ACS chemical biology

Spotlight

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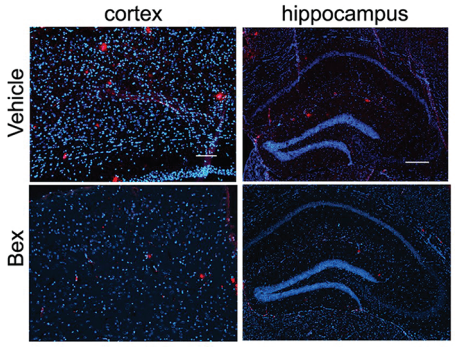
ESCORTING β-AMYLOID OUT OF THE BRAIN

Alzheimer's disease, a devastating brain disorder that slowly destroys memory and other intellectual and social abilities, affects over 5 million Americans. The disease is characterized by deposition of a peptide called β-amyloid in the brain. The protein apolipoprotein E is normally responsible for degrading β-amyloid and removing it from the brain, suggesting that compounds capable of increasing apolipoprotein E activity may have therapeutic potential against Alzheimer's disease. Now, Cramer *et al.* (*Science* published online February 9, 2012; DOI: 10.1126/science1217697) report the remarkable effects of a small molecule and known anticancer agent called bexarotene in mouse models of Alzheimer's disease.

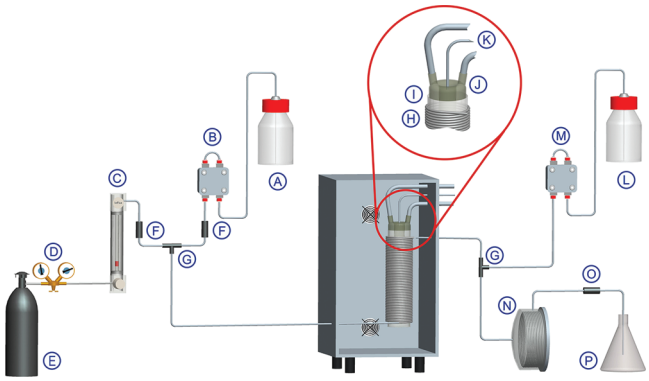


From Cramer, P. E., *et al.*, *Science*, February 9, 2012; DOI: 10.1126/science1217697. Reprinted with permission from AAAS.

Production of apolipoprotein E is regulated by a group of nuclear receptors including the retinoid X receptors (RXRs). Bexarotene is known to activate the RXR receptor, and thus the authors hypothesized that this anticancer agent may also have potential as an Alzheimer's drug by inducing increases in apolipoprotein E levels. Indeed, when mice genetically modified to exhibit symptoms of Alzheimer's disease were given bexarotene, numerous beneficial effects were observed. Both the soluble and aggregate forms of β-amyloid decreased in the brain, while apolipoprotein E levels increased. In addition, treated mice exhibited rapidly improved cognitive and behavioral abilities, endorsing the model that increases in apolipoprotein E levels lead to decreases in β-amyloid, which in turn leads to improvements in brain function. Together, the data support the strategy of targeting activation of apolipoprotein E for fighting Alzheimer's disease and point to bexarotene or similar drugs as exciting starting points for drug development. **Eva J. Gordon, Ph.D.**

GOING WITH THE FLOW TO CURE MALARIA

In Africa, a child dies every minute from malaria, a curable and preventable disease caused by infection from the parasite *Plasmodium falciparum*. The sesquiterpene endoperoxide artemisinin, a natural product of the sweet wormwood plant, is an effective treatment for malaria. However, global demand of the drug surpasses that which can be efficiently isolated from plants, and its complex structure has posed significant challenges in the development of a cost-effective chemical synthesis. Now, Lévesque and Seeberger (*Angew. Chem., Int. Ed.*, 2012, *51*, 1706−1709) present an exciting new strategy for the production of artemisinin: continuous-flow synthesis from dihydroartemisinic acid, a more readily available precursor of artemisinin produced by the same plant and also available *via* production in engineered yeast.



