Local drug delivery for oral mucosal diseases: challenges and opportunities

Sankar, V; Hearnden, V; Hull, K; Juras, D Vidovic; Greenberg, MS; Kerr, AR; Lockhart, PB; Patton, LL; Porter, S; Thornhill, M

Source / Izvornik: **Oral Diseases, 2011, 17, 73 - 84**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1111/j.1601-0825.2011.01793.x

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:127:528901

ORAL DISEASES

Oral Diseases (2011) 17 (Suppl. 1), 73–84. doi:10.1111/j.1601-0825.2011.01793.x

www.wiley.com

ORIGINAL ARTICLE

Local drug delivery for oral mucosal diseases: challenges and opportunities

V Sankar[1], V Hearnden[2,3], K Hull[4], D Vidovic Juras[5,6], MS Greenberg[7], AR Kerr[8], PB Lockhart[9], LL Patton[10], S Porter[11], M Thornhill[2]

[1]Department of Comprehensive Dentistry, The University of Texas Health Science Center at San Antonio, TX, USA; [2]Oral & Maxillofacial Medicine & Surgery, University of Sheffield School of Clinical Dentistry, Sheffield, UK; [3]Department for Engineering Materials, University of Sheffield, Sheffield, UK; [4]Department of Oral Medicine, Oral Pathology and Special Needs Dentistry, Westmead Centre for Oral Health, Westmead Hospital, Sydney, Australia; [5]Clinical Department of Oral Diseases, Dental Clinic, Zagreb University Hospital Center, Zagreb, Croatia; [6]Department of Oral Medicine, School of Dental Medicine, Zagreb University, Zagreb, Croatia; [7]School of Dental Medicine University of Pennsylvania, Philadelphia, PA, USA; [8]Department of Oral & Maxillofacial Pathology, Radiology & Medicine, New York University College of Dentistry, New York, NY, USA; [9]Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC, USA; [10]Department of Dental Ecology School of Dentistry, University of North Carolina, Chapel Hill, NC, USA; [11]UCL Eastman Dental Institute, University College London, London, UK

There are few topical formulations used for oral medicine applications most of which have been developed for the management of dermatological conditions. As such, numerous obstacles are faced when utilizing these preparations in the oral cavity, namely enzymatic degradation, taste, limited surface area, poor tissue penetration and accidental swallowing. In this review, we discuss common mucosal diseases such as oral cancer, mucositis, vesiculo-erosive conditions, infections, neuropathic pain and salivary dysfunction, which could benefit from topical delivery systems designed specifically for the oral mucosa, which are capable of sustained release. Each condition requires distinct penetration and drug retention profiles in order to optimize treatment and minimize side effects. Local drug delivery may provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. We identify those mucosal diseases currently being treated, the challenges that must be overcome and the potential of novel therapies. Novel biological therapies such as macromolecular biological drugs, peptides and gene therapy may be of value in the treatment of many chronic oral conditions and thus in oral medicine if their delivery can be optimized.

Oral Diseases (2011) **17** (Suppl. 1), 73–84

Keywords: drug delivery; oral mucosa; mucosal disease; transmucosal

Correspondence: Martin Thornhill, Academic Unit of Oral & Maxillofacial Medicine & Surgery, University of Sheffield School of Clinical Dentistry, Claremont Crescent, Sheffield S10 2TA, UK. Tel: +44 (0)114-271-7857, Fax: +44 (0)114-271-7863, E-mail: m.thornhill@sheffield.ac.uk
Received 23 December 2010; accepted 27 December 2010

Introduction: the need for topically delivered therapy

There are very few topical formulations that have been designed specifically for oral mucosal diseases. Most topical therapies currently used by oral medicine specialists for treating oral mucosal diseases are those used in the treatment of dermatological conditions. As such, they have not been designed to be used in an aqueous environment constantly bathed in saliva, which may cause much of the drug to be washed off and lost. Repeated dosing is also required to obtain a therapeutic dose. Delivery systems designed specifically for the oral mucosa capable of sustained release would be beneficial in the treatment of many oral diseases.

This review will examine both the properties of the oral mucosa that make topical drug delivery possible and the characteristics of the mouth that present challenges. Those mucosal diseases that could benefit from topical delivery technologies will be discussed, including oral cancer, mucositis, lichen planus, herpes simplex, candidiasis, recurrent aphthous stomatitis, vesiculo-bullous diseases, neuropathic pain and salivary dysfunction. A summary of current therapies will be provided, highlighting their limitations and exploring how existing and new topical therapies might benefit from improvements in drug delivery and facilitate improvements in treatment outcomes. In addition, the potential use of exciting novel biological therapies for the treatment of mucosal diseases will be covered.

Oral mucosa: structure and characteristics

Structure

Human oral mucosa is comprised of a stratified squamous epithelium and a connective tissue component,

separated by a basement membrane (Nanci, 2003). Adjacent to the basement membrane lies the basal keratinocytes that proliferate rapidly to repair and replenish the epithelium. Superficial to these are the partially differentiated supra-basal cells. In keratinized regions of the oral cavity (gingivae and hard palate), the most superficial layer of the epithelium is made up of terminally differentiated keratinocytes, which eventually die, are desquamated and shed (Nanci, 2003; Salamat-Miller *et al*, 2005).

The oral mucosa acts as a barrier between the all soft tissues and the environment, retaining tissue fluids and excluding extrinsic materials. The main permeability barrier to external materials is in the lower to middle third of the epithelium.

Where to deliver to?

Oral mucosal delivery has the potential to treat many different conditions and diseases. Each therapy requires distinct penetration and drug retention profiles in order to optimize treatment and minimize side effects (Figure 1). Superficial infections, such as candidiasis, affect only the most superficial epithelial cells and drugs used to treat these infections do not need to cross the permeability barrier but should be delivered to the surface of the epithelium.

Diseases such as oral dysplasia affect the epithelial cells themselves and drugs targeting epithelial diseases such as this need to penetrate and be retained within the epithelium with as little loss as possible from the surface or into the underlying connective tissue.

Oral lichen planus, like many other oral diseases, affects the basal cells and the adjacent connective tissue, the immune attack principally occurring in the upper connective tissue. In order for a drug to reach the basal cells it needs to cross the permeability barrier and penetrate deeply into the epithelium. It would be desirable if the drug was then retained in the epithelium and adjacent connective tissue rather than being lost systemically into the circulation and lymphatics.

It is not only the penetration and retention properties of drugs that should be considered but also their ease of uptake by cells. Drugs acting on intracellular targets or intracellular disease processes should be easily internalized by cells and cross the epithelium via the intracellular route (i.e. by passing through the epithelial cells). On the other hand, drugs that act on cell surface receptors would have increased efficiency if they were not internalized into cells but penetrated the epithelium via extracellular routes i.e. by passing around and between the epithelial cells.

