

# Crohn Disease : from gene to therapy

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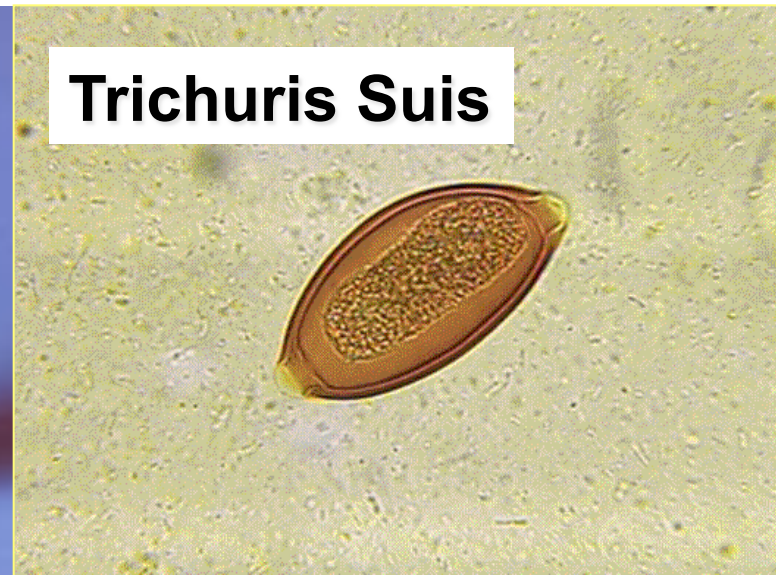
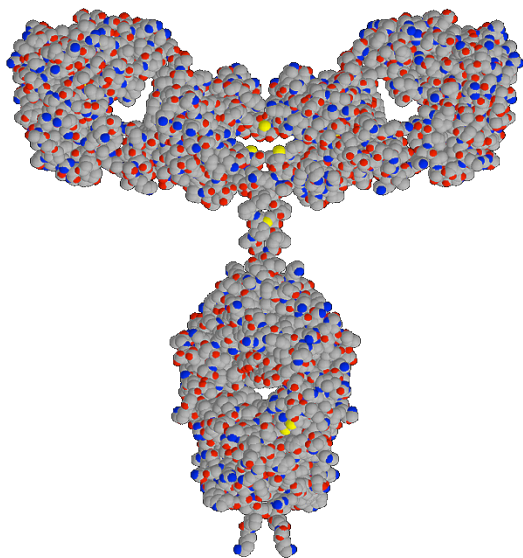


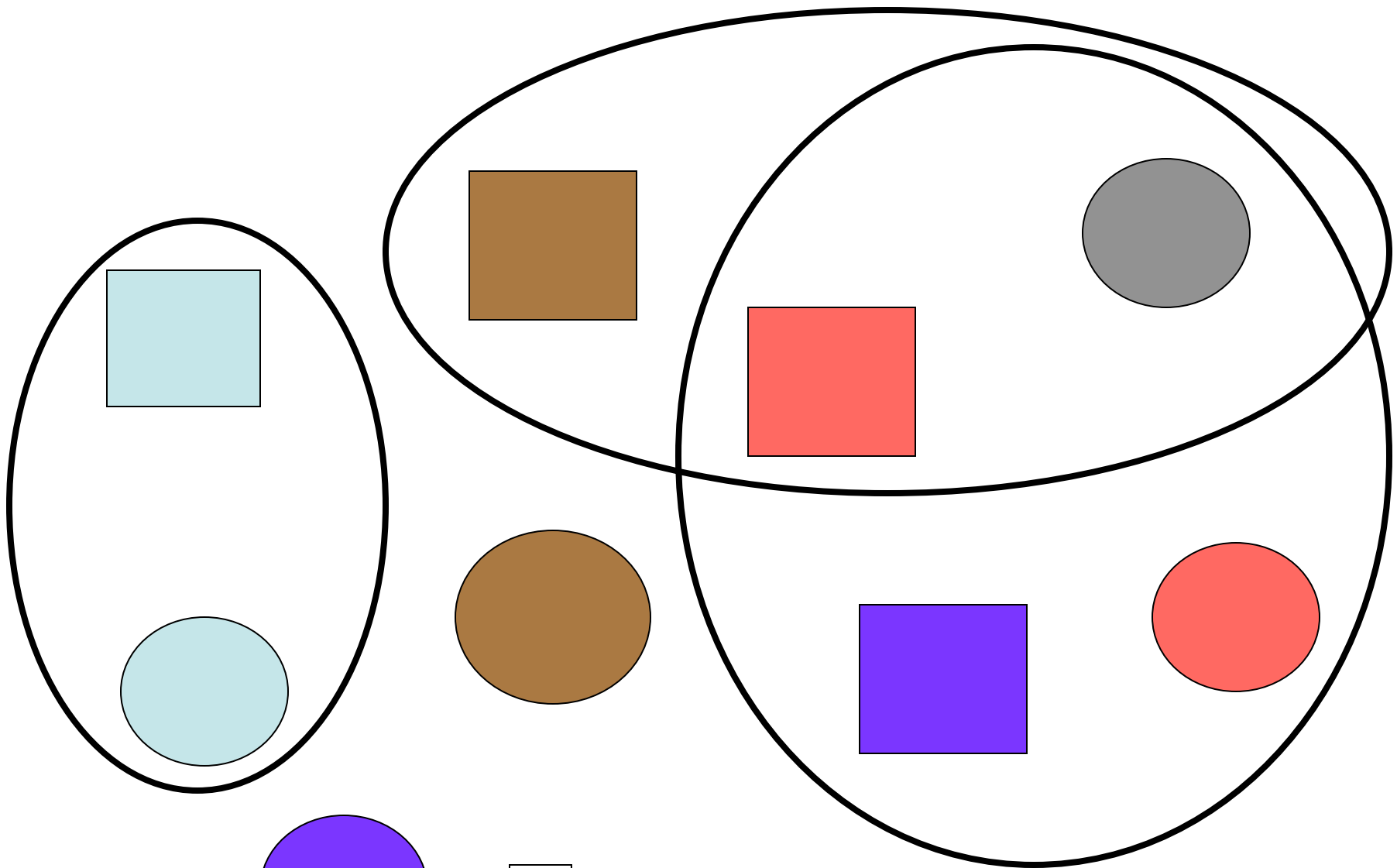
**Gordon Oppenheimer, Burill B Crohn and Leon Ginzburg, 1969**

From « BB Crohn, Life and Work », Falk Foundation 2000

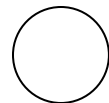
# Treatments for Crohn Disease

- Antibiotics
- Probiotics
- Nutritional support
- 5 amino-salicylates
- Steroids
- Immunosuppressive drugs
- Antibodies against TNF and other chemokines (IL12, ICAM,  $\alpha$ 4integrins)
- Pig parasites





