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# Prion meeting 2023: implications of a growing field

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**ABSTRACT**

The history of human prion diseases began with the original description, by Hans Gerhard Creutzfeldt and by Alfons Maria Jakob, of patients with a severe brain disease that included speech abnormalities, confusion, and myoclonus, in a disease that was then named Creutzfeldt Jakob disease (CJD). Later, in Papua New Guinea, a disease characterized by trembling was identified, and given the name "Kuru". Neuropathological examination of the brains from CJD and Kuru patients, and of brains of sheep with scrapie disease revealed significant similarities and suggested a possible common mode of infection that, at the time, was thought to derive from an unknown virus that caused slow infections. John Stanley Griffith hypothesized that the agent causing these diseases was "probably a protein without nucleic acid" and, in 1982, Stanley Prusiner reported the identification of a proteinaceous infectious particle (coining the term prion) that was resistant to inactivation methods that were at the time standard for nucleic acids, and identified PrP as the major protein component of the infectious agent in scrapie and in Creutzfeldt-Jakob disease, classifying this also as a prion disease. Interestingly, the prion concept had been previously expanded to yeast proteins capable of replicating their conformation, seeding their own aggregation and transmitting phenotypic information. The prion concept has been more recently expanded to refer to misfolded proteins that are capable of converting a normal form of a protein into an abnormal form. The quest to understand and treat prion diseases has united a specific research community around the topic, and regular meetings (Prion Meetings) have taken place over the years to enable discussions, train junior researchers, and inspire research in the field.

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## Prion diseases: the birth and growth of a global field of research

The history of human prion diseases began with the original description of patients with a severe unknown brain disease in 1920. The description was made, independently, by Hans Gerhard Creutzfeldt and by Alfons Maria Jakob, and included speech abnormalities, confusion, and myoclonus, in a disease that was then named Creutzfeldt Jakob disease (CJD). In the 1950s, in Papua New Guinea, a disease characterized by trembling was identified, and given the name 'Kuru', which is the Fore language word for trembling.

Neuropathological examination of the brains from CJD and Kuru patients, and of the brains of sheep with scrapie disease, revealed significant similarities and suggested a possible common mode of infection that, at the time, was thought to derive from an unknown virus that caused slow infections. However, in 1967, John Stanley Griffith hypothesized that the agent causing these diseases was 'probably a protein without nucleic acid' [1]. In 1982, Stanley Prusiner and his colleagues investigated the nature of the infectious agent in scrapie, and reported the identification of a proteinaceous infectious particle (coining the term prion) that was resistant to inactivation methods that were at the time standard for nucleic acids, i.e., for inactivating viruses [2–5]. In 1983, Prusiner's team identified PrP as the major protein component of the infectious agent in scrapie [6] and later confirmed that the molecular and biological properties of the agent were identical to that in Creutzfeldt-Jakob disease, classifying this also as a prion disease [7]. In the 1990s, the emergence of variant Creutzfeldt-Jakob Disease (vCJD), due to the ingestion of contaminated beef-products, constituted a hallmark in the field prion diseases [8]. This discovery, challenging the species barrier, underscored the complexity of prion transmission, and fuelled the field in subsequent years. More generally, prion diseases are transmissible spongiform encephalopathies (TSEs), i.e. transmissible, fatal neurodegenerative

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diseases in humans and animals that, upon neuropathological examination, display a typical 'sponge'-like appearance due to the holes observed in the brain.

Interestingly, the prion concept had been previously expanded to yeast proteins with the capability of replicating their conformation, thereby seeding their own aggregation and transmitting phenotypic information [9].

Although the 'original' human prion diseases (diseases caused by scrapie PrP) are rare, the prion concept has been more recently expanded to refer to misfolded proteins that are capable of converting a normal form of a protein into an abnormal form, which is thought to cause disease in humans. While recent research explores the extension of the prion concept to diseases such as Alzheimer's or Parkinson's, it underscores that actual infection appears to remain confined to the realm of PrP-associated disorders.

In short, this was the birth of an intriguing and exciting field of research that, after several decades of intense research, continues to intrigue the research community, and poses tremendous societal issues due to the severe public health implications for both animals and humans. The quest to understand and treat prion diseases has united a specific research community around the topic, and regular meetings (Prion Meetings) have taken place over the years to enable discussions, train junior researchers, and inspire research in the field.