Permeability of the oral mucosa

The permeability barrier is responsible for preventing exogenous and endogenous materials from entering the body across the oral mucosa and prevents loss of fluid from the underlying tissues to the environment. The permeability barrier is comprised predominantly of the lipid content of the upper layers of the epithelium. As supra-basal cells differentiate, they form strong intercellular desmosomal junctions and form membrane coating granules (MCGs) on their apical surfaces (Shimono and Clementi, 1976; Shojaei, 1998). These MCGs release lipophilic material into the intercellular spaces to ensure epithelial cohesion. This lipophilic material slows the passage of hydrophilic materials across the epithelium

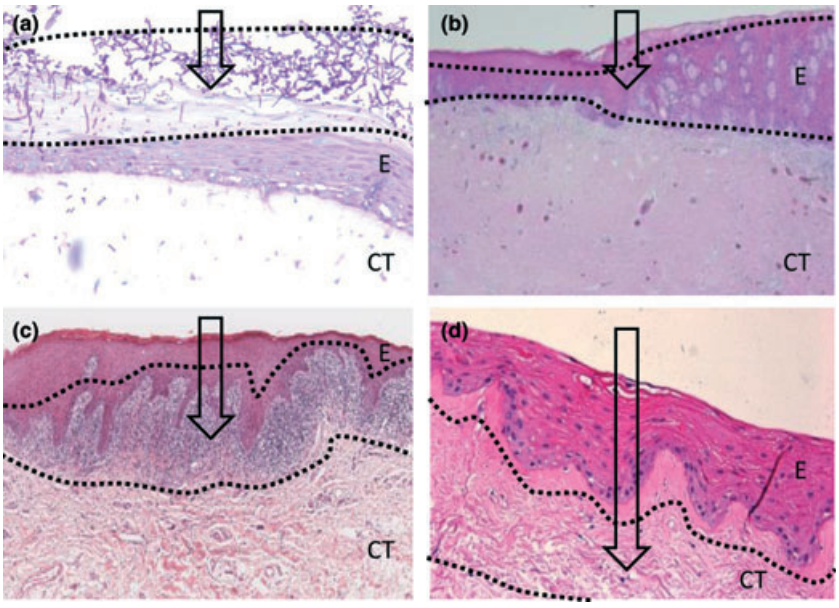

Figure 1 Level of drug penetration required depends on the condition requiring therapy. (a) Superficial infections such as candidiasis do not need to cross the permeability barrier. (b) Mucosal diseases such as dysplastic lesions require retained delivery to the affected epithelium. (c) Oral lichen planus affects basal cells and the adjacent connective tissue and requires delivery to these cells. (d) For systemic delivery, the therapeutic agent needs to cross the permeability barrier and should not be retained in the epithelium. Arrows show level of penetration required. Dotted lines show the desired area for drug retention. E, epithelium; CT, connective tissue

(Salamat-Miller *et al*, 2005). Kulkarni *et al* (2009) demonstrated that the epithelium is the major barrier to permeability with the connective tissue providing some resistance to lipophilic materials due to the connective tissue's high level of hydration.

There is variation in permeability across different regions of the oral mucosa due to the differing thickness of the epithelium and degree of keratinization at different sites. Keratinized tissues display a lower permeability than non-keratinized tissues; this is due to the lipid composition of the membrane coating granules in keratinized tissues rather than the presence of keratin alone (Ganem-Quintanar *et al*, 1997). The degree of permeability is lowest in gingivae and hard palate followed by the buccal mucosa with the most easily permeated area of the oral mucosa being the sublingual mucosa (Squier and Hall, 1985).

There are three methods of diffusion across the oral mucosa's permeability barrier (i) passive diffusion including trans-cellular (through cells) and para-cellular (where material passes through lipid rich domains around the cells), (ii) carrier-mediated transport and (iii) endocytosis/exocytosis where material is actively taken up and excreted by cells via the endocytic pathway (Li *et al*, 2005; Salamat-Miller *et al*, 2005; Sudhakar *et al*, 2006). The most easily diffusible materials are lipid soluble substances, non-ionized species and those with low molecular weights. Dextrans with a molecular weight below 20 000 Da is diffusible; however, dextran of higher molecular weight is not (Hoogstraate *et al*, 1994). The route of passive diffusion taken by a particular material depends on the material's lipophilicity, partition coefficient between lipophilic and hydrophilic regions, and the diffusion coefficient of the substance in the intercellular space (Sood *et al*, 2005). Drugs with a high pKa diffuse across the mucosa more efficiently (Madhav *et al*, 2009).

Increased permeability in diseased mucosa

Not surprisingly, the loss of the permeability barrier in ulcerated or eroded areas of oral mucosa means that drugs diffuse more freely into the tissue than in intact areas of mucosa. However, the reduced barrier function can also lead to faster loss of drug from ulcer sites (Harsanyi *et al*, 1986). Unpublished data show a marked increase in the permeability of lichen planus affected oral mucosa, even when not eroded or ulcerated, compared with normal oral mucosa (personal communication. A. Cruchley, Bart's and the London, Queen Mary, University of London). This may result in enhanced drug delivery into disease affected areas of mucosa compared with surrounding normal tissue.

The mucosa of malignant and potentially malignant oral lesions may exhibit altered permeability to different drugs. Bánóczy *et al* studied the permeability of nitrosonornicotine, a carcinogen found in cigarettes, in leukoplakic sites and their surrounding non-lesional areas. Both leukoplakia and the surrounding areas showed higher permeability than normal oral mucosa; however, only the non-lesional areas immediately surrounding the leukoplakia showed statistically significantly higher permeability (Bánóczy *et al*, 2003).

Oral mucosa: a site for local drug delivery

Advantages for drug delivery applications

The oral cavity has been proposed as a potential topical delivery site for the local and systemic delivery of therapeutic agents. Systemic drug delivery across the oral mucosa will be reviewed in a separate paper by the same group of authors.

Drug delivery via the oral mucosa has several advantages and disadvantages (Table 1). Drugs are self-administrable and well accepted by patients. The oral mucosa is easily accessible and rapidly repairs itself after damage or trauma. This short recovery time limits potential adverse side effects caused by long-term topical drug delivery (Sudhakar *et al*, 2006). In addition, there are fewer Langerhans cells in the oral mucosa than the skin reducing the risk of an allergic response, a drawback commonly experienced in transdermal delivery.

Disadvantages for drug delivery applications

Problems with oral mucosal delivery (Table 1) include developing drugs or delivery systems that (i) overcome the permeability barrier; (ii) protecting biological drugs such as peptides and proteins from enzymatic degradation; (iii) having an acceptable taste to patients; and (iv) are easily administered and are not easily swallowed by accident (Sudhakar *et al*, 2006). The oral mucosa has a small surface area compared with skin and limited exposure times make this delivery route most appropriate for drugs exhibiting high therapeutic potency as relatively small quantities of drug can be delivered (Madhav *et al*, 2009).

Table 1 Advantages and disadvantages of oral mucosal drug delivery for oral disease

Advantages	*Disadvantages*
Accessible	Permeability barrier of the oral mucosa
Self-administrable	Saliva washes away drug
Oral mucosa repairs rapidly	Mastication and speech may dislodge delivery device
Different areas of oral cavity have different permeability characteristics	Taste important consideration
Highly hydrated environment to dissolve drug	Highly enzymatic environment
Sustained delivery possible	Relatively small surface area
Potential reduction of systemic side effects	Risk of choking or swallowing on delivery device

Impact from saliva, mastication and speech. The constant washing of the oral cavity by saliva can limit the length of mucosal exposure to a drug both by diluting the drug in the oral cavity and clearance of a drug into the gastrointestinal tract by swallowing. Saliva is a particular problem when drugs are delivered sublingually as this area of the oral cavity is constantly bathed in saliva. Saliva, however, can also be beneficial in providing a highly hydrated environment in which to dissolve drugs to distribute around the entire oral cavity.

Mastication, the action of chewing food, can both hinder and enhance drug delivery in the oral cavity. It can also cause damage to or loss of mucoadhesive drug-delivery system but it can also be utilized by loading drugs into chewing gum, which are released when the gum is chewed (Maggi *et al*, 2005).

Local *vs* systemic drug delivery

Local drug delivery can provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. The main advantages of local drug delivery include (i) reduced systemic side effects, (ii) more efficient delivery as a smaller amount of drug is wasted or lost elsewhere in the body, (iii) targeted delivery as drugs can be targeted to the diseased site more easily when delivered locally, thereby reducing side effects.