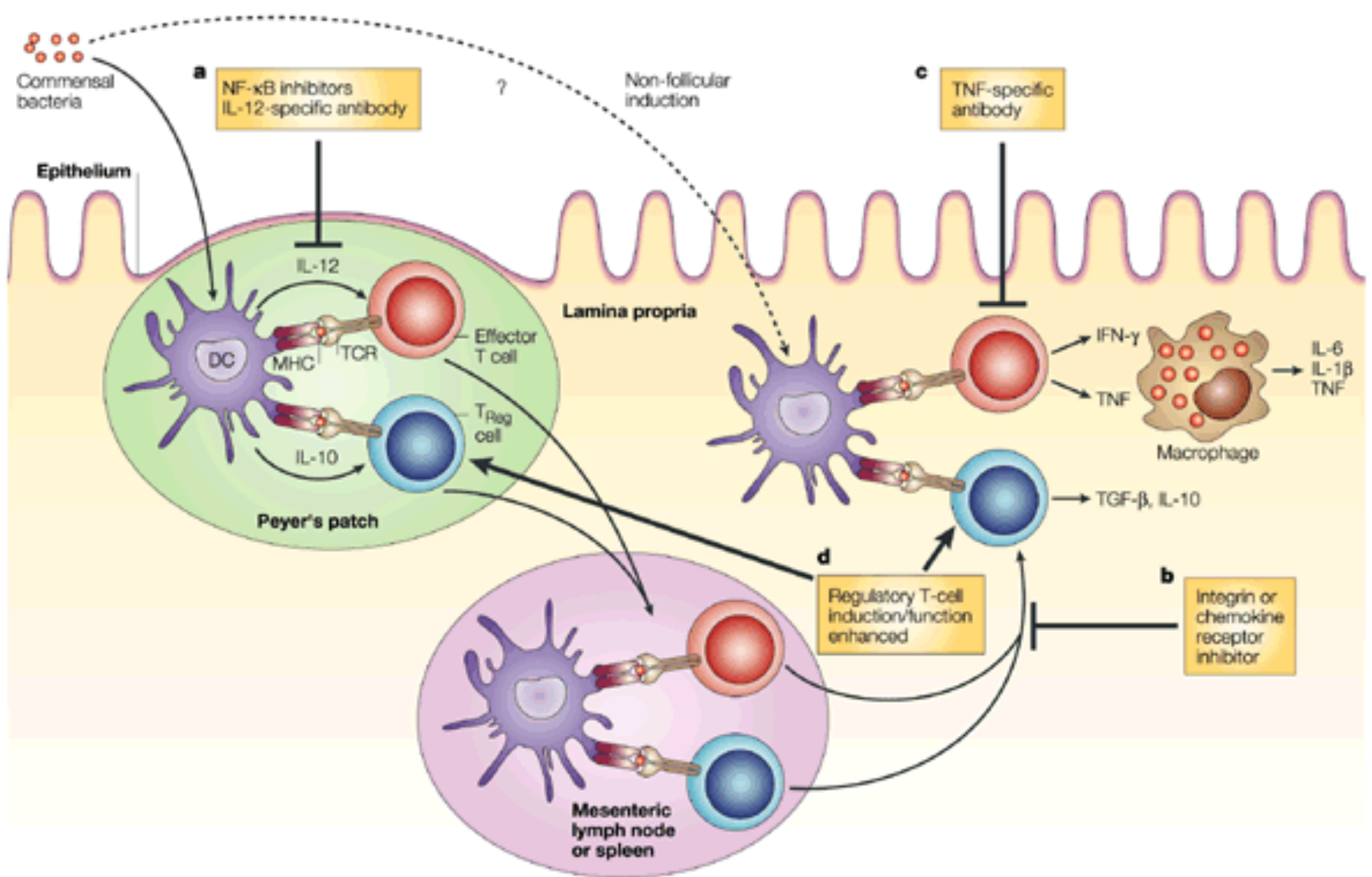
**Environnemental factor**



**Genetic factor**

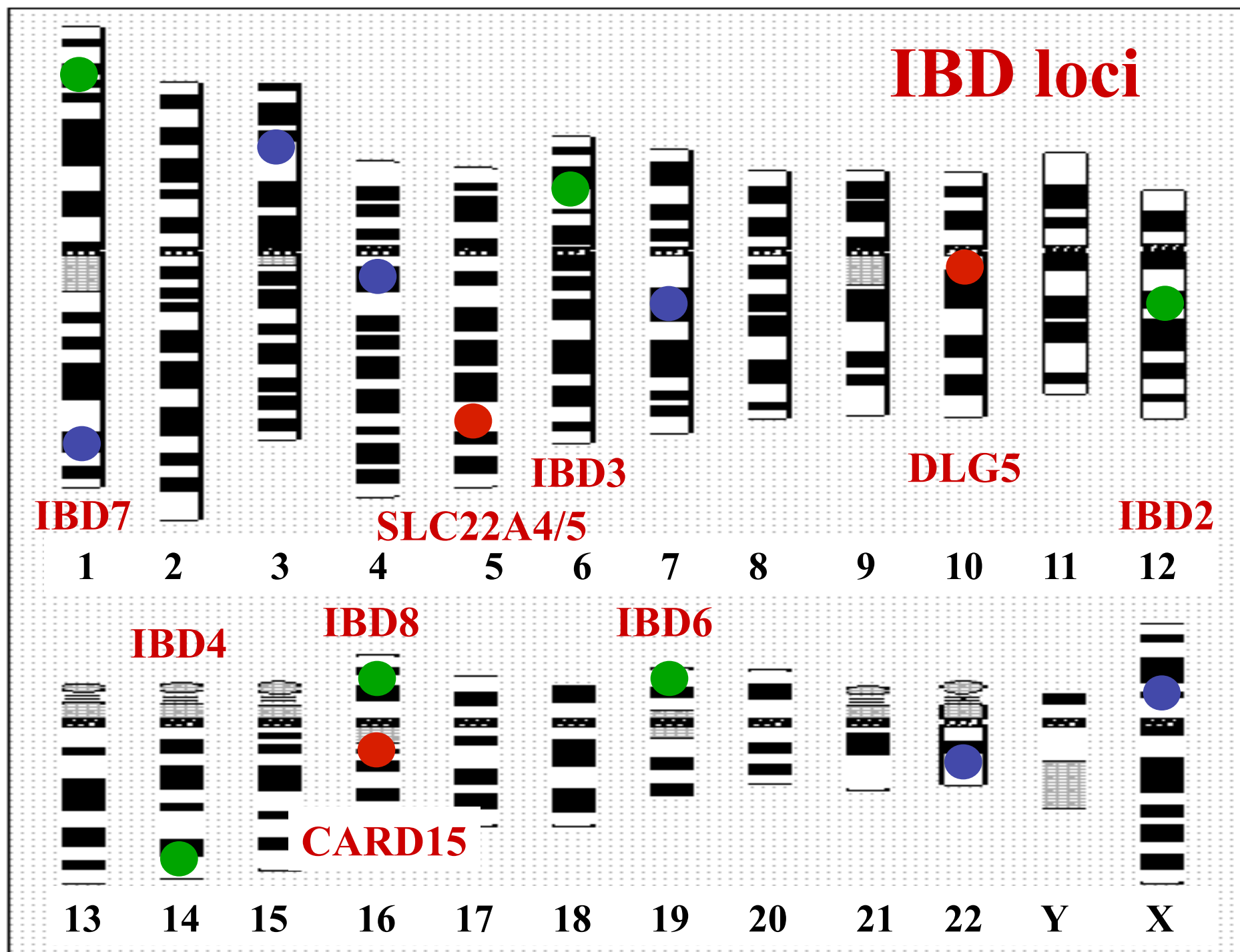






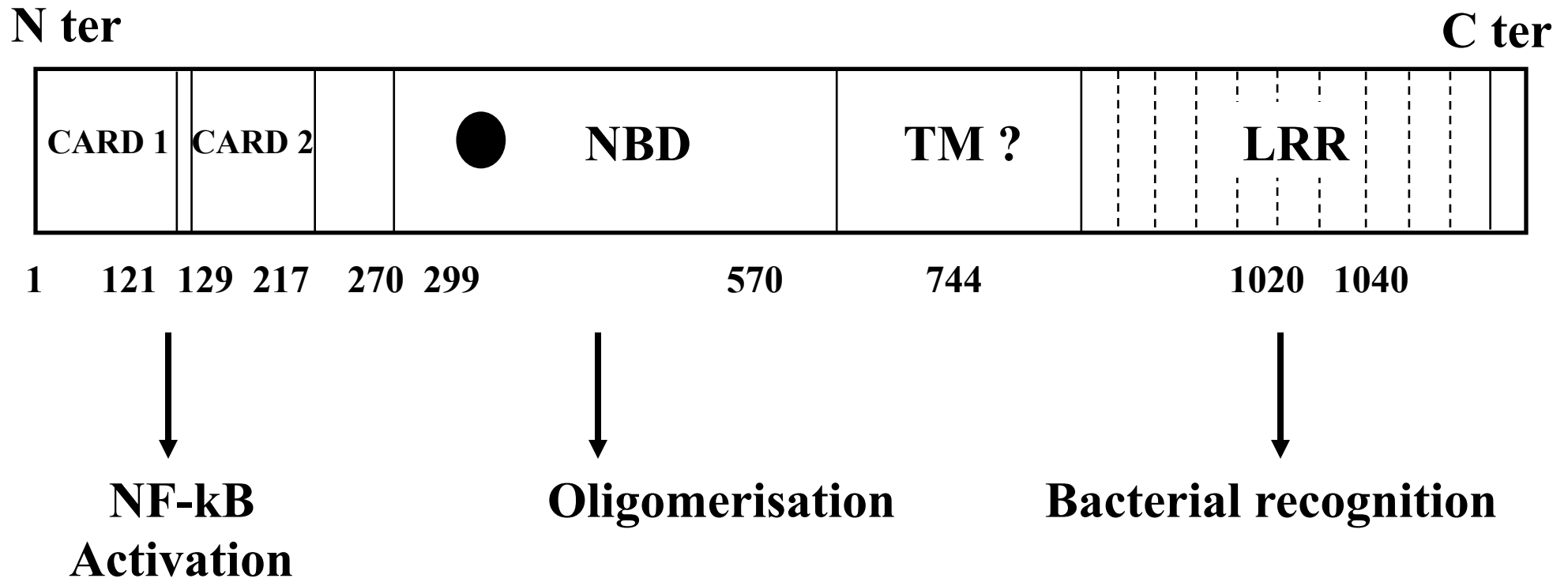
Bouma G et al. Nature Rev Immunol 2003







# *Ibd1-Nod2-Card15*

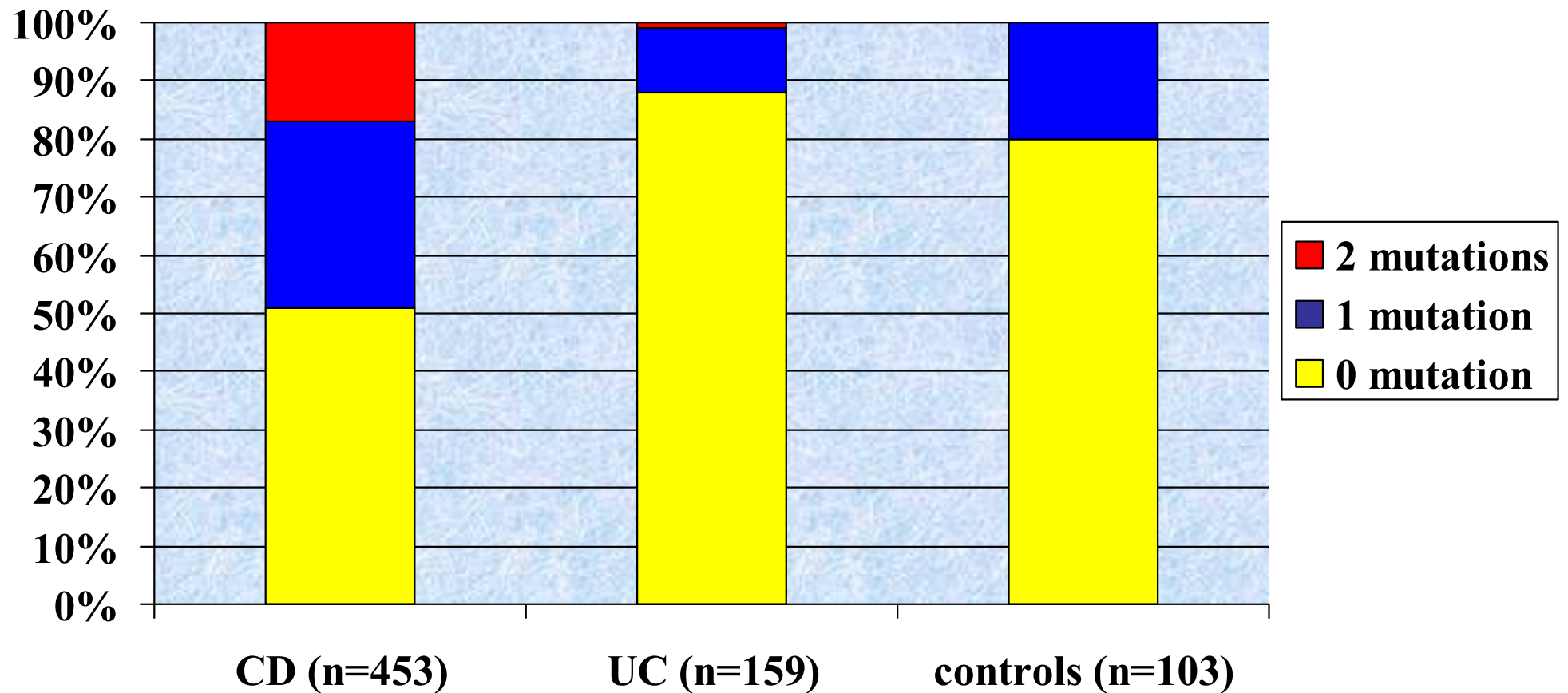




# Why to discover genes?

- To make a diagnosis
  - **Before disease occurrence (if prevention possible) or to avoid invasive procedures (sensitivity, sensitivity).**

# Proportion of mutated patients (all non conservative variations \*)



\*except P268S



# Why to discover genes?

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  - **To classify the disease (definition of disease subgroups)**

