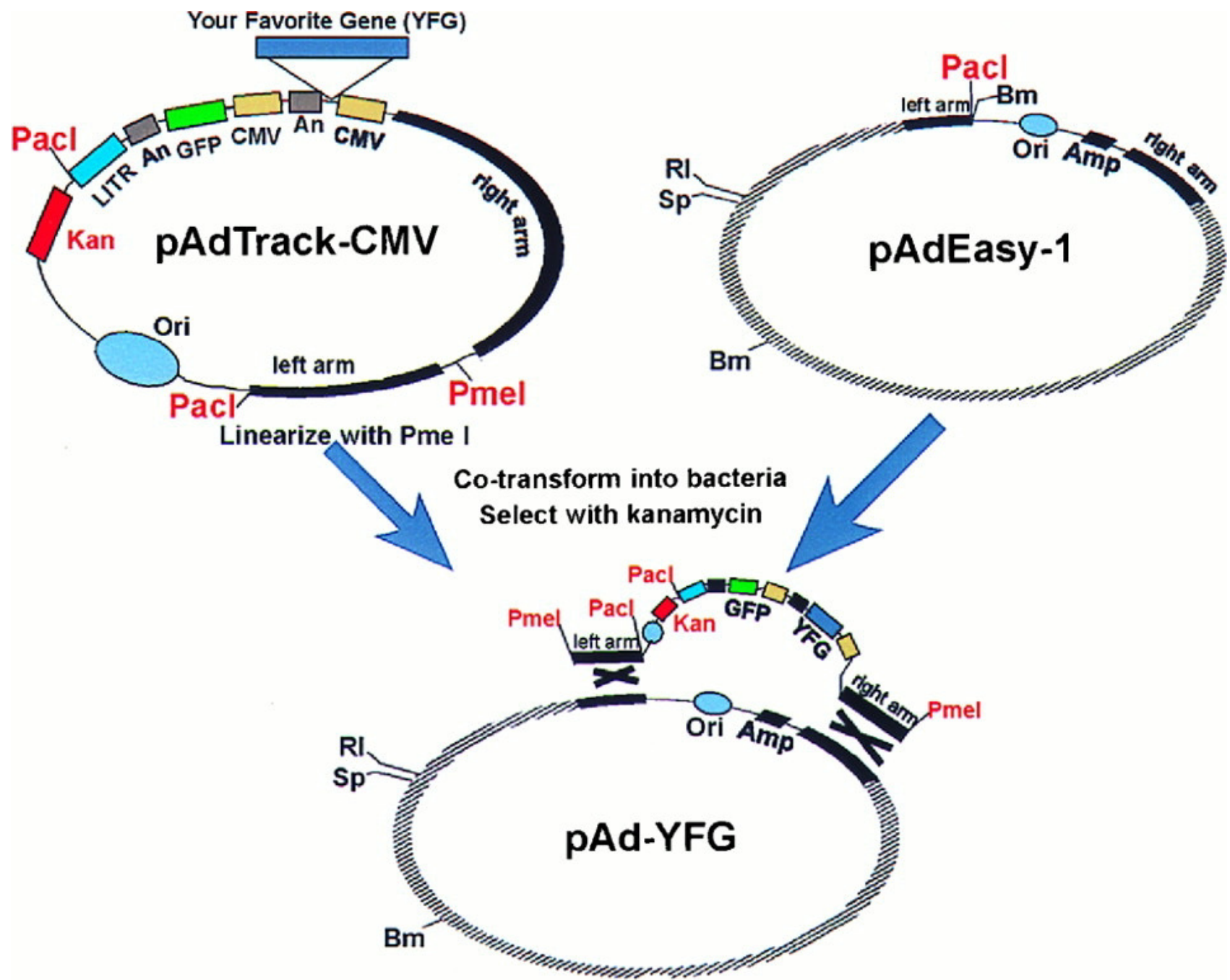
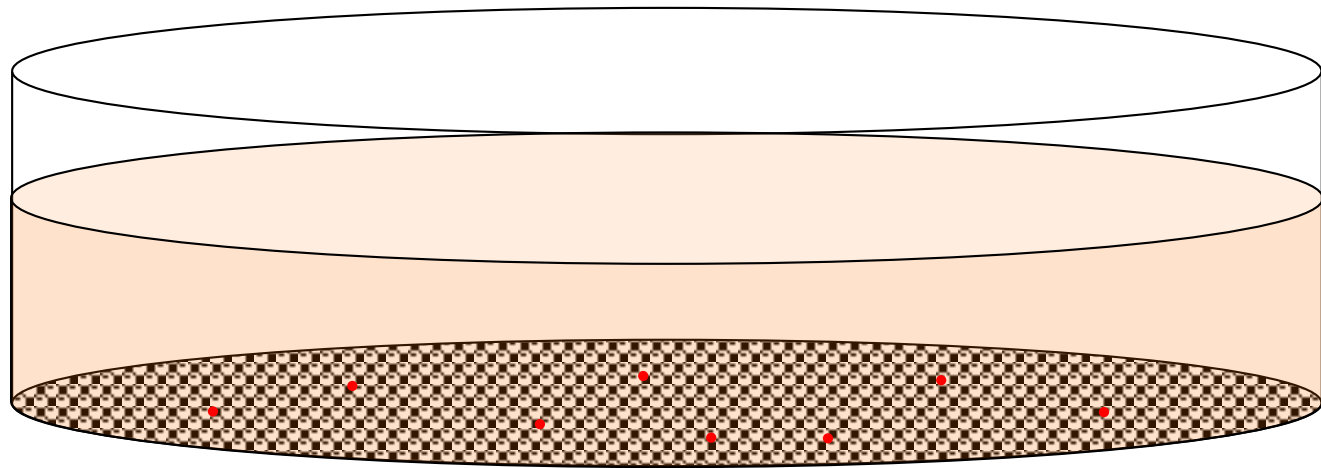


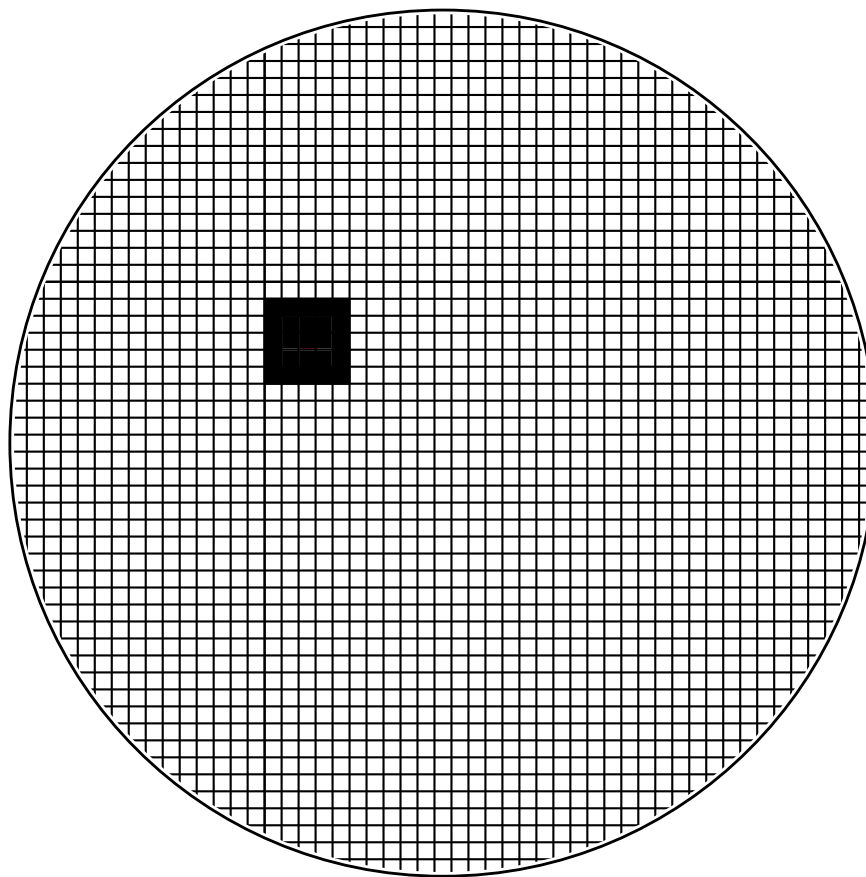
Adenovirus ricombinanti e loro applicazioni

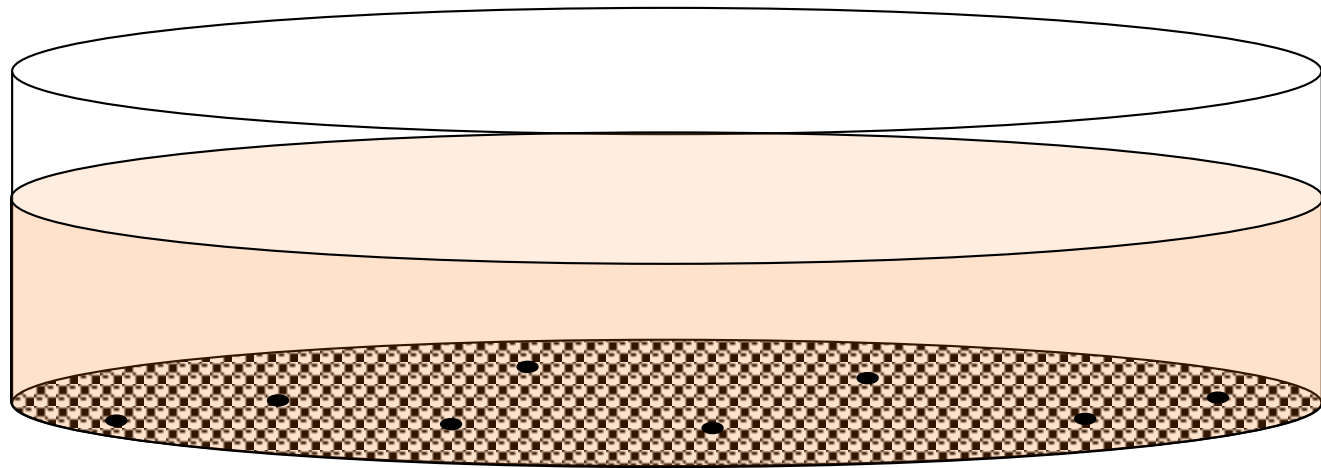
Marco Crescenzi, Istituto Superiore di Sanità – marco.crescenzi@iss.it

