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RHINOLOGY: TASTE AND SMELL DISORDERS (C PHILPOTT, SECTION EDITOR)

Novel Therapies in Olfactory Disorders

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Abstract
Purpose of Review To summarize and critically review the recent literature on novel treatments for olfactory disorders (OD).
Recent Findings Emerging therapies in the management of OD include multiple vitamins and supplements, biologics, neuromodulators, and intranasal agents. There is also an active investigation into treatments that harness the neuroregenerative properties of the olfactory epithelium, such as platelet-rich plasma and stem cell transplantation.
Summary Successful management of OD is multimodal and tailored to the underlying etiology. As the findings of further investigations accrue, the management of OD will undoubtedly continue to be advanced and refined, and likely harness the intrinsic neuroregenerative properties of the olfactory system.

Keywords Olfaction · Olfactory loss · Olfactory dysfunction · Olfactory disorders · Smell loss

Introduction

The frontiers in treatment for olfactory dysfunction (OD) are as broad and exciting now as they have ever been. While advances in the treatment of olfactory disorders have been building over the last few decades, the COVID-19 pandemic has bolstered a new wave of interest in the treatment of smell dysfunction among not only the scientific community but also the public zeitgeist worldwide. As a result, there has been a surge in recent data regarding new treatments for olfactory disorders that can serve to augment the established pillars of olfactory training and intranasal corticosteroids [1••, 2–5]. Here we discuss several emerging therapeutics for olfactory disorders.

Biological Agents

In chronic rhinosinusitis with nasal polyps (CRSwNP), inflammatory mediators acting at the olfactory epithelium have been implicated in the olfactory loss. In CRSwNP, interleukin (IL)-5 is present at elevated levels within the mucus of the olfactory cleft, and IL-5 levels are significantly associated with the severity of OD [6]. With the increasing role of biologics that target these inflammatory mediators in the management of CRSwNP, evidence of their efficacy in managing olfactory loss related to CRSwNP is also increasing.

Dupilumab, a monoclonal antibody against IL-4 and IL-13, has been demonstrated in RCT-level data to have significant improvement in UPSIT scores at 12, 24, and 52 weeks compared with placebo in patients with CRSwNP [7, 8]. Omalizumab, a monoclonal antibody against IgE, also demonstrates significant improvement in UPSIT scores at weeks 8 and 24 when compared with a placebo [9]. Interestingly, mepolizumab, a monoclonal antibody against IL-5, has not been shown to have significant improvement in olfactory outcomes compared with placebo, despite improving other clinical endpoints for CRS [10, 11]. Biologics may be an important tool in the near future in the management of CRS-related OD, with further study needed to better refine indications and patient selection.

Vitamins and Supplements

Numerous vitamins and supplements have been investigated in the management of OD and may represent important, accessible treatment adjuncts that assist the neuroregenerative properties of the olfactory epithelium. It should be noted; however, that the existing studies are of varying quality and quite heterogeneous in nature.

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Omega-3

Omega-3 fatty acids play an important role in lipid metabolism and have additional anti-inflammatory and antioxidant properties. Omega-3 supplements have been shown to have neuroprotective effects in diseases such as Alzheimer's disease or diabetic neuropathy [12, 13], and in rat models have been shown to improve performance in olfactory-cued tasks [14].

An Australian population study found that older adults with a high consumption of omega-3 fatty acids in their diet had lower odds of OD [15]. The benefit of omega-3 supplementation has also been investigated in the post-surgical setting in a recent double-blinded–placebo-controlled RCT [16]. Following endoscopic skull base surgery, patients that took omega-3 (1000 mg twice daily) experienced significantly higher UPSIT scores at 3 months and 6 months postoperatively [16]. While promising, additional studies are warranted to investigate the role of omega-3 in OD outside of the postsurgical setting.

