What’s Hot in IBD Research
“Future Therapies for IBD”

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Determinants of Gut Microbiota

- Environment
- Genetics
- Host Phenotype
- Antibiotics
- Inflammation
- Diet
Clinical Relevance of Diet and IBD

- CCFA maintains an Information Resource Center that receives more than 14,000 inquiries per year, of which, approximately 65% ask for dietary advice

- Patients desire therapies that do not suppress the immune system

- Diet and the gut microbiota are the two biggest environmental factors to which the gut is exposed
Diet is associated with new onset IBD

- High dietary intakes of total fats, PUFAs, omega-6 and meat were associated with an increased risk of CD and UC.

- High fiber and fruit intakes were associated with decreased CD risk.

- High vegetable intake was associated with decreased UC risk.

Enteral Nutritional Therapy For IBD

• A therapy which has been used for almost 4 decades

• Formula most often administered through an NG tube

• Exclusive (100% of calories) for a defined period of time versus...

• Partial (80-90% of calories) with the remainder of calories from normal food

Polymeric Diet Alone vs. Steroids for Active Pediatric Cron’s Disease (Induction Therapy)

Methods (n=37)
Prospective 10 week randomized controlled open-label trial
Newly diagnosis children receive:
    polymeric formula (n=18) or steroids (n=19)

Primary outcomes at 10 weeks
Clinical remission (PCDAI≤10)
Mucosal healing

Polymeric Diet Alone vs. Steroids for Active Pediatric CD (Induction Therapy)

- Clinical improvement
- Healing of GI tract

- Enteral nutrition
  - n=19

- Corticosteroids
  - n=18

Methods: 15 children with active CD

- 8 ileo-colonic
- 7 ileum
- 9 onset
- 6 relapse

In all patients CE was performed before and after an 8 week course of exclusive EN with the polymeric formula.
To assess the capacity of Enteral Nutrition to induced small bowel mucosal healing by Capsule Endoscopy

Results: clinical remission in all patients
To assess the capacity of Enteral Nutrition to induced small bowel mucosal healing by Capsule Endoscopy
Can a semi-vegetarian diet prevent relapse of Crohn’s disease?

- **Daily**
  - rice, miso soup
  - egg, yogurt, milk
  - vegetables, fruit, legumes, algae
- **Fish** once a week
- **Meat** once every 2 weeks

Can a semi-vegetarian diet prevent relapse of Crohn’s disease?

Prevention of Post-op Recurrence with Enteral Nutrition for CD

Methods: (prospective, control study)
After resection for ileal or ileocolonic CD

Patients received either:
50% of caloric needs from overnight elemental NG feed for 1 year (n=20)

OR

Normal diet (n=20)

Prevention of Post-op Recurrence with Enteral Nutrition for CD

At 1 year

Therapeutic Programs in IBD
Therapeutic Programs in IBD

Green: programs with a positive outcome
Orange: potentially effective with ongoing programs
Red: programs with negative outcomes

Danese S Gut 2012;61:918-932
The therapeutic pipeline in Crohn's disease.
The therapeutic pipeline in ulcerative colitis.
Therapies for IBD: The Pipeline

- Anti-TNF
  - Golimumab for UC

- Anti-Selective Adhesion Molecule
  - Anti-integrin antibodies
    - Vedolizumab (anti-α4β7)
    - Anti-β7
    - Anti-MAdCAM-1

- Chemokine antagonists
  - CCX282-B (Antagonist to chemokine receptor 9)

- Anti-Interleukin 12/23
  - Ustekinumab (CNTO 1275)

- Antagonist to Janus kinase 3 (JAK 3)
  - CP-690, 550
Humanization of Anti-TNF agents

Adapted from Rutgeerts Gastro 2009;136:1182
Adhesion Molecule Inhibition as an IBD Therapy

Reduced Leukocyte Infiltration and Gut Inflammation

Leukocyte Chemoattractant Signal

α4β7

α4β1 (VLA-4)

Blood Vessel Lumen

Endothelial Cells

Tissue

VCAM-1

MAdCAM-1

Reduced Leukocyte Infiltration and Gut Inflammation

Blocked
Anti-adhesion Therapy
\(\alpha 4\) integrin/VCAM-1 and MAdCAM-1 Pathway

- **Vedolizumab:**
  - Unique recognition of \(\alpha 4\beta 7\) in distinction to \(\alpha 4\) (Natalizumab)
  - Possible safety advantage due to increased gut specificity
Leukocyte Adhesion

Adapted from Rutgeerts et al. Gastro 2009;136:1182
Chemokine receptor 9 inhibitor: CCX-282B

Leukocyte Adhesion is a Multistep Process

Chemokines secreted from sites of inflammation diffuse through the endothelial layer and activate Leukocytes.

This process is inhibited by CCX-282B, an oral CCR9 inhibitor.

Adapted from Rutgeerts et al. Gastro 2009;136:1182
Inhibition of the Interleukin-12/23 Pathway

Adapted from Rutgeerts et al. Gastro 2009;136:1182
Tofacitinib (CP-690,550) an Oral Janus Kinase 3 Inhibitor

JAK3/γc inhibitors will block signalling by six cytokines

Receptors signalling through JAK3
IL-2
IL-4
IL-7
IL-9
IL-15
IL-21
Refining The Role of Serological Immune responses: Targeting Therapy

Clinical Phenotypes

Gene I
Gene II
Gene III

IBD 1
IBD 2
IBD 3

Bacteria X
Bacteria Y
Bacteria Z

Rx IBD1
Rx IBD2
Rx IBD3

Mild → Severe
Conclusion

- Targets which hold a great promise for the future include:
  - beta 7 integrin/MAdCAM-1
  - chemokine receptor 9
  - the p40 subunit of interleukin 12/23
  - JAK3
  - Diet??