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Spotlight

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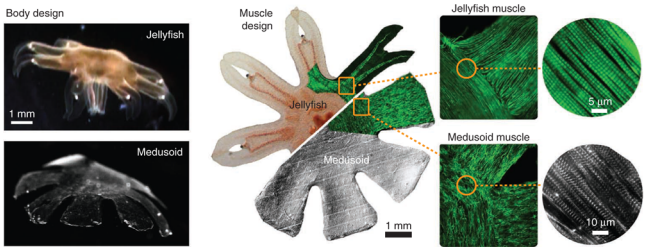
JELLYFISH BY DESIGN

Tissue engineering is an exciting field with various diagnostic and therapeutic applications. The relatively simplistic, umbrella-like motion used by adult jellyfish, also called medusae, to move through the water presents an attractive opportunity for designing a synthetic muscular pump. Jellyfish, made up of a bell-shaped, transparent body surrounded by a symmetric display of tentacles, require just a few specific cell types, including motor neurons and striated muscle cells, and efficient interactions with fluid to support their movement. Nawroth *et al.* (*Nat. Biotechnol.* 2012, *30*, 792−797) now combine computational design methods, rat tissue, and versatile biomaterials to reverse engineer a "synthetic jellyfish", referred to as a medusoid, capable of moving like a real jellyfish.



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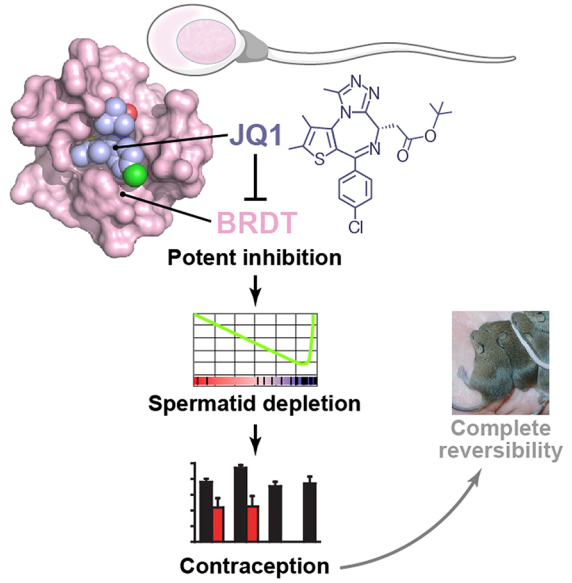
To simulate the rhythmic movement of the jellyfish body, the authors use a sheet of cultured rat cardiac muscle cells synchronized by an electrical field. To mimic the jellyfish contraction and expansion strokes, they construct a bilayer comprised of the muscle cells, which provide the force to contract the bell, and jelly fish shaped polydimethylsiloxane elastomer, which facilitates restoration of the original shape. Finally, the medusoid was designed to contain wedge-shaped lobes separated by gaps, a geometry that optimizes the efficiency of fluid transport in the construct. Remarkably, medusoids with these parameters achieved similar propulsion and contraction movements, velocities, and fluid currents as real jellyfish. The medusoids presented here highlight the incredible potential of tissue engineering for developing designed biomaterials with various functionalities, including those simulating entire organisms. **Eva J. Gordon, Ph.D.**

"THE PILL" FOR MEN!

Proteins involved in epigenetic regulation, such as the bromodomain and extraterminal (BET) subfamily of epigenetic reader proteins, have emerged as intriguing drug targets for various conditions such as cancer, inflammation, and metabolic disorders. The protein BRDT, a BET family member that recognizes acetyl-lysine moieties on histones, is expressed in testis and is essential for sperm production. The tissue-selective expression, coupled with the association of mutations in the *BRDT* gene with infertility in both animals and humans, points to BRDT as a potential target for the design of male contraceptives. To this end, Matzuk *et al.* (*Cell* 2012, *150*, 673−684) report that the small molecule JQ1, a known inhibitor of another BET family protein called BRD4, is a potent inhibitor of sperm production.



Reprinted from *Cell*, *150*, Matzuk, M. M., *et al.*, Small-Molecule Inhibition of BRDT for Male Contraception, 673−684. Copyright 2012, with permission from Elsevier.

