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Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

The Yeast Mating-Type Switching Mechanism: A Memoir

Amar J. S. Klar[1]

Developmental Genetics Section, Gene Regulation and Chromosome Biology Laboratory, National Institutes of Health, National Cancer Institute, Frederick, Maryland 21702-1021

ABSTRACT

It has been 33 years since I first presented results of genetic experiments that established the gene transposition model as the mechanism of mating-type switching in the budding yeast *Saccharomyces cerevisiae* at the Cold Spring Harbor Laboratory (CSHL) Yeast Genetics meeting in August 1977. Over two decades ago the Genetics Perspectives editors solicited a perspective on my participation in the studies that deciphered the mechanism of mating-type switching and revealed the phenomenon of gene silencing in yeast. Although flattered at the time, I thought that preparation of such an article called for a more seasoned researcher who had benefitted from seeing his contributions stand the test of time. Now realizing that our discovery of the transposition of a mutation from the *HM*α locus into the *MAT* (mating type) locus has provided the genetic evidence that established the gene transposition model, and having witnessed our conclusions confirmed by subsequent molecular studies, I decided that perhaps this is a good time to recount the chronology of events as they unfolded for me decades ago.

THE sexual cell types of yeast are designated **a** and α, which are correspondingly conferred by the *MAT***a** and *MAT*α alleles of the *ma*ting *t*ype locus (*MAT*). Cells of opposite type can mate to establish a cell of the *MAT*α/*MAT***a** diploid state (Figure 1). Because both *MAT* alleles are co-dominant, such diploid cells are sterile but can undergo meiosis and sporulation to form asci, each of which contains two *MAT***a** and two *MAT*α haploid spores. In so-called heterothallic strains (those containing the nonfunctional *ho* gene), the *MAT* alleles switch rarely ($<1 \times 10^{-6}$), but the unusual homothallic (those containing the functional *HO* gene) cells switch mating type remarkably efficiently, within a few cell divisions after the spore germinates. The cells in the incipient colony of the opposite type mate to reestablish *MAT*α/*MAT***a** diploid cells in which the *HO* gene and the switching process are shut off (Winge and Roberts 1949). This was an odd and fascinating phenomenon that workers in the field initially cracked open by conventional genetics. This Perspectives is about my postdoctoral training research, during which different aspects of the mystery were cleared up by a series of informative experiments. This is a personal account of the excitement I enjoyed through my own and my colleagues' genetic studies.

I started my graduate school training in 1969, working on yeast at the University of Wisconsin with Harlyn O. Halvorson, a prominent researcher of the cell cycle of yeast and of sporulation of yeast and Bacillus. His group moved from Madison, Wisconsin, to Brandeis University in Waltham, Massachusetts, in 1971. While conducting my thesis research on two other projects, two unrelated instances were instrumental in igniting my interest in the yeast mating-type switching phenomenon. First, Johanes van der Plaat, a visiting scientist from Gist-Brocades in Holland, related that controlling ploidy of industrial yeast strains was difficult. I proposed a project to test whether cells homozygous for the mating-type allele (*MAT***a**/*MAT***a** or *MAT*α/*MAT*α) containing the *D* (for *d*iploidization) gene (also called *HO*, for *ho*mothallism, Figure 1; Winge and Roberts 1949) would switch mating type, as haploid cells of either mating type do. I wondered if the *MAT***a**/*MAT*α constitution itself, and not the diploid state *per se*, turns off the switching process? Second, another visiting scientist in our group, Isamu Takano from Osaka University in Japan, handed me a couple of the Osaka group's articles to read, in which they had implicated two additional genes, *HM***a** and *HM*α, in *MAT* switching. In one of these papers, the Osaka group reported that an in-

I dedicate this contribution to my advisors, Harlyn O. Halvorson and Seymour Fogel, for training me to become an independent researcher.

