Forty-five years of cell-cycle genetics

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ABSTRACT **In the early 1970s, studies in Leland Hartwell's laboratory at the University of Washington launched the genetic analysis of the eukaryotic cell cycle and set the path that has led to our modern understanding of this centrally important process. This 45th-anniversary *Retrospective* reviews the steps by which the project took shape, the atmosphere in which this happened, and the possible morals for modern times. It also provides an up-to-date look at the 35 original *CDC* genes and their human homologues.**

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Forty-five years ago, a short paper was published (Hartwell *et al.*, 1970a) that launched the genetic analysis of the eukaryotic cell cycle and led (directly or indirectly) to most of our modern understanding at the molecular level of this centrally important process. It was the first published fruit of an intense collaboration between Lee Hartwell and Brian Reid that began in the Fall of 1968, when Brian was an undergraduate senior at the University of Washington and Lee was a newly arrived young faculty member. The two of them, plus part-time technicians Mary Ashton and Sue Purrington, constituted the lab group that year, but the intense collaboration expanded when Joe Culotti arrived in June 1969 to begin graduate work, Mimi Livesley replaced Mary and Sue as the lab technician, John Pringle arrived in July 1970 to begin postdoctoral work, and Lynna Hereford arrived in September 1970 as a transfer graduate student from Yale. This group worked closely together until 1974, when most moved on to the next stages in their careers. Although some of the papers took a few more years to come out, two 1974 articles (Hartwell, 1974; Hartwell *et al.*, 1974) were able to capture most of the progress to that point, which already incorporated many aspects of the modern understanding of the cell cycle in yeast and other eukaryotes, pointed the way to future studies, and provided 35 partially characterized cell division–cycle (*CDC*) genes as a substrate for those studies.

To recognize this anniversary, the editors of *Molecular Biology of the Cell* asked for a *Retrospective*, which we have provided here based on Brian's, Joe's, and John's memories and written records from the 1968–1974 period and Lee's recollections as recorded elsewhere (Hartwell, 1993, 2002a). To highlight the continuing influence of the studies performed 40–45 years ago, we also recruited Rob Nash of the *Saccharomyces* Genome Database to help us prepare a table of the original 35 genes.

LEE HARTWELL AND HIS EARLY LABORATORY

Although Lee had evinced curiosity about the natural world and a desire to understand it as a child, he did not focus in high school on building a strong precollege résumé (Hartwell, 2002b) and so began his further education at Glendale Junior College. However, his academic interests had been awakened by then, and his abilities had begun to show, so he was able to transfer to Caltech after just one year. While at Caltech, he spent much of his time on independent reading courses and research. He was influenced particularly by work with Bob Edgar on phage T4 morphogenesis (Hartwell, 1961), which gave him a strong belief in the value of conditional mutants for elucidating the organization of essential cellular pathways. After a quick PhD in bacterial biochemical genetics with Boris Magasanik at MIT (Hartwell and Magasanik, 1963, 1964) and an even quicker postdoc with Renato Dulbecco and Marguerite Vogt at the Salk Institute (Dulbecco *et al.*, 1965; Hartwell *et al.*, 1965), he began his independent career in 1965 at the newly established University of California–Irvine campus. Although he originally intended to study cell-proliferation control and cancer in mammalian cells (and secured a National Institutes of Health grant for this purpose), he quickly realized that fundamental understanding would come more easily in a system with genetic tools, and he began to work on yeast with lots of early help from Bob Mortimer in Berkeley and Herschel Roman and Don Hawthorne in Seattle.

True to Lee's early imprinting in the Edgar lab, he began by isolating a large collection of temperature-sensitive lethal (Ts^-) mutants

