Leveraging Data Across Multiple Immuno-Inflammation Indications: Early Clinical Development of a Novel Compound

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Content

- TNF-a Dependent Inflammatory Disease
- Overview of Experimental Medicine studies
- Overview of Each Indications Biomarkers & Efficacy
  - Psoarsis, Rheumatoid Arthritis, Ulcerative Colitis
  - Study Designs and Endpoints
- Leveraging Data Across Indications

TNF-α Mediated Inflammatory Disease

TNF-α Mediated Inflammatory Disease

- Tumor necrosis factor-a (TNFα) is a cell signaling protein (cytokine) involved in systemic inflammation
- TNF interacts with two different receptors, TNFR1 and TNFR2, which are differentially regulated on various cell types in normal and diseased tissues
  - resulting in a range of cellular responses, which include cell death, survival, differentiation, proliferation and migration
- Dysregulation of TNF production has been implicated in a variety of human diseases including a range of inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriasis
- Recent research has identified that necroptosis is the major driver of TNF-α dependent inflammation and disease
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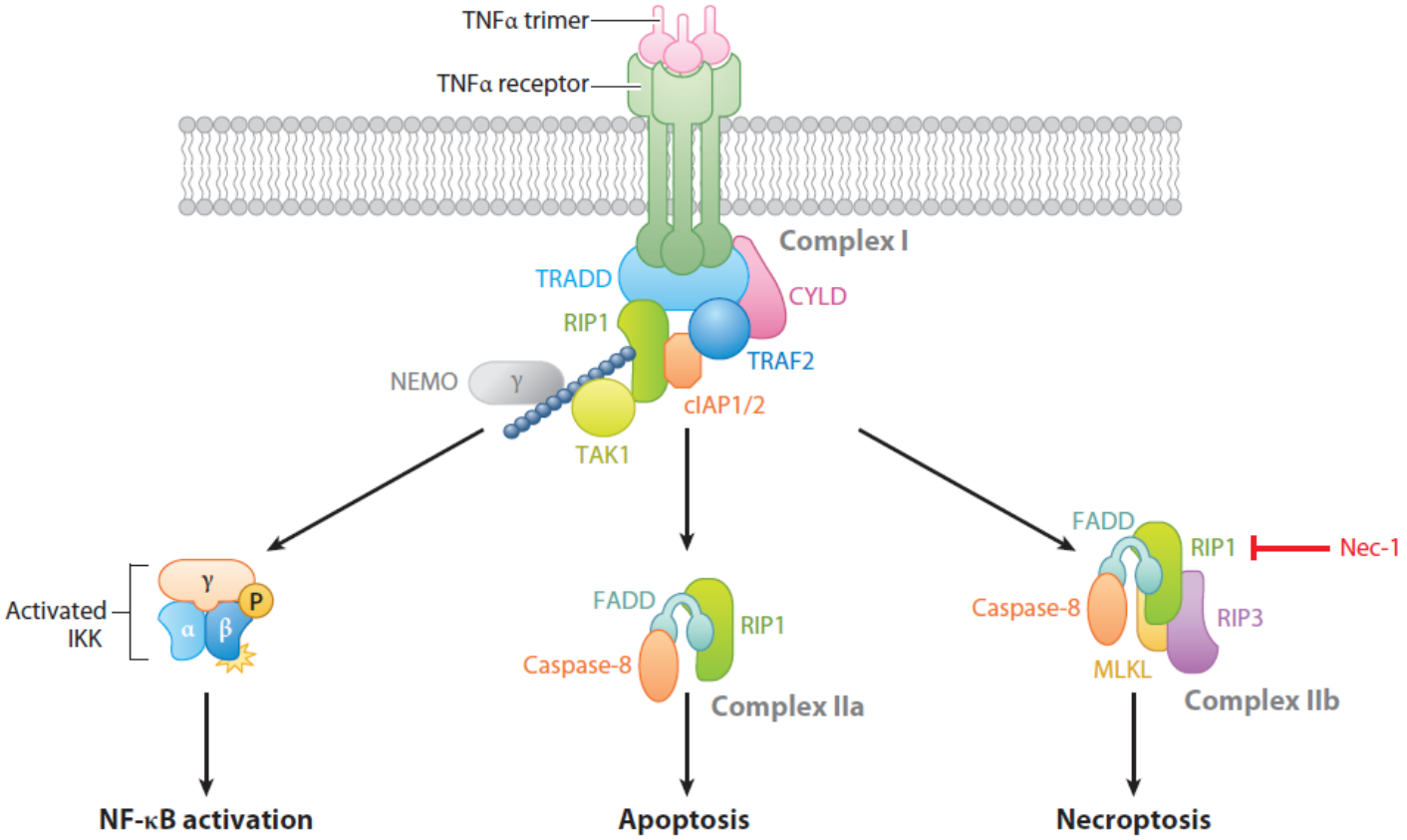
TNF-α Signalling Pathway



D(erived from Christofferson et al., Ann.Rev. Physiol. (2014) 76:129)

Experimental Medicine

What is Experimental Medicine?

"Investigation undertaken in humans, relating where appropriate to model systems, to identify mechanisms of pathophysiology or disease, or to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments."

UK Medical Research Council

At GSK, this translates into...

Clinical studies in a low number of patients or healthy volunteers, that are biomarker-rich, that address well-defined important questions which support 'go / no-go' decision-making

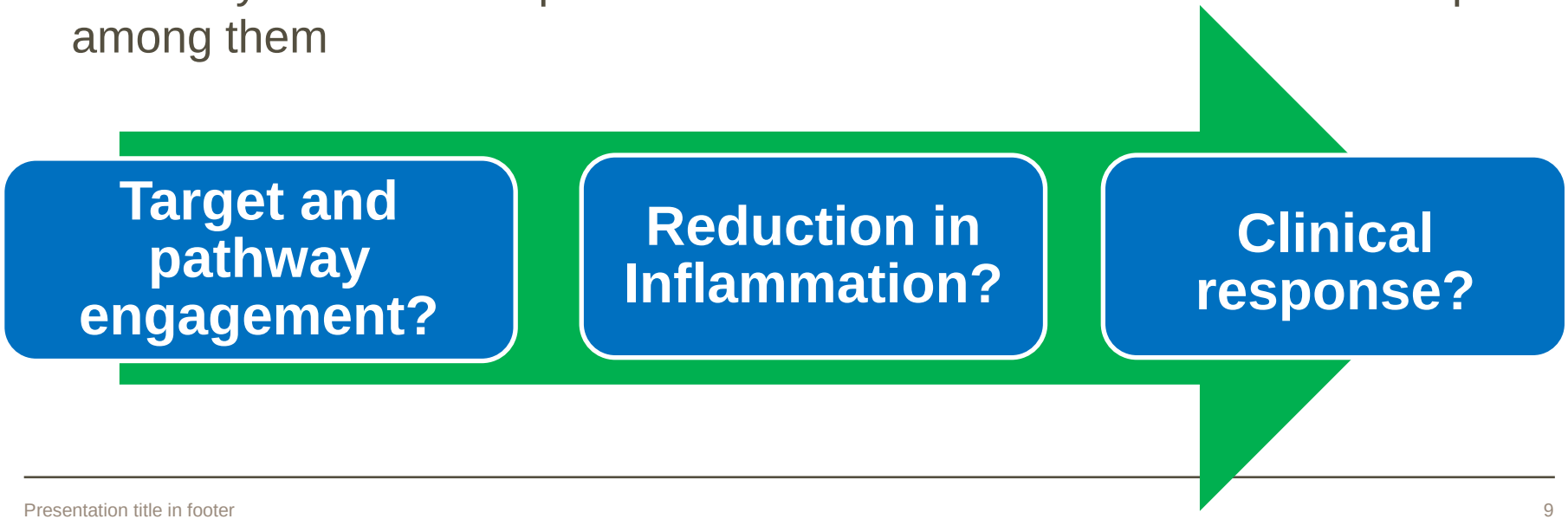
http://www.mrc.ac.uk/research/initiatives/experimental-medicine/

