ACS chemical biology

Spotlight

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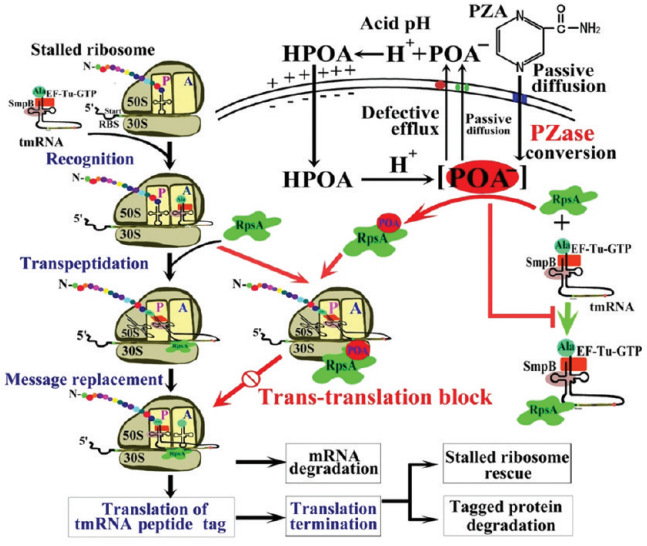
BEST OF CHEMICAL BIOLOGY 2011

2011 was an exciting year for chemical biology, and we've used our Spotlight section to highlight new developments every month. Now, looking back, the Editors have compiled a list of articles representing some of the most interesting and relevant research from all of 2011. As with our monthly Spotlights, it is simply not possible to recognize all of the amazing work being published, and this list is not meant to be comprehensive. However, we hope that this feature will at least provide a sense of the richness and quality of research being published in chemical biology as we move forward into a new decade. Happy New Year!

NEW TARGET FOR ANTI-TUBERCULOSIS DRUG DEVELOPMENT

Pyrazinamide (PZA) is a well-known frontline drug used in combination treatments for patients suffering from tuberculosis (TB). This drug has been shown to efficiently reduce treatment time from previously 9−12 months to 6 months. Although this nicotinamide analogue was first discovered more than 60 years ago, little is known about its target in *Mycobacterium tuberculosis*. However, the ability of PZA to target dormant *M. tuberculosis* bacilli specifically made it a highly desirable model drug that shortens the therapy. Now, Shi *et al.* (*Science* 2011, *333*, 1630−1632) identify the target of PZA and, in doing so, find a much-sought focus for anti-TB drug development.



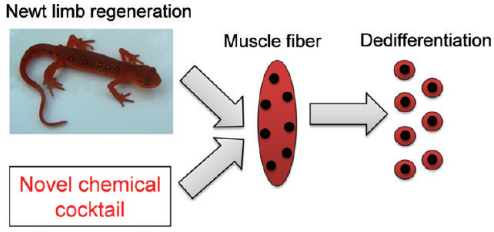
From Shi, W., et al., *Science*, **2011**, *333*, 1630−1632. Reprinted with permission from AAAS.

PZA is a prodrug that is functional as an anti-TB compound following hydrolysis in *M. tuberculosis* cells to pyrazinoic acid (POA) by the enzyme pyrazinamidase encoded by *pncA* gene. Using a combination of binding studies and mass spectrometry, the authors identified four possible targets. Of these four targets, the authors focused on ribosomal protein S1 (RpsA), a protein essential for the translation of proteins. RpsA is also involved in trans-translation, a process by which stalled ribosomes on mRNA are dislodged and replaced by transfer-messenger RNA (tmRNA). Specifically, RpsA binds tmRNA and subsequently complexes with other proteins involved in translation, *i.e.*, small protein B (SmpB) and elongation factor-Tu (EF-Tu) bound to GTP. This complex plays the essential role of removing stalled ribosomes and resuming translation. Overexpression of RpsA was found to increase resistance to PZA. The authors showed that POA bound directly to RpsA using an *in vitro* assay. The identification of RpsA as a target for persister drug PZA opens the door for developing more potent compounds against this target and related trans-translation pathway for more effective eradication of TB.

Jitesh A. Soares, Ph.D.

BREAKTHROUGHS IN REGENERATIVE MEDICINE

Urodele amphibians, which include salamanders and newts, have the remarkable ability to regenerate their limbs in response to injury. This process requires that skeletal muscle cells undergo a process called dedifferentiation. Dedifferentiated cells are multipotent, meaning they have the capacity to differentiate into one of multiple potential tissue types, which is a key aspect of the regeneration process. Unfortunately, mammalian skeletal muscle tissue does not respond in the same way to injury. To this end, Jung and Williams (*ACS Chem. Biol.* 2011, *6*, 553−562) now describe a chemical method to induce dedifferentiation in mouse skeletal muscle, findings that have exciting implications in regenerative medicine.



