Molecular arms races between primate and viral genomes

Part 1:
Viral evolution

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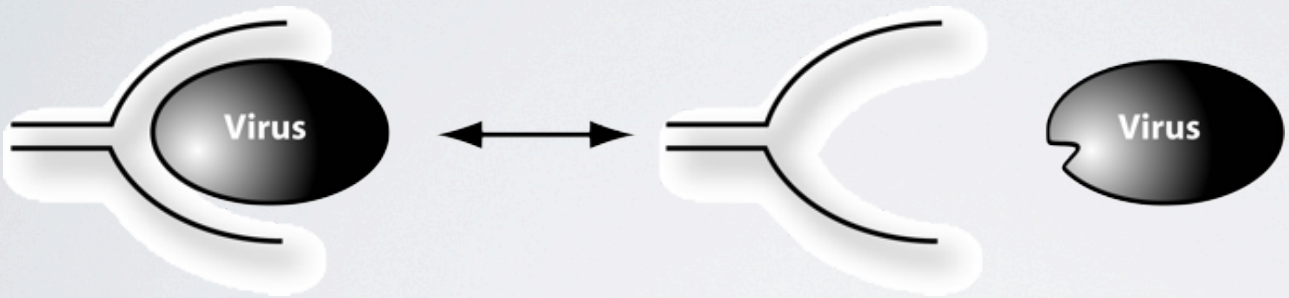
The Red Queen: “It takes all the running you can do, to keep in the same place.”

--Lewis Carroll,
“Through the Looking Glass”

The Red Queen Hypothesis: “For an evolutionary system, continuing development is needed just in order to maintain its fitness relative to the systems it is co-evolving with.”

--Leigh Van Valen (1973)

…the usual suspects



One party is always 'losing'.
There is always an evolutionary advantage
to be gained by innovation

Quantifying 'innovation' in protein-coding genes

(a brief primer)

```
...CAA ATG TGG...
   Q   M   W
```

```
CAG ATG TGG
 Q   M   W
```

Silent/Synonymous change

```
CAA ATC TGG
 Q   I   W
```

Non-synonymous (replacement) change

Quantifying 'innovation' in protein-coding genes

(a brief primer)

Diversifying selection

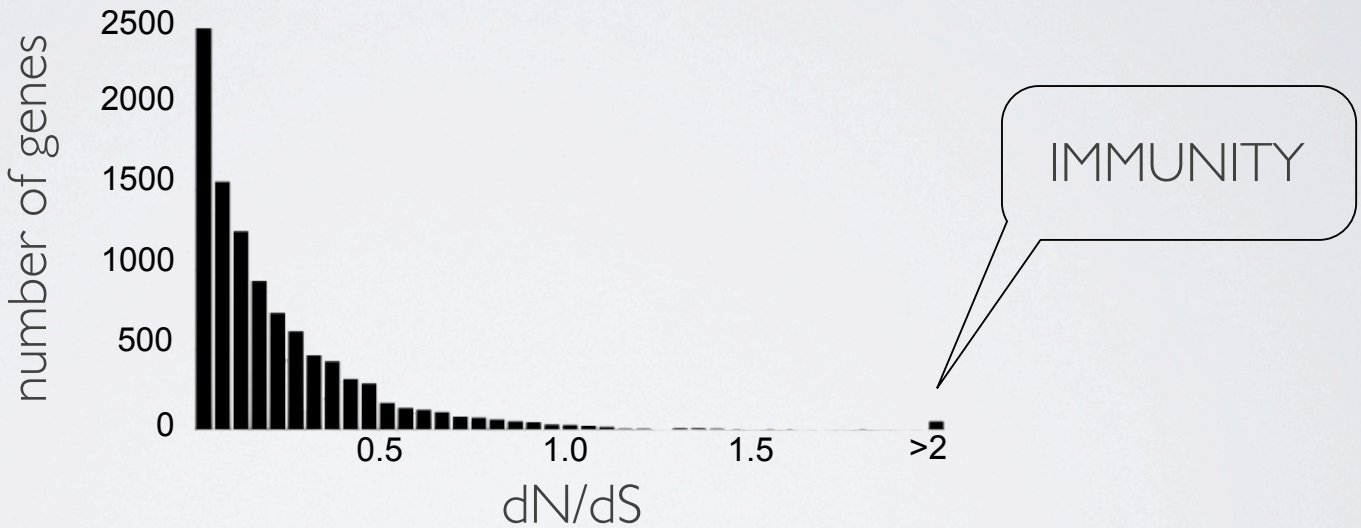
Positive selection (adaptive evolution)

```
... CAT GCG CGT ATG ATA ACT ... (..HARMIT..)
... CCT GCG CTT ATG ATG ACT ... (..pAlMmT..)
... CAT GTG CGA ATG ATA ACT ... (..HvRMIT..)
... CCT GCG AGT AGT GTA ACT ... (..pAssaT..)
```

$$\frac{\text{Actual number of synonymous changes}}{\text{Possible number of synonymous changes}} < \frac{\text{Actual number of replacement changes}}{\text{Possible number of replacement changes}}$$

$$K_S < K_{A \text{ or } R}$$

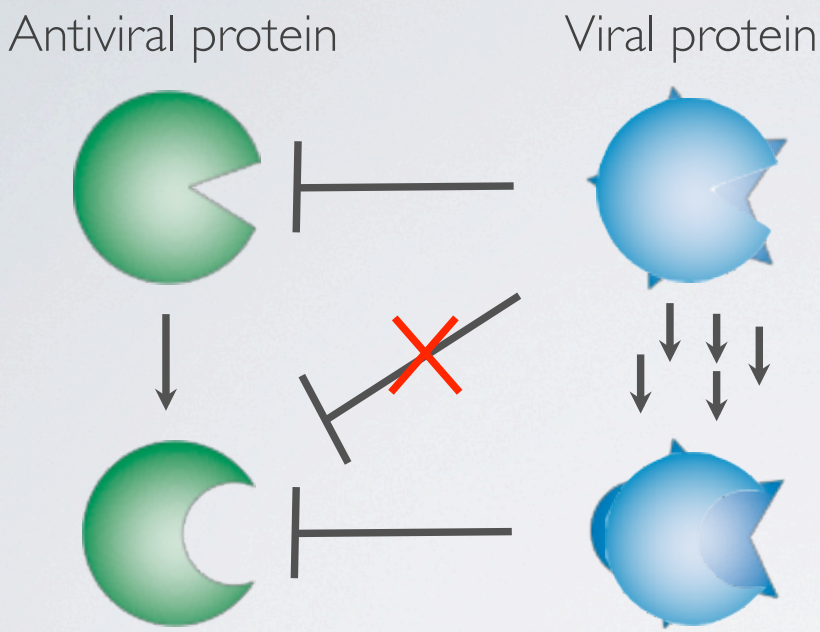
genomic view of selection



purifying —— neutral — positive selection

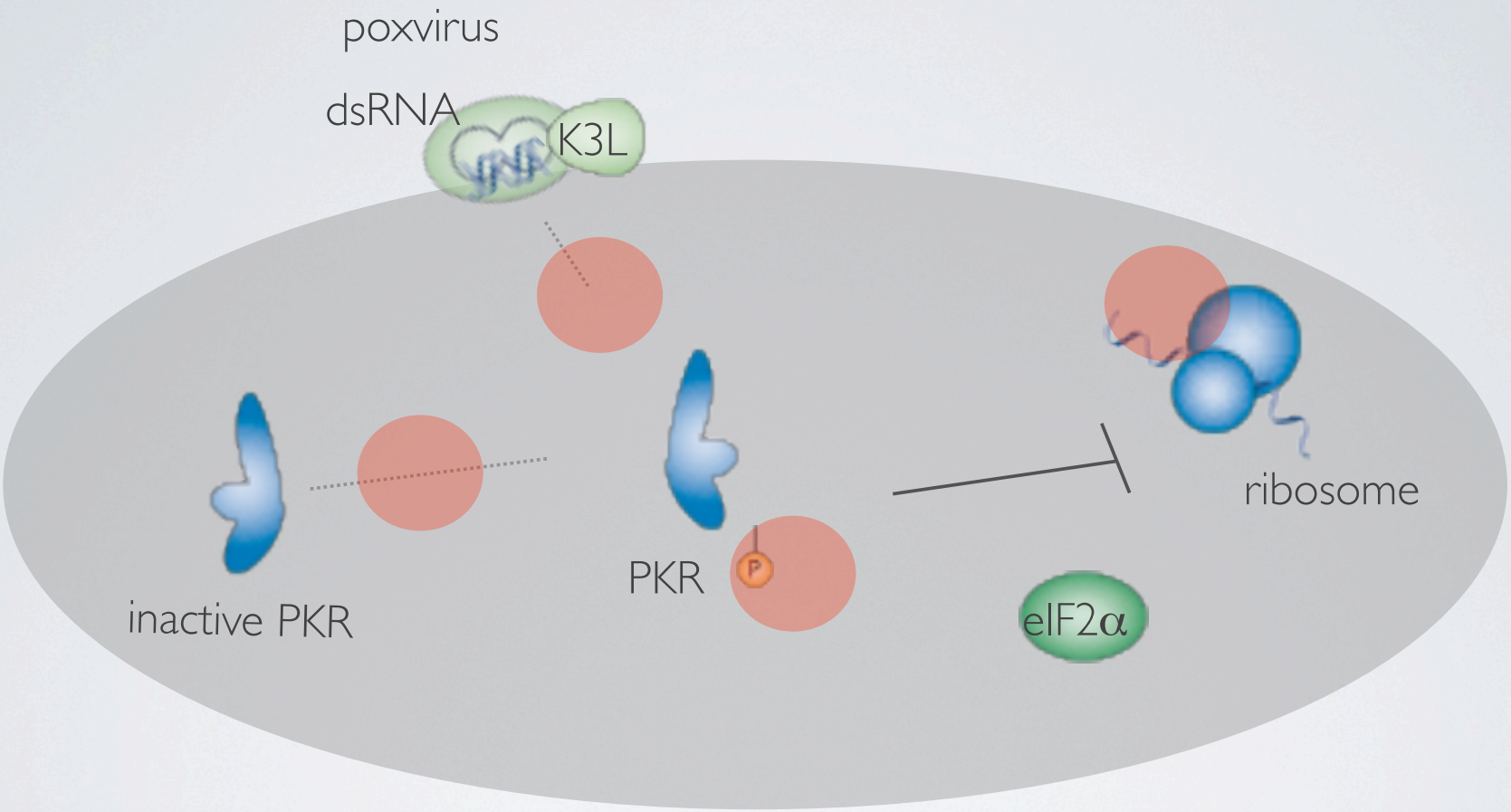
Siepel Lab

HOST-PATHOGEN EVOLUTION

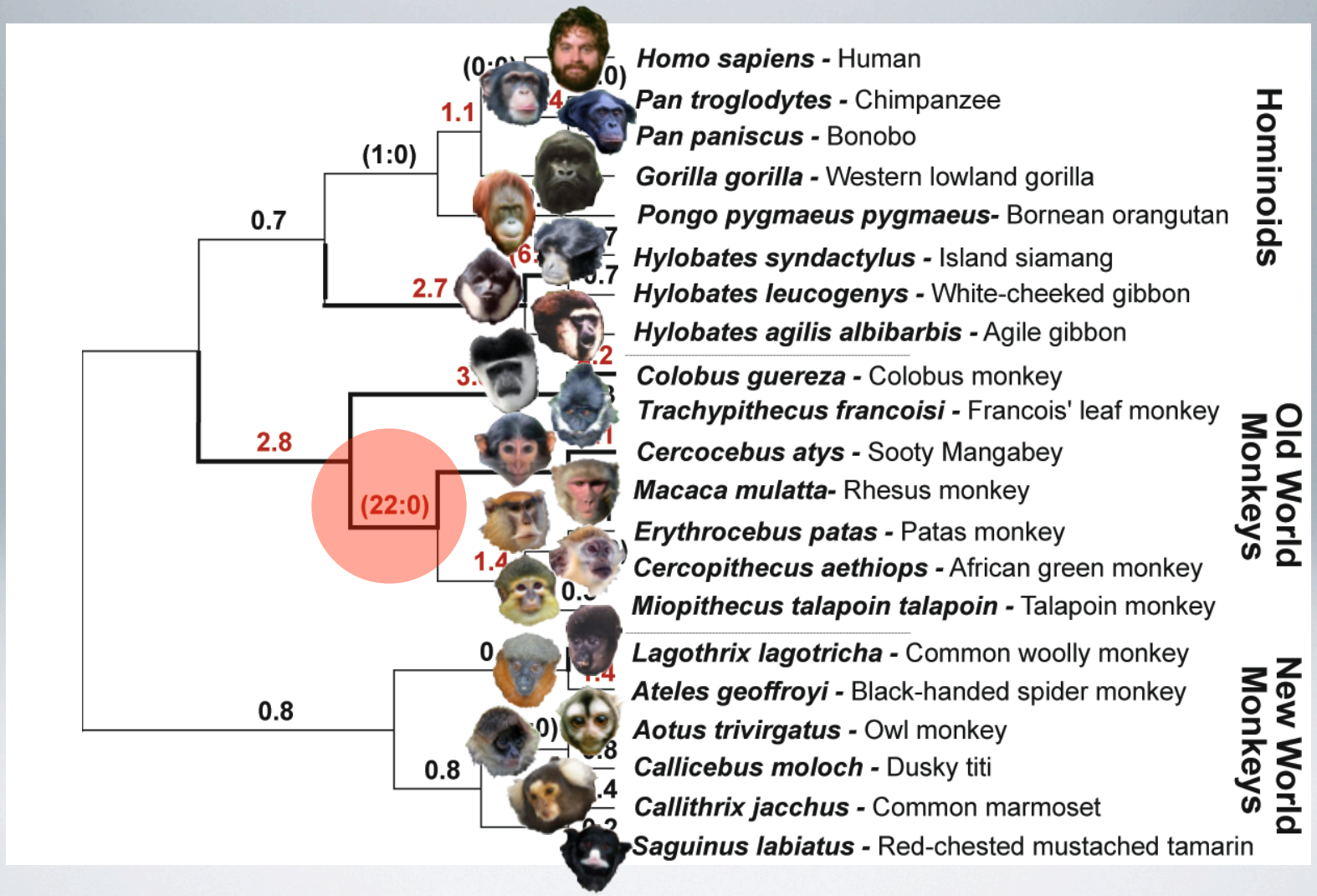


- the challenge of pathogen mimicry

protein kinase r (PKR)



