CANIBD

Canadian IBD Nurses
ANNUAL CONFERENCE

Saturday, November 4, 2017
Ritz-Carlton Hotel, Toronto

csgna
Canadian Society of Gastroenterology Nurses & Associates
Société canadienne des infirmières et infirmiers en gastroentérologie et travailleurs associés

Crohn's and Colitis Canada
Crohn et Colite Canada

CCF

Future landscape of IBD therapy

Claudio Fiocchi

Department of Pathobiology, Lerner Research Institute

Department of Gastroenterology & Hepatology

The Cleveland Clinic Foundation

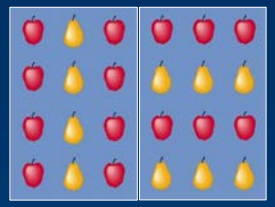
Cleveland, Ohio, USA

Conflict of interests

None

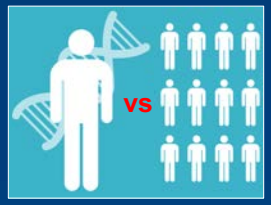
Session objectives

Review the most significant advances in our understanding of IBD pathogenesis and management over the past 10 years



Biosimilars – International perspective

IBD research:
Where are we going in the next 5-10 years?
Where will the next great breakthrough be?

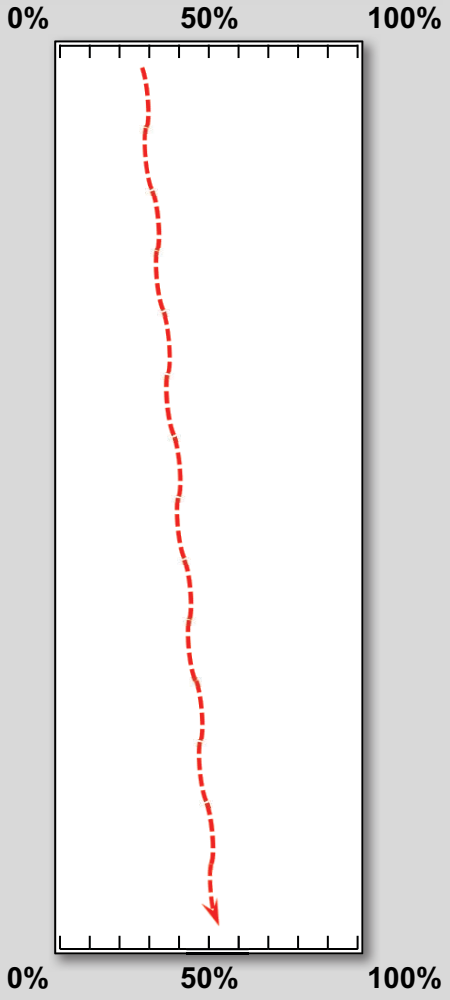


“Precision medicine”

Inspirational/visionary message

Evolution of IBD therapy: from empirical to pathophysiology-based

Year	Agent	Specificity
1940's	Sulfasalazine	No
1950's	Corticosteroids	No
1960's	Azathioprine	No
1970's	5-Aminosalicylic acid	No
1980's	6-mercaptopurine	No
	Metronidazole	No
	Elemental diets	No
1990's (early)	Cyclosporine	Yes
	Budenoside	No
	Methotrexate	No
	Antibiotics	No
1990's (late)	Biologics	Yes
	Probiotics, prebiotics	No
	Leukapheresis	No
2000's	Combination therapies	Yes, No



Evolution of IBD therapeutic goals: from few to multiple

Traditional

- Clinical response
- Clinical remission

Current

- Steroid-free remission
- Prevention of complications
- Prevention of dysplasia
- Avoidance of hospitalization
- Avoidance of surgery
- Good quality of life
- Sustained (deep) remission
- *Achieve mucosal healing*
- *"Treat to target"*

Ultimate goal: modification of the natural history?

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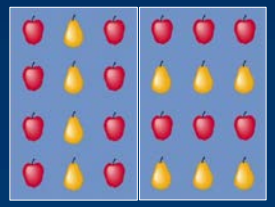

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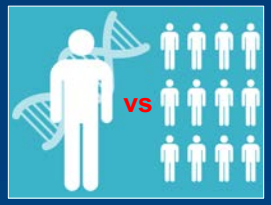
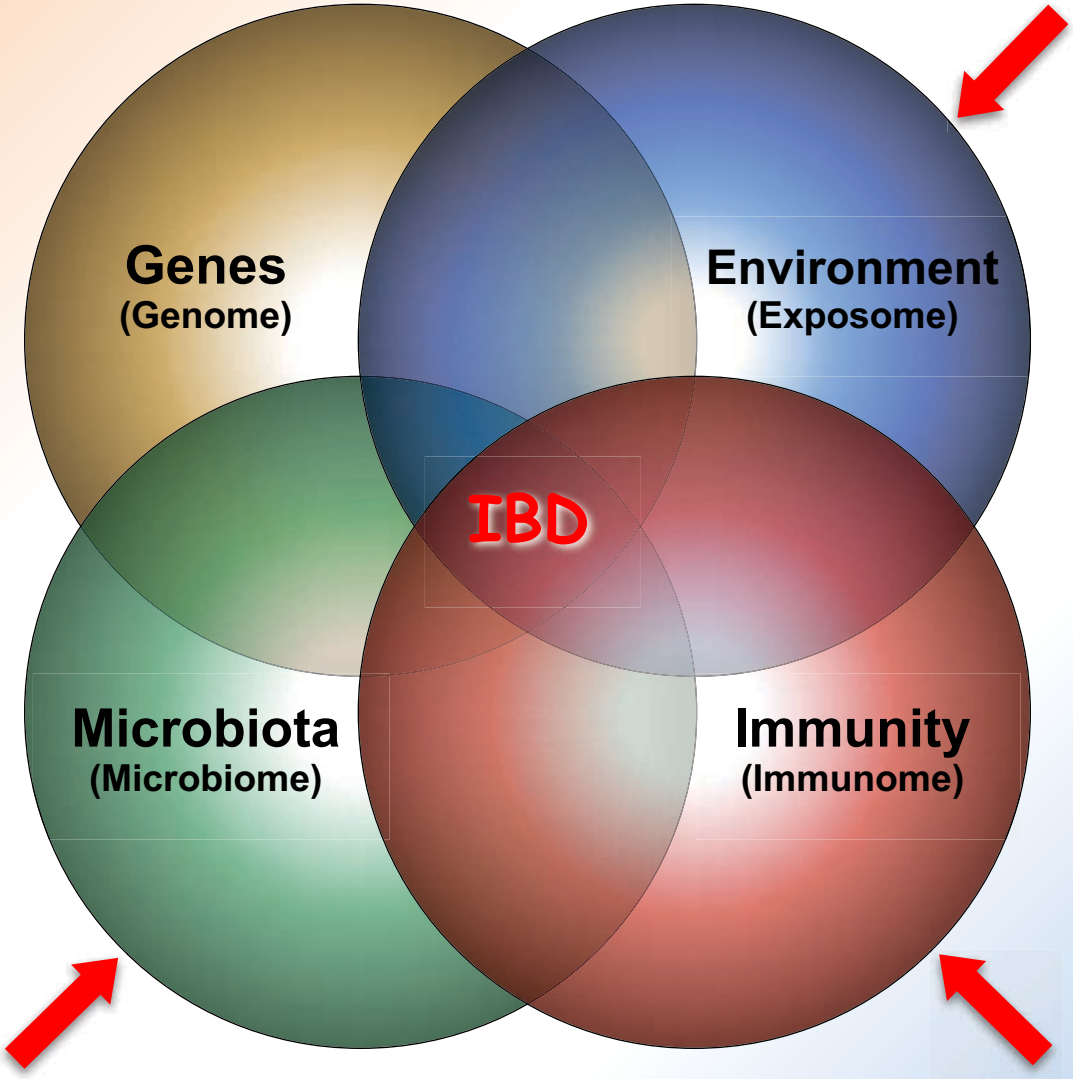


"Precision medicine"

Inspirational/visionary message

The IBD “omes” as individual therapeutic targets

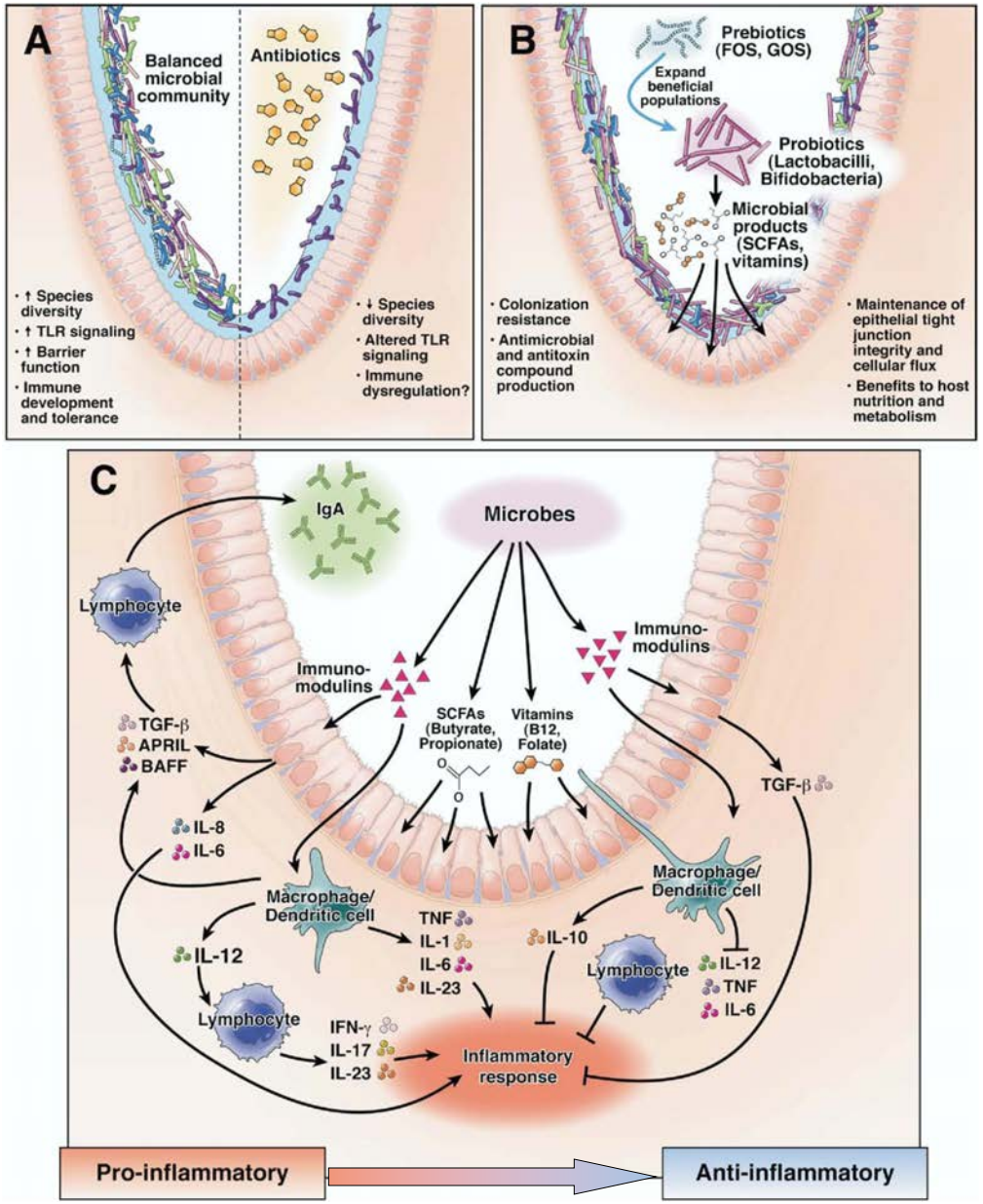


Where do we go from here?

Exposome-derived environmental factors: key determinants of gene function in health and disease

Microbial manipulation strategies in IBD: how effective they really are?

Antibiotics: removal or suppression of undesirable microbes



Probiotics: introduction of missing desirable microbes

Prebiotics: proliferation of beneficial microbes and probiotics

Fecal transplant: replacement of *"pathogenic"* microbiota with *"normal"* microbiota

Defensins: replenishment of antimicrobial peptides controlling the gut microbiota

Predeis GA & Versalovic J. *Gastroenterology* 2009;136:2015

Antibiotics in the management of IBD

Crohn's disease

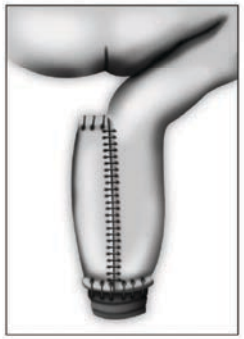
Induction of remission
Ciprofloxacin[70]
Clarithromycin[72]
Rifaximin/rifaximin-EIR[77,80,a]

Treatment of fistulizing disease
Ciprofloxacin[84,85]
Metronidazole[85]

Postoperative management
Metronidazole[66]
Ornidazole[67]

Ulcerative colitis

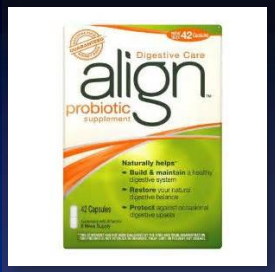
Induction and maintenance of remission
Ciprofloxacin[88]

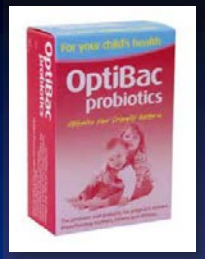


Pouchitis

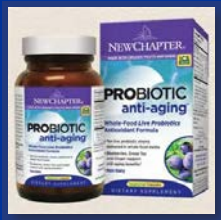
Ciprofloxacin[92]
Rifaximin[94,95]
Ciprofloxacin plus rifaximin[96]

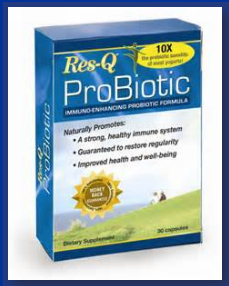
Kerman D & Deshpande A. *Postgraduate Medicine* 2014;Issue 4:7-19

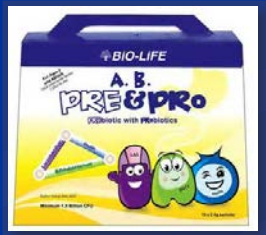


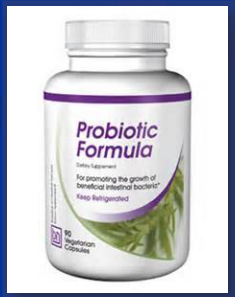


Which probiotic to use…?
How effective they really are?





