Received: 7 July 2022 | Revised: 6 October 2022 | Accepted: 9 October 2022

DOI: 10.1002/lio2.952

REVIEW

Laryngoscope Investigative Otolaryngology

# The current status of nanotechnological approaches to therapy and drug delivery in otolaryngology: A contemporary review

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## Abstract

**Objectives/Hypothesis:** To summarize the current standing of nanomedicine-based technology, particularly nanoparticles (NPs), for drug delivery and diagnostic mechanisms in otolaryngology and the otolaryngology subspecialties.

**Methods:** Literature searches were performed using PubMed and Ovid MEDLINE from 2010 to 2022. The search focused on original articles describing developments and applications of nanotechnology and drug delivery in otology, neurotology, cranial base surgery, head and neck oncology, laryngology, bronchoesophagology, and rhinology. Keyword searches and cross-referencing were also performed. No statistical analysis was performed.

**Results:** The PubMed search yielded 29 articles, and two Ovid MEDLINE searches both yielded 7 and 26 articles, respectively. Cross-referencing and keyword searches in PubMed and Google Scholar yielded numerous articles. The results indicate that currently, NPs are the most thoroughly studied nanotechnology for drug delivery and therapy in otolaryngology. Organic NPs have been utilized for drug delivery in otology and head and neck oncology due to their high biocompatibility. Inorganic NPs have similarly been utilized for drug delivery. However, inorganic NPs seem to be studied less extensively in these fields, likely due to an increased risk for heavy metal toxicity. Due to their magnetic properties, inorganic NPs have been utilized for magnetic-guided delivery in otology and thermoradiation and magnetic resonance imaging in head and neck oncology. Applications of nanotechnology to the fields of laryngology, bronchoesophagology, and rhinology have been studied less compared with otology and head and neck oncology. However, researchers have primarily employed NPs and other nanotechnologies such as nanofibers and nanoclusters for drug elution at mucosal surfaces to reduce airway and nasal inflammation.

**Conclusions:** Nanomedicine offers potential benefits in the treatment of patients in the field of otolaryngology due to enhanced control over drug release, cell-specific targeting, and the potential to reduce drug toxicity. Future work is needed to ensure the safety of these therapies to integrate this field of research into human therapies.

KEYWORDS
drug delivery, head and neck, laryngology, nanomedicine, nanoparticles, nanotechnology, otolaryngology, otology/neurotology

## 1 | INTRODUCTION

In recent decades, researchers have worked to advance "precision medicine" to help clinicians tailor care to the individual patient. Nanotechnology is a field of research that promotes individualized patient care with a focus on the nanoscale interactions within a system at a scale between ~1 and 300 nm. At this level, the properties of matter differ greatly from those with microscopic and particulate dimensions. Through an understanding of the principles governing these interactions, clinicians and researchers can control the macroscopic properties of a system.[1,2] Nanomedicine describes the application of these technologies to diagnose and treat patients at the molecular level.[3]

The unique properties of nanomaterials and nanoparticles (NPs) offer promising applications to patient care. Due to their small size, NPs can cross biological barriers that are otherwise inaccessible to traditional therapies. Other benefits include improved drug delivery and tissue specificity in the context of nanomaterial delivery systems. Finally, given their largely modifiable surface area, charge, and size, nanomaterials can be utilized for diagnostic purposes, often due to their unique light-scattering properties.[4]

Of the surgical subspecialties, otolaryngology is particularly suited to benefit from nanotechnological advances. Both the anatomy of the head and neck and the blood-labyrinth barrier impede drug delivery. Nanomedicine, including novel treatments, delivery mechanisms, and in vivo imaging, may overcome these complications by allowing for controlled release and targeted therapy.[5–8] Finally, systemic toxicity of modern chemotherapies and immunotherapies may be reduced by targeted therapy.[8]

Although articles have summarized the role of nanotechnology in the field of otolaryngology,[3,9,10] some time has passed since the last contemporary review. The purpose of this article is to describe the current standing of nanotechnology relating to drug delivery and diagnostic mechanisms in otolaryngology and the otolaryngological subspecialties.

## 2 | METHODS

A review of published studies and ongoing otolaryngological research involving nanomedicine and drug delivery was performed using PubMed, Ovid MEDLINE, and Google Scholar from January 2010 through May 2022. Our specific aim was to assess the standing of nanomedicine and nanotechnology involved in drug delivery mechanisms in the current otolaryngology literature. Keyword searches in Google Scholar and PubMed were also performed.

