2018 Virtual Regenerative Medicine Symposium

Hosted by BCRegMed and the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research of University of Southern California Keck School of Medicine

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October 11th 2018

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Contents:

BCREGMED

Agenda for the Day

9:00am-9:15am	**Registration and Coffee**		
9:15am-9:40am	**Welcome and Introductions**		
	Fabio Rossi (BCREGMED) Andrew McMahon (USC)		
9:40am-10:50am	**Theme 1: Stem Cells, Development & Disease**		
	15 mins	Pamela Hoodless	Epigenetic mechanisms regulating enhancer switching during hepatocyte differentiation
	15 mins	Min Yu	Circulating tumor cells as a "liquid biopsy" to inform mechanisms of metastasis
	10 mins	Joanna Smeeton (Crump Lab)	Arthritis and regeneration of the zebrafish jaw joint
	10 mins	Tracy Tran (McMahon Lab)	*In vivo* developmental trajectory informs in vitro differentiation of pluripotent stem-cell derived podocytes
10:50am-11:00am	**Break**		
11:00am-12:10pm	**Theme 1: Stem Cells, Development & Disease (continued)**		
	15 mins	Liam Brunham	Understanding mechanisms of chemotherapy-induced cardiotoxicity using patient-specific induced pluripotent stem cells
	15 mins	Qilong Ying	Understanding embryonic stem cell self-renewal
	10 mins	Ido Rafaeli (McNagny Lab)	Podocyte mutagenesis at distinct developmental time points during kidney organogenesis lead to different disease phenotypes
	10 mins	Jennifer Grants (Karsan Lab)	Loss of miR-146a links inflammaging with myeloid malignancy
12:10pm-1:10pm	**Lunch & Digital Poster Viewing**		
1:10pm-2:05pm	**Theme 2: Stem Cell and Tissue Engineering**		
	15 mins	Peter Zandstra	Engineering Development

	15 mins	Leonardo Morsut	Engineering cells with synthetic signaling pathways: A new way to control cell behaviors, from cell therapy to stem cell reprogramming
	10 mins	Mitch Bramm (Kieffer Lab)	Precise creation and correction of a neonatal diabetes-causing KATP-channel mutation in human iPSCs
2:05pm-2:40pm	**Theme 3: Chemistry and Translation**		
	10 mins	Ben Van Handel (Evseenko Lab)	Discovery and pre-clinical development of small molecule modulators of IL-6 family cytokine signaling
	15 mins	Michael Bonaguidi	Genomics-driven translation for human epilepsy
2:40pm-2:50pm	**Coffee break**		
2:50pm-3:50pm	**Theme 3: Chemistry and Translation**		
	15 mins	Michael Underhill	New genetics tools for investigating the fate and function of mesenchymal progenitors
	15 mins	Stephanie Willerth	3D bioprinting personalized neural tissues
	15 mins	Rong Lu	Tracking Hematopoietic Stem Cell and Leukemia Cell Clones in Mouse Models
3:50pm-4:50pm	**Poster Judging/Happy Hour**		
4:50pm-5:00pm	**Closing Remarks**		

Speaker Affiliations

Welcome and Introductions:

Fabio Rossi Professor, Department of Medical Genetics, UBC; Director, Biomedical Research Centre, UBC; Scientific Director, BC Regenerative Medicine Initiative

Andrew McMahon Director, Chair and W.M. Keck Provost Professor of Stem Cell Biology and Regenerative Medicine, and Biological Sciences, the Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research, USC

Presenters/Session Chairs:

Theme 1: Stem Cell and Organ Development

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Theme 2: Stem Cell and Tissue Engineering

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Leonardo Morsut Assistant Professor, Stem Cell Biology and Regenerative Medicine, Biomedical Engineering, Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC

Mitch Bramm PhD Candidate, Kieffer Lab, Diabetes Research Group, Laboratory of Molecular and Cellular Medicine, UBC

Theme 3: Chemistry and Translation

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Michael Bondaguidi Assistant Professor, Stem Cell Biology and Regenerative Medicine, Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC

Theme 4: Novel Technologies

T. Michael Underhill Professor, Department of Cellular and Physiological Sciences, UBC

Stephanie Willerth Associate Professor, Biomedical Engineering, Department of Mechanical Engineering, UVIC; Canada Research Chair in Biomedical Engineering

