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Commentary

Amar Klar: A giant among scientists (1947–2017)

At the outset, it is emphasized that this is not an obituary but a memorial to celebrate the genius and contributions of Amar Klar, who died from a freak head injury in his yard on March 5, 2017.

Amar Klar belonged to the generation of the 'Midnight's Children', many of whom went on to make a mark for themselves. He was born on April 1, 1947, to a farming family who migrated from Lyallpur in Pakistan to settle in Sangrur (Punjab, India). He obtained his BSc in biochemistry from Punjab Agriculture University, Ludhiana, in 1967 and MSc in microbiology from Haryana Agriculture University, Hisar, in 1969. Thereafter, he obtained his PhD in bacteriology under the supervision of Seymour Fogel at the University of Wisconsin in 1975. This was followed by a post-doctorate with Harlyn O Halvorson at the University of California at Berkeley, during which he contributed significantly to the emerging field of mating-type switching in budding yeast. He provided the key genetic evidence for the cassette model for mating type locus and co-discovered the trans-acting factor MAR1/SIR2, which keeps the silent cassettes repressed (Klar and Fogel 1979; Klar *et al.* 1979). These seminal discoveries were noticed by the upcoming group of Jeff Starthern and Jim Hicks at the Cold Spring Harbor Laboratory working to decipher the underlying molecular mechanisms of mating type. Based on their enthusiastic recommendation, Jim Watson, who received Nobel Prize for the discovery of the structure of DNA and was the Director of Cold Spring Harbor Laboratory, telephoned Amar Klar offering him the job at Cold Spring Harbor Laboratory. Here, together, Jeff Starthern, Jim Hicks and Amar Klar investigated threadbare the major aspects of regulation of mating-type switching, silencing and directionality, making the mating-type system a paradigm of gene regulation and recombination, which became the stuff of textbooks as reference for future students and researchers. In addition, Amar also jumped in to the newly discovered system of mating type in fission yeast *Schizosaccharomyces pombe*. Based simply on one report by Miyata and Miyata showing that cells of fission yeast undergo a switch to the opposite mating type in only one out of the four granddaughter cells following two asymmetric cell divisions, Amar Klar tested and confirmed that the asymmetric switching involves imprinting and segregation of the one of the two strands of DNA, the so-called strand segregation model (Klar 1987, 1990). In 1988 Amar Klar moved to NCI-ABL Basic Research Program at Frederick, MD.

It was a stroke of luck that I got to work under the guidance of Amar Klar. He hired me after a ten-minute telephonic interview while I was doing my first post-doctorate in Canada. Later, he confided that he liked my response to his query as to why I was interested in his lab, that the strand segregation may hold the key to asymmetric divisions during metazoan development. His first and very charitable remark after I joined him was, 'Jag, you are an expert in biochemistry and I in genetics. Let us work together'. I think he said so to make me feel at ease although I always remained in awe of the scientific luminaries like him and Jeff. Soon, I found him to be a most unusual type of researcher. Beneath his rugged exterior and down-to-earth behaviour was a rather astute, original and sharp intellect. The work environment in his lab and the

neighbouring labs of Jeff Strathern and Dave Garfinkel was full of energy, collegiality, excitement and rigorous discussions. Amar always laid stress on asking more causal rather than detailed mechanistic questions. His standard comment was, 'One can go on working on mechanisms till cows return home. It is more important to discover new phenomena'. And he certainly did. His parting advice when I left his lab to join at IMTECH was 'do difficult things; only they have impact'. In all of these he led by example.

While expounding on his results for feedback he always abhorred uncritical praise and welcomed critical inputs. He was an iconoclast by nature who boldly questioned the established theories, particularly the 'morphogen gradient' theory for development. His scepticism arose from an obvious caveat, that is, the theory only shifted the question of causality by one step more without really addressing the fundamental basis. Most experts in the field held on to the theory very religiously. In this regard, Amar Klar proposed the path-breaking 'strand segregation' model for dictating developmental asymmetry during mating type switching in fission yeast (Klar 1987). The simplicity and elegance of this model was in its obviousness … but only after it was successfully demonstrated by him! Further work showing that the developmental asymmetry was coupled to the process of asymmetric DNA replication and discoveries showing the ever increasing role of epigenetics in development, raised hopes that the mechanism of development proposed by Amar could be more general (Klar 1994). However, even before the above mechanisms came to be discovered in his lab, he embarked on a train of thought linking asymmetric processes of development to DNA strand imprinting and non-random chromatid segregation in diverse examples like situs invertus in mice, handedness in humans and its linkage to homosexuality, schizophrenia, etc. (Klar 2003, 2004). His theories were met with dismissal and stout resistance by the aficionados. In response, Amar provided evidence on his own by showing that the situs invertus could be generated by knocking down the left right dynein (*LRD*) gene (Armakolas and Klar 2006, 2007; Sauer and Klar 2012; Klar 2015). Fresh evidences are now emerging to lend support to his theories in other organisms like mouse, drosophila and humans (Merok *et al.* 2002; Richardson 2009; Huh *et al.* 2013; Elabd *et al.* 2013). He truly was ahead of his times. Quite befittingly, he was called the Father of Epigenetics by Dr JD Watson.

