PERSONALIZED MEDICINE: A NECESSITY OR AN OPPORTUNITY

The gastroenterologis perspectives

Massimo C Fantini MD, PhD
Dep of Systems Medicine
University of Rome «Tor Vergata»

Personalized medicine: a necessity or an opportunity

PERSONALIZED MEDICINE

Is this a relevant problem in IBD?

New therapeutic targets to hit!

OLD TARGETS

CLINICAL REMISSION

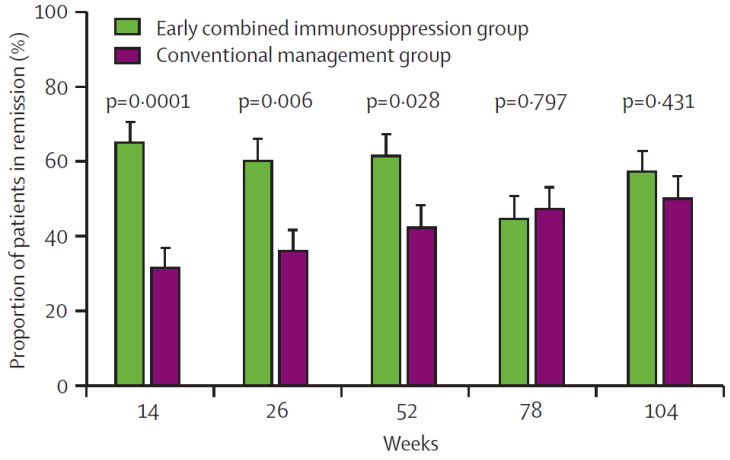
Clinical response

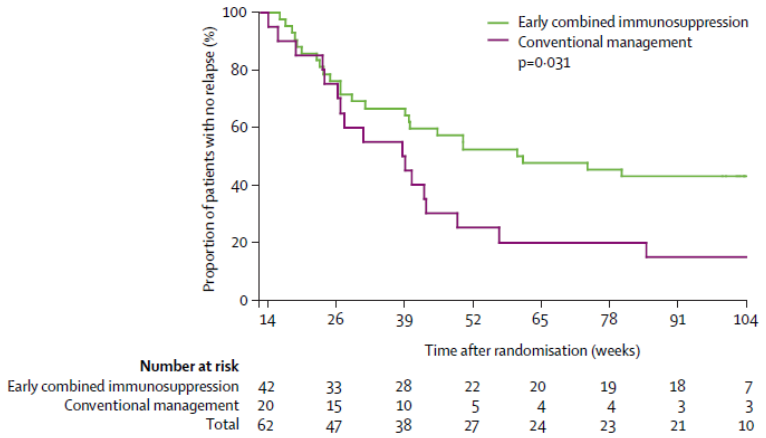
Steroid sparing

NEW TARGETS

Looking for new therapeutic **strategies** to reach ambitious targets

Step-up vs Top-down

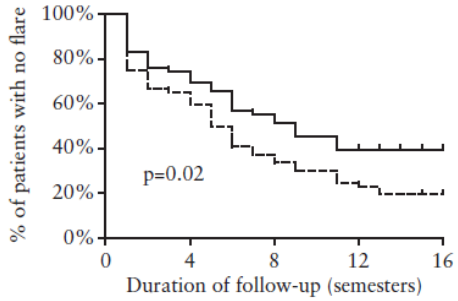




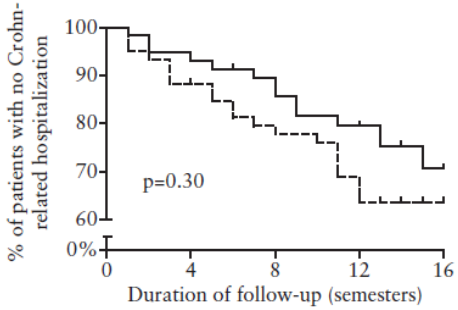
D'Haens G et al Lancet 2008

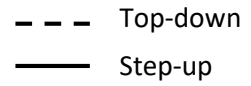
Step-up vs Top-down ....10 years later

% of Pts with no **Disease flare**

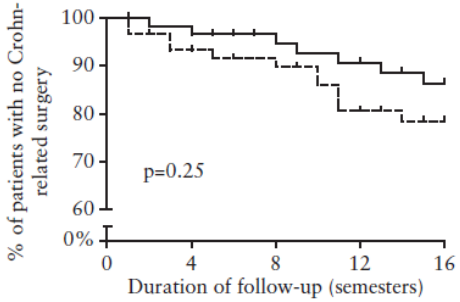


% of Pts with no **Hospitalization**

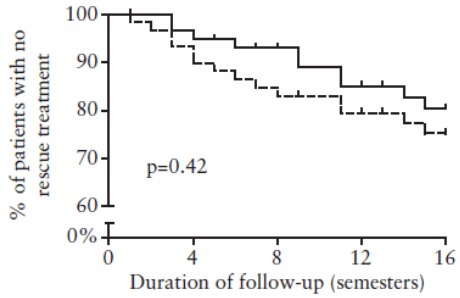




% of Pts with no **Surgery**



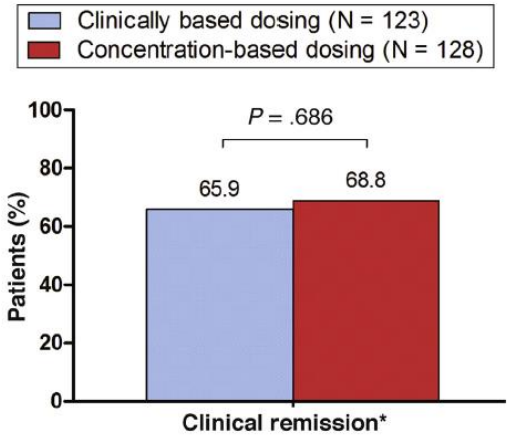
% of Pts with no **Rescue treatment**

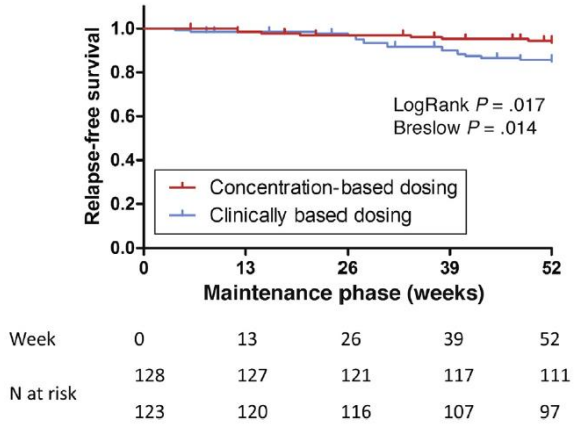


Hoekman DR et al J Crohns Colitis 2018

Exploring new strategies I

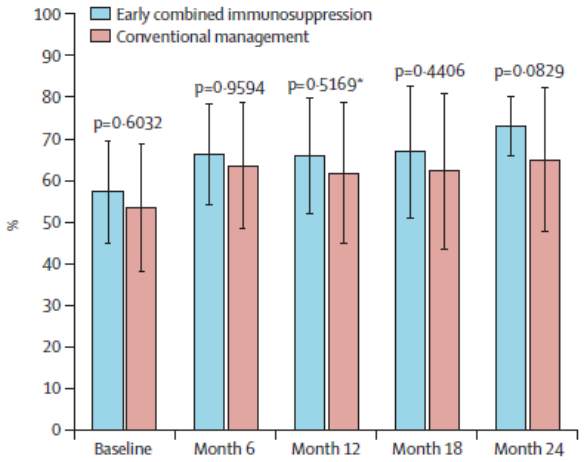
TAXIT study

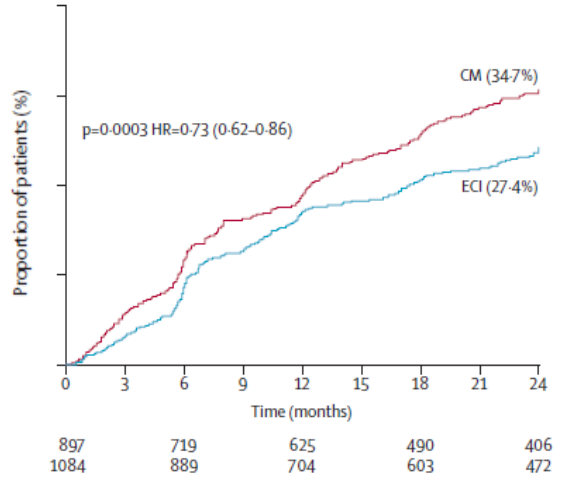




Casteele NV et al Gastroenterology 2015

REACT trial

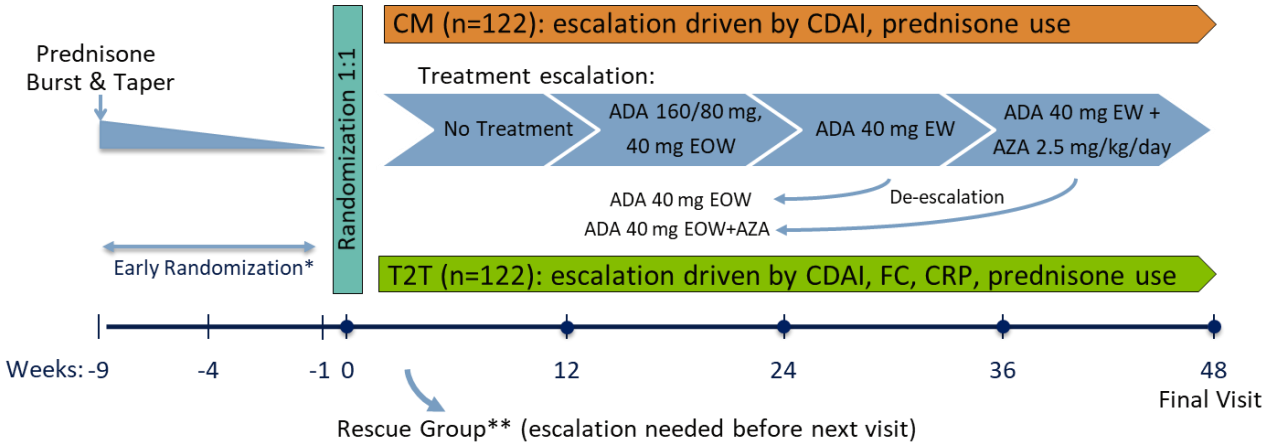




Khanna R et al Lancet 2015

Exploring new strategies II

The CALM study

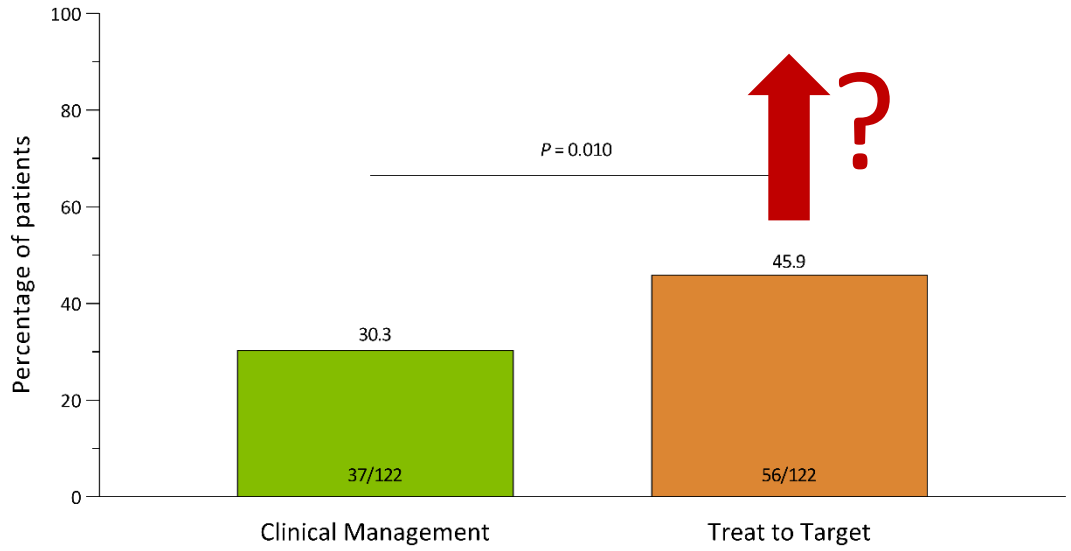


*CDAI>220 AND one of the following: steroid therapy > 4 weeks and best to taper per investigator assessment, intolerant/contraindication for steroid therapy, best interest of the patient per investigator assessment.

** CDAI > 300 for 2 consecutive visits 7 days apart or per investigator discretion (elevated CRP/FC, ulceration taken into consideration); moved to T2T group.

Primary Endpoint at 48 Weeks After Randomization

CDEIS < 4 AND NO DEEP ULCERATIONS



Colombel JF et al Lancet 2017

More drugs with different mode of action (MOA) to position

1st line

(*Its cheaper!!*)

