

Racing to a SARS-CoV-2 vaccine using platform technology

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Stages of Vaccine Development in a Pandemic

With a pandemic the key issue is speed.

- *Based on previous understandings, development and release of a vaccine must occur in months, not years.*

Safety demonstration is critical milestone for product advancement

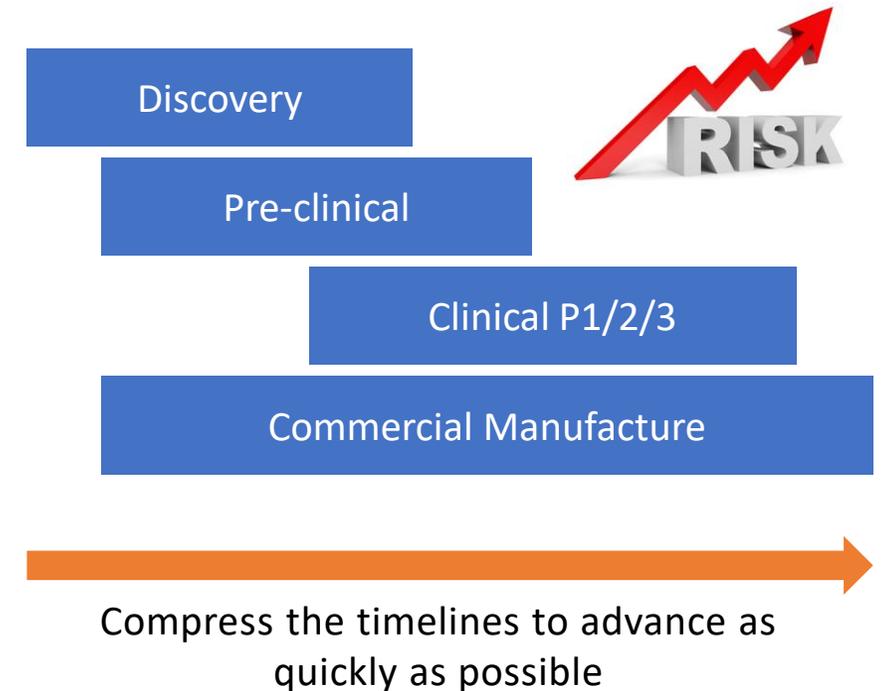
- *Initial signals on efficacy will be sought, but rarely sufficiently powered to demonstrate true efficacy.*

Work based on real-time data.

