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Large Chimeric Circular MACs for Gene Therapy and Animal Transgenesis

Two general strategies are being developed to engineer mammalian artificial chromosomes (MACs) as therapeutic vectors: (1) in vitro MAC cloning by enzymatic ligation of the individual MAC components followed by propagation in single cell organisms such as bacteria or yeast; and (2) in situ MAC assembly by co-introduction of the various MAC elements into an "incubator" mammalian tissue culture cell and use of it as a "foster parental" donor cell. Because of their organizational compactness, in vitro built MACs are suitable for somatic-based human gene therapy. In contrast, the long-term persistence of in situ built MACs can be capitalized to generate husbandry transgenic animals expressing therapeutic genes. While current MAC systems generally rely on cis-elements exclusively from viral or genomic origin, the next generation of MACs may combine both into chimeric systems. As illustration of the genetic flexibility and technological potential of chimeric MACs, the herpesviral oriP/EBNA1 system, paradigm of a self-replicating and -segregating episome in human cells, is discussed in terms of future therapeutic applications.

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Honors	
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