

# Thomas Andrew Longden, B.Sc. (Hons), PhD



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## Research Interests

The central theme of my research is the control of blood flow in the brain, with a focus on the moment-to-moment regulation of blood flow in response to neuronal activity—a process termed ‘functional hyperemia’ and mediated by a range of mechanisms collectively termed ‘neurovascular coupling’. This complex phenomenon, which forms the basis of fMRI, involves dynamic interplay between the cells of the neurovascular unit—neurons, astrocytes, pericytes, endothelial cells and arteriolar smooth muscle. To understand the mechanisms of neurovascular coupling in health and disease, I utilize a broad range of techniques, including multiphoton imaging *in vivo* and in brain slices, high-speed confocal imaging of calcium dynamics in the cells of the neurovascular unit, electrophysiology on freshly isolated vascular cells and on neurons and astrocytes in slices and *in vivo*, myography on isolated microvessels, whole-animal behavioral assays, molecular approaches, and vascular optogenetic approaches.

My current focus is on how capillary ion channel and GqPCR activity initiates and coordinates the blood flow response to local neuronal activity and how this is disrupted in disease. During my post-doctoral work, I completed a multidisciplinary study—spanning vascular biology, neuroscience, and psychology—which examined the effects of psychological stress on neurovascular coupling and identified a key ion ‘channelopathy’, in the form of  $K_{IR}$  channel dysfunction, which is now emerging as a common theme in a range of brain disorders. I am also interested in the impact of Alzheimer’s disease on cerebral blood flow control. To interrogate this research question, I have employed *in vivo* imaging of cerebral hemodynamics, single cell electrophysiology, and *ex vivo* arteriole studies to begin to explore the impact of this disorder on vascular smooth muscle and brain capillary endothelial function. I also have an interest in studying intracellular calcium dynamics in the choroid plexus epithelium, a tissue responsible for the production of cerebrospinal fluid which is essential for normal brain function, and calcium dynamics in astrocytes in health and disease.

## Academic Positions

July 2015-Present **Assistant Professor, Research Track, University of Vermont, USA**

## Postdoctoral Training

February 2011 **Postdoctoral Associate/AHA Postdoctoral Fellow, University of Vermont, USA**  
- June 2015  
Mentor: Prof. Mark Nelson.

## Education

2006-2010 **PhD, Pharmacology, University of Manchester, UK**  
Thesis: “Studies on the Expression of Calcium-Activated Potassium Channels in Astrocytes – A Potential Role in Neurovascular Coupling”.  
**Pass with no corrections.**  
Mentors: Prof. Arthur Weston and Dr. Gillian Edwards.  
Examiners: Prof. Christopher Garland (University of Oxford) and Dr. Paulo Tammaro (University of Oxford).  
My doctorate work was funded by a BBSRC CASE studentship, with the pharmaceutical company Boehringer Ingelheim acting as industrial sponsor. During my studies, I learnt a broad range of laboratory techniques including single cell and brain slice electrophysiology, calcium imaging in brain slices, immunohistochemistry, RT-PCR, fluorescence activated cell sorting, ELISA, and cell culture techniques.

2003-2006 **B.Sc (Hons), Pharmacology, University of Manchester, UK**  
Final Year Thesis: “Identification of GPRC6A in rat mesenteric arteries”  
2005 AstraZeneca Prize winner: Highest grade in pharmacology.

2001-2003 **Thomas Rotherham College, Rotherham, UK**  
Foundation Scholar Award winner.

1996-2001 **Old Hall Comprehensive School, Rotherham, UK**

## **Publications**

### Articles:

Harraz O, **Longden T**, Hill-Eubanks D, Nelson M (2018) "PIP<sub>2</sub> depletion promotes TRPV4 channel activity in mouse brain capillary endothelial cells" *eLife*. **7**: e38689.

Harraz O, **Longden T**, Dabertrand F, Hill-Eubanks D, Nelson M (2018) "Endothelial GqPCR activity controls capillary electrical signaling and brain blood flow through PIP<sub>2</sub> depletion" *Proceedings of the National Academy of Sciences USA*. In press.

