Clinical Trial Insight: cell and gene therapy

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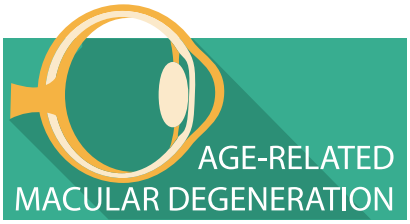
Dr Alexey Bersenev, Yale University, USA, providing an expert overview of the most important clinical trials, cases and cohort studies conducted in academic and industry with particular focus on later-stage efficacy data.



JAPANESE IPSC TRIAL SUSPENSION

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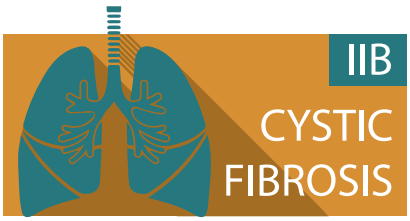
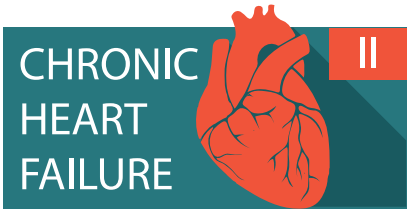
The most important news of this summer was a suspension of the first induced pluripotent stem cell (IPSC)-based clinical trial in Japan [1,2]. The trial, led by Dr Masayo Takahashi (RIKEN Institute), is assessing the safety of autologous iPSC-derived retinal pigment epithelium in age-related macular degeneration. The first patient was treated in September 2014 without any safety issues. While preparing the cell product for the second patient, some mutations were detected. The decision was made to not proceed with the second patient and to change strategy to partially matched, banked allogeneic iPSCs. Masayo Takahashi noted [3] that mutations were not the main reason for trial suspension, but rather a regulatory change, which came in effect after treatment of the first patient. While disappointing, this news could potentially have a big impact on the field.



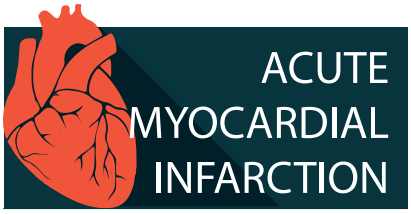
PHASE 2B CYSTIC FIBROSIS OUTCOMES

Results of a Phase 2 gene therapy trial for cystic fibrosis were published in the *Lancet Respiratory Medicine* [4]. The randomized, double-blind, placebo-controlled, Phase 2b trial [5], conducted in two UK centers, assessed non-viral *CFTR* gene therapy. The authors reported modest, but significant improvement in lung function in the experimental group over placebo. The team is now working on a follow-up study design.



MESOBLAST PUBLISHES PHASE 2 RESULTS

Australian stem cell therapeutic company Mesoblast Ltd, has published results [6] of their Phase 2 placebo-controlled trial, assessing allogeneic mesenchymal precursor cells in chronic heart failure patients [7]. The study included three cell doses (25, 75, or 150 million) groups of patients, randomized to receive cells versus placebo at a ratio of 15:5. The experimental treatment was safe and feasible (primary endpoints). As for efficacy, I interpret the results as mixed, because secondary endpoints were missed. In post-hoc analysis, however, the higher cell-dose group performed significantly better than controls. The authors concluded that "*high-dose allogeneic MPCs may provide benefits*". Larger or re-designed studies should be performed to conclude efficacy.



CHINESE CARDIAC TRIAL RESULTS

Another cardiac cell therapy clinical trial [8] conducted in China, yielded good results [9]. The randomized, placebo-controlled multicenter trial assessed allogeneic Wharton's jelly-derived (part of umbilical cord) mesenchymal stem cells in patients with acute myocardial infarction. 160 patients were randomized to cells versus placebo group at a 1:1 ratio. The 'cells' group significantly outperformed the placebo group, meeting efficacy endpoints.

PROMISING RESULTS FROM PHASE 3 TRIAL IN CROHN'S DISEASE

Belgian cell therapy company Tigenix announced preliminary results [10] of their Phase 3 trial assessing the efficacy of local injections of allogeneic adipose stem cells in Crohn's disease fistulas. The study met efficacy endpoints – moderate,

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but significant difference compared with placebo. In a population of 204 patients, "the combined remission rates at week 24 were 51.5% and 35.6%" for cells and placebo, respectively. This is a big event for the cell therapy industry, as for the first time Tigenix has demonstrated the efficacy of an allogeneic adipose-derived stem cell product in a Phase 3 trial. I'd like to draw your attention however to the very high remission rate (~35%) in the placebo group.

DISAPPOINTING OUTCOME FROM MACROCURE PHASE 3

Israeli-based company Macrocure announced preliminary results of their Phase 3 clinical trial using their cell product CureXcell in venous leg ulcers [11,12]. CureXcell is an allogeneic leukocyte product, which is injected directly into the skin wound. Although the results are preliminary, Macrocure states that "the study is not expected to meet its primary endpoint". This is very disappointing news.

ADAPTIMMUNE PUBLISH MYELOMA RESULTS

Immunocellular therapeutic company AdaptImmune published results of their myeloma trial [13,14]. Autologous T-cells were gene-modified with T-cell receptor recognizing cancer-testis antigens NY-ESO-1 and LAGE-1. Similar to CAR T-cell trials, TCR-modified T-cells engrafted and persisted in the bone marrow. T-cell persistence was observed in the majority of patients up to 2 years and was associated with good clinical response in 83% of patients.

POSTMORTEM ANAYLSIS PROVIDES INSIGHT INTO ALZHEIMER'S GENE THERAPY

A very interesting study, which cannot be missed, was published in *JAMA Neurology* [15]. This is an analysis of postmortem findings from Alzheimer's disease patients, who underwent experimental gene therapy treatment with nerve growth factor between 2001 and 2012. Brain pathology showed a response of degenerating neurons to growth factor stimulation evidenced by axonal growth. Though

the study does not provide any information regarding the efficacy of the experimental treatment, it does provide some insight into potential mechanisms of action of the gene therapy and the persistence of induced changes. Phase 2 of the trial is currently ongoing.

DISAPPOINTING EFFICACY DATA FROM BELLEROPHON

Finally, I cannot overlook the very important regenerative medicine industry trial [16], which assessed efficacy of implanted acellular biodegradable matrix in heart failure. The trial, sponsored by Bellerophon Therapeutics, was conducted in 61 sites in Europe, Australia and North America and involved 303 patients. According company's press release, there was no difference with placebo [17].This the first big failure of a commercial regenerative medicine trial using biomatrix implantation. Bellerophon licensed Bioabsorbable Cardiac Matrix from BioLineRx in 2009 [18].

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