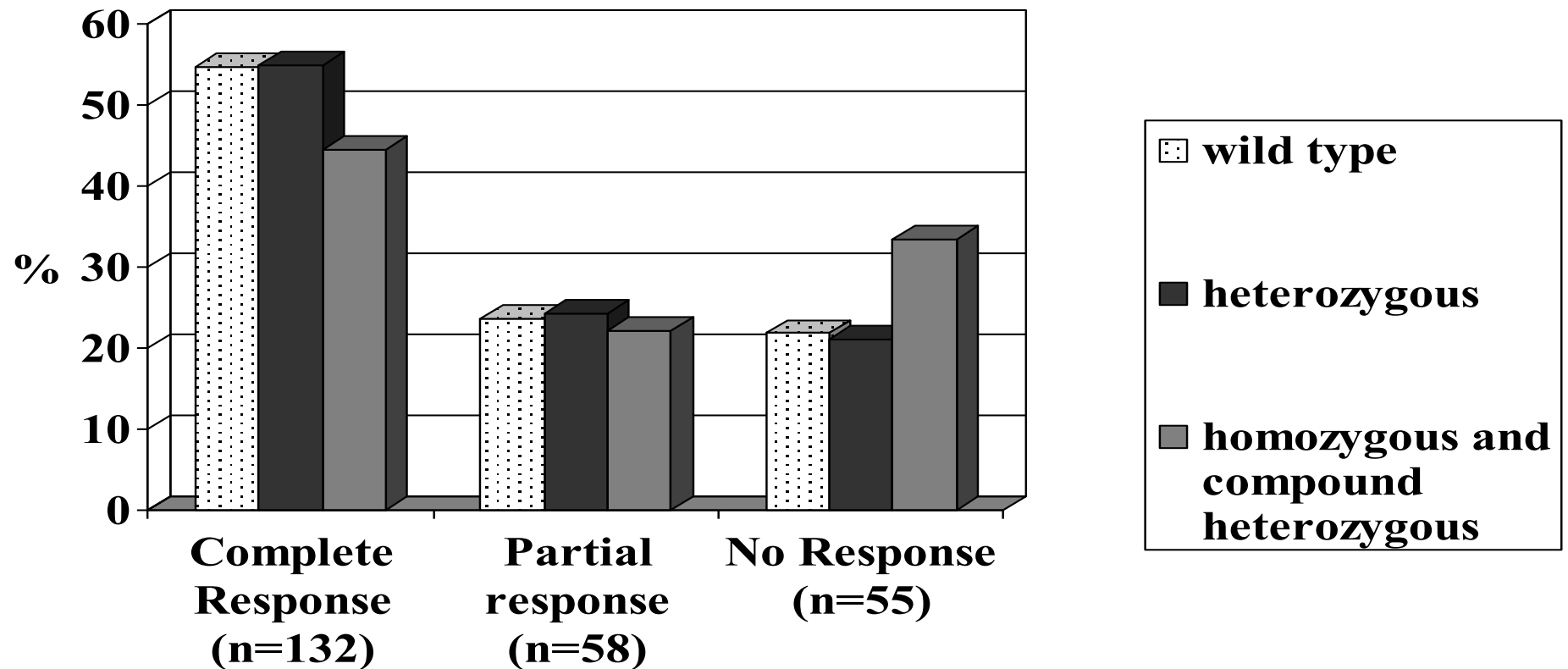
# NOD2/CARD15 mutations are associated with :

- A younger age of onset
- A more frequent ileal involvement
- An higher complication rate
  - Lesage et al. Am J Hum Genet 2002
  - Vermeire et al. Am J Hum Genet 2002
  - Cuthbert et al. **Gastroenterology 2002**
  - Hampe et al. Lancet 2002
  - Amhad et al. Gastroenterology 2002
  - Abreu et al. Gastroenterology 2002
  - Louis E et al. Gut 2003

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  - To classify the disease (definition of disease subgroups)
- To develop a treatment
  - Gene therapy (in the future?)
  - **Pharmacogenetics**

