*Cherish your doubts, for doubt
is the attendant of the truth*

Part A

Future - infos

Open desk for infos thesis and future

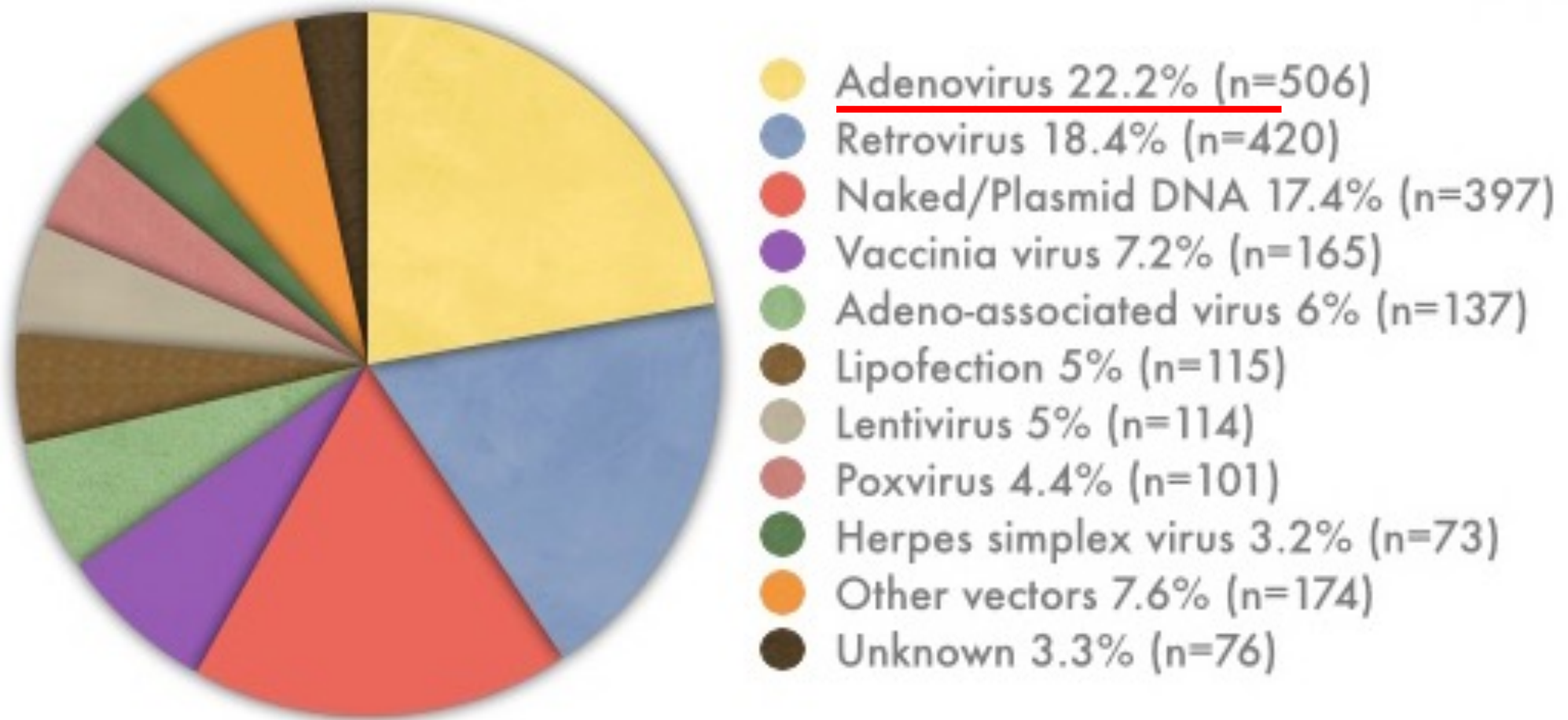Long term future:
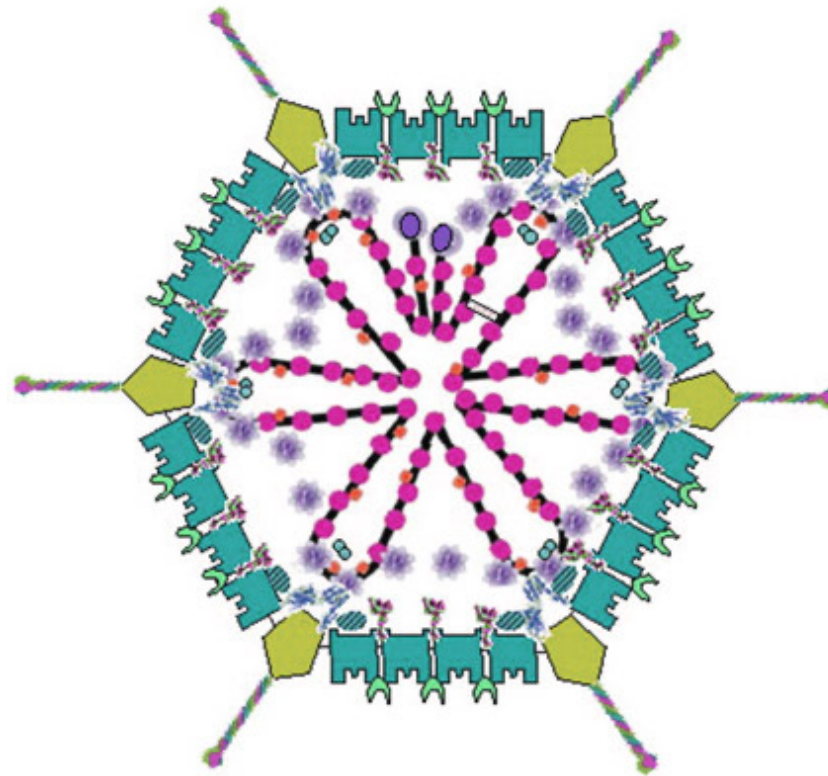
Master sgp
Master One Health analyst