selection on primate pkr



Elde, *et al.*, Nature 2009

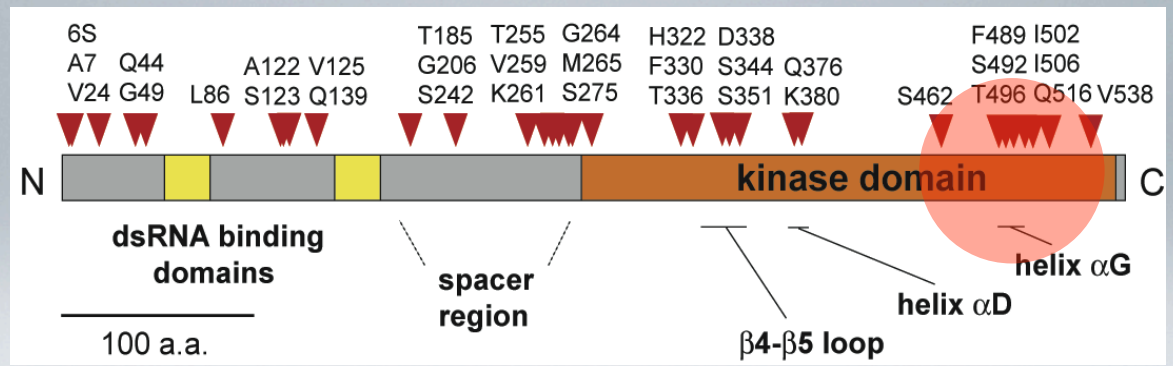
POSITIVE SELECTION ON PKR

Us11 (herpes virus)
NS1A (influenza)
E3L (poxvirus)

NS5A (HCV)

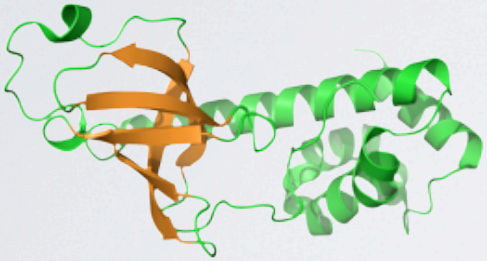
K3L & E3L (poxvirus)
RelF2H (ranavirus)

sites under positive selection:

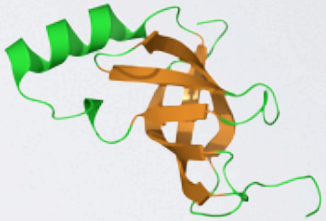


the origins of mimicry

eIF2α



K3L



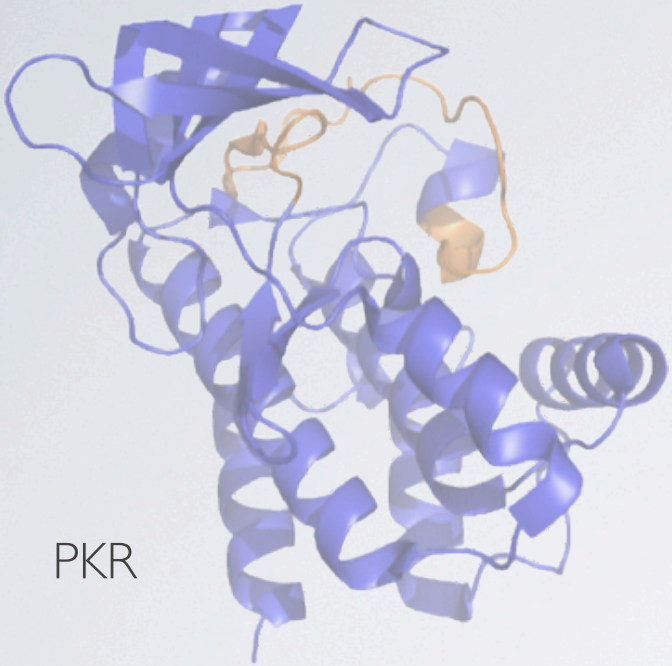
poxviruses (mammals)
iridoviruses (fish)
ranaviuses (amphibians)

