EDITORIAL

The call of the unknown: The story of $[PSI^+]$

Yury O Chernoff$^{1,2,*}$

$^1$School of Biology; Georgia Institute of Technology; Atlanta, GA USA;
$^2$Laboratory of Amyloid Biology and Institute of Translational Biomedicine;
St. Petersburg State University; St. Petersburg, Russia

The current issue of *Prion* marks the 50th anniversary of the discovery of the non-Mendelian element $[PSI^+]$ by Brian Cox in 1965.$^1$ The Profiles and Legacies paper, written by M. Tuite, G. Staniforth and B. Cox,$^2$ provides an excellent first-hand account of $[PSI^+]$ growing from a mysterious phenomenon of unknown nature into a well-documented example of the protein-based transmissible element, highlighting new mechanisms of inheritance and evolution. This paper is accompanied by reflections from several leading researchers in the yeast prion field, sharing their personal memories of being acquainted with $[PSI^+]$ and its discoverer. We hope that our readers will join us in celebrating this remarkable anniversary.

In addition to summarizing major achievements in studying this yeast prion, the story of $[PSI^+]$ teaches us a more general lesson. Prevailing rules of the game in the modern era of constant competition for research funding require grant applications to prove beyond any reasonable doubt that a success of the proposed research is essentially guaranteed. With rare exceptions, funding agencies no longer fund discoveries. Instead, they prefer to fund expansions or applications of existing knowledge. From their point of view, an investigator cannot start full scale research until he/she identifies a culprit. Following the same approach, many leading academic journals will not publish a paper until the authors have completely deciphered the mechanism of the observed phenomena.

No doubt, such an emphasis on guaranteed results and proven mechanisms does play an important role in shaping the scientific enterprise and making it highly productive. However, one might argue that it is also shaping a new generation of scientists for whom science may indeed become more an enterprise rather than a search for the unknown. $[PSI^+]$ provides an excellent example of how a research strategy, initially driven entirely by the researchers’
curiosity, can turn very productive and practical in the end.

Indeed, by now \(\text{PSI}^+\) has become the best understood example of a yeast prion, and arguably, the best understood example of a prion in general. As most of the readers of our journal undoubtedly know, prions are transmissible protein isoforms that can spread and proliferate by converting the non-prion isoform of the same amino acid sequence into a prion. First defined as infectious agents of certain neurodegenerative diseases by Stanley Prusiner,\(^3\) prions have now become linked to a variety of both pathological and possibly adaptive biological phenomena. Yeast prions represent a previously unknown protein-based mechanism of inheritance, based on structural templating rather than on the replication of a sequence (for review, see ref. 10). Chimeric constructs involving \(\text{SUP35}\), a protein that is responsible for the \(\text{tRNA}\) translation machinery of prion propagation was deciphered by employing \(\text{PSI}^+\) as a model (for review, see ref. 10). Chimeric constructs involving Sup35, a protein that is responsible for \(\text{PSI}^+\), were/are employed to identify other prions and study their properties (e.g., ref. 11). \(\text{PSI}^+\) was used to establish the first \textit{in vitro} assay for studying interactions between different prions (e.g., refs. 12, 13). This list is certainly incomplete, and more examples of the impact made by \(\text{PSI}^+\) on various directions of research in prion biology can be found in recent reviews, including the Tuite et al. paper.\(^2\) However, even from such an incomplete list, it is clear that the efforts spent on studying the initially mysterious and obscure non-Mendelian element were paid off by its contributions to understanding new principal mechanisms of biological and pathological phenomena.

While working on yeast translation in the Sergey G. Inge-Vechtomov group at St.-Petersburg University in 1980s, I became fascinated with the then unexplained phenomenon of \(\text{PSI}^+\). True, some older people told me: “How can you study this? No one knows what \(\text{PSI}^+\) is!” As I have realized later, they were speaking from experience. Fortunately, I was unexperienced then, and the mystery of \(\text{PSI}^+\) was exactly what made it interesting for me. Even more fortunately, my advisor, as well as other professors, Bun-ichiro Ono at University of Okayama and Sue Liebman at University of Illinois-Chicago, whose labs I joined subsequently (and Sue Lindquist with whom I started a collaboration while in Chicago), shared this attitude despite their experience. As a result, \(\text{PSI}^+\) has become an essential part of my scientific life, and later, I never had a reason to regret that I have yielded to the call of the unknown.

My first interaction with Brian Cox occurred when I submitted the manuscript to \textit{Current Genetics} in early 1990s. In this paper, we had described that \(\text{PSI}^+\) can be induced \textit{de novo} by a multicopy plasmid carrying the \textit{SUP35} gene. Obviously, we could not explain a mechanism of this phenomenon at that time, as “no one knew what \(\text{PSI}^+\) was.” Once again, a spark of fortune was that our manuscript was published,\(^{14}\) and I hope that it has provided some useful information to Reed Wickner when he came out with the prion model for \(\text{PSI}^+\) the following year.\(^{15}\) The breakthrough paper by Wickner entirely changed the landscape, and our next manuscript demonstrating the role of the chaperone Hsp104 in \(\text{PSI}^+\) propagation went to \textit{Science} in 1995.\(^{16}\) Surely \(\text{PSI}^+\) remains dear to my heart even after its nature has been deciphered. But what makes me especially happy is that I liked \(\text{PSI}^+\) as a frog even before it turned into a prince.

