F&F Research, Science and Technology Highlights

A review of recent work in new odorants, biotech and renewable materials, cooling compounds, encapsulation and more.

The largest flavor and fragrance houses spend about 7–10% of revenues on R&D activities, according to available annual reports. Investments have centered on everything from new molecule development and process engineering to sustainability innovations. Meanwhile, consumer products companies and academic and research institutions continue to invest in flavor, fragrance and taste research. This month, in the first of an occasional series, P&F *presents a survey of recent patent activity and research publications, providing a view into innovations being pursued throughout the industry.*

Odorants for Wound Healing

A recently published study by Daniela Busse et al. concludes that 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS# 65113-99-7; Givaudan trade name: Sandalore) interacts with chemoreceptors in keratinocytes in human skin to activate wound healing.[1]

Sandalore is a fragrance material with high tenacity and warmth, which can act as a sandalwood replacement in conjunction with materials such as 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS# 67801-20-1; Givaudan trade name: Ebanol). Sandalore is a colorless to pale yellow liquid that has a recommended use level of 0.5–10.0% in fine fragrance, beauty care, soap, laundry care and household applications, according to a Givaudan product specification sheet.

"Sandalore induces strong Ca_2+ signals in cultured human keratinocytes, which are mediated by OR2AT4, as demonstrated by receptor knockdown experiments using RNA interference," the study authors noted.

By unlocking this "increase in cell proliferation and migration," as co-author Hanns Hatt (Ruhr-Universität Bochum) put it in comments to *P&F*, skin regeneration and wound healing activities occur. Hatt noted that Sandalore was the sole material tested for this activity so far, but that it is possible that additional aromatic substances can interact with the same receptors. He also noted that there are 15 to 20 other olfactory receptors in keratinocytes, which could be activated by other substances, perhaps inducing similar reactions. Further work is necessary to untangle these questions.

In practice, Hatt noted that applying wound-healing-generating aromatic materials to skin via a cream or similar application is possible and could present a practical application of the present work.

By producing Reb M using fermentation, there is potential to produce the zero-calorie sweetener at a cost that is not feasible through conventional extraction of Reb M from the stevia leaf.

Optimizing Production Methods of Biotechnologically Produced Vanillin

Vanillin is a high-demand compound that has been produced via biotechnology methods such as yeast-based fermentation. A recent paper by Oliver Simon et al. examined the value of *Pseudomonas putida* KT2440 in the bioconversion of vanillin.[2] The work, according to the authors, "will deepen the understanding of metabolism of aromatic compounds in *P. putida* and may lead to a more comprehensive understanding of solvent tolerance mechanisms in Gram-negative bacteria in general. Moreover, it will serve as a basis for further strain developments for a biotechnological production of vanillin in *P. putida* KT2440 or other *Pseudomonas* strains, highlighting the role of proteomics surveys as a powerful screening technology." The authors also noted, "Aldehyde dehydrogenases, vanillin-specific porins and efflux pump systems identified in-study will be interesting targets for optimization of vanillin production in *Pseudomonas* bacteria."

Effects of Experience on Color-Odor Associations

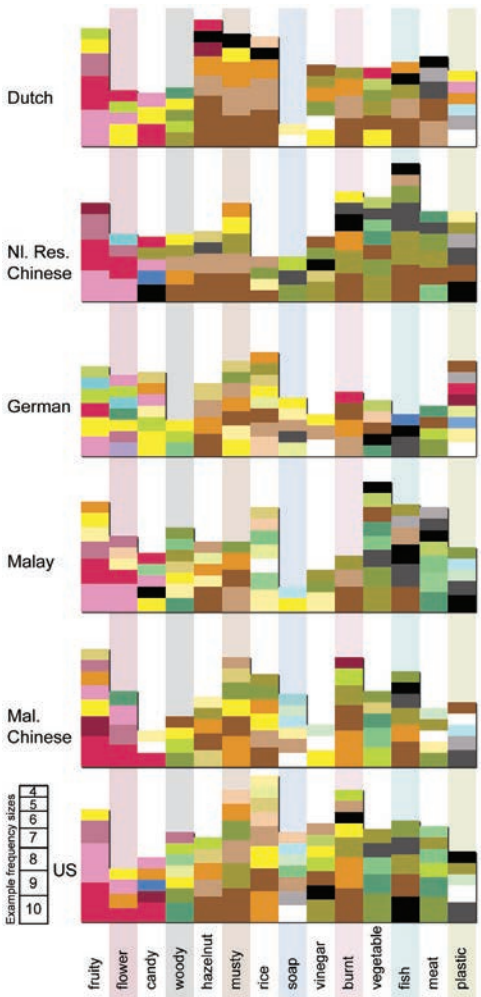
Experience is a significant driver of odor-color associations, according to a paper by Carmel Levitan et al.[3] The authors presented the same 14 odors to study participants, which included the following nationalities/groups: Dutch, Netherlands-residing