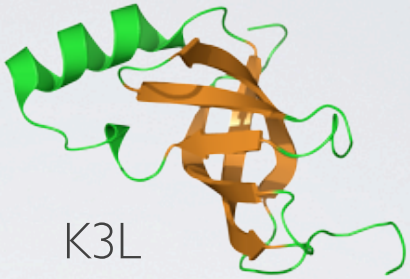
Mimicry and conflict

Henry Walter Bates, 1862

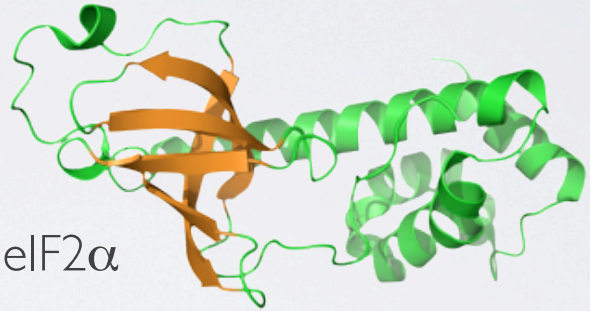
Dar, *et al*., Mol. Cell 2002

The Challenge of mimicry

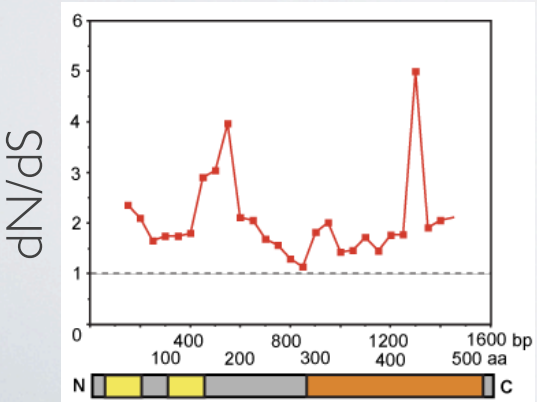




avoid this interaction

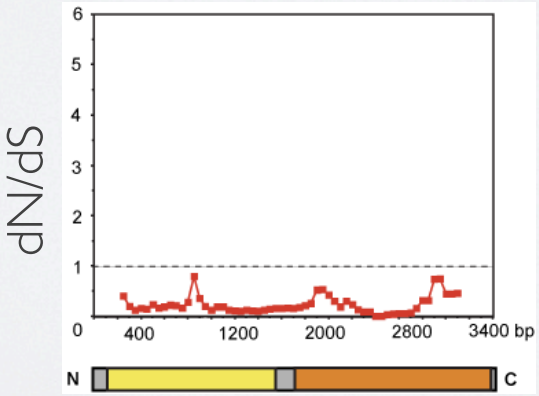


maintain
this interaction



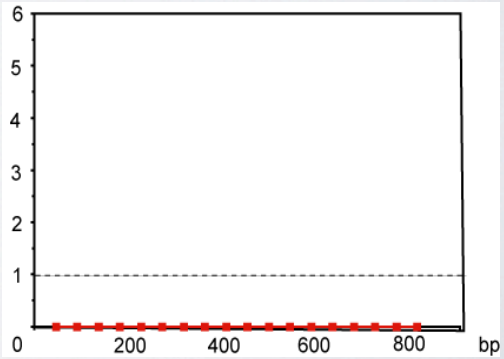
kinase domain

PERK



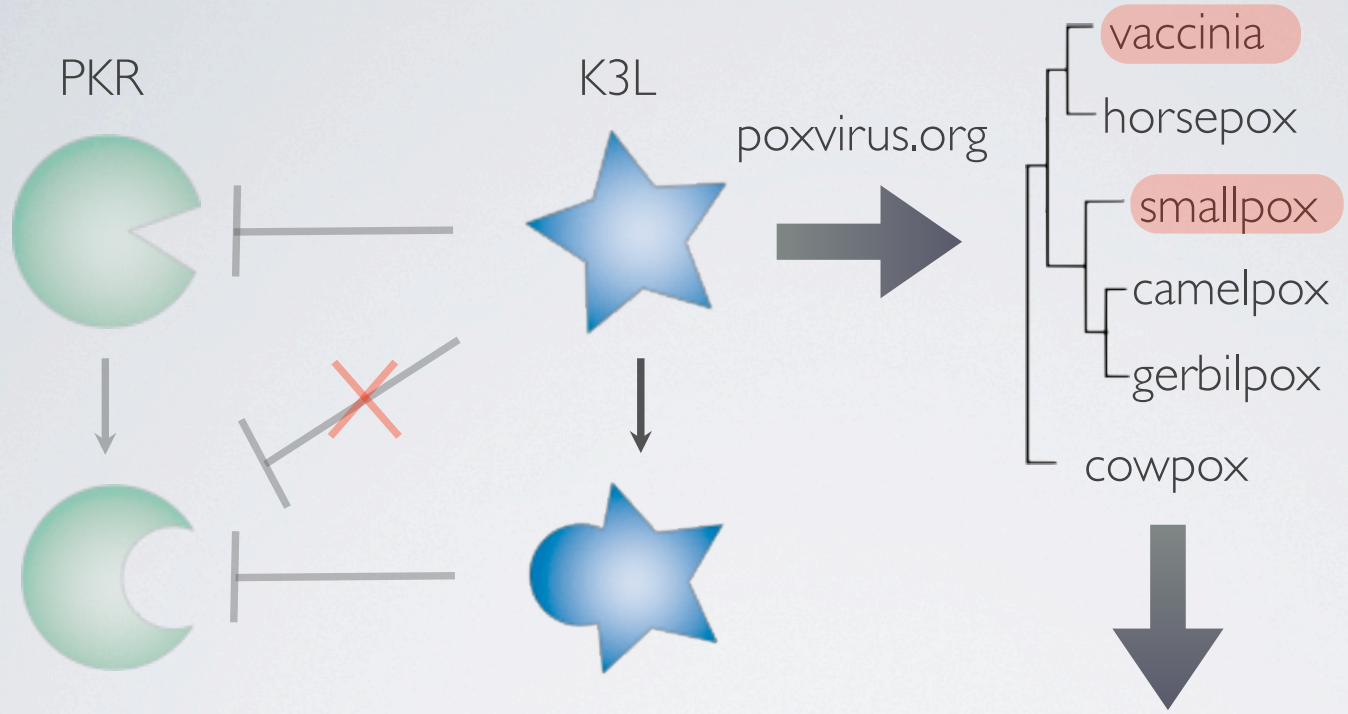
kinase domain

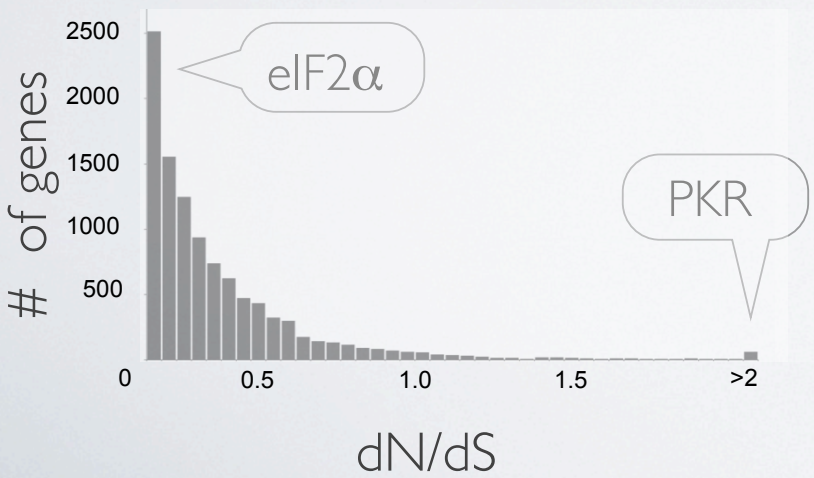
eIF2α

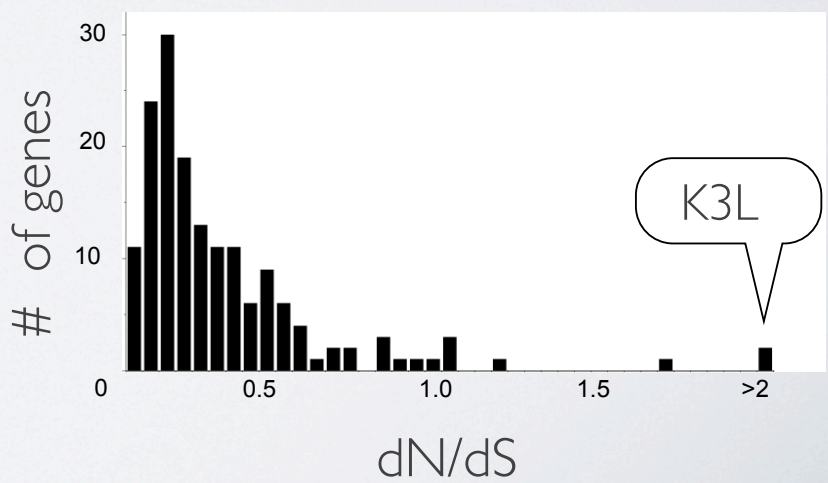


Dar, *et al.*, Cell 2005

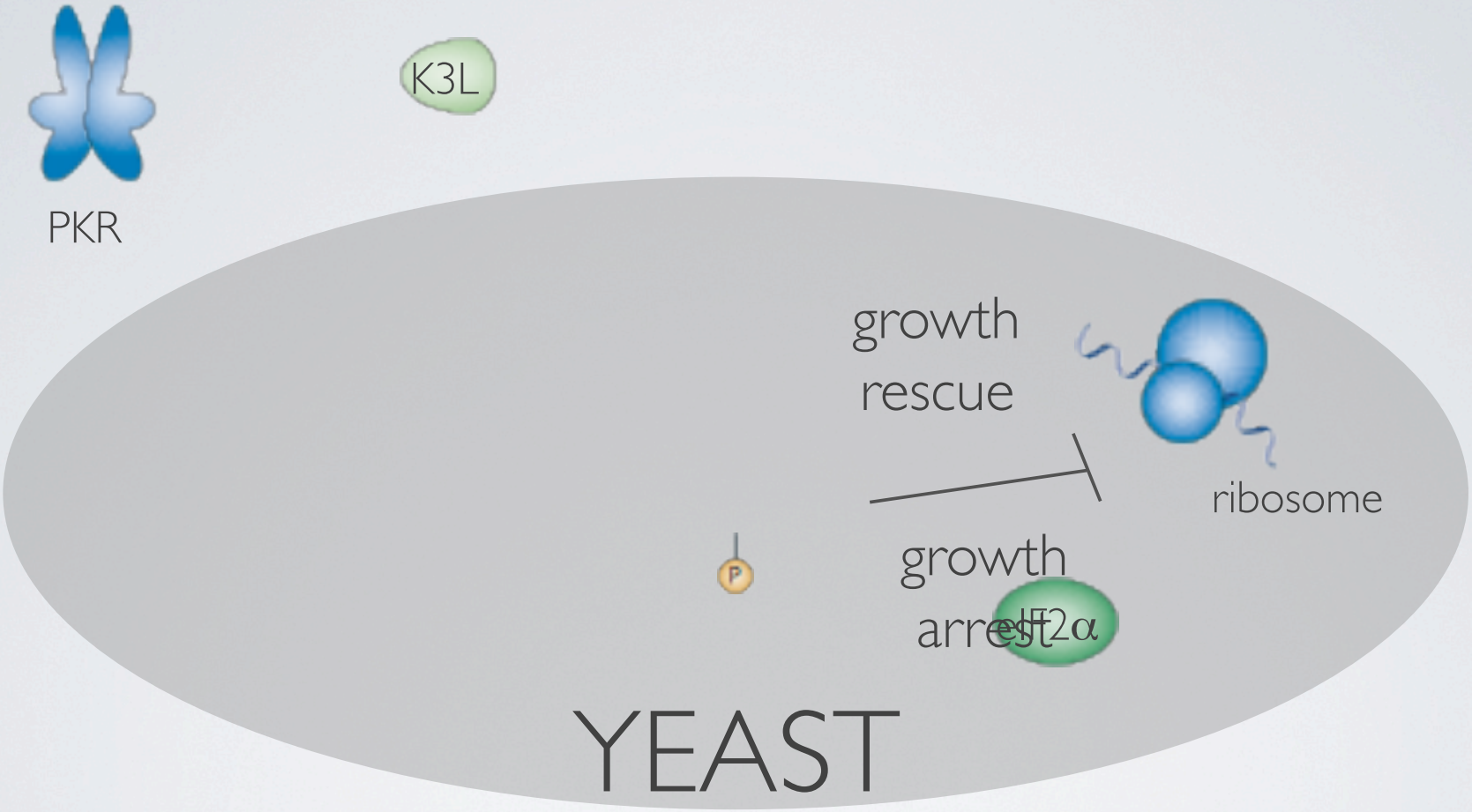
the evolution of mimicry





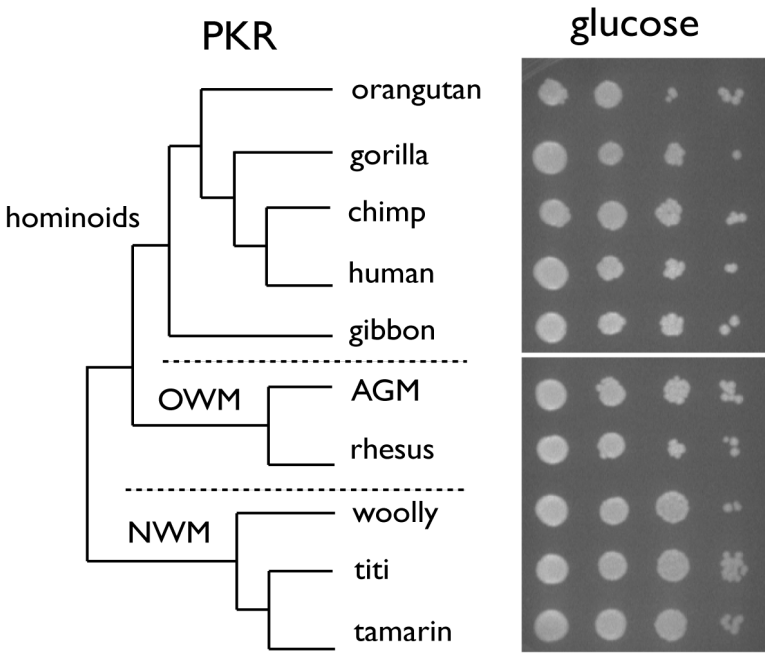


yeast assay for pkr activity



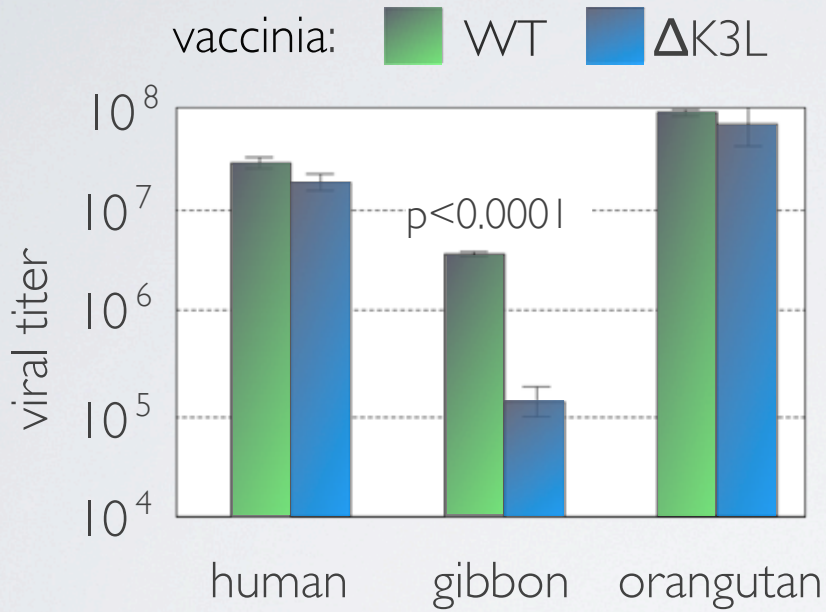
Hinnebusch Lab

yeast assay for pkr activity



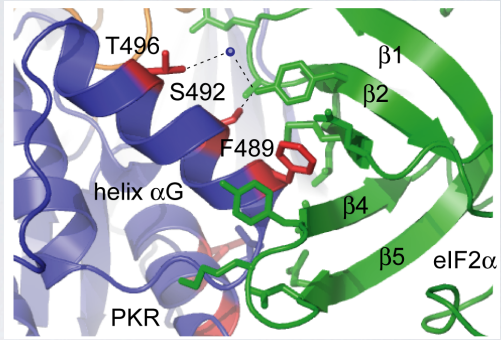
Elde, *et al*., Nature 2009

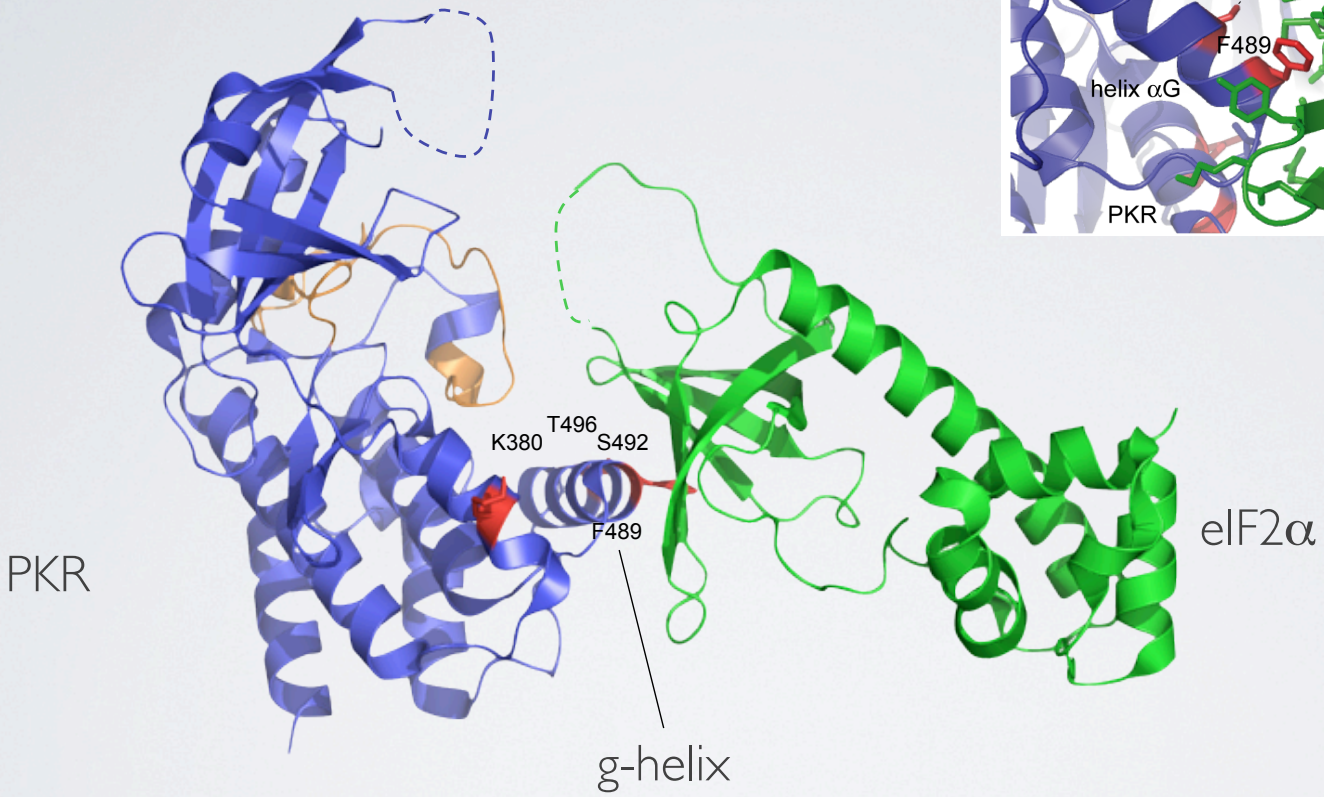
k3l & gibbon cell infection



Adam Geballe

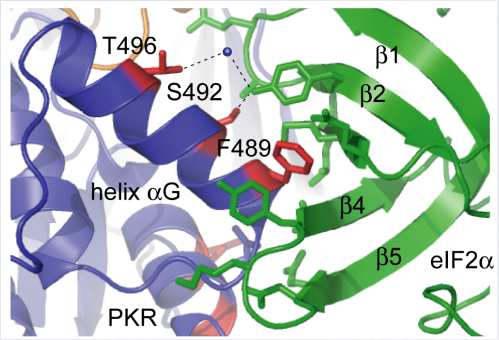
selection at the interface

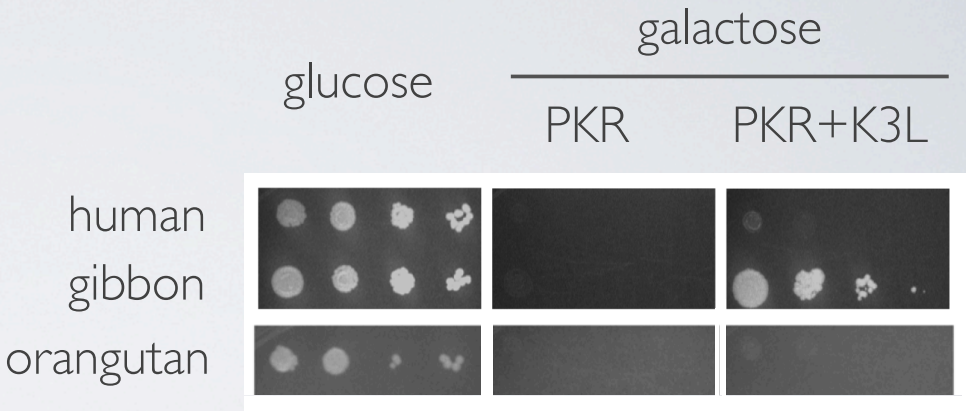




Dar, *et al.*, Cell 2005

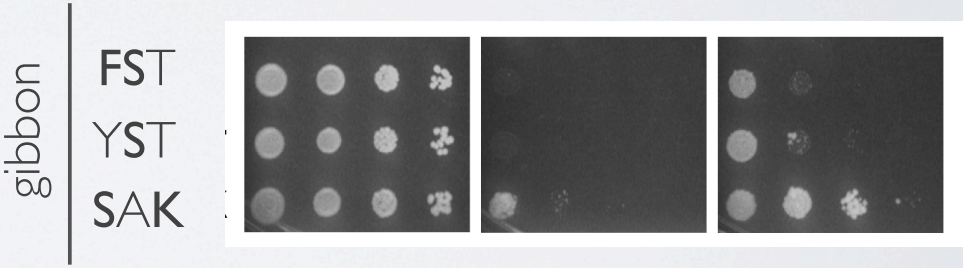
g-helix resists k3l





helix αG

```
                489  492   496
                ▼    ▼     ▼
human           DTAFETSKFFTDLR
gibbon          DTAYETAKFFTDLR
orangutan       DTASETAKFFKDLR
rhesus          DTASETLQLFRDLR
owl             DTALETSKFFGDLR
```



