

BY DAVID BALTIMORE

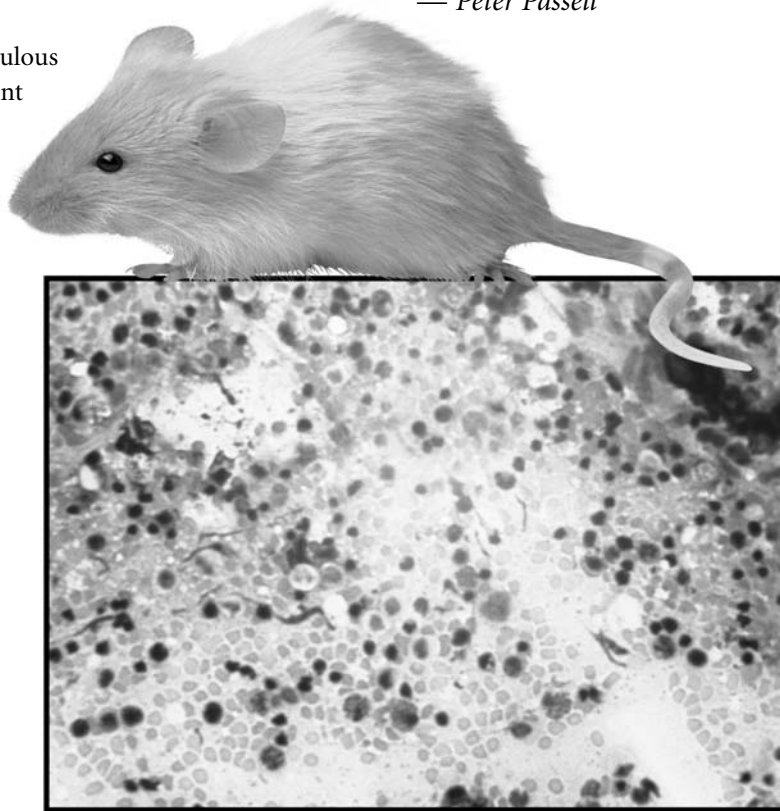
*The Center for Accelerating Medical Solutions (CAMS) is asking researchers from a variety of fields to suggest novel ways in which the system for producing medical treatments can be made more effective. Here, David Baltimore, the Nobel Prize-winning virologist who is now president of Cal Tech and a member of the CAMS board sketches one approach.*

— Peter Passell

Medical science has produced miraculous treatments for many diseases in recent years, but certain types remain intractable. Many cancers cannot be treated. Autoimmune diseases remain a plague. We can prevent many infectious diseases by vaccination – but not AIDS, tuberculosis or malaria. Medical science continues to work on these problems, but the longer we go without progress, the more we should be saying, “Perhaps these problems need a revolutionary approach.”

The Bill & Melinda Gates Foundation has set up special grants for “grand challenge” approaches to the killers of the less-developed world, primarily the three infectious diseases that have resisted efforts to design a vaccine. This represents recognition of the difficulty of dealing with these particular agents as well as the difficulty of doing medicine in circumstances where the infrastructure and resources for delivering care are very limited.

I suggest one general approach to these problems that would be revolutionary and which poses great challenges, but could pro-



vide new hope for dealing with these intractable problems. It derives from the insight that untreatable cancers – particularly solid tumors and recalcitrant infectious diseases – have one characteristic in common: they

## **WHAT I WOULD DO**

progress even though the immune system is trying its best to mount a defense against them. They slip through our defenses using many strategies – too many to list here. Suffice it to say that there is often a potentially effective immune response, but it lacks the power to totally control the pathogenic process.

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It is conventional wisdom that dietary supplements, positive thinking, stress control and other environmental manipulations can increase the effectiveness of the immune system, but none of these activities is of documented value. However, the immune system is genetically controlled and it is possible to manipulate its mechanisms using gene-therapy methods. All immune cells derive from so-called hematopoietic stem cells – cells found in adults in the bone marrow. So the gene therapy could be performed on bone marrow stem cells, mobilizing the cells from the bone into the blood by standard methods and allowing them to be harvested from the blood.

The procedure for modifying the genes of bone marrow stem cells has been well established in mice. The most efficient way to do it is to bring new genes into the cells using a virus as a carrier or vector. We and others

have achieved especially high efficiency using so-called lentivirus vectors as carriers of the new genes. Lentiviruses are the class of viruses that include HIV, but the vector is completely denuded of any genes that might cause disease and is purely a carrier of the modifying genes.

We have had good results with two kinds of genes, ones that encode negative regulators called small, interfering RNAs (siRNAs) and ones that encode the business end of certain immune cells called T-cell receptor (TCR) genes. There are other genes that could produce a therapeutic effect and could be used in such a protocol.

If siRNAs and TCRs have given such good results, why is such a gene therapy protocol considered a grand challenge? Because the method being proposed has never been used therapeutically in humans, and would create a number of potential dangers. For instance, the vector brings genes into cells by integrating its DNA with the cell's DNA. However, it integrates randomly and could integrate near a cancer-causing gene, activate it and produce a cancer cell.

This is not a theoretical issue: in a clinical trial using a virus related to the lentivirus, just such an integration potential was found. If this possibility can be circumvented, other problems loom. And if they can be solved, to export this methodology to the less-developed world would mean greatly simplifying it to drive the cost way down.

There are a few laboratories working along these lines. But I would encourage the National Institutes of Health to identify a series of really difficult but potentially valuable methodologies, like this, and to encourage their development with funds targeted to grand challenges that have huge payoffs. That could accelerate medical solutions to our most feared diseases. **M**