



Dr. Thomas Santangelo transferred his research group from Ohio State last July to join CSU in the Department of Biochemistry and Molecular Biology. For the past eight years Dr. Santangelo has been one of the few researchers in the world working on understanding the mechanisms of archaeal transcription.

RCO: To provide our readers a little background please explain what archaea are and why are you interested in using archaea in your research?

Dr. Santangelo: For ~200 years all life was divided into five kingdoms (Monera, Protista, Fungi, Plantae, Animalia), but even early on the microscopic Monera were difficult to catalogue. Pioneering efforts in the 1970s based on DNA sequencing led to the proposal - that has since been accepted - that extant life is more properly classified into three Domains: Eukarya, Bacteria, and Archaea. Eukaryotae contains four kingdoms, while the final kingdom, Monera, was split into the Bacteria and the Archaea. The three Domains share some common features, although there are many unique mechanisms utilized to support life within each Domain. Our current knowledge of archaeal biology is quite limited, and my group is focused on detailing how genes are expressed and regulated in archaeal systems.

RCO: Where did you obtain the Archaea used in your research?

Dr. Santangelo: Many archaea thrive in harsh environments that would kill other creatures: boiling water/mud, super-salty pools, sulfur-spewing volcanic vents, acidic pools, and even deep within Antarctic ice. These archaea are termed "extremophiles", meaning organisms that love extreme conditions. There is considerable interest in understanding how biology functions at the extremes of temperature, salinity, pressure, and pH. Our favorite organism, *Thermococcus kodakarensis*, was isolated from a hydrothermal vent in the Pacific Ocean.

RCO: What is the name of your research project and what are the project goals?

Dr. Santangelo: We have funding for three main projects, but the bulk of our radioisotope work is focused on an NIH-funded project entitled "Archaeal transcription termination". We are establishing the mechanisms employed to regulate gene expression and how such mechanisms influence the many activities of the archaeal RNA polymerase, the enzyme responsible for all RNA production in archaea.

RCO: Why are radioactive materials used for this research? What radioisotopes do you use and what determined this choice?

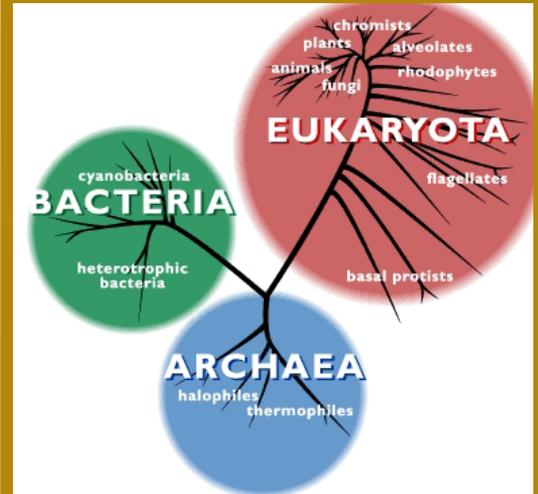
Dr. Santangelo: We use radioactive isotopes to monitor the synthesis and degradation of both DNA and RNA. We primarily use ³²P-labeled deoxy- and nucleotide triphosphates (NTPs and dNTPs) as a means to follow the progress of certain biological process. Incorporation of ³²P-labeled nucleotides in our reactions permits detection of extremely small quantities of DNA and RNA within our experiments that would be impossible to monitor with other techniques.

RCO: What are the results you are looking to gain from radiation use?

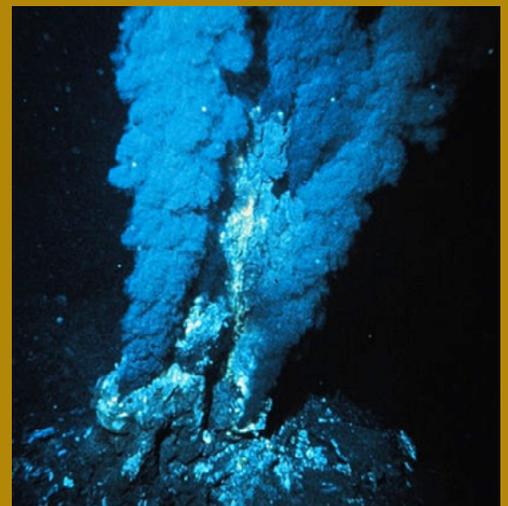
Dr. Santangelo: We aim to identify the signals that direct the archaeal RNA polymerase to continue or halt RNA synthesis under specific conditions.

