Creating a Multiplex Immunotherapeutic Virus

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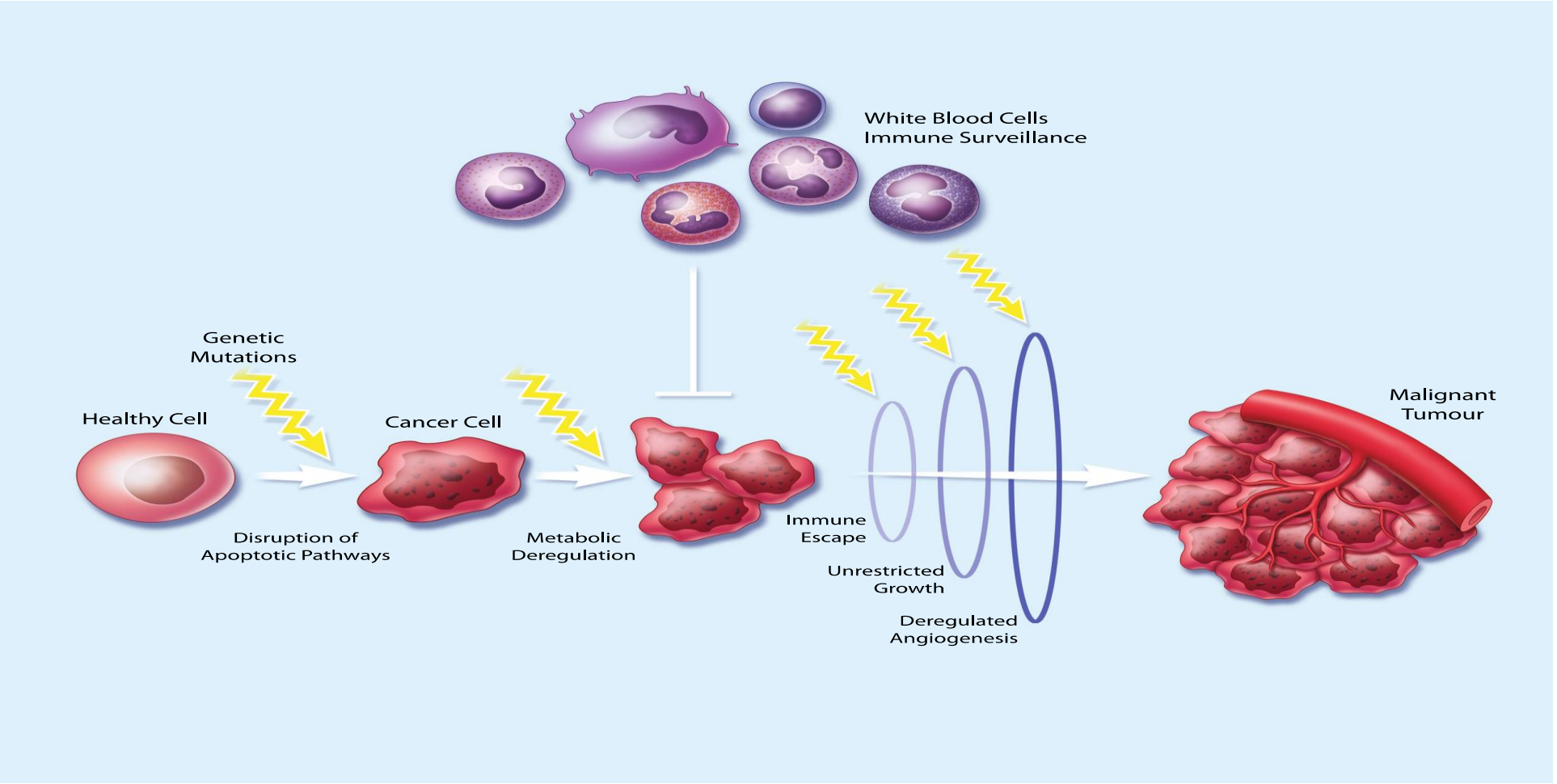
John C. Bell Disclosure

Scientific Co-Founder and Advisor

- Understanding virus -host cell interactions provides therapeutic opportunities – Oncolytic Virus Paradigm
- Multiplex Virus Therapeutic as a Strategy to Overcome Tumour Heterogenity
- Virally Programed Exosomes
- Virally Encoded T cell Engagers
- Virally Encoded Self Amplifying RNA Molecules

TUMOUR EVOLUTION

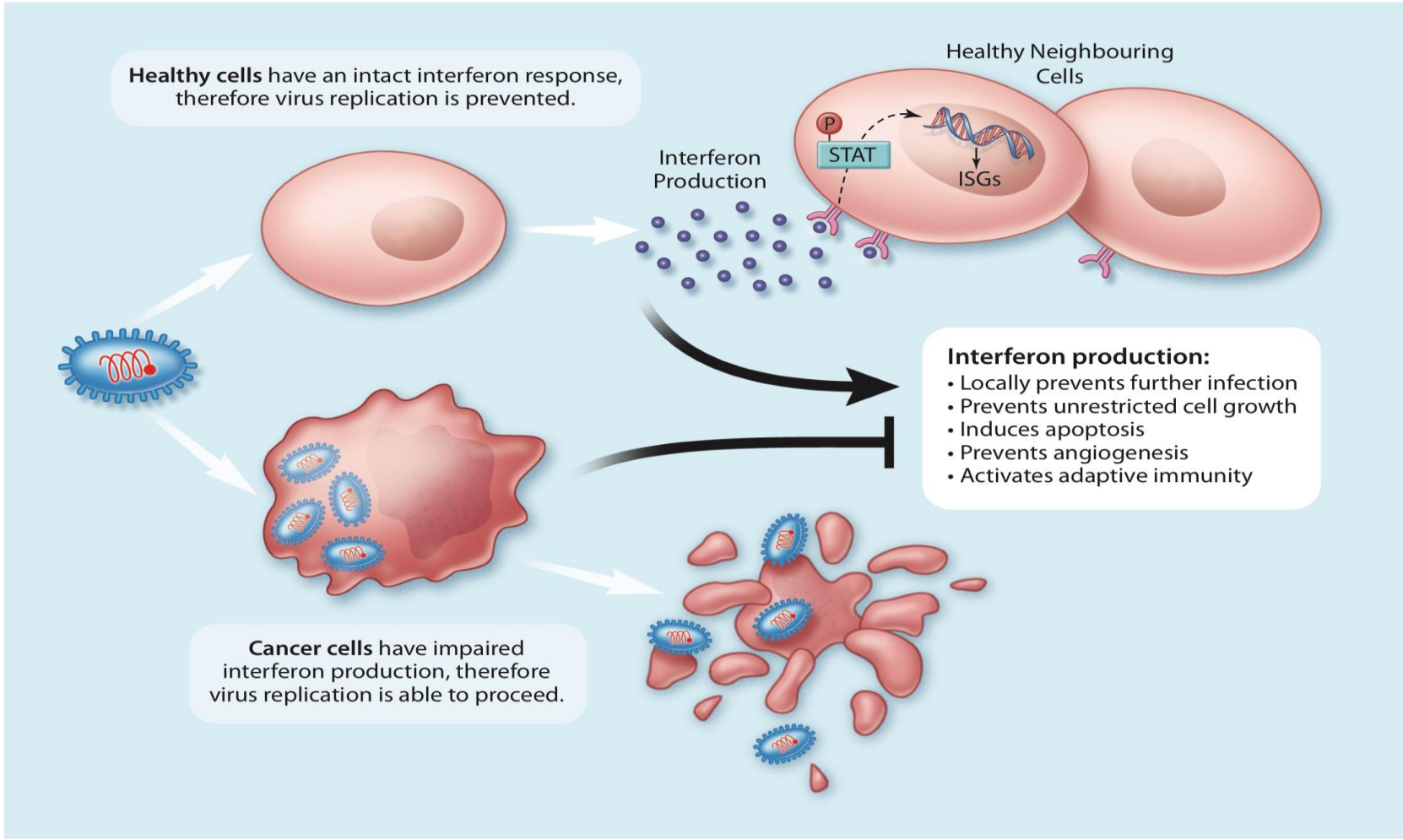


Pikor, Bell, Diallo (2015) Trends in Cancer Vol 1, 266-277

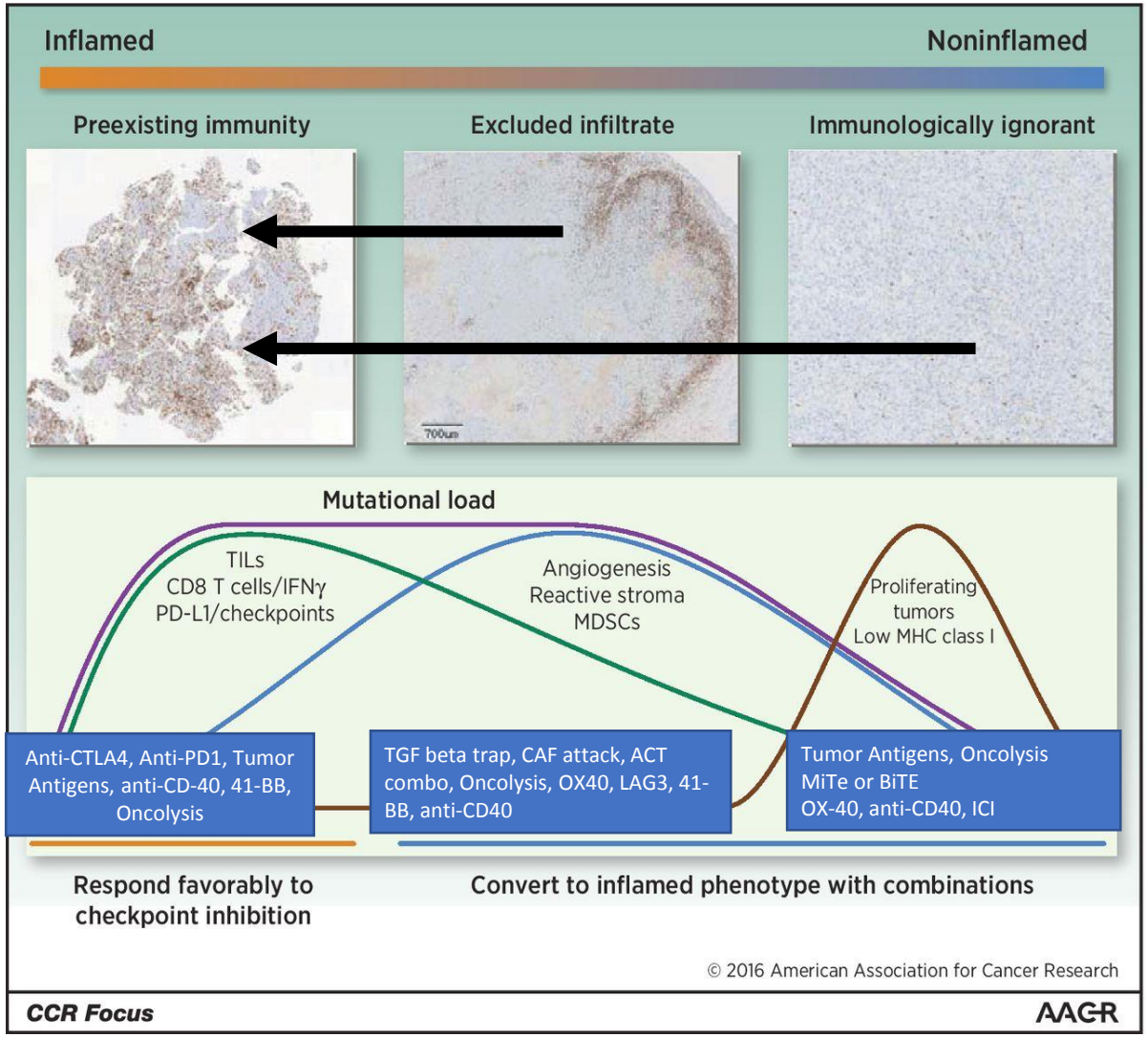
The Same Biological Processes that Control Cell Growth, Death and Metabolism also Control the Ability of Individual Cells to Fight Virus Infections!