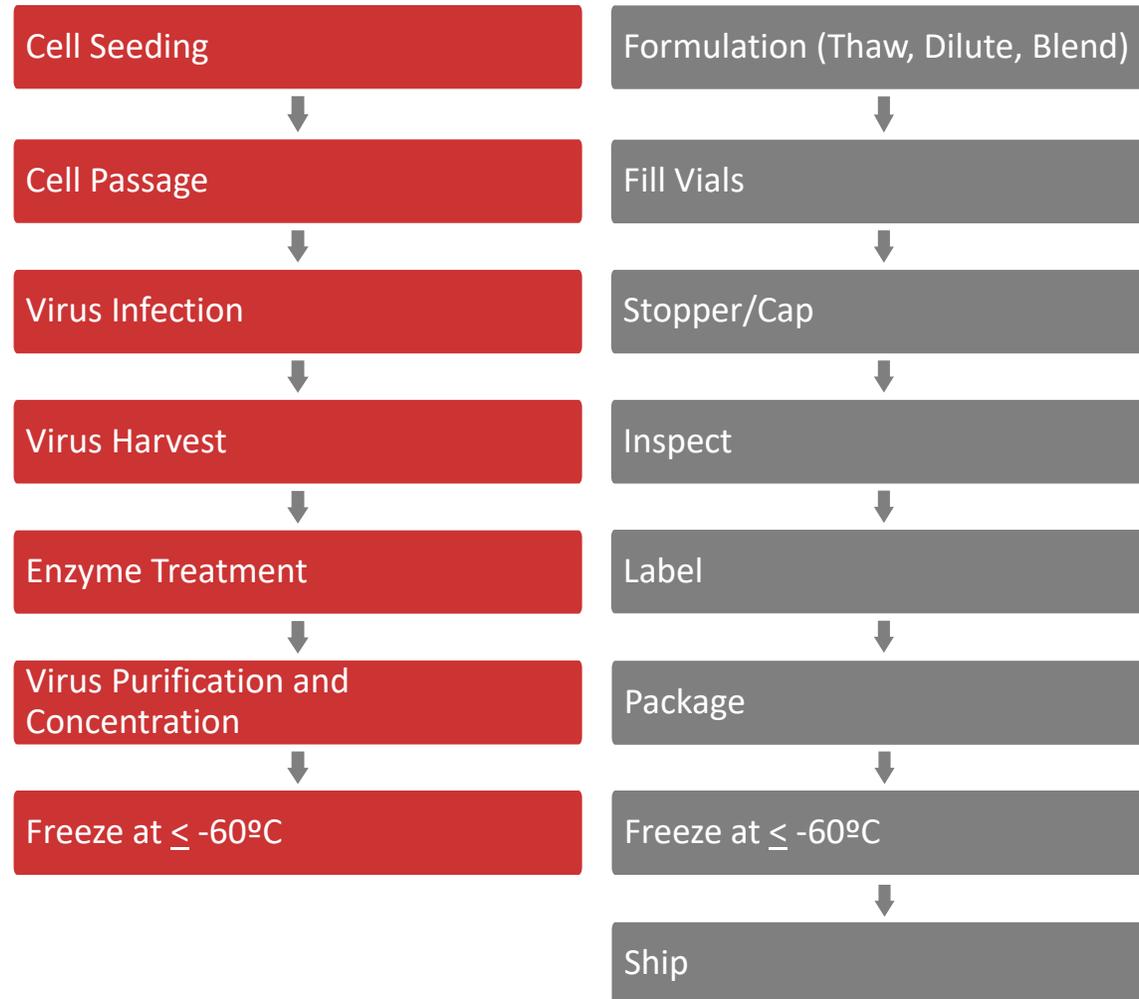
- *Information on the new pathogen is changing and increases our understanding with each new study.*

Risk profile is at its maximum.

- *Need to pre-invest in commercial manufacture at risk.*



Roller bottle process used with Ervebo[®]



- Drug Substance and Drug Product is stored and kept at $\leq -60^{\circ}\text{C}$
- Data indicates DP stable at $2-8^{\circ}\text{C}$ for up to 4 weeks

Supply for the world

Roller bottle production system



Increase in scalability and flexibility of supply



Need to create and adopt a scalable platform manufacturing technology that can be adopted to either vaccine candidate.