Chinese, German, Malay, Malaysian-Chinese and U.S. residents. Within each group, color-odor associations were consistent. Using representational dissimilarity analysis, the study authors discovered that the U.S. and German participants were the most alike in color-odor associations, followed by a less strong correlation between German and Malay participants. On the other hand, vast differences in associations were found between Malay and Netherlands-resident Chinese study participants and Dutch and Malaysia-Chinese participants. As a result, the authors explained, "We conclude that culture plays a role in color-odor crossmodal associations, which likely arise, at least in part, through experience." The color-coded responses can be seen in **F-1**.

Biorenewables for Fragrance Ingredient Production

A recent paper by Augosto de Meireles et al. examines the alkoxylation of monoterpenes for the sustainable production of fragrance compounds.[4] Using cesium salt of tungstophosphoric heteropoly acid as an "environmentally friendly" catalyst, the authors noted that fragrance materials such as camphene, limonene, α-pinene and β-pinene could be produced at "good to excellent yeilds."

F-1. Color congruency for each odor in each culture; courtesy of PLOS One[a]



[a]According to the original publication: "Colors per odorant per country are ordered by frequency (most frequent are shown lowest on their respective y-axis). Frequency is represented by the height of each color box; the box on the right of the figure shows the height a given box must be for there to be 10, 9, 8 etc. ratings of that color for a given odorant. Boxes have been given a slight shadow to help with the perception of harder to see light colors. The background bars are only colored so as to help with reading the figure."

Affordable Biotech Stevia

The patent application (WO 2014122227) for Evolva Holding SA's process to efficiently and sustainably produce next-generation sweeteners via fermentation, including rebaudioside M (reb M), has been published.[5] The patent application was originally filed on February 6, 2013. By producing reb M using fermentation, Cargill and Evolva have said they have the potential to significantly improve the flavor profile of zero-calorie sweeteners, especially at higher usage levels, and at a cost that is not feasible through conventional extraction of reb M from the stevia leaf. Conventional stevia materials are extracted from *Stevia rebaudiana*, typically grown in South America or Asia, and are purified to various extents for use in food systems or as standalone tabletop sweeteners.

Violet Leaf Odorants

Firmenich has published a patent for violet leaf odorants and their "use as [a] perfuming ingredient of a compound of formula in the form of any one of its stereoisomers or a mixture thereof."[6] The invention's compounds, listed with their odor notes in parentheses, include, but are not limited to: nona-1-en-4,8-diyne (green violet leaves, acetylene), non-1-en-4-yne (green, foliage, violet leaves, acetylene), tridec-1-en-4-yne (green, violet leaves) and 2-methylundec-2-en-5-yne (green, violet leaves, metallic, acetylene). Comparing the materials to existing violet leaf odorants, the applicant notes "the invention's compounds distinguish themselves by a clearly stronger green/galbanum and in some cases by having additional olfactive aspects (such as earthy or aromatic ones) and also by being more substantive."

Marine/Ozonic Notes

Many existing marine/ozonic notes have high production costs due to a large number of synthesis steps or expensive starting materials, according to a recent Mane patent publication.[7] The publication focuses on novel cycloalkane aldehydes for fragrance applications. These ingredients include 5-(2,4,4-trimethylcyclopentylidene)-pentanal, 6-(2-methylcyclohexylidene)-hexanal, 6-(4-tert-butylcyclohexylidene)-hexanal, 6-(4-tert-amylcyclohexylidene)-hexanal, 6-cyclooctylidenehexanal, 6-(3,3-dimethylcyclohexylidene)hexanal, 4-(2,4,4-trimethylcyclopentylidene)butanal, 4-(3,3-dimethyl cyclohexylidene)-butanal, 5-(4,4-diethylcyclohexylidene)-pentanal and 5-cycloheptylidenepentanal, and feature olfactive notes (at 5% by weight in dipropylene glycol) such as marine, ozonic, watery, cucumber, green applelike, dried seaweed, mineral, aldehydic, fatty, cardamomlike, flowery, salty, etc.

