

## Sample Abstract – *Biochemistry & Molecular Biology*

**Abstract Title:** Stereochemical and Mechanistic Investigation of the Reaction Catalyzed by Fom3 from *Streptomyces fradiae*, a Cobalamin-Dependent Radical S-Adenosylmethionine Methylase

Fom3, a cobalamin-dependent radical S-adenosylmethionine (SAM) methylase, has recently been shown to catalyze the methylation of carbon 2" of cytidyl-2-hydroxyethylphosphonate (HEP-CMP) to form cytidyl-2-hydroxypropylphosphonate (HPP-CMP) during the biosynthesis of fosfomycin, a broad-spectrum antibiotic. It has been hypothesized that a 5'-deoxyadenosyl 5'-radical (5'-dA<sup>•</sup>) generated from the reductive cleavage of SAM abstracts a hydrogen atom from HEP-CMP to prime the substrate for addition of a methyl group from methylcobalamin (MeCbl); however, the mechanistic details of this reaction remain elusive. Moreover, it has been reported that Fom3 catalyzes the methylation of HEP-CMP to give a mixture of the (S)-HPP and (R)-HPP stereoisomers, which is rare for an enzyme-catalyzed reaction. Herein, we describe a detailed biochemical investigation of a Fom3 that is purified with 1 equiv of its cobalamin cofactor bound, which is almost exclusively in the form of MeCbl. Electron paramagnetic resonance and Mössbauer spectroscopies confirm that Fom3 contains one [4Fe-4S] cluster. Using deuterated enantiomers of HEP-CMP, we demonstrate that the 5'-dA<sup>•</sup> generated by Fom3 abstracts the C2"-pro-R hydrogen of HEP-CMP and that methyl addition takes place with inversion of configuration to yield solely (S)-HPP-CMP. Fom3 also sluggishly converts cytidyl-ethylphosphonate to the corresponding methylated product but more readily acts on cytidyl-2-fluoroethylphosphonate, which exhibits a lower C2" homolytic bond-dissociation energy. Our studies suggest a mechanism in which the substrate C2" radical, generated upon hydrogen atom abstraction by the 5'-dA<sup>•</sup>, directly attacks MeCbl to transfer a methyl radical (CH<sub>3</sub><sup>•</sup>) rather than a methyl cation (CH<sub>3</sub><sup>+</sup>), directly forming cob(II)alamin in the process.

### KEY

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Abstract must contain a hypothesis, objective or statement about the problem under investigation

Abstract must contain a brief statement of the experimental methods/methodology used

Essential results must be present in summary form (even if preliminary)

Abstract must contain a conclusion that explains how the work contributes to the hypothesis, objective or statement of problem

**Abstract Source:** Wang B. et. al. (2018). *Biochemistry* Article ASAP DOI: 10.1021/acs.biochem.8b00693

## ABRCMS 2018

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract – *Cancer Biology*

**Abstract Title:** Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma

Understanding the profile of oncogene and tumor suppressor gene mutations with their interactions and impact on the prognosis of multiple myeloma (MM) can improve the definition of disease subsets and identify pathways important in disease pathobiology. Using integrated genomics of 1273 newly diagnosed patients with MM, we identified 63 driver genes, some of which are novel, including IDH1, IDH2, HUWE1, KLHL6, and PTPN11. Oncogene mutations are significantly more clonal than tumor suppressor mutations, indicating they may exert a bigger selective pressure. Patients with more driver gene abnormalities are associated with worse outcomes, as are identified mechanisms of genomic instability. Oncogenic dependencies were identified between mutations in driver genes, common regions of copy number change, and primary translocation and hyperdiploidy events. These dependencies included associations with t(4;14) and mutations in FGFR3, DIS3, and PRKD2; t(11;14) with mutations in CCND1 and IRF4; t(14;16) with mutations in MAF, BRAF, DIS3, and ATM; and hyperdiploidy with gain 11q, mutations in FAM46C, and MYC rearrangements. These associations indicate that the genomic landscape of myeloma is predetermined by the primary events upon which further dependencies are built, giving rise to a nonrandom accumulation of genetic hits. Understanding these dependencies may elucidate potential evolutionary patterns and lead to better treatment regimens.