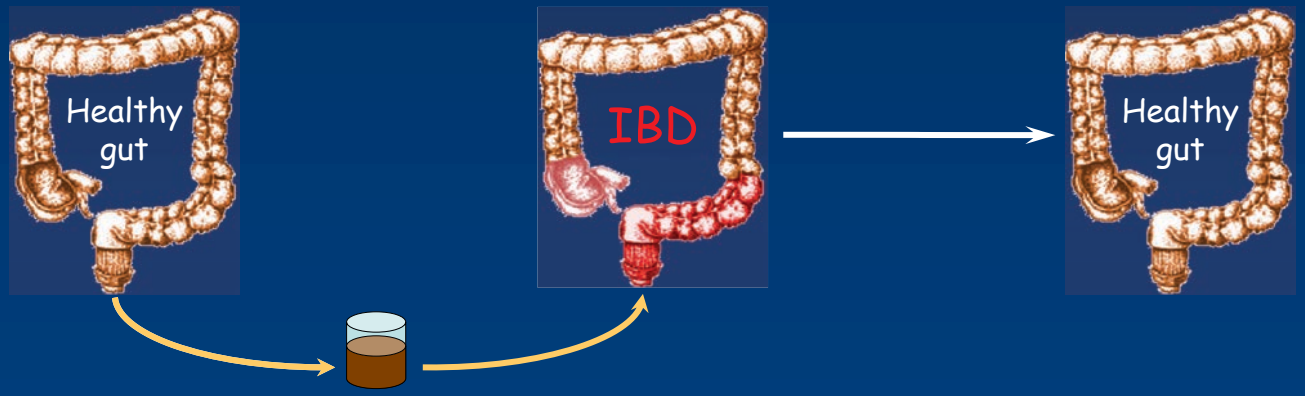




Fecal microbiota transplant (FMT): hope and reality

"Fecal microbiota transplant is the infusion of a fecal suspension of normal stools into the gastrointestinal tract of another person (patient) to cure a specific disease"

Aroniadis O & Brandt L. *Curr Opin Gastroenterol* 2013;29:79-84



So far, in IBD patients FMT only offers selective, donor- and recipient-dependent, transient modification of the gut microbiota with unpredictable clinical benefits

Changes in dietary habits and evolution of IBD incidence in Japan

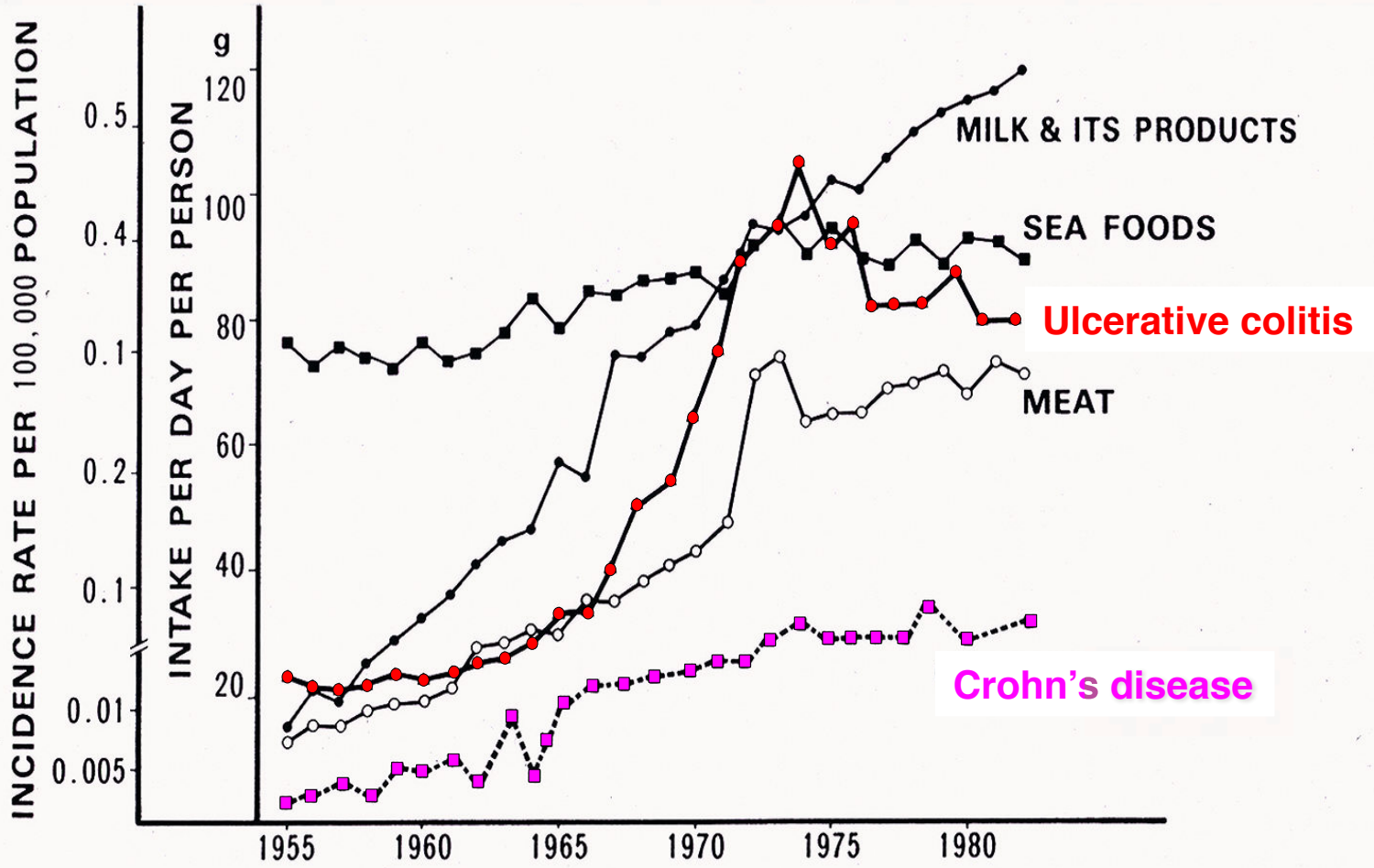


Figure 3. Annual intake dose of animal foods per day per person and annual incidence rates in ulcerative colitis and Crohn's disease in Japan, 1955–1982. (*From* Utsunomiya T, Suzuki K, Shinohara H, et al: Epidemiology of ulcerative colitis. Clin Gastroenterol 2:187, 1987; with permission.)

Food, food additives and xenobiotics: exposome-derived modulators of the microbiome and immunome

Artificial sweetener

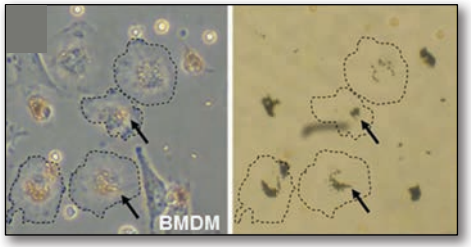
Emulsifiers

Smoking

Salt (excess)

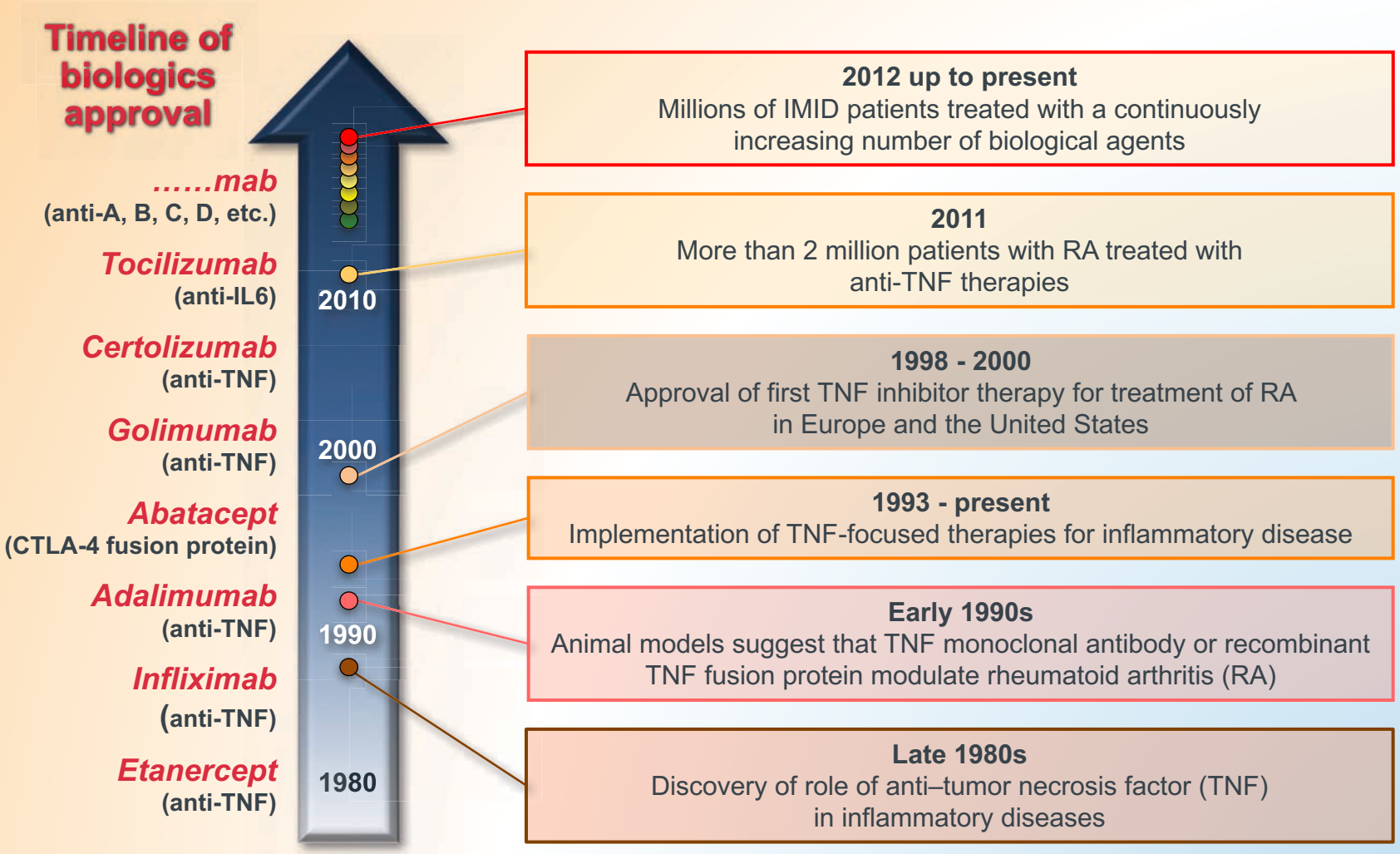
Fats

TiO_2 nanoparticles

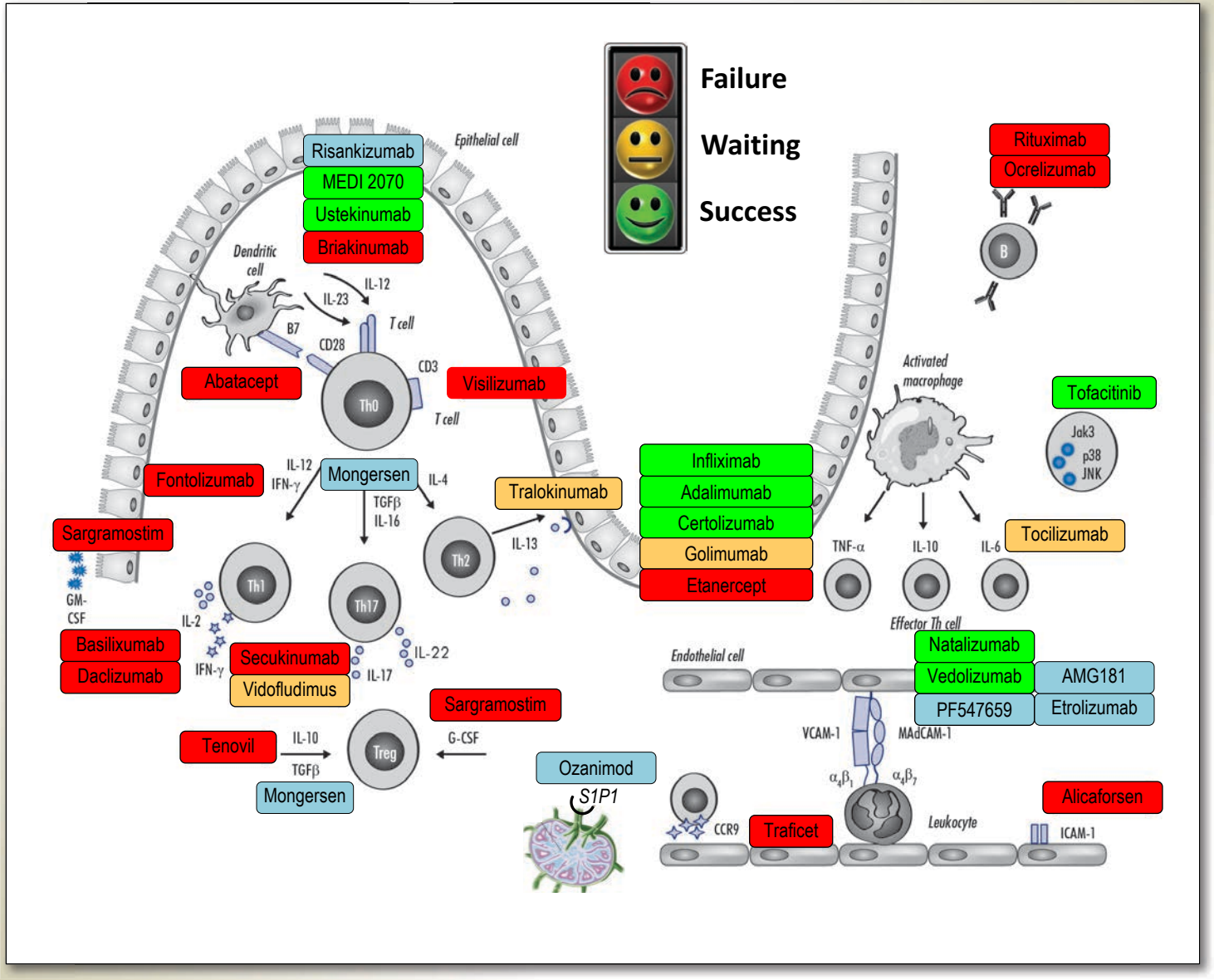


…and almost everything else

Evolution of biologic therapies for the treatment of immune-mediated inflammatory disorders (IMIDs)



