YONSEI UNIVERSITY

마이크로바이옴의 혈중 약동학 마커 탐색

보건복지부 KHIDI 한국보건산업진흥원 KONECT 국가임상시험지원재단 Korea National Enterprise for Clinical Trials

Severance

세브란스병원
김춘옥

첨단바이오분야 임상시험 기술개발

연구과제 개요

- 첨단바이오분야 등 신산업 분야의 초기 임상시험 진입·설계·수행 기술 개발을 통한 임상시험 수행기반 마련
  - ✓ 마이크로바이옴, 엑소좀, 오가노이드 등의 제조공정, 바이오마커 등 초기 임상시험 기술 개발, 규제 고려사항
  - ✓ 임상시험 수행(5년간 6건) 및 지침서 개발

과제명	첨단바이오분야 초기 임상시험 관련 기술 개발				
주연연구기관	가톨릭대학교 산학협력단	주관연구책임자	민창기 교수	총사업비	41억원

(주관) 가톨릭대학교 산학협력단

첨단바이오분야 초기 임상시험 관련 기술 개발

(1공동) 연세대학교 산학협력단	(2공동) 고려대학교 산학협력단	(3공동) 주식회사 입셀
첨단바이오분야 규제 돌파 및 다기관 연구 전략 마련	첨단바이오분야 임상시험 수행 체계 마련	엑소좀 활용 첨단바이오의약품 개발

(4공동) 주식회사 지놈앤컴퍼니	(5공동) (주)애임스바이오사이언스
마이크로바이옴 활용 첨단바이오의약품 개발	첨단바이오분야 임상시험기술개발 자문 및 규제실무

목차

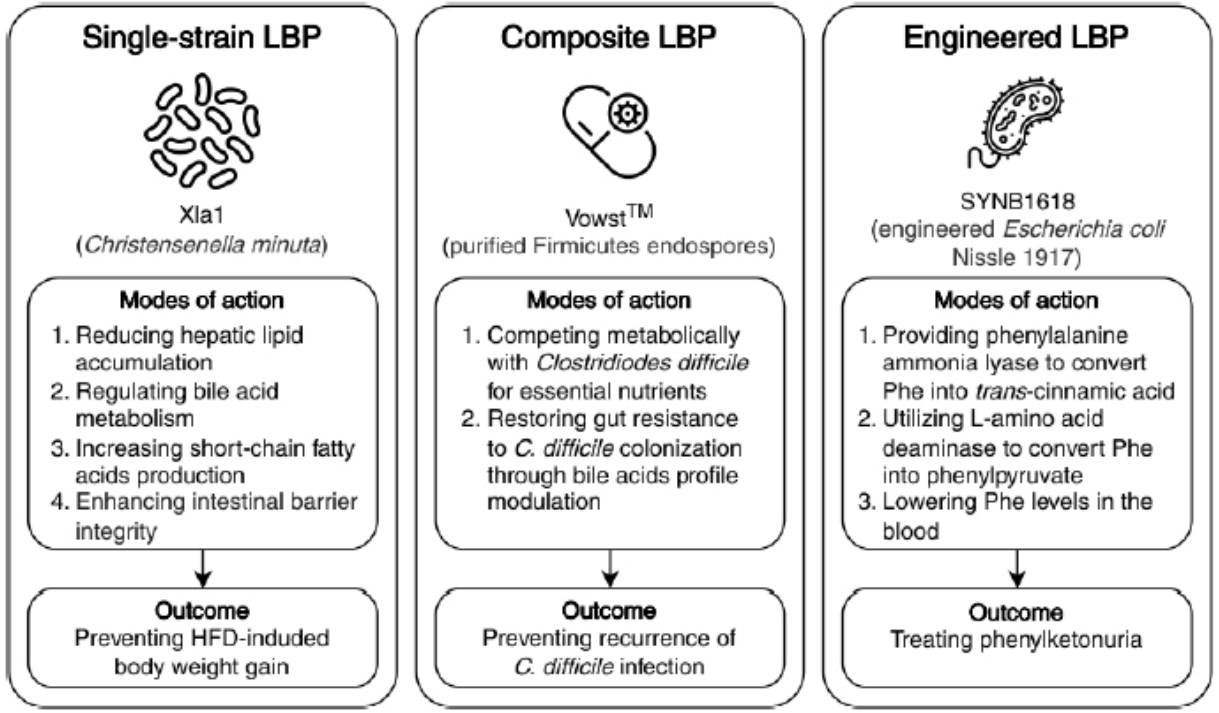
- 마이크로바이옴 임상시험의 어려움
- 신약, 마이크로바이옴 개발의 특수성
- 마이크로바이옴 PK/PD
- 마이크로바이옴-Drug Interaction

