Individualizing IBD therapy according to disease mechanism

3rd Annual Baylor University Medical Center IBD Conference
Dallas, TX
April 14, 2018

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Individualizing IBD therapy according to disease mechanism

- The ability to individualize IBD therapy according to mechanisms assumes that
  - We have characterized different pathways to disease (the same phenotype)
  - The different pathways have unique nodes for intervention
  - There exist effective therapeutic agents that can moderate the different pathways
  - We can identify which pathways are dominant in the disease in individual patients and be able to do this before treatment

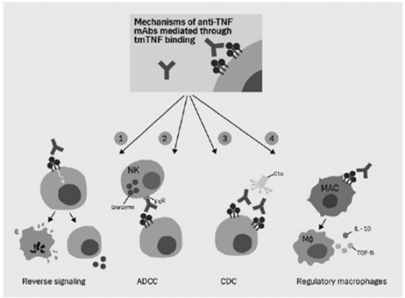
Individualizing IBD therapy according to disease mechanism

- Precision medicine provides care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling.
- Optimized versus precision medicine for IBD?
- We cannot individualize IBD therapy according to disease mechanism at this time

Current approaches to fulfilling individualized therapy in IBD

- Predicting non-response to anti-TNFs
- Lessons from targeting specific molecules
- Determining Endophenotypes of Disease: Hope for Improving Response to Therapy

Individualizing Therapy in IBD: anti-TNFα drugs



Indivdualizing Therapy in IBD: anti-TNFα drugs

- Pharmacokinetics: response related to tissue drug level
  - TNF/anti-TNF Ab ratio different between inflamed and non-inflamed mucosa Yarur, A. et al. Gu 2016 65, 249–255.
  - Optimized trough serum levels associated with increased CD remission Vande Casteele, N et al. (2015). Gastroenterology 148, 1320–1329.
  - Higher rates of anti-TNF Ab cleavage due to increased MMP expression Biancheri, P., Gastroenterology 2015 149, 1564–1574.
- Pharmacodynamics: is the signaling effect the same?
  - Seems that R and NR to IFX can have same profile for many TNF-responsive genes but other changes in IL1β and IL-17 supporting importance of "non-TNF-driven inflammation" Leal et al. Gut 2015 64, 233–242.
  - We have many examples of molecular profiles of gene expression that change differentially in R and NR but no pre-treatment discriminators

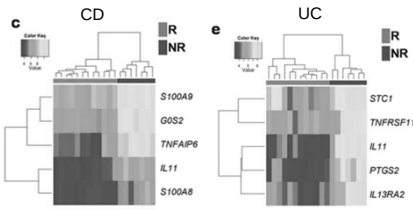
Individualizing Therapy in IBD: anti-TNFα drugs

- Pre-treatment molecular signatures of cell subsets in LP showed NRs had higher plasma and activated macrophages (Gaujoux et al Gut 2018;0:1–11.)
- NRs had lower expression of surface TNF in LP immunocytes
- Pre-treatment genotype IL17F (G/G) and the IL17R adaptor protein TRAF3IP2 (C/C or C/A) gene polymorphisms (Urabe et al Biomed Res Int 2015:416838)
- Pre-treatment mucosal molecular signatures of NR in CD and UC (Arijs et al Inflamm Bowel Dis 2010;16:2090–2098; Arijs et al. Gut 2009;58:1612–1619)

Individualizing Therapy in IBD: anti-TNFα drugs

Predictive Value of Epithelial Gene Expression Profiles for Response to Infliximab in Crohn's Disease

Ingrid Arijs, MS,*† Roel Quintens, MS,† Leentje Van Lommel, MS,† Kristel Van Steen, PhD,‡ Gert De Hertogh, MD, PhD,§ Katleen Lemaire, PhD,† Anica Schraenen, MS,† Clémentine Perrier, PhD,* Gert Van Assche, MD, PhD,* Séverine Vermeire, MD, PhD,* Karel Geboes, MD, PhD,§ Frans Schuit, MD, PhD,† and Paul Rutgeerts, MD, PhD, FRCP*¶



Mucosal biopsy-based, pre and post IFX induction

CD: fecal calprotectin heterodimeric complex of S100A9/S100A8, a lymphocyte cell cycle protein