**Longden T**, Dabertrand F, Koide M, Gonzales A, Tykocki N, Brayden J, Hill-Eubanks D, Nelson M (2017) "Capillary K<sup>+</sup>-sensing initiates retrograde hyperpolarization to locally increase cerebral blood flow" *Nature Neuroscience*, **20**: 717-726.

- Covered in a 'News and Views' article in *Nature Neuroscience* (doi:10.1038/nn.4542) and featured on the May 2017 cover.
- Recommended in *F1000Prime* as being of special significance in its field.

Tykocki N, Bonev A, **Longden T**, Heppner T, Nelson M (2017) "Inhibition of vascular smooth muscle inward-rectifier K<sup>+</sup> channels restores myogenic tone in mouse urinary bladder arterioles" *American Journal of Physiology Renal Physiology*, **312(5)**: F836-F847.

Klitgaard-Povlsen G, **Longden T**, Bonev A, Hill-Eubanks D, Nelson M (2016) "Uncoupling of Neurovascular Communication After Transient Global Cerebral Ischemia is Caused by Impaired Parenchymal Smooth Muscle K<sub>IR</sub> Channel Function" *Journal of Cerebral Blood Flow & Metabolism*, **36(7)**: 1195-1201.

**Longden T**, Hill-Eubanks D, Nelson M (2016) "Ion Channel Networks in the Control of Cerebral Blood Flow" *Journal of Cerebral Blood Flow & Metabolism*, **36(3)**: 492-512.

Balbi M, Ghosh M, **Longden T**, Vega M, Gesierich B, Hellal F, Loubopoulos A, Nelson M, Plesnila N (2015) "Dysfunction of mouse cerebral arteries during early aging" *Journal of Cerebral Blood Flow & Metabolism* **35(9)**: 1445-1453.

**Longden T**, Nelson M (2015) "Vascular Inward Rectifier K<sup>+</sup> Channels as External K<sup>+</sup> Sensors in the Control of Cerebral Blood Flow." *Microcirculation*, **22(3)**: 183-196.

- Selected as a 'Featured Article' in *The Microcirculatory Society Newsletter*, May 2015 issue.

Villalba N, Sonkusare S, **Longden T**, Tran T, Sackheim A, Nelson M, Wellman G, Freeman K (2014) "Traumatic brain injury disrupts cerebrovascular tone through endothelial inducible nitric oxide synthase expression and nitric oxide gain of function." *Journal of the American Heart Association*, **3(6)**: e001474.

**Longden T**, Dabertrand F, Hill-Eubanks D, Hammack S, Nelson M (2014) "Stress-Induced Glucocorticoid Signaling Remodels Neurovascular Coupling Through Impairment of Cerebrovascular Inwardly Rectifying K<sup>+</sup> Channel Function." *Proceedings of the National Academy of Sciences USA*, **111(20)**: 7462-7.

- Selected as Editor's Choice in the May 2014 issue of *Science Signaling*, doi: 10.1126/scisignal.2005510.
- Selected for Commentary in the July 2014 issue of *Channels*, doi: 10.4161/chan.29969.

**Longden T**, Dunn K, Draheim H, Nelson M, Weston A, Edwards G (2011) "Intermediate-Conductance Calcium-Activated Potassium Channels Participate in Neurovascular Coupling." *British Journal of Pharmacology*, **164(3)**: 922-33.

### Editorials:

Welsh D, **Longden T** (2017) "Endothelial Signaling and the Dynamic Regulation of Arterial Tone: A Surreptitious Relationship" *Microcirculation*, **24(3)**: 10.1111/micc.12370.

### Abstracts:

Moshkforoush A, **Longden T**, Dabertrand F, Nelson M, Tsoukias N (2017) "A Mathematical Model of Cerebral Blood Flow Control: Role of Kir Channels" *FASEB Journal* **31**: 684.20.

Harraz O, **Longden T**, Dabertrand F, Nelson M (2017) "Capillary endothelial Gq protein-coupled receptors and PIP<sub>2</sub> toggle signaling between TRPV4 and Kir2 channels in the brain" *FASEB Journal* **31**: 681.1

**Longden T**, Nelson M (2016) “Critical Role of Nitric Oxide in Capillary-to-Arteriole Electrical Signaling in the Brain” *Journal of General Physiology* **148(2)**: 22A-23A.

