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BLOCKING THE BITTER TASTE-SIGNALING PATHWAY

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BITTER-BLOCKING TECHNOLOGY

Biochemical Bitter Blocking for New Drug Formulations

By: F. Raymond Salemm, PhD

INTRODUCTION

The aversive taste of many active pharmaceutical ingredients (APIs) is a barrier to the creation of palatable liquid or other dosage forms that deliver the drug via absorption in the oral cavity. One commonly cited example is liquid pediatric formulations of antibiotics with poor taste, resulting in a lack of compliance and potential reemergence of resistant infections. Research studies have shown that palatability is particularly important to physicians prescribing liquid antibiotics for children. Other dosage forms, such as buccal delivery, lozenges, thin films, and orally disintegrating tablets, provide improved convenience and onset of action, as well as reduced hepatic drug metabolism for many APIs. However, in many cases, the aversive taste of the API is an impediment to their successful development and/or commercialization. The potential benefits of these improved formulation options motivate the development of new bitter blocking technology to overcome the aversive taste barrier.

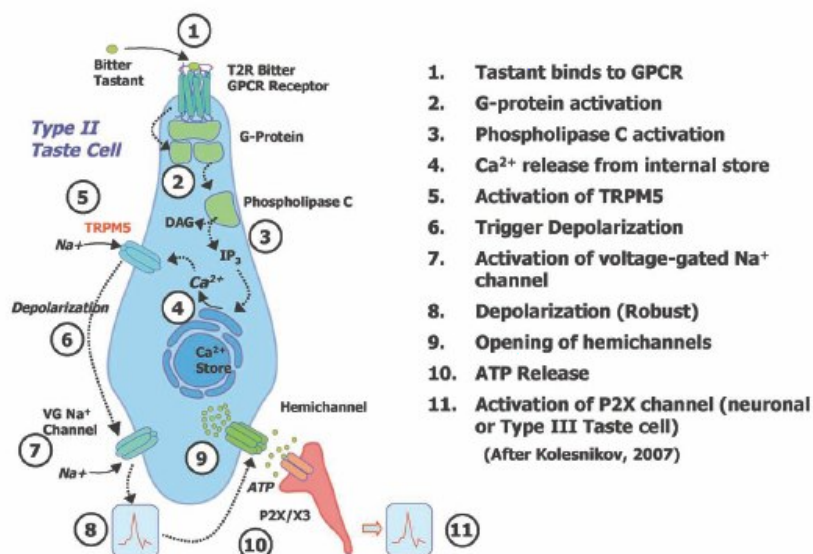
CURRENT STRATEGIES FOR TASTE MASKING

The classic pill is typically coated and formulated to dissolve in the gut, thus avoiding most issues with aversive API taste. In contrast, most liquid or buccal delivery formulations typically incorporate some type of taste-masking. Numerous technologies have been developed for taste-masking, ranging from the simple addition of sweeteners

and flavoring agents, to sophisticated methods of physical sequestration, such as API microencapsulation or complex formation with cyclodextrans or polymers. In many applications, substantial quantities of flavoring agents or sequestering agent are required to achieve effective taste-masking. In addition, many instances occur, due to the extreme bitterness of the API or the large quantities of API required for an effective dose, in which it is difficult to successfully mask the API aversive taste. There are over 100 commonly prescribed pharmaceutical and OTC products encompassing essentially all therapeutic areas that are known to have aversive API taste. Collectively, these products represent several billion dollars worth of annual sales.

FIGURE 1

The Bitter Taste Signaling Pathway



"BIOCHEMICAL" BITTER BLOCKERS

An alternative approach to the creation of better-tasting liquid and orally absorbed drug formulations involves the development of topically active compounds that can be formulated in very small amounts together with the API to biochemically block the bitter taste-signaling system. This approach is enabled by a recently emerging understanding of the molecular biology of taste.

An ideal biochemical bitter blocker is intended to be effective in quantities of approximately 100 micrograms per drug dosage form, which is about 100- to 1000-fold less than the typical quantity of API dosage. As outlined in Table 1, there are numerous advantages to the

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biochemical bitter-blocking approach that stem mainly from the very small amounts of compound required to transiently inhibit bitter taste perception in the oral cavity. There is also the potential for improved compatibility with orally absorbed drug delivery systems because there is no physical masking of the API to impede absorption through the oral mucosa. In addition, the small quantities of bitter blocker required can potentially reduce manufacturing complexity and lower overall formulation costs.