Viruses Can be Engineered to Exploit Tumour Specific Defects in Anti-Virus Defense Mechanisms

The Oncolytic Virus Paradigm



Tumor Heterogeneity Thwarts Monotherapeutic Strategies



Combination Therapy Will be Required to have Broadly Active Immunotherapeutics

Challenges:

(1) Systemic Combinations will/may have Compounded Toxicities
(2) Costs of Novel IO Combinations may not fit in our Health Care Systems

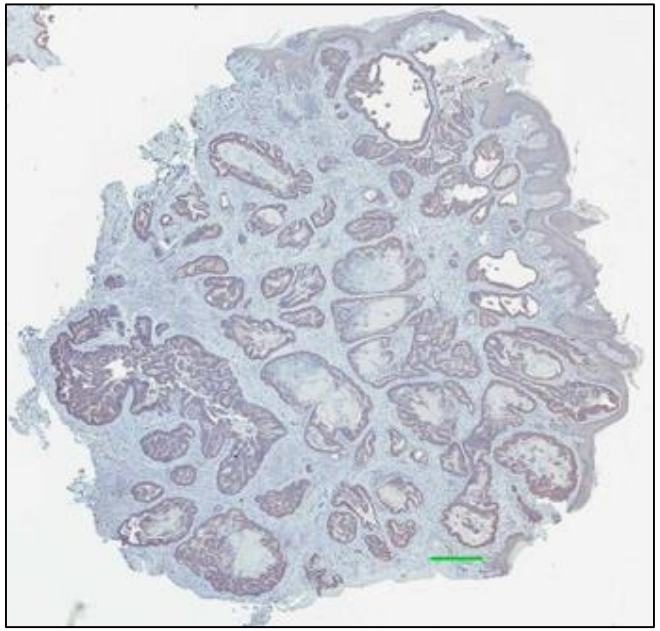
Our Solution - Create a Single Virus Therapeutic that Can Deliver Multiple Therapeutic Payloads

Characteristics of a Multiplex Virally Based Immunotherapeutic

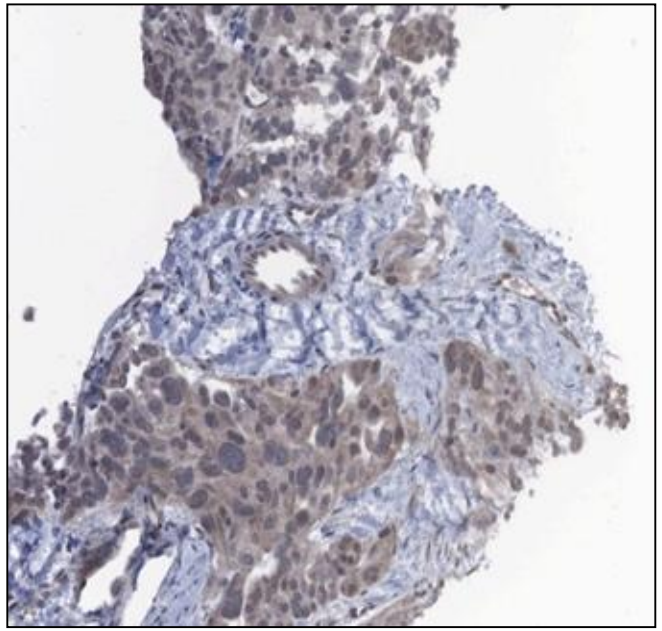
- Ideally, can be Delivered Systemically
- Highly Selective Replication only in Malignant Tissues
- Good Replication and Spread Within and Between Tumours
- Has Ample Coding Capacity for Therapeutic Transgenes