Mammalian skeletal muscle is comprised of multinucleated fibers that must fragment into proliferating mononuclear cells before dedifferentiation can occur. To accomplish this, mouse skeletal muscle fibers were treated with the trisubstituted purine myoseverin, a known tubulin-binding small molecule, and the activity of p21, a cyclin-dependent kinase inhibitor, was suppressed. Subsequent treatment of the resulting proliferating mononuclear cells with another small molecule purine derivative called reversine enabled their differentiation into nonmuscle cells, including fat and bone cells.

Wang *et al.* (*ACS Chem. Biol.* 2011, *6*, 192−197) describe another breakthrough in the field of tissue regeneration. The Wnt/β-catenin signaling pathway plays a role in guiding differentiation of pluripotent stem cells. The authors showed that a small molecule inhibitor of this signaling pathway could induce cardiomyogenesis of mouse embryonic stem cells.

Eva J. Gordon, Ph.D. and **Jitesh A. Soares, Ph.D.**

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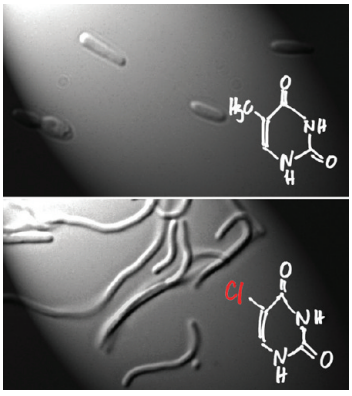
A CHEMICAL EVOLUTION

Manipulation of the chemical composition of RNA and DNA is a powerful method for investigating the biosynthetic and metabolic pathways that govern cell growth and reproduction. Noncanonical bases have been incorporated into RNA and DNA in some systems under defined conditions, but unlimited self-reproduction of an organism through complete genome or transcriptome substitution has not been achieved. Marlière *et al.* (*Angew. Chem., Int. Ed.* 2011, *50*, 7109−7114) now report a general method for evolving the DNA composition of a bacterial population.



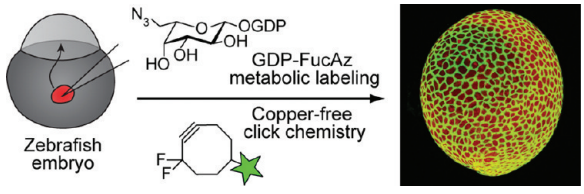
Reproduced with permission from *Angew. Chem., Int. Ed.* from Wiley-VCH, Marlière, P. et al., **2011**, *50*, 7109−14 DOI: 10.1002/anie.201100535.

The success of their approach relied on a cultivation process referred to as the conditional pulse-feed regime. The design consisted of a cultivation device connected to two nutrient reservoirs, one containing the canonical base thymine and the other containing the noncanonical base 5-chlorouracil. Thymine was selected to be replaced because it is present only in DNA, its metabolism is separate from that of RNA, and its biosynthesis can be abolished through the disruption of a single gene. 5-Cholouracil was selected as the replacement due to its structural similarity to thymine, its compatibility as a substrate for enzymes involved in thymine biochemistry, and its biochemical stability. A genetically modified strain of *Escherichia coli* unable to grow without a supply of thymine was used for transliteration with 5-chlorouracil. Growth conditions were set up such that every 10 min, the cultures received a pulse of either thymine or 5-chlorouracil. Over the course of approximately 25 weeks, the bacteria adapted to consume only 5-chlorouracil. Characterization of the adapted bacteria revealed that construction of DNA with 5-chlorouracil was inheritable, that 5-chlorouracil was largely encoded in the genomes of the adapted strains, and that numerous mutations including base substitutions or chromosome rearrangements were present, the relative amounts of which depended on the adaptation conditions.

Eva J. Gordon, Ph.D.

MONITORING FUCOSYLATION *IN VIVO*

Fucosylation is a post-translational modification crucial to cell fate decisions and organogenesis as well as in Notch signaling and brain development. Characterizing the precise function of fucosylation during these vital developmental processes is of great importance. However, monitoring this post-translational modification has been problematic due to the lack of reporters to analyze these modifications *in vivo*. To bridge this shortcoming, Carolyn Bertozzi (2012 *ACS Chemical Biology* lecturer) and co-workers (*ACS Chem. Biol.* 2011, *6*, 547−552) report the development of a new imaging tool for studying this process in zebrafish.