Novel local drug delivery and therapeutics for specific oral diseases

Potentially malignant oral disease and oral cancer
Potentially malignant oral disease is morphologically altered tissue that is present on clinical examination in which cancer is more likely to occur than in normal tissue. Examples include leukoplakia or erythroplakias. These lesions could be premalignant and exhibit dysplasia on histopathological exam. The overall risk for malignant transformation in oral dysplastic lesions is approximately 20% (Silverman *et al*, 1984). Approximately, 90% of oral cancers are squamous cell carcinomas.

Current treatment. Treatment of oral dysplastic lesions includes surgical management and the use of chemopreventive agents (Lodi *et al*, 2006). The treatment for oral squamous cell carcinomas may include single or combination modality surgery, radiotherapy, or chemotherapy [described in detail elsewhere (Haddad and Shin, 2008)]. As understanding of oral carcinogenesis has improved, it is now possible to target various operational mutations and aberrant molecular pathways. One targeted agent has been approved for the treatment of squamous cell carcinomas (cetuximab, an epidermal growth factor receptor antagonist), and several other agents are under development (Gold *et al*, 2009). Preventive activities, such as risk factor cessation coupled with close surveillance following treatment, are of paramount importance given the high rate of recurrent or new disease.

Problems with the current treatment. Aggressive treatment regimens associated with significant morbidity are used for treatment of later stage oral cancers. In the future, it is conceivable that targeted chemotherapies will become customized to an individual's malignant disease, thus limiting morbidity. Improvements are needed in preventive activities including risk factor avoidance or reduction, early stage disease detection, and identification of individuals (or lesions) at higher risk for developing oral cancer. Currently, there are no reliable treatments to prevent malignant transformation of dysplastic lesions or the development of recurrent/new disease in patients with a history of oral cancer (Kelloff *et al*, 2006; Lodi *et al*, 2006). The difficulty in developing such a reliable treatment is that each individual cancer (or premalignant oral lesion) is unique, carrying its own blend of mutations and thus not all patients will benefit from the same therapy.

Novel formulations and research into improved topical drug delivery for oral cancer. Opportunities for the topical treatment of oral cancer are limited by the ability for a putative agent to reach the tumour effectively. As such, topical treatments are generally indicated for local (early stage) cancers, premalignant oral lesions, or in patients with field carcinogenesis who are at a high risk for new or recurrent disease. Topical agents such as tolonium chloride (toluidine blue) might be used to identify subclinical or low-risk disease that is predictive of malignant transformation (Zhang *et al*, 2005). There is paucity of literature on topical therapies, and most studies have explored their efficacy in the treatment of oral premalignant lesions.

Topical retinoids have shown variable efficacy in oral premalignant lesions over the short term (Tradati *et al*, 1994; Epstein and Gorsky, 1999; Piattelli *et al*, 1999; Gaeta *et al*, 2000). There have been two RCTs; one used a mucoadhesive disc to provide an extended release of acitretin into the oral cavity (Gaeta *et al*, 2000) and the other used an isotretinoin gel (Piattelli *et al*, 1999). An RCT exploring the efficacy of a topical ketorolac oral rinse demonstrated no efficacy (Mulshine *et al*, 2004), although some investigators suggest that the differential permeation of topically delivered NSAIDS or COX-2 inhibitors may impact efficacy (Sood *et al*, 2005), or that novel mucoadhesive delivery systems, such as a polymer film, may be feasible (Wang *et al*, 2007). Two studies demonstrated variable efficacy of topical bleomycin (Epstein *et al*, 1994, 1998), one was an RCT (Epstein *et al*, 1994). One novel study explored the efficacy of a topical rinse containing an attenuated adenovirus engineered to destroy p53-mutant cells in three cohorts of patients with oral epithelial dysplastic lesions (Rudin *et al*, 2003). There were some complete responses, although most were transient. The delivery of black raspberry anthocyanins in a bioadhesive gel showed limited efficacy in reversing or down-grading oral dysplastic lesions (Mallery *et al*, 2008; Shumway *et al*, 2008). A study exploring the pharmacokinetics and distribution/uptake of this gel to target tissues in oral

lesion-free subjects demonstrated variability suggesting that these local factors could influence efficacy (Ugalde *et al*, 2009).

Observational studies using topical application of the photosensitizing agent 5-aminolevulinic acid applied to oral premalignant lesions followed by photodynamic therapy using a red light (630 nm) have reported a high response rate up to 6 months (Kubler *et al*, 1998; Sieron *et al*, 2003). The use of such topical photosensitizers may also facilitate early detection of potentially malignant oral lesions (Chang and Wilder-Smith, 2005). Further studies using this novel technique are needed.

Oral mucositis

Mucositis is an inflammatory condition of the oral mucosa, which results from cancer chemotherapy, particularly marrow conditioning regimens for bone marrow transplantation and head and neck radiotherapy, particularly for treatment of oral cancer. Dose-related mucosal damage results in painful ulceration and problems associated with eating, speaking and swallowing and an increased risk of infections. This can lead to significant morbidity and even delays or abandonment of anti-cancer treatment.

Current treatment. Current strategies for prevention and treatment of oral mucositis have been extensively reviewed in two recent Cochrane reviews (Worthington *et al*, 2007; Clarkson *et al*, 2010).

Problems with current treatment. Current treatments do not prevent patients developing mucositis; they are of low efficacy and mucositis still limits the use of chemotherapy and radiotherapy.

Novel formulations/research into improved topical drug delivery for mucositis. Intraepithelial delivery of transforming growth factor beta-3 (TGF-β3) to inhibit epithelial cell proliferation could have potential for the prevention of mucositis (Sonis *et al*, 1997; Squier *et al*, 1999). TGF-β3 temporarily arrests the cell division, protecting the cells from chemotherapy damage, but permits rapid proliferation and repopulation post-treatment. Topically delivered TGF-β3 was able to penetrate the epithelium and could be detected in the basal cell layer at therapeutically effective concentrations (Squier *et al*, 1999). Fifty per cent of TGF-β3 was found in the original homodimer state indicating that sufficient amounts of TGF-β3 remained stable in the epithelium and the saliva (Squier *et al*, 1999). Senel *et al* encapsulated TGF-β3 in a chitosan gel (a bioadhesive, biocompatible and biodegradable polymer commonly used as a permeability enhancer for medical applications) and demonstrated improved drug retention at the application site, six- to sevenfold increased permeability and protection against *Candida* infection (Senel *et al*, 2000). It is speculated that the chitosan could also provide a protective and lubricating barrier to reduce the discomfort experienced by patients suffering from the inflammatory and ulcerative condition of mucositis (Senel *et al*, 2000). There is also interest in the topical delivery of keratinocyte growth factor (KGF) for the prevention and treatment of mucositis. Currently, this drug is administered systemically (Spielberger *et al*, 2004).

Other treatment strategies include the use of mucoadhesive covering agents in the form of viscous mouthwashes and gels that provide physical coating and protection for thinned or ulcerated oral mucosa e.g. Gengigel®, Gelclair® and MuGard®. These agents do appear to provide some symptomatic relief for patients with mucositis. There is also some encouraging data on the potential beneficial effects of using a supersaturated calcium phosphate mouthwash to prevent oral mucositis (Papas *et al*, 2003).

Immunologically mediated diseases

Immunologically mediated diseases constitute one of the most common groups of disorders to affect the oral mucosa and thus form one of the main therapeutic challenges of contemporary oral medicine practice. These disorders usually centre upon T-cell [e.g. oral lichen planus (Sugerman *et al*, 2002; Lodi *et al*, 2005)] and/or B-cell [e.g. pemphigus (Mignogna *et al*, 2009) and mucous membrane pemphigoid (MMP) (Al-Johani *et al*, 2007)] dysfunction, although the precise immunological drivers of disorders such as recurrent aphthous stomatitis remain unclear (Jurge *et al*, 2006).