Vaccinia Virus – A Systemically Delivered Oncolytic Virus

Colon Cancer

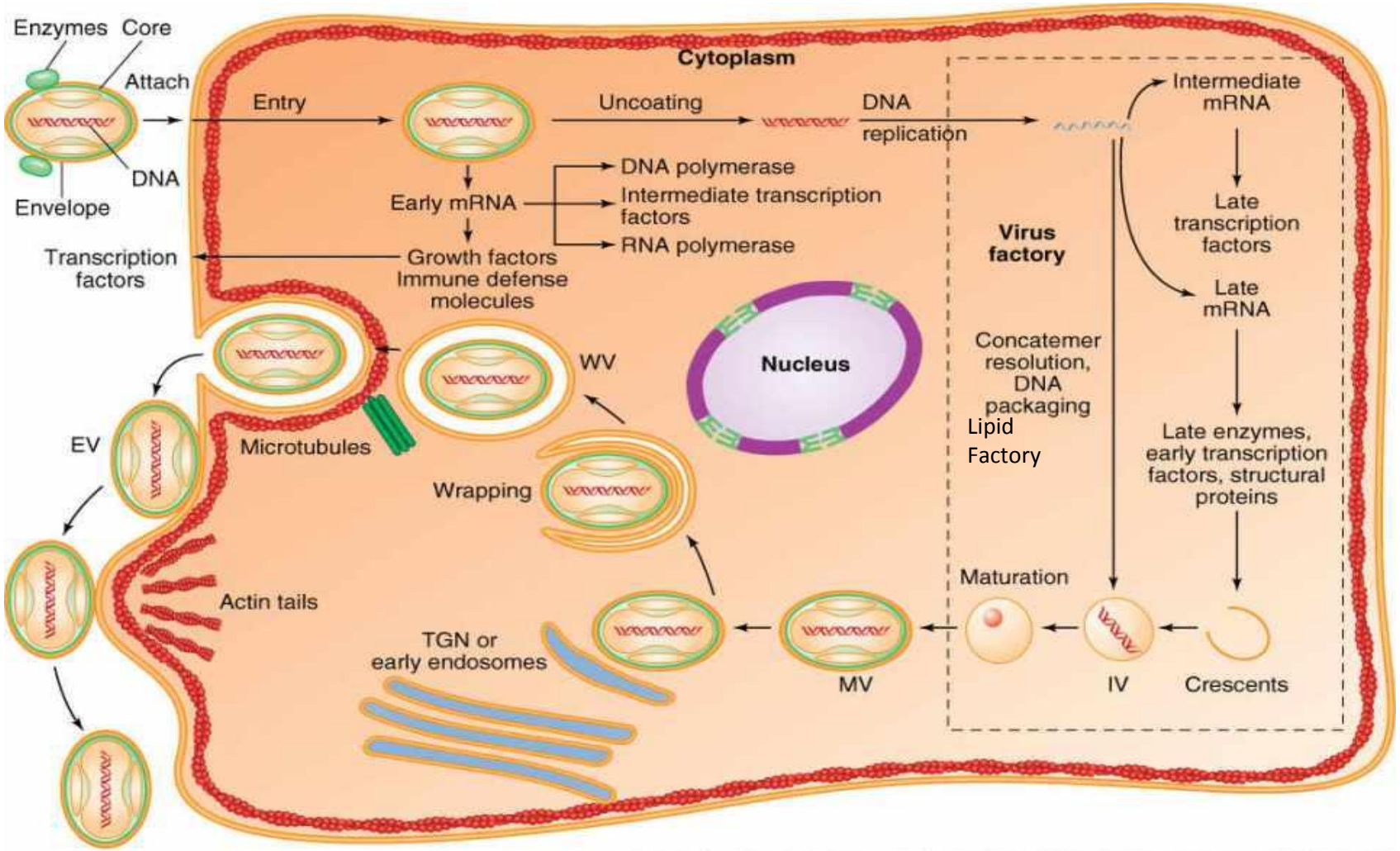


Ovarian Cancer



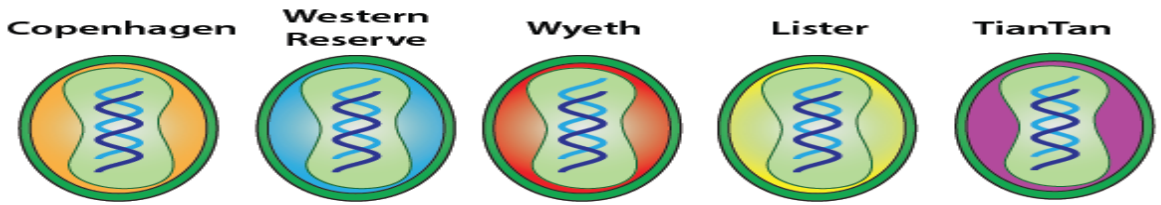
Breitbach et al Nature 2010

Vaccinia Virus Lifecycle



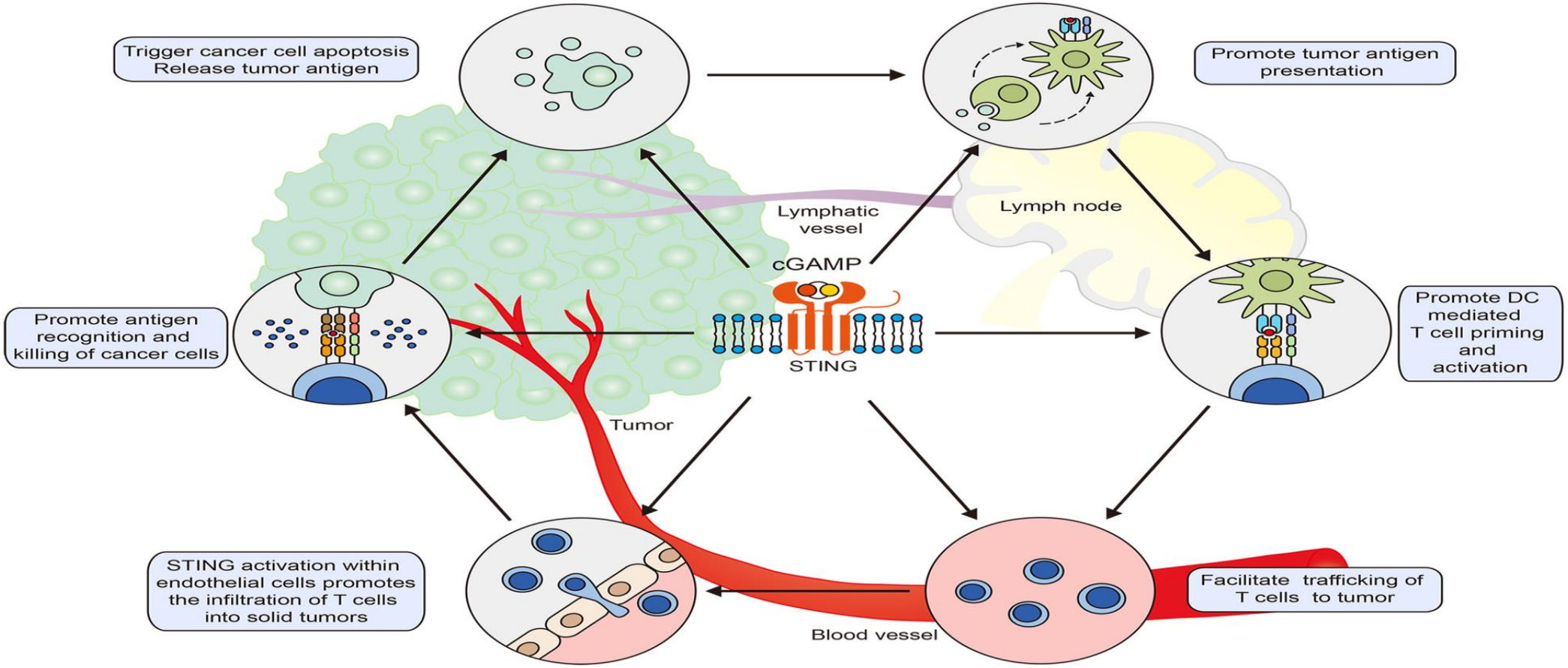
Information from Moss, B. *Poxviridae*. In *Fields Virology*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2013.

Bio-Selecting an Optimal Vaccinia Strain



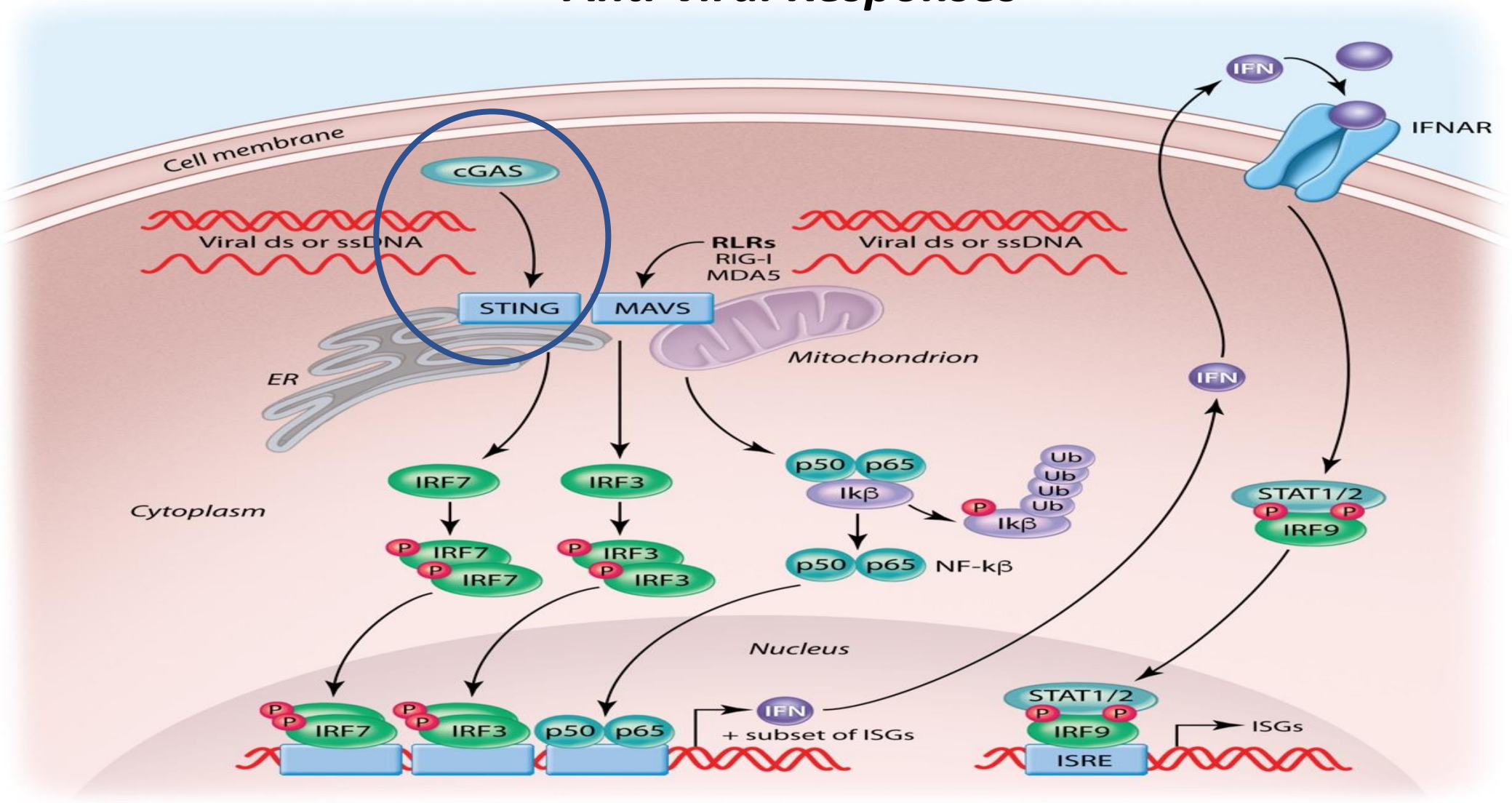
Enhancing “Tumour Selective” Oncolysis

STING: a master regulator in the cancer immunity cycle



Zhu et al Molecular Cancer 18:152 (2019)

STING Pathway Senses Virus Infection and Activates Anti-viral Responses



Suppression of STING Signaling through Epigenetic Silencing and Missense Mutation Impedes DNA-Damage Mediated Cytokine Production

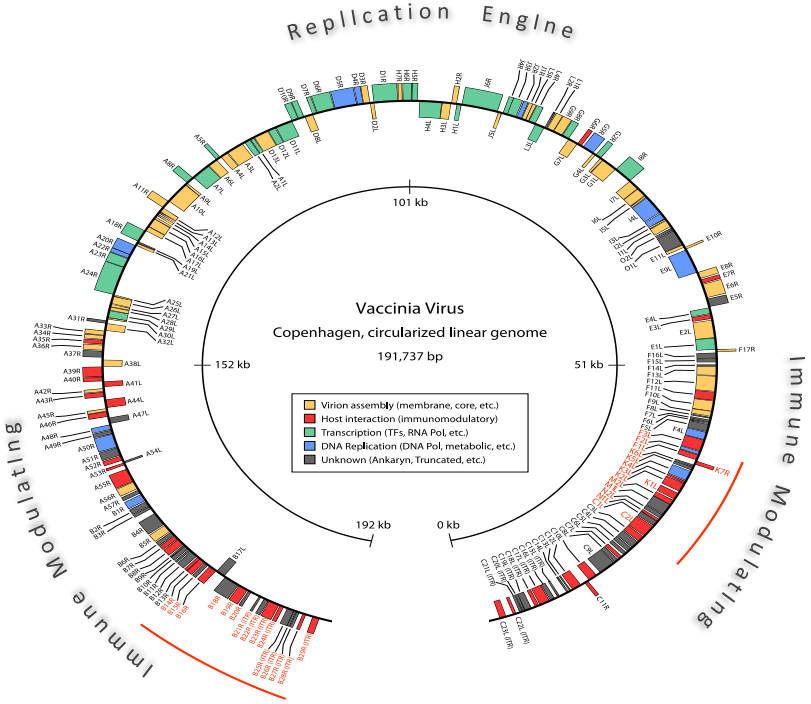
Hiroyasu Konno1, **Shota Yamauchi**1, **Anders Berglund**2, **Ryan M. Putney**2, **James J. Mulé**3,4, and **Glen N. Barber**1,*. **Oncogene. 2018 April ; 37(15): 2037–2051.**

80% of Human Tumour Samples Have Silenced or Mutated Sting Pathways

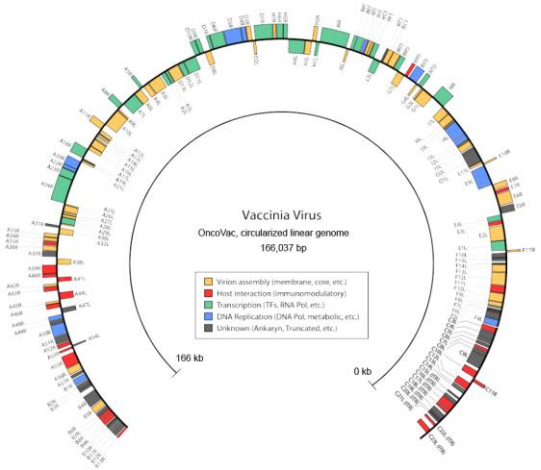
A STING Activating Virus Will be Rapidly Detected and Eliminated from Normal Tissues but Remain Stealth in Tumour Cells

