2009 Conference – January 23-25, 2009
Summary Report - Task Group 5 *- revised*

Task Group Challenge:

With the ultimate goal of improving vision of those with atrophic AMD, develop a plan for development of a stem cell product that could first come to clinical trial in the short term (as a proof of principle), and one (or more) that would ultimately be more effective, but may come to trial in a longer time frame.

Task Group Members:

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Science Writer's Summary Report:

by Alissa Poh

This group was charged with drawing up development plans for two stem cell products – one in the near future, as a proof of principle; the second and longer-term challenge- a form of therapy ready for efficacy testing in clinical trials, Each research project would ultimately contribute to improving vision in individuals with atrophic AMD.

The discussion opened with group members outlining several major goals of stem cell therapy for this disease. Chief among these goals was the regeneration of diseased Bruch's membrane through engraftment; another was using stem cells as a source of neurotrophic growth factors to protect the retina from further degeneration.

Therapy in four years – or less

Concerning a short-term stem cell product, the group felt that their best move would be to utilize the trophic support that such cells are capable of providing. Since the task group guidelines included suggestions of various stem cell-types that might be exploited for this purpose, the merits of each were debated early on. The group felt that final selection of stem cell-type(s) should be based on trophic factor measurement, and recommended three types of stem cells as current priorities: undifferentiated postnatal retinal stem cells; embryonic stem cells (ESCs) partially differentiated toward retinal pigment epithelium (RPE) cell or photoreceptor lineage; or induced pluripotent stem (iPS) cells, also partially differentiated toward RPE cells or photoreceptors.

The group proposed carrying out an initial safety trial in patients with advanced retinitis pigmentosa (RP), the rationale being that these patients, compared to those with advanced geographic atrophy (GA), have far more limited vision and would thus pose a lower risk/benefit ratio, in the event of unexpected adverse effects. Safety signals, or end points discussed by the group included teratoma development, antibody production in response to stem cell trophic factors, inflammation, further loss of visual acuity, and other local complications such as retinal necrosis, or hemorrhage. If this initial trial were to demonstrate reasonable safety, it could then be taken to the next level, using volunteers with advanced GA as the patient population, with end points similar to those of the first study. The overall goal here would be to monitor patients for approximately two years or less, ensuring safety.

A spirited discussion ensued on delivery methods for these stem cells, with the group considering both intravitreous and subretinal injections of cell suspensions, as well as encapsulating the cells, before abandoning these techniques as being considerably more invasive than implanting a single, sheet-like layer of cells into the subretinal space.

Looking ahead

Moving beyond trophic support and protection of the microenvironment in AMD, the group turned its focus to

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longer-term stem cell therapy that might ultimately repair and replace a patient's diseased Bruch's membrane. They outlined a step-wise approach for this process.

First, post-mitotic RPE cells (derived from one of the suggested stem cell sources) would be injected on a biodegradable polymer. A group member recommended using polycaprolactone (PCL) – shown to be well tolerated in the eye – and nanotexturing, or making tiny modifications to the polymer's surface. Following this, photoreceptor precursors would be implanted on a second piece of polymer, and both would then be combined in a newly-engineered outer retina that could be slipped beneath the retina, through a retinotomy or retinal incision.

Since the diseased Bruch's membrane found in patients with AMD would likely mar the effectiveness of any stem cell therapy, the group agreed that it might be necessary to first "till the garden," rehabilitating the membrane and creating a more permissive environment that would allow proper stem cell engraftment. The group suggested using remote laser therapy on Bruch's membrane, several months prior to implanting a new outer retina, as one possible way of remodeling this area of the eye.

The group also agreed that this approach of slipping a polymer-based sheet of stem cells beneath the retina, while less traumatic than injecting cell suspensions, would still be more invasive than one would like. An ultimate goal, then, would be figuring out a way to deliver these cells in a liquid form that would proceed to self-assemble in its final destination.

Sound check – assessing the end points

The group turned to optical imaging for this purpose, recommending the use of autofluorescence to measure the size of a patient's atrophic zone, by imaging for the presence of lipofuscin, a substance in RPE cells that fluoresces green at a wavelength of 550 nM. They also suggested using optical coherence tomography (OCT) to examine cross-sections of the retina, which would confirm the presence or absence of photoreceptors, as well as enable measurement of cone outer segment length, which degenerates as AMD progresses.

A group member brought up the idea of using adaptive optics to measure the survival of photoreceptor cones. This technology is relatively new, and it enables visualization of single retinal cells in the living eye, through the use of a deformable mirror that compensates for imperfect vision, uniquely adapting to individual eye differences. In terms of measuring cone sensitivity, microperimetry was discussed as a potential subjective test: the patient would be placed in a system that flashes light on specific areas of the retina, generating a sensitivity map.

As well, the group discussed a variety of in vitro tests for the engineered outer retina, their longer-term stem cell product. These included assessing the new retina for its ability to synthesize rhodopsin and other components of the phototransduction cascade, as well as examining its fine structure through electron microscopy. The retina's reactivity to light could also be tested via calcium imaging. One another point of assessment would be the ability of RPE cells in the newly-engineered retina to phagocytose cone outer segments, which are regularly sloughed off and would otherwise contribute to the accumulation of drusen, if uncleared.

Other considerations

The group spent some time discussing how nanomedicine might be exploited to improve their proposed stem cell therapy, and decided that it would be best used as a means of delivering additional trophic factors to keep stem cell grafts healthy. As well, since it would be very important to be able to track these cells in patients, via fluorescent tags or some other non-invasive method, the group wondered whether nanomedicine could play a role in this regard. There was, naturally, some debate around whether it would ever be possible to put labeled cells in humans, but the group chose to temporarily suspend disbelief and imagine that there would be a workable solution in the future.

Additionally, the group talked about potentially deriving iPS cells from skin fibroblasts of individuals with AMD, and

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differentiating these into RPE or photoreceptor cells that might once again form a diseased Bruch's membrane. As such, they could then assess in vitro the process by which this occurs, which could provide a window into the development of AMD. But they also acknowledged this to be only a theoretical possibility, for now, since a disease as complex and multifactorial as AMD could well be cell autonomous.

In conclusion, since no good animal models exist for the purpose of studying AMD – current knowledge indicates that, besides humans, only some birds of prey and specific primates possess a macula – the group concluded that, although hardly ideal, some of the necessary studies in preclinical models would have to be carried out using other types of retinal degeneration. Hence the rationale, at least in part, for moving into clinical trials relatively soon, as long as things look safe, because it's likely that the most pertinent answers to this disease will be found through human studies.

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