[1]*Author e-mail:* klara@mail.nih.gov

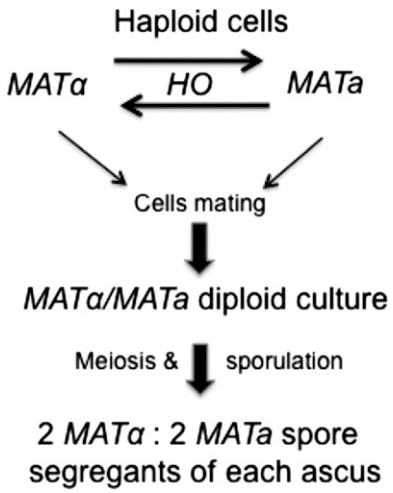


FIGURE 1.—The yeast mating-type switching homothallism phenomenon (see text for details).

efficiently switching *MAT*α-*inc* (*inc* for inconvertible, a naturally occurring variant) switches to the readily switchable *MAT***a** and *MAT*α (TAKANO *et al.* 1973). I was most impressed by this puzzle of repairing a switchability defect in *MAT*α by the switching process. Because the molecular nature of the *MAT*α-*inc* mutation was unknown, I proposed to conduct a similar switching experiment, but with a *mat*α-*ochre* mutation, because such a mutation must lie within the gene's coding region. Isamu Takano very much encouraged me to perform this experiment. I requested the mutant from Don Hawthorne of the University of Washington, but unfortunately I did not receive the strain. I later found out that Don Hawthorne knew the answer to this question (see below).

MAT ALLELE HOMOZYGOUS DIPLOID CELLS SWITCH

In the middle of 1975 I took up a postdoctoral position under Seymour Fogel of the University of California at Berkeley. As a side project, I explored whether the *HO* gene responds to diploidy or to the cell's mating-type constitution. An absolutely clear result was that cells homozygous for the *MAT* allele switched to establish a mixture of diploid *MAT***a**/*MAT*α cells by switching a single *MAT* locus and that tetraploid *MAT***a**/*MAT***a**/*MAT*α/*MAT*α cultures were due to switching of both *MAT* loci and subsequent mating between cells of opposite type. These results clearly showed that: (1) *HO* directs switching in diploid cells when they are homozygous for the *MAT* allele; (2) *HO* action is not influenced by ploidy; (3) *HO* action is turned off by *MAT***a**/*MAT*α heterozygosity; and (4) *HO* is dominant to the *ho* allele. I also noted a very interesting paradox in the literature and proceeded to employ our diploid cell's switching analysis to simplify the very confusing genetics of the switching specificity of *HM/hm* loci.

TABLE 1

***HM* loci nomenclature and *MAT* switching direction**

Old names	Year 1978 names	Switching direction
*HM***a**, *HM*α	*HML*α, *HMR***a**	**a** ↔ α
*hm***a**, *HM*α	*HML***a**, *HMR***a**	**a** ← α
*HM***a**, *hm*α	*HML*α, *HMR*α	**a** → α
*hm***a**, *hm*α	*HML***a**, *HMR*α	**a** ↔ α

*MAT*α SWITCHES BY *hm***a**

The *HM* genes and their *hm* alleles were identified as naturally occurring variants from different stocks (SANTA MARIA and VIDAL 1970; NAUMOV and TOLSTORUKOV 1973; HARASHIMA and OSHIMA 1976). The *HM***a** gene is required to switch *MAT***a** to *MAT*α, and *HM*α is required to switch *MAT*α to *MAT***a** (see Table 1). By convention, three letters are used in yeast gene nomenclature to designate a gene; uppercase letters are used for the dominant allele; lowercase letters are used for the recessive, usually nonfunctional allele. *HM***a**, *HM*α strains switch in both directions; *hm***a**, *HM*α switch only from *MAT*α to *MAT***a**; *HM***a**, *hm*α switch only from *MAT***a** to *MAT*α. This suggested that the *hm* genes are defective for the switching function normally directed by the *HM* loci. A beautiful paradox was that stocks containing *hm***a**, *hm*α switched in both directions, similar to the *HM***a**, *HM*α strains (Table 1). How could that be explained? *HM***a** maps near the left telomere, *HM*α near the right telomere, and *MAT* in the middle of chromosome III (HARASHIMA and OSHIMA 1976).

NAUMOV and TOLSTORUKOV (1973) theorized that perhaps *hm***a** performs the *HM*α function, and *hm*α performs the *HM***a** function. To test this conjecture, I made *hm***a**/*HM***a**, *MAT*α/*MAT*α, *hm*α/*hm*α diploid cells. Note that this strain does not contain *HM*α. If it switched, *hm***a** must have done the job of switching *MAT*α to *MAT***a**. The cells indeed switched! This showed that *hm***a** functions to switch *MAT*α to *MAT***a**, thus solving the paradox posed above. To answer such a question now, a new student would proceed to simply look up the *HM* gene sequence in the database. But that was not available at the time, so classical genetics tools had to be honed and used.