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**Abstract Source:** Walker B.A. et. al. (2018). *Blood* 132:587-597. DOI: <https://doi.org/10.1182/blood-2018-03-840132>.

## ABRCMS 2018

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## Sample Abstract – *Cell Biology*

**Abstract Title:** A novel microtubule nucleation pathway for meiotic spindle assembly in oocytes

The meiotic spindle in oocytes is assembled in the absence of centrosomes, the major microtubule nucleation sites in mitotic and male meiotic cells. A crucial, yet unresolved question in meiosis is how spindle microtubules are generated without centrosomes and only around chromosomes in the exceptionally large volume of oocytes. We hypothesized that oocytes have an alternative Augmin-independent pathway which recruits the  $\gamma$ -tubulin complex onto the spindle microtubules through Grip71. To test this hypothesis, an antibody was raised against Grip71 and used to immunostain mature WT oocytes which naturally arrest in metaphase I. We also hypothesized that these two pathways may act complementarily to assemble spindle microtubules. To test this, both Subito and Wac were simultaneously depleted from oocytes by expressing shRNA against Subito in ovaries of the wac null mutant. Here we report a novel oocyte-specific microtubule nucleation pathway that is essential for assembling most spindle microtubules complementarily with the Augmin pathway. This pathway is mediated by the kinesin-6 Subito/MKlp2, which recruits the  $\gamma$ -tubulin complex to the spindle equator to nucleate microtubules in Drosophila oocytes. Away from chromosomes, Subito interaction with the  $\gamma$ -tubulin complex is suppressed by its N-terminal region to prevent ectopic microtubule assembly in oocytes. We further demonstrate in vitro that the Subito complex from ovaries can nucleate microtubules from pure tubulin dimers. Collectively, microtubule nucleation regulated by Subito drives spatially restricted spindle assembly in oocytes.

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**Abstract Source:** Romé R. et. al. (2018). *Journal of Cell Biology* 218(8) DOI: 10.1083/jcb.201803172.

## ABRCMS 2018

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## Sample Abstract – *Computational & Systems Biology*

### Abstract Title: Coevolution-Based Inference of Amino Acid Interactions Underlying Protein Function

Protein function arises from a poorly understood pattern of energetic interactions between amino acid residues. Sequence-based strategies for deducing this pattern have been proposed, but lack of benchmark data has limited experimental verification. Here, we extend deep-mutation technologies to enable measurement of many thousands of pairwise amino acid couplings in several homologs of a protein family - a deep coupling scan (DCS). The data show that cooperative interactions between residues are loaded in a sparse, evolutionarily conserved, spatially contiguous network of amino acids. The pattern of amino acid coupling is quantitatively captured in the coevolution of amino acid positions, especially as indicated by the statistical coupling analysis (SCA), providing experimental confirmation of the key tenets of this method. This work exposes the collective nature of physical constraints on protein function and clarifies its link with sequence analysis, enabling a general practical approach for understanding the structural basis for protein function.

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**Abstract Source:** Salinas V. H. et. al. (2018). *eLife*. 7:e34300 DOI: 10.7554/eLife.34300.

