Introduction
- Feline Chronic Gingivostomatitis (FCGS) is a severe immune-mediated oral inflammatory disease that causes significant morbidity.
- Current treatment consists of full or near-full tooth extraction and life-long therapy with antibiotics, steroids and pain medication. There is currently no cure.
- Pathogenesis is poorly understood; may be a manifestation of an inappropriate host immune response to chronic oral antigenic stimulation secondary to other oral disease or viral infection.
- Identified similar diseases in human patients:
  - Oral Lichen Planus (OLP)
  - Pemphigus vulgaris
  - Aphthous stomatitis
- We propose that FCGS is a relevant, large animal, naturally occurring disease model for these human lesions; current clinical trial in cats demonstrates safety and efficacy of fresh autologous mesenchymal stem cells (MSCs) in cats with FCGS (Figure 1).
- Full pathological characterization of the immune cell subsets in human diseases is a critical step in model development and will greatly assist in appropriate translation to human beings.
- The goal of this study was to characterize the CD4+ and CD8+ T lymphocyte populations within a subset of human oral inflammatory diseases.
- We hypothesized that mucosal inflammation in cats with FCGS is most similar to humans with OLP.

Methods
- Formalin-fixed tissue samples (n=5 OLP, n=4 aphthous stomatitis, n=2 pemphigus vulgaris) were provided by Drs. Nasim Fazel and William Murphy, collaborators, UCD School of Medicine, Department of Dermatology.
- Fluorescent immunohistochemistry (IHC) was performed on tissue sections
- Primary antibodies: anti-human CD3, anti-human CD8, and anti-human CD4
- Secondary antibodies: Alexa fluor 488 and 594
- Slides were imaged via confocal microscopy.
- A hematoxylin and eosin (H&E) stain was also performed to a tissue section from each disease.

Results
- CD3+ T cell numbers were increased in all three human diseases (Figure 2).
- In pemphigus vulgaris and OLP, the CD3+ cells showed limited infiltration of the mucosa.
- In aphthous stomatitis, CD3+ cells were evenly distributed throughout the lesion, completely infiltrating the mucosa (Figure 2).
- CD3+ cells in OLP and pemphigus vulgaris had a follicular distribution.
- Aphthous stomatitis had the most noticeable increase in CD3+CD8+ cells, while OLP had a smaller ratio of CD3+CD8+: CD3+CD4+ cells (Figure 3).

Conclusion
- T cell inflammation in OLP and pemphigus vulgaris respects the mucosal border and assumes a follicular distribution, while T cells present in aphthous stomatitis lesions invade the mucosa in a diffuse pattern.
- Aphthous stomatitis lesions have the most apparent increase in CD8 positive T cells.
- FCGS is associated with increased CD8+ cells in blood and tissues, and histological evaluation of FCGS reveals immune cell invasion into the mucosa. As such, human aphthous stomatitis lesions most resemble FCGS lesions on initial histologic and immunofluorescent investigation.

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![Figure 1: MSC therapy resolves the oral manifestations of FCGS. An image prior to MSC therapy (left, A) demonstrates oral inflammation, bleeding and ulcerative lesions. 4 months after the 2nd MSC injection (right, B), there is complete resolution of oral inflammation. Other cats had substantial improvement (B, C-J) and others had no response to therapy (C, C).

![Figure 2: H&E and IF CD3+ cells in OLP, pemphigus vulgaris, and aphthous stomatitis oral lesions. A. OLP B. pemphigus vulgaris. C. aphthous stomatitis.

![Figure 3: A. CD3+ (red) and CD8+ (green) cells in OLP. B. CD3+ (red) and CD8+ (green) cells in pemphigus vulgaris. C. CD3+ (red) and CD8+ (green) cells in aphthous stomatitis. D. CD3+ (red) and CD4+ (green) cells in OLP (higher magnification). Blue= DAPI nuclei]