Anti-TNFs

Infliximab

Adalimumab

Golimumab

Certolizumab

2st line

Anti-Integrins

Vedolizumab

-IL12/IL23p40

Ustekinumab

Phosphodiesterase-4-inhibitors

Apremilast

Anti-IL23p19

Risankuzumab

Brazikumab, MEDI207

Guselkumab

Mirikizumab

Tofacitinib

Upadacitinib

Filgotinib

Peficitinib

S1PR agonists

Ozanimod

Etrasimod

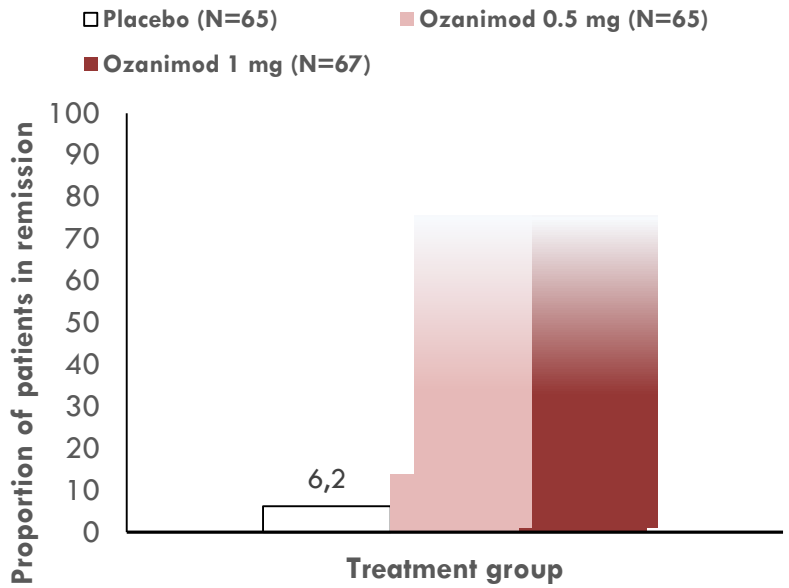
Anti MadCAM1

PF-00547659

Limited efficacy of the new drugs

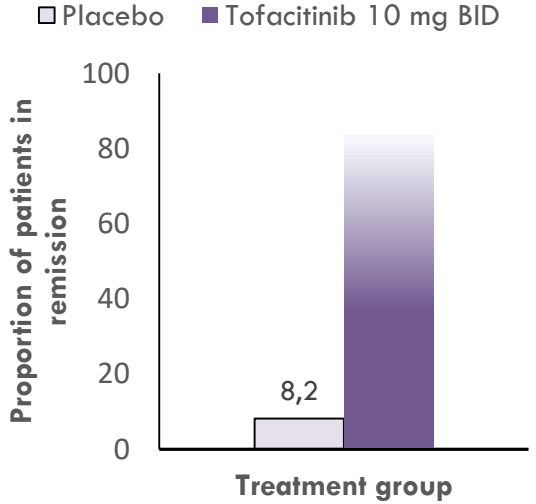
Ozanimod

TOUCHSTONE

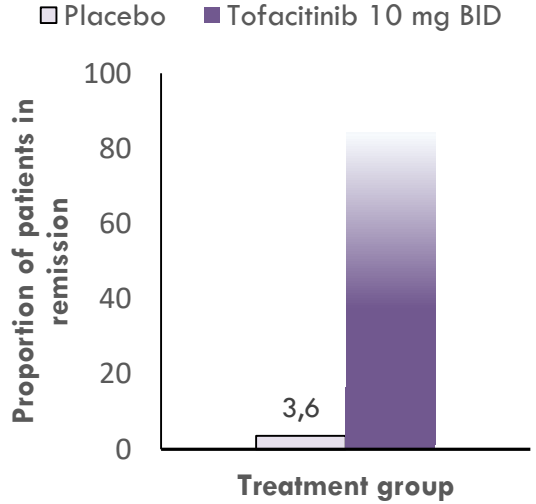


Tofacitinib

OCTAVE 1

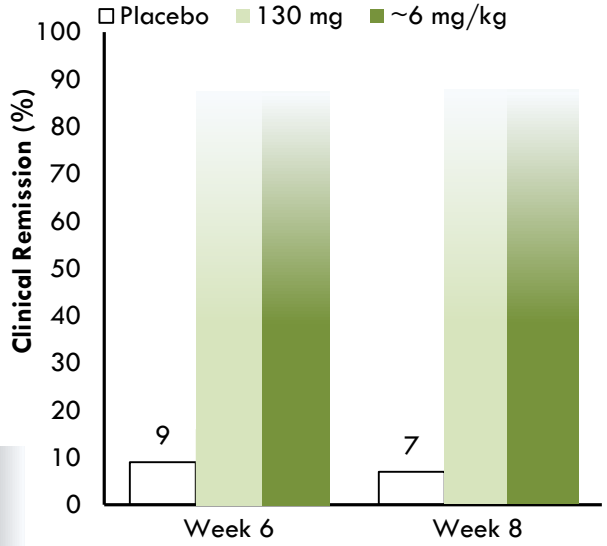


OCTAVE 2

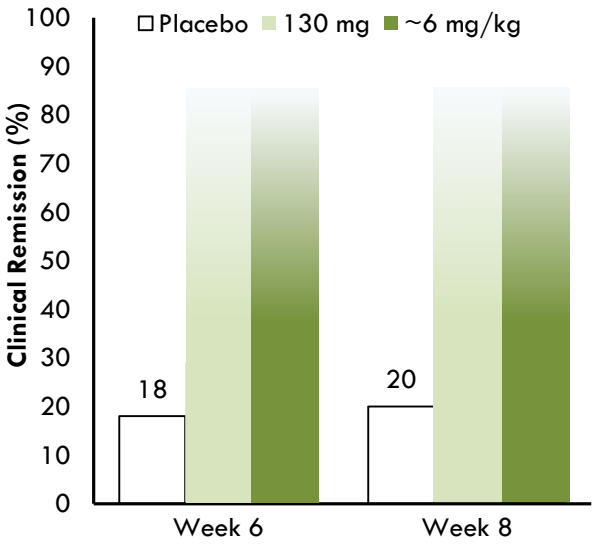


Ustekinumab

UNITI-1: antiTNF failure

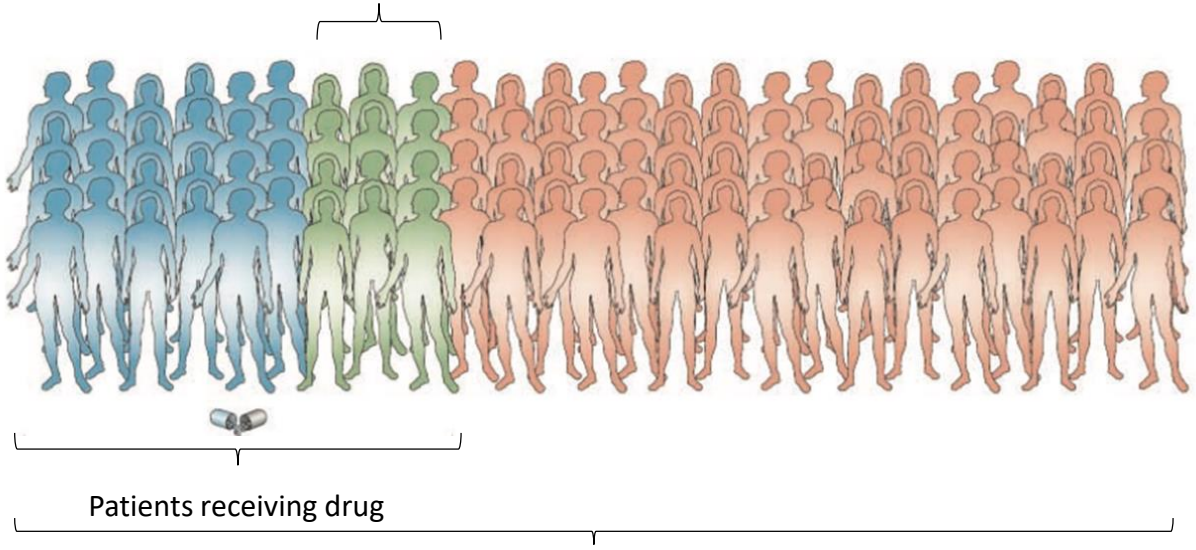


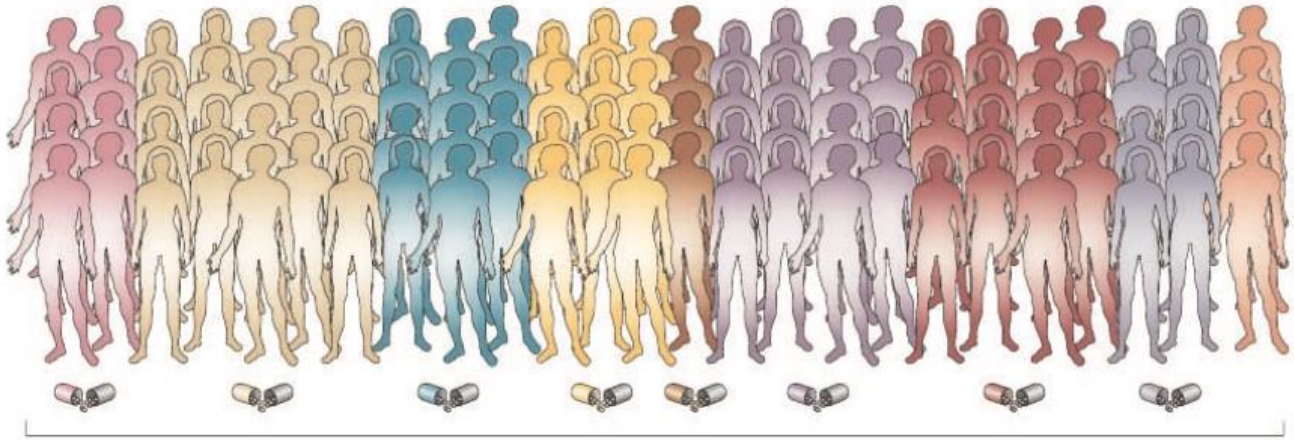
UNITI-2: Conv therapy failure



From a generalistic approach to personalized medicine

One-size-fits-all approach





Population of patients with given disease:
or or nearly all respond to different drugs

Personalized medicine

Where are we?.....The present

How to approach the problem

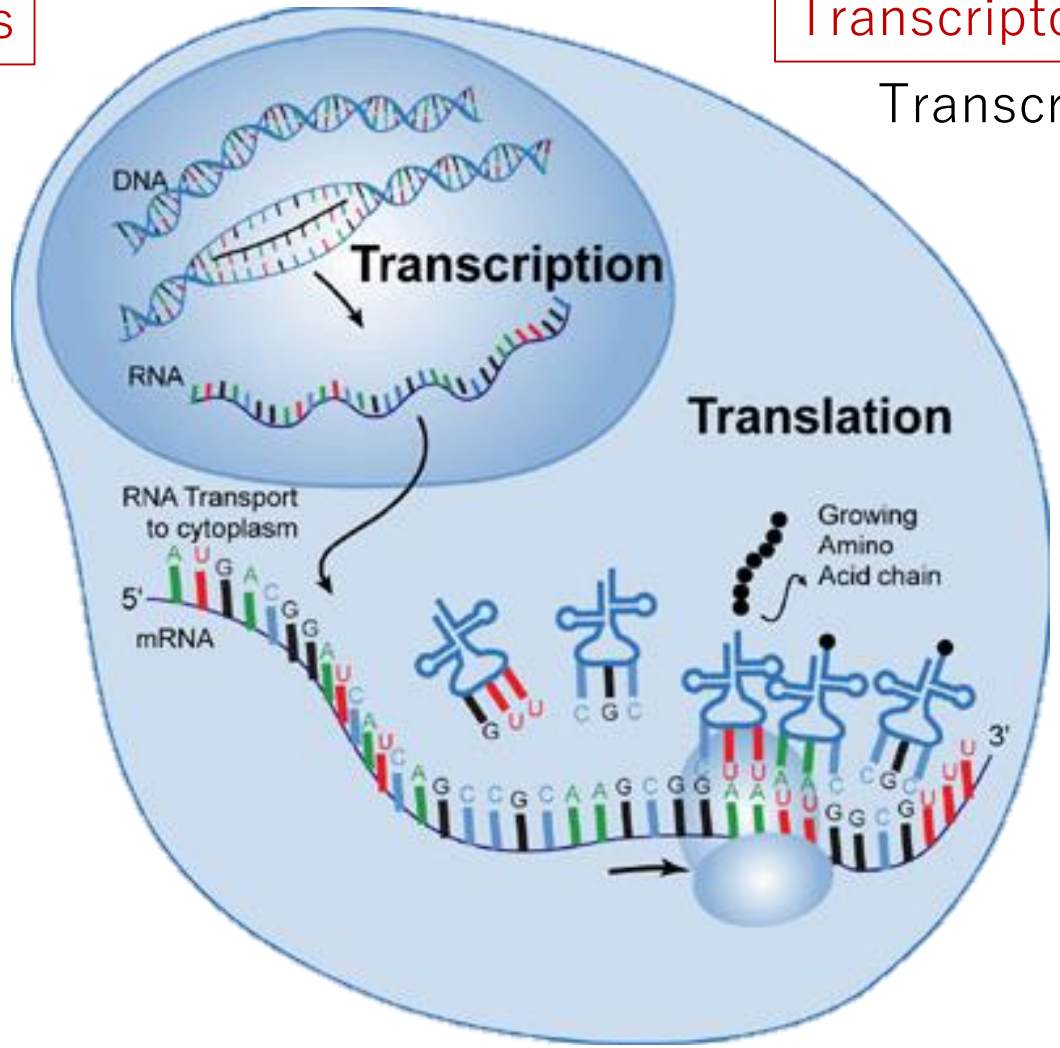
Genomics

Genes

Transcriptomics

Transcripts

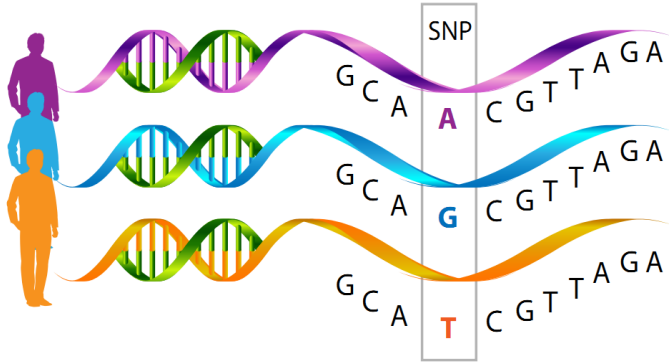
Response to therapies can be seen as a biologic pehnomen governed by the same mechanisms determining diseases.



Proteomics

Proteins

Pharmacogenomic to select the right drug



Point mutations and allele variants to predict response to therapy and side effects

Response to steroids:

- SNPs of **multidrug resistance protein 1 (MDR1)** conding gene are not association with steroid resistance in IBD while SNP at position **-308 of the TNFα** gene has been associated with an increased rate of both steroid resistance and requirment for surgery in pts with CD

  Cucchiara S et al J Pediatr Gastroenterol Nutr 2007
- SNPs in the **Glucocorticoid Receptor (GCR)** gene have been shown to decrease GCR protein level resulting in a drop of steroid potency, but no assocation with IBD pts not responding to steroid has been demonstrated.

  Koyano S et al J Pharmacol Exp Ther 2003

Response to methotrexate:

In patients with IBD, the homozygous **MTHFR 1298C** variant was found to be associated with toxicity to Methotrexate (MTX) whereas the 677T variant was not.

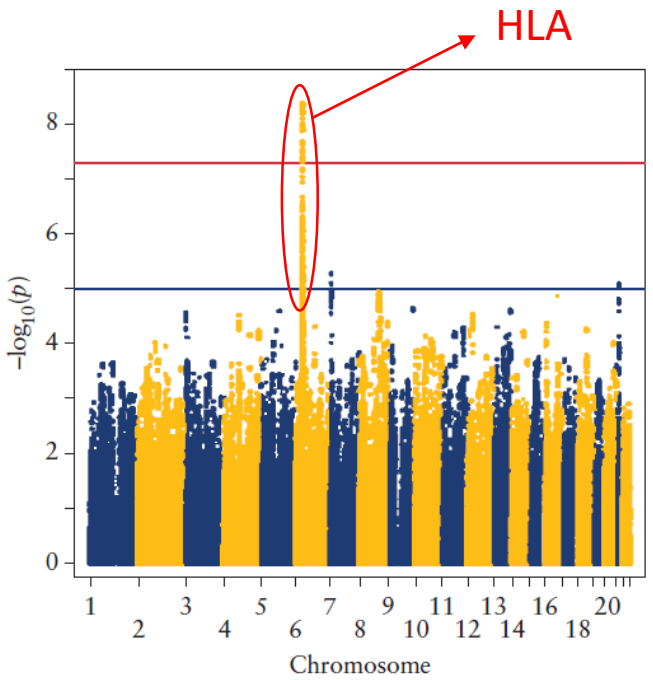
Herrlinger KR et al Pharmacogenet Genomics 2005

Pharmacogenomic to avoid side effects: 5-ASA

Clinical Features and HLA Association of 5-Aminosalicylate (5-ASA)-induced Nephrotoxicity in Inflammatory Bowel Disease

Graham A. Heap et al JCC 2015

Carriage of the risk allele (HLA region) is associated with a 3-fold increased risk of renal injury after 5-ASA administration.



Top genome-wide association study (GWAS) association signals from the combined GWAS and HLA imputation analysis.

Single-nucleotide polymorphism	Cohort	Chromosome	Position (hg19)	Effect allele	Control risk allele frequency	Risk allele frequency	Odds ratio (SE)	Odds ratio (95% confidence interval)	*p*-value
rs3135356	All	6	32391516	A	0.17	0.29	2.00 (0.13)		1×10^{-7}
	Biopsy only					0.39		3.11 (0.19)	4×10^{-9}
rs12204929	All	6	119396266	T	0.05	0.11	2.79 (0.20)		4×10^{-7}
	Biopsy only					0.10		2.26 (0.34)	0.02
rs10488193	All	7	12274220	G	0.11	0.21	2.15 (0.15)		3×10^{-6}
	Biopsy only					0.25		2.74 (0.23)	1×10^{-5}

- These data were not replicated in a validation cohort
- The high frequency of this SNP and the low frequency of the adverse event limits its clinical utility.
- Genetic testing could not be recommended in guiding treatment choice or monitoring intervals.