마이크로바이옴 임상시험의 어려움

용어

- **마이크로바이옴 (Microbiome)**
  - 특정 환경에 존재하는 미생물 군집과 그 유전체 정보를 총칭

- **생균치료제 (Live Biotherapeutic Product, LBP)**
  - 박테리아 등 살아있는 미생물을 주성분(유효성분)으로 하여 제조한 의약품
  - 세균 등 미생물을 함유
    + 사람의 질병 또는 상태의 예방이나 치료 또는 완치 목적으로 사용
    + 백신이 아님



1. 생균치료제의 임상시험 시 품질, 비임상 평가 가이드라인: 마이크로바이옴 기반 의약품. 2023.08.31
2. Tseng C-H, et al. Gut 2025; 0:1-8

2025년 마이크로바이옴 신약개발 현황

2개 FDA 허가 (Rebyota, Vowst)

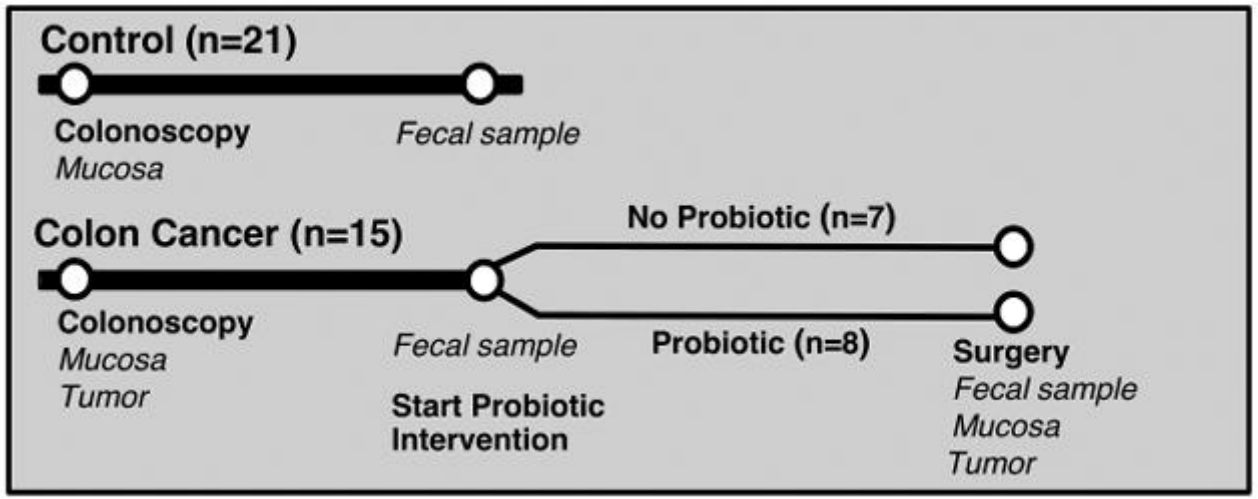
300여개
마이크로바이옴 기반 신약

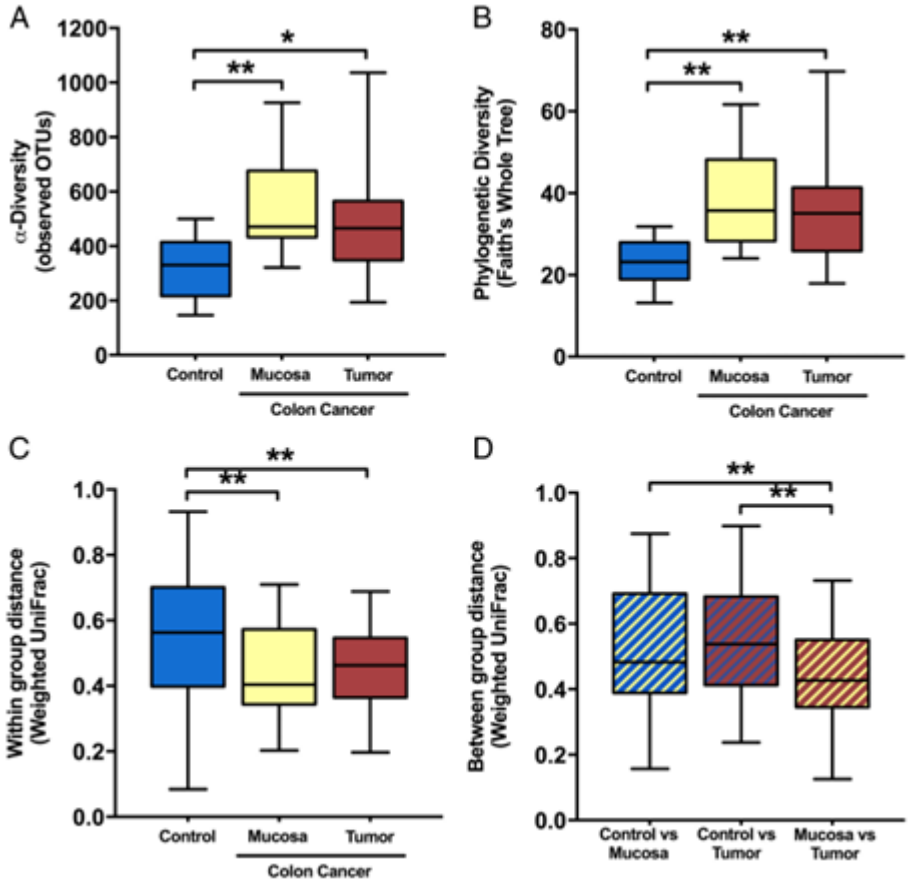
150여건
마이크로바이옴 임상시험

