A Mechanistic Overview of Taste Bud Maintenance and Impairment in Cancer Therapies*

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Abstract

Since the early 20th century, progress in cancer therapies has significantly improved disease prognosis. Nonetheless, cancer treatments are often associated with side effects that can negatively affect patient well-being and disrupt the course of treatment. Among the main side effects, taste impairment is associated with depression, malnutrition, and morbid weight loss. Although relatively common, taste disruption associated with cancer therapies remains poorly understood. Here, we review the current knowledge related to the molecular mechanisms underlying taste maintenance and disruption in the context of cancer therapies.

Key words: chemotherapy, Hedgehog signaling, Notch signaling, organoids, radiotherapy, Wnt signaling

A multitude of medical conditions and treatments are associated with altered (dysgeusia) or loss (ageusia) of taste, ranging from infection to cancer therapies. Regardless of the agent(s) causing taste alteration, this disruption is highly troubling to patients and often detrimental to their well-being and quality of life. Taste loss causes lack of appetite, which in turn can lead individuals to isolate socially and ultimately to depression (Leventhal 1959; Maes et al. 2002). The depth of psychological distress is well illustrated by Ethna MacCarthy-Leventhal, M.D., who described her “mouth blindness” after she was treated with radiotherapy for pharyngeal cancer: “What is it like to lose your sense of taste? To know that the most luscious fruit is a cinder, and its juice an acid liquid flavoured with bicarbonate of soda or copper, or that a Whitstable oyster is no more appetizing than a slug?” (Leventhal 1959). Physiologically, taste disruption impedes daily nutrient intake leading to malnutrition and dangerous weight loss (Ravasco et al. 2005; Ruo Redda and Allis 2006; Hutton et al. 2007; Mahdavi et al. 2007; Ogama et al. 2010; Deshpande et al. 2018), as Dr. MacCarty-Leventhal goes on to say: “If, by a mighty effort, the ‘cinders’ are forced down with copious fluid, the consequences are acute indigestion or vomiting. The patient is not hungry anyway, and it is easier to starve” (Leventhal 1959). Importantly, this distressing side effect can lead to poorer treatment outcomes, and in extreme cases, death may ensue (Bolze et al. 1982; Chencharick and Mossman 1983; Nelson 1998; Hutton et al. 2007; Zabernigg et al. 2012; Rathod et al. 2015).

The sense of taste, among our basic senses, seems particularly prone to perturbation. Like skin, taste bud cells continually and rapidly regenerate from adult stem cells, and disruption of taste function is thought broadly to be due to interruption of the renewal process. But given the complex regulation of renewing epithelia, the specific insults to this process in the taste epithelium by individual disease-causing agents or drugs are likely quite diverse, yet nonetheless result in a grossly similar impact on taste function. For example, inflammation can cause taste dysfunction...
environment (Landis et al. 2005; Sano et al. 2007; Goyal et al. 2020). Middle ear infection also can lead to distorted taste; nerve fibers that convey taste information from the anterior tongue to the brainstem travel through the middle ear and are exposed to the infected/inflamed environment (Landis et al. 2005; Sano et al. 2007; Goyal et al. 2009), damaging nerve fibers’ ability to transmit taste information, and/or to support taste bud maintenance (Oakley 1993; Miura et al. 2004; Oakley and Witt 2004).

Cancer therapies represent the largest category of taste-altering agents. A large majority of patients with head-and-neck cancer (HNC) are treated with targeted ionizing radiation that results in aguesia within weeks, followed by dysgeusia that can persist for months or years (Bolze et al. 1982; Chencharick and Mossman 1983; Nelson 1998; Maes et al. 2002; Ray-Chaudhuri et al. 2013; Irene et al. 2014). Additionally, an extensive list of chemotherapeutics used to treat a host of cancers lead to taste distortion or loss in large proportions of patients (e.g., see Vargas et al. 2017). Although the impact of cancer treatment on taste function is well recognized by clinicians and healthcare providers, little progress has been made on approaches to mitigate or prevent this debilitating side effect. This is in large part because it is difficult to ameliorate loss of taste if we understand so little mechanistically of how taste is maintained and how it is disrupted. Further, as there are so many different drugs and treatments that result in taste dysfunction, it is likely that maintenance of taste function is perturbed in a myriad of ways, depending upon the specific drug or treatment, yet a generally distorted sense of taste is the common complaint. Here we present examples of where we better understand how identifiable processes in taste bud renewal are regulated and discuss how specific cancer treatments perturb molecular regulators of discrete processes in taste regeneration. These studies reveal how the taste system can be “broken” by specific cancer treatments, shedding light on how we might devise approaches to “fix” taste dysfunction for patients.

