Justifying a pathway to reduced replication-competent lentivirus (RCL) testing

Adding the empirical to the theoretical.

Vector manufacturing and analytics

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Some graphics created in https://BioRender.com

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RCL testing impacts the full scope of LV product development

Why this talk has something for everyone

1

Patients

Trust us that we all take LV product safety testing seriously

2

Regulatory authorities

Need assurance that safety tests provide confidence that residual risks are acceptable

3

CMOs, CDMOs, CROs

Have to map resourcing/capacity to deliver on-time batch release to multiple clients simultaneously

4

The Sponsor (Spin-out/Biotech/Pharma)

Must understand how RCL assay development impacts their costs & timelines

5

Scientists and SMEs

Need to interpret regulatory guidance & deliver a sensitive, robust and meaningful RCL assay

6

What is the risk (and consequence) of RCL formation?

What's an appropriate test for a theoretical entity?

Years of effort & $$$ here

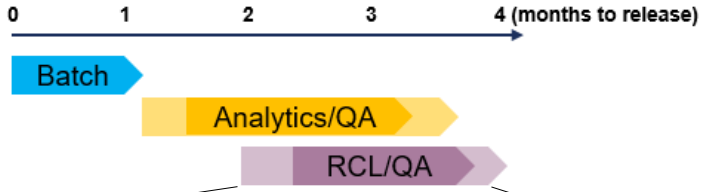
Surprisingly little here

Review article

OXB

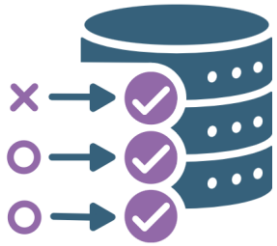
A birdseye view of RCL testing

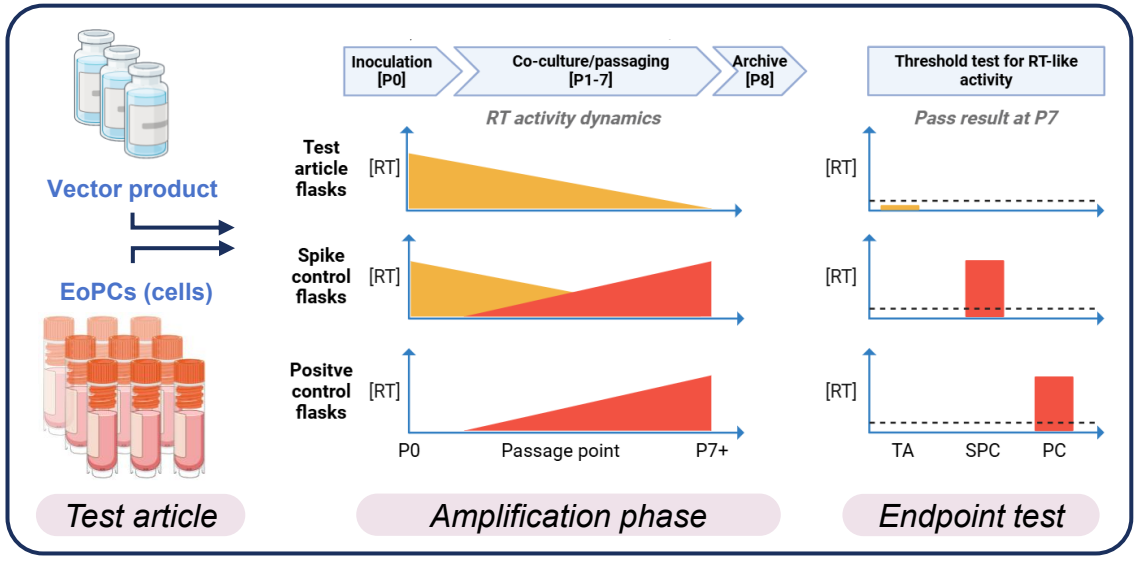
Will Development phase become a bottleneck?