THE SCIENCE OF TASTE

Discovery of a novel biochemical bitter blocker follows a classical drug discovery paradigm based on inhibiting a specific molecular target in taste signaling. This strategy is enabled by the recent advances in understanding the molecular signaling processes underlying the sense of taste.

Generally, there are considered to be five basic tastes: sweet, umami (savory), bitter, salt, and sour. Sweet, umami, and salt are appetitive tastes that provide positive reinforcement for the intake of carbohydrates, proteins and nucleic acids, and minerals, respectively. Sour and bitter are aversive tastes, evolved to discourage intake of acidic substances (sour) or alkaloids or other compounds (bitter) that could be toxic if consumed indiscriminately. Recent advances in the molecular biology of taste now make clear that sweet, umami, and bitter tastants are sensed by G-protein coupled receptors (GPCRs) and that salt and sour are most likely sensed by ion channels. In addition to the five basic senses, there are several "spicy" tastes that appear to be sensed through ligand-gated ion channels of the extensive transient receptor potential ion channel (or TRP channel) family.

The bitter taste sense may have evolved in part to prevent the excessive ingestion of alkaloids (eg, natural compounds like caffeine, nicotine, etc) and other aversive compounds produced by plants as their own

defensive mechanism to discourage consumption by animals. In fact, there is broad chemical diversity among the bitter compounds found in nature. Consequently, in contrast to the sweet and umami tastes, which

are each sensed by a single heterodimeric GPCR, bitter taste is sensed by over 25 different receptors that have evolved to sense the diversity of plant defensive chemistry. Many drug APIs are more or less similar in

FIGURE 2

TRPM5 Channel A Key Element in Taste Signaling

Ca²⁺ Gated Na⁺ Channel

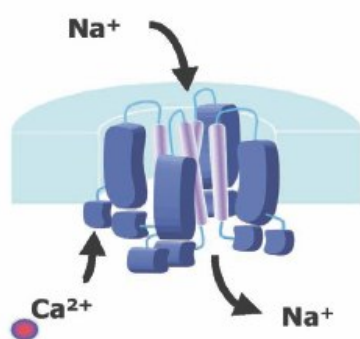
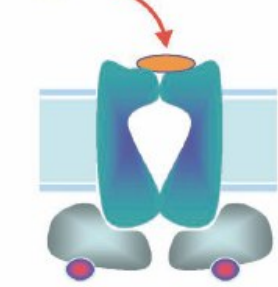


Fig 2A

Bitter Blocker



Blocker locks channel closed

Fig 2B

TABLE 1

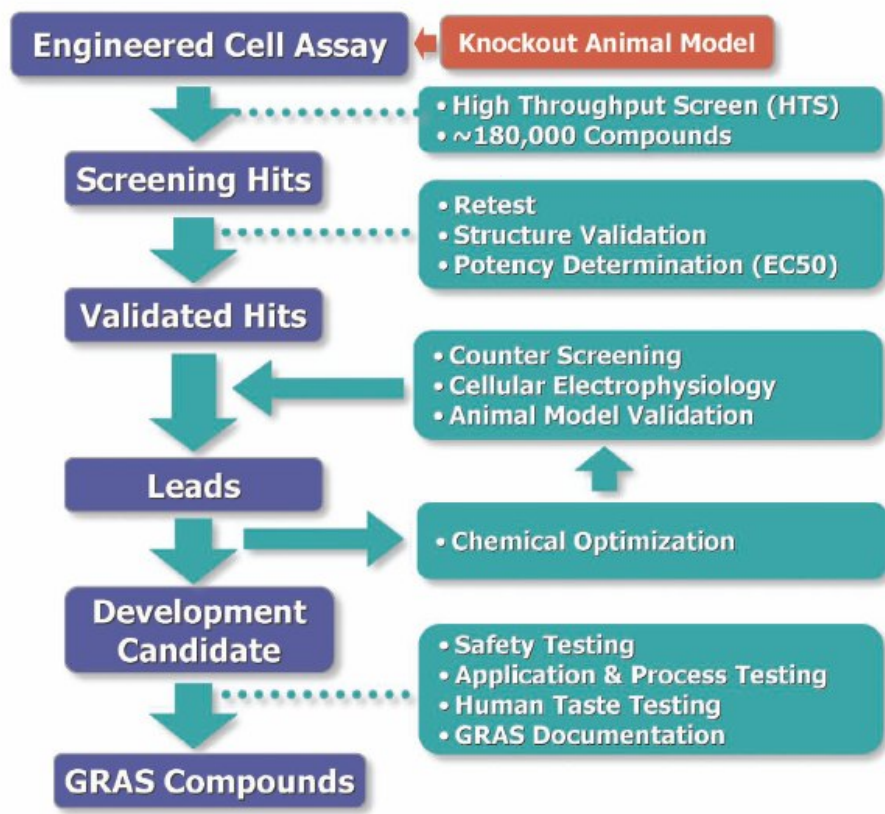
Potential Advantages of a "Biochemical" Bitter-Blocker