Targeting the immunome in IBD: successful and failed biological therapies



Adapted from Kennedy N & Jones G-R. *IBD Monitor* 2012:13;79-83

Adapted from Danese S. *Gut* 2012;61:918-932

Combined biological therapy in clinical practice

- Combination ***anti-TNF + an immunosuppressor should be the rule*** in immunomodulator-naive patients for at least one year (both UC and CD)

- Benefits and risks should be weighted for combination therapy in the following situations:
  - Adalimumab, certolizumab pegol in CD
  - Infliximab in AZA/6-MP failures
  - Patients with previous serious infections or malignancies

Monitoring biological therapy in IBD

Algorithm for loss of response in patients using infliximab

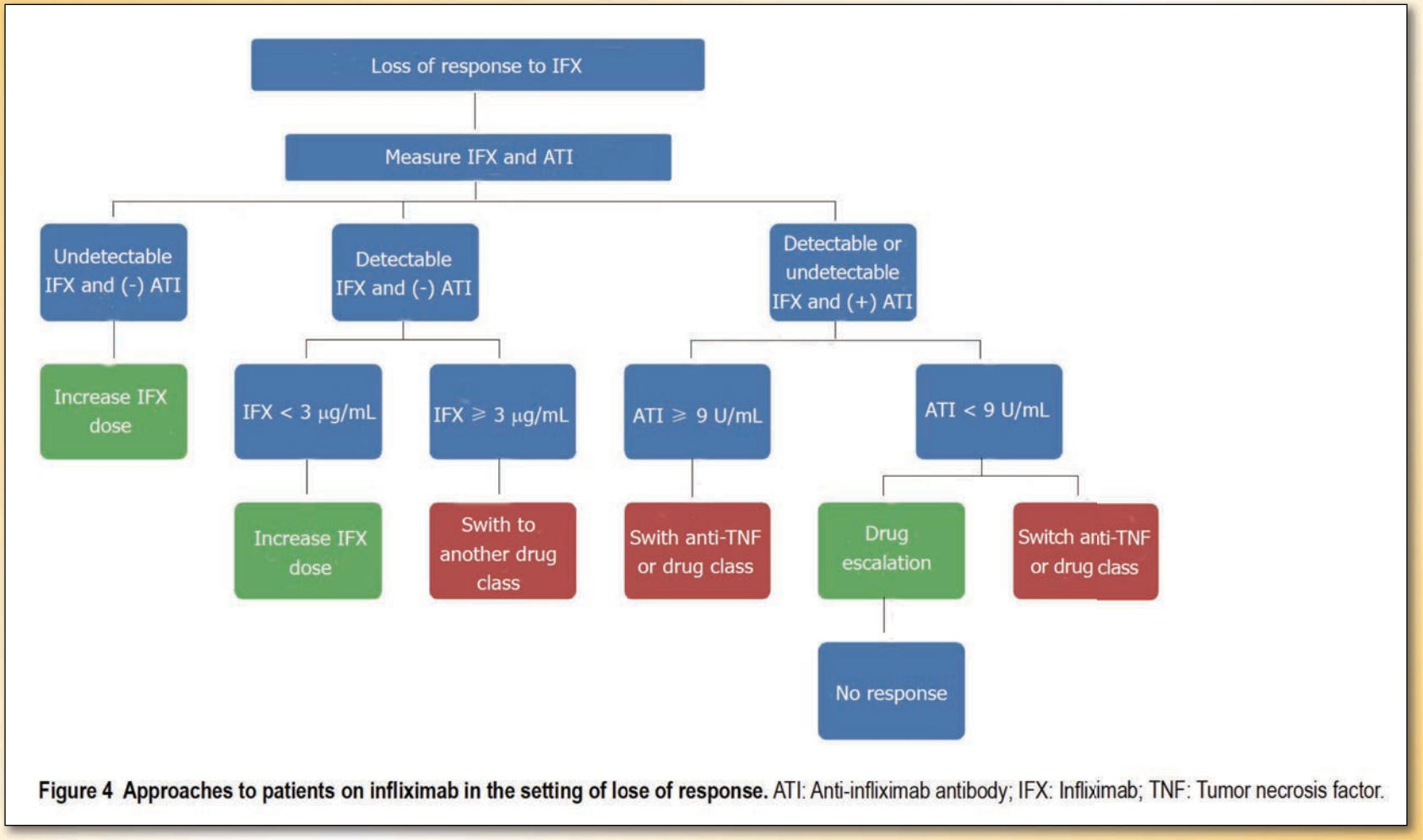
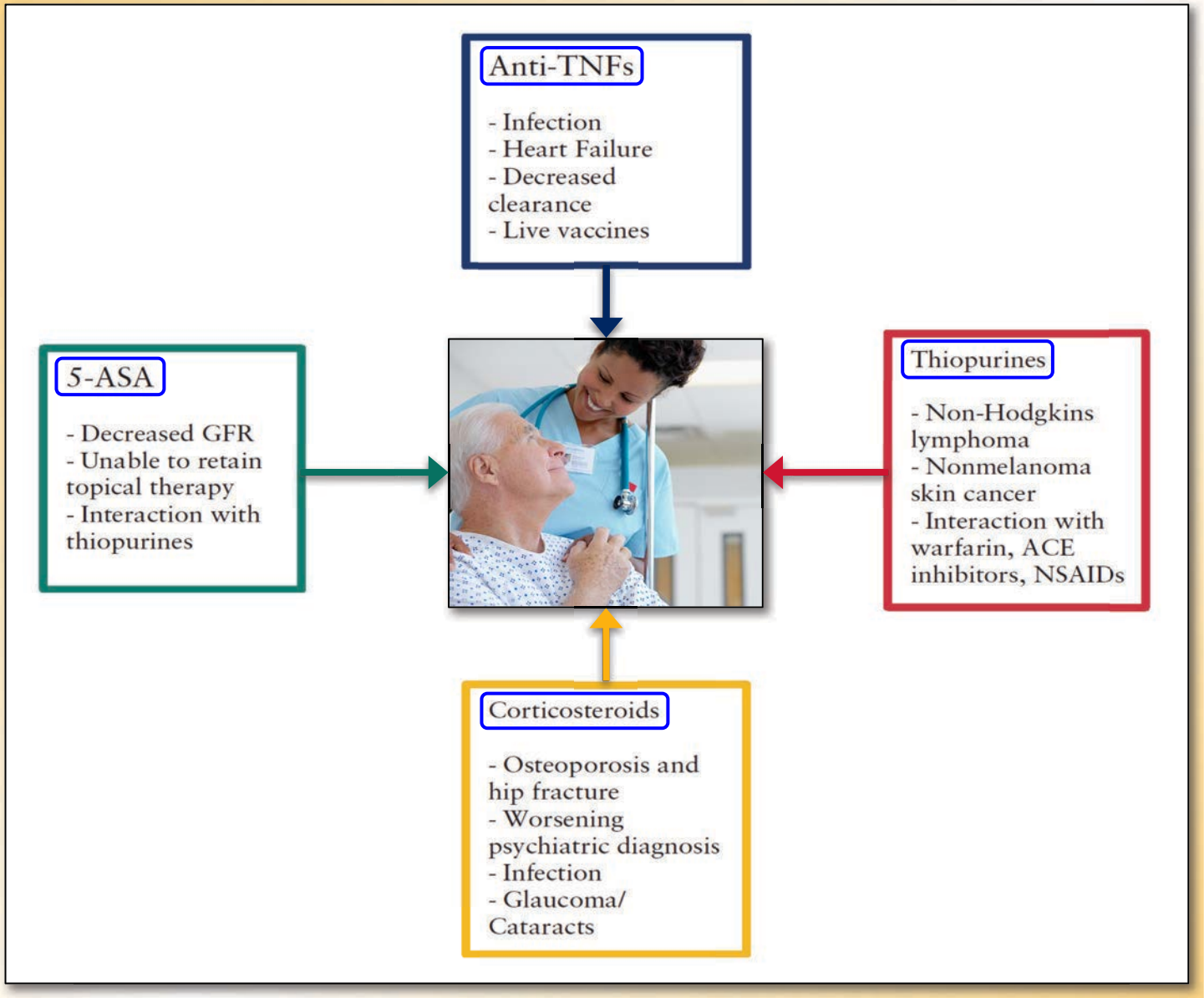


Figure 4 Approaches to patients on infliximab in the setting of lose of response. ATI: Anti-infliximab antibody; IFX: Infliximab; TNF: Tumor necrosis factor.

Yarur A et al. *World J Gastroenterol* 2014;20:3475-3484

Side effects and complication of IBD therapy



Taleban S et al. *J Crohn's & Colitis* 2015;9:507-515

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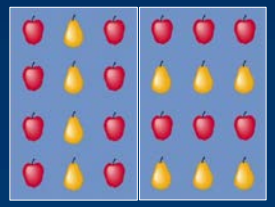

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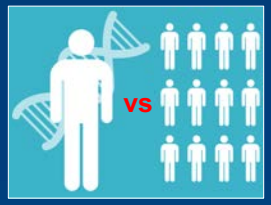
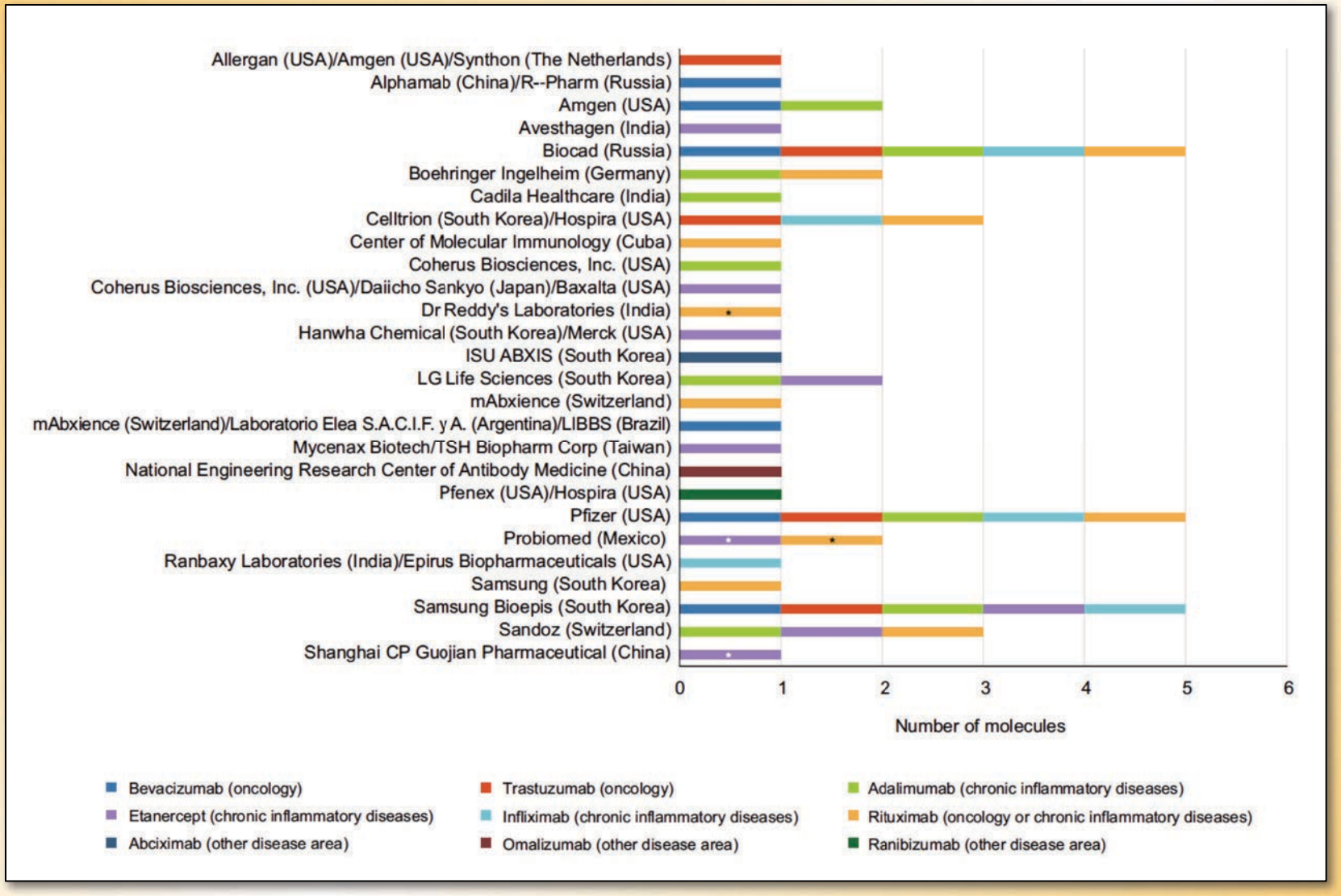


“Precision medicine”