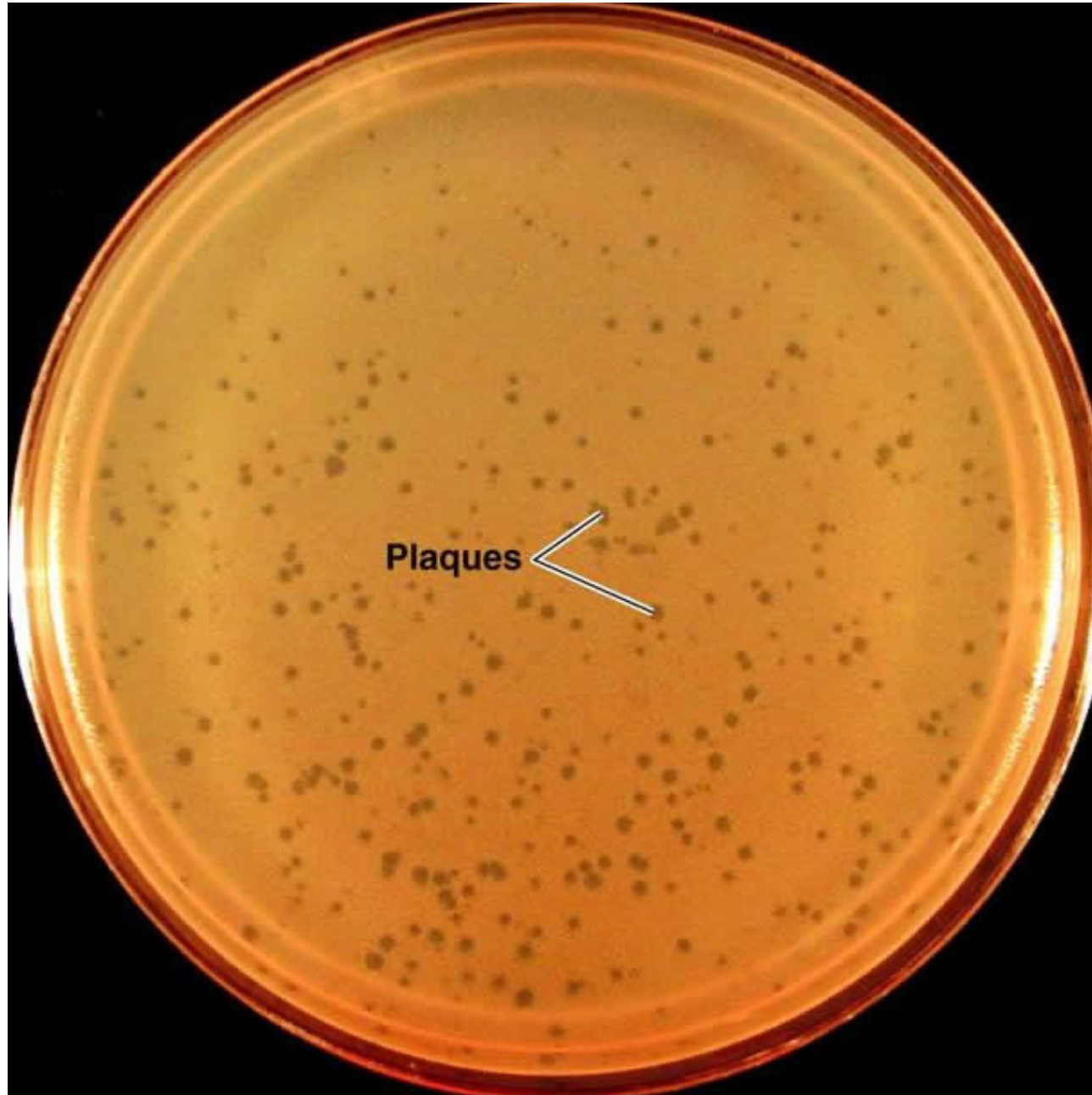
Generazione di adenovirus ricombinanti



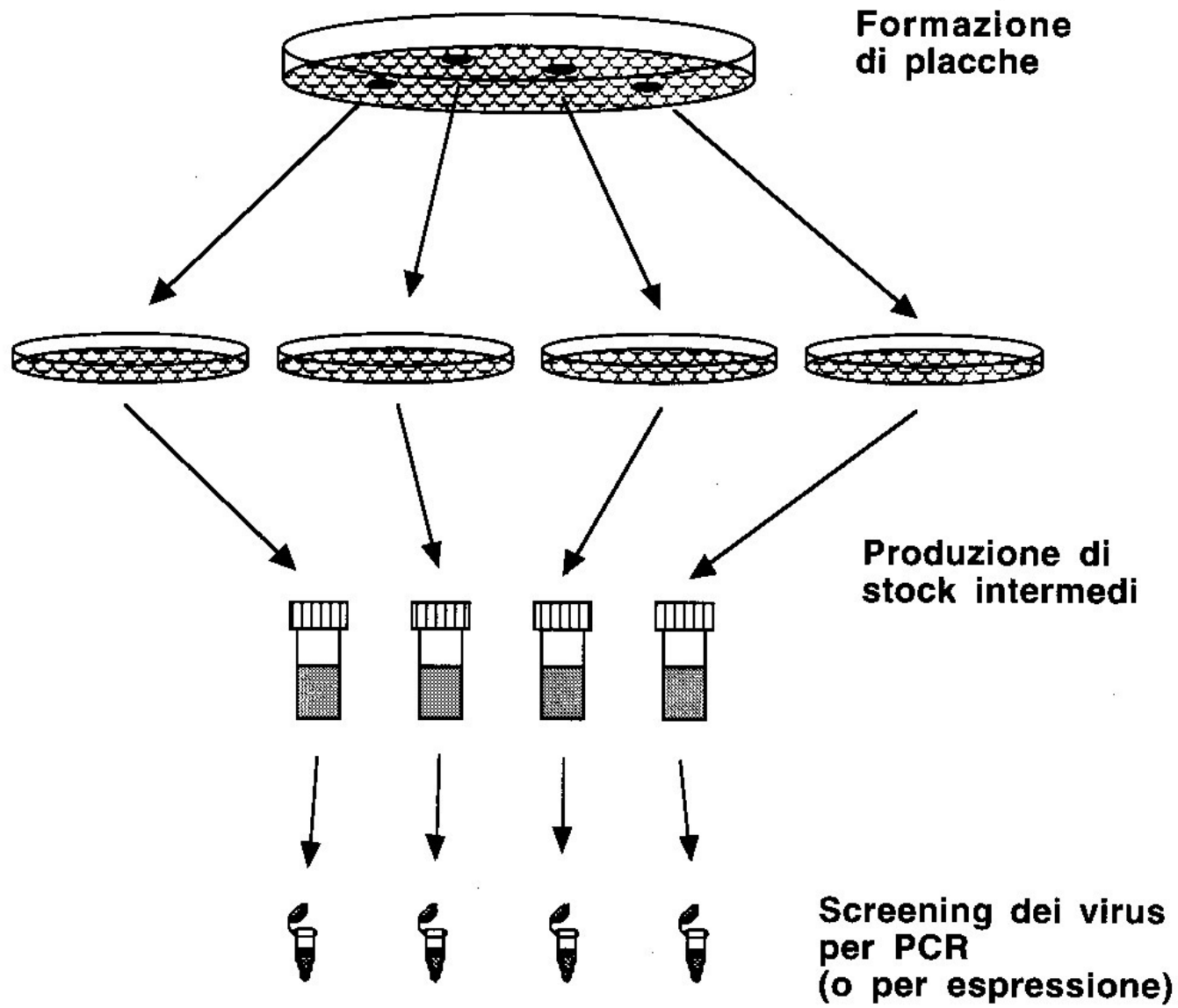


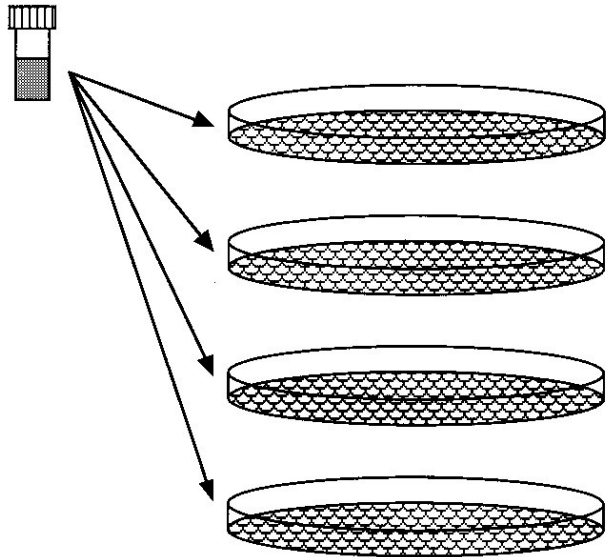




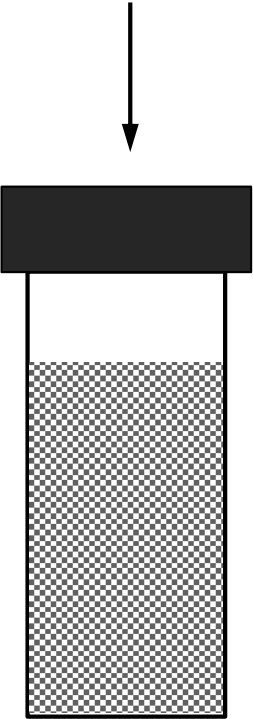


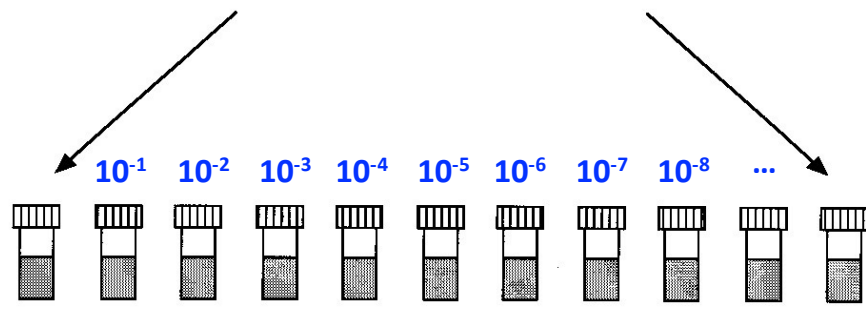
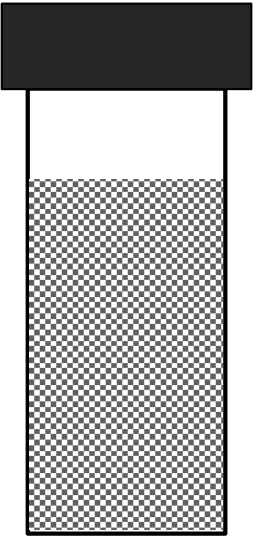
Plaques





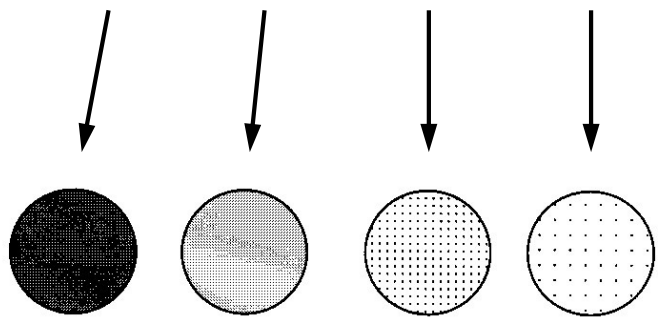
Produzione stock virale su larga scala





Diluizioni progressive

Titolazione per plaque test



Una applicazione clinica

CANCER

Therapeutic targeting of the RB1 pathway in retinoblastoma with the oncolytic adenovirus VCN-01

Guillem Pascual-Pasto^{1,2}, Miriam Bazan-Peregrino³, Nagore G. Olaciregui^{1,2}, Camilo A. Restrepo-Perdomo⁴, Ana Mato-Berciano³, Daniela Ottaviani^{5,6}, Klaus Weber⁷, Genoveva Correa^{1,2}, Sonia Paco^{1,2}, Monica Vila-Ubach^{1,2}, Maria Cuadrado-Vilanova^{1,2}, Helena Castillo-Ecija^{1,2}, Gaia Botteri^{1,2}, Laura Garcia-Gerique^{1,2}, Helena Moreno-Gilabert^{1,2}, Marta Gimenez-Alejandre³, Patricia Alonso-Lopez³, Marti Farrera-Sal³, Silvia Torres-Manjon⁸, Dolores Ramos-Lozano⁸, Rafael Moreno⁸, Isabelle Aerts^{5,6}, François Doz^{5,9}, Nathalie Cassoux^{5,9,10}, Elodie Chapeaublanc^{5,6}, Montserrat Torreadell^{1,2}, Monica Roldan^{1,4}, Andrés König¹¹, Mariona Suñol⁴, Joana Claverol^{1,12}, Cinzia Lavarino^{1,2}, Carmen de Torres^{1,2*}, Ligia Fu¹³, François Radvanyi^{5,6}, Francis L. Munier¹⁴, Jaume Catalá-Mora¹⁵, Jaume Mora^{1,2}, Ramón Alemany⁸, Manel Cascalló³, Guillermo L. Chantada^{1,2,16,17}, Angel M. Carcaboso^{1,2†}

Retinoblastoma is a pediatric solid tumor of the retina activated upon homozygous inactivation of the tumor suppressor *RB1*. VCN-01 is an oncolytic adenovirus designed to replicate selectively in tumor cells with high abundance of free E2F-1, a consequence of a dysfunctional RB1 pathway. Thus, we reasoned that VCN-01 could provide targeted therapeutic activity against even chemoresistant retinoblastoma. In vitro, VCN-01 effectively killed patient-derived retinoblastoma models. In mice, intravitreal administration of VCN-01 in retinoblastoma xenografts induced tumor necrosis, improved ocular survival compared with standard-of-care chemotherapy, and prevented micrometastatic dissemination into the brain. In juvenile immunocompetent rabbits, VCN-01 did not replicate in retinas, induced minor local side effects, and only leaked slightly and for a short time into the blood. Initial phase 1 data in patients showed the feasibility of the administration of intravitreal VCN-01 and resulted in antitumor activity in retinoblastoma vitreous seeds and evidence of viral replication markers in tumor cells. The treatment caused local vitreous inflammation but no systemic complications. Thus, oncolytic adenoviruses targeting RB1 might provide a tumor-selective and chemotherapy-independent treatment option for retinoblastoma.

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Government Works

Oncolisi: VCN-01 (Delta-24)

