

Preface

The more pity that fools may not speak wisely what wise men do foolishly. *Touchstone, As You Like It, Act 1, Scene 2, Line 85*

Truth's a dog must to kennel; he must be whipp'd out... *The Fool, King Lear, Act 1, Scene 4, Lines 109–110*

Foolery, sir, does walk about the orb, like the sun; it shines everywhere. *Feste, Twelfth Night, Act 3, Scene 1, Lines 37–38*

The fool doth think he is wise, but the wise man knows himself to be a fool. *Touchstone, As You Like It, Act 5, Scene 1, Lines 31–32*

Some of Shakespeare's most memorable characters are Fools. Whether in Comedy or Tragedy, the Fools in Shakespeare's plays serve an important role that mirrored their historical position. Whether by intellect, simplicity, or station, they embody the "other" in Shakespeare's worlds, standing outside the primary context of the play and thereby serving to provide an "honest" commentary on the proceedings, stripped of the social niceties and motivations that temper the comments of the other characters. Their position as Fools to a great degree protects them from the consequences of their statements and actions. In the historical (?) eras of Absolutism, Fools often provided the only means of vocalizing critiques of rulers and their societies; many scholars interpret their role as a vital social mechanism for funneling and focusing dissent in a nondisruptive and nonthreatening way. A Fool might make the comments regarding a Royal personage's peccadillos that are on the forefront of the court members' minds but about which are unable to note or speak of for fear of repercussion; however, spouting forth from the mouth of the Fool these exact same thoughts can safely be greeted with laughter (albeit a bit ostentatiously nervous and not too long or loud...).

Fools are intrinsically paradoxical. They are able to express the most cutting of critiques, but in so doing reinforce the stability of the societies they critique. They are outsiders, but often with the most intimate of relationships with their masters (i.e., Lear and his Fool, Viola and Feste, Rosalind and Touchstone). This paradoxical duality is even manifest in the most recognizable guise of the Fool: the harlequin costume of opposing and alternating color blocks. In Shakespeare's plays, his most notable Fools, such as Touchstone, Feste, and Lear's Fool, are often seen as mouthpieces for the plays' author. While this interpretation remains the subject of many an English Major's thesis and open to scholarly debate, there is something intrinsically consistent with the paradoxical nature of Fools in the belief that the author, who cannot be more intimately related to the piece he is writing, places his own truest words in the mouth of the plays' representative outsider. Regardless of whether they represent Shakespeare's opinions and beliefs, certainly these three Fools appear to possess a perspective more encompassing than the other characters in the plays they inhabit. Touchstone is the voice of logical reasoning and objective assessment among the refugees in the Forest of Arden; Lear's Fool provides the most comprehensive view and assessment of the madness and chaos following Lear's fateful decision; and Feste appears at sometimes an omniscient observer regarding the machinations taking place in the Duchy of Illyria.

Perhaps, the lesson to be taken from Shakespeare's Fools is that possession of the wider perspective, a grasping of the big picture, is what provides the most uncomfortable and disruptive conclusions, which, for the sake of the society, can only be spoken by Fools. It is truly ironic, then, that at the end of each of the plays noted above, there has been a dramatic disruption and reshuffling of the conditions at their respective beginnings, those same conditions that required the placement of disruptive comments in a Fool's mouth in an attempt to forestall the paradigmatic shifts that eventually would come to pass. Perhaps, then, the Fool is not such a fool after all.

We contend that the biomedical research community could potentially benefit from listening to a pair of Fools. Today, in biomedical research, paradoxes abound. We know more about the generative processes and mechanisms of disease than at any other point in history. The rate of this data acquisition shows no signs of slowing down, yet the introduction of new and more effective therapeutics for the diseases that most trouble us has never been less efficient. Many of those diseases that most trouble us—cancer, sepsis, obesity, autoimmune disorders—represent the hijacking of otherwise beneficial biological processes: cancer of growth and healing, sepsis of inflammation, obesity

of metabolism, and autoimmune disorders of immune protection. Even those therapeutics that have been life saving in the past (and still are in the present) have been revealed as producing a whole new set of problems that, in many ways, arise because of their initial success: antibiotics leading to increasingly lethal resistance, life support measures in the intensive care unit leading to the purgatory of chronic organ insufficiency and recurrent infections. Inside the biomedical community (for legitimate reasons we will discuss in this book), it is too easy to look only toward the patch of blue sky representing future technological and intellectual achievement. Yet, if one looks more widely (and not even much more widely, as the examples above can attest to) there are signs of the storm clouds building. This book is intended to help us turn around and look.