Pharmacogenomic to avoid side effects: Thiopurines

*Allele variants of the **Thiopurine S-Methyltransferase (TPMT)** affect the conversion rate of 6-MP to 6-MMP*

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 949–953, February 1995
Medical Sciences

A single point mutation leading to loss of catalytic activity in human thiopurine *S*-methyltransferase

EUGENE Y. KRYNETSKI, JOHN D. SCHUETZ, AMY J. GALPIN, CHING-HON PUI, MARY V. RELLING, AND WILLIAM E. EVANS*

Pharmaceutical Department, St. Jude Children's Research Hospital, and Center for Pediatric Pharmacokinetics and Therapeutics, Departments of Clinical Pharmacy and Pediatrics, University of Tennessee, Memphis, TN 38105

Communicated by Gertrude B. Elion, Burroughs Wellcome Co., Research Triangle Park, NC, November 1, 1994 (received for review October 6, 1994)

TPMT*2

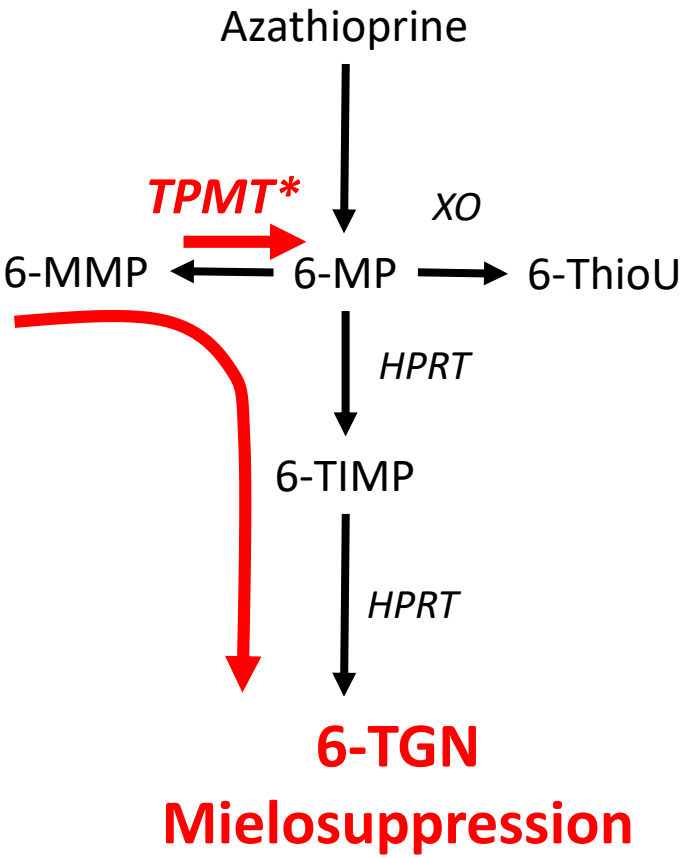
Am. J. Hum. Genet. 58:694–702, 1996

Thiopurine S-Methyltransferase Deficiency: Two Nucleotide Transitions Define the Most Prevalent Mutant Allele Associated with Loss of Catalytic Activity in Caucasians

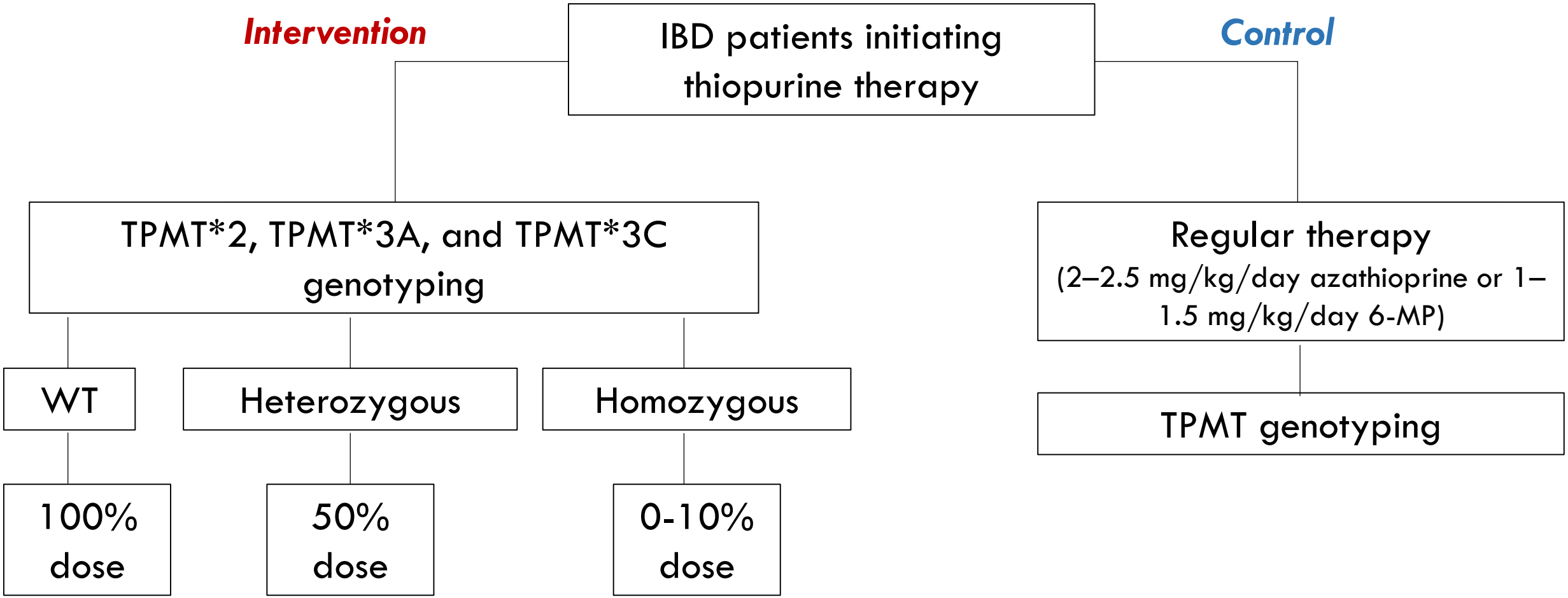
Hung-Liang Tai, Eugene Y. Krynetski, Charles R. Yates, Thrina Loennechen, Michael Y. Fessing, Natalia F. Krynetskaia, and William E. Evans

Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital; and Center for Pediatric Pharmacokinetics and Therapeutics, Departments of Clinical Pharmacy, Pharmaceutics, and Pediatrics, University of Tennessee, Memphis

TPMT*3A
TPMT*3B
TPMT*3C

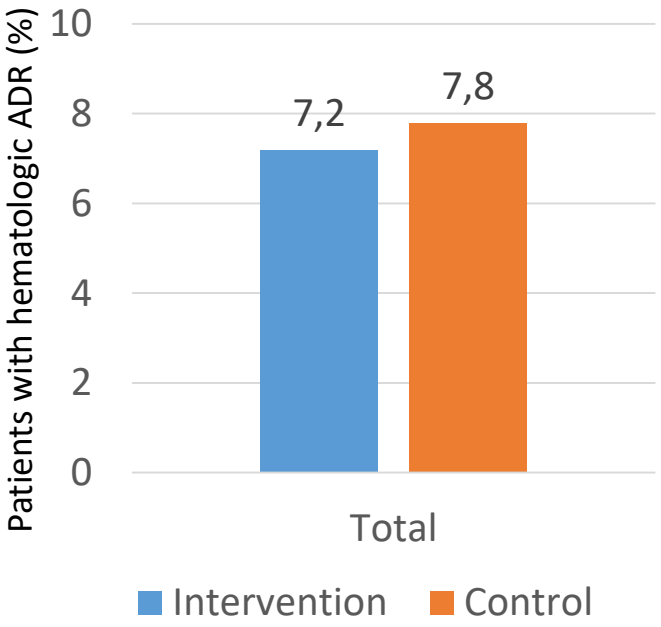


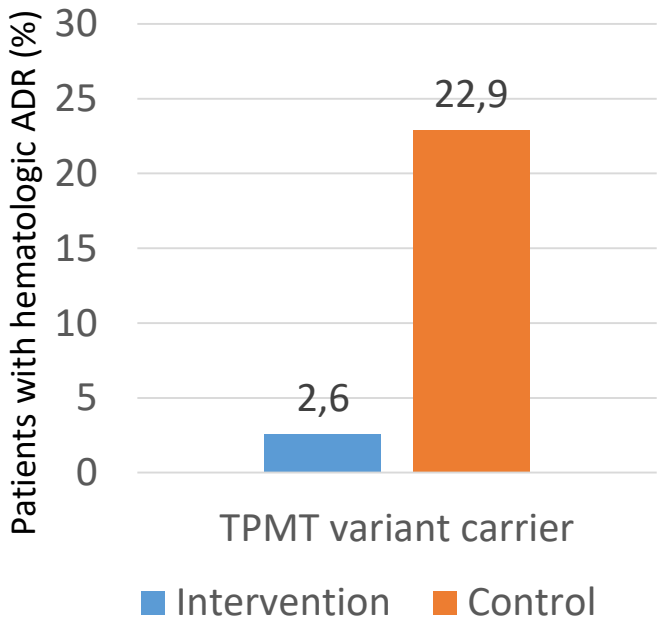
Pharmacogenomic to avoid side effects: **the TOPIC trial**



Coenen MJH. Gastroenterology 2015

Pharmacogenomic to avoid side effects: TOPIC trial results

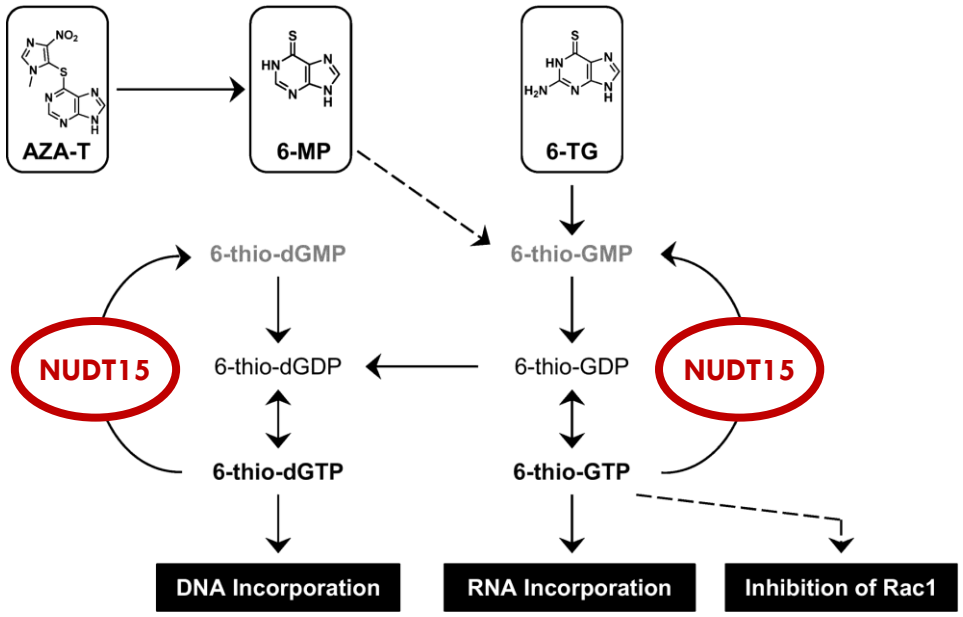




- Similar therapeutic efficacy
- 200 patients need to be genotyped to avoid 1 episode of hematologic ADR (7.4% vs 7.9%; i.e. 0.5% risk difference)
- Genetic testing should be considered as a cost-effective addition to hematological monitoring
- 1 patient of 11 with low enzyme activity TPMT variant developed leukopenia: **no all cases of leukopenia can be explained by the known TPMT known variants!**

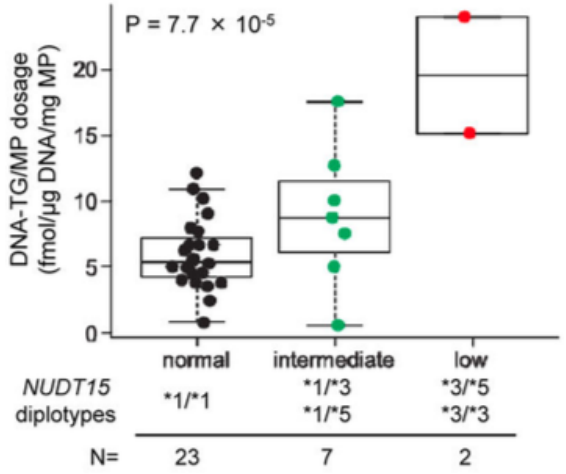
Coenen MJH. Gastroenterology 2015

NUDT15 genetic variants are associated with thiopurine-related toxicity



	Genotype			
	Homozygote (TT) (n = 14)	Heterozygote (CT) (n = 133)	Non-carrier (CC) (n = 199)	P value[b]
Azathioprine dose (mg/kg/d)[a]	0.86 (0.50–1.09)	1.06 (0.26–2.84)	1.53 (0.14–3.12)	4.93×10^{-11}
Interval from onset of therapy to leukopenia (d)[a]	19 (9–28)	135 (12–3,300)	465 (21–3,705)	1.03×10^{-17}
Leukopenia[c]				
Grade 3 or 4	14 (100.0)	10 (7.5)	4 (2.0)	4.85×10^{-19}
Grade 4	12 (85.7)	3 (2.3)	0 (0.0)	5.20×10^{-19}

Grade 3 leukopenia is defined by a WBC count between 1,000 and 2,000 cells/mm^3. Grade 4 leukopenia is defined by a WBC count of less than 1,000 cells/mm^3.



Yang SK. Nat Genet 2014

Genomic predictors of response to anti-TNF therapy

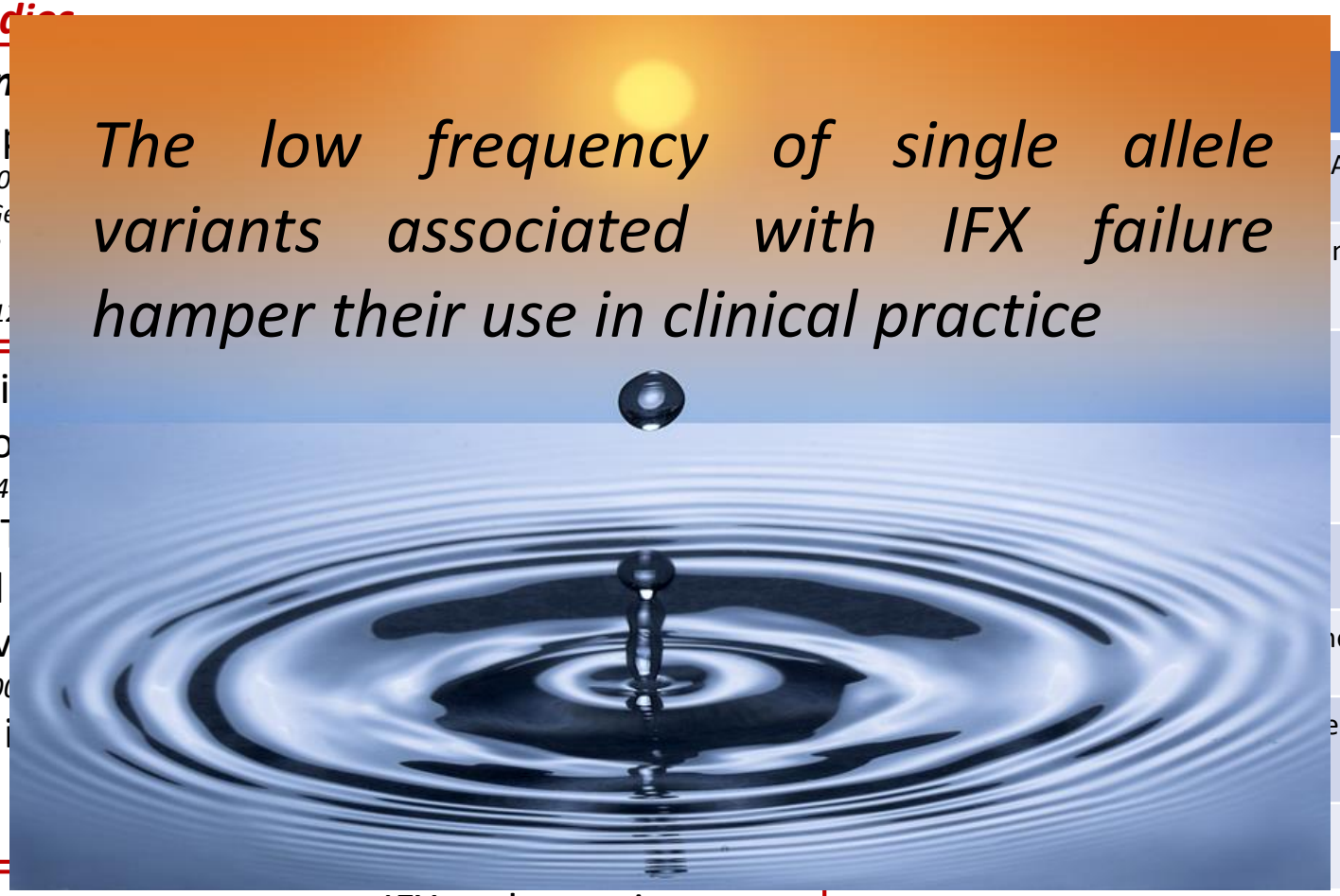
Single gene-association studies

SNPs of ***tnfrsf1a, tnfrsf1b, tn***
response to anti-TNFα therap
Matsukura H et al Aliment Pharmacol Ther 200
Magdelaine-Beuzelin C et al Pharmacogenet Ge
Prieto-Pérez R et al Pharmacogenomics J 2013
Prajapati R et al Pharmacogenomics 2011
Steenholdt C et al Aliment Pharmacol Ther 201

FCGR3A-158V/V polymorphi
perhaps clinical responses to
Louis EJ et al Aliment Pharmacol Ther 2004
A sub-analysis of the ACCEN
FCGR3A variants and clinical
greater decrease in C-reactiv
Louis EJ et al Pharmacogenet Genomics 20
FCGR3A-158 pplymorphism i
CD by affecting ADCC.
Moroi R et al Immunogenetics 2013

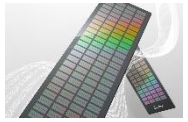
No associations was found between response to IFX and genetic variants of **NOD2/CARD15**, **TNFα** and **TNFαR** genes
Niess JH et al Dig Dis Sci 2012

The low frequency of single allele variants associated with IFX failure hamper their use in clinical practice



	Biologic
A and 1B)	Infliximab
ne)	Infliximab
	Infliximab
	Infliximab
	Infliximab
ne)	Infliximab
erization	Infliximab
	Adalimumab

Wide scale polymorphism association studies to predict response to IFX in CD



Illumina Immunochip-v1: genotyping platform containing 196 524 polymorphisms (718 small insertion deletions, 195 806 SNPs), with dense coverage of known major immune and inflammatory disease loci.