The quantum of work he accomplished reflected a high degree of originality and boldness, which is very rare given the pressure and competition to publish in modern science. His success was linked to his unique ability to identify the simplest common denominator in a complex problem, while others were busy wading through the mechanistic details. Thus, rather than being a career scientist, he was a scientific voyager who boldly went 'where no man had gone before'. Although a self-professed atheist, his insights into the biological phenomena had an element of spiritual epiphany.

As in science, so he was as a person. He was boisterous, eternally cheerful and infectiously enthusiastic. He was a doting father: I remember him picking and playfully throwing up his two young daughters in air when they would visit the lab sometimes. A caring husband:I remember him saying on the last day of the meeting in the Hague that he was missing his family and, shyly, his wife Kuljit. A real party animal and life of a party, he would talk to any unsuspecting delegate with his theories of handedness. On other occasions, he would collect a dozen people around him and regale them with his jokes. His gregarious nature and enthusiasm earned him a lot of admirers wherever he went, including India. He had the unique ability to relate to all types of people, be it a Nobel Laureate, a student or even a lay person. As an American scientist remarked, 'Amar is more American than Americans'

I also learnt from him how to face adversity. Even under most difficult scenarios he exuded confidence and positivity. 'Facing difficulties is important. It helps to build character.'

Opposition to his ideas and concerns about his credibility did not deter him from pursuing his inquiries. Whether it was a game of table tennis or state of research or life in general, he always exhorted his protégés, like me, by his words, 'You have to win under all circumstances'. Again, as in work, so in his attitude to life, he led by example. While discussing some issues, he would stress on deeper analysis, 'Doing is the easier part, thinking is the hard part. So, think!' For motivating, he would say 'Go for it. Sky is the limit'.

His larger-than-life persona has had such an impact that despite the deep feeling of sorrow and loss we all feel due to his untimely and premature passing, there is also a strong sense of being exhorted to live a life and work to its fullest. That would probably be his core legacy. His name will always remain immortal (अमर) in the world of science.

References

Klar AJ and Fogel S 1979 Activation of mating type genes by transposition in Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. U S A.* **76** 4539–4543

Klar AJ, Fogel S and Macleod K 1979 MAR1—a regulator of the HMa and HMalpha Loci in SACCHAROMYCES CEREVISIAE. *Genetics* **93** 37–50

Klar AJ 1987 Differentiated parental DNA strands confer developmental asymmetry on daughter cells in fission yeast. *Nature* **326** 466–470

Klar AJ 1990 The developmental fate of fission yeast cells is determined by the pattern of inheritance of parental and grandparental DNA strands. *EMBO J.* **9** 1407–1415

Klar AJ 1994 A model for specification of the left-right axis in vertebrates. *Trends Genet.* **10** 392–396

Klar AJ 2003 Human handedness and scalp hair-whorl direction develop from a common genetic mechanism. *Genetics* **165** 269–276

Klar AJ 2004 An epigenetic hypothesis for human brain laterality, handedness, and psychosis development. *Cold Spring Harb Symp Quant Biol.* **69** 499–506

Armakolas A and Klar AJ 2006 Cell type regulates selective segregation of mouse chromosome 7 DNA strands in mitosis. *Science* **311** 1146–1149

Armakolas A and Klar AJ 2007 Left-right dynein motor implicated in selective chromatid segregation in mouse cells. *Science* **315** 100–101

Sauer S and Klar AJ 2012 Left-right symmetry breaking in mice by left-right dynein may occur via a biased chromatid segregation mechanism, without directly involving the Nodal gene. *Front. Oncol.* **2** 1–10

Merok JR, Lansita JA, Tunstead JR and Sherley JL 2002 Cosegregation of chromosomes containing immortal DNA strands in cells that cycle with asymmetric cell kinetics. *Cancer Res.* **62** 6791–6795

Richardson MK Diffusible gradients are out- an interview with Lewis Wolpert. 2009 *Int. J. Dev. Biol.* **53** 659–662

Huh YN, Cohen J and Sherley JL 2013 5-hydroxycytosine identifies immortal DNA strand chromosomes in asymmetrically self-renewing distributed stem cells. *Proc. Natl. Acad. Sci, USA.* **110** 16862–16867

Elabd C, Cousin W, Chen RY, Chooljian MSD, Pham JT, Conboy IM and Conboy MJ 2013 DNA methyltransferase-3-dependent non-random segregation in differentiating embryonic stem cells. *J. Cell Biol.* **203** 73–85

Klar AJ 2015. Selective chromatid segregation mechanism proposed for the human split hand/foot malformation development by chromosome 2 translocations: A perspective. *Dev. Biol.* **408** 7–13

JAGMOHAN SINGH
Institute of Microbial Technology, Chandigarh, India
(Email, jag@imtech.res.in)