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and screening them for defects in macromolecule synthesis, morphology, and/or cell division (Hartwell, 1967). Although he was interested from the beginning in using the mutants to learn about the cell cycle, pursuit of this goal was initially blocked by 1) the lack of a way to recognize cell-cycle mutants among the many defective in other essential cellular processes and 2) the near impossibility, at the time, of identifying the molecular defect in any cell-cycle mutant that was identified. (Mutants with specific defects in DNA replication provided an early exception to both problems. The general solution to problem 2 did not appear until some years later, when the cloning of genes by complementation of the mutations became possible [Nasmyth and Reed, 1980].) Thus, Lee partnered with his UC Irvine colleague Cal McLaughlin in a series of studies of mutants with specific defects in RNA or protein synthesis (Hartwell and McLaughlin, 1968; Hartwell *et al.*, 1970b; and seven papers in between). In the midst of this period, Herschel Roman succeeded in convincing Lee to move from Irvine to the Department of Genetics at the University of Washington; he arrived in the Fall of 1968 unencumbered by lab members, except for one student who had finished his experimental work at Irvine and was writing his thesis. Mary Ashton was hired and began unpacking boxes several weeks before Lee himself arrived. By September 1970, the group had grown to eight full-time members (Lee, one technician, two postdocs, and four graduate students) and stayed that size during the next four years. Cal McLaughlin, at Irvine, continued to isolate many more Ts^--lethal mutants and send those with possible cell-cycle defects on to Seattle for further analysis.

Although the group was not large, it never seemed small, in part because interaction among the lab members was so constant and intense, and in part because we were embedded in a highly interactive department of other small groups. One lab room was shared with the group of Walt Fangman, frequently bringing him and his lab members—Tom Petes, Carol Newlon, and Walter Hill—into the conversations; the lab of collaborator Breck Byers was in the adjacent hallway; and the whole department attended weekly seminars and student/postdoc journal clubs, while all the yeast workers (from multiple laboratories) attended the weekly Yeast Meeting. Herschel himself missed none of these events, took care to ask frequent (and often seemingly naïve) questions in order to establish an atmosphere of open and uninhibited inquiry, and left no doubt whatsoever that everyone else's attendance and intellectual engagement at these events was expected.

All of us remember the atmosphere in the lab as simply *fun*. Lee himself was there all the time, doing his own experiments and discussing our experiments and ideas with us on a daily basis. He never joined in our silliest pursuits (Nerf and pipette-bucket basketball brought only a half-resigned shake of his head) but otherwise was part of the gang, even for much of our frequent out-of-the-lab socializing. Our scientific ideas did not always bring instant approval—indeed, sometimes Lee would give only a blank look and wander away without comment. But he would usually return to the idea later without further prompting, either to point out a fatal flaw or to provide a major conceptual improvement and/or suggest a new critical experiment. Lee's leadership style plus (we suppose) a fortunate confluence of personalities led to an atmosphere of total openness and high collegiality, in which no one worried about who would get credit for a particular idea. This was fortunate, because with the constant production, group dissection, and replacement of our often half-cocked models, it was usually impossible to reconstruct exactly who had contributed what facet of a new idea. As Lee himself put it: "Each new result generated vigorous discussions so that it is impossible to know who contributed a particular idea" (Hartwell, 1993); virtually identical wording appears in the acknowledgments section of Brian's PhD thesis. Importantly, we were excited about what we were doing and believed in its significance, even if others did not (see also below), and we *certainly* did not worry about what journals our papers would be published in or how many citations those papers would get in the next two years!

BRIAN REID AND THE "EUREKA" EVENING

Brian had begun college in 1965 with an interest in biology, but he was majoring in chemistry because he had found the biology courses boring. However, Dave Stadler's genetics course in the Spring of 1968 gave him new hope, so he inquired that Fall about research opportunities in the Department of Genetics. He was directed to the newly arrived Lee, who put him to work on a series of highly imaginative experiments that produced no useful results, while also giving him lots of one-on-one teaching about the important processes that had been elucidated using genetic approaches. One of the "unproductive" studies was an attempt to see whether mutants in the Ts^--lethal collection that made abnormal-shaped buds (thought of at the time as "cell-wall mutants"; later found to be defective in the septin proteins and thus in cytokinesis) would pass that trait on to their progeny after return to permissive temperature, as in the cortical inheritance that Tracy Sonneborn had described in *Paramecium*. On the evening of November 30, 1968, while examining the time-lapse experiments that Brian was doing for this project, he and Lee suddenly realized that the progressive growth in bud size during the cell cycle allowed them to recognize mutants that were competent for growth but defective in cell division. Establishing the pattern for the lab (see above), neither of them could remember afterward exactly how the idea had developed between them on that "Eureka!" evening and in the following months. However, by June 1969, it had progressed to the point that Brian spent most of the summer screening (with Mary Ashton's help) the hundreds of Ts^- mutants by time-lapse microscopy at 37°C, a project that was rather painful because the lack of a better method at the time forced them to do the screening while sitting and sweating at a microscope in the warm room.

