Diabetic Retinopathy:

Economic Evaluation and Cellular Functions

Julia Ho Yee, TING

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CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Julia Ho Yee, Ting

B Medical Science (Hons)

B Business

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Table of Content

CERTIFICATE OF AUTHORSHIP/ORIGINALITY ..... **ii**
Acknowledgement ..... **iii**
Publications arising from this thesis ..... **v**
Table of Content ..... **vi**
List of Figures ..... **viii**
List of Tables ..... **xi**
List of Abbreviations ..... **xiii**
Abstract ..... **xvi**

List of Figures

Figure 3.1: The Progression Of DR. 28

Figure 3.2: The Cohort Progression Of DR Over Time. 48

Figure 4.1: The Percentage Of Subjects In Sight Threatening Stage Of DR. 66

Figure 4.2: The Cost Effectiveness Analysis Plot For The Incremental QALY, Sight Year And Life Year Versus Incremental Costs. 72

Figure 4.3: The Cost Effectiveness Analysis Plot Of The Incremental QALY And Costs In Different Case Scenarios. 74

Figure 5.1: The Mechanism Of Prog-DR Test Prognosis. 88

Figure 5.2: The retina of a live streptozotocin-diabetic rats before (a) and after (b) stress drug application as imaged by slit lamp microscopy. 83

Figure 6.1: The water contact angle on different thin films. 106

Figure 6.2: Surface Roughness of Different thin films as measured by Root Mean Square (RMS) roughness (a) and average roughness (Ra) (b) 107

Figure 6.2: Atomic Force Microscopy images of glass coverslip (a), PSS (b), PAH (c), Ti (d), TiN120 (e) and TiN190 (f) thin films. 108

Figure 6.4: Cytotoxicity of 3T3-L1 (a) and HEK-293 cells (b). 109

Figure 6.5: The cytotoxicity (a) and viability (b) of SaOS-2 cells on different thin films as determined by PI assay (a) and Alamar Blue assay (b). 110

Figure 6.6: Proliferation of 3T3-L1 (a) and HEK-293 cells (b). 112

Figure 6.7: Proliferation of SaOS-2 cells. 113

Figure 6.8: The proportion of SaOS-2 cells at different stages of cell cycle 114

Figure 6.9: Morphology of SaOS-2 on tissue culture treated glass (a), PSS (b) and PAH (c). 115

Figure 6.10: The area (a) and length (b) of each individual SaOS-2 cell TCP, PSS and PAH terminating thin films. 116

Figure 6.11: The F-actin distribution of 3T3-L1 (a,b,c) and HEK-293 (d,e,f) cells on tissue culture treated glass (a,d), PSS (b,e) and PAH (c,f) coated surfaces. 117

Figure 6.12: The actin morphology of SaOS-2 on tissue culture treated glass (a), PSS (b) PAH (c), Ti (d), TiN120 (e) and TiN190 (f) 118

coated surfaces

Figure 6.13: The initial attachment of 3T3-L1 (a) and HEK-293 cells (b). 120

Figure 6.14: The initial attachment of SaOS-2 Cells as measured by PI assay (a) and Alamar Blue assay (b). 121

Figure 6.15: Adhesion of 3T3-L1 (a) and HEK-293 cells (b). 123

Figure 6.16: The Calcium Dependency of 3T3-L1 (a) and HEK-293 (b) Cell Adhesion on Different Surfaces. 124

Figure 6.17: Relative Collagen Production by 3T3-L1 (a) and HEK-293 cells (b). 125

Figure 6.18: Adhesion of SaOS-2 cells as measured by PI assay (a) and Alamar Blue assay (b). 127

Figure 6.19: Relative Collagen Production by SaOS-2 Cells. 128

Figure 6.20: The level of alkaline phospatase activity of SaOS-2 cells on different thin films as measured on day 10 130

Figure 6.21: The relative mineralisation of SaOS-2 cells on different surfaces. 131

Figure 6.22: The area (a) and number (b) of mineralised nodules produced by SaOS-2 cells on different surfaces 132

Figure 7.1: the Capsule Compression Equipment set-up. 167

Figure 7.2: The absorbance of polyelectrolyte thin films made in different pH environment and stained with 1% Coomassie blue. 171