Top down

Vectors Used in Gene Therapy Clinical Trials

- Adenovirus 22.2% (n=506)
- Retrovirus 18.4% (n=420)
- Naked/Plasmid DNA 17.4% (n=397)
- Vaccinia virus 7.2% (n=165)
- Adeno-associated virus 6% (n=137)
- Lipofection 5% (n=115)
- Lentivirus 5% (n=114)
- Poxvirus 4.4% (n=101)
- Herpes simplex virus 3.2% (n=73)
- Other vectors 7.6% (n=174)
- Unknown 3.3% (n=76)

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Adenovirus

Capsid proteins
- Hexon
- Penton base
- Fibre

Minor proteins
- IIIa
- VI
- VIII
- IX

Core proteins
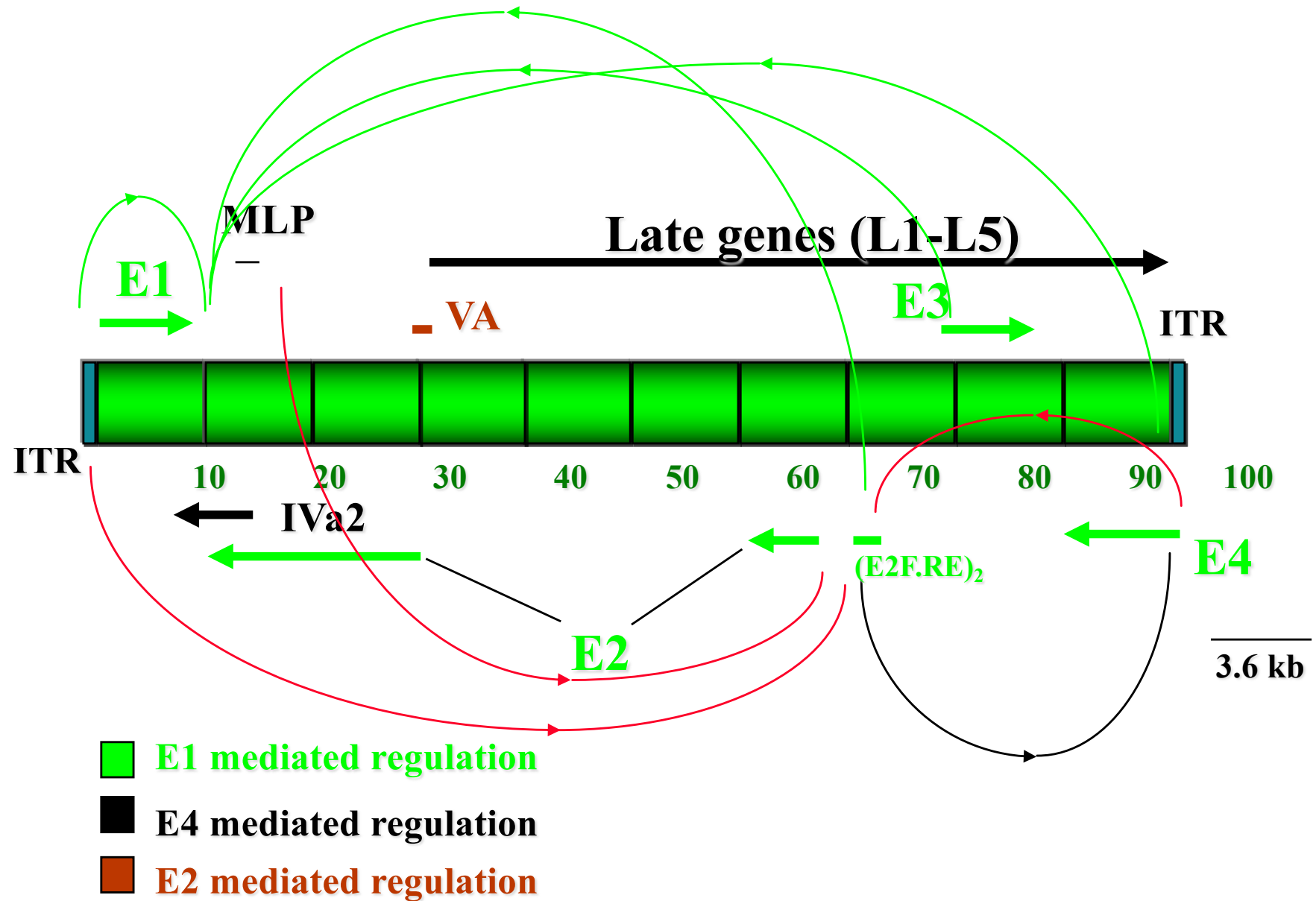- V
- VII
- Mu
- Terminal protein
- IVa2
- Protease

Adenovirus genome

MLP

Late genes (L1-L5)