By the time Brian left to start graduate school at MIT in September, they had identified 150 mutants with putative defects in "cell division" (rather loosely defined). Brian lasted less than a year at MIT before the lure of the cell-division mutants (and of the Washington mountains) drew him back to Seattle and the Hartwell lab; the activation energy for this move was lowered by Lee's having during the year acquired a warm-air blower and a Plexiglas box that fit over the microscope, so time-lapse analyses of the mutants at 37°C no longer needed to be done in the warm room! (Lee's discovery that conventional window screening provided a grid of just the right size to allow repeated relocation of the same field for time-lapse observations was another critical, "high-tech" advance.) Fortunately, Herschel had saved a slot on the training grant for just such an eventuality. Brian immediately resumed his role as an indefatigable discussant of ideas in the lab and solidified the idea of Start (see below) by using the mutants to show that mating was only possible in G1 before cells had initiated the cell cycle; the publication of this work (Reid and Hartwell, 1977) was held up by Brian's injudiciously beginning medical school in the Fall of 1975.

JOE CULOTTI, THE SOLIDIFICATION OF THE *CDC* MUTANT CONCEPT, AND EARLY IDEAS ABOUT PATHWAYS

Although Joe had also begun (as a freshman) at UC Irvine in 1965, he and Lee did not cross paths until a meeting in the summer of

1968 that almost ended Joe's career before it began. While doing undergraduate research in Cal McLaughlin's lab, Joe ran out of yeast medium and "borrowed" a flask of medium from Lee's lab. It happened to be the last such flask, and Lee needed it for an experiment in progress that thus needed to be aborted. Fortunately, his initial anger subsided when he recognized an innocent mistake by an eager student, and he responded positively when Joe contacted him later that year about coming to Seattle to do graduate work in his lab. Indeed, perhaps anxious that his tiny group would dwindle to nothing when Brian left, Lee suggested that Joe come early. Joe arrived on a weekend day in June, found Brian in the lab, and began a conversation that continued almost nonstop for the next five years.

Joe's arrival was propitious, because although Brian and Lee had identified many presumptive cell-division mutants by then, they did not really know whether these were *cell-cycle* mutants, because they had not yet been able to stain the nuclei in order to assess the status of the nuclear cycle. Brian mentioned this problem to Joe in their initial conversation, and Joe took up the challenge after only a short delay occasioned by a different (and now forgotten) project suggested by Lee that went nowhere. Joe was already making some headway when Lee learned that master cytologist Carl Robinow (Matile *et al*., 1969) was coming to Seattle for a conference and asked him to show Joe how to optimize his staining. Joe spent a month gathering and preparing the reagents for Robinow's staining protocol, but then forgot to start a culture of cells the night before the scheduled demonstration! Fortunately, he was able to "borrow" someone else's culture, Professor Robinow (a proper gentleman in a tweed suit) was able to overcome his instinctive aversion to Joe's "Seattle hippie" sartorial style (Joe still remembers Robinow's big sigh upon their first meeting at the hotel), the demonstration was duly made, and Joe's Giemsa staining of nuclei improved significantly. This immediately led Brian and Lee to conclude (in a closed-door meeting that Joe remembers well but Brian does not) that all the tools were now in place to declare a focus on the cell cycle, a decision whose rationale was explained to Joe and the lab helpers over pizza and beer at the Northlake Tavern (one of many key scientific conferences to occur at that conveniently located—and still operational—establishment). Nuclear staining using the Robinow procedure contributed importantly to all of the earliest papers on the *cdc* mutants (Hartwell, 1971a,b; Hartwell *et al*., 1970a; Culotti and Hartwell, 1971).

In late 1969 or early 1970, Joe and Lee also began the first attempts to use the mutants to organize the events of the cell cycle into pathways. There was not much to go on at first (too few mutants and too little information about them), and the first model was later shown to be largely incorrect. However, the effort continued more or less nonstop, particularly after Brian returned from MIT to help drive the frequent conversations. At various times, the models incorporated clocks, stopwatches, dependent series of events, events in independent pathways, and feedback loops that could enforce event dependencies. Such a feedback loop was present even in the very first model and was the forerunner of the now-famous cell-cycle checkpoints, but at the time we had neither a clear concept about how such feedbacks might work nor any experimental handle on them. Thus, the first model that we presented to the world offered no explanation for why some events would be dependent upon earlier events (Hartwell *et al*., 1974) and implicitly presumed that the progression of the cell cycle could be thought of like the sequential assembly of components during phage T4 assembly (the early Edgar influence again). Thus, the proper development of the checkpoint idea was delayed until Ted Weinert joined Lee's lab long after the rest of us had gone (Weinert and Hartwell, 1988; Hartwell and Weinert, 1989).