	Conventional Taste Masking	Biochemical Bitter Blocker
Technology	Microencapsulation, Cyclodextrin carriers, Polymer resins	TRPM5 Inhibitor
Quantity Required	Typically equals API quantity	10 ⁻³ × API quantity
Oral Cavity Absorption Compatibility	Poor	Excellent
Manufacturing Complexity	High	Low
COGs	Variable	Very Low

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FIGURE 3

Bitter Blocker Discovery & Development Process



chemical composition to alkaloids, and so are generally sensed as bitter.

Figure 1 outlines the bitter taste-signaling pathway.¹ The taste-signaling pathway is initiated when a bitter molecule, such as a drug API, binds to a bitter GPCR receptor on the surface of Type II taste cells found in taste buds on the surface of the tongue (Figure 1 No. 1). API binding causes a conformational change in the GPCR that initiates a G-protein signaling cascade (Figure 1 No. 2), resulting in activation of phospholipase C (PLC 3) (Figure 1 No. 3). This in turn, causes mobilization of internal cell calcium (Ca²⁺) stores (Figure 1 No. 4). Released calcium binds to a trans-membrane ligand-gated ion channel called TRPM5 (Figure 1 No. 5). Calcium binding to TRPM5 causes the channel to open, admitting sodium

into the cell interior. This produces a triggering depolarization that causes additional voltage-gated ion channels (Figure 1 No. 7) to open, admitting additional quantities of sodium and initiating a robust cellular depolarization (Figure 1 No. 8). Cell depolarization causes voltage sensitive hemichannels to open, resulting in the release of ATP, which in turn activates P2X/X3 channels on neuronal or Type III taste cells (Figure 1 No. 9), ultimately initiating a “taste” nerve signal to the brain (Figure 1 No. 10).

Many of the aforementioned molecular components are highly specific to taste tissue.² The circuitry was principally worked out through the use of transgenic animals, in which specific genes are “knocked-out” so that they are ineffective in the expression of a functional signaling protein. The phenotype of

animals with gene knock-outs of any of the key taste components is a greatly reduced capacity to taste bitter compounds. One of these signaling components, the calcium-gated channel TRPM5 in Figure 1 is an especially attractive target for pharmaceutical bitter blocking because it acts downstream of the 25+ bitter-sensing GPCRs. Thus, this target offers the potential to develop a single biochemical agent with the ability to broadly block bitter taste across a wide range of API chemotypes. Work carried out in Redpoint Bio’s labs shows that TRPM5 knock-out animals are indeed deficient in their ability to taste a wide range of chemically diverse, bitter APIs, as suggested by the circuitry outlined in Figure 1.

Figure 2a shows a schematic of the TRPM5 channel, which is a homo-tetramer incorporating four identical protein subunits of MW~ 131,000 Daltons, including both transmembrane and intracellular domains. TRPM5 is believed to bind calcium at domains on the intracellular membrane surface, triggering the channel to open and allow the influx of sodium. As outlined in Figure 2b, a blocker is envisioned to physically block the transmembrane sodium channel, although it is equally plausible that a blocker could bind elsewhere on the channel and cause the channel to remain closed.