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Two key steps in the continuous flow conversion of dihydroartemisinic acid to artemisinin are a photochemical reaction involving singlet oxygen and addition of triplet oxygen, which triggers a reaction cascade culminating in the formation of the endoperooxide group that is so crucial for the antimalarial activity of the drug. The continuous-flow synthesis design facilitates these reactions utilizing a reactor that receives dihydroartemisinic acid, oxygen gas, and photosensitizer. Appropriately timed introduction of trifluoroacetic acid, which triggers the second step of the reaction sequence, allows for the continuous production of artemisinin. Using this setup, artemisinin is produced without isolation and purification of intermediates and at a greatly reduced cost. The authors estimate that a single continuous flow setup could produce approximately 200 g of artemisinin each day. To accommodate the approximately 225 million doses needed worldwide, just 1500 similar continuous flow set-ups would be sufficient to supply the global population afflicted with malaria with this life-saving medication. **Eva J. Gordon, Ph.D.**

THE NEXT-GENERATION OF CANCER DISCOVERY

Many cancers arise from mutations in genes. These mutations can muck up cell function in a variety of ways, such as changing the amount of the gene that is expressed or altering the activity of the protein for which it encodes. Several anticancer drugs have been developed that specifically target such mutations, though determining which miniscule, needle-like mutations might be lurking in the haystack of genomic material is a formidable task. Now, Lipson *et al.* (*Nat. Med.* advance online publication January 13, 2012; DOI: 10.1038/nm.2673) describe their use of a next-generation sequencing assay to identify clinically relevant mutations in colorectal and lung cancers.

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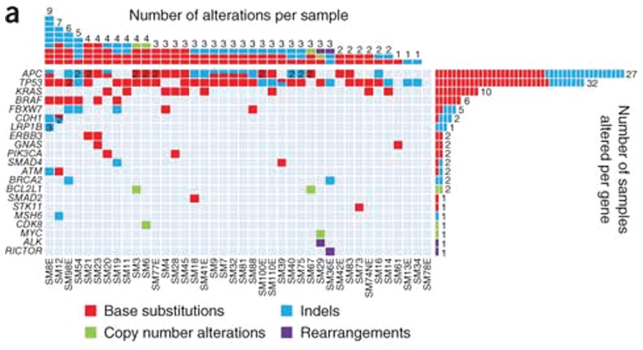

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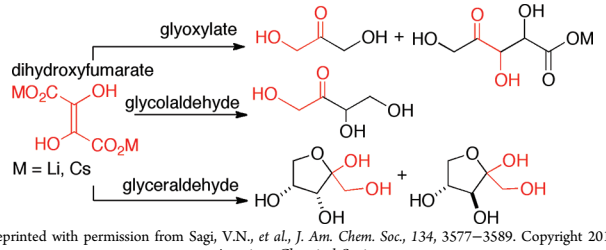
Next-generation sequencing methods, which have drastically reduced the time, cost, and labor involved in sequencing DNA, also enable identification of gene mutations that may be missed with other methods of tumor analysis such as immunohistochemistry and fluorescence *in situ* hybridization. Using a next-generation sequencing assay designed to interrogate genes associated with cancer-related pathways, 40 colorectal and 24 lung cancer specimens were analyzed. Over half of the colorectal specimens and over 70% of the lung cancer specimens contained mutations that could be linked with known treatments or drugs under investigation. In addition, in both the colorectal and lung cancer specimens, novel gene fusions were detected that are also candidates for known drugs. This analysis reveals the power of next-generation sequencing methods for identifying mutations in cancer specimens and uncovering critical therapeutic options that would be difficult to identify using standard genetic analysis methods. **Eva J. Gordon, Ph.D.**

ALTERNATE PREBIOTIC ROUTE TO SUGARS

Researchers have struggled to uncover the chemical mechanisms that could have converted an abiotic "primordial soup" into building blocks of biopolymers. In examining the formation of carbohydrates from fundamental components such as water and carbon dioxide, researchers initially proposed the formose reaction that converts formaldehyde to a mixture of aldoses and ketoses in a series of steps. But the complexity of the product mixture and the lack of specificity of that process have prompted questions about whether such a sequence could have generated essential sugars, such as ribose, that support biology.