Rong Lu Assistant Professor, Stem Cell Biology and Regenerative Medicine, Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC

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 # 09

High-Throughput Analysis of Cell Mechanical Response Using A Stretchable 3D Cell-laden Microgel Array

Kabilan Sakthivel, Grant Sonnenberg, Lukas Stracovsky, Justin Shim, Mark Verhalle, Andrew Reed, Homayoun Najjaran, Mina Hoorfar and Keekyoung Kim

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Cells *in vivo* are subjected to various mechanical stimuli from their microenvironment that include shear stress, cyclic mechanical strain and the stiffness of the extracellular matrix. These microenvironmental mechanical cues play a crucial role in regulating cell fate and function. Cell responses to externally applied strain field and matrix stiffness have been well studied in the past. However, most of these studies involve two-dimensional (2D) *in vitro* cell culture models which fail to approximate the *in vivo* physiological conditions. Cell behavior in three dimensions (3D) differs completely from that in 2D . Hence, it is crucial to study the cell responses to mechanical stimuli in a 3D environment. 3D miniaturized cell culture platforms have been generated using microarray bioprinting technology, however number of studies that evaluate the effects of mechanical cues on cellular microarrays remain meager. Recently developed platforms for screening the effect of mechanical cues in 3D neither offer high throughput nor evaluate multiple mechanical cues. To address this need, we report a deformable high throughput platform with easy fabrication steps that allows 3D dynamic stretching of cell-laden biomaterial microarray constructs.

The platform is based on the bio-printed cell-laden gelatin methacrylate (GelMA) microgel array on an elastic polymer membrane substrate that is later dynamically stretched to screen cell response. The substrate was fabricated by bonding a polyacrylamide (PAA) gel pad to a polydimethylsiloxane (PDMS) membrane using benzophenone. As PAA is hydrophilic, a fluoropolymer solution (Fluoropel) was spin coated on the PAA pad to turn its surface hydrophobic so that the printed GelMA droplets form the well-defined 3D structure. The strong covalent bonding between PAA and GelMA still existed despite the Fluoropel treatment which by itself had no role in bond formation. To test the feasibility of our approach, the GelMA prepolymer solution, containing a photoinitiator (VA-086) and green color dye, was printed as a droplet array on the substrate. Simultaneous crosslinking using a blue laser diode enabled the formation of microgel array. Strain transmission over 90% was also confirmed by measuring the displacement of the fluorescent microparticles embedded within the printed GelMA microgels when the PDMS membrane was stretched with 10% strain.

Fibroblasts-laden GelMA droplet microarray was printed on the substrate, which was then statically cultured as a control group. Live/dead assayed cells printed within microgels showed over 90% viability right after printing and 7 days culturing. Cell attachment and elongation were observed using F-actin and nuclei fluorescent staining. These results demonstrate that our developed platform favors high cell viability and allows to form a 3D cellular network within the GelMA microgels. The substrate printed with the cell-laden microgel array will be subjected to 10% strain at 1Hz for 3 days using a customized uniaxial stretcher. The cell alignment and cell

proliferation within the 3D microgels will be examined and compared between the stretched and non-stretched groups. Our platform can also be used to screen different biomaterials that support cell growth (especially the differentiation of stem cells) in the presence of mechanical cues for tissue engineering and regenerative medicine applications.

#10

On-chip Generation, Photocrosslinking, and Filtration of Uniform Microscale Cell-laden Hydrogel Spheroids

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In the recent years, several microfluidic techniques have been utilized to fabricate cell-laden photocrosslinkable hydrogel microdroplets. However, most of techniques relied on the ultraviolet light for crosslinking hydrogels and strong centrifugation for filtering oil that affected low cell viability. In addition, several rounds of off-chip centrifugation steps required relatively long duration, making the throughput very low for practical applications. Here, we present an integrated platform for the on-chip generation, photocrosslinking and filtration of cell-laden gelatine methacryloyl (GelMA) microgels.

