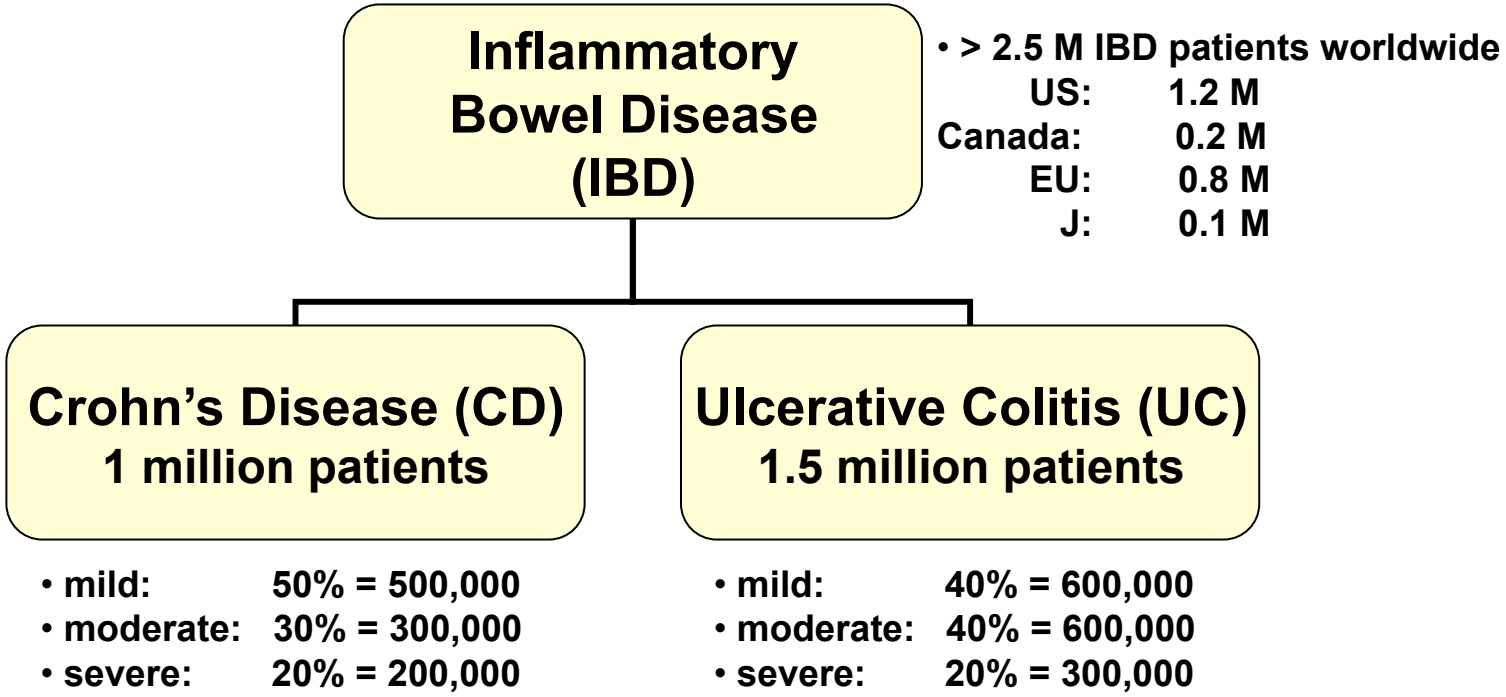
Exercise to discuss in class

- **Here are 3 target SWOTs**
  - Therapeutic area: Inflammatory Bowel Disease (IBD)

- **Which target would you move forward as a new small molecule biotech company ? #1, 2, 3? Why?**

- **All information needed provided in the slides below. No need for more literature search.**

IBD Populations (data from 2015)



- Most patients diagnosed between age 15 and 35
- Periods of flares and remission – can be a life long disease
- ~ 50% of all patients are in active disease (flare) or remission at any point of time
- Abdominal pain / cramping / urgency, weight loss, persistent diarrhea, rectal bleeding
- Current medical therapy is not curative
- Poor response to medical therapy leads to bowel surgery in most patients

APEH

- **Target Type**
  - **Enzyme**: Serine peptidase
  - This enzyme catalyzes the hydrolysis of the N-terminal peptide bond of an N-acetylated peptide to generate an N-acetylated amino acid and a peptide with a free N-terminus. It preferentially cleaves off Ac-Ala, Ac-Met and Ac-Ser.
  - It can also cleave peptides with n-acyl groups such as chloroacetyl, formyl & carbamyl
  - ACTIVATOR needed

- **Biological role**
  - The acylpeptide hydrolase is a homotetrameric protein of 300 kDa with each subunit consisting of 732 amino acid residues.
  - It can play an important role in destroying oxidatively damaged proteins in living cells; protein turnover

