Promise and Pitfalls of Microbiome-Modulating Methods for Inflammatory and Autoimmune Diseases

Arpita Maiti, PhD
Senior Director, External Science & Innovation
Pfizer Inc.

June 29, 2017
Boston
Forward-looking Statements

• This presentation includes forward-looking statements about, among other things, development of Pfizer’s products and product candidates, including their potential benefits, expected clinical trial study starts and expected regulatory submissions and approvals that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Additional information regarding these factors and other risks can be found in Pfizer’s most recent Annual Report on Form 10-K and subsequent reports on Form 10-Q and 8-K, all of which are available at www.sec.gov and www.pfizer.com.

• The forward-looking statements in this presentation speak only as of the original date of this presentation, and Pfizer undertakes no obligation to update or revise any of these forward-looking statements.
Factors affecting the stability and complexity of the gut microbiome in health and disease

Kostic A D et al. Gastroenterology 2014
Theme for today

- Correlation
- Causality
- Mechanism of Action
Dysbiosis is evident in the gut, salivary and oral microbiome in rheumatoid arthritis

Gut microbiome of control vs. RA patients

Microbiome as biomarker – MTX reversed dysbiosis / correlated to clinical markers

Zhang et al. Nat Med. 2015
Differential expression of multiple metabolic pathways in IBD patients vs. healthy individuals:

- Decrease in metabolism of short chain fatty acids (propionate and butyrate)
- Increase in Lipopolysaccharide biosynthesis
- Increase in β-lactam resistance metabolism

Morgan et al. Genome Biology 2012
Alterations in the gut virome in IBD

The enteric virome is abnormal in multiple inflammatory bowel disease patient cohorts.

The enteric virome richness increases in Crohn’s disease and ulcerative colitis.

Decreases in bacterial diversity and richness in IBD do not explain virome changes.

Virome changes in Crohn’s disease and ulcerative colitis are disease specific.

Norman et al. Cell 2015
Microbiome diversity and dysbiosis affect vaccine responses – the other side of the immunity coin


Oh et al. Immunity 2014
Immunotherapy responses are affected by the microbiome

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy
Microbiome / bacterial metabolites regulate cellular functions

Mechanisms by which bacterial metabolites affect biology

- Dietary fiber
- Acetylated histones, non-histone proteins
- SCFAs
- Metabolite-sensing GPCRs
- Immediate biological responses
  - Inhibition of NF-κB
  - Inflammasome activation, IL-18
  - MAP kinases, PI3 kinases

Cell Functions

- Inflammation
- Immune tolerance
- Gut permeability
- Metabolism
- Tissue repair
- Cardiovascular
- Neural functions

Zelante et al. Immunity 2013
Li et al. Cell 2011
Microbiome / bacterial metabolites regulate the immune system

Munn et al. Trends in Immunology 2013
Will the microbiome impact novel tolerogenic therapeutics for autoimmune disease?
What are central challenges on the path to microbiome-based therapeutics?

**Scientific**
- Evidence for causation? Are new associations between microbiome alterations and disease driving disease processes?
- Which bacterially derived molecule(s) drive key phenotypes at physiologically relevant concentrations?
- Are there appropriate experimental systems available to test activity of an individual molecule from a complex environment?

**Regulatory**
- Unclear how the agencies will assess new products *and modalities* as chronic therapies

**Clinical Development**
- How will trials be designed with new modalities and what will be required to demonstrate efficacy?
- Patient selection for trials and design/validation of surrogate biomarkers of efficacy

**CMC**
- Requires different approaches to manufacture product consistently and cross fertilization from other sectors for success

**Commercialization**
- Pricing versus standard of care which will include biologics and biosimilars for inflammatory diseases
- Education of physicians on new therapeutic modalities
- Convincing payers that microbiome-based therapeutics is a cost-effective part of the armory of therapeutics available