RCO: How many people beside yourself do you have working on this project?

Dr. Santangelo: The grant supports two graduate students and a technician who together contribute the bulk of the effort on archaeal transcription. My group also employs six undergraduates who work on different aspects of archaeal physiology, with most focused on our applied work directed towards biofuels and biorenewables.



The three domains of life



Black smoker at a mid-ocean ridge hydrothermal vent

Researching Archaeal RNA Transcription Termination (Continued)

RCO: What do you feel are the most beneficial aspects of your research to CSU and the community?

Dr. Santangelo: My group is - to my knowledge - the only group at CSU primarily focused on the archaea, and is one of only a handful of laboratories in the USA who center their efforts on archaea. As such, our research opens a new door to the archaeal community at CSU.

Further, as we learn more about archaeal physiology and gene regulation we consistently challenge and push the proposed limits of life, and the comparisons between archaeal vs. bacterial vs. eukaryotic biology encourage many interesting, and often evolutionary discussions. Commonalities between the activities of the archaeal RNAP and eukaryotic (including human) RNA polymerases also complement the studies of many researchers at CSU.

RCO: Do you have any preliminary results from the study that you can share?

Dr. Santangelo: We have very recently solved the atomic structure of the archaeal RNA polymerase which provides mechanistic insight into how the enzyme responds to specific sequences to tell the polymerase where to start and stop.

RCO: Where do you hope this research leads?

Dr. Santangelo: Our research will contribute to the overall comparisons made between the three Domains, and more specifically will detail the activities of RNA polymerase, an enzyme essential to all life.

RCO: Where do you see archaeal research heading in the next decade?

Dr. Santangelo: As environmental concerns continue to mount, greener routes of production – be it energy, consumables, pharmaceuticals, etc. – will be sought, and the chemistries encoded in archaeal genomes will continue to be exploited for such greener production schemes. Archaeal enzymes already dominate in many industrial (i.e. textile and paper processing) and biotechnology (i.e. PCR) applications due to their retained activities under demanding conditions. As we learn more concerning archaeal physiology, and learn how to manipulate such, it will become increasingly profitable and environmentally conscious to use enzyme-derived chemistry in production platforms. Archaea are most perhaps most prominently featured for their role in methane and biofuel production, a subject that I would predict will exponentially increase in the coming years.

Life's Extremists May Be an Untapped Source of Antibacterial Drugs

Story from newswise.com by David Salisbury November 21, 2014
Newswise — NASHVILLE, Tenn.

One of the most mysterious forms of life may turn out to be a rich and untapped source of antibacterial drugs. The mysterious life form is Archaea, a family of single-celled organisms that thrive in environments like boiling hydrothermal pools and smoking deep sea vents which are too extreme for most other species to survive. "It is the first discovery of a functional antibacterial gene in Archaea," said Seth Bordenstein, the associate professor of biological sciences at Vanderbilt University who directed the study, "You can't overstate the significance of the antibiotic resistance problem that humanity is facing. This discovery should help energize the pursuit for new antibiotics in this underexplored group of life." Vanderbilt University has applied for a patent on the newly discovered gene and is exploring industry partnerships and licensing opportunities. Until the late 1970s, biologists thought that Archaea were just weird bacteria, but then a landmark analysis of their DNA showed that they represent an independent branch on the tree of life that stretches back more than three billion years.

