Energy

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Energy-rich portfolio of new genome sequencing targets

Bioenergy crop plants switchgrass and cassava, other important agricultural commodities such as cotton, and microbes geared to break down plant material to render biofuels, round out the roster of more than 40 projects to be tackled by the U.S. Department of Energy Joint Genome Institute (DOE JGI) over the next year. The genomes of these organisms will be sequenced and characterized as part of the DOE JGI Community Sequencing Program (CSP).

"By coupling DNA sequencing technology with fundamental research, we seek to make cellulosic ethanol a major part of the nation's energy future," said DOE JGI Director Eddy Rubin. "The newest direction in biosciences research--systems biology--is built on a strong foundation of DOE's investment in genomics, with DNA sequence as the starting material of that endeavor and DOE JGI as the generator of that information through the CSP. Downstream characterization of the pathways inferred by the genetic code of the target CSP organisms is then supported through the DOE Genomics:GTL program."

In his 2006 State of the Union Address, President George W. Bush specifically cited the promise of switchgrass as a bioenergy crop. A tall perennial grass, a dominant species of the North American prairie, switchgrass (Panicum virgatum) is particularly compelling because of its relatively low production costs, minimal nutrient and pesticide requirements, perennial growth habit, as well as its ability to adapt to a broad range of growing conditions. The net energy gain for ethanol production from switchgrass is exceptionally favorable, coupled with low greenhouse gas emissions.

In complement to switchgrass, DOE JGI will be sequencing Brachypodium distachyon, a temperate grass model system with a simple genome more amenable to sequencing. This choice responds to the urgent need for developing grasses into superior energy crops and improving grain crops and forage grasses for food production. Brachypodium.
Another major CSP project is the selection of cassava (Manihot esculenta), an excellent energy source and food for approximately one billion people around the planet. Its roots contain 20 to 40 percent starch, from which ethanol can be derived, making it an attractive and strategic source of renewable energy. Cassava grows in diverse environments, from extremely dry to humid climates, acidic to alkaline soils, from sea level to high altitudes, and in nutrient-poor soil. "Sequencing the cassava genome will help bring this important crop to the forefront of modern science and generate new possibilities for agronomic and nutritional improvement," said Norman Borlaug, Nobel laureate. The cassava project will extend broad benefits to its vast research community, including a better understanding of starch and protein biosynthesis, root storage, and stress controls, and enable crop improvements, while shedding light on such mechanisms shared by other important related plants, including the rubber tree and castor bean.

Adding to the list of crops to be sequenced by DOE JGI is the oyster mushroom, Pleurotus ostreatus, for its prospective role in bioenergy and bioremediation. This white-rot fungus is an active lignin degrader in the forests. Lignin, a poly-aromatic hydrocarbon, is the second most abundant biopolymer on earth and its breakdown is a necessary step for making cellulose--the most abundant carbon biopolymer--available for conversion to biofuels. This organism will serve as a valuable comparison to the reference genome of white-rot fungus Phanerochaete chrysosporium, previously sequenced by DOE JGI.

Life Sciences

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Reawakened 'executioner' makes cancer self-destruct

A drug which exploits the cells' own suicide mechanism has specifically targeted cancer cells in mice without harming healthy tissue, a new study shows. The drug, which cured human lung and kidney cancers in the mice, may offer tailored treatments for individual cancer patients, the researchers hope.Called PAC-1, the drug converts a dormant protein called procaspase-3 into its active form, an "executioner" protein called caspase-3, which consigns the cell to death. In previous lab-based studies, the team has shown that PAC-1 successfully kills off a whole range of cancers, provided they are rich in procaspase-3.

The treatment works because procaspase-3 is often much more abundant in cancer cells than in healthy cells, says Paul Hergenrother at University of Illinois, who led the study: "In tissue from 23 colon cancer patients we found that, on average, levels of procaspase-3 are eightfold higher than in healthy cells – sometimes as much as 20-fold higher." In this latest study, Hergenrother and colleagues gave the drug to mice with human lung and kidney cancers, which contain about five times more procaspase-3 than healthy cells. After two months of treatment, the tumours were greatly reduced, while the mice that did not receive the drug had excessive tumour spread. "In the lung cancer experiments, the control mice ended up riddled with tumours, but in the treated lungs there was hardly any sign of the tumours," Moreover, the treatment worked when the drug was given orally, suggesting it could work as a pill and so be easy to administer.

One major benefit is that patients can be screened before treatment to check if they are eligible, Hergenrother says. If they have a big disparity in procaspase-3 levels between cancerous and healthy tissue, PAC-1 could be effective at quite low doses without harming healthy tissue, he says. "It means you'd have the executioner ready and waiting for activation in cancer cells," says Hergenrother. "And the more procaspase-3 there is relative to healthy cells, the more sensitive the cancer cells are to PAC-1, so the less you'd have to give the patient to kick-start action."