## ABRCMS 2018

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## Sample Abstract - *Developmental Biology & Genetics*

**Abstract Title:** Loss of Elongation-Like Factor 1 Spontaneously Induces Diverse, RNase H-Related Suppressor Mutations in *Schizosaccharomyces pombe*

A healthy individual may carry a detrimental genetic trait that is masked by another genetic mutation. Such suppressive genetic interactions, in which a mutant allele either partially or completely restores the fitness defect of a particular mutant, tend to occur between genes that have a confined functional connection. Here we investigate a self-recovery phenotype in *Schizosaccharomyces pombe*, mediated by suppressive genetic interactions that can be amplified during cell culture. We performed a survival competition assay, followed by calculating the frequency of phenotypic recovery and RNA-fluorescence *in situ* hybridization (RNA-FISH). Cells without Elf1, an AAA+ family ATPase, have severe growth defects initially, but quickly recover growth rates near to those of wild-type strains by acquiring suppressor mutations. *elf1Δ* cells accumulate RNAs within the nucleus and display effects of genome instability such as sensitivity to DNA damage, increased incidence of lagging chromosomes, and mini-chromosome loss. Notably, the rate of phenotypic recovery was further enhanced in *elf1Δ* cells when RNase H activities were abolished and significantly reduced upon overexpression of RNase H1, suggesting that loss of Elf1-related genome instability can be resolved by RNase H activities, likely through eliminating the potentially mutagenic DNA–RNA hybrids caused by RNA nuclear accumulation. Using whole genome sequencing, we mapped a few consistent suppressors of *elf1Δ* including mutated Cue2, Rpl2702, and SPBPJ4664.02, suggesting previously unknown functional connections between Elf1 and these proteins. Our findings describe a mechanism by which cells bearing mutations that cause fitness defects and genome instability may accelerate the fitness recovery of their population through quickly acquiring suppressors. We propose that this mechanism may be universally applicable to all microorganisms in large-population cultures.

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**Abstract Source:** Marayati B.F. et. al. (2018). *Genetics* 209(4): 967-981. <https://doi.org/10.1534/genetics.118.301055>

## Sample Abstract – *Engineering, Physics, & Mathematics*

### Abstract Title: A Tissue-Engineered Scale Model of the Heart Ventricle

Laboratory studies of the heart use cell and tissue cultures to dissect heart function yet rely on animal models to measure pressure and volume dynamics. Here, we report tissue-engineered scale models of the human left ventricle, made of nanofibrous scaffolds that promote native-like anisotropic myocardial tissue genesis and chamber-level contractile function. Incorporating neonatal rat ventricular myocytes or cardiomyocytes derived from human induced pluripotent stem cells, the tissue-engineered ventricles have a diastolic chamber volume of ~500 µl (comparable to that of the native rat ventricle and approximately 1/250 the size of the human ventricle), and ejection fractions and contractile work 50–250 times smaller and 104–108 times smaller than the corresponding values for rodent and human ventricles, respectively. We also measured tissue coverage and alignment, calcium-transient propagation and pressure-volume loops in the presence or absence of test compounds. Moreover, we describe an instrumented bioreactor with ventricular-assist capabilities, and provide a proof-of-concept disease model of structural arrhythmia. The model ventricles can be evaluated with the same assays used in animal models and in clinical settings.

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**Abstract Source:** MacQueen L. A. et. al. (2018). *Nat. Biomed. Eng.* DOI: <https://doi.org/10.1038/s41551-018-0271-5>.

## ABRCMS 2018

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract – *Immunology*

**Abstract Title:** Activation of Th1 Immunity within the Tumor Microenvironment Is Associated with Clinical Response to Lenalidomide in Chronic Lymphocytic Leukemia

Immune stimulation contributes to lenalidomide's antitumor activity. Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature, autoreactive B cells in secondary lymphoid tissues, blood, and bone marrow and progressive immune dysfunction. Previous studies in CLL indicated that lenalidomide can repair defective T cell function *in vitro*. Whether T cell activation is required for clinical response to lenalidomide remains unclear. In this study, we report changes in the immune microenvironment in patients with CLL treated with single-agent lenalidomide and associate the immunologic effects of lenalidomide with antitumor response. Within days of starting lenalidomide, T cells increased in the tumor microenvironment and showed Th1-type polarization. Gene expression profiling of pretreatment and on-treatment lymph node biopsy specimens revealed upregulation of IFN- $\gamma$  and many of its target genes in response to lenalidomide. The IFN- $\gamma$ -mediated Th1 response was limited to patients achieving a clinical response defined by a reduction in lymphadenopathy. Deep sequencing of TCR genes revealed decreasing diversity of the T cell repertoire and an expansion of select clonotypes in responders. To validate our observations, we stimulated T cells and CLL cells with lenalidomide in culture and detected lenalidomide-dependent increases in T cell proliferation. Taken together, our data demonstrate that lenalidomide induced Th1 immunity in the lymph node that is associated with clinical response.