Gonzales A, **Longden T**, Dabertrand F, Shui B, Kotlikoff M, Nelson M (2016) “Pericyte-Mediated Alterations of Blood Flow Distribution at Capillary Bifurcations in a Genetic Model of Cerebral Ischemic Small Vessel Disease” *Journal of General Physiology* **148(2)**: 13A.

Dabertrand F, Harraz O, **Longden T**, Brayden J, Nelson M (2016) “Remote Control of Intracerebral Arteriole Diameter by Capillary TRPV4 and TRPV3 Channels.” *FASEB Journal* **30**: Ib780.

Gonzales A, **Longden T**, Shui B, Kotlikoff M, Nelson M (2015) “Contractile Pericytes Determine the Direction of Blood Flow at Capillary Bifurcations.” *Journal of General Physiology* **146(3)**: 6A-7A.

**Longden T**, Nelson M (2015) “Potassium sensing by capillary K<sub>IR</sub> channels regulates cerebral blood flow” *Journal of General Physiology* **146(3)**: 10A.

**Longden T**, Nelson M (2015) “Unique Ion Channel Properties of Brain Capillary Endothelial Cells” *FASEB Journal* **29**: 832.9.

**Longden T**, Dabertrand F, Hill-Eubanks D, Hammack S, Nelson M (2014) “Glucocorticoid Signaling Mediates Stress-Induced Impairment of Neurovascular Coupling” *FASEB Journal* **28**: 841.4.

**Longden T**, Bonev A, Nelson M (2014) “Calcium Signaling in the Choroid Plexus Epithelium.” *FASEB Journal* **28**: 1097.11.

N Villalba, **T Longden**, M Nelson, G Wellman, K Freeman (2014) “Enhanced endothelial nitric oxide production impairs cerebrovascular tone after brain trauma” *FASEB Journal* **28**: 1070.1.

**Longden T**, Dabertrand F, Hammack S, Nelson M (2013) “Impairment of Neurovascular Coupling by Chronic Stress” *FASEB Journal* **27**: 925.9.

**Longden T**, Nelson M (2012) “Recruitment of the Vascular Endothelium into Neurovascular Coupling.” *FASEB Journal* **26**: 842.4.

**Longden T**, Nelson M (2011) “Recruitment of the Vascular Endothelium into Neurovascular Coupling” *Proceedings of the British Pharmacological Society* at [bps.conference-services.net/resources/344/2833/pdf/bpswinter2011\\_0113.pdf](http://bps.conference-services.net/resources/344/2833/pdf/bpswinter2011_0113.pdf)

**Longden T**, Draheim H, Weston A, Edwards G (2009) “The Expression of Small- and Intermediate-Conductance Calcium-Activated Potassium Channels in Astrocytes of the Mouse Brain” *Proceedings of the British Pharmacological Society* at [www.pA2online.org/abstracts/Vol7Issue4abst001P.pdf](http://www.pA2online.org/abstracts/Vol7Issue4abst001P.pdf)

**Longden T**, Edwards G, Weston A, Draheim H, Hengerer B (2008) “Evidence in favour of an intermediate-conductance calcium-activated potassium channel in cortical astrocytes” *Fundamental and Clinical Pharmacology* **22(2)**: 9.

Harno E, Weston A, **Longden T**, Absi M, Ruat M, Dodd R, Edwards G (2006) “Evidence for the presence of GPRC6A in the rat mesenteric artery.” *Acta Pharmacologica Sinica* **27 (1)**: 155-156.

