Introduction: Special Issue in Honor of Bruce Ransom

Helmut Kettenmann¹

Published online: 22 August 2017
© Springer Science+Business Media, LLC 2017

This Special Issue is devoted to Bruce Robert Ransom. All contributors of this special issue have a personal association with him during his long and successful scientific career. His research has focused on two main aspects. One is the role of glial cells in brain function and the second is the mechanism of white matter injury in ischemia.

Bruce was born in Santa Fe, New Mexico in 1945 and grew up in Minneapolis, Minnesota. He studied medicine at Washington University in St. Louis. Already as a

graduate student he started his first scientific project in the summer of 1969 and the topic was glial cells. Sidney Goldring, a neurosurgeon, was interested in the effects of direct electrical stimulation on the cerebral cortex. At that time very little was known about the physiology of glial cells. Only a few years earlier Steven Kuffler, John Nicolls and Richard Orkand had performed recordings from invertebrate and lower vertebrates glial cells. They demonstrated that the membrane potential was dominated by the transmembrane potassium gradient and that neuronal activity affected the membrane potential of these glial cells [11, 13]. In contrast, the properties of mammalian glial cells were largely unknown. At that time a prominent experimental model was the cat and Bruce's task was to record from the glial cells in the cat cortex. This was a very

---

✉ Helmut Kettenmann
kettenmann@mdc-berlin.de

¹ Max Delbrück Center for Molecular Medicine
in the Helmholtz Association, Berlin, Germany

challenging experiment, especially for an inexperienced student since the sharp electrodes were tedious to produce and handle. Moreover, the cat was anaesthetized and the brain surface was pulsating. At the end he succeeded and published a series of three important papers on membrane properties of glial cells in the cat cortex demonstrating that the membrane potential of these mammalian glial cells was dominated by the extracellular potassium concentration and sensitive to neuronal activity [17–19].

After finishing his MD/Ph.D. he went to the NIH to work in Phil Nelson's lab to study properties of neurons in cell culture. This was, at that time, a completely novel approach and it turned out that these cells in the dish could be manipulated in a way which was impossible in an intact animal. In a series of four papers published in 1977 in the *Journal of Neurophysiology*, Bruce was able to describe the basic electrophysiological properties, the chemosensitivity, the synaptic interconnections and the circuitry of cultured spinal cord neurons [10, 15, 16, 21]. These are highly cited landmark papers. In collaboration with Jeff Barker, a very successful side-project was undertaken to characterize glutamate and GABA receptors in these cultured mammalian neurons [14]. Shortly after I started my career, I visited the Nelson lab, which had become the Mecca for anyone who ever wanted to record from neurons in cell culture, and these four papers with Bruce were the blue print for me to start my electrophysiological recordings when I was back in Heidelberg. The NIH was also the place where Bruce met Joe Neale and Bill Catterall who became good friends and have contributed to this Special Issue in Bruce's honor. Bill Catterall summarized *40 Years of Sodium Channels: Structure, Function, Pharmacology, and Epilepsy*. Joe Neale, now at the end of his career, submitted (as he stated) the last paper of his long career to this Special Issue on *NAAG Peptidase Inhibitors Act Via mGluR3: Animal Models of Memory, Alzheimer's, and Ethanol Intoxication*.

In 1976 Bruce moved to Stanford for his clinical training. Three years later, David Prince, the chairman of Neurology recruited him to the faculty of Neurology at Stanford and Bruce build up his lab in the cramped basement of the building. Already there he shifted his interest from neurons back to glial cells, in particular to astrocytes. There he met colleagues like Barry Connors and Steve Waxman. Steve contributed to this Special Issue with something quite unique, namely a poem dedicated to Bruce, *Ode to Glia: A Tribute to Bruce Ransom*. At Stanford he got his first NIH funding and could hire his first postdoc, Elba Serrano. They discovered that relevant concentrations of anticonvulsive drugs could reduce neuronal dendritic complexity [26]. Elba contributed on *Post-translational Tubulin Modifications in Human Astrocyte Cultures* and on *A Hydrogel Environment Supports Cell Culture Expansion of a Female Grade IV Astrocytoma* to this Special Issue. Also part of