- **70%** 위장관 질환 (Gastrointestinal disease)
- **20%** 면역-종양 질환 (Immuno-oncology)

Business research insights: microbiome therapeutics market size, share, growth, and industry analysis, by type, by application, regional insights and forecast to 2035

왜 마이크로바이옴 임상시험 대부분이 실패하는가? (1)





Hibberd et al., BMJ open gastroenterology. 2017:17;4(1)

왜 마이크로바이옴 임상시험 대부분이 실패하는가? (1)

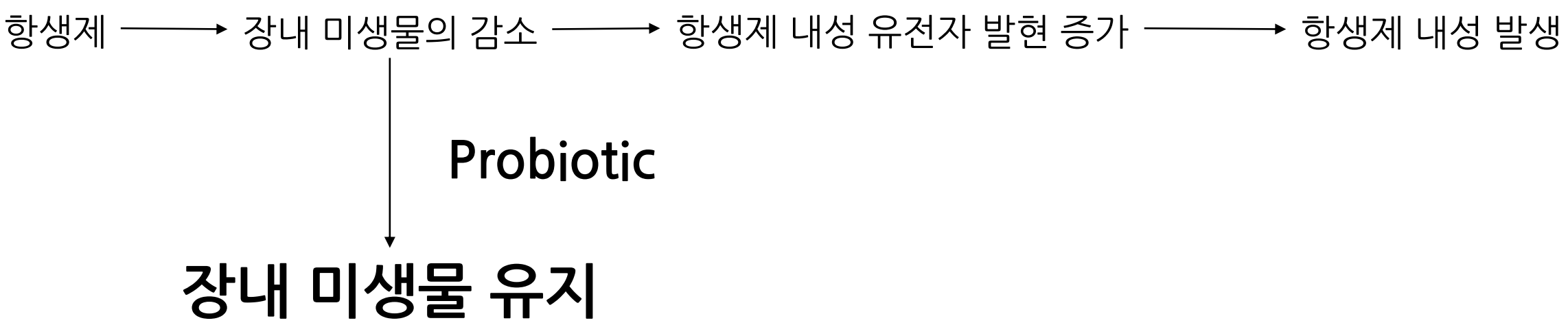
Table 3 Microbiota alterations with probiotic intervention in patients with colon cancer at surgery

