

19th International Neuroscience Winter Conference, Sölden Austria (March 26th-March 30th 2017, Das Central)

ISN Symposium on Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases, Thursday March 30th, 9:00-11:00, Symposium 8

Number of attending people: 25

Organized and chaired by Philip M. Beart (Australia) and Olga Corti (France)

Speakers:

- 1) Philip Beart (phil.beart@florey.edu.au), Florey Institute of Neuroscience and Mental Health, Melbourne, Australia.
Autophagy good and bad : Beneficial targeting in neuropathologies.
- 2) Angelo Poletti (angelo.poletti@unimi.it), Center of Excellence on Neurodegenerative Diseases, University of Milan, Italy.
Autophagy and polyglutamine diseases: The case for spinal and bulbar muscular atrophy.
- 3) Klas Blomgren (klas.blomgren@ki.se), Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg and Karolinska Institute, Stockholm, Sweden.
Neuroprotection by selective neuronal deletion of Atg7 in neonatal brain injury.
- 4) Olga Corti (olga.corti@upmc.fr), Institut du cerveau et de la Moelle épinière (Brain and Spine Institute), Paris, France.
Mechanisms of mitochondrial quality control and consequence of their dysfunction in autosomal recessive Parkinson's disease.

Highlights of the symposium:

Autophagy malfunction caused by gene mutations and/or aggregation-prone proteins is a hallmark of several human neurodegenerative diseases. Drugs that aid the clearance of potentially toxic debris or damaged organelles are now the focus of escalating attention as potential therapeutics.

This symposium covered basic aspects of brain autophagy with an emphasis on the roles of key genes and signaling pathways involved in ischemia, Parkinson's disease and polyglutamine diseases. The presentations integrated cellular, molecular and functional studies in diseased human brain, mouse models, neuronal and glial cells. The session provided an up-to-date overview of the critical functions of autophagy in these neurodegenerative conditions and highlighted prospects for therapeutic targeting.

Philip Beart, Florey Institute of Neuroscience and Mental Health (Australia), commenced the symposium with a talk addressing autophagy as a proteostatic mechanism for the clearance of damaged proteins/organelles to maintain cellular homeostasis, and which is increasingly proposed as a therapeutic target for neuropathologies. He presented evidence that "load" determines the recruitment of autophagy in "good" and/or "bad" modes in injured brain. His work addressed these concepts in oxidatively-stressed neurones, post-mortem brain tissue from stroke patients and a mouse model of motoneurone disease. In bioenergetic crisis complex I/II mediated effects were linked to mitochondrial autophagy. The FDA-approved molecule

rilmendidine showed potential as an autophagy activator in cellular models, but load of misfolded protein could result in detrimental “bad” autophagy. Targeting of autophagy has therapeutic possibilities but the pathology and its clinical stage need careful consideration.

This presentation was followed by that of the Angelo Poletti, Center of Excellence on Neurodegenerative Diseases, University of Milan (Italy), who discussed the role of autophagy- and proteasome-dependent protein quality control mechanisms in polyglutamine diseases. He focused on the example of the androgen receptor, which contains an expanded polyglutamine tract and accumulates in a toxic, misfolded conformation resistant to autophagic degradation in the motoneuron disease, spinal and bulbar muscular atrophy (SBMA). He showed in cell models that blocking autophagy by inhibiting the dynein-dependent retrograde transport of key chaperone complexes targets the misfolded androgen receptor towards an alternative, more efficient, proteasome-dependent clearance pathway. He further showed that manifestation of disease symptoms in a transgenic SBMA mouse model is associated with upregulation in the muscle of key autophagy components, as well as molecular chaperones that preferentially route the mutant receptor towards the autophagy system. Altogether the data presented open new therapeutic perspectives for SBMA and provide potential muscle-specific biomarkers to follow disease progression and evaluate the efficiency of treatments in patients.

The third speaker, Klas Blomgren, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg and Karolinska Institute (Sweden), focused his presentation on the role of autophagy in neuronal death and brain injury occurring during perinatal asphyxia. He presented the effects of the selective neuronal deletion of the autophagy-related 7 gene in a mouse model of severe neonatal hypoxia-ischemia caused by the unilateral ligation of the carotid artery. The results were consistent with “bad” autophagy in this model: autophagy blockade resulted in significant neuronal and brain tissue preservation, associated with reduced activation of caspase-dependent and independent cell death pathways and less extensive inflammation. A parallel analysis of key autophagy markers in the affected regions of the brains of severely asphyxiated human newborns revealed signs of autophagy exacerbation in the dying neurons. The data are altogether consistent with maladaptive neuronal autophagy in the immature brain and suggest that autophagy inhibition could improve the outcome of perinatal asphyxia.