We did worry in 1973 that the hypothesis that bud emergence and nuclear migration were in a pathway independent from that including DNA replication and nuclear division (Hartwell *et al*., 1974), which was based solely on the continuation of the nuclear cycle in the *cdc24* mutant, might be wrong if that mutant were missing a control that would normally slow or stop the nuclear cycle if bud formation were interrupted. It was this worry that led John to begin focusing on *cdc24* and similar mutants several years later in his own lab. However, this focus was ultimately more revealing about the mechanisms of cell polarization than about cell-cycle pathways per se, and it was many years later that Danny Lew and Steve Reed (himself a former Hartwell-lab postdoc) showed that there is indeed a "morphogenesis checkpoint" that normally delays mitosis when budding is defective (Lew and Reed, 1995; Short, 2015). This checkpoint was apparently defective in the heavily mutagenized *cdc24* strain that was examined in the original studies.

BOB MORTIMER, DON HAWTHORNE, AND THE MAPPING OF THE *CDC* GENES

In the days before genome sequences, the mapping of a gene gave it an aura of solid reality and helped to prove that it really was distinct from the other genes under study. In the early 1970s, it was also a time-consuming and often frustrating business. Thus, the Hartwell group was very lucky that Bob Mortimer came to spend a sabbatical with Don Hawthorne in 1972 and used the new *cdc* mutants to test some new mapping methods. Thus, the mapping of 14 *CDC* genes to distinct chromosomal positions was reported in the paper summarizing the genetic analysis of the mutants defining genes *CDC1*–*CDC32* (Hartwell *et al*., 1973). Rereading this paper many years after its publication reminded us of the craftsmanship that complemented the creativity: despite the brutally heavy mutagenesis that had been used (Hartwell, 1967), the mutations in the many mutants were neatly sorted into genes by a combination of complementation tests, linkage analysis, and mapping; the mutants carrying more than one relevant mutation were identified; and so on. Only minor tweaking of this initial analysis was required later.

JOHN PRINGLE, LYNNA HEREFORD, AND START

John had fallen in love with yeast, genetics, and cell biology during required courses as a first-year graduate student at Harvard. Undeterred by the complete absence of labs working on yeast in the Boston area in 1964, he began thesis work on some yeast proteins with protein chemist Guido Guidotti while plotting a path to Seattle, which at the time had the only concentration of yeast geneticists in the country. In 1968, Herschel agreed to sponsor him to come to the department but immediately began nudging him toward the lab of the newly recruited Lee. John initially resisted, because he was not excited about the work on RNA and protein synthesis, but when he heard about the cell-cycle project from Lee and Joe (Brian was already gone) during a visit in September 1969, he was immediately hooked and signed up on the spot to become Lee's first postdoc.

After arriving to stay in July 1970, John was trying to decide which *cdc* mutants to work on when he got distracted by the serendipitous observation that some cultures that had overgrown to stationary phase contained almost exclusively unbudded cells that varied enormously in size. These observations immediately suggested the existence of a control point in the unbudded (G_1) phase beyond which cells would complete a cell cycle even if nutrients were not sufficient for normal bud growth. Lee was initially uninterested, in part because Herschel argued in Yeast Meeting that this behavior was strain specific and thus not of general interest. However, Lee had already begun using a sonicator to separate clumps

of cells before counting with the Coulter Counter, and when John used this approach to separate postdivision cells in cultures of various strains that had been limited for carbon and energy, nitrogen, or sulfur, he found that the unbudded, size-heterogeneous arrest was quite general. Lee's interest was now awakened, and he politely vacated his office for hours at a time (to be sure, it also gave him a good excuse to do experiments rather than push paper!) while John worked in there with the lights off to do the critical experiment that established the cell-size requirement for cell-cycle initiation. (True to the low-tech spirit of the time, this involved using a filmstrip projector to project individual images from a time-lapse series of stationary-phase cells beginning to grow again onto a piece of white paper taped to the office wall, measuring the long and short axes of the cells with a ruler, and calculating their volumes using the formula for a prolate ellipsoid. See figure 5 of Johnston *et al.*, 1977.)