Vitamin A

Vitamin A is thought to play a role in the regeneration of olfactory receptor neurons, yet its role in the treatment of OD is currently questionable, with the need for higher-quality studies. Intranasal vitamin A with OT has been shown in a retrospective study to improve olfactory discrimination for all etiologies of OD, with the greatest improvements seen in the post-infectious OD group [17]. There is currently a double-blinded–placebo-controlled trial underway investigating the efficacy of intranasal drops of vitamin A for post-viral olfactory loss, which will assess both olfactory outcomes as well as volumetric change in the olfactory bulb on MRI [18].

Systemic vitamin A has not been shown to have benefit, as a double-blinded–placebo-controlled RCT found that vitamin A (10,000 ug daily for 12 weeks) did not demonstrate any improvement in olfactory scores [19].

Zinc

Zinc is an essential element for enzymes that participate in cell division and proliferation and may have a potential role in the maintenance of the olfactory epithelium. Specifically, in the setting of post-traumatic anosmia, oral zinc gluconate (10 mg three times per day) has been shown to have improvements in olfactory threshold testing [20]. However, in a study of post-chemotherapy OD, oral zinc had no benefit and even a trend toward worsening in the zinc group compared to placebo [21]. Similar to vitamin A, perhaps more study is needed before establishing the use of zinc for other etiologies of OD. Clinicians considering oral zinc supplementation for OD should be aware of the potential adverse effects, including gastric distress, neutropenia, and iron deficiency anemia. It should be noted that intranasal zinc is recommended *against* for the treatment of OD, as it has been shown to have potentially irreversible damage to olfaction function [1••, 22].

Toki-shakuyaku-san (TSS)

TSS is a Japanese herbal medicine with anti-inflammatory and immunomodulatory properties used to treat a multitude of diseases across the gynecological, gastrointestinal, and neurological systems. There is low-level evidence in the form of retrospective case serieses to suggest that oral TSS can also improve olfactory recovery in post-infectious OD, with reported rates of recovery ranging from 43–77% [23, 24]. Prospective, controlled studies are needed to better evaluate the efficacy of TSS in the management of OD.

Sodium Citrate

Free calcium in the olfactory epithelium may act to inhibit the processing of olfactory signals; therefore, it is thought that the introduction of a buffering solution such as sodium citrate to reduce free calcium may improve OD. Intranasal delivery of sodium citrate has shown early promise in the management of OD, particularly in the post-infectious setting, as two prospective trials showed improvements, albeit temporary, in olfactory outcomes following the administration of sodium citrate [25, 26]. In a study of 55 patients comparing 9% sodium citrate intranasal spray to sterile water, sodium citrate demonstrated significant improvement in olfactory threshold lasting up to 120 min after application, and the treatment response rate was 33% compared to 0% in the control group [26]. It should be noted that existing studies demonstrate olfactory benefit in the relatively short term following sodium citrate administration (on the magnitude of minutes to hours), and that it does not appear useful in terms of permanent or long-term efficacy. However, sodium citrate may still provide a useful therapy for patients in the time period when they are preparing to eat and enjoy their food and drink.

Insulin

Insulin receptors are present throughout the central nervous system, including the olfactory bulb, though their specific function in olfaction is not well understood. There

is some data to suggest that intranasal insulin may have a benefit in improving olfactory threshold. A pilot study found of 10 patients with post-infectious OD found a very small threshold improvement in 60% of patients [27]. In a placebo-controlled RCT of 36 patients with undifferentiated OD (18 in each treatment arm), patients underwent olfactory cleft placement of gel foam soaked with insulin versus placebo twice weekly for 4 weeks; intranasal insulin demonstrated a very slight improvement in the olfactory threshold, without significantly changing serum insulin or glucose levels [28].