# Genotype/phenotype relationship : response to Infliximab.

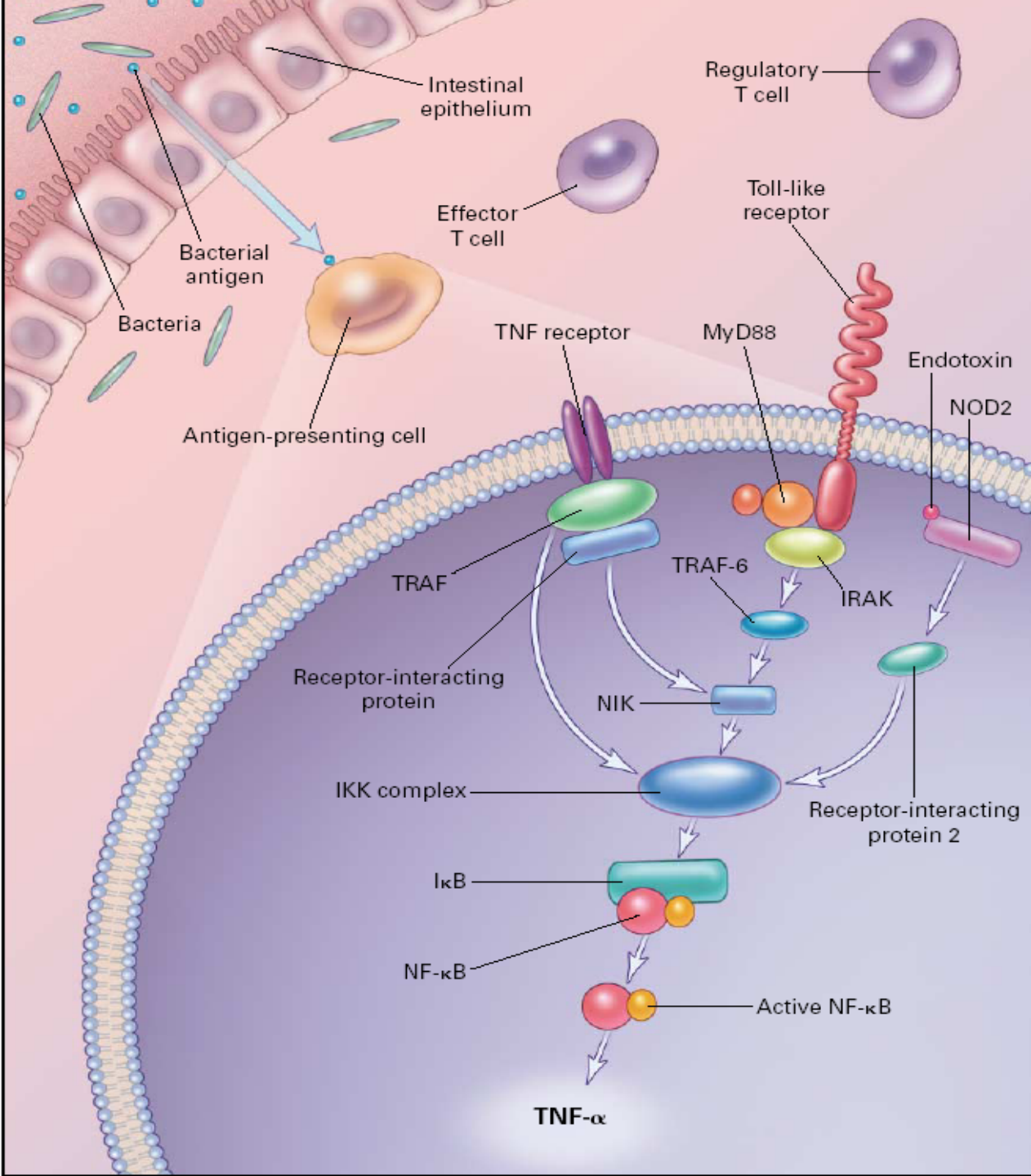


Vermeire S et al. Gastroenterology in press

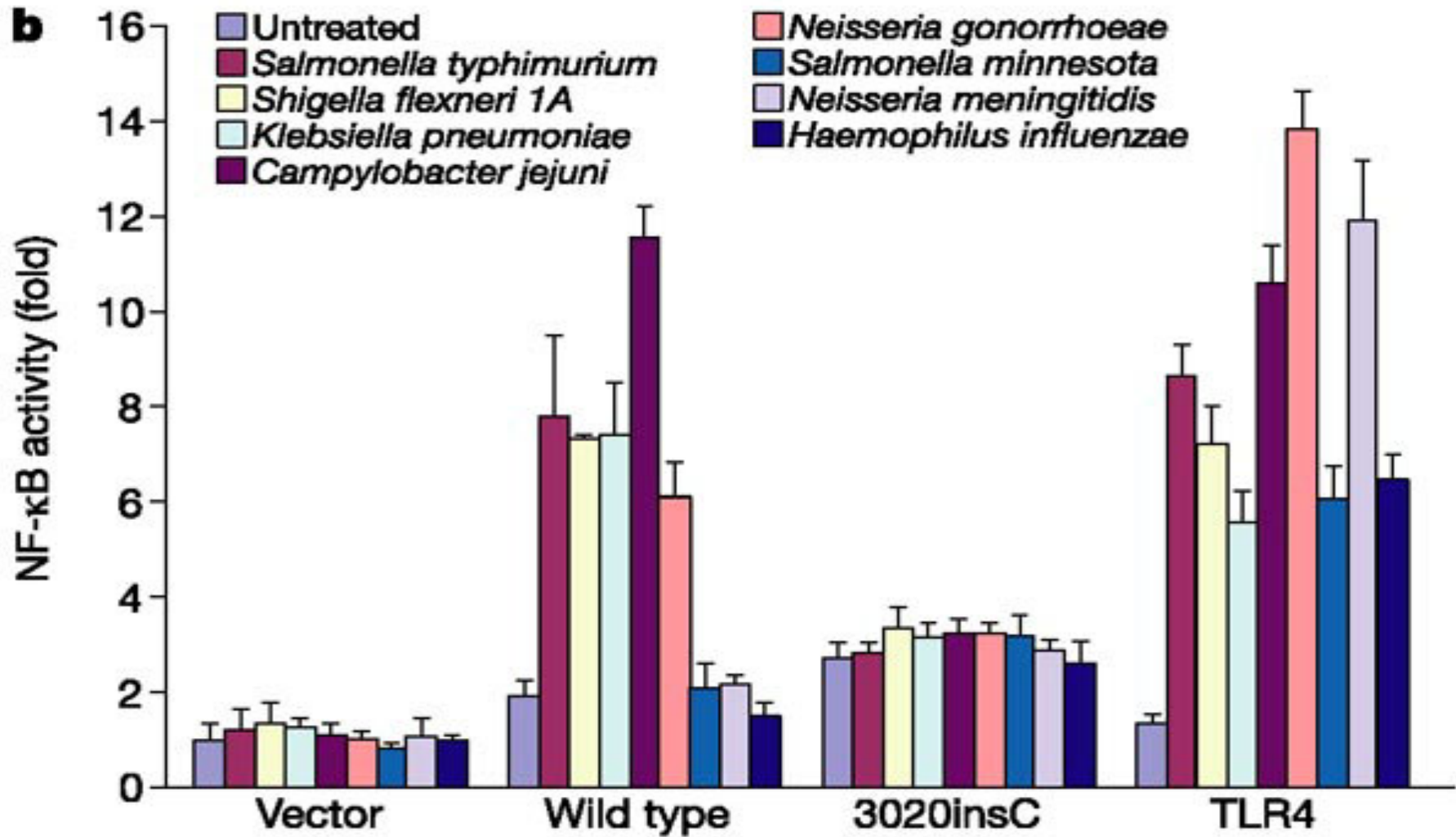


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  - Pharmacogenetics
  - **Drug discovery (disease mechanisms)**