Hergenrother says that the epithet "executioner" protein is well-deserved, because caspase-3 is the final and decisive step in the signalling pathway by which abnormal cells self-destruct through a process called apoptosis. The advantage of activating caspase-3 is that nothing can stop it once it is activated. This is preferential to other attempts to trigger apoptosis by repairing damaged signals - such as the protein p53 - further back in the signalling cascade. These approaches can fail if a repaired signal still does not make it through to caspase-3 due to an additional fault further down the line. "We've found a compound that can bypass the entire cascade, so you don't need to worry if there's any damaged machinery above caspase-3,"

Before clinical trials can begin, more toxicity and dosing data is needed in animals, and the Illinois group is screening for even better versions of PAC-1. The first targets could be cancers of the colon and lung.

No Cell Walls, No New Cancer Cells

Cancer cells, like houses, need building materials for their walls. And as with a house, the cell wall needs to be built at just the right moment to protect and allow the construction of internal components.

A team from the Uppsala Branch of the global Ludwig Institute for Cancer Research (LICR) has not only shown how the cell gets this timing right, but has also conducted proof-of-principle studies that indicate taking away the cell's bricks and mortar is a potential strategy for cancer control. "New cells are created by the duplication of existing cells through a highly-organized process known as the cell cycle," explains lead author, Dr. Maite Bengoechea Alonso. "Last year we discovered that a protein called SREBP1 that regulates the synthesis of lipids needed for new cell walls was regulated during the cell cycle. Now we show that the SREBP1 protein actually controls the cell cycle." The team of researchers realized that disrupting the function of SREBP1 might prevent the lipid synthesis required for new cell walls. "In fact, we literally stopped the cell cycle in its tracks by removing SREBP1 from cells. It seems that if you don't have SREBP1 activity, you can't make lipids, and if you don't have lipids, you can't make new cells. This approach might one day form the basis of a new strategy for the long-term control of cancer."

"Cancer cells divide uncontrollably, so their need for lipids is more urgent and continuous than normal cells. Treatment with an inhibitor of SREBP1 might reduce the rate of cancer cell proliferation to slow down tumor growth, or might enhance the effect of targeted therapies that aim to actually kill cancer cells."

Healing potential discovered in everyday human brain cells

Common brain cells may have stem-cell-like potential

University of Florida researchers have shown ordinary human brain cells may share the prized qualities of self-renewal and adaptability normally associated with stem cells.
Writing in Development, scientists from UF's McKnight Brain Institute describe how they used mature human brain cells taken from epilepsy patients to generate new brain tissue in mice. Furthermore, they can coax these pedestrian human cells to produce large amounts of new brain cells in culture. "We can theoretically take a single brain cell out of a human being and - with just this one cell - generate enough brain cells to replace every cell of the donor's brain and conceivably those of 50 million other people," said Dennis Steindler "This is a completely new source of human brain cells that can potentially be used to fight Parkinson's disease, Alzheimer's disease, stroke and a host of other brain disorders. It would probably only take months to get enough material for a human transplant operation."

The findings document for the first time the ability of common human brain cells to morph into different cell types, a previously unknown characteristic, and are the result of the research team's long-term investigations of adult human stem cells and rodent embryonic stem cells.Last year, the researchers published details about how they used stem-like brain cells from rodents to duplicate neurogenesis - the process of generating new brain cells - in a dish. The latest findings go further, showing common human brain cells can generate different cell types in cell cultures. In addition, when researchers transplanted these human cells into mice, the cells effectively incorporated in a variety of brain regions.

The human cells were acquired from patients who had undergone surgical treatment for epilepsy and were extracted from support tissue within the gray matter, which is not known for harboring stem cells.When the donor cells were subjected to a bath of growth agents within cell cultures, a type of cell emerged that behaves like something called a neural progenitor - a cell that is a bit further along in development than a stem cell but shares a stem cell's vaunted ability to divide and transform into different types of brain cells. Even when the cells from the epilepsy patients were transplanted into mice, bypassing any growth enhancements, they were able to take cues from their surroundings and produce new neurons."It was a long and difficult process, but we were able to induce what are basically support cells in the human brain to form beautiful new neurons in a dish. But what we really needed is for these support cells to turn into neurons in the brain, and we found we could get them to do it. Something in the environment in the rodent brain is sufficient to get these cells to become neurons."

Scientists speculate a small amount of existing progenitors may be emerging from the gray matter of the brain and multiplying in torrents, or perhaps the aging clock of the mature cells actually turns backward when the donor cells are in a new environment, returning them to past lives as progenitors or as stem cells.

In addition to using the cells in treatments to repair or replace damaged brain tissue, the ability to massively expand cell populations could prove useful in efforts to test the safety and efficacy of new drugs. It is also possible to genetically modify the cells to produce neurotrophins - substances that help brain tissue survive, researchers said.