Leu394 overrides k3l

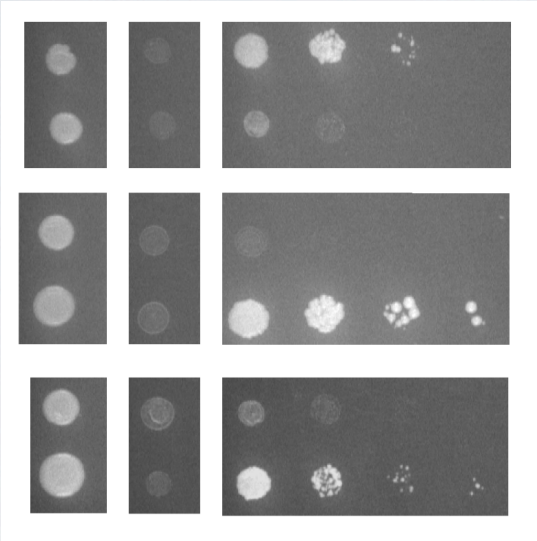
galactose

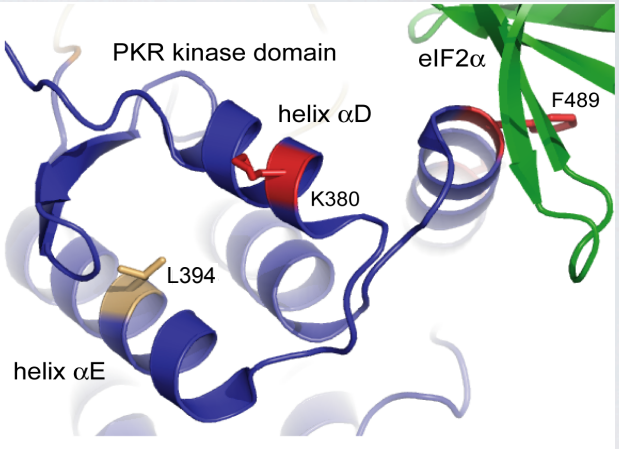
PKR PKR+K3L

gibbon F394L

orangutan L394F

human L394F F489Y S492A

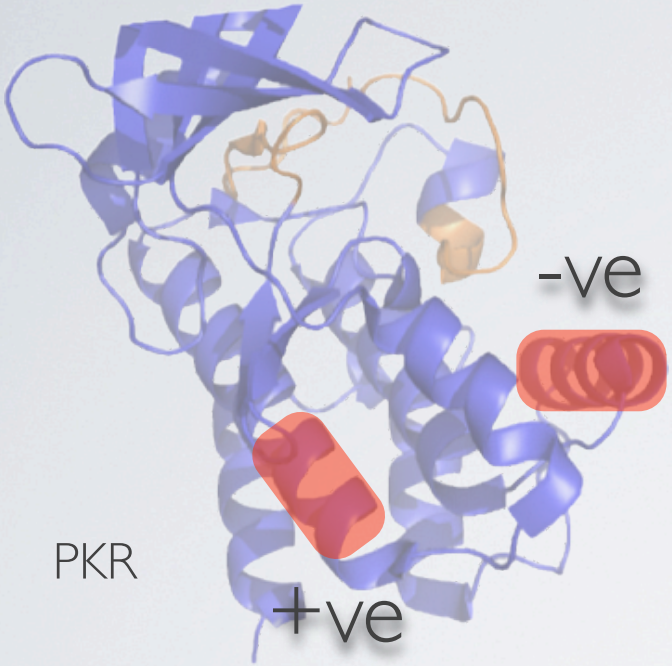


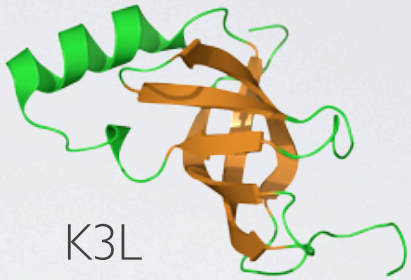


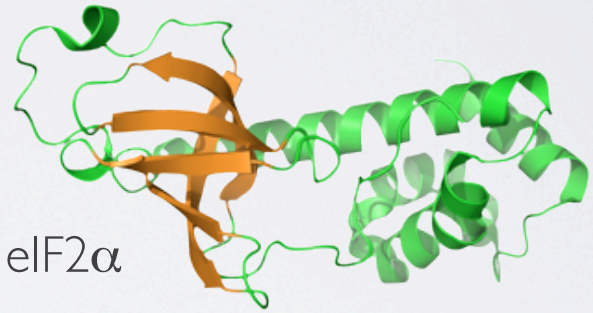
394

human	LELFEQ	primates
orangutan	LELFEQ	primates
gibbon	LEFFEQ	primates
rhesus	LELFEQ	primates
owl	FEFFEQ	primates
mouse	LDLYEQ	other mammals
rabbit	LEFFWQ	other mammals
dog	LELFEQ	other mammals
pig	LEFFEQ	other mammals