Taste bud cells are continuously and reliably renewed

In mammals, taste buds are found on the tongue housed in epithelial specializations termed gustatory or taste papillae (Figure 1A). Fungiform taste papillae are distributed on the anterior tongue, and in rodents, each contains a single taste bud while multiple taste buds can be found in a single human fungiform papilla. Foliate and circumvallate taste papillae are larger, more complex structures that house hundreds of taste buds and are situated posteriorly. In rodents, the foliate papillae comprise inward-folding epithelial trenches on each side of the posterior tongue, while a single circumvallate papilla sits posteriorly at the lingual midline (Figure 1A). Additionally, taste buds are found in the soft palate and upper respiratory tract epithelium (Henkin and Christiansen 1967; Purves and Williams 2001). Each bud, regardless of location, is made up of a collection of roughly 50–100 cells that historically have been categorized into three morphological types: I, II, and III. Over the past decades, these morphological types have been further refined to reveal their correspondence to functional and molecularly distinct subsets that detect sweet, bitter, umami, sour, and salt stimuli, as well as a glial-like population. Briefly, subsets of Type II cells make up roughly 15–20% of taste bud cells, and are sensitive to sweet, bitter, or umami stimuli, based on the G-protein-coupled taste receptor expressed by an individual cell (Adler et al. 2000; Clapp et al. 2001; Nelson et al. 2001; Kim et al. 2003; Zhang et al. 2003; Oka et al. 2013), whereas Type III taste cells are sour detectors and are the least common taste cell type (Huang et al. 2006; 2008; Ma et al. 2007; Kataoka et al. 2008; Ohturo and Yoshii 2011; Oka et al. 2013; Lewandowski et al. 2016; Teng et al. 2019; Wilson et al. 2019). An additional taste cell population that responds to salt (sodium) has been identified in fungiform taste buds, which does not fit criteria of either Type II or III cells in terms of morphology or molecular markers (Nomura et al. 2020). Finally, Type I cells are thought to function as support cells within buds (Pumplin et al. 1997; Lawton et al. 2000; Bartel et al. 2006; Yang et al. 2020), and this population makes up roughly half of the differentiated cells in each taste bud. For a more detailed account of functional and morphological characteristics of these taste cell populations, please see the review by Finger and Barlow (2021).

All taste cells, regardless of function, continually turn over throughout life. In textbooks, each taste cell is reported to live for 10 days, such that every ~10 days all cells within each bud are new. However, this metric is based on early birth dating studies where median lifespan of 10 days was reported for taste bud cells; in fact, many cells were found to live as long as 4 weeks, which was the duration of the study (Beidler and Smallman 1965). More recent work has confirmed a longer lifespan specifically for Type II and III taste bud cells. In particular, Type II cells have a populational half-life of 8 days, whereas long-lived Type II cells were evident at 40 days. Overall, Type III cells are more long-lived with a populational half-life of 24 days, and many surviving for up to 40 days (Perea-Martinez et al. 2013). Because of technical limitations, assessing the longevity of Type I cells has been difficult. Nonetheless, a population of short-lived taste cells has been identified, which do not express markers of Type II or III taste cells, and thus may be Type I cells (Hamamichi et al. 2006; Perea-Martinez et al. 2013). These findings suggest that the receptor cells detecting sweet, bitter, umami, salt, and sour have significantly longer lifespans than the glial-like cell population; these Type I cells appear to renew at a pace similar to the non-taste epithelial cells of the tongue, which turn over every 3–6 days (Hume and Potten 1976; Hill 1988; Potten et al. 2002).

Both taste bud cells and non-taste epithelia are generated from adult stem cells resident in taste papillae. These basal keratinocytes are located at the basement membrane and divided to replace themselves as well as produce both taste and non-taste daughter cells (Figure 1B,C). In the circumvallate papilla, roughly 80% of progenitors are actively proliferating (Nguyen et al. 2012) to accommodate the rapid replacement of the much more abundant non-taste differentiated cells in each taste bud. For a more detailed account of functional and morphological characteristics of these taste cell populations, please see the review by Finger and Barlow (2021).
lifespans, that is, Type I > Type II > Type III (Miura et al. 2014). Thus, we have termed these SHH+ cells “post-mitotic taste pre-
cursor cells.”