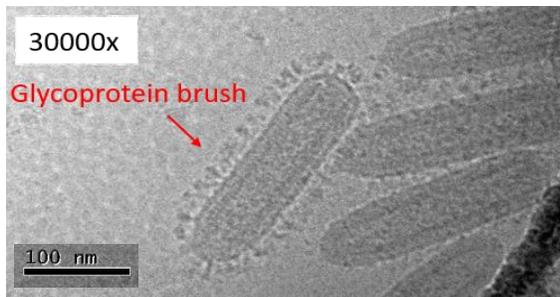
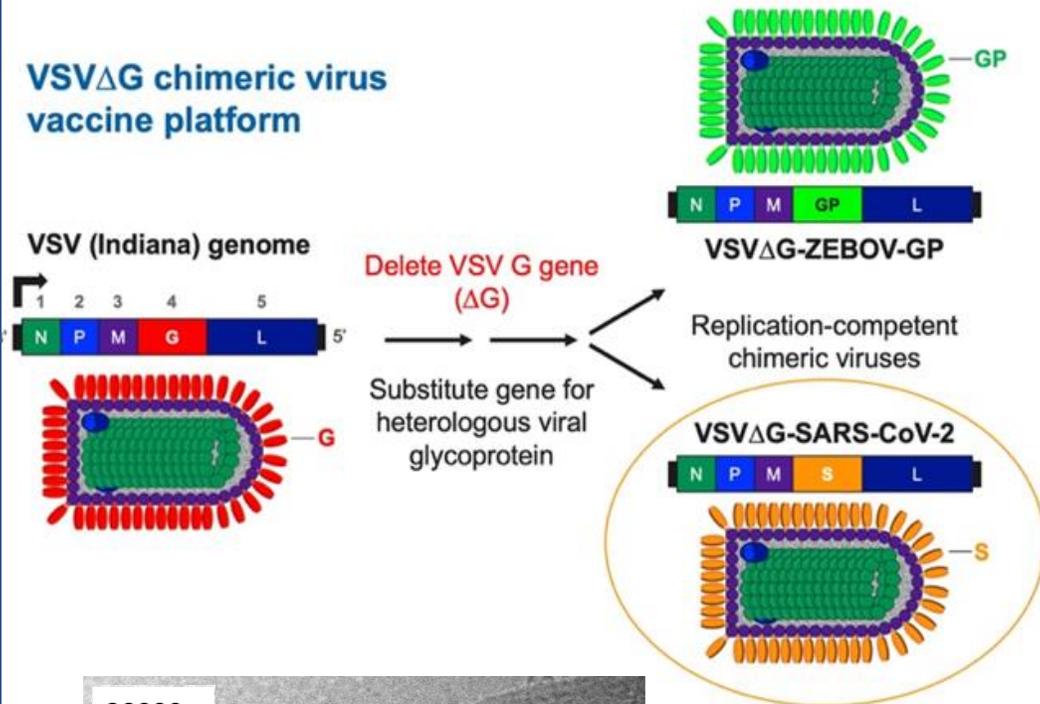
Bioreactor Production System



SARS-CoV-2 Vaccines Viral Vector Platform Approaches

Joint development with IAVI (International AIDS Vaccine Initiative)

VSV Δ G chimeric virus vaccine platform

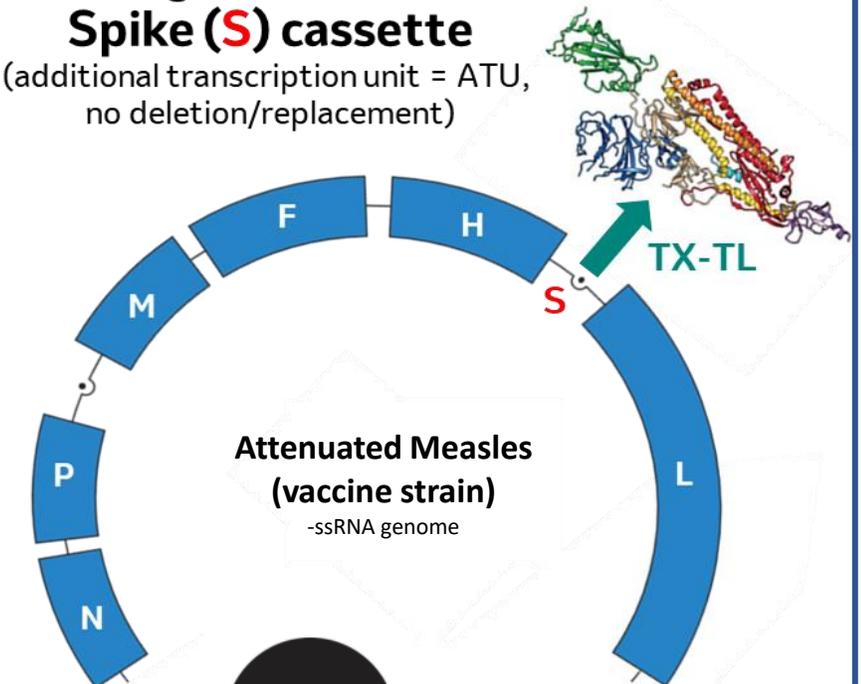


Themis Biosciences recently acquired by Merck

- Measles-vectored platform technology
- Replication competent viral vaccine potential for a single dose vaccine