Lee also made a critical experimental and conceptual contribution by showing (in collaboration with Tom Manney and Wolfgang Duntze) that the response of mating-type **a** cells to the mating pheromone from α cells could also be explained by a similar control point in G_1 (Bücking-Throm *et al.*, 1973). He also recognized that we, needed a name for this putative control step, which prevented cell-cycle initiation until certain threshold conditions had been met. He initially suggested "Sisyphier" (after the mythological Sisyphus, whose fate was to eternally try, and fail, to push his rock to the top of the hill), but this suggestion (which was perhaps not entirely serious) was quickly rejected, because we did not have any evidence that the cells actually approached cell-cycle initiation but then regressed. Extensive further discussions in the lab—and at the Northlake—then led to the highly imaginative "Start," which has endured.

Meanwhile, Lynna had joined the Genetics Department and the Hartwell lab in September 1970 and was contributing in multiple ways. Her good-natured mocking of our enthusiasms (G_1 was always "gee whiz" to her, and she posted a map of the London Underground system to spoof our early maps of cell-cycle pathways) helped us to sharpen our thinking. And although she preferred to work on the more concrete issue of DNA replication (Hereford and Hartwell, 1971, 1973), her most enduring contribution (probably to her chagrin) was to solidify the concept of Start by using epistasis analysis and the newly invented "reciprocal-shift" method to establish an order of dependent events (Start [defined by the *cdc28* mutation and the mating-pheromone-sensitive step] → Cdc4 function → Cdc7 function) leading up to the initiation of DNA replication (Hereford and Hartwell, 1974). This order of events was further solidified by the work of Breck Byers and Loretta Goetsch in the next hallway, who showed that these steps also corresponded to discrete stages in the duplication and separation of the spindle-pole body (Byers and Goetsch, 1974, 1975).

THE ORIGINAL *CDC* GENES TODAY

Although Lee's brilliance was certainly recognized early (e.g., by Hershel's recruitment of him in 1968 and the Eli Lilly Award from the American Society for Microbiology in 1973), the cell-cycle analysis did not immediately take the world by storm. Although it seems absurd in hindsight, at the time many doubted that yeast was even a bona fide eukaryote, much less that anything useful could be learned about animal cells by studying the evolutionarily distant yeast. An early seminar by Lee in Vancouver was attended almost exclusively by people from Seattle who drove up to hear him, and after a talk at Caltech, Max Delbrück commented that he did not expect to understand the cell cycle any better than he did black holes. And when Joe began his postdoc at Caltech and was asked at a dinner party to describe his graduate work, the entire party broke down in laughter when he suggested that his work in yeast might someday be relevant to understanding cancer! However, we had all benefited from the diverse faculty that Herschel had assembled in the Genetics Department, and we were aware of the emerging theory that cancer was a disease of clonal evolution, largely because of work in Stan Gartler's laboratory directly above our own (Linder and Gartler, 1965). Decades later, when Brian told another cancer researcher that he had decided during graduate school to study cancer because of insights into Start and cell-cycle control that came from the early yeast investigations, he got a surprised look and the comment that "you must have been the only one who thought that then."

Of course, it is now abundantly clear that the *CDC* genes have had the last laugh. Thirty-two such genes were described in the 1970–1974 papers, and an additional three were described in Joe's dissertation, although not in the papers. With only a few exceptions, these original 35 *CDC* genes have had major impacts on understanding of nearly all aspects of the cell cycle, not only in yeast but also in other organisms (Table 1). In most cases, the "official" names of the yeast genes are still the original CDC names, indicative of how the path to current understanding really did *begin* with the original *cdc* mutant. Many other *CDC* genes were named later, and some have also proved to be quite important in understanding cellular function in both yeast and animal cells, but *CDC1–CDC35* set a very high bar for subsequent studies!

