1682-Pos Board B574
Genomic Contingency and Protein Evolution: Accelerated Divergence of a DNA-Binding Module due to an Adjoining Micro-Satellite Invasion
Michael A. Weiss, Yen-Shan Chen.
Case Western Reserve University, Cleveland, OH, USA.
The sex-determining region of the mammalian Y chromosome encodes an architectural transcription factor containing a conserved sequence-specific high-mobility-group (HMG) box. Designated SRY, transient expression of this gene in the fetal gonadal ridge leads to Sertoli-cell differentiation and in turn testis formation. Mutations in human SRY are associated with 46, XY pure gonadal dysgenesis and somatic sex reversal. We have investigated the evolutionary history of SRY and its protein product SRY among placental mammals as a model for the conservation and divergence of a sequence-specific DNA-binding and DNA-bending module (the HMG box). Remarkably, the rate of divergence among mammalian SRY genes is markedly more rapid in Rodentia than among other Orders of placental mammals. Evidence will be provided that this accelerated evolution is a consequence of the in-frame insertion of a CAG triplet-expansion micro-satellite element, encoding a poly-glutamine or poly-alanine domain with autonomous biochemical properties. A model is proposed wherein relaxation of selective pressure on the HMG box has led to accumulation of deleterious amino-acid substitutions. Thus, a contingency of genomic dynamics (micro-satellite invasion) has led to a change in the pace of the mutational clock governing the evolution of a DNA-binding module.

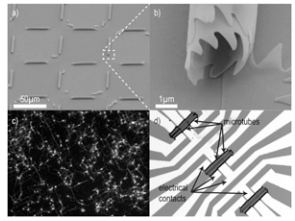
1683-Pos Board B575
Design and Synthesis of a Novel Photochromic HDAC Inhibitor and its Photo Reversible Inhibitory Effect
Keiko Tanaka, Shinsaku Maruta.
Soka University, Tokyo, Japan.
Core histone is composed of two H2A-H2B dimers and H3-H4 tetramers. Each histone have tail domain, which regulates dynamic structure of chromatin and transcription through posttranslational modifications. Histone acetylation-deacetylation is one of such epigenetic regulations of gene expression in eukaryotes. Histone deacetylase (HDAC) catalyze deacetylation of lysine residues in N-terminal domain of core histones and regulates gene transcription and expression. Inhibition of HDAC induces transcriptionally active chromatin, causing arrest of growth, differentiation and apoptosis. HDAC inhibitors are thought to be effective for neurodegenerative disorders, cardiac hypertrophy, inflammation and cancer. Photochromic molecule can be changed its property reversibly upon ultra-violet and visible light irradiations. using inhibitor composed of photochromic molecules, reversible site-directed regulation is thought to be achieved without displacement of solution or chemical modification. In this study, we designed and synthesized a novel photochromic HDAC inhibitor, N-(2-hydroxy-5-phenylphenyl)-4-[(E)-2-phenyldiazen-1-yl]benzamide, composed of azobenzene moiety which may bind specifically to surface region, benzamide group and phenyl group, which may bind to metal ion on active center, respectively. The design of the photochromic inhibitor was based on known HDAC inhibitor, N- (2-hydroxy-5-phenylphenyl) benzamide, which is known to affect HDAC class 1 selectively. Azobenzene moiety is placed in hydrophobic interacting region of inhibitor, therefore, it is expected that the light-induced structural change affects its affinity for HDACs. The synthesized photochromic HDAC inhibitor showed light-induced isomerization, derived from azobenzene moiety, and fluorescence, derived from biaryl moiety. Both of the cis and trans isomers of the inhibitor showed inhibitory effect of human whole HDAC activity. The trans-isomer of photochromic biaryl HDAC inhibitor showed higher affinity to HDAC in hela nuclear extract than cis isomer. Furthermore, other kind of photochromic biaryl inhibitor having functional group on azobenzene moiety was also examined.