CD

Primary Non-Response

Multivariable analysis of predictors of **PNR** to anti-TNF therapy in CD

	OR	95% CI	*P* value
Age at diagnosis	1.01	0.97–1.06	0.65
Disease duration	1.04	1.00–1.09	0.073
Disease location			
Ileal	1.00	–	–
Colonic	1.05	0.28–4.00	0.94
Ileocolonic	0.30	0.08–1.18	0.85
History of smoking	2.12	0.75–6.34	0.15
GRS (per 1 unit increase)	2.65	1.95–3.61	<0.001

Anti-TNF, anti-tumor necrosis factor therapy; CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; OR, odds ratio; PNR, primary non-response.

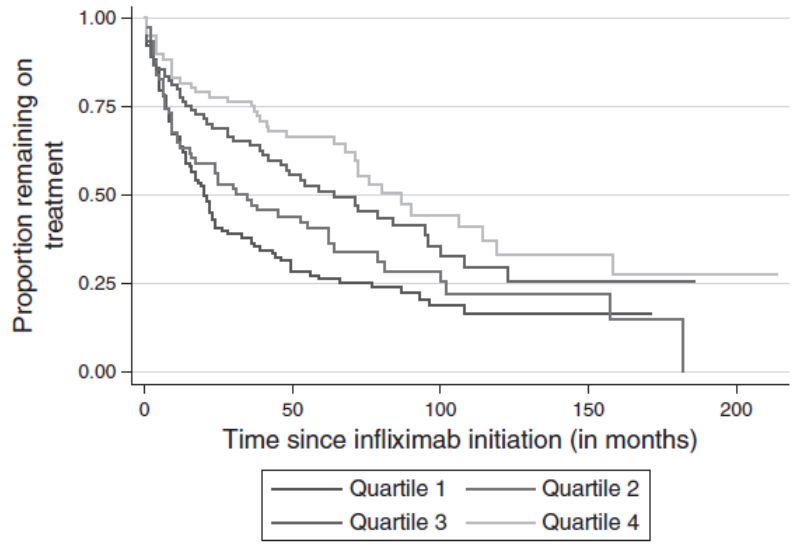
Durable Response

Multivariable analysis of predictors of **DR** to anti-TNF therapy in CD

	OR	95% CI	*P* value
Disease location			
Ileal (reference)	1.00	–	–
Colonic	1.89	0.60–5.97	0.28
Ileocolonic	1.50	0.63–3.57	0.36
Disease behavior			
Inflammatory (reference)	1.00	–	–
Stricturing	1.15	0.45–2.92	0.77
Penetrating	1.39	0.58–3.34	0.46
Immunomodulator	1.90	0.94–3.83	0.07
Prior resection	0.38	0.18–0.83	0.02
History of smoking	0.73	0.35–1.51	0.39
GRS (per 1 unit increase)	1.60	1.41–1.83	<0.001

Anti-TNF, anti-tumor necrosis factor therapy; CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; OR, odds ratio.

Durable Response



Genetic **R**isk **S**core (GRS) quartiles

<u>Genetic risk score (GSR)</u> for PNR could not predict DR (p=0.71) and vice versa (p=0.72; ρ0.02), suggesting that ***the mechanisms underlining the genetic predisposition to PNR and DR might be dinstinct.***

Barber GE et al Am J Gastroenterol 2016

Wide scale polymorphism association studies to predict response to IFX in UC

UC

Primary Non-Response

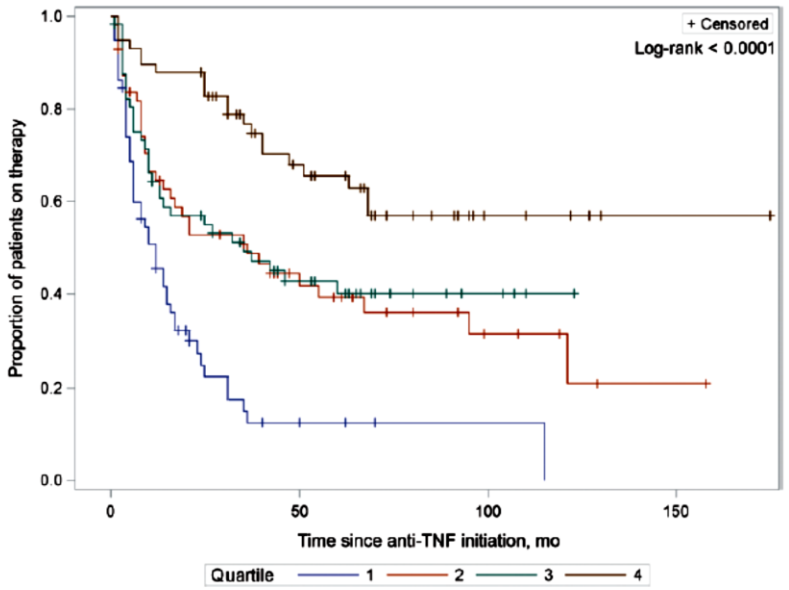
Multivariable analysis of predictors of **PNR** to anti-TNF therapy in UC

	Odds Ratio	95% Confidence Interval	*P*
Age at diagnosis	0.980	0.940–1.019	0.319
Disease duration	0.959	0.887–1.026	0.249
Sex	1.055	0.383–2.888	0.916
Disease extent (pancolitis vs not)	0.680	0.236–1.935	0.467
Active tobacco use	0.135	0.002–2.316	0.284
Genetic risk score (per 1-unit increase)	3.419	2.294–5.562	3.87×10^{-9}

Durable Response

Multivariable analysis of predictors of **DR** to anti-TNF therapy in CD

	Odds Ratio	95% Confidence Interval	*P*
Age at diagnosis	0.978	0.952–1.005	0.116
Disease duration	0.997	0.956–1.039	0.873
Sex	1.132	0.603–2.125	0.700
Disease extent	1.195	0.636–2.244	0.580
Active tobacco use	1.817	0.428–7.712	0.418
Genetic risk score (per 1-unit increase)	2.799	2.060–3.803	4.74×10^{-11}



Genetic **R**isk **S**core (GRS) quartiles

Predictors of PNR and DR were again mutually exclusive

No association between genetic risk score for DR and anti-IFX antibodies

Burke K et al Inflamm Bowel Dis 2018

From genes to their expression: the TRANSCRIPTOMICS

Gene-expression screening to predict response to IFX

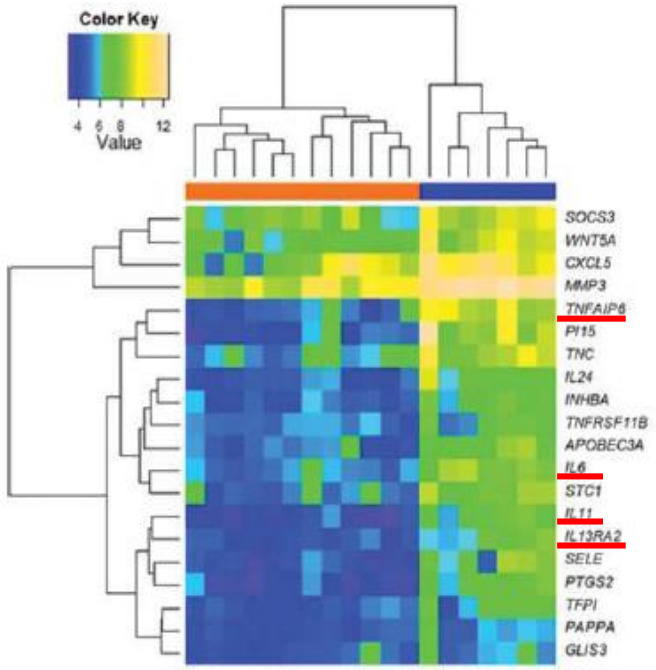
IFX

CDc
n=19

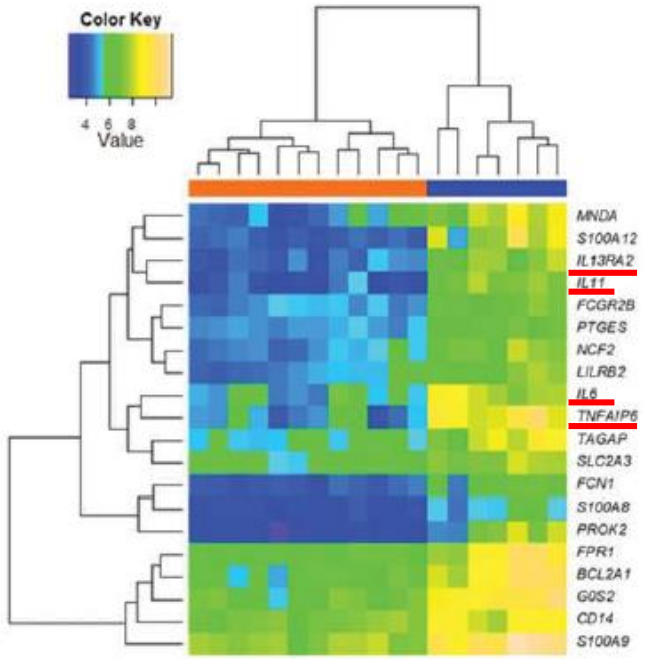
- Responsers
- Non Responsers

Gene expression comparison

CDc cohort



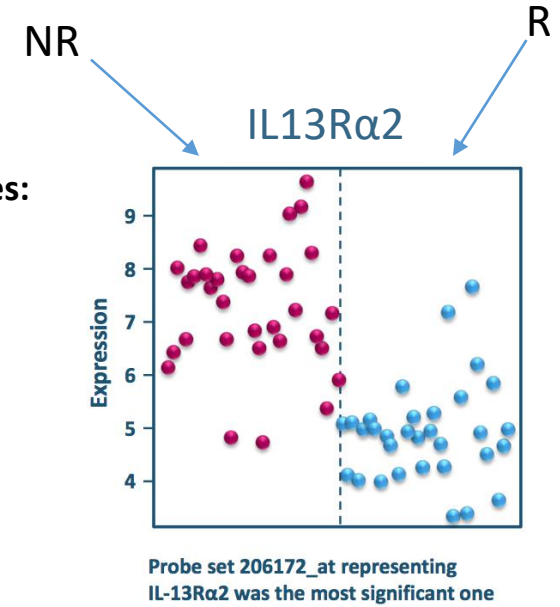
UC cohort



Arijs I et al Inflamm Bowel Dis 2010

4 overlapping genes:

- *IL13Rα2*
- *IL-11*
- *IL-6*
- *TNFAIP6*



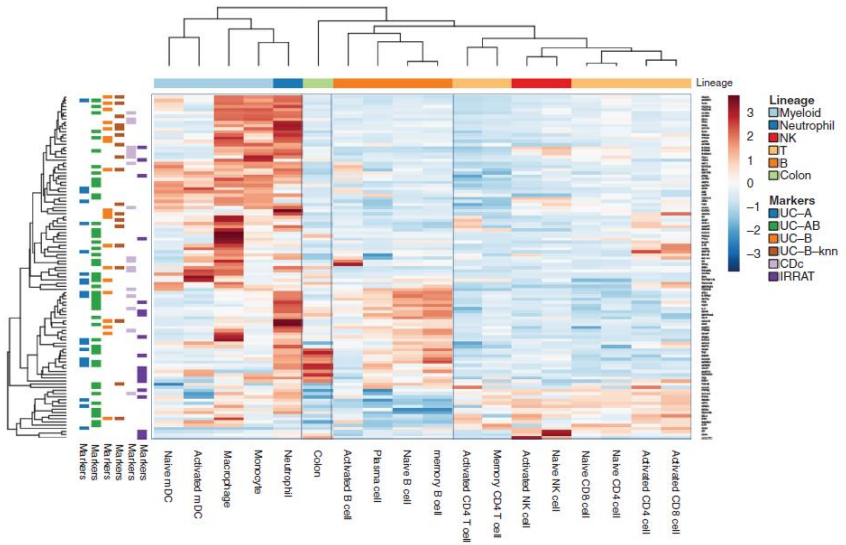
Probe set 206172_at representing IL-13Rα2 was the most significant one

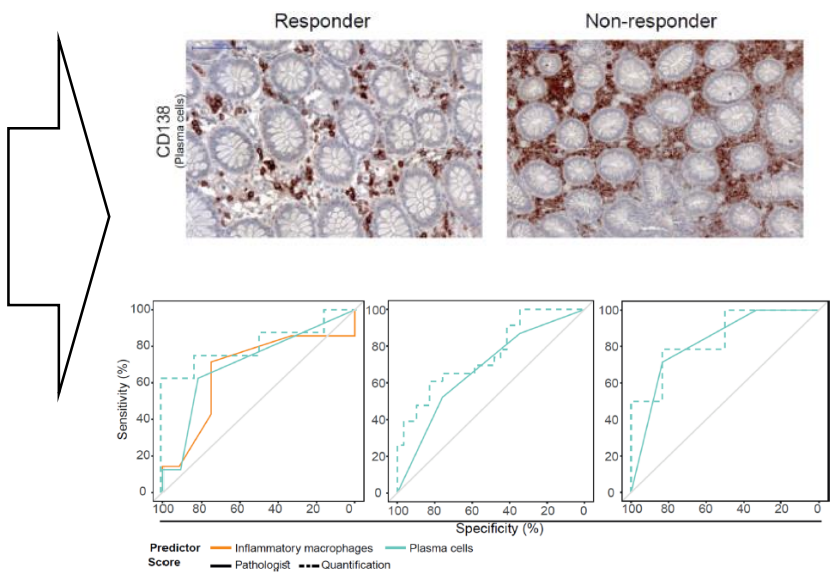
Gene-expression screening to predict response to IFX

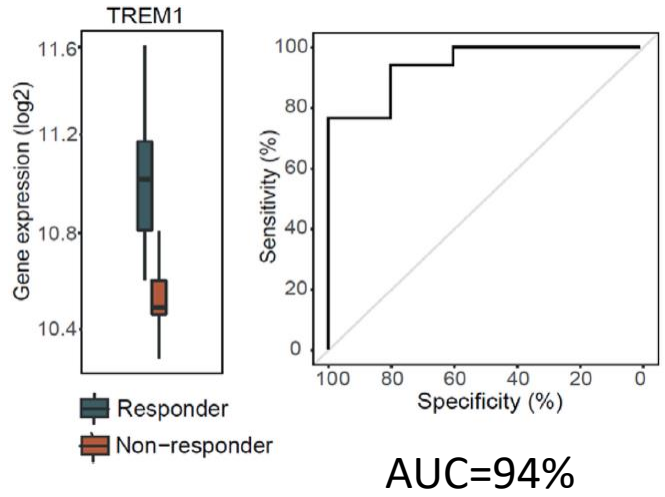
Gene expression profile

Predicition of cell subsets variation

Adjusting samples for cell subset variation unmasks upregulated pathways in biopsies of anti-TNF non-responders.



