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Fermenting knowledge: the history of winemaking, science and yeast research

Science & Society Series on Food and Science

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Wine has been with us since the dawn of civilization and has followed humans and agriculture along diverse migration paths (Fig 1). Serendipity presumably played a part in its genesis more than 7,000 years ago: damaged grapes spontaneously fermented in harvesting vessels; curious farmers tasted the resultant alcoholic beverage; the curious farmers liked what they tasted and enjoyed its effects; said farmers preferred fermented grape juice to the unfermented fruit. The fate of the grape was sealed.

One might argue that the seeds of science and technology, particularly biotechnology, were also sown at this time. Empirical observations of natural events and processes were harnessed in repeat 'experiments'—which is to say, vintages—and improvements were made by trialling modifications to practices, retaining those that were beneficial and discarding failures, with the results communicated down through the generations. At that time, there was no EMBO *reports* or alternative means by which to facilitate horizontal dissemination of information, but the principle of development—*sans* peer review—is clear: experimentation and invention lead to progress—technological and otherwise—and new knowledge is shared and built upon.

Of course, early inventions and innovations in grape and wine production were based on little or no knowledge of the biology of grapevines or the microbes that drive fermentation. In fact, it would be several thousand years before it was even known that microscopic organisms exist: using a primitive microscope, Antonie van Leeuwenhoek observed cells for the first time in 1680 (Fig 2).

Scientific knowledge grows at an exponential rate, and nowhere is this more evident than in the historical milestones of chemistry and biology that have shaped our understanding of the biology of the microorganisms that drive fermentation (Fig 2). This progress has been adorned with some of the most significant names in the chemical and biological sciences, including van Leeuwenhoek, Lavoisier, Gay-Lussac, Pasteur, Buchner and Koch. One might argue that the most important test tube in the birth and growth of the modern life sciences is the fermenter, and the most important model organism has been the yeast *Saccharomyces cerevisiae*—commonly known as baking, brewing or wine yeast. As readers might know, this is exemplified in the origin of the word enzyme—'en' meaning within and 'zyme' meaning leaven. Yeast has been integral to pioneering work in microbiology and biochemistry, particularly in the fields of metabolism and enzymology (Barnett, 1998, 2000; Barnett & Lichtenthaler, 2001).

Throughout the early decades of the twentieth century the place for *S. cerevisiae* in fundamental research was affirmed, and there are several good reasons for this. Our close relationship with this yeast in food and beverage production over millennia tells us that it is safe to work with; as confirmed by its 'Generally Recognised as Safe' designation by the US Food and Drug Administration. In addition, it is inexpensive, easy to grow and can be stored for long periods in suspended animation. Perhaps the most important thing is that it has accessible genetics that can be followed through sexual and asexual cycles (Barnett, 2007).

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The 1970s set the stage for another explosion of knowledge, sparked by the advent of gene technology and driven by a convergence of genetics, biochemistry, cell biology, microbiology, physical and analytical chemistry, as well as computing brought together under the banner of molecular biology (Fig 3). Yeast molecular biology was established when Gerald Fink's group in the USA demonstrated that yeast could be transformed with foreign DNA (Hinnen *et al*, 1978). In the same year, Jean Beggs in the UK developed a shuttle vector between *Escherichia coli* and *S. cerevisiae* that enabled cloning in yeast (Beggs, 1978). The research community now had a eukaryotic host that was amenable to genetic engineering, benefiting both fundamental research and offering the potential of precise engineering of novel strains for industrial applications. It

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was the first host cell for industrial-scale production of a recombinant vaccine against hepatitis B and a recombinant food-grade enzyme, chymosin, which is used in cheese processing (Pretorius *et al,* 2003).

Ever since, *S. cerevisiae* has been one of the most important model organisms in molecular biology and emerging fields; breakthroughs and technological advances in molecular, systems, and now synthetic biology rarely happen without *S. cerevisiae* figuring somewhere prominently in the story (Fig 3). The international yeast science community has been particularly progressive and proactive in establishing large collaborative projects and building resources that are available to the scientific community. *S. cerevisiae* was the first eukaryote to have its genome sequenced (Goffeau *et al*, 1996), a feat that was achieved through an international effort that involved 600 scientists, which paved the way for the first chip-based gene array experiments (Schena *et al*, 1995). It was the first organism to be used to build a systematic collection of bar-coded gene deletion mutants (Winzeler *et al*, 1999; Giaever *et al*, 2002), in which there are deletion strains for most of the open-reading frames in the *S. cerevisiae* genome. This has enabled high-throughput functional-genomic experiments, and anyone seeking information on just about any aspect of *S. cerevisiae* biology has access to the amazing community resource: the *Saccharomyces* Genome Database (SGD; http://www.yeastgenome.org/).