E1

VA

E3

ITR

ITR

10 20 30 40 50 60 70 80 90 100

IVa2

E2

(E2F.RE)₂

E4

3.6 kb

E1 mediated regulation

E4 mediated regulation

E2 mediated regulation

1ˢᵗ generation adenoviral vectors
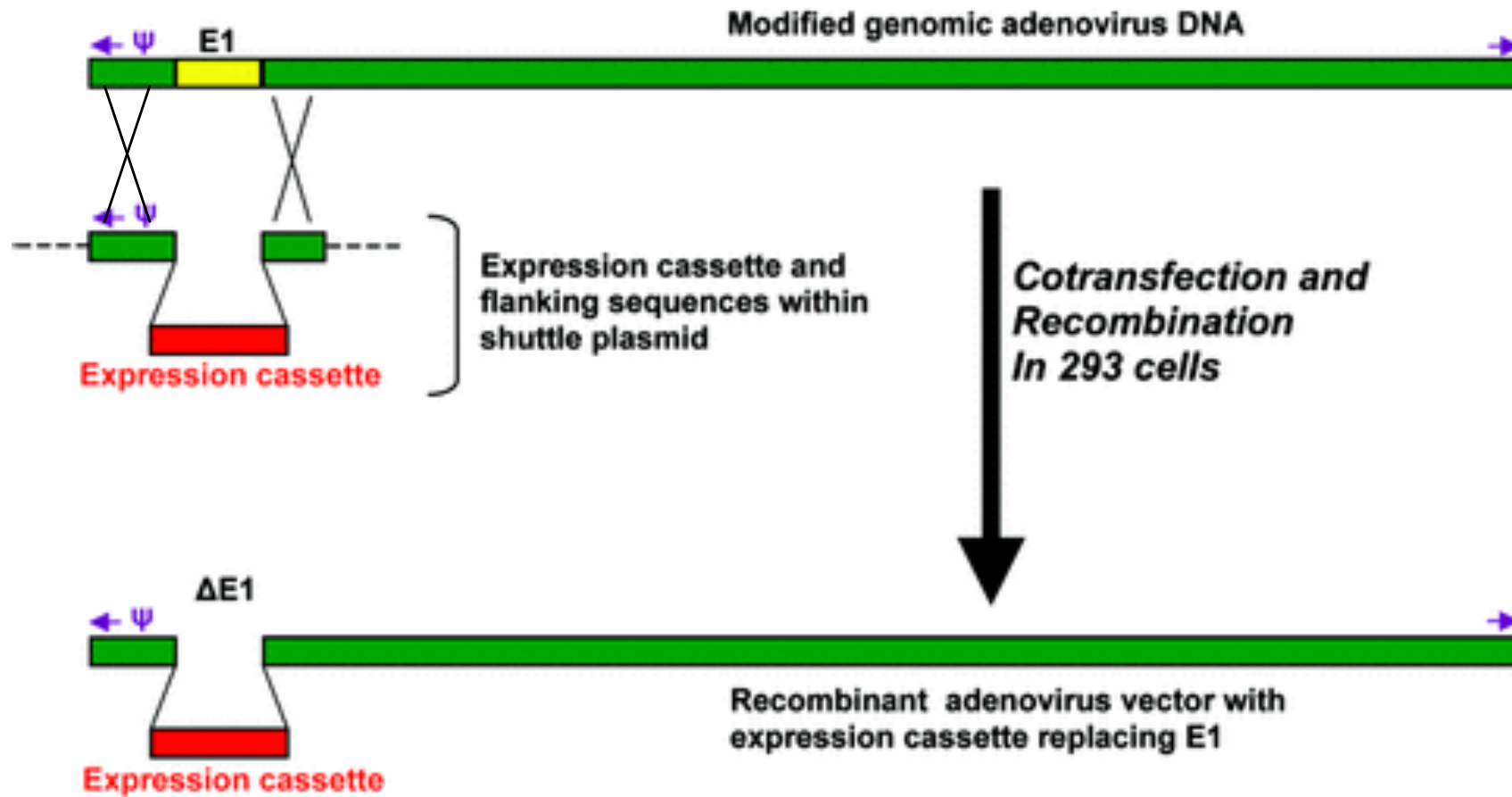
1ˢᵗ generation adenoviral vectors
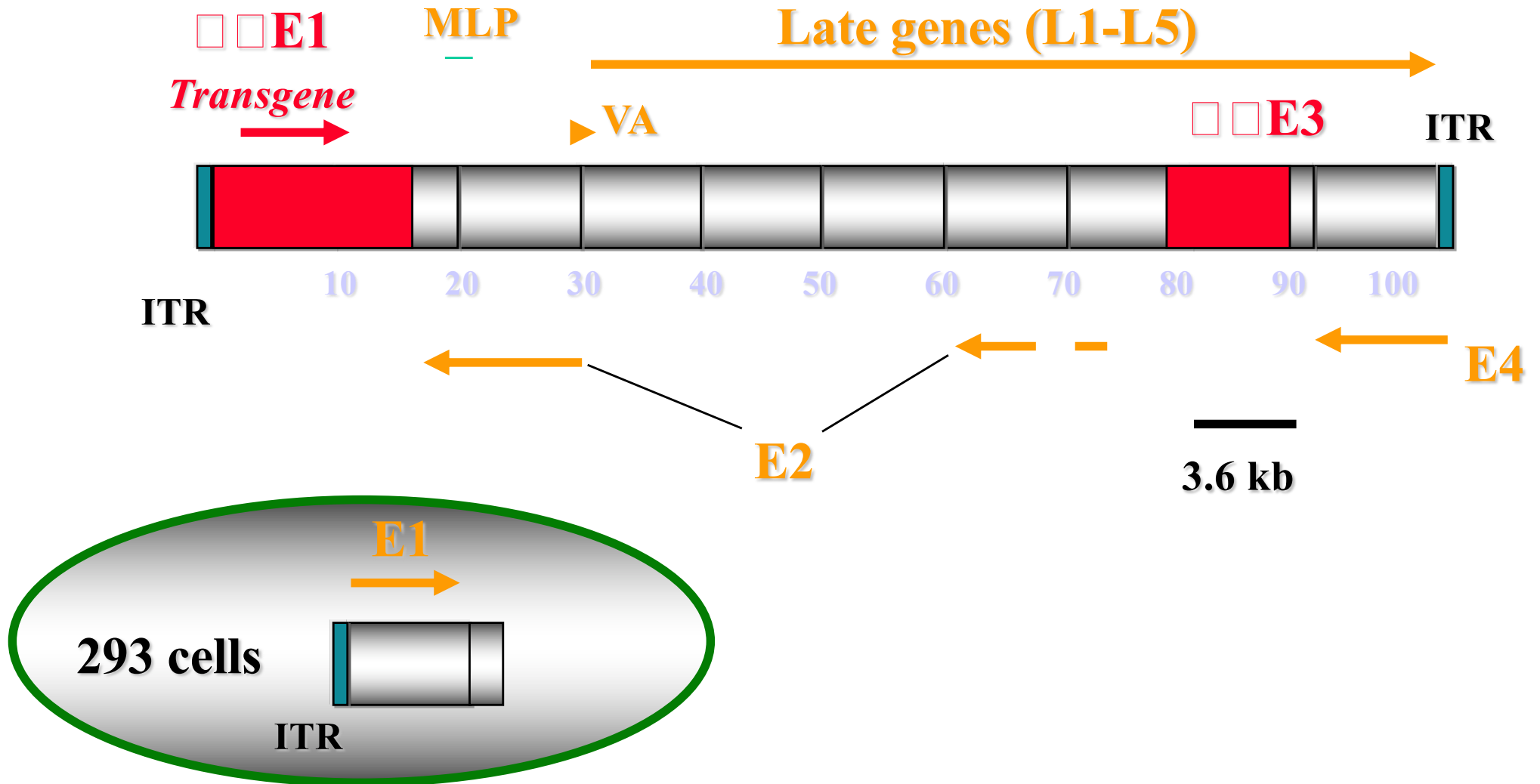
Problems and ameliorations of Ad vectors