The platform consists of three main parts: a flow-focusing junction, a photocrosslinking chamber, and an oil filtration unit. Design parameters the chamber, such as the lengths of the diagonal and each side, was optimized by computational simulation to obtain sufficient travel time of the GelMA microdroplets from entering to exiting the crosslinking chamber. The platform was fabricated by applying photolithography and softlithography methods. GelMA prepolymer was synthesized from porcine skin gelatin. NIH 3T3 mouse fibroblast cells were mixed with GelMA prepolymer solution and the VA-086 photoinitiator that can be initiated by a 405 nm laser beam illuminating over the crosslinking chamber to crosslink the GelMA prepolymer. The prepolymer-cell mixture was injected as the disperse phase into the continuous phase of oil to form droplets. After crosslinking, the microgels passed through the filter unit of the device where they were washed out from the oil.

These combined approaches resulted in a cell viability of around 85% at day 1 and was maintained throughout the 5 days. Cell elongation and 3D tissue network structure resulted in that the cells were integrated well with the GelMA hydrogel microstructure and exhibited a characteristic of polarized, polygonal morphology.

The analyzed cell viability and 3D tissue structure demonstrate that the developed platform is capable of fabricating highly viable, uniform cell-laden hydrogel spheroids that can be used for a variety of tissue engineering applications.

 # 11

Engineering Neural Tissue from Human Pluripotent Stem Cells Using Novel Small Molecule Releasing Microspheres

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Here a novel technique for engineering neural tissue consisting of motor neurons by combining human induced pluripotent stem cells (hiPSCs) with small molecule releasing microspheres is demonstrated. First, the small molecule purmorphamine (puro) was successfully encapsulated into poly ε-caprolactone (PCL) microspheres using a single emulsion oil-in-water (o/w) method for the first time with an efficiency of (84% ± 2.12%). These microspheres released 91 ± 1.7% of the encapsulated puro in a controlled fashion over 46 days. Puro microspheres, along with previously characterized retinoic acid (RA) releasing microspheres, were then incorporated into hiPSC aggregates to engineer neural tissue. This combination of puro and RA microspheres promoted hiPSC differentiation as indicated by the expression of multiple neural markers, including the neuronal marker β-tubulin III (βT-III), and the transcription factor Olig2 (7.69 ± 8.38 %) on day 28. These tissues expressed the motor neuron marker HB9 (24.85 ± 4.51 %) on day 35, and the mature motor neuron marker ChaT (12.35 ± 4.17 %) on day 60. These engineered tissues can be used for regenerative medicine applications such as treating spinal cord injury (SCI), disease modeling, and drug screening.

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PDGFRα expression is down-regulated by TGF-β signaling in Mesenchymal Progenitor Cells

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Mesenchymal Progenitor Cells (MPCs) are essential for tissue repair and regeneration. These stromal fibro-adipogenic progenitors (FAPs) are also responsible of skeletal muscle and heart fibro-fatty deposition under acute or chronic damage. PDGFRα is a classical marker of these cells and have been involved in MSCs fate regulation. Our aim was to study whether TGF-β signaling regulates PDGFRα expression in MSCs. The isolation through FACS of different MSCs populations from muscle allowed us to determine that PDGFRα expression is strongly reduced by TGF-β1 in FAPs, Hic1^{+} progenitors, and two different fibroblastic cell lines. Also, TGFBRI kinase activity and p38 MAPK pathway participates on this regulation. Moreover, PDGFRα immediate early genes (IEG) expression is altered during skeletal muscle regeneration and after TGF-β1 treatment as determined by RNAseq analyses from FAPs and corroborated by qPCR. Furthermore, PDGFRα promoter analyses showed putative transcription factor-binding sites related to TGF-β signaling, and Biogrid-based PDGFRα interactions network analysis suggest that PDGFRα and TGF-β signaling pathways cross-talk. Altogether, these data demonstrate for the first time that TGF-β signaling pathway regulates PDGFRα canonical marker for MSCs.

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 # 13

Deletion of podocalyxin in mature kidney podocytes leads to progressive renal failure and phenocopies human focal segmental glomerulosclerosis.