Touch alone makes stem cells differentiate

Researchers have managed to specify the type of cell an adult stem cell will become by altering the stiffness of the material they are grown on. Bone, nerve and muscle cell lines have been selectively initiated from human bone marrow cells by changing the physical consistency of the growth medium.
Previous studies have demonstrated that biochemical signalling strongly influences stem cell development. Now, researchers have shown for the first time that in the absence of any chemical signalling, adult bone marrow stems cells will begin to differentiate into unique cell types based solely on how tough the surrounding "tissue" is. Adam Engler at the University of Pennsylvania isolated adult stem cells in a series of three different polymer gels, each of a different stiffness. The softest corresponded roughly to the consistency of neuronal tissue; the middle to muscle tissue; and the hardest was similar to bone. When undifferentiated stem cells were placed in each of the gels – devoid of any biochemical signals – they began differentiating down the path to becoming exactly the type of tissue the gels' were designed to emulate.

Fully mature cells have been shown to be reliant on their physical surroundings for some time. A good example of this is fibroblasts – all-purpose mature cells found in connective tissue that can morph to form bone, cartilage, or even muscle cells. The cells in the study expressed just the first few steps in a progression of proteins necessary for differentiation into the various cell types, and had not to matured fully. Further work will be necessary to test whether cells can develop and form complex tissue structures without chemical signals. It also remains to be seen whether embryonic stem cells will display similar sensitivity to the mechanical properties of their surroundings.

"A first approach to stem cell therapies has been simply injecting cells into injured tissues.We would say that's not going to be sufficient because the cells would be entering an improper physical environment. That has been the dominant paradigm, but it's naïve. We need to learn how tissues repair themselves and mimic that."

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Nanowires Listen In on Neurons

Electrodes made of nanowires can measure the complex signals in a single brain cell.

Creating a tool with unmatched sensitivity, Harvard University researchers have made silicon nanowires that can precisely measure multiple electric signals within a neuron. These ultrasmall silicon wires could help brain scientists understand the underpinnings of learning and memory. They could also be used in neural prosthetics, providing electrodes far more sensitive than those currently used.

The research group, led by Charles Lieber, professor of chemistry at Harvard University, has developed techniques for synthesizing large arrays of silicon nanowires, which act as transistors, amplifying very small electrical signals from as many as 50 places on a single neuron. In contrast, the most precise existing methods can pick up only one or two signals from a neuron. By detecting electrical activity in many places along a neuron, the researchers can watch how it processes and acts on incoming signals from other cells. The nanowires are about the same size as the branches that neurons use to communicate with one another. William Ditto, professor of biomedical engineering at the University of Florida, says neurons probably send the same kinds of signals to the nanowires as they do to other neurons. As a result, the nanowires could provide a realistic view of a neuron's complex firing patterns.

Lieber and his coworkers make the silicon nanowires from silane gas in a vacuum furnace. Gold catalyst particles in the furnace determine the nanowires' diameters -- 20 nanometers for the neuron experiments. The nanowires are separated from one another and connected to electrical contacts made of nickel. The wires and their contacts are then mounted on a silicon chip that has been patterned with protein to promote neuron growth. Next, Lieber seeds a rat brain neuron on the chip and waits 7 to 10 days, while it grows. The neuron-friendly protein provides a path that directs a neuron's growth along the chip and ensures that it makes contact with the nanowires.

"The most interesting question is: How do cells in the brain actually communicate?" says Lieber. Electrical signals travel across neurons by means of an "action potential," a rapid swing in the cell's membrane voltage from negative to positive and back to negative within a few milliseconds. This voltage change doesn't occur throughout the whole cell at once, but rather spreads from a neuron's incoming branches, called dendrites, to the main body of the cell. Other branches, called axons, carry signals in the form of action potentials to other neurons' dendrites, as well as to muscle and other tissues. Neurons receive many incoming electrical signals through their dendrites that aren't carried even as far as the cell body. Although tiny changes in electrical conductivity within cells are the basis of normal learning and memory -- and many brain pathologies -- neuroscientists still have not been able to observe these small changes with the existing tools. The nanowires will be an important tool for studying neural circuits -- the networks of communicating neurons -- in great detail. And understanding neural circuits could provide insight into learning and memory, as well as advancing computer science. Lieber hopes the nanowires will find applications in medical devices. They might be used to "build an interface to the brain that's much more sophisticated" than current ones, which rely on large electrodes, he says. Such devices might help control epilepsy or pain, or, like cochlear implants for hearing, substitute for damaged sensory nerves.Lieber's group is also developing the nanowires to make even more sophisticated connections with neurons. The area where two neurons meet, a synapse, is characterized not just by electrical signaling but also by chemical signaling. In fact, the transfer of chemicals known as neurotransmitters at synapses is what allows the transmission of electrical signals from one neuron to another. Lieber has already demonstrated that his nanowires can act as sensitive chemical sensors. His group is now working to make nanowires that can detect -- and someday possibly release -- neurotransmitters.