the team at that time was Carole Poitry-Yamate starting as a technician and becoming an independent experimentalist. She started to work on astrocytes and they found that altered gliogenesis impacted neuronal function [31]. Bruce attracted Wolfgang Walz as a guest-scientist and they studied the changes in extracellular pH and potassium concentration after anoxia in the optic nerve [22], in one of Bruce's earliest papers on the pathophysiology of anoxic/ischemic injury to CNS white matter. Wolfgang provides here a contribution on *Neutrophil Infiltration and Matrix Metalloproteinase-9 in Lacunar Infarction*. Bruce was located in the Neurology 'basement lab' at Stanford which was an exciting place in those days (1980–1987). It was packed with extremely talented neuroscientists (Barry Connors, Scott Thompson, David McCormick, Arnold Kriegstein, Dennis Choi, David Prince and others) working in small adjacent labs, a situation that naturally promoted productive scientific discussions and collaborations.

Bruce was always a person between two worlds, science and clinics, and while being active in the lab he also saw patients at Stanford, among them the first patient ever to be intoxicated with a by-product of a new designer drug, MPTP, which resulted in symptoms of Parkinson's Disease. This drug is now widely used to generate animal models of Parkinson's Disease.

In 1987, he followed Steve Waxman to the Neurology Department at Yale University and started a lab that had a very strong focus on glial cells and white matter injury. His postdocs from this period are now Professors all over the world, including Harry Sontheimer, Peter Stys, Christine Rose, Arthur Butt, and Bob Fern. With Harry, he characterized sodium channels in astrocytes [27, 28]. With Arthur Butt, he studied the in vivo morphology of dye-filled oligodendrocytes and astrocytes during all stages of development using his favorite preparation, the optic nerve, and provided excellent images of these cells in situ that helped clarify their anatomic relationships to axons [3]. Arthur very successfully continued with that topic and now provides a contribution on *Metabotropic Glutamate Receptors Protect Oligodendrocytes from Acute Ischemia in the Mouse Optic Nerve*. Driven by a desire to better understand how stroke-like conditions affect CNS white matter, he embarked on a line of investigations that has persisted to the present. With Peter Stys, Bob Fern, Steve Waxman and others, important discoveries were made about how CNS white matter was damaged. Bob Fern contributes here on *The Leukocentric Theory of Neurological Disorder: a Manifesto*. Lastly, with Christine Rose, a series of papers analyzed intracellular sodium homeostasis and activity-related fluctuations in astrocytes [24] and neurons [25]. Christine has continued to study the role of sodium in glia and reports on that topic in this issue, *Astrocyte Sodium*

Signalling and Panglial Spread of Sodium Signals in Brain White Matter.

At Yale, Bruce also met George Richerson, a clinician and scientist who was doing his neurology residency there, and closely interacted with him. Mentioning George brings up the interesting subject of Bruce's oldest son, Christopher Ransom. Chris was undecided about his career as a 3rd year college student and arranged to spend 6 months at my newly established lab in Berlin-Buch shortly after the reunification of the two Germanies in 1992. This was his first scientific training and he greatly enjoyed the experience. Subsequently, Chris followed the path of his father and became both a scientist and clinician. In fact, Chris and his Dad have had the unique experience of publishing together [23]. Coming back to George Richerson, Chris did his neurology training at Yale where George was the program director and then his postdoc supervisor. Here George and Chris provide a contribution on *Modulation of Tonic GABA Currents by Anion Channel and Connexin Hemichannel Antagonists*. At Yale, Bruce interacted also closely with Jeff Kocsis who contributed a chapter on *Chronic TNF α Exposure Induces Robust Proliferation of Olfactory Ensheathing Cells (OECs), But Not Schwann Cells*.

