New strains for polio vaccines

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Ideal characteristics of new strains

	OPV	IPV
Yield in cell culture	+	+
Immunogenicity	+	+
Infectivity *in vivo*	+	-
Attenuation	+	(+)
Transmission	- ?	-
Genetic stability	+	+

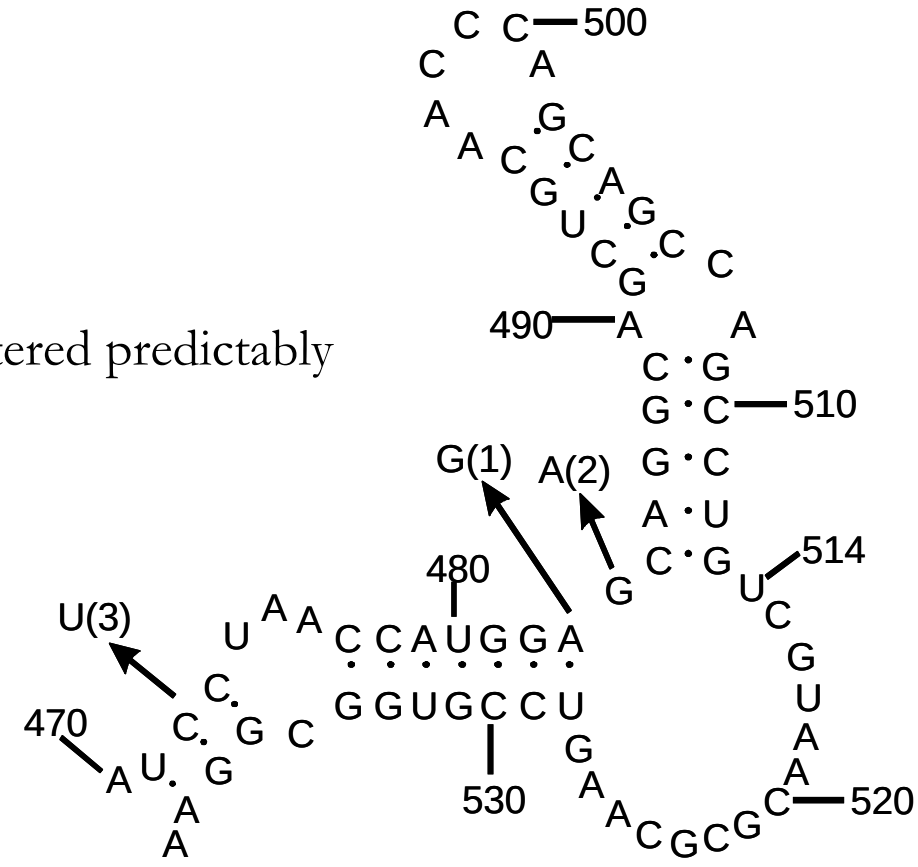
Recent approaches to new vaccines

	Potential use
Intergeneric 5'ncr recombinants Gromeier et al, 2000; Chumakov et al, 2001	Therapeutic, IPV
Genetic stabilisation of domain V Macadam et al, 2006; unpublished	OPV, IPV
Synonymous codon deoptimisation Burns et al, 2006; Mueller et al, 2006	OPV, IPV
Replication fidelity Andino, unpublished	OPV, IPV

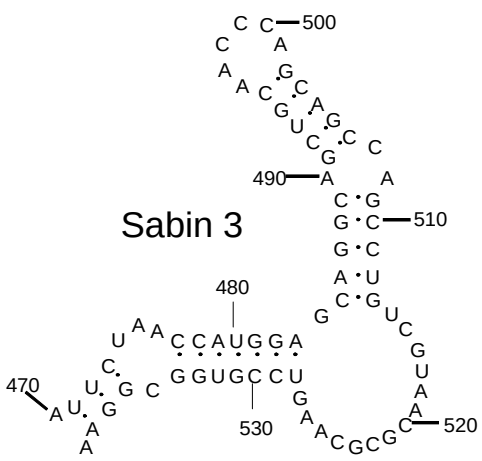
Why domain V?

