YOUR RELIABLE BIOSAFETY PARTNER, WE BRING NEAR-BY SERVICE CLOSER TO YOU

Detection of Replication Competent Lentivirus

Lentiviruses belong to the Retroviridae family, including a variety of pathogens (such as HIV, SIV, EIAV, etc.). By splitting the replication relative elements into different packaging plasmids and using a self-inactivation (Self Inactivation) constructed recombinant lentiviral vector. The gene delivery system has been successfully applied to the production of genetically modified cell therapy products.

Biosafety risks of Lentiviral vector in production and clinical applications:

- Production of replication-competent lentiviruses through recombination during the manufacturing process.
- Recombination with endogenous lentiviruses in clinical applications.
- Tumors caused by random insertion events in target cells.

Therefore, regulatory requirements demand the detection and control of biosafety risks that may be brought by replication-competent lentiviruses during the production and clinical application of recombinant lentiviral vectors.

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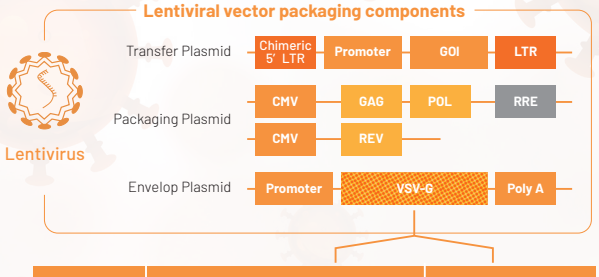
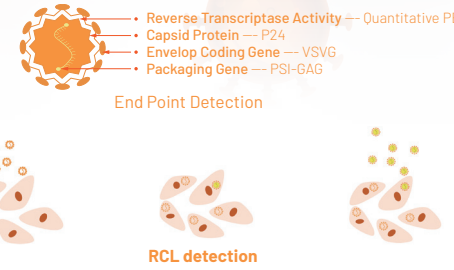
- Safety - Comprehensive Solutions for biosafety testing
- Efficiency – Automatic process empowering testing capabilities
- Compliance - Meet the requirements of different regulatory systems
- Scientific - Rigorous customization solution capability



Envelope type	Original	Recognition receptor
VSV-G	Vesicular Stomatitis Virus	LDL-R
BaEV	Baboon Endogenous Retrovirus	ASCT-1 & ASCT-2
RD114	Endogenous Feline Virus	ASCT-2
GALV	Gibbon Ape Leukemia Virus	GLVR1

BRC Biotech provides customized development of new enveloped RCL detection.



Mode of production	EOPC*	Viral vector	Post-transduction cells
Transient transfection	Lot testing	Lot testing	Lot testing

* RCR in vector production lots was not always consistently detected in both vector supernatant and EOP cells.
** Recommend each lot of *ex vivo* retroviral transduced cells be tested for RCR. Recommend archiving a sample for at least 6 months after the product expiration date. Recommend retaining a sufficient amount of the cell product to perform RCR testing in the future if necessary.

RCL detection

- Detection of Replication Competent Lentivirus in EOPC
- Detection of Replication Competent Lentivirus in Supernatant (C8166 co-culture and Quantitative Reverse Transcriptase Activity Assay)
- Detection of Replication Competent Lentivirus in Transduced Cells (C8166 co-culture and Quantitative Reverse Transcriptase Activity Assay)
- Rapid RCL Detection for Transduced Cell
- Integration Analysis with TLA-NGS

In a compliant biosafety level three laboratory, BRC Biotechnology has established and validated a replicating lentivirus detection using HIV-1 as a positive control. Additionally, we possess comprehensive capabilities for rapid RCL detection and clinical integration site analysis. For more information, please contact a BRC Biotechnology technical expert.