MORALS OF THIS STORY

The morals of this story are perhaps obvious, but we emphasize some of them here because of their relevance to the current troubled times in academic science. First, groundbreaking research does not require a large group. Indeed, we suggest (on the basis of this and many other examples) that it probably flourishes best when the group is small and the lab head is around most of the time and participating actively in the intellectual and experimental life of all group members on an almost daily basis. Second, such research benefits from an atmosphere in which all group members share new results and ideas freely with one another and without concern about the ultimate distribution of credit. Indeed, it is helpful when this attitude can be extended beyond the immediate group to others, as illustrated in this story by the critical early contributions of Don Hawthorne, Carl Robinow, Bob Mortimer, Tom Manney, Wolfgang Duntze, and Breck Byers. Third, if a research group is doing something that excites them, it does not really matter whether anyone else yet realizes that their line of work is important. Indeed, it is better if they *do not*, because that reduces any possible worries about being "scooped," encourages the full development of stories rather than the publication of half-baked ones, and suggests that what the group is doing is really *new*, rather than yet another variation on a well established theme. These consequences of genuine novelty are, of course, the fundamental—and fatal—flaw of any measure of scientific accomplishment that uses citation counts, particularly from the first few years after publication. Finally, despite the lack of respect they get from most current grant-review panels, "fishing expeditions"—in which one does not actually know beforehand what will be discovered—are often the most productive form of research, as not only the *CDC* story but many others clearly show.

CDC gene[a]	Functional description of the yeast gene product[b]	Human gene name(s) and BLASTP E-value(s)[c]	Functional description of the human gene product[d]
CDC1	Putative metallophosphodiesterase	*MPPE1*; 2e-11	Metallophosphodiesterase
CDC2 (now *POL3*)	DNA polymerase delta catalytic subunit	*POLD1*; 0.0	DNA polymerase delta catalytic subunit
CDC3	Septin family member; involved in cytokinesis	*SEPT1–SEPT14*; 3e-107 to 4e-61	Septin family members
CDC4	SCF E3 ubiquitin ligase F-box protein (substrate-specificity factor)	*FBXW7*; 3e-61	SCF(Fbw7) ubiquitin-ligase substrate receptor
CDC5	Polo-like kinase	*PLK1*; 1e-77	Polo kinase
CDC6	ATPase subunit of the prereplicative complex	*CDC6*; 6e-34	Replication origin licensing factor
CDC7	Catalytic subunit of the Dbf4-dependent kinase (DDK)	*CDC7*; 9e-30	Catalytic subunit of the Dbf4-dependent kinase
CDC8	Thymidylate/uridylate kinase	*DTYMK*; 1e-45	Thymidylate kinase
CDC9	ATP-dependent DNA ligase	*LIG1*; 8e-163	ATP-dependent DNA ligase
CDC10	Septin family member; involved in cytokinesis	*SEPT1–SEPT14*; 3e-91 to 1e-60	Septin family members
CDC11	Septin family member; involved in cytokinesis	*SEPT1–SEPT14*; 1e-68 to 4e-54	Septin family members
CDC12	Septin family member; involved in cytokinesis	*SEPT1–SEPT14*; 2e-78 to 5e-65	Septin family members
CDC13	Telomeric ssDNA-binding protein and telomere-cap–complex subunit	*POT1*; N/A[e]	Telomeric ssDNA-binding protein; subunit of the telomere cap and shelterin complexes
CDC14	Protein phosphatase subunit of the RENT complex	*CDC14A* and *CDC14B* (multiple isoforms); 1e-68 to 3e-27	Dual-specificity protein phosphatases
CDC15	Ser/Thr protein kinase of the mitotic exit network	None; N/A	The CDC15 subfamily has not been identified in humans
CDC16	Anaphase-promoting complex/cyclosome (APC/C) subunit	*CDC16*; 2e-90	Anaphase-promoting complex/cyclosome (APC/C) subunit
CDC17 (now *POL1*)	Catalytic subunit of the DNA pol I alpha–primase complex	*POLA1*; 0.0	Catalytic subunit of DNA pol I alpha–primase complex
CDC18	Unknown, not well studied; original alleles are leaky	N/A	N/A
CDC19	Pyruvate kinase	*PKM*; 6e-158	One of four pyruvate kinases
CDC20	Mitotic activator of the anaphase-promoting complex/cyclosome (APC/C)	*CDC20*; 7e-77	Mitotic activator of the anaphase-promoting complex/cyclosome (APC/C)
CDC21	Thymidylate synthase	*TYMS*; 8e-128	Thymidylate synthase
CDC22	Unknown, original isolates were multigenic	N/A	N/A
CDC23	Anaphase-promoting complex/cyclosome (APC/C) subunit	*CDC23*; 3e-63	Anaphase-promoting complex/cyclosome (APC/C) subunit
CDC24	Rho guanyl-nucleotide exchange factor for Cdc42p	*MCF2*; 2e-17	One of many CDC24 homologues
CDC25	Ras guanyl-nucleotide exchange factor (GEF)	*RASGRF1* and *SOS1*; 5e-13 and 6e-36	Ras guanyl-nucleotide exchange factors (GEF)
CDC26	Anaphase-promoting complex/cyclosome (APC/C) subunit	*CDC26*; 3e-05	Anaphase-promoting complex/cyclosome (APC/C) subunit
CDC27	Anaphase-promoting complex/cyclosome (APC/C) subunit	*CDC27*; 3e-64	Anaphase-promoting complex/cyclosome (APC/C) subunit