Inspirational/visionary message

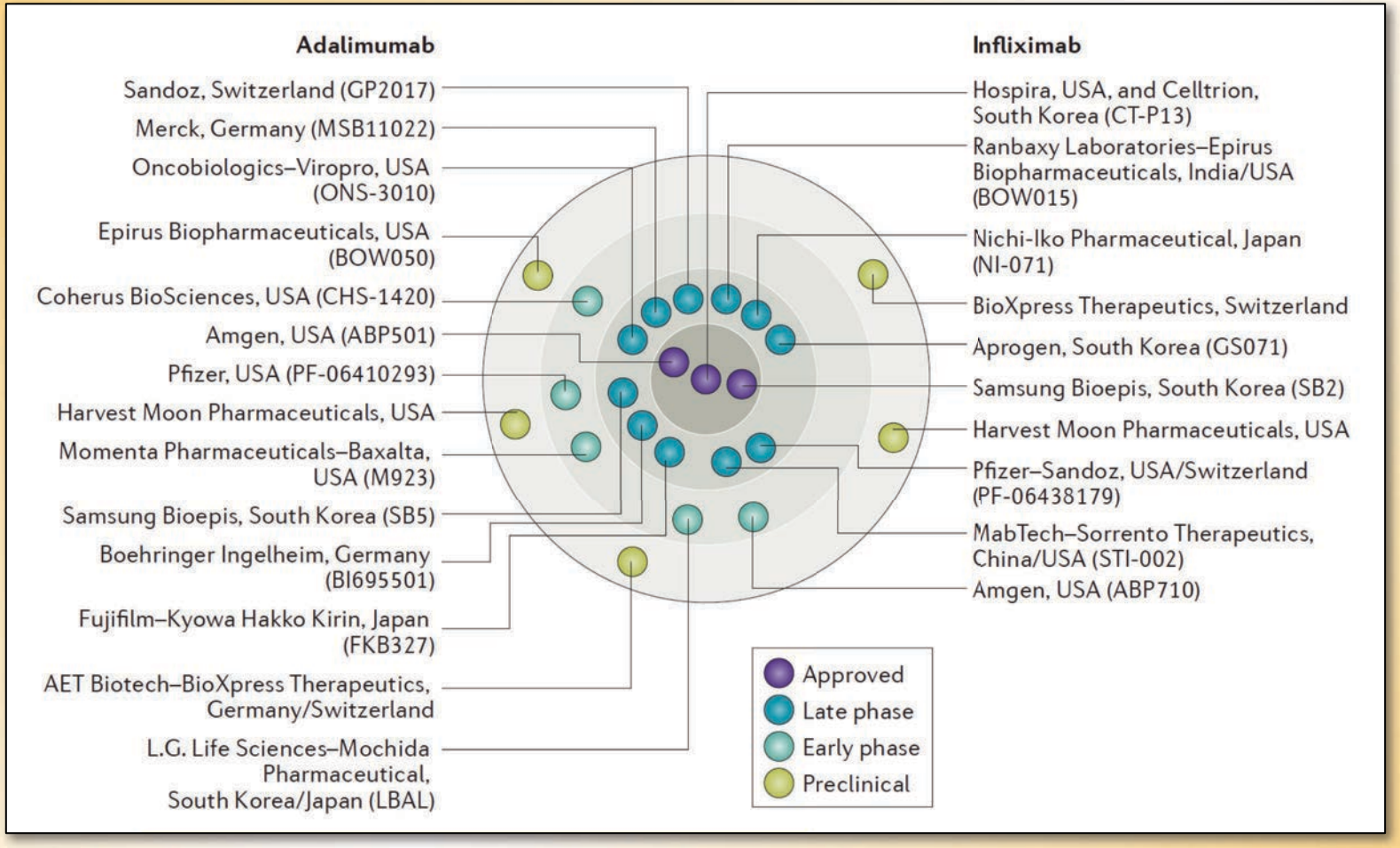
Biosimilars development pipeline*



*2016

Jacobs I et al. *Bio Drugs* 2016;30:489-523

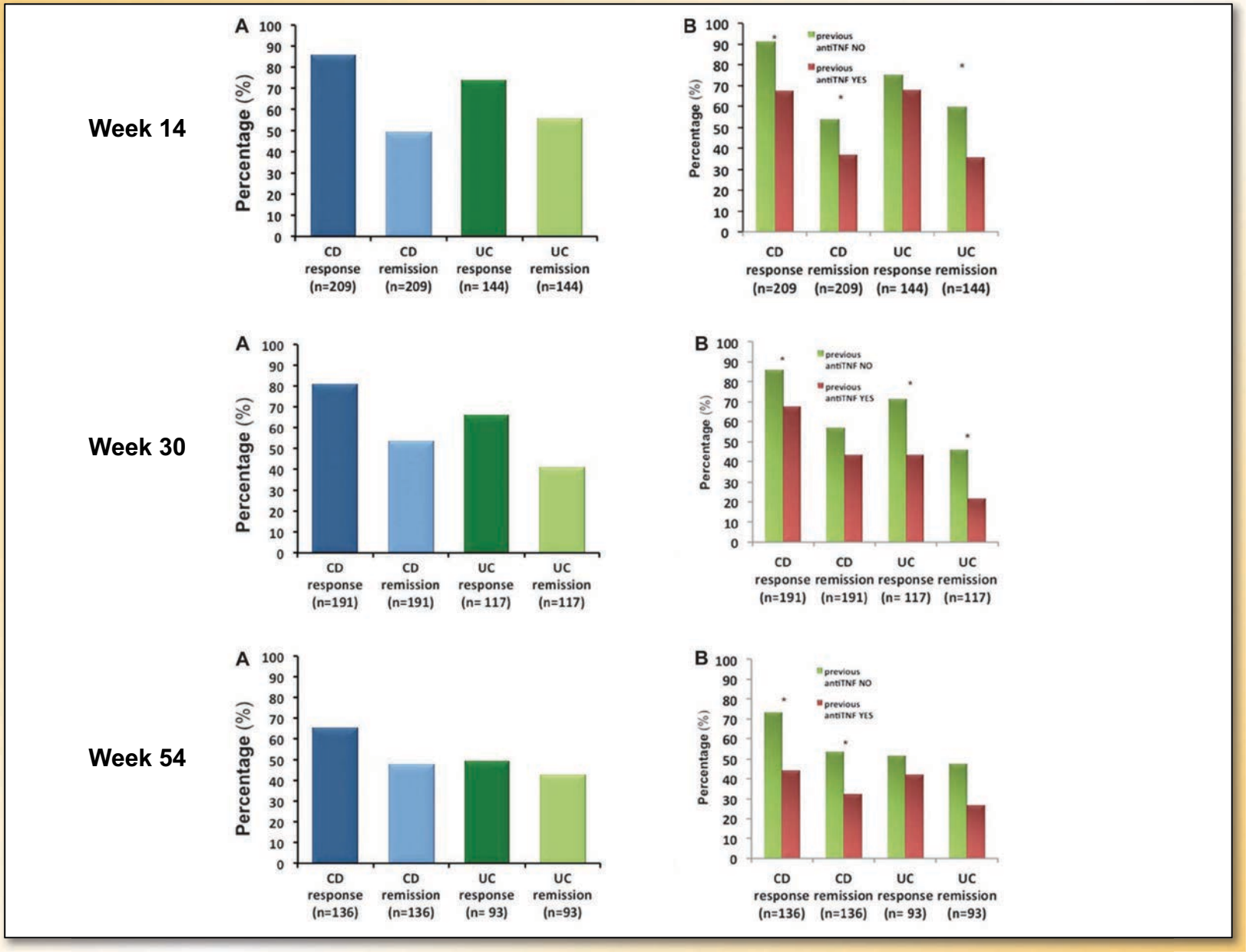
Pipeline of biosimilars for adalimumab and Infliximab*



*As of September 2016

Danese S et al. *Nat Rev Gastroenterol Hepatol* 2017;14:22-31

Long term efficacy of the infliximab biosimilar CT-P13



Gonzci L et al. *Inflam Bowel Dis* 2017 [ePub ahead of print]

Review article: pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases

K. Papamichael[*,†], T. Van Stappen[*], V. Jairath[‡], K. Gecse[§], R. Khanna[¶], G. D'Haens[¶,**], S. Vermeire[†], A. Gils[*], B. G. Feagan[¶], B. G. Levesque[¶,††] & N. Vande Casteele[*,††]

Conclusions

It is likely that biosimilars will be widely used for the treatment of IBD due to their cost savings and comparable efficacy. Nevertheless, robust post-marketing studies and pharmacovigilance are warranted in the coming years.

Aliment Pharmacol Ther 2015; **42**: 1158–1169

Biosimilars in inflammatory bowel disease: ready for prime time?

Fernando Gomollón

Summary

Biosimilars in IBD are here to stay. New data are awaited to settle the controversy of extrapolation, but only the complex behavior of markets will show whether biosimilars fuel competition and extend access to biologics with significant cuts in drug costs.

Curr Opin Gastroenterol 2015; **31**: 290-295

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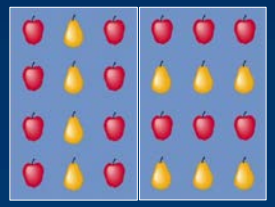

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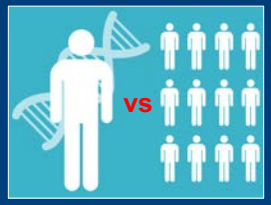
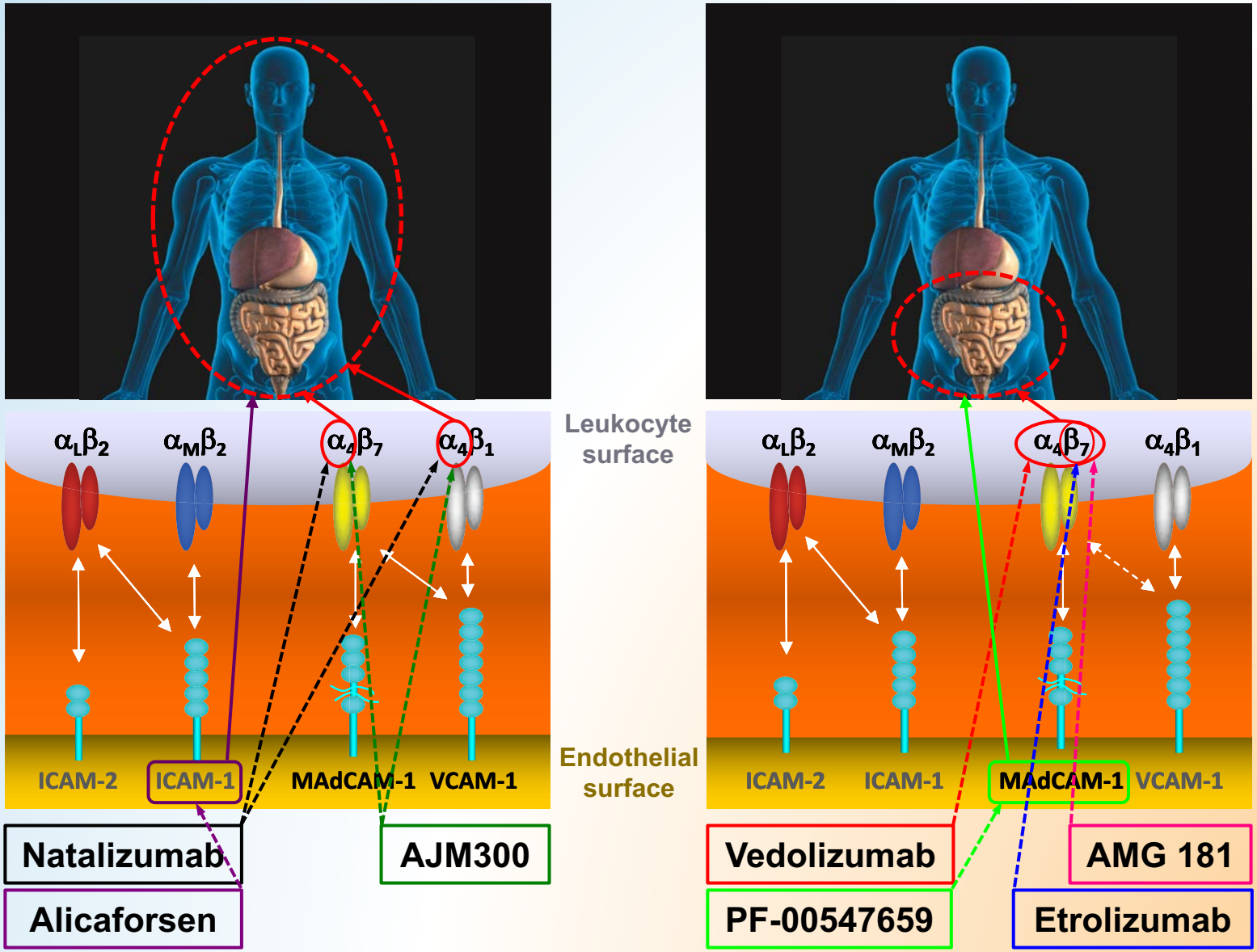


"Precision medicine"

