

마이크로바이옴 글로벌 연구동향 및 발전방향

November 29, 2018

GwangPyo Ko, Ph.D.

Professor@Seoul National University

Director@SNU Microbiome Center

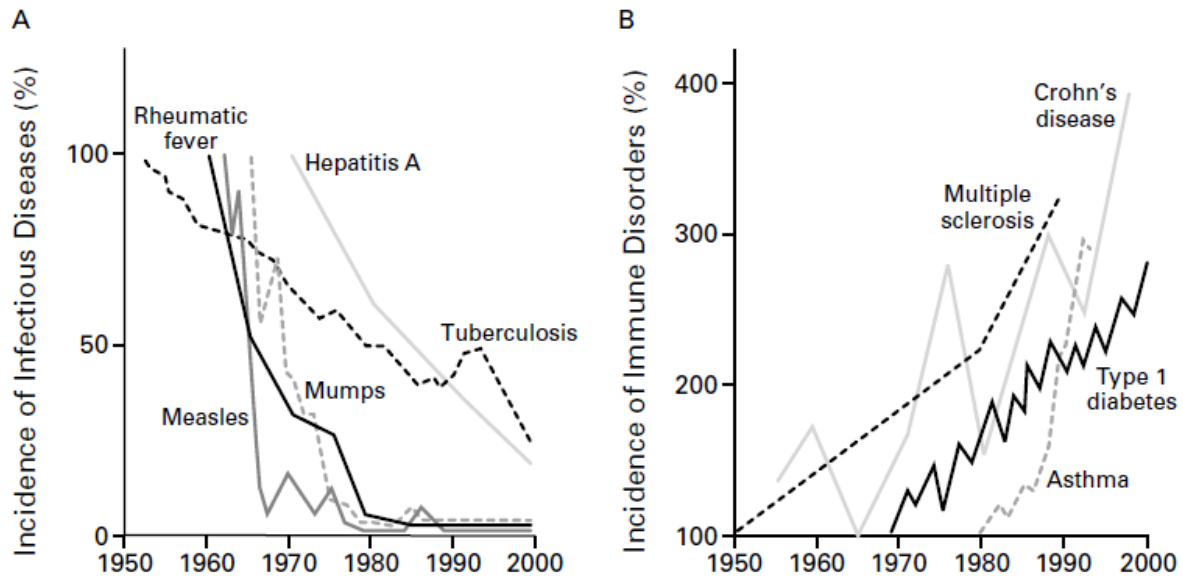
Founder/CEO@KoBioLabs



서울대학교
SEOUL NATIONAL UNIVERSITY



20th세기 인체 질병변화



J. Bach, 2002, NEJM, 347:911

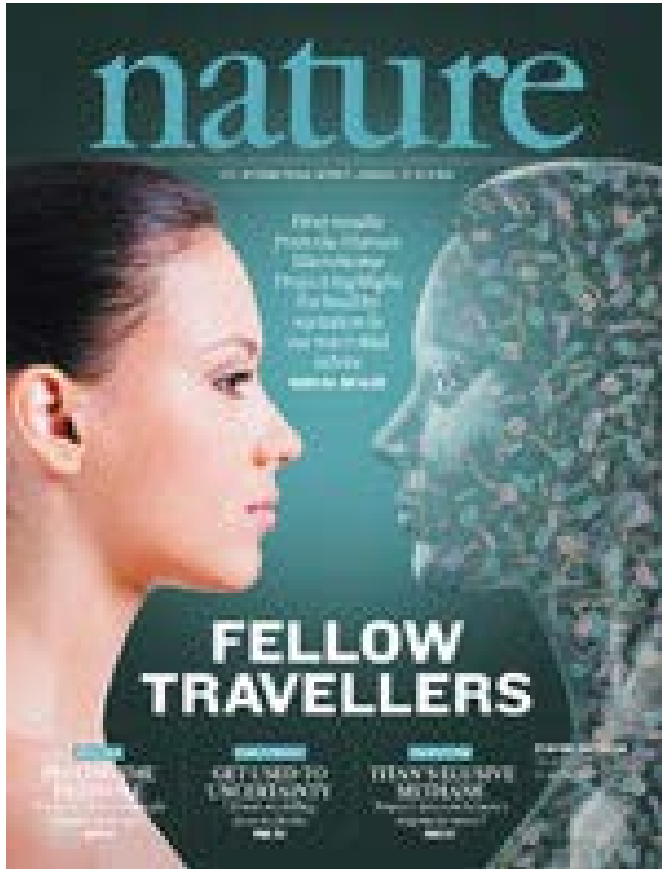
20th세기 인체 질병변화

- 알레르기 (allergies)
 - 1930's: 1 student per school
 - 1980's: 1 student per class
 - 현재: 1 in 4 children
- 제1형 당뇨 (Type 1 diabetes)
 - 20th 세기 초기: 매우 드문 병
 - 현재: 1 in 250 in Western country

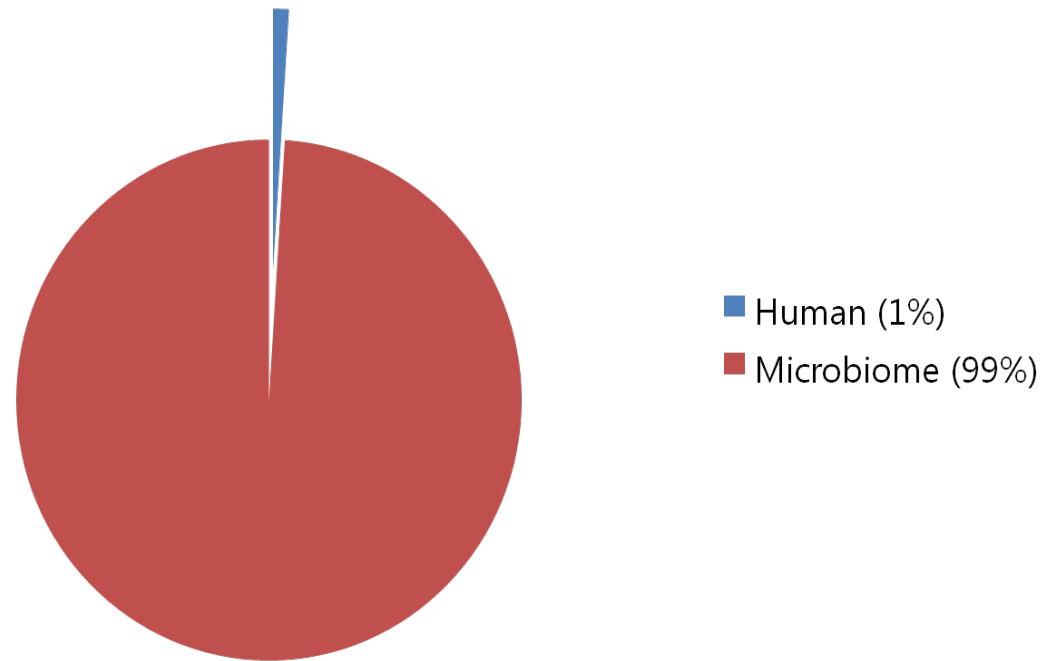
20th세기 인체 질병변화

- 비만 (obesity)
 - >50% of Western population: overweight or obese
 - T2D, 심장병, 암 등의 만성질환과 연관
- 장질환: 염증성 장염, 크론병 등
 - 20th 세기 초기: 매우 희귀한 병
- 정신질환 (mental health)
 - 1940년: 자폐증 진단의 부재
 - 현재: 1 in 68 children are on autism spectrum
 - 자폐증, 우울증과 장질환 연관성

The number of genes in human



Huttenhower et al, 2012, Nature



Who are we?

