MEETING REPORT

EN-ABL-ING RAS: ACTIVATION RE-EXAMINED

INDIANAPOLIS—In one of the livelier sessions at the recent symposium marking the dedication of the new \$60 million Eli Lilly Biomedical Research Building, David Baltimore (M.I.T.) described experiments that elucidate the structure of the cellular version of the *abl* oncogene of the Abelson murine leukemia virus. His work also offers some clues into the way transforming viruses might activate normal cellular genes to true oncogenes. As it exists in the virus, *abl* encodes a polypeptide of 403 amino acids that has a measurable tyrosine kinase activity. When Baltimore examined cellular mRNAs, he found four classes of message that hybridize with probes derived from this region. Their structures are intriguing. Each of the four types of "cellular-*abl*" genes consists of three basic parts: the exons representing the kinase domain, a common exon at the 5'-junction, and a type-specific exon at the extreme 5'-end. Although he did not speculate on the functions of these various genes, he did say that the Type I gene (the most abundant message) displays complete conservation in its type-specific exon between human and mouse cells.

Extrapolating, Baltimore said this suggests the domain is involved in key protein-protein interactions, which would tend to be preserved through evolution, and that perhaps the plethora of viral oncogenes represent a collection of truncated proteins that normally interact with internal regions of receptor proteins. Earlier in the day, Ora Rosen (Sloan-Kettering Institute, New York) had presented the latest refinement of her proposed structure for the insulin receptor in which the internal kinase domain contacts the transmembrane part of the receptor in exactly this manner.

As though intent on reinforcing Baltimore's truncation argument, Peter Duesberg, (University of California, Berkeley) presented evidence that the *v-ras* oncogene is also a truncated version of its cellular counterpart. He compared the published sequences of all known *v-ras* genes and the sequence of the upstream region of *ras*'s cellular homologue. Approx-

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Comparison of the structures (from top to bottom) of human and rat proto-*ras* oncogenes and their known viral counterparts. X-1 represents a proposed upstream exon various portions of which are found at the 5'-ends of the viral genes, and the rat pseudo-*ras* gene.

mately 1,000 base pairs upstream of the start of the viral p21 protein there is an open reading frame. Various portions of this presumptive exon are joined to each of the known *v-ras* genes at their 5'-ends (see illustration). As Duesberg pointed out, this

view (that *v-ras* is a truncated *c-ras*) brings it into line with the structures of all other viral oncogenes. And in this context, the current favored hypothesis—that *v-ras* is activated solely by point mutations—is open to re-examination.

—Harvey Bialy

MEETING REPORT

VIRAL CAVEAT FOR GENE THERAPY

INDIANAPOLIS—Producing safe retroviral vectors for delivering foreign genes to human cells may not be the straightforward procedure originally envisioned. According to Thomas Caskey (Baylor College of Medicine, Houston, TX), speaking at the Eli Lilly Dedicatory Symposium, when helper cell lines are transfected with DNA in which the foreign gene of interest is inserted between viral long terminal repeat (LTR) sequences, the progeny virus contain wild type infectious particles at frequencies between 10^{-4} and 10^{-5} . In the most widely used protocol, a helper cell line into whose genome a "packaging deficient" provirus has

been stably integrated is used to provide capsids for the introduced vector DNA (see *Bio/Technology* 3:689, August '85). Ideally, all virus produced in such cells should be incapable of further productive infection. Most likely, says Caskey, a recombination event in the helper line is responsible for the observed low frequency of wild type virus, although the activation of resident proviral genomes cannot be completely excluded.

Whatever the mechanism, the fact that preparations can be contaminated by infectious virus will have to be seriously considered when the risk: benefit ratios of retroviral delivery systems are finally assessed. —HB