Lentivirus Reference Standard Working Group Meeting

Location: Hilton Norfolk The Main in Energy, Third Floor, Norfolk, Virginia

Date: Tuesday March 6th 12:45 pm – 2:00 pm at 8th ISBioTech Spring Meeting.

Meeting notes

The Working Group (WG) Members that attended this meeting reviewed and discussed a previously distributed Request for Proposal for Lentiviral Vector Reference Material (LVV RM) Vector Production and Purification – RFP 1.0 (see attached).

Keith frame the discussion sharing previous experience with the development of an Ad5 vector Reference Standard Material

General comments:

In addition to Production and Purification, RFP1 contained requirements for Testing that seem to be extensive, including a comprehensive safety panel for release.

Some points made by attendees regarding RFP1.

- The material is not for patients, so safety testing could be part of the material characterization panel.
- Expect different titer values results from labs as they may have different 293 target cells
- Safety testing. Is adventitious agents testing needed?
- What would the minimum testing requirements for the organization offering production & purification be? Safety testing including RCL was the main candidate to be moved to the characterization RFP.
- Concerns around reducing testing for release of the Reference material included not knowing what the product quality is until characterization testing is performed.
- Around the need for Purity testing. The goal is to generate a material that is pure enough not to interfere with viral particle quantitation assays. The need for pDNA testing was brought up in case a transient transfection-based production process was proposed.
- Identity by the manufacturer could be performed by p24 ELISA instead of Western blot or sequencing as in RFP1.
- Requirements for titer (0.5-1x1-8 TU/mL in the final product) and number of vials (3000 vials) would be as in RFP1 as this was already agreed by the Working group in a previous meeting. However, the team brought up the possibility of shipping the bulk material for filling elsewhere. In this case, the titer assay would need to be repeated post vialing.
- Expectations for those donating the cell line and plasmids. Requirements for cell bank and pDNA concentration in vials requested for future productions were proposed and agreed upon: 10 million cells/vial and plasmid DNA 1 mg/ml. Both need to be well characterized and handled in separate RFPs. The number of vials requested should be reduced from 20 to 10. The remaining vials after production of the first Reference Material should be stored in a repository such as ATCC for future Reference Material production.
- The team wants to get away from prescribing the process, but rather meeting the specs.
- Future RFPs would include: Vialing, Repository, Cell Bank, Plasmids, Characterization testing, Consumables/Disposables and Long-term stability studies. Those activities would not be part of production. The content related to these activities should be removed from RFP1 or a clarification made.
- Production and vialing can occur at 2 sites. Concerns were raised as titer may change, but could be repeated post vialing.

- Concerns about being able to vial 3000 vials were reduced as robotic and automated systems can vial 1500 units/hour
- Concerns were raised by manufacturers regarding the scope of RFP1: produce, titer, fill, clean suites and give away protocols and material. Will we get enough bids?
- To these concerns, FDA members present at the meeting replied that being the producer of this Reference material puts your name out there, your vector is the standard and pointed out that in the small molecule industry, companies compete with each other to be the ones selected to manufacture the Reference material.
- In addition, it provides the advantage of not having to compare your product with another one generated by a process that is not yours. CMOs great candidates to participate in the bidding process for RFP1.
- The FDA standpoint for the development of this Reference Material is that they will encourage the use of it, but it will not be absolutely needed.
- Members of the working group were concerned that we are losing momentum and mentioned that this development should be the responsibility of the community using LVV. The community should be more proactive than reactive. Without this reference material we can't compare values between sites.
- The audience was reminded that 1) the process needs to be disclosed to be able to reproduce it for future reference materials and 2) no proprietary cell line could be used. There were concerns raised during the meeting regarding potential resistance to share information.
- To concerns raised regarding eventual changes in the manufacturing technologies with time, it was argued that this material represents a moment in time. The purpose of the material is to compare with new production systems.
- The working group reminded all that the intent is to have consumables and disposables donated to the producer of the material.
- NIBS is an excellent candidate to support vialing and storage for this reference material as they are currently involved in the generation of other reference standards for lentiviral vectors.
- Communication after the bidding process: team members suggested that more specific questions were posed to the working group going forward to attain better response rates, for instance by survey or during working group conference calls.