Accelerating Viral Vaccines Process Development

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SANOFI PASTEUR

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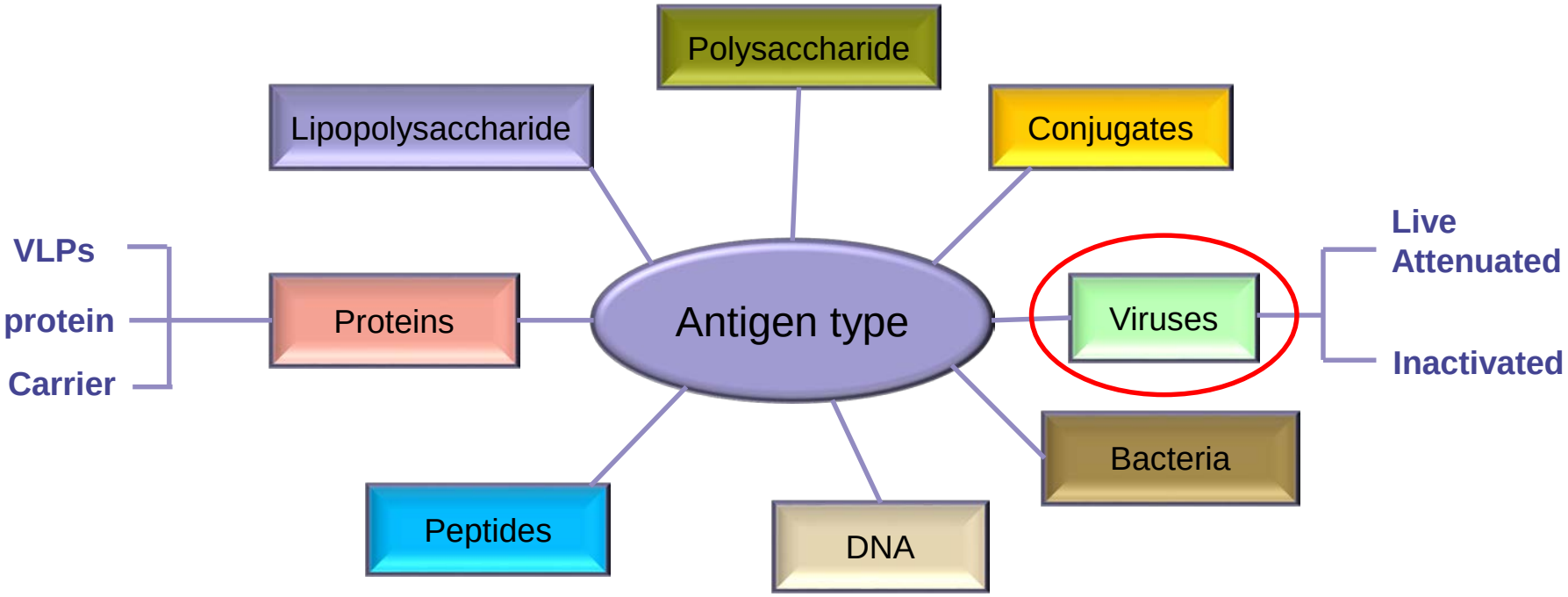
Arm-to-arm vaccination

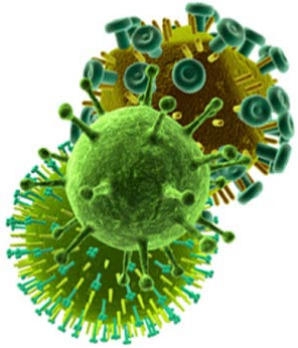
Evolution of Vaccine Technologies
(Susan & Stanley Plotkin)