- no integration => chimaeres AAV/ Retro
- seropositivity to Ad => change of serotype, higher doses, immunosuppression
- large tropism => **targeted transduction**, targeted expression
- immunogenicity => **immuno-suppression**, **new vectors**
- size of the insert => new vectors
- short term expr. => chimaeres AAV/Retro, immuno-suppression, new generation vectors
- RCA => new lines, new vectors
- transcomplementation => new vectors
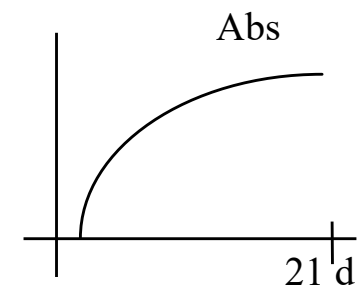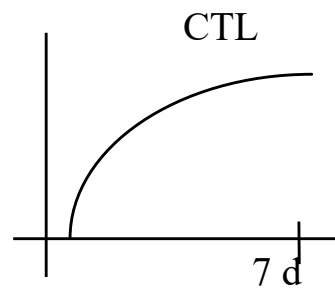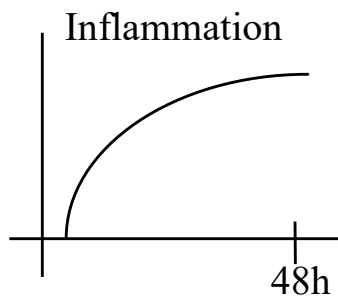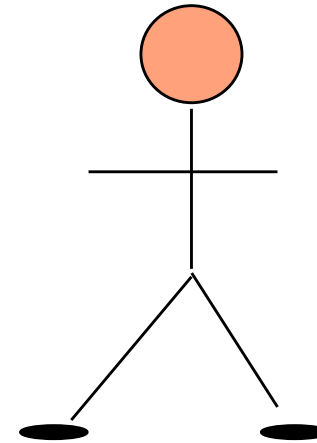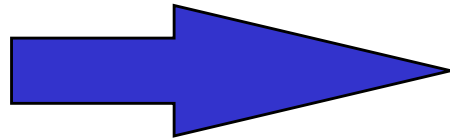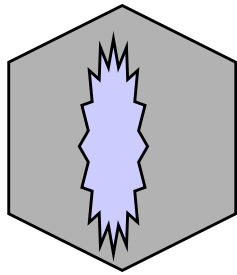
Ad modifications for targeting