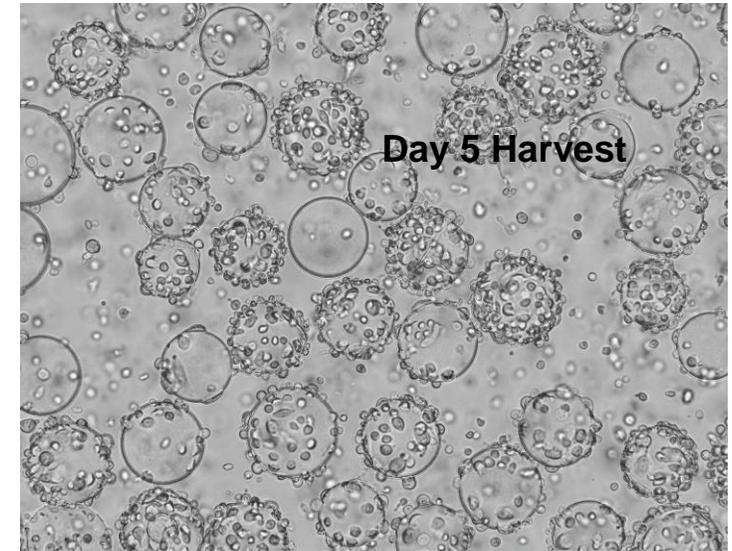
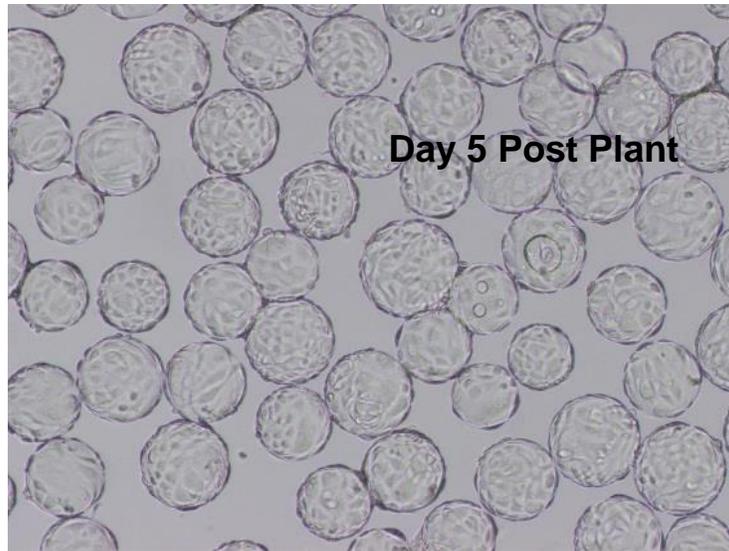
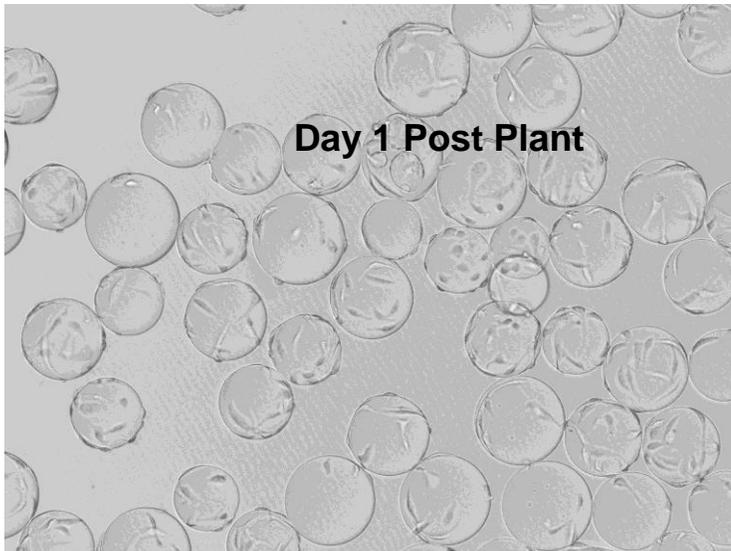
Full-length SARS-CoV-2 Spike (S) cassette