We submitted the *HO* dominance and *HM/hm* function results for publication in GENETICS. Apparently, Ira Herskowitz of the University of Oregon at Eugene received our article to review. He contacted Seymor Fogel and requested that he hold up our publication to publish it with an article from his group that addressed switching of *MAT* homozygous diploid cells. The two articles were published back to back in GENETICS (HICKS *et al.* 1977a; KLAR and FOGEL 1977).

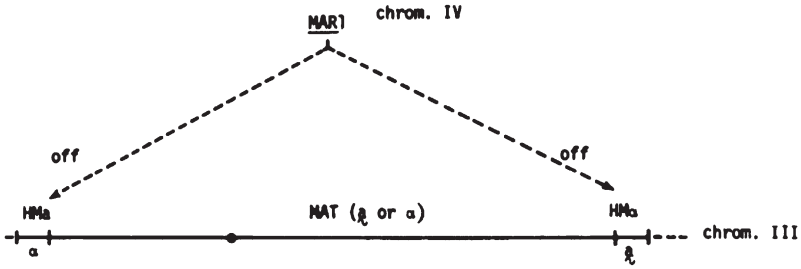


FIGURE 2.—Model for *MAR1* as the repressor of *HM* loci. Reproduced with permission from KLAR *et al.* (1979a).

THE OSHIMA GROUP'S CONTROLLING ELEMENT MODEL

Ever since my Brandeis days I have been very much influenced by the controlling element attachment/transposition model proposed for switching by Yasuji Oshima's group at Osaka University (TAKANO *et al.* 1973). By this model, the *HM***a** element "attached" to *MAT* constitutes the *MAT*α allele, whereas its replacement by the *HM*α-derived element forms the *MAT***a** allele. I had long appreciated the significance of the "healing" of the *MAT*α-*inc* allele for defining the mechanism of switching. My experiment to test the repair of the *mat*α-*ochre* mutation that should define the coding region of the *MAT* locus was borne of my desire to test whether the switching process transposes the structural part of the *MAT* locus or only some regulatory region of it. David Radin, a graduate student in our group at Berkeley, had isolated a *mat***a**$^-$ mutation in an *ho* strain as part of an unrelated project. We set out to test if the switching process could heal a *mat***a**$^-$ mutation as well. It did (KLAR *et al.* 1979b), a result in accord with the DNA transposition model for switching of both *MAT* alleles.

THE HERSKOWITZ GROUP'S CASSETTE MODEL

Ira Herskowitz learned the result of *mat*α-*ochre* mutation healing experiment from Don Hawthorne, and the University of Oregon at Eugene group showed healing of other *mat*α-*sterile* mutations by switching (HICKS and HERSKOWITZ 1977).Two key insights led the Eugene group to further define the transposition model as a mechanism for cell-type switching (HERSKOWITZ 1988; SATRATHERN 1992). The first was the insight that a fusion of the *MAT*α and *HM*α loci, caused by deletion of the interval between these loci called the Hawthorne deletion, caused the *MAT*α-to-*MAT***a** switch in *ho* strains. The second was the knowledge that bacteriophage λ mutations can be repaired by copying DNA from cryptic prophages residing in the bacterial genome.

In their cassette model (HICKS and HERSKOWITZ 1977; HICKS *et al.* 1977b), the Herskowitz group proposed that *HM***a** contains the library copy of the coding region of *MAT*α, that *HM*α likewise contains the *MAT***a** genetic information, and that *HM***a** and *HM*α remain unexpressed, possibly because they lack promoter elements. To activate the genetic information harbored at *HM***a** and *HM*α, a copy ("cassette") of one or the other "donor locus" is transposed into the *MAT* locus by a recombination/substitution reaction. I considered the cassette model to be a specific version of the controlling element model, and therefore it was very much in line with my thinking of the switching process. However, two other models were being considered at the time, which raised the possibility that the *HM* loci could function by reversibly "mutating" through DNA modification or by inverting a shared promoter located between *MAT***a** and *MAT*α coding sequences. Indeed, *HM* loci were sometimes referred to as "mutator" genes (NAUMOV and TOLSTORUKOV 1973). When Ira Herskowitz visited Berkeley in April 1977, he stopped by our laboratory, presumably because he knew we were working on *MAT* switching. In a very brief chat made to fewer than four of us standing around the chalkboard, Ira described the cassette model and the result of healing *mat*α mutations, and I related to him our unpublished result of healing the *mat***a**$^-$ mutation through switching (KLAR *et al.* 1979b).