## Prion meeting 2023: the logistics

The Prion Meeting 2023 (https://prion2023.org/) took place between October 16 and 19 at the University of the Algarve, in Faro, the capital city of the Algarve region in southern Portugal. Unexpectedly, as this is typically a dry and sunny region in Portugal, the 2023 meeting was blessed by rain, to ensure the participants were not distracted by the beautiful landscapes, white sandy beaches, famous golf courses, or the peaceful shaded areas of the university campus, and stayed focused on prions.

The University of the Algarve, the Faculty of Medicine and Biomedical Sciences, and the Algarve Biomedical Center (ABC, https://abcmedicalg.pt/) were instrumental partners, ensuring the success of the meeting focused on a topic of growing importance, given the general ageing of the human population. In fact, as we learned, this tri-partite endeavour aims at not only training a differentiated group of physicians and researchers in the field of medicine and biomedicine but also to act as a reference centre for active and healthy ageing. Impressively, the ABC is deeply committed to promoting active ageing by preparing and supporting the local communities for an active and healthy life.

The Prion Meeting 2023 also benefited from the generous support of a number of sponsors (full list at https://prion2023.org/), which enabled the organizers to offer travel awards to all junior scientists who applied for financial support and to award prizes to the best poster and the best junior oral presentation. In recognition of the strategic importance of the meeting, which brought together >320 leading experts in the field from 26 countries, the meeting also received the high patronage of the President of Portugal, himself an academic albeit in the field of law.

## Prion meeting 2023: the scientific programme

As in previous editions, the meeting started on October 16 with pre-meeting workshops designed to train junior scientists on specific topics. We kicked off with two introductory lectures on the History of animal prion diseases, by Prof. Jason Bartz, and on the History of human prion diseases, by Prof. Richard Knight. Prof. Markus Glatzel organized the workshop on 'Neuropathology and clinicopathological correlation of human prion diseases and related dementias', where participants were introduced to key neuropathology concepts of CJD, Alzheimer's and Parkinson's disease. Prof. Tiago Outeiro organized the workshop on 'Cell and animal models of prion and prion-like diseases', where the speakers discussed cell and animal models used in the study of the molecular underpinnings of prion diseases. Prof. Tuane Vieira organized the workshop on 'Structural biology techniques for studying prion protein in vitro and in silico', a topic of growing importance given the need to understand the structural determinants of protein aggregation to enable the development of therapeutics.

The main programme of the meeting took place between October 17 and 19 and included 12 scientific sessions, and each session included 1 or 2 keynote lectures. Session 1 was focused on Protein structure, function, conversion and dysfunction, and started with the keynote lecture by Dr Szymon Manka on the structural biology of prions in 4D, covering their findings using *ex vivo* material, *in cellulo*, and with the goal of achieving *in situ* resolution. Session 2 focused on Yeast prions and on functional protein aggregates such as stress granules. The keynote speaker, Dr Reed Wickner, presented their recent work on anti-prion systems and how they function in cells. On session 3, the focus was on the spreading of pathology in prion-like diseases, and started with the lecture by Dr Mathias Jucker on amyloid-beta seeds and how they spread. Session 4, the last talk on the first day of the meeting, focused on pathogenic mechanisms in prion diseases, and opened with the lecture by Dr David Westaway on the endoproteolysis of the cellular prion protein and on how this is relevant for pathogenesis. Session 5 explored the connection between prion diseases and other disorders. This is a broad topic, so