SKV – A Novel Oncolytic Vaccinia Virus Platform

Wild-type Copenhagen



SKV



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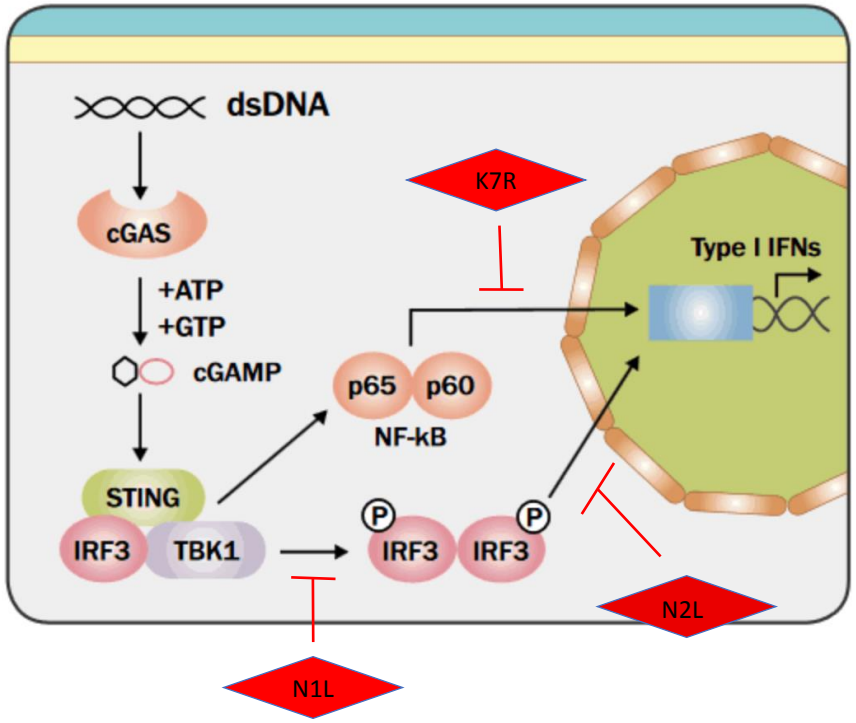
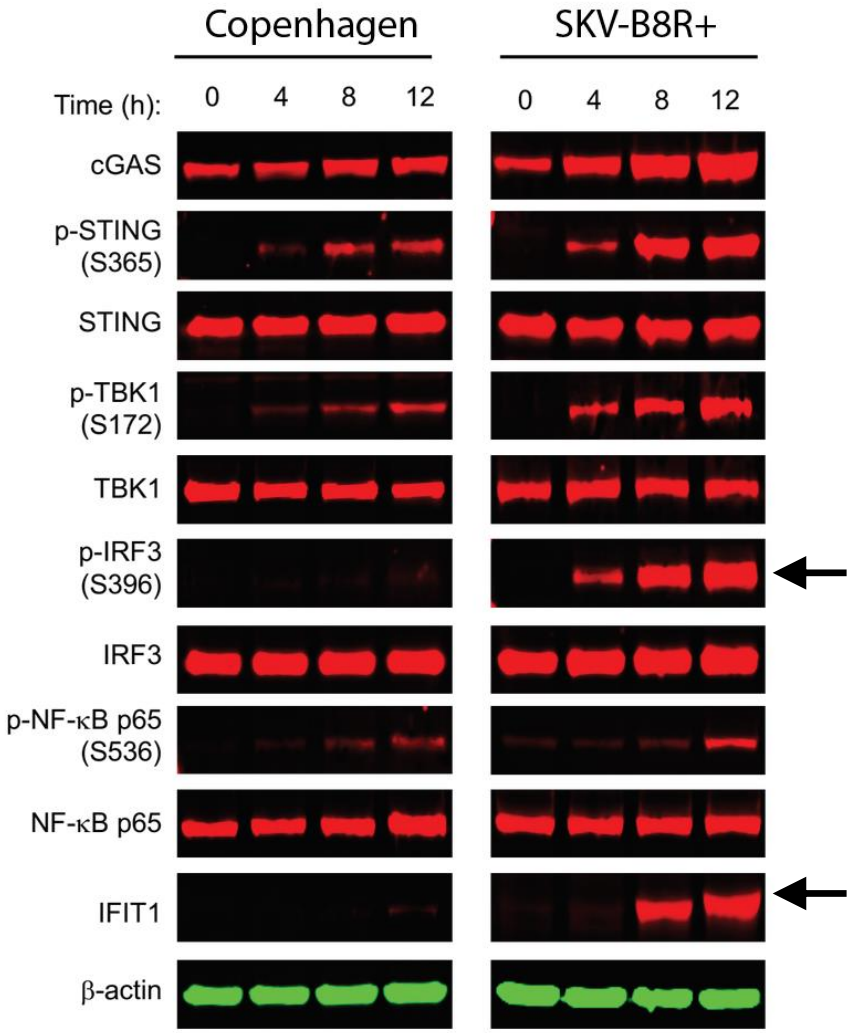
Integration of Biological Data Led to the Development of SKV

Adrian Pelin

SKV Activates the cGAS-STING Pathway

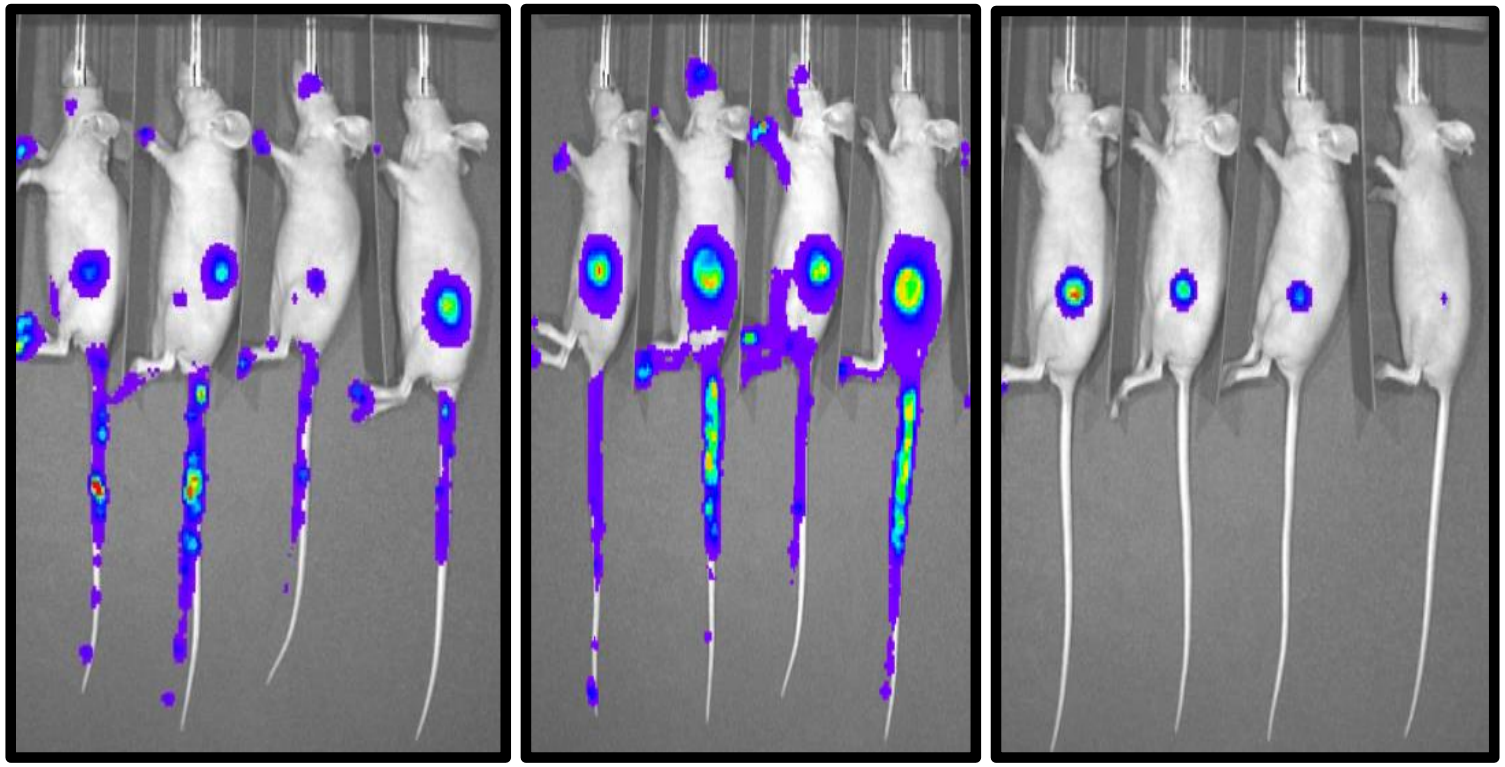
Ragunath Singaravaleu





Fuan Wang

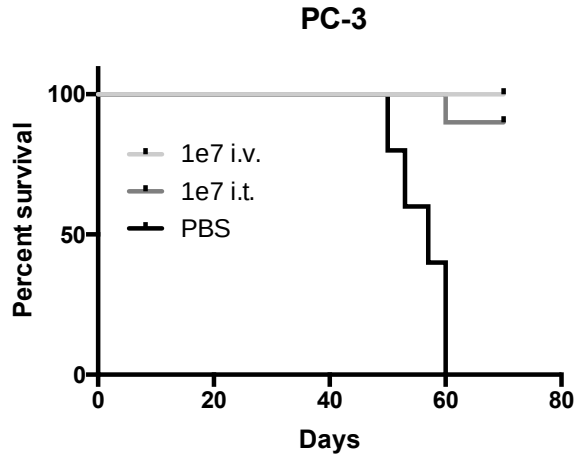
SKV – Highly Selective for Cancer Cells

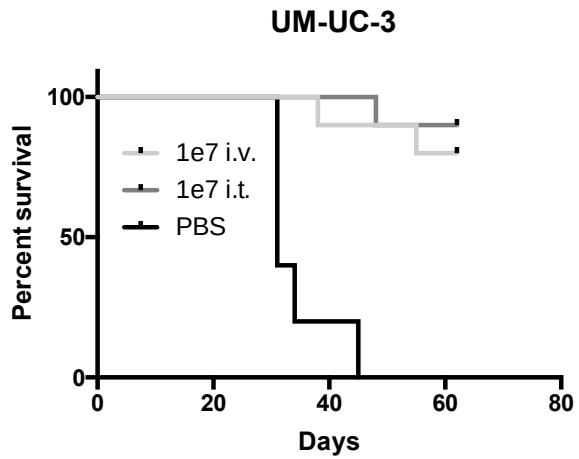


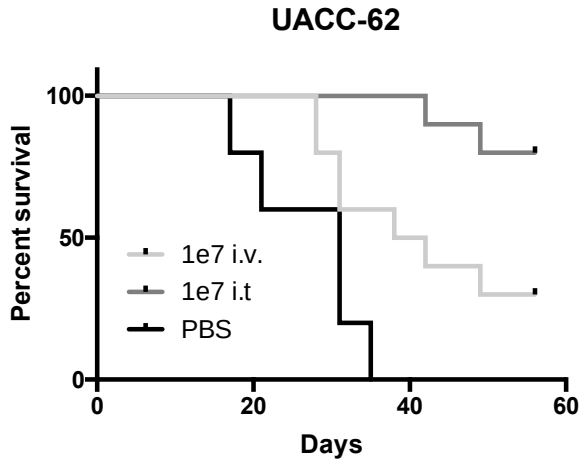
Wyeth TK- Copenhagen TK- SKV

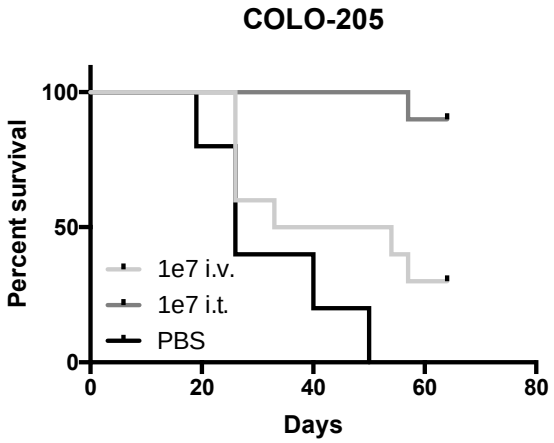
Adrian Pelin

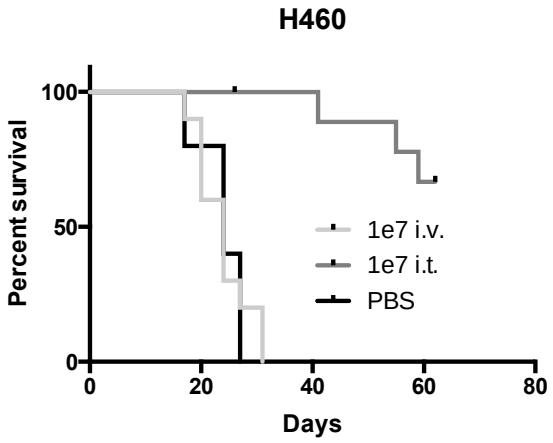
SKV is Active in a Spectrum of Human Tumours