DISCOVERY OF THE *MAR1* GENE AS A REPRESSOR OF THE *HM/hm* LOCI

Over a year before Ira's visit to our laboratory, we had been working on a spontaneous mutation that prevented yeast cells from mating with cells of either mating type. The mutant strain (*MAT***a**, *ho*) had misbehaved several times over the years in two different laboratories at Berkeley. In our laboratory a spontaneous diploid arose from this strain during routine culturing. Kathy Macleod, a technician in our laboratory, found that, upon sporulation, each ascus produced four spores that gave rise to non-mating cells that maintained the size of a haploid, but that exhibited behavior expected of *MAT***a**/*MAT*α cells: polar budding pattern and insensitivity to the α-factor. In the past, such sterile derivatives were discarded in the laboratory, but since I was working on *MAT* switching, I entertained the possibility that the *ste* phenotype might have resulted from the mutation of a gene that represses the *MAT* cassettes thought to reside at the *HM* loci. My co-workers argued that my proposal was inconsistent with the cassette model because the absence of promoter regions in *HM* loci would preclude their

expression. I countered that the model could be revised so the entire *MAT* locus, including its promoter, resides at both *HM* loci and that the *MAR1* (*ma*ting type *r*egulator *1*) gene that I proposed as the site of this *ste* mutation might function to keep them repressed.

My hypothesis was that the expression of the *HM* loci in the *mar1-1* mutant causes the *ste* phenotype by making the cell think that it is a diploid due to the expression of both *MAT***a** and *MAT*α information.(Figure 2). In support of this idea, the haploid cells exhibited incipient sporulation, a phenotype possibly resulting from aberrant meiosis due to expression of both *MAT***a** and *MAT*α genes in a haploid cell. We occasionally found fully matured meiotic products (asci) in a culture of *mar1-1*, where each ascus produced four-haploid, sterile meiotic products.

In crosses with wild-type strains, Kathy Macleod found that the *mar1* mutation segregated as a single gene in one hybrid strain, but the pattern was much more complicated in other hybrids that had acquired *mar1* suppressor mutations. The *MAR1* gene was found to be linked to *TRP1*, located on chromosome IV. Luckily, *mar1* mutant spores derived from the *MAR1/mar1* heterozygous strain showed mating competence during spore germination. This spore-to-cell mating technique greatly facilitated analysis of the *mar1* mutant.

THE NATURAL *hm***a** AND *hm*α ALLELES SUPPRESS STERILITY OF THE *mar1-1* MUTANT

The controlling/cassette model predicted that *hm***a** and *hm*α alleles should suppress the *mar1* mutant's sterile phenotype in predictable ways. For example, the *hm***a**, *MAT***a**, *HM*α (Table 1), and *mar1* mutant should exhibit the **a**-mating type because all cassettes are expected to contain the *MAT***a** information. By the same logic, the *HM***a**, *MAT*α, *hm*α, and *mar1* cells should be of the α-mating type. Indeed, these predictions were precisely borne out by our genetic analysis (Klar *et al.* 1979a). This analysis confirmed that *HM* and *hm* loci contain functional *MAT* information and that their expression is repressed by *MAR1* (Figure 2).

HM LOCI MUTATIONS AND SWITCHES DISCOVERED AS SUPPRESSORS OF THE *mar1-1* MUTATION

The *mar1* mutant showed a very tight sterile phenotype, but its cells could acquire mating capacity due to rare, spontaneous, unlinked suppressor mutations. We found two types of suppressors and, most tellingly, both classes mapped to the *HM* loci! One class of suppressors was composed of those changing from *HM* to *hm* alleles; the other class carried novel mutations of *HM* cassettes. By employing this "rare mating" selection, we identified several *hm*α$^-$ and *hm***a**$^-$ mutants. (The entire *mar1* mutant analysis was conducted in *ho* strains in which the *MAT* locus is highly stable.)