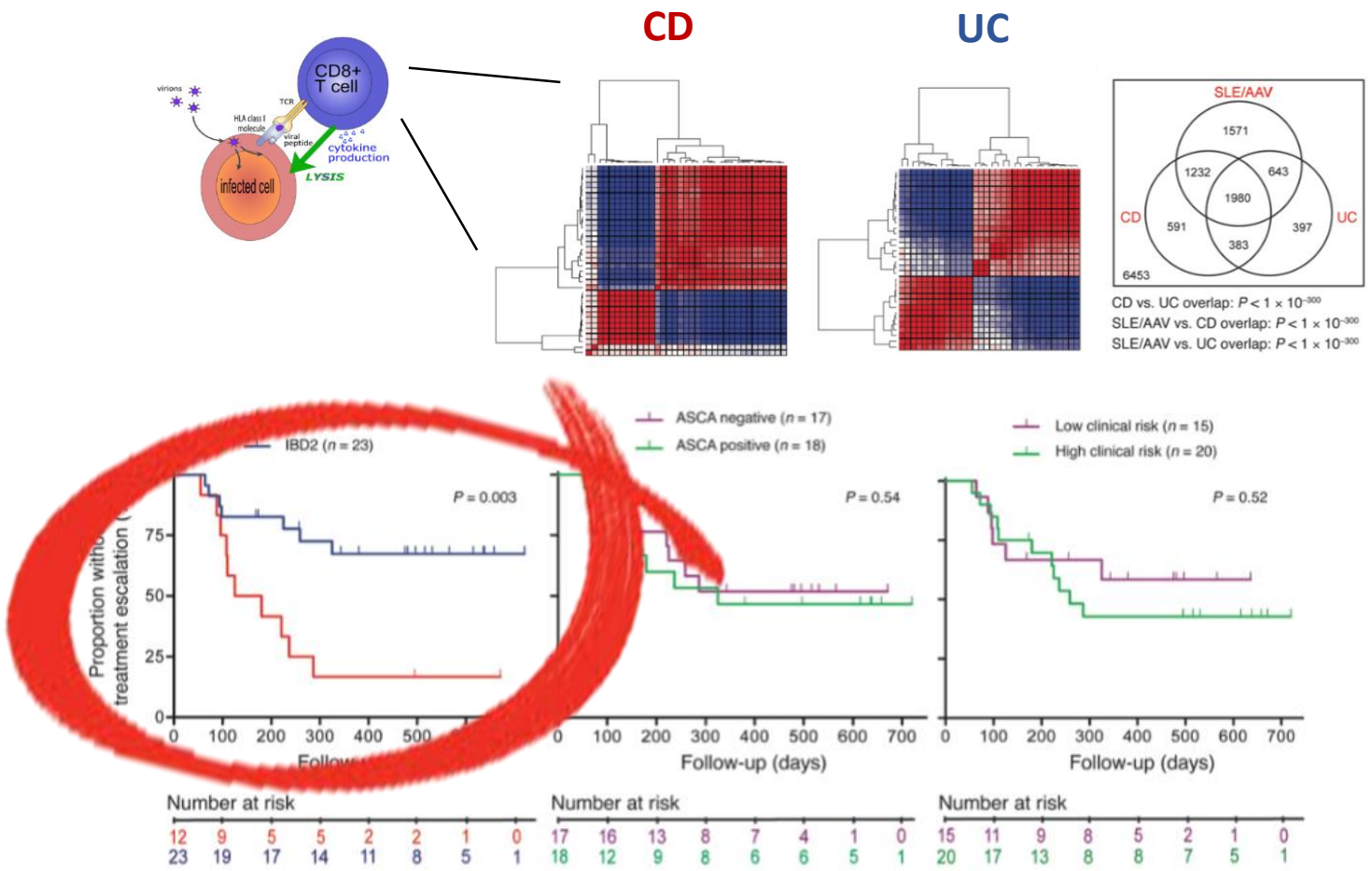




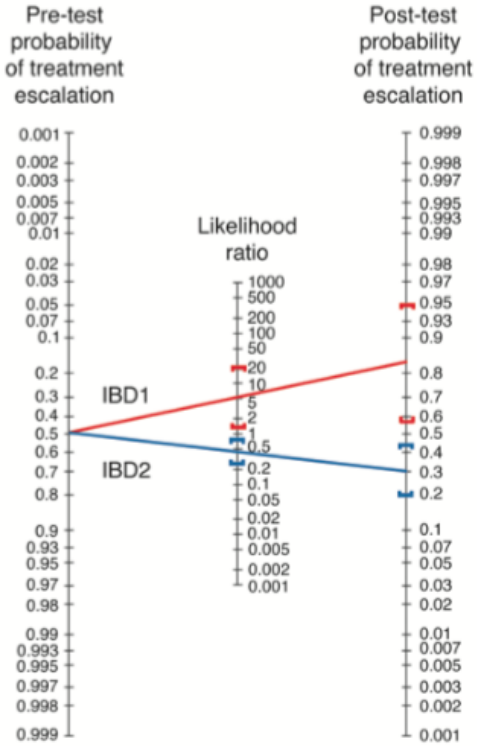
AUC=94%

Gaujoux R et al GUT 2018

Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn's disease and ulcerative colitis



End point: treatment escalation

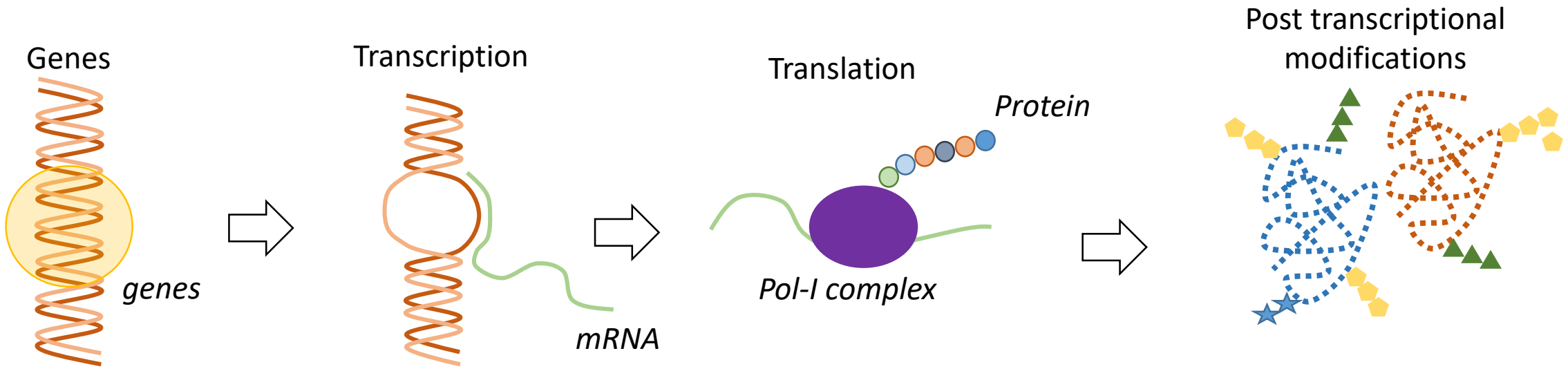


Lee JC. J Clin Invest 2011

From Genes to Proteins

The **Proteome** is defined as the full complement of proteins encoded by a genome.

- ❑ Allelic variants predisposing to disease are generally present in the general population thus limiting their use as diagnostic tool.
- ❑ The effect size of associations of genetic factors with clinical phenotypes is often small
- ❑ Biological and functional output of cells is governed primarily by proteins



20.000
protein-coding genes

100.000
Transcribed mRNAs

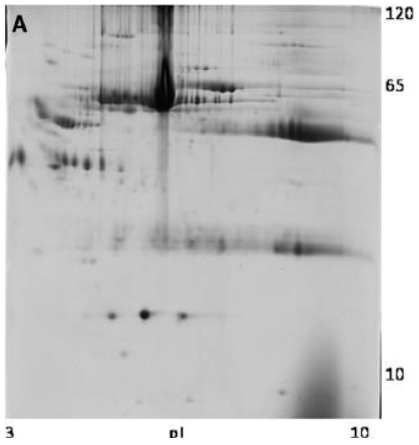
100.000
Differents proteins

1.000.000
Proteoforms

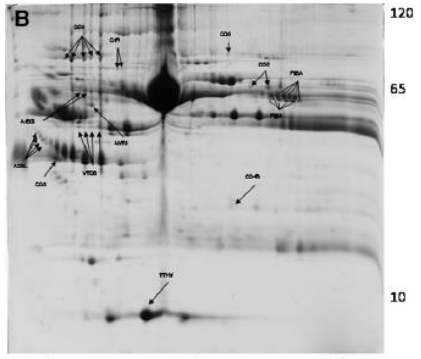
Proteomics to predict response to IFX

Fifteen proteins corresponding to 240 spots were identified (more than one spot correspond to the same protein)

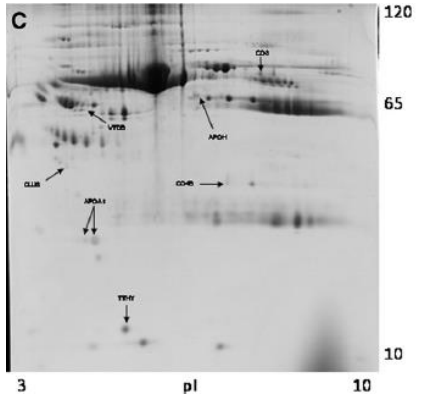
Contol (pre treatment)



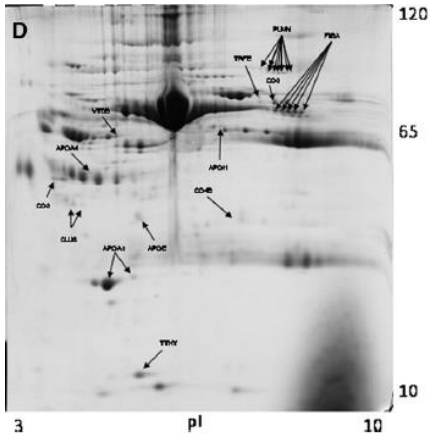
Remission (Rm)

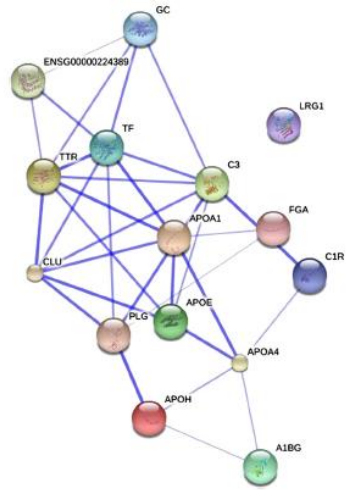


Response (Rs)

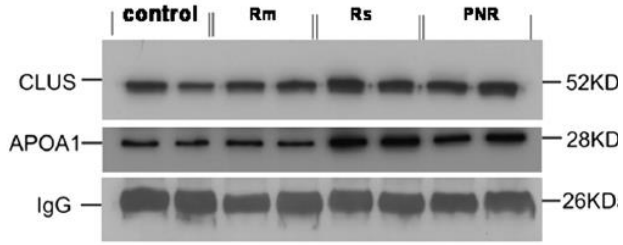


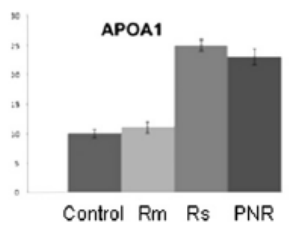
Primary Non-responder (PNR)

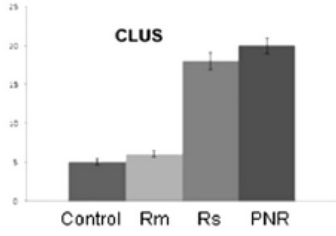




Protein name	Protein symbol	MW	pI	Mascot score	Coverage	Expression levels		
						Rm	Rs	PNR
Leucine-rich alpha-2-glycoprotein	A2GL_HUMAN	38,382.00	6.50	97	32	3.8**	0.94	0.74
Apolipoprotein A-I	APOA1_HUMAN	30,759.00	5.50	261	59	1.07	3.75**	3.24**
Apolipoprotein A-IV	APOA4_HUMAN	45,371.00	5.20	231	57	1.02	0.49*	1.65*
Apolipoprotein E	APOE_HUMAN	36,246.00	5.50	170	51	0.96	1.02	2.02*
Complement C3	CO3_HUMAN	188,569.00	6.00	367	37	2.4*	1.33*	2.17*
Complement C4-B	CO4B_HUMAN	194,247.00	6.70	208	23	2.21*	3.57*	4.21**
Plasminogen	PLMN_HUMAN	93,247.00	7.30	311	50	1.13	0.78	3.65**
Transthyretin	TTHY_HUMAN	15,991.00	5.40	162	64	5.84**	1.62*	5.55**
Serotransferrin	TRFE_HUMAN	79,280.00	7.00	257	43	0.24**	1.08	1.652*
Vitamin D-binding protein	VTDB_HUMAN	54,526.00	5.30	245	55	4.01**	1.47*	2.71*
Alpha-1B-glycoprotein	A1BG_HUMAN	54,809.00	5.50	195	46	2.15*	1.05	0.98
Beta-2-glycoprotein 1	APOH_HUMAN	39,584.00	9.49	128	58	0.98	1.51*	1.91*
Complement C1r subcomponent	C1R_HUMAN	81,606.00	5.80	158	42	3.35**	0.96	0.97
Clusterin	CLUS_HUMAN	53,031.00	5.90	75	21	1.09	3.33**	4.28**
Fibrinogen alpha chain	FIBA_HUMAN	95,656.00	5.60	250	36	1.64*	0.91	1.94*







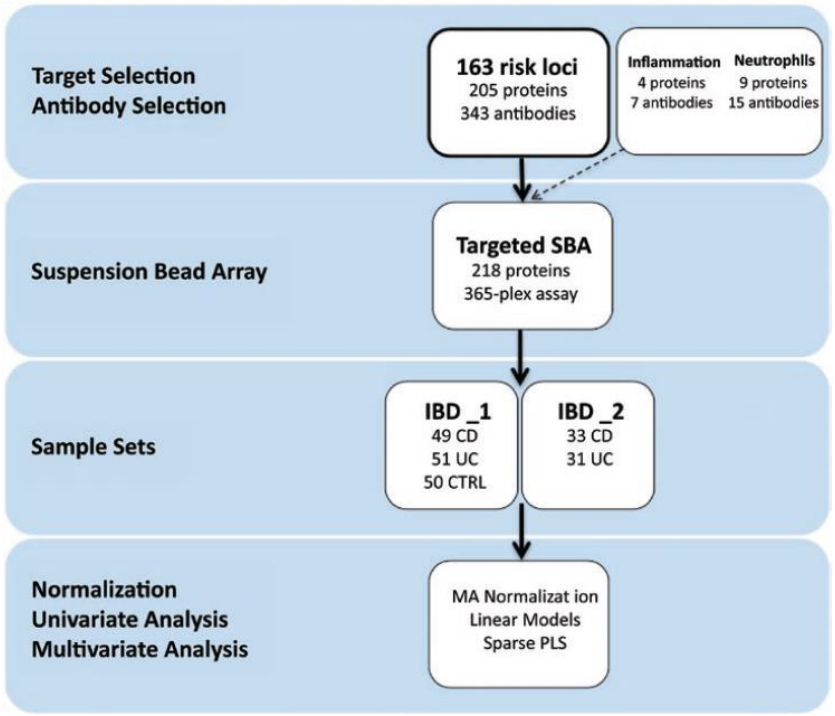
Gazouli M et al J Crohn Colitis 2013

Proteomic approach for the indetification of disease markers

Targeted Analysis of Serum Proteins Encoded at Known Inflammatory Bowel Disease Risk Loci