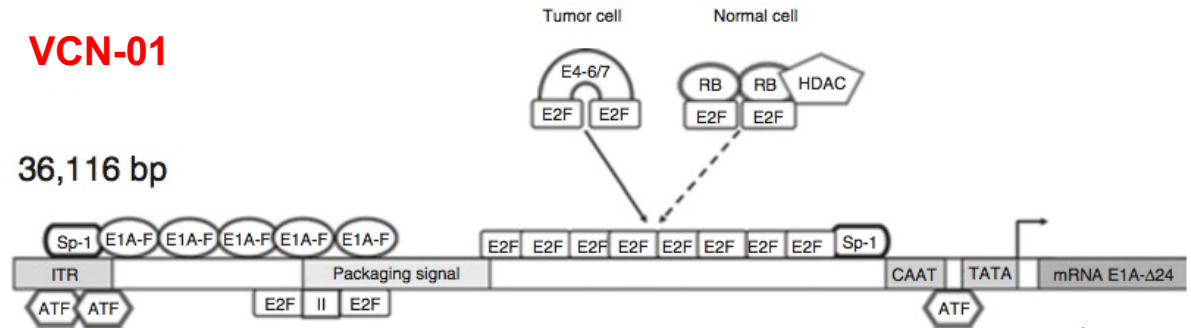
wild type

35,965 bp



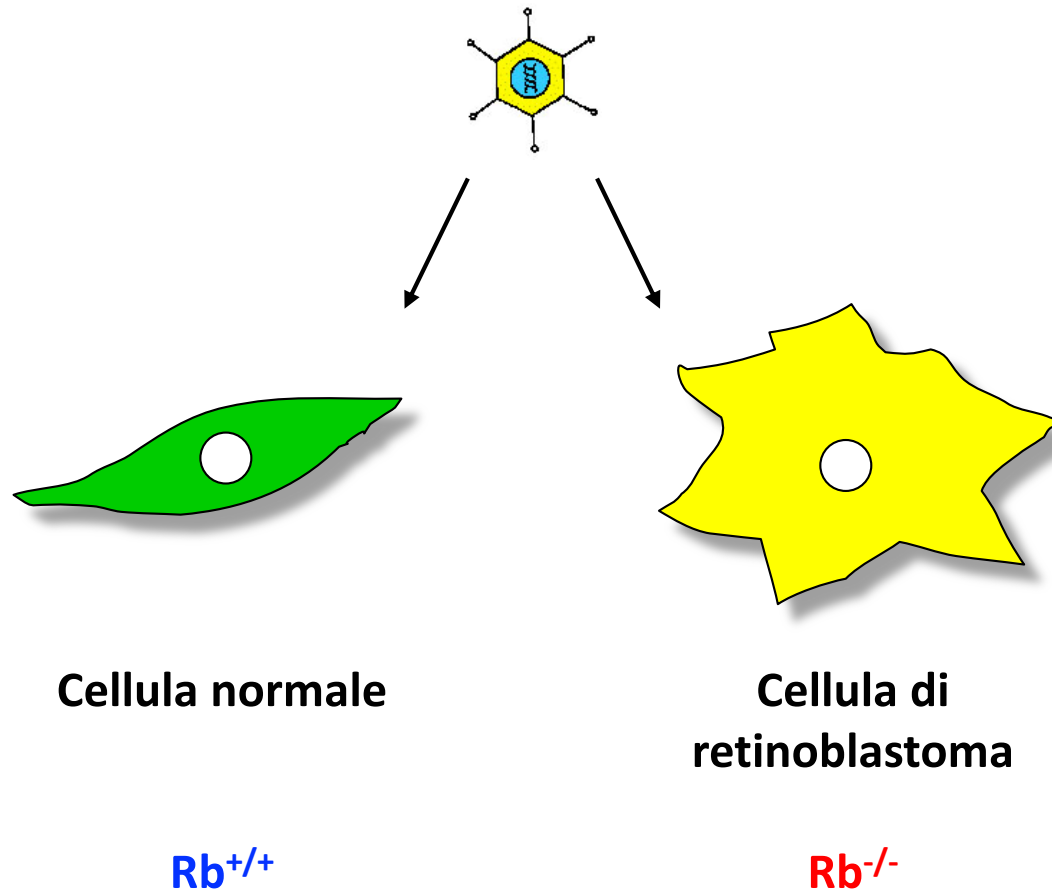
VCN-01

36,116 bp

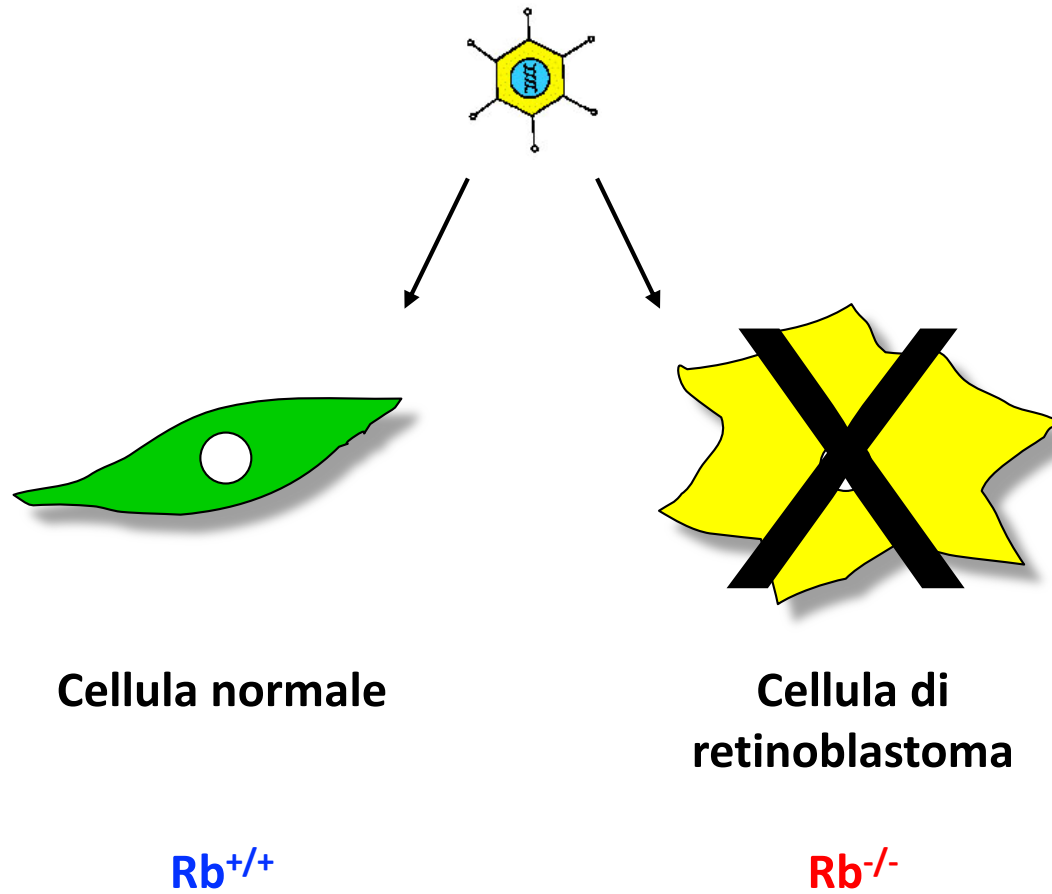


E1A Δ24

Oncolisi: VCN-01 (Delta-24)



Oncolisi: VCN-01 (Delta-24)



Delta-24 adenoviral therapy for glioblastoma: evolution from the bench to bedside and future considerations

Chibawanye I Ene ¹, Juan Fueyo ^{1 2}, Frederick F Lang ¹

Affiliations + expand

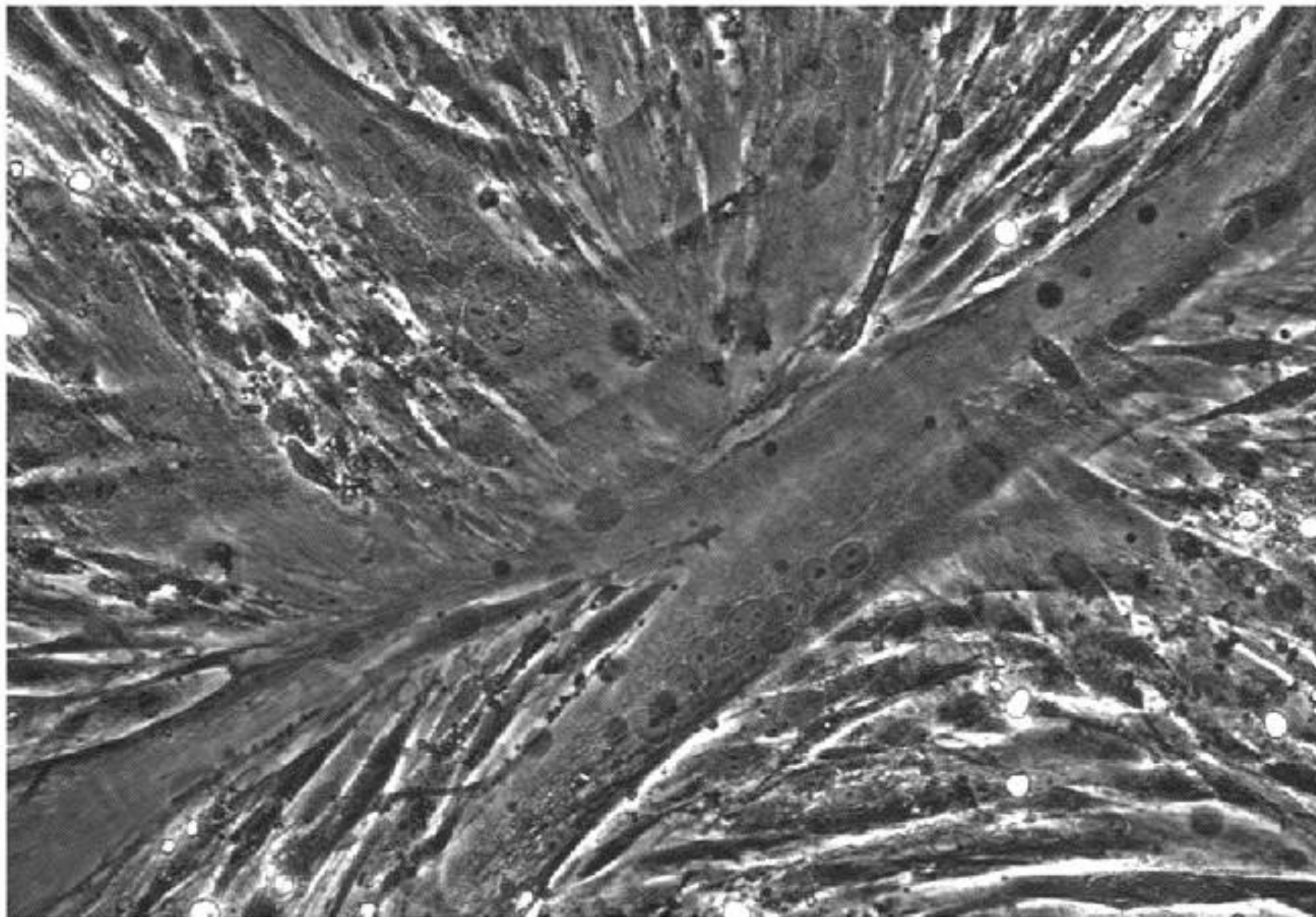
PMID: 33524949 DOI: [10.3171/2020.11.FOCUS20853](#)