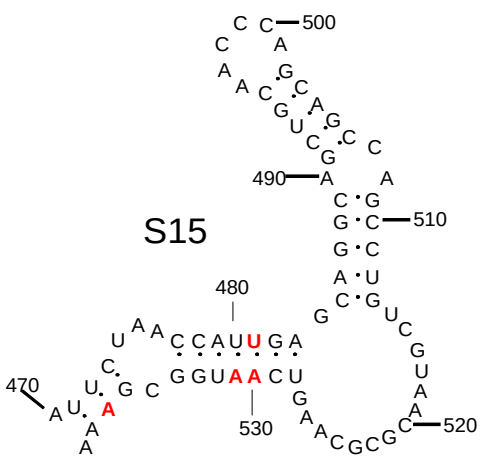
Attenuating residues in this region:

- reduce infectivity in the human gut
- lower growth temperatures
- act through RNA structure so:
  - ➢ biological properties can be altered predictably
    - • in a genetically stable way
- inhibit translation initiation



Design


Sabin 3
500
490
480
470
510
520
530


S15
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490
480
470
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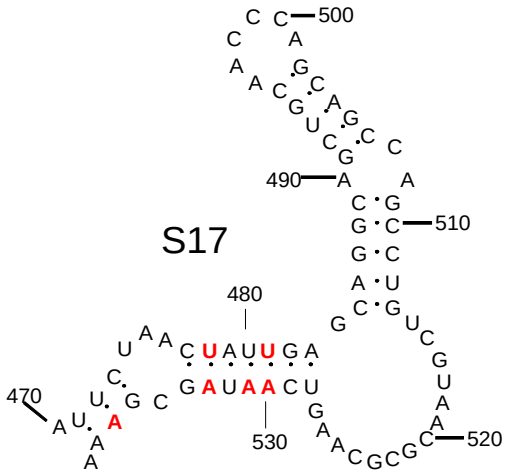
520
530


