

Review

Yeast Hybrids in Brewing

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Abstract: Microbiology has long been a keystone in fermentation, and innovative yeast molecular biotechnology continues to represent a fruitful frontier in brewing science. Consequently, modern understanding of brewer's yeast has undergone significant refinement over the last few decades. This publication presents a condensed summation of *Saccharomyces* species dynamics with an emphasis on the relationship between; traditional *Saccharomyces cerevisiae* ale yeast, *S. pastorianus* interspecific hybrids used in lager production, and novel hybrid yeast progress. Moreover, introgression from other *Saccharomyces* species is briefly addressed. The unique history of *Saccharomyces cerevisiae* and *Saccharomyces* hybrids is exemplified by recent genomic sequencing studies aimed at categorizing brewing strains through phylogeny and redefining *Saccharomyces* species boundaries. Phylogenetic investigations highlight the genomic diversity of *Saccharomyces cerevisiae* ale strains long known to brewers for their fermentation characteristics and phenotypes. The discovery of genomic contributions from interspecific *Saccharomyces* species into the genome of *S. cerevisiae* strains is ever more apparent with increasing research investigating the hybrid nature of modern industrial and historical fermentation yeast.

Keywords: hybrid; lager; yeast; introgression; interspecific; domestication; phylogeny; brewing; molecular; genomics



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1. Species of *Saccharomyces*

Saccharomyces cerevisiae may be one of the oldest domesticated organisms known to humans. Domestication events imposed on brewing strains of the budding yeast species *S. cerevisiae* resulted in unique strains similar to the divergence seen in animal lineages of *Canis familiaris* breeds or the plant lineage of *Brassica oleracea* foods. It has been suggested that *S. cerevisiae* behaved as a synanthropic species, following human settlements as a commensal organism residing in gardens and vineyards, although the time period and location of the yeast's origins has been the subject of much debate throughout history. Domesticated *Saccharomyces* brewing strains feature flocculation capabilities, fast fermentation rates, malt sugar utilization, pleasant aromas, and are largely negative for production of phenolic off flavors (POF) [1,2].

Nearly two centuries have passed since the first accessible description was produced regarding brewer's yeast and its recognition in fermentation [3,4]. Recently, phylogenetic research utilizing genomics and modern molecular biology techniques has shed some light on the historically convoluted nomenclature surrounding this budding yeast. Genomic analysis of the *Saccharomyces* genus has consolidated many variations into eight individual species: *S. cerevisiae*, *S. paradoxus* (syn. *S. cariocanus*, *S. cerevisiae* var. *tetraspora*, *S. cerevisiae* var. *terrestris*, *S. douglasii*), *S. uvarum* (syn. *S. bayanus* var. *uvarum*), *S. mikatae*, *S. kudriavzevii*, *S. arboricola* (syn. *S. arboricolus*), *S. eubayanus*, and *S. jurei* [3,5–19] (Table 1). Moreover, two natural hybrids are recognized in the *Saccharomyces* clade: *S. pastorianus* (syn. *S. carlsbergensis*, *S. monacensis*) and *S. bayanus* [20–22]. Most modern lager fermentations utilize *S. pastorianus* yeasts.

Table 1. Current *Saccharomyces* Yeast Species History.

<i>Saccharomyces</i>	Described	Substrate	Location	Reference
<i>cerevisiae</i>	1838	Beer	Germany	[4]
<i>uvarum</i>	1898	<i>Ribes rubrum</i> , redcurrant juice	South Holland, The Netherlands	[16,17]
<i>paradoxus</i>	1914	Tree sap	Russia	[15]
<i>kudriavzevii</i>	1991	Decayed leaf	Japan	[18]
<i>mikatae</i>	1993	Decayed leaf	Japan	[19]
<i>arboricola</i>	2008	<i>Fagaceae</i> spp.	West China	[6]
<i>eubayanus</i>	2011	<i>Nothofagus</i> spp. & parasitic fungi <i>Cyttaria</i> spp.	Andean, Patagonia	[11]
<i>jurei</i>	2017	<i>Quercus robur</i>	Saint Auban, France	[14]