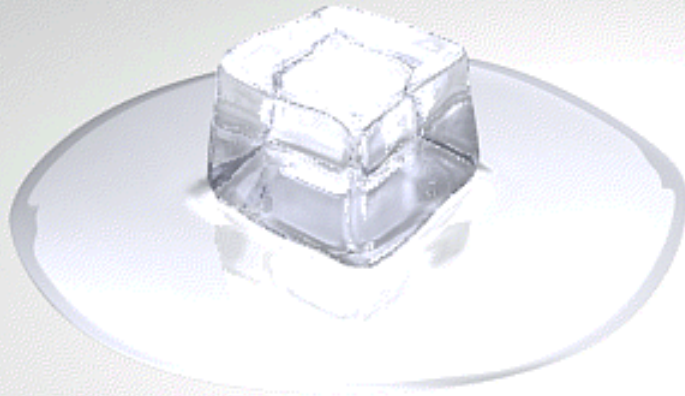


**From Elson C.  
N Eng J Med 2002**



From Ogura et al. Nature 2001

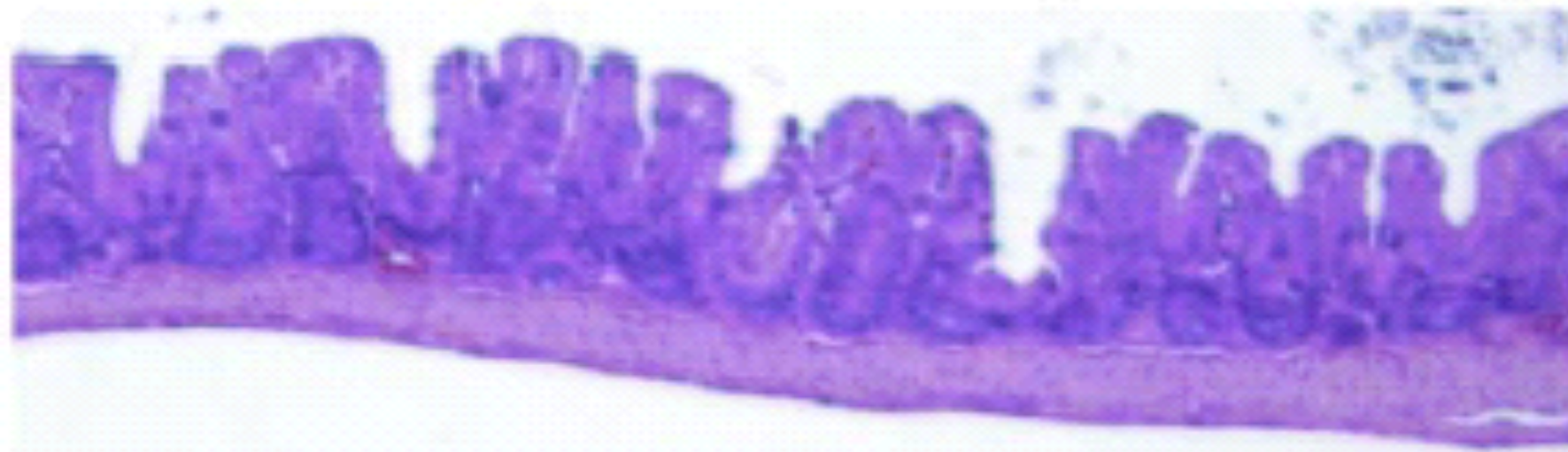
**How a defect in a  
proinflammatory molecule...**