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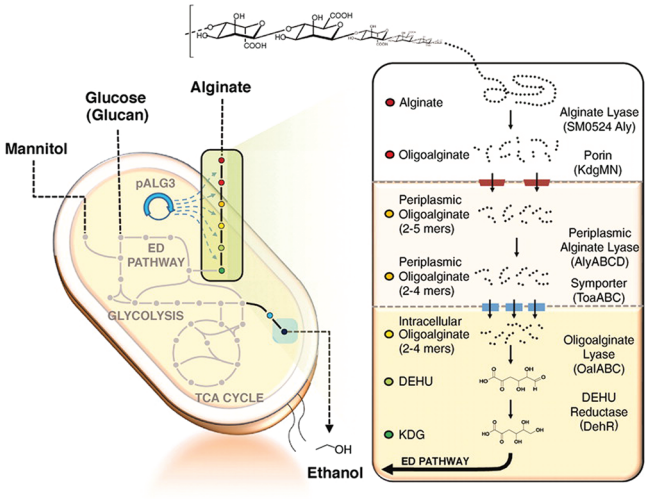
Recently Albert Eschenmoser proposed that glyoxylate and dihydroxyfumarate (DHF), instead of formaldehyde, could serve as cornerstones for generating carbohydrates from abiotic sources. Now Sagi *et al.* (*J. Am. Chem. Soc.*, 2012, *134*, 3577−3589) have shown in a series of initial experiments that this "glyoxylate scenario" produces a specific set of ketoses. The researchers carried out a series of aqueous reactions of DHF with glyoxylate, glycoaldehyde, and glyceraldehyde, varying factors including reactant equivalents and Lewis Acid content. They monitored the reactions using ^{13}C NMR. These careful experiments give detailed analysis of the intermediates and products, including two pentuloses, and expand the known palette of aqueous chemistry for DHF. In these reactions, other than a dimerization reaction, DHF serves as a carbon nucleophile with a variety of α-hydroxyaldehydes.

Because DHF reacts readily with aldehydes but slowly with ketones, these reactions are more selective and produce a narrower range of unbranched ketose products than the formose reaction. The pentuloses produced, ribulose and xylulose, have relevance on their own, and further research may lead to a direct path to ribose. Experiments are also needed to verify that DHF and glyoxylate can be generated under prebiotic conditions. Overall, this research proposes an uncluttered route for producing biologically relevant sugars under mild conditions. **SarahA. Webb, Ph.D.**

AN ALGAE-EATING BACTERIUM FOR BIOFUEL PRODUCTION

Biofuels represent a promising alternative to traditional fossil fuels, but efficient conversion of plant or algal biomass into usable fuels remains a central challenge. One hurdle with these organisms is the particular oligomeric configurations in which they store sugars. To address this problem, researchers often search for microorganisms that can metabolize these polysaccharides into more simple sugars and ultimately ferment them into ethanol. This approach can be difficult to scale from the laboratory to a production setting due to the culture conditions of these special microorganisms. Now, a new study (Wargacki *et al.*, *Science* 2012, *335*, 308−313) borrows the enzymatic cascade from an algal-metabolizing organism and transplants it into a familiar and more scalable host, *E. coli*.



From Wargacki, *et al.*, *Science*, 2012, *335*, 308. Reprinted with permission from AAAS.

To unleash the energy in the algal polysaccharide, alginate, the researchers first engineered a secreted enzyme system for depolymerizing the long alginate chains. Then, they queried bacterial genomic data for an organism that might contain a complete alginate metabolism system in one contiguous segment of DNA. By transferring segments from the candidate *Vibrio splendidus* genome into *E. coli*, the researchers uncovered a 36 kilobase region that could transform the *E. coli* into a alginate-metabolizing microbe. Surveying the flanking regions in the *Vibrio* genome revealed several more enzymes that could

be involved in alginate metabolism or transport, so these were engineered into the bacterial strain as well. These iterative changes to the bacteria resulted in faster growth rates and density while culturing on alginate, plus the alginate in the culture was more fully digested into monomers. Finally, this finely tuned strain of *E. coli* containing 20 *Vibrio* genes, the secreted alginate lyase system and the ethanol pathway was put to the test by growing it with brown algae and measuring production of ethanol. The experimental yield was an impressive 80% of the theoretical yield. This study indicates another route to breaking down a hard-to-digest polysaccharide and it represents a promising new direction for eventual biofuel production on an industrial scale. **JasonG. Underwood, Ph.D.**

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