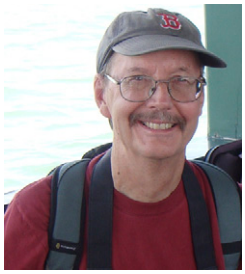
The 2013 Thomas Hunt Morgan Medal
Thomas Douglas Petes



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 32 years. The George W. Beadle Award 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 2013 awards.

THOMAS (Tom) Douglas Petes is the recipient of this year's Thomas Hunt Morgan Medal for life-long contributions to the field of genetics. Tom's career has been devoted to understanding basic mechanisms that govern DNA transactions and regulate genetic stability in *Saccharomyces cerevisiae*. He is a geneticist's geneticist, approaching the study of fundamental problems through the design and use of clever genetic assays. This award acknowledges a career that has been punctuated by seminal discoveries that extend well beyond the budding yeast system.

The Formative Years

Tom grew up in suburban Maryland, where there were two major influences on his eventual career path. The first was his father, a physicist whose education was disrupted by World War II. Having only a bachelor of science degree eventually limited his father's career advancement and instilled in Tom the importance of postgraduate education. The second influence was an excellent high school biology teacher (Mr. LaRue) who engaged students through an unusually lab-centric curriculum. Tom majored in Biology at Brown University, where a genetics course provided a very welcome problem-solving rather than a rote-memorization experience, and he became a convert to the field. This led to graduate school in the Genetics Department at the University of Washington, a department that housed luminaries such as Herschel Roman, Lee Hartwell, and Larry Sandler. Tom's contemporaries at the University of Washington were equally impressive and included John Pringle, housemates Mike Liskay and Jeff Hall, Bruce Baker, Adelaide Carpenter, Jim and Anita Hopper, Joe Culotti, Carol Newlon, Hannah Klein, and the late Lynna Hereford (who co-occupied with Tom what other students referred to as the "Bay of Pigs"). It was also here where Tom met Rosann Farber, a human geneticist who has been his wife, as well as occasional collaborator, for almost 40 years. Their two most notable collaborations are their daughters: Laura, a marine biologist at the National Oceanic and Atmospheric Administration and Diana, a yogurt/granola entrepreneur in San Francisco.

Tom's thesis research was performed in the lab of Walt Fangman, with the goal of providing evidence that individual yeast chromosomes were indeed composed of a single, duplex DNA molecule. He proved that they were, first sizing DNA molecules using sucrose gradients (Petes and Fangman 1972) and then via direct examination by electron microscopy (Petes *et al.* 1973). An unexpected bonus of the latter work was subsequent confirmation (in collaboration with Carol Newlon and Lynna Hereford) that the branched molecules observed were replicating yeast chromosomes (Newlon *et al.* 1974). Following the completion of graduate training in 1973, Tom spent 2 years as a Jane Coffins Child postdoctoral fellow with Don Williamson at the National Institute for Medical Research in London, where he continued to study DNA replication in yeast. He then began a second National Institutes of Health-funded postdoctorate with Joel Huberman at Harvard University, with the intent of using SV40 as a model system to study replication. Huberman shortly moved to the University of Rochester, however, and Tom's search for an

doi: 10.1534/genetics.113.150664

alternative postdoctorate position landed him in David Botstein's lab at the Massachusetts Institute of Technology from 1975 to 1977. Botstein, who was well known for his phage work, was just beginning to move into yeast, an experimental organism that Tom was happy to return to. Yeast genomic DNA fragments were just beginning to be isolated, and Tom's initial project was to clone chromosome III by classic chromosome walking. When it became clear that the walk was more akin to a very slow crawl, his attention turned to a restriction fragment length polymorphism (RFLP) associated with rDNA clones isolated from the genomic library constructed for the chromosome walk. As luck would have it, the library had been derived from a diploid strain, and this led to the discovery that the RFLP originated from a sequence difference in the rDNA arrays in the component haploid parent strains. Following this difference through meiosis, via Southern blots of genomic DNA from tetrad-dissected spores, provided a clever way to monitor meiotic recombination within the rDNA array and was one of the first uses of an RFLP for mapping purposes (Petes and Botstein 1977). The general use of direct DNA-based alterations, such as RFLPs (by Southern blots) or variable number tandem repeats (by PCR tests), as heterozygous genetic markers later proved to be key in the early identification of human disease-causing genes as well as in the construction of a high-resolution genetic map of the human genome.