THE HUMAN PROTEIN ATLAS

Drobin K et al J Crohn Colitis 2018

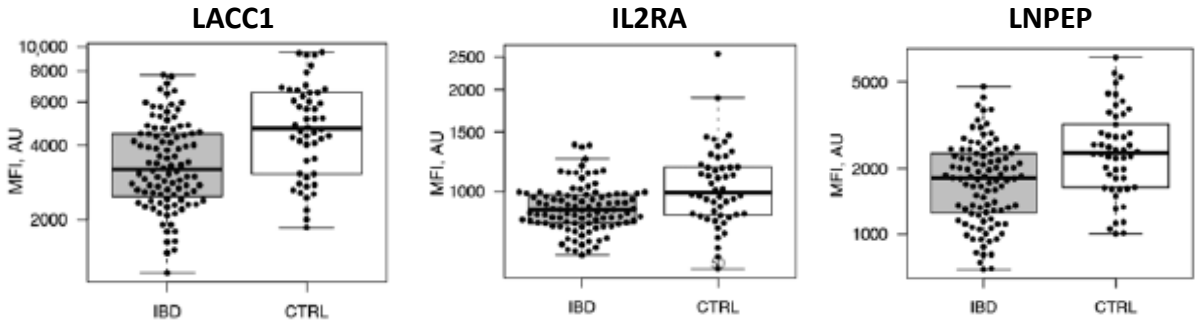


IBD risk loci

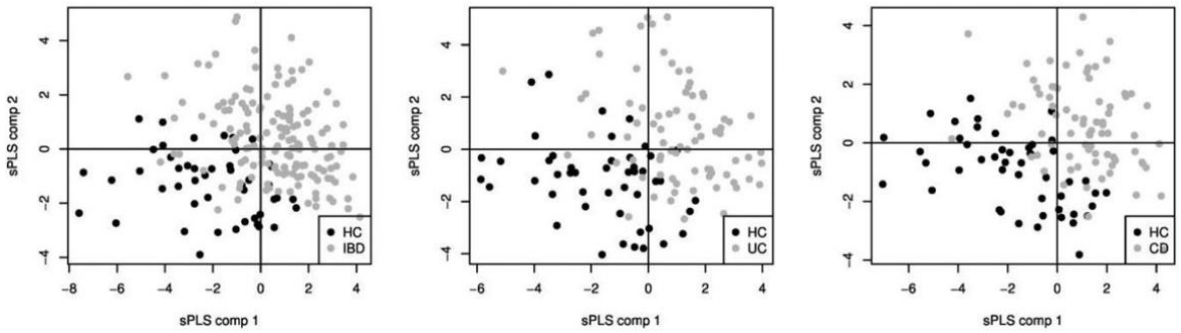
Candicate proteins

Proteomic analysis

Serum markers identification



Sparse PLS (sPLS) discriminant analysis



LOO-hit rate 0.83 p<0.0001

LOO-hit rate 0.80 p<0.0001

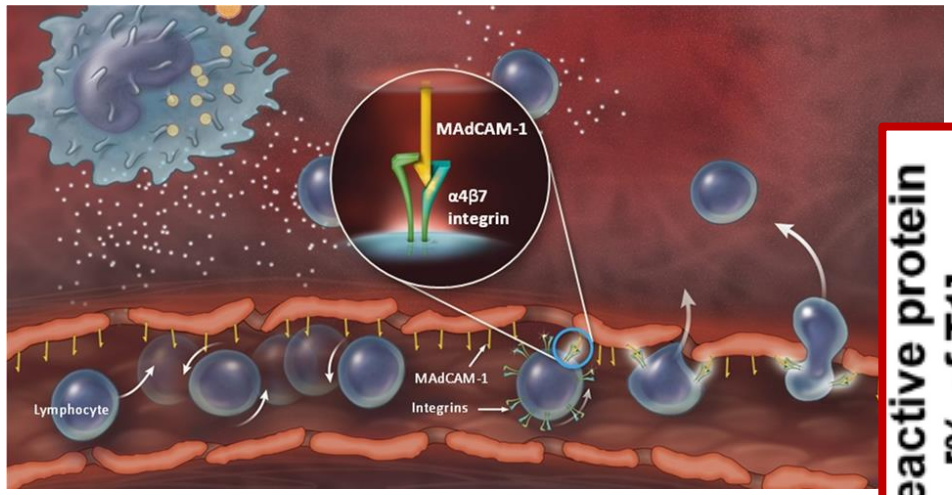
LOO-hit rate 0.76 p<0.0001

Profiling based on the drug specific mechanism of action

The candidate target approach

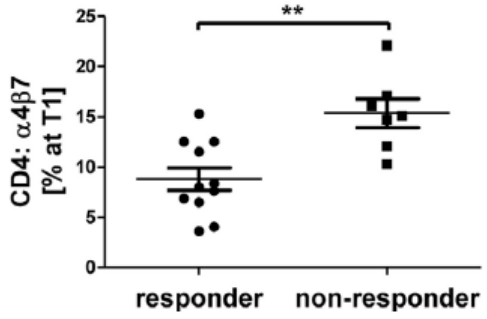
The expression of α4β7 and α4β1 integrin expression predict response to Vedolizumab

Vedolizumab (VDZ) mechanism of action



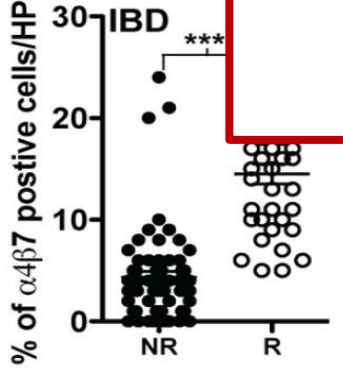
α4β7

Peripheral blood



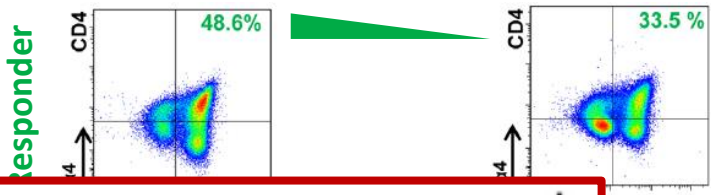
Fuchs F et al Front Immunol 2017

Intestinal m



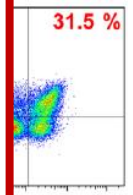
Rath T et al Front Immunol 2018

α4β1

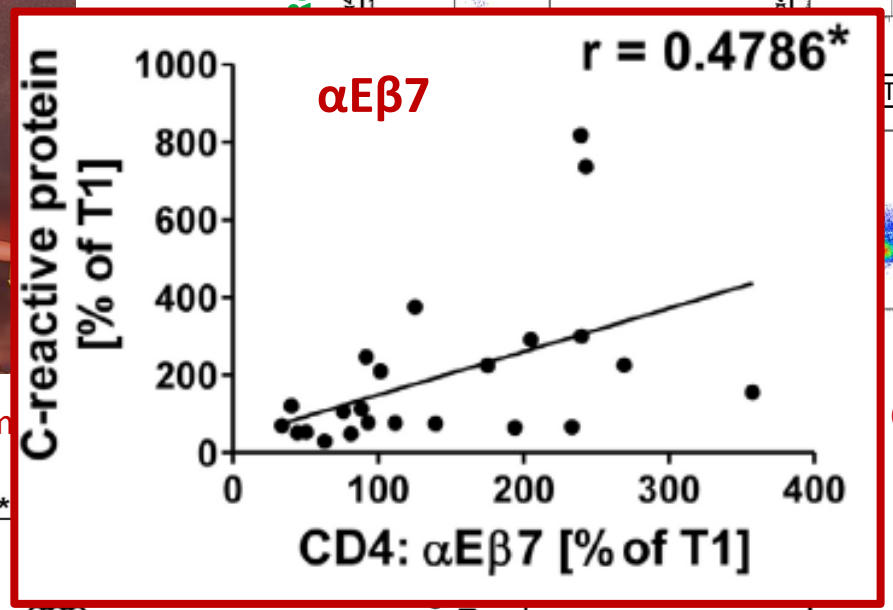


MCS:1

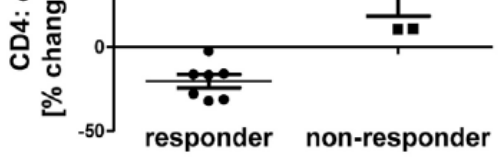
T3 T4 T5

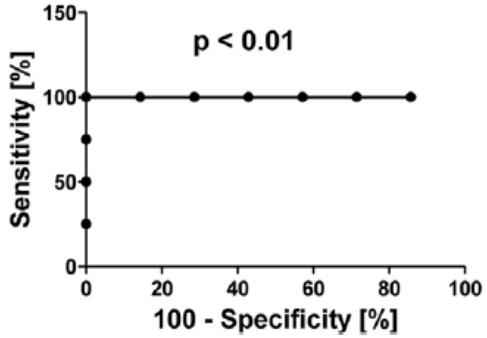


MCS:5



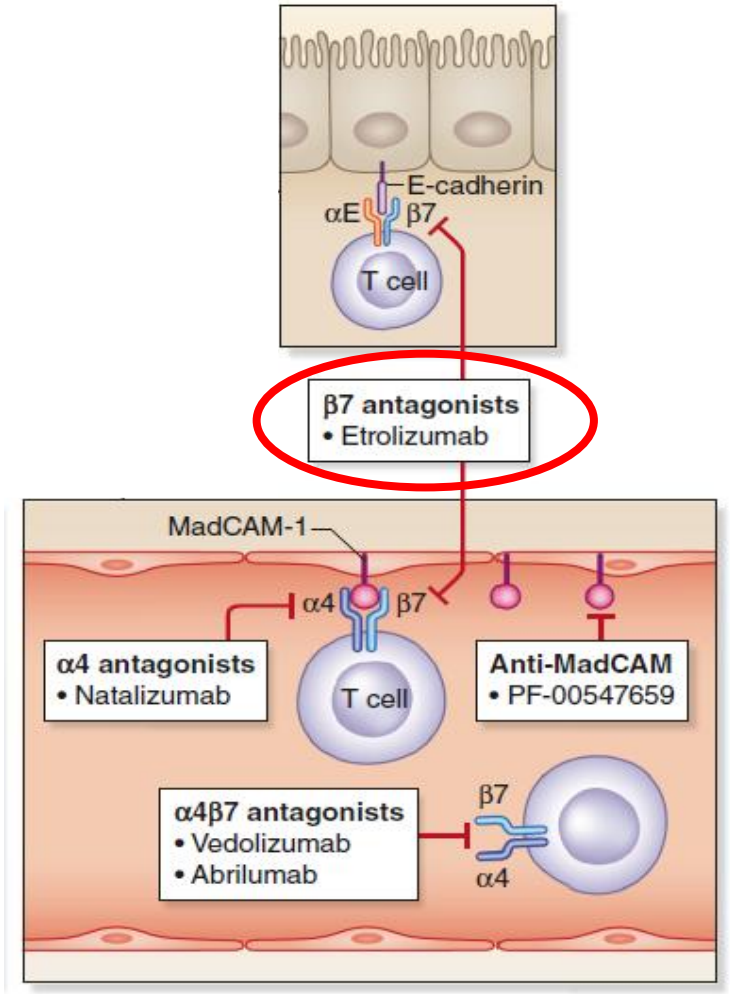
α4β1





Fuchs F et al Front Immunol 2017

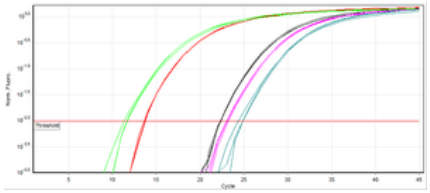
The expression of αE integrin predicts response to Etrolizumab



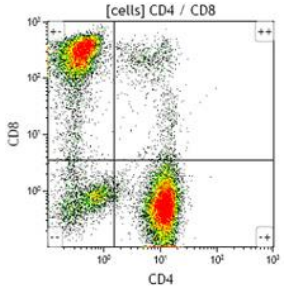
Paramsothy S et al Mucosal Immunol 2018

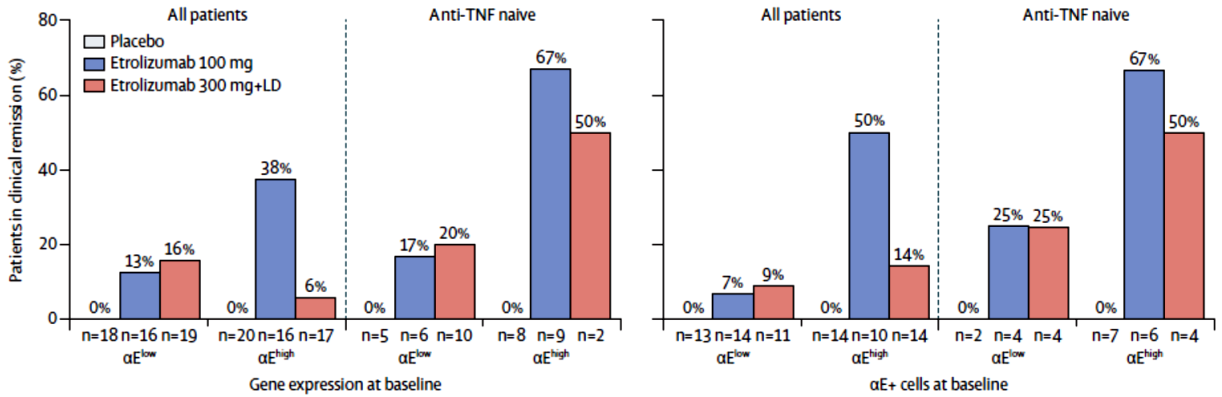
Colonic biopsies

αE gene expression



αE protein expression





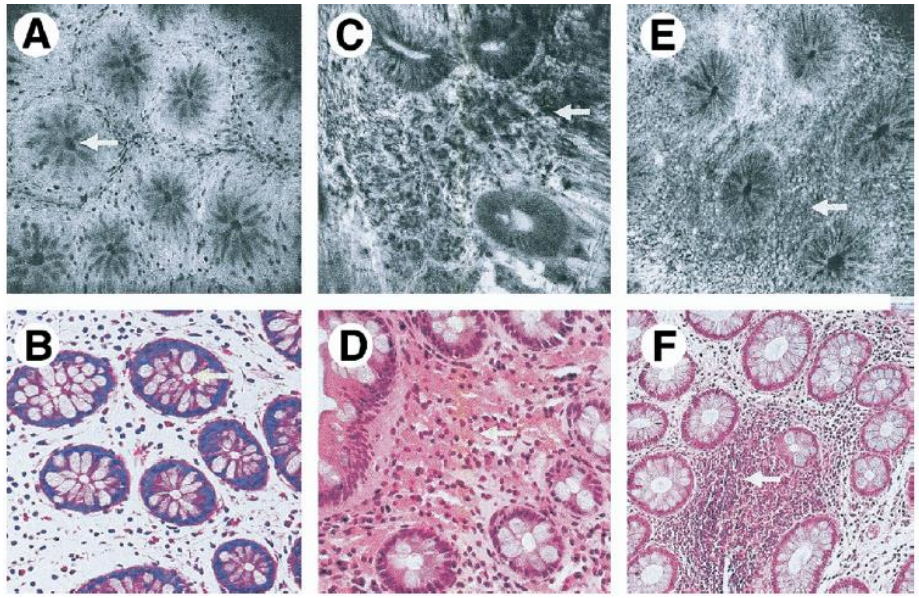
Vermeire S et al Lancet 2014

Novel imaging modalities for immune cell monitoring in the intestine

2005

Neumann H et al Gastroenterology 2010

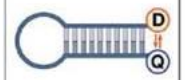
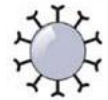
Fluorescein-aided endomicroscopy



