Harnessing Gene-Expression 'Noise' for Therapy

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Over the past decade, a stubborn debate has persisted in biology regarding the role and importance of stochastic fluctuations (probabilistic 'noise') in gene-expression. The debate roughly parallels the early 20th century "Bohr-Einstein" debates in Physics between the deterministic classical-mechanics view and the probabilistic quantum-mechanical view (emblemized by Einstein's grand indictment of quantum mechanics: "God does not play dice with the universe"). Clearly, quantum mechanics prevailed and is a cornerstone of modern physics, in large part because of its practical utility to atomic-orbital theory and semiconductor applications. In Biology, there have been no analogous applications for 'noise'; the debate will likely continue until practical uses for noise are identified.

I will present a set of newly identified noise-modulating chemicals (Dar et al. ***Science*** 2014). These compounds modulate noise in HIV expression and synergize with conventional activators to reactivate HIV from latency.

By screening a diverse library of bioactive small molecules, we identified over 80 compounds that modulated HIV gene-expression fluctuations ('noise'), without changing mean expression. These noise-modulating compounds would be neglected in conventional screens and strikingly they synergized with conventional transcriptional activators. Noise enhancers reactivated latent cells significantly better than existing best-in-class reactivation while noise suppressors stabilized the latent state. Noise-modulating chemicals synergized with in both cell-culture lines and human primary cells and are all FDA-approved compounds that exhibit minimal cytotoxicity. Noise-modulating chemicals may provide novel probes for the physiological consequences of noise and may provide an unexplored axis for drug discovery, allowing enhanced control over cell-fate decisions in diverse biological systems.