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Fig 1 | A generalized scheme of the spread of *Vitis vinifera* noble varieties of grapevine and winemaking from their centre of origin in Asia Minor to other parts of the world.

All of this is important to wine research; our winemaking workhorse is centre stage in thousands of research projects worldwide, so we know more about this humble eukaryote than any other organism on the planet. It is therefore unsurprising that wine research has benefited enormously from the privileged place that *S. cerevisiae* occupies in life sciences research. This is particularly evident in the impact that advances in molecular biology and related fields have had on winemaking.

In the hands of molecular biologists, *S. cerevisiae* is the most tractable of organisms; it is amenable to almost any modification that modern biology can throw at a cell. This makes it an ideal host for generating variants with improved and even exotic phenotypes that will benefit winemaking. The following gives some examples of current research and directions in this field.

In modern winemaking, fermentations are driven largely by single-strain inoculations; pure cultures of selected strains of *S. cerevisiae* are added to grape must as soon as possible after crushing. This ensures greater control of vinification, leads to more predictable outcomes and decreases the risk of spoilage by other microorganisms. There are many—probably hundreds of—different yeast strains available, and the winemaker's choice can substantially effect the quality of the wine (Lambrechts & Pretorius, 2000; Swiegers *et al*, 2005).

One of the reasons for the yeast-induced variation in wine quality is that, during fermentation, *S. cerevisiae* produces an abundance of aroma-active secondary metabolites and releases many aroma compounds from inactive precursors in grape juice, which greatly affect the sensory properties of the wine (Swiegers & Pretorius, 2007). Thus, any genetic variation in wine yeast that affects the production or release of sensorially important molecules will affect wine quality. In this context it has been demonstrated, for example, that different commercial yeast strains generate wines with very different profiles of volatile thiols (Swiegers *et al,* 2009). These thiols—which are present in grape juice as non-volatile cysteinylated precursors (Tominaga *et al*, 1998)—are often described as 'passionfruit', 'tropical fruits'

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2010 The Australian Wine Research Institute publishes the genome sequences of 4 more *Saccharomyces* wine strains (AWRI 796, QA23, VL3 and VIN13)

2008 The Australian Wine Research Institute publishes the first genome sequence of a wine strain (AWRI 1631) of *Saccharomyces cerevisiae*

2002 Construction of the first systematic, almost complete, collection of *Saccharomyces cerevisiae* gene disruption mutants, enabling high throughput functional genomics

1996 André Goffeau and co-workers publish the genome sequence (12,068 kb) of a laboratory strain of *Saccharomyces cerevisiae* (S288c)

1995 Pat Brown and co-workers conduct the first chip-based gene array experiments in *Saccharomyces cerevisiae*

1978 Gerald Fink and co-workers transform plasmid DNA into *Saccharomyces cerevisiae* and Jean Beggs develops a *S. cerevisiae* episomal vector enabling high frequency transformation

1965 The first two active dried wine yeast strains were produced commercially for a large winery in California

1943 Carl Lindegren discovers the two mating types, a and α, in *Saccharomyces cerevisiae* and elucidates the lifecycle of yeast

1940 The elucidation of the glycolytic pathway based on the work of Gustav Embden, Otto Meyerhof, Jakub Parnas, Otto Warburg, Carl Neuber, and others

1935 Øjvind Winge discovers that diploid yeast cells come from haploid ascospores

1900 Robert Koch demonstrates that inoculation with malolactic bacteria (*Oenococcus oeni*) can reduce wine acidity (malolactic fermentation)

1897 Eduard Buchner demonstrates that a cell-free extract of yeast cells can ferment sugar to ethanol

1891 Hermann Müller-Thurgau demonstrates that bacteria are responsible for acid reduction (malolactic fermentation) noted in wine