		Faecal			Mucosa			Tumour		
Genus	Effect of probiotic	No Probiotic abundance (%), n=7	Probiotic abundance (%), n=8	p Value (FDR)	No probiotic abundance (%), n=6	Probiotic abundance (%), n=7	p Value (FDR)	No probiotic abundance (%), n=5	Probiotic abundance (%), n=7	p Value (FDR)
Clostridiales spp	Increase	3.5±3.1	8.5±4.1	0.02 (0.3)	2.8±2.0	7.5±3.3	0.01 (0.3)	1.9±1.7	6.7±2.8	0.01 (0.3)
Faecalibacterium	Increase	3.2±2.6	6.5±2.0	0.02 (0.3)	3.3±2.8	8.1±3.5	0.02 (0.3)	2.7±2.8	6.8±3.1	0.03 (0.4)
[*Eubacterium*]	Increase	0.86±1.8	2.9±2.7	0.05 (0.3)	0.50±0.73	2.1±1.9	0.04 (0.3)	–	–	–
Roseburia	Increase	–	–	–	0.05±0.07	1.7±2.2	0.04 (0.3)	0.04±0.03	1.9±2.2	0.007 (0.3)
Lachnospira	Increase	–	–	–	0.10±0.08	1.4±0.85	0.03 (0.3)	0.10±0.07	1.3±0.78	0.03 (0.4)
Fusobacterium	Decrease	0.81±0.87	0.03±0.05	0.01 (0.3)	–	–	–	–	–	–
Erysipelotrichaceae spp	Increase	0.42±0.59	1.3±1.0	0.02 (0.3)	–	–	–	–	–	–
Coriobacteriaceae spp	Increase	0.49±0.46	1.3±0.75	0.04 (0.3)	–	–	–	–	–	–
Porphyromonas	Decrease	0.43±0.56	0.00±0.00	0.05 (0.3)	–	–	–	–	–	–
[*Prevotella*]	Decrease	0.22±0.38	0.00±0.00	0.05 (0.3)	–	–	–	–	–	–
Peptostreptococcus	Decrease	0.42±0.71	0.04±0.06	0.05 (0.3)	–	–	–	–	–	–
Unclassified *Rikenellaceae*	Increase	–	–	–	0.03±0.08	1.1±2.1	0.03 (0.3)	–	–	–
Bacteroidales spp	Decrease	–	–	–	0.68±1.6	0.00±0.00	0.04 (0.3)	–	–	–
Unclassified *Clostridiales*	Increase	–	–	–	–	–	–	0.12±0.14	0.72±0.72	0.01 (0.3)
[*Barnesiellaceae*] spp	Increase	–	–	–	–	–	–	0.07±0.11	0.24±0.15	0.03 (0.3)

Data are presented as mean±SD.
Wilcoxon rank sum test comparing no probiotic with probiotic for each sample type.
Square brackets indicate the Greengenes database notation for proposed taxonomy.
Only p≤0.05 are shown.
FDR, false discovery rate (Benjamini-Hochberg).