TABLE 1: The 35 original *CDC* genes today, and their human homologues.

Continues

CDC gene[a]	Functional description of the yeast gene product[b]	Human gene name(s) and BLASTP E-value(s)[c]	Functional description of the human gene product[d]
CDC28	Cyclin-dependent kinase (CDK) catalytic subunit	*CDK1*; 1e-98	Cyclin-dependent kinase (CDK) catalytic subunit
CDC29	Unknown, not well studied; exists only as a genetic locus	N/A	N/A
CDC30 (now *PGI1*)	Glucose-6-phosphate isomerase	*GPI* (multiple isoforms) 0.0 to 4e-74	Glucose-6-phosphate isomerase
CDC31	Centrin	*CETN3*; 3e-57	Centrin
CDC32	Unknown, genetically intractable	N/A	N/A
CDC33	mRNA m^7G cap-binding protein (eIF4E)	*EIF4E*; 6e-36	mRNA m^7G cap-binding protein (eIF4E)
CDC34	SCF ubiquitin-conjugating enzyme (E2)	*CDC34*; 9e-42	SCF-associated ubiquitin-conjugating enzyme (E2)
CDC35 (now *CYR1*)	Adenylate cyclase	Multiple structurally distinct human *ADCY* genes	Adenylyl cyclase family members

[a]*CDC* name (with current standard name, where different, in parentheses); entries link to the *Saccharomyces* Genome Database (SGD) (PMID: 22110037).
[b]Summarized from information provided in the SGD entries.
[c]As approved by the HUGO Gene Nomenclature Committee. E-values were obtained by querying the NCBI human taxon (taxid:9606), restricted, nonredundant protein sequence data set with the predicted amino acid sequence of the yeast genes using BLASTP.
[d]Summarized from the literature; see the Supplemental Material for details and references.
[e]Cdc13 and Pot1 do not have detectable sequence similarity but are considered to be structurally similar (see the Supplemental Material for relevant references).

TABLE 1: The 35 original *CDC* genes today, and their human homologues. Continued

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We dedicate this article to the memory of Lynna Hereford, a critical member of the early 1970s Hartwell group who, sadly, did not live long enough to fully enjoy the fruits of its labors.

REFERENCES

Bücking-Throm E, Duntze W, Hartwell LH, Manney TR (1973). Reversible arrest of haploid yeast cells at the initiation of DNA synthesis by a diffusible sex factor. Exp Cell Res 76, 99–110.

Byers B, Goetsch L (1974). Duplication of spindle plaques and integration of the yeast cell cycle. Cold Spring Harbor Symp Quant Biol 38, 123–131.

Byers B, Goetsch L (1975). Behavior of spindles and spindle plaques in the cell cycle and conjugation of *Saccharomyces cerevisiae*. J Bacteriol 124, 511–523.

Culotti J, Hartwell LH (1971). Genetic control of the cell division cycle in yeast. III. Seven genes controlling nuclear division. Exp Cell Res 67, 389–401.

Dulbecco R, Hartwell LH, Vogt M (1965). Induction of cellular DNA synthesis by polyoma virus. Proc Natl Acad Sci USA 53, 403–410.

Hartwell LH (1961). An upper limit to the map distance separating the two cistrons of the *rII* region of bacteriophage T4B. Virology 15, 510–511.

Hartwell LH (1967). Macromolecule synthesis in temperature-sensitive mutants of yeast. J Bacteriol 93, 1662–1670.