1890 Hermann Müller-Thurgau introduces the concept of inoculating wine ferments with selected pure yeast cultures

1888 Emil Hansen perfects the method of Louis Pasteur for the isolation of pure yeast cultures

1878 Wilhelm Kühne coins the term ‘enzymes’ (meaning ‘in yeast’ in Greek) for the catalytic agents in cell-free extracts

1870 Louis Pasteur postulates that fermentation is an energy-yielding process for microbes such as bacteria and yeast under anaerobic conditions

1837 Julius Meyen uses the term *Saccharomyces* (‘sugar fungus’) for budding yeast

1835 The so-called ‘vitalistic’ theory proposes that living yeast cells convert sugar into alcohol and CO_2

1825 Charles Cagniard de la Tour, Friedrich Kützing and Theodore Schwan independently demonstrate that wine yeast reproduce by budding

1818 Friedrich Erxleben postulates that yeast consist of living vegetative organisms

1815 Joseph Gay-Lussac revises the chemical stoichiometry for fermentation

1789 Antoine Lavoisier describes wine fermentation as a chemical reaction of ‘grape must = carbonic acid + alcohol’

1680 Antonie van Leeuwenhoek observes yeast cells using a primitive microscope

Fig 2 | Selected milestones that mark the path of research in microbiology and yeast biology that have affected, directly or indirectly, wine science and winemaking.

and ‘citrus’ by tasters, flavours that are particularly important in wine varieties such as Sauvignon Blanc (Dubourdieu *et al*, 2006).

Molecular biology and its tools are crucial to our understanding of the genetic and molecular bases of yeast-driven volatile thiol release from non-volatile precursors in grape juice. Howell *et al* (2005) have used bioinformatic tools and the SGD to identify candidate *S. cerevisiae* carbon–sulphur lyase genes that might be involved in the release of volatile thiols from cysteinylated precursors during fermentation. The researchers used targeted gene deletion to remove these candidate carbon–sulphur lyases from the wine and laboratory yeast strains, and they identified four genes that potentially contribute to the release of these important aroma molecules.

Swiegers *et al* (2007) then engineered a wine yeast, VIN13, to constitutively express a carbon–sulphur lyase gene, *tna*A, from *E. coli*. Sensory analysis revealed that, compared with its non-engineered relative, this transgenic yeast, VIN13 (CSL1), had a positive impact on the release of volatile thiols from a Sauvignon Blanc grape juice. The authors commented that wine assessors preferred the VIN13 (CSL1)-derived experimental wines to the relatively neutral VIN13-derived wines.

A similar approach has been used to engineer yeasts for the enhanced production of fruity esters (Lilly *et al*, 2006a) and to increase the production of higher, fusel alcohols (Lilly *et al*, 2006b)—all of which contribute to the flavour profiles of wines. Although this work is in the early stages of development, it shows the value of yeast molecular biology, and the amazing resources that come with it.

Wine alcohol content is of growing importance to the wine industry. In some wine regions, it has been increasing during recent decades (Godden & Muhlack, 2010). The main reason for this increase is that grapegrowers tend to leave fruit on the vine as long as possible to increase fruity characters—which develop as berries mature—and reduce undesirable ‘green’ characters. This practice, however, produces fruit with a higher sugar content, which translates to higher ethanol concentrations in the wine.

A recent review by Kutyna *et al* (2010) discusses several metabolic engineering strategies that have been explored to generate wine yeasts that can divert some carbon metabolism away from ethanol production, with the aim of decreasing ethanol yields during vinification. Understanding the central metabolism of yeast and the genes that drive it has been crucial to this work. Candidate genes that are likely to influence ethanol yields can be identified from a range of sources, including the SGD, and then manipulated and cloned as required. Several laboratories have targeted the glycerol-3-phosphate dehydrogenase isozymes *GPD1* and *GPD2*, which divert carbon from glycolysis to glycerol production (Michnick *et al*,

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1997; Remize *et al*, 1999; de Barros Lopes *et al*, 2000).