Current treatment and future treatment directions by disorder. *Oral lichen planus (OLP):* To date, the mainstay of therapy of OLP has been topical corticosteroids, but there have been few randomized controlled trials to definitively prove effectiveness (Zakrzewska *et al*, 2005). There is evidence that topical application of corticosteroids such as betamethasone mouthwash, fluticasone spray, fluocinolone cream, fluocinolone acetonide gel or in adhesive paste, dexamethasone mouthwash, clobetasol propionate (as cream, aqueous solution, ointment or in an oral adhesive paste) and mometasone furoate can each cause a lessening of the symptoms of OLP [reviewed by (Thongprasom and Dhanuthai, 2008)]. In recent years, there have been several studies of the potential efficacy of topical calcineurin inhibitors, notably tacrolimus and pimecrolimus for the treatment of OLP, but as yet there remain no well-powered studies that truly demonstrate clinical efficacy – although they may have a therapeutic role in the management of OLP that is recalcitrant to topical corticosteroids [reviewed by (Al Johani *et al*, 2009; Lopez-Jornet *et al*, 2010)].

Oral lichen planus has been suggested to be a TNF-α-driven disorder (Thornhill, 2001, 2010; Sugerman *et al*, 2002) and of relevance topical thalidomide (1% in paste) may be as effective as topical 0.043% dexamethasone in paste for the short-term treatment of OLP. Similarly, there are reports of systemic thalidomide being effective for mucocutaneous LP (Maender *et al*, 2005; Petropoulou *et al*, 2006). However, the use of thalidomide, even topically, is of concern because of its known adverse side effect profile (Porter and Jorge, 2002); however, the advent of thalidomide analogues with fewer side effects may provide the opportunity for

local application of such anti-TNF-α agents. The human anti-TNF-α monoclonal adalimumab has been reported to cause resolution of cutaneous and vulval LP (Chao, 2009); however, LP-like disease has been reported as an adverse side effect of infliximab and adalimumab (Asarch *et al*, 2009), indeed OLP secondary to thalidomide has previously been reported (Bez *et al*, 1999). There are no open or randomized controlled studies of the efficacy of infliximab, adalimumab or etanercept for the treatment of LP. Similarly, the role of TNF-α in the pathogenesis of LP remains unclear. These, together with the challenge of the known adverse side effects of TNF-α agents, and the possible risk of reactivation of TB, would suggest that their systemic use for OLP may be questionable. Delivery systems that facilitate topical delivery of these to affected areas of mucosa could, however, revolutionize the treatment of OLP.

Similar to the TNF-α biological agents, there are almost no data on the potential efficacy of rituximab [an anti-CD 20 (B-cell) monoclonal antibody], although there is one report of clinical efficacy in a patient with oral, cutaneous and oesophageal disease (Parmentier *et al*, 2008). In view of the likely central role of T-cells in the pathogenesis of OLP (Thornhill, 2001, 2010; Carrozzo and Thorpe, 2009) it would be challenging, if not unjustifiable, to develop a therapeutic strategy based around rituximab.

Pemphigus. The clinical spectrum of pemphigus vulgaris (PV) (the most common form of oral mucosal pemphigus) (Black *et al*, 2005) suggests that topical agents are likely to have a role in the management of oral disease, although this will depend upon the severity of disease. As with OLP, the topical agents that have previously been employed have largely comprised different corticosteroids, and there have been some reports of efficacy with topical ciclosporin or tacrolimus for corticosteroid-recalcitrant oral disease [reviewed by (Al Johani *et al*, 2009)]. Systemic corticosteroids are the first-line therapy for severe oral and/or cutaneous PV (Knudson *et al*, 2010) and a spectrum of corticosteroid sparing agents have been proposed as adjuvant therapies. The latter include azathioprine, methotrexate, mycophenolate mofetil (Beissert *et al*, 2010; Koga *et al*, 2010), cyclophosphamide, ciclosporin (Knudson *et al*, 2010) and perhaps systemic tacrolimus (Busing *et al*, 2010). Intravenous immunoglobulin (IVIG) is suggested by some authorities to be effective for rapidly progressing, severe and/or treatment-resistant PV (Mignogna *et al*, 2010). There is some evidence that the anti-TNF-α biological agents or rituximab are of benefit in the treatment of PV that involves the oral mucosa [reviewed by (Mignogna *et al*, 2009)]. Again, topical delivery systems that could efficiently deliver antibody based biological agents to oral lesions could avoid the necessity for systemic administration with its attendant side effects. Of relevance to local application of drugs, adjuvant perilesional or intralesional triamcinolone acetonide injections may lessen or cause resolution of signs and symptoms of oral PV (Mignogna *et al*, 2010).

Mucous membrane pemphigoid. Strategies for MMP disease that are severe and/or recalcitrant to topical corticosteroids include azathioprine, dapsone (Gurcan and Ahmed, 2009) and other conventional corticosteroid-sparing agents. There are some data suggesting that anti- TNF-α agents or rituximab may be of potential benefit but most information is based upon case reports and small case series of severe disease (Peterson and Chan, 2009). As PV and MMP are antibody-mediated autoimmune diseases, it could be argued that anti-B-cell therapies might be a more logical choice in these conditions than OLP.

Recurrent aphthous stomatitis. Although a wide range of therapeutic strategies have been suggested [reviewed by (Scully *et al*, 2003; Jurge *et al*, 2006)], there are few well-designed randomized controlled trials of possible therapies for recurrent aphthous stomatitis (RAS). The mainstays of therapy across the globe remain topical antimicrobials (of which chlorhexidine is the most common and assessed agent) and topical corticosteroids (Porter and Scully, 2005; Jurge *et al*, 2006; Scully and Porter, 2008). Amlexanox (as cream or Oradisk) has been suggested as an effective therapy for the management of both preventing and resolving the oral ulceration (Khandwala *et al*, 1997; Murray *et al*, 2005, 2006), but this agent remains unavailable throughout Europe. There is some evidence that systemic immunosuppressives such as azathioprine and colchicine may lessen the severity or recurrence of RAS but disease may still arise. In contrast, thalidomide (and perhaps pentoxifyline) reduces the frequency and severity of ulceration, suggesting perhaps that TNF-α may be of pathogenic significance. Certainly RAS would seem to reflect a local immunologically driven cytotoxic effect (Jurge *et al*, 2006); hence, agents that locally target such responses would seem to be key to future therapy. As with OLP, topical drug-delivery systems that cover lesional tissue and deliver anti-TNF-α biological agents, thalidomide or reduced side effect thalidomide analogues could result in more effective treatments for RAS without the need to resort to systemic therapies (such as thalidomide) with their associated side effects.

Future directions for immunologically mediated oral disease. The vast majority of studies of local therapeutic approaches to immunologically mediated oral mucosal disease have centred upon use of commercially available preparations that have principally been designed for cutaneous application. These preparations are highly unlikely to be appropriate for the mouth and as such probably have a suboptimal effect on the target disease. The recent report that mucoadhesive prolonged-release clobetasol tablets may be more effective than clobetasol ointment for the treatment of OLP would suggest that this is indeed true at least with respect to OLP (Cilurzo *et al*, 2010). There are now several potent systemic drugs and antibody-based biological agents with the potential to interfere more effectively in the disease processes of immunologically mediated oral diseases. Currently, these drugs must be given systemically and they have

serious side effects that limit their use to severe and recalcitrant cases. However, the development of effective topical oral mucosal delivery systems for these drugs would simplify their use, target treatment to disease-affected mucosa, thereby reducing the risk of systemic side effects, and raise the prospect of providing more effective treatments to a much wider range of patients affected by these diseases.