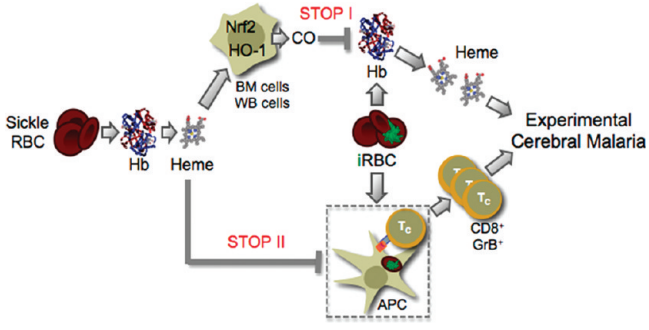


The authors "tricked" the metabolism of zebrafish cells into incorporating azide-based fucose analogs (FucAz) on cell-surface glycans by microinjecting embryos with azido fucose analogs modified at the C6 position. The incorporated fucose analogs were then visualized using a fluorophore probe using copper-free click chemistry. However, the incorporation of these unnatural azide analogs was inefficient due to low tolerance by the fucose salvage pathway. To circumvent this problem, GDP-FucAz derivatives were microinjected into zebrafish embryos. Confocal microscopy and flow cytometry showed efficient incorporation of this analog into cell-surface glycans. Using this approach, the authors were able to follow fucosylation in embryos with stunning clarity. This new imaging tool provides researchers with a much-needed chemical reporter to monitor this crucial post-translational modification in living cells which will provide a better understanding for the developmental processes involved in the early stages of life.

Jitesh A. Soares, Ph.D.

HOW SICKLE CELL MUTATIONS THWART MALARIA

Malaria infects 250 million people each year, and its cerebral form where sticky blood cells can plug up brain capillaries is particularly dangerous for young children. For decades researchers have known that carrying the sickle cell gene helped individuals survive malaria infections, and earlier research had suggested that the mutations in the hemoglobin protein might help decrease the *Plasmodium* pathogen load. Now, Ferreira *et al.* (*Cell* 2011, *145*, 398−409) provide a new molecular mechanism that explains why altered hemoglobin helps people tolerate malaria infections.



Reprinted with permission from Elsevier, Inc., Ferreira, A et al, *Cell*, **2011**, *145*, 398−409.

People with hemoglobin S, the mutated form of the protein, tend to leach free heme from their red blood cells. High concentrations of free heme in the plasma are toxic but can

prompt the expression of heme oxygenase-1 (HO-1), an enzyme that protects against many inflammatory diseases.

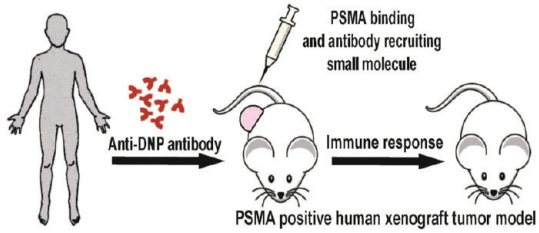
In detailed studies with transgenic mice that serve as a model for mild sickle cell disease, Ferreira *et al.* show that this uptick in HO-1 expression in blood cells, not a decrease in pathogen load, is responsible for the increased tolerance to malaria among carriers of the sickle cell gene. Previous work had demonstrated the transcription factor, NF-E2-related factor (Nrf2), regulates HO-1 expression. The researchers confirm that Nrf2 also controls HO-1 expression in response to the release of free heme in the plasma of sickle cell gene carriers.

The enzyme HO-1 breaks down free heme molecules to produce biliverdin, iron, and carbon monoxide. Carbon monoxide inhibits the oxidation of hemoglobin, blocking the release of more molecules of free heme that can lead to the symptoms of cerebral malaria and of sickle cell anemia. Free heme also appears to block the expansion of T-cells in brain tissue that can lead to disease symptoms, but not *via* the HO-1/Nrf2 mechanism. This pathway represents a promising potential target for new treatments for severe malaria.

Sarah A. Webb, Ph.D.