I had met Bruce in 1983 at his first meeting outside of the US, at Castle Rabenstein in Germany on 'Theory and Application of Enzyme and Ion Electrodes in Biology and Medicine'. At that time it was quite fashionable to use ion-selective microelectrodes to measure intracellular and extracellular ion concentrations in brain, especially fluctuations of potassium concentration in and outside of cells. Both of us used that technique to study potassium changes in the extracellular space and within glial cells [7, 31]. I had admired his papers and I was very delighted to see him the first time as a person and we very rapidly got familiar with each other. Since our common interest was glial cells,

I invited him for his first scientific interaction in Europe and we worked together in the lab of Neurobiology at the University of Heidelberg, at that time headed by Melitta Schachner. We focused on characterizing gap junctions between the different types of glial cells, astrocytes and oligodendrocytes and from this interaction we published our first common papers describing the junctional properties between these glial cells. There he met my post-doc of that time, Frank Kirchhoff and they continued to see each other over the years. Frank's contribution here is on *The Role of the Oligodendrocyte Lineage in Acute Brain Trauma*. His interest in gap junctions brought him together with Christian Giaume and Luc Leybart who contributed a chapter on *Connexin Channels at the Glio-Vascular Interface: Gatekeepers of the Brain*.

I visited Bruce at Stanford and he came back as a guest scientist to Heidelberg and it was during one of those collaborations that he started to discuss an idea to create a new journal on the topic of glial cell biology. It was in Heidelberg where we had the first contact to a publisher discussing our new idea, namely at Springer Verlag. Eventually we made a deal with Alan A. Liss in 1986 in New York and the first issue of the new journal GLIA appeared in 1988. Our first study on the glial gap junctions was published in that first issue [4] followed up by four more publication on glial gap junctions, all published in GLIA [6, 20, 29, 32]. Since then we have been chief editors and we are now completing our 30th year of that enterprise. Another common project was to edit a basic text book on neuroglia and the first edition appeared in 1995 followed by a second in 2005 and the third edition in 2013 [5].

In 1995 Bruce moved to Seattle to become the Chair of a new Department of Neurology at the University of Washington. He continued to combine clinics with basic science. The postdocs during that period were Zucheng Ye

At a meeting in New York with Maiken Nedergaard, Bruno Weber, Pierre Magistretti, Phil Haydon, Bruce Ransom, Christian Giaume, Ben Barres, Brian MacVicar, Helmut Kettenmann (from left to right) (2009)

(co-author of Chris' paper), Thomas Möller who contributed on *Senicapoc: Repurposing a Drug to Target Microglia KCa3.1 in Stroke*, Jonathan Weinstein on *Microglial Interferon Signaling and White Matter* and Angus Brown on *A Lifetime Adventure in K^+ Regulation—the Scottish Connection*. Angus and Bruce have been very productive and have published 20 papers analyzing the pathophysiology and molecular mechanism of white matter injury due to ischemia, and the dynamics and physiology of astrocyte glycogen in optic nerve astrocytes [2]. During that time he also met Carlos Matute, an oligodendrocyte specialist, and they collaborated on reviews on various aspects of the pathophysiology of white matter injury [9]. Carlos here provides a contribution on *Inwardly Rectifying K^+ Currents in Cultured Oligodendrocytes from Rat Optic Nerve Are Insensitive to pH*. With Maiken Nedergaard Bruce supervised a common PhD student, Nancy Oberheim who analyzed and characterized human astrocytes and demonstrated unique features of these cells including a highly

Helmut Kettenmann, Bruce Ransom and Brian MacVicar in Helsinki (from left to right) (1989)

Bruce Ransom and Helmut Kettenmann in Berlin (from left to right) (about 1995)

complex morphology [12]. Maiken and Nancy contributed the chapter *Do Evolutionary Changes in Astrocytes Contribute to the Computational Power of the Hominid Brain?*