- bispecific ABs antifiber/antireceptor (nabs)

- bispecific abs anti fiber insert/antireceptor (antiflag/antireceptor)

- fiber inserts (RGD)
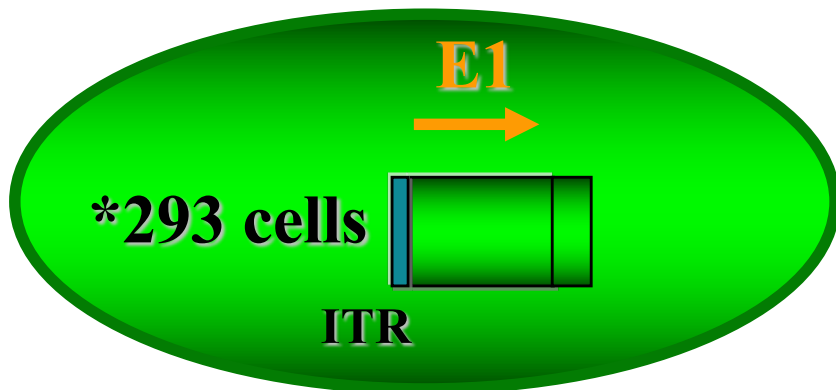
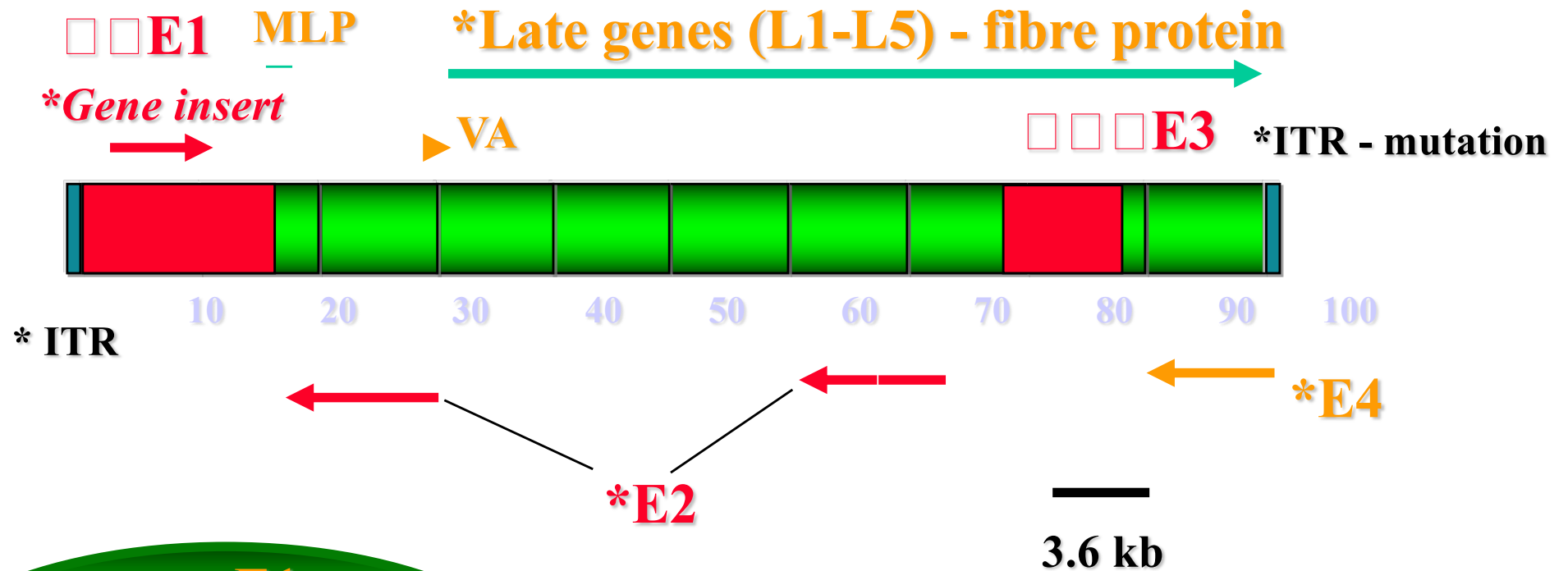- hexon inserts

