AQUAPORINS: GATEKEEPERS OF OEDEMA IN TRAUMATIC BRAIN INJURY

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Prof. Robert Vink
Prof. Andrea Yool
DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Joshua Luke Burton

2014
DEDICATION

"How much truth can a spirit endure; how much truth can it dare? This became for me more and more the actual test of value. Error (the belief in the ideal) is not blindness; error is cowardice. Every conquest, every step forward in knowledge is the outcome of courage, of hardness towards one’s self; of cleanliness towards one’s self." - Ecce Homo, Preface, Friedrich Nietzsche

This thesis is dedicated in memory of Lesley Gillian and John Rex Kimber who instilled in me the significance and value of study. For without them I would not have come this far.
ACKNOWLEDGEMENTS

From my earliest recollection I was blessed by Lesley and John by their imparting to me the true value of knowledge. Thus my decision to undertake a PhD was not one of if, but rather when. Indeed Plato’s infamous Allegory of the Cave has remained a key part of my own ideology and in many respects has mirrored the early challenges I have so far faced throughout my life with an undying desire to seek the light.

There is also unquestionably a deep sense of sadness in closing this part of my studies, for not only am I taking a step away from a place of self-growth but so too the presence of those who have inspired me. My mentor and principle supervisor Prof. Robert Vink has not only guided me throughout my candidature academically, but so too has continually inspirited within me my thirst for learning by his vast research experience and unique teaching approach, epitomising the ideal of evolving academia. There is yet so much I could and dearly wish to learn from him in all aspects of my life and so I only hope that I am fortunate enough to one day be in a position to continue my tuition. Thank you Bob, you will always remain to me a pillar of insight.

Next I would like to thank my secondary supervisor Prof. Andrea Yool, for whom without the studies conducted within this thesis would simply not have been possible. With her immense understanding of physiology and great expanse of research to support her claims, she was singularly responsible for having developed \textit{in vitro} the novel pharmaceutical agents used within this research.

I would also like to thank the various members of the Vink laboratory who have either assisted in experimental protocol or provided valued feedback on my work throughout my candidature. Indeed arguably the special maxim of the Vink team is one of comradely and so should be cherished as an example for other research groups to follow.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
</tr>
<tr>
<td>AMDA</td>
<td>A-amino-3-hydroxy-5-methyl-4-isoxazolpropionate</td>
</tr>
<tr>
<td>AQP</td>
<td>Aquaporin</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine-5'-triphosphate</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain-barrier</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>DAI</td>
<td>Diffuse axonal injury</td>
</tr>
<tr>
<td>EAA</td>
<td>Excitatory amino acid</td>
</tr>
<tr>
<td>ECF</td>
<td>Extracellular fluid</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>Hypoxia-inducible factor 1-alpha</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>ISF</td>
<td>Interstitial fluid</td>
</tr>
<tr>
<td>Kir4.1</td>
<td>Inward-rectifying potassium channel</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinases</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Na⁺/K⁺-ATPase</td>
<td>Sodium-potassium adenosine triphosphatase pump</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>OAP</td>
<td>Orthogonal array of particles</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial cell growth factor</td>
</tr>
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