2. Hybrid Nature of Yeast

Interspecific hybrids are not unique to lager brewing. For example, the livestock and agricultural industries commonly employ selective breeding to alter species' properties or increase yields [23–25]. A time-honored showpiece of hybrid vigor is the mule, a great pack animal known for its hardiness and longevity. For over 4000 years, the mule has been bred as the hybrid progeny of a male donkey and a female horse. Since the early 1900s, maize has been hybridized to increase yields and introduce biodiversity [26]. Similarly, hybrid yeasts have been isolated from fermentation processes on numerous occasions [27] (Figure 1). A hybrid between *S. cerevisiae* and *S. kudriavzevii* was isolated from Belgian Trappist beers [28]. Popular in wine production, strain VIN7 is a hybrid of *S. cerevisiae* and *S. kudriavzevii* [29]. Other interspecific *S. cerevisiae* and *S. uvarum* hybrids are also regularly used for production of wines [29,30]. Spontaneous fermentations have yielded *Pichia apotheca*, a hybrid of *P. membranifaciens* and an unknown species [31]. Hybrid vigor, or heterosis, confers a competitive advantage by facilitating transgressive phenotypes in changing environments, and is known to be a driver of fungal evolution and adaptation [32]. This is especially important for yeast as the many stages of fermentation and maturation create a microbially competitive environment in which rapid adaptation may be advantageous.

The mule of the brewing industry is the lager yeast *S. pastorianus*, an interspecific hybrid that produces the lion's share, in volume, of the global beer production. Although its use is widespread, the biodiversity is limited to two main lineages, Saaz/group I (*syn. S. carlsbergensis*, L12: Noble, Imperial Yeast Culture Collection, type strain CBS1513) and Frohberg/group II (L13: Global, Imperial Yeast Culture Collection, type strain-Weihenstephan 34/70). Saaz and Frohberg lineages vary in their genomic composition from each parent species, *S. eubayanus* and *S. cerevisiae*, which influences important fermentation characteristics. Genomic analysis demonstrated a genomic composition of 1:2 *S. cerevisiae* to *S. eubayanus* sub genome in the Saaz lineage and 2:2 *S. cerevisiae* to *S. eubayanus* sub genome in the Frohberg lineage supporting the traditional designations used by brewers [33–35]. Saaz lineage hybrids are very well adapted to cold fermentations and many of these strains lack maltotriose utilization [27]. The Frohberg hybrids contain more *S. cerevisiae* genomic content conferring greater attenuation, higher ethanol production, differing ester profiles, and higher typical viabilities [36]. The composition of genetic material transferred and retained in these hybrids impart important fermentation characteristics and phenotypes such as the POF (phenolic off flavor) trait, efficient fermentation of maltose and maltotriose, reduction of diacetyl, flocculation, and production of unique volatile metabolite profiles that are low in off-aroma/flavors. Investigation into these hybrid lineages supports bolstering the fermentation capacity of *S. cerevisiae* with hybrid vigor from *S. eubayanus* incorporation and conveyance of a positive phenotype.