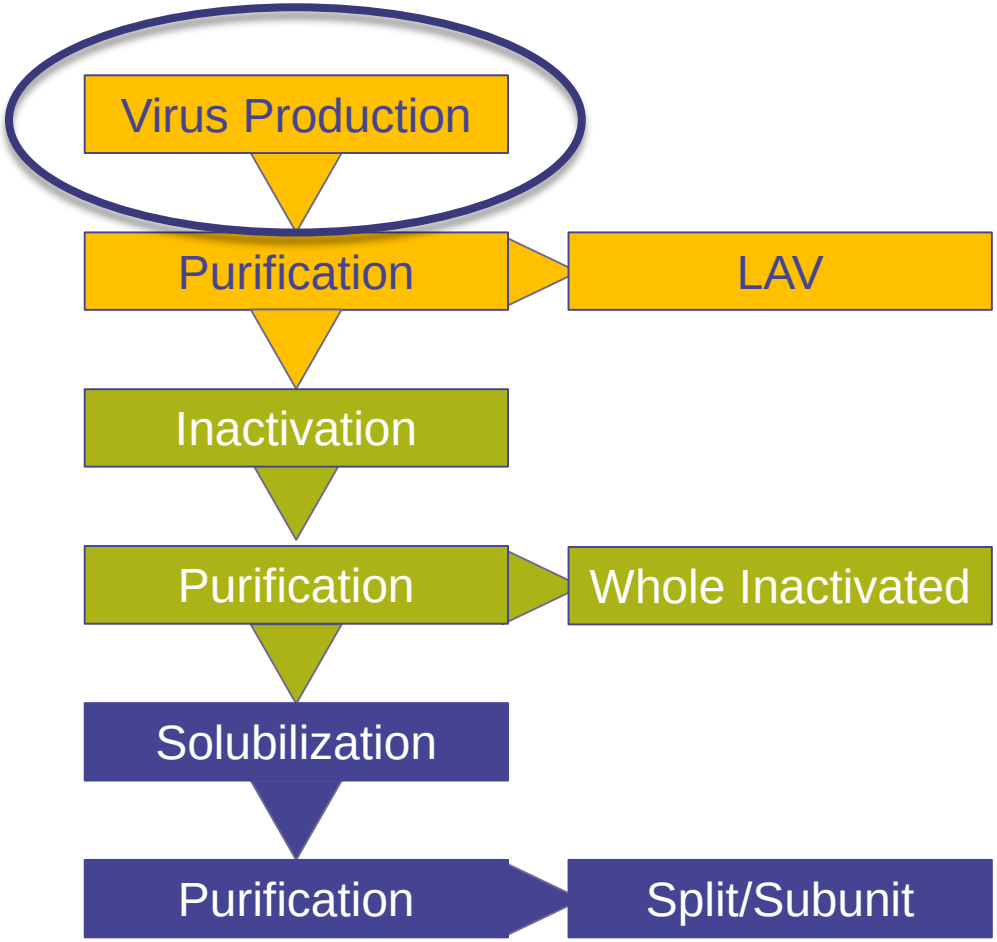
Live Attenuated	Killed Whole Organism	Protein or Polysaccharide	Genetically Engineered
18th + 19thCentury			
Smallpox (1798)			
Rabies (1885)	Typhoid (1896)		
	Cholera (1896)		
	Plague (1897)		
First Half 20th Century			
Tuberculosis (BCG 1927)	Pertusis (1926)	Diphtheria toxoid (1923)	
	Influenza (1936)		
Yellow Fever (1935)	Thyphus (1938)	Tetanus toxoid (1926)	
Second Half 20th Century			
Polio (oral)	Polio (injected)	Pneumococcus polysaccharide	HepB surface antigen recombinant
Measles	Rabies (cell culture)	Meningococcus polysaccharide	Lyme OspA
Mumps	Japanese encephalitis	HiB polysaccharide	Cholera (recombinant toxin B)
Rubella	Tick-borne encephalitis	Meningococcal conjugate	
Adenovirus	Hepatitis A	H. influenzae conjugate	
Typhoid (salmonella Ty21a)		Hepatitis B (plasma derived)	
Varicella		Typhoid (Vi) polysaccharide	
Rotavirus reassortants		Acellular pertusis	
Cholera		Anthrax secreted proteins	
21th Century			
Cold-Adapted Influenza		Pneumococcal conjugates	Human papillomavirus recombinant
Rotavirus attenuated and new reassortants		Meningococcal quadrivalent conjugates	
Zoster			

