NEW HOT PAPERS - 2008

July 2008

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Philippe Horvath talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Microbiology. The author has also sent along images of their work.

Article Title: CRISPR provides acquired resistance against viruses in prokaryotes
Authors: Barrangou, R;Fremaux, C;Deveau, H;Richards, M;Boyaval, P;Moineau, S;Romero, DA;**Horvath , P**
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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

Our work provides the first biological evidence showing that CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), along with CRISPR-associated (*cas*) genes, functions as a new antiviral system in prokaryotes. Discovered fortuitously in 1987, and described as a widespread family of prokaryotic DNA repeats in 2002, CRISPRs have gained considerable interest in 2005-2006 when distinct publications hypothesized a role in cellular defense against invading DNA.

The popularity of CRISPR is undoubtedly linked to its putative mechanism of action, which is probably analogous to RNA interference (RNAi). Furthermore, in contrast to the eukaryotic immune system based on antigens, the acquired CRISPR immunity is based on nucleic acids.

Figure 1: + details

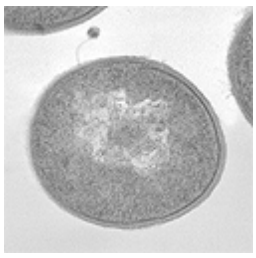


Figure 2:

However, prior hypotheses were based on *in silico* observations, and remained purely theoretical until the publication of our paper. Our experimental results on *Streptococcus thermophilus* combine biology of viral-host interactions, genetic engineering of CRISPR/*cas* structures for demonstration purposes, and CRISPR sequence comparison across a large number of bacterial strains.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Our paper represents the first demonstration of the functionality of CRISPR/*cas* as a new microbial immune system. It is essentially the validation of a

putative hypothesis. This achievement is mostly due to the concomitant availability, within Danisco, of two large and complementary collections: bacterial strains and their corresponding bacterial viruses.

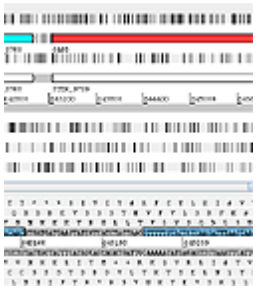
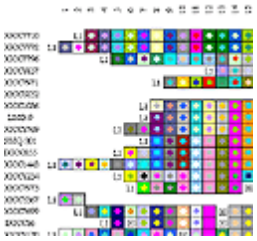


Figure 3:



SW: Would you summarize the significance of your paper in layman's terms?

Bacteria and bacterial viruses (bacteriophages, or phages) behave like prey and predators in a ruthless fight. Since the dawn of time bacteria have developed a variety of resistance mechanisms against viral infection. In response, phages continuously evolve wily strategies to skirt around bacterial defenses.

Our results show for the first time that a peculiar structure previously identified within bacterial genomes constitutes a new antiviral system. CRISPR structures can be seen as an archive of past encounters, where the bacterium stores short fragments of viral genomes. The presence of these viral fragments provides to the bacterium a kind of immunity against any forthcoming virus containing the same fragment.

Our discovery opens new perspectives in the fight against viruses, notably in the field of microbial food fermentations (dairy, meat, and wine industries, for instance). It could also impact our use of viruses to fight against undesirable bacteria (phage therapy), an approach that is currently considered as a credible alternative to antibiotics.

SW: How did you become involved in this research, and were there any problems along the way?

Danisco is a world-leading company for food ingredients. In order to provide starter cultures with enhanced robustness, Danisco Innovation explores any new track that could improve our knowledge on bacterial resistance against phages. Our interest for CRISPR goes back to 2002, while we were involved in the genome sequencing projects for *Lactobacillus acidophilus* NCFM® and *Streptococcus thermophilus* LMD-9 (a Danisco strain). Shortly after having discovered CRISPR structures in these two genomes, the analysis of CRISPR arrays across a diversity of bacterial strains from the same species suggested unambiguously a link with phage resistance. Experiments were then designed to test our hypotheses.

SW: Where do you see your research leading in the future?

Based on the knowledge we have added on CRISPR, we are actively implementing this strategy and we now concentrate our efforts on the development of natural approaches that will provide, in a near future, new starter cultures for the food industry. Our initial publication on CRISPR has also opened new doors to collaborations with academic teams across the world.

SW: Do you foresee any social or political implications for your research?

Our research does not have any social nor political implication. Nevertheless, in addition to improving the quality of functional food ingredients, it should have a significant impact on the population of…bacterial viruses!

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Keywords: CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats, CRISPR-associated, cas, CRISPR/cas structures, prokaryotes, prokaryotic DNA, RNA interference, RNAi, microbial food fermentations, undesirable bacteria, phage therapy, Lactobacillus acidophilus NCFM, Streptococcus thermophilus LMD-9, Danisco strain, Danisco Innovation.

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