The realization that Archaea could be a source of novel pharmaceuticals emerges from a study of widespread horizontal gene transfer between different species conducted by a team of scientists from Vanderbilt University and Portland State University in Oregon. The researchers were investigating a gene that produces a type of enzyme found in tears, saliva, milk and mucus called a lysozyme. This particular lysozyme possesses broad-spectrum antibacterial action and remarkably jumped from bacteria to all major branches of life. They discovered it in an extremely unlikely source: an Archaea microorganism that inhabits deep sea areas surrounding jets of superheated mineral water spewing from hydrothermal vents. The paper that describes this discovery is titled "Antibacterial Gene Transfer Across the Tree of Life" and was published online on Nov. 25 in the new science journal eLife. The authors are Jason Metcalf, who is pursuing both Ph.D. and M.D. degrees, doctoral student Lisa Funkhouser-Jones and Bordenstein from Vanderbilt and postdoctoral student Kristen Brileya and Professor Anna-Louise Reysenbach from Portland State University in Oregon. "We found that this Archaea lysozyme kills certain species of firmicutes bacteria, a large group of bacteria that contains the classic drug resistant bacterium *Staphylococcus aureus*, *Bacillus anthracis*, which causes anthrax, and the gut infection *Clostridium difficile*," said Bordenstein.



Life's Extremists May Be an Untapped Source of Antibacterial Drugs (Continued)

Before now scientists had largely ignored Archaea as a source of drugs because they don't cause any diseases in humans and experts thought they didn't interact much with the other forms of life because they were limited to extreme environments. In recent years, however, investigators have found that significant numbers of bacteria co-exist with Archaea in extreme environments and that Archaea themselves are not limited to such environments but also live in milder environments, such as within marine algae and in mammalian guts. "The fact that Archaea are interacting with other forms of life a lot more than we thought means that they are competing for resources," said Metcalf. "And, if they are competing for resources, then they are creating chemicals to attack and defend against other organisms: compounds that could be effective against bacteria resistant to our current antibiotics."

The scientists first encountered this antibacterial gene, a GH25-muramidase, in a bacteriophage virus that attacks Wolbachia, a bacterial parasite that infects insects and other invertebrates worldwide. It is a member of a family of enzymes that are common in bacteria, which use them to remodel their cell walls. Bacteriophages use the same enzymes to invade bacteria by chewing holes in their cell walls. In addition, the gene's presence in an insect, the pea aphid, had previously been reported. But when they examined its evolutionary history, the researchers were surprised to find that the gene also popped up in an ancient lineage of plants (*Selaginella moellendorffii*) and many species of fungi including *Aspergillus oryzae*, a mold used in Asian cooking to make soy sauce, miso and alcoholic beverages like sake. "That was completely unexpected," said Metcalf. "But the weirdest occurrence was in an Archaea species *Aciduliprofundum boonei* that lives in hydrothermal vent communities. Why in the world would it need such an enzyme?" In order to explore this question, Metcalf tracked down one of the few groups of scientists in the world who specialize in collecting and growing Archaea species, including *A. boonei*: the Reysenbach Lab at Portland State. With their aid, he was able to purify *A. boonei*'s GH25-muramidase domain, a step that was needed to determine the enzyme's function.

"What is really cool about these results for me comes from an ecological perspective," said Reysenbach. "These Archaea live in close proximity, in biofilms, to extremophile bacteria and need to compete for resources. I have often wondered, 'How do Archaea do it?' Through this paper, we show that the smart archaeal 'bugs' do so by stealing genes from their bacterial 'mates' and competitors. This points to Archaea being good, as yet relatively untapped targets for exploring new antibacterial drugs."

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Radiation Do's and Don'ts

LSC Cocktails Cannot be Poured Down the Drain

Even "Biodegradable" cocktails must go into Hazardous Waste

All Liquid Scintillation Counter cocktails are now considered Hazardous Wastes by the city of Fort Collins and must be submitted to the EHS Hazardous Waste program for disposal. Do not pour any LSC cocktails down the drain in the lab even if you have done so in the past. If you have any questions please contact the Radiation Control Office at 491-4835 or the Chemical Management Unit at 491-6745.