Contrary to genius, which is born, Fools might be made, through the correct and fortuitous mix of temperament, training, timing, and terrain. Two decades ago, the intellectual terrain of critical illness was ripe for disruption: clinical trials for the treatment of sepsis that, by all ostensible criteria for success, should have worked, did not. There was the beginning of an existential crisis in the biomedical research community that persists to this day in the Translational Dilemma. The traditional community would quickly retrench and retool, but for those with the right level of training (i.e., not too deeply embedded in the traditional academic paths) and the appropriate temperament (i.e., curious, contrarian, and stubborn about it), this was an opportune time to learn to become a Fool. About 15 years ago, working separately and initially without knowledge of each other's work, two very different people with very different backgrounds and for very different reasons began to question the state of biomedicine in the context of critical illness. Gary, a trauma surgeon and intensive care physician, saw a clinical dilemma, and being outside the academic research structure, was unburdened by knowledge and possessing of procedural naiveté. As such, he started on his own, on the fringe, with the naïve concept that if he, as someone without formal research training, could apply these new techniques to the challenges facing the translation of basic research knowledge, then surely just that demonstration would be enough to lead to adoption (after all, what could possibly go wrong!). Yoram, a researcher, a biochemist and immunologist, had experienced the academic biomedical research community at near its highest level, but with enough insight and perspective to recognize both its best and worst characteristics. He, too, pursued an unorthodox path, forming part of the leadership of an interdisciplinary team before that description had become *de rigueur*, and enlisting the potential of industry by helping to start a biosimulation company. This odd couple had absolutely no reason to ever meet, to find common ground, to have compatible personalities, much less to collaborate. But, in 2002, they, as they say, "met cute" by total coincidence at lunch at the 25th Annual Meeting of the Shock Society. Conversation ensued, connections and common interests were identified, and a collaboration was born. Time and terrain contributed to foster the conditions that would enhance this collaboration, as at that 2002 meeting, Gary and Yoram were invited, along with their collaborators, to a workshop in Germany on complex systems approaches to critical illness. This led to the formation of the Society for Complex Acute Illness, which has and continues to serve as the focal point for the most dynamic discussions and developments in this still-growing field.

The simple fact that pursuing this line of investigation required the formation of a new scientific society points to the "outsider" nature of the endeavor. Yet while they remained outsiders, they kept hearing from many people that they were on the right track (perhaps the surreptitious support of the members of court that have an inkling that these Fools spoke some truth?). Self and system analysis ensued, and the germ of an idea grew out many late night discussions: what was it that they were doing that resonated with individual people but was distrusted, misunderstood, or ignored by so many others primarily at an organizational level? Were the problems, deficiencies, successes, and failures they observed specific to critical illness or a more general phenomenon?

Translational Systems Biology was the product of these discussions, disseminated since through multiple manuscripts on the topic, but facing a fair amount of resistance and indifference (after all, how dare the Fools try to be members of the court!). Hence the paradox of being the Fool, able to speak certain truths, but only given the freedom to do so because their voices serve to preserve the *status quo*. But, as seen in *King Lear*, *Twelfth Night*, and *As You Like It*, change will come. When the offer to write this book came along, we viewed this as perhaps a qualitative shift in how our message could be delivered, and hence, how it would be received. Few Fools are given this opportunity, to potentially have their words actually have real and tangible meaning. When exercising that opportunity, we realized that there needed to be a balance between tempering the traditional level of agitation that is the domain of Fools, but retaining the disruptive quality of the Foolery that first brought it attention. As such, readers should consider themselves warned that they may be rattled, that our chosen tone might bite, and that the images cast by the mirror provided might not be ones they would prefer to see. If, at some point, the reader might feel too accused, they should perhaps take at least some comfort in that, as all Fools are, the authors are part of the same system they are critiquing, and their reflections are present in that same mirror.

No one would subject themselves to that degree of uncomplimentary self-reflection unless it was for a hope that somehow doing so would make things better. It is all too easy to critique without providing an alternative solution.

We believe that we have avoided this trap: this is why we present Translational Systems Biology as a potential pathway to address what we interpret as the roadblocks and barriers to enhancing human health for the remainder of the twenty-first century and hopefully beyond. Consistent with our strategy of founding things on the fundamental principles of Science, we do not claim that this is a unique or even necessarily effective solution. Rather, we claim, that given a transparent analysis of the preponderance of the evidence, a problem with the structure and operations of the biomedical research community has been identified and we have proposed a *plausible* solution to that problem. If the result of this book is the establishment of new, competing views of how we as a research community can move forward, and these and our strategies are given the opportunity to be given the test of real-world implementation, then we can consider our endeavor a success. This, after all, is how Science progresses.

This book includes an *Acknowledgments* section, but we would like to take the last space of our *Preface* to give special thanks to those who most suffered the company of Fools, our families. Gary wishes to thank his lovely wife Melanie, who always wondered where this time consuming, semiprofessional hobby would lead, and his daughter Madeline, who may be cursed with too many similarities to her father; and Yoram wishes to thank his better half, Xing, who stood by his side and provided grounding, and his daughter Lena and his son Ethan, who grew up surrounded by the good and bad of Science.