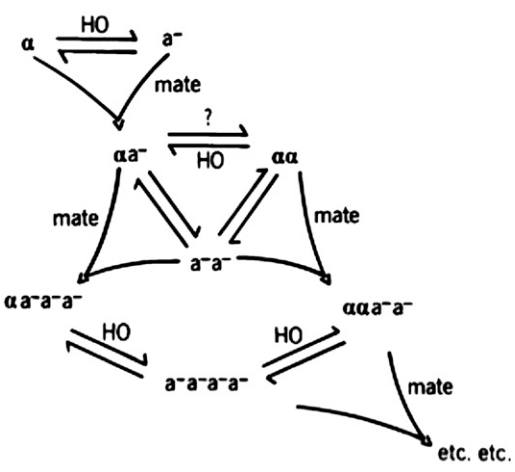
*hm*α$^-$ MUTATIONS TRANSPOSE TO GENERATE ONLY MUTANT *mat***a**$^-$ SWITCHES

A critical prediction of the transposition model is that cells containing the *hm*α$^-$ mutation should switch *MAT*α to mutant *mat***a**$^-$ because the donor locus contains the mutant copy. This prediction was satisfyingly realized (Figures 3 and 4). With just one look at the cells, we got the "aha" feeling. Most tellingly, the *hm*α$^-$ mutant culture kept on switching and mating: the switching was not shut off because of the *mat***a**$^-$ mutation. Consequently, the cells continued to increase in ploidy. Indeed, such cultures produced smaller colonies because of the *hm*α$^-$ mutant's uncontrolled sexual activity (Figure 4). This *MAT* "wounding" result satisfied a key prediction of the transposition model (Klar and Fogel 1979). This result meant that the mutation from *hm*α$^-$ is transmitted to *MAT* by the switching mechanism. We tested four such *hm*α$^-$ mutants; all produced similar results.

RESULTS PRESENTED AT THE 1977 CSHL YEAST MEETING

We submitted an abstract to the CSHL yeast genetics conference describing the *mat***a**$^-$ "healing" by switching. After submitting the abstract, we made the advances described above. I sought Ira Herskowitz's opinion about our findings before my formal presentation, scheduled for the first session of the conference, on the steps of the Blackford Hall cafeteria: Ira Herskowitz, David Kaback, my friend from my graduate school days, and two other people who were unknown to me at the time. I quickly described to them that we had found a mutation that causes derepression of the *HM* loci, that the mutation maps near the *TRP1* marker on chromosome IV, that the mutant is sterile, that the suppressors of the sterile mutation map at *HM* loci, and so on. One of the two strangers inquired with urgency about what happens when we use the *hm*α$^-$ mutant for switching. After I had described the meager details of how the mutations were isolated and characterized, I answered that the *hm*α$^-$ mutant alternates between *MAT*α and mutant *mat***a**$^-$ and that it keeps on switching back and forth. The stranger became very excited and stomped the ground a few times while yelling, "A shrine should be made for mating type right there." Then Ira introduced me to the two strangers: his student Jasper Rine and a former student, Jeffrey N. Strathern (the stranger who stomped). They immediately understood what I had described. Within minutes I was introduced to James B. Hicks, another former student of Ira's who also had worked on *MAT* switching for his thesis research.

MAT was put on the agenda of the first session of the meeting because the organizers thought that the presentations would be an exciting start to what



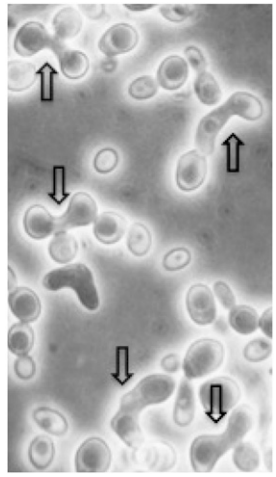


FIGURE 3.—The mating orgy of the *hmα⁻-2* mutant. The *HO*, *HM***a**, and *hmα⁻-2* mutant switches continuously between *MAT*α and mutant *mat***a**⁻ (left). Reproduced from KLAR and FOGEL (1979). The *mata⁻* cells mate as **a**-mating type. Photograph of promiscuous matings between switched cells show dumbbell-shaped zygotic cells (marked by arrows, right).