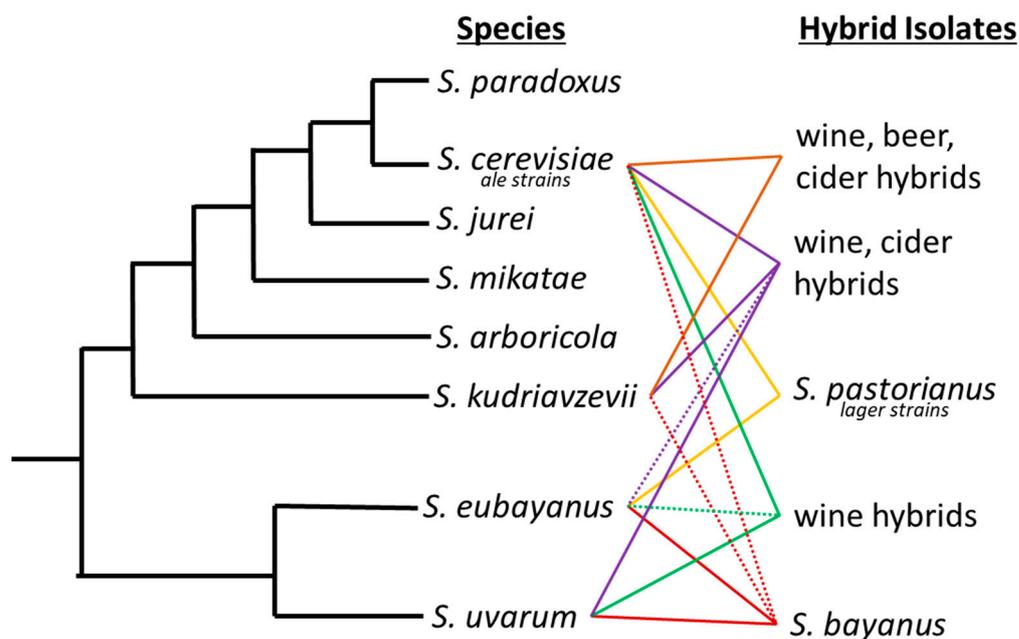


Figure 1. *Saccharomyces* phylogenetic tree with industrially important hybrids. Industrial hybrids are listed to the right by the fermentation they have predominately been associated with. Solid lines between two species signifies the interspecific hybrids and dashed lines denote introgression from a third or fourth species that may not always be present in each hybrid strain.

3. Novel Hybrid Development

The first yeast breeding experiments aimed at combining desirable traits of brewing strains were conducted by Ojvind Winge during his tenure at the Carlsberg Laboratory in the 1930s [37]. Hybrid yeast development has been carried out for over half a century since then, aimed predominantly at increasing attenuation and fermentation rates via intraspecific crosses with ale and lab strains [38–40]. Modern fermentations benefit from many innate and acquired hybrids that have been isolated or developed [11,27,28,41–52]. Early efforts in brewing science established the fundamentals necessary to explore the phylogeny, genomics, and strain development for *Saccharomyces* fermentation. During typical rich nutrient propagations of yeast in a brewing environment, mother cells reproduce asexually to bud off small daughter clones (Figure 2). Under poor nitrogen conditions, such as proline, yeast growth changes to a pseudohyphal form [53,54]. The complete absence of a nitrogen source and the presence of a non-fermentable carbon source, such as acetate, will sporulate yeast cells [55]. Sporulation transforms the cell wall into the ascus, or sack, that holds four spores termed a tetrad. Analogous to the human egg and sperm, these spores divide equally into mating types as either a or α [56]. When conditions improve for yeast growth, new haploid (*1n*) yeast can conjugate with the opposite mating type yeast as they form a shmoo. Depending on the genomic make up of each parental strain or species, there is some genomic instability or rewiring that occurs during the following mitotic budding growth.

Interspecific hybridization is seen as a valuable tool for yeast strain development, enabling the combination and enhancement of characteristics from both parental strains or species [57]. The development of hybrids is executed via three primary methodologies: spore–spore mating, rare mating, and protoplast fusion (Figure 2). Spore to spore mating is most similar to what would be considered natural mating, as outlined in Figure 2b. This approach bears a high success rate, high genomic stability, and can avoid the aid of selection markers such as drug resistance or autotrophies. Rare mating utilizes a described spontaneous loss of heterozygosity at the mating type locus. Normal diploid cells carry two sets of chromosomes with both the MAT α and MAT a genetic alleles and do not respond to sex pheromones for mating purposes. The spontaneous loss of either sex allele tolerates yeast mating to a yeast cell of complimentary sex. This results in yeast

with high chromosome counts, influencing gene dosage during cellular processes and partially explains the outperformance over a diploid yeast of the same background [57]. Rare mating, as the name implies, is uncommon and selection markers are needed to perform this technique. The frequency of rare mating is estimated to occur in 1 out of 10 million cells [58]. This procedure is beneficial in overcoming poor sporulation but produces hybrids prone to high genomic instability. Lastly, protoplast fusion is performed by removing the cell wall and fusing the protoplasts of two cells together before the cell wall is repaired. This technique generates cells with a high chromosome copy number and higher genomic instability but overcomes low sporulation. This technique can be used in the laboratory to combine yeast from different genera such as the brewer's yeast *S. cerevisiae* and other yeast outside of the *Saccharomyces* genera which are otherwise incompatible [59]. Protoplast fusion is considered genetic engineering in many parts of the world. Recent select investigations into *Saccharomyces* hybrid application in beverage fermentations are listed in table format (Table 2).