Increased expression of either of the *GPD* paralogues increased glycerol and decreased ethanol yields. However, increased Gpd activity also led to increased amounts of acetic acid in the fermentation product. This was probably owing to rectification—by one or more of the five aldehyde dehydrogenase isozymes—of a redox imbalance that resulted from excessive Gpd-driven oxidation of NADH. Aldehyde dehydrogenase isozymes drive the oxidation of acetaldehyde to acetic acid with concomitant reduction of coenzymes NAD^+ or NADP, depending on which isozyme is involved (Navarro-Aviño *et al*, 1999). This might be good for a yeast cell struggling with an imposed redox imbalance, but an increase in acetic acid production is not good news for winemakers; excessive vinegar is not desirable in wine. This problem was alleviated by knocking out one of the five aldehyde dehydrogenase isozymes, *ALD6* (Eglinton *et al*, 2002; Cambon *et al*, 2006).

Similar approaches have targeted *S. cerevisiae* pyruvate decarboxylase isozymes, alcohol dehydrogenase isozymes and glycerol transporters, leading to increased glycerol yields and reduced ethanol production (Kutyna *et al*, 2010). However, while there are probably several good candidate 'low-ethanol' wine yeast strains sitting in various labs around the world, none have been tested in commercial-scale, industrial fermentations. This is largely because consumers are generally unaccepting of genetically modified organisms (GMOs) in foods and beverages.

Another area of ongoing research in wine yeast molecular biology is the development of strains that flocculate—that is, form clumps—at the end of fermentation. This facilitates the process of settling them out of suspension and separating them from the wine, thereby reducing the need for clarification. The timing of flocculation is crucial; it must not happen too early, as yeast in large flocs are inefficient at sugar utilization and can generate suboptimal—stuck or sluggish—fermentations (Pretorius, 2000).

Generally, wine yeasts are not good at flocculation; they do not form large clumps that settle out of suspension. Many years of research using laboratory strains of *S. cerevisiae* led to the identification and characterization of genes that encode cell-surface glycoproteins—including lectin-like flocculins—that cause, among other things, flocculation and subsequent settling to the bottom of the fermentation vessel (Pretorius, 2000).

- **2010** Synthetic life generated: Craig Venter and colleagues generate a synthetic bacterial genome form *Mycoplasma mycoides* and use it to replace the native genome of a closely related species, *Mycoplasma capricolum*
- **2008** Genome sequencing of a wine yeast strain of *Saccharomyces cerevisiae*
- **2007** Genome sequencing of a grapevine cultivar, *Vitis vinifera* var. Pinot Noir
- **2005** Genome sequencing of a malolactic bacterium, *Oenococcus oeni*
- **2003** Genome synthesis of a virus, *Phi-X174*
- **2002** Construction of the first systematic, almost complete, collection gene disruption mutants for a species is completed in *Saccharomyces cerevisiae*, enabling high throughput functional genomic analysis
- **2000** Genome sequencing of humans, *Homo sapiens*
- **1996** Genome sequencing of a eukaryote, a laboratory yeast strain of *Saccharomyces cerevisiae*
- **1995** Genome sequencing of a prokaryote, *Haemophilus influenzae*
- **1995** Using *Saccharomyces cerevisiae*, Pat Brown and co-workers conduct the first chip-based gene expression array experiments
- **1985** *In vitro* amplification of DNA by the Polymerase Chain Reaction method
- **1984** Karyotyping of yeast through pulsed-field-gel-electrophoresis
- **1983** Genome sequencing of a virus, *phage lambda*
- **1978** Genetic engineering of *Saccharomyces cerevisiae* yeast by transformation with recombinant plasmid DNA
- **1977** Development of rapid DNA sequencing procedures
- **1972** Genetic engineering of *Escherichia coli* by transformation with recombinant plasmid DNA
- **1966** Unravelling of the universal genetic code for all lifeforms
- **1953** Postulation of a complementary double-helical structure for DNA
- **1943** DNA proves to be the genetic molecule capable of altering the heredity of bacteria via transformation, conjugation and transduction
- **1935** Discovery of two mating types in the yeast *Saccharomyces cerevisiae*
- **1928** Discovery that bacteria are capable of transferring genetic information from cell to cell via transformation
- **1871** Discovery of DNA in the sperm of trout
- **1860** Postulation of Gregor Mendel's laws of inheritance

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Fig 3 | Selected milestones that mark the path of research in genetics and molecular biology that have affected, directly or indirectly, wine science and winemaking.