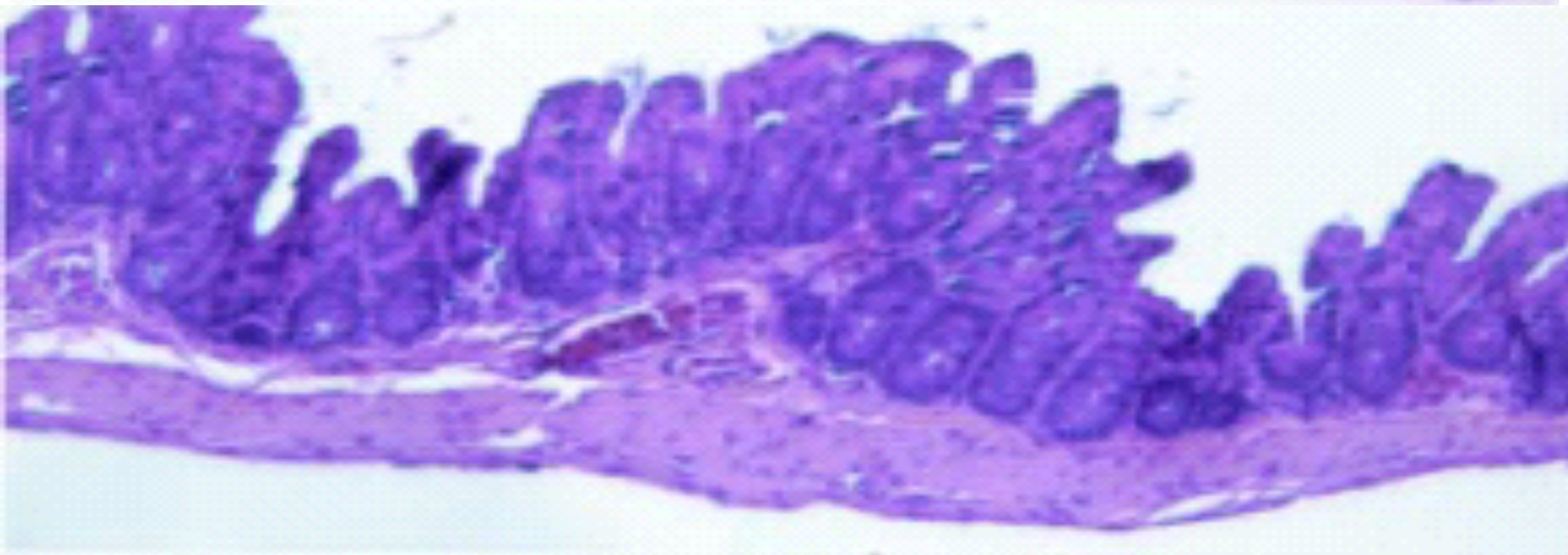
**..can induce an inflammation?**



# CARD15 $-/-$ mouse

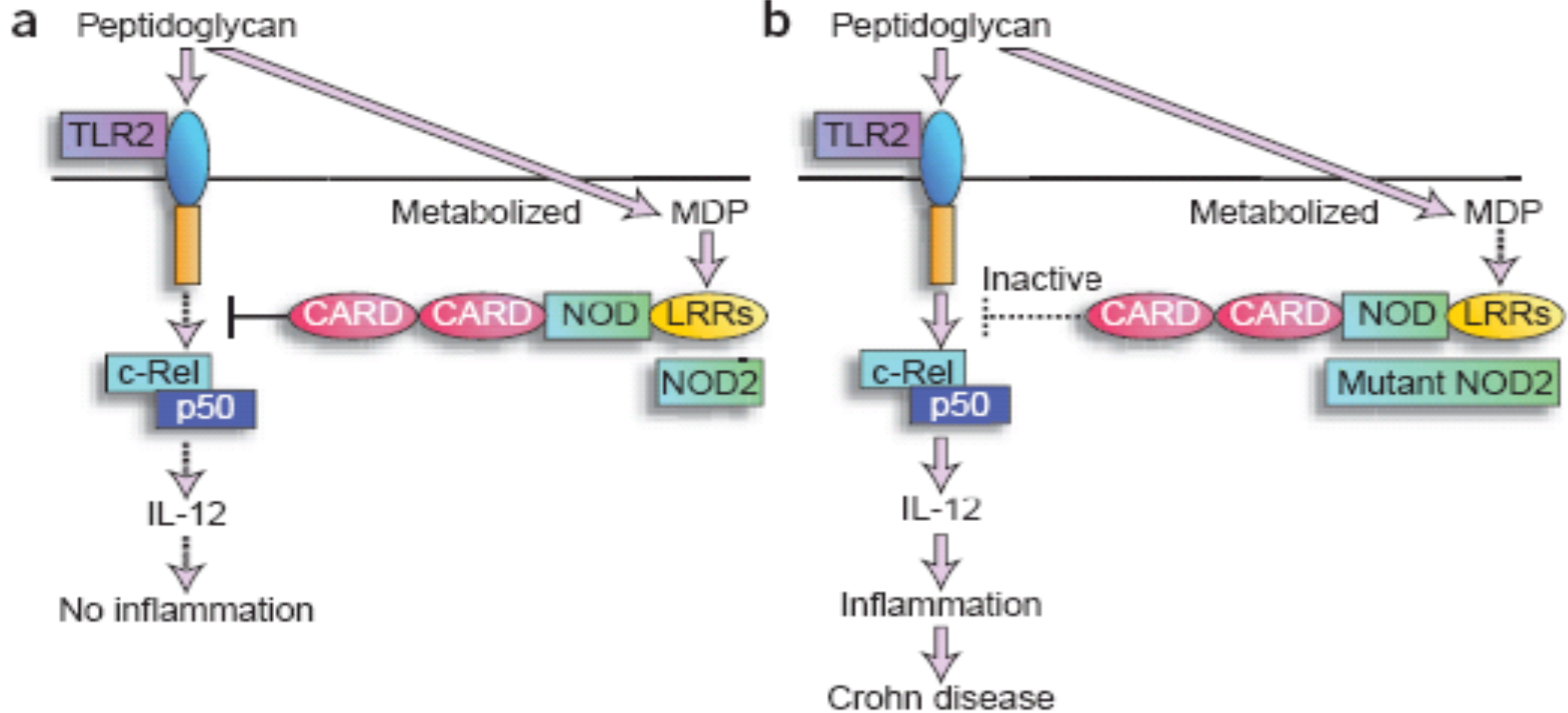


$+/+$



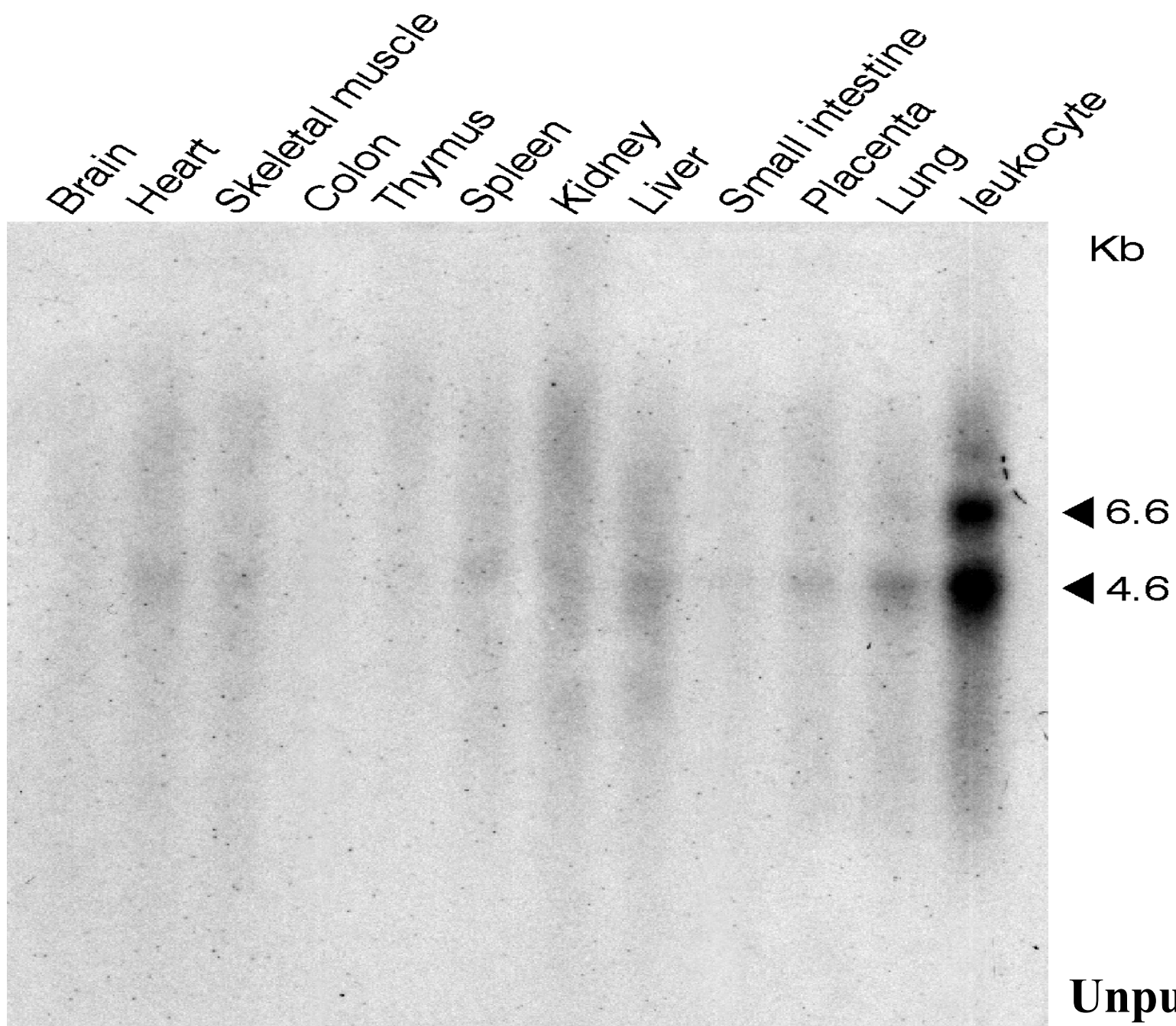
$-/-$

# Interaction between TLR2 and NOD2



# How CD mutations induce the inflammation?

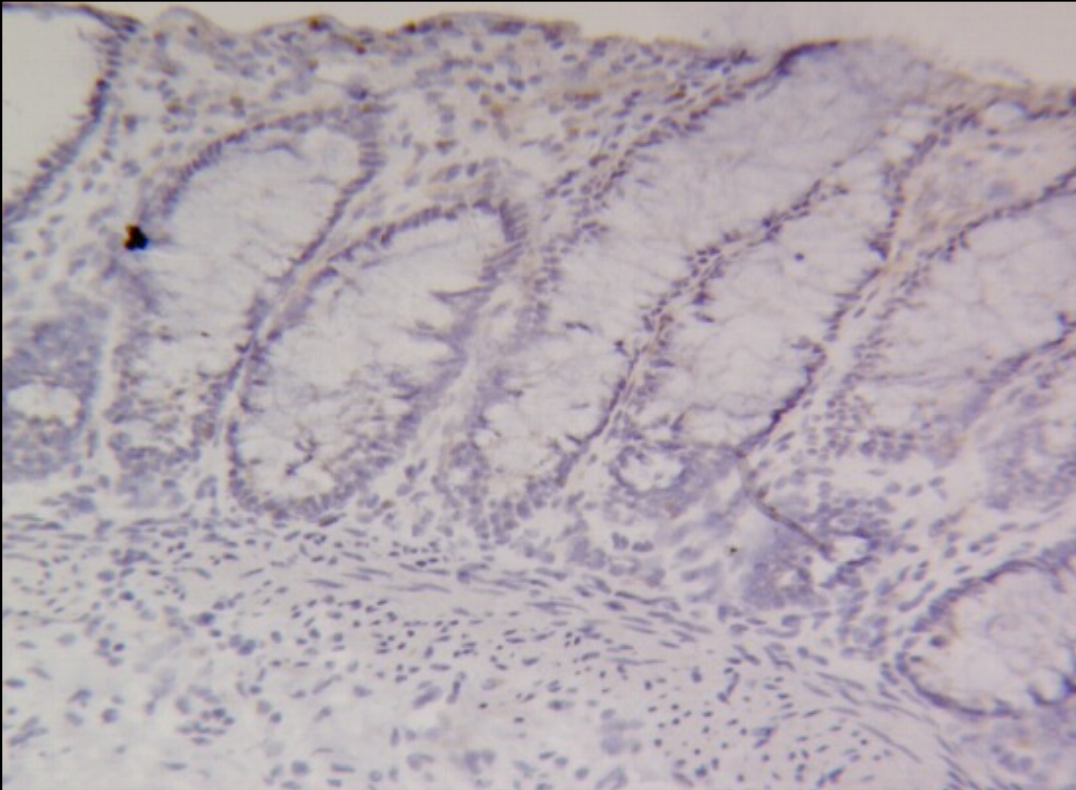
- A defect in the innate immunity induces an excess of response by the adaptive immunity which is deleterious for the mucosa.
- CD mutations are gain of function mutations (Maeda S Science 2005)
- CD mutations do not inhibit pro-inflammatory pathways (Watanabe T Nature Immunol 2004; Chen CM J Biol Chem 2004)
- CD mutations no more activate anti-inflammatory pathways (IL10) (Netea MG Eur J Immunol 2004)