### 2.1 | Definitions and search strategies

The following search was performed on PubMed between 2010 and 2022: ((otolaryngology[MeSH Terms]) OR (otorhinolaryngology[MeSH Terms]) OR (laryngology[MeSH Terms]) OR (otology[MeSH Terms]) OR (cranial base[MeSH Terms]) OR (cancer of head and neck[MeSH Terms]) OR (rhinology[MeSH Terms])) AND (((nanotechnology[MeSH Terms]) OR (nanomedicine[MeSH Terms])) AND (drug delivery systems [MeSH Terms])). The following searches were performed on Ovid MEDLINE with the resource Journals@Ovid Full Text: (1) "nanotechnology" AND "drug delivery" AND "otolaryngology" AND "nanoparticles," (2) "drug delivery" AND "otolaryngology" AND "nanoparticles." The searches were restricted to articles published in English. The Ovid searches were limited to articles. Google Scholar was additionally queried for articles containing the keywords "otolaryngology", "head and neck surgery," "laryngology," "otology," "rhinology," "drug delivery," and "nanomedicine." Results that were not relevant to otolaryngology were excluded. Data extraction was performed by author Clayton Prakash Burruss and reviewed by authors Clayton Prakash Burruss and Ashutosh Kacker.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Search results

The PubMed search resulted in 29 articles, abstracts, and book chapters. The first and second Ovid MEDLINE searches resulted in 7 and 26 results, respectively. Google Scholar keyword searches and cross-referencing yielded additional resources. Of the PubMed articles, 16 were included in the review. Others were omitted if they were reviews or did not pertain to otolaryngology and/or nanotechnology drug delivery mechanisms. The Ovid searches yielded numerous review articles and articles not directly pertinent to otolaryngology. Duplicates from the PubMed search were excluded. No new resources were utilized from the Ovid search. A total of ninety-four resources were found using the Google Scholar keyword search and result cross-referencing. Duplicates were excluded. In total, 110 articles contained relevant information for this review. Relevant studies and technologies are displayed in Table 1.

### 3.2 | Nanomedicine and nanomaterial/NPs subtypes

Nanomedicine is the study of materials on the nanoscale and, thus, can be used for a wide array of applications in medicine and other fields. As a result of their small size, nanomaterials have unique physical properties

**TABLE 1** Summary of data for nanomaterials used in otology, neurotology, cranial base surgery, head and neck surgery, laryngology, bronchoesophagology, and rhinology

| | Study | Year | Description |
|---|---|---|---|
| Otology, neurotology, and cranial base surgery | | | |
| Organic NPs | | | |
| Liposomes | Buckiová et al.[17] | 2012 | Disulfiram-loaded NPs delivered to cochlea |
| | Zou et al.[19] | 2012 | Transtympanic injection of gadolinium-containing NPs to spiral ganglion |
| | Lajud et al.[23] | 2015 | Liposomal NPs in a CGP-hydrogel delivered across round window |
| Polymersomes | Zhang et al.[20] | 2010 | Fluorescently labeled NP uptake in spiral ganglion |
| | Buckiová et al[17] | 2012 | Disulfiram-loaded NPs delivered to cochlea |
| Polymeric NPs | Zhang et al.[21] | 2011 | Hyperbranched poly-lysine NPs delivered to organ of Corti and spiral ganglion |
| Inorganic NPs | | | |
| SPIONs | Du et al.[30] | 2013 | Dexamethasone-loaded SPION-PLGA NPs delivered with magnetic guidance |
| | Ramaswamy et al.[32] | 2017 | prednisolone-loaded SPIONs delivered to cochlea |
| | Shimoji et al.[33] | 2019 | Dexamethasone-loaded chitosan polymer and SPIONs delivered to cochlea |
| Other nanomaterials | | | |
| Nanotubes | Senn et al.[5] | 2017 | Carbon nanotubes on platinum with inorganic/metallic CuZnO NPs for cochlea implant improvement |
| Head and neck oncology and surgery | | | |
| Organic NPs | | | |
| Liposomes | Strieth et al.[53] | 2014 | Phase I/II clinical study on safety and antivascular effects of paclitaxel-loaded cationic liposomes for targeted therapy in advanced HNC |
| | Basak et al.[55] | 2015 | Curcumin-difluorinated-loaded liposomes for cisplatin-resistant HNC |
| | Mohan et al.[54] | 2016 | Trans-resveratrol (Res) and doxorubicin-containing PEGylated liposomal NPs for HNC |
| | Xu et al.[58] | 2017 | Docetaxel and siRNA-containing NPs with EGFR-binding peptides for laryngeal cancer |
| | Li et al.[48] | 2019 | dihydroartemisinin-loaded NPs for HNSCC |
| | Zheng et al.[57] | 2019 | Resveratrol-containing NPs with EGFR-binding peptides for HNSCC |
| | Wang et al.[49] | 2020 | Fully human anti-EGFR fragment liposomes containing doxorubicin and vinorelbine |
| | Yang et al.[50] | 2020 | Doxorubicin-loaded liposomes for HNSCC |
| Micelles | Cohen et al.[51] | 2010 | PHOTOSENSITIZER-loaded NPs for PDT in HNSCC |
| | Master et al.[43] | 2013 | photosensitizer-loaded NPs decorated with EGFR-binding peptides for PDT in HNSCC |
| | Wang et al.[46] | 2016 | PEG-coated cisplatin-containing micelles for CD44-positive HNCs |
| | Liu et al.[59] | 2020 | Photosensitizer-loaded NPs decorated with EGFR-binding nanobodies for PDT in HNSCC |
| Protein NPs | Rioja-Blanco et al.[65] | 2022 | Protein NPs with *Pseudomonas aeruginosa* exotoxin A and *Corynebacterium diphtheria* exotoxin for HNSCC |
| Polymeric | Lukianova-Hleb et al.[42] | 2012 | Anti-EGFR labeled gold NPs with plasmonic nanobubbles containing cisplatin, doxorubicin, and encapsulated doxorubicin liposomal for HNSCCs |
| | Wang et al.[44] | 2015 | Cisplatin-loaded PLGA-PEG NPs with an EGFR-targeting peptide for HNSCC |