Recent findings have identified a problem with extrapolating basic research on laboratory strains to those used in industry; yeasts domesticated for different purposes have different phenotypes. Work by Govender *et al* (2008) on the flocculation genes *FLO1*, *FLO5* and *FLO11*, for example, demonstrated the potential ability of engineered *ADH2*- or *HSP30*-promoter/*FLO* gene combinations to switch on flocculation at the end of fermentation; *ADH2* and *HSP30* are both upregulated in stationary-phase cells, so their promoters are suitable candidates to drive the expression of genes in later stages of wine fermentation.

The results of this work were promising, but, when they were carried over to wine yeast, the findings were rather different. There were even substantial differences between wine yeast strains, leading the authors to caution that "optimisation of the flocculation pattern of individual commercial strains will have to be based on a strain-by-strain approach" (Govender *et al*, 2010). Nonetheless, controlled expression of *FLO* genes at the end of fermentation remains a plausible technique for improving the performance of wine yeast, but the strategies required to achieve a desirable outcome might be more complex than was originally thought.

While the complexity of biological systems is a cause for excitement and wonder to most biologists, it can make engineering novel strains for industrial applications trickier than molecular biology and biotechnology textbooks might suggest. For those of us working on industrial yeast strains, it might be pertinent to directly tackle the issue of complexity and use systems biology approaches to better understand the workings of yeast metabolism. This should lead to more accurate modelling of metabolic processes for better-informed manipulations, to achieve targeted, predictable outcomes.

> **However, molecular biologists face one important obstacle to this progress: near worldwide refusal to permit the use of GMOs in the production of foods and beverages...**

S. cerevisiae has been at the forefront of '-omics' research. This provides us with enormous opportunities to improve understanding of wine yeast complexity, which, in turn, will inform the design of new strains for industrial applications. Increased and improved knowledge from a huge number of studies investigating strains of *S. cerevisiae* at the various -omic levels gives wine yeast scientists a head start in this field (Borneman *et al*, 2007; Petranovic & Vemuri, 2009).

One of the most interesting developments has come from the sequencing of a wine yeast genome, and its comparison with the genomes of a laboratory strain and an opportunistic pathogenic *S. cerevisiae* (Borneman *et al*, 2008). The authors found a difference of about 0.6% in sequence information between the wine yeast and the other strains. They also found, perhaps more importantly, 100 kb of additional genome sequence in the former; enough to carry at least 27 genes. Open reading frames (ORFs) in the additional sequences do not resemble anything found in other strains of *S. cerevisiae*, but seem to be similar to genes found in distant fungal relatives. BLAST searches have indicated that some of the genes that are specific to wine yeast are similar to those encoding cell-wall proteins. This might contribute to the greater robustness of wine yeast, compared with laboratory strains. Other genes might encode proteins associated with amino acid uptake, which is significant in the context of wine sensory attributes; amino acid metabolism is central to the production of many sensorially important volatile aroma compounds.

Novo *et al* (2009) published similar findings from a different wine yeast strain (EC1118) and suggested that the extra sequence was probably the result of horiziontal gene transfer. Further work using functional genetics—to determine the effects of knocking out and overexpressing the ORFs—should enable characterization of the phenotypes of these ORFs, determine their relevance in the context of winemaking and might also reveal their origins.

There have also been numerous studies describing transcriptomic, proteomic and metabolomic analyses of wine-yeast fermentations. This work is beginning to provide insights into wine-yeast fermentations, but it is still early days. It should also be noted that much of the -omics work on wine yeast has used resources and databases that are based on laboratory strains. It is now clear that there are genomic differences between wine and lab strains of *S. cerevisiae*, and these might affect -omics data acquisition and analysis. For example, gene-array chips based on the reference laboratory strain S288c will not include the additional ORFs found in wine strains. This does not suggest that earlier work is invalid, but that there are likely to be gaps in it.

As the various -omics fields progress, it should be possible to build systems-based mathematical models of metabolism that will facilitate the *in silico* design of new wine yeast strains (Borneman *et al*, 2007). In parallel, we see the emergence of synthetic biology where, yet again, *S. cerevisiae* is a key player. It should not be too long before we have customised *S. cerevisiae* genomic components—regulatory elements to control the expression of targeted genes, or cassettes carrying genes encoding metabolic pathways to shape wine-relevant traits, for example—available 'off the shelf' for designing, building and refining metabolic processes in our wine yeast. But are consumers ready for this brave and exciting new world?