Efforts to catalogue and understand the human microbiome are opening up a whole new research frontier. But the earlier Human Genome Project should provide a cautionary lesson about overselling.

“Who am I?” is a question that is often asked and seldom answered. But as several articles in this issue suggest, the question itself may need to be reframed: biologists are discovering that it is frequently more informative to ask, “Who are we?”

example, anyone so inclined can now pay genetic-testing companies for a preliminary rundown of the genetic variations associated with his or her risk of developing cancer, obesity and other conditions. But the risks identified are often so low or unclear that people are questioning whether the information will actually prompt the changes

INSIGHT FEATURE

NATURE|Vol 449|18 October 2007|doi:10.1038/nature06244

The Human Microbiome Project

Peter J. Turnbaugh, Ruth E. Ley, Micah Hamady, Claire M. Fraser-Liggett, Rob Knight & Jeffrey I. Gordon

A strategy to understand the microbial components of the human genetic and metabolic landscape and how they contribute to normal physiology and predisposition to disease.

Before the Human Genome Project was completed, some researchers predicted that ~100,000 genes would be found. So, many were surprised and perhaps humbled by the announcement that the human genome

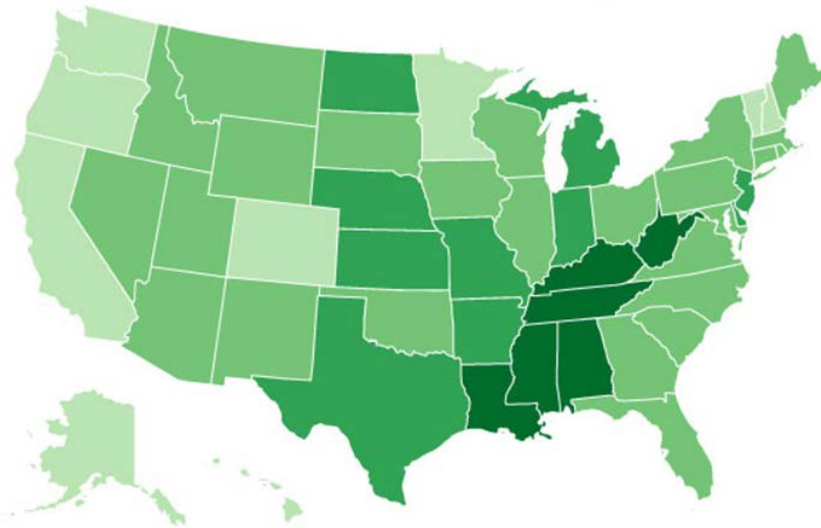
Ecology and considerations of scale

Questions about the human microbiome are new only in terms of the system to which they apply. Similar questions have inspired and con-