we had a lecture by Dr Jerson Silva, on the prion-like aggregation and phase transition of mutant p53 and how this is relevant in cancer, and Dr Sophie Mouillet-Richard explored the role of PrP in neurodegeneration and cancer. Session 6 focused directly on the cell biology of PrP. Again, since this is a broad topic that can be explored from multiple angles, we started with a lecture by Dr Christina Sigurdson on deranged synaptic signalling in experimental models of prion disease, and followed with a lecture by Dr Chiara Zurzolo on the role of tunnelling nanotubes in the spreading of various prions. In session 7 the focus was on animal prion diseases, and started with the keynote lecture by Dr Glenn Telling on strategies to characterize emerging and established strains of chronic wasting disease. Session 8 focused on the transmission of prions and prion-like proteins and started with the lecture by Dr Jiyan Ma on understanding the seeding capability, transmissibility and pathogenicity of prions. Finally, the last day of the meeting started with session 9 on Biomarkers for prion and other neurodegenerative diseases, and opened with the lecture by Dr Inga Zerr on their recent work on biomarkers for prion and other neurodegenerative diseases. Session 11 focused on therapeutic approaches in neurodegeneration. This session included lectures by Dr Jeffrey Kordower on current approaches in neurodegeneration, by Dr Sonia Vallabh on the benefit of lowering PrP in various models, by Dr Pekka Kallunki on the use of novel antibodies for lowering the seeding of pathology of alpha-synuclein, and by Dr Warren Hirst, who reviewed the status of therapeutic approaches in Alzheimer's disease. In each session, the keynote lectures were followed by three presentations selected from the abstracts submitted. This format, used already in previous meetings, ensures ample opportunities for both senior and junior scientists to present their work at the Prion meetings. Session 12 included presentations selected from the abstracts submitted, which were considered late breaking news.

As in previous meetings, the programme included a special lecture and, in this edition, we heard from Prof. John Collinge about the history of prions. This was a remarkable and engaging overview of the field that attracted the attention of both junior and senior participants.

The main topics of the meeting ranged from basic studies of protein structure and function, to biological roles of prions and mammalian functional aggregates, and to pathogenic mechanisms and transmission of pathological proteins in both animal and human prion diseases. Knowledge of these topics has fuelled the discovery and biomarkers that are now widely used in the clinical practice in prion diseases, inspiring the development of a variety of therapeutic strategies in neurodegenerative diseases.

One highlight of the meeting was session 10, organized by the 'CJD International Support Alliance', with the involvement of patient organizations from the USA, France, Australia, and Portugal. These organizations play key roles in supporting patients and family members,


**Figure 1.** Photograph of the art of science panel. the creativity of a local artist connecting scientific images using graffiti.

providing guidance, advice, and support during the devastating journey of the various terrible prion diseases. Importantly, they enable people to share their experiences, fears, and hopes, inspiring us researchers to continue the quest to stop these diseases from taking human lives, most of the time way too early.

At the end of day 1, the 'Art of Science' event (https://science-artof.org/) created a relaxing moment where science was connected by art, engaging the participants as they watched a local artist create (Figure 1).

The programme was a remarkable gathering that not only delved into the intricacies of prion proteins but also showcased a noteworthy expansion of the scientific discourse to encompass related proteins. The breadth of topics covered revealed the interconnectedness of research in neurodegenerative diseases. While the primary focus of the meeting remained on prion-related disorders, the large number of presentations exploring various other proteins emphasized the broader implications of prion research over the years. Thus, it is evident that investigations of prions, initially associated with rare diseases, have far-reaching implications, and resonate beyond the immediate scope of the prion community. The meeting served as a testament to the collaborative efforts to unravel the complexities of protein misfolding disorders, and highlighted the potential for cross-disciplinary insights to contribute significantly to understanding these intricate biological phenomena.

## Prion meeting 2023: overview and outlook

In a field where hopes are, invariably, shattered by devastating suffering and loss, the Prion Meetings serve the unique purpose of bringing scientists and caregivers together, under the universal umbrella of science. At the Prion Meeting 2023, we learned about significant advances in both basic science and in the forthcoming therapeutic arena. Importantly, the meeting highlighted that, despite tremendous progress, we still need to seriously invest in basic science to fuel translation in order to ease human suffering. The Prion Meetings will continue to serve this purpose, and the 2024 edition will take place on October 21–25, in Nanchang, Jiangxi Province, in China.

In conclusion, the success of the Prion Meeting 2023 also demonstrates that the Algarve region of Portugal is not just a beautiful place for vacation and retirement, but it is also a great place for scientific meetings of the highest calibre.

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## Author contributions

Both authors Tiago Outeiro and Tuane Vieira conceived, wrote and are accountable for all aspects of the manuscript.

## Data sharing

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