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The CD34-related sialomucin, podocalyxin, is the most abundant cell surface glycoprotein of kidney podocytes. Previous studies in mouse and human have shown it plays a critical role in morphogenesis of podocyte precursors and development of the urinary filtration apparatus, and that in its absence, both mice and humans die perinatally from anuria and hypertension. Despite this, its functional significance on mature, terminally differentiated podocytes remains unknown. Here we employ conditional deletion from differentiated podocytes to show that podocalyxin is essential to the maintenance of foot process architecture and appropriate targeting of slit diaphragm proteins. Its loss from mature podocytes leads to all the major hallmarks of focal segmental glomerulosclerosis and proteinuria, and eventual death in adolescence. These data suggest two critical roles for podocalyxin in podocytes, the first in facilitating the appropriate morphogenesis of podocyte precursors and the second in maintaining foot process integrity and urinary filtration in mature podocytes once morphogenesis is complete. Because shedding of podocalyxin in the urine is a common feature of several nephrotic syndromes, these data also suggest its loss from mature podocytes is a functional hallmark of disease progression and a therapeutic target for intervention.

 # 14

Idiopathic Pulmonary Fibrosis mechanism exploration using a combination of MDCT, microCT, histology and next generation sequencing

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RATIONALE

Since little is known about the pathogenesis mechanism of Idiopathic Pulmonary Fibrosis (IPF), there is no treatment to intervene the progression of the disease. This project aims to identify the potential mechanism of IPF pathogenesis by integrating MDCT, microCT, histology and next generation sequencing analysis on the identical fibrosis lung tissue.

METHODS

Explanted lungs from patients with IPF and unused donor control lungs were inflated with air and frozen solid. Each frozen lung specimen was scanned with CT, and cut into serial slices from apex to base. Cores of lung tissue removed from these slices were scanned with microCT at -30°C. Following microCT, cores were fixed with alcohol based formalin at -4°C, embedded, and cut into serial sections for histology and next generation sequencing (NGS) profiling. The results of MDCT, microCT, histology and NGS would be integrated to explore the changes in fibrosis samples and further explore the potential pathogenesis mechanism of IPF.

RESULTS

MDCT scan discriminated the minimal and established fibrosis cores. Based on following microCT scan, terminal bronchiole is destructed right from the minimal fibrosis stage, which is different from the previous cognitions that airways are not destructed in IPF. Histological data illustrate that the infiltration of distinct immune cells, including CD4 T cells, CD8 T cells, and B cells, are significantly infiltrated in IPF cores. The NGS RNA seq offers the expression level of distinct genes. The integrative analysis of NGS RNA seq and disease related index, such as Ashcroft score and Picro sirius red staining, identified a group of genes that have strong association with the pathogenesis of the disease. These genes are enriched in the functions, such as wound healing, regulation of immune system, apoptosis and epithelial development.

CONCLUSIONS

Terminal bronchioles of IPF patients were badly destroyed. Both the histological and expression profiles illustrate the activation of immune response in IPF lungs, which is further supported by the activation of immune related pathways, such as TGFbeta, NFkB, TLRs and immune-check-point genes related pathways. These pathways might be promising therapeutic targets or biomarkers of IPF on the basis of their expression patterns in IPF samples.

 # 15

Activation of fibro-adipogenic progenitors plays a key role in cardiac pathologies

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Others and we identified a population of multipotent mesenchymal progenitors (fibro-adipogenic progenitors; FAPs) resident in the heart that expresses platelet-derived growth factor receptor alpha (PDGFRα) and stem cell marker Sca-1. These cells respond to damage by marked proliferation and differentiation at the injury site.

In the present work, we identify the transcriptional repressor Hic1 as a novel marker of FAPs in the heart and show that, PDGFRa+, Sca-1+, Hic1+ cells are multipotent mesenchymal progenitors while the PDGFRa+, Sca-1-, Hic1- cells are the more differentiated fibroblasts.

Using lineage tracing with Hic1 Cre^{ERT2} or PDGFRaCre^{ERT2}/tomato, we found that FAP fate was injury model-dependent. In ischemic injury, FAPs differentiated only along the fibrogenic lineage to a phenotypically distinct Sca-1- fibroblast population responsible for the formation of fibrous tissue replacing damaged myocardium. We investigated this fibrogenic differentiation hierarchy by performing single cell RNA sequencing on healthy and infarcted cardiac tissue. We found that a new PDGFR+ population that was highly enriched with fibrogenic genes only emerged after damage.