항생제 사용과 비만

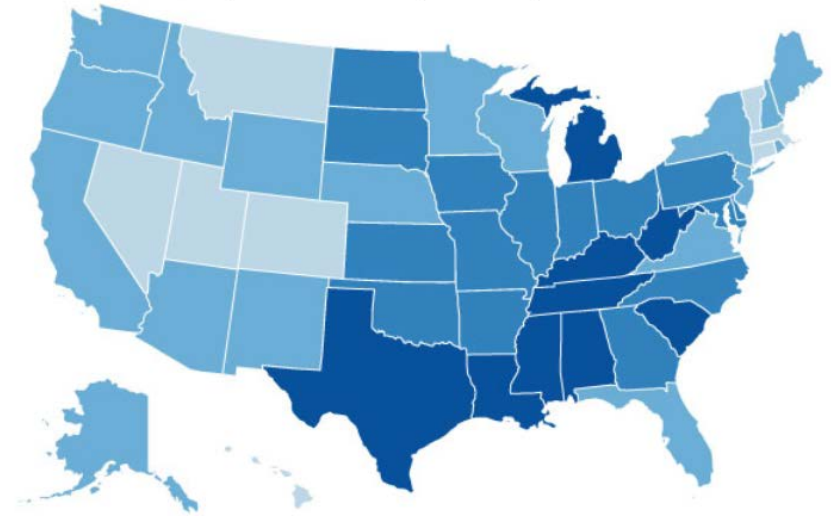
● Antibiotics treatment per 1,000

500-699 700-899 900-1,099 1,100-1,299

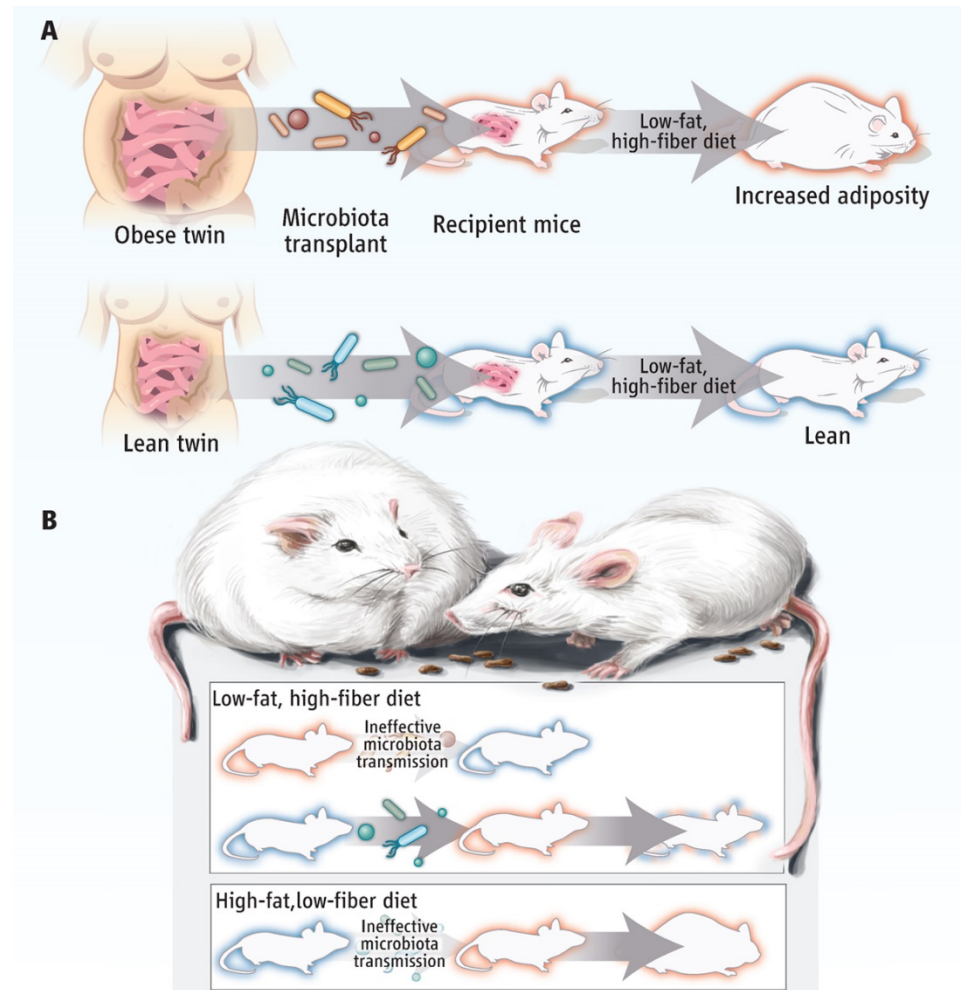


● Obesity prevalence

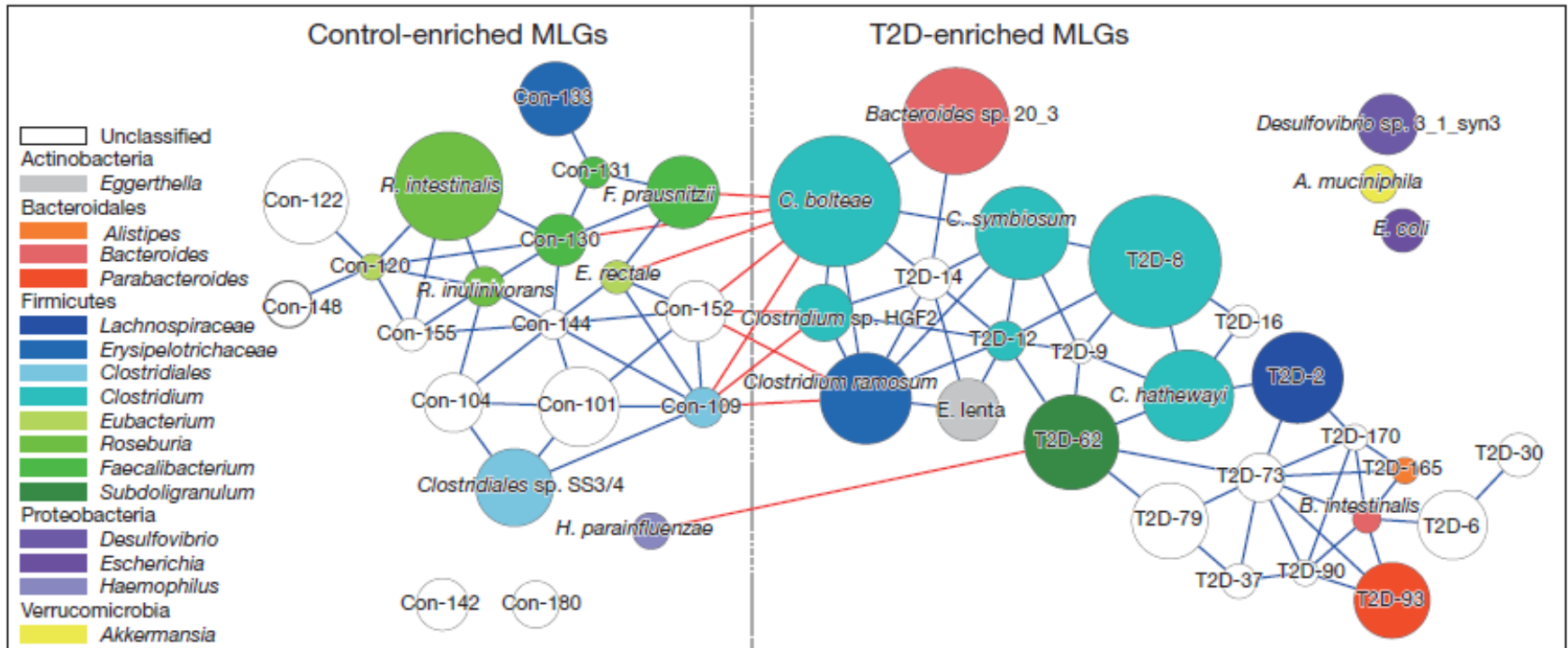
20-23,5% 23,5-27% 27-30,5% 30,5-34%



Obesity & gut microbiota



T2D & gut microbiota



J. Qin et al., 2012, Nature

The Promise of Poop

Fecal transplants offer hope for treating many diseases. But they need to be studied more scientifically, says one of the treatment's pioneers

AMSTERDAM—Soon after Max Nieuwdorp started his residency at the internal medicine department of the Academic Medical Center (AMC) here in 2006, he was confronted with a sad case: an 81-year-old woman hospitalized for a complication after a urinary tract infection who seemed unlikely to survive. She had bed sores and high fevers and was unable to eat. After antibiotics had wiped out her colon's microbial population, an opportunistic bacterium called *Clostridium difficile* had taken over, causing terrible diarrhea and bowel inflammation.

C. difficile is a notorious pathogen that kills at least 14,000 patients a year in the United States alone; many patients suffer repeated bouts with the microbe. To treat

it, the woman was given several courses of vancomycin, the standard antibiotic in such cases. But, as often happens, the bacteria had become resistant.

Nieuwdorp refused to accept the patient's fate—"I was young and naive," he says—and started searching PubMed for anything that could save her. When he found a 1958 paper by Ben Eiseman, a physician who was then at the University of Colorado, Denver, he knew what to do. "I want to try a fecal transplant," he told his supervisor, Joep Bartelsman.

Once he realized that Nieuwdorp wasn't joking, Bartelsman agreed. The plan was simple: The duo would flush the contents from the woman's colon, including, hope-

fully, the *C. difficile* population, and replace it with the healthy bacterial flora from a donor, in this case her son. To do so, they would mix the son's feces with saline in a blender and squirt it straight into the patient's duodenum, the upper part of her intestine, via a thin plastic tube inserted through her nose.

Three days after her treatment, the woman left the hospital—walking. Nieuwdorp and Bartelsman decided to treat another six *C. difficile* patients in the following months. Embarrassed about the unusual experiment, they waited for colleagues to break for lunch before infusing the stools. Four patients recovered immediately, the other two after another transplant from a second donor. The transplanted bacteria were apparently restoring the intestinal flora to health.

But when Nieuwdorp presented the results at a hospital meeting, an internist approached him with a condescending smile. "If you seriously want us to treat our *C. diff* patients with poop, why don't you infuse our cardiovascular patients as well?" the man asked, and left the room.

CREDIT: TIM WONG/AMC PRESS OFFICE



A new study coats babies born by C-section with the microbes in their mother's vagina, in an effort to alter the microbial community that's a part of them. STEVE DEBENPORT/ISTOCKPHOTO

How to give a C-section baby the potential benefits of vaginal birth

By Jennifer Couzin-Frankel | Feb. 1, 2016 , 11:00 AM

Babies born vaginally are thought to have an edge over those born via cesarean section. They pick up bacteria from their mother's birth canal, which scientists believe helps protect them from asthma, obesity, and other health issues as they grow older. Now, a new study offers hints that

J Couzin-Frankel, 2016, Science Mag

엄마 마이크로바이옴과 아이들 질환 연관

LETTER

doi:10.1038/nature23910

Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring

Sangdoon Kim^{1*}, Hyunju Kim^{1*}, Yeong Shin Yim², Soyoung Ha¹, Koji Atarashi³, Tze Guan Tan⁴, Randy S. Longman⁵, Kenya Honda³, Dan R. Littman^{6,7}, Gloria B. Choi² & Jun R. Huh^{1†}