OVERCOMING MIMICRY

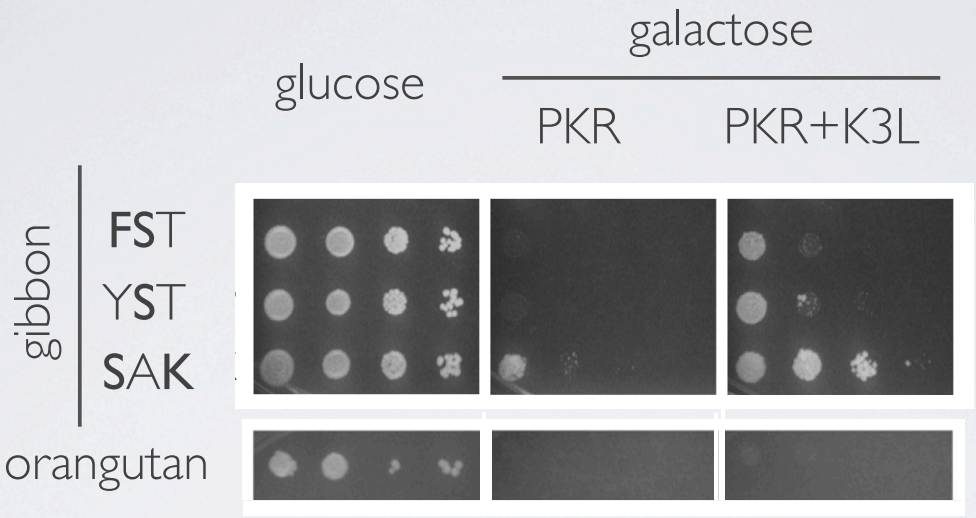






- evolution on multiple surfaces
- flexibility for substrate recognition

Elde, Child, Geballe, Malik Nature 2009



Intragenic "restoration" of function

A cost to flexibility

```
          αG helix
          489 492 496     530 533 537     1024 1027 1031     944 947 951
human     TAFETSKFFTDLRD  TEMERAEVLTGLRT  TQMERVRTLTDVRN  TASERIFVLNQLRD
rhesus    TASETLQLFRDLRG  TEMERAEVLTGLRT  TQMERVRTLTDVRN  TASERIFVLNQLRD
mouse     TESEKIKFFESLRK  TEMERATVLTGVRT  TQMERVRILTDVRN  TASERIFVLNQLRD
cow       TSLETQKFFDDLRN  TEMERAHVLTGLRT  TQMERVRILTDVRD  TASERIFVLNQLRD
dog       TVSETLKIFKELRA  TEMERVHILTGLRS  TQMERVRVLTDVRN  TASERIFVLNQLRD
          *  *     *  **  *****  :***:*  ******* *****  **************