**TABLE 1** (Continued)

| | Study | Year | Description |
|---|---|---|---|
| | He et al.[73] | 2017 | Anti-EGFR antibody labeled doxorubicin-containing PLGA/polydopamine NPs for PDT of HNSCC |
| | Wang et al.[74] | 2018 | Phase-changeable cetuximab-containing PLGA NPs for anaplastic thyroid cancer |
| | Lang et al.[47] | 2018 | Saracatinib-loaded PEG NPs with Src kinase-blocking for HNSCC |
| | Song et al.[70] | 2020 | Cisplatin-loaded PEG NPs with a photosensitizer for PDT of HNSCC |
| | Deng et al.[71] | 2020 | Docetaxel and curcumin-loaded PEG NPs for esophageal cancer |
| | Haider et al.[72] | 2020 | Paclitaxel-loaded PLGA NPs for HNSCC |
| | Wang et al.[68] | 2021 | Photosensitizer-loaded chitosan NPs with GBAS gene plasmid DNA for PDT of HNC |
| | Wang et al.[69] | 2021 | Photosensitizer-loaded chitosan NPs with MTHFD1L shRNA for PDT of HNC |
| | Chen et al.[79] | 2021 | PEG NPs with an HNSCC cell and red blood cell hybrid membrane for HNC bony metastasis |
| Inorganic NPs | | | |
| Gold NPs | Li et al.[81] | 2017 | Folate and cisplatin-containing SPIONs with a polymer shell for T2-weighted MR imaging of nasopharyngeal carcinomas |
| | Davidi et al.[67] | 2018 | Gold NPs coated in cisplatin acting as a CT-contrast agent for HNSCC |
| SPIONs | Zhao et al.[82] | 2012 | Spions for thermoradiation of HNSCC |
| | Su et al.[83] | 2019 | SPIONs with EGFR-binding peptides for CD44-positive HNSCC |
| Zinc NPs | He et al.[84] | 2015 | Cisplatin and photosensitizer-loaded Zn-based NPs for PDT for cisplatin-resistant HNC |
| Manganese NPs | Zhou et al.[86] | 2021 | pH-sensitive Mn-based NPs for the hypoxic environment of HNSCC |
| MOF NPs | Lu et al.[87] | 2014 | Zn-containing MOFs for PDT of HNSCCs |
| Laryngology, bronchoesophagology, and rhinology | | | |
| Organic NPs | | | |
| Chitosan NPs | Shahnaz et al.[106] | 2012 | Leuprolide-containing thiolated chitosan NPs for nasal administration |
| | Gulati et al.[107] | 2013 | Sumatriptan succinate-loaded chitosan NPs for migraine therapy |
| Inorganic NPs | | | |
| SPIONs | Dobretsov et al.[101] | 2015 | Amoxicillin-clavulanate-containing SPIONs for chronic nasal inflammation |
| Other nanomaterials | | | |
| Nanofibers | Abu Ammar et al.[94] | 2018 | Mometasone furoate-loaded PLGA nanofibers for reduced airway inflammation |
| | Abu Ammar et al.[95] | 2021 | Mometasone furoate-loaded PLGA nanofibers for reduced airway inflammation at longer intervals |
| Nanocrystals | Valiense et al.[98] | 2015 | Strontium-containing carbonated hydroxyappetitie/sodium alginate nanocrystals for sinus lifts in rabbits |
| Nanoclusters | Li et al.[108] | 2019 | Polyoxometalate nanoclusters as nano-antioxidants for neuronal protection in cerebral ischemia/reperfusion injury |