Maternal immune activation (MIA) contributes to behavioural abnormalities associated with neurodevelopmental disorders in both primate and rodent offspring^{1–4}. In humans, epidemiological studies suggest that exposure of fetuses to maternal inflammation increases the likelihood of developing autism spectrum disorder^{5–7}. In pregnant mice, interleukin-17a (IL-17a) produced by T helper 17 (T_H17) cells (CD4⁺ T helper effector cells involved in multiple inflammatory conditions) induces behavioural and cortical

social interaction deficits (decreased interaction with a social stimulus) in adult male offspring (Fig. 1b–d). These behavioural phenotypes did not emerge from changes in activity or arousal levels as the total investigation time and the total distance travelled during the sociability test remained comparable (Extended Data Fig. 1b, c). To investigate whether maternal commensal bacteria influence MIA-associated behaviours, we treated wild-type C57BL/6 mice from our vivarium with the broad spectrum antibiotic vancomycin before phosphate buffered

Microbiome Projects Worldwide

Korean Microbiome Diversity Using Korean Twin Cohort
(National Research Foundation)



Human Microbiome Project
(NIH Common Fund)



Metagenomics of the Human Intestinal Tract
(European Commission)



Canadian Microbiome Initiative



MicroObes, Human Intestinal Microbiome
in Obesity and Nutritional Transition
(French National Agency for Research)



Australian Human Microbiome Project



Medical Research Council (Gambia)

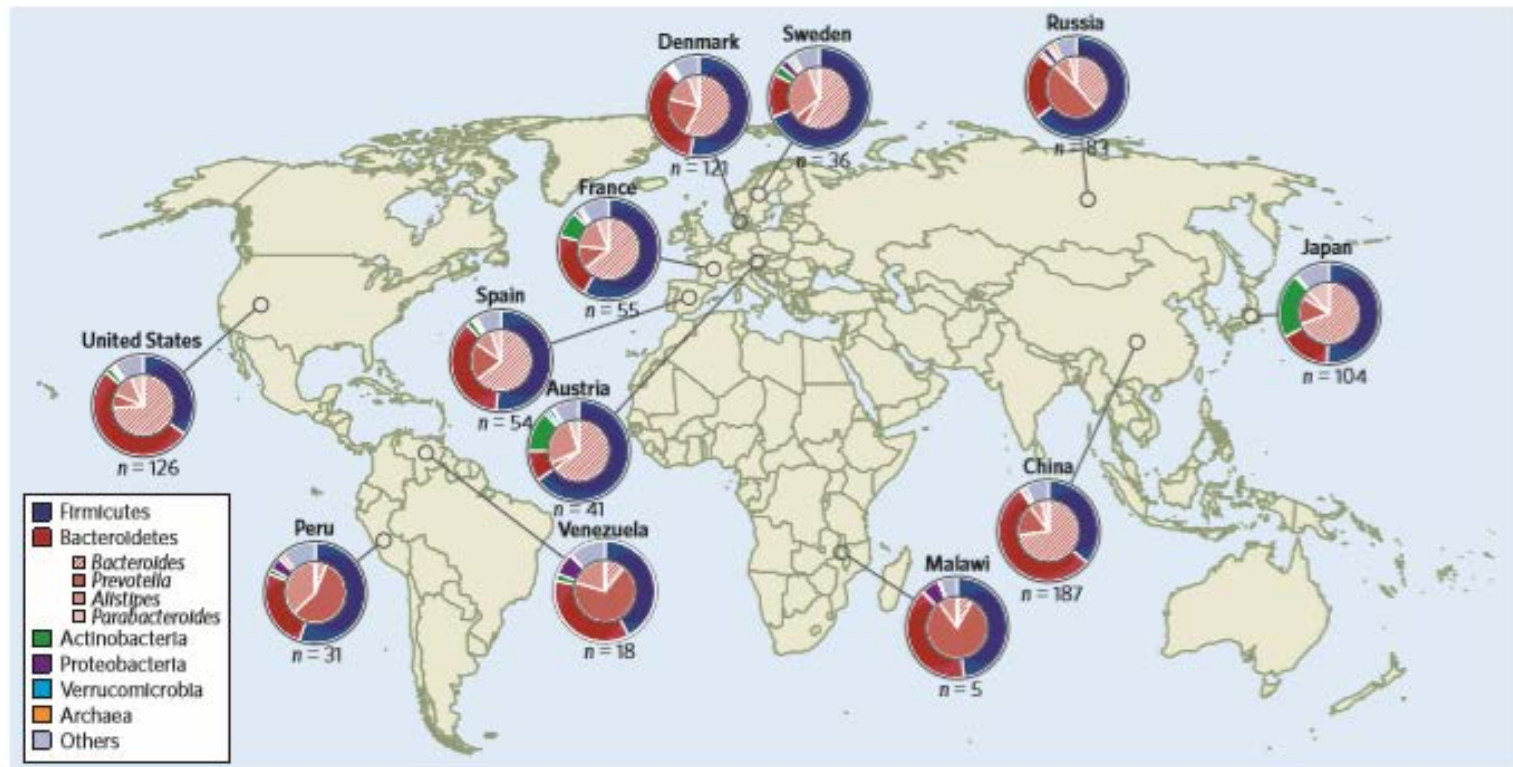
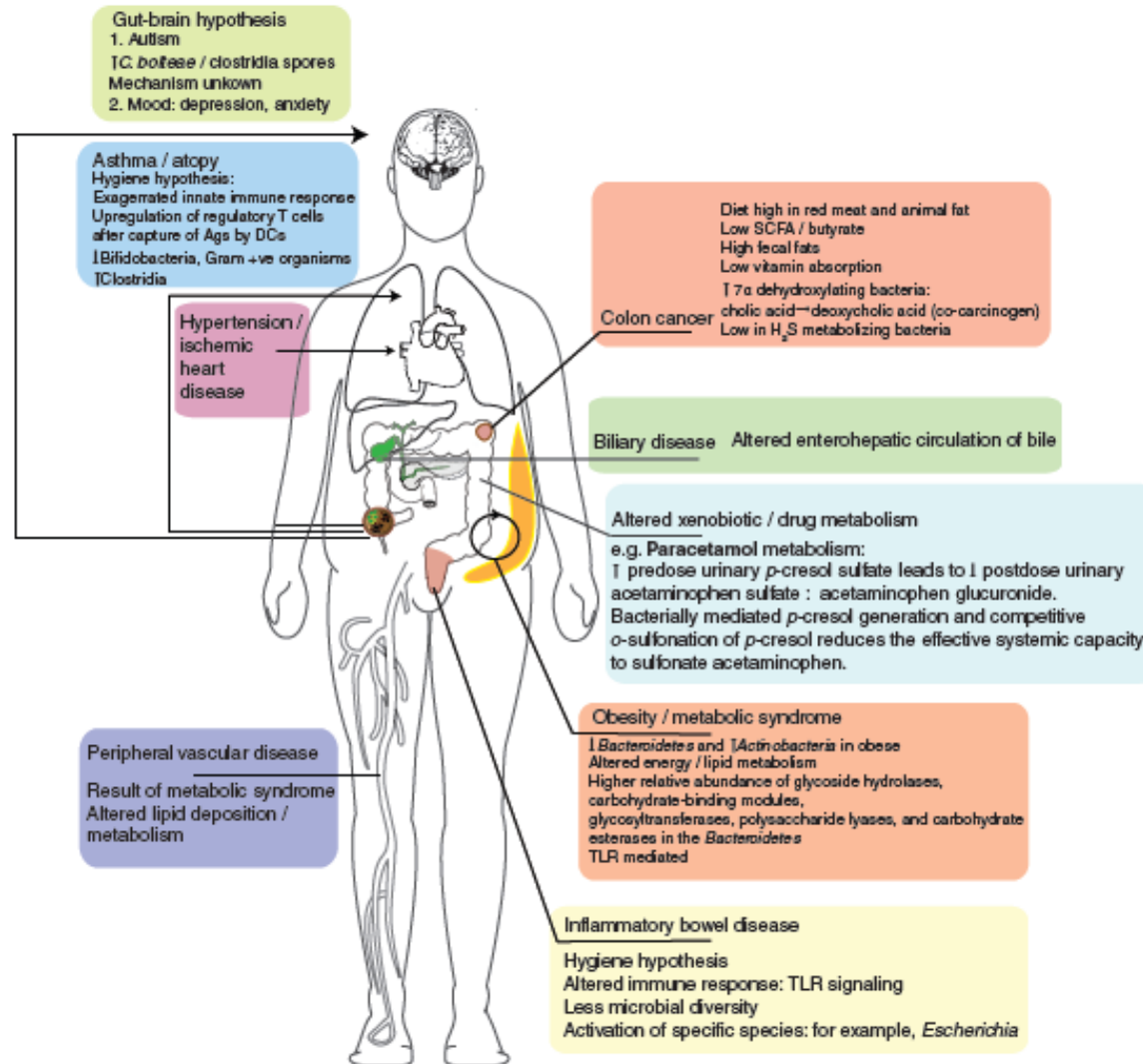


