Clinical Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

UCD School of Medicine
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Charles Institute of Dermatology

Special delivery

The UCD Charles Institute Derma Seminar series recently heard a talk by ***Prof David Brayden*** *on his research into administering peptides via oromucosal routes*

The Charles Institute, Ireland's national dermatology research and education centre, hosts a range of guest speakers who cover a variety of topics ranging from skin cancer to psoriasis, among others. The series, which is sponsored by RELIFE (part of the A.Menarini group), is designed to provide expert advice from a range of distinguished national and international experts in their respective fields and is chaired by Prof Desmond Tobin, Full Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars are broadcast to attendees with a special interest in dermatology and cutaneous science in other locations, who access the talks remotely via an audio-visual link.

Attendees heard a presentation from Prof David Brayden, Full Professor of Advanced Drug Delivery at the School of Veterinary Medicine, UCD, and Senior Fellow at the UCD Conway Institute. A pharmacologist, Prof Brayden spent 10 years as a senior scientist with a major pharmaceutical company and is the author or co-author of more than 200 research publications and patents, predominantly in the areas of oral peptide delivery, epithelial drug transport, and nanomedicine formulation. He is currently a co-lead Principal Investigator in the Research Ireland CURAM Centre for Medical Devices and is the Coordinator of the EU Horizon Consortium, BUCCAL-PEP.

Prof Brayden explained that buccal and sublingual epithelia have been used for decades as an administration site for small molecules in the form of tablets, lozenges, and dissolvable films. Research shows that this method of administration achieves blood levels quickly and helps to avoid the first liver pass effect, which represents a major advantage over oral administration.

He provided an overview of the BUCCAL-PEP EU consortium, which was designed to address the novel question of whether peptides can now be administered via oro-mucosal routes. This may be possible through multiple strategies, including patch and film synthesis, permeation enhancers, peptide selection and patient involvement, as well as the use of large animal models for assessment of performance.

Potential

"Following on from my research into oral peptides, I saw that there was a niche potential in looking at the buccal cavity and the inside of the cheek as a route for administration for peptides," Prof Brayden told the attendees. "This is because while oral [administration] is a fantastic achievement if it can be done for peptides, there are some disadvantages with oral that buccal administration can address."

The 'mission statement' of the BUCCAL-PEP concept is stated as: "To make a rapid-acting, once-a-day buccal device

Prof David Brayden

containing a glucacon-like peptide-1 receptor agonist (GLP-1 RA) and a permeation enhancer to deliver the required blood levels and where the patch dissolves and the remaining components are swallowed in 15-30 minutes."

In practice, this involves the BUCCAL-PEP patch, which is placed on the inner cheek. The mucoadhesive layer expands, releasing the enhancer, GDC (sodium glycodeoxycholate), which temporarily increases the permeability of the mucosa. The peptide analogue can then travel through the first layer and diffuse across the epithelium, and the entire patch then disintegrates and a small proportion of the peptide analogue reaches the blood circulation.

Knowledge gaps

Describing his research in this area so far, Prof Brayden told the seminar there are knowledge gaps when it comes to permeation pathways through the buccal epithelium. "We think of it in terms of a paracellular pathway 'sneaking' around between these fatty cells within the epithelium," said Prof Brayden. "And yet, there is also a transcellular pathway, which is obviously going to favour lipophilic small molecules with low molecular weight. When we are working with peptides, we want to exploit that paracellular pathway, because there will be potential to have a hydrophilic route there as well… but we don't really know the details about this. We don't know if there are carriers on buccal epithelia that we have in the small intestine for amino acids and so on, or if we have proper tight junctions, so there is a lot to discover here and hopefully we can address such questions along the way during this project."

This will be one of the main priorities of the BUCCAL-PEP project and will seek to address this knowledge gap using a patch made from biomaterials — the first of its kind to surmount these challenges by combining a permeation enhancer with biomaterials and a peptide analogue in a patch system. Delivering peptide analogues orally has presented a major challenge for researchers up to now, and only five peptide analogues have so far been made into tablets or capsules for oral delivery. As well as low bioavailability, other problems with the oral delivery route have included dose control issues, inconvenient administration, and interactions with food.

Advantages

Prof Brayden and his colleagues in the BUCCAL-PEP project will seek to exploit and develop the advantages of buccal administration for peptides, which include ease of accessibility, rapid onset of action, no liver first-pass, and crucially, good patient adherence. Other advantages include low proteolysis, low level of damage to the tissue, and that patients are free to eat and drink once the patch has dissolved.

However, there are challenges, he pointed out, including obtaining high enough peptide loading in the device, as well as inherently low buccal permeability and the fact that peptides will not cross this barrier without assistance. Other obstacles include the foreign body sensation in the mouth, meaning that the patch must act fast or patients will reject it, and that the device components must be swallowed, so all component materials must be biologically safe.

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"Some of the advantages of the oral route also apply to this route of administration," Prof Brayden told the attendees. "What we are seeing with the small molecules story is good compliance. However, we prefer to use the word 'adherence' rather than compliance. 'Compliance' sounds a little like the doctor talking down to the patient, whereas 'adherence' is more about the patient telling us what they want."

He spoke about synthesis methods in the laboratory and described the process of connecting ex vivo to in vivo studies in pig models. Prof Brayden also presented data that were accrued over several months of work: "We have been working on different ratios of our GLP-1 analogue with GDC, working in 1:1 ratios, 1:2 ratios, and so on," said Prof Brayden.

'Sweet spot'

"We have now reached a ratio 'sweet spot' where we are getting around 8 per cent permeation across pig tissue using a Hill Top Chamber ex vivo, and we have some histology to go with that." The Hill Top Chamber is a patented, widely-used system for administration in a range of areas, including cosmetics and diagnostics, as well as patch testing in animals. It allows assessment of the enhancer and the GLP-1 RA on a cotton pad before moving to the patch designs.

Describing the development of the BUCCAL-PEP mode of delivery, he told the seminar that patients were consulted during the design process. "We decided on 1.5cm x 1.5cm square design," he said. "We saw that the backing layer has to dissolve the slowest — if it dissolves too quickly, everything will just go backwards… you also have to use materials with a history of safe use in humans. The peptide needs to be released in about 15-to-20 minutes; we are also aware that there is a maximum foreign body toleration that we are going to have to deal with."

Prof Brayden concluded: "We are currently investigating a range of prototypes made by five different methods and supported by two formulation approaches, and pig studies are starting this month," he said. These studies will begin with proof of principle studies with GLP-1 RA with GDC in Hill Top Chambers and patches. "We have manufacturing ready to go on a scale that we know works for small molecules," he said, adding that informative reports on economic and healthcare benefits of these potential innovations are also in progress.

Medical approach

In a lively clinical discussion and Q&A following the presentation, Prof Tobin further explored the bench-to-bedside element of Prof Brayden's work, from both the medical and cosmetic perspectives.

He briefly mentioned research on small peptides in which he was previously involved to modulate skin pigmentation. "We were trying to keep things happening only within the skin epidermis, whereas you are trying to get through the epidermis to provide more systemic benefits," said Prof Tobin. "… the strategy for cosmetic skin people is to [work on] the superficial epidermis, but for a medical, metabolic, system-wide approach, you have to try to deliver deeper from say a patch, and perhaps from swallowing?"

"We don't expect residual to [be delivered via] swallowing, because it will be too diluted and not formulated," commented Prof Brayden. "But I do think there is opportunity there for delivery into the epithelium in the mouth for mucositis, for example, or even in oral cancers. So there are definitely opportunities for off-shoots from this work."

RELIFE has had no input into the content of this article or series of seminars.