The Different Types of Vaccine Antigens



Viral Vaccine Manufacturing





OPV

MMR

Rota

YF

Dengue

JEV

IPV

Hep A

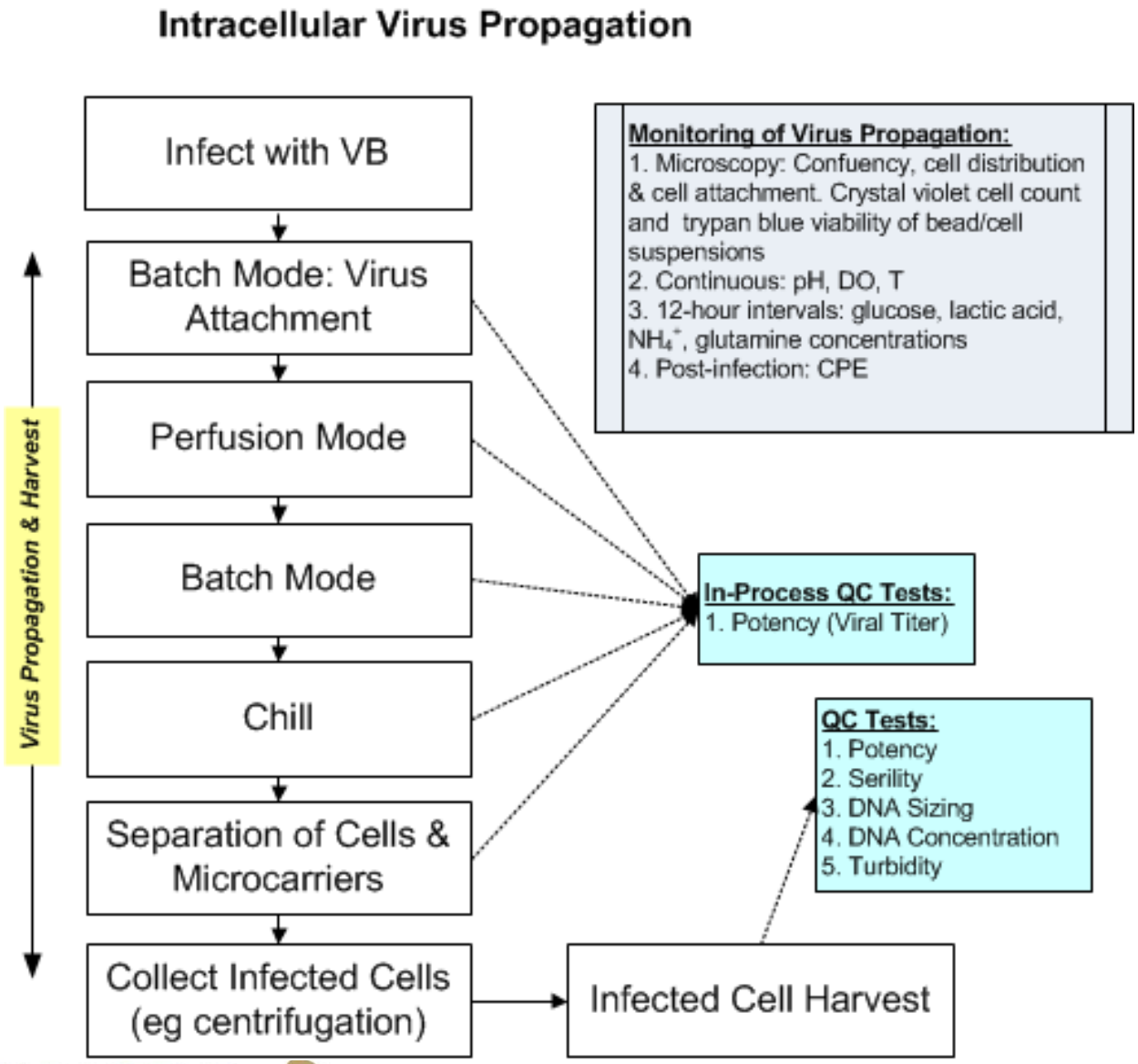
Rabies

Flu

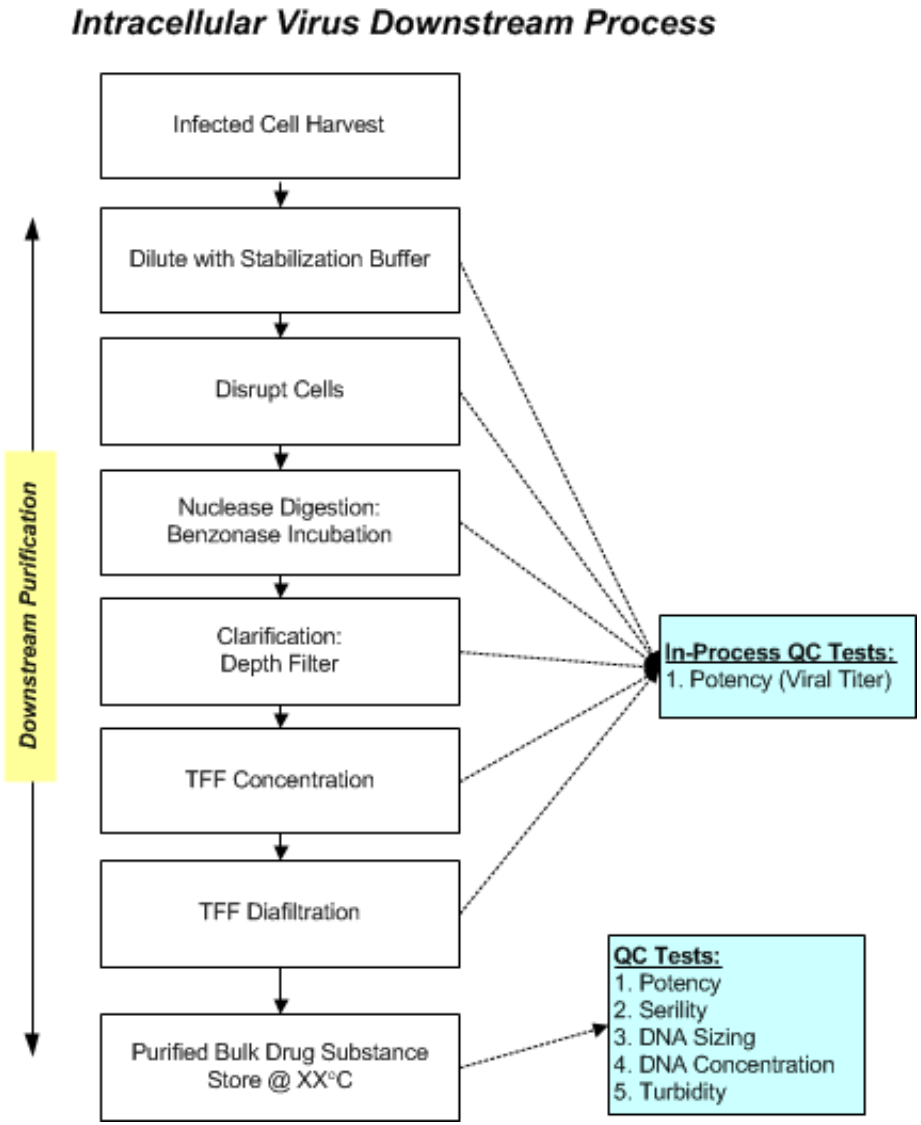
Vaccine Process Development: Goals

- Based Upon the Target Product Profile (TPP)
  - **Stable Form**
  - **Patient Population**
  - **Dose(s)**
  - **Route-of-Administration**
  - **Regulatory Guidance**
- Product Critical Quality Attributes
  - **Potency**
  - **Stability**
  - **Purity**
  - **Identity**