Bruce's studies on white matter injury sparked his interest in brain energy metabolism and he studied basic mechanisms with the focus on astrocytes as the glycogen stores of the brain. This brought him in contact with Arne Schousboe and Arne's colleague Helle Waagepetersen to discuss brain glycogen metabolism and the three had a successful collaboration [1, 30]. Arne, as the editor-in-chief of *Neurochemical Research* initiated this special issue to recognize Bruce and Helle and Arne provided their paper on *Glycogen Shunt Activity and Glycolytic Supercompensation in Astrocytes May Be Distinctly Mediated via the Muscle Form of Glycogen Phosphorylase*. Another Copenhagen contact is Nanna MacAulay, who has collaborated with him on astrocyte hemichannels. She provides here a contribution on *Connexin Hemichannels in Astrocytes—an Assessment of Controversies Regarding Their Functional Characteristics*. Bruce's devotion to down-hill skiing led him to attend many of the Winter Conferences on Brain Research (WCBR) where we also skied together. There he met his long-term friend Brian MacVicar with whom he also collaborated on a project seeking to explain intrinsic optical signals in optic nerve astrocytes, published in *GLIA* [8]. Brian's contribution here is entitled *Astrocytes Provide Metabolic Support for Neuronal Synaptic Function in Response to Extracellular K^+* . His many international contacts led him to travel all over the world and one of his long-term collaboration partners is Mami Noda from Fukuoka, Japan. She provides here a contribution on *Complexity of Stomach–Brain Interaction Induced by Molecular Hydrogen in Parkinson's Disease Model Mice*.

Bruce has contributed many excellent papers to the scientific community. He has an h-factor of 69 which is mainly based on basic scientific papers, but he also published some papers on clinical topics. The highlights are the first studies of mammalian neurons in the dish, ionic mechanisms of white matter injury, the role of hemichannels on astrocytic glutamate release and the role of astrocytes as glycogen stores for maintaining axonal function.

Me and all the contributors to this Special Issue in your honor, wish you all the best for the years to come. We are looking forward to a continuation of our professional relationships with you and, more importantly, to your enduring friendship.

References

1. Brown AM et al (2005) Astrocyte glycogen metabolism is required for neural activity during aglycemia or intense stimulation in mouse white matter. *J Neurosci Res* 79(1–2):74–80

