Journal of Nutrition & Food Sciences
ISSN: 2155-9600

RC Bird and BF Smith, J Nutr Food Sci 2016, 6:1
DOI: 10.4172/2155-9600.1000448

Review Article Open Access

The Impact of Yeast Genomics on Brewing

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Rec date: Nov 15, 2015; **Acc date:** Dec 14, 2015; **Pub date:** Dec 22, 2015

Abstract

Beer is an agricultural product that has been brewed since the dawn of civilization. Several species and countless strains of yeast are employed to ferment beer but little has been known regarding the differences and origins of these yeast strains as many were serially passaged over many years in breweries. Recently, the science of genomics-the ability to determine, analyze and compare the sequences of every DNA base pair that defines an organism-has promoted investigation of these genome differences among domesticated and wild populations of brewer's and related yeast. This is allowing a detailed comparison of strains from different fermentations and beer styles as well as comparisons to wild populations. It has also revealed the potential origins of several of these important commercial strains. New genetic analysis designed to correlate sequence with phenotype are being attempted and new genetically modified yeasts are on the horizon. The modern era of brewing is witnessing the merging of these two very different disciplines – one from serious academic science and the other from the beverage production industry. This review discusses the current state of knowledge regarding the genomics of brewer's yeast and the impact such investigations may have on the future of the brewing industry.

Keywords: Brewing yeast; Saccharomyces; Brettanomyces; Genomics; DNA sequencing

Introduction

Beer is an agricultural product made from water, barley, and hops according to the *Reinheitsgebot*, or German Beer Purity Law, with versions dating from 1487 to 1516 and amended to also include yeast in 1993 [1]. It has been brewed since the dawn of civilization and perhaps as long ago as the Neolithic era. Little seems to have changed for hundreds of years in the components that go into making beer, even in the face of rampant industrialization and commercialization throughout the nineteenth and twentieth centuries. Yet, with the advent of craft brewing, and home brewing in the U.S. in the 1970s, and the concurrent resurgence of craft brewing in many European countries, interest in beer styles beyond light lager, as well as the *terroir* of locally produced beer, has exploded [2]. Enter the science of genomics and big data-the ability to determine, analyze and compare the sequences of every DNA base pair that defines an organism and then investigate genome differences among domesticated and wild populations [3]. The modern era of brewing is witnessing the merging of these two very different and very separate disciplines-one from serious academic science and the other from the beverage production industry-and the combination is turning out to be, to say the very least, interesting, with ramifications that could well affect the contents and quality of pints served around the world. Much of the interest in brewing yeast genomics appears driven by this concurrent interest in *terroir*, or place, as it affects the quality and style of the beer being brewed and it should be no surprise that much of this local character is the result of local yeast strains.

Introduction to Modern Genomics

For most living organisms, the information that encodes the functional molecules that make up that organism, and their organization into the recognizable components of that organism, are stored in DNA. This information is organized into units that are called genes that typically contain all of the information for one protein. Genes are copied or transcribed into RNA, which is subsequently translated into the amino acid chain that makes up a protein. While the collection of all of the genes in an organism, or the genome typically does not vary from cell to cell, different genes can be turned on, or expressed, at different times in response to the needs of that cell. The genes that are turned on at any given time make up the transcriptome.

With the advent of the science of molecular biology, scientists began to develop tools that allowed genes and genomes to be manipulated and studied. It became possible to sequence DNA, and in doing that, to learn and understand the precise genetic code that determines the biologic functions of a cell. As the field progressed through the last 2 decades of the 20th century, it became possible to sequence entire genomes; first small genomes such as bacteria, then yeast and eventually culminating in the sequencing of the human genome, published in 2001 [3]. Much of this project was accomplished by sequencing the genome one gene at time, and cost approximately 2.7 billion dollars to complete. Following this landmark achievement, sequencing technologies have continued to advance rapidly as the focus has shifted from sequencing one genome per species to sequencing hundreds or even thousands of genomes to better understand how the differences between genes result in differences in function. These new technologies are known colloquially as "Next-Generation" (NextGen), "deep sequencing" or "massively parallel

sequencing" approaches and they allow millions of bases of DNA sequence to be read nearly simultaneously. This has resulted in the time necessary to sequence a genome being reduced from years, to months, and now to just days. The cost of sequencing has also dropped and a complete human genome can now be sequenced for around $3,000. The availability of these technologies and their relatively low cost now makes genomic analysis a practical tool to understand the biology involved in the process of brewing beer.