Hartwell LH (1971a). Genetic control of the cell division cycle in yeast. II. Genes controlling DNA replication and its initiation. J Mol Biol 59, 183–194.

Hartwell LH (1971b). Genetic control of the cell division cycle in yeast. IV. Genes controlling bud emergence and cytokinesis. Exp Cell Res 69, 265–276.

Hartwell LH (1974). *Saccharomyces cerevisiae* cell cycle. Bacteriol Rev 38, 164–198.

Hartwell LH (1993). Getting started in the cell cycle. In: The Early Days of Yeast Genetics, ed. MN Hall and P Linder, Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 307–314.

Hartwell LH (2002a). Yeast and cancer. In: Les Prix Nobel: Nobel Prizes, Presentations, Biographies and Lectures, ed. T Frängsmyr, Sweden: Norstedts Tryckeri AB, 246–265.

Hartwell LH (2002b). Leland H. Hartwell. In: Les Prix Nobel: Nobel Prizes, Presentations, Biographies and Lectures, ed. T Frängsmyr, Sweden: Norstedts Tryckeri AB, 243–245.

Hartwell LH, Culotti J, Pringle JR, Reid BJ (1974). Genetic control of the cell division cycle in yeast. Science 183, 46–51.

Hartwell LH, Culotti J, Reid B (1970a). Genetic control of the cell-division cycle in yeast. I. Detection of mutants. Proc Natl Acad Sci USA 66, 352–359.

Hartwell LH, Magasanik B (1963). The molecular basis of histidase induction in *Bacillus subtilis*. J Mol Biol 7, 401–420.

Hartwell LH, Magasanik B (1964). The mechanism of histidase induction and formation in *Bacillus subtilis*. J Mol Biol 10, 105–119.

Hartwell LH, McLaughlin CS (1968). Mutants of yeast with temperature-sensitive isoleucyl-tRNA synthetases. Proc Natl Acad Sci USA 59, 422–428.

Hartwell LH, McLaughlin CS, Warner JR (1970b). Identification of ten genes that control ribosome formation in yeast. Mol Gen Genet 109, 42–56.

Hartwell LH, Mortimer RK, Culotti J, Culotti M (1973). Genetic control of the cell division cycle in yeast. V. Genetic analysis of *cdc* mutants. Genetics 74, 267–286.

Hartwell LH, Vogt M, Dulbecco R (1965). Induction of cellular DNA synthesis by polyoma virus. II. Increase in the rate of enzyme synthesis after infection with polyoma virus in mouse kidney cells. Virology 27, 262–272.

Hartwell LH, Weinert TA (1989). Checkpoints: controls that ensure the order of cell cycle events. Science 246, 629–634.

Hereford LM, Hartwell LH (1971). Defective DNA synthesis in permeabilized yeast mutants. Nature 234, 171–172.

Hereford LM, Hartwell LH (1973). Role of protein synthesis in the replication of yeast DNA. Nature 244, 129–131.

Hereford LM, Hartwell LH (1974). Sequential gene function in the initiation of *Saccharomyces cerevisiae* DNA synthesis. J Mol Biol 84, 445–461.

Johnston GC, Pringle JR, Hartwell LH (1977). Coordination of growth with cell division in the yeast *Saccharomyces cerevisiae*. Exp Cell Res 105, 79–98.

Lew DJ, Reed SI (1995). A cell cycle checkpoint monitors cell morphogenesis in budding yeast. J Cell Biol 129, 739–749.

Linder D, Gartler SM (1965). Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas. Science 150, 67–69.

Matile P, Moor H, Robinow CF (1969). Yeast cytology. In: The Yeasts, ed. AH Rose and JS Harrison, London: Academic, 219–302.

Nasmyth KA, Reed SI (1980). Isolation of genes by complementation in yeast: molecular cloning of a cell-cycle gene. Proc Natl Acad Sci USA 77, 2119–2123.

Reid BJ, Hartwell LH (1977). Regulation of mating in the cell cycle of *Saccharomyces cerevisiae*. J Cell Biol 75, 355–365.

Short B (2015). The first buds of Cdc42. J Cell Biol 209, 780.

Weinert TA, Hartwell LH (1988). The RAD9 gene controls the cell cycle response to DNA damage in *Saccharomyces cerevisiae*. Science 241, 317–322.