QUEEN'S UNIVERSITY BELFAST | WELLCOME-WOLFSON INSTITUTE FOR EXPERIMENTAL MEDICINE

Queen's University Belfast
IENGAGE Program

MBRU

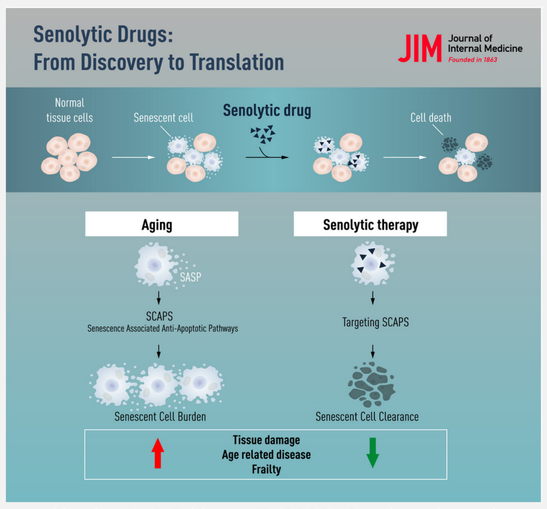
OBJECTIVES

6-week course comprised of:

- Daily seminars delivered by world-leading experts in the areas of immunobiology and microbes, vision and vascular medicine and respiratory medicine.
- Weekly roundtables hosted by PhD students and postdoctoral fellows, providing us with insights on their researches and their personal experience from their postgraduate programs.
- Each group was allocated with a supervisor whose role was to guide us through our research projects presented below:

Senolytics in Cardiovascular Disease; Systematic Review

Senolytics are a class of drugs that selectively clear senescent cells by inducing apoptosis that regulates senescence cells gene (BCL-2, p16, p53 and p21)



Kirkland, J. L., & Tchkonia, T. (2020). Senolytic drugs: from discovery to translation. *Journal of internal medicine*, *288*(5), 518–536.

METHODS

Reviewing articles published in 2020 and 2021 about senolytics targeting vascular and endothelial components of cardiovascular diseases.

RESULTS

Navitoclax	Inhibition of BCL-2 antiapoptotic protein
Dasatinib + Quercetin	Clearing cells positive for p21 (Cdkn1a) and alleviating renal dysfunction and damage

CONCLUSION

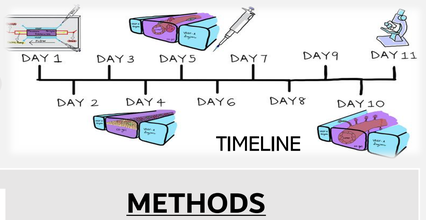
Senolytics represent a potential new treatment for age-related diseases, but more research is needed to facilitate translation into clinics.

A Novel in vitro model of Angiogenesis

Angiogenesis refers to formation of new blood vessels from preexisting vessels. Sprouting angiogenesis is initiated in response to a hypoxic environment by secreting proangiogenic growth factor called Vascular Endothelial Growth Factor A (VEGF-A)

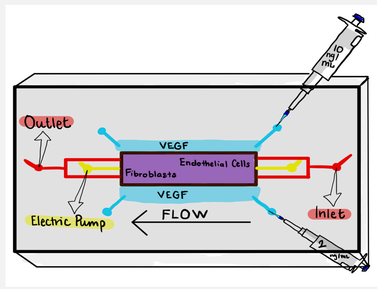
GOAL

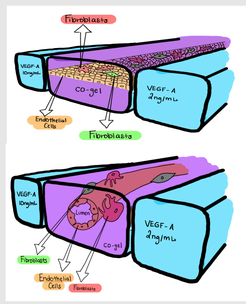
To create a model that represents in vivo conditions of angiogenesis in the presence of a parent vessel under VEGF A concentration gradient.



VESSEL ON A CHIP

scaffold engineering with microfluidics and co-culture



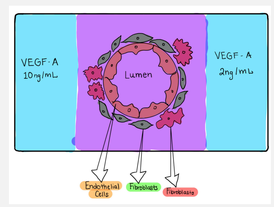


METHODS

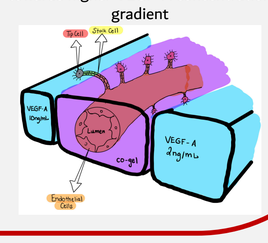
a. CHIP ASSEMBLY
The Chip is made from Polyethylene glycol (PEG)
b. Co-Culture
Endothelial cells are cocultured with fibroblasts on an extracellular matrix to aid in lumen formation and an electric pump is attached to create a flow of endothelial cells from the inlet to the outlet.
c. VEGF-A Gradient
Two syringes are used to add high (10ng/ml) and low (2ng/ml) concentration of VEGF-A, hence forming a gradient.

RESULTS

1. Establishing a parent vessel



2. Sprouting angiogenesis takes place towards higher VEGF-A concentration gradient



CONCLUSION

- The advantages (parent vessel, flow) of our proposed in vitro model- vessel on a chip will expand our current knowledge on how angiogenesis occurs in the human body.
- Secondly the model can also be used to replicate various disease conditions for example cancer and gain deeper insights about its angiogenic influence.