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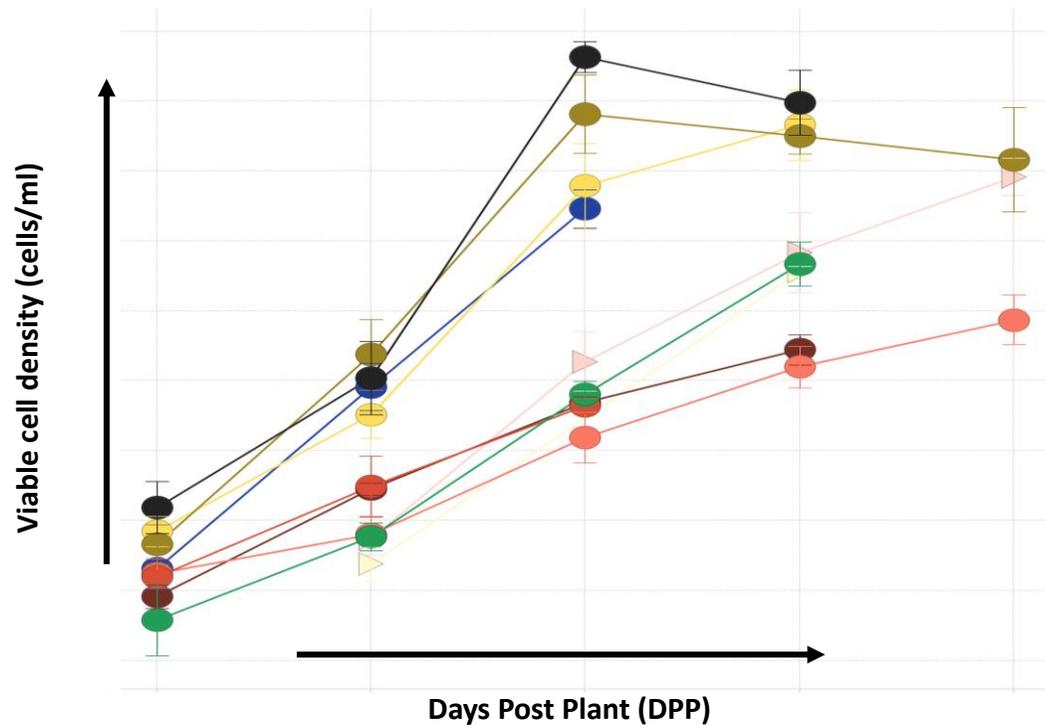
Vero Cells

- Anchorage dependent and continuous.
- One of the most common mammalian cell lines used in research. Vero cells have been licensed in the US for both live (rotavirus, smallpox) and inactivated (poliovirus) viral vaccines. Throughout the world, Vero cells have also been used for production of other vaccines such as Rabies, Reovirus, and Japanese encephalitis.
- Industrially, over 25 years experience with vero-derived human vaccines, and MM doses distributed worldwide.