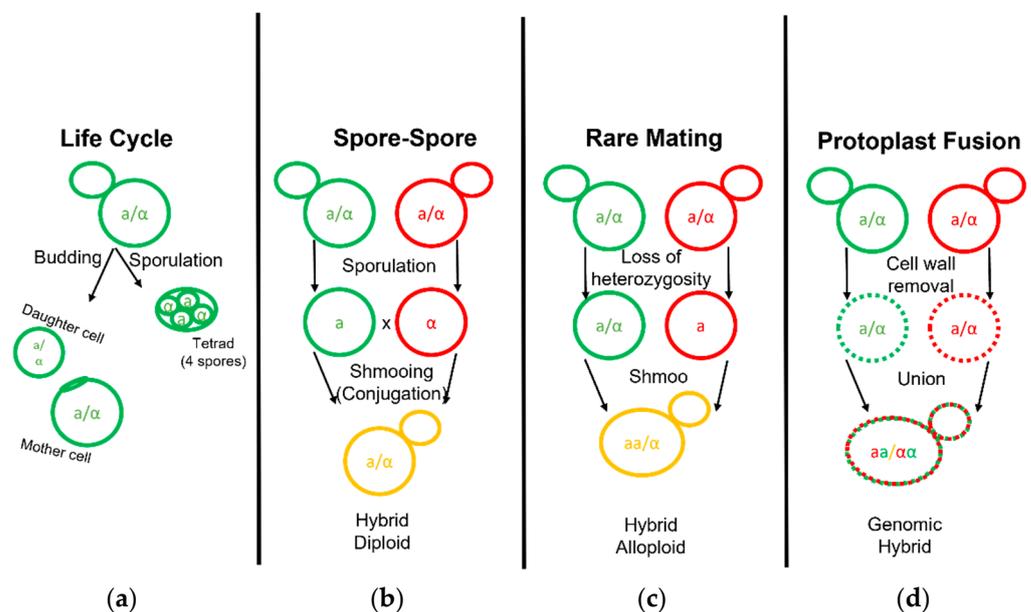


Figure 2. Life and Mating of *Saccharomyces* Yeast. Diagram pertaining to the clonal growth typical of yeast fermentation cultures and the various known techniques employed to generate yeast hybrids. (a) Diploid yeast cells may bud and grow clonally to form a mother and daughter cell or undergo sporulation to form a tetrad. (b) Yeast hybridization may form by direct spore to spore mating. (c) Yeast hybridization may form by rare mating events in which one or both diploid parent cells gain competency by becoming hemizygous or MATa/MATa and MATα/MATα diploids. (d) Yeast hybridization may also form by fusion of two separate yeast cell protoplasts with their cell wall removed.

Utilizing advanced molecular biology techniques for the modification of yeast strains presents an ongoing endeavor by many academic labs and some commercial yeast laboratories. Several research groups have developed protocols that use plasmids carrying genetic markers for drug resistance or functional enzymes that target the mating system in yeast. Industrial strains are well-known for their poor ability to adhere to laboratory techniques including sporulation and transformation [60]. One strategy developed at the University of Wisconsin generates allotetraploid strains of prototrophic yeast without the need for sporulation or modification to the nuclear genome of parental yeast strains [61]. This method leverages a series of inducible plasmids coined HyPr (Hybrid Production) containing compulsory drug markers and an inducible HO cassette. HO encodes an endonuclease that performs a double stranded break in the DNA that determines the *Saccharomyces* sex type. To repair this damage, the yeast cell will copy the silenced sex type already present in