Neuromodulators

There is very little evidence regarding the management of parosmia/phantosmia, with the majority of existing studies as level 3 or level 4 evidence [29•]. However, there is an urgent and increasing need for treatments with the rise of parosmia/phantosmia associated with COVID-19 [30]. Neuromodulating agents with antipsychotic, antiseizure, and/or antimigranous properties such as haloperidol, topiramate, verapamil, gabapentin, and nortriptyline may have some benefit in preliminary studies assessing parosmia/phantosmia [29•, 31, 32]. Preliminary data also suggests that gabapentin may improve COVID-19 related parosmia, where 5 of 9 patients experienced significant improvements in UPSIT scores [33]. It should be noted; however, that 2 of these 9 patients had to discontinue gabapentin due to adverse effects. Given the potentially significant side effects of these neuromodulating agents, the further rigorous study is certainly needed to evaluate their risk and benefit, and close monitoring of patients prescribed these medications is warranted.

Platelet Rich Plasma

Platelet-rich plasma (PRP) is an autologous blood product that has both anti-inflammatory and pro-regenerative properties, used in many inflammatory and neuropathic conditions. In anosmic mouse models, topical application of PRP in the olfactory cleft induced significantly more growth in olfactory epithelium thickness and exhibited less epithelial damage compared to saline application [34]. There have been two pilot single-arm studies investigating the efficacy of intranasal PRP for OD in humans, and although relatively small, these early studies are promising. In a study of 5 patients where PRP was injected into the olfactory groove 4 times over the course of 7 months, 4 patients recovered subjective olfaction and had a mean improvement from a pretreatment score of 0.19–4.92 out of 10 [35]. Another study of 7 patients performed a single injection of PRP and found significant improvements in TDI score in patients starting with hyposmia ($16 < TDI < 30$), while those starting with anosmia ($TDI < 16$) did not have significant improvement [36•]. A recent randomized placebo-controlled trial demonstrated that PRP injections into the olfactory cleft can have significant improvements in olfactory threshold and discrimination for COVID-19-related olfactory loss [37]. In this RCT of 26 patients, 8 of 14 (57.1%) patients treated with PRP achieved clinically meaningful improvement ($\Delta > 5.5$ points) in Sniffin' Sticks testing compared to 1 of 12 (8.3%) placebo subjects (adjusted odds ratio 19.2, 95% CI 1.3–291, $p = 0.03$), without any adverse effects noted.

Electrostimulation

Electrical stimulation therapy represents another novel area of exploration in the treatment of OD, as it has been shown to help nerve regeneration in other conditions such as traumatic brain injury and peripheral neuropathy [38, 39]. In a pilot study of 5 patients with OD following endoscopic sinus surgery, electrical stimulation delivered through electrodes positioned at the lateral lamella of the cribiform induced subjective smell perception in 3 patients [40•]. The senior author (ZMP) is also carrying out translational studies evaluating electrical stimulation to the olfactory system via other mechanisms. While additional more rigorous studies are needed to validate and correlate subjective smell perception with objective electrophysiologic findings, the results of these studies suggest that electrostimulation may be a potential treatment option for OD in the future.

Stem Cell Therapy

The olfactory epithelium is uniquely one of the few sites of the human body where neurogenesis continues into adulthood. This is thought to be mediated by two populations of stem cells: globose basal cells (GBCs), which actively replace cells in the olfactory epithelium, and horizontal basal cells (HBCs), which are dormant cells whose differentiation into GBCs is activated following acute epithelial injury [41]. There is an early but promising investigation being performed in harnessing the regenerative properties of these stem cells in the olfactory epithelium for the treatment of OD. GBCs have been successfully cultured [42, 43], and recently, the ability to culture HBCs from the human olfactory epithelium has been established [44•]. This has given investigators the opportunity to better understand molecular mechanisms driving multipotency as well as the ability to test stem cell potency via

transplantation. In mouse models of anosmia induced by olfactotoxic gas methyl bromide, HBCs transplantation yielded multiple cell types in the olfactory epithelium, including neuronal cells with apical processes and sustentacular cells, demonstrating that the multipotency of stem cells can be maintained through transplantation [44•]. An additional mouse study found that intranasal delivery of GBCs via intranasal drops induced new olfactory neuron formation in the olfactory bulb and restored food-smelling behaviors [45]. Further validation in animal models is needed, and no testing of olfactory progenitors has been performed yet in humans. Nonetheless, therapeutic strategies that harness the unique regenerative property of the olfactory system may be promising avenues in the future of olfactory loss treatment.