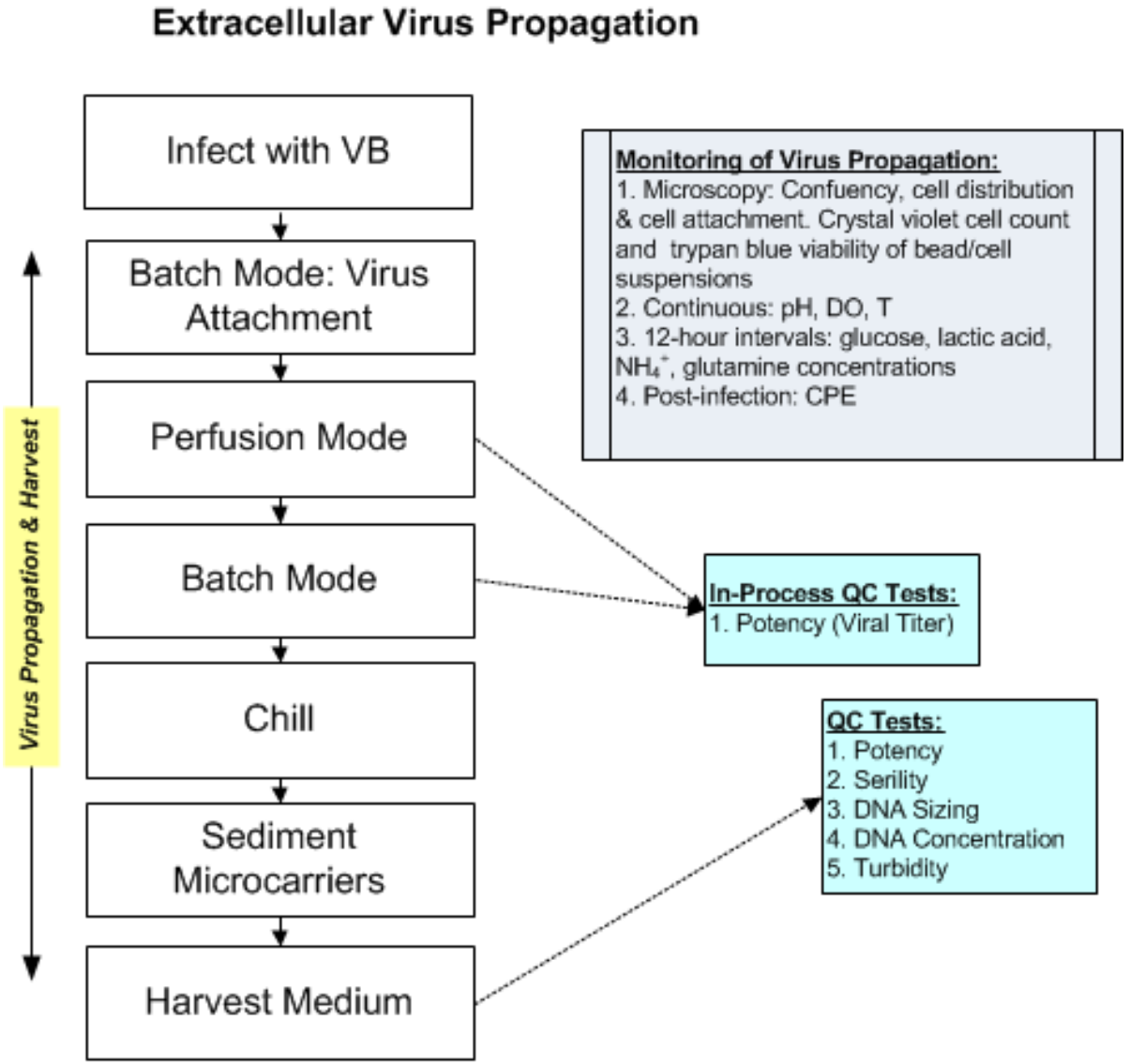
Upstream Process Development (1)