Olga Corti, Brain and Spine Institute, ICM, Paris (France), concluded the symposium by addressing the role of dysfunctional mitochondrial quality control in familial Parkinson’s disease forms linked to the PINK1 kinase-driven Parkin ubiquitin ligase system. She provided evidence in primary neurones from a knock-out mouse model that Parkin-deficiency not only impairs mitophagy but also disrupts the establishment of other cell-protective pathways under mitochondrial stress, including mitochondrial biogenesis. In microglial cells, Parkin-deficiency was associated with exacerbated responses to activation by proinflammatory stimuli and, specifically, with overactivation of the NLRP3 inflammasome. This defect that was also observed in human macrophages from patients with Parkin-linked Parkinson’s disease. Finally, a new role of the PINK1/Parkin system in the regulation of mitochondrial protein import through the translocase of outer mitochondrial membrane was presented, identified in cell models by the use of a new genetically encoded reporter of the import process.

The audience sought clarification on specific issues arising from each presentation. It was apparent that the symposium was well structured and that the talks, which complemented each other nicely, were well received by the audience.

ISN budget utilization

Speaker	O. Corti	Phil Beart	K. Blomgren	A. Poletti
Registration	415	Free	415	415
Accommodation Das Central, 4 nights (single occupancy)	695	695	695	695
Budget flight	360	1,235	400	350
Airport transfer	none	210	210	210
TOTAL	1470\$	2140\$	1720\$	1670\$

13th April, 2017

Roberto Cappai - Attendee report on ISN Symposium on Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases.

I attended the ISN Symposium on Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases, which was held on Thursday, 30th March, 9:00-11:00am, as part of the 19th International Neuroscience Winter Conference, Sölden Austria, March 26th - 30th 2017.

I rate this ISN sponsored symposium highly. The introductory talk by Philip Beart (Australia) provided an excellent summary on autophagy for the general audience and established important background information for the other speakers. The next three speakers Klas Blomgren (Sweden), Angelo Poletti (Italy) and Olga Corti (France) gave detailed talks on the role of autophagy in different brain diseases / injury. All three talks were high quality and utilised sophisticated animal and cell culture models and state of the art techniques in cellular and molecular biology and neurobiology. The talks described the positive and negative roles of autophagy in response to neurodegeneration and injury, and the neurochemical basis for its actions. The symposium succeeded in educating the audience on the role of autophagy in neurodegeneration and resulted in a robust and active question time by the participants. Overall, a very successful symposium.



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To whom it may concern

I attended the ISN Symposium on Autophagy in neurodegeneration on 30th March 2017, as part of the 19th International Neuroscience Winter Conference in Sölden, Austria. My overall impression was very positive (the quality of the speakers, timeliness of topics and intensity of discussions were all in the top 10% range). The presentations covered a wide range of cellular, molecular and functional studies in experimental models pointing to novel autophagy mechanisms in neurons or glial cells. The first talk was given by Philip Beart (Australia) who introduced the general audience to the topic. Klas Blomgren (Sweden), Angelo Poletti (Italy) and Olga Corti (France) then gave very informative presentations on the role of autophagy in various neurological diseases (including ischemia, Parkinson's disease, polyglutamine diseases, and spinal motoneuron atrophy). All four speakers provided excellent up-to-date overviews of the critical functions of autophagy in neurodegenerative conditions and highlighted prospects for therapeutic targeting.

Lars Klimaschewski MD PhD

21 April 2017

Björn Falkenburger - Attendee report on ISN Symposium on Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases.

I attended the ISN Symposium on Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases, which was held on Thursday, 30th March, 9:00-11:00am, as part of the 19th International Neuroscience Winter Conference, Sölden Austria, March 26th - 30th 2017.

For me, this ISN sponsored symposium was the best symposium of the Neuroscience Winter Conference. Philip Beart (Australia) provided an introduction on autophagy and an in depth discussion of the various roles autophagy can play in the course of disease processes. Specifically, he explained that autophagy can on the one hand serve protective roles by removing toxic cellular content and on the other hand constitute a form of cell death. For instance, blocking autophagy can reduce toxicity of H₂O₂ in neurons. Klas Blomgren (Sweden) detailed the role of autophagy for ischemic damage in neonate rodents. Again, mice with impaired autophagy showed smaller infarcts, indicating that in this model autophagy contributes to cell death. Angelo Poletti (Italy) described a detailed analysis of autophagic degradation of polyglutamine aggregates. He demonstrated that two protein complexes containing small heat shock proteins deliver cargo either to the proteasome or to the aggresome for autophagic degradation. In addition, he pointed out that inhibition of one pathway can stimulate degradation through the other pathway. In contrast to the first two talks, autophagy here serves a protective role by removing polyglutamine aggregates. Similarly, the data presented by Olga Corti (France) on mitophagy detailed a protective role of autophagy. Damaged mitochondria through the TOM complex recruit PINK and parkin for autophagic degradation. In addition, however, parkin and the TOM proteins participate in import of proteins into mitochondria. This was demonstrated by an elegant BRET biosensor specifically taken up into mitochondria. Overall, the symposium thus provided a very balanced overview of the multiple roles of autophagy in neuronal cells.



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Group Photo, Speakers of ISN Symposium on Autophagy in neurodegeneration, 19th International Neuroscience Winter Conference, Sölden Austria, March 29 2017. From left to right: Klas Blomgren, Philip Beart, Olga Corti, Angelo Poletti