Key Benefits of EM Approaches

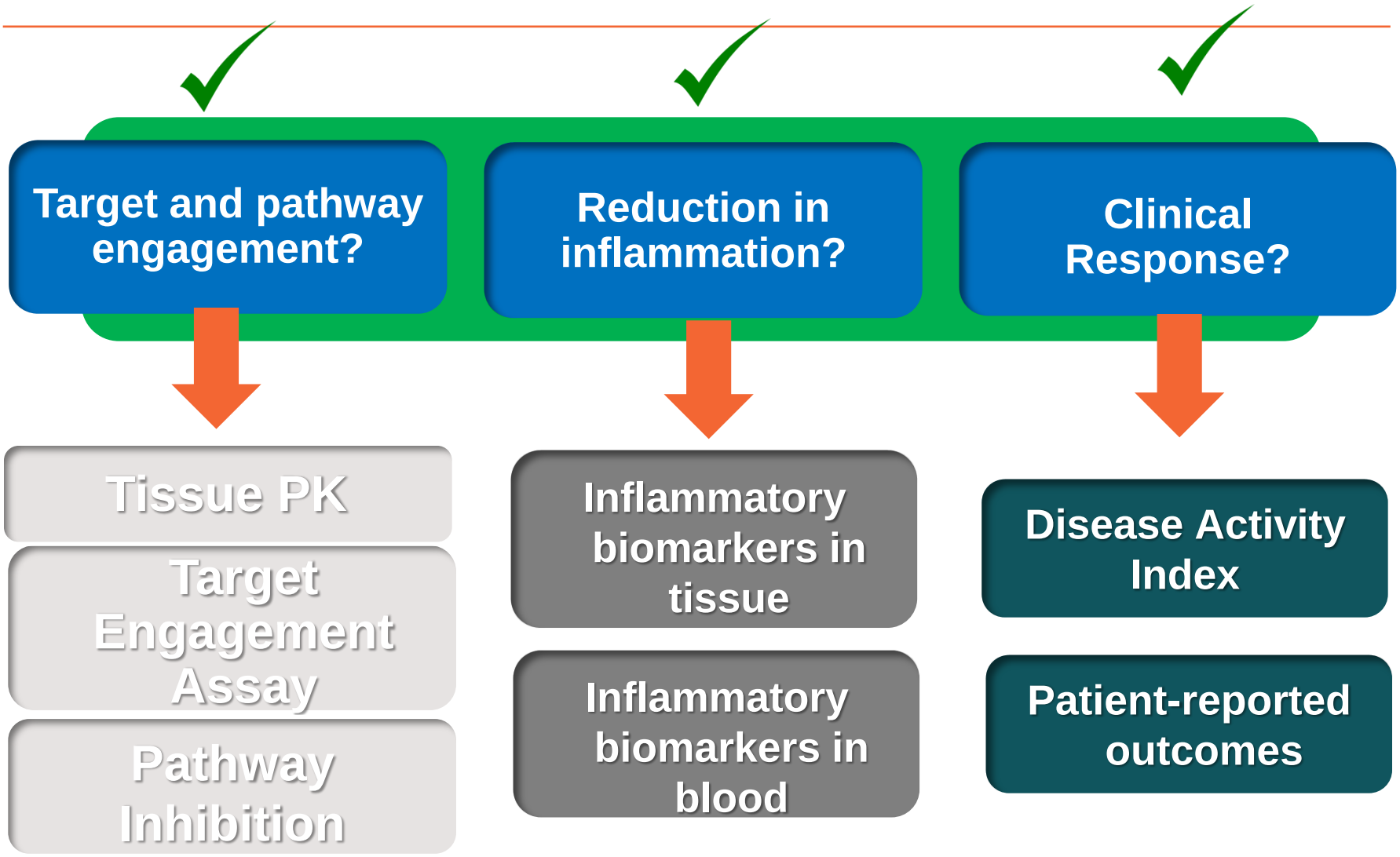
- Early understanding of candidate potential in man
  - enable earlier investment/de-investment decisions
  - reduce overall resource burn
- Enhance probability of phase 2 success
  - inform potential adaptive designs or stratification approaches
  - may inform dose selection
- Enhance mechanistic and disease understanding
  - early decisions on target validation in humans
- Enhance smart decision making
  - evidence based decisions made against preset criteria

Understanding of the Compound and Mechanism Early in Clinical Development

- Questions still to be answered
  - Does blocking solely the TNF-α necroptosis pathway result in a reduction of inflammatory biomarkers
  - Does a reduction in inflammatory biomarkers result in an improvement in clinical endpoints
- To ensure a correct interpretation of these multidimensional data, appropriate statistical modelling needs to be formally incorporated into the analysis of EM endpoints and in the estimation of the relationships among them

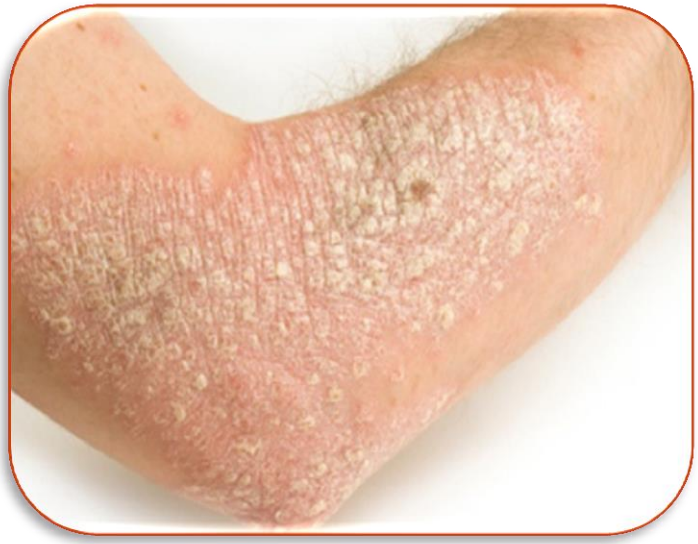


Experimental Medicine Criteria



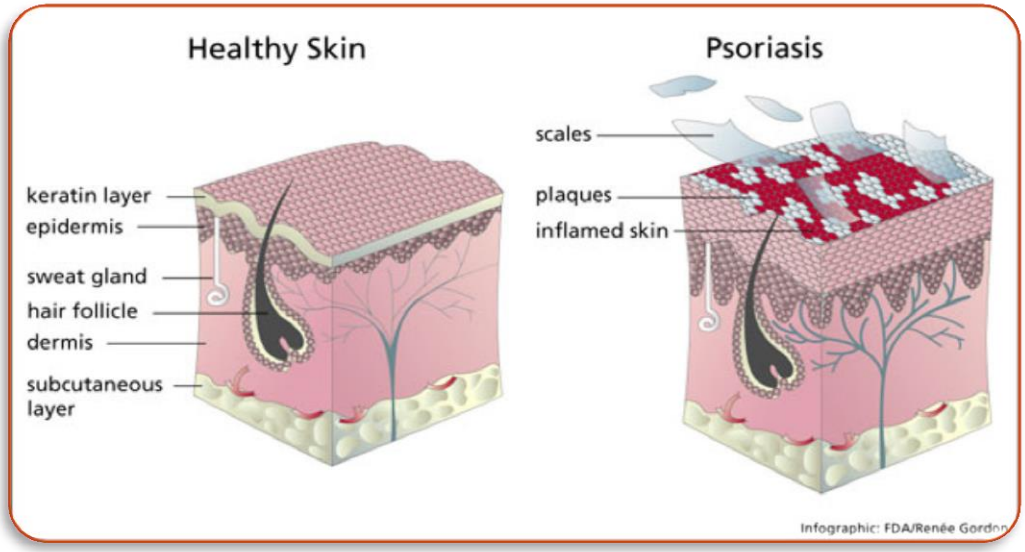
Psoarsis

Psoriasis: Disease Overview



- Common, chronic, autoimmune skin disease
  - 1-3% General population
  - Bimodal distribution with peaks in early(late teens to 20s) and late adulthood (50s and 60s)
- Pruritic, erythematous, lichenified plaques with silvery scales and inflammation.
- Elbows, knees, scalp, lower back, face, palms and soles of the feet, but may occur on any other part of body skin
- Approx 15%-30% of psoriatic patients develop Psoriatic Arthritis