In sum, lingual progenitors must maintain proliferation and
daughter cell generation to balance taste versus non-taste lineages with
vastly different lifespans as well as generate the proper ratio of the dif-
ferent taste cell types again with different longevities. How each of these
lineage decisions is deployed must be tightly regulated in order to main-
tain taste function; and each step of this lineage generation is likely sus-
ceptible to perturbation by subsets of different cancer treatments. Below

Figure 1. Anatomy of the tongue and taste cell renewal. (A) Taste buds (yellow) are embedded in taste papillae in the tongue epithelium. The number of taste buds in fungiform papillae, which are located in the anterior two-thirds of the tongue, is species-dependent; rodent fungiform papillae each contain a single taste bud while multiple taste buds can be found in a human fungiform papilla. Hundreds of taste buds line the trenches (epithelial invaginations) of foliate and circumvallate papillae in the posterior tongue. In human circumvallate papillae, taste buds are mostly found in the inner wall of the trench. Foliate papillae lie laterally while circumvallate papillae are organized in a central V-shaped formation. Rodents possess only a single circumvallate papilla. (B) Taste buds are made of 50–100 cells that are continually replaced throughout life. Progenitor cells (dark blue) reside along the basement membrane outside taste buds and actively divide to self-renew and produce taste cells and non-taste keratinocytes (light gray) that surround taste buds. Following mitosis, taste-fated lingual progenitors enter taste buds and specify into post-mitotic SHH+ taste precursor cells (magenta). Precursor cells then differentiate into most prevalent Type I glial-like cells (tangerine), Type II sweet/bitter/umami receptor cells (green), and least common Type III sour receptor cells (yellow). (C) Fate decision is regulated by the Wnt pathway, Hedgehog, and Notch signaling. The Wnt/β-catenin pathway controls all steps of taste and non-taste cell renewal, while SHH instructs progenitors to differentiate into taste cells. Notch signaling represses Type II cell fate via HES1 and transcriptionally represses ASCL1 to control Type III taste cell differentiation. Illustrations are modified from Servier Medical Art licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com/).
we discuss the impact of radiotherapy and specific chemotherapies on taste function in patients in the context of identified molecular and cellular regulators of taste cell renewal elucidated using animal models.

How is taste cell homeostasis impacted by cancer therapies?