Blood-Retina-Barrier: Changes in Diabetic Retinopathy; Systematic Review

Blood-retina-Barrier (BRB) functions to maintain homeostasis in the retina to avoid entrance of blood-borne proteins, maintain metabolic + ionic gradients. BRB is divided into inner BRB (2/3rds of retina) and outer BRB (1/3rd of retina)
The earliest and most significant change in Diabetic Retinopathy is **BRB disruption/breakdown.**

RESULTS

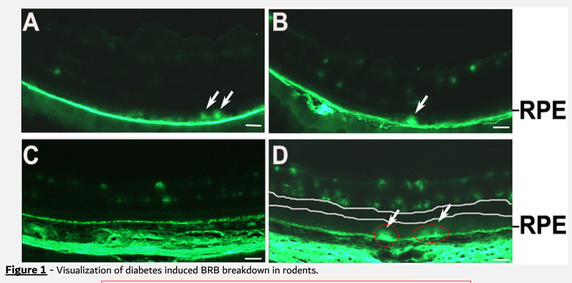


Figure 1 - Visualization of diabetes induced BRB breakdown in rodents.

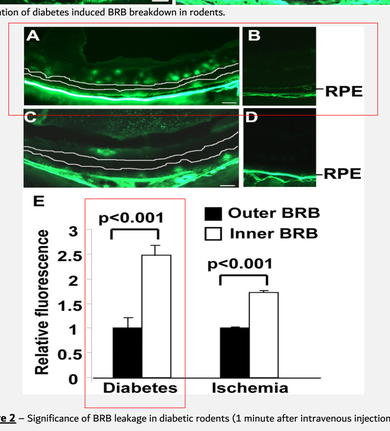


Figure 2 – Significance of BRB leakage in diabetic rodents (1 minute after intravenous injection)

GOAL

Visualize and evaluate outer vs inner BRB breakdown as a consequence of Diabetic Retinopathy. Determined via "BRB-specific leakage in diabetic rodents by fluorescent microscopy"

METHODS

Visualize and evaluate outer vs inner BRB breakdown as a consequence of Diabetic Retinopathy. Determined by systematic review of articles on "BRB-specific leakage in diabetic rodents by fluorescent microscopy"

CONCLUSION

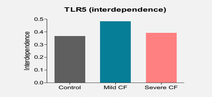
Fig. 1,2 show that FITC-dextran fluorescent dye leaked through outer BRB of DR rodents, suggesting blood-retina-barrier breakdown as a significant pathophysiological component of Diabetic Retinopathy.

REFERENCE:

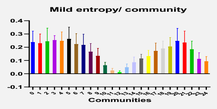
Xu, Hui-Zhuo, and Yun-Zheng Le. "Significance of Outer Blood-Retina Barrier Breakdown in Diabetes and Ischemia. Investigative Ophtalmology & Visual Science, 1 Apr. 2011.

AI derived gene networks to identify markers of phenotypical variability in Cystic Fibrosis (CF) inflammation

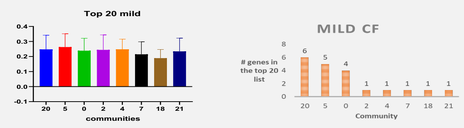
RESULTS



Entropy of the top 20 genes were calculated for each CF severity

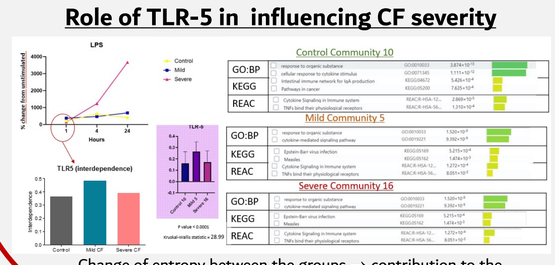


Significance of each community within Mild CF



Even though communities 20, 5, and 0 contained the majority of the 20 most significant genes, they were not more significant than other communities as a whole

Role of TLR-5 in influencing CF severity



Change of entropy between the groups → contribution to the network and phenotypic variability

GOAL

To identify patterns among the modifier genes within communities that influence the severity of cystic fibrosis

METHODS

1. Gene expression data is collected from CF primary nasal epithelial cells for the ΔF508/ΔF508 genotype with cystic fibrosis lung disease and controls
2. Self-supervised machine learning is applied
3. 10 RT² Profiler PCR Arrays (commercially available) to identify relevant inflammatory genes (total n=637 genes)
4. The top genes involved in the inflammatory networks in control, mild CF and severe CF are identified
5. Gene expression is confirmed using quantitative PCR
6. Bioinformatical analyses to gain further knowledge into the 'known' connection of these genes using pathways analyses g:profiler

CONCLUSION

	Network interdependence	Contribution to phenotypic variability	Epithelial gene expression
TLR5	High in mild CF	yes	Low but variable

CONCLUSION

- During iENGAGE we generated networks and links with students from all around the world, worked in groups on various projects and presented our results by the end of the program.
- The program aided in enhancing our presentation skills, scientific writing, critical thinking and teamwork spirit.

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