Floral-Green Notes

There is constant demand for improved or modified floral and green odor notes, according to a patent publication from Givaudan.[8] The publication details substituted 4-cyclopentylidenebutanals, which reportedly possesses floral and green odor

New violet odorants are the subject of a recent patent publication.

notes appropriate for aromatic compositions, in which it imparts floral, muguet and green odor notes. In a demo unisex floral fragrance composition, the publication notes that the inclusion of 25 parts of (E/Z)-4-(3,3-dimethylcyclopentylidene)butanal "results in a vibrant opening and enhancement of the exuberant orange, increasing the exotic florality and giving the composition a touch of sophistication."

Effect of Coolants on Athletic Performance

A recent paper from Florence Riera et al. suggests that the addition of menthol aroma to "cold water or ice-slush" boosts athletic endurance.[9] The study, which focused on male cyclists and triathletes, examined the impact of a menthol-aromatized cold water and ice-slush consumed before and after warm-up, and before and during exercise. Performance improved exponentially with the coldness of the beverage and menthol inclusion, so that the best performance was achieved with the ice-slush + menthol, followed by the cold water + menthol. According to the authors, "Cold water or ice-slush with menthol aroma seems to be the most effective beverage for endurance exercise in a tropical climate. Further studies are needed to explore its effects in field competition."

n-Hexane Extraction Alternatives

Blackcurrant bud extracts contain aromatic compounds such as sabinene, δ-3-carene, terpinolene, β-caryophyllene, α-phellandrene, *cis*-β-ocimene, α-terpinene, terpinen-4-ol and limonene. A recent paper from representatives of Firmenich, ERINI Institute, Université Nice Sophia-Antipolis and Université d'Avignon examines alternative solvents for the extraction of aroma compounds from blackcurrant buds.[10] The researchers concluded that 2-methyltetrahydrofuran (MeTHF; CAS# 96-47-9) presents the best alternative solvent for n-hexane, offering "good yield and selectivity of aromas." Other solvents examined included α-pinene, ethyl acetate, methyl acetate, ethyl lactate, butanol, isopropanol, ethanol and CO_2 supercritical fluid.

Synthesis of α-Santalol

"[A]ll known [α-santalol] syntheses are lengthy, require expensive starting materials and/or reagents, or even steps which are too expensive for an industrial process or generate unacceptable quantities of waste," according to a recent patent publication from Firmenich.[11] The publication goes on to explain that, as a result, synthetic α-santalol is not generally commercially available. The component, a key odorant found in *Santalum album* Indian sandalwood, is highly sought-after. However, Indian sandalwood availability is hampered by shortages and protected status under the Convention on International Trade in Endangered Species. At the same time, West Australian sandalwood oil (*Santalum spicatum*) contains just 3–8% α-santalol. The publication concludes that "There is an urgent need for alternative syntheses to produce α-santalol and its derivatives. The publication comprises the use of a described compound for the synthesis of α-santalol."

Rose and Rhubarb Fragrance Notes

There is a need for fragrances with rose notes, a recent patent publication from BASF argues, as are efficient preparation modes for materials, higher stability and tenacity, improved sensory profile and synergistic activity with other fragrances.

"4,8-Dimethyl-3,7-nonadien-2-ol in which the weight ratio of (E)-4,8-dimethyl-3,7-nonadien-2-ol to the sum of (E)- and (Z)-4,8-dimethyl-3,7-nonadien-2-ol is at least 80% or in which the weight ratio of (Z)-4,8-dimethyl-3,7-nonadien-2-ol to the sum of (E)- and (Z)-4,8-dimethyl-3,7-nonadien-2-ol is at least 80%, is used as fragrance," the publication states.[12]

When applied to fragrance compositions, the publication explains that the scents have a floral, roselike character, while rhubarblike, citrusy and minty notes can be detected. Rose notes are detectable at low use levels.

At different ratios of (E)- isomer to (Z)-isomer, the material can have a profile that is rosy-green-minty, rosy-floral-green-minty, rosy-floral-citrus-rhubarblike or rosy-floral, citrus-fruity-rhubarblike-herbaceous.

"All of the isomer mixtures have the desired rose component," the publication explains. One-to-one and one-to-two mixtures feature "fresh minty accompanying notes," while one-to-four and one-to-five mixtures "have attractive fruity accompanying notes of citrus and rhubarb."

