their statistical power to about $10^6$. While larger companies and research institutes do have robotics that can improve upon current throughputs, "most small- to medium-sized enterprises do not enjoy such resources," Hidalgo said.

Using Metafluidics' envisioned microfluidics platform, assay throughput would increase from $10^6$ to $10^8$," Hidalgo said.

"Since the volume of a droplet is 20 picoliters, compared to microliters [used in conventional assays] the reduction of cost could be impressive," he speculated. "Microfluidics is definitely easier to implement in most laboratories and not the price of a high-throughput robotics platform," he added.

**'Central nodes'**

According to the Metafluidics grant abstract, the group imagines offering high-throughput screening in picoliter droplets that will lower the cost per assay to well below $0.01 cents.

The Metafluidics teams will also develop workflows that streamline and increase the yield of library construction and functional expression, as well as workflows for "efficient bioinformatic analysis" of discoveries based on user-friendly software solutions for metagenome analysis.

Potential application areas include identification of enzymes for biosynthesis of therapeutic small molecules, green bioenergy conversion, bioremediation, and food chemistry. All 13 participants are working on different aspects of the effort.

"There are two central nodes to this project: microfluidics and metagenomics," said Hidalgo. "Some partners develop microfluidics and others have expertise in metagenomics. Everybody is moving toward the interface."

Drop-Tech, a spin-out of the University of Cambridge, will be providing much of the microfluidics knowhow for Metafluidics. Liisa van Vliet, managing director of the six-year-old firm, told GenomeWeb that Drop-Tech will "highlight pathways to commercialization" for the metagenomics technologies that Metafluidics produces.

"We are particularly interested in high-throughput functional metagenomic screenings using microfluidic droplets and how the discovery of novel industrial biocatalysts from unknown genomic libraries can be commercialized," said van Vliet.

Drop-Tech has developed a droplets-on-demand sampler that allows the creation of microfluidic droplet sequences from up to 24 samples, van Vliet said. The company claims that its tool allows screening to be performed using "a million times less reagent" than competitive systems, and enables the detection of multiple markers on single cells. Drop-Tech has partnered with Dolomite Microfluidics to make its technology available as an instrument, the Mitos Dropix.

According to Hidalgo, each company participating in Metafluidics provides an output for commercializing technologies developed in the project. In addition to Drop-Tech's path to market, Hidalgo noted that Novozymes could potentially offer bulk enzymes developed via Metafluidics, just as Prozomix could sell any enzymes for biocatalysis it designs.

Qiagen is Metafluidics' main bioinformatics partner, though, and Hidalgo said that the consortium will use Qiagen's CLC Genomics Workbench and CLC Genomics Server software in the project. CLC Workbench includes tools for analyzing next-generation sequence data, including de novo assembly and mapping. The package also includes MetaGeneMark Plugin, which enables gene finding in bacterial genomes and metagenomes. Hilden, Germany-based Qiagen gained the tools through its acquisition of Aarhus, Denmark-based CLC Bio in 2013.

"They have this great tool for NGS assembly," said Hidalgo. "They will make it a little friendlier for metagenomics, to build modules that will be more user-friendly compared to what they have already," he said.

Michael Lappe, a senior bioinformatics scientist at Qiagen, said that the company will focus on developing an integrative, next-generation sequencing data analysis and visualization platform for metagenomic data as part of Metafluidics. At the first stage of the project, Lappe said that consortium members will be provided with a server for data exchange and analysis and that all partners will receive installations of CLC Genomics Workbench. Toward the end of the project, Qiagen will update its software based on its findings. "The bioinformatics tools developed in this project will contribute to Qiagen's competitiveness in this growing market," he said.

Lappe said that projects like Metafluidics are a "key innovation driver" for the company as they "allow us to explore new concepts to be turned into potential products." By interacting with its partners in Metafluidics, Qiagen will "gather feedback on the capabilities of current microbial analysis pipelines," Lappe said. The company will specifically focus on metagenome assembly, as well as developing multiple genome and metagenome alignment and visualization tools, he said. Qiagen will also work on gene finding and annotation, functional pathway annotation, taxonomic profiling, and search algorithms.

"We will gain valuable insight as to how we can best serve the research community with respect to current and future applications of NGS technologies in the metagenomics market," Lappe said.

**'Diverse objectives'**

While Metafluidics' commercial partners may be able to parlay their participation into new instruments, bioinformatics tools, and enzyme products, each of the consortium's academic members aims to develop or improve its own tool set when it comes to functional metagenomics.

Anton's lab at the University of Alicante, for instance, intends to use the tools offered in the project to explore viral communities from hypersaline environments, with the potential to apply any discoveries in aquaculture.

"The combined technologies of metagenomics and microfluidics will allow us to develop new tools to investigate virus-hosts interactions in nature in unprecedented ways," said Anton. "This would allow us, for example, to monitor the evolution of both host and virus at a single virus-host pair resolution or to follow the spreading of a virus within a microbial community," she said.

Eduardo González-Pastor's lab at the CSIC's Center of Astrobiology in Madrid, has a somewhat different objective: studying microorganisms that thrive in extreme environments that may be similar to conditions in outer space and other planets.

González-Pastor told GenomeWeb that his lab is particularly interested in the mechanisms by which these extremophile organisms adapt to different extreme conditions such as acid pH, toxic metals, ultraviolet radiation, and high salt concentration.

While the lab has traditionally relied on functional metagenomics as its main experimental approach, González-Pastor said that the method is hindered by the poor expression of proteins from extremophiles in the mesophile *Escherichia coli* used to screen the metagenomic libraries.

"Therefore, our research team will develop a novel set of tools to explore more efficiently the mechanisms involved in resistance to extreme conditions of these microorganisms," said González-Pastor. Specifically, the lab will develop new vectors and hosts for the construction of metagenomic libraries from extremophiles and their expression in microfluidic droplets, he said.

INSA Toulouse, meantime, hopes to use metagenomics to identify new enzymes that can be exploited in manufacturing processes, Gabrielle Potocki-Veronese, a research director at the French engineering university, told GenomeWeb.

According to Potocki-Veronese, the high-throughput screening strategies developed within Metafluidics will accelerate the rate at which new functions of carbohydrate metabolization can be discovered, a research interest at INSA Toulouse with potential industrial applications.

"Decrypting the molecular bases of catalysis of the best … targets will guide their integration into in vitro or in vivo synthetic platforms for bioconversion of renewable biomass into carbohydrate-based compounds for the food, health, chemical, energy, or environmental sectors," she said.

"Along with technology platform development, members of Metafluidics will in parallel develop expression vectors and systems as part of the project," Hidalgo commented. "Their aims are to increase the number of individuals that are expressed functionally in a metagenome library," he said. All this, according to Hidalgo, should be accomplished by the time the project ends in 2021.

"What we aspire to do in this project is to prove that the technology works and can be used with very diverse objectives," he said.

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