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SPOTLIGHT

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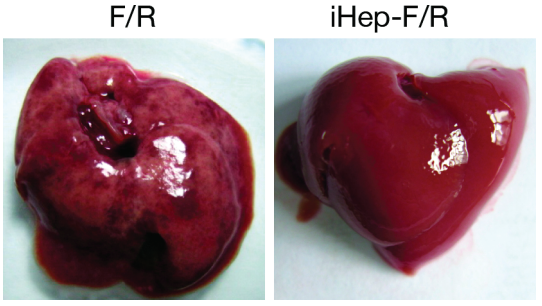
A Tail of a Liver Transplant

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 a new study by Huang *et al.* (*Nature* 2011, advance online publication May 11, 2011; DOI: 10.1038/nature10116), mouse fibroblast cells induced to make hepatocyte-like cells were put back into the living mouse to repopulate an ailing liver.



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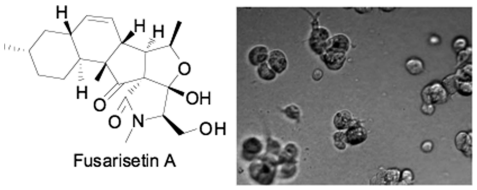
The researchers started with adult tail-tip fibroblast cells from mice deficient in the proliferation inhibitor gene, p19Arf, and expressed 14 transcription factors that are important for liver function in the cells. The resulting cells adopted an epithelial morphology and began expressing many markers 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 that 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 With a drug in their water supply, these animals function normally, but when the drug is withdrawn, they experience liver failure and death within weeks.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 repopulated 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. **Jason G. Underwood, Ph.D.**

Extracting Novel Anticancer Agents

Together, microorganisms such as bacteria and fungi produce an enormous collection of natural products with diverse and intriguing biological and medicinal properties. Finding such natural products from the plethora of microorganisms that roam the planet, however, can be a tedious process, though one that is greatly facilitated by the development of a meaningful biological assay. Jang *et al.* (*J. Am. Chem. Soc.* 2011, *133*, 6865−6867) describe their use of a three-dimensional cellular assay to identify fusarisetin A, a structurally novel compound produced by a fungus of the *Fusarium* species. Their chemical and biological characterization of fusarisetin A illuminates its unique structural and biological properties.



Fusarisetin A

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Extracts from the fungus were screened for their ability to disrupt the behavior of breast cancer cells suspended in a three-dimensional gel composed of various structural proteins and growth factors. In the gel, the cells can engage in numerous activities that mimic normal and cancer cell behavior, including forming berry-like structures called acini. One fungal extract inhibited acinar formation, and chromatographic purification followed by extensive structural characterization using mass spectrometry, nuclear magnetic resonance, infrared spectroscopy, X-ray crystallography, and circular dichroism revealed a compound containing a novel pentacyclic ring system with an impressive 10 stereogenic centers. Further biological characterization demonstrated that the compound inhibited the migration and the invasive capabilities of the cells, with limited toxicity. Investigation into potential biological targets of the compound eliminated several signaling molecules commonly associated with cancer cell migration and invasion, suggesting that further characterization of the compound may point to the discovery of a novel target for the development of anticancer drugs. **Eva J. Gordon, Ph.D.**

Giving Blood Vessels a Little More Muscle

Angiogenesis, the growth of new blood vessels, is a fundamental component of numerous normal and pathological processes including proper organ development, wound healing, and the progression of cancer. Angiogenesis is mediated in part by specific angiogenic factors that promote the growth of endothelial cells, which make up the blood vessel walls. However, the limited success of exploiting such growth factors as therapeutic agents for vascular disease suggests that other factors are also at play. Vascular smooth muscle cells play an important role in the

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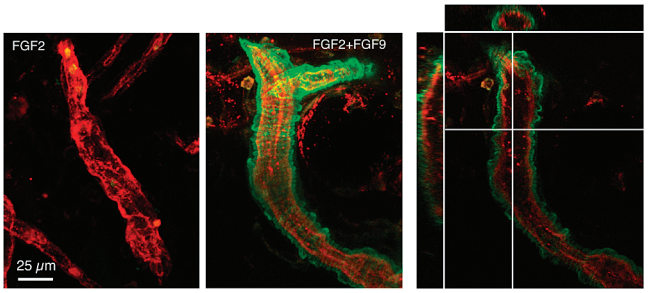
proper functioning of new blood vessels by enabling the dynamic regulation of blood flow through the vessels, which facilitates oxygen and nutrient delivery to the tissue. Frontini *et al.* (*Nat. Biotechnol.* 2011, *29*, 421−427) now demonstrate that the growth factor fibroblast growth factor 9 (FGF9) promotes the muscularization of new blood vessels, which may be an essential component of vascular regeneration in damaged tissues.