Psoriasis Pathobiology

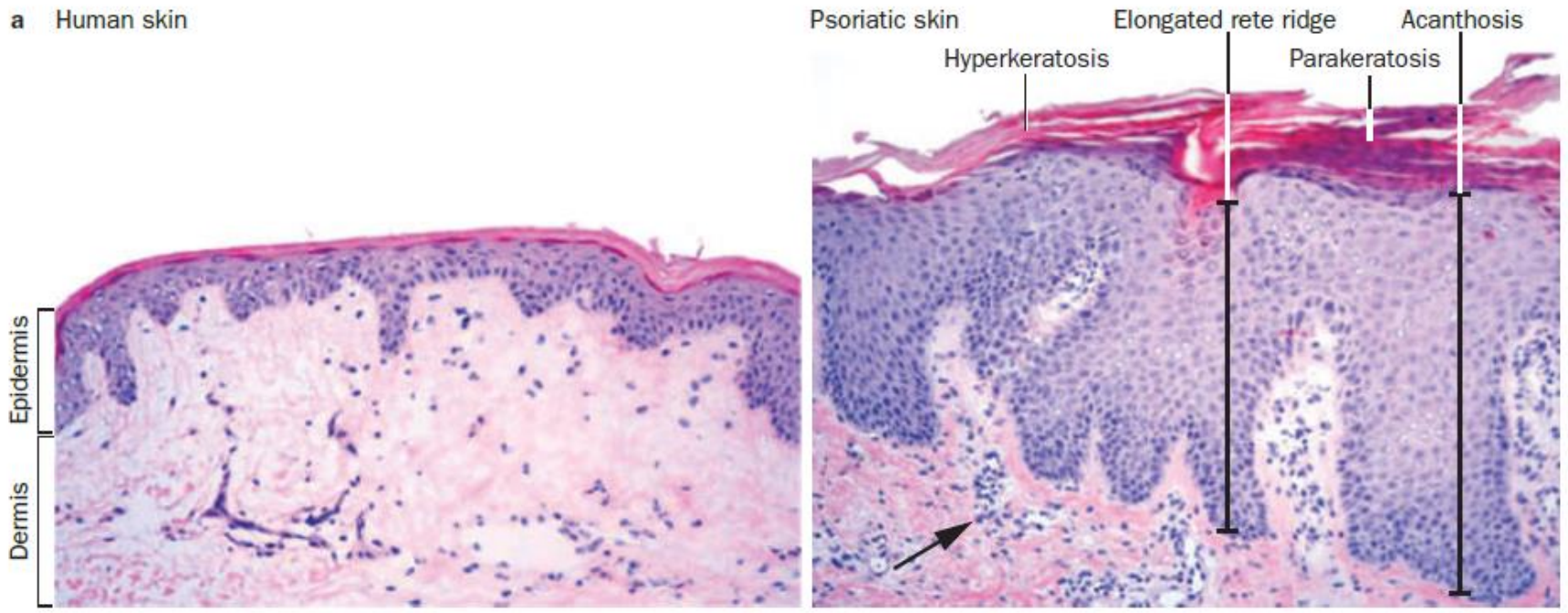


- Excessive growth and aberrant differentiation of keratinocytes which is triggered by the activation of cellular immune system
- Keratinocytes replicate at an extremely rapid rate--about eight times faster than normal, but the rate at which old cells slough off is unchanged
- This causes cells to build up on the skin's surface, forming thick patches, or plaques, of red sores (lesions) covered with flaky, silvery-white dead skin cells (scales)

PsO: Experimental Medicine Study Endpoints

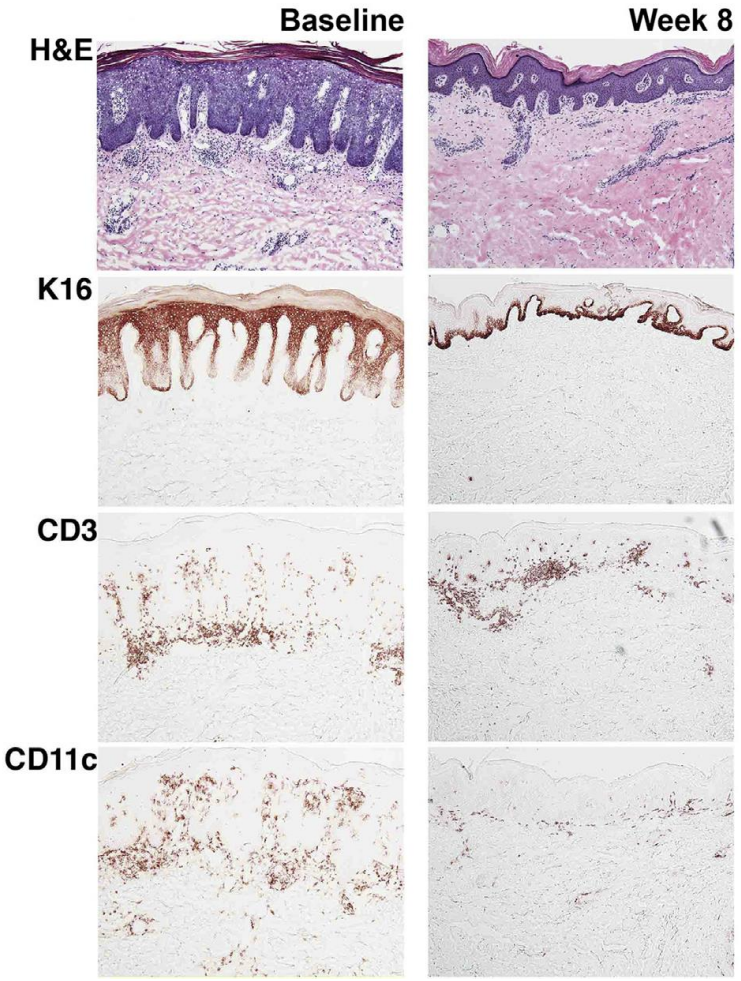
- Target Engagement
  - Assay available to determine target engagement and downstream activity
- Pharmacokinetics in Blood and Psoriatic Skin Lesions
- Biomarkers in Psoriatic Skin Lesions
  - Histopathological scoring
  - mRNA expression of inflammatory gene transcripts
- Biomarkers in Blood
  - Inflammatory markers
    - e.g. CRP, VEGF, IL-17, IL-22, TNF
- Clinical Endpoints and PROs
  - PGA
  - PLSS
  - PASI
  - DLQI