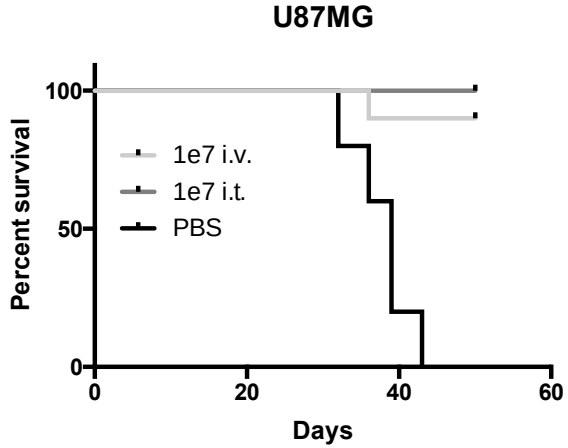


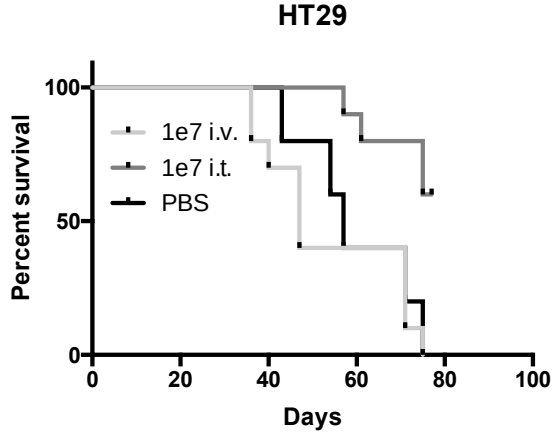




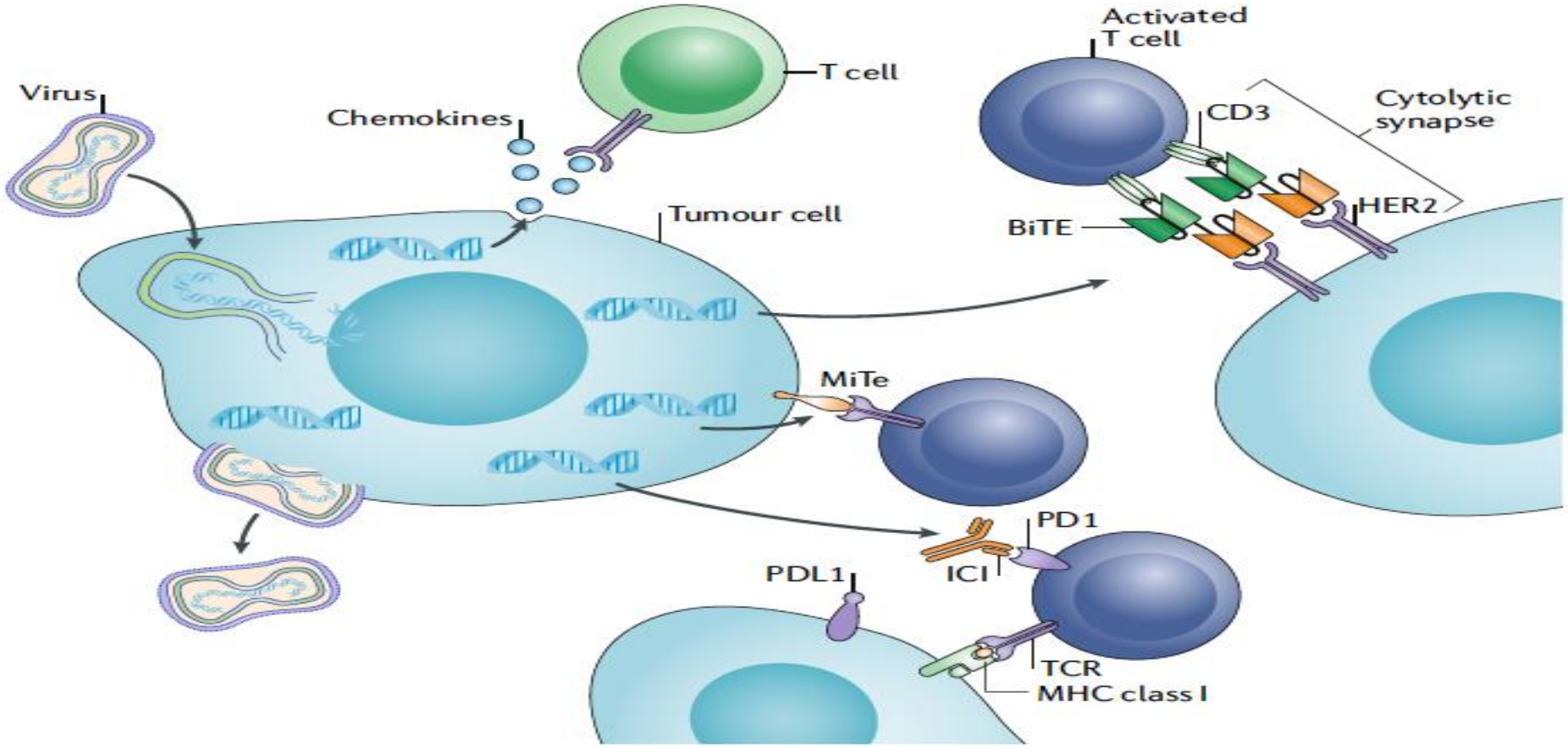






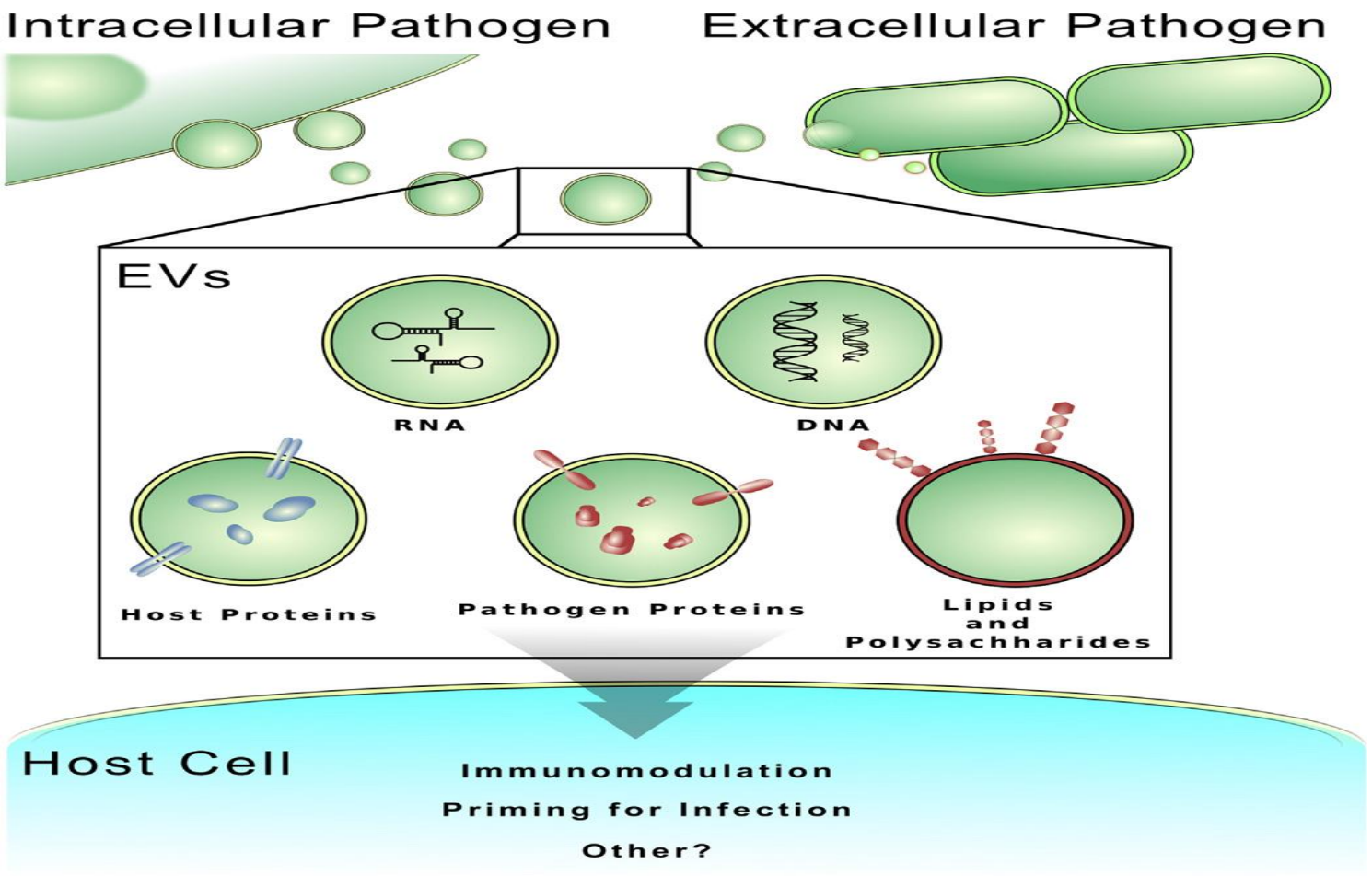


Attacking Cancers with a Multiplex Virus Based Immunotherapeutic
Poster P811 Friday AM

