

# Establishment of a Novel Prediction System of Intestinal Absorption using Human Fresh Inflammatory Bowel Disease Intestinal Tissue

Graeme MacLuskie & Michael Finch

REPROCELL (Biopta), West of Scotland Science Centre, Glasgow, Scotland, G20 0XA

## ABSTRACT

The present study aimed to establish a novel prediction system of drug permeability in Inflammatory Bowel Disease (IBD) and determine how intestinal drug absorption is modified by this condition. Using transport studies using inflamed ulcerative colitis (UC) intestinal resections were used to estimate the permeation of atenolol and sulfasalazine in two IBD patients. The Ussing model was established successfully, results suggesting that IBD affects the intestinal absorption of drugs.

## INTRODUCTION

The incidence of Inflammatory Bowel Disease (IBD) is increasing<sup>1</sup>, and the majority of IBD compounds are administered orally, meaning that estimation of fraction of dose absorbed ( $f_a$ ) or bioavailability (BA) early in drug development is critical<sup>2</sup>. By performing ADME/DMPK studies during lead optimisation, researchers can estimate the *in vitro* measurement of absorption and identify potential limitations of BA before clinical trial<sup>2</sup>.

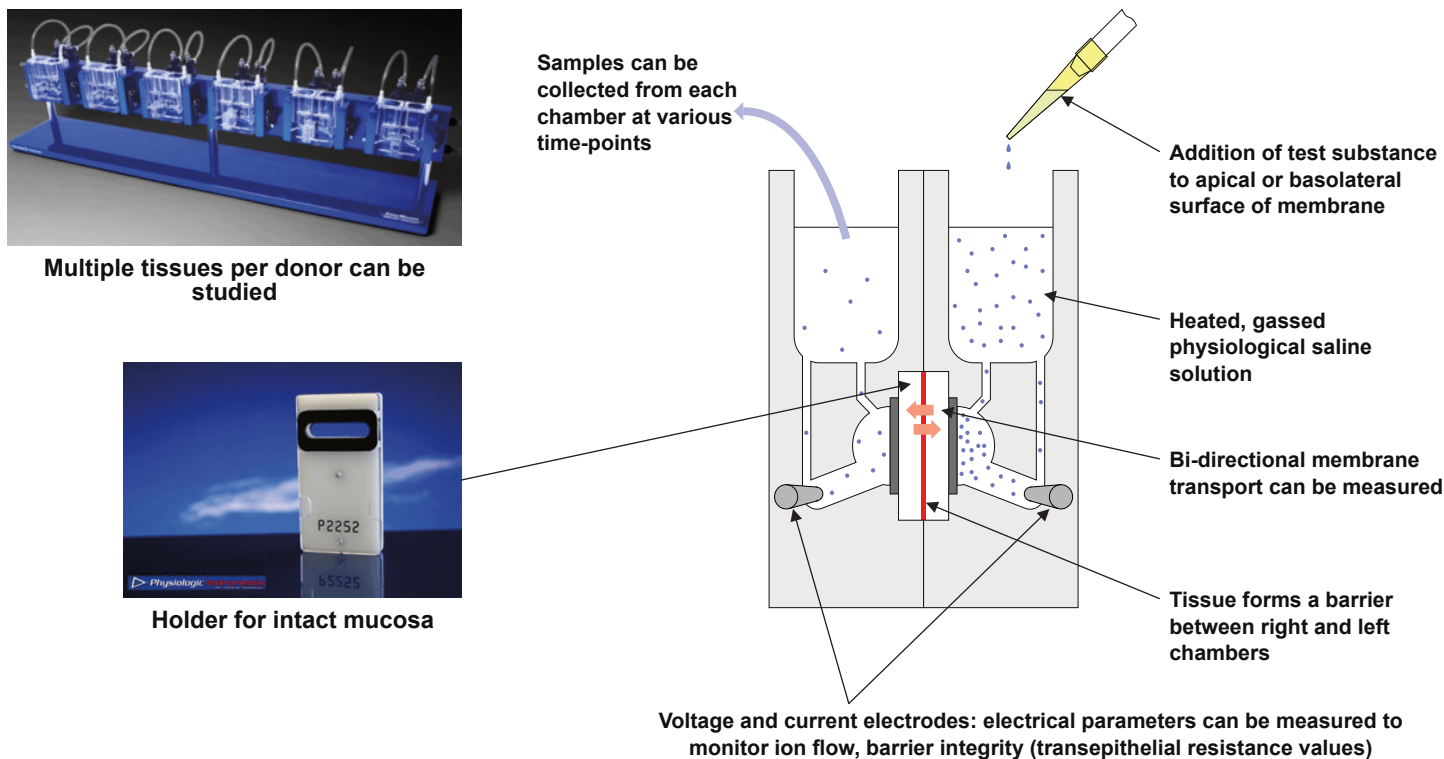
However, these studies are often limited by species differences and a lack of physiologically relevant preclinical models; leading to inaccurate prediction of compound behaviour in humans<sup>2</sup>. Commonly used absorption models are not reflective of the genetic variability in humans which can cause variation in patient drug response. In addition,

Miyake *et al*<sup>2</sup> determined that the absorption profile across various IBD patients is varied, and Schork<sup>3</sup> estimates that only 25% of individuals respond to drugs commonly used to treat IBD.