## Awards

### Research Support

July 2017- June 2020	<b>American Heart Association Scientist Development Grant</b> “Vascular signaling plasticity in the brain” Priority score: 1.19. Score percentile: 0.28 Total awarded: \$231,000
May 2017 – May 2020	<b>Vermont Center for Behavior and Health Project Directorship</b> “Impact of stress on capillary-to-arteriole communication” Total awarded: \$561,600
July 2014 - July 2015	<b>American Heart Association Founders Affiliate Postdoctoral Fellowship</b> “Hemodynamic contributions to the control of neuronal function” Priority Score: 1.36 Score percentile: 6.10 Total awarded: \$47,000
July 2012 - July 2014	<b>American Heart Association Founders Affiliate Postdoctoral Fellowship</b> “Neurovascular Coupling in Chronic Stress” Priority Score: 1.20 Score percentile: 2.83

Total awarded: \$87,000

#### Other Awards

- September 2016 **Society of General Physiology Travel Award**  
Society of General Physiology 2016 Annual Meeting
- October 2015 **Japanese Microcirculatory Society Travel Award**  
10<sup>th</sup> World Congress for Microcirculation
- September 2015 **Cardiovascular Research Institute of Vermont Travel Award**  
Society of General Physiology 2015 Annual Meeting
- March 2015 **Cardiovascular Research Institute of Vermont Travel Award**  
Experimental Biology 2015
- April 2012 **ASPET Young Scientist Travel Award**  
Experimental Biology 2012

#### Honors

- 2016 **Young Investigator Award**  
Awarded by the CVRI at Society of General Physiologists Annual Meeting 2016.
- 2015 **Symposium Award winner**  
Society of General Physiologists Annual Meeting 2015.
- 2014 **Cardiovascular Pharmacology Postdoc Competition, first runner-up**  
American Society for Pharmacology and Experimental Therapeutics. Experimental Biology 2014.
- 2014 **Durwood J Smith Award for Excellence in Pharmacology**  
Best presentation. University of Vermont Annual Pharmacology Retreat.
- 2013 **Durwood J Smith Award for Excellence in Pharmacology**  
Best presentation. University of Vermont Annual Pharmacology Retreat.
- 2012 **Durwood J Smith Award for Excellence in Pharmacology**  
Best presentation. University of Vermont Annual Pharmacology Retreat.

#### Teaching Experience

- 2011-Present During my time at UVM I have lectured for undergraduate- and graduate-level courses on ion channel biophysics and membrane potential, electrophysiology, state-of-the-art calcium imaging techniques, the cerebral circulation, and vascular function and disease. I have also mentored several undergraduates through their final year lab projects and I have mentored a research associate in the Nelson lab. I have also taught technical skills to several graduate students, technicians, and colleagues.  
2017 student teaching evaluation average score: **4.52/5.00**  
2018 student teaching evaluation average score: **4.43/5.00**  
**Mentored Students:** Benjamin Dahlgren (M.Sc in Pharmacology). Present position: Associate Biochemist at GlaxoSmithKline.  
Matthew Broomer (B.Sc in Psychology). Present position: PhD Candidate, University of Vermont.  
Julia Campbell (B.Sc in Psychology final year thesis). Present position: Masters Candidate, Boston University.
- 2006-2010 **Postgraduate Demonstrator, University of Manchester**  
During my PhD studies, I regularly taught in several classes. A colleague and I ran a full module on pharmacology.

#### Conferences and Seminars

- 2018 **11<sup>th</sup> World Congress for Microcirculation.** Vancouver, Canada. Platform talk. "Capillary Ca<sup>2+</sup> Signals Generate Nitric Oxide to Tune Local Brain Blood Flow."  
**UC Davis, CA.** Seminar. "Food for Thought: Capillary Control of Cerebral Blood Flow."  
**University of Pennsylvania, PA.** Seminar. "Food for Thought: Capillary Control of Cerebral Blood Flow."
- 2017 **NBH Research Forum.** Vermont chapter of the Society for Neuroscience. Speaker. "Brain capillaries act as a sensory web to translate neural activity into blood flow".