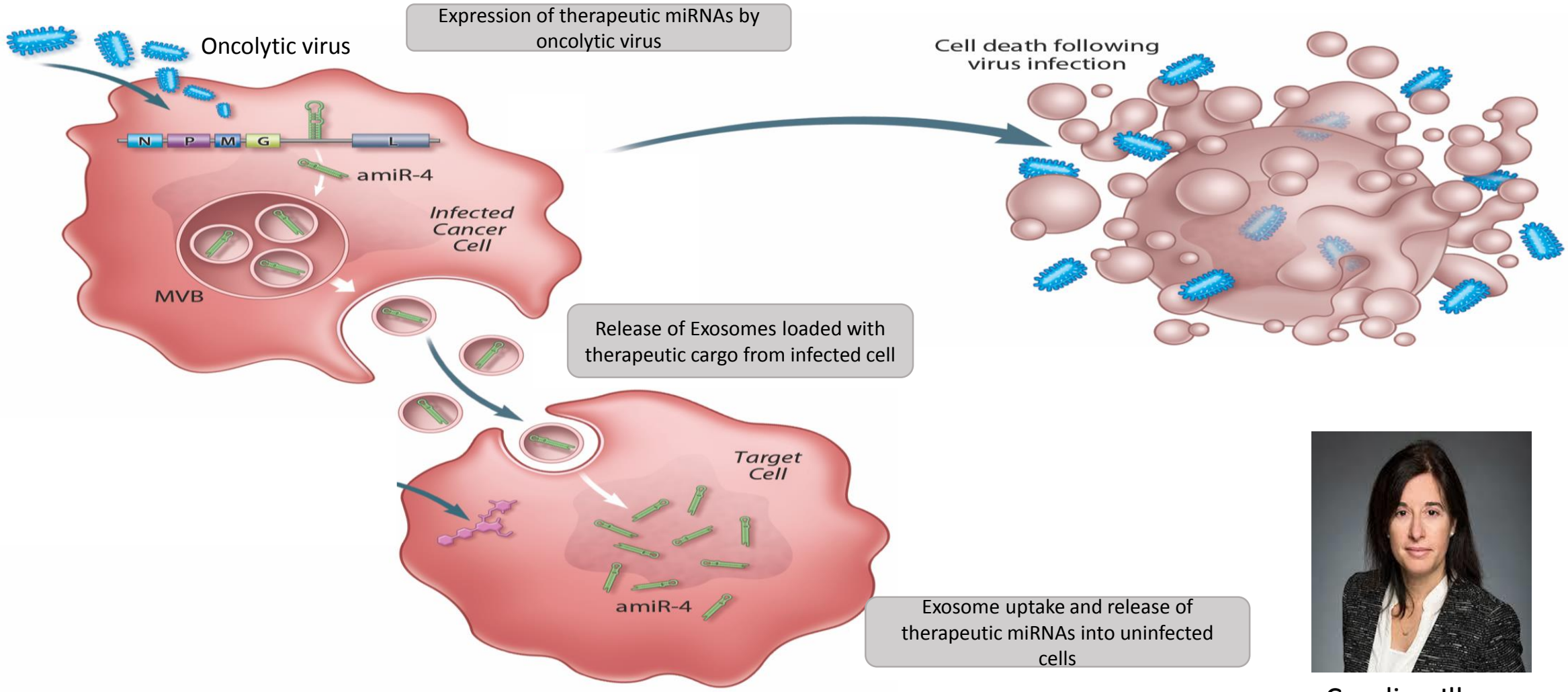


Twumasi-Boateng, Pettiogrew, Kwok, Bell, Nelson (2018) Nature Reviews Cancer

Exosomal Transport of MicroRNAs



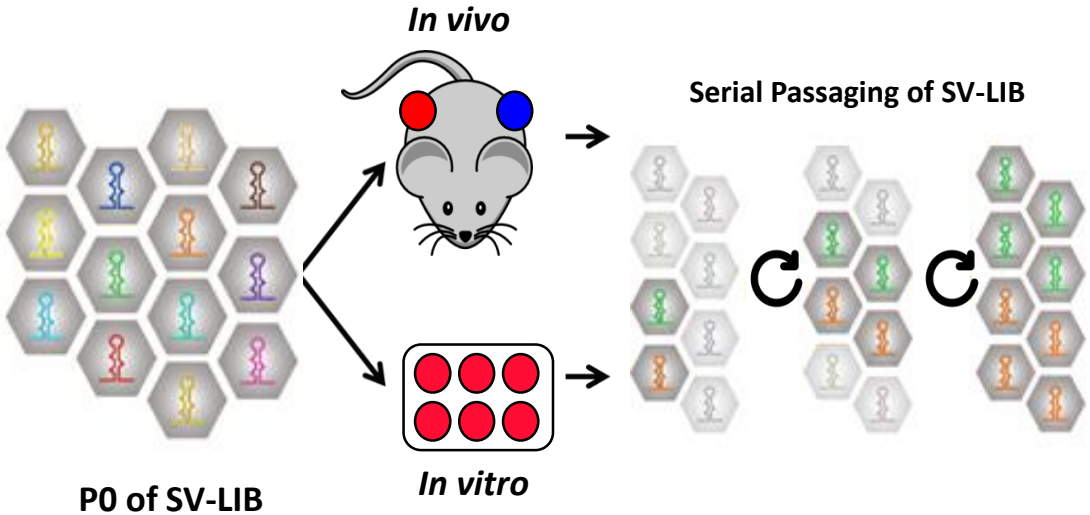
Strategies for Reprogramming the Tumour Microenvironment with Virally Expressed microRNAs



Carolina Ilkow

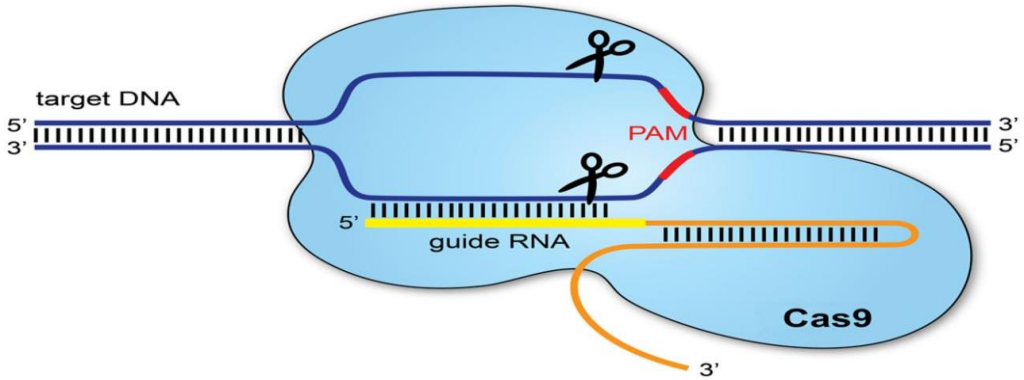
Genetic Strategies to Enhance OV Replication

Carolina Ilkow

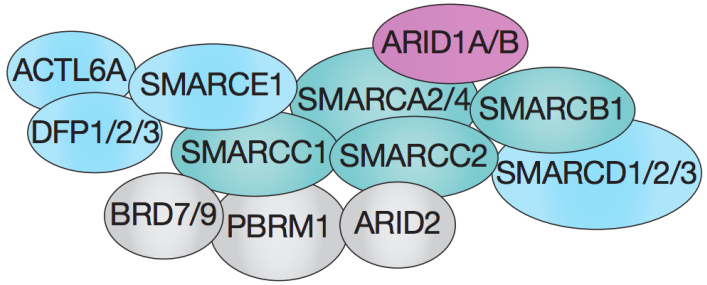


P0 of SV-LIB
(16,000 unique clones)

Larissa Pikor



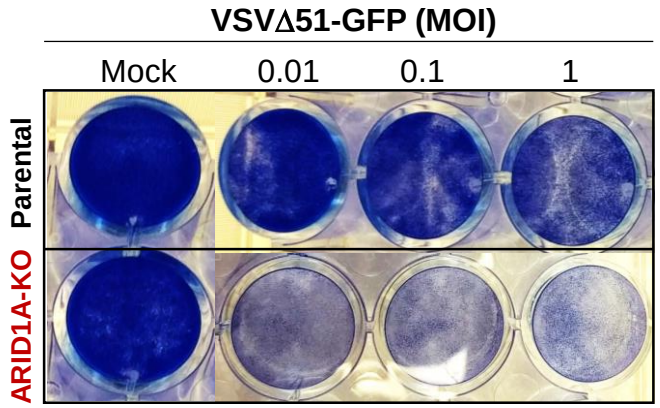
CRISPR-Cas 9 Screen of Virus Resistant Tumour Cells