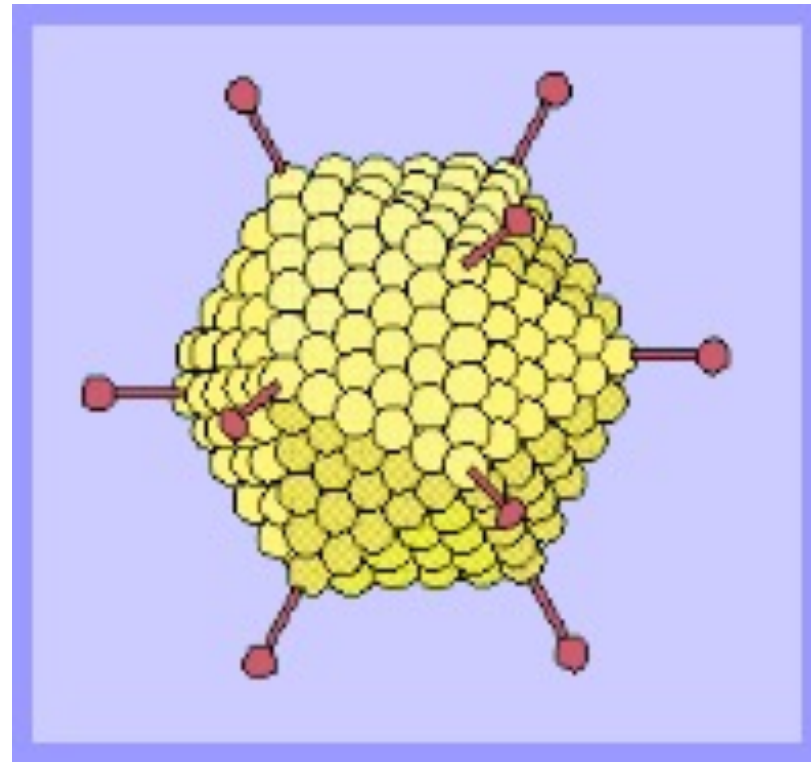
Abstract

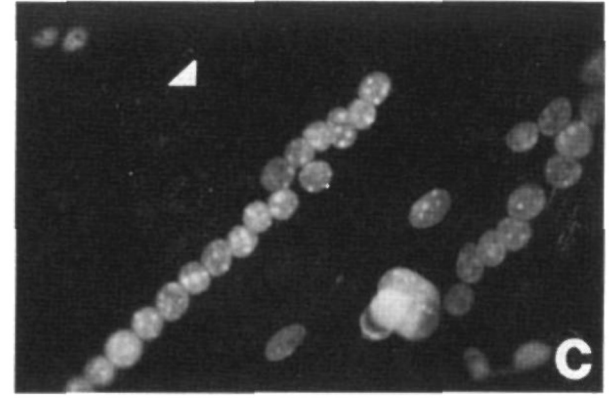
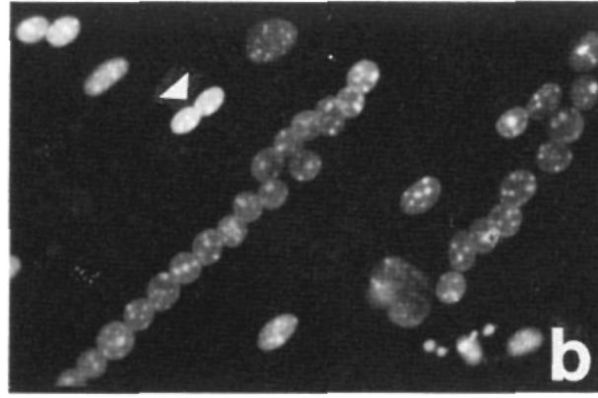
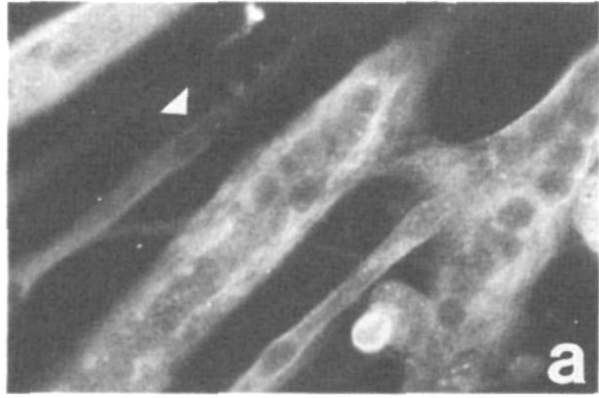
Delta-24-based oncolytic viruses are conditional replication adenoviruses developed to selectively infect and replicate in retinoblastoma 1 (Rb)-deficient cancer cells but not normal cell with intact Rb1 pathways. Over the years, there has been a significant evolution in the design of Delta-24 based on a better understanding of the underlying basis for infection, replication, and spread within cancer. One example is the development of Delta-24-RGD (DNX-2401), where the arginine-glycine-aspartate (RGD) domain enhances the infectivity of Delta-24 for cancer cells. DNX-2401 demonstrated objective biological and clinical responses during a phase I window of opportunity clinical trial for recurrent human glioblastoma. In long-term responders (> 3 years), there was evidence of immune infiltration (T cells and macrophages) into the tumor microenvironment with minimal toxicity. Although more in-depth analysis and phase III studies are pending, these results indicate that Delta-24-based adenovirus therapy may induce an antitumor response in glioblastoma, resulting in long-term antitumor immune response. In this review, the authors discuss the preclinical and clinical development of Delta-24 oncolytic adenoviral therapy for glioblastoma and describe structural improvements to Delta-24 that have enhanced its efficacy in vivo. They also highlight ongoing research that attempts to address the remaining obstacles limiting efficacy of Delta-24 adenovirus therapy for glioblastoma.

Keywords: Delta-24; adenovirus; glioblastoma; oncolytic virus; retinoblastoma gene mutation.

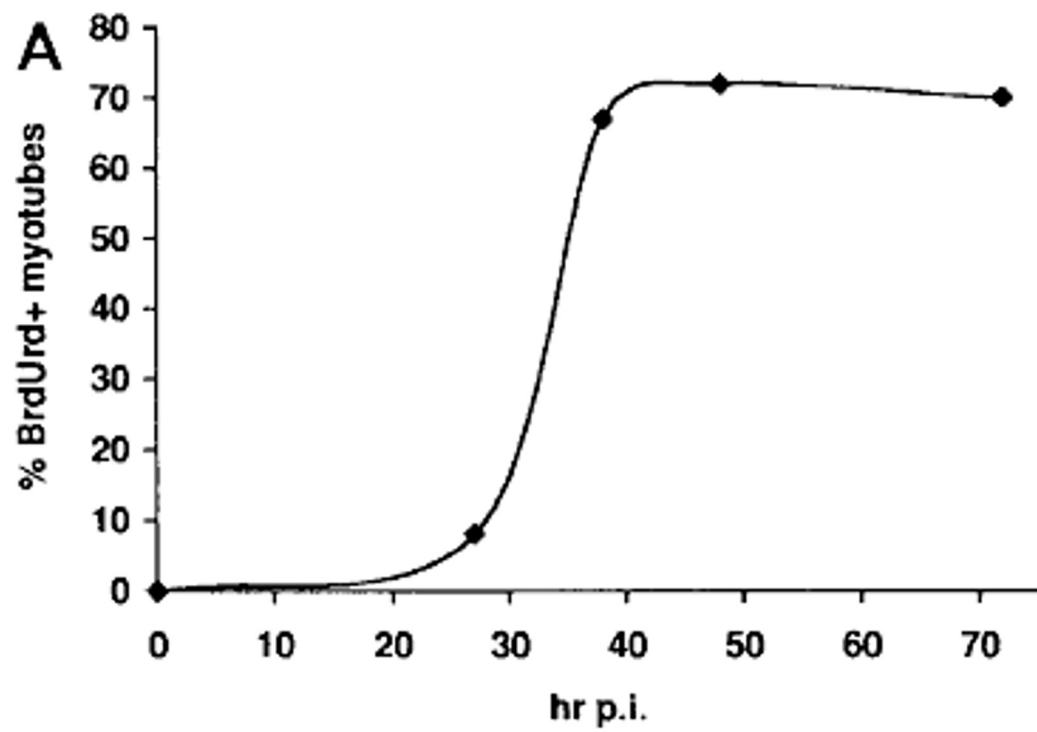
Applicazioni nella ricerca

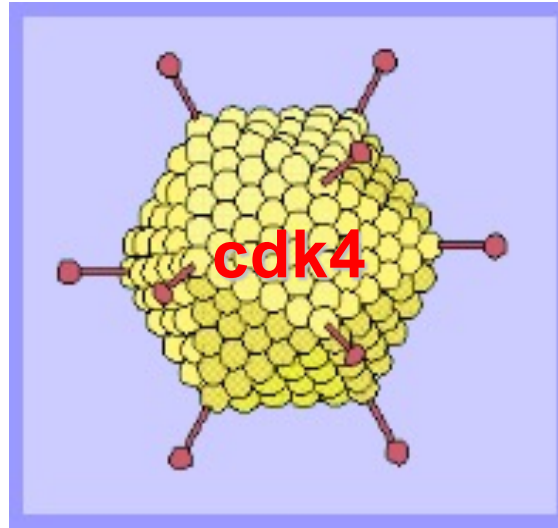
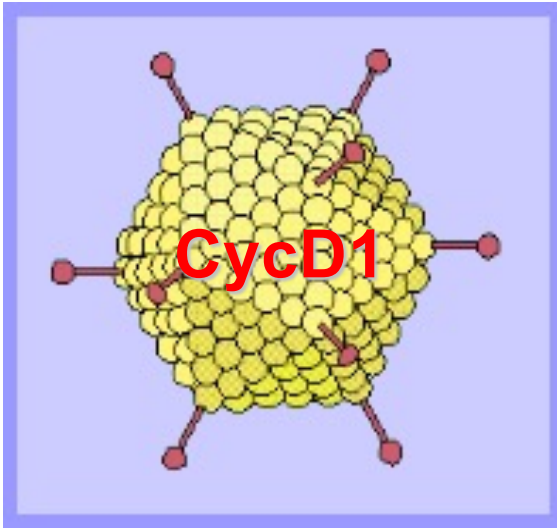