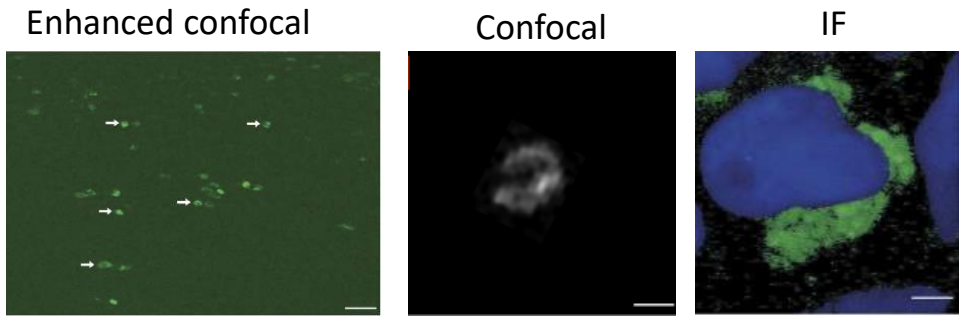
Kiesslich R et al Gastroenterology 2007

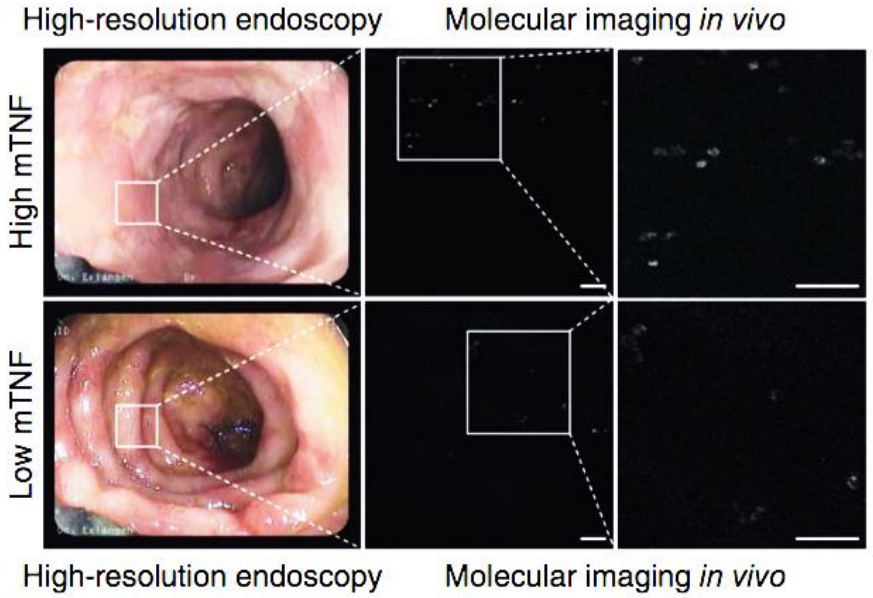
Ralf Kiesslich

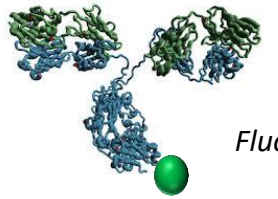
2014

Type	Peptide	Antibody	Activatible probe	Nanoparticle
				
Advantages	• Easy delivery to target structure • Low immunogenicity • Low cost	• High specificity • Defined target • Defined and approved therapeutic ab may be labeled	• Specific activation • Optimized signal-to-noise ratio	• Loading with multiple proteins for multivalent targeting • Strong fluorescence
Disadvantages	• Variable affinity	• Potential immunogenicity	• Internalization frequently required for activation • Undefined safety profile	• Potential toxicity of non-biocompatible core • Renal clearance

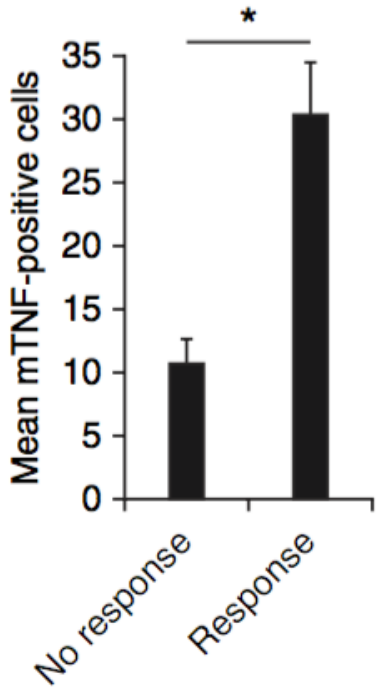
Mucosal expression of mTNF as predictor of response to ADA

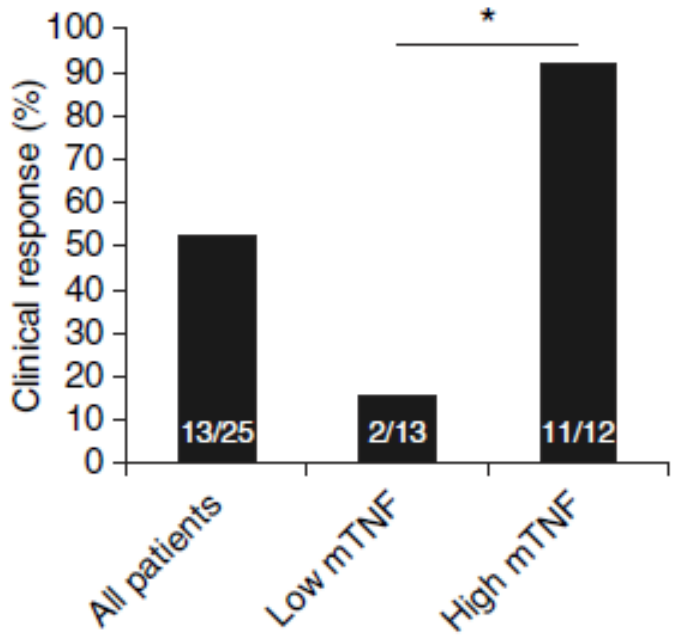






Fluorescein (FITC)-labled ADA



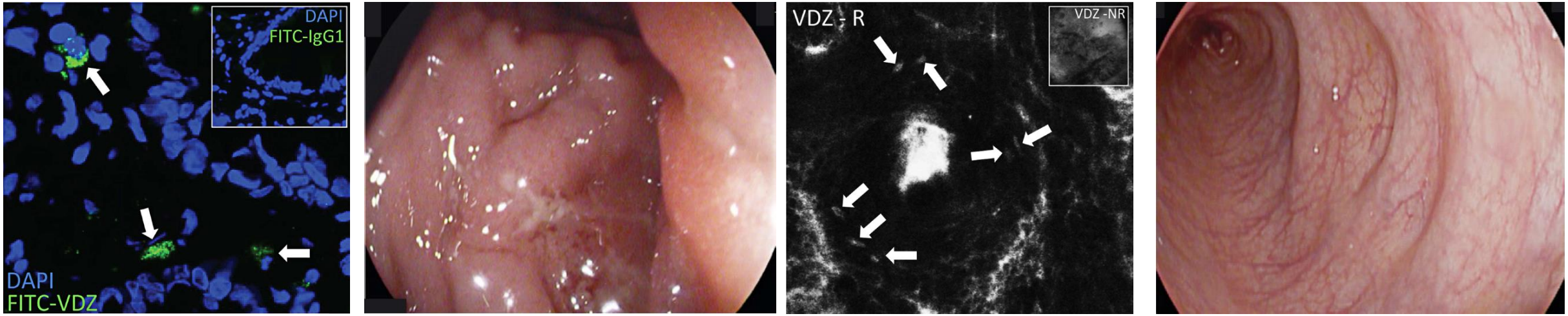


Atreya R et al Nat Med 2014

Vedolizumab *in vivo* mucosal staining as predictor of response

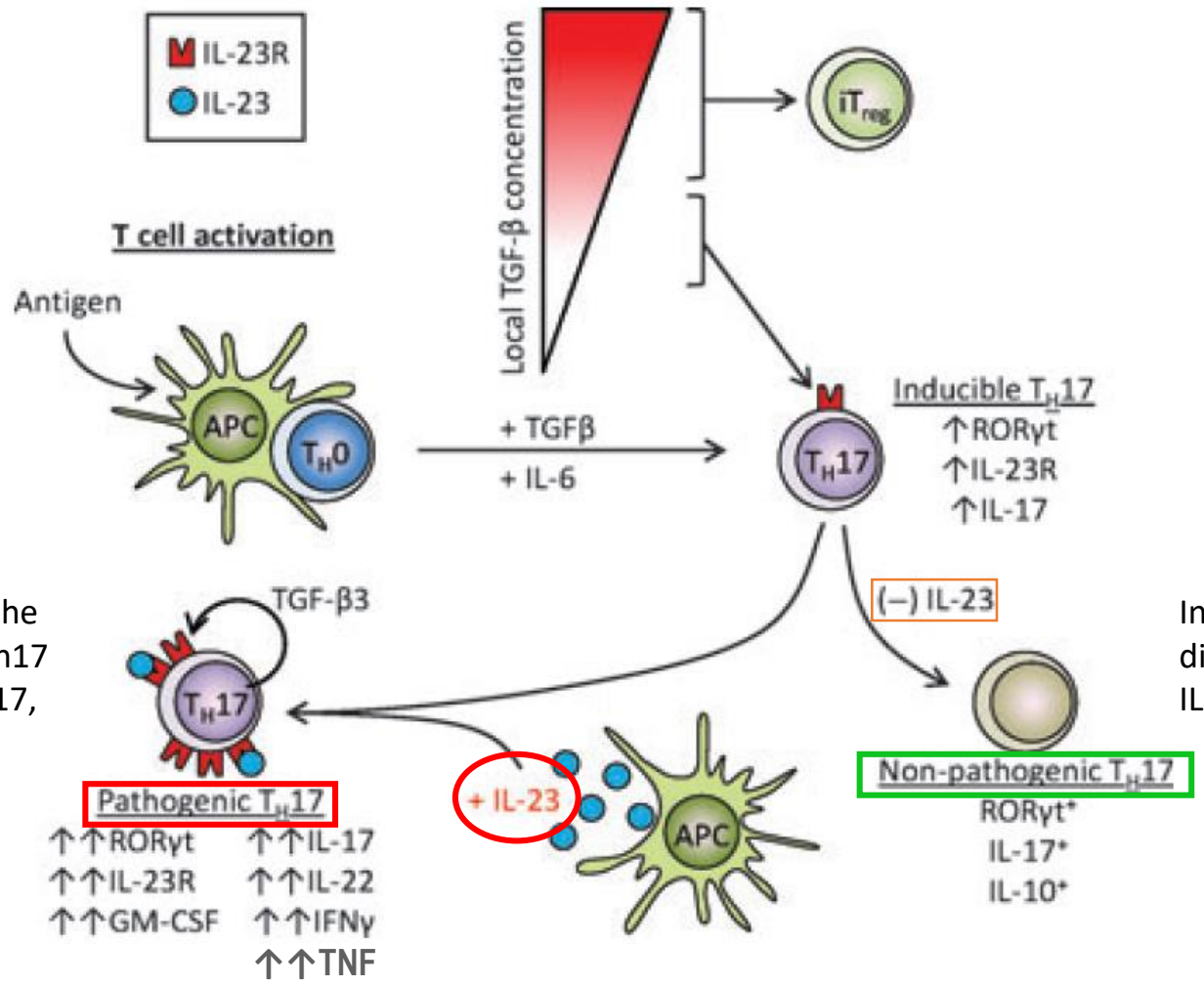
5 anti-TNF refractory CD patients with active mucosal inflammation underwent high definition endocopy and evaluated for VDZ labeling by confocal endomicroscopy.

2 of the five Pts who showed pericryptal FITC-VDZ in vivo staining responsed to VDZ therapy.



Rath T et al Gastrointest Endoscopy 2017

Predicting response to anti-(IL23)p19



Exposure to IL-23 is needed for the development of inflammatory Th17 cells producing high levels of IL-17, IL-22, IFNγ, and TNF.

In the absence of IL-23, Th17 cells differentiate into non-pathogenic IL-17+ and IL-10+ cells.

Zuniga LA, et al. Immunol Rev. 2013;252:78–88
Gaffen SL, et al. Nature Rev Immunol 2014;14, 585-600

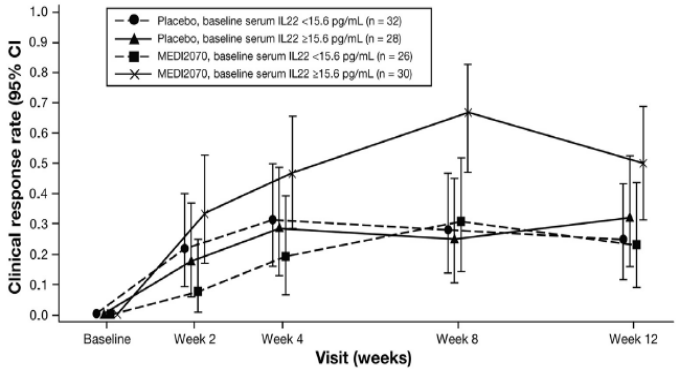
IL-22 basal serum expression predicts response to MEDI2070

Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study

Bruce E. Sands,[1] Jingjing Chen,[2] Brian G. Feagan,[3] Mark Penney,[4] William A. Rees,[2] Silvio Danese,[5] Peter D. R. Higgins,[6] Paul Newbold,[2] Raffaella Faggioni,[7] Kaushik Patra,[2] Jing Li,[7] Paul Klekotka,[8] Chris Morehouse,[2] Erik Pulkstenis,[2] Jörn Drappa,[2] René van der Merwe,[4] and Robert A. Gasser Jr[2]

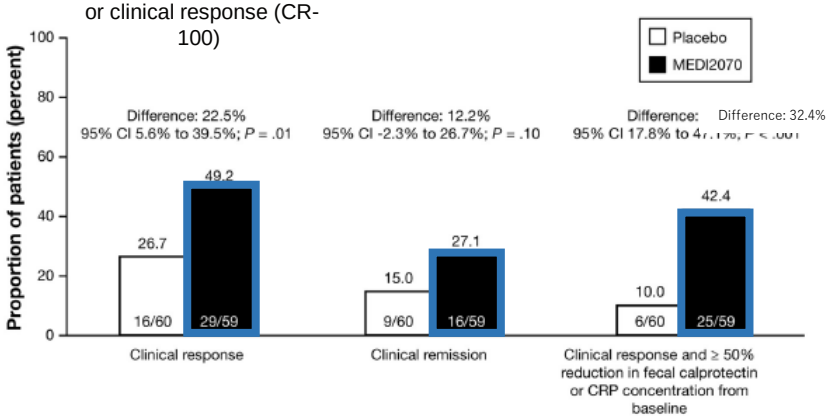
- IL22 serum level decreases after exposure to MEDI2070.
- Pretreatment serum IL22 above **15.6 pg/ml** is associated with higher rate of clinical response and remission.

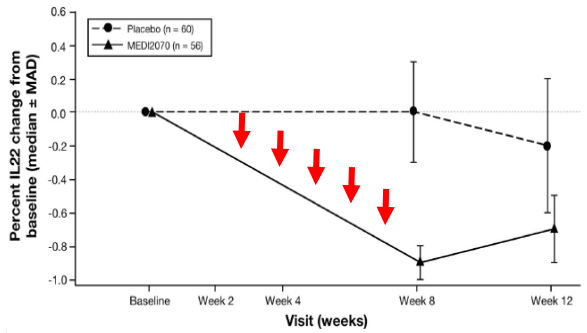
Clinical Response



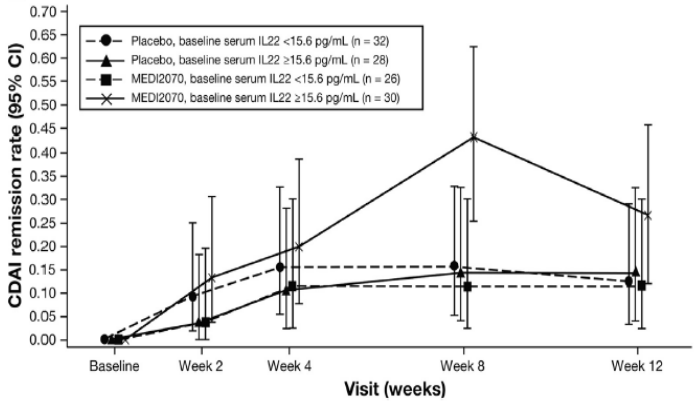
Primary endpoint:
Clinical remission (CDAI<150) or clinical response (CR-100)