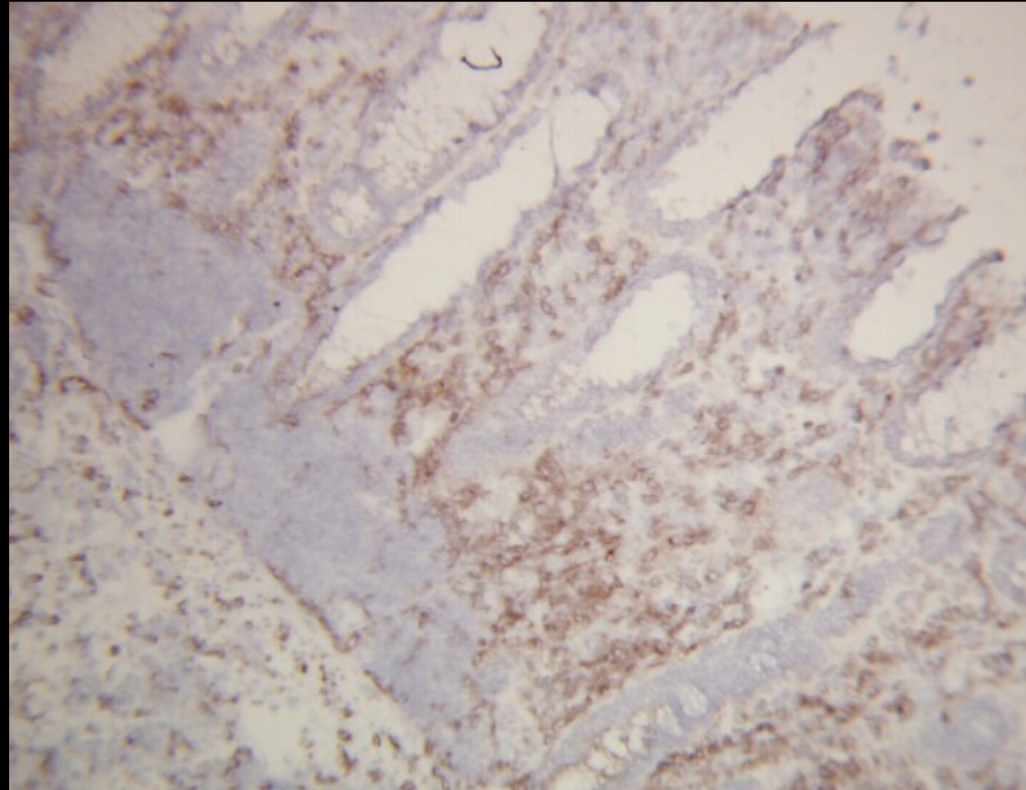


# CARD15 immunohistochemistry

normal colon

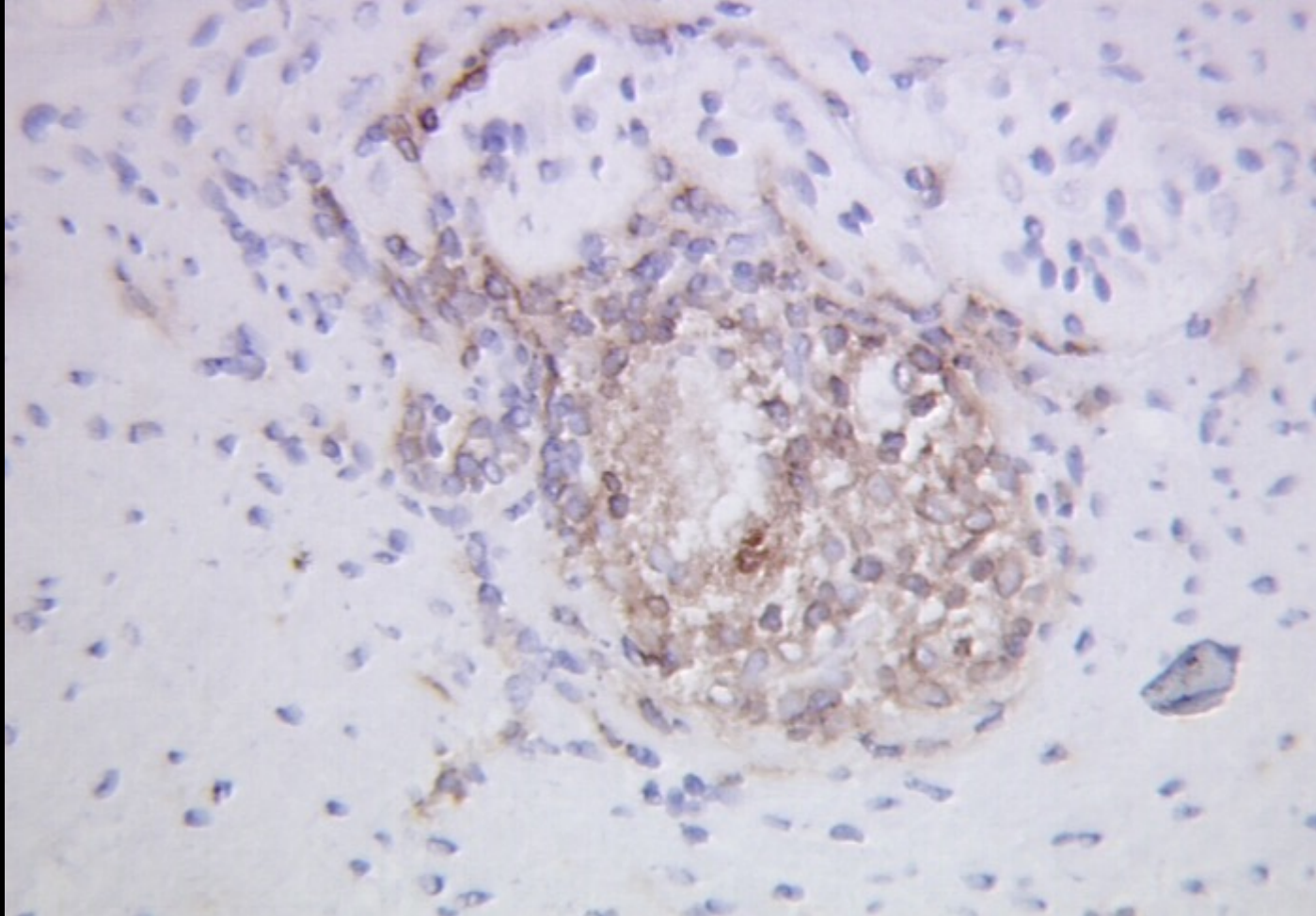


Crohn



Berrebi D et al. Gut 2003

# Card15 immunohistochemistry

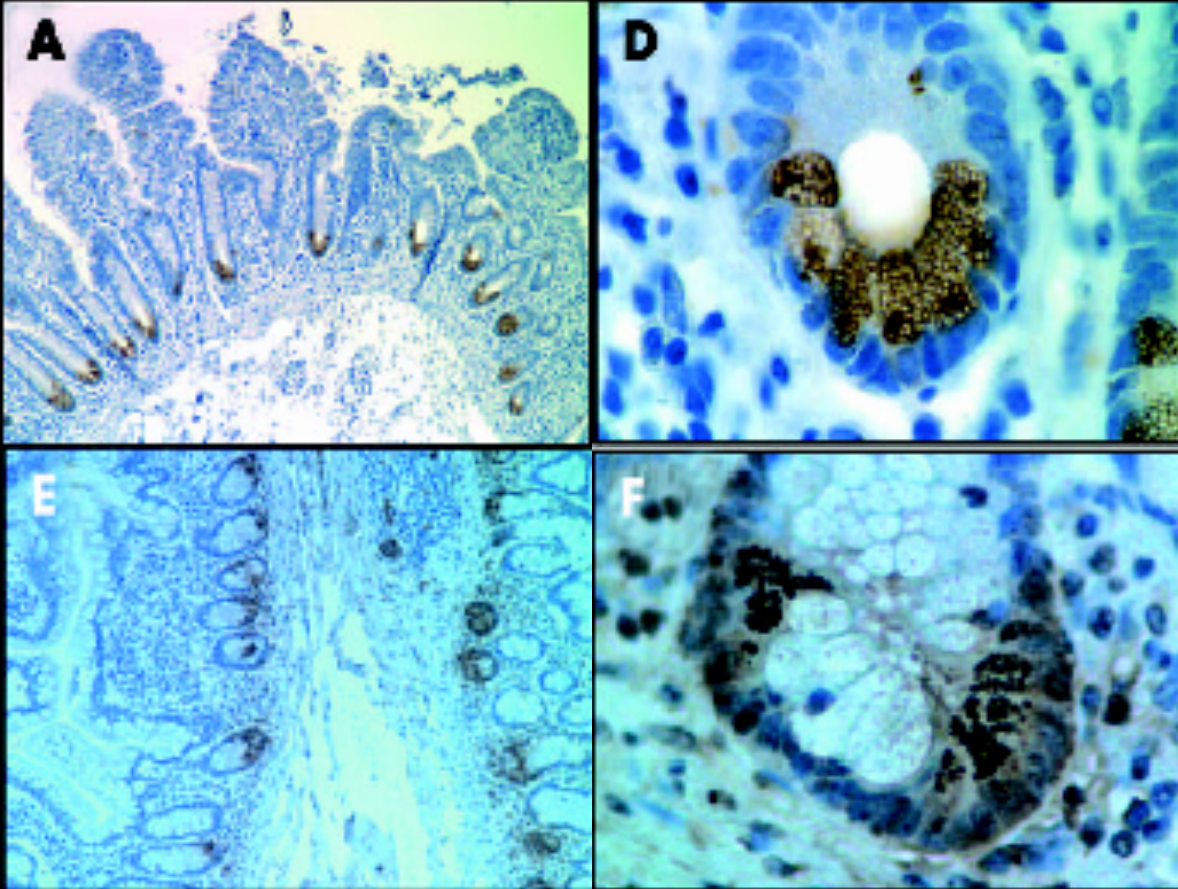


Berrebi D et al. Gut 2003



# NOD2 and Paneth cells

Crohn normal ileum



**Card15**

**Lysozyme**

Ogura Y et al. Gut 2003

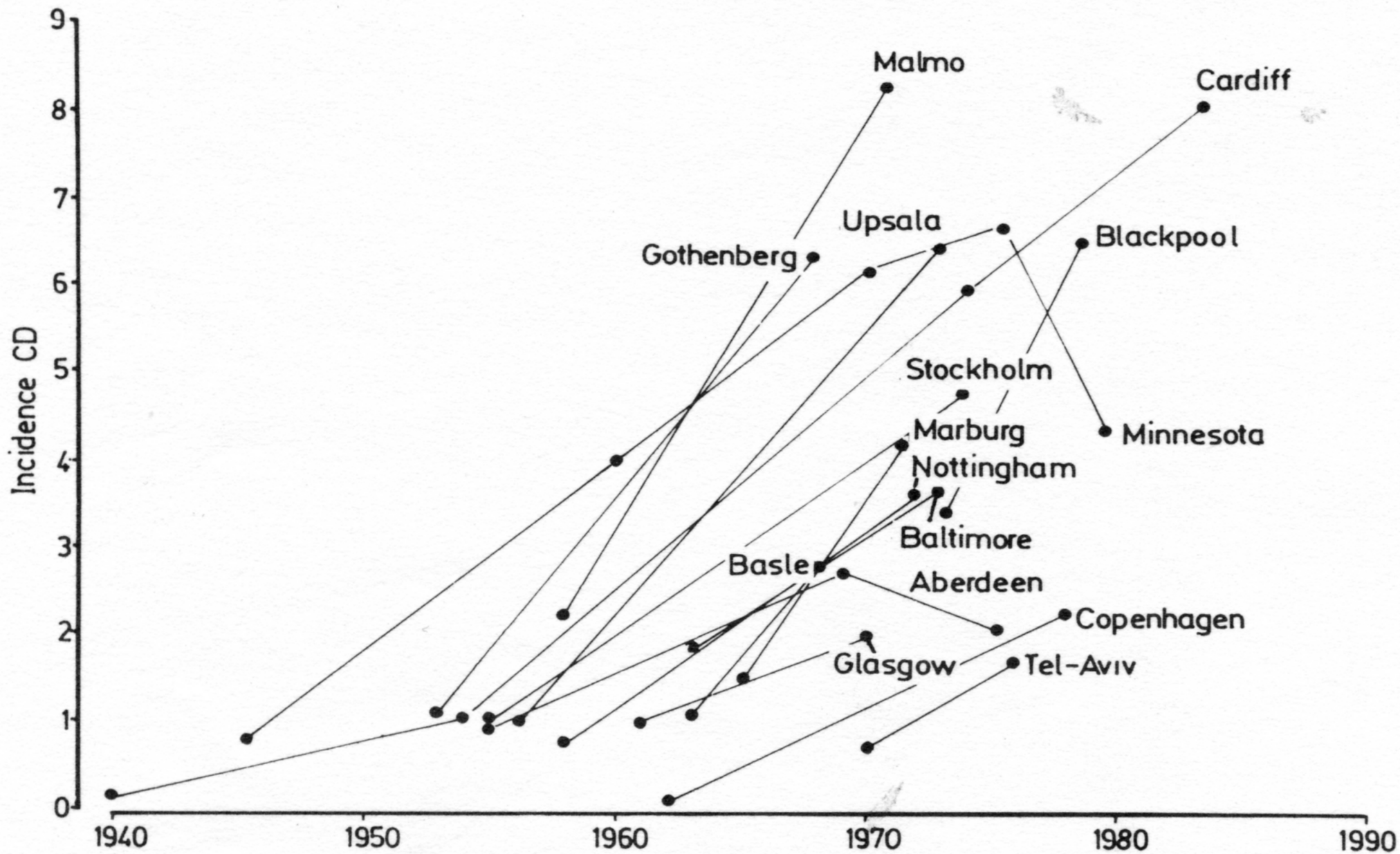
# Screening for Card15/Nod2 interacting small molecules

- Loss or gain of function?
- Which cell line?
- Role of MDP?

Toward a specific curative therapy?

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  - To classify the disease (definition of disease subgroups)
- To develop a treatment
  - Gene therapy (in the future?)
  - Pharmacogenetics
  - Drug discovery (disease mechanisms)