Review article

Development phase | **Qualification phase** | **Final RCL assay (routine testing)** | **Batch release**





- **Amplification cell engineering?**
- Suitability/robustness?
- Sensitivity?
- Reg guidance

- Virus & cell banks
- Assay validation pack
- Inhibition studies
- Operator training
- SOPs & COPs

- Separate vector and EoPC tests
- Amplification phase = ↑ RCL
- Positive & Spike controls
- Endpoint test on RT activity / p24 ELISA

Pass result

=

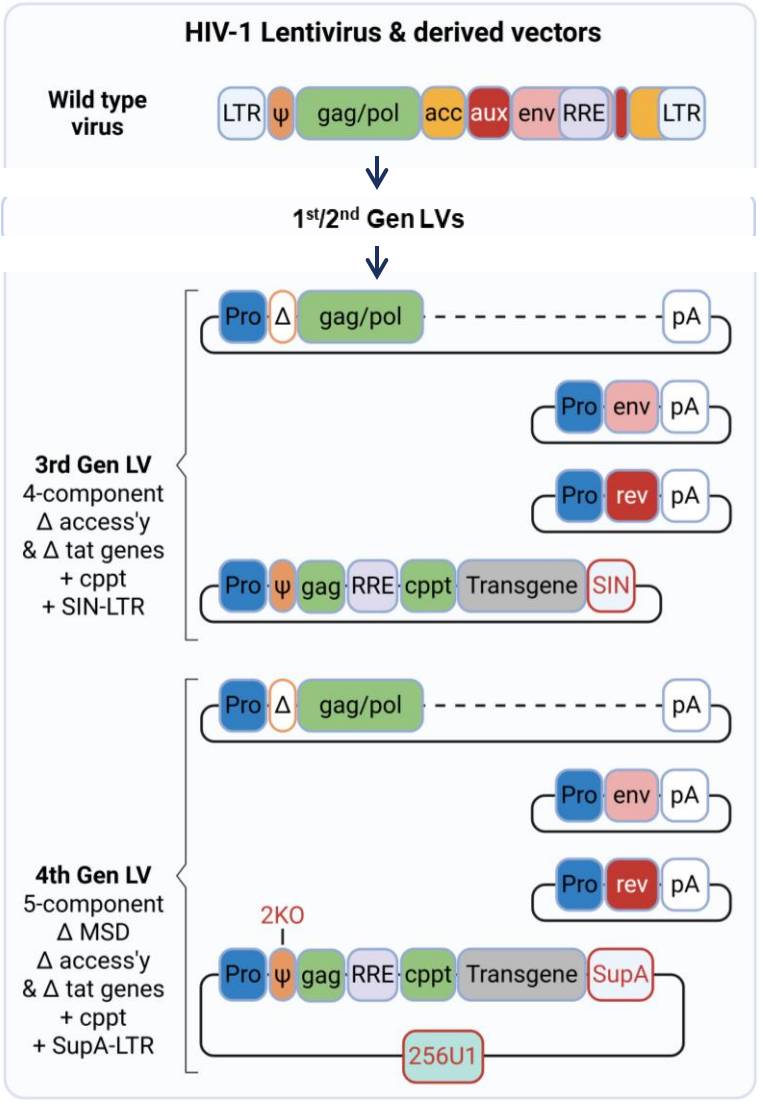
Batch release

12+ months | ***6 months*** | ***2 months***

➢ **A bespoke cell line for each retargeted LV envelope?** (RCL will most likely acquire envelope of the LV system employed)

Safety features of contemporary LV systems

Why no RCL has been detected in their 25 year history



Safer 3rd Gen RV/LV systems & improved in 4th Gen LV

- Components split into separate cassettes and plasmids
- Reduced homology (codon optimised GagPol – relevant later)
- Self-inactivating [SIN]-LTR & removal of tat
- Major splice donor mutation [2KO] and SupA-LTRs (OXB's SupA2KO-LVs)