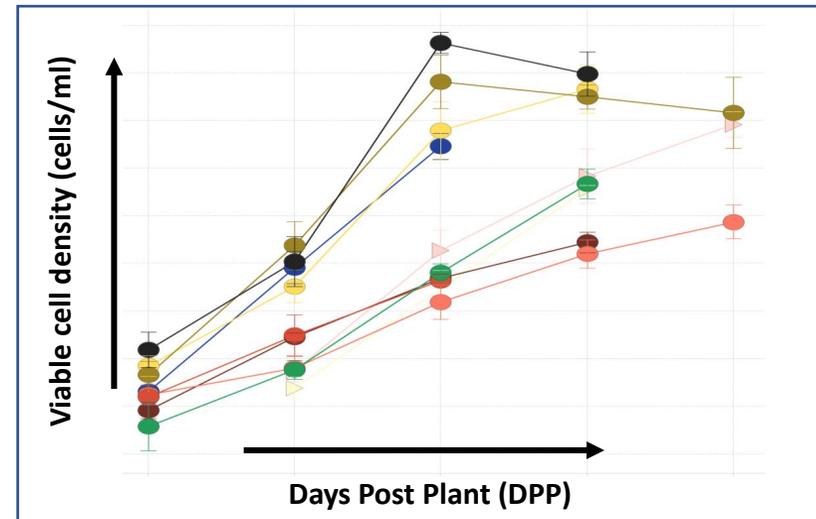
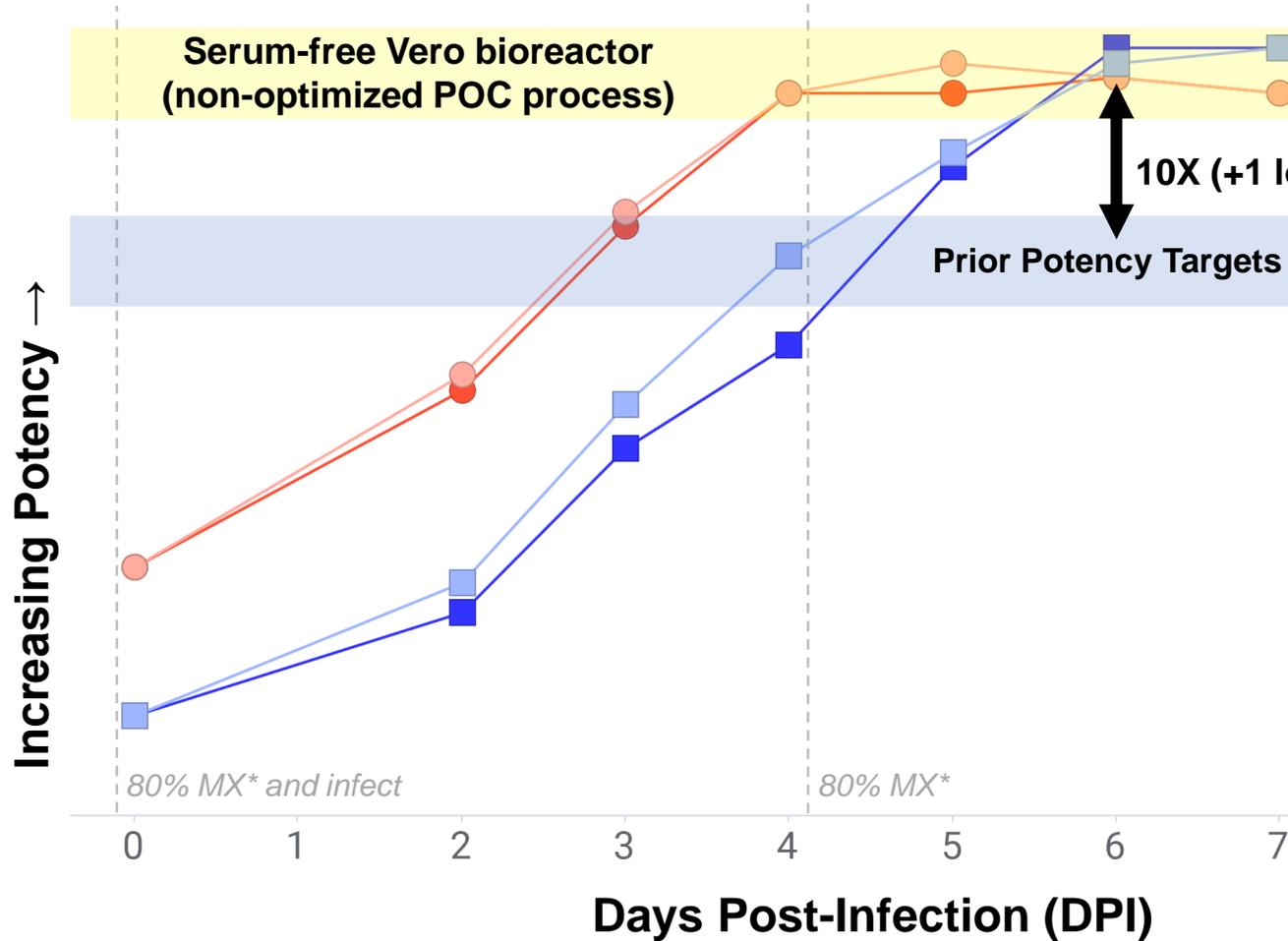