UC: genes involved in adaptive immune response, TNF pathway

IL-11: hematopoetic sten cell and megakaryocyte growth factor

These results have not been validated in larger studies

Individualizing Therapy in IBD: anti-TNFα drugs

Experience with the best used biologic in IBD has identified primary non-response with:

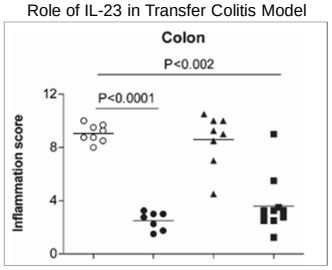
- Suboptimal drug levels
- Non-TNF-driven inflammatory pathways
- IL17F and receptor adaptor protein gene polymorphisms (of unclear functional consequence)
- Profiles of gene expression present at pretreatment that predict NR

Therapy Based on Disease Mechanism: Highlighted Experiences

- Can we identify subjects who will do better with one targeted drug over another?
- Targeted mechanisms
  - IL-12/INFγ and IL-23/IL-17 dominant in Crohn's disease
  - Anti-IL-17A and anti-IL-17RA trials
  - Anti-p40 (IL-12/23): briakinumab, ustekinumab (Stelara)
  - IL-13 associated with ulcerative colitis (Th2-like)
  - Inhibited TGFβ signaling by excess SMAD7 (Mongersen) (no apparent regulatory defect in CD and UC despite the VEO-IBD and checkpoint inhibitor IBDs not withstanding)

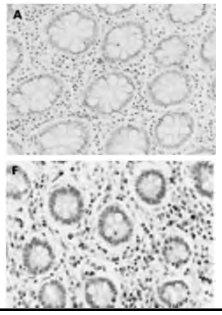
The Origins of IL-23/IL-17 Contributions to Crohn's disease

Role of IL-23 in Transfer Colitis Model

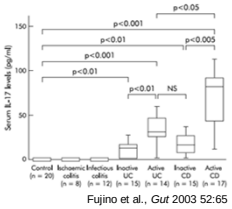


Hue et al., *JEM* 2006 203:2473

IL-23/IL-17 Association with IBD

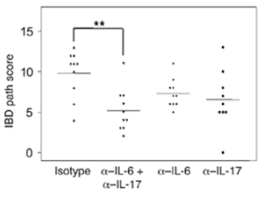


Elevated IL-17 in Active IBD



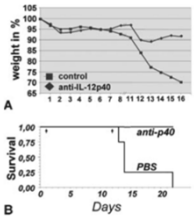
Fujino et al., *Gut* 2003 52:65

Targeting IL-17 in IL-10$^{-/-}$ Colitis Model Does not Fully Inhibit Inflammation



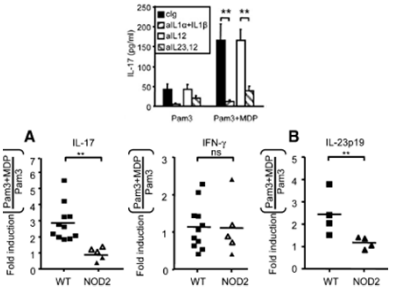
Yen et al., *JCI* 2006 116: 1310

Targeting IL-17 in TNBS Colitis Model Worsens Outcome in IL-23 Deficiency (p19 KO)



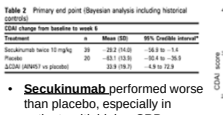
Becker et al. *J Immunol* 2006; 177:2760-2764

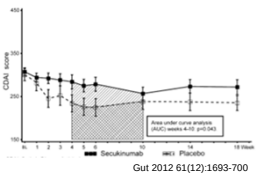
Human Crohn's NOD2 Defect Impairs IL-23 and IL-17 Development in Response to TLR Ligands



Immunity 2007 27(4):660-9

Experience with anti-IL-17 Agents in Crohn's Disease

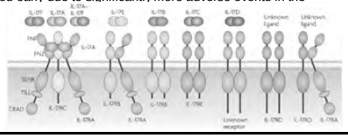




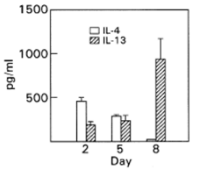
- **Secukinumab** performed worse than placebo, especially in patients with higher CRPs
- 43% infection rate vs 0% placebo; 4 with severe mucocutaneous Candidiasis

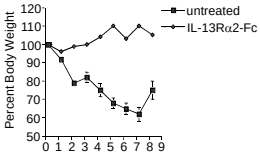
Gut 2012 61(12):1693-700

Brodalumab (anti-IL-17AR) clinical trial results have not been published but this study was stopped early due to significantly more adverse events in the study drug arm.