Week 8

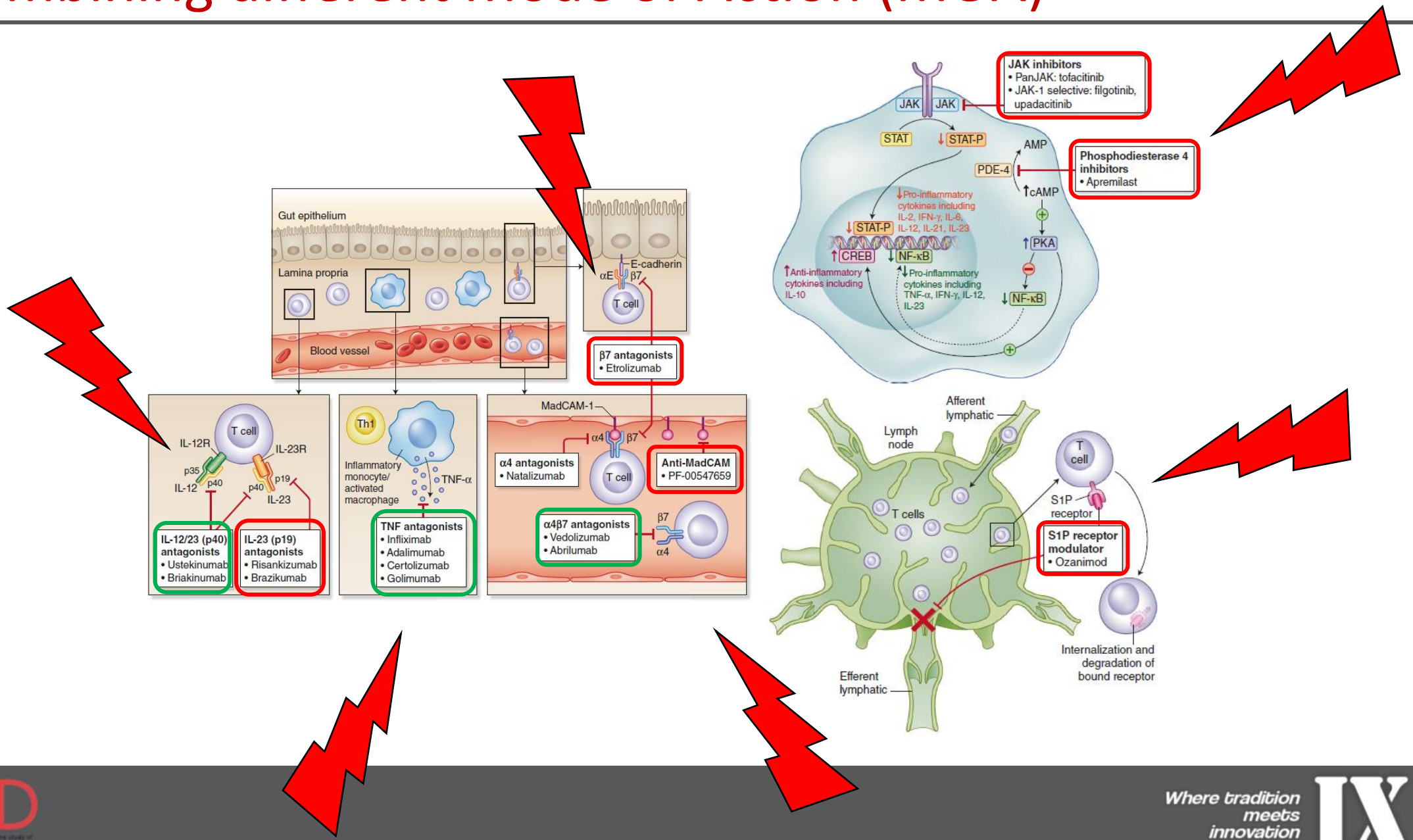




Clinical Remission



Combining different Mode of Action (MOA)

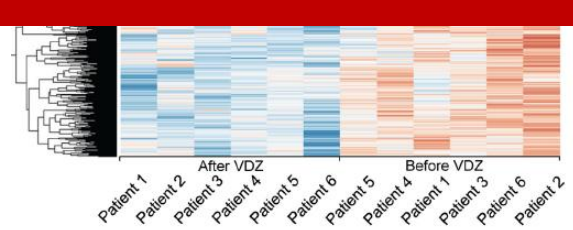


Combining different Mode of Action (MOA)

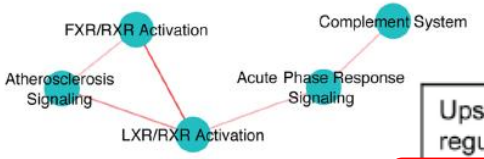
Gene expression in intestinal mucosa at week 0 and week 14 after VDZ therapy

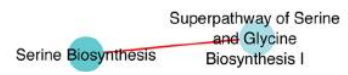
	CD	
	Remitters	Non-remitters
Baseline characteri		
Sex (m/f)		
Age (years)		
Mean ± SD		
Disease manifestatior		
Ileum		
Ileum + colon		
Ileum + colon + upper GI tract	2	1
Disease duration		
Mean ± SD (years)	6.7 ± 1.6	7.3 ± 4.5
Prior anti-TNF treatment	3	3
Concomitant medication		
Glucocorticoids only	1	1
Immunosuppressants only[a]		1
No glucocorticoids and immunosuppressants	2	1

Might these patients benefit from an anti-integrin plus an anti-TNF combined therapy?



Upstream regulators associated with Non-Response





Upstream regulators	p-value of overlap	Activation Z-Score	Predicated Activation
TNF	4.81E-20	4.374	Activated
TGFB1	1.43E-17	4.357	Activated

Rath T et al Front Immunol 2018

Combining different MOA

NO SAFETY ISSUES WERE REPORTED

FUTURE DIRECT

Combining Anti-TNF-α and Vedolizumab in the Treatment of Inflammatory Bowel Disease: A Case Series

Lydia C.T. Buer MD[,†,1], Marte L. Høivik MD, PhD[*], David J. Warren MD[‡], Asle W. Medhus MD, PhD[*] and Bjørn A. Moum MD, PhD[*,†]*

Bruet L et al Inflamm Boel Dis 2018

Long-term Combination Therapy with Anti-TNF plus Vedolizumab Induces and Maintains Remission in Therapy-refractory Ulcerative Colitis

Sarah Fischer, MD[1], Timo Rath, MD[1], Carol-Immanuel Geppert, MD[2], Bernhard Manger, MD[3], Georg Schett, MD[3], Markus F. Neurath, MD[1] and Raja Atreya, MD[1]

Fischer S et al An J Gastroenterol 2017

WILEY AP&T Alimentary Pharmacology & Therapeutics

Safety, efficacy and pharmacokinetics of vedolizumab in patients with simultaneous exposure to an anti-tumour necrosis factor

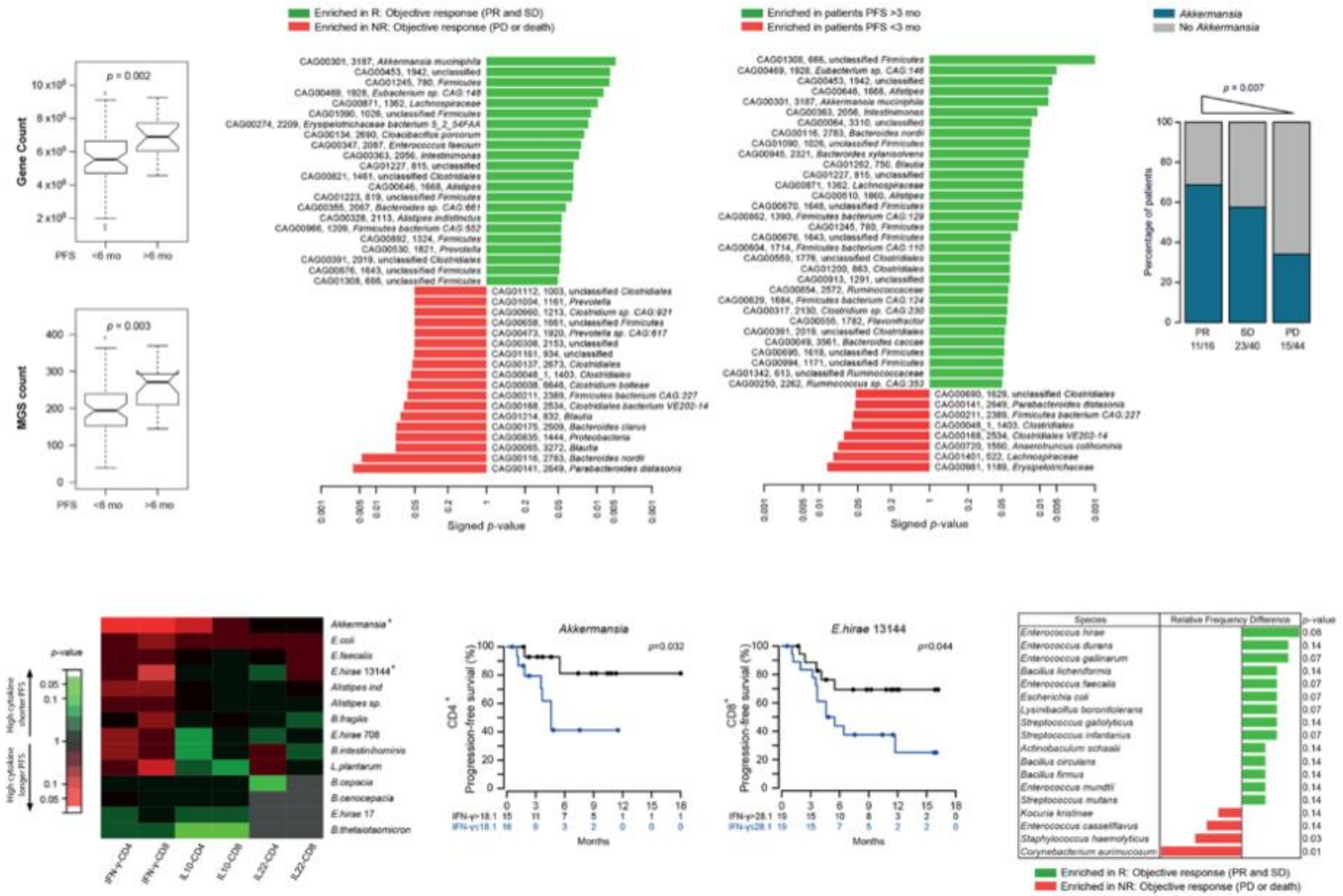
S. Ben-Horin[1,2] | B. Ungar[1] | U. Kopylov[1] | A. Lahat[1] | M. Yavzori[1] | E. Fudim[1] | O. Picard[1] | Y. Peled[3] | R. Eliakim[1] | E. Del Tedesco[4] | S. Paul[4] | X. Roblin[4]

Ben-Horin S et al Aliment Pharmacol Ther 2018

Microbiota

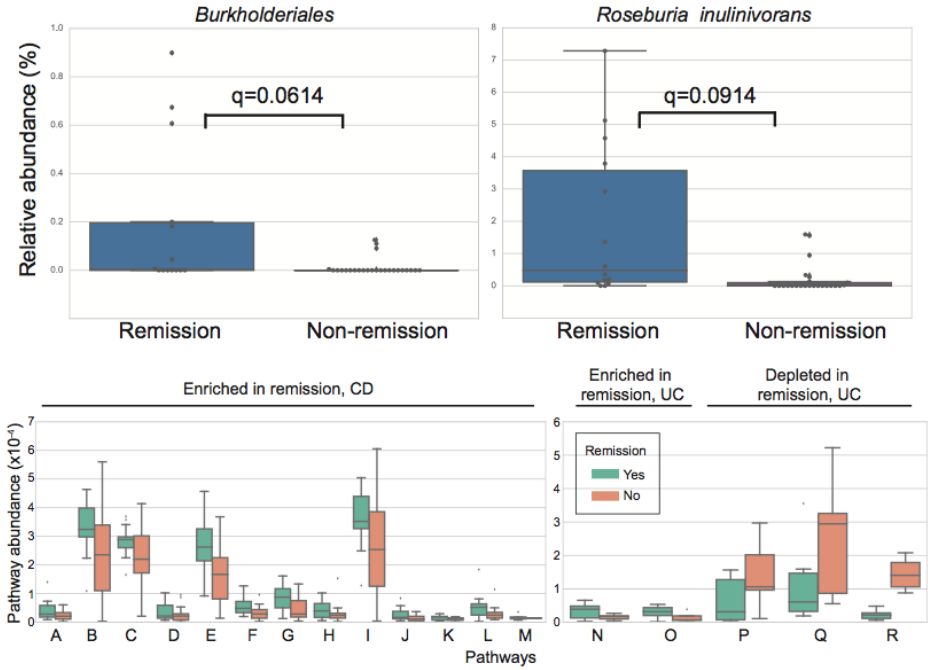
Microbiota and pesonalized medicine: does it play a role?

Role of microbiome in anti PD-1 response

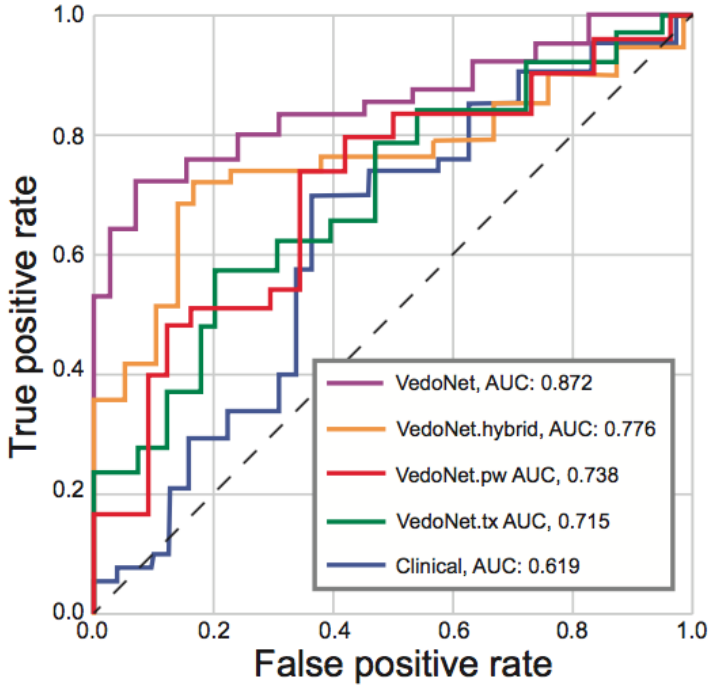


Routy B et al Science 2017

Role of microbiome in predicting response to VDZ



VedoNet (a neural network algoritm) incorporates microbiome and clinical data

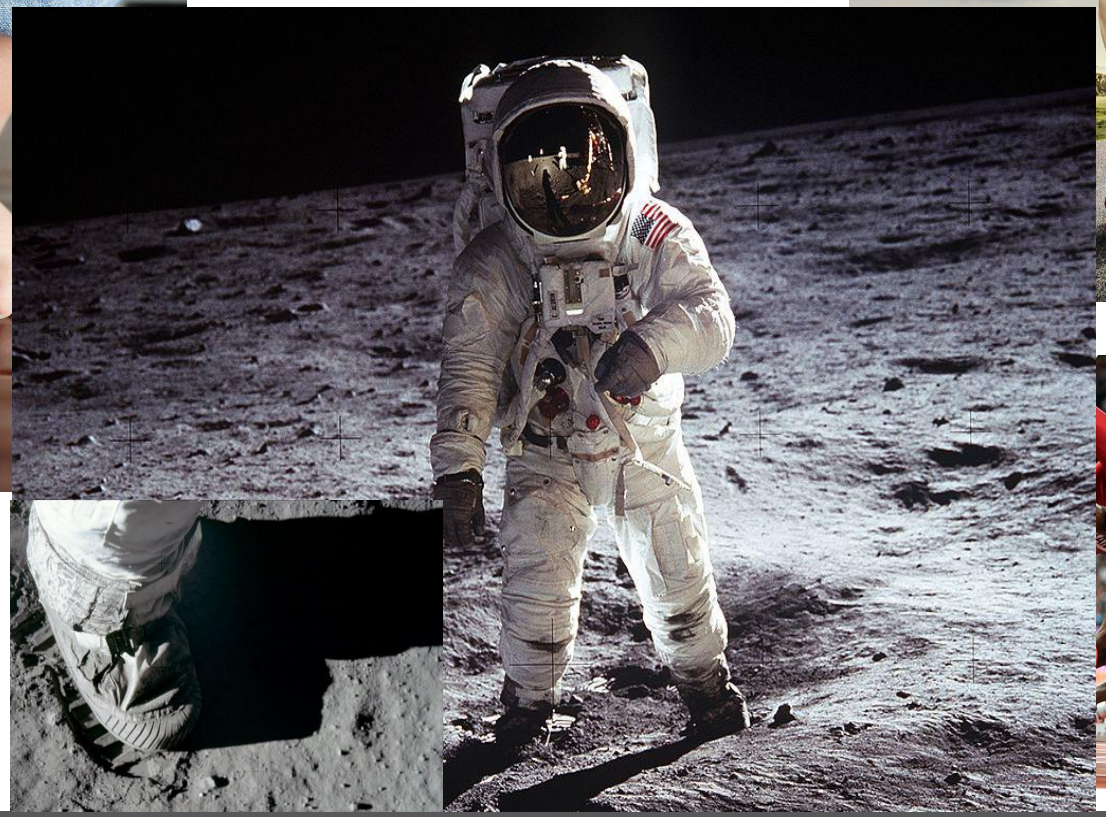


VedoNet containing 40 microbiome variables provided the highest classifiing power (AUC=0.872), >80 of true positive discovery rate and <25% false negative discovery rate.

Ananthakrishnan AN et al Cell Host & Microbe 2017

The long way to success

The **infancy** of personalized medicine in IBD



Signals from the future

Thanks for you attention