Normal vs. Psoriatic Skin Histology



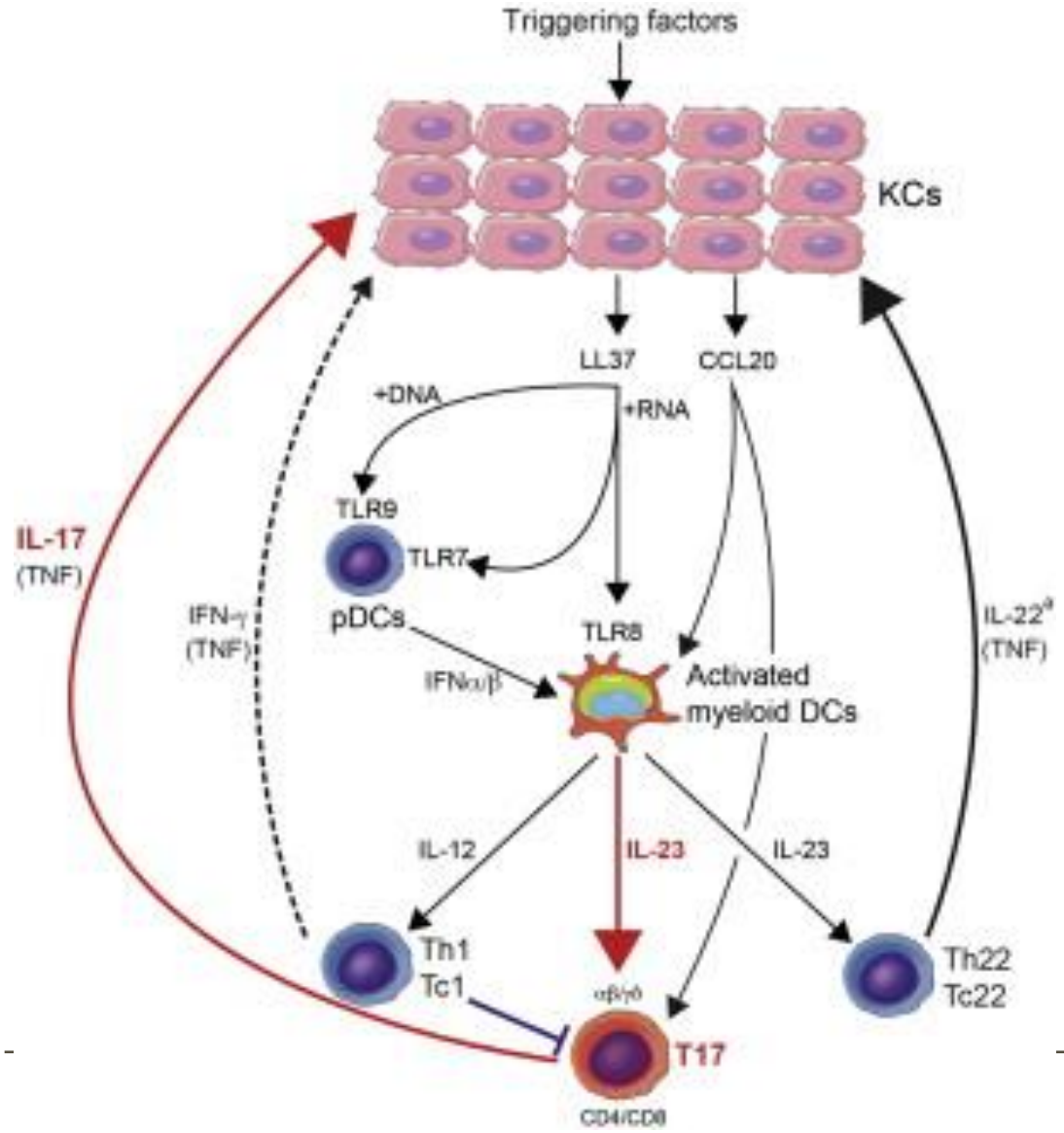
Histopathological Scoring

– Change in expression of genes/proteins in key pathways in psoriatic skin after a single dose of BI 655066 (anti-IL23 mAb)



Krueger et al. *JACI* 2015, VOLUME 136, NUMBER 1

Psoriasis Immunopathology



- T-cell dependent immune response that drives the accelerated growth of epidermal and vascular cells in psoriatic lesions.
- Critical events include inflammatory cytokine and chemokine cascade in skin lesions, activation of Langerhans cells and T cells, selective trafficking of activated T cells to the skin.
- Each of these steps provides an opportunity for drug intervention

Physician Global Assessment (PGA)

- **0** - Clear: no signs of psoriasis
- **1** - Almost clear: slight elevation, scale and/or erythema
- **2** - Mild: slight plaque elevation, scale and/or erythema
- **3** - Mild to moderate: mild plaque elevation, moderate erythema and/or scale
- **4** - Moderate: moderate plaque elevation, scaling and/ or erythema
- **5** - Moderate to severe: marked plaque elevation, scaling and/ or erythema
- **6** - Severe: very marked plaque elevation, scaling and/ or erythema

Psoriasis Area and Severity Index (PASI)

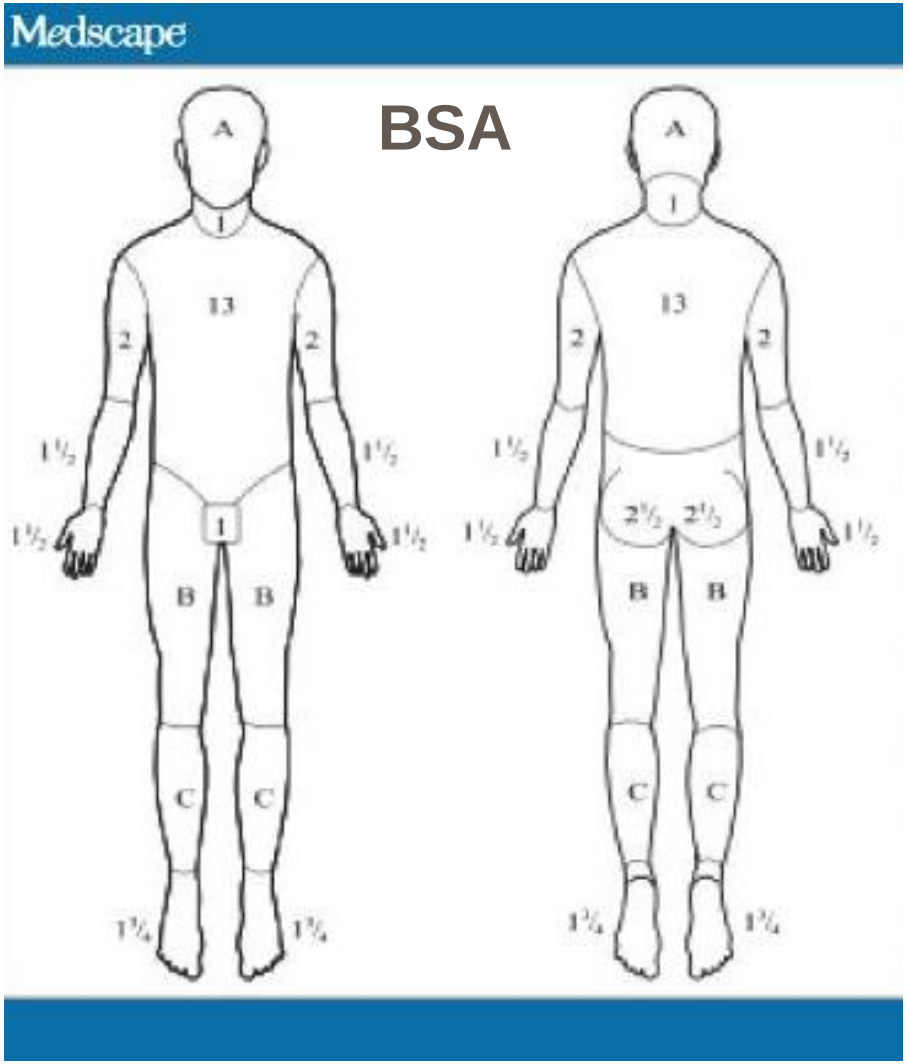


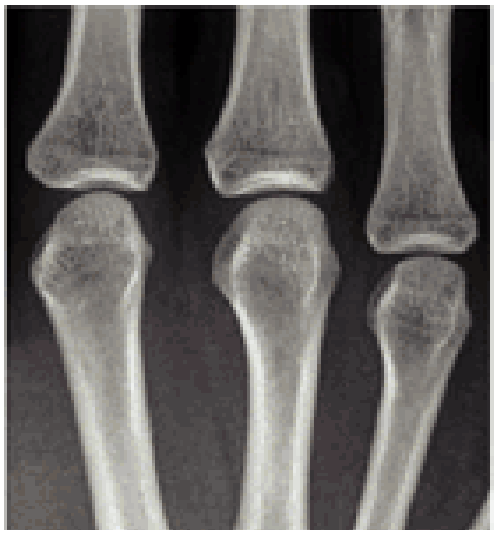
Table 1: Calculation of the Psoriasis Area and Severity Index