Figure 1 | Global distributions and abundances of human gut microorganisms at the phylum and genus levels. Of the gut microbial taxa represented among healthy adult human populations, the Gram-positive Firmicutes and the Gram-negative Bacteroidetes appear to be universal. While different microbiota can appear similar at the phylum level (for example, Sweden versus Russia), they often differ significantly at lower taxonomic levels. In this figure, each pie chart represents an average per cohort, with outer pies depicting phylum-level taxa and Archaea, and inner pies depicting genus-level taxa within Bacteroidetes. Inter-personal variation within each country is also significant. Data adapted from ref. 147.

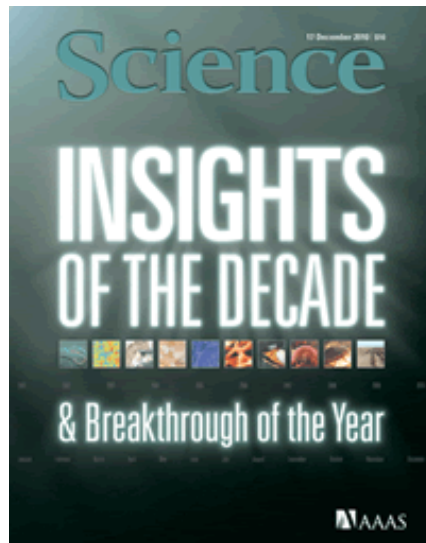
AG Wexler and AL Goodman, 2017, Nature Microbiol.

Microbiota in our health and diseases



Microbiome therapeutics

- 2011년 Science誌 선정 10대 breakthrough 기술 선정
- 2014년 World Economic Forum에서 21세기 차세대 핵심 부가가치 산업으로 마이크로비옴 기술 선정:
“미래를 바꿀 10대 신기술”





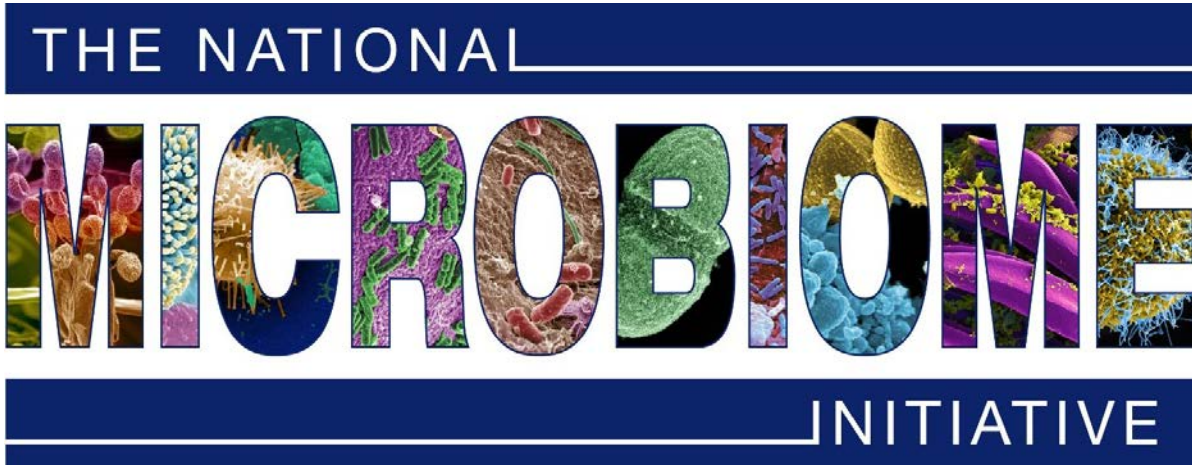
HOME · BLOG

Announcing the National Microbiome Initiative

MAY 13, 2016 AT 6:00 AM ET BY JO HANDELSMAN



Summary: The new National Microbiome Initiative aims to advance microbiome science in ways that will benefit individuals, communities, and the planet.



분변이식 기술 (Fecal microbiome transplantation)



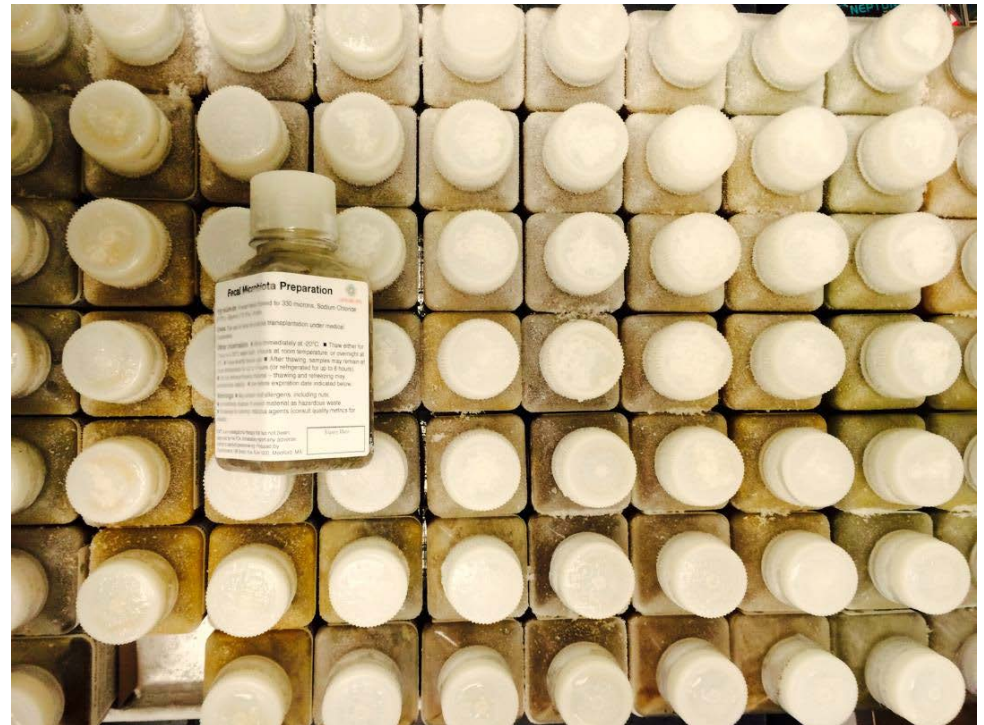
FMT LOWER DELIVERY
microbiota preparation



FMT UPPER DELIVERY
microbiota preparation



FMT CAPSULE G3
microbiota preparation
with MEM technology



마이크로바이옴 치료제 개발

'Bugs as Drugs'

'Drugs from Bugs'

Consortia of bacteria

Single bacterium (strain)

Bioactive Molecule

Undefined mixture (FMT)

Defined Mixture

Single strain Native

Single strain modified

Protein
Polysaccharide
Metabolite ...