the genome, effectively performing a sex change and allowing the cell to mate with other cells of the opposite mating type. Using drug resistance markers and the HO cassette, hybrids are produced and serial growth in the absence of drug selection purges cells of exogenous DNA [61]. Similarly at the Advanced Industrial Science and Technology Center of the Biomedical Research Institute of Japan, another plasmid utilizing system aimed at exploiting the loss of heterozygosity of yeast cells was developed. A series of three to four plasmids allows for isolating α - and α - type cells from mixed cell populations and subsequent continual cross breeding [62]. CRISPR/Cas9 has also been utilized to force double stranded breaks in the MAT locus in order to increase the diversity of industrial yeast strains and their hybrids [63]. In the coming years, industrial yeasts will be designed by utilizing these protocols and molecular toolkits.

Currently, the options for strain selection in *S. cerevisiae* yeast are plentiful, but the criteria for fermentation performance in the brewing environment remains selective. Strains are employed largely by beer style, equipment availability, and supporting knowledge base. Certain beer styles also contain defining features from specific yeast flavor active molecules [64]. Banana and clove flavors are derived from isoamyl acetate and 4-vinyl guaiacol (4VG) in Weissbier [64–66]. Hybridization of yeast bears several advantages in brewing to include transgressive phenotypes such as increased ethanolic fermentation performance or stress tolerance, shifting fermentation temperatures beyond traditional inhibitory conditions, and creating a mosaic blend of parental fermentation profiles [24,51,57,63,67]. Targets of yeast hybridization may include increased formation of glycerol for an enhanced mouthfeel, alternative carbon source metabolic ability, reduced off-flavor production, increased formation of antioxidants that increase beer flavor stability, or increase production of yeast longevity molecules such as trehalose. The methodologies to create yeast hybrids vary in their specificity to target genetic or phenotypic results, but efforts to harness yeast hybrids in brewing broadly increase the biodiversity of fermentation yeast, add depth to the complexity of fermentation profiles, and advance brewing science knowledge.

Table 2. Interspecific Yeast Hybrids in Fermentation.

History	Parents	Reference
Isolated	<i>S. cerevisiae</i> × <i>S. eubayanus</i>	[11]
Isolated	<i>S. cerevisiae</i> × <i>S. eubayanus</i> × <i>S. uvarum</i>	[41]
Isolated	<i>S. cerevisiae</i> × <i>S. uvarum</i>	[68]
Isolated	<i>S. cerevisiae</i> × <i>S. kudriavzevii</i>	[27,28,42]
Isolated	<i>S. uvarum</i> × <i>S. eubayanus</i>	[27,42]
Developed	<i>S. cerevisiae</i> × <i>S. eubayanus</i>	[43,45–47,69]
Developed	<i>S. cerevisiae</i> × <i>S. mikatae</i>	[48]
Developed	<i>S. cerevisiae</i> × <i>S. kudriavzevii</i> × <i>S. paradoxus</i>	[49]
Developed	<i>S. cerevisiae</i> × <i>S. kudriavzevii</i>	[52]
Developed	<i>S. cerevisiae</i> × <i>S. arboricola</i>	[48,51]
Developed	<i>S. cerevisiae</i> × <i>S. jurei</i>	[70]

4. Natural Considerations and State of the Field

Outside of industrial fermentations and laboratory settings, *Saccharomyces* yeast is readily obtained from tree sap exuded seasonally from oaks and beech tree bark, part of the *Fagaceae* family. The natural fluctuation of available carbon, nutrition, and climate influences the state cells between active replication, a non-dividing state termed quiescence, and sporulation [71]. During industrial use, yeast spend their time in active growth and metabolism.