- **Fit in Franchise**
  - Proliferative and wound healing potential?
  - Effects of microbiome by-products
  - Innate immune response-mediated

APEH SWOT analysis

Strengths

- Druggable target; enzyme
- GWAS studies link APEH to IBD (directionality unknown)
- Fits with IBD Disease Area strategy
- Biology is understood
- Assays/ enzymes are described & available for HTS
- Inhibitors are described in the lit & can be used for an *in vitro/ vivo* POC

Weaknesses

- Conflicting data about effects on cell proliferation (pro vs anti)?
- Effect on protein turnover; ER stress unknown?
- Effects on mounting immune response to bacterial infection unknown?
  - Gut targeting to prevent potential AEs
- No KO mouse
- Activator needed; no chemical know-how

Opportunity

- Potential proliferative & wound healing effects
- Effects of microbiome by-products

Threats (competition)

- none

CD48

- **Target Type**
  - Glycosyl-phosphatidyl-inositol (GPI) anchored protein
  - **Cell surface receptor** & soluble form detected
  - Ligand for CD2 & CD244 (2B4). Might facilitate interaction between activated lymphocytes. Probably involved in regulating T cell activation
  - Inhibitor needed (antibody or small molecule)

- **Biological role**
  - Adhesion and co-stimulator molecule
  - The encoded protein is found on the surface of lymphocytes and other immune cells, dendritic cells and endothelial cells, and participates in activation and differentiation pathways in these cells. The encoded protein does not have a transmembrane domain, however, but is held at the cell surface by a GPI anchor via a C-terminal domain which maybe cleaved to yield a soluble form of the receptor.

- **Fit in Franchise**
  - Adaptive immune response-mediated (T & B)
  - Innate immune response-mediated (neutrophils, mast cells, eosinophils, NK)
  - Involved in FimH binding to cell surface – microbiome
  - Anti-cancer therapeutics

CD48 SWOT analysis

Strengths

- Druggable target; cell surface molecule
- Fits with IBD Disease Area strategy
- Biology is understood
- Inhibition of CD48 prevents FimH-expressing *E. coli* from adhering & invading cells
- Anti-CD48 antibody decreased experimental colitis in mice (prophylactic & therapeutic modes)
- GWAS studies link CD48 to IBD (directionality unknown)

Weaknesses

- Antibody needed? Inhibition of protein-protein interaction extremely difficult with a small molecule
- Immune suppression? Autoimmunity?
  - Gut targeting to prevent potential AEs

Opportunity

- Anti-cancer effect – colorectal cancer?
- Effects of microbiome & immune system at once
- Osaka University looking to outsource anti-CD48 antibody

Threats (competition)

- Osaka University

GPR35

- **Target Type**
  - **GPCR**; receptor for kynurenic acid (KYNA)
  - AGONIST needed; gut-targeted (none-brain penetrant)

- **Biological role**
  - Highly expressed in small intestine, colon, spleen, PBMCs
  - Gq & Gi signaling
  - Kynurenic acid is a product of the normal metabolism of amino acid L-tryptophan. It has been shown that kynurenic acid possesses neuroactive activity. It acts as an antiexcitotoxic and anticonvulsant, most likely through acting as an antagonist at excitatory amino acid receptors
  - Potentially a receptor for 2-acyl lysophophatidic acid (natural ligand of GPR55)

- **Fit in Franchise**
  - Anti-inflammatory
  - Innate immune response-mediated
    - neutrophils & monocytes chemotaxis & adhesion
  - Anti-bacterial activity
  - Anti-nociception
  - Anti-proliferative?

GPR35 SWOT analysis

Strengths

- Druggable target; GPCR
- Fits with IBD Disease Area strategy
- Biology is understood
- Several agonists and antagonists available for POC
- GWAS studies link GPR35 to IBD (directionality unknown)
- Potential anti-bacterial, anti-nociception & anti-proliferative effects

Weaknesses

- Activity in brain and anticonvulsant
  - Gut targeting to prevent potential AEs (or non-brain permeable)

Opportunity

- Broader therapeutic uses - see table

Threats (competition)

- none

Table 2. Therapeutic potential for GPR35 ligands

Disease indication	Supporting evidence
Diabetes	Thiazolidinediones with agonist action at GPR35 promote glucose-dependent insulin secretion Such ligands also improve glucose handling
Hypertension	GPR35 knockout mice have markedly elevated blood pressure
Coronary artery disease	Association with Ser294Arg polymorphism
Asthma	Anti-asthma medications cromolyn disodium and nedocromil sodium are agonists of GPR35
Pain	Expression of GPR35 in mouse dorsal root ganglion and spinal cord Effects of agonist ligands in acetic acid-induced writhing models
Early-onset inflammatory bowel disease	Genetic linkage to a 5′ untranslated single nucleotide polymorphism of GPR35