plantation and growth of transplanted human cells. The other important marker used by the authors is the production of human albumin in mice with chimeric livers. (A note of caution: Although the title gives the impression that the infected mice have human livers, in reality they have mouse livers that contain a variable proportion of human hepatocytes.)

The viral titers in the blood of the infected mice are high—equal to or higher than those present in patients with chronic hepatitis C. The detection of HCV replicative-intermediate RNA (negative strand) inside the human cells in the mouse liver and western-blot analysis showing the expression of viral proteins during the course of the infection would have provided a stronger demonstration that the virus indeed infected the human cells.

A major puzzle in the experimental data is that Mercer *et al.* detected the presence of the HCV genomic strand (positive strand) for a much longer period of time than the replicative strand. If the virus stopped its replication, it would be highly unusual for the genomic strand to persist. The puzzle might have been solved by carrying out serial measurements of viral titers to determine how long the virus

can persist in mice in which replication should not occur (non-transplanted mice, for instance). These experiments would also strengthen the important evidence for serial passage of the virus to naive mice.

The system described by Mercer *et al.* is laborious and requires special expertise to isolate and transplant human hepatocytes and maintain a colony of fragile immunodeficient mice with an approximately 35% mortality in newborns due to a defect in blood coagulation. I suspect that not many virologists will jump into hepatitis C research upon reading this paper. Nevertheless, the results should have a major impact in the field for testing antiviral agents and, if nothing else, as a proof of principle that a mouse model for HCV infection is feasible. It is thought that in human chronic hepatitis C, hepatocyte injury is not directly caused by HCV infection, but is a consequence of the destruction of infected hepatocytes by cytotoxic lymphocytes. My question to the authors and others who may use and optimize this system is this: Will these mice develop liver disease confined to the transplanted human hepatocytes or will the immunosuppressed mice be infected

but free of disease?

And by the way, the alphabet soup of viral hepatitis has expanded to six viral types.

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Anticancer squirt

A compound derived from a marine organism defines a new class of anticancer drugs that targets the nucleotide excision repair system of cells.

Ecteinascidin 743 (Et743) is an alkylating agent that tightly binds DNA in the minor groove. It was originally isolated from the Caribbean sea squirt, *Ecteinashidia turbinata*, shown in the photograph. In Phase II/III trials, the compound has shown remarkable activity against a number of advanced cancers, including sarcomas.

On page 961 of this issue, Takebayashi *et al.* show that Et743 DNA adducts are recognized by a cell's nucleotide repair system, which ends up killing the cell instead of repairing the damage caused by the adducts. What is particularly interesting, and relevant to cancer therapy, is that the killing is only seen if the repair occurs in transcribed genes.

Nucleotide excision repair (NER) is a mechanism for removing and repairing lesions that distort the DNA helix, such as ultraviolet-light-induced cyclobutane pyrimidine dimers or adducts caused by alkylating anticancer drugs. There are

two pathways of NER—one which recognizes damage localized to transcribed regions and the other damage in the global genome. Several proteins that have critical roles in one or both pathways are known.

The link between Et743 and NER was uncovered by the authors by generating two Et743-resistant cell lines and showing that both have defects in the gene encoding xeroderma pigmentosum (XPG), an endonuclease involved in NER. Restoring XPG activity in these cells restored their ability to repair DNA damage induced by ultraviolet light and also Et743 sensitivity.

Cell lines deficient in other genes that, similar to XPG, are essential to both transcription-coupled and global genome NER were also found to be resistant to Et743. However, cells deficient in XPC, which encodes a protein that only recognizes damage in the global genome, were sensitive to Et743 killing. This find-

ing suggested that ecteinascidin cytotoxicity is specifically associated with transcription-coupled NER.

In each cell tested, Et743 cytotoxicity correlated with functional transcription-coupled NER activity as well as with the presence of single-stranded DNA breaks in transcribed genes. Based on these observations, the authors suggest that when the NER system detects Et743 adducts in genes it makes single-stranded DNA breaks on either side of the lesion. These breaks are what cause the cells to die.

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