The University of Chicago

Following a productive postdoctorate with Botstein, Tom began his independent career in 1977 as an assistant professor in the Department of Microbiology at the University of Chicago. He spent 12 very productive years at the University of Chicago, rapidly rising to the rank of full professor. During this time he also spent two summers at Cold Spring Harbor, where he taught the renowned Yeast Genetics course with Fred Sherman and Gerry Fink. Though Tom's early work continued to focus on recombination within the yeast rDNA array, the development of yeast transformation in the late 1970s (Hinnen *et al.* 1978), combined with extraordinarily efficient homologous recombination in this system, provided a tool to modify the yeast genome in very precise and predetermined manners (Rothstein 1991). Tom cleverly exploited this new technology to construct defined recombination substrates, publishing a seminal study of meiotic recombination between direct repeats (Klein and Petes 1981) and later demonstrated efficient ectopic recombination between repeats positioned on nonhomologous chromosomes (Jinks-Robertson and Petes 1985). Analyses were soon extended to study interactions among dispersed copies of the endogenous Ty retrotransposon (Kupiec and Petes 1988), a line of work that continues in his lab to this day. Tom's lab also pioneered the use of engineered sequence polymorphisms to follow the extent of DNA exchanged during recombination (Symington and Petes 1988). Finally, his group examined the integration of restriction fragments that had no homology to the yeast genome, and this led to the discovery of a novel type of insertional mutagenesis (restriction enzyme-mediated integration, REMI) mediated by restriction enzymes that piggy-back into cells with exogenous DNA fragments (Schiestl and Petes 1991). REMI subsequently has been exploited to randomly integrate exogenous DNA into the genomes of other, less genetically amenable organisms, especially *Dictyostelium* (Kuspa 2006).

In addition to recombination-related studies, Tom began to pursue a long-standing interest in simple repeated sequences, especially the dinucleotide repeats that are so prominent in the human genome. Using radioactively labeled poly(GT/CA) as probe in Southern blots, his lab discovered that this sequence hybridizes to yeast telomeres (Walmsley *et al.* 1983). This insight not only aided in the basic characterization of telomeres, it was used as a tool to identify the first yeast mutants with altered telomere length (Lustig and Petes 1986). The eventual cloning of the corresponding *TEL1* gene in 1995 revealed it to be a central DNA-damage checkpoint protein related to the human ataxia telangiectasia gene (Greenwell *et al.* 1995). Tom's lab has continued to study the critical roles that Tel1 as well as partially redundant Mec1 checkpoint protein play in maintaining the mitotic genome stability, recently extending analyses to the entire yeast genome (McCulley and Petes 2010).

The University of North Carolina at Chapel Hill

In 1988, Tom moved to the Biology Department at the University of North Carolina, Chapel Hill. It was here that forward and reverse mutation assays were developed to study the instability of simple repeats (Henderson and Petes 1992). The ability to quantitatively monitor expansion/contraction of simple repeats in yeast had an unanticipated, but profound, impact on biomedical research. During the mapping of a human mutation that caused hereditary predisposition to colon cancer (HNPCC), it was noted that a secondary phenotype of "microsatellite instability" was co-segregating with the cancer predisposition phenotype. This work, published in back-to-back *Science* articles in the spring of 1993, signaled the beginning of a labor- and resource-intensive process to positionally clone the relevant gene (Aaltonen *et al.* 1993; Thibodeau *et al.* 1993). Petes realized that his new yeast assays presented an opportunity to systematically test DNA-metabolism mutants for an associated microsatellite instability phenotype. In a beautiful article published in *Nature* in the fall of 1993, Tom (together with Mike Liskay) documented an extraordinary instability of dinucleotide repeats in mismatch repair (MMR)-defective mutants (Strand *et al.* 1993). This led to the realization that the human homologs of yeast MMR genes were cross-species candidates for HNPCC genes. Indeed, just a few months later, two groups showed that mutations in human MSH2, a homolog of bacterial MutS class of MMR proteins, were indeed responsible for HNPCC (Fishel *et al.* 1993; Leach *et al.* 1993). When a second HNPCC locus associated with microsatellite instability was subsequently