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**Abstract Source:** Aue G. et. al. (2018). *J. Immunol.* ji1800570 DOI: <https://doi.org/10.4049/jimmunol.1800570>.

## ABRCMS 2018

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract – *Microbiology*

**Abstract Title:** Identification, Cloning, and Characterization of *Staphylococcus pseudintermedius* Coagulase

Coagulase activation of prothrombin by staphylococcus induces the formation of fibrin deposition that facilitates the establishment of infection by Staphylococcus species. Coagulase activity is a key characteristic of *Staphylococcus pseudintermedius*; however, no coagulase gene or associated protein has been studied to characterize this activity. We report a recombinant protein sharing 40% similarity to *Staphylococcus aureus* coagulase produced from a putative *S. pseudintermedius* coagulase gene. Prothrombin activation by the protein was measured with a chromogenic assay using thrombin tripeptide substrate. Stronger interaction with bovine prothrombin than with human prothrombin was observed. The *S. pseudintermedius* coagulase protein also bound complement C3 and immunoglobulin. Recombinant coagulase facilitated the escape of *S. pseudintermedius* from phagocytosis, presumably by forming a bridge between opsonizing antibody, complement, and fibrinogen. Evidence from this work suggests that *S. pseudintermedius* coagulase has multifunctional properties that contribute to immune evasion that likely plays an important role in virulence.

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**Abstract Source:** Sewid A.H. et. al. (2018). *Infect. Immun.* 88(8): e00027-18. DOI: 10.1128/IAI.00027-18.

## ABRCMS 2018

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract – Neuroscience

**Abstract Title:** Posterior Parietal Cortex Dysfunction is Central to Working Memory Storage and Broad Cognitive Deficits in Schizophrenia

Prefrontal cortex (PFC) dysfunction is widely believed to underlie working memory (WM) deficits in people with schizophrenia (PSZ), but few studies have focused on measures of WM storage devoid of manipulation. Research in neurotypical individuals has shown that storage capacity is more closely related to posterior parietal cortex (PPC) than PFC, suggesting that reductions in WM storage capacity in schizophrenia that are associated with broad cognitive deficits may be related to neural activity in PPC. In the present human neuroimaging study, 37 PSZ and 37 matched healthy control subjects (HCS) of either sex completed a change detection task with varying set sizes while undergoing functional Magnetic Resonance Imaging. The task was designed to emphasize WM storage with minimal top-down control demands. Whole-brain analysis identified areas in which BOLD activity covaried with the number of items maintained in WM ( $K$ ), as derived from task performance at a given set size. Across groups,  $K$  values independent of set size predicted BOLD activity in PPC, including superior and inferior parietal lobules and intraparietal sulcus, and middle occipital gyrus. Whole-brain interaction analysis found significantly less  $K$ -dependent signal modulation in PSZ than HCS in left PPC, a phenomenon that could not be explained by a narrower  $K$ -value range. The slope between  $K$  and PPC activation statistically accounted for 43.4% of the between-group differences in broad cognitive function. These results indicate that PPC dysfunction is central to WM storage deficits in PSZ and may play a key role in the broad cognitive deficits associated with schizophrenia.

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**Abstract Source:** Hahn B. et. al. (2018). *J. Neurosci.* 0913-18; DOI: <https://doi.org/10.1523/JNEUROSCI.0913-18.2018>.

