their lymphoid cells were also of the donor type. Eight months following engraftment, the stem-cell deficient hosts' bone marrow and spleen were heavily populated with donor cells, while the thymus was not. In the T- and B-cell deficient hosts, the opposite was true. Mintz adds that she does not yet know anything substantial about the expression of the genes of interest in the host, although *myc* and *neo* can be expressed in B-cell lines, with 20–40 percent efficiency.

The human gene for HPRT (hypoxanthine guanine phosphoribosyl transferase) is expressed very poorly in mouse bone marrow cells. Theodore Friedmann (University of California, San Diego) says that when he looked at the expression of this marker, he found that the activity was very low, evanescent, and certainly not very efficient. This led him to change targets and concentrate on liver cells instead. Friedmann used murine retroviral-based vectors expressing a mutagenized human HPRT gene and a bacterial neomycin resistance gene. Friedmann's *in vitro* experiments on infecting adult rat liver hepatocytes with these retroviral vectors demonstrate that hepatocytes are indeed targets for retroviral gene transfer. Although Friedmann has yet to do the *in vivo* experiments, the system makes available in principle a means to cure hepatic and metabolic diseases.

HPRT is an important enzyme in purine biosynthesis. Mammalian cells normally have two major routes for making purines: *de novo* synthesis and a salvage pathway (driven by HPRT). Some cells, however, have marginally functional *de novo* pathways and depend on the HPRT route. These cells are in the basal ganglion of the brain; the absence of HPRT activity results in Lesch-Nyhan disease.

When Friedmann introduced HPRT cDNA into retroviral vectors, he found that he could transfect both the gene and its function back into cells from Lesch-Nyhan patients. The enzymatic activity was restored to levels close to those in HeLa cells; moreover, the aberrant metabolic features of the cells—including altered purine pools—were corrected toward normal.

In principle, gene therapy should work. In practice, researchers are far from that goal. For any human work, Mulligan cautions, better methods to infect large numbers of cells are needed. Scientists need to develop *in vitro* assays for human cells that will allow them to determine that they have infected the crucial stem cells to reconstitute patients.

—Jennifer Van Brunt

MIAMI SYMPOSIUM

JUMPING PHENOTYPES ARE HARD TO KEEP UP WITH

MIAMI—The yeast *Candida albicans* is more than a useful laboratory tool: this pathogenic organism kills more people than all other fungi combined. *Candida* kills one-quarter of all AIDS patients and one-quarter of all terminal leukemics. Even worse, the yeast's prevalence is on the rise: whereas 20 years ago it was extremely rare to find a systemic *C. albicans* infection, today one-third of all bone marrow transplant recipients carry the yeast.

And the situation could get worse. David Soll (University of Iowa, Iowa City) and his colleagues have identified three different high-frequency phenotype switching systems in *Candida*; Soll warns that this has "extraordinary implications for the pathogenicity of this organism."

Each high-frequency switching system gives *Candida* a second level of variability, built over its basic dimorphic differentiation pattern (budding yeast vs. hyphae formation). Soll and his colleagues discovered the first switching system (3153A) in the laboratory when a variant kept "popping out of the population" at a frequency of one in one hundred (much too high for a mutation). Moreover, this variant could itself switch to six other phenotypes, again at a frequency of one in one hundred. And any of these phenotypes could jump to any of the others. Once a cell has switched—whether spontaneously or induced by ultra-violet light—it is in a high frequency mode. The system is heritable and reversible. (For details see *Science* **230**:666, 1985.)

A second switching system, picked up in yeast isolated from a systemic infection, is termed the white/opaque transition. Again, the frequencies of phenotypic switching are one in one hundred. (Several other phenotypes appear at lower frequencies, as well.) In this system, when a cell switches, virtually everything changes. In fact, Soll says that the opaque state is so different from the white that it has been mistaken for a different genus in the literature. Soll says that the opaque cell buds differently, has a different volume, a different nuclear structure, different actin distribution patterns, and differences in the synthesis of a few major polypeptides. (See *J. Bacteriol.* **169**:189, 1987 for details.)

How can one keep track of a particular *Candida* strain in a case like this? Soll says that his lab, in collaboration with James Hicks (Research Institute of Scripps Clinic, La Jolla, CA), has isolated chromosomal mid-repeat sequences that are non-mobile. These mid-repeats can act as fingerprints for the different strains. Two different switch phenotypes from one strain give identical mid-repeat banding patterns on Southern blots.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Phenotypic switching in the 3153A system. The switch from ring to star can occur at frequencies of one in one hundred.

There is also a mid-repeat that jumps. Soll says that he and Hicks have recently demonstrated that the sequence is telomeric, residing on many chromosomes. He adds that they have not yet correlated this jumping with phenotypic switching.

Switching is not just a laboratory phenomenon: It occurs at the site of infection, as well. Soll has recently demonstrated that, in women infected with *Candida*, switching in the vagina happens at extraordinarily high rates. Four out of 11 vaginal isolates contained multiple switch phenotypes, and nine of them were already in high-frequency mode. Southern blots of cellular DNA to compare the non-mobile mid-repeat sequences demonstrated that multiple phenotypes at the site of a single infection did represent the same strain.

According to Soll, every time *Candida* switches (in the white/opaque transition system, as well as the 3153A system), it changes its resistance to the known antifungal agents. In some cases it changes its antigenicity, as well. This does not bode well for treating systemic infections. Concludes Soll: "It's scary."

—Jennifer Van Brunt