Overview of yeast genomics

The budding yeast species *Saccharomyces cerevisiae* is the principle, though not the only, yeast used in brewing beer, baking bread and even fermentation of wine. And, *Saccharomyces* was the first eukaryotic species to have its complete genome fully sequenced in 1996 (reviewed in Dujon [4]). Additionally, the *Saccharomyces* Genome Database (http://www.yeastgenome.org) was established as the first model organism genome database containing the complete DNA sequences of many strains [5]. Yet, the genome sequencing and characterization of strains of *Saccharomyces* used to brew beer has lagged far behind the scientific efforts to define the biochemistry and genetics of these wonderfully facile organisms. This has been due, to some extent, to resistance by the brewing industry to embrace new genetic technologies [6].

Saccharomyces cerevisiae is primarily the traditional ale yeast species and occurs widely throughout Europe and Asia as an agricultural isolate found on malt, grapes and many other crops. *Saccharomyces cerevisiae* was domesticated millennia ago as a brewing organism even in the absence of knowledge of the microbe. For example, German brewers would serially passage yeast cultures by inoculating new batches with the healthy foaming *Kräusen* on the top of aggressively fermenting batches. Lager yeast, by contrast, are separated into a discrete species by brewing scientists, named *S. pastorianus*, and appears only to be found in lager fermentations. Extensive searches for a wild source in Europe and Asia had failed to discover a natural reservoir for this species. Genome sequencing and analysis suggested that *S. pastorianus* was a combination of the *S. cerevisiae* genome and an unknown wild cryotolerant (cold-tolerant) yeast species but until recently the source and character of this yeast remained unknown.

Ale yeast-*Saccharomyces cerevisiae*

Historically, brewers have identified more species diversity among cultured yeast strains than research scientists have been willing to recognize. Research scientists, focused on budding yeast, have tended to lump all of these strains into the species *Saccharomyces cerevisiae*. Brewers, on the contrary, have tended to differentiate yeast strains based on fermentation characteristics. The advent of genome sequencing has allowed both sides of this argument to view the evolutionary relationships and uncover some surprising genetics as well as some controversial theories as to the origins of some of the most well-known brewing yeast strains. Because *S. cerevisiae* has been used as a simpler, small genome, model eukaryotic organism for decades of genetic analysis it was among the very first eukaryotes to have its genome completely sequenced [5,7,8]. Although the genomes of laboratory strains of these versatile yeast have been extremely well characterized there is much less known regarding the genetic diversity present in brewing strains and even less regarding the complexities of wild mixed fermentations by multiple *S. cerevisiae* species/isolates.

S. cerevisiae has been characterized as possessing approximately 5,780 protein encoding genes on 16 chromosomes, most of which have been functionally characterized [4,7]. Although extremely well characterized as an experimental cell system, relatively little is known regarding the subtleties of sequence and function that underlie the differences in different strains of ale yeast. One of the key problems with genomic analysis of brewing yeast strains is that they frequently contain significant aneuploidy (or abnormal chromosome number) compared to laboratory strains including polyploidy (multiple complete genomes) and allopolyploid (multiple genomes from multiple species) and also have relatively high levels of heterozygosity [8]. They are also typically selected for stability, which has resulted in low spore viability and a lack of sexual recombination [9,10]. This challenge has recently been engaged with the sequencing of *S. cerevisiae* GSY2239, a strain derived from the industrial ale brewing strain Wyeast 1388 (Wyeast Laboratories). Analysis of this genome has revealed 5,365 putative open reading frames (protein encoding genes) of which all but 11 genes could be mapped to other laboratory strains of *S. cerevisiae* [11]. The number and extent of genomic differences between laboratory *S. cerevisiae* type-strains and Wyeast 1388 suggest many important metabolic differences could exist between these different strains.

The evolution of *S. cerevisiae* spp. used in fermentation has been investigated in an attempt to describe the strain heterogeneity evident in brewing and wine fermentation systems and the complexity of such populations was found to be very large even among geographically close locations [12]. The complexity of *S. cerevisiae* strains in use in the brewing industry appears to be extremely large with differences in ploidy, as noted, and other changes commonly evident. Extensive analysis of the genomics of these strains is the right approach to investigate the relationships among such strains, the complexity of these genomic differences and their characteristics with respect to brewing phenotype. Only genome analysis can hope to rigorously describe the strain heterogeneity evident in brewing strain populations.