## ABRCMS 2018

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract – *Physiology*

**Abstract Title:** Effect of Dietary Nitrate Supplementation on Conduit Artery Blood Flow, Muscle Oxygenation, and Metabolic Rate During Handgrip Exercise

Dietary nitrate supplementation has positive effects on mitochondrial and muscle contractile efficiency during large muscle mass exercise in humans and on skeletal muscle blood flow ( $\dot{Q}$ ) in rats. However, concurrent measurement of these effects has not been performed in humans. Therefore, we assessed the influence of nitrate supplementation on  $\dot{Q}$  and muscle oxygenation characteristics during moderate- (40 %peak) and severe-intensity(85% peak) handgrip exercise in a randomized, double-blind, crossover design. Nine healthy men (age:  $25 \pm 2$  yr) completed four constant-power exercise tests (2/intensity) randomly assigned to condition [nitrate-rich (nitrate) or nitrate-poor (placebo) beetroot supplementation] and intensity (40 or 85% peak). Resting mean arterial pressure was lower after nitrate compared with placebo ( $84 \pm 4$  vs.  $89 \pm 4$  mmHg,  $P < 0.01$ ). All subjects were able to sustain 10 min of exercise at 40% peak in both conditions. Nitrate had no effect on exercise tolerance during 85% peak (nitrate:  $358 \pm 29$ ; placebo:  $341 \pm 34$  s;  $P = 0.3$ ). Brachial artery  $\dot{Q}$  was not different after nitrate at rest or any time during exercise. Deoxygenated [hemoglobin + myoglobin] was not different for 40% peak ( $P > 0.05$ ) but was elevated throughout 85% peak ( $P < 0.05$ ) after nitrate. The metabolic cost ( $\dot{V}O_2$ ) was not different at the end of exercise; however, the  $\dot{V}O_2$  primary amplitude at the onset of exercise was elevated after nitrate for the 85% peak work rate ( $96 \pm 20$  vs.  $72 \pm 12$  ml/min,  $P < 0.05$ ) and had a faster response. These findings suggest that an acute dose of nitrate reduces resting blood pressure and speeds  $\dot{V}O_2$  kinetics in young adults but does not augment  $\dot{Q}$  or reduce steady-state  $\dot{V}O_2$  during small muscle mass handgrip exercise.

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**Abstract Source:** Craig J. C. et. al. (2018). *J. Appl. Physiol.* 125(2):254-262.; DOI: <https://doi.org/10.1152/japplphysiol.00772.2017>.

**ABRCMS 2018**

Abstract Submission Site: [bit.ly/abrabstracts18](http://bit.ly/abrabstracts18)

## Sample Abstract –*Social & Behavioral Sciences and Public Health*

**Abstract Title:** Unmet Social Support Needs among College Students: Relations between Social Support Discrepancy and Depressive and Anxiety Symptoms

Social support is a widely studied construct due to its associations with physical and emotional well-being outcomes. However, little research examines the context within which receiving support may be helpful. Whereas examinations of support adequacy are present in the literature, limited research considers the difference between support needs and support received when the 2 are separated as distinct constructs. The current study consisted of 428 undergraduate college students and examined how the relation between social support needs and received social support relates to depressive and anxiety symptoms via a statistical approach suggested for need-actual discrepancy analysis (polynomial multiple regression, PMR, with response surface analysis). Results indicated that greater discrepancy between needed support and received support was related to greater depressive, but not anxiety, symptoms. Specifically, when emotional support needs exceeded emotional support received, depressive symptoms tended to be highest. Moreover, perceptions of needed support were significantly greater than perceptions of received support, suggesting that college students in general perceive receiving less support than they need, and this discrepancy is related to greater depressive symptoms.

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**Abstract Source:** Rankin J.A. et. al. (2018). *J. Counseling Psych.* 65(4):474-489. DOI: <http://dx.doi.org/10.1037/cou0000269>.

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