promised to be a great meeting. Jasper Rine from the Eugene group led off with a talk about a suppressor of a *mat*α*-sterile* mutant, called *ssp1*, and I learned for the first time of their proposal for its function in gene silencing of *HM* loci. At the time Jasper thought that the *ssp1* gene was probably allelic to *MAR1*, as it was linked to *TRP1*. [I later tested their allelism and found that it was a different gene, which they named *SIR1* (*s*ilent *i*nformation *r*egulator *1*).] In my turn, I presented an analysis of the *mar1* mutant (Figure 2) and of the transposition of a mutation from *hmα⁻* to generate the *mat***a**⁻ mutant allele (Figures 3 and 4). My talk, embarrassingly, went on past the buzzer, taking me out of the running for a bottle of champagne promised by organizers for the shortest talk of the meeting. However, Jim Hicks called out from the audience, "I'll buy you champagne, keep going." I finished by concluding that both results genetically support the cassette model.

I felt that only a few people understood my presentation because many people asked me to explain our results during the conference. It must have been difficult for most people to follow the complex analysis of four genes segregating in crosses, one of which switches between two alleles. James Broach from the CSHL characterized my presentation as a "bombshell." Seymor Fogel was overjoyed for me and remarked, "Amar, your talk was so well received. I don't think such a wonderful reception could happen to you in the future." I was happy for the pat on the back from my advisor, but luckily this was not to be the single most important day of my career.

MY FIRST TASTE OF COMPETITION

One of the participants who must have understood my talk was James E. Haber of Brandeis University. After hearing my presentation, ANITA HOPPER (personal communication) from the University of Massachusetts told Haber that the *cmt* (*c*hange of *m*ating *t*ype) mutation that she had published in 1975 had properties exactly like those of the mutant that I had presented. She speculated that the *CMT* gene is probably *MAR1*. Haber promptly requested the mutant from HOPPER, and a manuscript describing a *MAR1*-related explanation for the *cmt* mutation was prepared quickly before our results had been published. The findings about *MAR1* and *CMT* in *HM* loci gene silencing came out in the September issue of GENETICS (HABER and GEORGE 1979; KLAR *et al.* 1979a). In the acknowledgment of the *CMT* article, the authors noted that "We began to study the *cmt* mutation after Amar Klar communicated to us his characterization of the *MAR1* mutation, which has a phenotype appar-

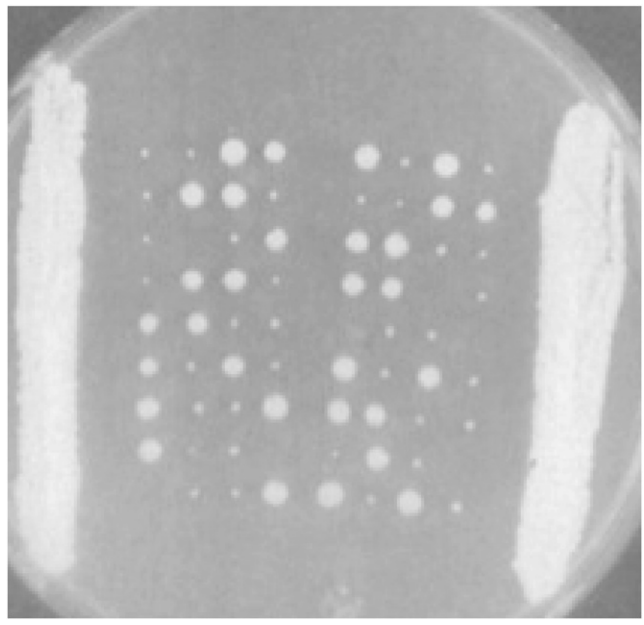


FIGURE 4.—Segregant analysis of *HO/HO*, *HM***a**/*HM***a**, *MAT***a**/*MAT*α, and *hmα⁻-2*/*hmα⁻-2* strain (KLAR and FOGEL 1979). Four-spore segregants from each ascus were planted to grow in a horizontal line on solid medium in two parallel columns. In each tetrad, the two *MAT***a** spores produced standard-size *MAT***a**/*MAT*α diploid segregants due to homothallism, and two *MAT*α spores produced much smaller colonies due to continuous switching and mating.

ently identical to *cmt*." The *SIR1* article was published later in the December 1979 issue of Genetics (Rine *et al.* 1979).