APPROACH FOR PROSTATE CANCER VACCINE DEVELOPMENT

Prostate cancer is a leading cause of cancer-related death among men, which has led to the search for effective therapies. A recent line of research is the development of cancer vaccines that target tumor-associated antigens. Dubrovska *et al.* (*ACS Chem. Biol.* 2011, *6*, 1223−1231) report the development of a vaccine strategy that exploits a ligand with high affinity to a tumor-associated antigen.

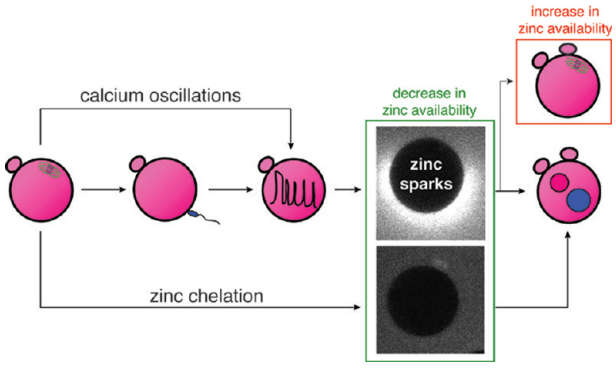


The redirection of the immune system to attack tumors is an attractive approach for cancer treatment. The authors used bifunctional ligands comprising of a ligand that targets a prostate cancer related antigen, prostate specific membrane antigen (PMSA), conjugated to a dinitrophenyl hapten for antibody recruitment. Importantly, this bifunctional conjugate showed significant antitumor response against human prostate cancer cell lines when studied in relevant murine xenograft model.

Jitesh A. Soares, Ph.D.

ZINC SPARKS LIFE

The role of cellular zinc is typically associated with its function as a cofactor or with structural maintenance in enzymes. More recent observations also point to its involvement in the regulation of the cell cycle in egg development. It is now known that the mouse oocyte absorbs billions of zinc atoms during the final stages of egg maturation prior to fertilization. Kim *et al.* (*ACS Chem. Biol.* 2011, *6*, 716−723) reveal the mechanism behind the role of zinc in egg development with sparkling results.

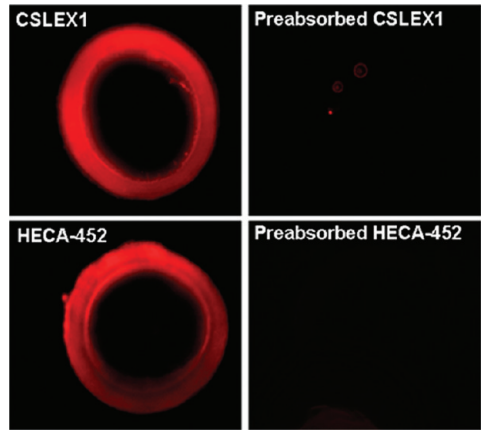


As a mammalian egg matures, it becomes enriched with zinc. Upon fertilization, calcium levels fluctuate within the cell and influence oocyte development. Using several chemical and fluorescent probes as well as metal-modulating small molecules, the authors investigated the cellular dynamics of calcium and zinc. Calcium spikes elicited the quick release of zinc, termed zinc sparks, into the extracellular milieu within two hours of egg fertilization. The decrease in intracellular zinc releases the egg from cell cycle arrest and initiates the earliest stages of embryonic development. This visually spectacular observation invites further research on the role of transition metals in developmental processes.

Jitesh A. Soares, Ph.D.

ELUCIDATION OF THE ZONA PELLUCIDA

We all know that the initial step of human fertilization occurs when a sperm cell, or spermatozoan, binds to an egg cell, or ovum. Perhaps less well-known is that this binding event is mediated by the interaction between a protein on the sperm cell surface and carbohydrate moieties on glycoproteins present in the zona pellucida, which is the outer coating of the ovum. However, the challenges associated with obtaining human eggs for research purposes and the notorious complexities in the characterization of cell surface oligosaccharides have hindered the identification of the specific carbohydrates and proteins involved. Pang *et al.* (*Science* 2011, *333*, 1761−1764) now report that sperm binds to the zona pellucida through a well-known tetrasaccharide moiety called sialyl-Lewis^x.



From Pang, P.-C., et al., *Science*, **2011**, *333*, 1761−4; DOI: 10.1126/science.1207438. Reprinted with permission from AAAS.