On the other hand, in non-ischemic injury as in arrhythmogenic cardiomyopathy (AC), an inherited disease characterized by fibrofatty infiltrations and ventricular arrhythmias, FAPs generated intramyocardial adipocytes as well as fibroblasts, leading to fibrous/fatty lesions.

Interestingly, FAP activation in the absence of damage, by deletion of Hic1, was *per se* sufficient to produce a cardiac phenotype that mimicked AC in humans. Additionally, breeding a murine AC model with Hic1 KO mice resulted in a markedly accelerated AC phenotype. Finally, pharmacologic inhibition of FAP differentiation significantly improved cardiac function and mitigated remodeling post injury. This suggests that, *independent of cardiac damage*, activation of FAPs is a key pathogenic event that could be targeted for treatment of cardiac pathologies that involve fibrosis or fibrofatty lesions.

 # 16

Pericytes: novel insights about their heterogeneity in adulthood from mouse to human

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The World Health Organization reports that cardiovascular diseases are the number one cause of death globally. Surgical revascularization is the most common intervention, however, not always successful or achievable. The mesenchymal stem cells (MSCs) therapeutic potential has been explored as an alternative or adjuvant angiogenic therapy, which aims at growing new blood vessels in the ischemic tissue. However, the results of individual trials involving MSCs are rarely in agreement. We believe part of this confusion stems from the underappreciated heterogeneity of mesenchymal progenitors. In fact, our results indicate that at least two distinct cardiac-resident perivascular mesenchymal progenitors reside in the heart: multipotent fibro/adipogenic progenitors, which generate new matrix and modulate inflammation; and pericyte likely involved in regenerative angiogenesis. Despite the richness of proposals regarding the embryonic origin of pericytes in different organs, much less is known about how pericytes are maintained and spread along growing vessels in adulthood. We tackled this performing Single Cell Sequencing on murine cardiac-pericytes purified based on a marker suggested by previous studies. The cluster analysis revealed two subgroups, one of which was associated with mature pericytic genes, and the second with progenitor-like genes. We took advantage of novel tracing systems we generated to address the relation between these pericyte subpopulations after myocardial infarction. We found that the putative progenitors increased the expression of mature pericytic markers and underwent proliferation more efficiently than the mature pericytes. Same results were obtained in murine skeletal muscle. Interestingly, we confirmed this pericyte-heterogeneity in human adipose, cardiac, and skeletal muscle tissue. Ongoing experiments both in mouse and human will address the therapeutic potential of the novel pericyte-progenitors we described.

 # 17

The recapitulation of human embryoid bodies *in vitro* using embryonic stem cells to study early human development

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Stem cells hold great promise in regenerative medicine because of their pluripotent nature and self-renewal capacities. Notably, human embryonic stem cells (hESCs) have the ability to self-organize into embryoid structures observed in early human development. This inherent ability of hESCs to perform tissue level organization needs to be further understood in order to improve tissue engineered products and applications. Early human embryogenesis is a highly ordered process with many complex steps governed by multiple genetic factors. These critical processes are difficult to study directly in human embryos due to practical and ethical reasons. In early development, the first round of differentiation occurs through spatial cues, but it is not clear how the second round of differentiation occurs. More specifically, it is not understood how the inner cell mass (ICM) differentiates and segregates into the epiblast and hypoblast layers. Afterwards, the epiblast cells go on to create all the tissues and organs of the adult human body. As these early stages of human development are the first to create the adult human tissues and organs, these stages are the logical place to turn to for a means of repair and regeneration. Studies performed in mouse embryos show that the mouse ICM cells decide their fate first and then organize into the epiblast and hypoblast layers. It is hypothesized that the human ICM cells also pre-determine their fate prior to segregation. Current results show that embryoid bodies made from multiple hESC lines organize into the epiblast and hypoblast layers as seen in early development. These studies were performed using size controlled embryoid bodies that were fixed and visualized through immunohistochemistry. The next objective is to visualize this organization occurring in real time. A better understanding of these complex processes is an essential step in harnessing the full potential of stem cells to advance the field of tissue engineering and human development.