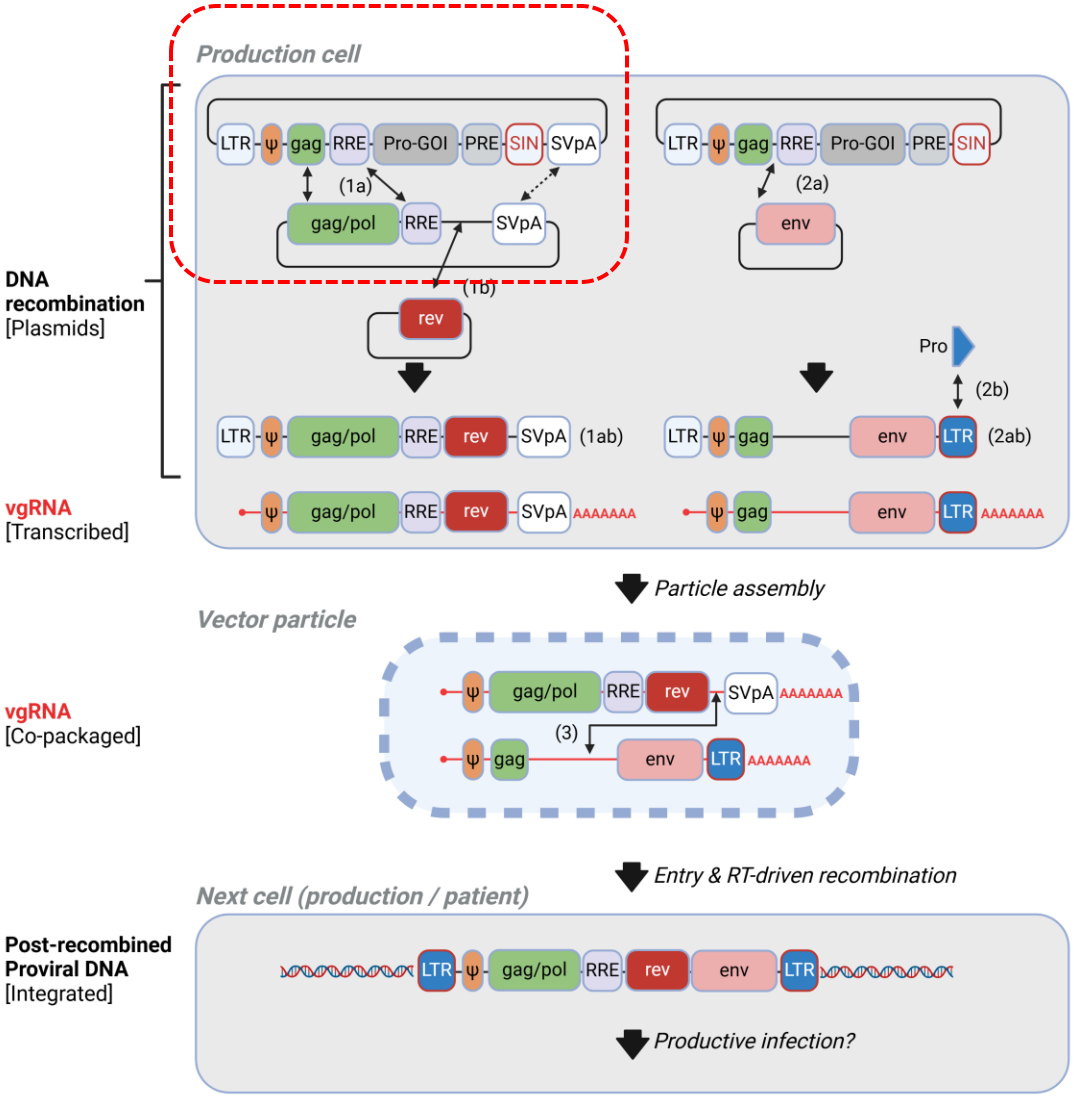
➢ **The more serial steps required to 'reverse' safety features, the less likely an RCL will form.**