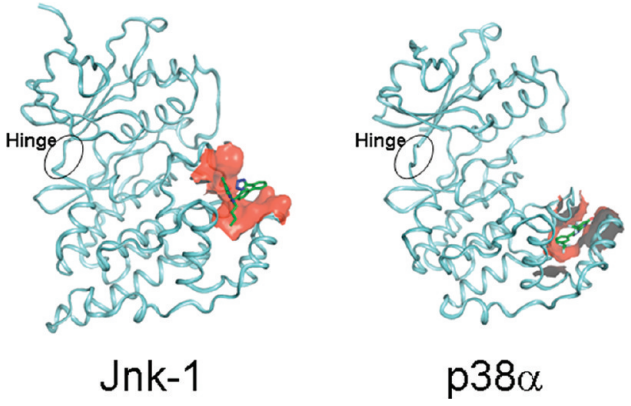
dx.doi.org/10.1021/cb200550s | *ACS Chem. Biol.* 2012, 7, 6−11

Nearly 20 years ago, evidence was presented that the major carbohydrate sequences presented on the human zona pellucida reacted with adhesion molecules known as the selectins. Selectins mediate cell adhesion during the initial stages of the inflammatory response, and sialyl-Lewis^x is their universal ligand. Now, mass spectrometry analyses demonstrated that sialyl-Lewis^x is the most abundant terminal oligosaccharide sequence present in the zona pellucida, and surprisingly it was present at significantly higher densities than those found in other cells. The interaction was characterized using the hemizona assay, in which nonliving human eggs are split into two equivalent hemispheres to provide an internal control for sperm binding. Sperm were prevented from binding to the zona pellucida in the presence of sialyl-Lewis^x-BSA or antisialyl-Lewis^x antibodies, and when solubilized zona pellucida was desialylated. In addition, fluorescently labeled sialyl-Lewis^x-BSA bound to sperm but not the hemizona. These findings are an exciting step forward in understanding the molecular underpinnings of human fertilization. Notably, since selectins are not expressed on the sperm surface, the hunt for the sperm protein that binds sialyl-Lewis^x continues.

Eva J. Gordon, Ph.D.

AN ALTERNATIVE APPROACH TO PROTEIN KINASE INHIBITION

Protein kinases play an important role in cellular signaling. Given their significance in several diseases, they are also considered attractive drug targets. It is estimated that over 200 kinase inhibitors are currently under clinical development. An overwhelming majority of these potential drugs are small molecules that inhibit binding to conserved ATP-binding site. However, an inherent drawback of this strategy is non-specificity, which often results in unexpected toxicity and side effects. Comess *et al.* (*ACS Chem. Biol.* 2011, *6*, 234−244) present a unique approach to identifying new compounds that specifically inhibit a target protein kinase by binding a novel allosteric site on two different target kinases of high therapeutic importance.

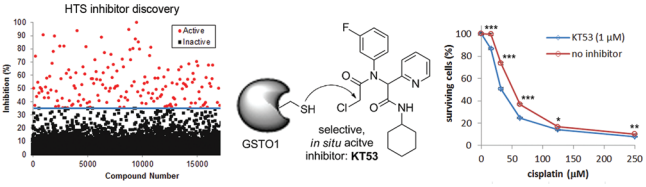


The authors focused on serine/threonine protein kinases c-Jun N-terminal kinase 1 (Jnk-1), implicated in type-2 diabetes and p38α, associated with the inflammatory response in rheumatoid arthritis. Using an affinity-based, high-throughput screening technique, compounds that bound to all sites on the protein kinases were studied. In addition to compounds that bound the ATP-site, the screen identified several compounds that bound kinases in an allosteric manner. Allosteric ligands that bound to a previously unknown allosteric site distant from the active site of Jnk-1 and p38α were characterized using NMR spectroscopy, X-ray crystallography, surface plasmon resonance and activity assays. One of the allosteric inhibitors to Jnk-1 was used as a lead compound to develop a synthetically superior ligand, which specifically inhibited Jnk-1 activation in human adipocyte and hepatocyte cells. Thus, the identification of a novel druggable site and associated inhibitor in kinase enzymes has significant implications for drug discovery.

Jitesh A. Soares, Ph.D.

ATTACKING THE RESISTANCE

Some cancer cells have a notorious talent for resisting the actions of chemotherapeutic drugs. Glutathione *S*-transferase omega 1 (GSTO1), a member of the glutathione *S*-transferase (GST) superfamily of enzymes, has been implicated in chemotherapeutic resistance. However, the lack of potent and selective GSTO1 inhibitors has hindered exploitation of this potential target for combating drug resistance. Tsuboi *et al.* (*J. Am. Chem. Soc.* 2011, *133*, 16605−16616) now report the discovery of novel GSTO1 inhibitors and demonstrate their efficacy in sensitizing otherwise resist cancer cells to traditional chemotherapeutic agents.