N-1 Bioreactor Stage Development

- Identify ideal impeller configuration
- Demonstrate optimal microcarrier bead density
- Optimize cell growth, timing of harvest and harvest recovery
- Determine feed strategy (Medium exchange vs. bolus shots)
- Demonstrate cell growth and productive infection at the production scale

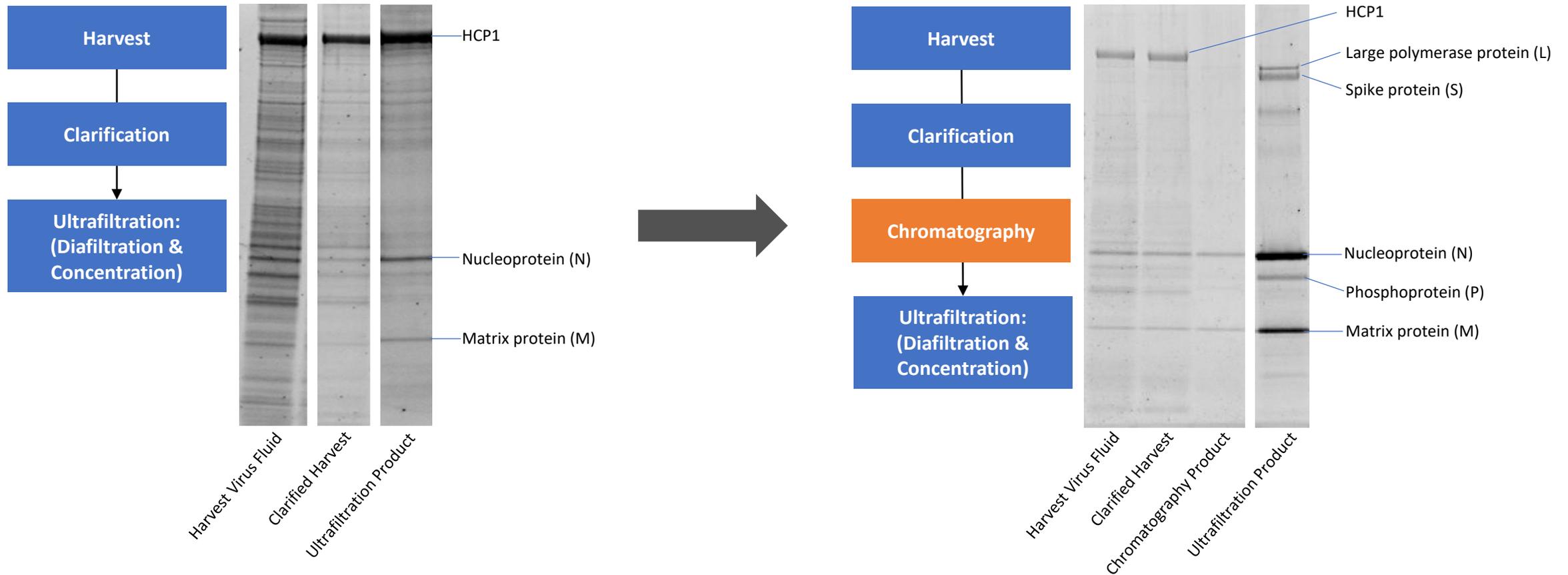


Viral Potency in serum-free Vero / microcarrier bioreactor exceeded prior process yields