S17
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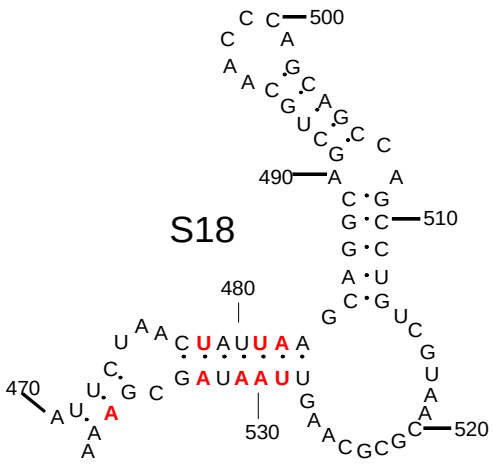
S18
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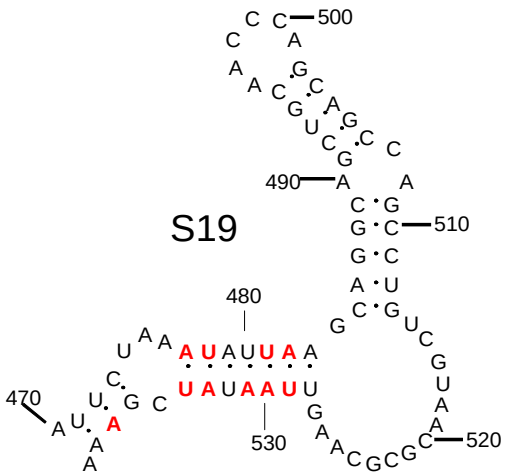
S19
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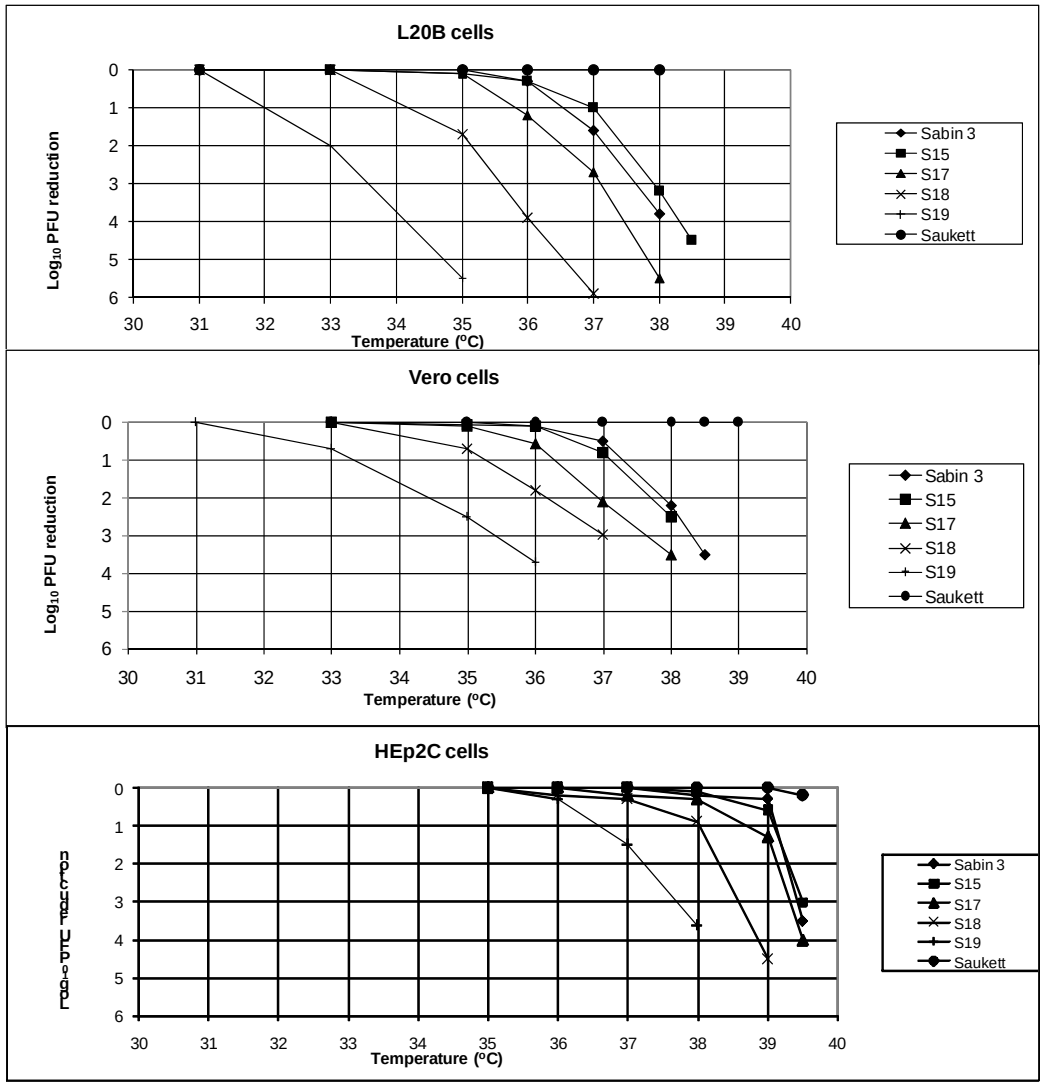
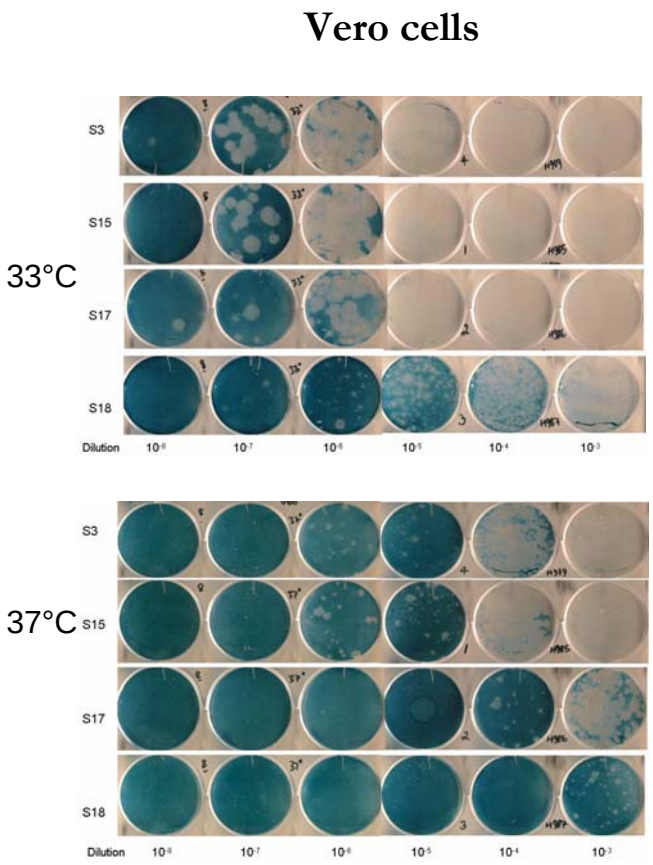
Temperature-dependence of virus replication in cell culture