Abbreviations: EGFR, epidermal growth factor receptor; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinomas; MR, magnetic resonance; NP, nanoparticles, PDT, photodynamic therapy; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); SPIONs, superparamagnetic iron oxide nanoparticles.

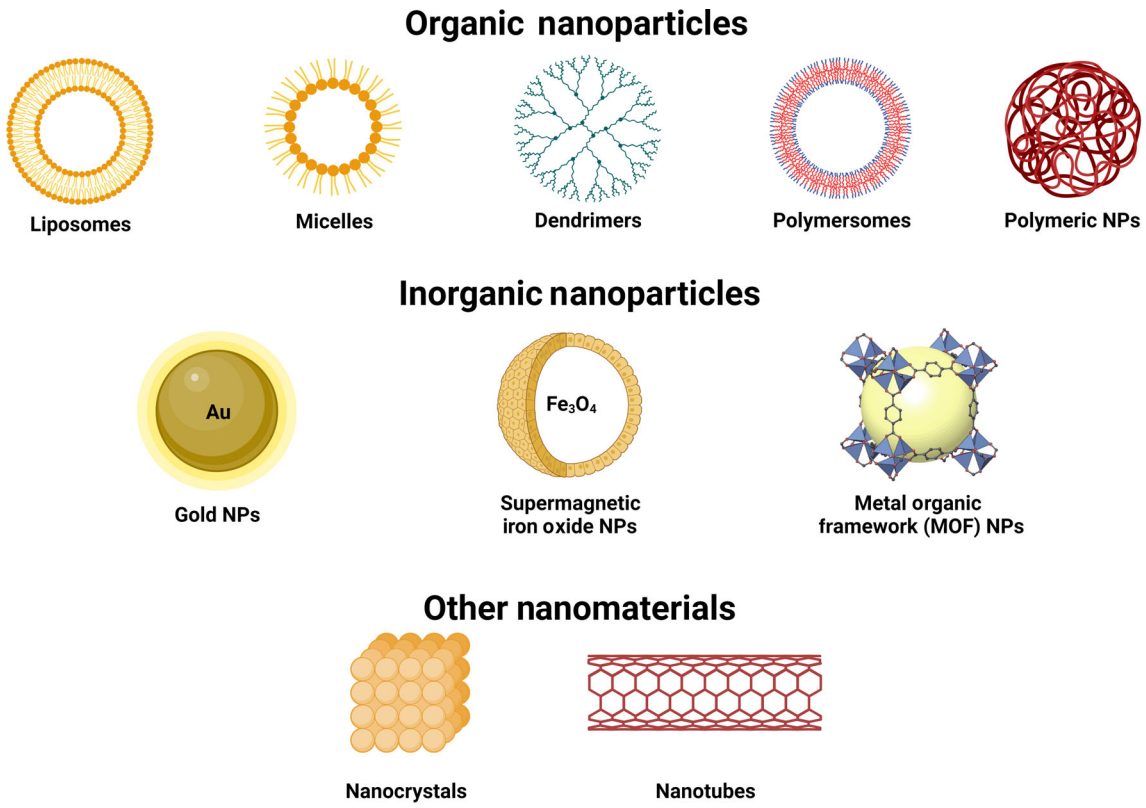


**FIGURE 1** Common organic and inorganic nanoparticles (NPs) and nanomaterials used in otolaryngology. Created with BioRender.com.

including increased surface area, variable thermal conductivity based on composition, magnetism, and increased mechanical strength.[11]

Nanomaterials currently utilized in the field of nanomedicine can be broadly separated into material-based categories.[12] These include (1) organic, (2) inorganic/metal, (3) carbon, or (4) composite-based nanomaterials. Organic-based nanomaterials exclude carbon-based and inorganic-based nanomaterials.[12] NPs are a particular subset of nanomaterials and are commonly classified as (1) organic or (2) inorganic (see Figure 1). Organic NPs are a subclass of organic nanomaterials that include liposomes, micelles, dendrimers, and polymeric NPs.[13] Inorganic NPs include gold NPs, quantum dots, silica NPs, and other metal NPs.[14] In all subspecialties of otolaryngology, there is ongoing research into the applications of these technologies.