Radiation therapies for HNCs

About 900,000 new cases of HNCs are reported annually worldwide, representing more than 5% of all cancers and leading to ~500,000 deaths (Bray et al. 2018). HNCs are treated with radiotherapy alone or in association with surgery and/or chemotherapy. Radiation therapy reduces tumor size by inducing DNA damage in dividing cells, leading to cell death (Surova and Zhivotovsky 2013; Wang 2019). The use of radiation in medical applications is more than a century old. The first documented use of radiotherapy to treat cancer dates back to 1896 and targeted radiotherapy for HNCs was made possible with the development of new X-ray irradiators in the 1920s and 1930s (Lederman 1981; Holsti 1995; Gianfaldoni et al. 2017). Efficacy of head-and-neck radiotherapy significantly improved in the second half of the 20th century with technological innovation and new treatment protocols (Cognetti et al. 2008). Patients receive daily fractionated X-ray doses of 1–2 Gy administered for up to 7 weeks (Deloch et al. 2016) via a variety of protocols, including volumetric modulated arc therapy, intensity-modulated radiation therapy, image-guided radiation therapy, and radiosurgery (Cognetti et al. 2008; Deloch et al. 2016; De Felice et al. 2018). These paradigms are designed to specifically target tumor sites and spare healthy tissues from radiation damage. However, HNC patients treated with radiotherapy suffer taste dysfunction associated with taste pore loss, suggestive of taste bud degeneration (Just et al. 2005; Deshpande et al. 2018). Noticeably, taste impairment is often accompanied by xerostomia (dry mouth) and mucositis (oral inflammation, ulceration, and blistering) resulting in difficulty chewing and swallowing, which contributes to reduced quality of life in patients (Bolze et al. 1982; Chencarick and Mossman 1983; Nelson 1998; Ray-Chaudhuri et al. 2013). Nonetheless, the extent of salivary dysfunction and of taste loss are not necessarily correlated (Temmel et al. 2005), suggesting that dysgeusia originates from direct effects on taste tissues. Importantly, taste disruption is prolonged in the months and years following the end of treatment suggesting that depleted taste buds do not fully regenerate after injury (Bolze et al. 1982; Chencarick and Mossman 1983; Nelson 1998; Maes et al. 2002; Ray-Chaudhuri et al. 2013; Irene et al. 2014; Deshpande et al. 2018; Barbosa da Silva et al. 2019; Chen et al. 2019). In addition to perturbed taste bud regeneration, authors have postulated that gustatory nerve damage and improper reinnervation may contribute to long-term taste distortion (Nelson 1998; Sandow et al. 2006; Barlow 2015; Deshpande et al. 2018). Because actively dividing cells are significantly affected by radiation, it has been assumed that like tumor cells, proliferating taste progenitor cells are primarily impacted by radiation, altering their ability to generate new taste cells. Mouse models have been instrumental to explore the mechanisms underlying radiation-mediated taste disruption. Exposing the head-and-neck region of mice to a single 8 Gy dose of radiation results in a dramatic reduction in proliferation of taste progenitors. Depletion of the progenitor population is associated with augmented cell death, resulting in a transient drop followed by a rapid recovery in the number of differentiated taste cells (Nguyen et al. 2012) and sensitivity to sweet (Jewkes et al. 2017). Although these studies provide exhaustive data about the behavior of irradiated taste progenitors in mice, a single dose of radiation does not mirror conventional fractionated radiotherapy for patients. Studies employing fractionated irradiation paradigms in mice report longer-lasting drops in proliferation and taste bud cell count (Dorr et al. 1994, 1996; Gaillard et al. 2019) compared with single-dose irradiation (Nguyen et al. 2012). Surprisingly, progenitor loss upon fractionated irradiation does not seem to result from cell death; we proposed that lower repeated doses may induce progenitors to prematurely differentiate or activate autophagy and senescence pathways (Gaillard et al. 2019). Altogether, these findings using rodent models show that the dose regimen is critical to trigger long-term taste loss, supporting variable degrees of taste impairment in patients who received different radiation doses (Chen et al. 2019).

Chemotherapies and targeted therapies

Dating back to the early 1900s, alkylating agents were developed as chemotherapies to induce DNA damage and subsequent cell death in quickly dividing cancer cells, but started to be widely used in the 1960s (DeVita and Chu 2008). Since the turn of the century, targeted therapies have been the center of attention with the promise of minimizing undesired side effects by developing small molecules and antibodies that target mutated or upregulated signaling pathways in cancers (Dobosz and Dzieciatkowski 2019; Bedard et al. 2020). Although more specific than chemotherapeutics, targeted therapies disrupt oncogenic molecular programs that may also be required for the maintenance of taste cell renewal, resulting in ageusia and dysgeusia.

Inhibition of the SHH signaling pathway

The Hedgehog (Hh) pathway is a key regulator of the development and homeostasis of multiple tissues (Varjosalo and Taipale 2008; Petrova and Joyner 2014). In the absence of Hh ligand, protein patched homolog (PTCH) binds the transmembrane protein Smoothened (SMO) inhibiting activation of the pathway. When SHH binds PTCH, SMO is released from PTCH inhibition, turning on transcription of Hh target genes including the GLI1 transcription factor and PTCH (Figure 2A); the latter then feeds back to reduce Hh signaling via resumed inhibition of SMO (Varjosalo and Taipale 2008; Petrova and Joyner 2014).

The Hh pathway is also activated in multiple types of cancer, including basal cell carcinoma (BCC), medulloblastoma, rhabdomyosarcoma, prostate, and lung cancers (Rubin and de Sauvage 2006). Inhibitors of SHH, SMO, and GLI1 have been tested to disrupt the Hh pathway in cancer tissues (Figure 2A; Carpenter and Ray 2019). Small molecule inhibitors of SMO, Vismodegib and Sonidegib, are currently used for the treatment of BCC (Carpenter and Ray 2019) and are undergoing multiple clinical trials to treat other types of malignancies (Girardi et al. 2019). Dysgeusia is among the most prevalent side effects reported in patients treated with these SMO antagonists (LoRusso et al. 2011; Sekulic et al. 2012; Tang et al. 2012; Rodon et al. 2014; Basset-Seguin et al. 2015; Le Moigne et al. 2016) and occasionally leads to treatment discontinuation (Basset-Seguin et al. 2015). Noticeably, gustatory function recovers when the treatment is halted (Tang et al. 2012). Dysgeusia appears within weeks of BCC treatment initiation, suggesting that taste bud maintenance is disrupted (Tang et al. 2012).