Infections

Infectious agents targeting the oral mucosa include viral, fungal and bacterial species. The diversity and scope of these infections were recently reviewed (Dahlen, 2009; Sallberg, 2009; Samaranayake *et al*, 2009; Slots, 2009). Host exposure to infectious agents, changes in the oral environment, interactions with the oral microbiome (Dewhirst *et al*, 2010) and reduced host defences all potentially contribute to development of opportunistic and non-opportunistic infections of the oral mucosa. Topical and locally delivered antibiotics and antiseptics for the oral and periodontal diseases, such as chlorhexidine, tetracycline, doxicycline, minocycline and metronidazole, have been reviewed elsewhere (Etienne, 2003) and will not be discussed here.

Current treatment. Antifungal drugs are commonly delivered topically to the oral mucosa to treat oral candidiasis (Zhang *et al*, 2007). The most commonly used formulations include topical nystatin, clotrimazole, miconazole and itraconazole. Currently, there are no effective topical treatments available for intra-oral infections caused by the human herpes viruses or the human papilloma viruses or picornaviruses. Antiviral topical therapies (5% acyclovir cream, 1% penciclovir cream, 10% docosanol cream and 3% foscarnet cream) are available for recurrent labial herpes (Woo and Challacombe, 2007) and some providers have used dermatologic antiviral or sclerosing preparations in the mouth.

Problems with current treatment. One component of difficulty in effective management of infections is the development of drug resistance. Azole drug resistance is the most common problem encountered in managing oral candidiasis and is related primarily to systemic drug therapy (Yang *et al*, 2008). Acyclovir and penciclovir resistance is also a growing problem particularly among immune-compromised patients (Woo and Challacombe, 2007). The efficacy of local drug delivery may not be sufficiently high to resolve infections. In addition, yeasts may play a synergistic pathogenic role with opportunistic bacterial pathogens in oral mucosal infections, making multipathogen infections more complex to manage.

Novel formulations/research into improved topical drug delivery for oral infections. Advances in prevention and management of oral mucosal infections will require new agents and improved mechanisms of topical drug delivery. A phase III randomized clinical trial of a diluted 0.00165% topical gentian violet mouthrinse (Traboulsi *et al*, 2008) compared with nystatin mouthrinse to treat oral candidiasis associated with human immunodeficiency virus is currently being conducted by international investigators in the U.S. AIDS Clinical Trials Network. Use of probiotics delivered by lozenges or in chewing gum has been suggested for altering oral infectious disease susceptibility (primarily to dental caries and periodontitis, but to a lesser extent oral fungal infections) via inter-microbial species interactions and induction of immuno-stimulatory effects (Meurman, 2005; Stamatova and Meurman, 2009).

Antiviral and antifungal pharmacokinetics need to be altered to allow targeted delivery, rapidly followed by sustained release and prolonged retention of high drug concentration localized at the oral infection site. To enhance the bioavailability and therapeutic efficacy of existing azole antifungals, new drug delivery strategies and drug formulations are needed to improve the aqueous wetting and dissolution properties of azole antifungals by increasing their chemical potential, stabilizing the drug-delivery system and targeting high concentration of the azoles to the infection sites (Yang *et al*, 2008).

A mucoadhesive buccal slow-release tablet formulation containing 50 mg of miconazole applied once daily to treat pseudomembranous candidiasis has shown efficacy and reduces the need for the repeated applications associated with conventional topical antifungal agents (Vazquez *et al*, 2010). A similar product containing acyclovir has been developed and is in phase III clinical trials for once daily local treatment for recurrent herpes labialis. An occlusive hydrocolloid patch, devoid of any medication has shown similar efficacy to topical acyclovir in the management of herpes labialis (Karlsmark *et al*, 2008).

Neuropathic pain

Neuropathic pain, defined as a condition that is initiated or caused by a primary lesion or dysfunction in the nervous system, has various aetiologies from local trauma to central nervous system pathologies (Colombo *et al*, 2006). In the orofacial region, this can be caused by deafferentation pain, traumatic neuroma, or trigeminal or glossopharyngeal neuralgia. Additional orofacial neuropathic conditions include atypical odontalgia and burning mouth syndrome. Neuropathic pain has a severe psychosocial impact on quality of life and mood of affected patients and substantial societal costs.

Current treatment. There are numerous systemic treatments for neuropathic pain (Dworkin *et al*, 2010). Burning mouth syndrome is a neuropathic pain managed initially with topical clonazepam and then with other neuropathic drugs (Zakrzewska, 2010). Currently, topical formulations of capsaicin (cream) and lidocaine (patch) are available for treating neuropathic pain in humans. Topical medication in combination with systemic medications can reduce orofacial neuropathic pain severity (Heir *et al*, 2008).

Problems with current treatment. Systemic pharmacologic treatment is often accompanied by unpleasant side effects such as sedation, dizziness and drug interactions. In the majority of patients, existing therapies for neuropathic pain are far from effective and are symptomatic rather than disease modifying or curative. Topical medications seem to have increased effectiveness when initial pain levels are mild to moderate (Heir *et al*, 2008).

Novel formulations and research into improved topical drug delivery for neuropathic pain. Advances in appreciation of the molecular entities involved in initiation of pain, the role of particular afferents (small and large diameter, injured and uninjured), and the contribution of inflammation will open doors to novel formulations and local delivery modes (Sawynok, 2005). Emerging therapeutic modalities targeting a variety of mechanisms associated with neuropathic pain disorders should be given priority as should the development of increasingly sophisticated tools for measuring and categorizing neuropathic pain (Backonja and Woolf, 2010).

Preclinical studies provide evidence that peripheral applications of opioids, alpha-adrenergic agents and antidepressants also may be beneficial in neuropathic pain, and some clinical reports provide support for topical applications of such agents (Sawynok, 2005). Finding effective topical drug-delivery systems for these agents will be crucial in optimizing their therapeutic potential and efficacy.

Salivary hypofunction and xerostomia

Salivary hypofunction is associated with a reduction in salivary fluid volume and/or a change in salivary composition. It often correlates with xerostomia, the subjective experience of a dry mouth. There are numerous causes including xerogenic medications, systemic diseases such as Sjögren's syndrome, diabetes, or HIV infection or radiotherapy for head and neck cancer. Salivary hypofunction may be reversible or irreversible and if chronic can have a number of consequences including increased dental caries, oral candidiasis, problems associated with eating, speaking, use of dentures and general mouth comfort.

Current treatment. Treatment is contingent upon the degree of hypofunction and includes the use of systemic sialogogues, electrical stimulation, gustatory agents and saliva substitutes/lubricants. In Sjögren's syndrome and postradiation patients with some residual function, the systemic use of the muscarinic agents pilocarpine and cevimeline shows benefit (von Bultzingslowen *et al*, 2007; Jensen *et al*, 2010; Ramos-Casals *et al*, 2010). Palliative therapy includes the use of gustatory agents (sugar free chewing gum, mints, lemon drops), saliva substitutes and lubricants in various formulations (gels, rinses, sprays).

Problems with current treatment. Problems with current treatment are that muscarinic agonists have potential cardiorespiratory and other unpleasant side effects and palliative therapies have no sustained effect.

Novel formulations and research into improved topical drug delivery for salivary dysfunction. In Sjögren's syndrome and postradiation salivary gland dysfunction, evidence from controlled trials suggests benefit of salivary gland stimulation from systemically ingested muscarinic agonists, pilocarpine and cevimeline, for sicca features. Palliative therapy includes replacement of lost fluid with artificial salivary formulations or mucosal lubricants (gels, rinses, sprays) and sugar-free gums and mints.