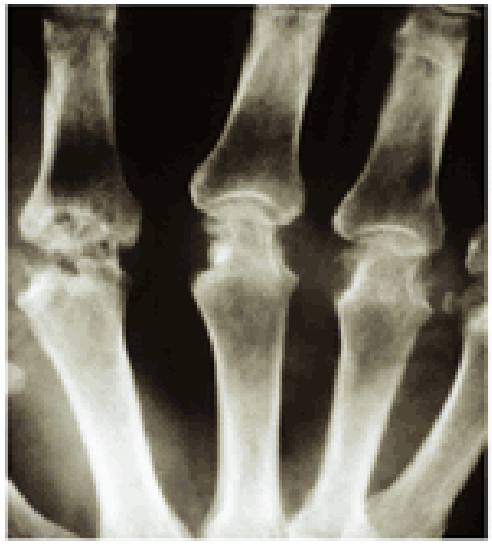
Severity of psoriatic lesions (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe)				
	Head	Trunk	Upper limbs	Lower limbs
Erythema	0-4	0-4	0-4	0-4
Induration	0-4	0-4	0-4	0-4
Scaling	0-4	0-4	0-4	0-4
Total score = TS	Sum of the above	Sum of the above	Sum of the above	Sum of the above
Area of psoriatic involvement 0 = none, 1 = <10%, 2 = 10-30%, 3 = 30-50%, 4 = 50-70%, 5 = 70-90%, 6 = 90-100%				
Degree of involvement = DI	0-6	0-6	0-6	0-6
Multiply TS × DI	TS × DI	TS × DI	TS × DI	TS × DI
Correction factor for area of involvement = CF	0.10	0.30	0.20	0.40
TS × DI × CF	A	B	C	D
A + B + C + D = total PASI				

Adapted from table 8.2, Calculation of the Psoriasis Area and Severity Index (PASI), from Bolognia JL[13]

Rheumatoid Arthritis

RA Disease Overview



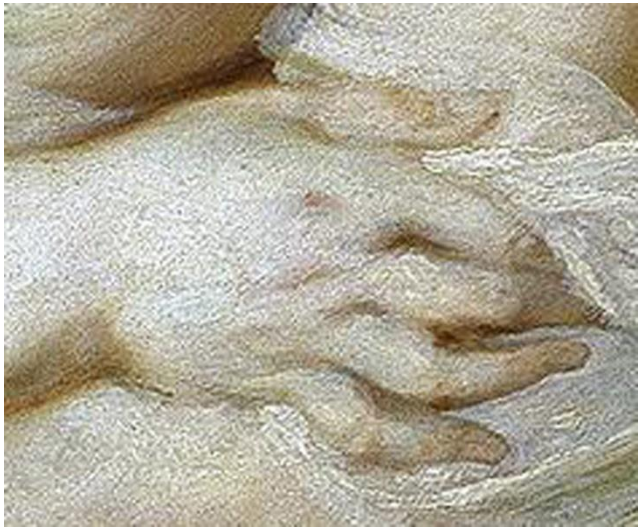


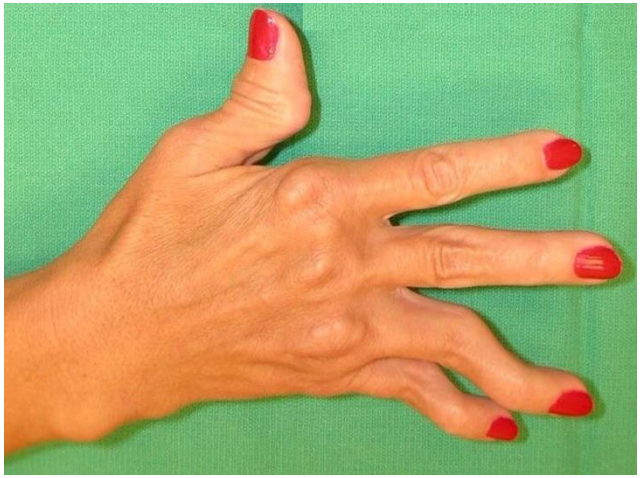
- **Natural history**
  - –progressive (10%)
  - –relapsing/remitting (70%)
  - –self-limiting arthritis (20%)
- **Poor prognostic factors**
  - –Severe baseline disease (No.of swollen & tender joints; erosions; extra-articular disease)
  - –RF^+, HLA DR4 alleles, ACPA
  - –Smoking; male gender
  - –Functional limitation
  - –Extraarticular disease (Rheumatoid nodules, vasculitis, Felty's)
- **Increased mortality: CVD, metabolic syndrome.**
- **Prevalence is 0.95% for US and 0.71 % for EU**

Smolen JS & Steiner G. Nature Reviews Drug Discovery 2, 473-488 (2003)

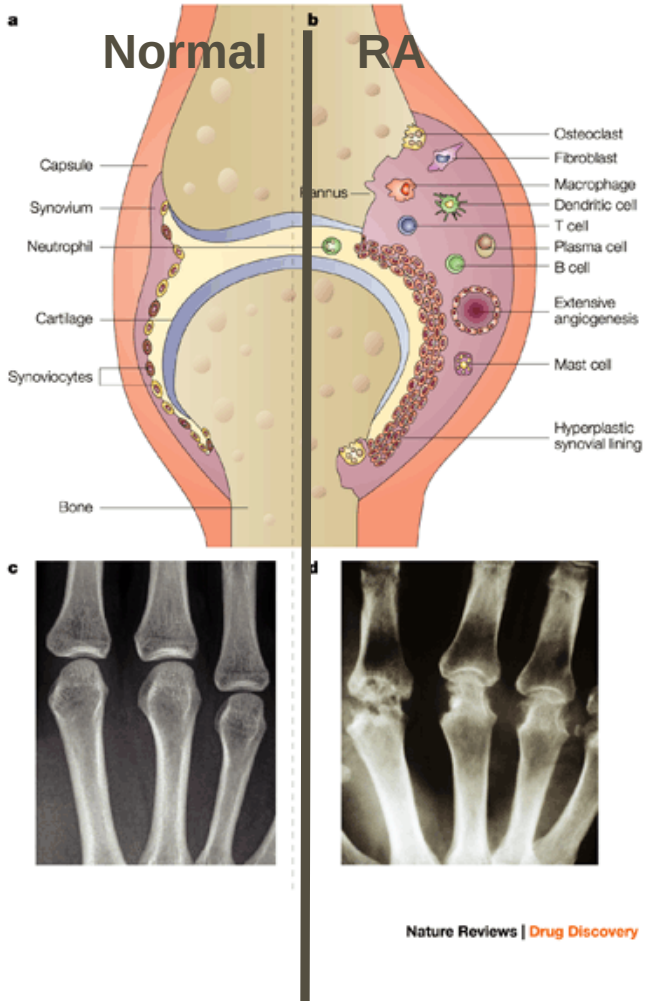
The Three Graces (1638)

Peter Paul Rubens (1577-1640)





