

## Meeting report series

### Report of the 3<sup>rd</sup> Teleconference of the WG on Biotechnology-derived products including cell & gene-based therapies

21 November 2014

#### Organization

Organized by: Scientific Secretariat

#### Participants

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#### Agenda

- ▶ Update
- ▶ Progress in the field
- ▶ Bottlenecks
- ▶ Next steps

## REPORT

### Update

Members of the WG received the report of the last meeting of the Therapies Scientific Committee (TSC) that was held on 6 October 2014. There was no feedback from the TSC as there was no teleconference of the WG since the previous TSC meeting. Members did not have any comment on the report.

Members were reminded that the purpose of the WG is to define bottlenecks and potential opportunities in the area of biological, biotechnology and gene-based therapies to provide recommendations to funder members of IRDiRC on what type of direction their future calls should go. It is an opportunity to consult with the expert field on what they think is funding opportunities at relatively short notice.

Members commented that area of research that needs to be funded will be different from a country to another country. The situation is very different in US, Canada and Europe in term of support for RD research. In Canada, at this point, the RD does not have any status; there is no special activity for RD research, it is much less advanced than the situation in Europe where RD program running in Europe has benefit in some of the field of RD such as neuromuscular, neurodegenerative and kidney field. Moreover, there is no IRDiRC process adopted worldwide on how to fund these things. All the different funding agencies participating to IRDiRC have their own scheme for funding.

The Chair of the WG also bring to the attention of the Scientific Secretariat that a list of projects in the field would help define gaps for funding. The lists previously received were rather difficult to read and digest.

### Progress/development in the field

Promising techniques:

- ▶ Clustered Interspaced Short Palindromic Repeats (CRISPR) is a gene editing technology in development that will allow correcting genes in iPS cells, a potential for better cell therapies.
  - ⇒ Field of genome editing (CRISPR, targeted transposon strategy, meganucleid, zinc-finger strategy) should be further developed.
- ▶ There is also a lot of interest for direct differentiation of cells, without reaching the stage of iPS cells.
- ▶ Adeno-associated virus (AAV) approach is promising
  - Local administration of an AAV vector carrying a transgene for the exon skipping led to a 40-60% expression of dystrophin in muscles of a canine model of Duchenne muscular dystrophy ([press release](#)). Clinical trials are expected to take place next year.
  - Genethon has another program using µdystrophin AAV approach. Toxicology study is planned for the next few months.

- In the field of lysosomal storage disorders, a clinical trial was launched last year using intracerebral AAV administration for Sanfilippo syndrome.
- ▶ In the field of siRNA, there is a clinical trial for Transthyretin amyloidosis (knockdown of transthyretin protein). Phase 1 results were published in 2013.
  - ⇒ RNA therapeutics is also a good approach for RD.

#### Progress in the field:

- ▶ A follow up study shows a long term expression of factor IX, 4 years after a single injection of AAV for gene therapy, in patients with hemophilia B (New England Journal of Medicine, 2014, 371:21).
- ▶ A recent article reported the long-term efficacy of modified gamma-retrovirus vector for X-linked severe combined immunodeficiency (New England Journal of Medicine, 2014, 371:15).
- ▶ Increasing the expression of jagged (jagged/notch pathway) in the muscle could have some benefit for many different muscle diseases. Dogs with a mutation in the jagged notch pathway were not as sick as other dogs without dystrophin. The mutation created a myogenin binding site for jagged molecules that caused an enormous enhancement in the generation of satellite cells (presentation at ASHG 2014).
- ▶ There is a phase 3 clinical trial in the field of blindness. Results are expected in the second half of 2015.

#### Bottlenecks

##### **Harmonization of some of the requirements around cell- & gene-therapies products between the US, the EU and Japan**

- ▶ A clear definition of what is a medicinal product in cell therapies would be of much help. In homologous re-implantation of cell transformed ex-vivo with plasmids and transposons (non viral gene therapy), depending on the agencies, either the transformed cells or the plasmid/transposon is considered as the medicinal product. Quality controls are very difficult to develop for transfected cells.
- ▶ Harmonization would also benefit the CMC process.
- ▶ Clinical trials with gene targeting and gene therapies are not evaluated in the same centers of regulatory agencies (Center for durgs/ center for biologics).
- ▶ Harmonization would facilitate international clinical trials as shown by the example of a gene therapy trial in which "harmonization" of the protocol across sites in US, Canada and the EU is being dictated by perceived regulatory requirements of FDA, Health Canada and the EU respectively, as the study moves into Phase 2.

Regulatory agencies are working with researchers, clinicians and patient representatives to provide input and guidance through participation/hosting of workshop. For example, report of such a workshop on translational and regulatory hurdles of developing Exon skipping for RD was published in Human Gene Therapy ([Link to PubMed abstract](#); [link to document for general public](#)). A workshop hosted by EMA on Exon skipping for Duchenne is scheduled on 29 April 2015 in London.

## Power of local Ethics Committees

Ethical approval of experimentation in children is a bottleneck that is aggravated by the power of local Ethics Committee that seems to have too much power to stop a clinical trial.

Members reported several examples where a clinical trial could not be conducted or was delayed for several months due to a refusal of the local committee when the clinical trials were already approved by regulatory agencies (EMA, FDA, Health Canada). This delays therapy development.

- ⇒ Problem is often in the interpretation of the law in different field (European/national; federal/ provincial). There is a need for harmonization of experimentation in children.

## Heterogeneity of patients

Heterogeneity of patient population can bias the outcomes of a clinical trial. Such heterogeneity can appear when too many patients are included in the trial (example of Duchenne clinical trial). However, compared to small size trial where heterogeneity can also be present, large size trials allow stratification analysis afterward.

## Placebo control in clinical trials

In some clinical trials, it is impossible to have a proper placebo control trial as patients receiving placebo are easily identifiable or giving placebo would not be ethical. For example, in a disease characterized by extreme sensitivity to sun-light, phase 3 clinical trial shows that administration of a pre-hormone reduces the pain level in patients exposed to more than 30 min daylight.

- ⇒ It is important to develop other readout than the p-value readout.

## Next steps

- ▶ Provide revised lists.
- ▶ Exchange by email on expertise and analysis on potential gaps in the area of biological, biotechnology and gene-based therapies.
- ▶ Organize a teleconference to finalize the analysis and reach a consensus

## WG Deliverables

- ▶ Consider the possibility to prepare more practical lists of research projects (Scientific Secretariat).