SCV platform: A novel replication-incompetent Vaccinia viral vaccine vector system

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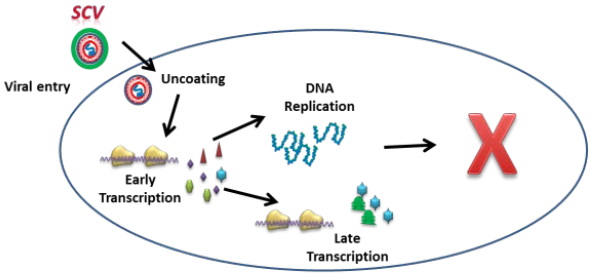
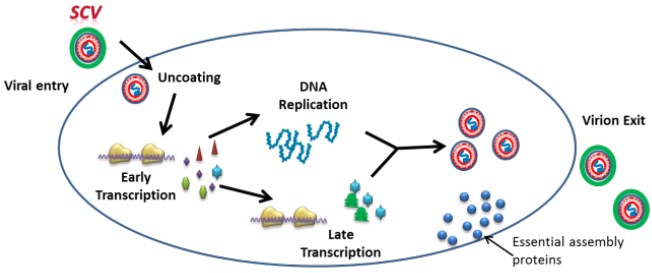
Introduction:

The SCV system is a novel vaccine platform designed to confer the advantages of a live vaccinia virus vector (VACV) including a large heterologous gene capacity, high immunogenicity and long-lived immune responses without the safety concerns associated with using a replication-competent virus.

The SCV vector was rendered replication-defective by deletion of an essential assembly protein and a complementary rescue cell line (RCL) was constructed for production of SCV-derived vaccines using the well-characterized and fast-growing CHO cell line to express essential viral assembly host range genes while providing manufacturing advantages of scalability and batch-to-batch consistency.



VACV PERMISSIVE CELL



RESCUE CELL

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Results:

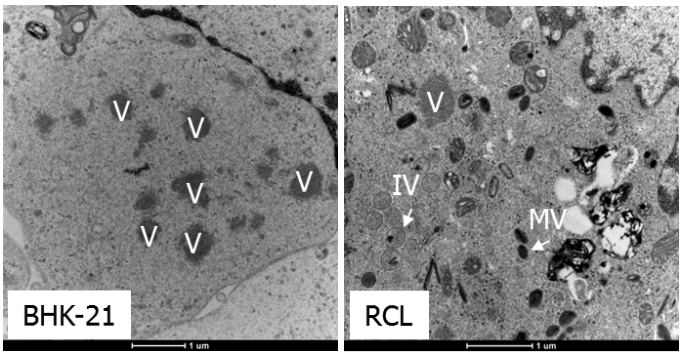

Fig 1: SCV morphogenesis in RCL. VACV permissive BHK-21 and RCL were infected with SCV and viral maturation / assembly was examined by electron microscopy. Production of mature virions was restricted to the RCL.

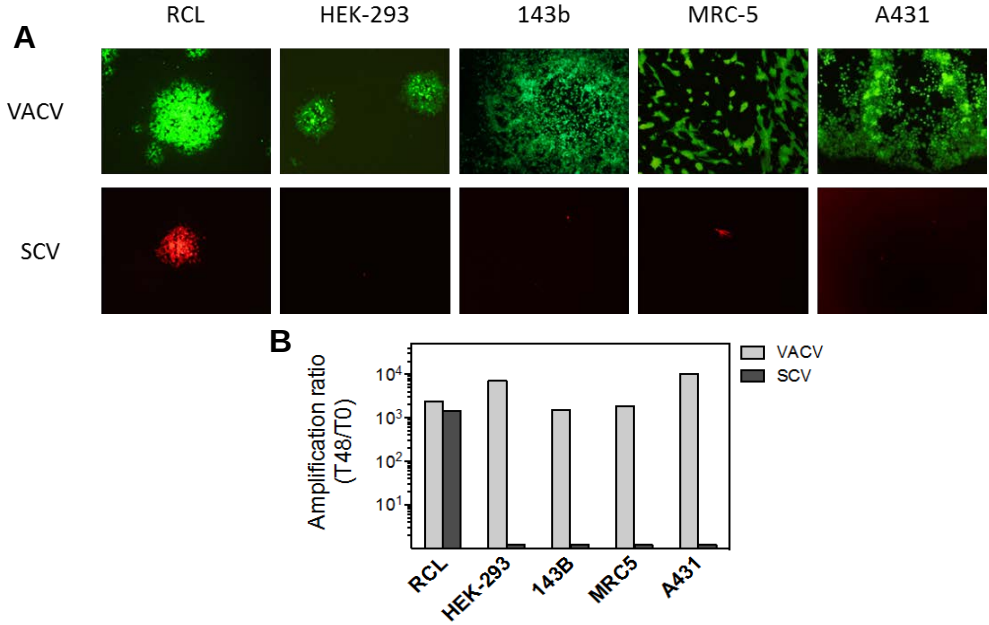

Fig 2: Replication and spread of SCV was confined to the RCL. **(A)** Monolayers of indicated human cell-lines were infected with GFP-expressing VACV or dsRed-expressing SCV to study cell-to-cell spread and plaque morphology. **(B)** Viral plaque assay to detect production of infectious progeny virus confirmed that none of the human cell lines tested supported SCV growth.

