

JOINING ASTROBIOLOGY TO MEDICINE. RESURRECTING ANCIENT ALCOHOL METABOLISM.

M. A. Carrigan^{1,2}, O. Uryasev^{1,2}, Ross W. Davis^{1,2}, S. G. Chamberlin^{1,2}, and S. A. Benner^{1,2}, ¹Foundation for Applied Molecular Evolution (P. O. Box 13174, Gainesville FL 32604), and ²The Westheimer Institute for Science and Technology (720 S. W., 2nd Avenue, Gainesville FL 32601).

Introduction: Any system, natural or human-made, can be better understood if we understand *both* its structure *and* its history [1]. In biology over the past century, analyses of the structure of living systems has come to dominate, especially in biomedical research, with the analysis extending to the molecular level. Indeed, it is difficult to find a biological phenomenon that is *not* today associated with its underlying chemistry. These applies to much of human disease, and includes adaptation and evolution, the hallmarks of biological systems.

Astrobiology as a field and the NASA Astrobiology Institute specifically have made major contributions to fill the gap created by a 50 year focus on the chemistry of biology. With its appreciation of natural history, astrobiology has much to say to complement the lack of historical perspective in modern medical research. Setting aside infectious disease and diseases (such as cancer) that arise from a failure of the human genetic program to do what it has evolved to do, much of human disease is the consequence of maladaptation to current environments of genetic structures that were, in the hominoid past, adaptive. This includes mundane diseases (e.g., flat feet and lower back pain), but also some of the principal killers in the developed world, including hypertension, obesity, the metabolic syndrome, and diabetes.

Research program. Alcoholism most likely falls into this class as well. Evidence shows that human populations adapted to different environments (for example, Inuits versus Mediterranean Caucasians) are also differentially adapted at the genetic level to the ill effects of ethanol ("alcohol"). Further, it is clear that this differentiation in human populations is only the latest example of primate adaptation to ethanol.

Some time ago, we used paleogenetic experiments to resurrect the enzyme that is the primary producer of ethanol in the human environment, the alcohol dehydrogenase from yeast [2]. These showed that bulk

ethanol first emerged in primate environments approximately 80 million years ago (Ma), when angiosperms first produced fleshy fermentable fruits.

With funding from the National Institute for Alcohol Abuse and Alcoholism (NIAAA), we have applied an astrobiological approach to understanding how primates responded to the emergence of ethanol in their environment. In this work, we are resurrecting two enzymes involved in the degradation of ethanol, alcohol dehydrogenase (Adh) and aldehyde dehydrogenase (Aldh) (Figure 1). Adh is a multilocus family of paralogs in humans, including three that belong to the Adh1 family that arose after primates diverged from other mammal orders.

To support the resurrections, we have collected a large number of sequences of genes encoding these proteins from mRNA in livers and kidneys from a range Old and New World primates, as well as lemurs from Madagascar. This work, combined with database mining, has discovered a new paralog of Adh1. This discovery was made by realizing that the databases were incorrectly annotated, a common problem in modern bioinformatics.

Progress will be reported on the resurrection of Aldh2, the mitochondrial aldehyde dehydrogenase that is most important in the detoxification of ethanol in humans. Also in progress are kinetic studies on contemporary lemur and marmoset Adhs. These will be applied to ancestral resurrected proteins to determine which of our primate ancestors used ethanol, which tolerated ethanol, and which avoided ethanol.

References:

[1] Benner, S. A. (2009) *Life, the Universe, and the Scientific Method*, Gainesville, Foundation Press, 322 pp. [2] Thomson, J. M., Gaucher, E. A., Burgan, M. F., Aris, J. P., Benner, S. A. (2005) Resurrecting extinct proteins from ancient yeast at the origin of fermentation. *Nature Genetics* **37**, 630-635

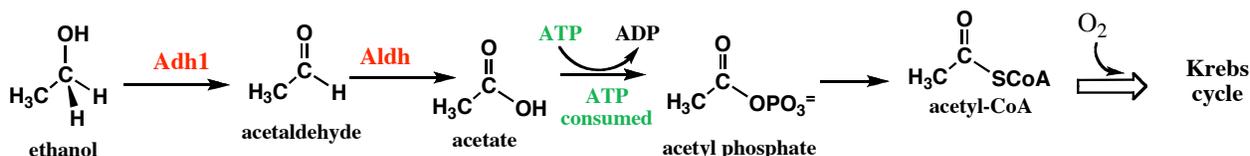


Figure 1. The pathway for detoxification of ethanol in primates. Alternatively, acetate is carboxylated to give propionyl-CoA, which then is used as a precursor for the biosynthesis of fatty acids.