## 3.3 | Otology, neurotology, and cranial base surgery

The inner ear demonstrates numerous barriers to drug delivery, both due to the complex anatomical structures surrounding the inner ear and the need for precise rather than systemic therapy. Zou et al.[7] describe these barriers in two parts: the round window (RW) and oval window (OW) for the middle-inner ear barrier, and the blood-inner ear barrier consisting of the blood-perilymph and blood-endolymph barriers. Currently, local therapy exists in the form of intratympanic drug injection. However, diffusion limitations at the level of the RW and OW and transient drug loss in the middle ear through the Eustachian tube often reduce inner ear drug concentrations to undesirable or ineffective levels.[15,16] Nanotechnology provides a unique avenue to avoid these barriers.

### 3.3.1 | Organic NP technology and the inner ear

Buckiová et al.[17] described the transport and localized drug delivery of two organic NPs, liposomes and polymersomes, from the middle ear to the cochlea in a mouse model. Polymersomes, or polymeric vesicles, are a fully synthetic counterpart to liposomes constructed from amphiphilic block co-polymers made into a vesicle with a spherical bilayer. Liposomes are instead constructed of lipids.[18] In this study, cases exposed to both NPs demonstrated fluorescent uptake in the cochlear tissues, particularly the spiral ganglion. Additionally, when these NPs were loaded with disulfiram, researchers observed cellular destruction in the spiral ganglion compared with a lack thereof when free disulfiram was injected into the RW. These results demonstrate both functional organic NP drug delivery to the inner ear and a measurable readout of localized drug release in the inner ear. Zou et al.[19] similarly studied the delivery of liposomal NPs through transtympanic injection instead of direct application to the round window. Liposomal uptake was exhibited in the utricle, spiral ganglion region, and spiral ligament capillaries. Similar studies have demonstrated organic NP uptake in the spiral ganglion with polymersomes[20] and organ of Corti with hyperbranched polylysine NPs.[21]

Hydrogels offer a similar method of localized and prolonged drug release in the inner ear. Hydrogels are cross-linked networks of

hydrophilic polymers with a high capacity for binding hydrophobic and hydrophilic compounds. They can be classified as organic, inorganic, or composite depending on functional groups.[22] By definition, hydrogels are not inherently nanomaterials. However, recent studies have demonstrated successful drug delivery to the inner ear using hydrogels and improved drug delivery when integrating hydrogels with liposomal NPs.[23] Paulson et al.[24] initially demonstrated the applications of chitosan-glycerophosphate (CGP)-hydrogel for the sustained release of dexamethasone at the RW. Xu et al.[25] subsequently utilized CGP technology for gentamicin delivery to the inner ear as a possible application for the treatment of Meniere's disease. CGP hydrogel modularity acting as an "off switch" was added through the introduction of chitosanase,[26] a hydrolytic enzyme that depolymerizes chitosan and catalyzes the cleavage of β-1,4-linked glycosidic chitosan linkages.[27] This holds important implications for minimizing the ototoxicity of ototoxic therapies delivered by hydrogel technology. More recently, Lajud et al.[23] incorporated liposomal NPs into this CGP-hydrogel to produce nanohydrogels. The hydrogel-liposomal technology allowed for sustained release of liposomal NPs without disrupting the integrity of the RW. This research serves as a proof of concept for future applications of NPs that integrate biomaterials such as antibodies, peptides, and other cell-specific ligands for the treatment of inner ear pathologies.

### 3.3.2 | Inorganic NP technology and the inner ear

Although liposomal NPs and other organic nanomaterials have been effectively transported to the inner ear, they often rely on passive diffusion across the RW to access the inner ear. Certain inorganic NPs such as superparamagnetic iron oxide nanoparticles (SPIONs) have been studied due to their ability to be magnetically guided to the inner ear and subsequently be used for magnetic resonance (MR) imaging.[28,29] Although SPIONs cannot directly encapsulate a pharmaceutical,[28] they can be integrated with other organic materials such as poly(lactic-co-glycolic acid) (PLGA) or chitosan for subsequent drug delivery.[30,31] Du et al.[30] used this technology to transport dexamethasone-loaded SPION-PLGA NPs to the cochlea under magnetic guidance and compared mass transfer rates to that of diffusion alone. Similar magnetic NPs have been successfully integrated with prednisolone for the treatment of cisplatin-induced ototoxicity.[32] In another study, Shimoji et al.[33] compared the safety of cochlear magnetic delivery of a chitosan polymer loaded with dexamethasone and SPIONs to intratypmpanic injection of steroids in a rodent model. Magnetic delivery was not associated with scarring, worse hearing loss outcomes, or increases in systemic iron levels compared with intratympanic injection after 90 days.

