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MEETING REPORT

25 years of yeast prions

Symposium honouring the 25-year anniversary of Reed Wickner's discovery of yeast prions

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In the early 1990s, Reed Wickner developed a novel hypothesis. For decades it was known that two phenotypes of the yeast *Saccharomyces cerevisiae* followed non-Mendelian patterns of inheritance [1,2]. These phenotypes were designated [PSI+] and [URE3]. When yeast strains were mated, if either parental strain had one of these phenotypes, all daughter spore clones would inherit the phenotype, although only half would be expected to if the phenotypes were governed by a nuclear gene. Instead, the genetic element resided in the cytoplasm as if it were one of the many yeast viruses. However, unlike yeast viruses, no nucleic acid could be identified. To explain these observations, Reed postulated that the genetic element was composed of protein, not nucleic acid.

In 1994, Reed solo-authored an article in *Science* titled, '*[URE3] as an altered URE2 protein: evidence for a prion analog in Saccharomyces cerevisiae*', where he described how the puzzling [URE3] and [PSI+] phenotypes could be explained simply as self-propagating misshapen forms of the Ure2 and Sup35 proteins, respectively [3]. His experiments elegantly demonstrated that the Ure2 protein was itself the critical factor for the formation and propagation of the [URE3] prion, and he proposed that it was a yeast analog of mammalian prions. Noting the logical parallels with [PSI+] and the Sup35 protein, he extended his hypothesis to include [PSI+] as a prion analog of the Sup35 protein, opening the door for discovery of other prions in yeast.

At that time, the prion concept – suggesting a form of the protein PrP was the infectious entity responsible for prion disease – was controversial and applied solely to the infectious species that caused transmissible spongiform encephalopathies of mammals (*e.g.* scrapie, Kuru and Mad Cow disease). Little else was known of PrP extracted from infectious brain aside from it being fibrous aggregates enriched in beta-sheet structure. Whether PrP was *a* prion component, *the* prion component, or merely a propagation factor for another pathological agent, was arguable. The question of whether prions existed in nature as defined (*i.e.* infectious proteins) remained unresolved.

The enormous impact of Reed's short paper is made obvious by the suddenly renewed and widespread interest in non-Mendelian genetic elements and the dramatic evolution of the scientific community's view of prions in the 25 years since its publication. The broad acceptance of prion mechanisms is largely based on work and ideas pioneered by Reed and colleagues in the yeast model system. These studies provided the first confirmation of protein-only infectious elements and identified a common structural model that enabled a mechanism of protein infectivity: self-propagating amyloid with parallel in-register beta-sheet architecture [4]. This conceptual framework established how prion, or prion-like, mechanisms could be involved in human diseases, especially neurodegenerative disorders that commonly feature pathological protein aggregation in neuronal networks. This structural insight also explained how a variety of prion strains (or variants, with subtle differences in phenotype) could be 'encoded' and perpetuated by molecular variations in the underlying amyloid configuration. Reed thus provided a mechanism by which proteins could act as genes by templating their own conformation, just as DNA mediates inheritance by templating its sequence [5].

Recognizing that the misfolded proteins underlying prion phenotypes were a disease state [6], Reed also astutely identified that the domains facilitating prion formation were serving cellular functions that were independent of their amyloid-forming properties [7]. These intrinsically disordered domains with low-sequence complexity are found in dozens of different yeast proteins that appear to have at least some

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prion-forming capacity. Therefore, many researchers speculated that the purpose of these domains was to form functional self-propagating amyloid in yeast. However, these domains are now largely considered critical to assembly into distinct and reversible subcellular liquid-like phases, while transition into an insoluble amyloid phase is considered more indicative of molecular pathology [8]. In fact, Reed showed that yeast prion amyloid is generally toxic [9], and he exploited this property to identify and characterize many 'anti-prion' systems that typically, and logically, involve factors that act in cellular protein quality control [10].

With his single publication in 1994, Reed Wickner launched new fields of study. Hundreds of papers that address everything from fungal prions to protein quality-control mechanisms cite his 1994 Science paper and the scores of subsequent articles Reed has corresponded. To recognize and publicize the breadth of his impact and to celebrate the 25-year anniversary of his seminal Science paper, a symposium was held on October 28 at the National Institutes of Health in Bethesda, MD, where Reed is currently the Chief of the Laboratory of Biochemistry and Genetics of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). During the day-long event, many highly accomplished prion and structural biologists discussed their science and acknowledged Reed's outsized contributions to their research programs. Speakers included Sue Liebman, Mick Tuite, Yury Chernoff, Marie-Lise Maddelein, Rob Tycko, Tatiana Chernova, Byron Caughey, Herman Edskes, Dan Masison, Frank Shewmaker and Eric Ross. The symposium's topics (mammalian prions, yeast protein chaperones, structures and sequence-determinants of prion domains, yeast viruses, etc.) could all be linked to work originating in Reed Wickner's lab at the National Institutes of Health. The research community is grateful to Reed for his significant contributions to science.

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References

[1] Lacroute F. Non-Mendelian mutation allowing ureidosuccinic acid uptake in yeast. J Bacteriol. 1971 May;106 (2):519–522.
[2] Cox BS, Tuite MF, McLaughlin CS. The psi factor of yeast: a problem in inheritance. Yeast. 1988 Sep;4(3):159–178.
[3] Wickner RB. [URE3] as an altered URE2 protein: evidence for a prion analog in Saccharomyces cerevisiae. Science (New York, NY). 1994 Apr 22;264(5158):566–569.
[4] Tycko R, Wickner RB. Molecular structures of amyloid and prion fibrils: consensus versus controversy. Acc Chem Res. 2013 Jul 16;46(7):14–96.
[5] Wickner RB, Edskes HK, Bateman DA, et al. Amyloid diseases of yeast: prions are proteins acting as genes. Essays Biochem. 2014;56:193–205.
[6] Wickner RB, Edskes HK, Bateman D, et al. The yeast prions [PSI+] and [URE3] are molecular degenerative diseases. Prion. 2011 Oct-Dec;5(4):258–262.
[7] Shewmaker F, Mull L, Nakayashiki T, et al. Ure2p function is enhanced by its prion domain in Saccharomyces cerevisiae. Genetics. 2007 Jul;176 (3):1557–1565.
[8] Franzmann TM, Alberti S. Prion-like low-complexity sequences: key regulators of protein solubility and phase behavior. J Biol Chem. 2019 May 3;294 (18):7128–7136.
[9] McGlinchey RP, Kryndushkin D, Wickner RB. Suicidal [PSI+] is a lethal yeast prion. Proc Natl Acad Sci U S A. 2011 Mar 29;108(13):5337–5341.
[10] Wickner RB. Anti-prion systems in yeast. J Biol Chem. 2019 Feb 1;294(5):1729–1738.