- penton base inserts
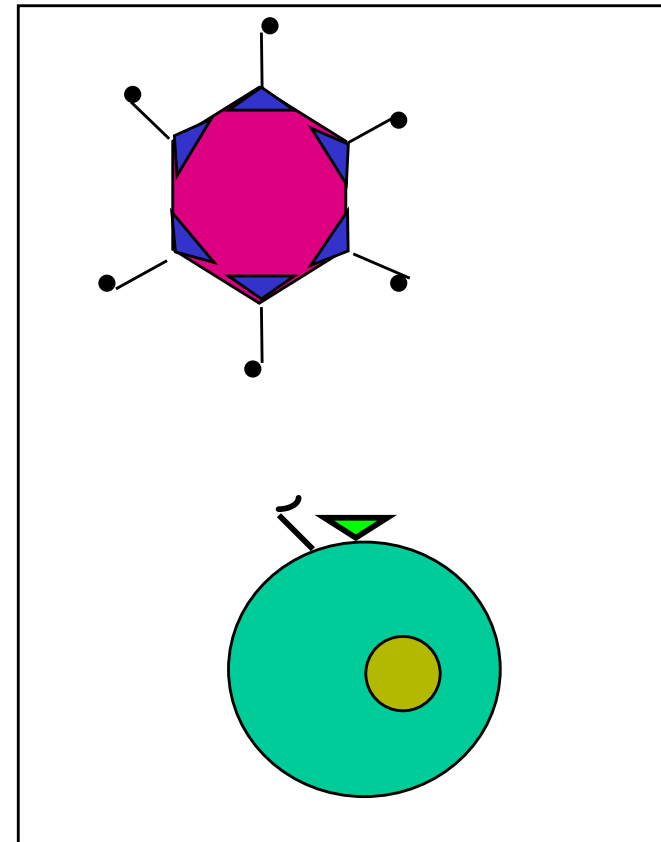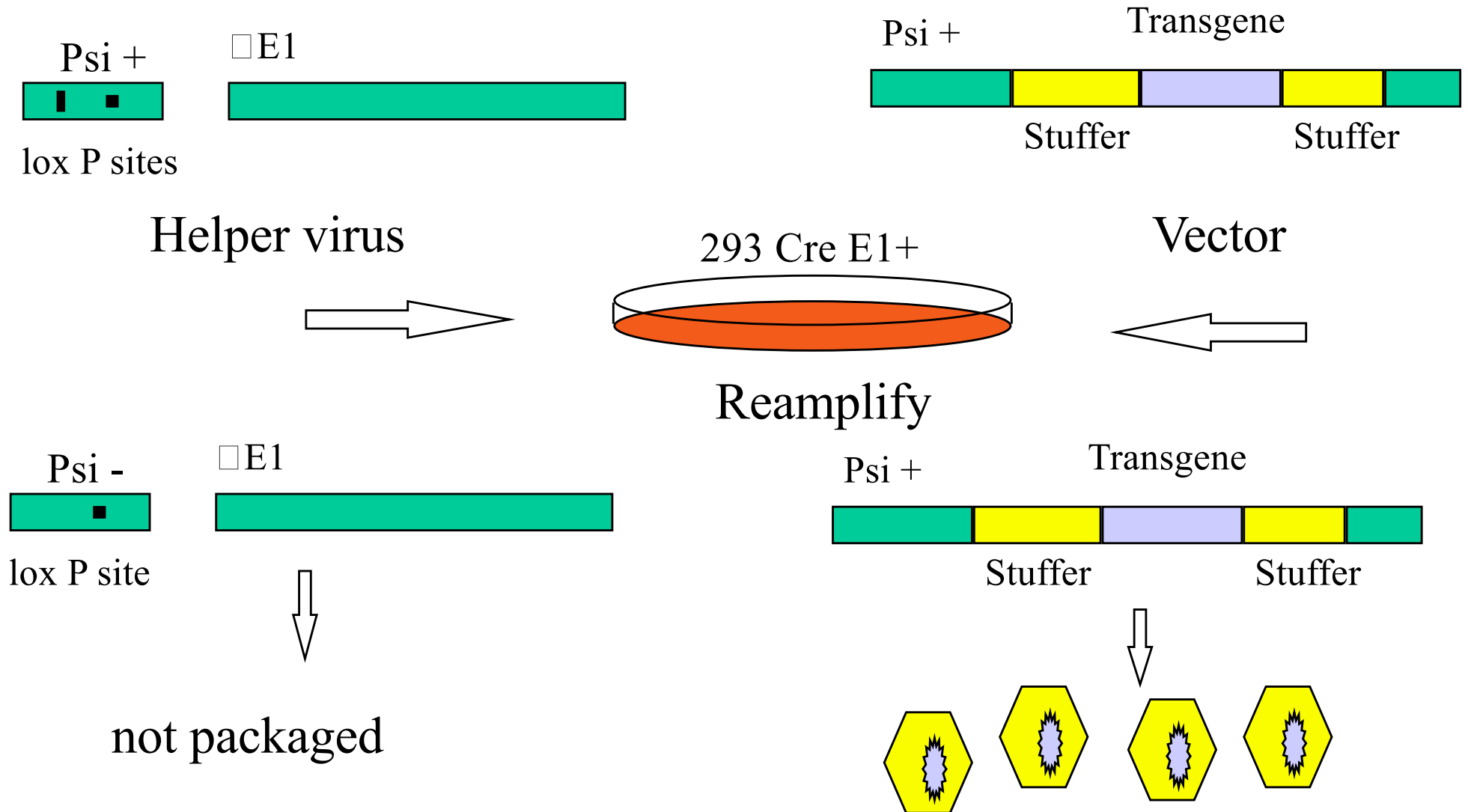
Immune response to adenoviral vectors

Inflammation

48h

CTL

7 d

Abs

21 d

2ⁿᵈ generation Adenoviral vectors

3rd generation Adenoviral vectors

Psi +   E1

lox P sites

Helper virus

Psi +   Transgene

Stuffer   Stuffer

Vector

293 Cre E1+

Reamplify

Psi -   E1

lox P site

not packaged

Psi +   Transgene

Stuffer   Stuffer

3rd generation Ad vectors: advantages

- size of the insert (36kb)
- low immunogenicity (no viral sequences)
- long term expression

3rd generation ad vectors: disadvantages

- titers
- instability
- helper contaminations
- stuffer?