DON HAWTHORNE BELIEVED OUR STORY

A few months after the CSHL meeting, Leland Hartwell of the University of Washington invited me to Seattle, having heard about my talk from his students. There I met Don Hawthorne, a legendary yeast geneticist who favored the hypothesis of *MAT* switching occurring by directed mutations. Being aware of the Hawthorne deletion, and his unpublished work on the *mat*α*-ochre* mutation's healing result, I was therefore most interested in Don's opinion for my presentation. He said, "I believe you. It's neat." I was elated by his response. A few years later, I related to Don that by not publishing the *mat*α*-ochre* healing result in due time he had held back the field for 10 years. He countered, "Five years."

JOINING THE CSHL YEAST GROUP IN 1978

Jeff Strathern and James Broach were already working as postdoctoral fellows at CSHL, and Jim Hicks was a postdoctoral fellow at Cornell University. [With several Jim's (Hicks, Broach, and Watson) who figure in this story, hereafter I will identify them by their last names.] Both Hicks and Jeff proposed that I be asked to join the CSHL yeast group that included Jeff, Broach, and Hicks (Hicks 2009). According to Hicks (personal communication), for his job seminar he presented *MAT* studies to a handful of CSHL senior scientists, which included the director, James D. Watson. All went well for Hicks's appointment, but a question was raised as to why I should be hired into the group. After some silence, one inquisitor asked for a summary of what I had done in research, a summary that Hicks gave. Some silence ensued, and then one committee member said, "I got it. You guys proposed a model, Klar established it. Is that why you want him to join the group?" Hicks agreed.

Jim Watson tracked me down while I was in the middle of delivering a seminar at the University of California at Irvine. Perhaps because of Watson's insistence, my host's secretary walked into the seminar room and politely interrupted my seminar to tell me that Watson wanted to talk to me right away. Immediately after finishing my talk, I got on the phone: "Hello, Dr. Watson; this is Amar Klar." Abruptly, Watson replied, "Oh, yes, I know you; I know what you do. We are opening a yeast lab to work on mating-type switching. Whatever you need, I will arrange for it. You should realize your appointment has to go through a committee, but I will send you the appointment letter tomorrow. You should sign it and send it back to my assistant director, Mr. Bill Udry. Bye" (Klar 2003).

I joined the yeast group in the summer of 1978. At the yeast meeting held in Rochester, New York, that year, Ira Herskowitz presented his version of the *MAT* wounding experiment of the *hm***a**$^{-}$ mutant in support of the cassette model. Yasuji Oshima stood up after Ira's presentation to ask the first question, "How is your model different from the controlling element model?" Ira replied, "They are similar." This answer clarified the intellectual linkage between these gene transposition models, and subsequently the *MAT* controlling elements came to be referred to as cassettes.

My postdoctoral work paved the way for me to join a wonderful group of colleagues at CSHL. Initially, there were four of us. Broach soon moved to Stony Brook, leaving Hicks, Jeff, myself, other colleagues from CSHL, and our postdoctoral colleagues to work on the mating-type story. Our long-term collaboration led to many discoveries in an exciting research environment. This group (1) cloned the *MAT* gene, molecularly confirming conclusions derived from the genetics studies described above; (2) discovered that *MAT* switching is initiated by a double-stranded DNA break at *MAT*; (3) showed that *HO* encodes the endonuclease that cleaves *MAT*; (4) established that switching occurs by gene conversion; (5) showed that *MAR/SIR*-promoted gene silencing prohibits *HM* loci from switching; and (6) found that the directionality of *MAT* switching (*MAT***a** prefers to switch to α, and vice versa) results from a specific chromosomal location and not from the genetic content of *HML* and *HMR*.

This Perspective narrates my participation in the mating-type story from my postdoctoral research. Descriptions of related contributions are presented in other commentaries (Herskowitz 1988, 1992; Klar 1992; Strathern 1992; Oshima 1993; Hicks 2009). Time has flown quickly since the 1977 yeast meeting, but thankfully the people I met along the way have made the intervening time very exciting for me. I am sad that this story has not been shared until this time because several of the personalities who figured prominently in it—Harlyn Halvorson, Seymor Fogel, Ira Herskowitz, and Don Hawthorne—have passed away. I wish I could have refreshed their memory about the story with this Perspective.

I very much appreciate the research experience with Jim Hicks, Jeff Strathern, Jim Broach, and numerous postdoctoral associates and collaborators and visiting scientists over the years. I thank David Kaback for his suggestions on the manuscript. The Intramural Research Program of the National Institutes of Health, National Cancer Institute, Frederick, Maryland, has supported my research for the past 22 years.

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