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The active site cysteine in GSTO1 distinguishes it from the majority of other GSTs, which utilize serine or tyrosine as their active site nucleophiles. Inhibitors specific for GSTO1 are thus likely to possess thiol-reactive moieties such as sulfonate esters and haloacetamides. A strategy called fluorescence polarization activity-based protein profiling ((fluopol)-ABPP) was used to identify such GSTO1 inhibitors. The 300,000+ public NIH small-molecule library was screened for the ability to block binding of a fluorescent GSTO1 activity-probe to the enzyme. From an initial ∼3200 hits, retesting and various secondary assays led to the selection of 10 compounds, 9 α-chloroacetamides and 1 α-aryl chloride, for selectivity testing and structure optimization. Ultimately, a compound referred to as KT53 was chosen for further testing in cells due to its superior potency, selectivity, and pharmacological properties. In addition, an alkyne analogue of KT53 called KT59 was synthesized so that click chemistry could be used to assess the presence of additional inhibitor-reactive proteins in cells. Notably, KT53 alone showed limited toxicity in cells, but when given to cancer cells in combination with the common chemotherapy drug cisplatin, the cells were significantly more sensitive to the cytotoxic effects of the drug. This study offers pharmacological evidence for the involvement of GSTO1 in chemotherapy resistance and delivers exciting lead compounds for future development.

Eva J. Gordon, Ph.D.

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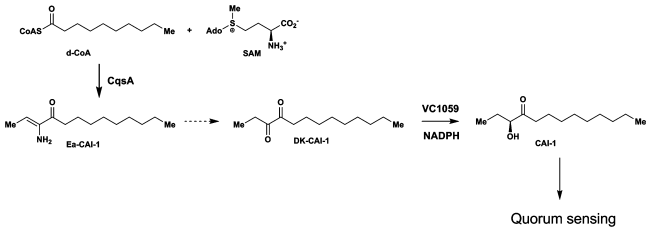
BIOSYNTHESIS OF A BACTERIAL COMMUNICATION SIGNAL

Bacteria can coordinate their gene expression by assessing their population density through cell-to-cell communication known as quorum sensing. Communication occurs *via* the production of freely diffusible signal molecules known as autoinducers. Extracellular concentrations of autoinducers increase with the proportional rise in bacterial cell-density. Once autoinducer levels reach a threshold concentration, bacteria that sense these small molecules alter their gene expression patterns in a coordinated manner. Several pathogenic bacteria use quorum sensing as a means to control the production of virulence factors. Wei *et al.* (*ACS Chem. Biol.* 2011, *6*, 356−365) describe the biosynthesis of a key signal molecule involved in virulence, CAI-1, in the human pathogen *Vibrio cholerae*.



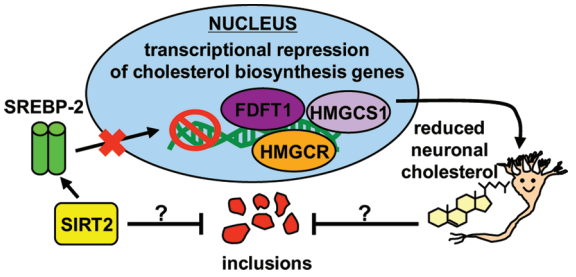
Previous studies have identified CqsA as a key biosynthetic enzyme of autoinducer (*S*)-3-hydroxytridecan-4-one (CAI-1). However, the pathway for CAI-1 production remained elusive. In an elegant study, the authors provide substantial evidence for a three-step process in the biosynthesis of CAI-1. In a never before reported reaction, CsqA couples (*S*)-adenosylmethionine (SAM) with a second substrate, decanoyl-coenzymeA, producing the previously unidentified intermediate signaling molecule, 3-aminotridec-2-en-4-one. The unique mechanism of CsqA activity involves a single step enzymatic PLP-dependent β,γ-elimination of SAM and a acyltransferase catalyzed reaction. The second step is presumed to involve the spontaneous conversion of 3-aminotridec-2-en-4-one to tridecane-3,4-dione. A newly identified dehydrogenase, VC1059 was shown to be involved in the subsequent NADPH-dependent conversion of tridec-3,4-dione to CAI-1. Given the involvement of the CAI-1 signaling pathway in the life cycle and virulence of *V. cholerae*, the current study provides new targets for the development of therapeutics.

