The 2009 GSA Honors and Awards

The Genetics Society of America annually honors members who have made outstanding contributions to genetics. The Thomas Hunt Morgan Medal recognizes a lifetime contribution to the science of genetics. The Genetics Society of America Medal recognizes particularly outstanding contributions to the science of genetics over the past 25 years. The George W. Beadle Medal recognizes distinguished service to the field of genetics and the community of geneticists. The Elizabeth W. Jones Award for Excellence in Education recognizes individuals or groups who have had a significant, sustained impact on genetics education at any level, from kindergarten through graduate school and beyond. The Novitski Prize recognizes an extraordinary level of creativity and intellectual ingenuity in solving significant problems in biological research through the application of genetic methods. We are pleased to announce the 2009 awards.

John Roth

The 2009 Thomas Hunt Morgan Medal

John Roth

THE field of genetics has been strongly influenced by work of John Roth and his laboratory. While this work focuses on genetic analysis of bacteria, it has had general implications for gene regulation, translation, metabolism, genome organization, and evolution.

While an undergraduate at Harvard University, John Roth became fixated on bacterial genetics. His career trajectory was set by a bacterial physiology course with William Sistrom, a genetics laboratory course with Robert Riseborough, and an evolution course with E. O. Wilson. Sistrom made science come alive by presenting new research articles in the context of current scientific debate. Riseborough introduced the then budding field of bacterial genetics, stimulating Roth to take a French class so as to read Jacob and Monod's initial reports on repressor control of the *lac* operon in the French Academy's "Comptes Rendu" (Pardee *et al.* 1958; Jacob and Monod 1959; Jacob *et al.* 1960; Buttin *et al.* 1960; Perrin *et al.* 1960). Wilson made it clear that you cannot fully understand a mechanism until you can visualize how it might evolve. The possibility of a science career opened for Roth only after the medical school interview process demonstrated conclusively the inhuman side of medicine. James Watson saved the day by offering, on the strength of a felicitous student essay, to help an otherwise unknown undergraduate achieve last-minute admission to graduate school and a position as a summer researcher in the Undergraduate Research Program (URP) at Cold Spring Harbor. The joys of Salmonella genetics became apparent under the influences of Paul Margolin (URP mentor), Phil Hartman (Ph.D. advisor), and Bruce Ames (postdoctoral sponsor). All of these initial influences contributed repeatedly to Roth's later career in science.

Roth's graduate work with Phil Hartman at Johns Hopkins University focused on the regulation of histidine biosynthesis. At that time many labs were trying to fit all regulatory processes into the repressor model for operon control devised by Jacob and Monod. It was therefore disappointing that Roth's analysis of the histidine operon (*his*) revealed no evidence of a repressor. The regulatory mutations were scattered widely around the genome and affected functions involved in the process of code translation (*e.g.*, histidyl-tRNA synthetase, $tRNA^{His}$, and tRNA modifying and processing enzymes). Genetic characterization of these mutants relied on a discovery by Bruce Ames that mutants overexpressing the histidine operon formed "wrinkled" colonies, a phenotype that allowed genetic mapping. Roth later did a postdoctoral stint with Ames at the

National Institutes of Health, where many of these mutants were characterized biochemically. Genetic work on the *his* control mechanism continued after Roth started his own lab at the University of California at Berkeley. Once DNA sequencing became possible, the control region structure suggested a model that explained the regulatory mutations (extending prior work by Charlie Yanofsky's lab at Stanford). According to this model (Johnston *et al.* 1980), the histidine operon sensed the level of his-tRNA by measuring the rate at which seven adjacent histidine codons are translated. Any limitation of this rate by a his-tRNA shortage changed RNA secondary structure and allowed transcription of operon coding sequences. (In current parlance, the operon is regulated by an RNA ribo switch, not by a repressor protein.)

Interest in the genetics of tRNA led Roth's lab to work on a variety of informational suppressors, including recessive nonsense suppressors and many classes of frameshift suppressors in which altered tRNAs caused translation to the shift reading phase. In essence (if not quite in fact) some suppressor tRNAs can read a four-base codon. Nonsense suppressors revealed the effects of a codon context on suppression efficiency. Roth contributed to several reviews on suppression, including one broad survey written by Phil Hartman and Roth (Hartman and Roth 1973). Now 40 years old, this review still provides a clear and comprehensive overview of the many levels of genetic suppression.

Roth's failure to find a repressor for the *his* operon led to a second attempt using the proline utilization genes (*put*). Alas, a thorough genetic analysis revealed no standard dedicated allosteric repressor. Instead, the second enzyme in the pathway (the PutA dehydrogenase) served as a constant repressor but allowed operon transcription whenever proline demanded a PutA membrane association, "an allo-positional repressor." This provided the first clear example of autogenous regulation by an enzyme that was not intimately involved in nucleic acid metabolism—a concept that had been previously proposed for many other enzymes but that was invariably found erroneous due to inadequate genetic analysis.