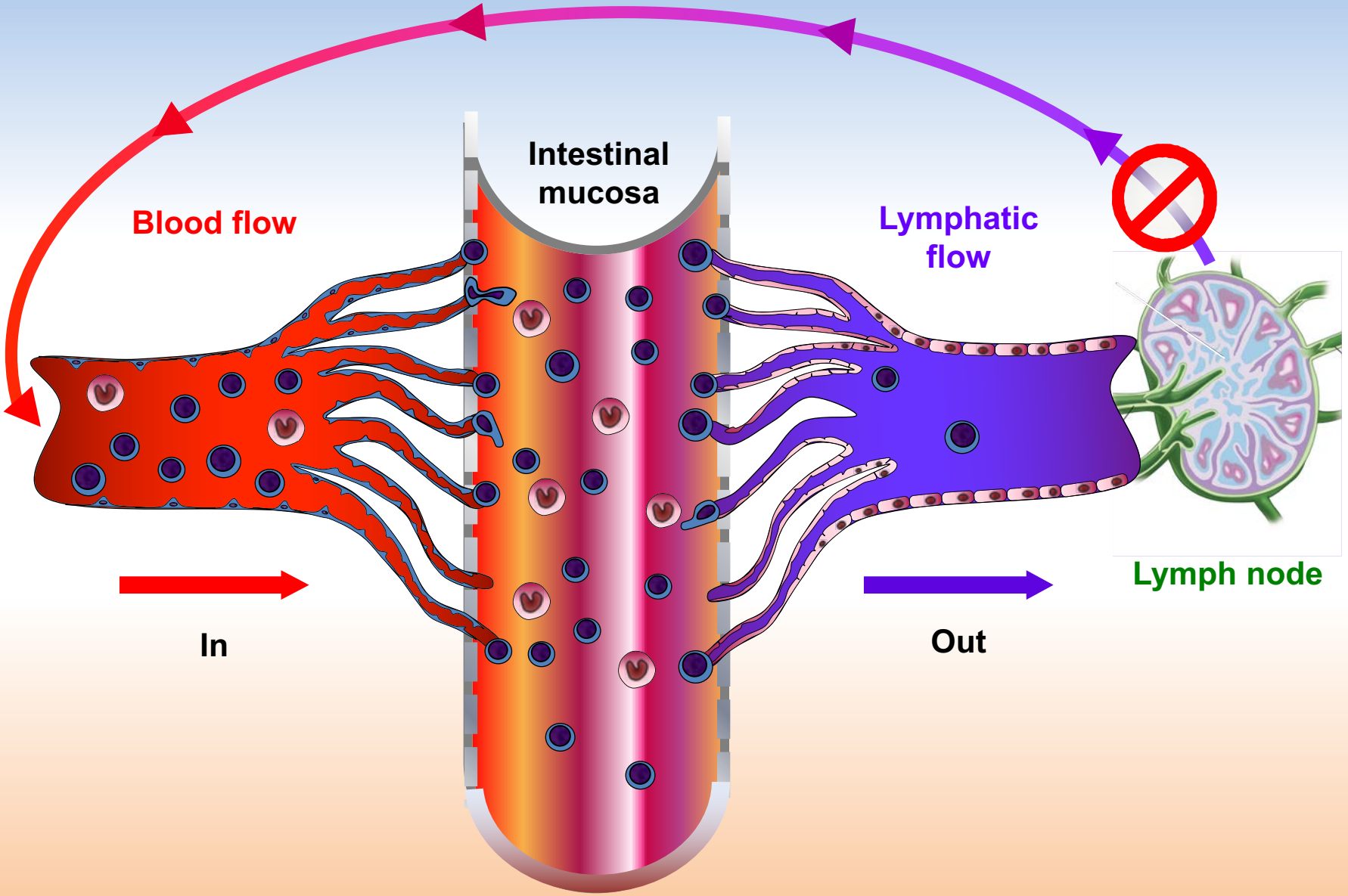
Inspirational/visionary message

Importance of gut selectivity for therapeutic success

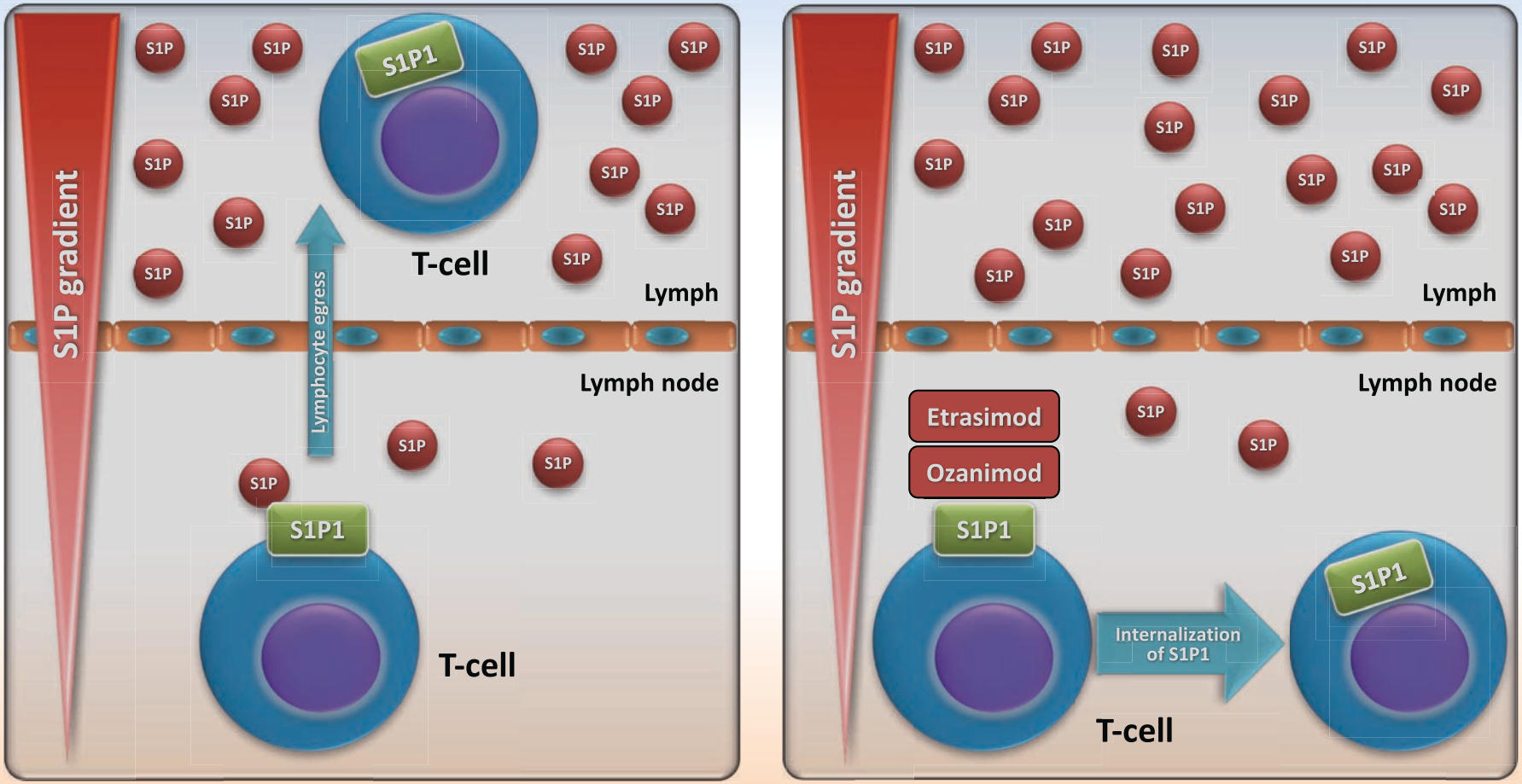


Danese S & Panes J. *Gastroenterology* 2014;147:981-9

In and out intestinal leukocyte trafficking



Inhibition of lymphocyte egression from lymph nodes by S1P receptor modulators



Olivera P et al. *Gut* 2017;66:199-209

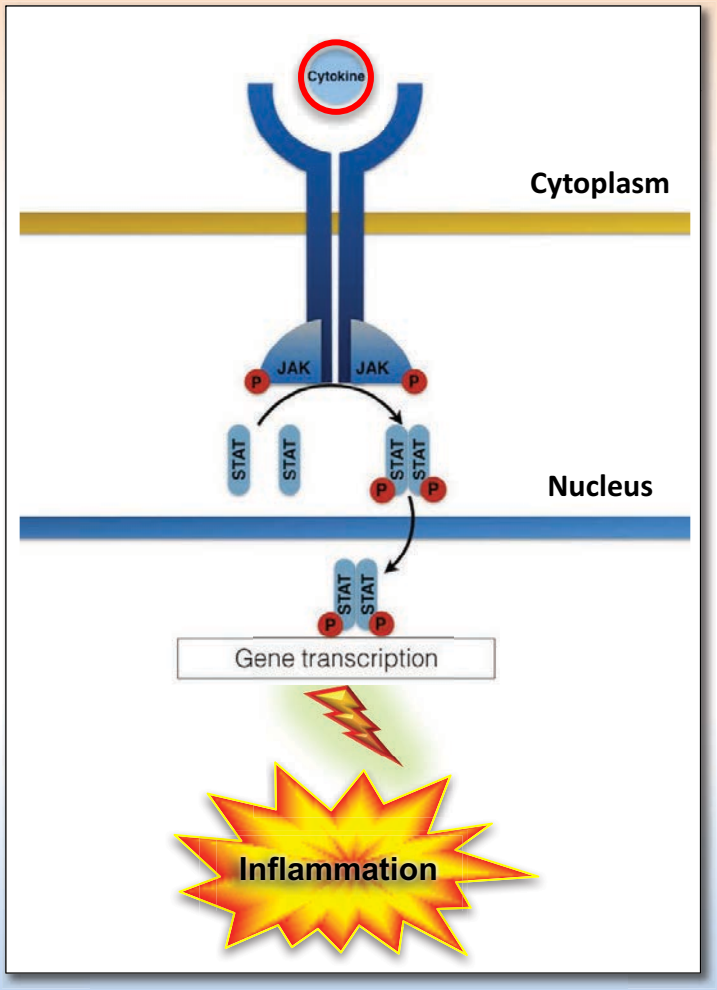
Small molecule drugs: an alternative to biologics

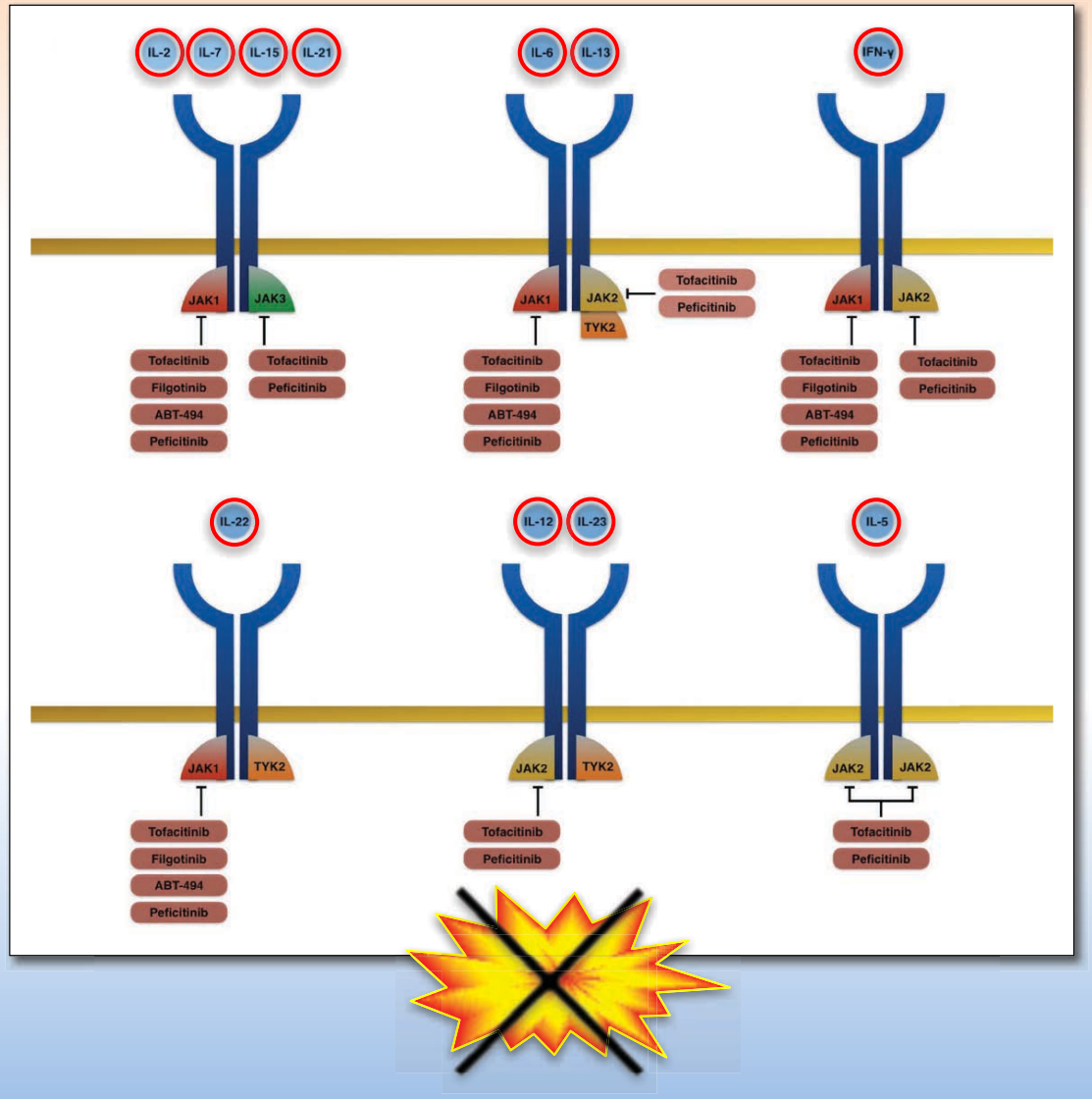
Table 1 Differences between small-molecule drugs (SMDs) and biologics

	SMDs	Biologics
Molecular weight (Da)	<1000	>>1000
Chemical structure	Small organic compounds	Proteins
Location of target	Intracellular	Extracellular
Mechanism of action	Receptor or enzyme inhibition	Depletion
Route of administration	Oral	Parenteral
Distribution	Variable	Limited to plasma and extracellular fluids
Degradation	Metabolism	Proteolysis
Serum half-life	Short	Long
Antigenicity	Non-antigenic	Potentially antigenic
Drug–drug interactions	Possible	Infrequent
Toxicity	Specific toxicity due to the parent compound or metabolites. Possible 'off-target' effects	Receptor-mediated toxicity
Production	Chemical synthesis	Biological production
Cost of production	Variable	High
Generics	Identical	Biosimilar

Olivera P et al. *Gut* 2017;66:199-209

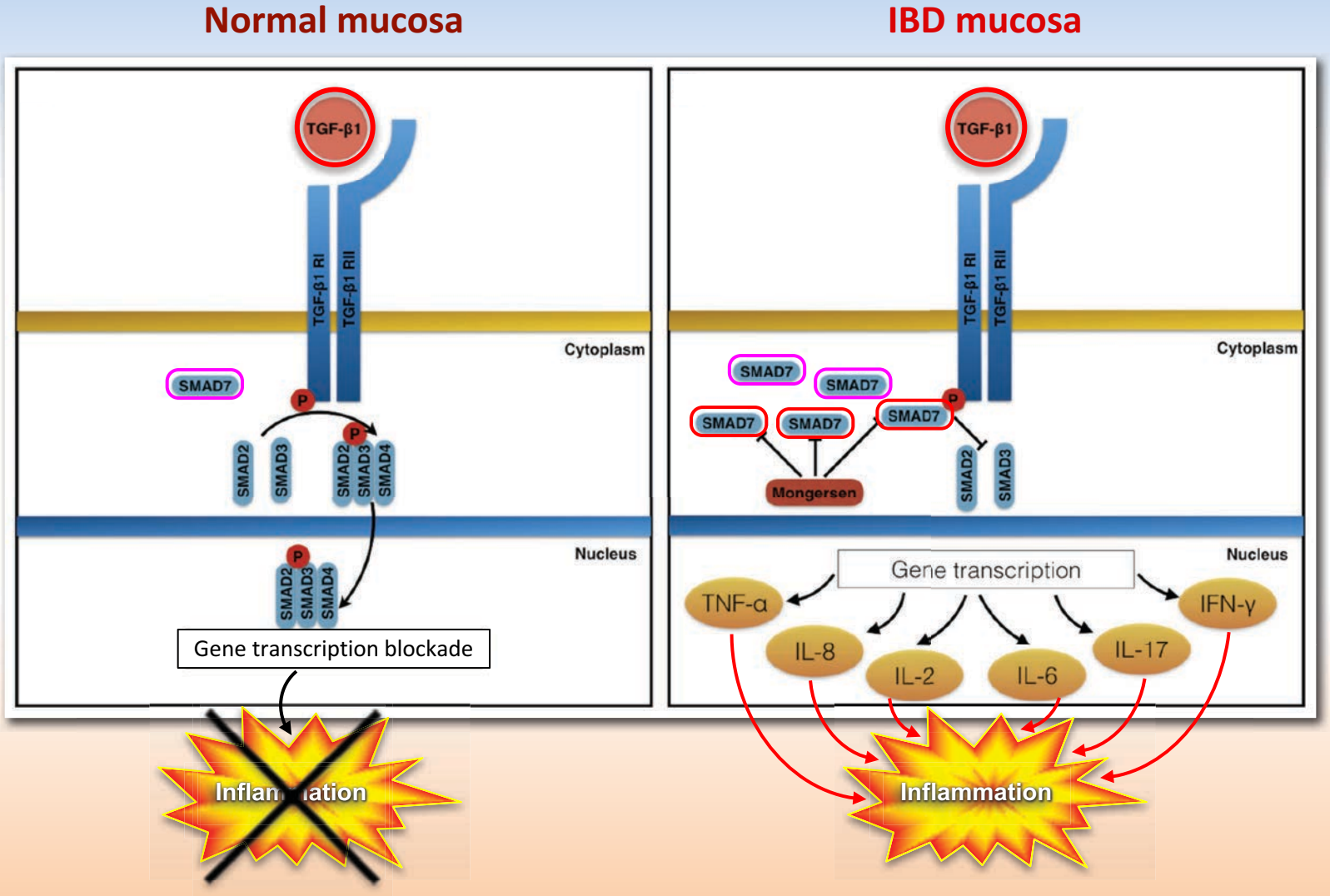
Cytokine activation of downstream signaling molecules JAKs and STATs and respective blockers





Olivera P et al. *Gut* 2017;66:199-209

Promotion of TGFβ1 suppressor/anti-inflammatory activity by oligonucleotide*-induced inhibition of SMAD7



*Mongersen

Adapted from Olivera P et al. *Gut* 2017;66:199-209

New IBD drugs: hopes and realities

Healio > Gastroenterology > Inflammatory Bowel Disease

Celgene halts mongersen trials in Crohn's disease

October 20, 2017

COMMENT

SAVE

Celgene announced it has discontinued two trials of drug candidate GED-0301 (mongersen) in Crohn's disease due to disappointing results.