2KO/U1

SupA-LTR

A new model for assessing RCL formation risk

Possible vs Plausible vs Reasonable



RCL model

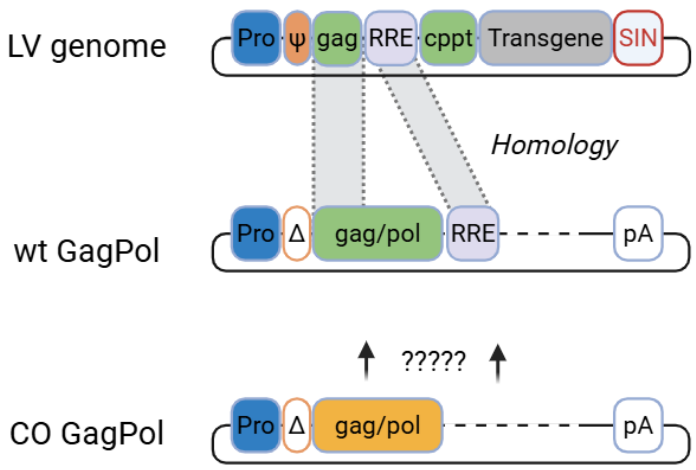
The ‘minimal’ RCL model

- Probability of the arrival of a single RCL genome molecule in first cell
- Based on known cellular and HIV-1 biology mechanisms
- Using conservative assumptions and published data
- For 4x component transient: p[RCL formation] = 1 in 10,000 bioreactors (200L)
- Probability reduces further with more components and more safety (SupA2KO-LV)
- **We are now adding empirical data from LV production cells, starting on Step 1a: genome x gagpol recombination….**

Empirical detection of genome x gag/pol cassette recombination

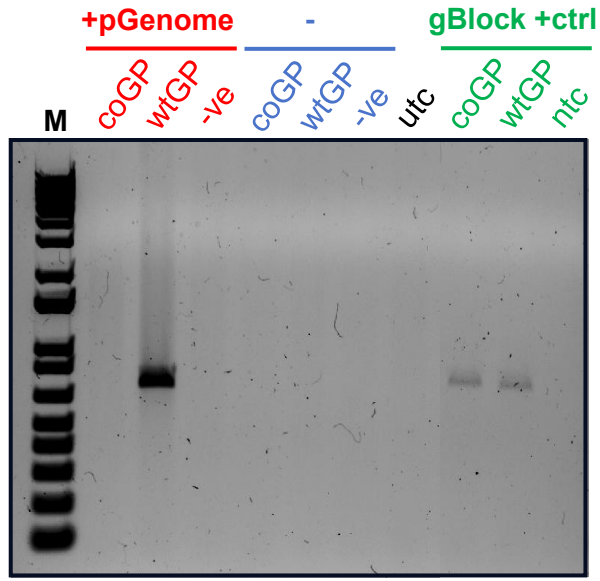
A comparison of wild type HIV-1 vs codon-optimised gag/pol in HEK293T cells

coGP has minimal homology to genome



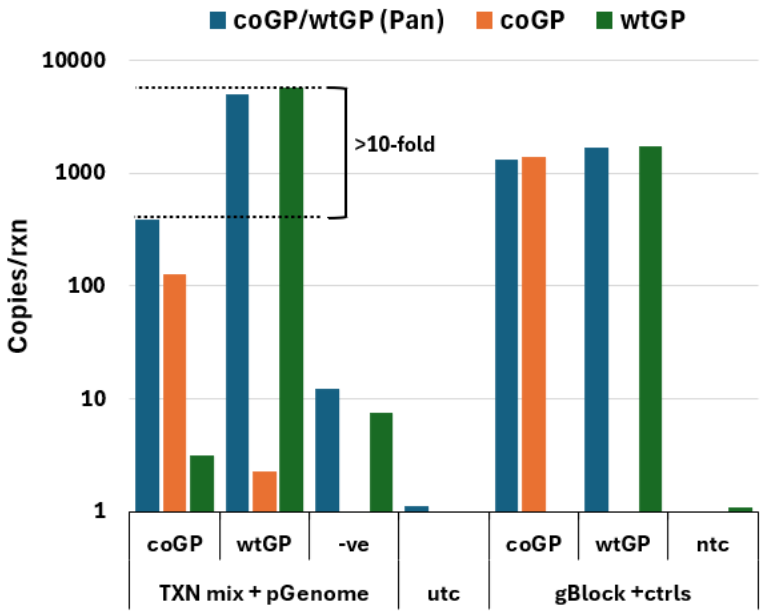
- wtGP shares Gag and RRE regions with genome
- coGP has minimal homology