The fermentation of sugars into ethanol, carbon dioxide, and flavor molecules is utilized to prepare food or drink for human consumption. The brewer's and baker's yeast have secured a niche ecological space in industry via an advantage in high sugar environments. The Crabtree effect is a critical microbial factor for beer production and occurs when fermentation of sugars is the preferred metabolic route instead of aerobic respiration in the presence of oxygen. This metabolic capability is estimated to have evolved

during the Cretaceous period, ca. 125 million years ago, when modern fruiting plants also appeared and humans were absent [72,73]. Bacteria present in these environments competed for resources, but the make–accumulate–consume provided a winning strategy for yeast. By producing inhibitory concentrations of alcohol for later consumption via a diauxic shift the yeast continued to occupy these environments over time [71,72,74].

The production of fruity esters may be an advantageous evolutionary trait developed to allow the passage of non-mobile unicellular fungi yeast from one rich environment to the next either via insect or brewer [75–78]. One theory suggests insect vectors' intestines act as a vessel for facilitating natural yeast hybridization events [76,77]. Unfortunately, the microscopic nature of yeast impose a limit for scientists to infer retrospectively on yeast mating modes and frequency by analyzing genomic data sets [79,80].

Interspecific hybridizations facilitate exchange of DNA which intertwine lineages and blur traditional species boundaries [32]. In yeast, the newly developed hybrids can rapidly adapt by filtering their diverse chromosomes and retaining advantageous portions via the loss of heterozygosity [81–83]. Cells experiencing a stressor, such as a drug or environmental condition, appear to prioritize genomic filtering early in growth, demonstrated by *Saccharomyces* interspecific hybrids subjected to various temperatures. *S. cerevisiae* and *S. uvarum* hybrids retained the cryotolerant subgenome of *S. uvarum* during cold adaptation, but retained the *S. cerevisiae* subgenome during warm environmental growth [83,84]. The dynamics between interspecific hybridization, adaptation, and evolution in *Saccharomyces* is not fully understood, but recent evidence suggests that this exchange of DNA components has and will continue to play a pivotal role as new yeast hybrids are described.

5. Conclusions

The quest to gain diverse and novel fermentation characteristics from a pure culture remains an overarching goal for brewing molecular biologists. Flavor attributes and temperature phenotypes were investigated by many research groups; however, gaps in knowledge remain concerning yeast fermentation and the evolution field. Efforts large and small are being exerted worldwide to explore the awesome power of yeast genetics in brewing sciences, yet many questions continue to surround the budding fungus akin to the brewers and bakers of the globe. Are interspecific hybrids naturally abundant under the correct environmental conditions or are they rare success stories? To what extent are yeast present in various natural climates and substrates, what vectors are involved in mobility, what interactions occur with other microbes, what is the typical lifecycle timeline of wild yeast, do *Saccharomyces* yeast originate out of Asia, or will researchers ever obtain adequate and representative environmental samples? Yeast phenotypes that, to the authors knowledge, remain unexplored by targeted hybridization include formation of antioxidants that increase flavor stability, formation of glycerol for an enhanced mouthfeel in low alcohol beverages, and reduced off-flavor production.

Many recent interspecific hybrids developed have largely focused on reinventing the lager yeast, *S. pastorianus*, by crossing *S. cerevisiae* with *S. eubayanus*. As research continues, understudied *Saccharomyces* species may serve as a reservoir for diverse genomic contributions. Natural isolates of *Saccharomyces* hybrids suggest that interspecific mating is not as uncommon as previously thought and recent investigations continue to redefine species whilst uncovering genetic exchange events. The ability of yeast to participate in interspecific hybridization and avoid hinderance by large genetic distances between parent species is promising and illustrative of the introgression likely yet to be discovered in many preserved isolates. While there are many yeast strains favored for production of quality fermented foods and beverages, their status as species or hybrids may be adjusted over time owing to the continual refinement of phylogenetics, the advancement in genome sequencing technology, and increased accessibility to genomic sequencing capabilities. By increasing yeast sampling, focusing on metabolic specifics, and facilitating collaboration, the yeast of tomorrow will be driven by scientific innovation in the laboratory today.