Lactate producers
(e.g., lactobacilli,
bifidobacteria)

Methanogens
(e.g., methanogenic
archaea)

Mucin degraders
(e.g., Bacteroidetes)

Short chain fatty acids
producers
(e.g., *Clostridium*)

Lactate
producers

Lactobacillus rhamnosus

p40¹⁷



Specificity

Ecosystem Effects

(colonization/alteration of ecosystem composition, pathogen exclusion)



Cell

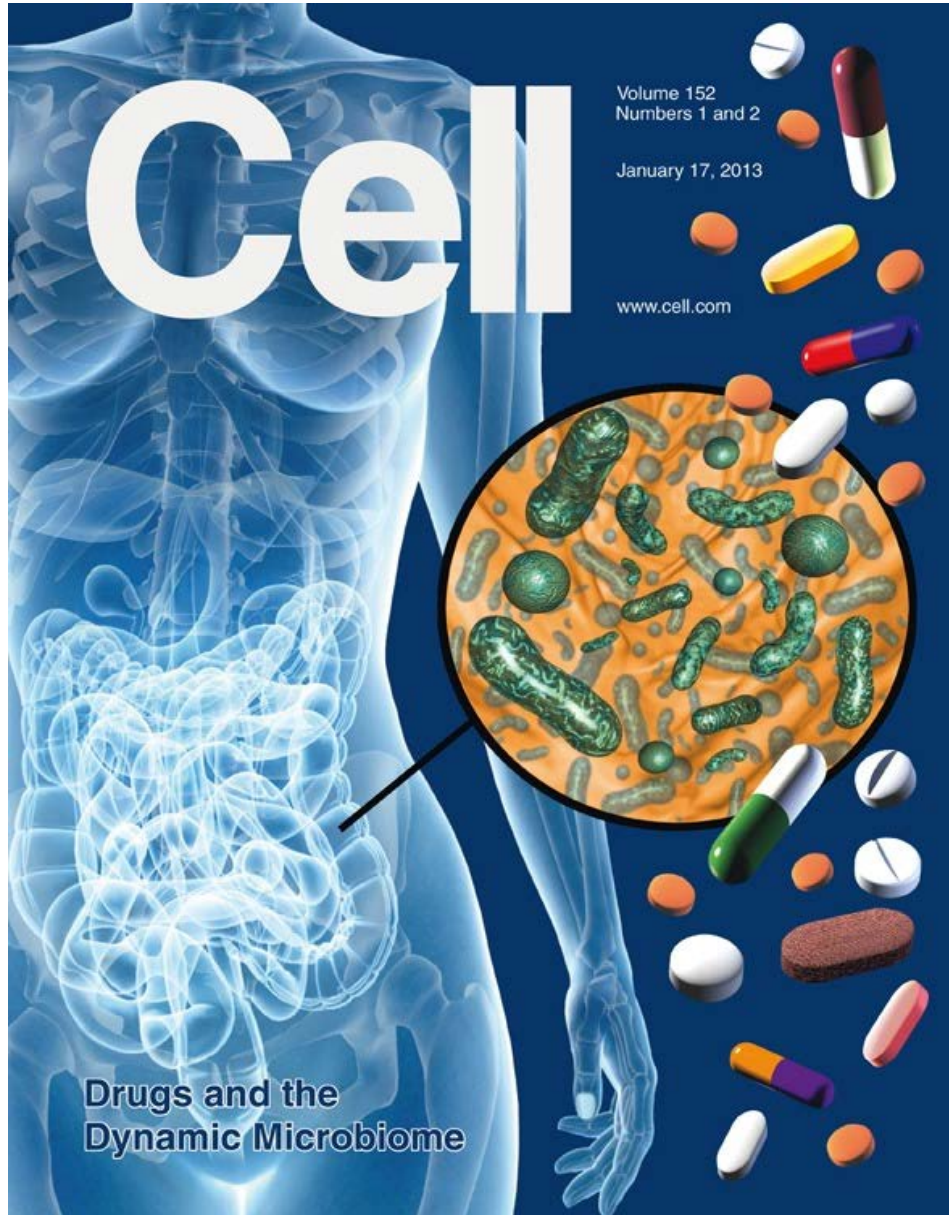
Volume 152
Numbers 1 and 2

January 17, 2013

www.cell.com

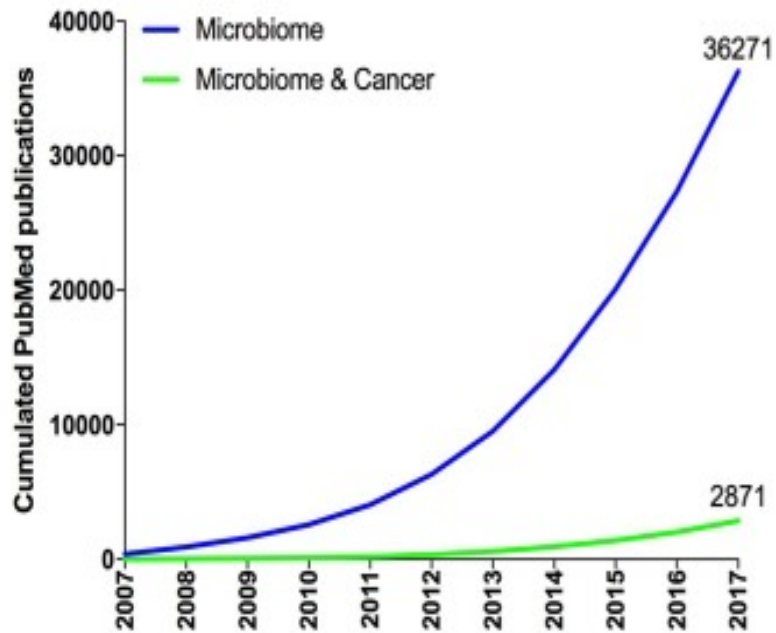


Drugs and the
Dynamic Microbiome

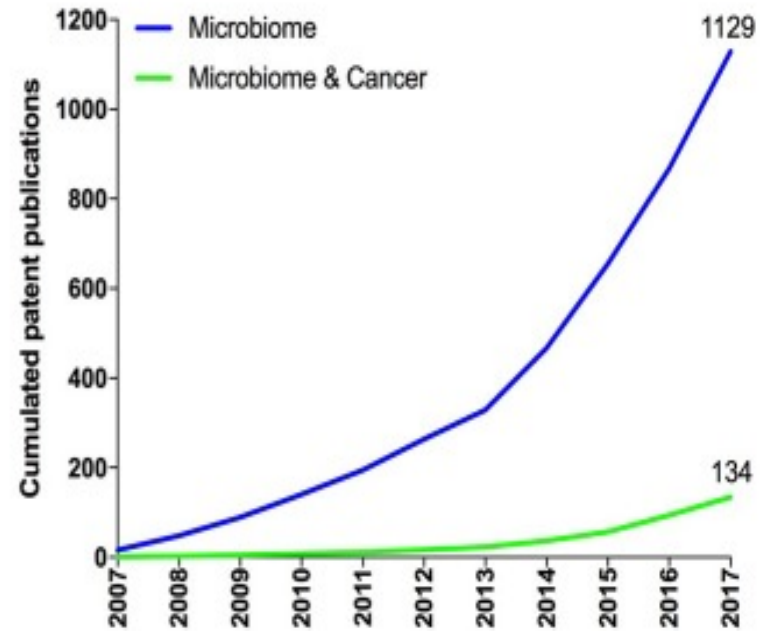