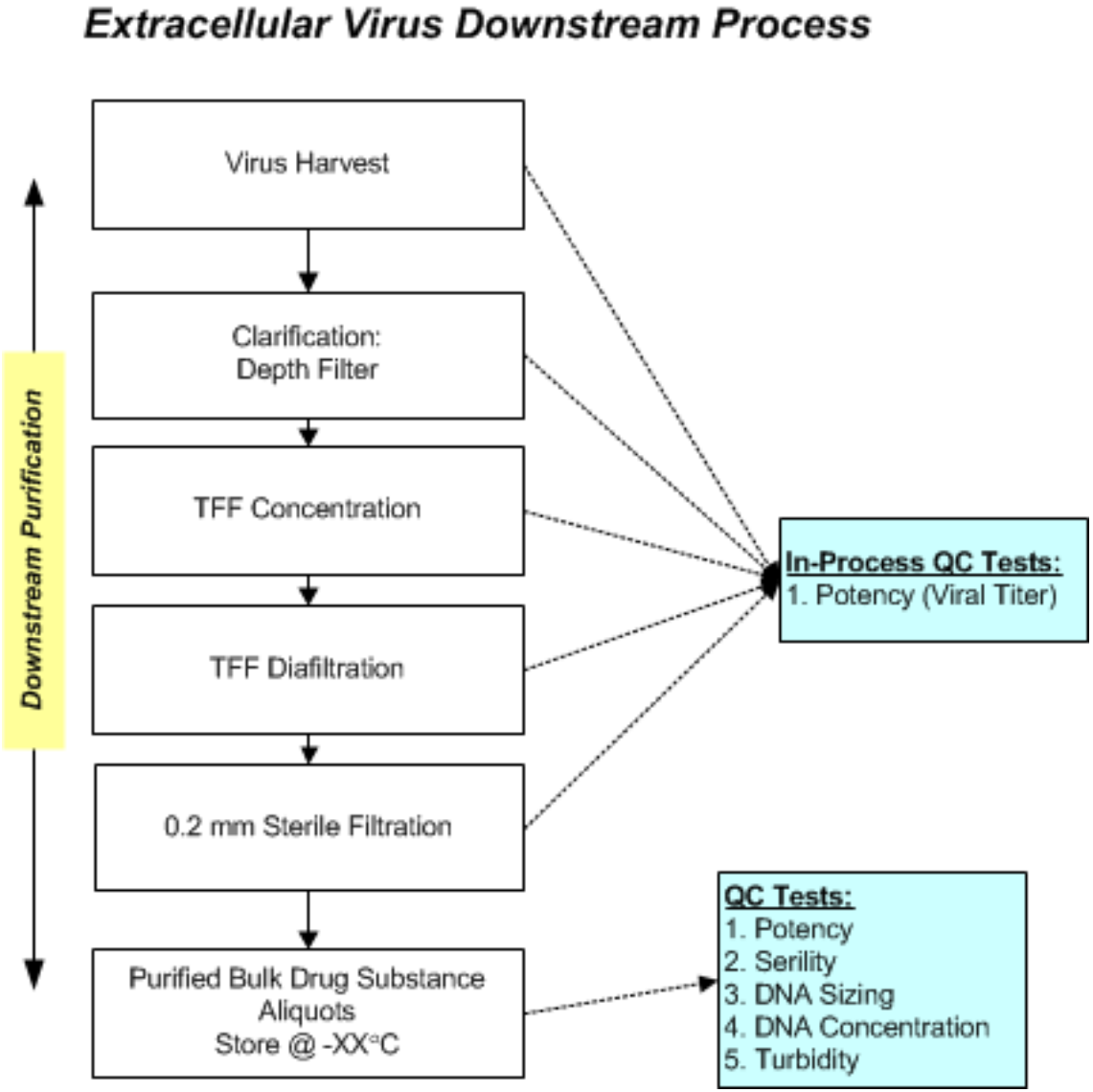
Downstream Process Development (1)



Upstream Process Development (2)



Downstream Process Development (2)



