

Mechanism of Tissue Engineered Small Intestine Formation

Grant Award Details

Mechanism of Tissue Engineered Small Intestine Formation

Grant Type: New Faculty II

Grant Number: RN2-00946

Project Objective: To generate a Tissue Engineered Small Intestine (TESI) and test efficiency and reproducibility of TESI formation in a mouse model
They overall objective is to engineer large and small intestine from human progenitor cells for the treatment of short bowel syndrome.

Investigator:

Name:	Tracy Grikscheit
Institution:	Children's Hospital of Los Angeles
Type:	PI

Disease Focus: Intestinal Disease, Metabolic Disorders, Pediatrics

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: \$3,211,122

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Reporting Period: Year 4

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Reporting Period: Year 5

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Grant Application Details

Application Title: Mechanism of Tissue Engineered Small Intestine Formation

Public Abstract: Short Bowel Syndrome is an expensive, morbid condition with an increasing incidence. Fundamental congenital and perinatal conditions such as gastroschisis, malrotation, atresia, and necrotizing enterocolitis (NEC) may lead to short bowel syndrome (SBS). NEC is the most common gastrointestinal emergency in neonates and primarily occurs in premature infants. As rates of prematurity are increasing, so are the numbers of children with SBS and NEC. In addition, prevalence is increased for other diagnoses such as gastroschisis, which has nearly doubled. Medical and surgical treatment options carry high dollar and human costs and morbidities including multiple infections and hospitalizations for vascular access, liver failure in conjunction with parenteral nutrition-associated cholestasis, and death. Small bowel transplant has a reported 5 year graft survival of 48%, but is attended by rejection, the morbidity of major surgery, and a lifelong need for anti-rejection medication. A report on 989 grafts in 923 patients by the Intestine Transplant Registry reveals improving outcomes, but one year graft/ patient survival rates are 65%/77%. Tissue engineered small intestine (TESI) offers a potential alternative durable autologous therapy that avoids the problems of donor graft supply for intestinal transplant and long term immunosuppression. TESI exactly recapitulates native intestine histology. All four epithelial lineages are seen in conjunction with a lamina propria, nerve elements, and muscularis mucosa. OU, when reduced to single cells or the single cell fraction obtained in the purification of OU do not form TESI. This multicellular OU transplantation strategy is distinctive in producing full-thickness TESI that recapitulates all the layers of native intestine, and in the Lewis rat, intact function. In order to meet regulatory requirements and to guarantee the best chance of success by optimizing all conditions, we must define the necessary and sufficient progenitor cell population that will be transplanted. In addition, defining the mechanisms by which TESI forms and therefore can be impelled will underpin the best chance of success in human trials. This grant proposal seeks to identify and surpass the barriers to using TESI as a human therapy for SBS.

Statement of Benefit to California: Short Bowel Syndrome is an expensive, morbid condition with an increasing incidence. Fundamental congenital and perinatal conditions such as gastroschisis, malrotation, atresia, and necrotizing enterocolitis (NEC) may lead to short bowel syndrome (SBS). NEC is the most common gastrointestinal emergency in newborn babies in California and primarily occurs in premature infants. As rates of prematurity are increasing, so are the numbers of children with SBS and NEC. In addition, more babies in California are getting SBS associated with other diagnoses such as gastroschisis, which has recently nearly doubled. Medical and surgical treatment options carry high dollar and human costs and children suffer from problems such as infections and hospitalizations for vascular access, liver failure, and death. The only therapy currently is small bowel transplant, but a recent study showed that the transplant only has a 65% chance of surviving in the first year, and the child has only a 77% chance of surviving that same year. We need to give these children a better future measured in decades. Tissue engineered small intestine (TESI) offers a potential therapy. This would come from the patient's own cells, and therefore would avoid the problems of finding a donor for small bowel transplant, and also would not require life-long medicine for immunosuppression as children must take who have had a transplant. In this proposal, we seek to identify and surpass the barriers to using TESI as a human therapy for SBS. This would benefit the children of California as well as the field of Regenerative medicine as these advances might also help with further somatic stem cell-based therapies to treat a wide range of problems for both children and adults.

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