### 3.3.3 | Implants and other nanotechnologies used for hearing loss

Otologic implants such as the cochlear implant (CI), bone conduction hearing implants, middle-ear implants, and auditory brainstem implants are the most common implants utilized in otolaryngology.[34] Auditory implants have become the treatment of choice for patients with severe to profound hearing loss due to their high efficacy. Despite the success of these implants, there is considerable user variability due to the anatomical gap between the CI electrodes and the firing neurons which may impede sound quality with music or loud environments.[35] Senn et al.[5] and the NANOCI project worked to address this problem using a variety of nanomaterials. The researchers describe the anatomical limitation of modern CI's due to the minimal proximity between electrodes which, when exceeded, causes a reduction in spatial resolution due to the electric crosstalk through overlapping electric fields. These researchers worked to integrate neurotrophic factors such as brain-derived neurotrophic factor into gel matrices to induce auditory neuron production and functionally decrease the anatomical gap to promote a "gapless interface" in vivo. The in vivo electrode array utilized conductive carbon nanotubes bound on platinum, parylene-coated array with inorganic/metallic CuZnO NPs, and 7,8,3-trihydroxyflavone, thereby demonstrating a possible future application of nanomedicine and NPs to improve outcomes and quality for otologic conditions.

## 3.4 | Head and neck oncology and surgery

Traditional treatment of oral cancers includes surgery, radiotherapy, and chemotherapy. Due to the anatomical sensitivity of these tumors and surrounding tissues, current treatment modalities may result in adverse effects such as mucositis, neurotoxicity, tissue/bone necrosis, fibrosis, or infection.[36] Although head and neck cancer (HNC) outcomes are improving,[37–39] new therapies should be pursued to improve patient quality of life and care. Nanomedicine has immense potential in the treatment of cancers of the head and neck due to its targeted approach and potential for reduced side effects.[40] In head and neck oncology, recurrence or advanced disease often occurs due to late detection, micrometastasis, multidrug resistance, or therapy toxicity.[41] Nanomaterials can be designed in a way to meet these specific disease requirements. Current nanotechnological research in HNC focuses greatly on enhanced drug delivery to specific or resistant cell lines. Targets include cell lines with increased transmembrane growth factor receptors,[42–44] specific signal transducers,[45] variant cell-surface adhesion receptors,[46] and nonreceptor tyrosine kinases.[47]

### 3.4.1 | Organic NP technology in head and neck oncology

Organic NPs such as liposomes, micelles, protein-based NPs, and some nonmetal-containing polymeric NPs have been studied for the diagnosis and treatment of HNCs.[43,48–51] These NPs are often favorable due to the biocompatibility of lipids and low cost.[52] Given their low toxicity, liposomes have been studied as carriers and adjuvants for a variety of chemotherapies for the treatment of HNCs, including paclitaxel,[53] doxorubicin,[54] and cisplatin.[55] Although enhanced drug delivery is desirable, certain cell lines can often avoid chemotherapy-induced cell death through damage repair, drug efflux, increased

growth signaling, and apoptosis inhibition.[56] Researchers have taken advantage of increased growth signaling in head and neck squamous cell carcinomas (HNSCCs) by conjugating both variable fragments[49] and peptides[57,58] that selectively bind receptors such as epidermal growth factor receptor (EGFR) to liposomal NPs. Similarly, micelle NPs have been used to both encapsulate drugs such as cisplatin[46] and target EGFR using peptides and other novel NP surface conjugates.[43,59,60] Master et al[43] evaluated the efficacy of organic micelle NPs with EGFR-targeting peptide ligands and an added photosensitizer for the added benefit of photodynamic therapy (PDT). PDT involves photon-induced activation of a photosensitizer to generate reactive oxygen species (ROS) and promote cell death. PDT offers a unique approach to aggressive HNCs and has demonstrated promise in HNSCCs.[61–63] These technologies not only allow for the localization of NPs to tumor cells but also the release of chemotherapies and subsequent cellular destruction through PDT. There is additional work looking at the integration of nanotechnology with bacterial machinery using synthetic biology,[64] and, more recently, the incorporation of bacterial toxins into protein NPs to target HNSCCs.[65] Rioja-Blanco et al.[65] describe the incorporation of *Pseudomonas aeruginosa exotoxin A and the diphtheria exotoxin from Corynebacterium diphtheriae* into protein NPs to target HNSCCs.