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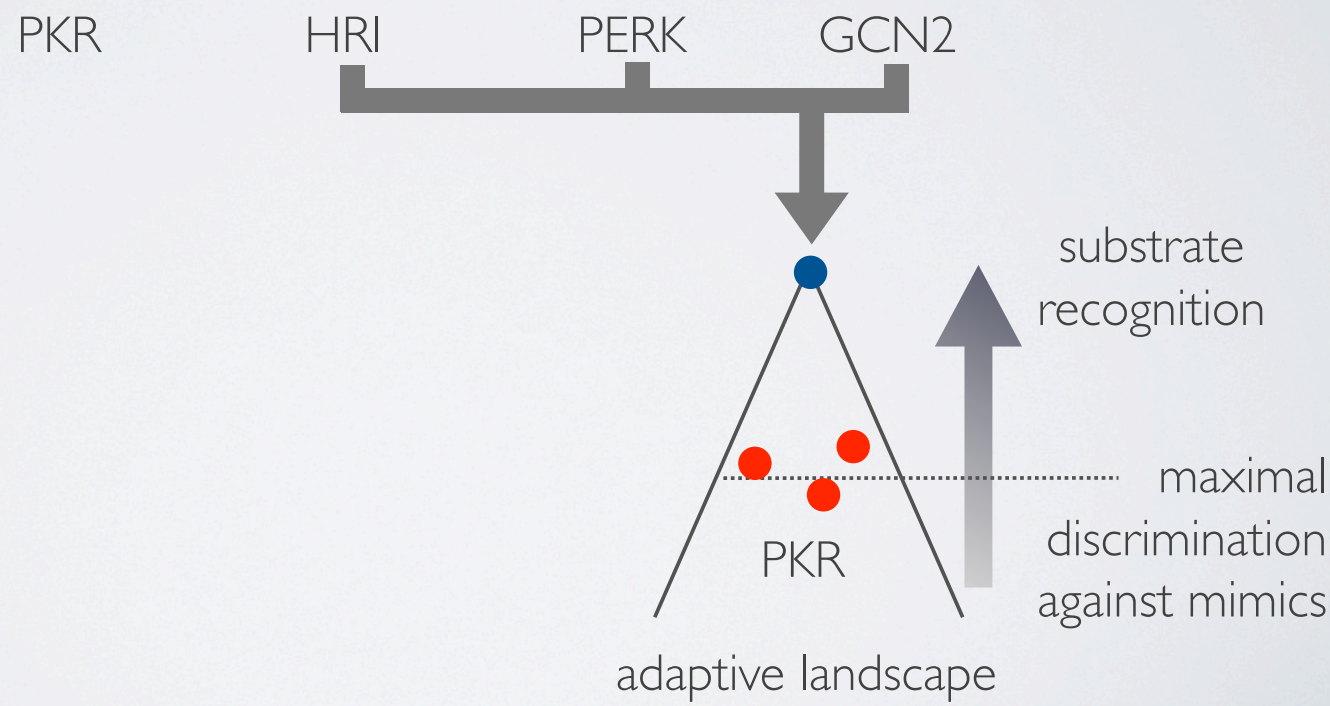
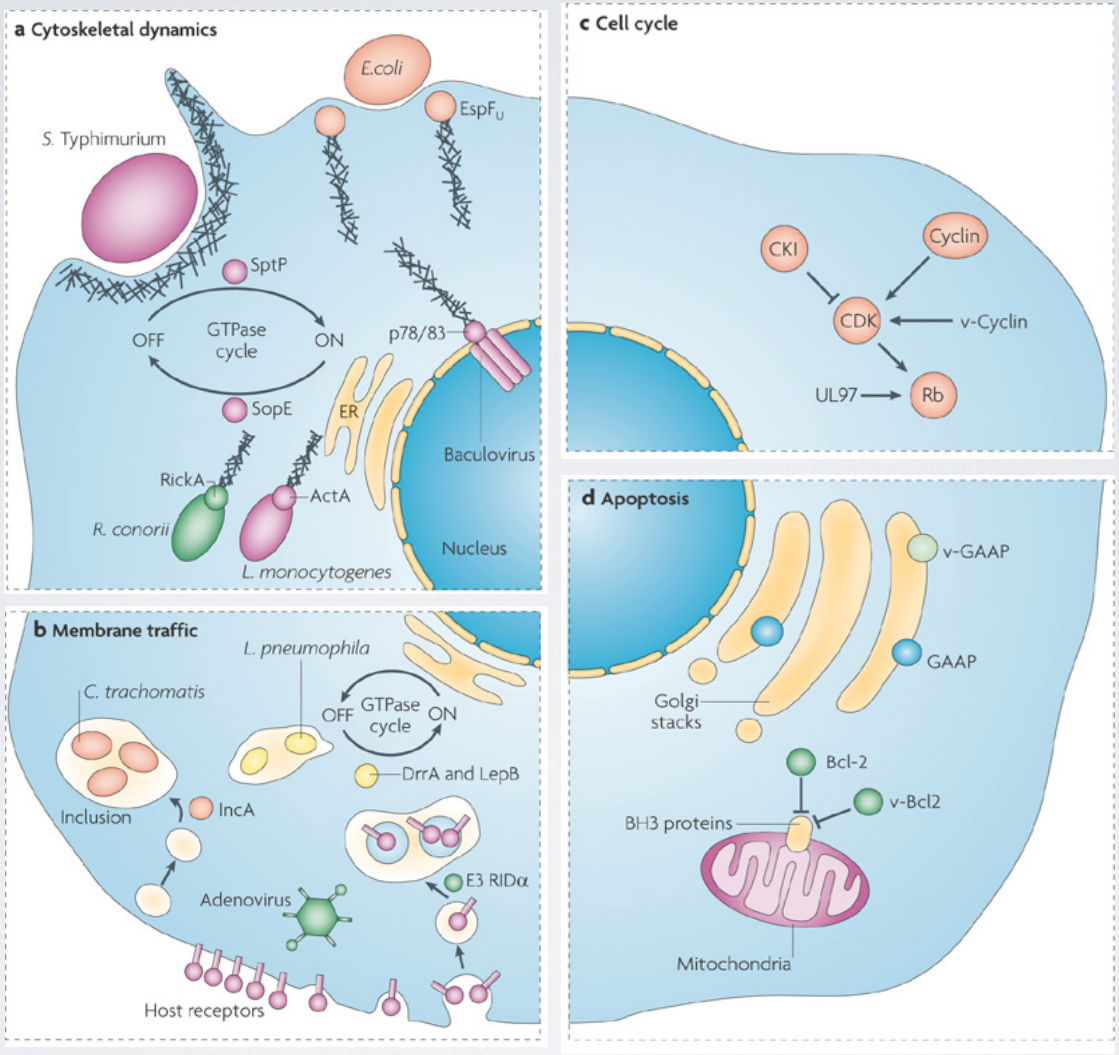


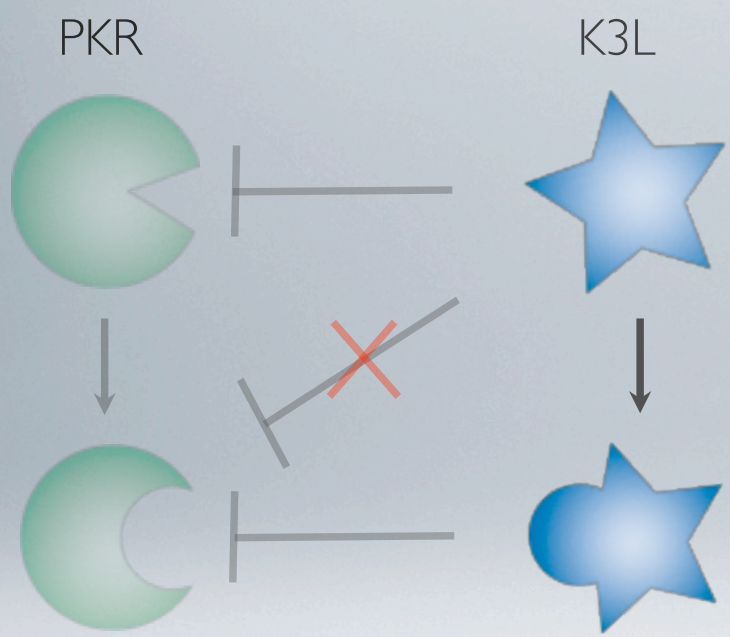
MIMICRY AGAINST THE CELL



Evolutionary "winners" may in fact be losers...

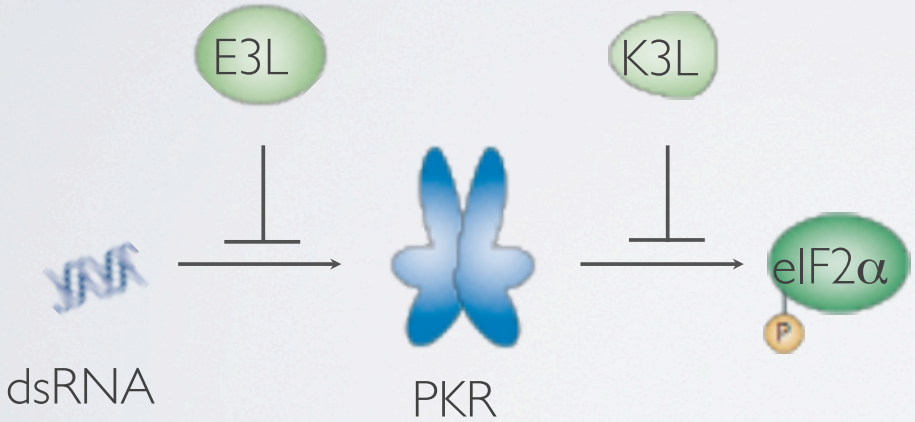
Elde, Malik Nature Rev Microbiol 2009

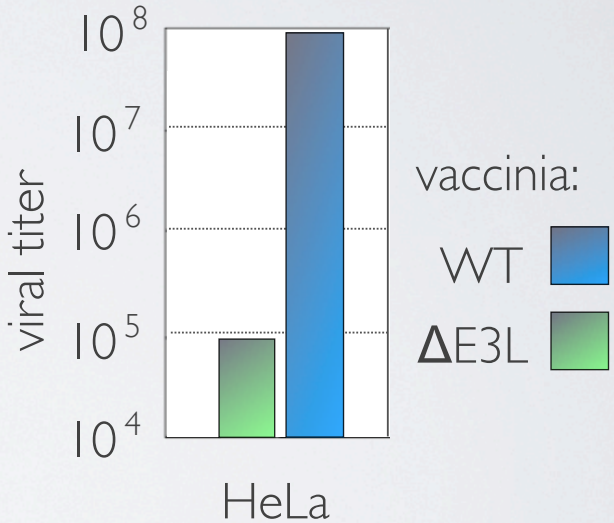
PKR versus K3L



EXPERIMENTAL EVOLUTION

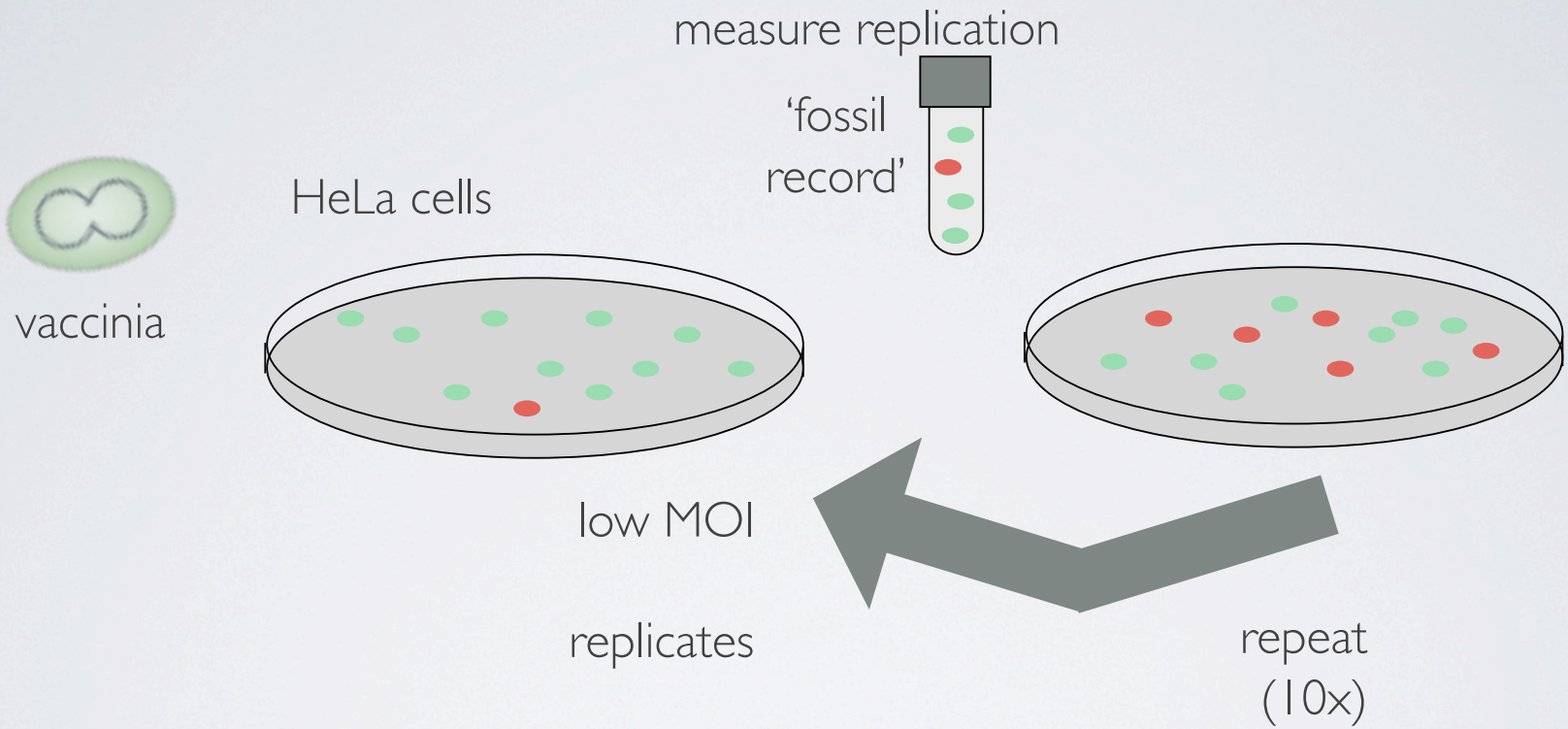
vaccinia
ΔE3L
(β-gal)





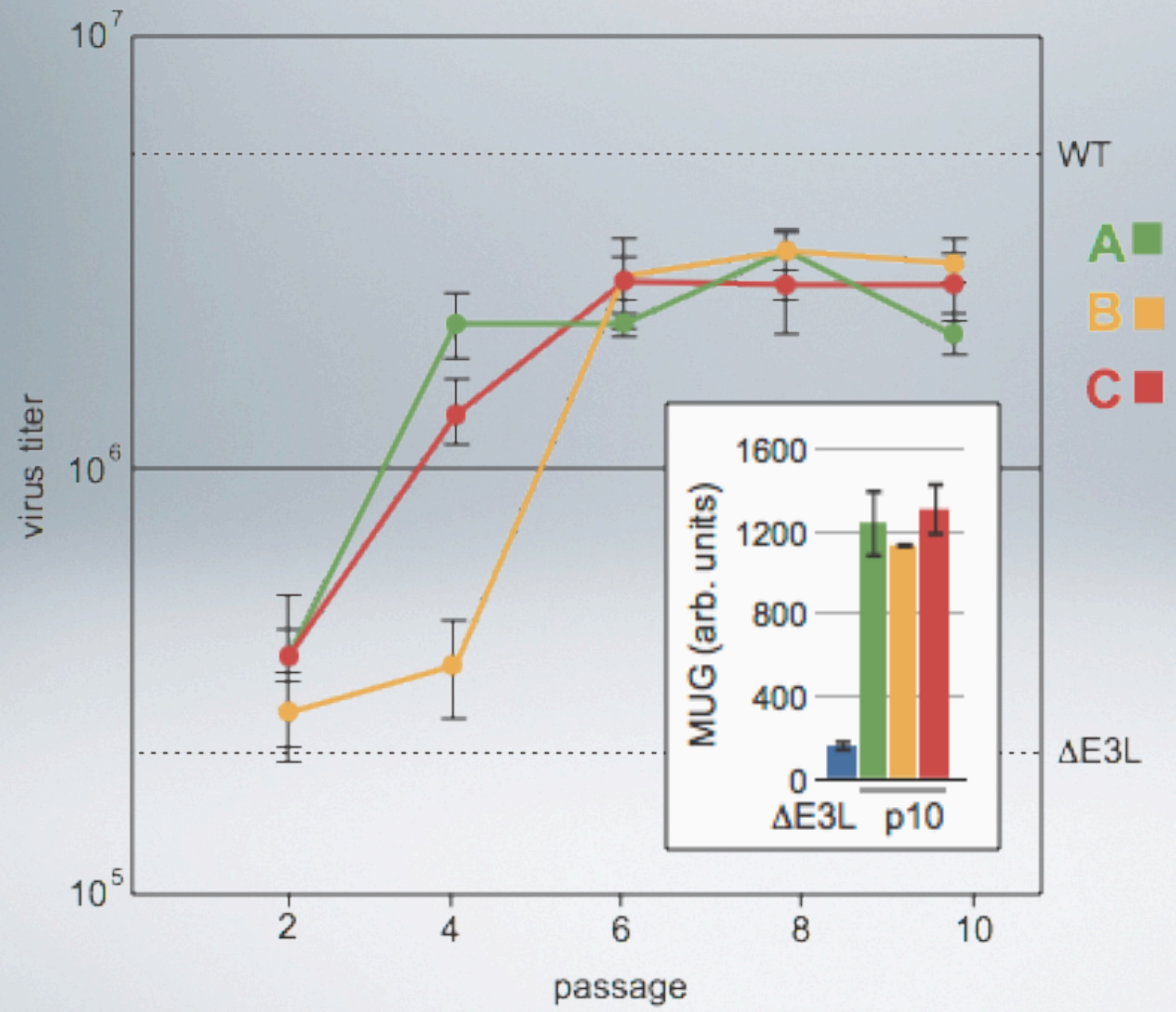
adapted from
Langland and Jacobs, Virology, 2002

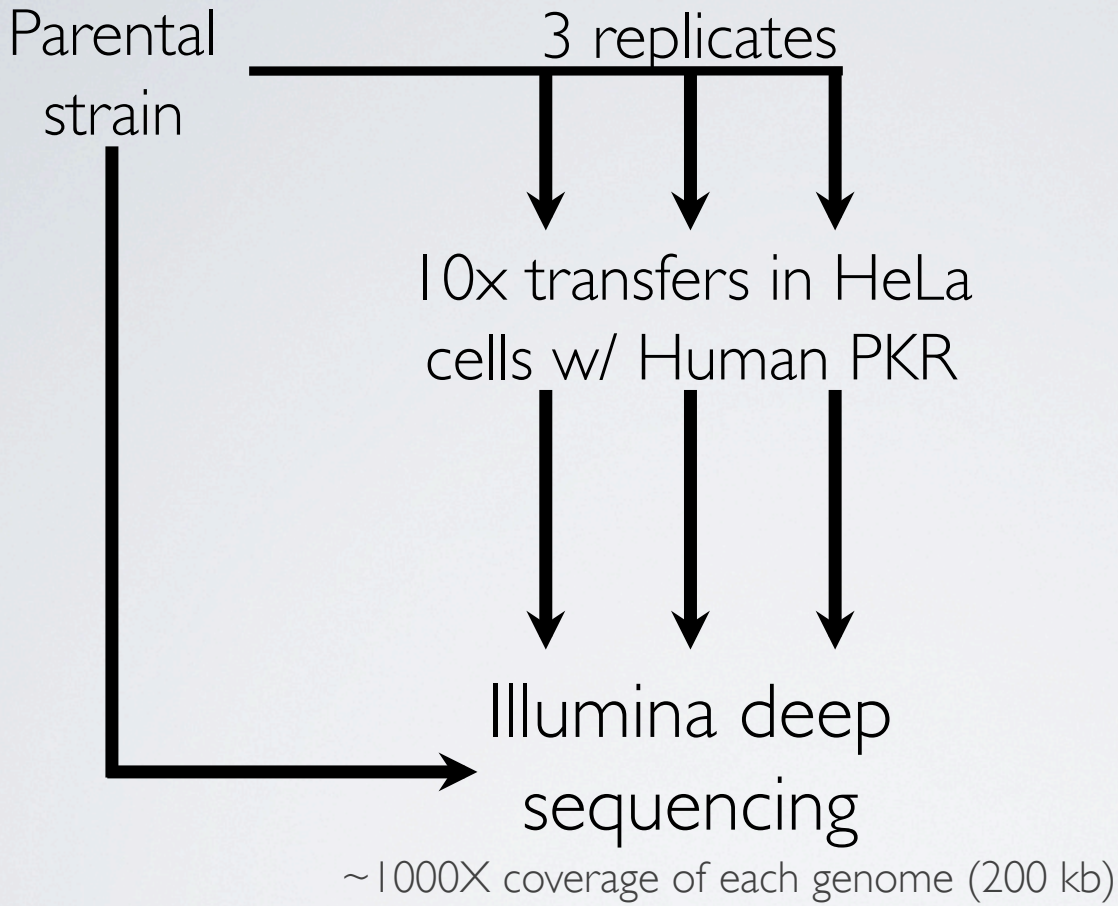
experimental evolution



Geballe Lab

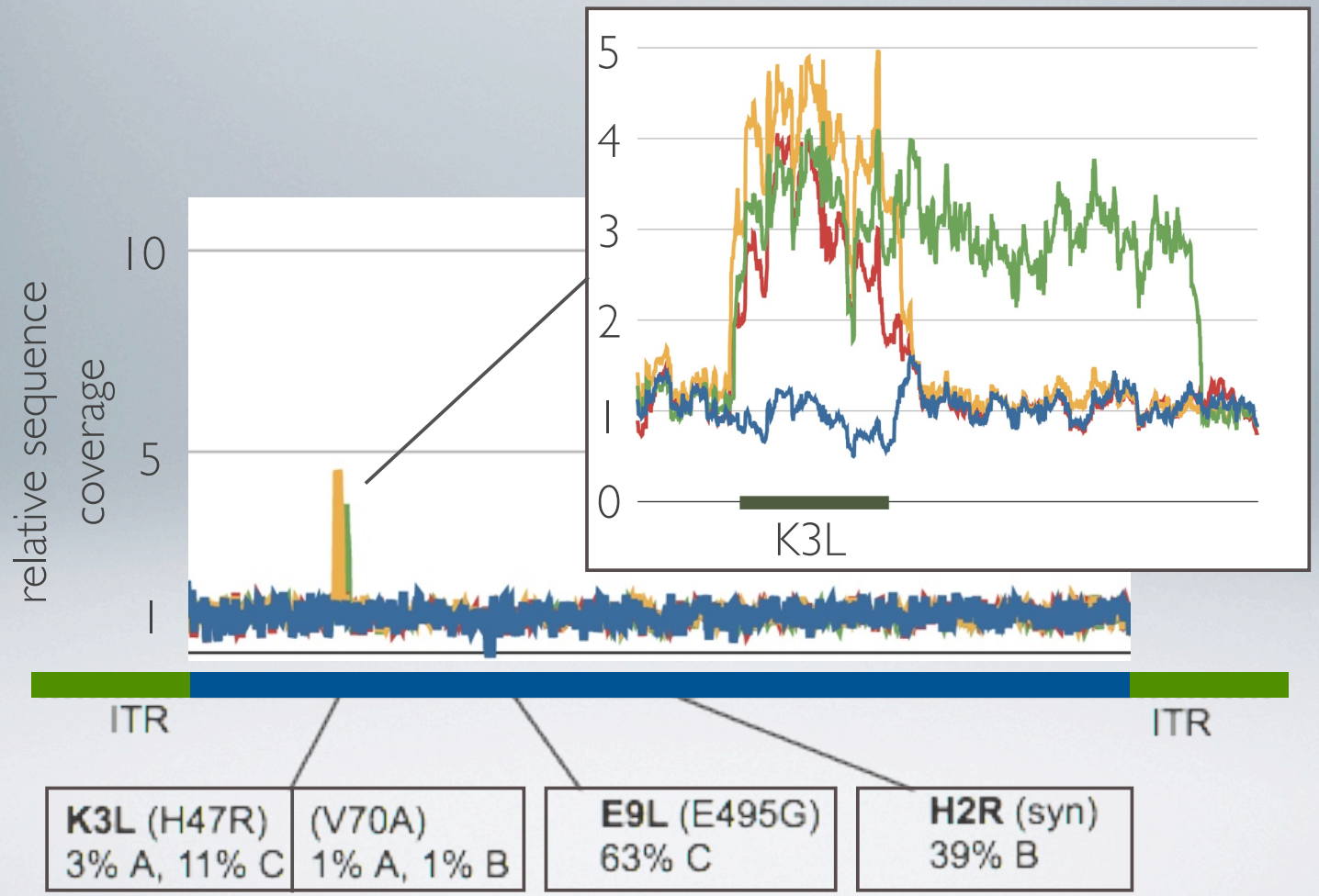
evolution of vaccinia



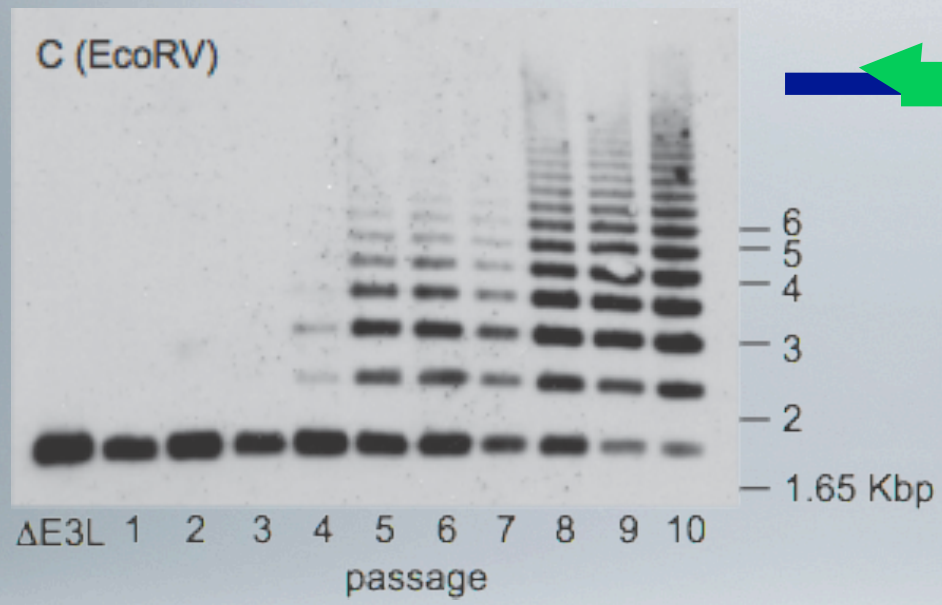


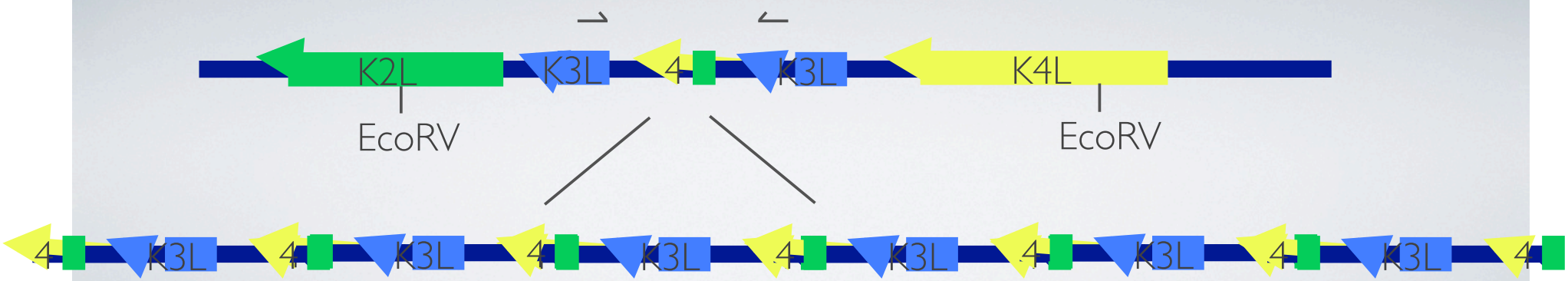
Shendure Lab

evolution of vaccinia