The engineered wine yeast strains described in this paper show the potential of novel yeast strain development to improve wine quality. But molecular biologists face a major obstacle to this progress: near worldwide refusal to permit the use of GMOs in the production of foods and beverages, at least in 'developed' countries (Gross, 2009; Pretorius & Høj, 2005). Wine industries in most parts of the world have eschewed the use of GMOs in commercial winemaking, leaving most new-generation wine yeasts on the laboratory shelf, where they await more enlightened times.

Two genetically modified wine yeast strains have been released to market in a limited number of countries including the USA, Canada and Moldova: ML01 and 522^{EC-}. ML01, a transgenic wine yeast, has genes that enable it to perform malolactic fermentation (MLF), a deacidifying secondary fermentation in which malic acid—present in grape juice—is decarboxylated to lactic acid. MLF is usually performed by the lactic acid bacterium *Oenococcus oeni* after alcoholic fermentation. However, this bacterium is rather fastidious, being inhibited by a range of conditions that are typical of fermented grape juice—low pH, high alcohol content, poor nutrient availability and the presence of sulphur dioxide—and can become 'stuck' or take considerable time to complete fermentation (Davis *et al*, 1985). In addition, lacitic acid bacteria can produce a range of biogenic amines, which are associated with health risks (Lonvaud-Funel, 2001).

A wine yeast that completes both primary and secondary fermentations should therefore have great potential in the wine industry. The genetically modified wine yeast ML01 carries two foreign genes—the *Schizosaccharomyces pombe* malate transporter gene (*mae1*) and the *O. oeni* malolactic enzyme gene (*mleA*)—which are both chromosomally integrated and regulated by the *S. cerevisiae PGK1* promoter and terminator (Husnik *et al*, 2006). This enables the host wine yeast to perform MLF, in parallel with alcoholic fermentation.

The researchers went to great lengths to ensure the safety of ML01. The transgenes came from microorganisms found in wine, there were no antibiotic resistance genes or vector sequences carried by the yeast and transcriptome and proteome analysis showed no important differences in gene expression profiles between the genetically modified strain and its parent. The FDA granted 'Generally Regarded As Safe' status to ML01,

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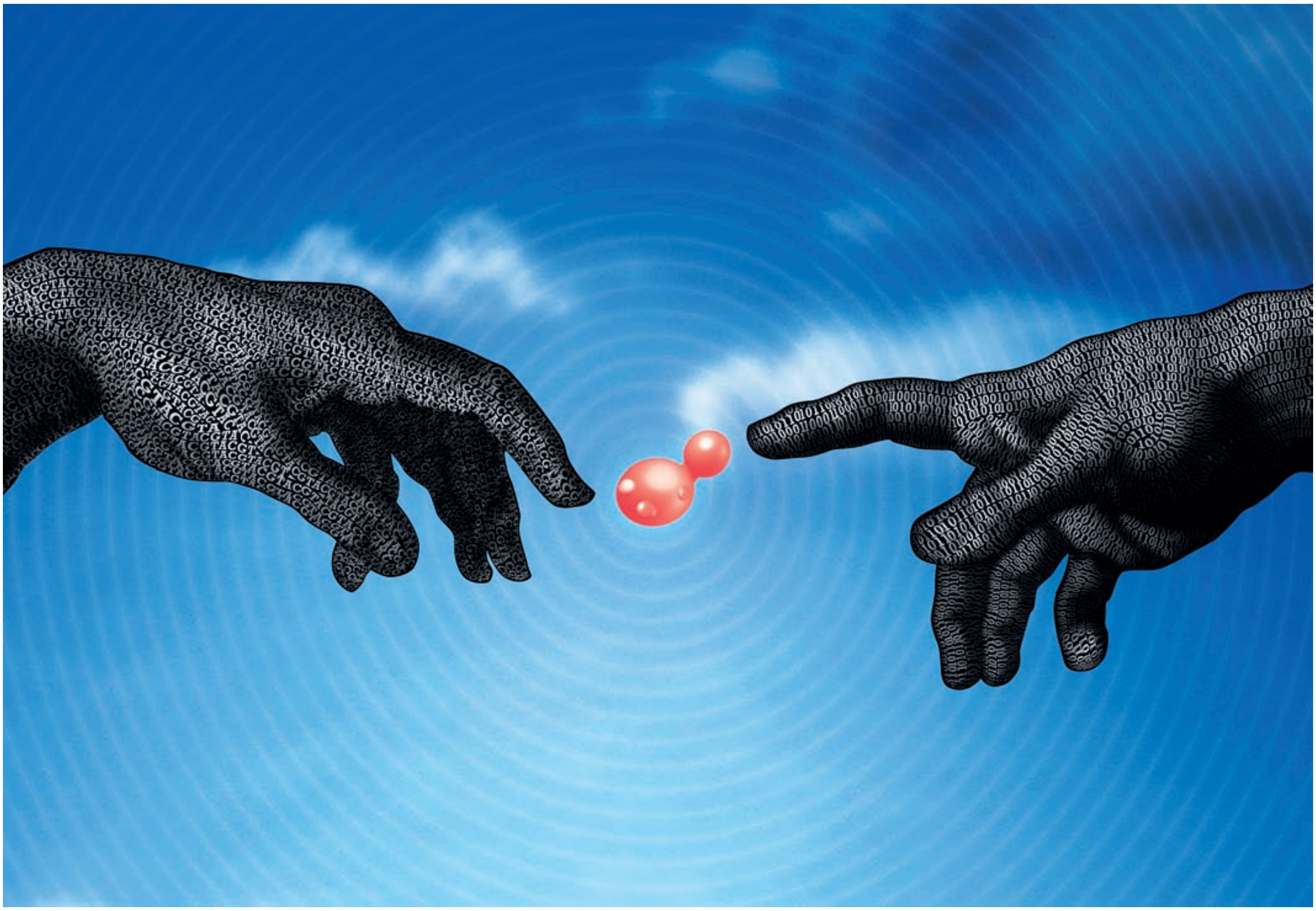