Problems with current treatment. Problems with current treatment are that muscarinic agonists have unpleasant side effects and palliative therapies have no sustained effect.

Novel formulations/research into improved topical drug delivery for salivary dysfunction. As reviewed in Thelin *et al*, 2008, preventing fluid absorption from the oral cavity will improve oral hydration and prevent the clinical symptoms and discomfort associated with dry mouth. Therapeutic strategies that prevent fluid absorption and improve oral fluid balance may provide relief for those suffering from dry mouth. Epithelial sodium channel blockers, such as P-552 under phase II study by Parion Sciences, Durham NC, USA, are unique therapeutic agents developed to maintain and stimulate hydration on the body's mucosal surfaces, including those of the lung, mouth, nose, eye and gastrointestinal tract. Topical delivery is possible by oral rinse or oral spray to provide lasting effect.

In a small double-blind, crossover, randomized controlled trial, locally applied physostigmine (1.8 mg) gel produced long-lasting (120 min) relief in the feeling of dryness among subjects suffering from dry mouth and with hyposalivation (Khosravani *et al*, 2009). In addition, there is some suggestion that 150 IU interferon-alpha lozenges three times daily may enhance salivary secretion in patients with primary Sjögren's syndrome (Cummins *et al*, 2003; von Bultzingslowen *et al*, 2007). Anhydrous crystalline maltose, a food stabilizer and desiccant for use in foods, cosmetics, and pharmaceuticals, when delivered orally as a 200-mg lozenge three times daily for 24 weeks in patients with primary Sjögren's syndrome, resulted in improved salivary output and decreased complaints of dry mouth (Fox *et al*, 2002). Moreover, the presence of a mucoadhesive in the mouth three times a day appears to increase salivary flow and the subjective impression of moisture (Kerr *et al*, 2010).

Currently clinical investigations are underway using aquaporin gene therapy for restoring function of salivary gland tissues in patients with postradiation therapy salivary hypofunction and there is a potential application for this gene therapy in patients with Sjogren's syndrome as well (Baum *et al*, 2010).

Future drugs: challenge of delivery

Antibody-based drugs, peptides and other biological agents

Novel macromolecular biological drugs, including antibody based drugs (e.g. rituximab and infliximab), peptides, other biological molecules and gene therapy, have the potential to improve dramatically the treatment of many chronic oral conditions if their delivery can be optimized. Currently, delivery of these drugs can only be achieved by injection as they are destroyed in the gastrointestinal tract when delivered orally. This severely limits their usefulness for treating chronic diseases including most immune-inflammatory oral diseases. Although some of these drugs could be applied topically to oral mucosal lesions, buccal delivery exposes the drugs to the enzymatic activity of saliva and epithelial cells and can reduce the bioavailability of protein or peptide drugs by 95% (Madhav *et al*, 2009). Attempts to protect biological drugs from the enzymatic environment (e.g. in nanocarriers) or reduce the enzymatic activity of the epithelium (e.g. with enzyme inhibitors) may overcome this problem and enable therapeutic proteins and biological drugs to be delivered topically to oral mucosal lesions or systemically *via* the oral mucosa. Due to the size and other physical properties of many protein and antibody-based biological agents, mucosal penetration is extremely poor and permeability enhancers or drug carrier systems are necessary to improve penetration.

Therapeutic anti-TNF-α antibodies and peptides and other similar 'biologicals' have huge potential for improving the treatment of common oral mucosal diseases such as OLP and RAS. Currently, this is precluded by the need for long-term parenteral administration and the risk of potentially serious systemic side effects. However, the use of topical delivery systems that could deliver these agents directly across the oral mucosa to the site of disease could dramatically improve the treatment of these conditions whilst limiting the potential of systemic complications.

Conclusions

Topical delivery of drugs for the treatment of mucosal diseases is able to reduce side effects and improve treatment outcomes. The potential for topical delivery systems in oral medicine has not yet been fully realized and further research targeted to oral medicine applications is needed in order to improve treatment outcomes for the diseases and disorders discussed here. Currently used dermatological topical treatments have not been designed for oral applications and are therefore often inappropriate for oral mucosa use. Many of the challenges in delivery relate to overcoming the permeability barrier, protecting drugs from enzymatic environments and ensuring that drugs reach their target at therapeutic concentrations, and these are being investigated with novel formulations and technologies. Many of the formulations and technologies that could enhance topical and systemic drug delivery across the oral mucosa are explored in more depth in a separate review by the same group of authors.

Acknowledgements

Sankar, Hearnden, Kerr, Patton, Porter, Hull,Vidovic Juras and Thornhill were all involved in analysing the data and drafting the paper. Authors Thornhill, Greenberg, and Lockhart were involved with designing the review, determining the scope and structure as well as editing the paper. Some of the work undertaken by SR Porter was within UCL/UCLH who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

References

Al Johani KA, Hegarty AM, Porter SR *et al* (2009). Calcineurin inhibitors in oral medicine. *J Am Acad Dermatol* **61:** 829–840.

Al-Johani KA, Fedele S, Porter SR (2007). Erythema multiforme and related disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103:** 642–654.

Asarch A, Gottlieb AB, Lee J *et al* (2009). Lichen planus-like eruptions: an emerging side effect of tumor necrosis factor-alpha antagonists. *J Am Acad Dermatol* **61:** 104–111.

Backonja M, Woolf CJ (2010). Future directions in neuropathic pain therapy: closing the translational loop. *Oncologist* **15**(Suppl. 2)**:** 24–29.

Bánóczy J, Squier CA, Kremer M *et al* (2003). The permeability of oral leukoplakia. *Eur J Oral Sci* **111:** 312–315.

Baum BJ, Adriaansen J, Cotrim AP *et al* (2010). Gene therapy of salivary diseases. In: Seymour GJ, ed. *Oral biology*, *Methods Mol Biol*, Springer, New York., pp. 3–20.

Beissert S, Mimouni D, Kanwar AJ *et al* (2010). Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebo-controlled trial. *J Invest Dermatol* **130:** 2041–2048.

Bez C, Lodi G, Sardella A *et al* (1999). Oral lichenoid lesions after thalidomide treatment. *Dermatology* **199:** 195.

Black M, Mignogna MD, Scully C (2005). Number II. Pemphigus vulgaris. *Oral Dis* **11:** 119–130.

von Bultzingslowen I, Sollecito TP, Fox PC *et al* (2007). Salivary dysfunction associated with systemic diseases: systematic review and clinical management recommendations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103**(Suppl.)**:** S57e1–S57e15.

Busing V, Kern JS, Bruckner-Tuderman L *et al* (2010). Recalcitrant pemphigus vulgaris responding to systemic tacrolimus. *Dermatology* **221:** 122–126.

Carrozzo M, Thorpe R (2009). Oral lichen planus: a review. *Minerva Stomatol* **58:** 519–537.

Chang CJ, Wilder-Smith P (2005). Topical application of photofrin for photodynamic diagnosis of oral neoplasms. *Plast Reconstr Surg* **115:** 1877–1886.

Chao TJ (2009). Adalimumab in the management of cutaneous and oral lichen planus. *Cutis* **84:** 325–328.

Cilurzo F, Gennari CG, Selmin F *et al* (2010). A new mucoadhesive dosage form for the management of oral lichen planus: formulation study and clinical study. *Eur J Pharm Biopharm* **2010:** 11.

Clarkson JE, Worthington HV, Furness S *et al* (2010). Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* **8:** CD001973.

Colombo B, Annovazzi PO, Comi G (2006). Medications for neuropathic pain: current trends. *Neurol Sci* **27**(Suppl. 2)**:** S183–S189.