Publications and Patents Related to Microbiome Research

A Academic publications



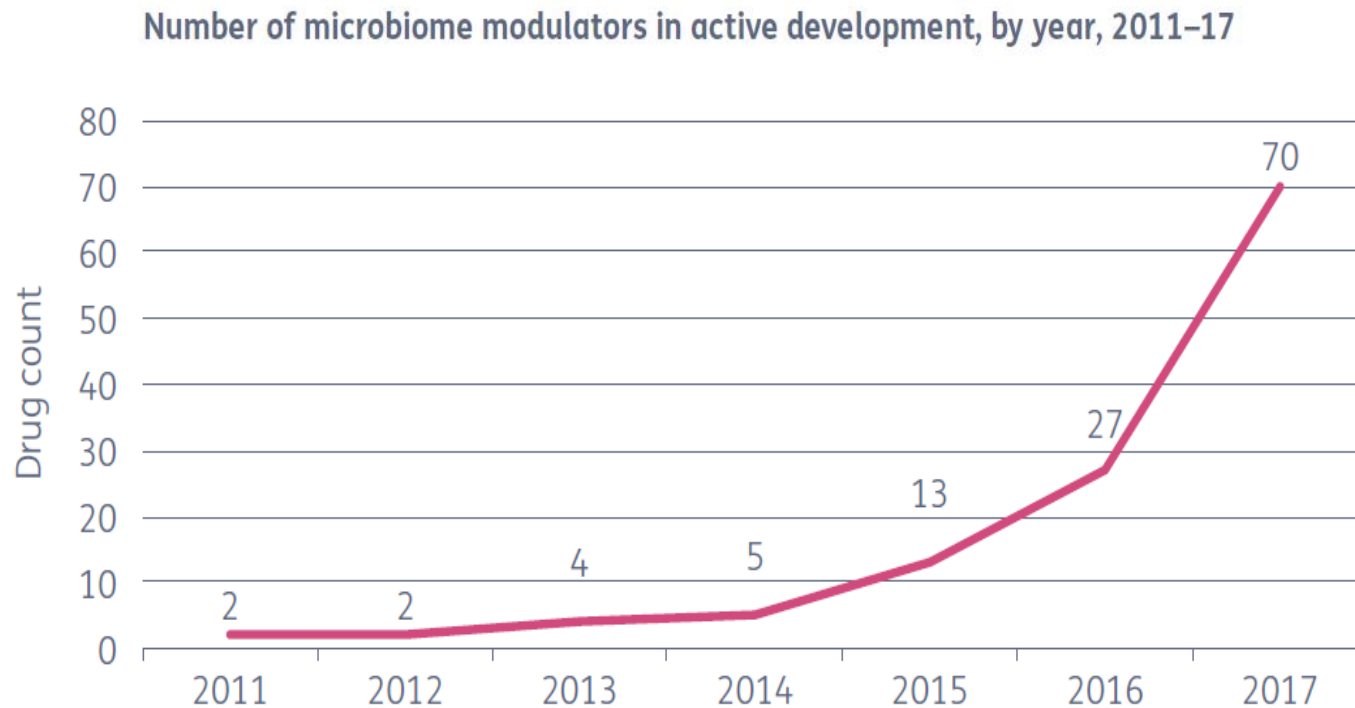
B Patents



Source) *Frontiers in Bioengineering and Biotechnology*, 2018; volume 6, 84

Microbiome Therapeutics Development Landscape

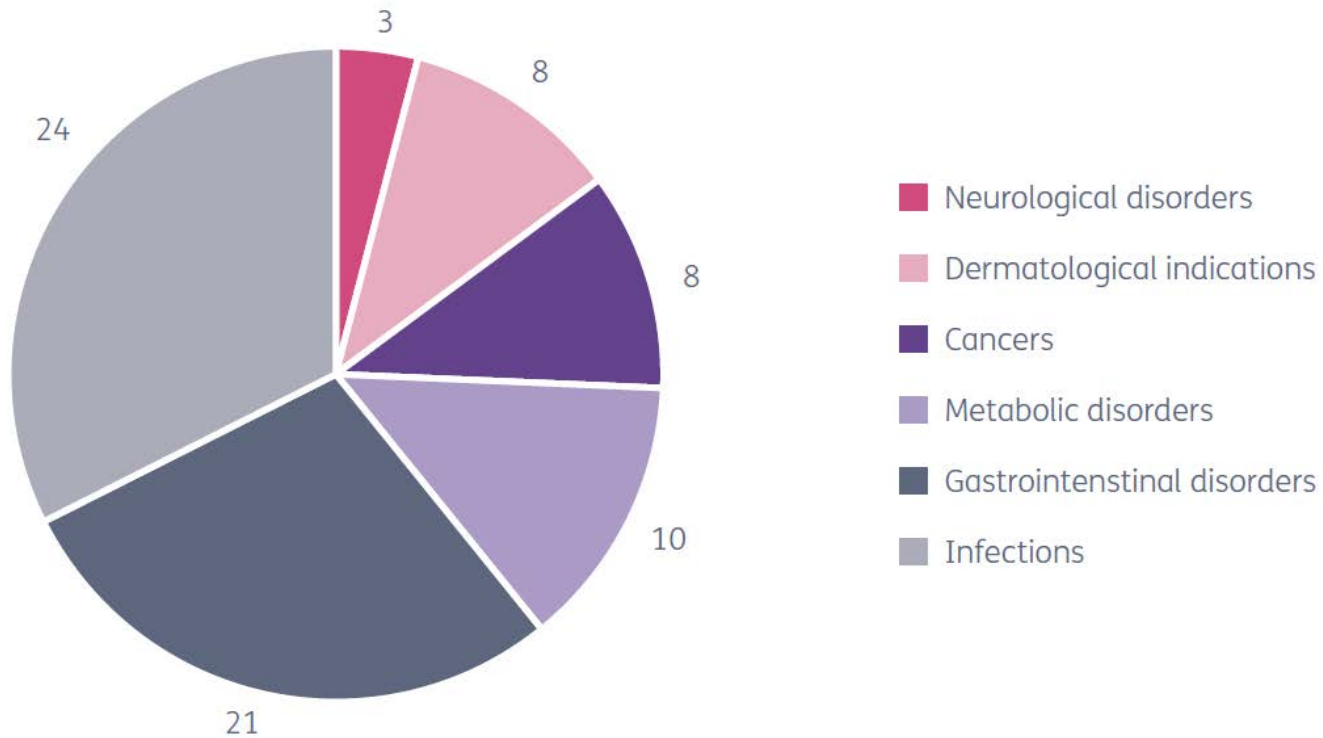
- As of January 2018, the number of microbiome therapeutics in development (preclinical to clinical stage) stands at **70**
- The sudden spark in industrial interest is recent, as seen by the **65% increase in the number of microbiome modulators being developed over the past two years**



