

INTEGRATION OF HIV DNA: MECHANISTIC AND THERAPEUTIC IMPLICATIONS

Frederic D. Bushman¹, Gary P. Wang¹, Troy Brady¹, Keshet Ronen¹, Tracy Diamond, Angela Ciuffi¹, Nirav Malani¹, Philippe Leboulch⁴, Marina Cavazzana-Calvo³, and Charles C. Berry²

¹University of Pennsylvania School of Medicine, Department of Microbiology, 3610 Hamilton Walk, Philadelphia, PA 19104-6076; ²Department of Family/Preventive Medicine, University of California, San Diego School of Medicine, San Diego, CA 92093; ³Department of Biotherapy, Hôpital Necker-Enfants Malades, 75743 Paris, France; ⁴CEA, Institute of Emerging Diseases and Innovative Therapies (iMETI), Fontenay-aux-Roses 92265, France

Integration of retroviral vector DNA into host cell DNA is a defining feature of retroviral replication. The integration system is important as a new drug target, as a model for function of molecular machines that change genomes, and as a tool for use in human gene therapy. The lecture will cover the mechanisms underlying integration and the consequences for the host cell. One line of work to be discussed centers on the mechanisms by which retroviruses select integration target sites in chromosomes. HIV integration is known to be favored in active transcription units, which promotes efficient transcription of the viral genes. A host cell factor, PSIP1/LEDGF/p75 acts as a tethering factor to direct local integration, accounting for part of the effect. These findings suggest possible new drug targets. In addition, the methods devised for basic studies of retroviral integration targeting are useful for analyzing integration sites generated during human gene therapy, including the first uses of HIV-based vectors in humans. Selected results from such studies will also be discussed.