LTR-Psi-Gag ddPCR product analysis



- Gel analysis of pooled ddPCR products
- Genome x wtGP recombination detected

LTR-Psi-Gag ddPCR outcome



- ddPCR analysis show >10-fold lower signal for Genome x coGP
- Use of coGP strengthens case for reduced RCL testing

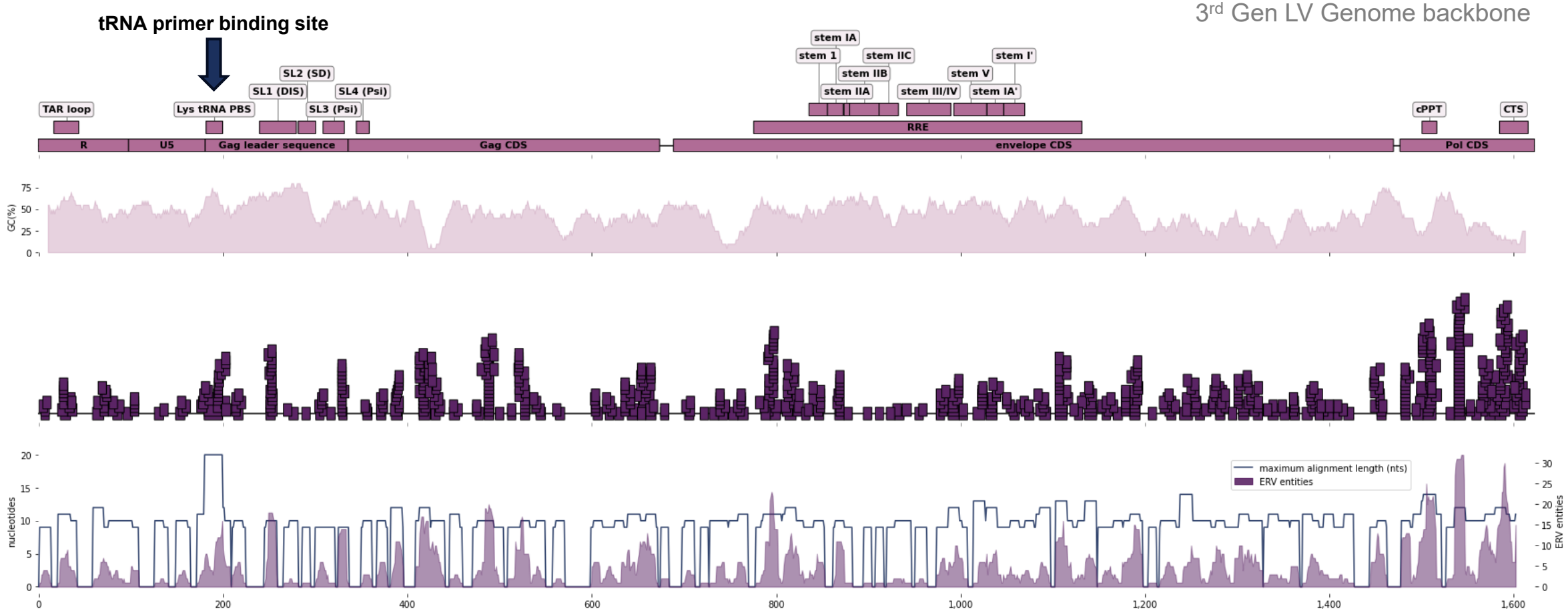
➢ **Data indicates our predictions genome x wtGP recombinants per cell to be very close to reality (within 2-fold).**