Reference

CHP	• 2017 Technical Guidelines for Research and Quality Control of Human Cell Therapy Products. • 2018 Key Considerations for Quality Control Testing, Research, and Non-Clinical Studies of CAR-T Cell Therapy Products. • 2020 "Technical Guidelines for Pharmaceutical Research and Evaluation of Gene Therapy Products (Draft for Comment)"
USP	• 2005, Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors • 2020, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) • 2020, Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry • 2020, Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry • 2022, Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (For comments)
EP	• 2005, Guideline On Development and Manufacture of Lentiviral Vectors • 2019, Guideline on Quality, Non-clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials • EP5.14 Retroviridae-derived Vectors for Human Use

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Detection of Replication-competent AAV

Recombinant Adeno-associated Virus (rAAV) can efficiently transduce exogenous genes and achieve long-lasting *in vivo* expression, and it has been successfully used in gene therapy for a variety of rare genetic diseases. Although rAAV is a replication-defective companion virus, the biological events of homologous/non-homologous recombination that may occur within the cell nucleus mean that the potential risk of producing replication-competent AAV (rcAAV) cannot be completely ruled out during large-scale preparation of rAAV. Therefore, in actual clinical applications, comprehensive and compliant safety testing of rAAV packaging cells, rAAV virus stock, and final rAAV products is required.

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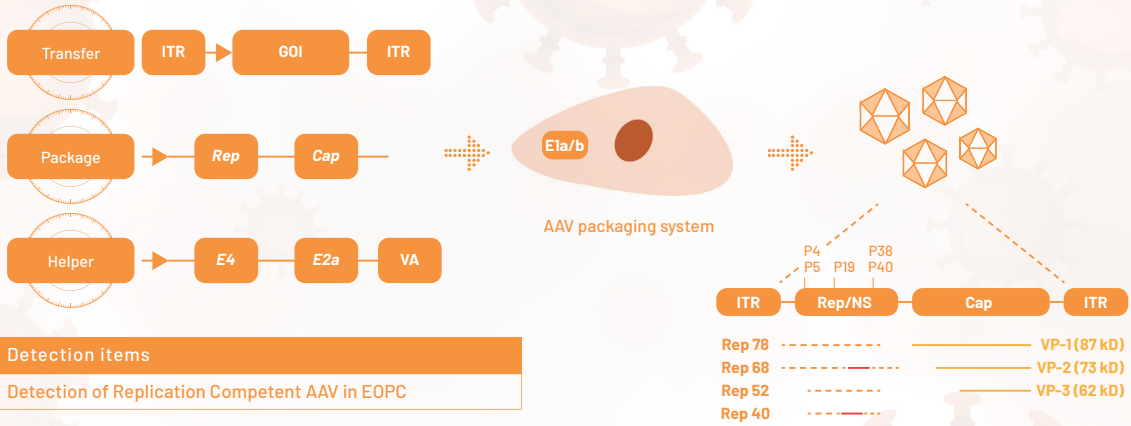
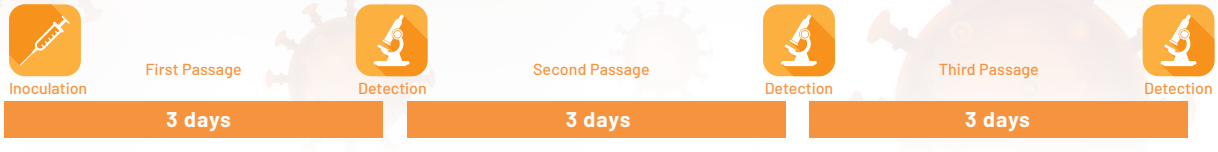


Detection items

Detection of Replication Competent AAV in EOPC



Detection and analysis of Rep2 gene in each passage.

Reference

CHP	• 2020 "Technical Guidelines for Pharmaceutical Research and Evaluation of Gene Therapy Products (Draft for Comment)" • 2020 Edition of the Pharmacopoeia - General Principles of Gene Therapy Products for Human Use. • 2021 "Technical Guidelines for Non-Clinical Research and Evaluation of Gene Therapy Products (For Trial Implementation)" • 2022 "Technical Guidelines for Pharmaceutical Research and Evaluation of In Vivo Gene Therapy Products (For Trial Implementation)"
USP	• 2008 Guidance for FDA Reviewers and Sponsors Content and review of Chemistry, Manufacturing and Control CMC Information for Human Somatic Cell Therapy Investigational New Drug Applications • 2020, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
EP	• EP5.14 Adeno-associated Virus Vectors for Human Use
ICH	• ICH Q5A (R1) Viral Safety evaluation of biotechnology products derived from cell lines of human or animal origin

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