Figure 7.3: Chitosan-cored Polyelectrolyte capsules with PSS (a) and PAH (b) as the starting coating material. 172

Figure 7.4: Collapsed polyelectrolyte capsules (a, b) and rods (c, d) made from chitosan cores with PSS (a, b) and PAH (b, d) as the start coating material. 173

Figure 7.5: Confocal images of FITC-dextran stained chitosan-cored polyelectrolyte capsules with PAH as the start coating material in PBS (a), after washing with 2% acetic acid (b) follow by 1% acetic acid incubation overnight (c). 174

Figure 7.6: Confocal images of Rhodamine stained walls of chitosan-cored polyelectrolyte tubes with PSS (a) and PAH (b) as the starting coating material. 175

Figure 7.7: Confocal images of FITC-dextran stained walls of chitosan-cored polyelectrolyte capsules with PSS (a) and PAH (b) as the start coating material. 176

Figure 7.8: The wall thickness of capsules with PSS or PAH as the start coating material. Wall thickness of capsules with PSS and PAH as the start coating material were measured on their optical sections. 176

Figure 7.9: Permeability of polyelectrolyte capsules as measured by the change in fluorescent intensity over time, of capsule with PSS and PAH as the start coating material. 177

Figure 7.10: Chitosan-cored PE-PAH capsule with CFDA-stained 3T3-L1 cells. 178

Figure 7.11: Chitosan-cored polyelectrolyte capsule auto-fluorescence in green (a) and red (b). 178

Figure 7.12: ESEM image of a polyelectrolyte tubes made from agarose cores seeded with RAW cells. 179

Figure 7.13: ESEM image of Polyelectrolyte tubes made from chitosan cores seeded with 3T3-L1 (a) and HEK-293 (b) cells. 179

Figure 7.14: ESEM image of polyelectrolyte capsules made from chitsan spheres (PAH as the starting PE), collapsing under vaccum (a) and seeded with 3T3-L1 cells in (b). 180

Figure 7.15: TEM image of 3T3-L1 cell on chitosan-cored PE-PAH capsule (a) and at higher magnification (b). 181

Figure 7.16: The force versus deformation graph of the PE-PAH capsule with the cores still intact, PE-PSS capsules, PE-PAH capsules and PE-PAH capsules in buffer. 182

Figure 7.17: The force versus deformation graph of the PE-PSS capsules, PE-PAH capsules and PE-PAH capsules in buffer. 183

Figure 7.18: The mean change in area over time of 3T3-L1 seeded polyelectrolyte capsules. 185

Figure 7.19: The actin distribution of 3T3-L1 cells in culture media (a) and post 20minutes exposure to 10μM Forskolin (b) and 10μM Cytochalasin D (c). 186

Figure C.1: The change in free intracellular calcium levels upon high potassium in retinal microvascular cells over time. 211

Figure C. 2: The change in free intracellular calcium levels upon 10μm Glibenclamide in retinal microvascular cells over time. 212

Figure E.1: The proportion of 3T3-L1 (a) and HEK-293 (b) cells at different stages of cell cycle 215

List of Tables

Table 3.1: Method Of Determining The Number Of Patients In The Cohort For Evaluation By The Markov Model. 32

Table 3.2: Lifestyle Characteristics Of Lean And Overweight Subjects. 34

Table 3.3: The Transition Probabilities For Non-Sight Threatening DR. 36

Table 3.4: The Transition Probabilities To Blindness From Different Stage Of DR. 39

Table 3.5: Transitional Probabilities To Death By Diabetes-Related Complications And Other Causes. 40

Table 3.6: The Quality Of Life Scores For Different Stages Of Diabetic Retinopathy. 41

Table 3.7: Cost Of Blindness. 45

Table 4.1: The Differences In Behaviour Of Diagnosed (With Prog-DR Test) And Non-Diagnosed (Without Test) Subjects. 62

Table 4.2: The Cost For Pre-DR Screening. 64

Table 4.3: Matrix Of The Scenarios Examined With Varying Compliance To NHMRC Guideline And Blood Glucose Management. 68