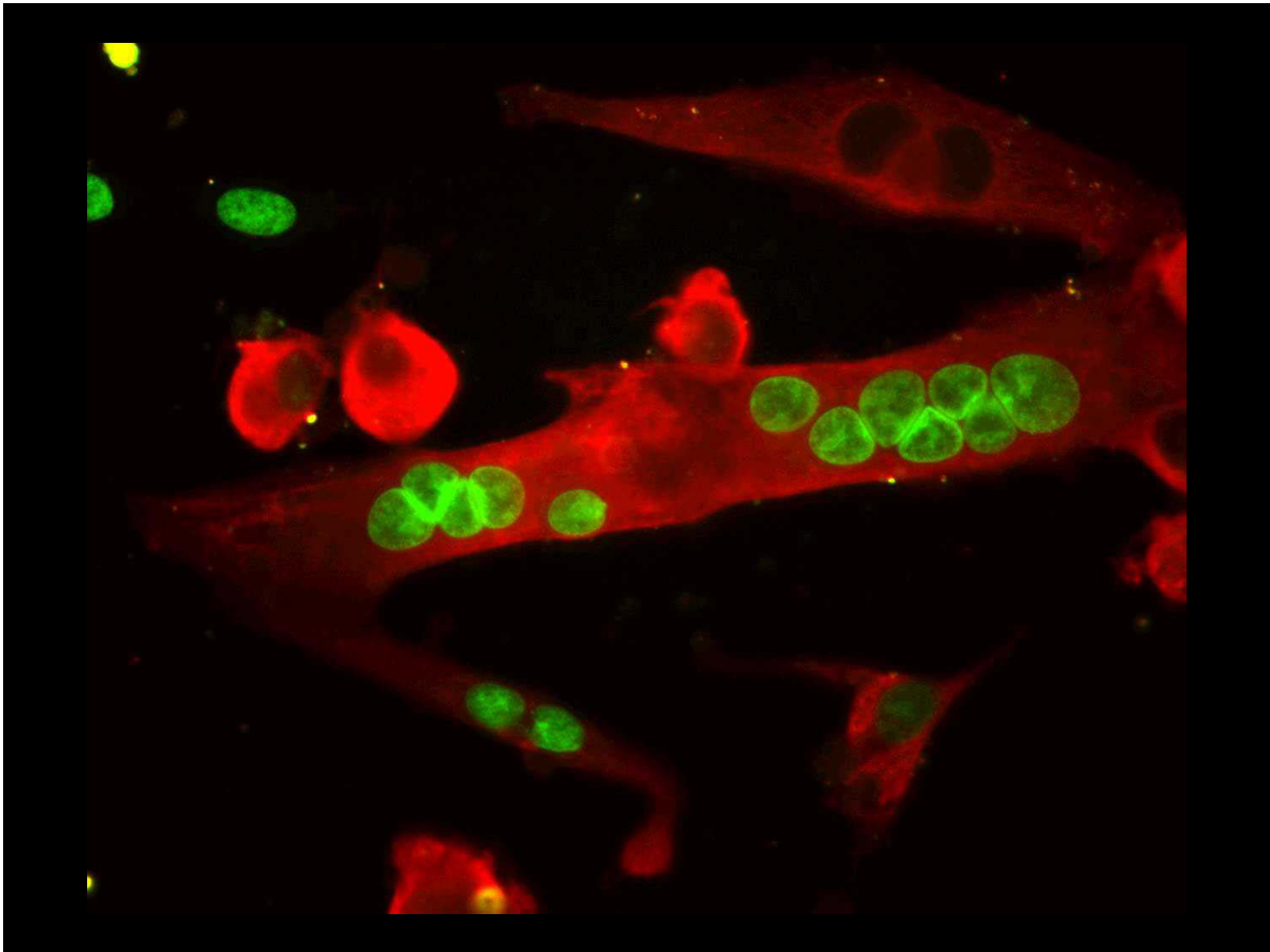




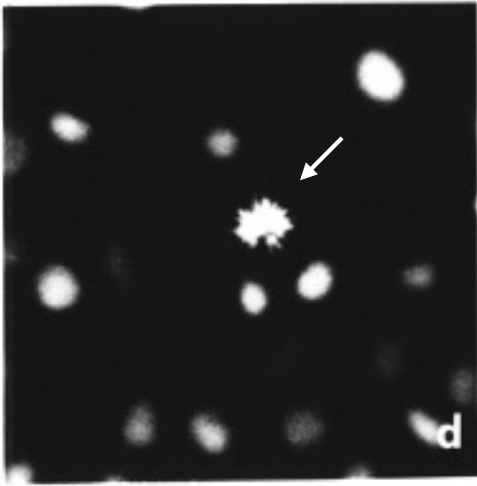
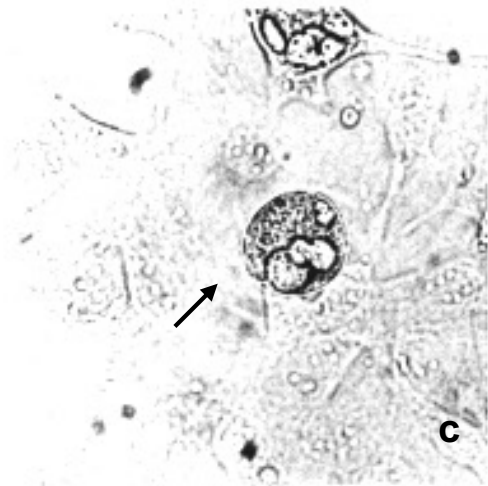
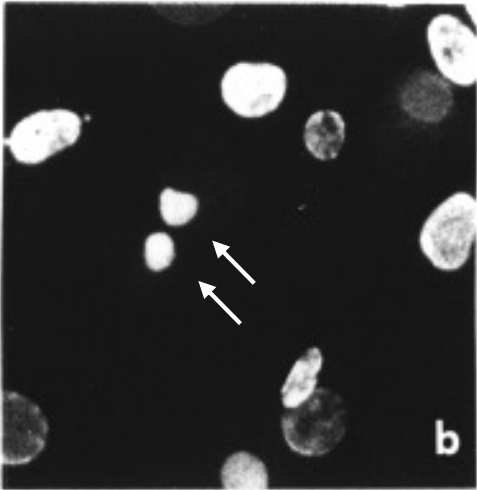
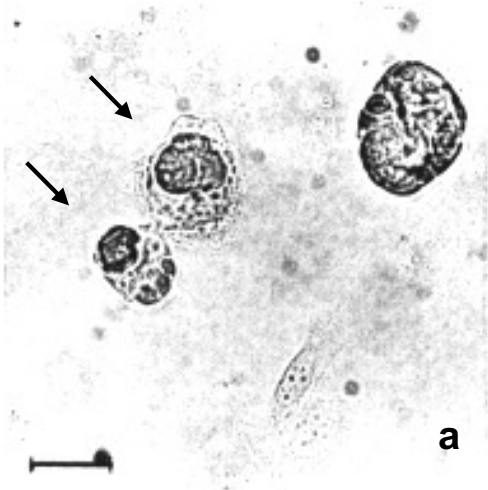
Virus	E1A 13S	E1A 12S	E1B 19 kDa	E1B 55 kDa	% mitotubi BrdU+
wt Ad5	+	+	+	+	1
dl520	-	+	±	±	80
pm975	+	-	+	+	35
dl338	+	+	+	-	30
dl313	tronca	tronca	-	-	30
dl312	-	-	±	±	0



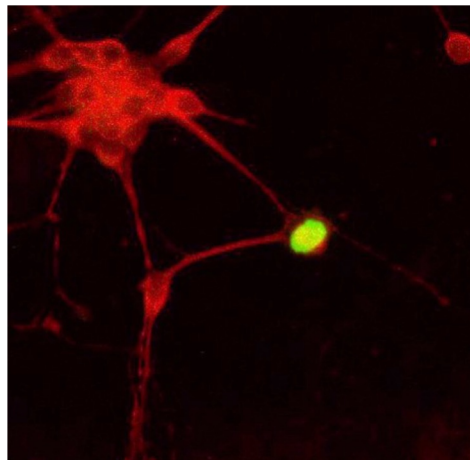
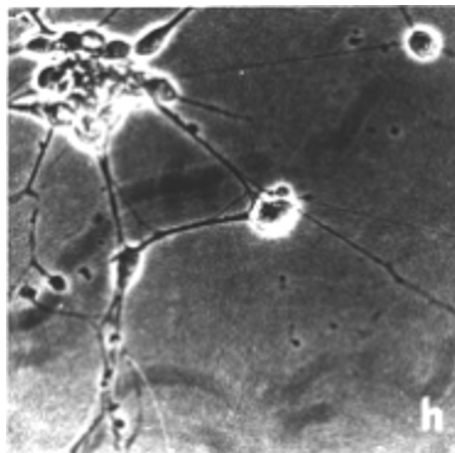
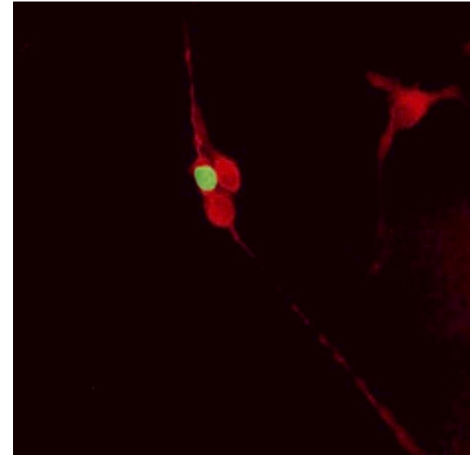
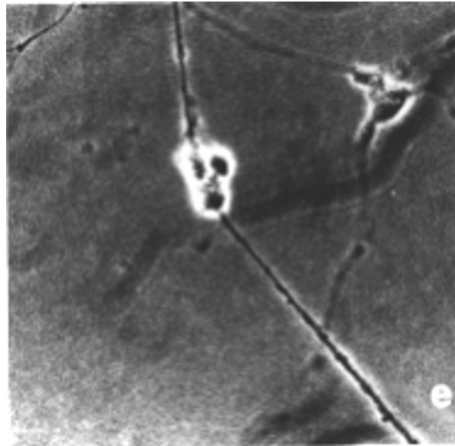




Cyclin D1/cdk4 induce DNA synthesis in 3T3-L1-derived adipocytes....