Cummins MJ, Papas A, Kammer GM *et al* (2003). Treatment of primary Sjogren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. *Arthritis Rheum* **49:** 585–593.

Dahlen G (2009). Bacterial infections of the oral mucosa. *Periodontol 2000* **49:** 13–38.

Dewhirst FE, Chen T, Izard J *et al* (2010). The human oral microbiome. *J Bacteriol* **192:** 5002–5017.

Dworkin RH, O'Connor AB, Audette J *et al* (2010). Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* **85:** S3–S14.

Epstein JB, Gorsky M (1999). Topical application of vitamin A to oral leukoplakia: a clinical case series. *Cancer* **86:** 921–927.

Epstein JB, Wong FL, Millner A *et al* (1994). Topical bleomycin treatment of oral leukoplakia: a randomized double-blind clinical trial. *Head Neck* **16:** 539–544.

Epstein JB, Gorsky M, Wong FL *et al* (1998). Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer* **83:** 629–634.

Etienne D (2003). Locally delivered antimicrobials for the treatment of chronic periodontitis. *Oral Dis* **9**(Suppl. 1)**:** 45–50.

Fox PC, Cummins MJ, Cummins JM (2002). A third study on the use of orally administered anhydrous crystalline maltose for relief of dry mouth in primary Sjogren's syndrome. *J Altern Complement Med* **8:** 651–659.

Gaeta GM, Gombos F, Femiano F *et al* (2000). Acitretin and treatment of the oral leucoplakias. A model to have an active molecules release. *J Eur Acad Dermatol Venereol* **14:** 473–478.

Ganem-Quintanar A, Falson-Rieg F, Buri P (1997). Contribution of lipid components to the permeability barrier of oral mucosa. *Eur J Pharm Biopharm* **44:** 107–120.

Gold KA, Lee HY, Kim ES (2009). Targeted therapies in squamous cell carcinoma of the head and neck. *Cancer* **115:** 922–935.

Gurcan HM, Ahmed AR (2009). Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol* **10:** 383–396.

Haddad RI, Shin DM (2008). Recent advances in head and neck cancer. *N Engl J Med* **359:** 1143–1154.

Harsanyi BB, Hilchie JC, Mezei M (1986). Liposomes as drug carriers for oral ulcers. *J Dent Res* **65:** 1133–1141.

Heir G, Karolchek S, Kalladka M *et al* (2008). Use of topical medication in orofacial neuropathic pain: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **105:** 466–469.

Hoogstraate AJ, Cullander C, Nagelkerke JF *et al* (1994). Diffusion rates and transport pathways of fluorescein isothiocyanate (FITC)-labelled model compounds through buccal epithelium. *Pharm Res* **11:** 83–89.

Jensen SB, Pedersen AM, Vissink A *et al* (2010). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. *Support Care Cancer* **18:** 1061–1079.

Jurge S, Kuffer R, Scully C *et al* (2006). Mucosal disease series. Number VI. Recurrent aphthous stomatitis. *Oral Dis* **12:** 1–21.

Karlsmark T, Goodman JJ, Drouault Y *et al* (2008). Randomized clinical study comparing Compeed cold sore patch to acyclovir cream 5% in the treatment of herpes simplex labialis. *J Eur Acad Dermatol Venereol* **22:** 1184–1192.

Kelloff GJ, Lippman SM, Dannenberg AJ *et al* (2006). Progress in chemoprevention drug development: the promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer – a plan to move forward. *Clin Cancer Res* **12:** 3661–3697.

Kerr A, Corby P, Shah S *et al* (2010). Use of a mucoadhesive disk for relief of dry mouth. A randomized, double-masked, controlled, crossover study. *J Am Dent Assoc* **141:** 1250–1256.

Khandwala A, Van Inwegen RG, Alfano MC (1997). 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **83:** 222–230.

Khosravani N, Birkhed D, Ekstrom J (2009). The cholinesterase inhibitor physostigmine for the local treatment of dry mouth: a randomized study. *Eur J Oral Sci* **117:** 209–217.

Knudson RM, Kalaaji AN, Bruce AJ (2010). The management of mucous membrane pemphigoid and pemphigus. *Dermatol Ther* **23:** 268–280.

Koga H, Ishii N, Hamada T *et al* (2010). Successful treatment with mycophenolate mofetil of four Japanese patients with pemphigus vulgaris. *Eur J Dermatol* **20:** 472–475.

Kubler A, Haase T, Reinwald M *et al* (1998). Treatment of oral leukoplakia by topical application of 5-aminolevulinic acid. *Int J Oral Maxillofac Surg* **27:** 466–469.

Kulkarni U, Mahalingam R, Pather SI *et al* (2009). Porcine buccal mucosa as an in vitro model: relative contribution of epithelium and connective tissue as permeability barriers. *J Pharm Sci*. **98:** 471–483.

Li N, Sood S, Wang S *et al* (2005). Overexpression of 5-lipoxygenase and cyclooxygenase 2 in Hamster and human oral cancer and chemopreventive effects of zileuton and celecoxib. *Clin Cancer Res* **11:** 2089–2096.

Lodi G, Scully C, Carrozzo M *et al* (2005). Current controversies in oral lichen planus: report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **100:** 40–51.

Lodi G, Sardella A, Bez C *et al* (2006). Interventions for treating oral leukoplakia. *Cochrane Database Syst Rev* **18:** CD001829.

Lopez-Jornet P, Camacho-Alonso F, Salazar-Sanchez N (2010). Topical tacrolimus and pimecrolimus in the treatment of oral lichen planus: an update. *J Oral Pathol Med* **39:** 201–205.

Madhav NVS, Shakya AK, Shakya P *et al* (2009). Orotransmucosal drug delivery systems: a review. *J Control Release* **140:** 2–11.

Maender JL, Krishnan RS, Angel TA *et al* (2005). Complete resolution of generalized lichen planus after treatment with thalidomide. *J Drugs Dermatol* **4:** 86–88.

Maggi L, Segale L, Conti S *et al* (2005). Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. *Eur J Pharm Sci* **24:** 487–493.

Mallery SR, Zwick JC, Pei P *et al* (2008). Topical application of a bioadhesive black raspberry gel modulates gene expression and reduces cyclooxygenase 2 protein in human premalignant oral lesions. *Cancer Res* **68:** 4945–4957.

Meurman JH (2005). Probiotics: do they have a role in oral medicine and dentistry? *Eur J Oral Sci* **113:** 188–196.

Mignogna MD, Fortuna G, Leuci S (2009). Oral pemphigus. *Minerva Stomatol* **58:** 501–518.

Mignogna MD, Fortuna G, Leuci S *et al* (2010). Adjuvant triamcinolone acetonide injections in oro-pharyngeal pemphigus vulgaris. *J Eur Acad Dermatol Venereol* **2010:** 5.

Mulshine JL, Atkinson JC, Greer RO *et al* (2004). Randomized, double-blind, placebo-controlled phase IIB trial of the cyclooxygenase inhibitor ketorolac as an oral rinse in oropharyngeal leukoplakia. *Clin Cancer Res* **10:** 1565–1573.

Murray B, McGuinness N, Biagioni P *et al* (2005). A comparative study of the efficacy of Aphtheal in the management of recurrent minor aphthous ulceration. *J Oral Pathol Med* **34:** 413–419.

Murray B, Biagioni PA, Lamey PJ (2006). The efficacy of amlexanox OraDisc on the prevention of recurrent minor aphthous ulceration. *J Oral Pathol Med* **35:** 117–122.

Nanci A (2003). *Ten Cate's oral histology-development, structure and function*. Mosby: MO, USA.