Table 6.1: Summary Of Studies On Cell Response To PSS And PAH Polyelectrolyte Thin Films. 97

Table 6.2: The Cell Density And Time Used In Propidium Iodide Assays. 102

Table 6.3: The Size Of Peaks On Different Surfaces As Measured By Atomic Force Microscopy. 107

Table 7.1: Characteristics Of Chitosan-Cored Scaffolds. 172

Table 7.2: Mechanical Strength Of Polyelectrolyte Capsules As Measured By Ultrasonic Treatment. 182

Table 7.3: The Least Square, Linear Regression Of Force Versus Deformation Data Of PE-PAH Before Core Dissolution, PE-PSS And PE-PAH Capsules And PE-PAH In HBS Buffer. 184

187

Table 7.4: Calculation Of The Force Exerted Per Cell To Reach The Level Of Deformation.

Table A.1: Univariate Sensitivity Analysis On Health Outcomes And Costs. 207

Table B.1: Summary Of The Percentage Change In Life Years, Sight Years, QALYs, Costs And Cost Per QALY With A 10% Change In Parameters. 208

Table B.2: Summary Of The Percentage Change In Cost Per QALY With A 10% Change In Cost Parameters. 209

Table D.1: The Prices Of Collagen And Polyelectrolyte. 213

List of Abbreviations

3D	Three Dimensional	**DR**	Diabetic Retinopathy
3T3-L1	Mouse Embryonic Adipose-Like Fibroblast	**HRQoL**	Health Related Quality Of Life
AFM	Atomic Force Microscopy	**ECM**	Extracellular Matrix
AGE	Advanced Glycation End Product	**EDTA**	Ethylenediaminetetraacetic Acid
AIHW	Australian Institute Of Health And Welfare	**EGTA**	Ethylene Glycol Tetraacetic Acid
ALP	Alkaline Phosphatase	**ESEM**	Environmental Scanning Electron Microscope
ANOVA	Analysis Of Variance	**FAK**	Focal Adhesion Kinase
Ar	Argon gas	**FBS**	Fetal Bovine Serum
BMI	Body Mass Index	**FGF**	Fibroblast Growth Factors
BSA	Bovine Serum Albumin	**FITC**	Fluorescein isothiocyanate
CAM	Cell Adhesion Molecules	**FPG**	Fasting Plasma Glucose
CFDA	5-Carboxyfluorescein diacetate	$\mathbf{Hb_{A1c}}$	Glycosylated Hemoglobin
CVD	Cardiovascular Disease	**HBS**	HEPES buffered Saline
DM	Diabetes Mellitus	**HCl**	Hydrochloric acid
DMEM	Dulbecco's Modified Eagle's Medium	**HCS 2/8**	Human Chondrocyte Cell
DNA	Deoxyribonucleic Acid	**HEK 293**	Human Embryonic Kidney 293 Cells

HUVEC	Human Umbilical Vein Endothelial Cells	**nSTDR**	Non-Sight Threatening Diabetic Retinopathy
ICER	Incremental Cost Effectiveness Ratio	**OAA**	Optometrists Association Australia
IGT	Impaired Glucose Tolerance	**OGTT**	Oral Glucose Tolerance Test
IL-8	Interleukin-8	**PAA**	Poly(Acrylic Acid)
LBL	Layer-By-Layer	**PAH**	Poly(Allylamine Hydrochloride)
LY	Life Years	**PBAC**	Pharmaceutical Benefits Advisory Committee
MA	Micro-Aneurysm	**PBS**	Phosphate Buffered Saline
MBS	Medicare Benefit Schedule	**PBS**	Pharmaceutical Benefits Schedule
ME	Maculopathy	**PDDA**	Poly(Diallyldimethylammonium Chloride)
mfERG	Multifocal Electroretinogram	**PDGF**	Platelet-Derived Growth Factor
MSAC	Medical Services Advisory Committee	**PD-L**	PEriodontal Ligament Cells
N_2	Nitrogen gas	**PDR**	Proliferative Diabetic Retinopathy
NaCl	Sodium Chloride	**PE**	Polyelectrolyte
NaOH	Sodium hydroxide	**PEI**	Polyethylenimine
NHMRC	National Health And Medical Research Council	**PEM**	Polyelectrolyte Multi-Layers
nPDR	Non-Proliferative Diabetic Retinopathy	**PE-PAH**	Polyelectrolyte Capsule With PAH As The Start Coating Material

