SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

BIOPHARMA

Engineered human alveolar-like macrophages as a cell therapy for respiratory diseases

BACKGROUND

In recent years, directed differentiation of pluripotent stem cells (PSCs) has become a major focus of regenerative medicine to help address the shortcomings of pulmonary therapeutics or transplantation. Specific efforts have focused on endoderm-derived lung epithelium tissue regeneration, while mesoderm-derived tissues in the lungs, such as non-circulating hematopoietic lineages, have received minimal attention. This oversight in pulmonary stem cell regenerative medicine has led to a failure to appropriately address the importance of the innate immune system of the lungs, particularly its most abundant population of airway cells, the alveolar macrophage (AM). This cell type is an environmentally-adapted phagocytic macrophage, unlike those of other tissues.

Currently, there are inadequate therapeutic options for a variety of major respiratory diseases, including: bronchopulmonary dysplasia, RSV, COPD, and bacterial infections due to cystic fibrosis. Many of these diseases result from prolonged inflammatory states and compromised innate immunity leading to further tissue damage and infection. Bolstering the immune system could provide acute therapeutic relief and promote positive health outcomes in paediatric populations.

DESCRIPTION OF THE INVENTION

The Post lab has developed an *in vitro* differentiation protocol whereby human embryonic stem cells can be differentiated into human alveolar-like macrophages (hALMs) in xeno-free media (seeder/feeder independent). The protocol that was originally developed from murine PSCs (mPSC) has been successfully translated to human PSCs. AMs are highly phagocytic cells of the pulmonary innate immune system that represent the primary hematopoietic cells of the airways.

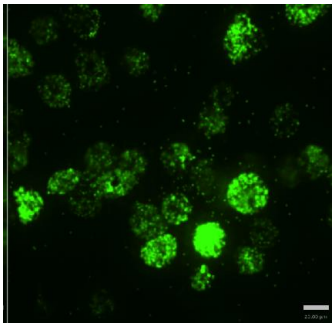

Fig 1: Internalization of GFP-expressing bacteria by hALMs

Their identity was phenotypically confirmed via co-expression of F4/80:CD11c:SIRPalpha and functionally characterized by their ability to phagocytose (Fig 1) and to remain functionally active in healthy, injured and injury-resolving mouse lungs without an obvious compromise in immune response. Furthermore, the mPSC-AM remained viable in

KEYWORDS
Pluripotent stem cells, alveolar macrophages, lung, cell therapy, respiratory diseases

culture for several months using expansion and maintenance media. Following xeno-transplant, hALMs did not appear outside the lungs after 2 weeks and did not elicit T-cell response, showing potential for allogenic and autologous transplants (Fig 2).

	Week 1	Week 2
Spleen	NS	NS
Thymus	NS	NS
Airways	ND	ND

Fig 2: CD4 and CD8 Tcell detection after 1 and 2 weeks following intratracheal hALM administration in mice.

COMMERCIAL APPLICATIONS & ADVANTAGES

This invention is a platform technology which permits the ex-vivo generation and transplant of hALMs that can be engineered to express several factors which become active in the lungs and has the potential to treat several respiratory illnesses.

- hPSC-AMs as a cell therapy tool: treatment with exogenous macrophage may mitigate the pathophysiological effects and/or progression of genetic or acquired lung diseases, including pulmonary alveolar proteinosis, cystic fibrosis, adenosine deaminase deficiency, infectious diseases, or chronic obstructive pulmonary disease (COPD).
- Robust model with human translation: mPSC-AMs have been extensively characterized phenotypically and functionally, *in vitro* and *in vivo*, and protocol has been successfully translated to human PSCs.

DEVELOPMENT STAGE

In vivo work evaluating hALMs therapeutic effect on RSV, BPD etc. are ongoing.

PATENT STATUS

- US 2017/0335282 A1: “Alveolar-like macrophages and method of generating same” – allowed in the US and Europe
- US Patent Application No. 62/825352: “Method of generating haemangioblasts” filed March 28, 2019

IP&C is seeking venture capital investment to create a company and/or a strategic partnership with a pharmaceutical company to complete the development and commercialization of the hALMs.

LEAD INVENTORS:
Dr. Martin Post, PhD, Senior Scientist, Translational Medicine, The Hospital for Sick Children

LICENSING CONTACT:
Konrad Powell-Jones, Director of Business Development, Tel. 416.813.7654 ext. 309572, konrad.powell-jones@sickkids.ca
IP&C Ref. | RDLP 1175