The RA Joint

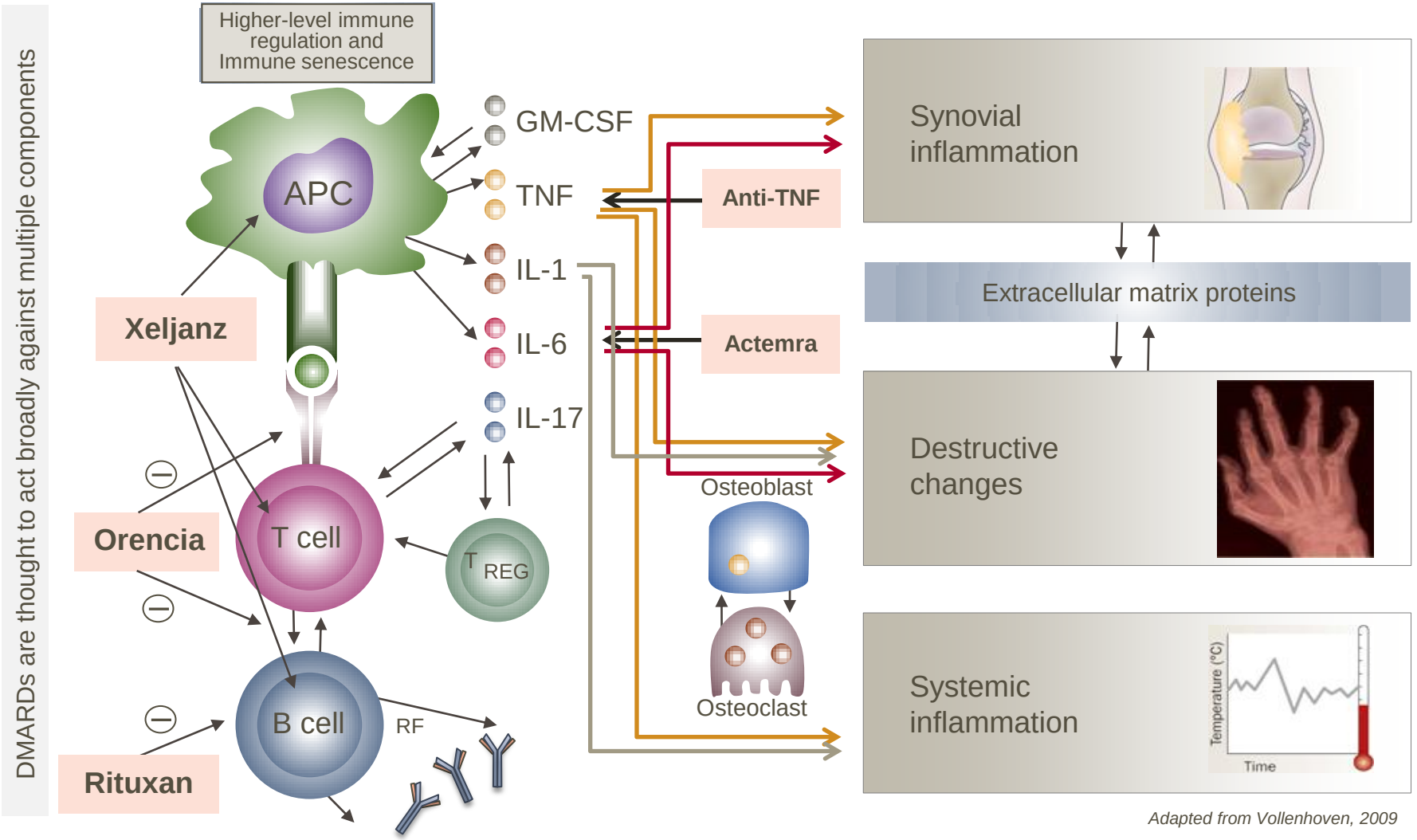


- **Synovial inflammation**
  - Lymphocytes, plasma cells, macrophages, dendritic cells, mast cells
- **Synovial hyperplasia** – fibroblasts
- **Angiogenesis** – endothelial cells
- **Cartilage matrix damage** – chondrocytes
- **Bone joint erosion & peri-articular osteopenia** – osteoclasts

Smolen JS & Steiner G. Nature Reviews Drug Discovery 2, 473-488 (2003)

Pathophysiology

RA is a syndrome with multiple pathological mechanisms, requiring a range of targeted treatments



Adapted from Vollenhoven, 2009

Source: van Vollenhoven RF., Nat Rev Rheumatol., 2009,10, 531-41

ACPA, anti-citrullinated protein/peptide antibodies; APC, antigen presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; RF, rheumatoid factor; TNF, tumour necrosis factor; TREG, regulatory T cell.

Experimental Medicine Study Endpoints

- Target Engagement
  - Assay available to determine target engagement and downstream activity
- Pharmacokinetics in Blood and Synovial Tissue
- MRI changes
  - Bone and synovial inflammation
- Inflammatory Markers in Synovial Tissue
  - e.g. CD68+ macrophages, CD3, CD22, CD138, TNF, IL6, VEGF, IL-1B
- Inflammatory Markers in Blood
    - e.g. CRP, IL-6
- Clinical Endpoints and PROs
  - DAS28-CRP
  - ACR
  - HAQ-DI

Efficacy Measures in RA

Components	Key primary end point
Improve signs and symptoms of the disease	– ACR 20/50/70/90 •Pain •Patient global assessment •Physician global assessment •Function •Acute phase reactants
Inhibit progression of joint damage	Mean change from baseline in Sharp Score (TSS), a lower score indicates less progression of structural damage
Improve physical function	Improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) : Impact on daily activities
Reduce disease activity	Mean improvements in DAS or DAS28 scores
Induce remission	DAS28 < 2.6 at a specified time point

ACR: American College of Rheumatology; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; TSS: Total Sharp Score

Source: Decision Resources Report, Dec. 2015 (Rheumatoid Arthritis)

Refer notes section for further details

Clinical diagnosis: 2010 ACR/EULAR Classification

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

More sensitive in identifying early RA

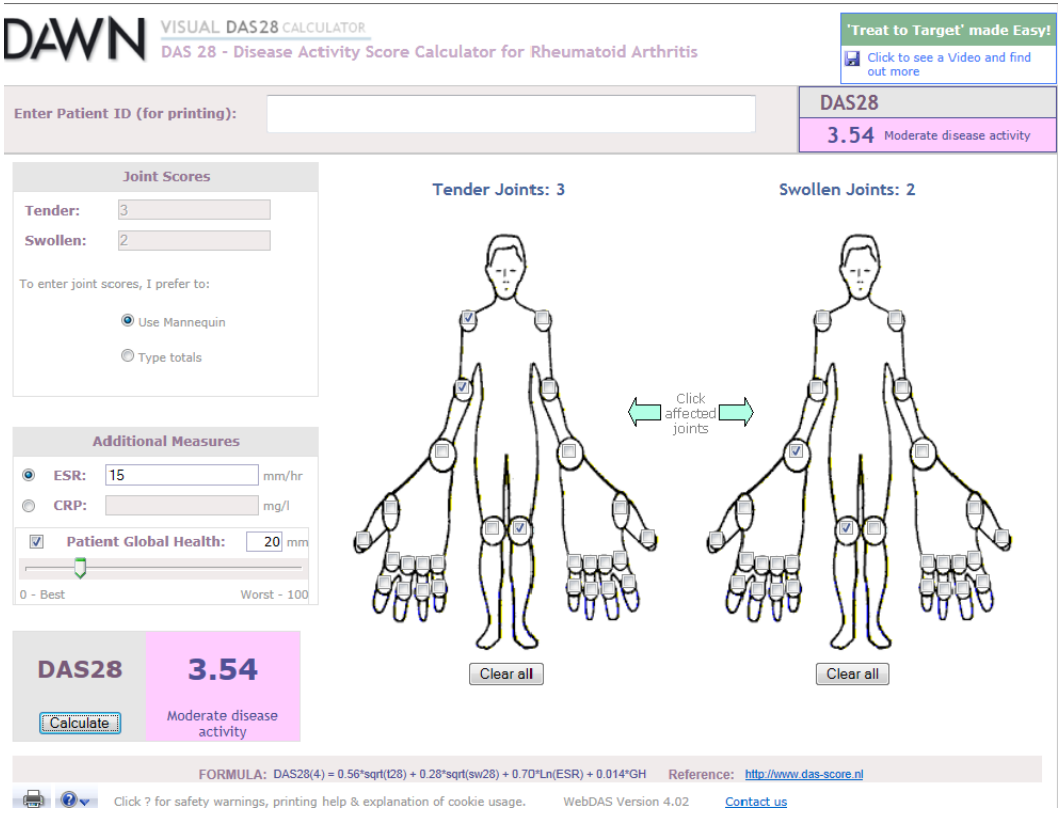
≥6/10 = Definite RA

ACR: American college of rheumatology; EULAR: European League Against Rheumatism

Sources: 1. ACR-endorsed criteria for rheumatic diseases (accessed on 6 Jan'16); 2. Scott DL et. al., Lancet, 2010, 376, 9746, 1094-108; 3. Rheumatoid Arthritis, Medscape (accessed on 5 Jan'16)

DAS28

28 day Joint Disease Activity Score



- **DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR or CRP) + 0.014 * Global Health Assessment VAS**