Lager yeast-*Saccharomyces pastorianus*

The plausible origins of the lager yeast species, *S. pastorianus*, have only recently been discovered even though this species is thought to have inhabited the fermenters and barrels of German and Czech breweries for centuries. Cold-adapted strains of brewing yeast were known, even before yeast itself was known as an organism, as lagering was common in caves in Germany throughout the medieval period. German brewers have used *Kräusening* techniques to serially passage the cold adapted *Kräusen*-i.e., the healthy yeast from primary fermentation-to inoculate subsequent batches. Continuous serial dilution and propagation would very quickly select for a cold-adapted rapidly growing strain. In this environment, any genetic changes that enhanced these characteristics would be strongly selected for.

Early sequencing efforts revealed that *S. pastorianus* was a hybrid of *Saccharomyces cerevisiae* and another unknown yeast strain. Despite extensive efforts to discover the wild reservoir of this wild species the source remained elusive until 2011 when the species *S. eubayanus* was discovered inhabiting galls living on the bark of Southern Beech trees in temperate rain forests in Patagonia in the central parts of southern Argentina [13]. DNA genome sequencing revealed this new species to be the likely source of the wild portion of the lager yeast, *S. pastorianus*, and genome. This discovery led to speculation regarding the pathway by which a yeast species, from deep in the southern

hemisphere of the new world, could make its way to the breweries and lagering caves of central Europe where lagering began about the end of the fourteenth century. This seems to have occurred even though Spanish explorers did not start exporting commodities from South America until well into the sixteenth century around 200 years later. Speculation as to the vehicle by which such yeast could have made the journey have included raw lumber and other exports, the gut or appendages of fruit flies associated with food stuffs and even migratory birds [14]. It appears that once it made its way to Europe, soon after the discovery of the new world, it was able to find its way into lager fermentations. In this environment it found very rich wort medium at cool temperatures where it did not have to compete against warmer adapted *S. cerevisiae*. Once in the presence of more cool-adapted *S. cerevisiae*, which were being selected during the early years of the lagering process, *S. eubayanus* combined with *S. cerevisiae* and new hybrid strains appeared with greatly enhanced cold adaptation as well as the flavor profiles desired for lagered beers. Continual selection of these naturally occurring hybrid yeasts by brewers appears to have resulted eventually in the modern strains of the lager yeast we know as *S. pastorianus* today (Figure 1).

Further investigations revealed that this story was, or could be, much more complicated with threads of its origin potentially emanating from further afield. Recent genome sequencing of different isolates of lager yeasts has revealed what appear to be two distinct lineages of *S. pastorianus* that share the distinct cold-adapted physiology [14]. The two strains appear associated with either Czech breweries or breweries in Germany and Denmark [14]. The *S. pastorianus* Czech strain genomes are composed of most of the *S. eubayanus* genome and a partial *S. cerevisiae* genome while the German/Danish strain genomes appear to be composed of equal but partial genomes from both parental species (Dunn and Sherlock 2008). These two isolates are currently thought to represent two different hybridization events probably occurring in different geographic locations in Europe.

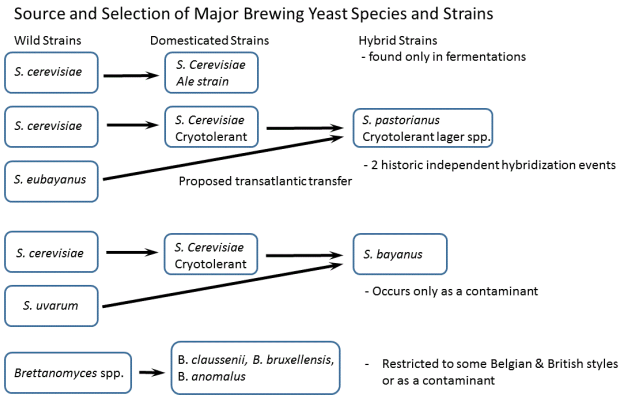

Figure 1: Source and Selection of Major Brewing Yeast Species and Strains. The putative evolution of brewing yeast species and strains is shown including the proposed parentage of the current modern ale and lager hybrid brewing strains.