The company said it decided to stop the phase 3 REVOLVE trial (CD-002) and the extension trial (SUSTAIN, CD-004) based on the Data Monitoring Committee's recommendation in October following an interim analysis of observed risks and benefits. A press release noted this analysis showed "no meaningful safety imbalances."

SEE ALSO

Galapagos initiates phase 3 trial of filgotinib in Crohn's...

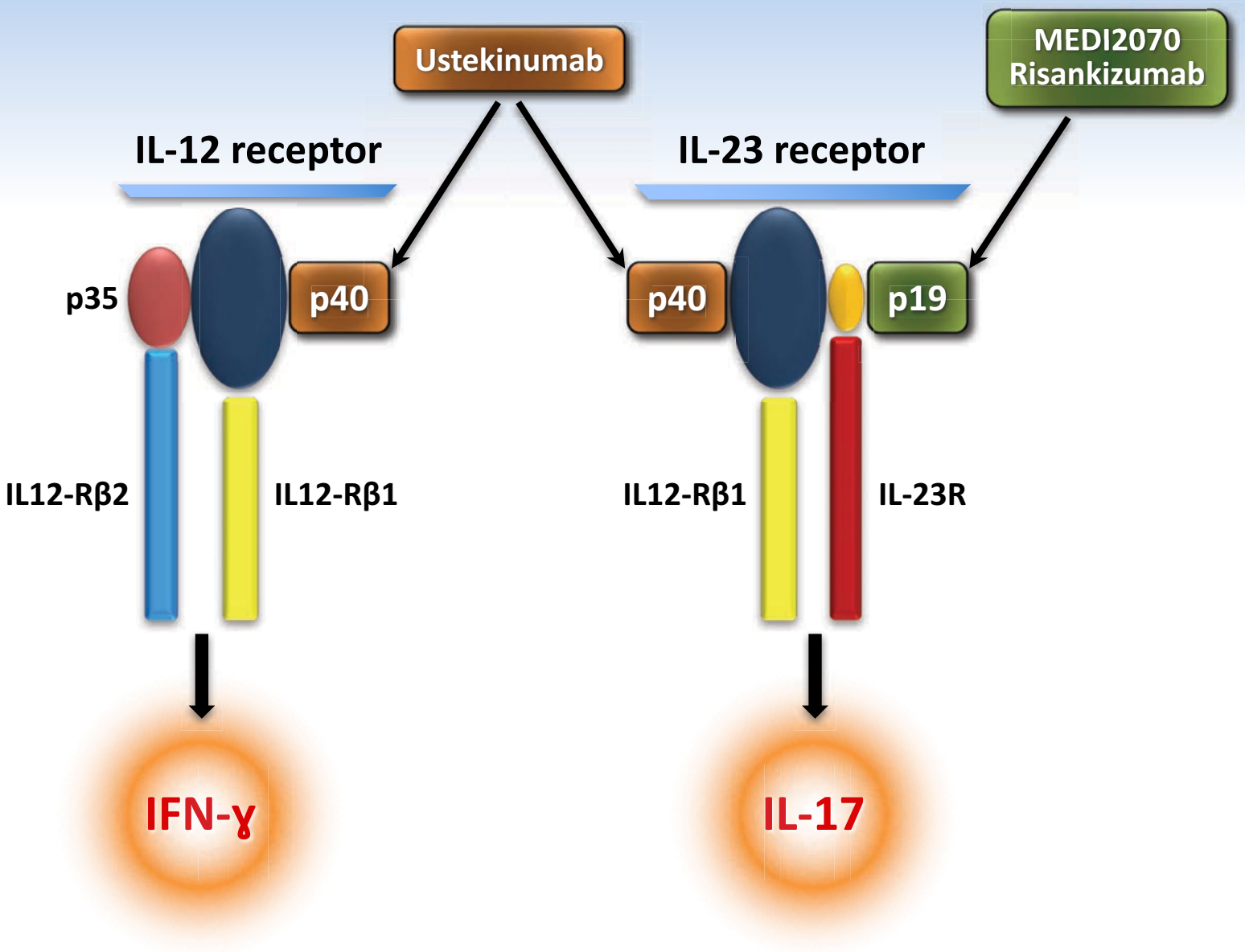
Axsome launches phase 2/3 trial of AXS-05 for agitation in...

CDC: Nearly 500,000 C. difficile infections in US in 2011

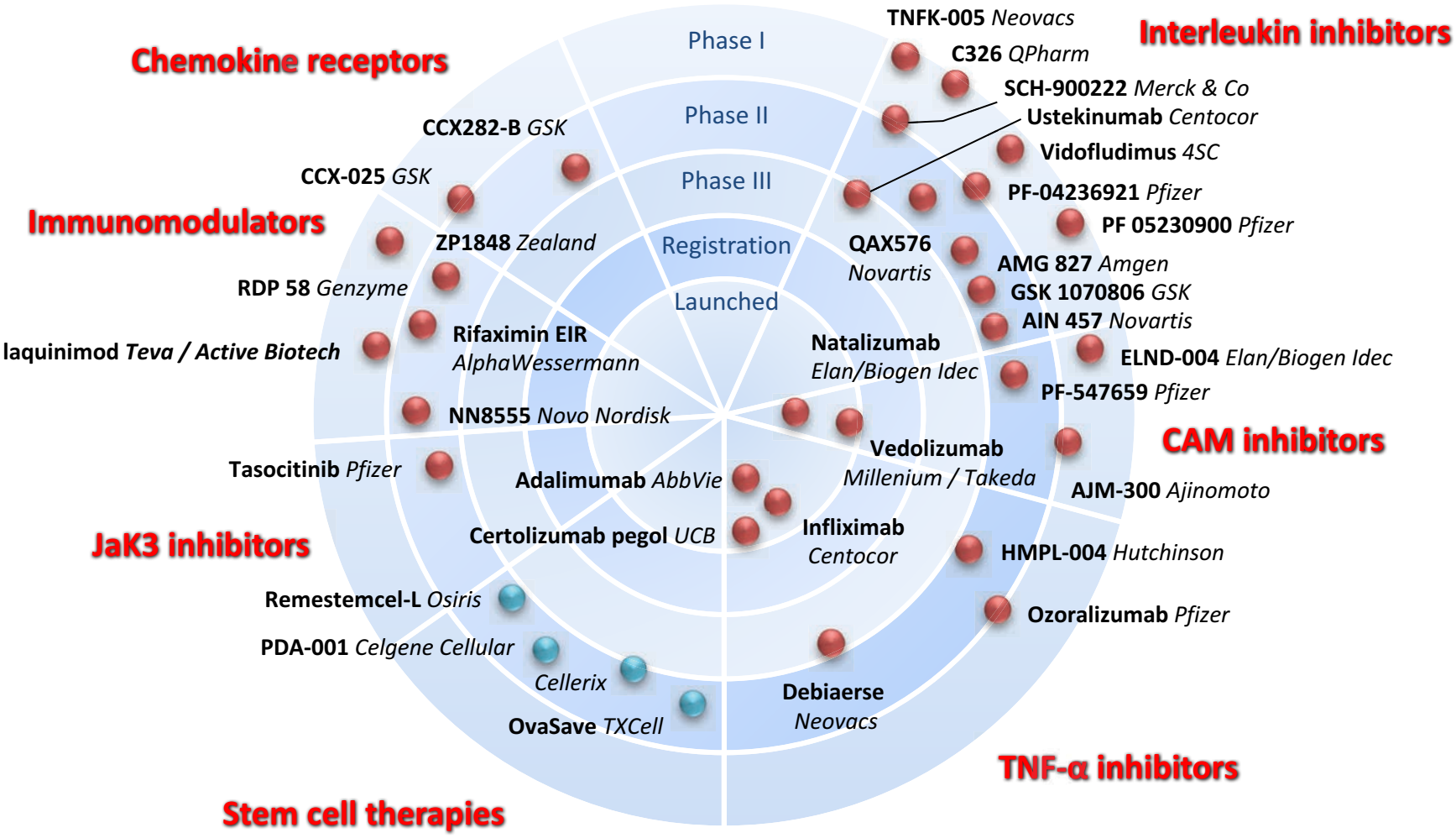
As a result, the company said it will not begin the phase 3 DEFINE trial (CD-003) in Crohn's disease, and will decide if it will continue developing mongersen for ulcerative colitis after reviewing full data from a phase 2 trial.

This oral antisense therapy, which is investigational and not approved for use in any country, "is an oligonucleotide that decreases Smad7 protein, thereby potentially impacting [TGF-beta 1] signaling," according to the press release. "In patients with Crohn's disease, abnormally high levels of Smad7 interfere with [TGF-beta 1] anti-inflammatory pathways in the gut, leading to increased inflammation."