Jitesh A. Soares, Ph.D.

BREAKTHROUGH IN DRUG DEVELOPMENT AGAINST PARKINSON'S AND HUNTINGTON'S DISEASES

The blood−brain barrier is a major obstacle for the development of drugs against diseases affecting the central nervous system. Novel ways of delivering drugs to the brain hold the key for treatment against debilitating neurodegenerative disorders such as Huntington's and Parkinson's diseases. Taylor *et al.* (*ACS Chem. Biol.* 2011, *6*, 540−546) provide a major breakthrough in drug delivery by identifying a compound that can cross this protective barrier and lower cholesterol levels in the brain.

Sirtuin 2 (SIRT2) is a NAD-dependent deacetylase that has recently emerged as a drug target. It is involved in the regulation of sterol biosynthesis, which has been linked to

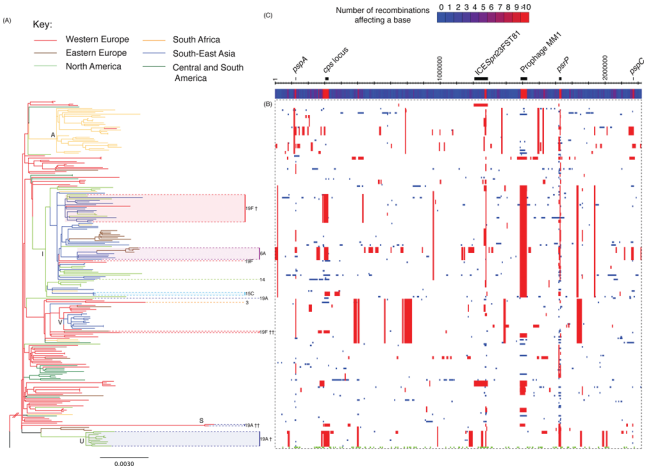


Parkinson's and Huntington's disease progression. Inhibition of this enzyme has been shown to significantly reduce cholesterol levels. The authors performed an arduous screen of a large library of compounds using mammalian-cell based assays to identify sulfobenzoic acid derivatives as a structural scaffold that inhibits SIRT2 while possessing brain-permeable properties. This scaffold led to the identification of AK-7, a brain penetrable compound that showed remarkable antineurogenerative properties by reducing neuronal cholesterol levels *via* SIRT2 inhibition. The identification of this lead compound has significant implications on drug development in treating chronic brain diseases.

Jitesh A. Soares, Ph.D.

THE EVOLUTION OF RESISTANCE

The alarmingly rapid emergence of microbial pathogens that have acquired drug and vaccine resistance has fuelled exploration into strategies for the discovery of effective new treatments, as well as investigations into the mechanisms that underlie the acquisition of resistance. Indeed, delineation of the genetic changes that accompany drug and vaccine resistance may enable the development of new strategies to target drug-resistant strains. To this end, Croucher *et al.* (*Science* 2011, *331*, 430−434) examined the genome sequences of 240 isolates of *Streptococcus pneumoniae*, a bacteria capable of causing numerous, potentially life-threatening infections including pneumonia and meningitis, and offer insight into how the genomic plasticity of this shrewd pathogen facilitates its rapid adaptation to clinical interventions.



From Croucher, N. J., et al., *Science*, **2011**, *331*, 430−434. Reprinted with permission from AAAS.

Lineages derived from the first recognized multidrug-resistant *S. pneumoniae* clone, called Pneumococcal Molecular Epidemiology Network clone 1, have been found throughout

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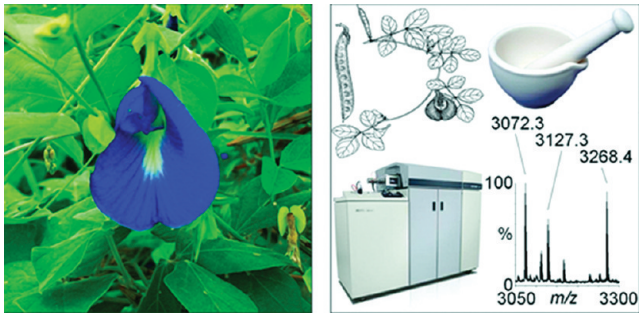
the world. Sequencing of 240 members of this global collection enabled construction and detailed analysis of the phylogeny. Over 57,000 single-nucleotide polymorphisms, including 702 recombination events, were identified. Close examination revealed that the sequence variations likely arose primarily through incorporation of imported DNA, not the accumulation of base substitutions, and the sequence changes often affected genes that encoded major antigens. Further analysis suggested that the human immune system drives increased recombination at specific loci, and that *S. pneumoniae* has distinct responses to different anthropogenic pressures. For example, changes in serotype (subgroups defined by cell surface antigen expression) that follow vaccine introduction appear to result from the depletion of the resident population and expansion of preexisting capsular variants, as opposed to a change in capsule type. In contrast, evolution of resistance to various antibiotics, including fluoroquinolones, rifampicin, and macrolides, occurred on numerous occasions and involved supplementation or replacement of the affected gene. These insights into the remarkable adaptability of this organism will inform efforts to control future, drug-resistant *S. pneumoniae* strains and guide investigations of other drug-resistant pathogens.