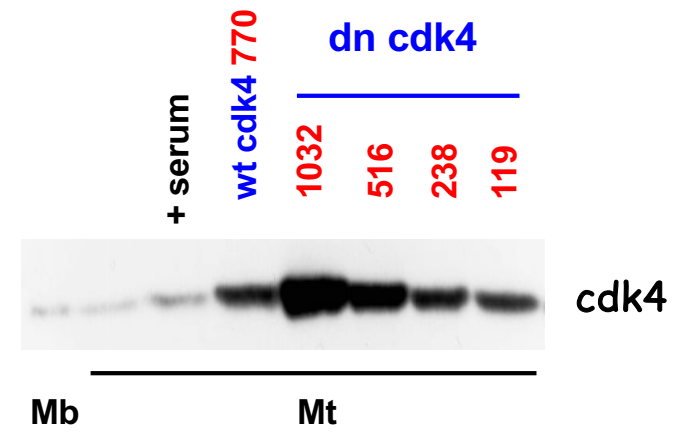


....and in P19-derived neurons

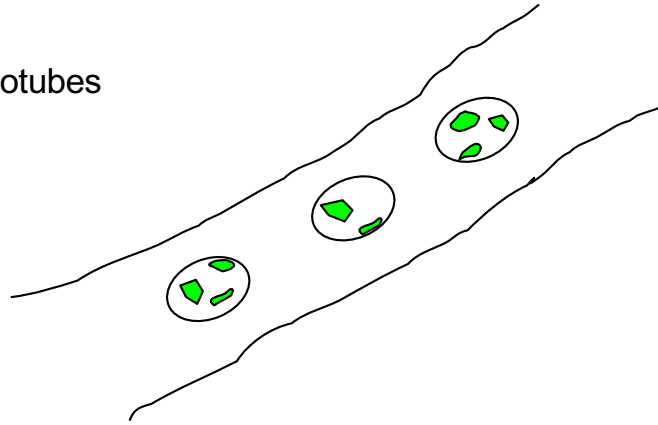


		Ad-cycD1 - moi				
		60	30	15	7,5	0
Ad-cdk4 moi	770	72	44	10	21	0
	255	30	8	12	1	0
	85	1	0	1	1	0
	28	1	0	0	0	0
	0	0	0	0	0	0

