BEERS WITH ENHANCED FLAVOUR STABILITY

The brewing industry protects its investment in farsighted research and development.

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A striking feature of all branches of the brewing industry, today, is their use of high-tech engineering solutions to secure streamline production and maximise output capacity. Individual players within the industry (including barley breeders, maltsters and brewers) can further improve their relative market position and competitive edge by strategic investment in research and development (R&D). New types of beer with improved or new flavours, new yeast strains for brewing, new malting barley varieties, new hop additives, and new forms of beer packaging can each contribute to capturing market share within the industry. However, brewers, or their suppliers, can only capture the full benefit of their investment if they secure market exclusivity for their new products. Patent rights provide companies with the most powerful legal tool to protect their valuable R&D technology, excluding their competitors from using patented technology for a period long enough to gain market share and a return on their investment. This article illustrates how strategic investment in R&D combined with a complementary patent strategy has been implemented with a view to improving market position and competitive edge within the brewing industry.

R&D ADDRESSES THE PROBLEM OF 'CARDBOARD' OFF-FLAVOUR

The fresh and delicate flavour of a lager beer, which is the goal of all brewers, is easily spoiled by off-flavour compounds that can develop in bottled or canned beer. All brewers are familiar with the unpleasant 'cardboard' flavour sometimes found in beers stored for several months or exposed to elevated storage temperatures. Overcoming this problem could be of considerable commercial value to the industry, both in terms of extending the shelf life of the beer and maintaining its high quality, as well as reducing the need for cold storage facilities for beer marketed in hot climates.

The culprit of this off-flavour is a lipid oxidation product called trans-2-nonenal (T2N), now known to originate from polyunsaturated lipids in the barley grain/malt used in brewing. Attempts to solve this problem are challenging in the extreme, since as little as 0.05 ppb T2N in a beer is sufficient to spoil its organoleptic flavour profile.

In the past, brewers have relied on sulphite to prevent or delay the formation of off-flavour compounds in beer, since sulphite forms adducts with carbonyl precursors and blocks their conversion into free T2N. Addition of sulphite to control and maintain sufficient sulphite levels in packaged beer products is not, however, a universally accepted practice.

Finding a better solution has been hampered by a lack of hard evidence as to how T2N is formed. An enzymatic route, involving the enzyme lipoxygenase, was a potential candidate since off-flavours in several food products (soybean and rice seed) had been attributed to the lipoxygenase pathway. On the other hand, alternative mechanisms based on a chemical auto-oxidation route were thought equally likely. Since barley mutants lacking the relevant lipoxygenase in the enzymatic route were unknown, there was no quick and easy way to address this question.

Any R&D department wishing to find a solution to T2N off-flavour in beer would need to think long and hard before embarking on such an undertaking. If the problem lay in lipoxygenase enzyme activity (lox1), then lox-deficient barley mutants would be needed, as well as the tools for both producing and identifying such mutants. Generating a lox1$^-$ barley would require several years of classical mutation breeding, since a lack of public acceptance has excluded the use of genetically engineered barley. Even then, proof of concept would still lie several years away, since the selected lox1$^-$ mutant seed would need to be scaled up through many crop generations in order to produce sufficient quantities of barley malt to conduct pilot scale brewing trials. Finally, accurate analytical assays would be needed to measure T2N sub ppb, →

supported by trained taste panels to detect any cardboard off-flavour in the brewed beer. While the cost of such an R&D project might represent many millions of euros, the commercial value of a solution, having worldwide utility for the brewing industry, could be considerable.