A further complication has recently arisen that casts some doubt on this whole hypothetical construction of new world yeasts traveling to Europe at the dawn of the discovery of South America. A separate source of what appears to also represent a wild reservoir of *S. eubayanus*-related isolates has been reportedly discovered in Tibet [1]. This discovery has raised the possibility that *S. eubayanus* arrived in Europe, via the Silk Road, perhaps much earlier than originally anticipated. The authors of both hypothetical sources of *S. eubayanus* have made attempts to investigate wild strain genome diversity and homogeneity with the portion of the *S. pastorianus* genome contributed by *S. eubayanus*, however, to date the source of these strains remains controversial. The origins of the actual *S. eubayanus* strain thought to have been the parental strain for *S. pastorianus* may also be a hybrid itself as recent genome analysis provided evidence suggesting its genome is composed of portions of *S. uvarum*, *S. eubayanus*, and *S. cerevisiae* genomes. It has also been hypothesized that the reason it has not been found in Europe is that it is a product of the brewing environment where these yeast strains found themselves growing together [15]. Early fermentation is known to have resulted in mixed fermentations that included wild yeast strains that could have supported such hybridization. In summary, sometime in the last 600 years bottom-fermenting cryotolerant yeast seem to have emerged by hybridization probably in or after the early 1400s, in at least two different locations in central Europe. How *S. eubayanus* came to be associated with European yeast strains remains controversial. However, the resulting cold-tolerant yeast hybrids have adapted well through serial passage during the lagering process and have become the dominant strain used in lager brewing today.

Other brewing yeast species

Some 350 yeast species are known and several have been identified as contributing to fermentation including at least three distinct species of *Brettanomyces* [5]. Other yeast species, including wild-captured strains and species in open fermentations, are also used for brewing. In Belgium, and to a lesser extent in the United Kingdom, *Brettanomyces* species have been, and are, particularly important in some beer styles. "Brett", as it is commonly known, lives naturally on the skins of fruit in the environment. The *Brettanomyces claussenii* strain was originally identified in 1904 at the Carlsberg Brewery by N. Hjelte Claussen [2]. He identified it as a cause of spoilage in English ales particularly those identified as "stale" or "stock"-meaning aged-usually in wooden barrels. *Brettanomyces* means "British fungus" although the strains of this species are more common as intentional fermenting species in Belgium. Currently, 5 species of *Brettanomyces* have been identified of which 3-*B. claussenii*, *B. bruxellensis* and *B. anomalus*-have been associated with brewing styles although wild spoilage strains are known to exist [4].

Several strains of *Brettanomyces* have been sequenced, at least as laboratory strains, although little has been known regarding the strain diversity of these organisms in brewing cultures. Recently, an effort to determine genomic differences between wild spoiling strains of *Brettanomyces*, isolated from wine fermentations, compared to brewer's strains of *Brettanomyces bruxellensis*, typically employed in Belgian lambic and gueuze beers, revealed considerable numbers of differences that allowed them to be easily distinguished [4]. Classical DNA fingerprinting had revealed unique profiles that allowed brewer's strains to be distinguished from spoilage strains but genomic sequencing revealed 20 genes in the spoilage strains that had been deleted from the brewer's strain, many of which appear to be involved in carbon and nitrogen metabolism pathways. The brewer's strain also encoded large duplications of at least 4 regions of the genome encompassing approximately 69 genes. These genomic alterations suggest real potential to affect flavor profiles and further that this brewer's strain is, like *Saccharomyces* strains, highly selected from

adaptive modifications by the brewing process. Much more investigation of these deleted and duplicated genes is necessary to associate them with specific phenotypic characteristics but it is clear that significant differences between domesticated and wild strains of *Brettanomyces* exist.

New efforts to characterize brewing yeast genomes

There has recently been an effort to rigorously and aggressively track down different and notable brewer's yeast strains and sequence them through collaboration by scientists at White Labs and the Kevin Verstrepen Lab in Belgium, which specializes in applied bioinformatics [13]. They have sequenced a variety of brewer's and other strains of *Saccharomyces cerevisiae* in an attempt to characterize this quite diverse population of organisms. The goals of the project have been reported to be the creation of the first genetic family tree for brewing yeasts by associating them with the beers they are used to ferment.