*MX = medium exchange

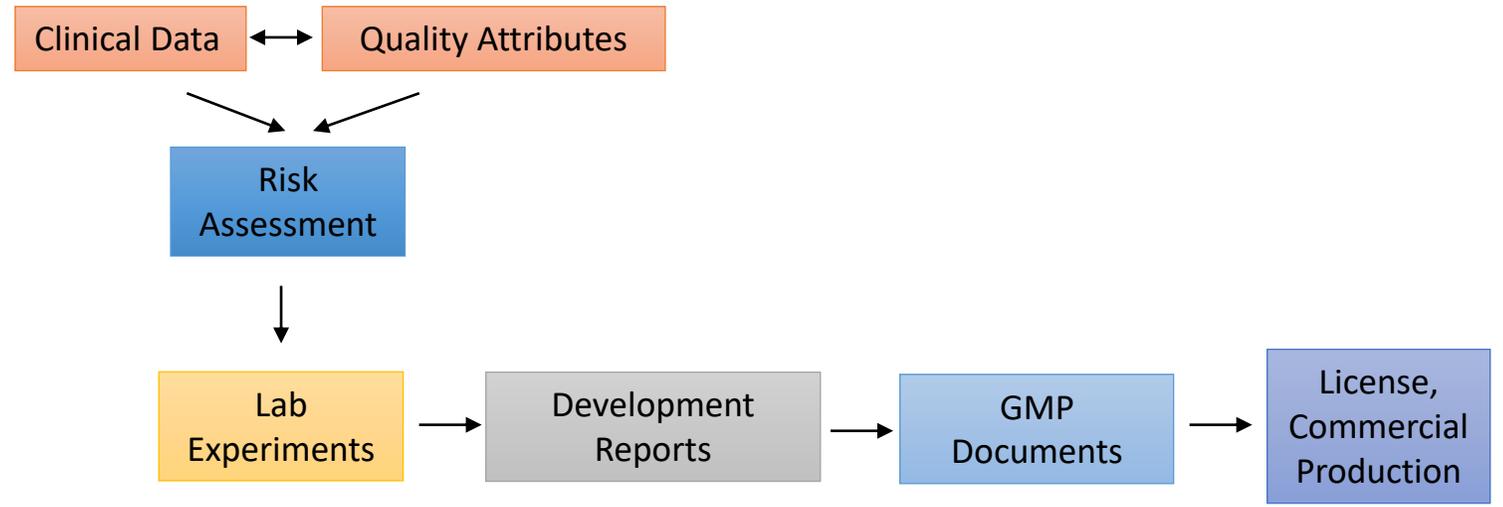
V590 Chromatography



- Large Host cell Protein was not cleared by ultrafiltration
- Added chromatography step and optimized process parameters.
 - 2-log clearance of target HCP >10-fold clearance in other HCPs ~2-fold clearance dissociated S1.

Approaches to expedite process development and characterization

1. Clinical, process development and manufacturing scale-up teams working in parallel
2. Use a risk-based approach to prioritize development studies
3. Use of scale-down models to increase experiment throughput
4. Implementation of single-use standard solutions
5. Implement a documentation strategy with the marketing application in mind



V59X Proposed Process



- Adapted from process used to make ERVEBO®
- Converted Vero cell expansion and virus propagation steps from roller bottles to single-use bioreactor
- Multiple changes to increase manufacturability and improve impurity clearance
- Modified composition of Drug Substance and Drug Product buffers to maintain virus morphology and improve stability

Network of Operations to enable Supply Chain

- Unprecedented speed for facilities construction & start-up across DS, DP, Packaging
- Manufacturing and testing footprint to ensure global access
- Building product-agnostic facilities with equipment flexibilities to enable V59X manufacture
- Commissioning and Qualification Strategy aligned across all nodes
- Leveraging single-use designs incorporating Merck standards for speed
- Building flexibility for supply swing factor considerations
- Full scale development strategy in parallel with process development
 - ✓ Early demonstration and de-risking of process scalability
 - ✓ Enables early process optimization and 'Right First Time' technology transfer
 - ✓ Early supply of representative commercial-scale materials for Analytical and DP workstreams

Conclusions

- Typical timelines for vaccine development are on the order of years, and frequently depends on introduction of novel technology
- Rapid pandemic response required target identification, development and deployment be completed in months and in parallel
- To achieve this strategy, existing technology, experimental methodology, and business systems were used to greatest extent possible to achieve target timelines
- **Vaccine selection at Merck centered on live viral candidates as vectors for introduction of the SARS-COV2 spike protein where prior experience and capability already existed**
- **Leveraging a platform within vaccine development and commercialization at Merck has enabled us to meet ambitious and needed process objectives.**
- Development of this platform approach can be beneficial to other viral vaccines, examples below:
 - Enables standard approaches for process characterization with product specific refinements
 - Accelerating equipment design and procurement
 - Facility readiness

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