➢ **Total pDNA is closer to our assumed transcriptionally active number (i.e. over-conservative)**

Data from Jordan Wright

Assessing risk from human endogenous RVs (hERVs)

Recombination risk from hERVs appears low



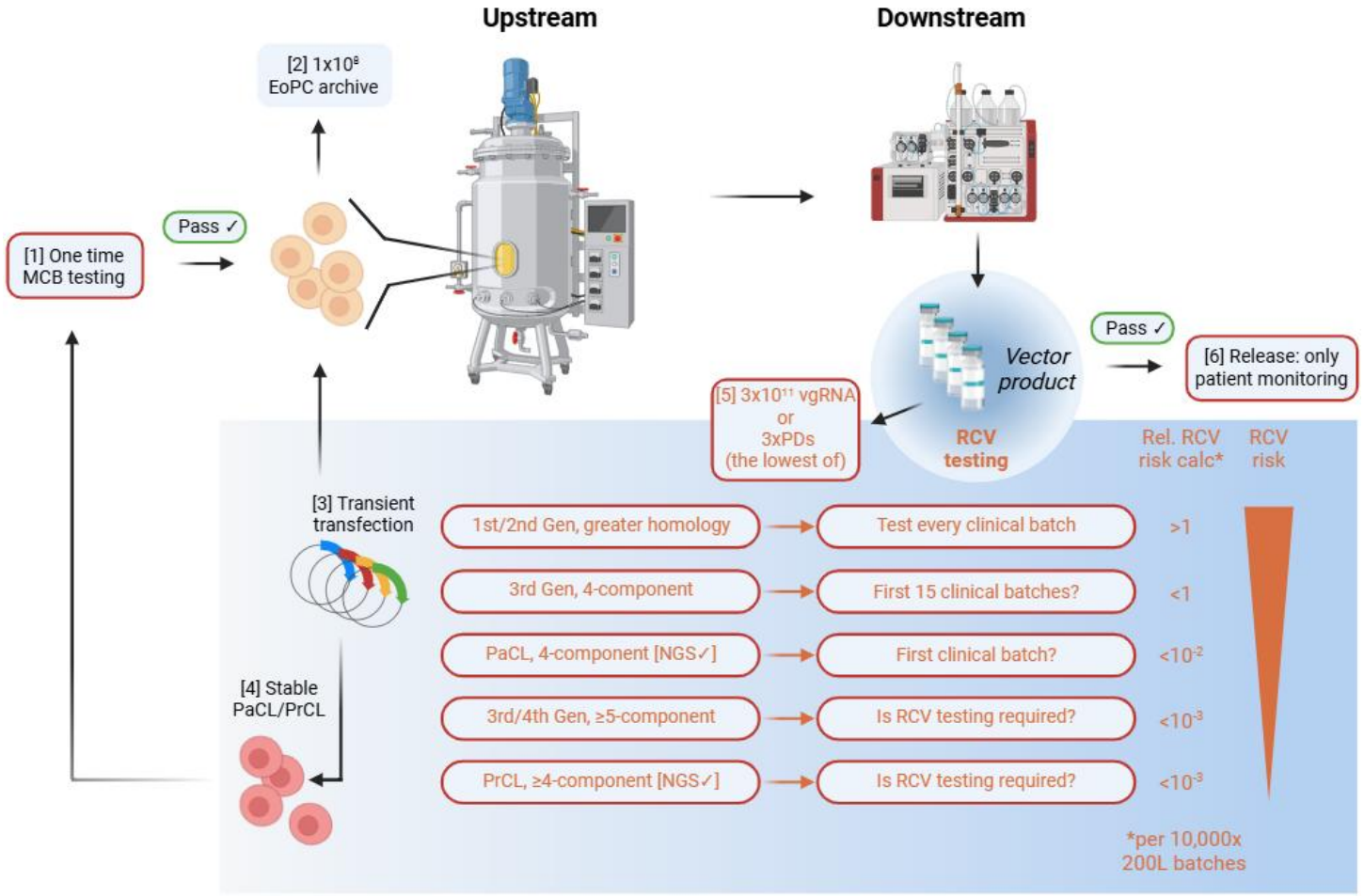
- Nucleotide alignment with **HERVd** database sequences (containing >0.5m endogenous HERV sequences) identified **HERV-K entities** as sharing greatest unbroken sequence homology with LV genome (~20 nts)
- Homologous alignments appear to cluster with **PBS**, **RRE** and **cPPT/CTS** regions