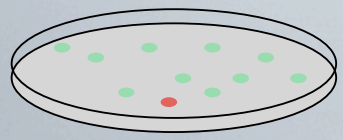


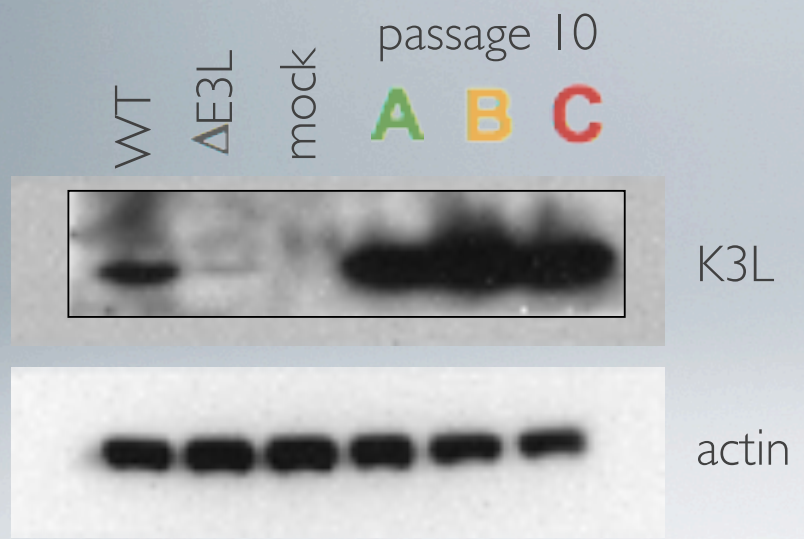
evolution of CNV

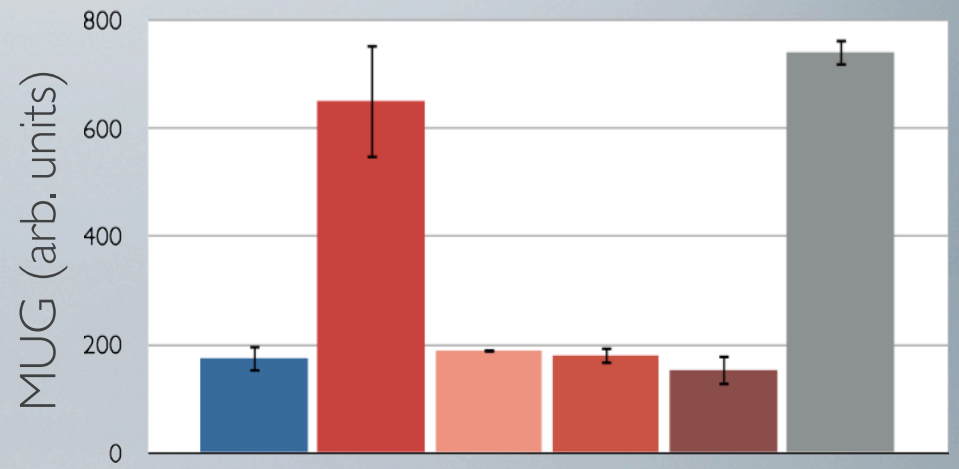


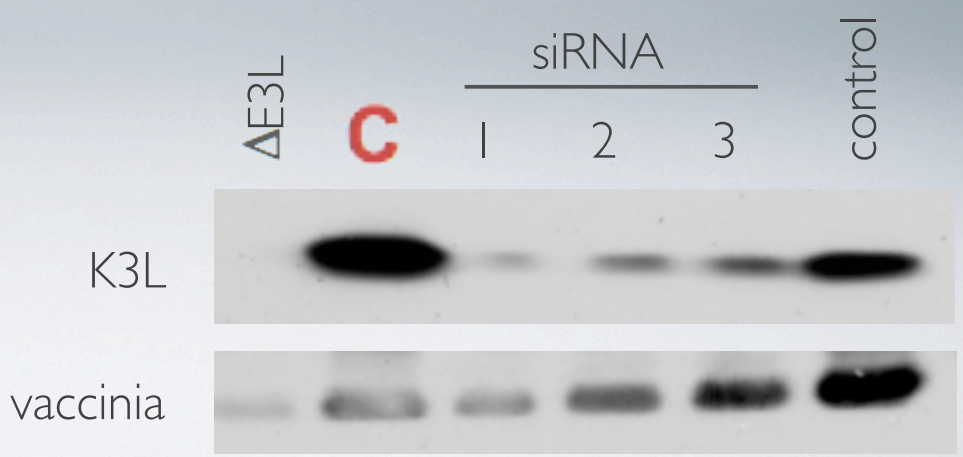


adaptive K3l duplications

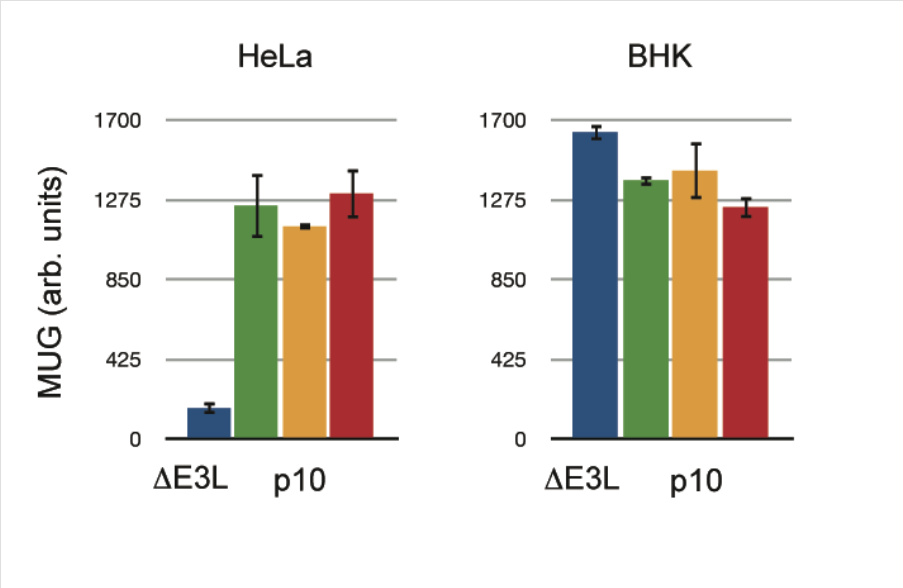


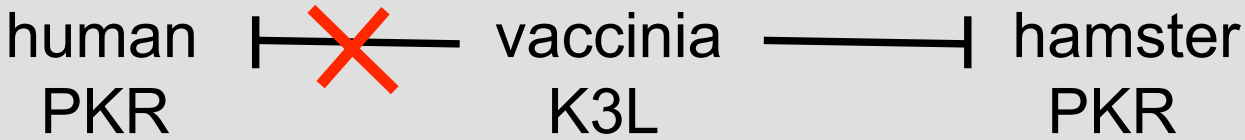


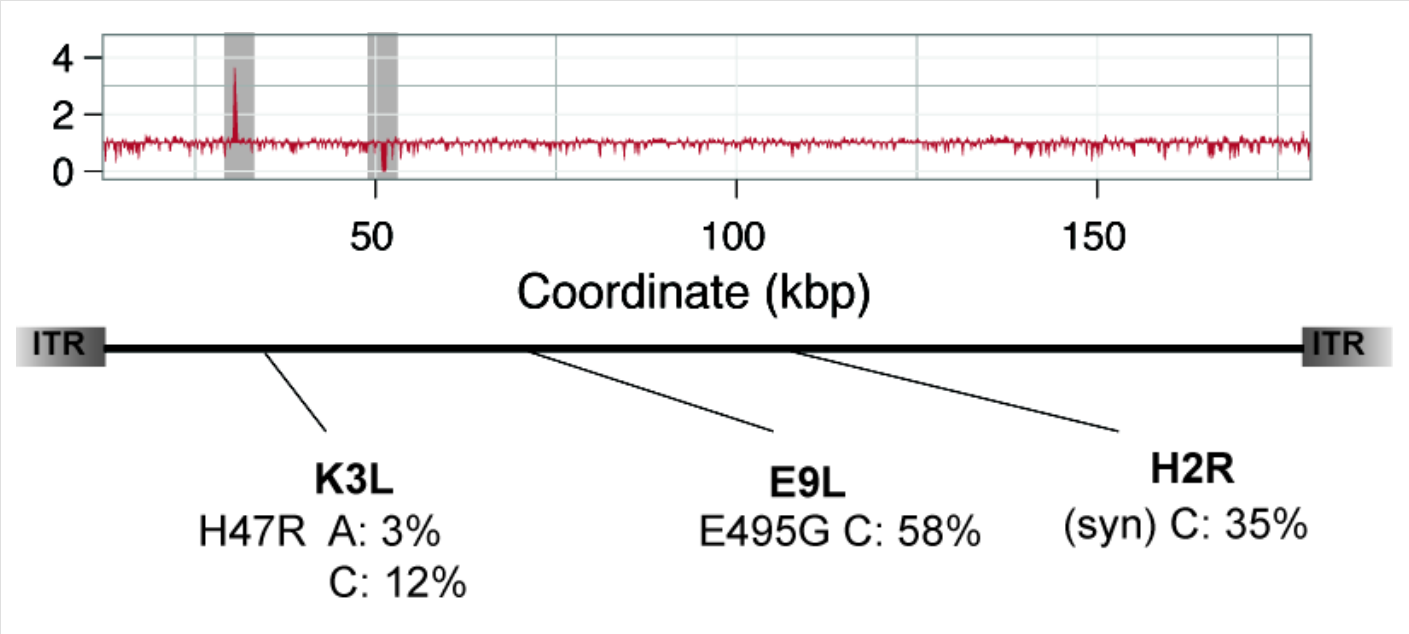


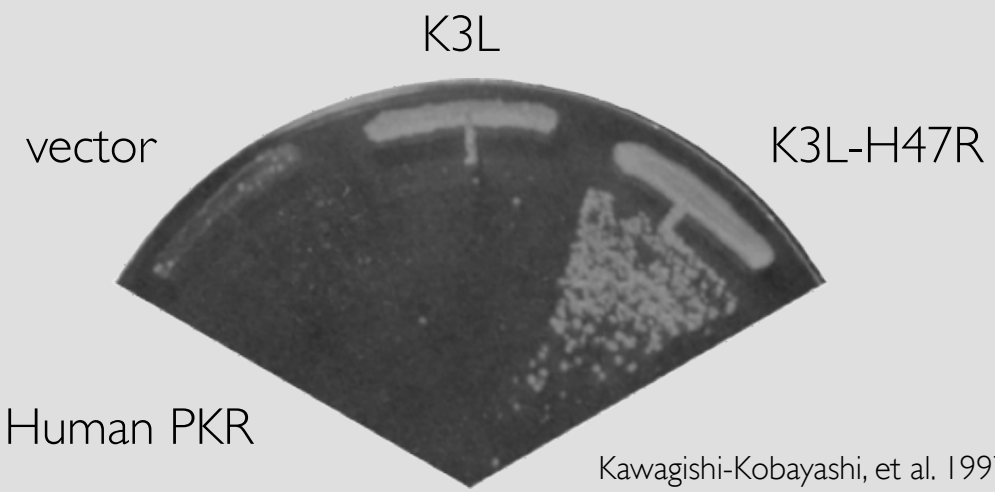


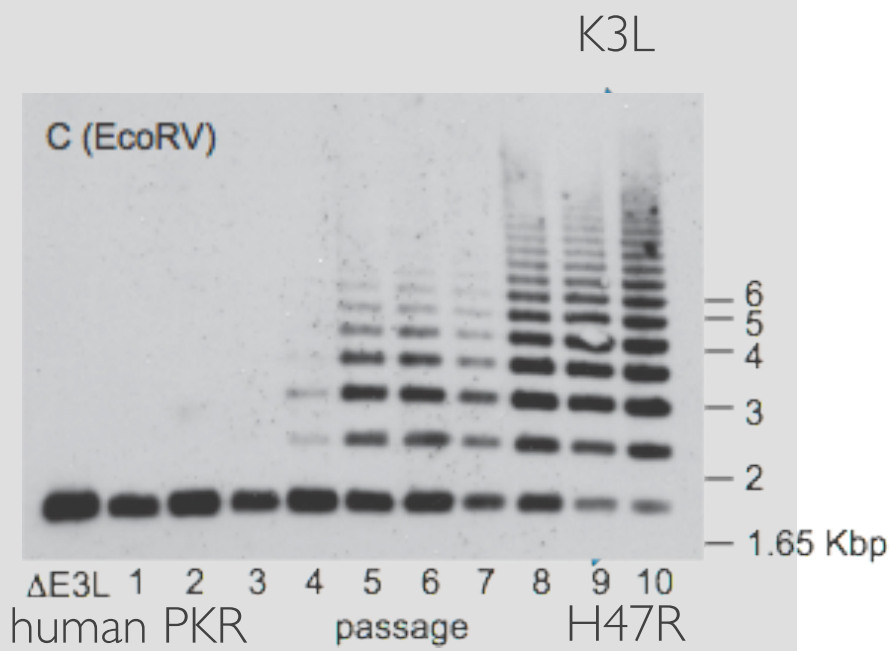
A trade-off associated with K3L gene expansion





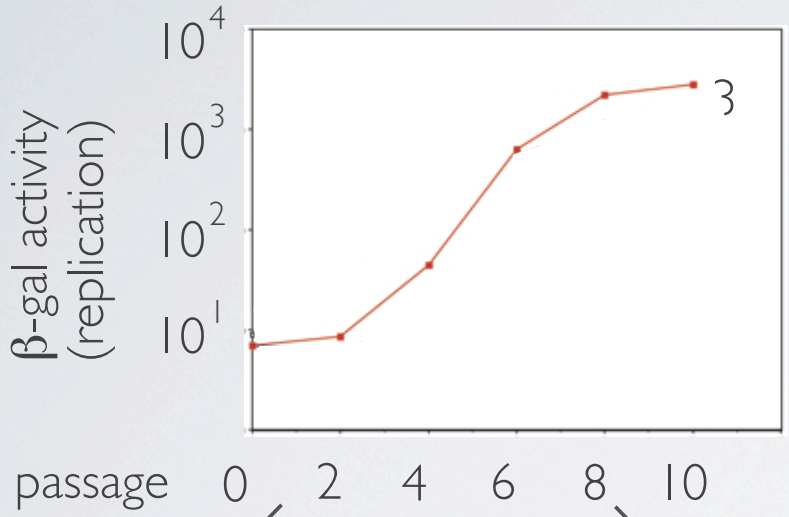


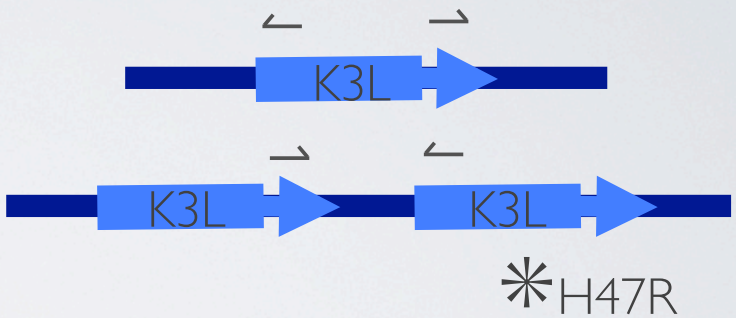


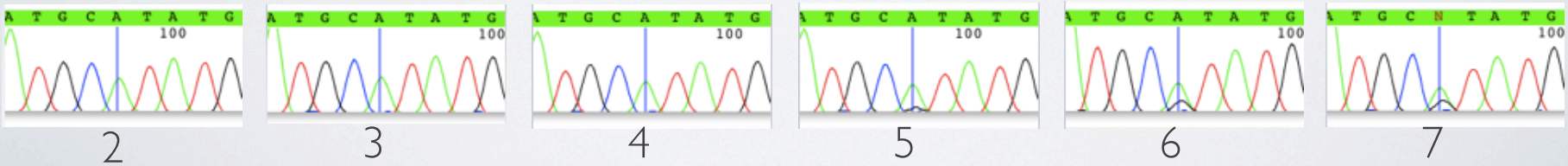


Kawagishi-Kobayashi, et al. 1997 & 2000

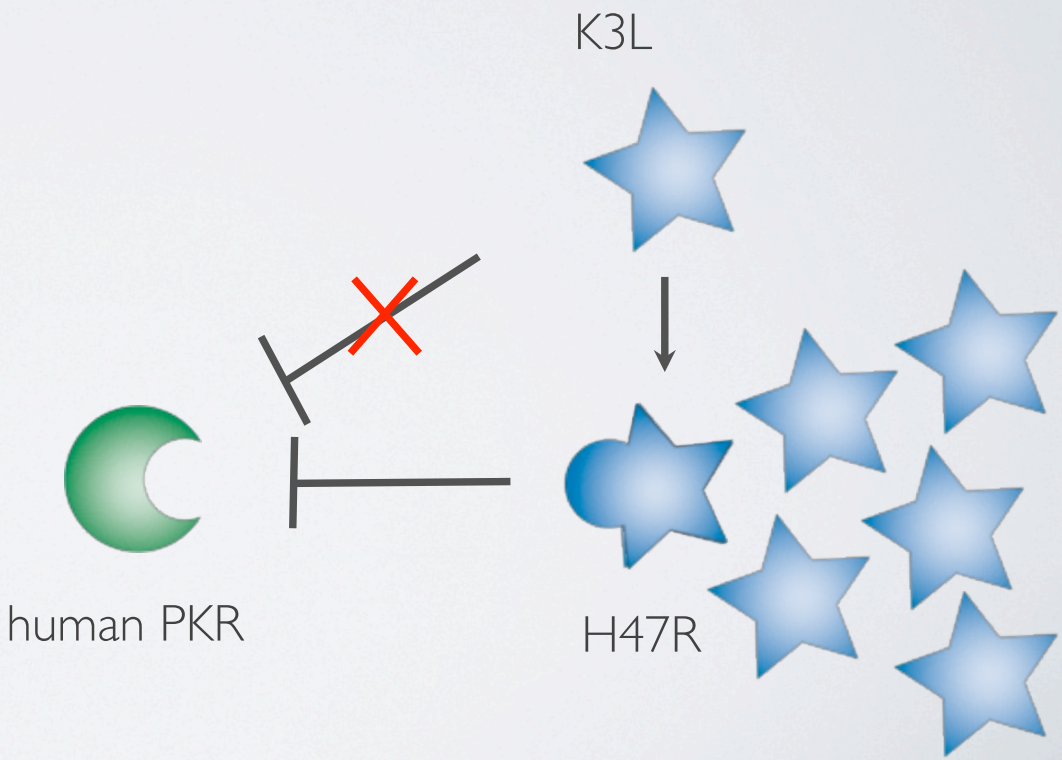
adaptation via duplication



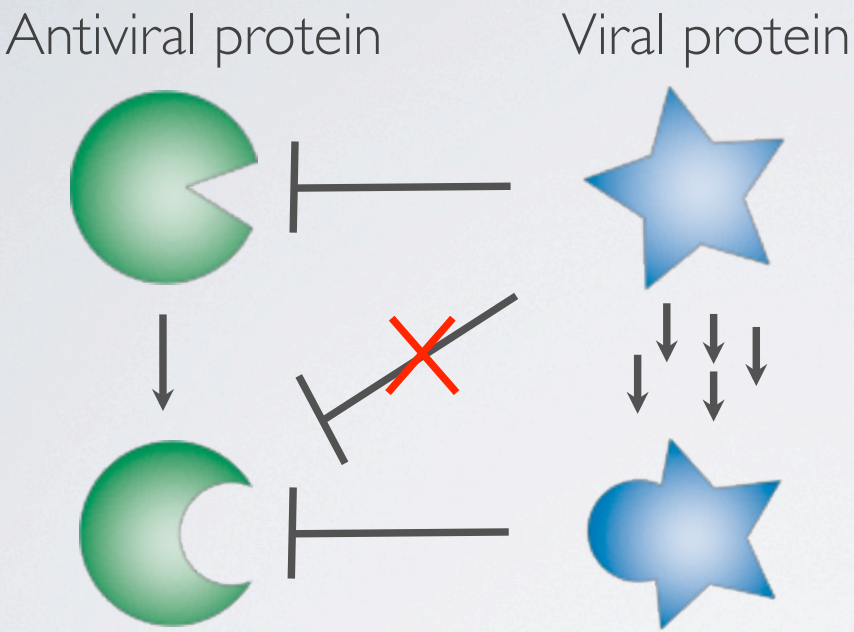




Does the Red Queen always play the accordion?