Increasing molecular specificity of antibody targeting

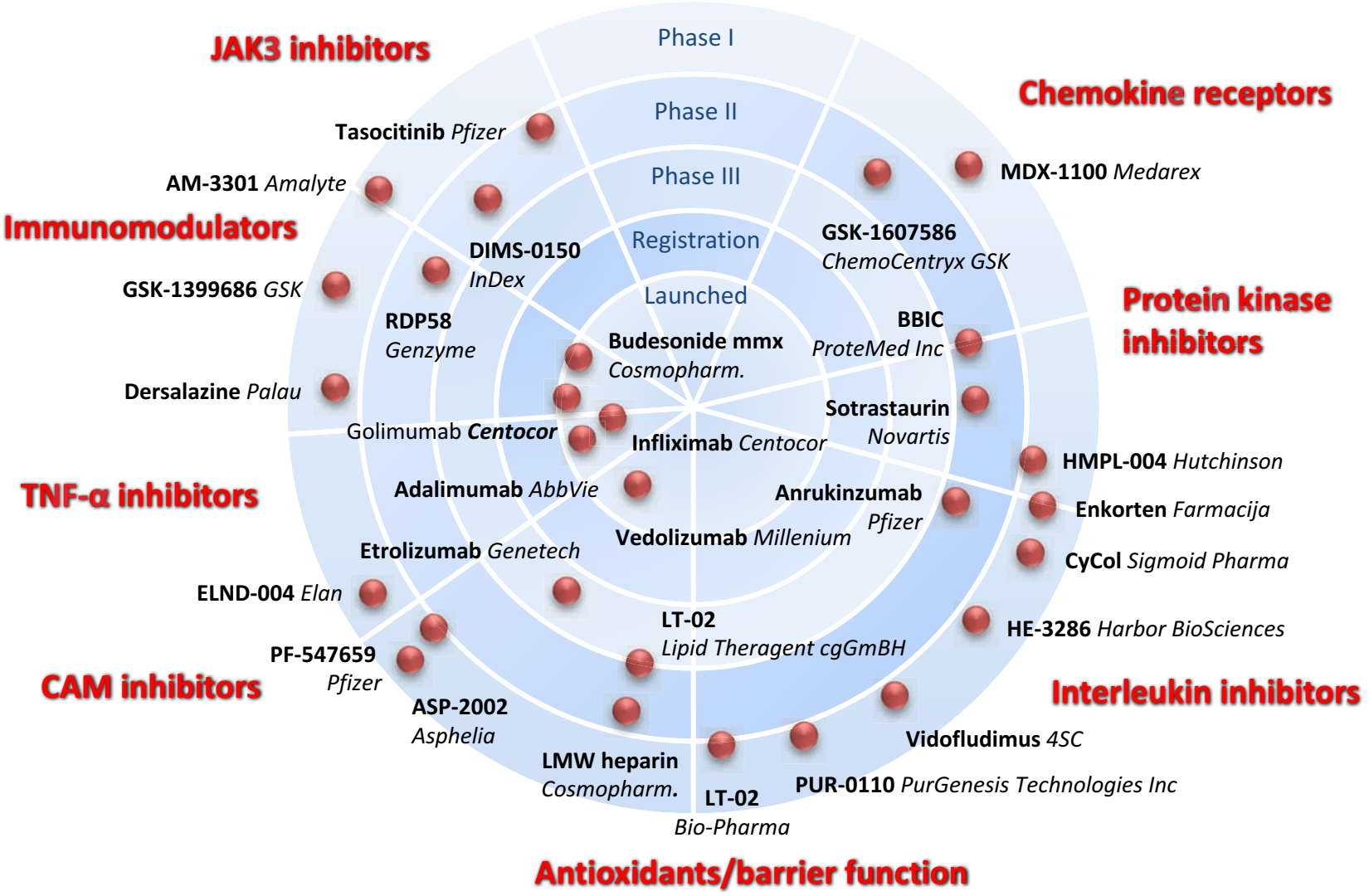


The Crohn's disease therapeutic universe



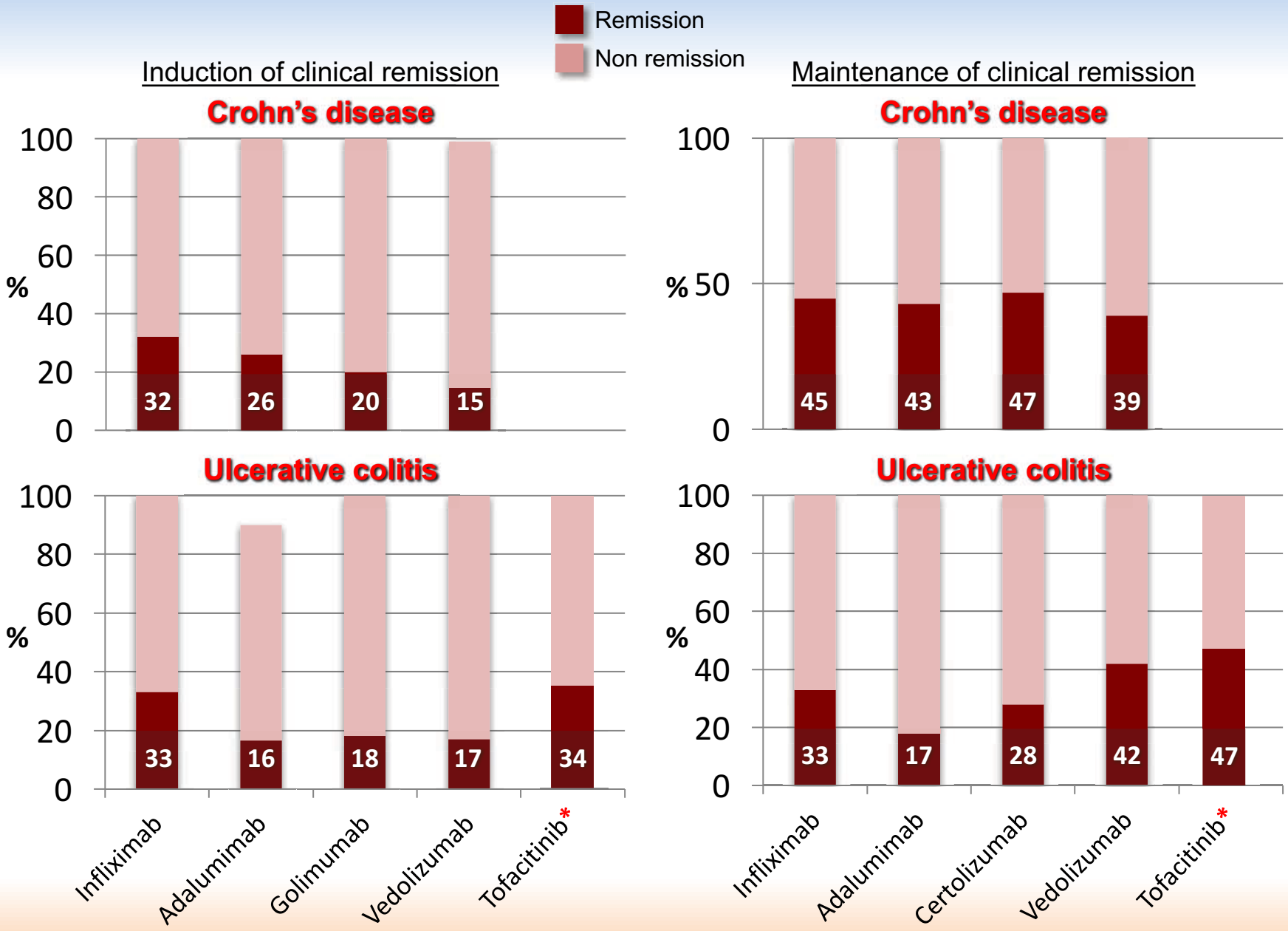
Courtesy of S. Danese

The ulcerative colitis therapeutic universe



Courtesy of S. Danese

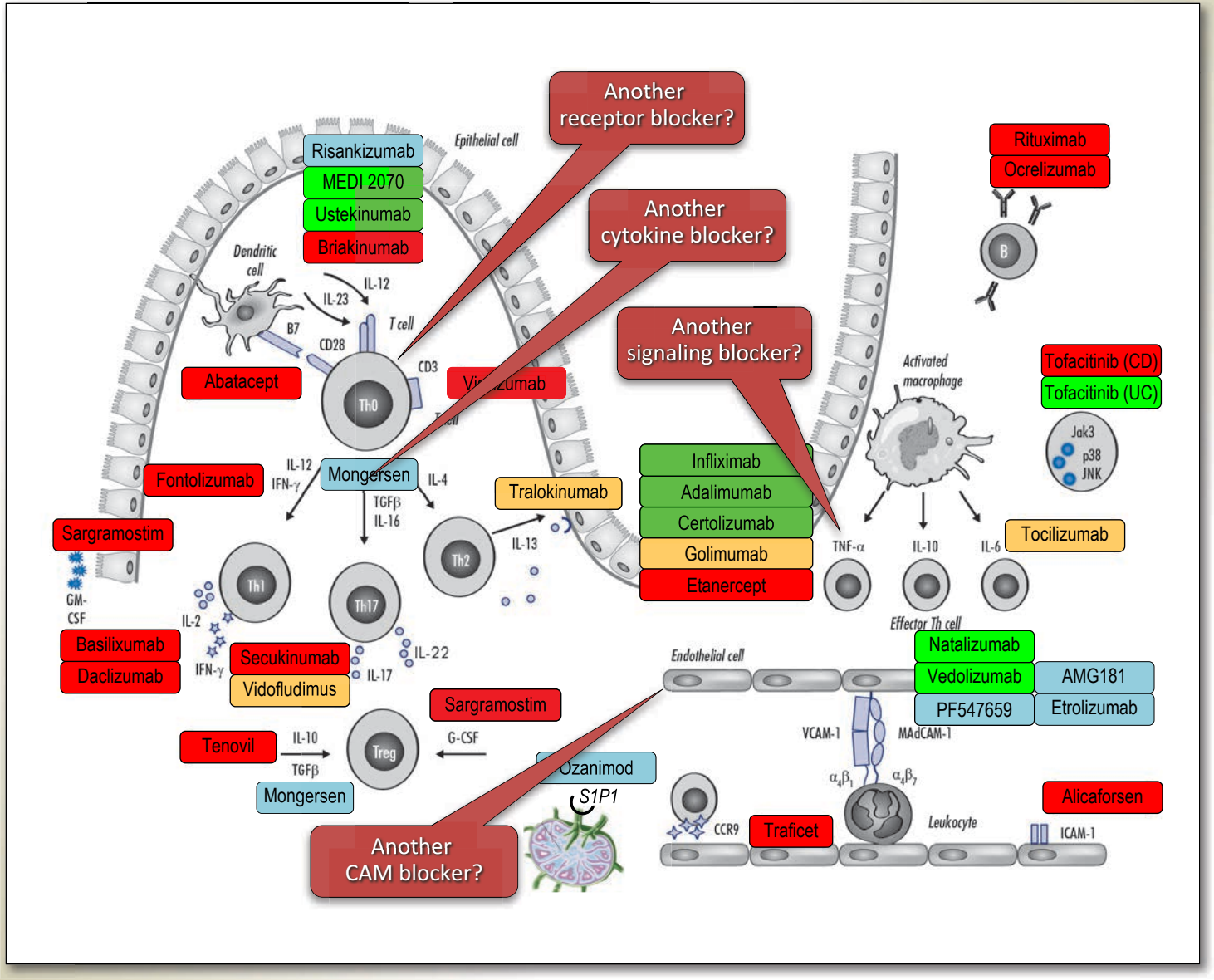
The most advanced treatments for IBD are still suboptimal



*OCTAVE Sustain

Adapted from Courtesy of Dr. M. Gassull

Targeting the immunome in IBD: successful and failed biological therapies

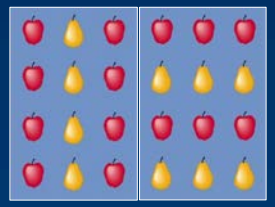


Adapted from Kennedy N & Jones G-R. *IBD Monitor* 2012:13;79-83

Adapted from Danese S. *Gut* 2012;61:918-932

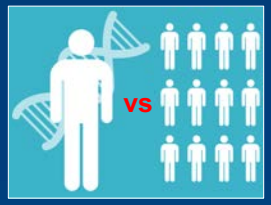
Session objectives

Review the most significant advances in our understanding of IBD pathogenesis and management over the past 10 years



Biosimilars – International perspective

IBD research:
Where are we going in the next 5-10 years?
Where will the next great breakthrough be?



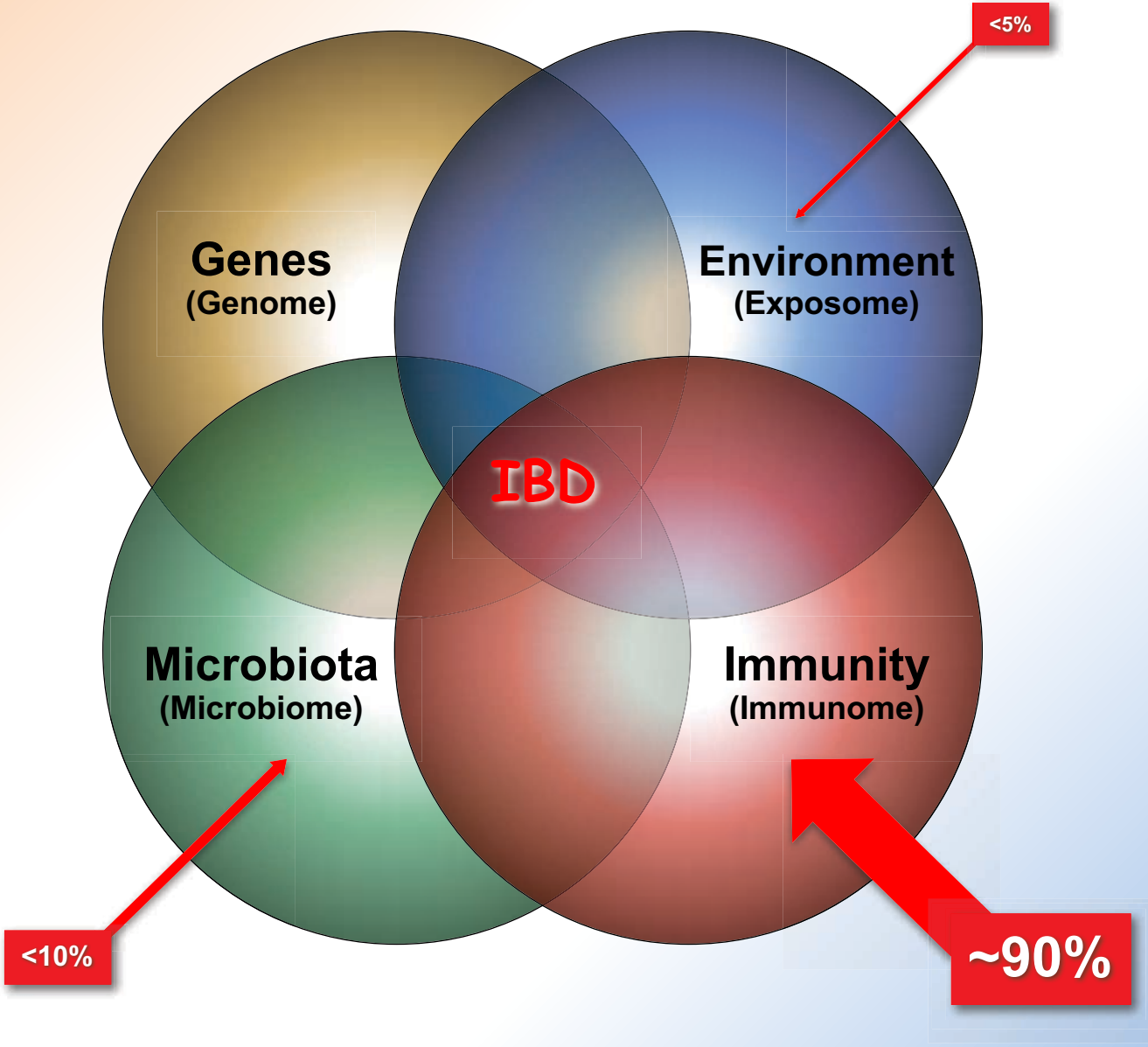
"Precision medicine"

Inspirational/visionary message

“What is precision medicine?”

According to the Precision Medicine Initiative of the NIH, precision medicine is *"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"*

IBD: a complex disease with a lopsided therapeutic approach



science & society

Complex diseases require complex therapies

SSS Science & Society series on drugs and science

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EMBO *reports* (2013) **14**, 1039–1042; published online 15 November 2013; doi:10.1038/embor.2013.177

1 Drugs, by and large, work at a molecular level, just as diseases originate from molecular malfunctions

2 Malfunctions differ from person to person owing to variations and changes in the person's genome and environment

3 Current approaches might have reached their limits and we need new thinking to drive drug discovery and use

4 Systems biology-based treatments are likely to be of increasing value because most diseases undergo multiple molecular changes as they progress

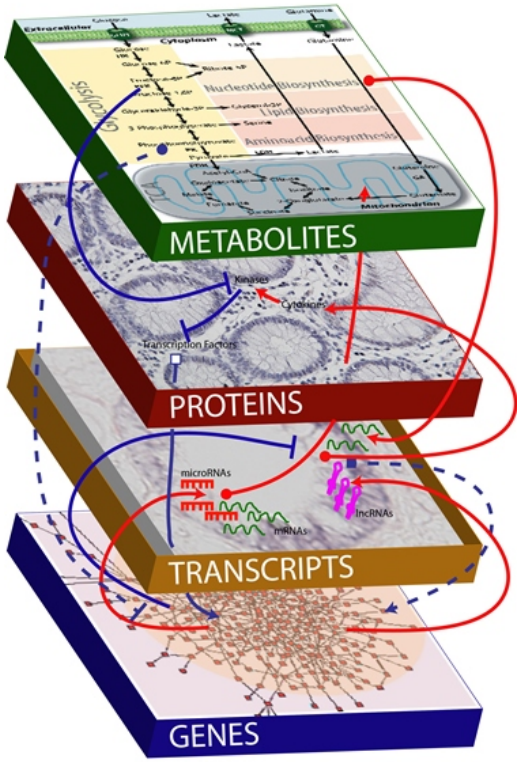
5 Complex diseases cannot be treated effectively by modulating a single target

6 Combining drugs that act on different targets within a network could be more efficacious than treating diseases with one drug

EMBO Rep 2013 Dec;14(12):1039-42

IBD is a highly complex disease:

multiple molecules, multiple interactions, multiple effects



DNA —transcription→ RNA —translation→ Protein

Genome
- SNPs
- Mutations

Transcriptome
- Coding RNAs
- Non-coding RNAs

Proteome
Metabolome

Epigenome
- DNA methylation
- Chromatin modifications

Courtesy of Dr. D. Iliopoulos

Multiple IBD "omics" data integration:
genome, exposome, microbiome, immunome, etc.