Various biocompatible polymers have been integrated into NP technology for the treatment of HNCs.[66] These include natural polymers such as chitosan and synthetic polymers such as PLGA and polyethylene glycol (PEG). Polymeric NPs can exist alone or as add-on coatings with other NP technologies such as micelles[46] or inorganic NPs.[67] Chitosan NPs have been used for both PDT and gene therapy for HNSCCs.[68,69] PEG NPs have been used to transport cisplatin,[70] docetaxel,[71] and tyrosine kinase inhibitors[47] to HNC cells; PLGA NPs have been used to transport paclitaxel,[72] doxorubicin,[73] and cetuximab[74] to HNSCC cells.

Similar to the technology described above with EGFR-targeting liposomes and micelles, He et al.[73] report a PLGA NP that employs an anti-EGFR antibody and a photosensitizer core for PDT. Wang et al.[44] similarly studied cisplatin-loaded NPs with a PLGA-PEG shell and a peptide with EGFR affinity.[75] Their results demonstrated increased cell cytotoxicity compared with free cisplatin and PLGA-PEG NPs lacking the peptide. The design allows for rapid tumor cell-specific endocytosis and subsequent shell destabilization in a lysosomal environment, resulting in increased cytotoxic activity in the presence of the targeting peptide. In addition to EGFR-localized NPs, Lang et al.[47] demonstrated PEG NPs with Src kinase-blocking activity through the incorporation of saracatinib. Cancers including HNSCCs have shown increased levels of Src, which acts as a molecular switch in signal transduction.[76,77] Uniquely, the polymer shell of these NPs was sensitive to cathepsin B (CTSB), an enzyme commonly increased in HNSCCs.[78] The result of CTSB sensitivity was increased NP specificity and reduced systemic toxicity of saracatinib as measured by aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine.[47] PEG NPs have also been altered to target bony metastasis of HNSCC using cancer cell/erythrocyte coatings.[79]

PEG NPs have similarly been used to target the CD44-variant cell line of HNSCC.[46] The CD44 cell line has previously exhibited drug resistance attributed to an increase in glutathione and enhanced cellular protection.[80] This delayed-release technology, therefore, protects the drug from glutathione-induced reduction and increases active therapy at the level of the nucleus. Finally, Wang et al.[74] applied phase-changeable PLGA NPs to treat anaplastic thyroid cancer. These NPs can undergo ultrasound-driven drug release which they used for in vivo imaging and the release of cetuximab.

### 3.4.2 | Inorganic NP technology in head and neck oncology

Inorganic and metallic NPs for the treatment of HNCs have previously been constructed of gold,[42,67] iron oxide,[81–83] zinc,[84,85] manganese dioxide,[86] metal-organic frameworks (MOFs), and various other metals.[87] Inorganic NPs often have higher toxicity than organic NPs,[88] but they are useful for both drug delivery mechanisms and imaging due to their metallic properties.[89] Gold NPs may also deliver thermoradiation to various cancers.[90,91] However, like PDT, issues arise due to the heating of surrounding tissues in the absence of cell-specific uptake. Lukianova-Hleb et al.[42] demonstrated the production of plasmonic nanobubbles (PNBs), a unique technology derived from gold NPs, conjugated to EGFR-antibodies for HNSCC cell-specific death. This study compared cisplatin, doxorubicin, and doxorubicin liposomal (Doxil) as monotherapies and combination therapies with PNBs for HNSCCs and saw that, when administered together, tumor cell death increased compared with that achieved by chemo-monotherapy. Additionally, the combination therapy spared normal tissues and reduced the required chemotherapeutic concentration 10-fold compared with monotherapy to achieve the same cell death. Other research has worked to coat gold NPs with cisplatin to promote cell uptake.[67] This study had the added benefit of demonstrating enhanced tumor imaging utilizing the NPs as a radio-sensitizing computed tomography (CT)-contrast agent. Li et al.[81] studied discovered similar applications of folate and cisplatin-containing SPIONs with a polymer shell. This magnetic NP was further utilized for T2-weighted MR imaging of nasopharyngeal carcinomas. SPIONs have also been used for thermotherapy of HNSCCs[82] and antibody-targeting of the CD44-overexpressing HNSCCs.[83]

Zinc NPs have been studied for drug delivery and PDT of HNCs.[84,85] He et al.[84] described cisplatin-PDT combination therapy using zinc-based NPs loaded with a photosensitizer and cisplatin for a cisplatin-resistant HNSCC murine model. When compared with chemo-monotherapy, the NPs demonstrated a greater tumor cell death without enhanced cytotoxicity in the absence of irradiation, furthering the result that this nanotechnology provides modular antitumor apoptosis. Finally, NPs derived from zinc-containing MOFs have been reported for PDT of HNSCCs.[87] MOFs are a class of porous solids with tunable sizes and structures.[92] Given their extremely large surface areas and, drug carrying capacity, they are of particular interest. Future research is required to analyze their safety profiles and efficacy.