BITTER-BLOCKER DISCOVERY & DEVELOPMENT

The pharmaceutical industry has developed an extensive tool set to discover drugs directed to specific molecular targets. Redpoint Bio’s bitter-blocker discovery process is outlined in Figure 3. The process begins much like a conventional therapeutic drug discovery campaign with the development of a high throughput screening assay and screening of a synthetic chemical or natural products compound library to find active “hits.” Hits are then validated and begin iterative cycles of chemical diversification to optimize a continually expanding and more

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rigorous set of evaluation criteria (eg, potency, selectivity, efficacy in animal models, etc) until a compound is selected as a development candidate. Computational chemistry tools are extensively employed throughout compound optimization to guide the process and to identify and correct potential liabilities with respect to compound efficacy and safety. Because taste is a characteristic shared in common with higher vertebrates, Redpoint makes use of operant animal models to evaluate its taste modulators throughout the optimization process. The company has developed novel approaches to traditional technology for animal behavioral testing that enable the in vivo testing of hundreds of compounds in usefully short timeframes.

Development candidates meeting initial selection criteria are scaled up for additional evaluation of safety, application suitability, and human taste testing. As noted previously, development compounds for pharmaceutical bitter-blocking applications are intended to be effective in quantities of approximately 100 micrograms per drug dosage form, which is about 100- to 1000-fold less than the typical quantity of the API dosage. Novel compounds used as flavor modifiers in foods and pharmaceutical products go through an extensive safety testing procedure, but are ultimately certified as safe for use through the Generally Recognized As Safe or GRAS approval process. GRAS is the category established by the 1958 Food Additive Amendment to the Federal Food, Drug and Cosmetic Act that applies to natural or artificial chemicals that can be added to food, beverage, and pharmaceutical products within a defined level of usage. New compounds can gain GRAS approval through a review of scientific material by an expert panel qualified by training and experience to determine safety. The current GRAS list contains approximately 2000 compounds, of which approximately 1400 are "nature identical" and 600 are synthetic. Many entries on the current GRAS list were reviewed and approved by the Flavor and Extract Manufacturers Association (FEMA) Expert

Panel that has operated since the early 1960s. The FEMA expert panel requires a data package for GRAS status approval that generally includes extensive testing to demonstrate an adequate safety margin relative to the expected use level in any marketed product. GRAS Certification requires that the reviewing expert panel agree that the compound is safe at the anticipated use levels. Although FDA notification is not formally required, the GRAS data package is provided to the FDA so that the agency has the opportunity to review and/or challenge the GRAS status of flavor ingredients as determined by the FEMA expert panel.

PRODUCT APPLICATIONS

An effective biochemical bitter blocker is anticipated to improve a wide range of pediatric, geriatric, OTC, and consumer products that currently have taste problems, and to enable new liquid formulations that have previously been technically challenging. In addition, significant opportunities exist to create new dosage forms, such as lozenges, orally disintegrating tablets, and thin films, with bitter-tasting APIs. These formulations can offer improved convenience, more rapid onset of action, and potentially greater safety owing to bypass of hepatic metabolism. This technology is potentially applicable across numerous therapeutic indications, including pain, CNS, anti-infective, cardiovascular, gastrointestinal, genitourinary, and respiratory/allergy.

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BIOGRAPHY



Dr. F. Raymond Salemme is the CEO of Redpoint Bio, a biotechnology company leveraging recent discoveries in

taste biology to discover and develop novel taste modifiers for the pharmaceutical, food, and beverage industries. Prior to Redpoint Bio, Dr. Salemme founded 3-Dimensional Pharmaceuticals, a company integrating structure-based design and combinatorial chemistry for drug discovery. Prior to 3DP, he worked in drug discovery at Sterling Winthrop and DuPont Merck Pharmaceuticals, and in basic materials science at DuPont CRD. Before joining industry, Dr. Salemme was Professor of Biochemistry at the University of Arizona. He earned his PhD in Chemistry from UCSD and his BA in Molecular Biophysics from Yale University. He is an inventor on 30 US patents and an author of over 90 publications.