Asthma and Fragrance: It's Not What You Smell, It's What You Think You Smell

An asthma sufferers' perception of an odor as harmful may in fact trigger an asthmatic reaction, rather than the odorant itself, a recent study from Monell explains.[13]

"Predictably," the authors noted, "manipulations of perceived risk altered both the quality ratings of the fragrance as well as the reported levels of asthma symptoms. Perceived risk also modulated the inflammatory airway response."

The asthmatics in the study group were exposed to an odorant characterized as "asthmogenic" or "therapeutic," with the result that the negative reaction was "elevated" in response to the supposedly asthmogenic odorant. According to the authors, "The asthmogenic group showed a rapid and persistent increase in airway inflammation."

As a result, it appears that physiological and psychological factors play into asthmatic reactions, rather than merely the composition of fragrances or strong odors.

"Asthmatics often are anxious about scents and fragrances," said lead author Cristina Jaén of Monell. "When we expect that an odor is harmful, our bodies react as if that odor is indeed

harmful. Both patients and care providers need to understand how expectations about odors can influence symptoms of the disease."

Senior author Pamela Dalton noted, "Can we improve health outcomes by reducing concern or fear in a disease where emotional arousal is counter-productive?"

Jaén added, "It's not just what you smell, but also what you think you smell."

Off-note Blocking Compounds

A recent patent publication from Givaudan explores the use of compounds to counteract off notes in formulations containing sweeteners such as aspartame, saccharin, acesulfame K, sucralose, stevioside and rebaudioside A.[14] The numerous off-note blocking compounds discussed include, but are not limited to, 4-(2,2,3-trimethylcyclopent-3-enyl)but-2-enoic acid, 4-(2,2,3-trimethylcyclopentyl) butanoic acid and 4-(2,2,6-trimethylcyclohexyl)butanoic acid. In an aspartame/acesulfame-K-containing diet energy drink, the applied off-note blocker diminished bitterness compared to the control. In a sucrose/glucose-sweetened energy drink containing ingredients such as taurine, caffeine, niacin, and vitamins B6 and B12, the off-note blocker decreased off notes, bitterness and astringency, compared to the control. Applied to dark chocolate, the blockers decreased bitterness. In a daytime cough syrup containing acetaminophen, dextromethorphan and phenylephrine HCl, the off-note blocker reduced bitterness. Meanwhile, in a low-sugar iced coffee the off-note blocker reduced bittermness and astringency, compared to the control.

Mood-enhancing Fragrances

"Our research has shown that the ability of odors to enhance mood is related to their complexity," notes a recent patent publication from Givaudan.[15] "Complex odors in a similar olfactory category were generally more effective than simple blends, and simple blends were more effective than single materials and oils."

The publication details formulation rules for the creation of fragrances with "a high probability" of invigorating and energizing users. The ingredients used were segmented into various categories, including "IMP" (comprising materials such as coriander oil, allyl amyl glycolate, fir balsam and bergamot oil), "HMR" (comprising materials such as allyl ionone, *cis*-jasmone, geranium oil and lemon oil, "HMI" (comprising materials such as β-damascone, dihydromyrcenol, eugenol, mandarin oil and orange oil), "HMP" (comprising materials such as allyl cyclohexylpropionate, allyl heptanoate, cassis base, *cis*-3-hexenyl salicylate and damascenone), "RMP" (comprising materials such as anisic aldehyde, benzoin Siam resinoid, ethyl vanillin, hexyl salicylate and vanillin) and "GEN" (comprising materials such as hexyl cinnamic aldehyde, β-ionone, isobornyl cyclohexanol, linalool and methyl dihydrojasmonate). The ratios by group are described as follows: "(a) IMPs>=HMPs+HMRs; (b) IMPs+HMIs+GENs>=70%; (c) $(IMP+HMI)/(IMP+HMI+RMP+HMR)>=0.7$;

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The addition of a coolant to water consumed by bicyclists improved athletic endurance in one study.

(d) IMPs/(HMPs+RMPs+IMPs)>=0.5; and (e) IMPs/[(HMPs+RMPs+IMPs)+(100–TOTAL)]>=0.3." Low-odor and odorless solvents are excluded from these calculations.