Percentuale di mitotubi BrdU+



BrdU-labeled myotubes



Extract DNA

Separate on CsCl gradient



Unsubstituted

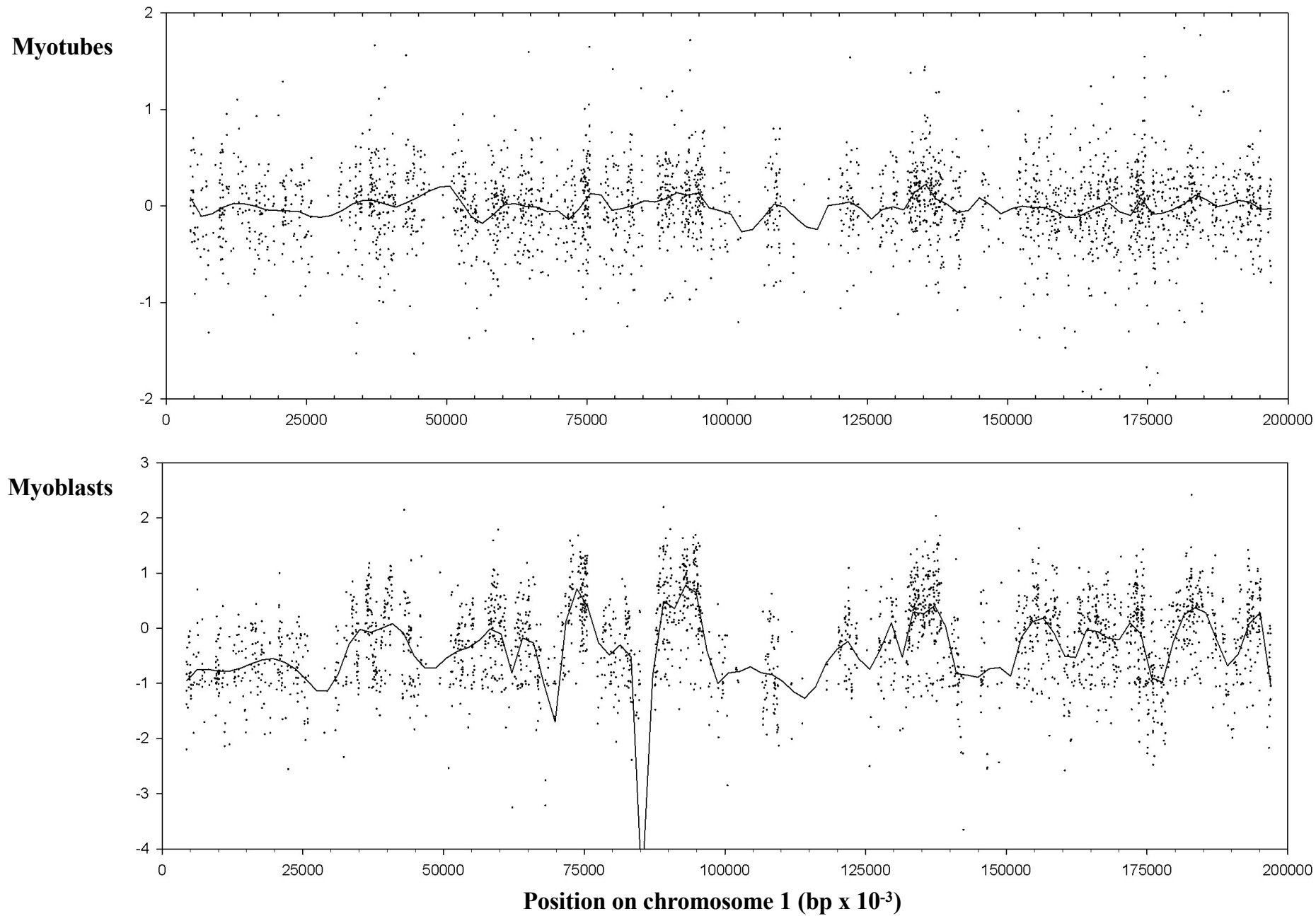
Hemisubstituted

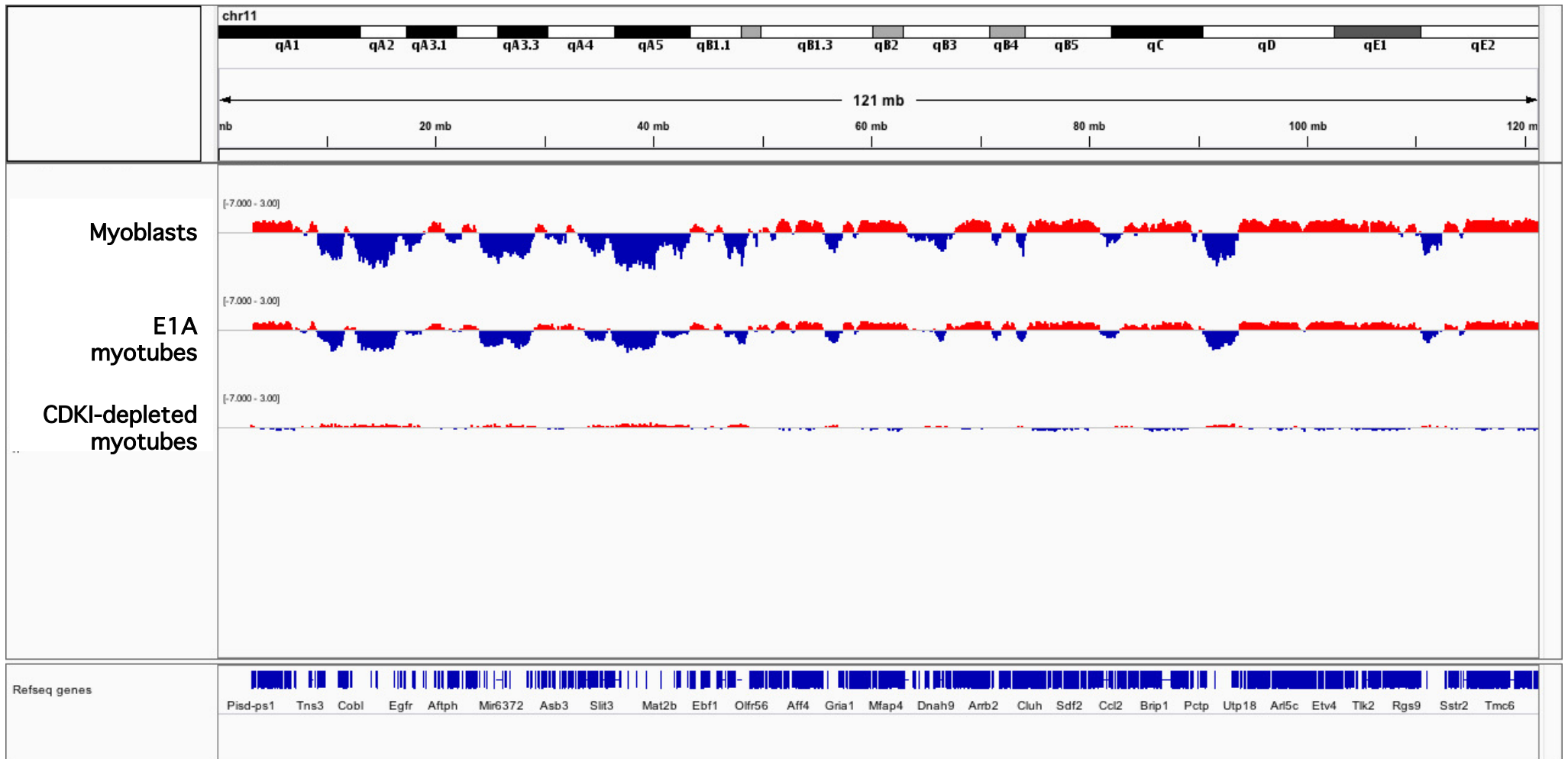
Totally substituted

Hybridize to genomic microarrays



Reactivated myotubes lack a replication timing program





I vettori adenovirali nella ricerca e nella clinica

Sono dotati di ampio tropismo; l'infezione non dipende dalla replicazione cellulare