Excitable Systems

1684-Pos Board B576
Modeling K_{ATP}-Dependent Excitability in Pancreatic Islets
Jonathan R. Silva[1], Colin G. Nichols[2].
[1]Washington University in St. Louis, Saint Louis, MO, USA, [2]Washington University School of Medicine, Saint Louis, MO, USA.
In pancreatic beta cells, K_{ATP} channels respond to changes in blood glucose to regulate cell excitability and insulin release. Confirming this role, gain or loss of function mutations in K_{ATP} are linked to neonatal diabetes or hyperinsulinism, respectively. Compared to neurons or cardiac myocytes, cellular models of beta-cell electrical activity have remained relatively rudimentary, but a recent detailed computational model of single cell pancreatic beta cell excitability (Cha et al., J Gen Physiol. 2011 138:21-37) accurately reproduces the beta cell response to varying glucose concentrations. Our aim was to test whether the model could also reproduce experimentally observed changes in excitability when K_{ATP} conductance is altered by genetic manipulation. Since the experiments were conducted in islets, we extended the model from a single cell to a 3D model (10x10x10 cell) islet with 1000 cells. For each cell, the conductances of the major currents were allowed to vary as was the gap junction conductance between cells. Initial simulations showed that the model was unable to reproduce K_{ATP} conductance-dependent changes in glucose-responses of excitability. By altering the ATP dependence of the L-type Ca^{2+} channel and the Na^{+}-K^{+} pump to better match experiment, appropriate K_{ATP} dependence was quantitatively reproduced. In extending and refining the previous model, these simulations highlight the criticality of these parameters and suggest further experiments to improve characterization of beta cell excitability.

1685-Pos Board B577
Wavefronts and Mechanical Signaling in Early Drosophila Embryos
Timon Idema[1,2], Julien O. Dubuis[3], M. Lisa Manning[4], Philip C. Nelson[2], Andrea J. Liu[2].
[1]Delft University of Technology, Delft, Netherlands, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Princeton University, Princeton, NJ, USA, [4]Syracuse University, Syracuse, NY, USA.
Many developmental processes use signaling for synchronization. One possible and well-known method is for each component to measure the local concentration of some diffusing biochemical species, and if that concentration exceeds a certain threshold, to release more of the same biochemical, giving rise to wavefront propagation in the chemically excitable medium. There are however more ways in which a medium can be excited and wavefronts can be formed. We suggest a new kind of signaling based not on diffusion of a chemical species, but on the propagation of mechanical stress. We construct a theoretical approach to describe mechanical signaling in an overdamped system as a nonlinear wavefront propagation problem. We apply the theory to mitosis in the early syncytial Drosophila embryo, which is highly correlated in space and time, as manifested in mitotic wavefronts that propagate across the embryo. We compare our results to data taken on Drosophila embryos in which histones in the nuclear chromosomes are labeled with GFP. By analyzing confocal microscopy videos of the mitotic wavefront, we find that the wavefront can be resolved into two distinct wavefronts in each cycle, corresponding to the onset of metaphase and of anaphase, respectively. The two wavefronts have the same speed and are separated by a time interval that is independent of cycle, indicating that they are two different markers for the same process. We find that the dependence of wavefront speed on cell cycle number is most naturally explained by mechanical signaling via stress diffusion, and that the entire process suggests a scenario in which biochemical and mechanical signaling are coupled.

1686-Pos Board B578
Guided Growth and Electrical Probing of Neurons on Arrays of Biofunctionalized GaAs/InGaAs Semiconductor Microtubes
Cornelius S. Bausch[1], Aune Koitmäe[1], Eric Stava[1], Daniel Diedrich[1], Amanda Price[2], Pedro J. Resto[2], David Sonnenberg[1], Christian Heyn[1], Williams Justin[2], Erik Dent[2], Robert H. Blick[1].
[1]University of Hamburg, Hamburg, Germany, [2]University of Wisconsin-Madison, Madison, WI, USA.
We demonstrate embedded growth of cortical mouse neurons in dense arrays of semiconductor microtubes (see Figure (a,b)). The microtubes, fabricated from a strained GaAs/InGaAs heterostructure, guide axon growth through them and thus, enable the outgrowth of complex, artificial neuronal networks (see Figure (c)). At the same time, in situ electrical sensing is made possible. We present methods of stimulating and sensing action potentials, where electrodes are embedded inside the microtubes (see Figure d)). The wrapping of these electrodes around the axon greatly increases the contact area, and, with the fabrication of multiple electrodes along the tube length allow for the measurement of action potential propagation along single axons. The coaxial nature of the microtubes - similar to myelin - is expected to enhance the signal transduction along the axon.



Our choice of GaAs, an optical III-V semiconductor, offers a variety of advantages over Si despite its toxicity: Its electron velocity and mobility is generally higher than, resulting in lower noise levels of possible electronic devices. We present a technique of suppressing arsenic toxicity and prove its efficiency by the results of neuronal cell culture.