The laboratories have reported sequencing genomes from more than 240 Brewer's and other strains in an attempt to build a genomic relationship tree (a dendrogram) relating brewing style and genome. Unfortunately there is a temptation to ascribe individual phenotype characteristics (for example the ability to synthesize a particular flavor molecule) to single genes. This can lead to a tendency to over-interpret the effects of different gene sequences-different alleles of a single gene locus-and their effects on specific phenotypic characteristics. This has been a wide-spread phenomenon where, in the extreme, single gene differences are even credited with encoding specific human behaviors. Genes encode RNA which can be a functional product itself or can further encode protein. While such products do influence many organismal characteristics they do not encode them directly. Such over-interpretation can be evident in yeast genomics where attempts have been made to associate yeast strain fermentation differences with differences in specific gene sequences.

The numbers of differences are generally too numerous when comparing whole genomes and the association too difficult to correlate directly with specific phenotypic traits. Considerable additional effort is required to demonstrate cause and effect between specific sequence differences and metabolic characteristics in the absence of most other differences. Although frequently performed for laboratory strains, little of this type of molecular genetics has been applied to brewing strains. However, it will be possible to determine lineages where related yeast strains can be associated using classical evolutionary criteria and methods based on sequence similarity. Indeed, this is exactly the approach that has yielded what appears now to be the true hybrid parent of *S. pastorianus* in *S. eubayanus*. This identification has eliminated the species previously thought have been the parent-*S. bayanus*-which now appears to have also been created as a result of hybridization itself in a brewery setting involving *S. uvarum* with small amounts of the *S. cerevisiae* genome added [5]. Indeed, *S. pastorianus*, *S. bayanus* and *S. uvarum* have only ever been isolated from human-associated fermentation environments.

Yeast transcriptome and noncoding RNAs

Beyond the linear sequence of bases found in DNA there are other means by which organisms can be characterized using modern omics technologies and some of these technologies are more informative both in characterizing the specific organism under study but also in developing the metabolic pathway networks that typify eukaryotic cells [8]. Two different approaches, focused on two populations of primary RNA products of genes, have generated the most interest. These include complete sequence characterization of the mRNAs, or protein encoding RNA products of genes, and the noncoding RNAs (ncRNAs). Yeast express nearly 6,000 genes, of which most are protein coding, although at least 86 have been characterized as ncRNAs and the remainder encode structural RNAs such as tRNAs and rRNAs. Yeast genomes have, to date, been characterized as having no known microRNAs (miRNAs or miRs), RNAs that are known to regulate target gene expression by causing gene silencing in higher eukaryotes [16]. Nearly 2000 of the 6000 genes in *S. cerevisiae* have been mapped at some level to explore interactions among pairs of proteins to develop a yeast interactome [3]. This data has allowed some of these protein encoding genes to be assigned functions and these functions to be associated with metabolic functions. Some of these are known or suspected of affecting fermentation though it is likely that a majority of genes functioning in yeast affect this process either directly or indirectly (Figure 2).

Recently both protein coding and ncRNA populations have been integrated into a global pathway network described as an interact-ome that accounts not only for the expression and repression of each mRNA but also attempts to link individual proteins together into interactive networks that influence the same pathways and to some extent each other. Their importance is only just being described as they represent a large complex set of new transcripts with complex regulatory functions. These functions have been characterized as both gene activation and silencing activities but it is becoming clear that other forms of regulation of expression are possible and are likely key to understanding the metabolome of eukaryotic organisms in general and yeast in particular. As the understanding of these complex pathways and interactions grows, so will the ability to map these to specific phenotypes in brewing yeasts, and to thereby understand and ultimately use and manipulate these pathways to affect fermentation characteristics.

Genetically engineered yeast

Due to their facile genetics and haploid nature, yeast has been among the earliest and most aggressively genetically modified organisms, although this has largely remained the province of basic biological science. Driven by the desire to understand biochemical and biological systems shared by all eukaryotes, yeast were the first organisms in which human genes were shown to be able to compliment yeast mutations in *Trans* [17]. More recent investigations have proposed genetic modification of the flavor-associated metabolic pathways of brewing yeast to, in effect, customize the flavor profiles produced. While some of these yeast proteins are clearly involved in flavor molecule production they do not actually encode such flavors, as noted previously. Most of these phenotypic characteristics are very likely to be multigene characteristics and subject to complex gene and regulatory control. Such over interpretation is evident in recent attempts to genetically modify *S. cerevisiae* and its fermentation characteristics [18].