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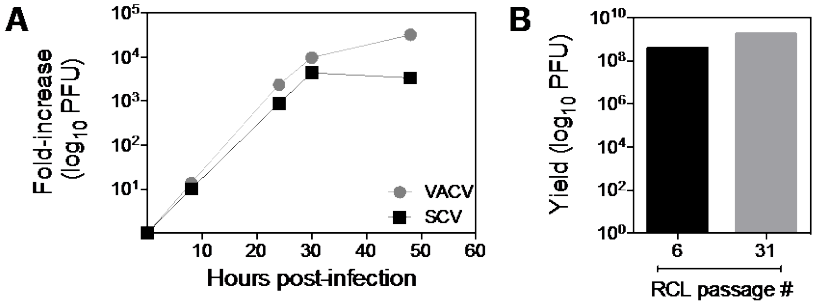
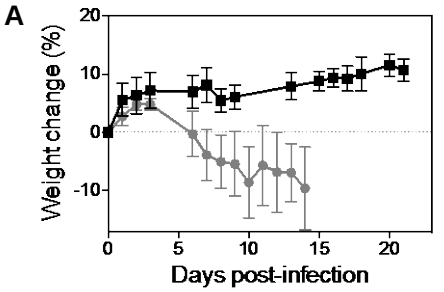
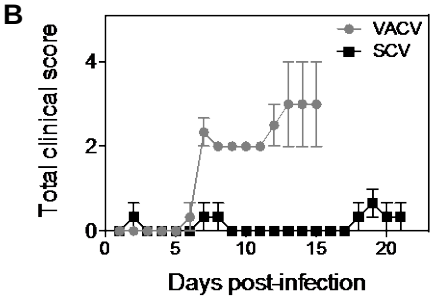
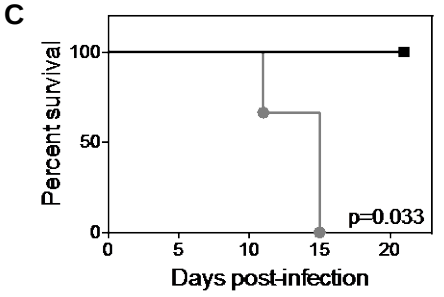


Fig 3. High yield and stable production of SCV vaccine platform in RCL. (A) RCL provides sufficient essential assembly protein to produce yields of SCV similar to VACV. **(B)** The yield of SCV was maintained after multiple RCL passages.







D

		Day1		Day3		Day5		Day9		Day15	
		VPA	PCR	VPA	PCR	VPA	PCR	VPA	PCR	VPA	PCR
Lung	VACV	+		+		+		+		+	
	SCV	-	+	-	+	-	-	-	-	-	-
Kidney	VACV	+		+		+		+		+	
	SCV	-	+	-	+	-	-	-	-	-	-
Spleen	VACV	+		+		+		+		+	
	SCV	-	+	-	+	-	-	-	-	-	-
Ovaries	VACV	+		+		+		+		+	
	SCV	-	+	-	+	-	+	-	+	-	-

Fig 4: The SCV platform is safe to use in immunocompromised mice. Groups of 6-8 weeks old SCID mice were infected intraperitoneally with 10^7 PFU VACV or SCV and monitored daily. **(A)** Percentage weight loss, **(B)** clinical scores and **(C)** survival during the course of infection. **(D)** At time-points indicated, mice were sacrificed and the presence of virus in liver, kidney, spleen and ovaries was detected by viral plaque assay (VPA) and PCR-based detection methods

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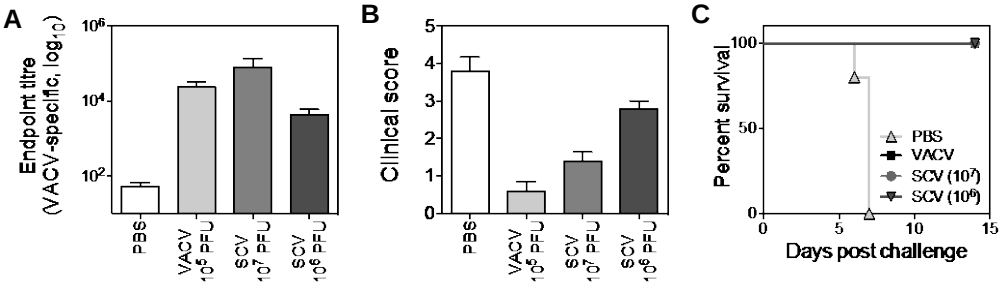

D

	Ovary	Spleen	Liver	LN	Lung
PBS	++	+++	+++	++	++
VACV (10^5 PFU)	-	-	-	-	-
SCV (10^7PFU)	-	-	-	-	-
SCV (10^6 PFU)	-	-	-	-	-

++ : 10^4 -10^6 PFU/organ
+++ : 10^6 – 10^8 PFU/organ
- : No infectious virus

Fig 5: **SCV vaccination protects against heterologous lethal challenge with Ectromelia (ECTV).** BALB/c mice were vaccinated with either VACV (10^5 PFU), SCV (10^6 or 10^7 PFU) or sterile PBS and challenged with a lethal dose of ECTV (500 LD_{50}) 4 weeks post-vaccination **(A)** Anti-VACV antibody levels pre-challenge, **(B)** clinical score (d7) **(C)** survival and **(d)** viral load in key organs at the termination of the experiment

Conclusions:

- SCV is replication-defective *in vitro* and *in vivo* suggesting the viral vector is a safe vaccine platform.
- A stable rescue cell line derived from biotech-proven CHO cells can provide for scalable production of SCV vaccines.
- Immunogenicity is maintained, evidenced by protection from heterologous poxvirus challenge in mice.
- The SCV platform can be tailored to an array of prophylactic or therapeutic vaccine applications requiring antigen-driven humoral and cell-mediated immune responses and applications for infectious disease, allergy and cancer are under investigation.

(Talk #2167, Session:Vaccine 3, Thursday 25th August)

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