 # 18

Tissue-resident PDGFRa+ Fibro-adipogenic progenitors with inherent osteogenic potential are the source of heterotopic lesions

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Heterotopic ossification (HO), in which bone forms in soft tissues outside of the skeleton, can arise as a result of many different conditions including genetic mutations, CNS injuries, hip arthroscopy, severe burns, or large traumatic injuries. Mesenchymal progenitors have been suggested as the source of these heterotopic lesions, however their identity and origins have remained controversial. Further, in patients suffering from large traumatic injuries resulting in HO, the trigger for osteogenic differentiation remains unknown. Our lab previously identified tissue-resident PDGFRa+ fibro-adipogenic progenitors (FAPs) that provide trophic support during muscle regeneration and hypothesized they may have a role in the development of ectopic lesions. Using an rh-BMP2 induced model of HO and an endogenously regulated inducible PDGFRaCreERT2 lineage tracing model, we show that PDGFRa+ FAPs are the source of ectopic lesions. Using a parabiosis model, we further demonstrate that these ectopic lesions arise from existing tissue resident PDGFRa+ FAPs, and not from circulating bone marrow-derived progenitors. Lastly, we demonstrate that beyond the administration of exogenous BMPs, PDGFRa+ FAPs have inherent osteogenic potential that can be triggered after muscle damage. Using a CCR2 knock-out mouse model in which inflammatory responses are impaired, we show that after muscle damage, the altered inflammatory milieu can lead to the expansion of PDGFRa+ FAPs and their expression of osteogenic genes that results in the formation of heterotopic lesions. By identifying the cellular source and a possible mechanism for the formation of heterotopic lesions, we may provide new cellular and molecular targets for therapeutic interventions aimed at those suffering from or most at risk of developing HO after injury.

 # 19

Gelatin Methacryloyl-based Visible Light Stereolithography System for Multi-scale 3D Bioprinting

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In the present decade, tissue engineering research has become highly focused on 3D bioprinting of tissues. This focus is driven by the requirement of rapid and efficient fabrication of cell-laden scaffolds for application as high throughput assays and in-vivo models. The scaffolds fabricated with various 3D bioprinting methods can mimic the in-vivo microenvironment with varying degrees. Stereolithography has emerged as one of the significant bioprinting methods for rapid fabrication of complex 3D scaffolds supporting cell encapsulation. Most of the present system utilize UV light (UV-A, 365nm) for crosslinking the methacrylated hydrogel in presence of a phototoinitiator. Some systems also utilize near UV light (405nm) for crosslinking and fabricating the scaffold. Although, stereolithography bioprinting is faster than other common bioprinting methods, fabrication of human scale tissues can take long hours. Long duration exposure to UV and near-UV lights have been found to be harmful for cells and hence, there is a need to restrict the use of UV light for bioprinting. To address this need, we present a visible light based stereolithography bioprinting system using Gelatin methacryloyl (GelMA) and Eosin Y (EY-GelMA) operating within the visible light spectrum. Through systematic experiments, we developed the bioprinting system and compared it with the commonly use UV light based stereolithography system using Irgacure and GelMA. The cell viability is found similar for day 1 and day 6 for both systems. EY-GelMA exhibited more cell attachment and elongation on day 6. Further, we characterize our system by comparing mechanical properties and cell viability with the Irgacure-GelMA system (Irgacure 2959 as photoinitiator). In order to optimize the bioprinting process of the developed system, effect of GelMA and Eosin-Y concentration is examined on the mechanical strength and biocompatibility of the crosslinked EY-GelMA. Next, we investigate the time required for crosslinking of EY-GelMA for various concentration of Eosin-Y and GelMA in order to optimize the bioprinting process. Our observations for studying the effect of generated free radicals and the exposure light on the cell viability demonstrate significant decrease in cell viability for Irgacure-GelMA system in the presence of free radicals and UV-A exposure for a long duration (~1 hour). On the other hand, the EY-GelMA based visible light bioprinting system exhibited higher cell viability for long term exposure without any significant difference which points towards more feasibility and compatibility of the presented visible light stereolithography system for long duration bioprinting processes.

 # 20

The Anti-inflammatory Effect of Human Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome with Extracorporeal Membrane Oxygenation

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Background: Acute respiratory distress syndrome (ARDS) can be triggered by a variety of direct or indirect pulmonary insults, which is characterised by widespread inflammation in the lungs. Currently, the only effective intervention is limited to supportive care. Mesenchymal stem cells (MSCs) have recently demonstrated their pleiotropic immunomodulatory abilities to reduce lung injury in animal models. This study aims to investigate the combination of stem cell therapy and extracorporeal membrane oxygenation (ECMO) for the treatment of severe ARDS.