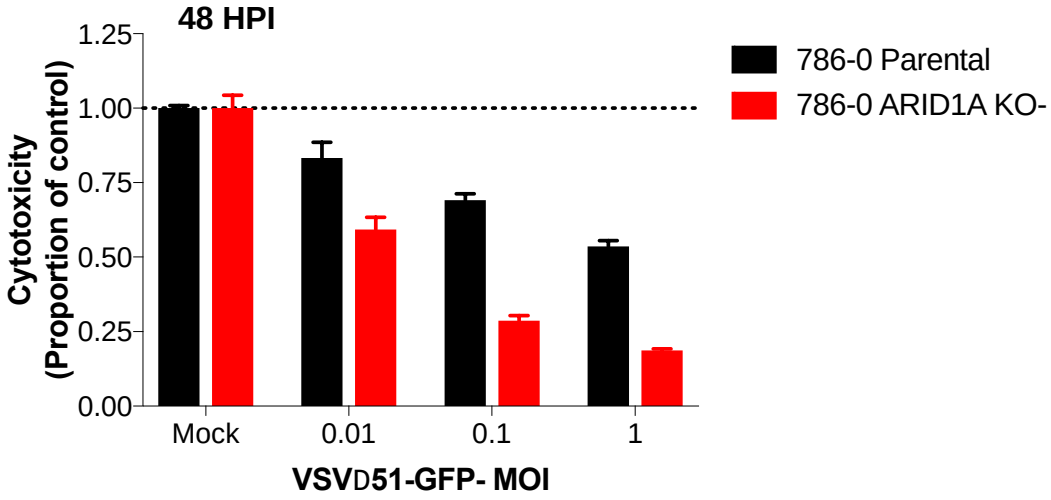


SWI/SNF Chromatin
Re-modelling complex

Marie-Eve Wedge

Larissa Pikor



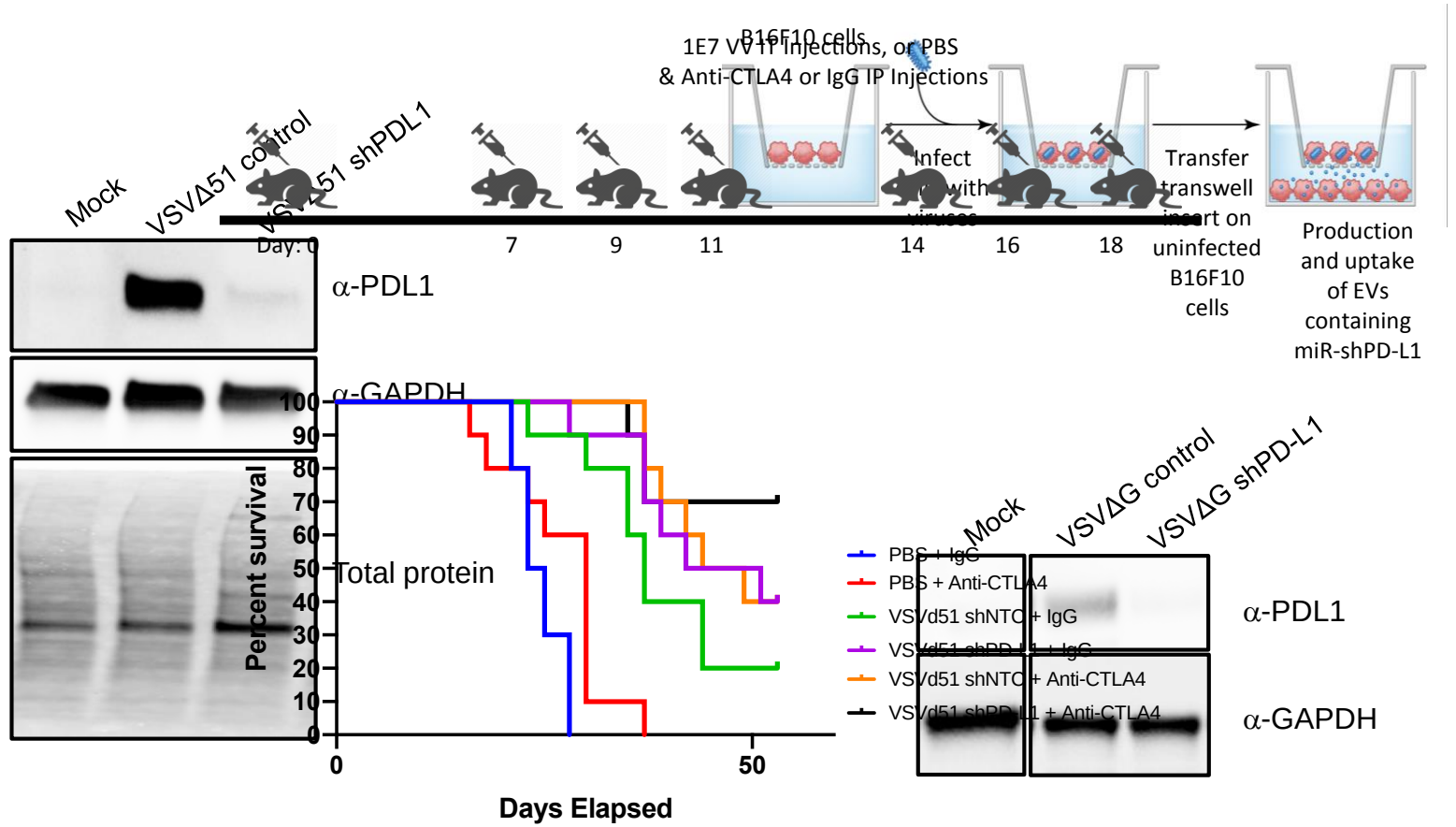


Can we Develop a Strategy to Spread amiRNAs from Infected to Un-infected Cells

Virally Programmed Exosomes to Modify the Tumour Microenvironment

Giuseppe Pugiliese

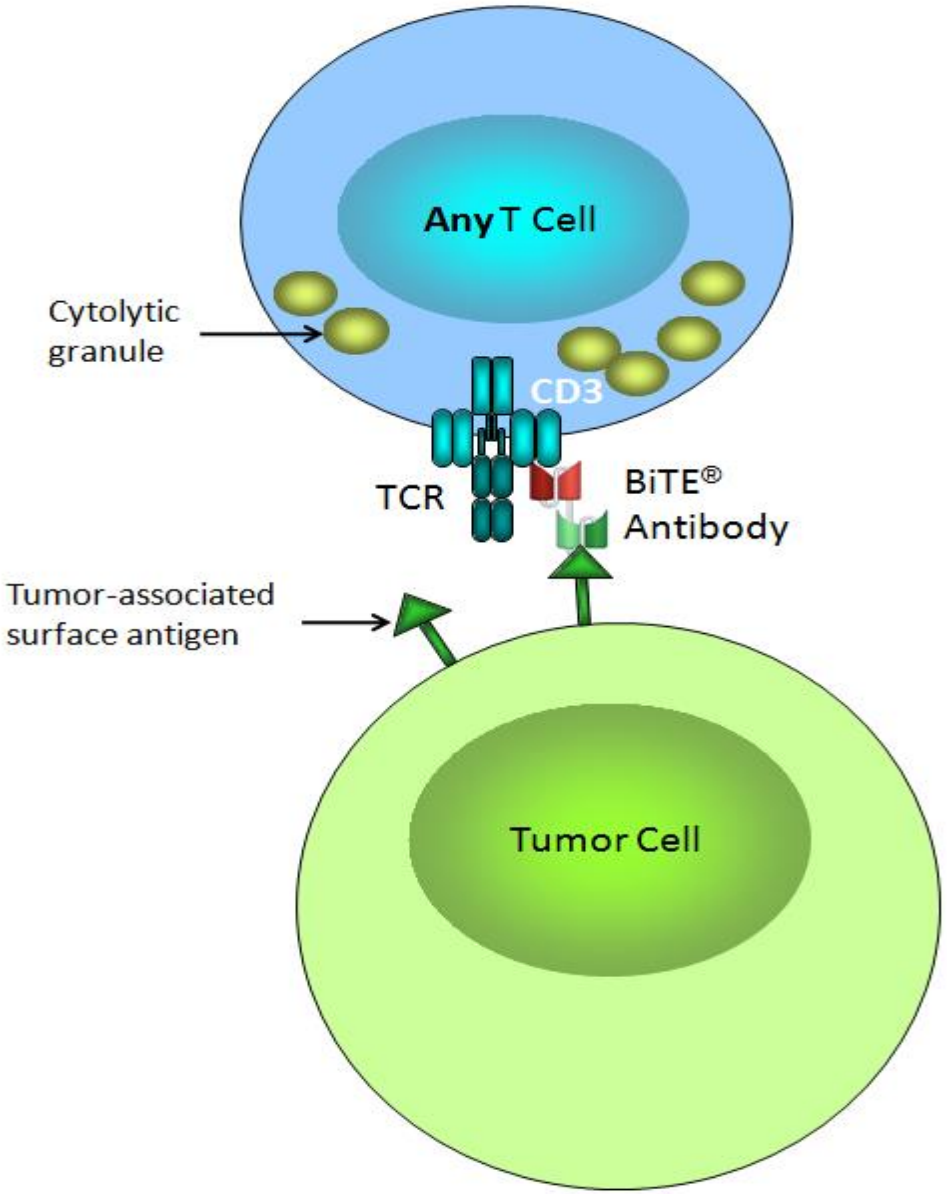
Mathieu Crupi.

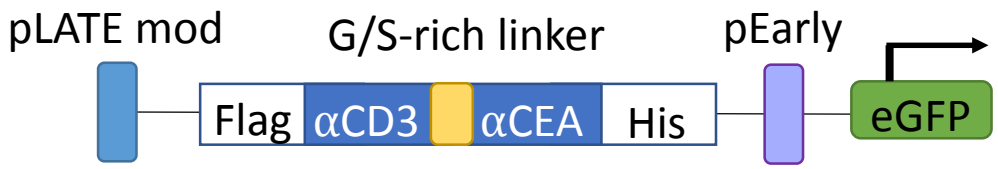


VSVΔ51-shPDL1 downregulates PD-L1 levels in B16-F10 cells (MOI 0.1, 18 hpi)

EVs–derived from B16-F10 VSVΔG-shPDL1 infected cells downregulate PD-L1 levels in uninfected cells