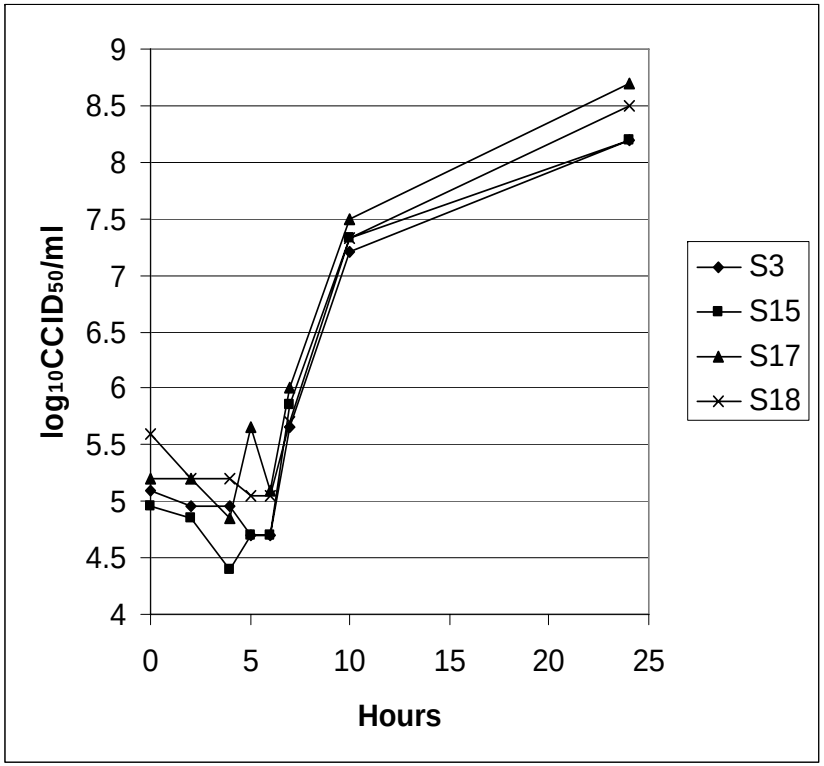
Infectivity *in vivo*

Virus	PD_{50} *i.s.* /$\log_{10}$ $CCID_{50}$
Sabin 1	2.25
S18/1	> 8.6 (1/16)*
Mahoney	≤ 0.7
Sabin 2	6.4
S18/2	> 8.1 (0/8)*
Sabin 3	3.6
S15	3.7
S17	> 7.1 (4/16)*
S18	> 8.4 (0/16)*
S19	> 8.2 (0/16)*
Leon	0.7

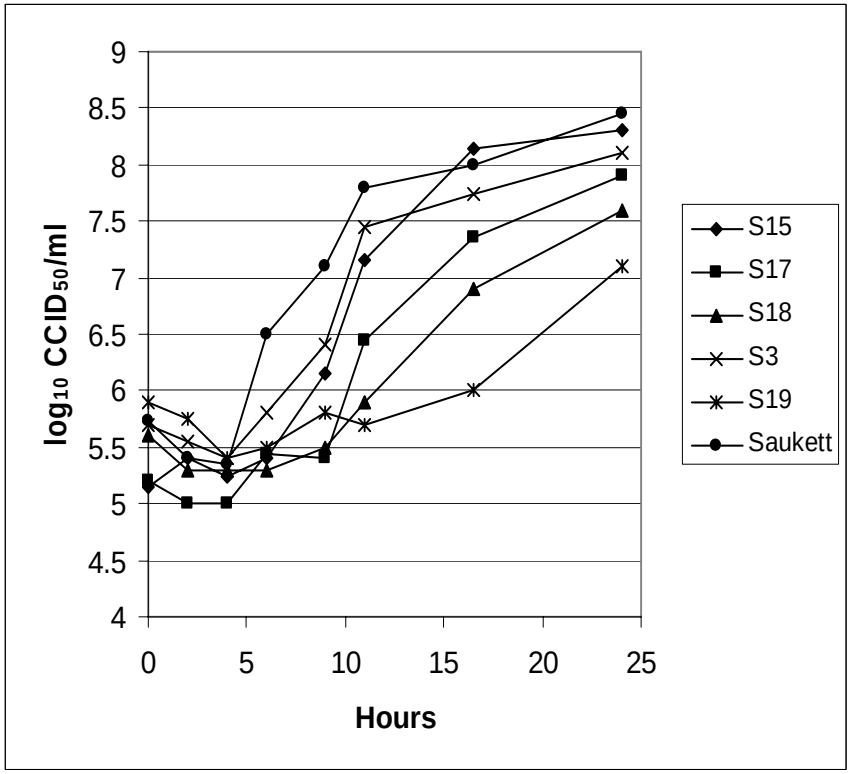
* paralysed/total at highest dose

One-step growth at 33°C

HEp2C cells



Vero cells



Stability

- Selection
  - Passage at supra-optimal temperature
  - Cloning at supra-optimal temperature
- Phenotypic changes
  - Partial loss of temperature sensitivity (Vero cells)
  - No increase in infectivity *in vivo*
- Genotypic changes
  - Domain V sequence stable
  - Substitutions selected in protease 2A (Vero cells)

Potential applications of self-containing viruses

- S19, S19/1 & S19/2 could be used as laboratory reagents in HEp2C cell based assays
- S18, S18/1 & S18/2 or S18/Mahoney-P1, S18/MEF-P1 & S18/Saukett-P1 (under construction) could be used for IPV production in Vero cells