Eva J. Gordon

DISCOVERY OF NOVEL CYCLOTIDES

Cyclotides are gene-encoded, backbone-cyclized plant protein made up of 28−37 amino acids with three intramolecular disulfide bonds. More than 150 cyclotides have been discovered in plant families such as Rubiaceae, Violaceae, and Cucurbitaceae. Not only are these cyclized proteins highly resistant to proteolysis, but they possess therapeutically and economically significant properties. Poth *et al.* (*ACS Chem. Biol.* 2011, *6*, 345−355) report the discovery of twelve new cyclotides in Fabaceae (Legume) making it the largest plant family from which cyclotides have been isolated.



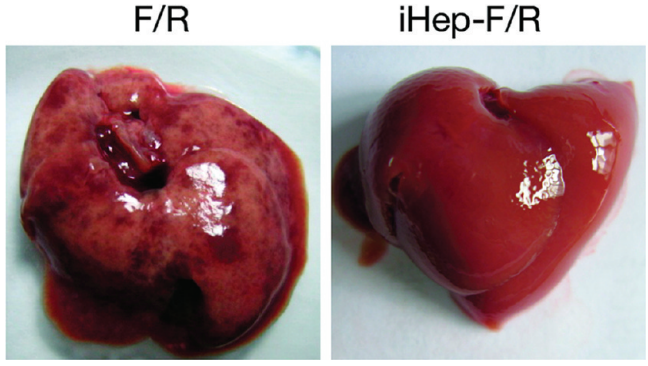
Using mass spectrometry and amino acid analysis, the authors characterized 12 novel cyclotides from the seed extracts of Butterfly Pea, a member of the Fabaceae plant family. Additionally, the authors observed unusual sequence motifs near the presumed cyclization site that provide new insight into cyclotide biosynthesis. Overall, this report reveals the presence of cyclotides in a large and important family of flowering plants offering a new understanding of their distribution in plants.

Jitesh A. Soares, Ph.D.

A TAIL OF A LIVER TRANSPLANT

Not long ago, turning a differentiated mammalian cell into a new type of cell was mere science fiction, but breakthroughs with induced pluripotent stem (iPS) cells have proven otherwise. Today, a fibroblast cell dosed with the proper medley of transcription factors can be turned into an iPS cell or even directly converted to new fates such as neural or cardiac cells. Methods like these offer great promise in the clinic, but making the transition from the Petri dish to the organism can be especially challenging. In Huang *et al.* (*Nature* 2011, *475*, 386−389), mouse fibroblast cells induced to make hepatocyte-like cells were put back into the living mouse to repopulate an ailing liver.

The researchers started with adult tail-tip fibroblast cells from mice deficient in the proliferation inhibitor gene, p19Arf, and



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expressed 14 transcription factors that are important for liver function in the cells. The resulting cells adopted an epithelial morphology and began expressing many markers of the hepatic lineage. Then, using a reductionist approach guided by previous studies, fewer transcription factors were assayed until a combination of just three genes showed the ability to induce a hepatocyte-like fate when p19Arf was inactivated genetically or by RNA interference. These induced hepatocyte-like cells, or iHep cells, shared many metabolic and gene expression patterns with primary hepatocytes. Next, the iHep cells were tested for their ability to restore liver function by using the $Fah^{-/-}$ mouse line which lacks an enzyme key for tyrosine metabolism. With a drug in their water supply, these animals function normally, but when the drug is withdrawn, they experience liver failure and death within weeks. Transplantation of iHep cells into livers significantly extended the life of these mice and cell staining post-mortem indicated that iHep cells became repopulating the liver. Though iHep cells are not the same as primary hepatocytes, this study demonstrates that induced cells could have powerful therapeutic potential if these findings can be extended from the mouse to human.

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