While such projects pose interesting academic questions and fruitful approaches for research, the complexity of the problem, the conservatism of brewers and customers, as well as broad resistance to genetically modified foods argues that this is unlikely to have any impact in the near future.

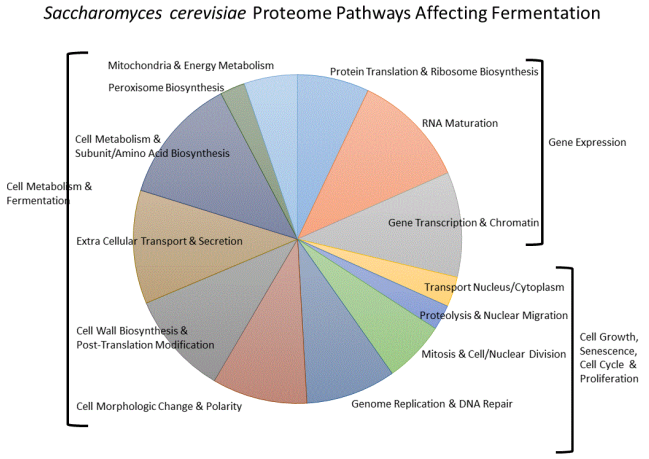

Figure 2: *Saccharomyces cerevisiae* Proteome Pathways Affecting Fermentation. Nearly 2000 of the 6000 genes in *S. cerevisiae* have been mapped at some level to explore interactions among pairs of proteins to develop a yeast interactome [3]. Much of this data has been developed using yeast 2-hybrid analysis to explore even relatively transient unstable protein-protein interactions. This data has allowed some of these proteins with known functions to be associated with metabolic functions such as fermentation. It is likely that a majority of genes functioning in yeast affect this process either directly or indirectly. The size of each region is an approximate estimate of the percent of genes involved in the function noted among genes for which functions have been determined and was derived from published data [3]. In most cases functions are not exhaustive and further research will be required to develop this interactome further.

An alternative approach that carefully avoids the genetically modified organism label is an attempt to recreate the historic and natural hybridization of *S. cerevisiae* and *S. eubayanus* that resulted in *S. pastorianus* and such an attempt has been reported [19-23]. Such new lager strains were reported to have improved fermentation efficiency, alcohol production and general hybrid vigor, compared to parental strains, but also included improvements in desirable fermentation characteristics including cryotolerance, maltotriose utilization and flocculation. Such new hybrid lager strain recreations are unlikely to be exactly the same as modern *S. pastorianus* as the original cold-adapted parents are not available, since current parental strains are very modern and not the original archaic strains [24]. Additionally, the exact combination of parental genes is unlikely to be recapitulated. It is too early to know whether such new lager strains can be used for commercial brewing but they do offer an alternative approach to analysis which, if coupled to extensive genome analysis, could be used to further probe the contributions of individual genes and gene pathways affecting specific flavor profile production [25].

Conclusions

In summary, the current state of yeast genomics is moving well beyond the standard laboratory strains of this organism and is now embracing many of the brewing strains typical of beer styles and cultures throughout the world. Although much remains to be done regarding the functional association of flavor profile production during fermentation and individual gene sequences and alleles it is clear that this effort has begun and should continue to provide important insights into the differences and commonalities between yeast strains and the beer they produce. Whether this knowledge will result in genetically modified brewing strains is unclear at present and unlikely in the near future although the potential will be developed as these projects move forward. Brewers can look forward to a much more complete and thorough description of the genotypes of brewing yeast in the near future. The most likely impact of our greater understanding of the genetics and biology of brewer's yeast will be in the ability of the brewer to better appreciate the yeast that they already use, both for metabolic optimization and flavor development. In addition, brewers will be able to precisely select yeasts to use for specific beers based on these criteria to optimize their brewing. Thus, our ever increasing understanding of the yeast genome will lead to both economic advantages and potentially, enhanced or novel flavor characteristics.

Acknowledgements

The authors would like to thank the Auburn University Brewing Science Program for continued support and Allison Church Bird for critical reading of the manuscript.

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