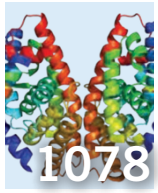
Flu fix:
A small genetic tweak promises safer influenza research



Gamma gamble:
Drugmakers double down on RORγt inhibitors

Inducing aura:
Neurologists strive to trigger migraine auras in human subjects

After 40 years, fate of recombinant DNA committee under review

WASHINGTON, DC — Engineering a gene into a treatment destined for human patients was once a frightening concept, and perhaps still is to some. As a result, gene therapy has always undergone an extra level of scrutiny in the US, in the form of the Recombinant DNA Advisory Committee (RAC). But the RAC now faces a potential reduction or modification of its powers, with some scientists proposing it should evaluate only protocols that involve substantially new types of genetic manipulation.

On 6 August, gene therapists, bioethicists and lawyers debated whether to let the RAC be, reshape its role or abolish it altogether before a team of independent reviewers convened here by the US Institute of Medicine (IOM). "We've now had, I think, quite astonishing improvements in our knowledge of the basic science, coupled with clinical trials that have demonstrated that gene transfer is no more risky than other new therapies," Carl June, director of translational research at the University of Pennsylvania Abramson Family Cancer Research Institute in Philadelphia, said at the meeting.

"In a sort of Darwinian world, the question is which are the characteristics of the RAC that make it fit for survival, and which, as in past evolutions, are ready to drop away," said Alexander Capron, a former RAC member and a healthcare law specialist at University of Southern California in Los Angeles, who spoke at the IOM meeting.

Detailed protocol review may be one such characteristic. Today clinical investigators must still submit protocols for the 20 members of the RAC to consider if they or the institutions involved in the study receive funding from the US National Institutes of Health (NIH). With an annual operating cost of more than $680,000, the RAC holds four public meetings each year and selects about 20% of the roughly 70 protocols submitted each year for full review.

The NIH established the RAC in 1974 to alleviate public anxiety over the possible ethical and scientific consequences of manipulating DNA in the lab. But over the ensuing decades the primary fears of new, uncontrolled pathogens created through experiments and foreign genes entering the human germline have not materialized. Since 1989, almost 2,000 clinical trials involving gene therapy have taken place worldwide. During the same timeframe, the RAC has seen degrees of change, narrowing its jurisdiction mainly to novel gene-therapy experiments and vectors. With gene therapies already approved in Europe and China, some feel that the US has lagged behind and that the extra oversight wrought by the RAC is partly to blame.

Helen Thompson

Splicing opinion: The IOM reviews discuss their views of the RAC's value.

The extra scrutiny imposed by the RAC is not necessary, says Xandra Breakefield, a neuroscientist at Harvard Medical School in Boston and former president of the American Society of Gene and Cell Therapists (ASGCT). "To take the level of detail they're taking now, which in my view is microscopic, you really just bog everything down," says Breakefield, who has written on the subject in *Nature Medicine* (*Nat. Med.* **18**, 1007, 2012). Slowing down the review of experimental protocols frustrates clinicians and patients alike, and in March 2012, the ASGCT asked the NIH to do away with the RAC's review of individual study proposals. Many gene-therapy vectors, such as those developed from the adeno-associated virus (AAV), have also become ubiquitous in experimental vaccines and other treatments in development, but the RAC still takes time to do a full review of some AAV protocols.

Transparent benefits

One area where experts agree that the RAC has made a unique mark is in its transparency. All RAC meetings and data are open to the public, and occasionally, the RAC also holds special workshops on trials or issues in the field. "The RAC has been held up as a model of what you can do by promoting public trust and public discourse and scientific discourse about a field," says Jacqueline Corrigan-Curay, acting director of the NIH's Office of Biotechnology Activities, which houses the RAC.

None of the experts disagree that RAC review can potentially inform experiments involving new vectors and future therapies involving induced pluripotent stem cells. Most speakers agreed that the RAC needs to be scaled back—either to reviewing only first-in-class experiments or to serving purely as a registry—but not nixed completely.

The IOM is expected to release a report of its findings in December. It may recommend modifying or axing individual protocol review by the RAC or expanding the RAC to fields outside of gene therapy. Although doing away with the RAC is on the table, it seems unlikely.

"We have these dueling understandings," says Lawrence Gostin, a health law scholar at the Georgetown University Law Center in Washington, DC, who chairs the IOM review committee. "The RAC is a model. It's got expertise. It's got public engagement. It's open. Perhaps the individual protocol reviews have limited utility, but if we get rid of it, perhaps we run the risk of making it less relevant."

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