  - **Prevention (environmental factors)**



From Rose J et al. Gut 1988



# ENVIRONMENTAL FACTORS FOR CD

- **Tobacco**
- Refined sugars
- Fast-food and Cola
- Microparticles
- Tooth paste
- Chewing-Gum
- Margarin
- Fibres
- Backer yeast
- Alcohol
- Caffè
- Corn-flakes
- Curry
- Hot water
- Refrigeration
- Perinatal Infections
- Infections in childhood
- Antibiotics
- Adenoïdectomy
- Breast feeding
- Life events
- Oral contraceptives



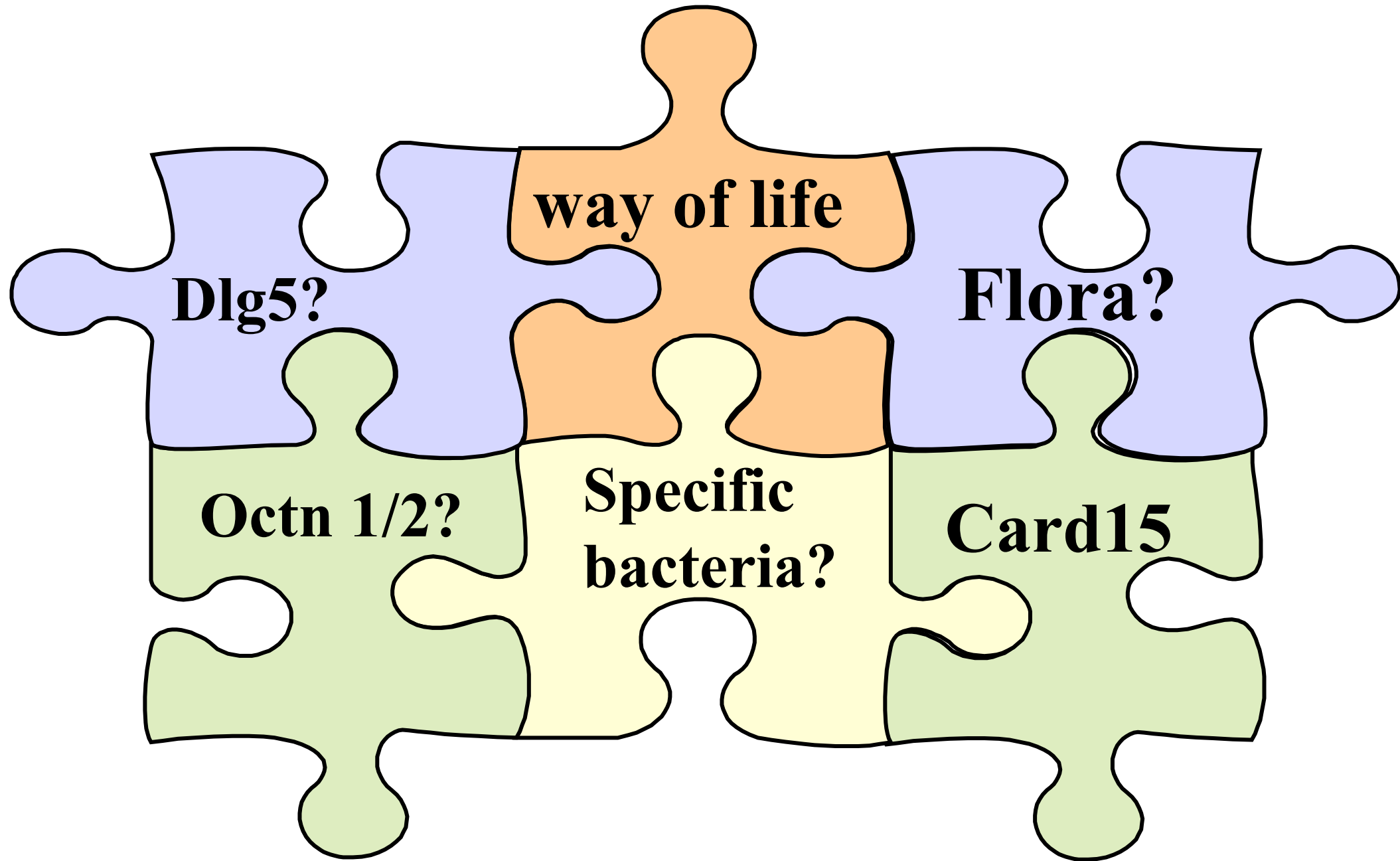
Commensal flora....

Or specific pathogenic bacteria ?



# Most popular infectious agents for CD

- *Mycobacterium paratuberculosis*
- *E coli*,
- *Y enterocolitica*
- *L monocytogenes*
- *Pseudomonas species*



**way of life**

**Dlg5?**

**Flora?**

**Octn 1/2?**

**Specific  
bacteria?**

**Card15**