Conclusions

OD is complex in nature, as there are multiple etiologies, clinical manifestations, and varying prognoses to treatments. In general, successful management of OD is multimodal and tailored to the underlying etiology and clinical nature of the OD. While olfactory training and intranasal corticosteroids serve as the foundational regimen in the management of OD, there may be opportunities to improve benefit in through the emerging therapies discussed here. Future potential avenues in the management of OD will likely harness the neuroregenerative properties of the olfactory system. While meaningful progress has been made in understanding OD over the last 2 decades, there remains a tremendous amount to learn and refine in the treatment of OD. Knowledge in the management of OD will undoubtedly continue to accelerate with more intriguing discoveries in the coming years.

Declarations

Conflict of Interest Michael T. Chang declares that he has no conflict of interest. Zara M. Patel reports royalties or licenses from Springer and Wolters Kluwer; consulting fees from Medtronic, Wyndly, Dianosic, Ethicon/Johnson & Johnson, Mediflix, and Consumer Medical; patent pending (S15-465 63/076,656 [S31-06935.PRO]); participation on a Data Safety Monitoring Board or Advisory Board for Optinose and Regeneron/Sanofi; and stock or stock options for Olfera Therapeutics.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Patel ZM, Holbrook EH, Turner JH, et al. International consensus statement on allergy and rhinology: Olfaction. Int Forum Allergy Rhinol. 2022;12(4):327–680. https://doi.org/10.1002/alr.22929. **This newly published international consensus statement on olfaction from multidisciplinary experts summarizes the existing evidence regarding the clinical management of olfactory disorders.**
2. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory training in patients with olfactory loss. Laryngoscope. 2009;119(3):496–9. https://doi.org/10.1002/lary.20101.
3. Liu DT, Pellegrino R, Sabha M, et al. Factors associated with relevant olfactory recovery after olfactory training: a retrospective study including 601 participants. Rhinology. Published online September 9, 2020. https://doi.org/10.4193/Rhin20.262
4. Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2020;10(9):1065–86. https://doi.org/10.1002/alr.22624.
5. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. Int Forum Allergy Rhinol. 2018;8(9):977–81. https://doi.org/10.1002/alr.22140.
6. Schlosser RJ, Mulligan JK, Hyer JM, Karnezis TT, Gudis DA, Soler ZM. Mucous cytokine levels in chronic rhinosinusitis-associated olfactory loss. JAMA Otolaryngol Head Neck Surg. 2016;142(8):731–7. https://doi.org/10.1001/jamaoto.2016.0927.
7. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA. 2016;315(5):469–79. https://doi.org/10.1001/jama.2015.19330.
8. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638–50. https://doi.org/10.1016/S0140-6736(19)31881-1.
9. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146(3):595–605. https://doi.org/10.1016/j.jaci.2020.05.032.
10. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9(10):1141–53. https://doi.org/10.1016/S2213-2600(21)00097-7.
11. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. J Allergy Clin Immunol. 2017;140(4):1024-1031.e14. https://doi.org/10.1016/j.jaci.2017.05.044.