Data from Charles Moore-Kelly

Using the model to justify reduced RCL testing

A roadmap driven by data and probablistic + logical arguements

Review article



Considerations for a roadmap to reduced / no testing

1. No more EoPC testing (archive cells only)
2. No testing of *ex vivo* modified cells (already close)
3. Fixed amount testing: 3-5x10^{11} vgRNAs?
4. Fixed-and-finite testing? Only initial batches? 1-in-10 batches?
5. ≥5 components systems: only a supplementary assay?
6. PaCL and PrCLs: single, one-off testing?

Launching the RADAR network

RCV **A**ssay **D**evelopment, **A**lignment & **R**egulation: consensus from the census

↑ **Join RADAR** ↑

1. **Connecting stakeholders from all parts of the industry**
   SMEs, Sponsors, CROs/CDMOs, Regulatory-advisors
2. **Surveys & feedback**
   Opportunity to feedback on the idea of the roadmap, RCL model, own experience and our surveys
3. **Sign-up for latest information**
   OXB feedback from surveys and progress
4. **Opportunity to input on navigating the regulatory pathway on RCL testing**
   If reduced testing is justified, how and who drives the change?

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OXB booth #1331
Come chat further, sign-up to RADAR, take the survey, get connected.

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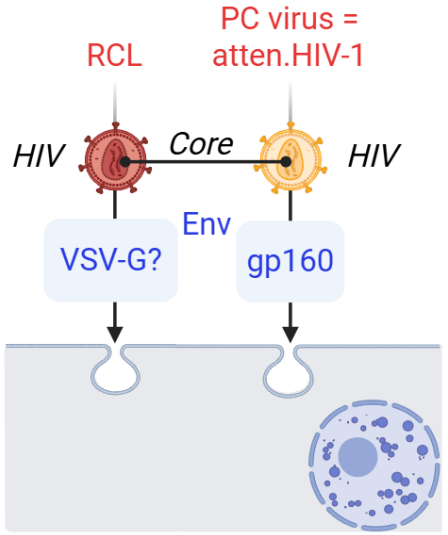
Developing an RCL assay: no longer plug-and-play?

Beyond VSV-G; how bespoke, retargeted envelopes may bottleneck RCL testing

Review article

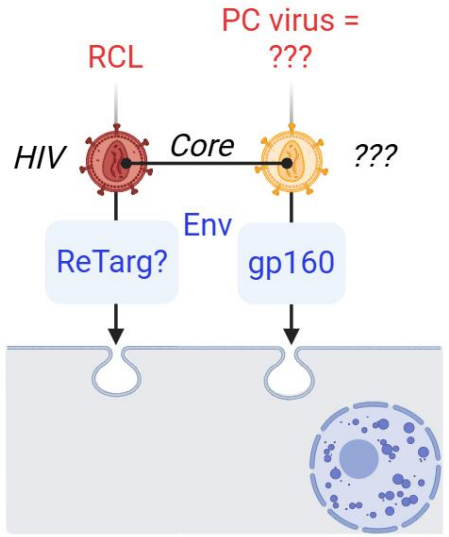
Amplification cell and PC virus choices in Development

LV/VSVG (off-the-shelf)



C8166 cells

Retargeted LVs



C8166? cells + receptor

↑Essential properties↑

Desirable properties

Bespoke RCL assay = Development bottleneck?