Methods: A total of 14 healthy sheep was randomly divided into two groups; ECMO only (n=7) or ECMO-MSC treatment (n=7). The injury was induced by intravenous oleic acid and intrabronchial *E. coli* lipopolysaccharide. Seven ARDS sheep were treated with ECMO support one hour after the injury criteria were reached. Seven ARDS sheep received a 3 x 10^8 cells/kg dose of mesenchymoangioblast-derived human MSCs intra-bronchially 2 hours after the injury, followed by ECMO support. The protein levels of four cytokines, IL1β, IL6, IL8, and IL10, were assessed through ELISA assays. While quantitative RT-PCR was performed to examine the mRNA expression of genes associated with the pathophysiological process of ARDS.

Results: The blood gas results indicate the successful development of ARDS in sheep. Our data suggest that in the broncho-alveolar lavage fluid, IL10 ($p = 0.025$) significantly increased while IL1β, IL6, IL8 concentrations declined ($p < 0.001$) over time. In addition, the gene expression of pro-inflammatory mediators matrix metalloproteinases (MMPs) and von Willebrand factor (vWF) was shown to be down-regulated in the MSC-treated sheep.

Conclusion: Our findings provide a beneficial evidence for the use of combined stem cell therapy and ECMO support on less inflammation in severe ARDS. Future studies will be warranted to further assess the anti-inflammatory potential of MSCs as a novel treatment option for the modern critical care.

 # 21

Loss of *miR-146a* links inflammaging with myeloid malignancy

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Background: Hematopoietic stem cells (HSCs) are specialized bone marrow cells capable of differentiation to produce all mature blood cell types and self-renewal to maintain the HSC pool. Both chronic inflammation and aging impair HSC function, with strikingly similar effects on HSC self-renewal, propensity toward myeloid differentiation, and cell cycle quiescence. Chronic low-grade inflammation in the absence of infection, or sterile inflammation, is a hallmark of aging termed "inflammaging". It is possible that HSC aging occurs by a process of inflammaging, but the underlying molecular mechanisms remain poorly understood. In this study, we demonstrated that loss of *miR-146a* is a common mechanism linking inflammation, HSC aging, and leukemic transformation.

Results: Previous research has shown that loss of *miR-146a* is sufficient to cause features of myeloid malignancy in mouse models; however, the effect of *miR-146a* loss on HSC function prior to the onset of overt malignancy remains poorly characterized. In the present study, we found that loss of *miR-146a* produces features reminiscent of HSC aging in young, undiseased mice. Specifically, loss of *miR-146a* in young mice expanded the immunophenotypic HSC pool but severely reduced the serial transplantation ability of HSCs, similar to reports in aging mice. Single-cell resolution analyses of HSC quiescence, stemness, differentiation potential, and epigenetic state revealed multiple characteristics of HSC aging in young *miR-146a* null mice. Intriguingly, *miR-146a* expression decreased significantly in HSCs isolated from aged wild type animals, suggesting that loss of *miR-146a* may be a driver of normal HSC aging. HSC aging in *miR-146a*$^{-/-}$ coincided with low-grade sterile inflammation, a hallmark of inflammaging. Transcriptome profiling of *miR-146a*$^{-/-}$ hematopoietic stem and progenitor cells identified interleukin 6 (IL6) and tumor necrosis factor (TNF) signaling as potential drivers of HSC inflammaging. Reducing inflammation mediated by IL6 or TNF restored *miR-146a*$^{-/-}$ HSC function in single-cell assays, and delayed the onset of myeloid malignancy-like disease in aging *miR-146a*$^{-/-}$ mice.

Conclusion: Our results support a model in which *miR-146a* promotes HSC inflammaging, leading to development of myeloid malignancy. Our findings provide direct evidence that inhibiting inflammation not only restores HSC function, but also reduces the predisposition to developing myeloid malignancy. As aging-associated disruption of the hematopoietic system is associated with pathogenic aging of non-hematopoietic organ systems, our findings may potentially have wider applications in ameliorating age-related disease.

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