12. Canhada S, Castro K, Perry IS, Luft VC. Omega-3 fatty acids' supplementation in Alzheimer's disease: a systematic review. Nutr Neurosci. 2018;21(8):529–38. https://doi.org/10.1080/1028415X.2017.1321813.
13. Lewis EJH, Perkins BA, Lovblom LE, Bazinet RP, Wolever TMS, Bril V. Effect of omega-3 supplementation on neuropathy in type 1 diabetes: a 12-month pilot trial. Neurology. 2017;88(24):2294–301. https://doi.org/10.1212/WNL.0000000000004033.
14. Hichami A, Datiche F, Ullah S, et al. Olfactory discrimination ability and brain expression of c-fos, Gir and Glut1 mRNA are altered in n-3 fatty acid-depleted rats. Behav Brain Res. 2007;184(1):1–10. https://doi.org/10.1016/j.bbr.2007.06.010.
15. Gopinath B, Sue CM, Flood VM, Burlutsky G, Mitchell P. Dietary intakes of fats, fish and nuts and olfactory impairment in older adults. Br J Nutr. 2015;114(2):240–7. https://doi.org/10.1017/S0007114515001257.
16. Yan CH, Rathor A, Krook K, et al. Effect of omega-3 supplementation in patients with smell dysfunction following endoscopic sellar and parasellar tumor resection: a multicenter prospective randomized controlled trial. Neurosurgery. 2020;87(2):E91–8. https://doi.org/10.1093/neuros/nyz559.
17. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. Eur Arch Otorhinolaryngol. 2017;274(7):2819–25. https://doi.org/10.1007/s00405-017-4576-x.
18. Kumarisan K, Bengtsson S, Sami S, et al. A double blinded randomised controlled trial of vitamin a drops to treat post-viral olfactory loss: study protocol for a proof-of-concept study for vitamin a nasal drops in post-viral olfactory loss.https://assets.researchsquare.com/files/rs-1587149/v1_covered.pdf?c=1656513062. Published June 29, 2022.
19. Reden J, Lill K, Zahnert T, Haehner A, Hummel T. Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope. 2012;122(9):1906–9. https://doi.org/10.1002/lary.23405.
20. Jiang RS, Twu CW, Liang KL. Medical treatment of traumatic anosmia. Otolaryngol Head Neck Surg. 2015;152(5):954–8. https://doi.org/10.1177/0194599815571272.
21. Lyckholm L, Heddinger SP, Parker G, et al. A randomized, placebo controlled trial of oral zinc for chemotherapy-related taste and smell disorders. J Pain Palliat Care Pharmacother. 2012;26(2):111–4. https://doi.org/10.3109/15360288.2012.676618.
22. Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. Altern Ther Health Med. 2006;12(1):34–8.
23. Uchida J, Furuta A, Suzaki H. Kampo treatment on the cases of olfactory dysfunction. Otorhinolaryngol Neurosci. 2009;23:20–1.
24. Ogawa T, Nakamura K, Yamamoto S, Tojima I, Shimizu T. Recovery over time and prognostic factors in treated patients with post-infectious olfactory dysfunction: a retrospective study. Ann Otol Rhinol Laryngol. 2020;129(10):977–82. https://doi.org/10.1177/0003489420922563.
25. Whitcroft KL, Ezzat M, Cuevas M, Andrews P, Hummel T. The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients. Clin Otolaryngol. 2017;42(3):557–63. https://doi.org/10.1111/coa.12789.
26. Philpott CM, Erskine SE, Clark A, et al. A randomised controlled trial of sodium citrate spray for non-conductive olfactory disorders. Clin Otolaryngol. 2017;42(6):1295–302. https://doi.org/10.1111/coa.12878.
27. Schöpf V, Kollndorfer K, Pollak M, Mueller CA, Freiherr J. Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: a pilot study. Rhinology. 2015;53(4):371–8.
28. Rezaeian A. Effect of intranasal insulin on olfactory recovery in patients with hyposmia: a randomized clinical trial. Otolaryngology-Head and Neck Surgery. 2018;158(6):1134–9.