Expression analysis data from rodents have long supported a role for the Hh pathway in adult taste cell renewal. In adult mouse tongue, SHH is expressed by post-mitotic precursor (Type IV) cells within taste buds, whereas PTCH and GLI1 are expressed by taste progenitors outside of taste buds (Figure 1; Miura et
This arrangement led to the testable idea that signaling from SHH+ precursor cells regulates renewal of taste receptor cells from taste progenitors, but left open the specific aspects of renewal that might depend on Hh signaling (Miura et al. 2001, 2004, 2014; Liu et al. 2013). Genetic gain-of-function (GOF) and loss-of-function (LOF) studies have revealed the pathway is required for taste bud differentiation from lingual progenitors, independent of an impact on progenitor proliferation (Castillo et al. 2014; Ermilov et al. 2016; Castillo-Azofeifa et al. 2017, 2018).

Similar to results from Hh pathway LOF studies, taste buds progressively shrink and are lost within 2–3 weeks in mice treated with a SMO inhibitor (Kumari et al. 2015, 2017, 2018; Castillo-Azofeifa...
et al. 2017); further, all taste cell types are depleted (Yang et al. 2015; Kumari et al. 2017), consistent with SHH promotion of differentiation of Type I, II, and III taste cells (Castillo et al. 2014). In addition, gustatory signals in the seventh cranial nerve are virtually abolished within ~2 weeks of treatment (Kumari et al. 2015, 2017, 2018). Similar to patients, drug withdrawal results in taste function recovery via taste bud regeneration and restoration of gustatory nerve signals (Kumari et al. 2017). The mechanisms of action of SMO inhibitors in the taste system remain under debate, specifically whether SMO inhibition hinders proliferation or differentiation of taste tissues. Proliferation was unchanged in taste papillae of mice treated for up to 21 days with one SMO inhibitor (Castillo-A佐ofeira et al. 2017), while it was reduced in other reports using a different antagonist (Kumari et al. 2015, 2017, 2018). However, genetic constitutive expression of SHH in lingual progenitors induces taste bud differentiation (Castillo et al. 2014), supporting a model where SMO antagonists cause taste loss by inhibiting taste cell differentiation rather than progenitor proliferation.

**Inhibition of Wnt/β-catenin pathway components**

Wnt/β-catenin is a major developmental pathway that controls embryonic development and tissue homeostasis (Clevers 2006; Nusse and Clevers 2017). WNTs comprise a family of 19 secreted ligands that are processed in signal-producing cells by PORCN, a palmitoleoyl transferase (Nusse and Clevers 2017). Secreted WNTs bind to Frizzled (FZD) receptors and low-density lipoprotein receptor-related protein (LRP) co-receptors at the cell membrane of signal-receiving cells (Figure 2B). In the absence of ligand, the degradation complex keeps cytosolic β-catenin levels low. Specifically, GSK3β phosphorylates β-catenin, leading to the latter's degradation. Upon WNT binding to FZD, the destruction complex is dismantled, and β-catenin accumulates and translocates to the nucleus where it complexes with transcription factors to activate Wnt target gene expression (Figure 2B).

Dysregulation of the Wnt/β-catenin pathway is associated with multiple types of cancer, including colorectal, pancreatic, and breast cancers (Jung and Park 2020), making it a target of interest for therapeutic applications. Different approaches to inhibit (1) the secretion of Wnt ligands, (2) ligand/receptor interaction, or (3) intracellular signaling are currently in clinical trials (Figure 2B; Takebe et al. 2015; Siebel and Lendahl 2017). A wide array of drugs has been developed to inhibit Notch signaling and reduce tumorigenesis (Takebe et al. 2015). Gamma-secretase inhibitors (GSI) tested in clinical trials aim to broadly block the Notch pathway by inhibiting the cleavage of Notch receptors and subsequent intracellular signaling (Figure 2C). Unsurprisingly, GSI treatments result in dysgeusia in cancer patients (Lee et al. 2015; Massard et al. 2018; Even et al. 2020); The Notch pathway is active in taste tissues of mice (Seta et al. 2003, 2006, 2011; Hsu et al. 2020) and zebra fish (Kapsimali et al. 2011) and has been implicated in sour cell fate decision by controlling the expression (Figure 2C). Unsurprisingly, GSI treatments result in dysgeusia in cancer patients (Lee et al. 2015; Massard et al. 2018; Even et al. 2020); The Notch pathway is active in taste tissues of mice (Sota et al. 2003, 2006, 2011; Kapsimali et al. 2011; Kito-Shingaki et al. 2014; Hsu et al. 2020). In addition, a Notch target gene, Hes1, restricts the development of Type II taste cells as HES1-null mice produce more Type II cells in late mouse embryos and new-born pups (Ota et al. 2009). Taste cell balance is also shifted in taste organoids treated with GSI; γ-secretase inhibition results in more Type II and III taste cells and fewer Type I cells (Ren et al. 2017). Altogether, mouse data support the importance of targeting Notch pathway elements that are more prevalent in cancer tissues than healthy cells to minimize taste disruption.