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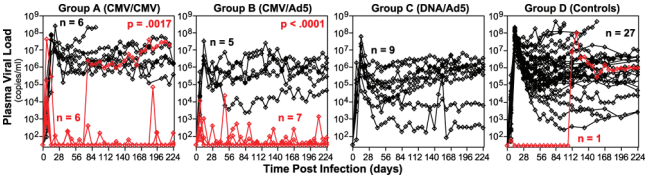
A three-dimensional cellular assay designed to assess the ability of smooth muscle cells to wrap around a tube network of endothelial cells was used to facilitate the search for factors involved in blood vessel muscularization. Microarray expression analysis revealed that FGF9 was highly upregulated in during this process. It was further demonstrated that FGF9 activated FGF receptor-dependent signaling pathways in the cells and enhanced cell survival, attributes likely important in tissue regeneration. FGF9 also promoted the wrapping of small blood vessels by muscle cells and induced expression of two signaling molecules, platelet-derived growth factor receptor b and sonic hedgehog, pointing to the signaling pathways involved in the muscularization process. Finally, imaging methods in mice showed that FGF9 facilitates regulation of blood flow through new vessels, and promotes the maturation and recovery of vessels in damaged areas. These findings represent an exciting advance in the development of new strategies for vascular regeneration therapy. **Eva J. Gordon, Ph.D.**

Nipping Viral Infection in the Bud

The human immunodeficiency virus (HIV) and its simian counterpart SIV viciously attack the immune system of their hosts, rendering their prey incapable of mounting an effective immune response and effectively evading detection by the immune system once an infection is established. However, the first few days after infection, before the virus has had a chance to disseminate and replicate, may present a window of opportunity to nip viral infection in the bud using immune intervention, provided an effective immunization strategy is available. Hansen *et al.* (*Nature* advance online publication May 11, 2011; DOI: 10.1038/nature10003) now report the development of novel SIV vaccines that exploit the vulnerability of the virus in those early days of infection.



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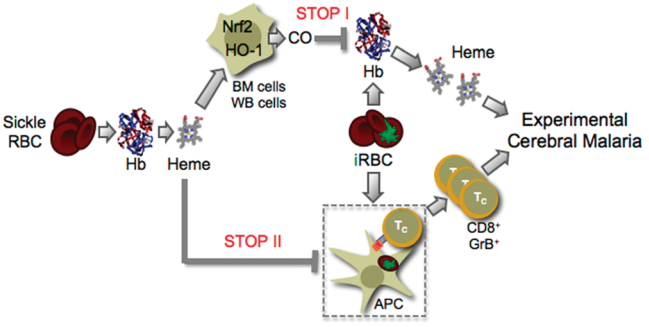
The success of the SIV vaccines was based on the incorporation of pieces of the rhesus cytomegalovirus (RhCMV), which are highly persistent and are known to induce the generation of effector memory T-cells, into the vaccine. Effector memory T-cells are better suited to mount an immune response against the localized virus present in the first few days of infection than the central memory T-cells generated by nonpersistent agents typically used in vaccine development. Thirteen of 24 rhesus macaques vaccinated with the RhCMV-based vaccines were able to control initial SIV infection. In addition, when the animals were subjected to SIV exposure approximately 1 year after vaccination, 12 of those 13 remained protected from infection, in striking contrast to the animals in the control groups who all became infected with SIV. Examination of immune activity in the RhCMV-vaccinated animals indicated the execution of a highly controlled immune response to SIV infection mediated by the effector memory T-cells. The incorporation of elements from persistent viral agents such as CMV into vaccines targeting members of the HIV/SIV family presents an exciting new approach for vaccine development in the fight against AIDS. **Eva J. Gordon, 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 from *Cell*, *145*, Ferreira *et al.*, Sickle hemoglobin confers tolerance to Plasmodium infection, 398−409. Copyright 2011, with permission from Elsevier.

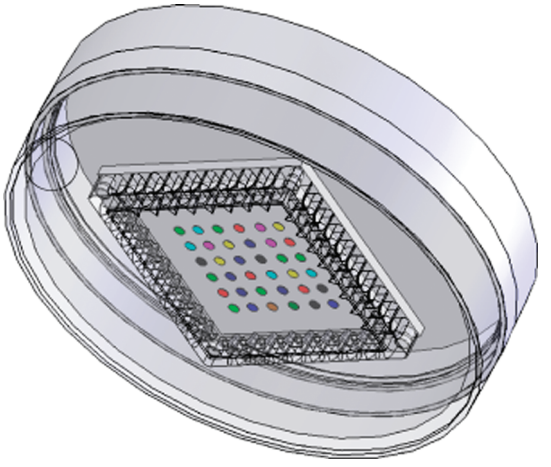
People with hemoglobin S, the mutated form of the protein, tend to leach free heme from their red blood cells. High concentrations of free heme in the plasma are toxic but can prompt the expression of heme oxygenase-1 (HO-1), an enzyme that protects against many inflammatory diseases. In detailed studies 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.**

Sniffing out Pathogenic Bacteria

Sepsis is one of the leading causes of death in the developed world. Lacking methods to rapidly identify pathogenic bacteria, physicians are unable to treat patients with suitable antibiotics in a timely fashion. Available identification procedures are typically tedious and require long culturing periods overseen by highly skilled staff. To circumvent this problem, Carey *et al.* (*J. Am. Chem. Soc.* 2011, *133*, 7571−7576) report the development of an exciting new method for the rapid identification of bacteria by detecting their characteristic "smell."



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Bacteria produce their own distinctive metabolites, a signature composed of volatile organic compounds (VOCs) unique to individual bacterial strains. Taking advantage of this strain-specific identification, the authors developed a colorimetric sensing array for the detection of VOCs from complex heterogeneous mixtures. The colorimetric sensing array is placed into a Petri dish with growth media in which the pathogens can proliferate. This sensor array consists of 36 chemically diverse dyes, composed of pH indicators, metal salts, metalloporphyrins, solvatochromic dyes, *etc.* that change color depending on the VOCs present. The color maps of 10 different bacterial strains such as *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *etc.* and their antibiotic-resistant forms can be accurately identified after a relatively short (10 h) incubation period. The implications of this new rapid and cost-effective colorimetric sensor array are enormous in the quick and precise diagnosis of patients suffering from bacterial infections. **Jitesh A. Soares, Ph.D.**