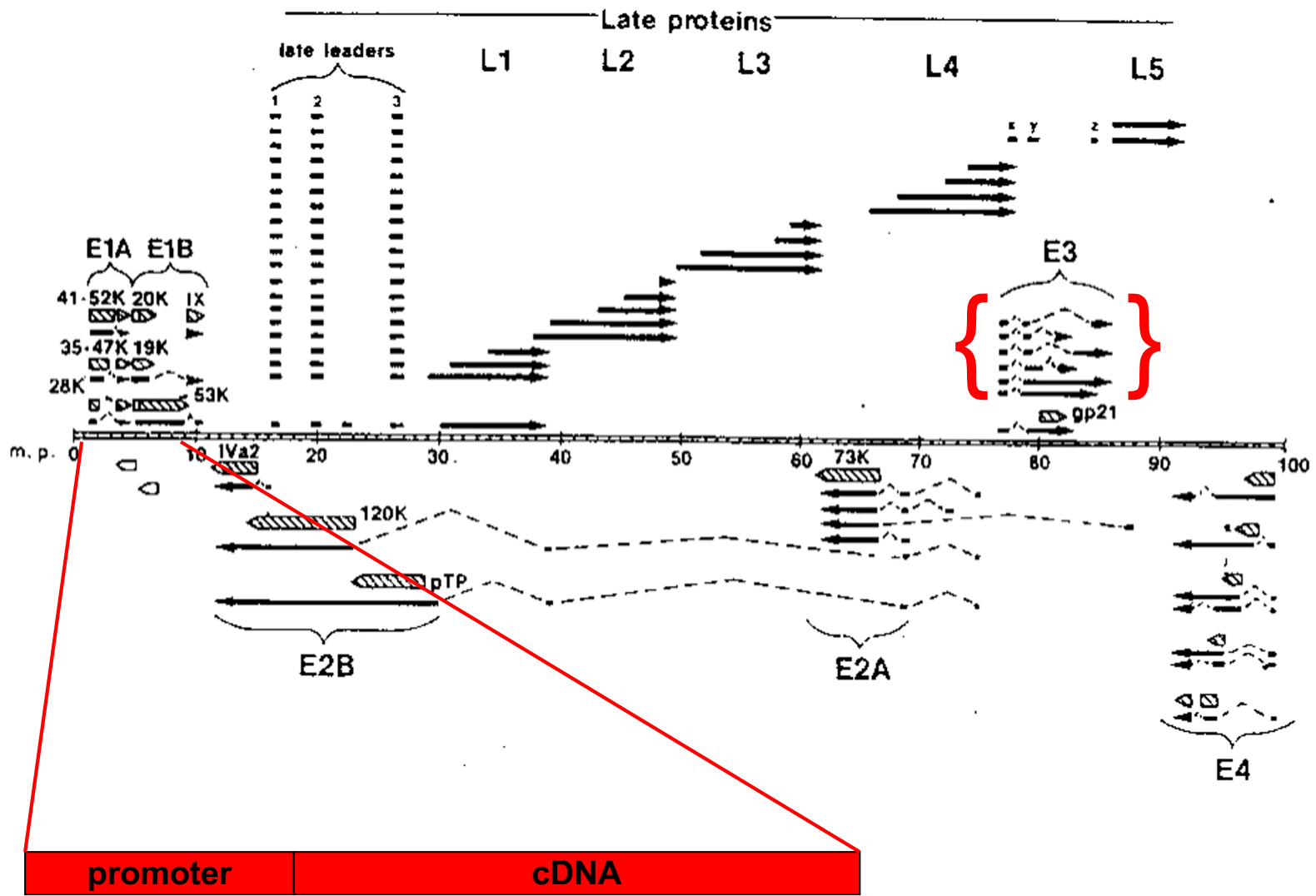
L'espressione genica può essere modulata variando la molteplicità di infezione

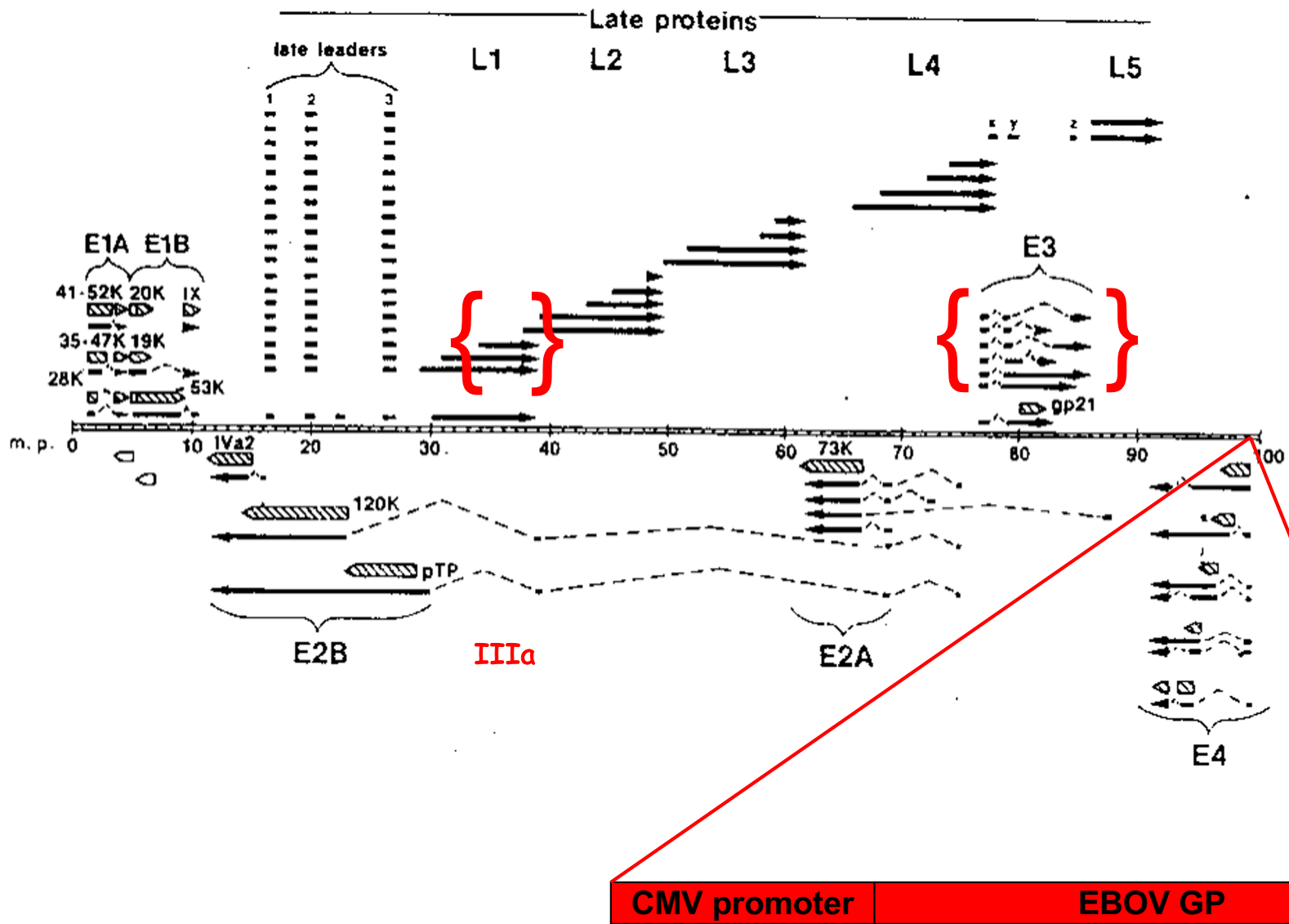
L'infezione avviene in maniera sincrona, facilitando le procedure e le analisi successive

Gli adenovirus sono utilizzabili per studi in vivo

In vivo, gli adenovirus sono fortemente immunogenici e possono esserlo anche i prodotti dei geni veicolati

Single-cycle adenovirus (SC-Ad)





293-III