**Targeting the Notch pathway in cancer treatment**

Other signaling pathways are associated with the development of various cancers. For instance, the Notch pathway is abnormally active in forms of lung, liver, brain, and breast cancers (Takebe et al. 2015; Siebel and Lendahl 2017). A wide array of drugs has been developed to inhibit Notch signaling and reduce tumorigenesis (Takebe et al. 2015). Gamma-secretase inhibitors (GSI) tested in clinical trials aim to broadly block the Notch pathway by inhibiting the cleavage of Notch receptors and subsequent intracellular signaling (Figure 2C).

**Taste organoids as a high-throughput drug screening tool**

We reviewed different cancer therapies that cause dysgeusia and highlighted the importance of characterizing the function of potential molecular targets in taste bud cell renewal to develop drugs with reduced side effects. In addition to radiotherapy and targeted therapies inhibiting the Wnt, Hh, and Notch pathways, a multidude of therapies target other critical developmental signals. For example, more than 25 tyrosine kinase inhibitors (TKIs) inhibit a variety of protein tyrosine kinases activated in certain cancers (Jiao et al. 2018; Wing Tung Ho et al. 2019). Taste impairment has been reported for a number of them, including in the treatment of metastatic renal
cell carcinoma (van der Werf et al. 2017; Vigarios et al. 2017). The advent of next-generation genomic and proteomic tools, including single-cell RNA sequencing and proteomics, offers incredible opportunities to explore the expression of this multitude of targets at single-cell resolution in healthy and diseased tissues. However, animal models remain a costly and time-consuming tool to screen the side effects of so many drugs in development. Further, to date, no immortalized taste cell line is available. Alternatively, taste organoids have become common in taste biology (Ren et al. 2014, 2017, 2020; Aihara et al. 2015; Qin et al. 2018; Guo et al. 2019; Matsumoto et al. 2019; Takai et al. 2019; Feng et al. 2020; Lin et al. 2021) and offer high-throughput drug screening possibilities. Murine taste organoids can be generated in multi-well plates from single cells isolated from whole taste papillae or from discrete taste stem cell populations such as Lgr5+ progenitor cells (Figure 1C; Ren et al. 2014, 2017). Single taste stem cells incubated in the right culture media proliferate and produce taste cell-replete organoids within 10 days (Ren et al. 2014, 2017). Quick generation of taste organoids in large numbers makes these organoids a promising model to address the effect of a multitude of injuries (Feng et al. 2020), including cancer therapies on taste bud cell renewal (Ren et al. 2017; Guo et al. 2019). Taste organoids allow screening of cancer therapies for impacts on taste stem cell proliferation and survival, taste cell differentiation and function (e.g., calcium imaging), and could be co-cultured with gustatory neurons to reproduce in vivo nerve inputs in organoid generation, as reported in other systems (Pastula et al. 2016; Chukwurah et al. 2019).

Within the past decades, the fight against cancer has been marked by significant progress with early detection and development of state-of-the-art technologies and protocols that maximize cure and survival rates. As much as modern therapies are targeted, side effects remain common and are occasionally detrimental to the course of the treatment. For instance, patients can experience taste impairment that is so unbearable that treatment must be paused. Thus, there is a need for more comprehensive investigations of potential side effects of anticancer therapies on the peripheral taste system upstream of clinical trials. The recent developments in taste organoid culture will speed up the process, and combined with in vivo and next-generation molecular tools, will help design more effective therapies.

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**Conflict of interest**

The authors declare no competing interests.

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