The use of human tissue models could therefore enable more precise predictions of IBD drug permeability in humans, reduce drug attrition rates and allow the development of more targeted patient therapies<sup>2</sup>. The aim of the present study was to evaluate the absorption profile of IBD donors compared with healthy donors in order to establish a preclinical absorption model.

## METHODOLOGY

Human intestinal tissue resections were ethically obtained from one healthy donor and two UC



**Figure 1: Cross-section of an Ussing chamber.** This diagram highlights how the Ussing system can be used to measure different test article characteristics. The same experimental set-up can be used whether the experiment aims to explore drug permeability or ion-channel function

donors, and mounted vertically in Ussing chambers (Figure 1) in physiological solution at 37°C aerated with O<sub>2</sub> (95% ) and CO<sub>2</sub> (5%). Test articles were administered to the apical side of the Ussing chambers at a concentration of 10 µM/ml for 2 hours, then the tissue was homogenised to determine drug accumulation. *Papp* values were calculated as a mean of four baths for each donor and plotted against reference data for normal donors.

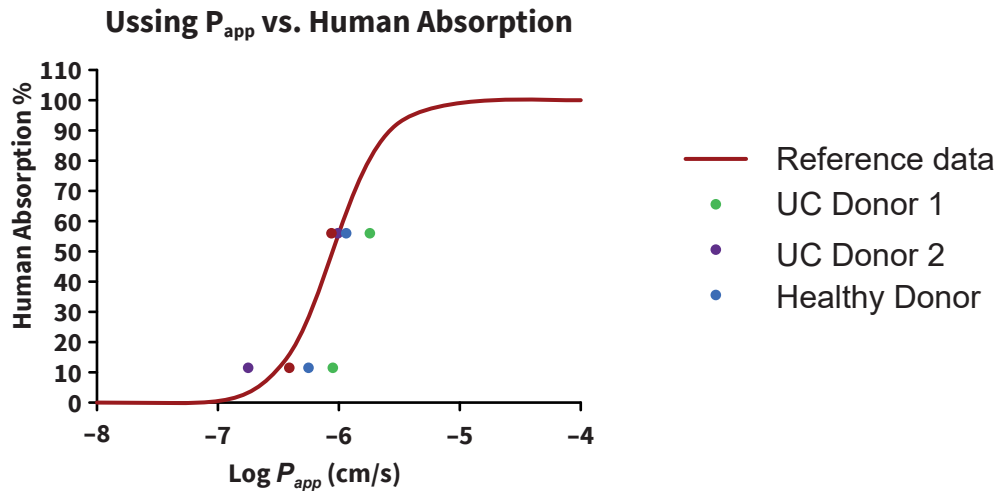
## RESULTS

The mean *Papp* values were plotted against REPROCELL’s reference data in Figure 2. Tissue from

the healthy donor showed permeability comparable with the reference data [Atenolol, 1.15e<sup>-6</sup>; Sulfasalazine, 5.74e<sup>-7</sup>]. Tissue from one UC donor displayed a higher rate of absorption than the reference data [Atenolol, 1.80e<sup>-6</sup>; Sulfasalazine, 8.99e<sup>-7</sup>] while the other showed a lower absorption rate for Sulfasalazine [Atenolol, 9.44e<sup>-7</sup>; Sulfasalazine, 1.79e<sup>-7</sup>].

## PRELIMINARY CONCLUSION

This study shows that human tissue absorption studies can be established using inflamed intestinal tissue. The present work suggests that IBD can affect



**Figure 2: Graph showing relationship between Ussing  $P_{app}$  and Human Absorption in intestinal resections.** The  $P_{app}$  values were calculated as a mean of four baths from each donor and then plotted against the reference data. The absorption profile for the healthy donor was comparable to the reference data, whilst data for the Ulcerative Colitis patients varied from the reference data.

the intestinal absorption profile; either increasing or decreasing permeability to test articles. Future studies aim to increase the number of subjects to obtain a clearer picture of the effects of IBD on drug absorption.

## REFERENCES

1. Ananthkrishnan. [Epidemiology and risk factors for IBD.](#) *Nature Reviews: Gastrointestinal and Hepatology* 12:205 – 17 (2015).
2. Miyake *et al.* Establishment of Novel Prediction System of Intestinal Absorption in Humans using Human Intestinal Tissues. *Journal of Pharmaceutical Science* (2013).
3. Kristensen *et al.* The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. *Scandinavian Journal of Rheumatology* 36:6 (2007).

**If you would like to find out more about REPROCELL's (Biopta) absorption studies, visit our website, or contact one of our team.**