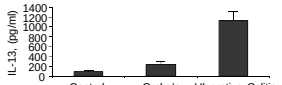


IL-13 Is the Effector Cytokine in Experimental Oxazolone Colitis



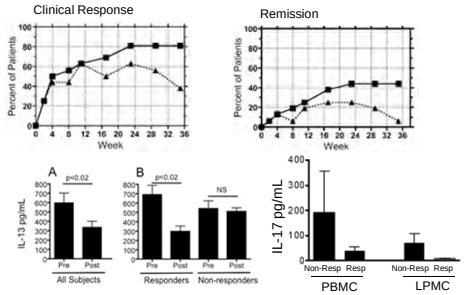


(Heller, *Immunity* 2002)



(Fuss, *JCI* 2004)

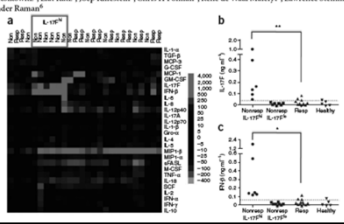
Results of Interferon-beta Trial in UC



High IL-17 Production Accompanies Non-response to Interferonβ in Multiple Sclerosis

T helper type 1 and 17 cells determine efficacy of interferon-β in multiple sclerosis and experimental encephalomyelitis

Robert C Axtell[1], Brigit A de Jong[1–3], Katia Boniface[4], Laura F van der Voort[1], Roopa Bhat[1], Patrizia De Sarno[5], Rodrigo Naves[6], May Han[1], Franklin Zhong[1], Jim G Castellanos[1], Robert Mair[1], Athena Christakos[1], Ilan Kolkowitz[1], Liat Katz[1], Joep Killestein[3], Chris H Polman[3], René de Waal Malefyt[4], Lawrence Steinman[1] & Chander Raman[6]



Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study

Walter Reinisch,[1,2] Julián Panés,[3] Sunil Khurana,[4] Gabor Toth,[5] Fei Hua,[6] Gail M Comer,[6] Michelle Hinz,[6] Karen Page,[6] Margot O'Toole,[6] Tara McDonnell Moorehead,[7] Hua Zhu,[8] YanHui Sun,[8] Fabio Cataldi[6]

Reinisch W, et al. Gut 2015;64:894–900

Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study

Silvio Danese,[1] Janusz Rudziński,[2] Wolfgang Brandt,[3] Jean-Louis Dupas,[4] Laurent Peyrin-Biroulet,[5] Yoram Bouhnik,[6] Dariusz Kleczkowski,[7] Peter Uebel,[8] Milan Lukas,[9] Mikael Knutsson,[10] Fredrik Erlandsson,[10] Mark Berner Hansen,[10] Satish Keshav[11]

Danese S, et al. Gut 2015;64:243–249.

Individualizing Therapy in IBD: Insights from Monogenic diseases associated with IBD

- Subsets of IBD pts with NADPH oxidase hypomorphic phenotype and treatment with G-CSF or GM-CSF
- Subsets of IBD pts with hyper-inflammatory phenotypes may resemble mevalonate kinase deficiency or FMF pts with IBD who respond well to IL-1β antagonists
- Endophenotype of high IL-17 production

Individualizing Therapy in IBD Based on Mechanism of Disease

- Optimizing therapy versus individualizing for now
- Working to establish endophenotypes of disease that expand beyond excess cytokine production
- Continued focus on conventional and experimental therapies with comprehensive study of pre-treatment and post-treatment genetic, epigenetic, and molecular measures linked to robust outcomes
- Paying attention to the extremes of outcomes to differentiate dominant effects for robust predictors of outcomes to highly targeted therapies