Various biochemical and structural characterization methods, including a homogeneous luminescence proximity assay, isothermal titration calorimetry, and X-ray crystallography demonstrated that JQ1 is a potent and competitive inhibitor of BRDT. Pharmacokinetic studies in male mice showed that JQ1 can effectively permeate the blood:testis barrier. In addition, it was shown that JQ1 treatment significantly reduces testis volume, sperm number and motility, and production of new sperm, and genome-wide expression analysis demonstrated a reduction in expression of a number of spermatogenic genes. Notably, mice treated with JQ1 were phenotypically similar to mice deficient in BRDT, supporting the notion that JQ1 acts through inhibition of BRDT. The contraceptive effect of JQ1 was shown to be dose-dependent and reversible within a few months, and the compound did not appear to affect testosterone levels, mating behaviors, or developmental processes in offspring. These compelling results designate JQ1 as a promising lead compound for development of an oral contraceptive drug for men. **Eva J. Gordon, Ph.D.**

THE ENEMY NEXT DOOR

Tumors often acquire resistance to anticancer drugs, which frequently leads to treatment failure, especially in late stage cancers. This ominous conduct has been attributed to the ability of tumor cells to export or metabolize the drugs and/or alter their survival mechanisms, but numerous investigations have also uncovered a role for the tissue surrounding the tumor, called the stroma, in drug resistance mechanisms. To explore how stromal cells might contribute to drug resistance, Sun *et al.* (*Nat. Med.* advance online publication August 5, 2012; DOI:

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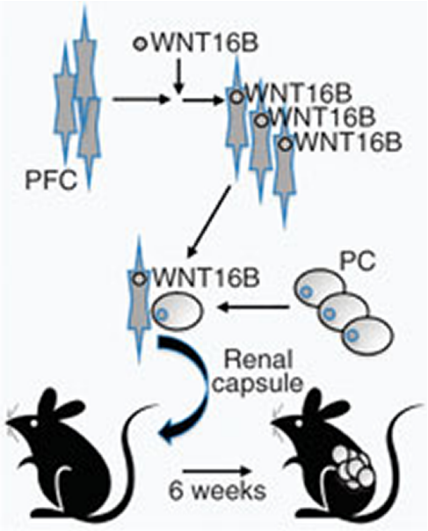
10.1038/nm.2890) conducted a genome wide analysis of transcriptional responses to cancer drugs in prostate cancer tissue.



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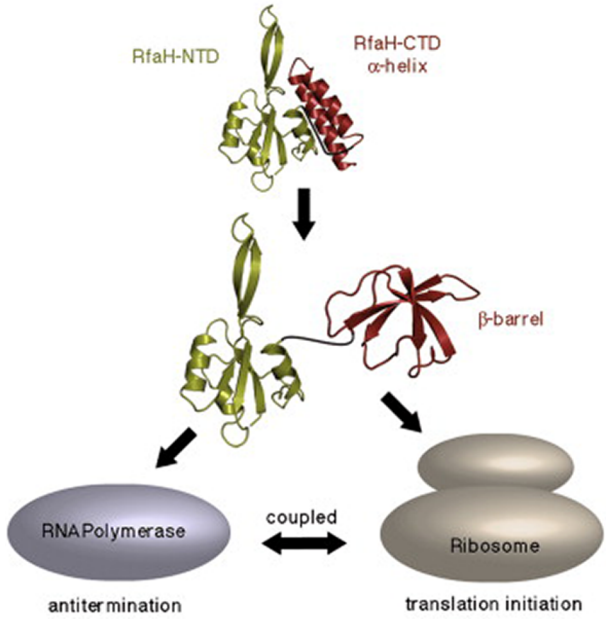
The authors initially noted that noncancerous stromal cells that surround prostate tumor tissue, including fibroblasts and muscle cells, exhibited DNA damage in response to chemotherapy treatment. They also found that prostate fibroblasts treated with anticancer agents had increased expression of various secreted proteins, including the Wnt family member WNT16B. To probe the role of WNT16B expression in drug resistance, the authors generated engineered fibroblast cell lines expressing the protein. They showed that the conditioned medium from the cells, which contains the secreted protein, had a number of telling effects on cancer cells, including: increased proliferation and invasiveness; activation of the cell adhesion and signaling protein β-catenin; promotion of the loss of adhesion and increased motility; reduction of chemotherapy-induced cytotoxicity; and increased viability. They also determined that WNT16B activity is regulated by the transcription factor NF-κB, which is known to be involved in DNA repair mechanisms. Together, the study puts forth a compelling model in which treatment-induced damage to stromal cells leads to secretion of WNT16B, which in turn activates survival pathways in neighboring cancer cells and promotes the development of drug resistance. The results outline a path forward for targeting drug resistance in anticancer strategies. **Eva J. Gordon, Ph.D.**