identified, other genes encoding MMR homologs were immediately tested as candidates. The dramatic outcome in the spring of 1994 was the identification of MLH1, a homolog of bacterial MutL, as the second HNPCC gene (Bronner *et al.* 1994). The yeast-HNPCC story provided a stunning example of how basic studies in model organisms can impact biomedical research and came at a time when the relevance of such studies was not universally accepted in the medical genetics community. At the annual Jackson Laboratories Short Course on Medical and Experimental Mammalian Genetics in the summer of 1994, Victor McKusick came up to one of us following a lecture that recounted the yeast-HNPCC story, and proclaimed, "Now I get it!" This was a watershed moment for the establishment of yeast as a model for human disease and contributed, in part, to Tom's election to the National Academy of Sciences in 1999.

Following release of the yeast genome sequence in 1996 and the rapid development of microarray-based approaches that followed, Tom's lab exploited these technologies to study meiotic and mitotic recombination and mitotic chromosome stability on a genome-wide scale. This led, for example, to use of ChIP-chip to construct the first map of meiotic double-strand breaks across the yeast genome (Gerton *et al.* 2000) and the use of comparative genome hybridization (CGH) arrays to characterize the mitotic genome instability (Lemoine *et al.* 2005). Last, but not least, Tom gave back to the genetics community during this period, serving as Secretary of the Genetics Society of America from 1995 to 1998 and as its president in 2002.

Duke University

Tom moved to Duke University in 2004 to be chair of the Molecular Genetics and Microbiology Department, a position that he relinquished in 2009 to return his focus to basic research. At Duke, his experimental toolbox has continued to evolve and most of his work now focuses on mitotic recombination in diploids, an area that has been propelled by two key innovations. First, Tom's group developed a clever sectoring-based assay that can be used to identify and thus study both products derived from mitotic crossover events between homologs (Barbera and Petes 2006). Use of diverged haploid strains to construct the diploid then allows conversion of single-nucleotide polymorphisms (SNPs) associated with the primary crossover event to be monitored (Lee *et al.* 2009). Though this began with simply monitoring SNPs that altered restriction sites on the relevant chromosome, the second key development was the design of SNP microarrays ("Jordan" arrays) that can monitor mitotic gene conversion, crossover, and/or nondisjunction events across the entire yeast genome (St Charles *et al.* 2012). As in Tom's prior studies, recent results from his lab are shifting basic paradigms of mitotic recombination and chromosome stability. It appears, for example, that most mitotic recombination between homologous chromosomes is initiated by double-strand breaks that occur in G1 and are passed on to both sister chromatids (Lee *et al.* 2009) and that uniparental disomy can result from a meiotic-like disjunction of homologs, giving rise to "reciprocal" uniparental disomy in the daughter cells (Andersen and Petes 2012).

Concluding Remarks

Using genetic approaches to study genome stability, Tom has made fundamental discoveries that have extended well beyond the yeast system. He has consistently asked interesting and important scientific questions, designed clever genetic assays to address these questions, and has done rigorous follow-up experiments to test the models that emerge. We would be remiss if we did not also note the profound influence that Tom has had on his students, his postdocs, and his colleagues. He has been a superb role model, providing both guidance and an exceptional training environment for the large number of independent scientists who have emerged from his lab. Beyond his scientific contributions, those of us who know Tom especially appreciate his warm personality, his generous spirit, his collaborative nature, and his quick sense of humor. Though the Thomas Hunt Morgan Medal recognizes life-long contributions to the field of genetics, we are happy to report that Tom's research has yet to slow down. It is indeed a pleasure to recognize this year's recipient of this prestigious award.

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