### 3.5 | Laryngology, bronchoesophagology, and rhinology

Although NPs are commonly employed in otology and HNC research, they have been less studied in other subspecialties. Instead, other nanomaterials such as drug eluting nanofibers and stents have been more thoroughly researched in laryngology, bronchoesophagology, and rhinology.

In laryngology and bronchoesophagology, implants are regularly used in the form of tracheostomy tubes, tracheoesophageal voice prostheses, tracheal stents, and injectable vocal cord implants.[34] Eluting implants in the larynx and pharynx may be employed to reduce inflammation or infection.[93] Abu Ammar et al.[94] demonstrated a steroid delivery mechanism through endotracheal tubes coated in PLGA nanofibers loaded with mometasone furoate (MF). Cases with the PLGA-MF tube saw a reduction in laryngeal mucosal thickness postintubation compared with animals in vivo compared with controls without tube coating. More recently, Jahshan et al.[95] performed a similar study analyzing the effect of the same PLGA-MF tube after a 1-week intubation interval. In the absence of MF, subjects exhibited significant increases in tracheal fibrosis, demonstrating a possible intraoperative intervention to reduce the incidence of laryngotracheal stenosis. Of the polymers studied for steroid elution, PLGA seems to offer the best biodegradability and promising clinical utility.[93]

The major applications of nanomedicine in rhinology and sinus surgery currently involve nasal packing and implants used to prevent and treat nasal valve collapse in functional endoscopic sinus surgery (FESS).[34] Nasal packings are often denoted as absorbable or nonabsorbable packings. Absorbable stents are often comprised of biodegradable polymers with modular extracellular matrices, allowing for microscopic temporal and spatial release of therapeutics and macroscopic structural support. When compared with onabsorbable packings, absorbable packings have demonstrated reductions in postoperative synechia and postoperative bleeding in FESS.[96] Stents[97] and nanocrystals[98] made from calcium and sodium alginates, a gel-transforming material, are currently being studied to reduce inflammation in the nasal mucosa and provide structural support in the sinuses.[97] Additional studies are analyzing bioabsorbable PLGA-stents that elute MF, similar to the laryngology discussion above.[99,100] When compared with saline controls, these stents reduced inflammation, polyp formation, and adhesion. Finally, Dobretsov et al.[101] analyzed SPIONs containing amoxicillin clavulanate for rapid cellular uptake of antibiotics in the nasal mucosa. This research demonstrates the feasibility of nanotechnology to improve therapeutic options for chronic rhinosinusitis and inflammation of the sino-nasal mucosa.

One final application of NPs in rhinology is the treatment of anosmia. With the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the incidence of persistent loss of taste and smell has increased.[102] Previous work has demonstrated the feasibility of using NP technology in the treatment of neurodegenerative disorders.[103] One barrier in the delivery of NP therapy to the olfactory system is mucociliary clearance.[104] Chitosan NPs, among other chitosan-containing nanomaterials,[105] have been studied to overcome this barrier due to their positive charge and ability to bind negatively charged mucous.[106,107] Additional NP structures have integrated ROS-scavenging ligands to reduce oxidative damage, demonstrating the potential for COVID-19 management.[108,109] Yoo et al.[110] highlight the novel NP technologies currently under review to treat anosmia.

## 4 | CONCLUSION

In the future management of otolaryngological conditions, nanotechnology may offer a controlled and precise approach for drug delivery and imaging. Current research demonstrates numerous in vivo applications of NPs in many otolaryngology subspecialties. Microscopically, these technologies have the benefits of cell-specific drug delivery, reduced systemic toxicity, and controlled time-dependent drug release. Future work needs to further consider the safety profiles of these new technologies to ensure there is an ethical and efficacious translation into human studies. Finally, as highlighted by the breadth of specialists cited in this paper, it is likely that cross-functional teams that extend beyond medical professionals will be essential to eventually convert this technology into a form that can benefit humans in modern medicine.


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**How to cite this article:** Burruss CP, Kacker A. The current status of nanotechnological approaches to therapy and drug delivery in otolaryngology: A contemporary review. *Laryngoscope Investigative Otolaryngology*. 2022;7(6):1762-1772. doi:10.1002/lio2.952