PE-PSS	Polyelectrolyte Capsule With PSS As The Start Coating Material	**SWAP**	Short Wavelength Automated Perimetry
PI	Propidum Iodide	**SY**	Sight Years
pKa	Acid Dissociation Constant	**TCP**	Tissue Culture Plastic
pNPP	Alkaline Phosphatase Yellow	**TGF**	Transforming Growth Factor
pre-DM	Pre-Diabetes Mellitus	**Ti**	Titanium
pre-DR	Pre-Diabetic Retinopathy	**TiN**	Titanium Nitride
PSS	Poly(Sodium 4-Styrene Sulfonate)	**TiN120**	Titanium Nitride Thin Film Made With 120 Watts
QALY	Quality Adjusted Life Years	**TiN190**	Titanium Nitride Thin Film Made With 190 Watts
QoL	Quality Of Life	**TNF α**	Tumour Necrosis Factor A
Ra	Average Roughness	**UKPDS**	UK Prospective Diabetes Study
RAW	Mouse Leukaemic Monocyte Macrophage	**VEGF**	Vascular Endothelial Growth Factor
RCT	Randomized Controlled Trial	**VIPP**	Vision Impairment Prevention Program
RMS	Root Mean Square Of Roughness	**WESDR**	Wisconsin Epidemiological Study Of Diabetic Retinopathy
RNAse	Ribonuclease		
STDR	Sight Threatening Diabetic Retinopathy		

Abstract

This thesis reports an investigation from the “bedside” back to the “bench”. That is, from the economic evaluation of a medical intervention to basic research and development of a contractility assay. The underlying theme of this thesis is cellular contractility, which was stimulated from our laboratory’s work in the microvascular complications of Diabetic Retinopathy (DR).

The health economic perspective of this thesis evaluates the cost effectiveness and cost utility of DR prognosis using the prog-DR test. This novel prognostic test developed in our laboratory relies on the contractile response of blood vessels to detect subjects with high risk of developing DR. Markov modeling based on information in the literature was used to estimate the outcomes of a hypothetical population. The costs, health and utility outcomes of DR were compared to the potential outcomes if the prog-DR test was used. The model show that the prog-DR test can improve the health of the hypothetical population as measured in the number of life years (LY), sight years (SY) and quality-adjusted life years (QALY). The prog-DR test was more cost effective than the benchmark of annual or bi-annual screening and the incremental cost effectiveness ratio (ICER) appears to be at an acceptable level. Scenario and sensitivity analysis also show that the cost effectiveness of the prog-DR test can be improved by (i) better blood glucose management post prog-DR test, (ii) targeted screening (as opposed to population-wide screening) and (iii) reduced costs of both screening and management of DM and DR.

The physiological perspective of the thesis aimed to develop a contractility assay for DR that was based on a 3D scaffold, which was affordable, easy to make and mimicked the three dimensional physiological environment of blood vessels. The contractility assay was developed using a 3D, hollow scaffold (PE-PAH capsule) and involved (i) the selection of the optimal core material, (ii) optimisation of the manufacturing process, (iii) characterisation of the scaffold and (iv) ensuring that cells can be grown on it. The cyto-biocompatibility of the candidate polyelectrolyte Poly(Sodium 4-Styrene Sulfonate) (PSS) and Poly(Allylamine Hydrochloride) (PAH) in the thin films format were investigated using three different cell lines and the effects of these thin films were also

compared to titanium and titanium nitride thin films. In essence, PSS and PAH are not cytotoxic and was used to develop the contractile scaffold, PE-PAH capsule. This scaffold is relative elastic and the contractile force exerted by the 3T3-L1 cells was calculated based on the deformation of the PE-PAH capsule. The contractility assay was sufficiently sensitive to detect the nano-Newton magnitude of force developed by individual cells and discriminated the change in force due to disruption of the F-actin cytoskeleton by forskolin and cytochalasin D.