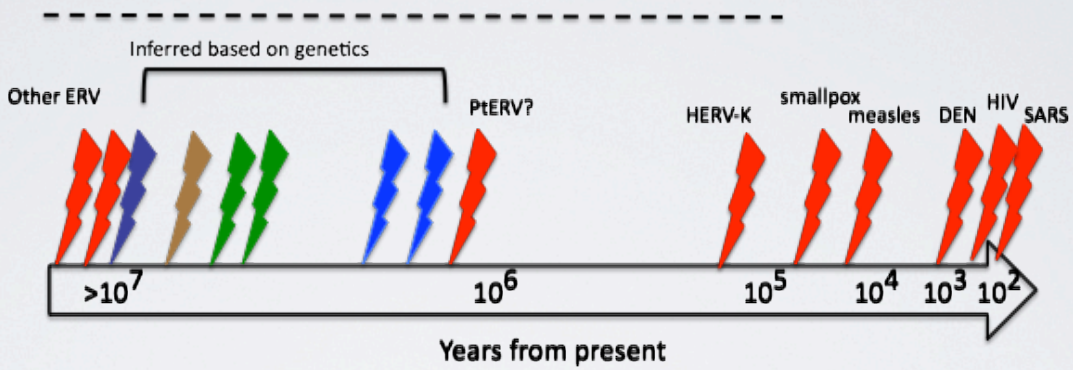
the usual suspects



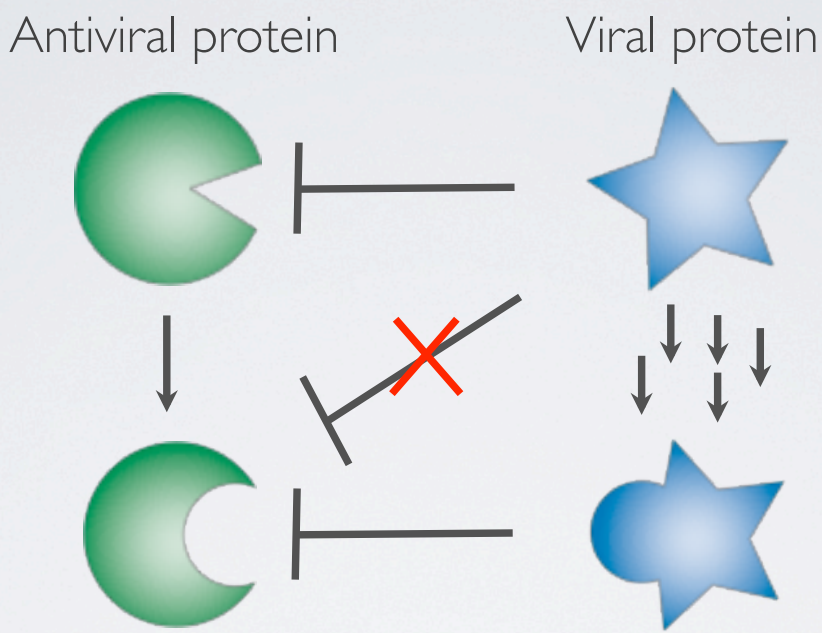
Conflict → 'Rapid evolution'

Host evolution and paleovirology

Plate 5.1. The mummified head of Ramses V of Egypt (died 1157 BC) showing the pustular eruption that may have been due to smallpox. (From Smith, 1912.)

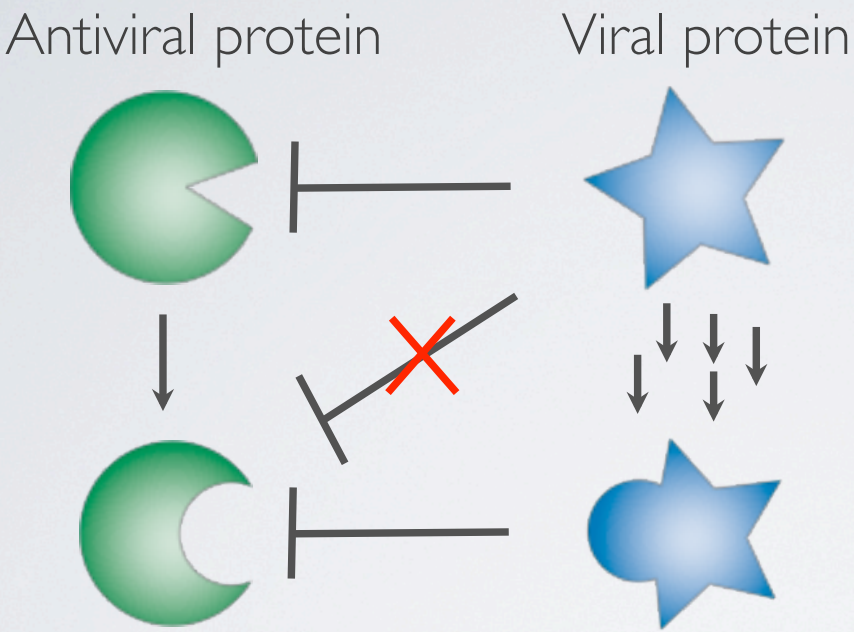

Inferred based on genetics
Other ERV
PtERV?
HERV-K
smallpox
measles
DEN
HIV
SARS
>10^7
10^6
10^5
10^4
10^3
10^2
Years from present

the usual suspects



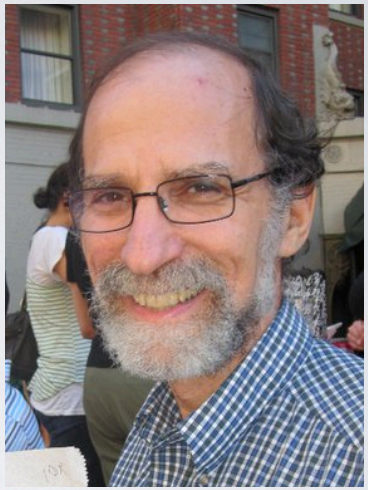
Conflict → 'Rapid evolution'

the usual suspects



Conflict → 'Rapid evolution'

Adam Geballe



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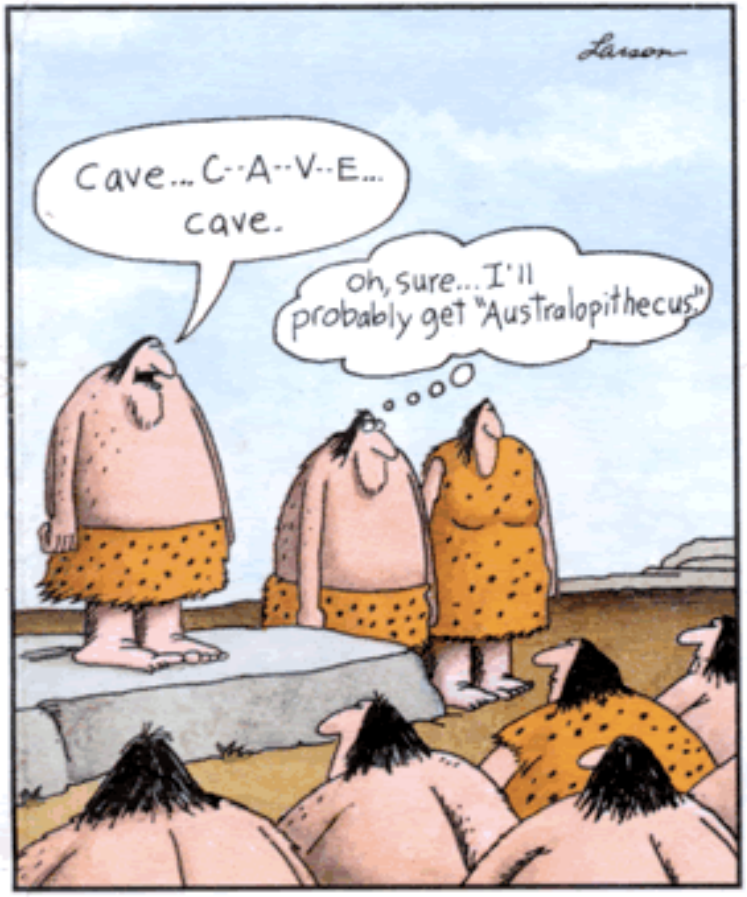
Questions?



Primitive spelling bees