- ISRA 2017.** Manchester, UK. Invited speaker. Title: “Capillary-to-arteriole communication regulates blood flow into the brain”. Session chair.
- University of Maryland, MD.** Invited seminar. Title: “Control of brain blood flow by capillary calcium signaling.”
- 2016 **Experimental Biology.** San Diego, CA, USA. Invited speaker. “Potassium Sensing by Capillary  $K_{IR}$  Channels Regulates Cerebral Blood Flow”.
- FASEB Smooth Muscle Congress.** Lisbon, Portugal. Invited Speaker. “Control of brain blood flow by capillary-to-arteriole communication”.
- Society for General Physiologists Annual Meeting.** Woods Hole, MA, USA. Poster presentation.
- UC Davis Distinguished Lecture in Physiology.** Invited seminar. “Translating thought into blood flow: Capillary-to-arteriole communication in the brain.”
- University of Reno, NV.** Invited seminar. “Translating thought into blood flow: Capillary-to-arteriole communication in the brain.”
- 2015 **10<sup>th</sup> World Congress for Microcirculation.** Kyoto, Japan. Poster presentation.
- 2015 **Society for General Physiologists Annual Meeting.** Woods Hole, MA, USA. Poster presentation.
- 2014 **NBH Research Forum.** Vermont chapter of the Society for Neuroscience. Speaker. “Neurovascular coupling in the stressed amygdala.”
- Neuroscience.** Washington DC, USA. Nanosymposium speaker. “Stress-induced glucocorticoid signaling remodels neurovascular coupling through impairment of cerebrovascular  $K_{IR}$  channel function”.
- University of Oxford, UK.** Invited seminar. As above.
- Smooth Muscle Underground.** San Diego, CA, USA. Invited speaker. As above.
- 2012-2015 **Experimental Biology.** I presented posters each year on my work on capillaries, endothelial recruitment into neurovascular coupling, and stress.
- 2006-2011 **British Pharmacological Society Winter Meetings.** I have been closely involved with the British Pharmacological Society and I attended the annual winter meetings between 2006 and 2011. I presented talks in both 2009 and 2011.
- 2010 **World Pharma.** In addition to presenting a poster I carried out various duties on behalf of the British Pharmacological Society including organizing and compering an international networking event for young pharmacologists.
- 2008 **EPHAR.** I presented an elevated talk at the 2008 European Federation of Pharmacological Societies meeting in Manchester.

### Courses

- 2009 **Microelectrode Techniques for Cell Physiology workshop.** I attended this two-week course at the Marine Biological Association in Plymouth to enhance my understanding of patch clamp electrophysiology.

### Positions of Responsibility

#### Peer review

*Journals:* Journal of Cerebral Blood Flow and Metabolism, Journal of Physiology, American Journal of Physiology, British Journal of Pharmacology, Journal of Molecular and Cellular Cardiology, Frontiers, Advances in Pharmacology, Neurosignals, Microcirculation.

*Grants:* American Heart Association (Founders Affiliate Student Task Force, Allen Initiative in Brain Health and Cognitive Impairment), French National Research Agency.

**Guest editor** *Microcirculation* Special Themed Issue, January 2017.

**Committee memberships** 11<sup>th</sup> World Congress for Microcirculation Scientific Advisory Committee.  
ISRA 2020 Scientific Advisory Committee.  
Cardiovascular Research Institute of Vermont Early Career Advisory Committee.

**Conference organizer** SMUG 2019, Experimental Biology 2019 Satellite, Orlando FL.

2012-2014 **Postdoctoral Representative for the Society for Neuroscience, Vermont Chapter.** As a postdoctoral representative I was involved in organizing the annual UVM Neuroscience Behavior and Health Research Forum.

2007-2010 **British Pharmacological Society Young Pharmacologists Committee.** The aim of this committee is to raise awareness of pharmacology as a career choice for young people.

2008 **British Pharmacological Society winter meeting.** I was part of a team of PhD students recruited to help run the winter BPS conference.

2008 **Biotech YES (Young Entrepreneurs Scheme).** I was part of a team of five PhD students who entered this competition, aiming to give early career scientists an insight into the biotechnology sector. Teams were given tuition on the many aspects of managing a biotech start-up company, then asked to prepare a pitch for a panel of venture capitalists, who then chose

2007-2008

the best business plan. After winning a regional heat in Manchester, our team went on to the London finals, where we won an award sponsored by Syngenta.

**Young Physiologists' Symposium (*Cations in Physiological Signalling*)**. Over the course of a year I was part of a team of PhD students who organized a full two-day conference for early career life scientists, held in the Core Technology Facility at the University of Manchester.