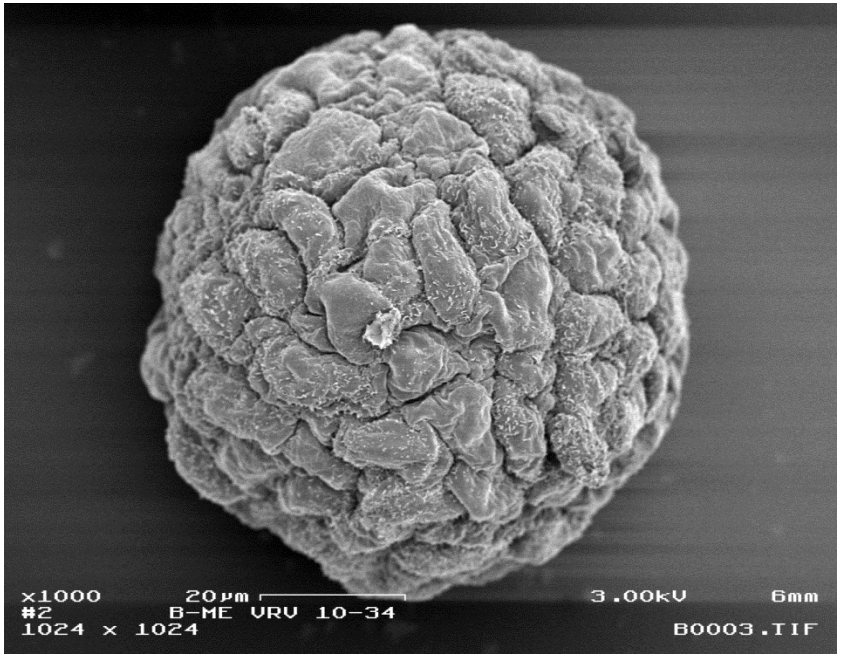
Viral Vaccine Cell Lines

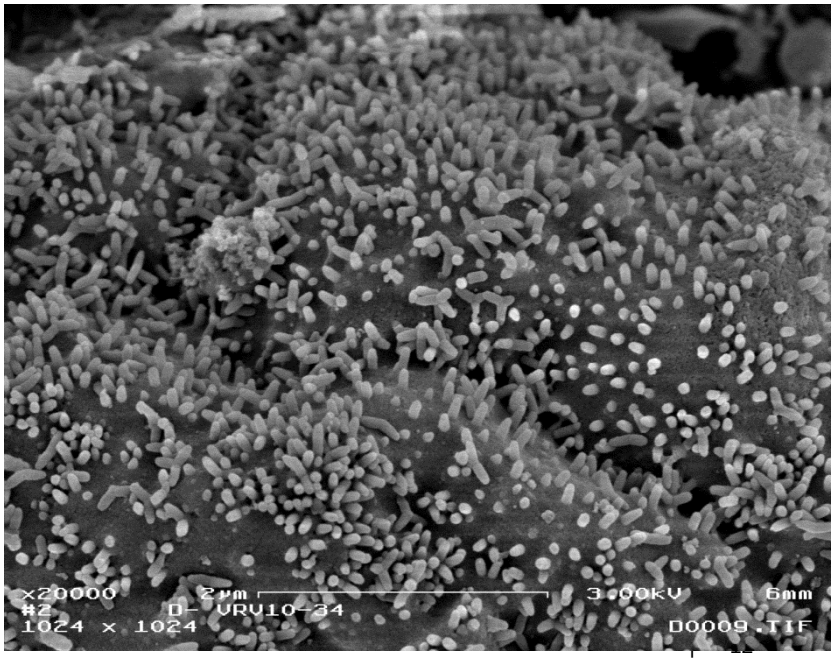
- Adherent cells
  - MDCK
  - MRC5
  - Vero
  - BHK
  - CEF
  - …

Legacy processes

- Suspension cells
  - EB66
  - PerC6
  - HEK293
  - …

New products





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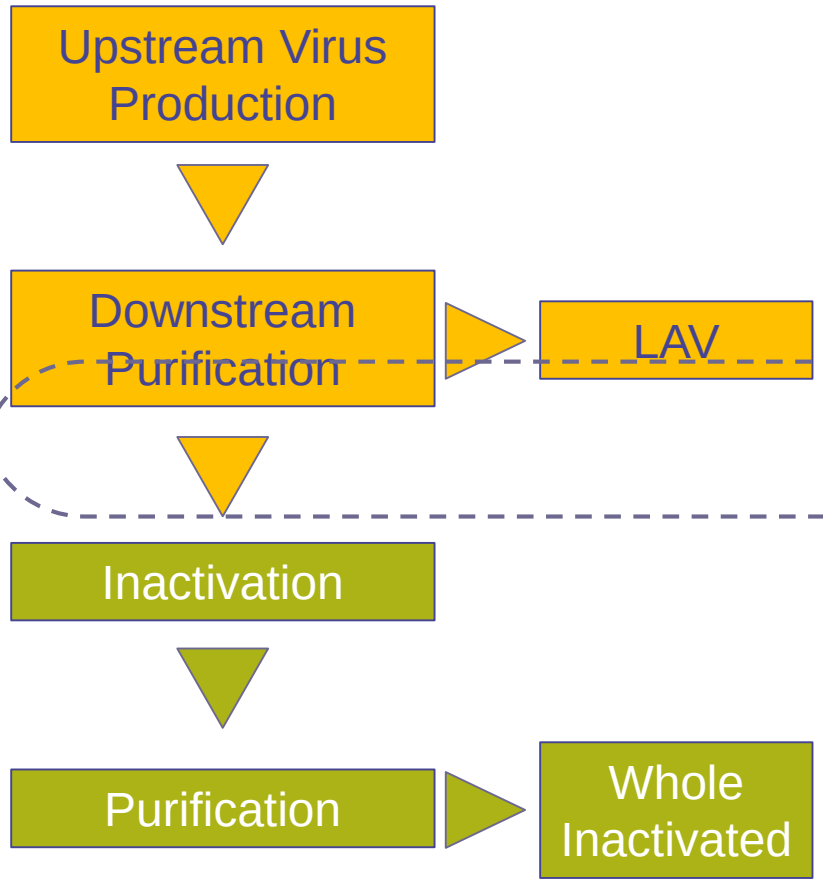
L B C – Microscopie Electronique, Université François Rabelais, Faculté de Médecine et CHRU de Tours