Water-fragrance Spray

Organic solvents allow for fragrance to be dispersed using a minimum of fragrance and without emitting an overwhelming odor.[16] Ethanol, for example, allows for both of these goals to be met. However, according to a recent patent publication from Givaudan, "there is a desire to move away from these formulations on cost and environmental grounds."

While water is a desirable, alternative, there are numerous associated technical challenges, including the hydrophobicity of many fragrance ingredients, necessitating the use of significant amounts of emulsifiers. In addition, water emulsion systems have a diminished shelf life because of their thermodynamically unstable nature—a negative from economic and sustainability perspectives. At the same time, the publication notes, "emulsifiers can leave undesirable residues on substrates, especially skin, and produce thereby sticky or simply unpleasant residues." Emulsifiers also reduce the rate of evaporation, resulting in an unpleasant "moist feeling" on-skin, induce undesired foaming, and cause fragrance material retention, which reduces performance and induces "perfume profile distortion."

The patent publication proposes a dispersal solution employing "separate reservoirs of water and fragrance and the conveying of the liquids through separate conduits to at least one spray nozzle, the liquids being combined immediately prior to or immediately after spraying from at least one nozzle." The system could include a single nozzle, and two conduits with separate entrances feeding into a mixing chamber "adjacent to the spray nozzle," which may contain a static mixer.

To avoid unintended mixing via flow-back, "the conduits are concentric for the final parts of their lengths to the chamber," according to the publication. "An example is a spring-loaded ball valve at the bottom of the chamber." Regarding the aerosol, the publication notes: "it is believed that fragrance is adsorbed on to the surface of water droplets formed by the spraying action, and are thus carried into the atmosphere, or on to a surface."

The twin nozzles produce discrete water and fragrance sprays, which can be combined by means of cross-angling or perpendicular positioning.

The publication adds, "[O]ne or both liquids may be under pressure, and depression of valves releases them. Another possibility is to use a spray pump of the type … in which the depression of a cap causes liquid to be pumped. This is configured such that the appropriate amounts of liquid are metered for spraying. A further possibility is the use of compressed gas as release agent."

Bitter Blocker Efficacy and Age

A recent study from Monell notes that bitter blockers are less effective in children, which raises the question of the role of genotyping and adult panelists in medicinal flavor development.[17]

The authors note, "Bitter taste is the primary culprit for rejection of pediatric liquid medications. We probed the underlying biology of bitter sensing and the efficacy of two known bitter blockers [sodium gluconate and monosodium glutamate] in children and adults."

The blockers were tested against food-grade bitter compounds, including quinine, denatonium benzoate, caffeine and propylthiouracilin.

"Bitter blocking was less effective in children, and the efficacy of blocking was both age and compound specific," the authors explain. They add, "This knowledge will pave the way for evidence-based strategies to help develop better-tasting medicines and highlights the conclusion that adult panelists and genotyping alone may not always be appropriate in evaluating the taste of a drug geared for children."

Boosting Fragrance Release During Ironing

A recent patent publication from Colgate-Palmolive focuses on increasing the release of fragrance during the ironing process to enhance consumer experience.[18] The described solution includes a composition "comprising a linear polyether having a weight average molecular weight less than 5,000 that is terminated with —N—(—CH2—CH(OH)—CH2—Cl)2, and fragrance." While odor is released during ironing of the fragrance-only comparative solution described in the patent publication, blooming is enhanced in the polyether-containing

A recent patent publication focuses on increasing the release of fragrance during the ironing process.

composition. After five washings, the polyether-containing comparative has significant fragrance blooming.

"The presence of the polyether helps to provide unexpected blooming of fragrance when the towels are washed multiple times (more than three times)," the publication notes. "[O]ne possible hypothesis is that unlike fragrance, there may be build-up of polymer due to multiple washings and thus deposited polymer may help to provide increased blooming of fragrance. It is also possible that the polymer may have the characteristics to deposit fragrance at increased levels."

Temperature- and pH-Activated Fragrance Encapsulation

A recent paper from Ines Hofmeister et al. describes the use of polymer nanocapsules for encapsulating α-pinene.[19] The miniemulsuion-analagous free radical polymerization process led to the formation of capsules that could be triggered by temperature and pH changes, according to the authors. The paper notes, "In contrast to more frequently applied barrier microcapsules the nanocapsules provide drastically improved colloidal stabilities."

Furthermore, the barrier nanocapsule approach is principally not restricted to fragrances and is expected to be compatible with other hydrophobic actives.

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