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Nomenclature

Terminology	Description
a/ α	The two mating types of <i>S. cerevisiae</i> that enable cellular fusion when the complimentary pheromone is detected. The mating type and sexual state is largely determined by the MAT locus on chromosome III.
Allele	A variant of any particular gene found at the same genomic location. The mating type of yeast is determined by which allele, MATa or MAT α , is present at the MAT locus.
Allopolyploids	A hybrid organism or cell composed of two or more sets of chromosomes obtained from two separate species.
Auxotrophy	The loss of a functional gene needed for growth. This is particularly relevant for amino acid synthesis and metabolism during yeast genetics experiments where controlling growth is needed.
Ascus	The sack like structure enclosing the four spores of <i>Saccharomyces</i> , this characteristic is important in classification of the <i>Ascomycota</i> (sac fungi) yeast.
<i>Brassica oleracea</i>	Important food crop plant species. It is wild cabbage in the uncultivated form, but cultivation has yielded varieties over time to include broccoli, brussels sprouts, kale, cauliflower, cabbage, and collards.
Crabtree Positive	Microorganism that preferentially metabolizes sugar into ethanol in the presence of oxygen instead of cellular respiration.
Diauxic Shift	The shift from fermentation to utilizing ethanol for cellular respiration and cell growth.
Diploid	An organism with a paired set of chromosomes creating a (2n) genome, such as a human with a set of genomes from each parent.
<i>Fagaceae</i> spp.	Family of <i>Angiosperms</i> (flowering plants) that include the beech and oak trees.
Frohberg	One of two primary lineages of modern lager yeast known to brewers originally used in Germany.

Terminology	Description
Gene	The basic unit of heredity which is composed of a sequence of DNA. It is characterized by a start sequence, genomic segment that often is translatable into a protein of function, and a stop sequence.
Genomics	The study of all of an organism's complete sequences of genetic materials composed of DNA (deoxyribonucleic acid) including structure, function, evolution, mapping, editing, and environmental interactions.
Haploid	An organism with one set of chromosomes composing their genome (<i>1n</i>).
Hemizygous	A condition of diploid cells where only one copy of a gene or other genetic component is present.
Hybrid Vigor (<i>syn.</i> Heterosis)	The tendency for the hybrid progeny between two species to outperform their parents in traits such as strength, size, or yield.
Interspecific	Arising or existing between separate species.
Intraspecific	Arising or existing within a species or individuals from the same species.
Locus	A specific fixed position on an individual chromosome where particular genetic content is present.
Make Accumulate Consume	<i>S. cerevisiae</i> yeast survival strategy that invokes the ability to make ethanol from saccharides, the ability to survive accumulation of the toxin, and the ability to consume ethanol for energy post fermentation.
Maltotriose	Prominent trisaccharide typical of beer wort and is enzymatically derived from starch. It is composed of three glucose molecules linked together by α -1,4 glycosidic bonds.
Nomenclature	The terminology and language used to categorize and communicate in various disciplines.
Out of Asia/Silk Road Hypothesis	The idea that <i>Saccharomyces</i> yeast originate from an Asian geographical region because of the abundance natural biodiversity found in that region.
Phenotype	A characterized trait, best exemplified by measurable qualities such as color or yield.
Phylogeny	The lineage and evolution of relative organisms.
Progeny	The offspring or descendants of an organism.
Quiescence	A state of inactivity, dormancy, or a period of idleness in yeast ecology.
Saaz	One of two primary lineages of modern lager yeast known to brewers originally used in Bohemia region of the Czech Republic where the town Žatec/Saaz is located.
Shmoo	The distinct physical form of two <i>Saccharomyces</i> yeast cells mating. This terminology originated from the morphological similarity to an Al Capp cartoon popular in America during the early 1950s.

Terminology	Description
Synanthropic Species	An undomesticated organism that habitually exists with human populations and benefit from non-natural environments. Their life cycles are adapted fully or in part to conditions created by human activity.
Tetrad	Four spores produced via meiosis of <i>Ascomycota</i> yeast, specifically focused on yeast <i>S. cerevisiae</i> in this article.
Transgressive Phenotype	Formation of extreme phenotypes that surpass the ability of parental lineages, often found in hybrids and can be positive or negative for fitness of the individual.

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