Viral Vaccines & Candidates

Disease Virus type	Family	Representative Vaccine Strain	Host-Cell Death Rate	Capacity to infect single-cell suspensions	Genome	Enveloped
YF	Flaviviridae	YF17D	+++	YES	RNA +ss	YES
JEV	Flaviviridae	SA-14-14-2	+++	YES	RNA +ss	YES
Dengue	Flaviviridae	NA	+++	YES	RNA +ss	YES
Smallpox	Poxviridae	Vaccinia	+	LOW	DNA ds	YES
Flu	Orthomyoxyviridae	« seasonal »	+++	YES	RNA –ss	YES
Rota	Reoviridae		++	YES	RNA ds	NO
Polio	Picornaviridae		++++	YES	RNA +ss	NO
Rabies	Rhabdoviridae		+	YES	RNA –ss	YES
HepA	Picornaviridae		+	NO	RNA +ss	NO
Measles	Paramyoxyviridae		+++	?	RNA –ss	YES
Mumps	Paramyoxyviridae		+++	?	RNA –ss	YES
Rubella	Togaviridae		+++	?	RNA +ss	YES
Canarypox	Poxviridae	NA	++	LOW	DNA ds	YES

Genetic Stability: DNA > + SS RNA > - SS RNA

Traditional Viral Vaccine Analytics (1)



- Infectivity Assays
  - Plaque Assay
  - Endpoint Dilution Assay (TCID50)
  - Immunofocus Assay
- Physical Methods
  - TEM, Light-scattering
- Immuno-Assays
  - Single radial immunodiffusion assay (SRID)
- Protein Assays
  - Hemagglutination

Traditional Viral Vaccine Analytics (2)

- None of these Assays are At-line or Rapid
  - **Hours-to-Days of often cumbersome Sample Preparation**
  - **Often limited by the number of samples that can be processed in parallel**
- Infectivity Assays
  - **Highly dependent upon consistency of substrate cell monolayer**
  - **Limited linear range (1-2 log)**
  - **Multi-day incubation for CPE to develop**
  - **DIPs can interfere**
  - **Best performance: ± 0.3 log**
- Physical or Protein-based assays
  - **TEM & Light Scattering: no distinction between live and dead virus particles**

Limitations on Experimental Turnaround, Extending Development Time

Meeting Analytical Needs (1)

- ViroCyt VirusCounter
  - Next Generation Tool based on well-understood technology
  - At-line (< 15 minutes)
  - Autosampler Option
  - Requires Some Sample Preparation for Intracellular Viruses
  - Correlation with existing methods
  - Yet to be Fully Validated

Meeting Analytical Needs (2)

- Virus Counter: Potential Impact on Vaccine PD
  - **Reduce Experimental Turnaround 30 – 50% (!!!)**
  - **Reduce Analytical Complexity**
  - **Increase Statistical Significance via high throughput (increased *n*)**
  - **Facilitates increasing multiplex capability allowing true DOE approach**

"If your dreams don't scare you, you don't dream big enough"

Thank You

(only the dress-code has changed…)