After moving from Berkeley to the University of Utah, Roth developed close scientific interactions with his new colleague, Baldomero (Toto) Olivera, a biochemist whose discovery of DNA ligase had prompted an interest in NAD. In collaboration, their labs dissected NAD biosynthesis and recycling, providing insights into the mechanisms for regulatory integration of energy metabolism, oxidative stress, DNA repair, and recombination. Studies of NAD metabolism led to an interest in cobalamin (vitamin B_{12}). Roth's lab found that Salmonella could synthesize this huge cofactor only under anaerobic conditions, explaining why this pathway had escaped detection for so long. They analyzed operons for B_{12} synthesis (*cob*) and for B_{12}-dependent use of two carbon sources: ethanolamine (*eut*) and propanediol (*pdu*). Detailed genetic studies revealed that Salmonella invests nearly 1% of its genome in B_{12} synthesis and another 1% in B_{12}-dependent metabolism. On a sabbatical leave at George Church's lab at Harvard Medical School, Roth used Church's multiplex sequencing methods to determine the DNA sequence of the *cob* and *pdu* operons. This sequence suggested that both operons had entered Salmonella by horizontal transfer, suggesting a model for the evolution of the prominent clustering of related genes in bacterial genomes. As an aside, the *cob* operon also failed to reveal a standard repressor and appeared to be controlled primarily by an allosteric mRNA that recognizes cobalamin and regulates translation of the first gene in the operon.

In the course of this work, Roth's lab developed many genetic tools, of which transposons are most noteworthy. While on sabbatical at Cold Spring Harbor Laboratory, Roth collaborated with David Botstein and Nancy Kleckner to devise a variety of ways in which transposable drug-resistance elements (*e.g.*, Tn*10*) could be used in genetic analysis (Kleckner *et al.* 1977). They pointed out that insertion mutations could cause a recessive null phenotype (useful in physiology) that is completely associated with a dominant drug-resistance phenotype (useful in strain construction). Transposons also provide "portable regions of homology," and recombination between such regions can be used to construct deletions, duplications, and Hfr's. Many of these approaches were later exploited in Roth's lab and taught in the Advanced Bacterial Genetics course at Cold Spring Harbor Laboratory taught by David Botstein, Ron Davis, and John Roth (among others). This technology was disseminated through the microbiology community by the scientists who took this course and by the course lab manual—a luscious intellectual meal that was gleefully gulped down by a generation of growing scientists and their advisors. Roth's lab also exploited and developed the phage Mu-derived gene fusion elements (Mud) developed by Malcomb Casadaban for studies of gene regulation and chromosome rearrangments.

Chromosomal duplications were encountered during early studies on nonsense suppressor tRNAs. Suppressor mutations that alter an essential tRNA type are lethal unless they arise in one copy of a preexisiting duplication of the tRNA gene. This provided a duplication phenotype and revealed that duplications form and decay at extremely high frequency in bacteria. Transposons facilitated duplication maintenance by allowing selection for both copies of the duplicated region: one allele was functional and the other carried the insertion and provided drug resistance. Roth's lab demonstrated that the frequency of cells with a tandem duplication increases when the level of a particular gene product limits population growth. This demonstrated the rapid copy-number variation in bacterial populations and

presaged the more recent discovery of common copy-number variants in many organisms. Transposons also provided a novel tool to show that inversions occur rarely. The methods for selecting recombination between transposons were used by Pat Higgins to demonstrate independent supercoiling of chromosomal domains. The genetic tools developed in Roth's lab helped to change our perspectives on the pulsating rhythms of chromosome organization.

The frequent formation and loss of duplications caused Roth's group to think about population biology and evolution. The willingness to enter this foreign turf was supported by Roth's early undergraduate course with Ed Wilson and later instruction by Jeffrey Lawrence and Utah colleague Jon Seger. Forays include attempts to understand why all Salmonellae (but no *Escherichia coli*) conserve a constellation of genes, including *cob*, *pdu*, and *eut*. Other work led to ideas on the evolution of bacterial operons by horizontal transfer and on the origins of new genes by selective amplification. The most recent population work from Roth's group came in response to a provocative article by Cairns *et al.* (1988). This publication suggested that selective stress might induce mutations or even "direct" them to sites that improve fitness. Roth's lab in collaboration with the Swedish labs of Dan Andersson and Diarmaid Hughes has published substantial evidence that growth limitation enhances mutant frequency by favoring mutant growth, not mutagenesis. Selection allows frequent mutations with weak phenotypes to evolve subclones with full fitness. The effect of selection is large because the duplication and higher amplification are surprisingly frequent and because growth with an amplification adds mutational targets to the selection plate. (If only there had been a repressor of mutagenesis.)

In addition to his research accomplishments, Roth is an enthusiastic, stimulating teacher. He is a master of Socratic discipline, encouraging critical, creative thinking and problem solving. Over the years he has encouraged many undergraduates to pursue graduate training. He has also trained many graduate students and postdoctoral fellows who have gone on to successful careers in academia and industry. He took personal responsibility for ensuring that anyone who entered his lab would succeed. He has an amazing gift for stimulating those in his lab to perform at their very best. For students and postdocs who had the great fortune to work with John, it was always hard to move on.

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