RFAH: MORE THAN MEETS THE EYE

In all kingdoms of life, the NusG-like transcription factors play a central role in committing a transcription complex to a processsive, elongation state. Mechanistically, it is thought that the N-terminal domain of NusG proteins bind and bridge two subunits of the RNA polymerase to lock down the enzyme into a processive mode. In *E. coli*, where the founding family member NusG was identified, a second NusG-like protein, RfaH, is also encoded and has always appeared to play a specialty role. While NusG participates in the transcription of most loci, RfaH is only recruited to a few horizontally transferred operons displaying a conserved recognition site in their DNA. These sibling proteins share a structurally identical N-terminal domain, but the C-terminal end of NusG and RfaH appeared completely different. In previously solved structures, NusG's C-terminus adopts a β barrel motif while RfaH adopts an α helical hairpin motif. Now, a new study indicates a dramatic structural rearrangement by the RfaH C-terminus, transforming this domain to a β fold.

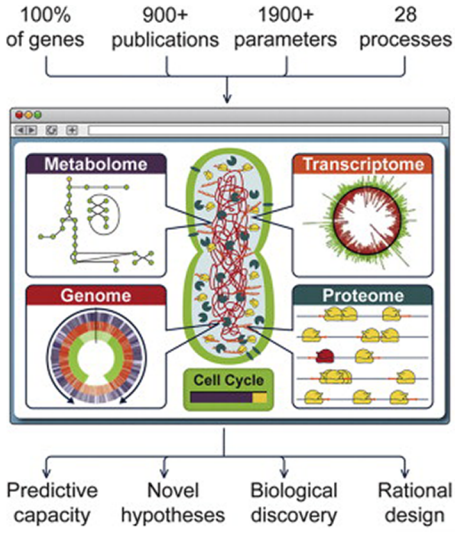


Reprinted from *Cell*, *150*, Burmann, B. M., *et al.*, An α Helix to β Barrel Domain Switch Transforms the Transcription Factor RfaH into a Translation Factor, 291−303. Copyright 2012, with permission from Elsevier.

Burmann *et al.* (*Cell* 2012, *150*, 291−303) used NMR to show that in the full length protein context, RfaH's C-terminal region formed an α helical fold, but curiously, when this domain was studied alone, the fold was almost identical to the β fold of NusG. But was this an artifact of isolated proteins or does structural rearrangement play a role in the biology of RfaH? Interestingly, the subsequent experiments show that this interconversion actually switches RfaH from a transcription factor to a translation factor. When RfaH takes on the β fold, the protein enhances translation of the operons that are being transcribed. The authors show that this is through an interaction with S10, a component of the 30S subunit of the ribosome. This is biologically important for the RfaH-dependent operons since they do not naturally possess canonical ribosome binding sites and, as such, coupling transcriptional elongation to protein synthesis can greatly boost protein output. While there are certainly many cases of gene expression machines being coupled to one another, this study shows that a single protein can sometimes shape shift to play a dual role in both transcription and translation. **Jason G. Underwood, Ph.D.**

ENTER THE AGE OF "VIRTUAL CELL BIOLOGY"

Computer models are powerful tools for understanding and predicting biological phenotypes. An elusive goal has been to understand individual interactions on a "whole-cell" scale which lead to complex phenotypes .With the coming of age of genomics and high-throughput techniques, however, characterization has begun to reach a level of accuracy where comprehensive phenotypic prediction is within reach. In a recent article, Karr *et al.* (*Cell*, 2012, *150*, 389−401) provide a revolutionary study that thrusts us into a new era of "virtual cell biology".



Reprinted from *Cell, 150,* Karr, J. R., *et al.*, A Whole-Cell Computational Model Predicts Phenotype from Genotype, 389−401. Copyright 2012, with permission from Elsevier.

The authors selected *Mycoplasma genitalium*, a human urogenital parasite with a small genome size (525 genes), for "whole-cell" computational modeling. The functionality of cells was subdivided into 28 independent modules (*e.g.*, metabolism, protein degradation, *etc.*) with each module modeled by an appropriate mathematical representation. These independent modules were subsequently integrated to interact and exchange variables in other modules at 1 s intervals. This integrated simulation was subsequently repeated several thousand times until termination when cell division is simulated to cease upon the septum diameter variable reaching zero. This "whole-cell" computational model accurately predicted known experimental data across multiple biological functions. Interestingly, the model also provided new insight into previously unobserved cellular behavior, such as predicting factors that regulate cell-cycle duration. On the basis of these predictive models it is easy to envision integrative "whole-cell" models revolutionizing experimental design and stimulating biological discovery. **Jitesh A. Soares, Ph.D.**

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