Client 1	*Development (12+ mths)*	*Qual (6 mths)*	*Batch testing*
Client 2	*Development (12+ mths)*	*Qual (6 mths)*	*Batch testing*
Client 3	*Development (12+ mths)*	*Qual (6 mths)*	*Batch testing*
Client 4	*Development (12+ mths)*	*Qual (6 mths)*	*Batch testing*
Client 5	*Development (12+ mths)*	*Qual (6 mths)*	*Batch testing*

Considerations for the CRO/CDMO, clients and the LV field regarding capacity

- Number project client batches?
- Number bespoke assays do you need to develop?
- The present solution is to amplify expensive RCL lab footprints
- Client expectation versus the reality of CRO/CDMO capacity.
- Competitive edge: non-viral platforms don't need any RCL testing!

➢ **Is this burden of testing justified?**

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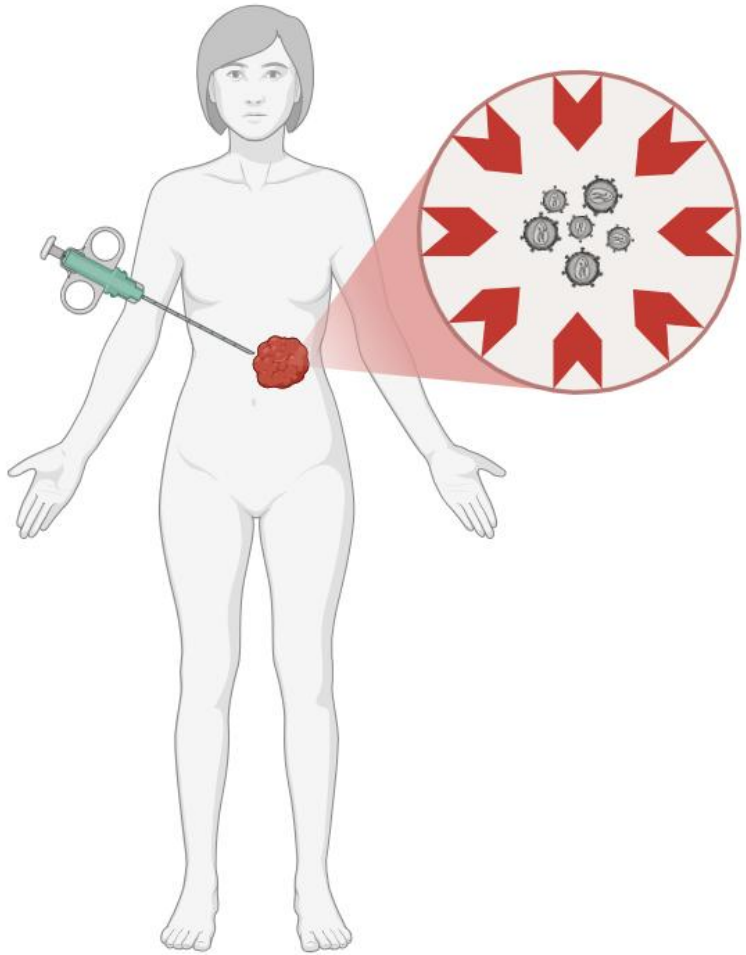
What would we expect if an RCL was administed to a patient?

Reasonable inferences from what we actually know about HIV-1 and oncolytic RVs



Administration to patients

- **Highly unlikely** that a **minimal RCL** would be able to **replicate efficiently**
- Minimal RCL will **not encode accessory genes**: innate **restriction factors** will **block replication**
- No known strains of HIV-1 isolated from infected humans that **lack nef** lead to **pathogenic disease**
- **Vif and Vpr** expression are highly correlated with **lytic HIV-1 infection** of primary T-cells
- Minimal RCL will 'look' more like a simple RV like MLV: **MLV does not replicate in humans**
- MLV-based replicating **oncolytic RVs** (e.g. Toca 511) were injected into tumours (**no RCR testing was performed**, because they *are* replication-competent by definition!).
- Basis for **oncolytic RV safety** was in-patient 'containment' to tumour environment, relying on somatic tissue's **innate immune response** and slower cell division.