29.• Saltagi MZ, Rabbani CC, Ting JY, Higgins TS. Management of long-lasting phantosmia: a systematic review. In: International Forum of Allergy & Rhinology. Vol 8. Wiley Online Library; 2018:790–796. **This systematic review summarizes the available evidence for medical and surgical treatments for parosmia and phantosmia.**
30. Campbell M, Hopkins C, Smith B, Kelly C, Deary V. Altered smell and taste: anosmia, parosmia and the impact of long Covid-19. Plos one. 2021;16(9).
31. Coleman ER, Grosberg BM, Robbins MS. Olfactory hallucinations in primary headache disorders: case series and literature review. Cephalalgia. 2011;31(14):1477–89.
32. Morrissey DK, Pratap U, Brown C, Wormald PJ. The role of surgery in the management of phantosmia. Laryngoscope. 2016;126(3):575–8.
33. Cho DY, Pena-Garcia J, Woodworth B. Gabapentin for COVID-19 induced parosmia. Presented at: American Rhinologic Society, 68th Annual Meeting; September 10, 2022; Philadelphia, PA.
34. Yasak AG, Yigit O, Araz Server E, Durna Dastan S, Gul M. The effectiveness of platelet-rich plasma in an anosmia-induced mice model. Laryngoscope. 2018;128(5):E157–62. https://doi.org/10.1002/lary.27029.
35. Mavrogeni P, Kanakopoulos A, Maihoub S, Krasznai M, Szirmai A. Anosmia treatment by platelet rich plasma injection. Int Tinnitus J. 2017;20(2):102–5. https://doi.org/10.5935/0946-5448.20160019.
36.• Yan CH, Mundy DC, Patel ZM. The use of platelet-rich plasma in treatment of olfactory dysfunction: a pilot study. Laryngoscope Investig Otolaryngol. 2020;5(2):187–93. https://doi.org/10.1002/lio2.357. **This pilot study suggests potential benefit in olfactory outcomes with direct injection of the olfactory epithelium with platelet-rich plasma.**
37. Yan CH, Patel, Zara M. Platelet-rich plasma for COVID-19 smell loss, a randomized controlled trial. Presented at: American Rhinologic Society, 68th Annual Meeting; September 8, 2022; Philadelphia, PA.
38. Shin SS, Dixon CE, Okonkwo DO, Richardson RM. Neurostimulation for traumatic brain injury. J Neurosurg. 2014;121(5):1219–31. https://doi.org/10.3171/2014.7.JNS131826.
39. Willand MP, Nguyen MA, Borschel GH, Gordon T. Electrical stimulation to promote peripheral nerve regeneration. Neurorehabil Neural Repair. 2016;30(5):490–6. https://doi.org/10.1177/1545968315604399.
40.• Holbrook EH, Puram SV, See RB, Tripp AG, Nair DG. Induction of smell through transethmoid electrical stimulation of the olfactory bulb. Int Forum Allergy Rhinol. 2019;9(2):158–64. https://doi.org/10.1002/alr.22237. **This pilot study provides a proof of concept that olfaction may be able to be recapitulated through electrical stimulation of the olfactory epithelium.**
41. Schwob JE, Jang W, Holbrook EH, et al. Stem and progenitor cells of the mammalian olfactory epithelium: taking poietic license. Journal of Comparative Neurology. 2017;525(4):1034–54.
42. Goldstein BJ, Goss GM, Hatzistergos KE, et al. Adult c-Kit (+) progenitor cells are necessary for maintenance and regeneration of olfactory neurons. Journal of Comparative Neurology. 2015;523(1):15–31.
43. Beites CL, Kawauchi S, Crocker CE, Calof AL. Identification and molecular regulation of neural stem cells in the olfactory epithelium. Exp Cell Res. 2005;306(2):309–16. https://doi.org/10.1016/j.yexcr.2005.03.027.

44.• Peterson J, Lin B, Barrios-Camacho CM, et al. Activating a reserve neural stem cell population in vitro enables engraftment and multipotency after transplantation. Stem Cell Reports. 2019;12(4):680–95. **This study establishes the ability to reliably culture horizontal basal cells and maintain their multipotency in transplantation into a mouse olfactory epithelium.**
45. Kurtenbach S, Goss GM, Goncalves S, et al. Cell-based therapy restores olfactory function in an inducible model of hyposmia. Stem cell reports. 2019;12(6):1354–65.