- ≥5.1= high disease activity
- 3.2-0-5.0=moderate disease activity
- ≤3.1= low disease activity
- ≤2.6 = remission

- **CONS**:
  - Not useful if feet are affected
  - **In EU a DAS28>5.1 is required for biologics**
  - Hard to interpret with normal inflammatory markers
  - Confounded by co-morbidities (fibromyalgia)

HAQ-DI

Health Assessment Questionnaire Disability Index

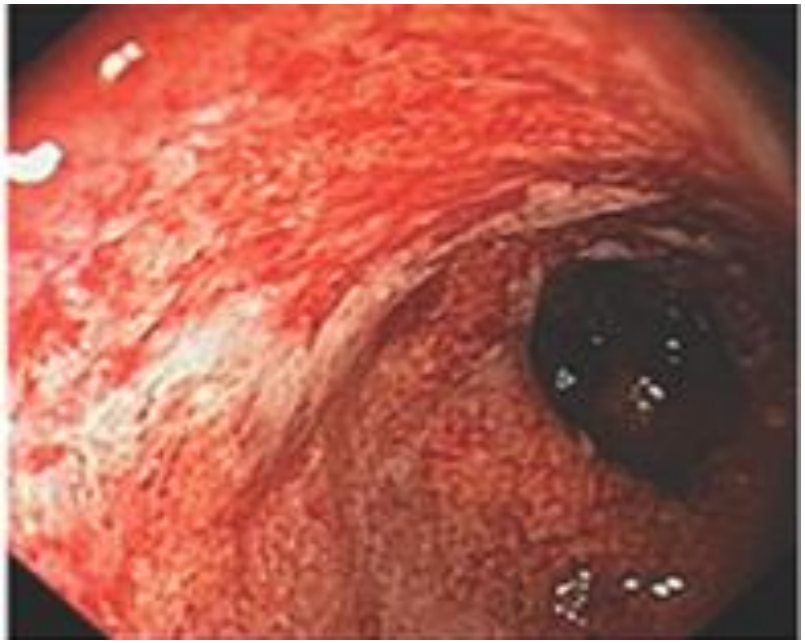
8 Categories

- Dressing
- Arising
- Eating, Walking
- Aids/Devices
- Hygeine
- Reach
- Grip
- Activities

- **Validated scoring tool for PROs**
- **Scoring: Overall 0-3**
  - "No difficulty" to "Not able to do" (0-3)
  - Highest subscore in each of 8 categories=score
  - Add categorical scores, divide by # completed

Ulcerative Colitis

Ulcerative Colitis (UC)



- Chronic disease that causes inflammation, affecting the mucosa of the colon and rectum

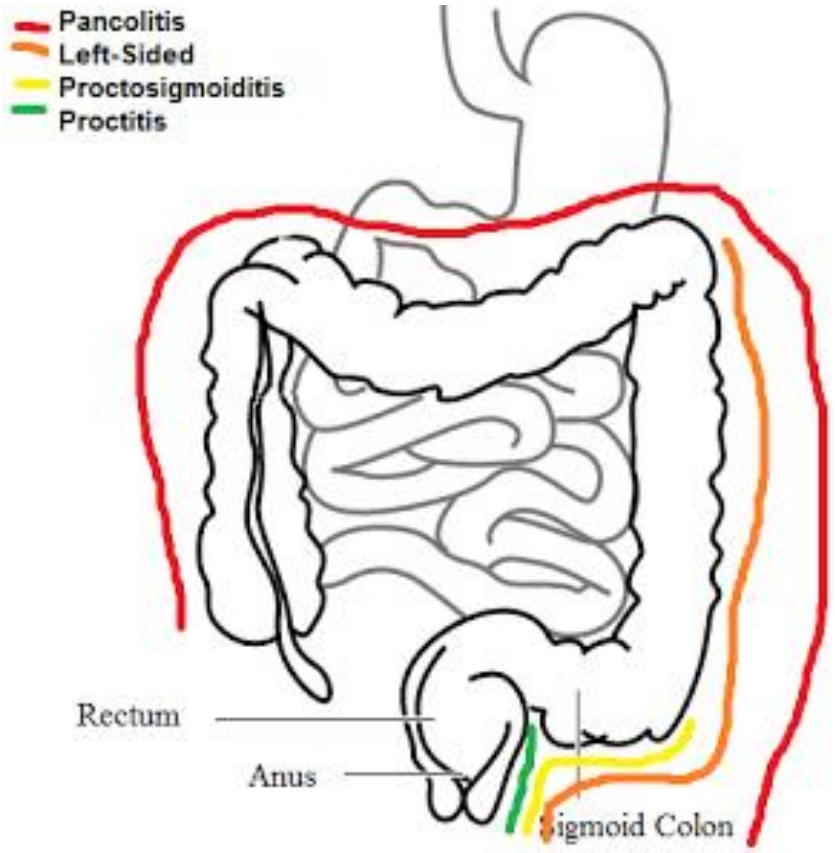
- Symptoms: Intermittent bloody diarrhoea, rectal urgency (tenesmus), weight loss/anaemia, fever, tachycardia

- Bimodal incidence:
  - 2nd decade of life
  - 6th decade of life

- Gold standard dx: Colonoscopy/ileoscopy

- Risk factors : Age, Race/Ethnicity, genetic factors, microorganisms, diet, stress, smoking (protective?), etc.