2. Brown AM et al (2001) Ionic mechanisms of aglycemic axon injury in mammalian central white matter. *J Cereb Blood Flow Metab* 21(4):385–395
3. Butt AM, Ransom BR (1989) Visualization of oligodendrocytes and astrocytes in the intact rat optic nerve by intracellular injection of lucifer yellow and horseradish peroxidase. *Glia* 2(6):470–475
4. Kettenmann H, Ransom BR (1988) Electrical coupling between astrocytes and between oligodendrocytes studied in mammalian cell cultures. *Glia* 1(1):64–73
5. Kettenmann H, Ransom BR (eds) (1995, 2005, 2013) *Neuroglia*. Oxford University Press, New York.
6. Kettenmann H et al (1990) Intracellular pH shifts capable of uncoupling cultured oligodendrocytes are seen only in low HCO_3^- solution. *Glia* 3(2):110–117
7. Kettenmann H et al (1983) Exclusive potassium dependence of the membrane potential in cultured mouse oligodendrocytes. *J Neurosci* 3(3):500–505
8. MacVicar BA et al (2002) Intrinsic optical signals in the rat optic nerve: role for K^+ uptake via NKCC1 and swelling of astrocytes. *Glia* 37(2):114–123
9. Matute C, Ransom BR (2012) Roles of white matter in central nervous system pathophysiology. *ASN Neuro* 4(2)
10. Nelson PG et al (1977) Mouse spinal cord in cell culture. IV. Modulation of inhibitory synaptic function. *J Neurophysiol* 40(5):1178–1187
11. Nicholls JG, Kuffler SW (1964) Extracellular space as a pathway for exchange between blood and neurons in the central nervous system of the leech: ionic composition of glial cells and neurons. *J Neurophysiol* 27:645–671
12. Oberheim NA et al (2009) Uniquely hominid features of adult human astrocytes. *J Neurosci* 29(10):3276–3287
13. Orkand RK et al (1966) Effect of nerve impulses on the membrane potential of glial cells in the central nervous system of amphibia. *J Neurophysiol* 29(4):788–806
14. Ransom BR, Barker JL (1975) Pentobarbital modulates transmitter effects on mouse spinal neurones grown in tissue culture. *Nature* 254(5502):703–705
15. Ransom BR et al (1977) Mouse spinal cord in cell culture. III. Neuronal chemosensitivity and its relationship to synaptic activity. *J Neurophysiol* 40(5):1163–1177
16. Ransom BR et al (1977) Mouse spinal cord in cell culture. II. Synaptic activity and circuit behavior. *J Neurophysiol* 40(5):1151–1162
17. Ransom BR, Goldring S (1973) Ionic determinants of membrane potential of cells presumed to be glia in cerebral cortex of cat. *J Neurophysiol* 36(5):855–868
18. Ransom BR, Goldring S (1973) Slow depolarization in cells presumed to be glia in cerebral cortex of cat. *J Neurophysiol* 36(5):869–878
19. Ransom BR, Goldring S (1973) Slow hyperpolarization in cells presumed to be glia in cerebral cortex of cat. *J Neurophysiol* 36(5):879–892
20. Ransom BR, Kettenmann H (1990) Electrical coupling, without dye coupling, between mammalian astrocytes and oligodendrocytes in cell culture. *Glia* 3(4):258–266
21. Ransom BR et al (1977) Mouse spinal cord in cell culture. I. Morphology and intrinsic neuronal electrophysiologic properties. *J Neurophysiol* 40(5):1132–1150
22. Ransom BR et al (1992) Anoxia-induced changes in extracellular K^+ and pH in mammalian central white matter. *J Cereb Blood Flow Metab* 12(4):593–602
23. Ransom CB et al (2000) Activity-dependent extracellular K^+ accumulation in rat optic nerve: the role of glial and axonal Na^+ pumps. *J Physiol* 522(Pt 3):427–442
24. Rose CR, Ransom BR (1996) Intracellular sodium homeostasis in rat hippocampal astrocytes. *J Physiol* 491(2):291–305
25. Rose CR, Ransom BR (1997) Gap junctions equalize intracellular Na^+ concentration in astrocytes. *Glia* 20(4):299–307
26. Serrano EE et al (1988) Effects of chronic phenobarbital exposure on cultured mouse spinal cord neurons. *Ann Neurol* 24(3):429–438
27. Sontheimer H et al (1991) Na^+ -current expression in rat hippocampal astrocytes in vitro: alterations during development. *J Neurophysiol* 65(1):3–19
28. Sontheimer H et al (1991) Relationship between Na^+ current expression and cell-cell coupling in astrocytes cultured from rat hippocampus. *J Neurophysiol* 65(4):989–1002
29. Von Blankenfeld G et al (1993) Development of cell-cell coupling among cells of the oligodendrocyte lineage. *Glia* 7(4):322–328
30. Walls AB et al (2008) Characterization of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) as an inhibitor of brain glycogen shunt activity. *J Neurochem* 105(4):1462–1470
31. Yamate CL, Ransom BR (1985) Effects of altered gliogenesis on activity-dependent K^+ accumulation in the developing rat optic nerve. *Brain Res* 353(2):167–173
32. Ye ZC et al (2009) Pharmacological “cross-inhibition” of connexin hemichannels and swelling activated anion channels. *Glia* 57(3):258–269