Mathematical model

$$D_t^{\frac{1}{2}} u_1 = d\sqrt{2}/3\left[-CD_t^{\frac{1}{2}} u_1\tau + Cf_1\tau\right],$$

$$D_t^{\frac{1}{2}} u_2 = d\sqrt{6}/5\left\{-C^3 D_t^{\frac{1}{2}} u_1\tau - \frac{C}{2} D_t^{\frac{1}{2}} u_2\tau + C^3 f_1\tau + \frac{C}{2} f_2\tau\right\},$$

$$D_t^{\frac{1}{2}} u_k = d\sum_{m=2}^{k-1}\left\{\left[(k-m)\lambda(k-m) + \mu(k-m)\right]\right.$$

$$\times\left[-\sum_{s=1}^{m-2} B^{m-2-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{m-2} B^{m-2-s} Cf_s\tau\right]$$

$$+\left[(2m-2k-1)\lambda(k-m) - 2\mu(k-m)\right]$$

$$\times\left[-\sum_{s=1}^{m-1} B^{m-1-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{m-1} B^{m-1-s} Cf_s\tau\right]$$

$$+\left[(k-m+1)\lambda(k-m) + \mu(k-m)\right]$$

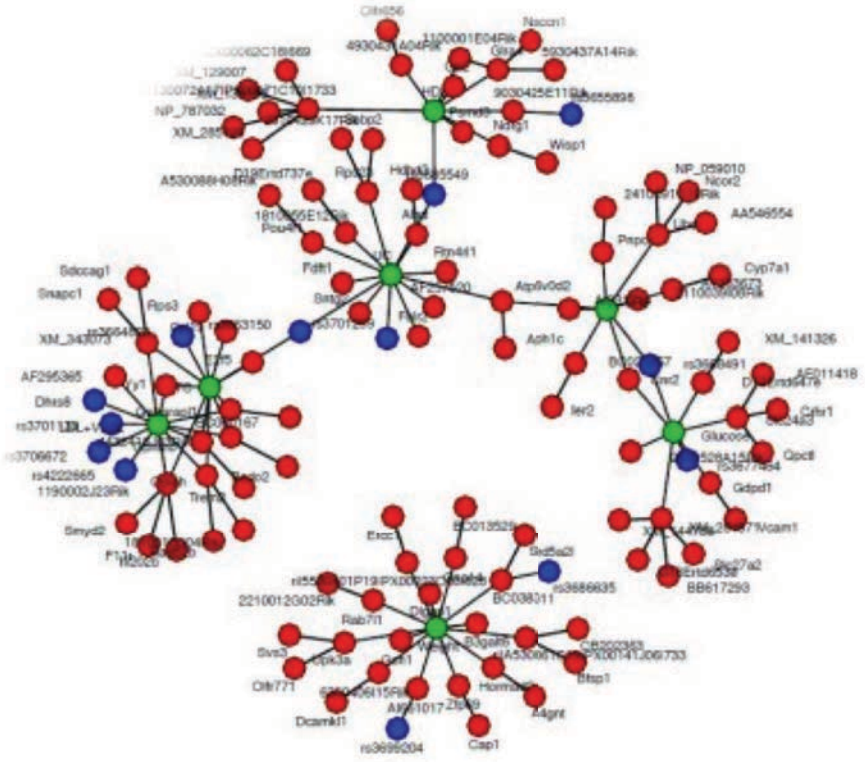
$$\left.\times\left[-\sum_{s=1}^{m} B^{m-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{m} B^{m-s} Cf_s\tau\right]\right\}$$

$$+\frac{d}{6\sqrt{2}}\left\{-\left[-\sum_{s=1}^{k-2} B^{k-2-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{k-2} B^{k-2-s} Cf_s\tau\right]\right.$$

$$-4\left[-\sum_{s=1}^{k-1} B^{k-1-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{k-1} B^{k-1-s} Cf_s\tau\right]$$

$$\left.+5\left[-\sum_{s=1}^{k} B^{k-s} CD_t^{\frac{1}{2}} u_s\tau + \sum_{s=1}^{k} B^{k-s} Cf_s\tau\right]\right\}, \quad 3 \le k \le N.$$

Organize information in networks



Identification of the central regulators (●) of IBD pathogenesis

Courtesy of Dr. D. Iliopoulos

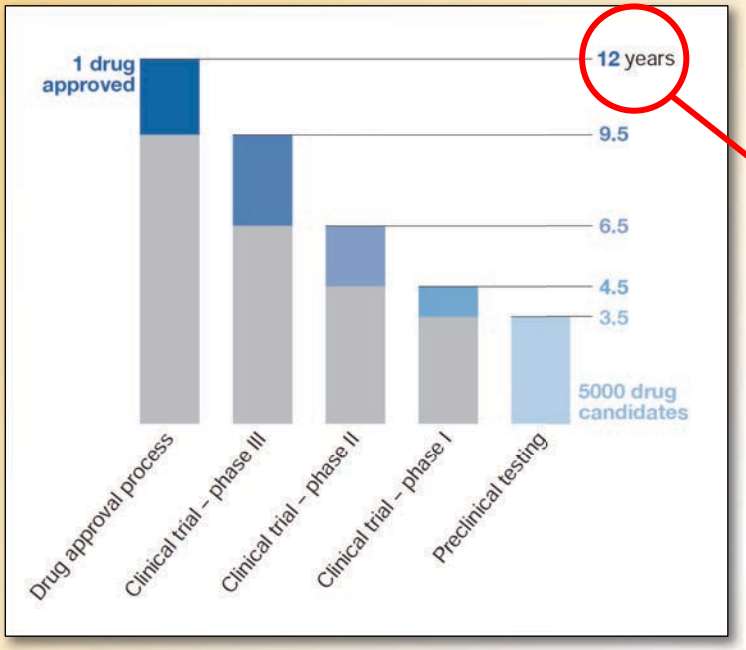
CSB technology platforms

High throughput drug discovery platform

- An integrated robotic system for pharmaceutical discovery
- Collection of >500,000 compounds
- Ability to test ~200,000 compounds in a single screen in ***7 days***
- A single laboratory would perform the same analysis in ***2 years***

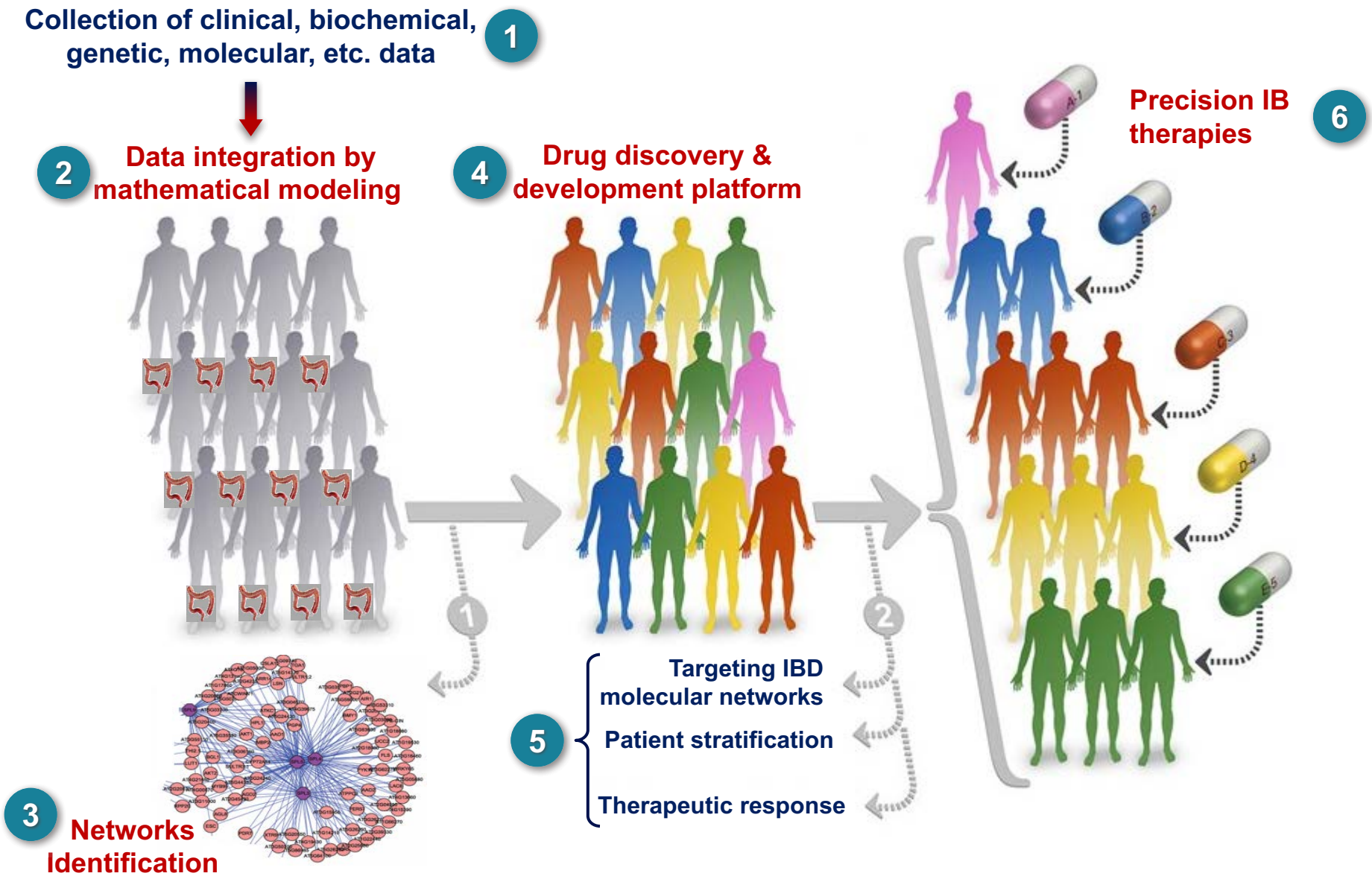
Courtesy of Dr. D. Iliopoulos

Omics accelerated drug discovery



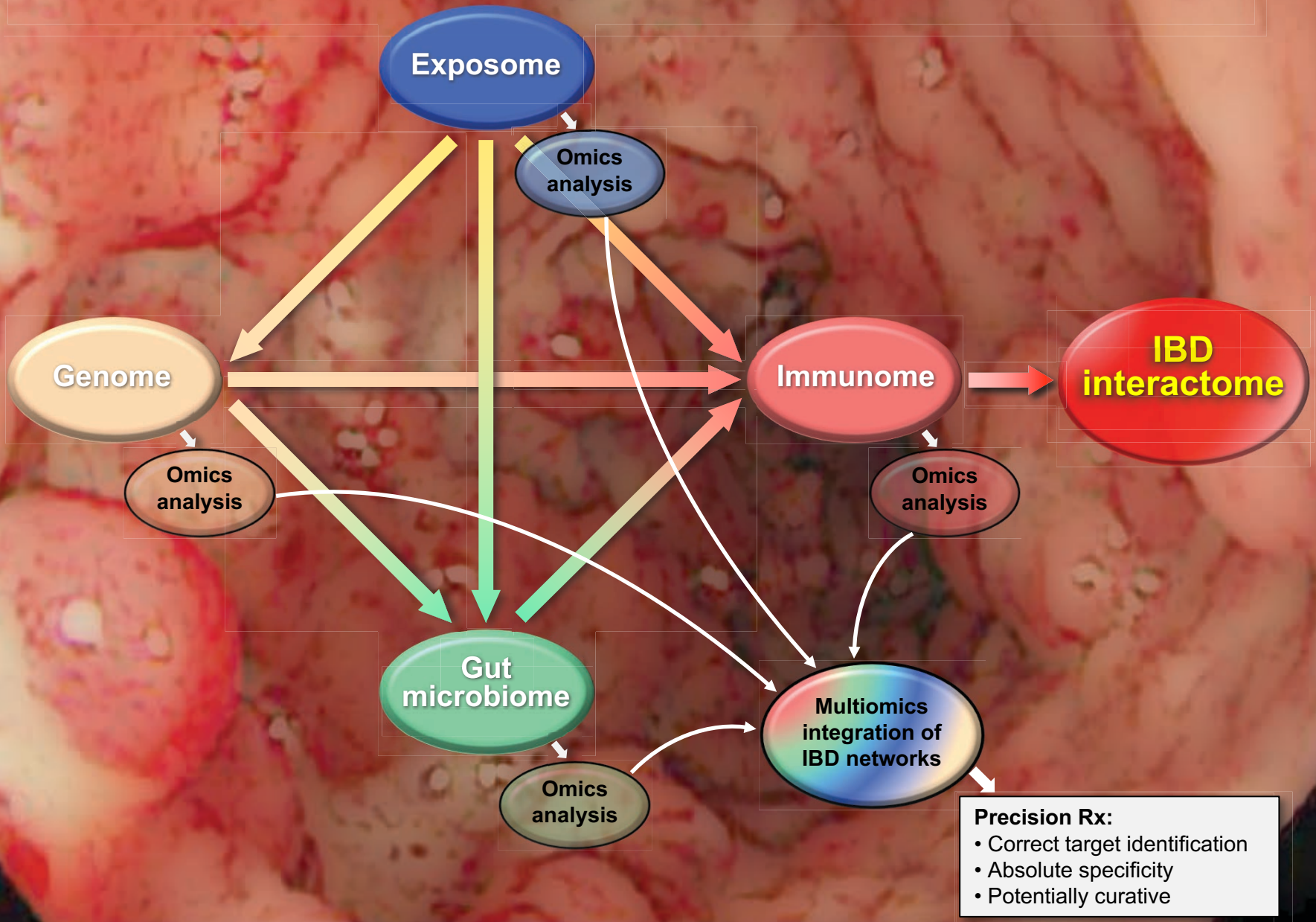
Kraljevic S et al. *EMBO Reports* 2004;5:837-842

A systems biology approach to IBD therapy



Courtesy of Dr. D. Iliopoulos

The future of IBD: a therapeutic approach based on systems biology



Thank you!