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but it has not been widely adopted, even in countries where it is approved for use. This is largely owing to concerns about export markets that do not tolerate GMOs. In fact, wine industries in many countries have banned the use of GMOs in wine production, in order to avoid jeopardizing their exports.

The genetically modified wine yeast 522^{EC-} was engineered to reduce the risk of ethyl carbamate production during fermentation. Ethyl carbamate, a potential carcinogen, is the product of yeast-derived urea reacting with ethanol. It is usually produced at such low levels—if at all—that it is not a cause for concern, but it sometimes can make an appearance in some wine-producing regions.

S. cerevisiae is able to degrade urea before it is secreted and release ammonia instead, thereby reducing the risk of generating ethyl carbamate. This is achieved by the action of an enzyme encoded by *DUR1,2*, but this gene is repressed by nitrogen and therefore downregulated throughout much of wine fermentation. Coulon *et al* (2006) placed a copy of *DUR1,2* behind a constitutive (*PGK1*) *S. cerevisiae* promoter, which led to a reduction in ethyl carbamate yields. Interestingly, this genetically modified yeast is self or *cis* cloned; it carries no foreign DNA and therefore is not transgenic. Nonetheless, because it was generated by using techniques that involved the manipulation of DNA *in vitro*, the regulations of many countries classify it as a GMO. Again, to the best of our knowledge, this yeast is not being used in the industry. This might be because ethyl carbamate production is not a widespread problem, but it probably also reflects the influence of GMO bans and the reluctance of winemakers to risk losing market share in countries that harbour strong anti-GMO sentiment.

Winemaking, science and technology have interwoven histories and have grown together over the millennia, benefiting from each other. Although science is an important part of an

Who knows what bottled masterpieces await us as we sculpt novel yeast strains in the laboratory using molecular, systems and synthetic biology

oenologist's training and scientific methods and equipment are routinely employed in the winery, winemakers are not scientists *per se*. They are, perhaps more appropriately regarded as artisans, with the emphasis on the 'art'. As for many human endeavours, the Arts progress with developments in technology; think of the use of acrylic paint in the fine arts since its introduction in the 1950s, or David Hockney's use of a Polaroid camera to create photocollages. In the way that acrylic paint and photography have provided more options to artists, enabling them to broaden their horizons, yeast science and technology is adding to the winemaker's palette. Who knows what bottled masterpieces await us as we sculpt novel yeast strains in the laboratory using molecular, systems and synthetic biology. The only real obstacle that we face is consumer acceptance of GMOs; we can only hope that rationality will eventually prevail.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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