Encoding T Cell Engagers in SKV

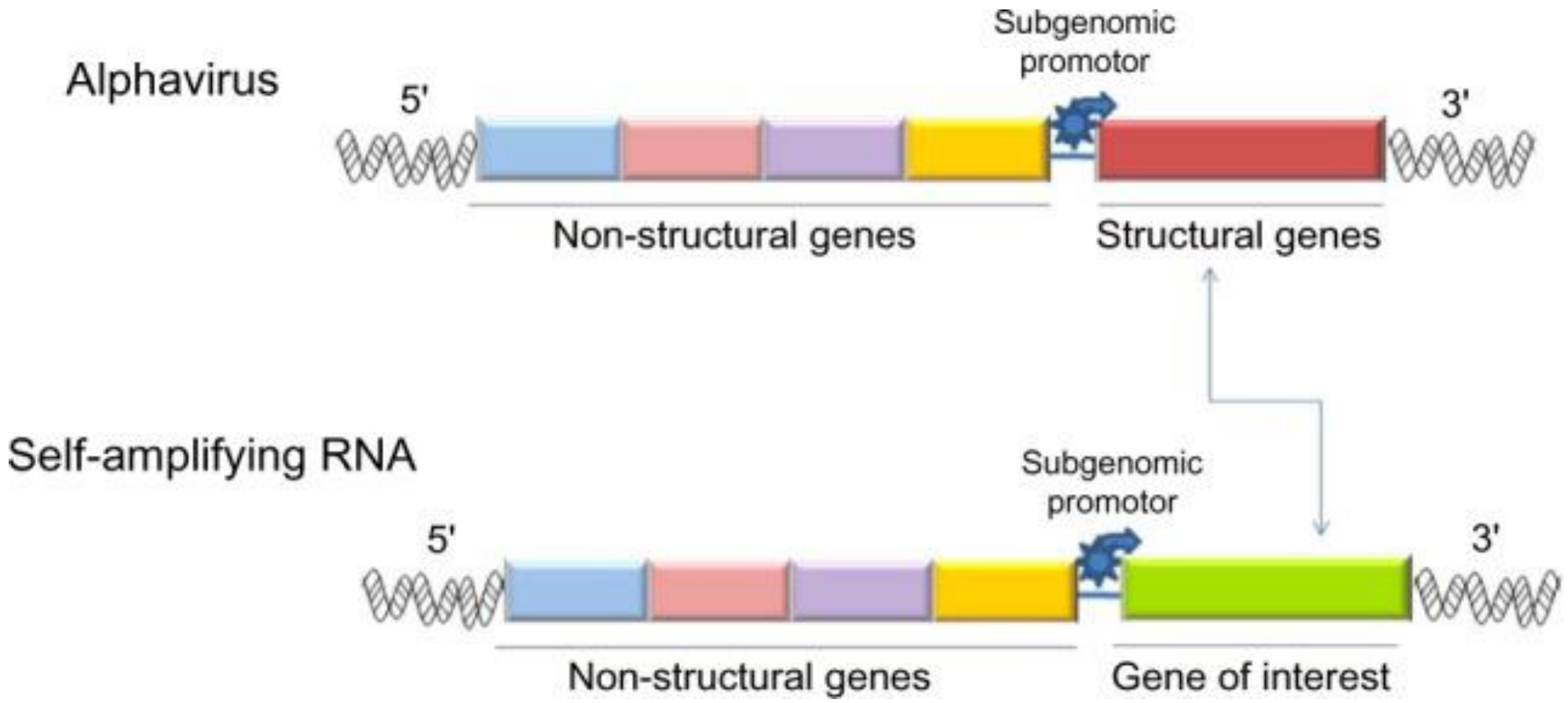




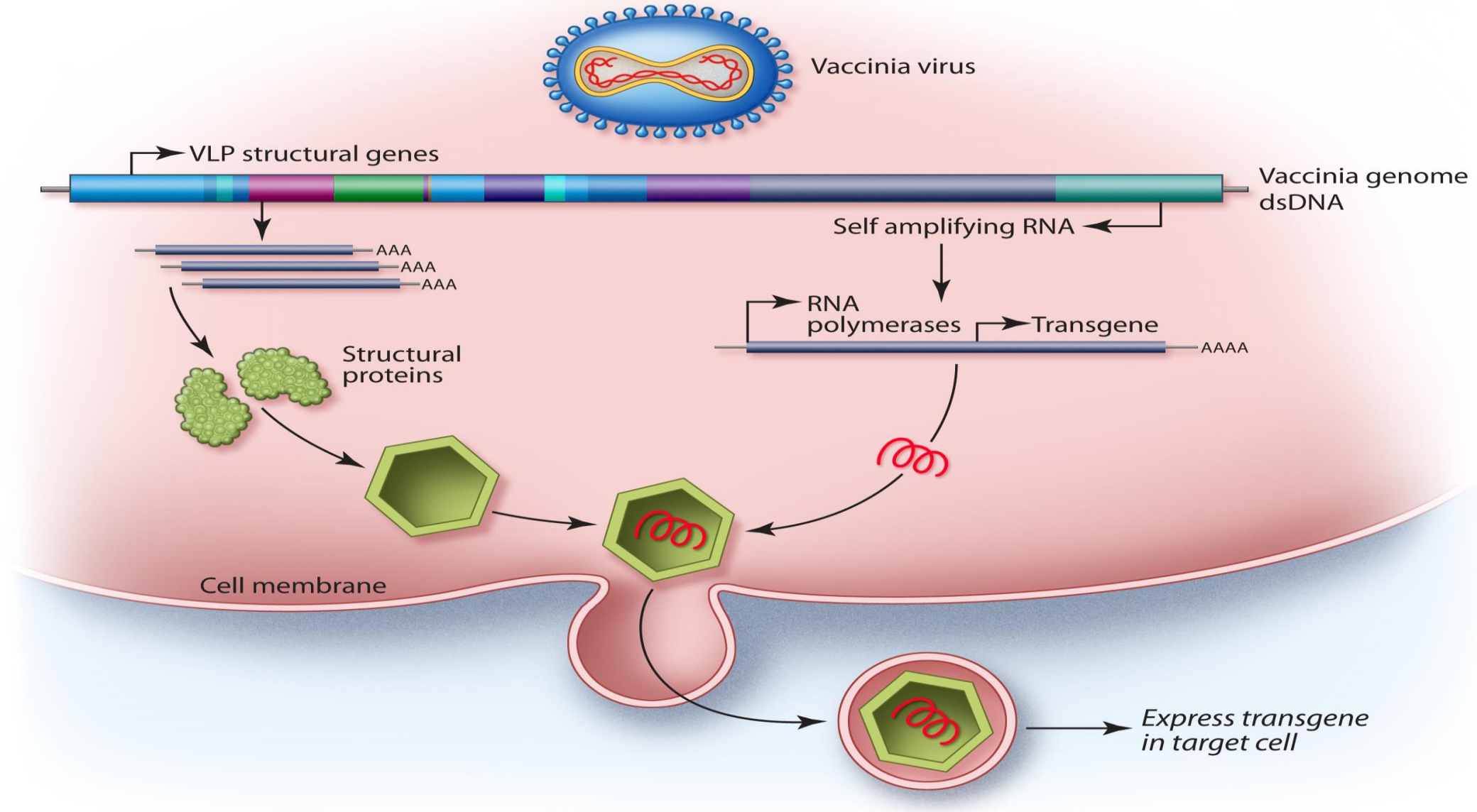
SKV – A Therapeutic Aircraft Carrier?

Nikolas Martin

Self Amplifying RNA Vectors

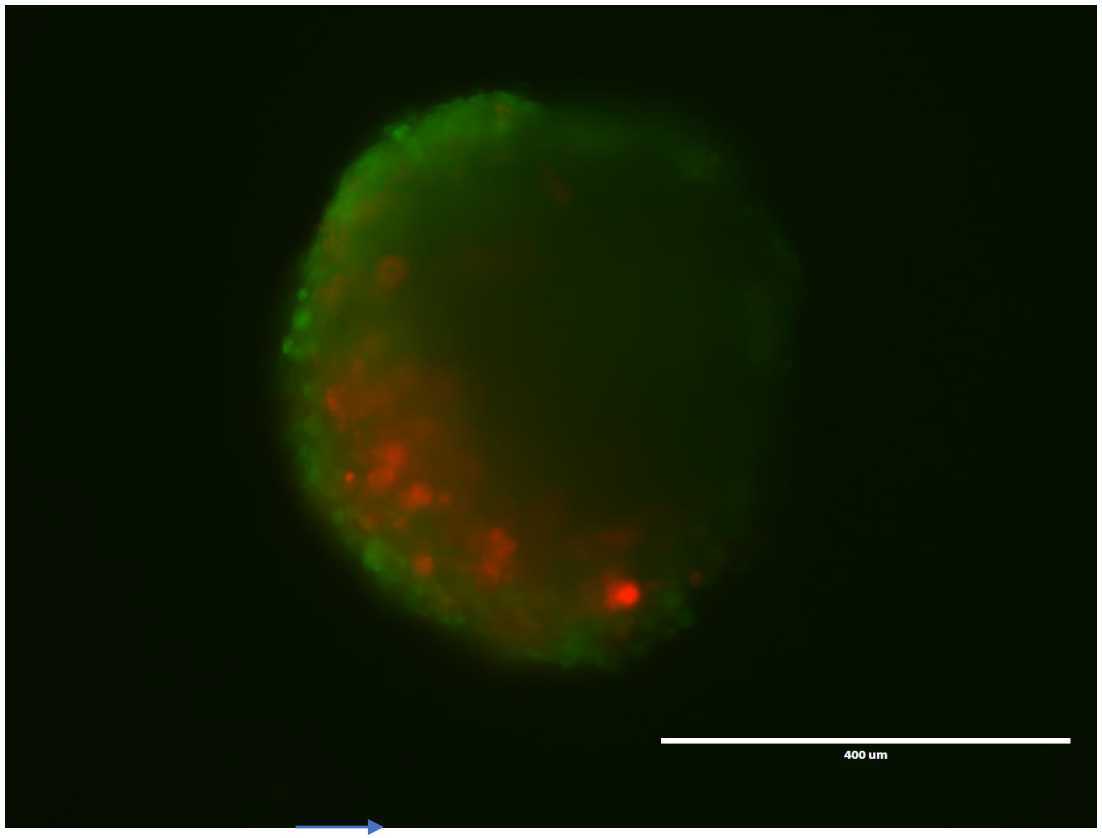


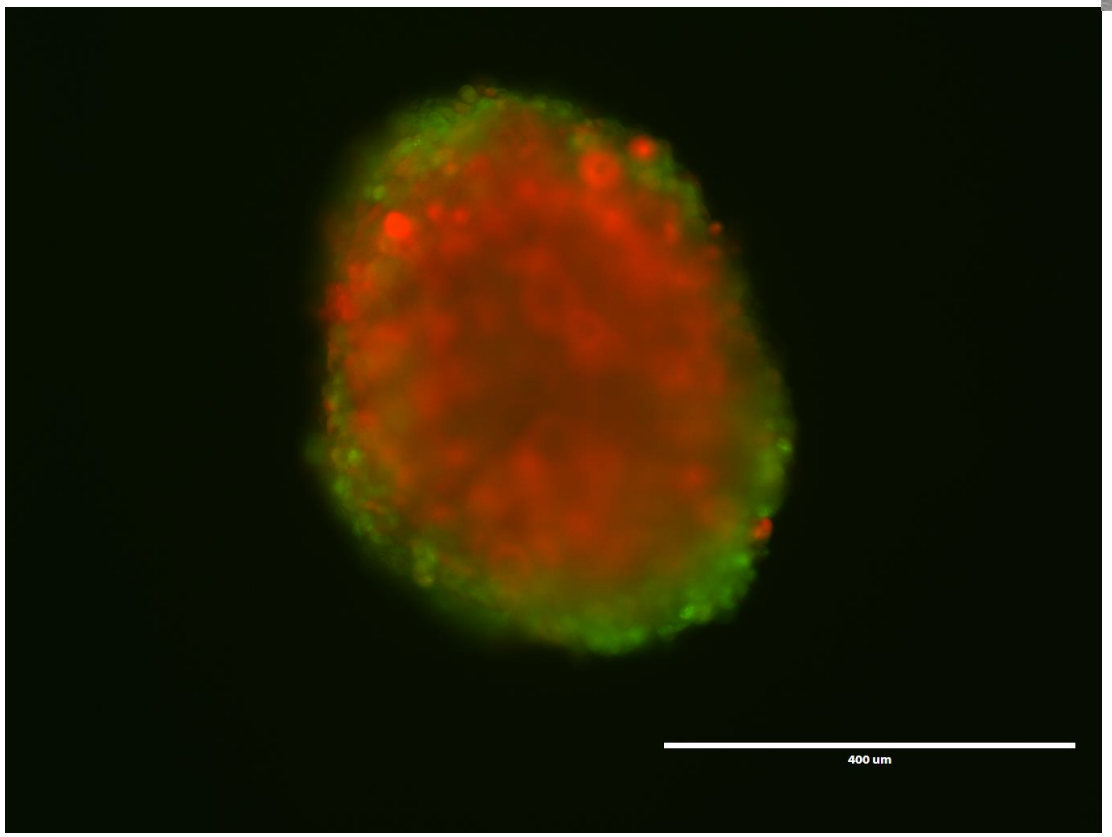
Transfer of saRNA from Infected to Non-Infected Cells



SKV – Disseminating saRNA within the Tumour Microenvironment

Nikolas Martin





SKV – Green
saRNA - Red

Time

Prostate Cancer Canada Network

OICR Ontario Institute for Cancer Research

Canadian Cancer Society

BioCanRx

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Leeds University
Vicky Jennings
Institute of Cancer Research
Alan Melcher
Turnstone Biologics
Mike Burgess
Caroline Breitbach
Steve Berinstein
Dave Stojdl
NCT Germany

OHRI
Carolina Ilkow
Jean Simon Diallo
Marie-Eve Edge
Brian Keller
McMaster University
Brian Lichty
Fuan Wang
NCT Heidelberg
Guy Ungerechts