Source) Pharmaprojects, January 2018

Microbiome Therapeutics Development Landscape

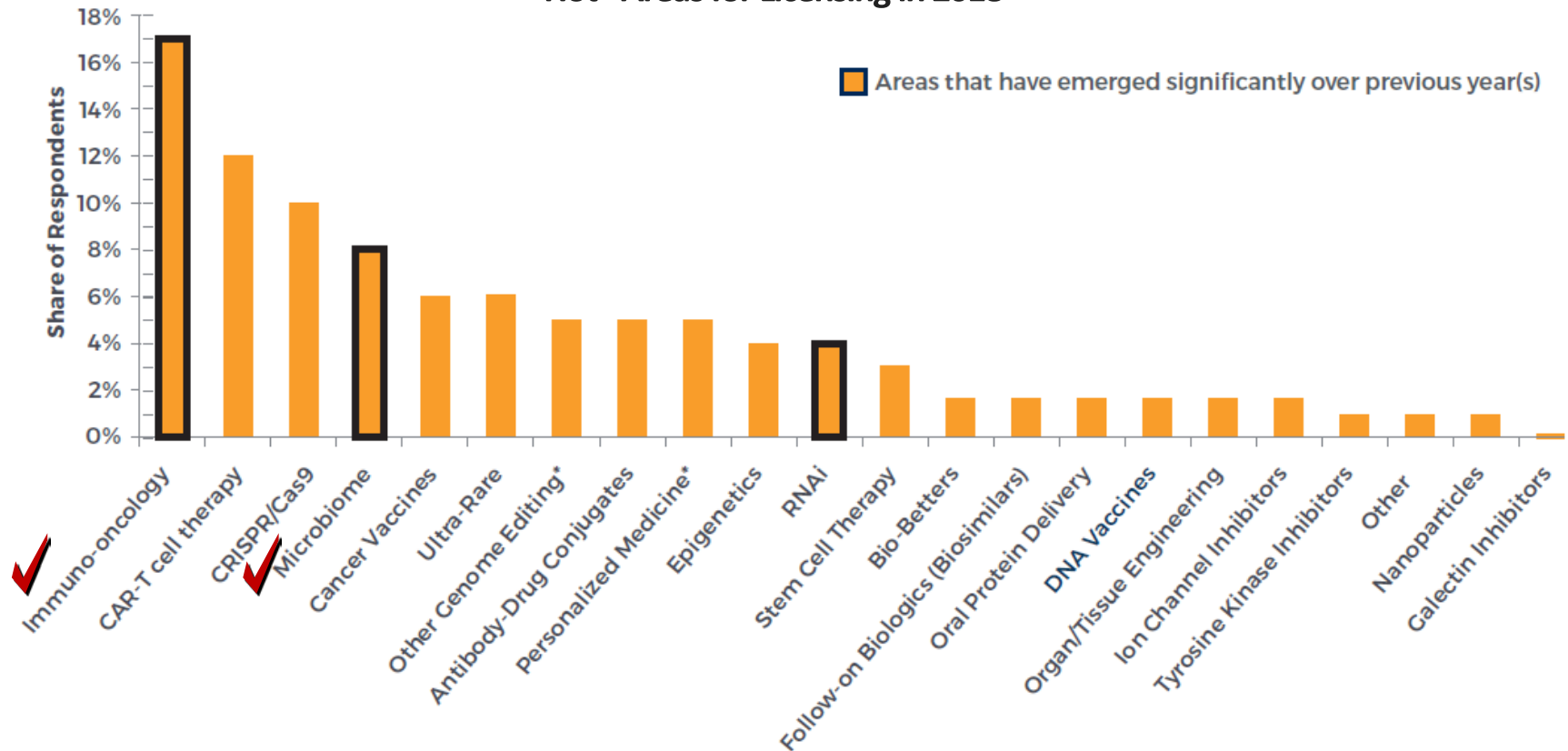
Number of Microbiome Therapeutics by Therapeutic Area



Hot Areas for Licensing in 2018

» CAR-T and CRISPR/Cas9 continue to be among the “hottest” areas for licensing in 2018 but interest in immuno-oncology and microbiomes has increased considerably since 2017.

“Hot” Areas for Licensing in 2018



*Other Genome Editing / Gene Therapy (Viral / Non-Viral)

*Personalized Medicine / Companion Diagnostics

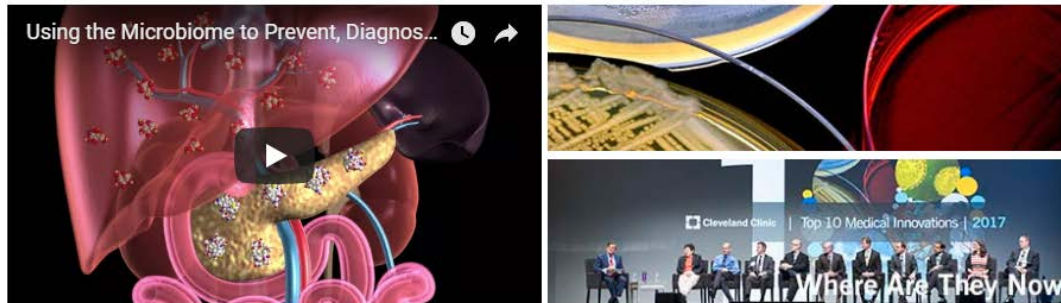
Source: Syneos Health Consulting Dealmakers' Intentions 2018. Includes answers from 66 respondents. Respondents could select multiple areas.

Cleveland Clinic Innovations in 2017: #1 Microbiome



TECHNOLOGIES VENTURES SERVICES SUMMIT RESOURCES ABOUT US 

#1 The Microbiome to Prevent, Diagnose, and Treat Disease



Overview

When it comes to life-saving potential and market opportunities, it turns out the gut is a gold mine. The trillions of bacteria making up communities in our body, referred to as the microbiome, are unlocking mysteries at an incredible pace, and the market is aligning and realigning to keep up with the endless possibilities.

Interview: KoBioLabs Pioneering The Microbiome Landscape In Korea

04 Jun 2018 | NEWS

Executive Summary

Industry interest in the development of microbiome modulators is noticeably increasing worldwide. In South Korea, KoBioLabs is leading the charge to microbiome drug development, helped by a sizable database and biobank. Its founder and CEO GwangPyo Ko talked to Scrip about its core technology, pipeline progress, and general strategy.



GWANGPYO KO, FOUNDER AND CEO OF KOBIO LABS

Source: KoBioLabs Inc.

Bill Gates at JP Morgan Conference in 2018

- “It is also increasingly clear that the gut microbiome and nutrition, and the interplay between the two, is a big factor in the survival and healthy development of children, no matter where they live”



감사합니다 Natick

Grazie Danke Ευχαριστίες Dalu

Thank You Köszönöm

Спасибо Dank Gracias Tack

谢谢 Merci Seé
ありがとう

Obrigado