To conclude, perhaps the most important lesson that we can learn from the \(\text{PSI}^+\) story is that one should not resist the call of the unknown even when the results are not guaranteed. The fearless crusade that Brian Cox, Mick
Tuite and their coworkers pursued with the aim to decipher the true nature of [PSI+] eventually resulted in the elimination of all “conventional” explanations and laid a foundation for new revolutionary developments. This is the effort put forth by the founder of the [PSI+] story and by other scientists who subsequently joined and advanced the field that we applaud today in the anniversary issue of Prion.

ACKNOWLEDGMENTS

I thank P. Chandramowlishwaran, Z. Deckner and R. Howie for helpful comments.

FUNDING

This publication was supported by grant 14-50-00069 from Russian Science Foundation.

REFERENCES

1. Cox BS. $\psi$, a cytoplasmic suppressor of super-suppressors in yeast. Heredity 1965; 20:505-21; PMID:NOT_FOUND; http://dx.doi.org/10.1038/hdy.1965.65
2. Tuite MF, Staniforth GL, Cox BS. [PSI+] turns 50. Prion 2015; 9(this issue)
3. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science 1982; 216:136-44; PMID:6801762; http://dx.doi.org/10.1126/science.216.4532.136
4. Liebman SW, Chernoff YO. Prions in yeast. Genetics 2012; 191:1041-72; PMID:22379407; http://dx.doi.org/10.1534/genetics.111.137760
5. Bailey CH, Kandel ER, Si K. The persistence of long-term memory: a molecular approach to self-sustaining changes in learning-induced synaptic growth. Neuron 2004; 44:49-57; PMID:15450159; http://dx.doi.org/10.1016/j.neuron.2004.09.017
6. Glover JR, Kowal AS, Schirmer EC, Patino MM, Liu JJ, Lindquist S. Self-seeded fibers formed by Sup35, the protein determinant of [PSI+], a heritable prion-like factor of S. cerevisiae. Cell 1997; 89:811-9; PMID:9182769; http://dx.doi.org/10.1016/S0092-8674(00)80264-0
7. Paushkin SV, Kusnirov VV, Smirnov VN, Ter-Avanessyan MD. In vitro propagation of the prion-like state of yeast Sup35 protein. Science 1997; 277:381-3; PMID:9219697; http://dx.doi.org/10.1126/science.277.5324.381
8. King CY, Diaz-Avalos R. Protein-only transmission of three yeast prion strains. Nature 2004; 428:319-23; PMID:15029195; http://dx.doi.org/10.1038/nature02391
9. Tanaka M, Chien P, Naber N, Cooke R, Weissman JS. Conformational variations in an infectious protein determine prion strain differences. Nature 2004; 428:323-8; PMID:15029196; http://dx.doi.org/10.1038/nature02392
10. Chernova TA, Wilkinson KD, Chernoff YO. Physiological and environmental control of yeast prions. FEMS Microbiol Rev 2014; 38:326-44; PMID:24236638; http://dx.doi.org/10.1111/1574-6976.12053
11. Alberti S, Halfmann R, King O, Kapila A, Lindquist S. A systematic survey identifies prions and illuminates sequence features of prionogenic proteins. Cell 2009; 137:146-58; PMID:19345193; http://dx.doi.org/10.1016/j.cell.2009.02.044
12. Derkatch IL, Bradley ME, Hong JY, Liebman SW. Prions affect the appearance of other prions: the story of [PIN+]. Cell 2001; 106:171-82; PMID:11511345; http://dx.doi.org/10.1016/S0092-8674(01)00427-5
13. Osherovich LZ, Weissman JS. Multiple Gln/Asn-rich prion domains confer susceptibility to induction of the yeast [PSI+] prion. Cell 2001; 106:183-94; PMID:11511346; http://dx.doi.org/10.1016/S0092-8674(01)00440-8
14. Chernoff YO, Derkach IL, Inge-Vechtomov SG. Multicopy SUP35 gene induces de-novo appearance of psi-like factors in the yeast Saccharomyces cerevisiae. Curr Genet 1993; 24:268-70; PMID:8221937; http://dx.doi.org/10.1007/BF00351802
15. Wickner RB. [URE3] as an altered URE2 protein: evidence for a prion analog in Saccharomyces cerevisiae. Science 1994; 264:566-9; PMID:7909170; http://dx.doi.org/10.1126/science.7909170
16. Chernoff YO, Lindquist SL, Ono B, Inge-Vechtomov SG, Liebman SW. Role of the chaperone protein Hsp104 in propagation of the yeast prion-like factor [psi+]. Science 1995; 268:880-4; PMID:7754373; http://dx.doi.org/10.1126/science.7754373