Papas AS, Clark RE, Martuscelli G *et al* (2003). A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* **31:** 705–712.

Parmentier L, Bron BA, Prins C *et al* (2008). Mucocutaneous lichen planus with esophageal involvement: successful treatment with an anti-CD20 monoclonal antibody. *Arch Dermatol* **144:** 1427–1430.

Peterson JD, Chan LS (2009). Effectiveness and side effects of anti-CD20 therapy for autoantibody-mediated blistering skin diseases: a comprehensive survey of 71 consecutive patients from the Initial use to 2007. *Ther Clin Risk Manag* **5:** 1–7.

Petropoulou H, Kontochristopoulos G, Kalogirou O *et al* (2006). Effective treatment of erosive lichen planus with thalidomide and topical tacrolimus. *Int J Dermatol* **45:** 1244–1245.

Piattelli A, Fioroni M, Santinelli A *et al* (1999). bcl-2 expression and apoptotic bodies in 13-cis-retinoic acid (isotretinoin)-topically treated oral leukoplakia: a pilot study. *Oral Oncol* **35:** 314–320.

Porter SR, Jorge J Jr (2002). Thalidomide: a role in oral oncology? *Oral Oncol* **38:** 527–531.

Porter S, Scully C (2005). Aphthous ulcers (recurrent). *Clin Evid* **13:** 1687–1694.

Ramos-Casals M, Tzioufas AG, Stone JH *et al* (2010). Treatment of primary Sjogren syndrome: a systematic review. *JAMA* **304:** 452–460.

Rudin CM, Cohen EE, Papadimitrakopoulou VA *et al* (2003). An attenuated adenovirus, ONYX-015, as mouthwash therapy for premalignant oral dysplasia. *J Clin Oncol* **21:** 4546–4552.

Salamat-Miller N, Chittchang M, Johnston TP (2005). The use of mucoadhesive polymers in buccal drug delivery. *Adv Drug Deliv Rev* **57:** 1666–1691.

Sallberg M (2009). Oral viral infections of children. *Periodontol 2000* **49:** 87–95.

Samaranayake LP, Keung LW, Jin L (2009). Oral mucosal fungal infections. *Periodontol 2000* **49:** 39–59.

Sawynok J (2005). Topical analgesics in neuropathic pain. *Curr Pharm Des* **11:** 2995–3004.

Scully C, Porter S (2008). Oral mucosal disease: recurrent aphthous stomatitis. *Br J Oral Maxillofac Surg* **46:** 198–206.

Scully C, Gorsky M, Lozada-Nur F (2003). The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc* **134:** 200–207.

Senel S, Kremer MJ, Kas S *et al* (2000). Enhancing effect of chitosan on peptide drug delivery across buccal mucosa. *Biomaterials* **21:** 2067–2071.

Shimono M, Clementi F (1976). Intercellular junctions of oral epithelium. I. Studies with freeze-fracture and tracing methods of normal rat keratinized oral epithelium. *J Ultrastruct Res* **56:** 121–136.

Shojaei AH (1998). Buccal mucosa as a route for systemic drug delivery: a review. *J Pharm Pharm Sci* **1:** 15–30.

Shumway BS, Kresty LA, Larsen PE *et al* (2008). Effects of a topically applied bioadhesive berry gel on loss of heterozygosity indices in premalignant oral lesions. *Clin Cancer Res* **14:** 2421–2430.

Sieron A, Adamek M, K-K A *et al* (2003). Photodynamic therapy (PDT) using topically applied [delta]-aminolevulinic acid (ALA) for the treatment of oral leukoplakia. *J Oral Pathol Med* **32:** 330–336.

Silverman S Jr, Gorsky M, Lozada F (1984). Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer* **53:** 563–568.

Slots J (2009). Oral viral infections of adults. *Periodontol 2000* **49:** 60–86.

Sonis ST, Van Vugt AG, Brien JP *et al* (1997). Transforming growth factor-beta 3 mediated modulation of cell cycling and attenuation of 5-fluorouracil induced oral mucositis. *Oral Oncol* **33:** 47–54.

Sood S, Shiff SJ, Yang CS *et al* (2005). Selection of topically applied non-steroidal anti-inflammatory drugs for oral cancer chemoprevention. *Oral Oncol* **41:** 562–567.

Spielberger R, Stiff P, Bensinger W *et al* (2004). Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* **351:** 2590–2598.

Squier CA, Hall BK (1985). The permeability of skin and oral mucosa to water and horseradish peroxidase as related to the thickness of the permeability barrier. *J Invest Dermatol* **84:** 176–179.

Squier CA, Kremer MJ, Bruskin A *et al* (1999). Oral mucosal permeability and stability of transforming growth factor beta-3 in vitro. *Pharm Res* **16:** 1557–1563.

Stamatova I, Meurman JH (2009). Probiotics: health benefits in the mouth. *Am J Dent* **22:** 329–338.

Sudhakar Y, Kuotsu K, Bandyopadhyay AK (2006). Buccal bioadhesive drug delivery – a promising option for orally less efficient drugs. *J Control Release* **114:** 15–40.

Sugerman PB, Savage NW, Walsh LJ *et al* (2002). The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med* **13:** 350–365.

Thelin WR, Brennan MT, Lockhart PB *et al* (2008). The oral mucosa as a therapeutic target for xerostomia. *Oral Dis* **14:** 683–689.

Thongprasom K, Dhanuthai K (2008). Steriods in the treatment of lichen planus: a review. *J Oral Sci* **50:** 377–385.

Thornhill MH (2001). Immune mechanisms in oral lichen planus. *Acta Odontol Scand* **59:** 174–177.

Thornhill MH (2010). The current understanding of the aetiology of oral lichen planus. *Oral Dis* **16:** 507–508.

Traboulsi RS, Mukherjee PK, Ghannoum MA (2008). In vitro activity of inexpensive topical alternatives against Candida spp. isolated from the oral cavity of HIV-infected patients. *Int J Antimicrob Agents* **31:** 272–276.

Tradati N, Chiesa F, Rossi N *et al* (1994). Successful topical treatment of oral lichen planus and leukoplakias with fenretinide (4-HPR). *Cancer Lett* **76:** 109–111.

Ugalde CM, Liu Z, Ren C *et al* (2009). Distribution of anthocyanins delivered from a bioadhesive black raspberry gel following topical intraoral application in normal healthy volunteers. *Pharm Res* **26:** 977–986.

Vazquez J, Patton L, Epstein J *et al* (2010). Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of Miconazole Lauriad® efficacy and safety (SMiLES). *HIV Clin Trials* **11:** 186–196.

Wang Y, Spitz MR, Lee JJ *et al* (2007). Nucleotide excision repair pathway genes and oral premalignant lesions. *Clin Cancer Res* **13:** 3753–3758.

Woo SB, Challacombe SJ (2007). Management of recurrent oral herpes simplex infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103**(Suppl.)**:** S12e1–S12e18.

Worthington HV, Clarkson JE, Eden OB (2007). Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* **17:** CD000978.

Yang W, Wiederhold NP, Williams RO III (2008). Drug delivery strategies for improved azole antifungal action. *Expert Opin Drug Deliv* **5:** 1199–1216.

Zakrzewska JM (2010). Medical management of trigeminal neuropathic pains. *Expert Opin Pharmacother* **11:** 1239–1254.

Zakrzewska JM, Chan ES, Thornhill MH (2005). A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. *Br J Dermatol* **153:** 336–341.

Zhang L, Williams M, Poh CF *et al* (2005). Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. *Cancer Res* **65:** 8017–8021.

Zhang AY, Camp WL, Elewski BE (2007). Advances in topical and systemic antifungals. *Dermatol Clin* **25:** 165–183.