FOUR COMPANIES TOOK ON THE CHALLENGE:

Not surprisingly, all of them were brewers with a strong track record in R&D and the technical expertise to support such a major endeavour. Between the years 2000-2004, three international patent applications were filed describing solutions to the T2N problem. Publication of each application, some 18 months from its earliest claimed filing date, revealed the following details about the applicants and their solution:

The first application, WO02/053721, was filed by Carlsberg Research Laboratory*, Heineken Technical Services BV and Brasseries Kronenbourg**, acting as joint applicants. A team of eight co-inventors describe both the isolation of Line G barley with a mutant lipoxygenase 1 (low-lox1) with low activity; the genetic tools for detecting the mutant gene in malting quality barley varieties; as well as two brewing trials on a 30 hl scale, using the low-lox1 mutant malt, combined with forced aging tests on the finished beer to demonstrate its improved flavour stability. Lipoxygenase activity in this mutant barley was reduced to nine per cent of normal barley, due to a substitution of a critical residue in the enzyme's sequence.

The next application, WO2004/085652, filed by Sapporo Breweries Ltd, was published some two years later. The team of six co-inventors were no doubt encouraged when they read the published application WO02/053720, since it confirmed their own evidence that lox1 was the key to controlling T2N formation. However, their own invention, filed eight months later, would now need to be both novel and inventive over all the knowledge disclosed in the published WO02/053720 in order to be granted patent protection. In common with the majority of inventions, Sapporo's application provides an incremental improvement over the art, in that all detectable lox1 activity is eliminated in barley lines comprising their null-lox mutant barley gene (Lox1-5'splice site mutant).

Carlsberg A/S alone filed the next application, WO2005/087934, providing their own incremental improvement on Line G, in the form of new null-lox mutants.

THE SCOPE OF GRANTED INTELLECTUAL PROPERTY RIGHTS

So far, only two patents have issued from the first of the three applications (WO02/053721), while the remainder are all in patent office pipelines, which may take several years. New Zealand Patent 527171 grants the joint patentees (Carlsberg/Heineken) exclusive rights to barley plants/grain/malt comprising any mutant lox1 enzyme with reduced activity, its use in a brewing process, as well as the end products (e.g. beer). The exclusive rights granted in the USA by US patent 6,660,915 are narrower and only protect barley plants/grain/malt comprising the low lox1$^-$ mutation described in the patent, and its use in brewing. The two subsequent applications include patent claims to each their own null-lox barley mutants and their use in brewing.

EXPLOITING INTELLECTUAL RIGHTS

The exclusive rights granted by US 6,660,915 and NZ 527171 extend to 2021, after which the public is free to exploit the invention in the US and New Zealand without risk of an infringement suit. This gives the patentees ≤17 years to recover their investment. Since breweries can only gain full benefit of a reduced lox1 activity once a lox$^-$ mutation has been bred into top malting barley varieties, the speed and success of the breeding programme is critical. The patentees could then choose to reserve their exclusive rights to use of the low lox1$^-$ barley malt for brewing their own flavour-stable beers in the US, New Zealand and all other countries in which this ➜

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patent is eventually granted. Alternatively, they could seek to license their invention to seed merchants, maltsters or their brewing industry competitors, in return for a royalty on the low lox1⁻ barley grain/malt or its use in beer production. The same will apply to any patent rights granted for the null-lox barley inventions. Securing patent rights in Europe and other regions of the globe where barley is grown, malted, and/or used to brew beer may greatly increase the value of the low-lox1⁻ and null-lox1 inventions.

From the perspective of patent rights, it is important to note that in some jurisdictions, e.g. New Zealand, the exclusive rights granted in NZ 527171 are dominant with respect to null-lox barley, since they extend to any barley containing a mutant lox1 enzyme with reduced activity. Thus, the right to grow or use a mutant null-lox1 barley will require a license from the NZ 527171 patentee. If the second generation null-lox1 barley is a real improvement, the parties will have every reason to cross-license their respective inventions once patented.

COST EFFECTIVE R&D

If the first low-lox1 and the second generation nul-lox1 barley lines live up to their expectations, the farsighted brewers will be a step ahead of their competitors, with the resources to invest in new challenges, provided that their inventions are patent protected in their key markets.

* *Carlsberg Research Laboratory is a Research Division within Carlsberg A/S*

** *Brasseries Kronenbourg is now a subsidiary of Carlsberg A/S*

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