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Celebrating the work of Nobel Laureate Paul Modrich

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On October 7, 2015, the Nobel Prize Committee announced that the 2015 Nobel Prize in Chemistry had been awarded jointly to Professors Paul Modrich, Tomas Lindahl and Aziz Sancar (Figure 1), each of whom made ground-breaking discoveries about the molecular mechanisms of DNA Repair. In one of life's unpredictable turns, Paul was among the last individuals in his entire personal, professional and social network to learn of the Committee's decision, because Paul was very far "off-the-grid" at the time of the announcement. The news that he had been selected as a 2015 Nobel Laureate may have taken Paul by surprise, but it certainly was not a surprise to most, if not all, of Paul's colleagues, students, family and friends.

As a scientist and person, Paul exemplifies excellence, dedication and the highest level of commitment to science and the scientific process, to the extent that he stands head and shoulders apart and above the rest of us. Paul is also modest, approachable, honest, unpretentious and an excellent mentor to the young scientists in his laboratory. I had the honor of working for Paul from 1991 to 1995, one of the most exciting times in the field of DNA repair, and certainly, at least so far, the highlight of my personal and professional life.

Paul was born and grew up in Raton, New Mexico. His interest in DNA and nucleic acids was inspired by his father, the local high school biology teacher, who encouraged him to learn about the DNA when Paul was a high school student. His father's advice had influenced Paul to obtain his BS degree in biology at Massachusetts Institute of Technology. As a doctoral student, Paul studied nucleic acid metabolism and the enzymes that carry out DNA transactions in Dr. I. Robert Lehman's laboratory at Stanford University. Paul characterized DNA ligase from *Escherichia coli* (Modrich et al., 1973; Modrich and Lehman, 1970, 1971; Modrich et al., 1972), an enzyme that performs an essential step, and often the critical last step, in multiple pathways of DNA replication and repair. After postdoctoral training with Charles Richardson at Harvard University, studying bacteriophage T7 DNA polymerases (Modrich and Richardson, 1975a, b), Paul took a faculty position at the University of California, Berkeley in 1974. He then joined Duke University's faculty in 1976, where he currently holds the position of James B. Duke Professor of Biochemistry and an investigator at the Howard Hughes Medical Institute.

Figure 1 (color online) Paul Modrich, Aziz Sancar and Tomas Lindahl share the 2015 Nobel Prize in Chemistry. The photo was taken at the Nobel Award Ceremony on December 10, 2015, when professors Lindahl (left), Modrich (middle) and Sancar (right) received their awards from the King of Sweden, Carl XVI Gustaf, in the Concert Hall, Stockholm, Sweden.

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Paul's early studies concentrated on the *E. coli* experimental model system, arguably the most important experimental model system for analyzing and understanding the molecular mechanisms of DNA replication and repair. His seminal work on the molecular mechanism of DNA mismatch repair (MMR) in *E. coli* laid the groundwork for later breakthroughs in understanding the biochemical basis of human colon carcinogenesis and for understanding cellular resistance to some classes of chemotherapeutic drugs for treating human cancer.

In his early *E. coli* studies, Paul provided an unequivocal mechanistic basis for the strand-specificity (and accuracy) of MMR, which had remained an unsolved question and a major roadblock to progress in the field. Based on earlier observations that nascent *E. coli* DNA is transiently under-methylated at duplex d(GATC) sites (Marinus, 1976), and a hypothesis first advanced by Matthew Meselson (Wagner and Meselson, 1976), Paul, Meselson and their colleagues provided definitive evidence that the asymmetry of hemi-methylated nascent DNA confers strand-specificity on *E. coli* MMR (Pukkila et al., 1983). It is important to realize that in the absence of strand-specificity, the MMR system would be entirely useless, because the accuracy of a non-strand-specific MMR reaction cannot exceed 0.5 (*i.e.*, 50% chance of correct repair).

In the early 1980s, Paul developed a powerful *in vitro* assay for strand-specific methyl-directed MMR (Lu et al., 1983). Using this assay, Paul's lab identified, purified and characterized *E. coli* MutS (Su and Modrich, 1986), MutL (Grilley et al., 1989) and MutH (Welsh et al., 1987), the three *E. coli* proteins whose dedicated primary role is in MMR. As the milestone achievement in the late 1980s, Paul's laboratory reconstituted *E. coli* MMR *in vitro* using purified components (Lahue et al., 1989). This groundbreaking work led to Paul's later studies elucidating the mechanism of *E. coli* methyl-directed MMR (Allen et al., 1997; Au et al., 1992; Cooper et al., 1993; Dao and Modrich, 1998; Grilley et al., 1993; Grilley et al., 1990; Grilley et al., 1989; Worth et al., 1994; Yamaguchi et al., 1998).

In the 1990s, Paul and his colleagues extended these studies to eukaryotic cells, demonstrating that human and *Drosophila* cells express enzymes that carry out strand-specific MMR, in a reaction that resembles, but is significantly different from *E. coli* MMR (Holmes et al., 1990). In 1993, Bert Vogelstein (Aaltonen et al., 1993), Stephen Thibodeau (Thibodeau et al., 1993) and Manuel Perucho (Ionov et al., 1993) independently reported that instability of microsatellite sequences is associated with hereditary non-polypopsis colorectal cancer (HNPCC, also called Lynch Syndrome) and a subset of sporadic colorectal cancers. This correlation, and the fact that simple repetitive sequences are also highly unstable in MMR-deficient *E. coli* (Levinson and Gutman, 1987a, b), led to the next milestone discovery out of Paul's laboratory: namely, that cancer cells displaying microsatellite instability are defective in MMR (Parsons et al., 1993). This discovery is consistent with genetic studies from the laboratories of Richard Kolodner, Bert Vogelstein and Mike Liskay, which showed that mutations in *hMSH2, hMLH1* and *hPMS2* genes, the human homologs of *mutS* and *mutL*, are causally linked to HNPCC (Bronner et al., 1994; Fishel et al., 1993; Kolodner et al., 1994; Leach et al., 1993; Nicolaides et al., 1994; Papadopoulos et al., 1994).

Collectively, these discoveries elevated the whole field of DNA repair, previously thought of as a collection of "housekeeping" pathways, to a new level of significance. DNA repair, largely as a result of the work of Paul Modrich, Richard Kolodner and Bert Vogelstein, but also complemented by the work of Aziz Sancar, Phil Hanawalt, Richard Wood and others, was named *Science* magazine's Molecule of the Year in December, 1994 (Koshland, 1994).

Paul's laboratory went on to purify and characterize key human MMR proteins hMutLα (Li and Modrich, 1995), hMutSα (Drummond et al., 1995), DNA polymerase δ (Longley et al., 1997), hMutSβ (Genschel et al., 1998) and exonuclease I (Genschel et al., 2002), taking advantage of both MMR-deficient cancer cell lines and biochemical "mutants" generated by fractionation, which ultimately allowed Paul's lab to reconstitute and elucidate the mechanism of human MMR (Constantin et al., 2005; Dzantiev et al., 2004; Kadyrov et al., 2006).

In summary, Paul's laboratory, working over three decades, was always at the forefront of the field, being the first to answer the unanswered questions about MMR and its impact on human health. Therefore, Paul, Aziz Sancar, and Tomas Lindahl are three scientists who are highly deserving of the 2015 Nobel Prize in Chemistry. All who know Paul are extremely grateful to him for his invaluable contribution to this field of research.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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