Disease Extent

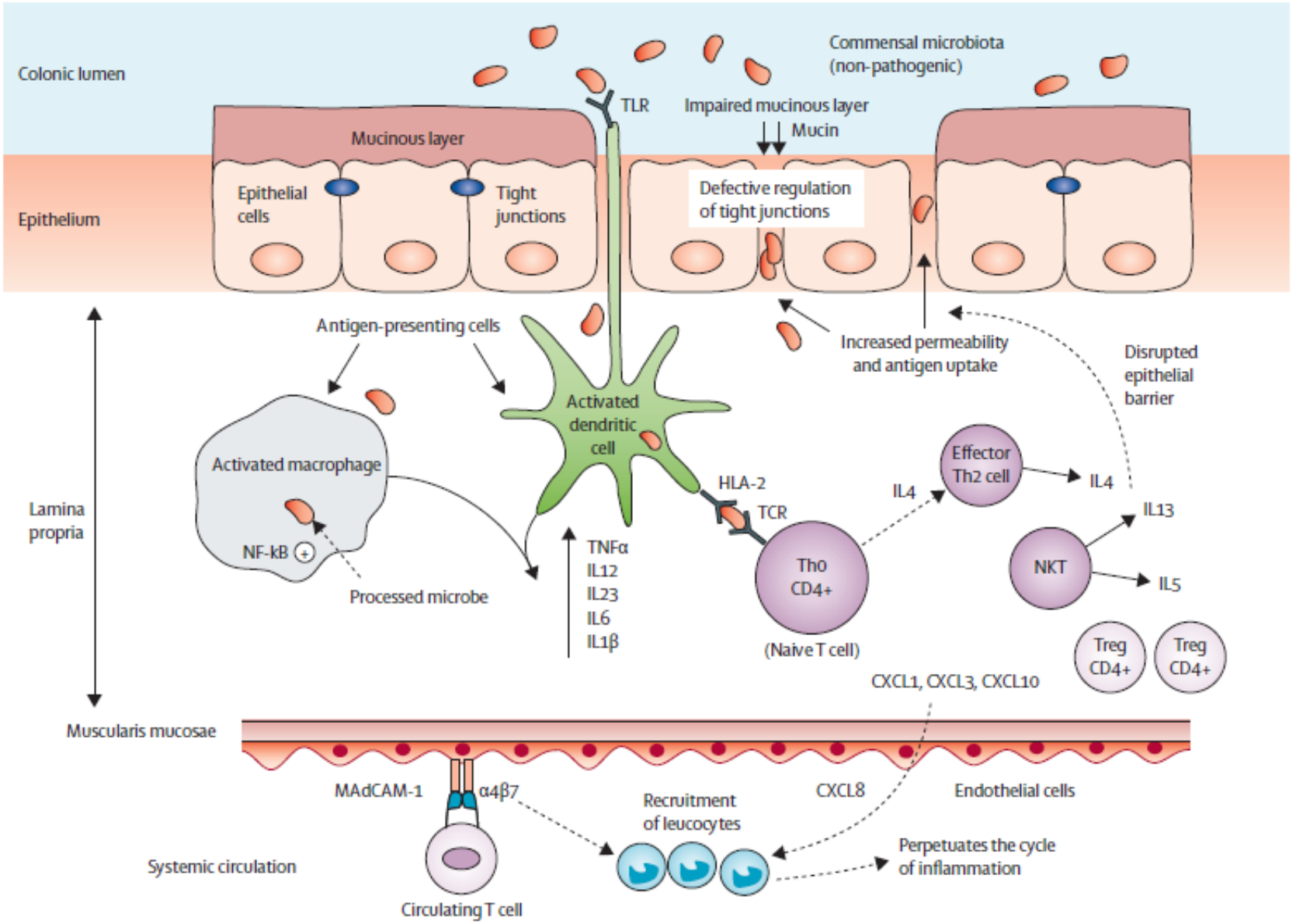


- 25% Proctitis
- 25% Rectosigmoid
- 30% Left sided
- 20% Pancolitis

PEDIATRICS

5%	Proctitis
10-15%	Rectosigmoid
30-40%	Left-sided
50%	Pancolitis

Pathophysiology



Experimental Medicine Study Endpoints

- Target Engagement
  - Assay available to determine target engagement and downstream activity
- Pharmacokinetics in Blood and Biopsies
- Stool Biomarkers
  - CRP and FCP
- Inflammatory Markers in Biopsies
  - e.g. IL-1, IL-6, IL-8, MMP3, TNFα, IFNγ.
- Stool Biomarkers
  - CRP and FCP
- Clinical Endpoints and PROs
  - Mayo
  - UCEIS
  - Modified Riley
  - Geboes
  - IBDQ

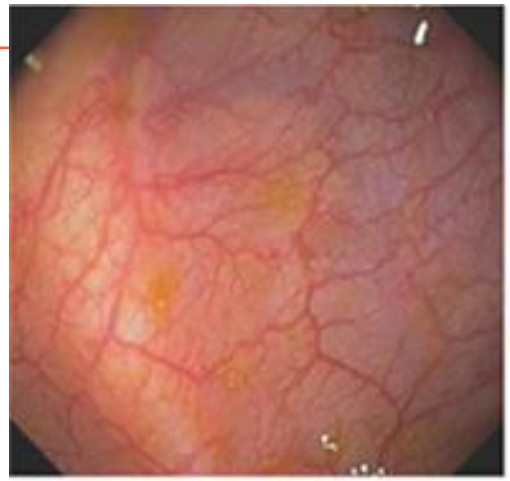
Mayo Scoring System

Table 2 Mayo scoring system for assessment of ulcerative colitis activity

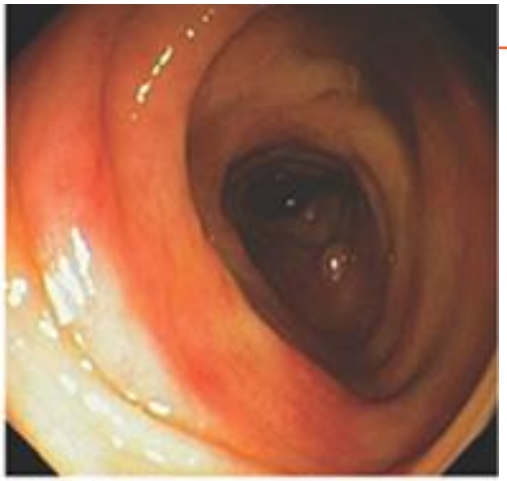
Measure	Scoring system
Stool frequency (per day)	0 = normal number of stools for patient
	1 = 1–2 more stools than normal
	2 = 3–4 more stools than normal
	3 = 5+ more stools than normal
Rectal bleeding	0 = no blood seen
	1 = streaks of blood with stool less than 50% of time
	2 = obvious blood with stool most of time
	3 = passes blood without stool
Findings on endoscopy	0 = normal or inactive disease
	1 = mild disease
	2 = moderate disease
	3 = severe disease
Physician's global assessment	0 = normal
	1 = mild disease
	2 = moderate disease
	3 = severe disease

Endoscopy sub-score

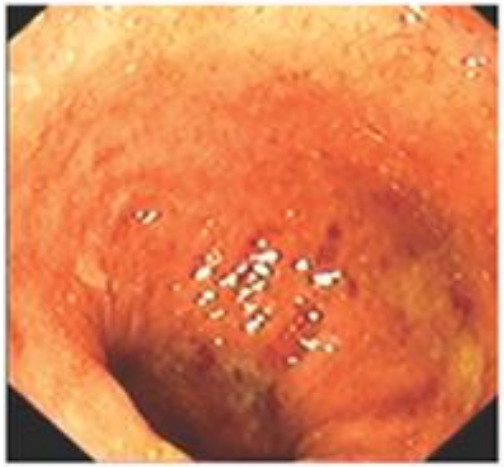
Mayo Endoscopic Subscore



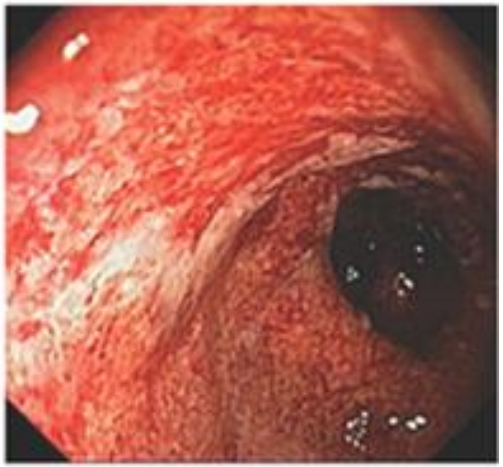
0 Normal or inactive disease



1 Mild disease (erythema, decreased vascular pattern, mild friability)



2 Moderate disease (marked erythema, absent vascular pattern, friability, erosions)



3 Severe disease (spontaneous bleeding, ulcerations)

UC Endoscopic Index of Severity

UCEIS

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visible oozing from the mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

- Travis SP et al. *Gastroenterology* 2013
- Satisfactory intra and interobserver variability
- Not yet validated prospectively in a RCT

UC PROs

Health-related QOL tools

- Inflammatory Bowel Disease Questionnaire (IBDQ)
  - Used most frequently in CD RCTs
  - 32 questions
  - 4 domains:
    - Bowel symptoms
    - Systemic symptoms
    - Emotional function
    - Social function

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
  - 10 questions (90% of the variance of the IBDQ), same 4 domains
  - 10 (worst) to 70 (best)

Leveraging Data Across Indications

Clinical Development in Multiple Concurrent Indications

- All three studies will be conducted in parallel, presenting an unique opportunity to leverage data across studies and clinical development plans
  - 12 week placebo-controlled studies, with biopsies/MRIs at baseline, 6 and 12 weeks

- More than just an opportunity to pool data across studies
  - Target Engagement and Down-stream activity in blood
  - Pharmacokinetics in blood
  - Safety data

- What about inflammatory biomarkers and clinical endpoints?
- Studies wont all complete at same time, how can one indication benefit from data collected in another indication?

Bayesian Decision Criteria to Inform Clinical Development Across Indications

- Changes in Inflammatory Biomarkres
  - Number of options to investigate
    - EM approach to relationship between TE and normalised inflammatory biomarker
    - Defining a “responder” for each biomarker to compare across indications

- Changes in Clinical Endpoints
  - PsO, RA and UC all have clearly defined definitions of a responder based on clinical endpoints
  - Bayesian inference will be performed to determine the responder rate in each study, weighted appropriately for the indication
  - Resulting posterior probability distribution will be compared to the aTNF probability distribution obtained from appropriate historical data

  - Will allow a greater understanding of the whether the mechanism provides a similar clinical response with aTNFs, which in turn will aid Go/No-Go decisions

Thank You