Hibberd et al., BMJ open gastroenterology. 2017:17;4(1)

왜 마이크로바이옴 임상시험 대부분이 실패하는가? (1)



John et al., Front. Microbiomes, 2024

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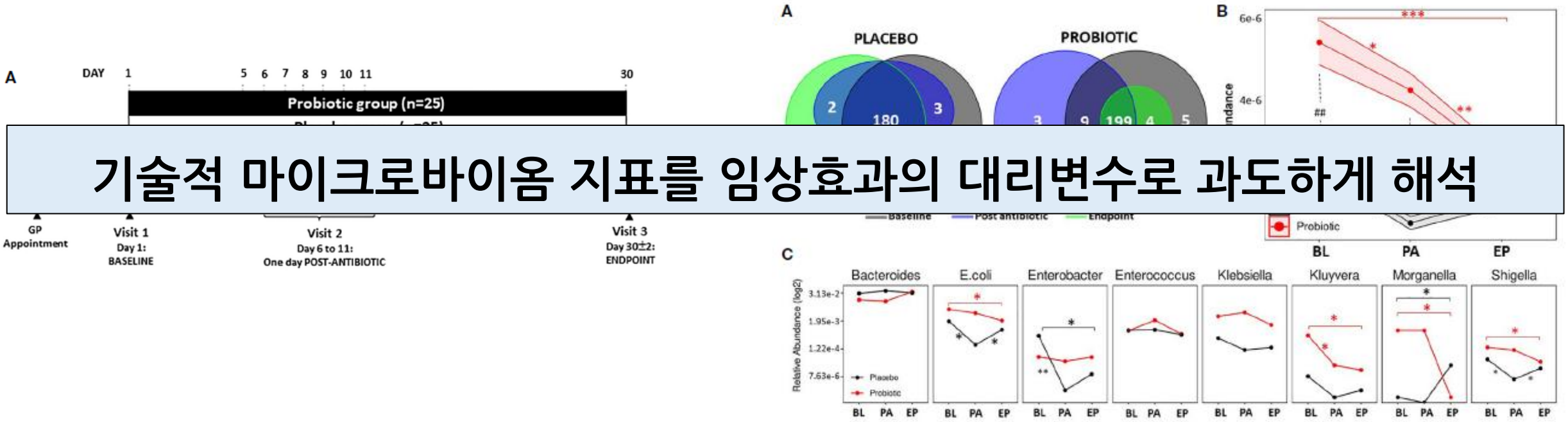
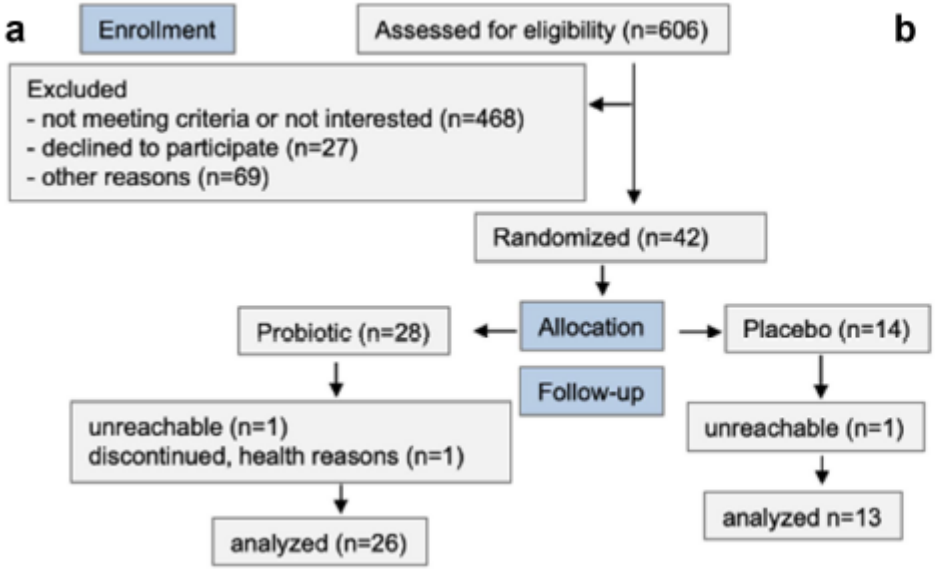


기술적 마이크로바이옴 지표를 임상효과의 대리변수로 과도하게 해석

John et al., Front. Microbiomes, 2024

왜 마이크로바이옴 임상시험 대부분이 실패하는가? (2)

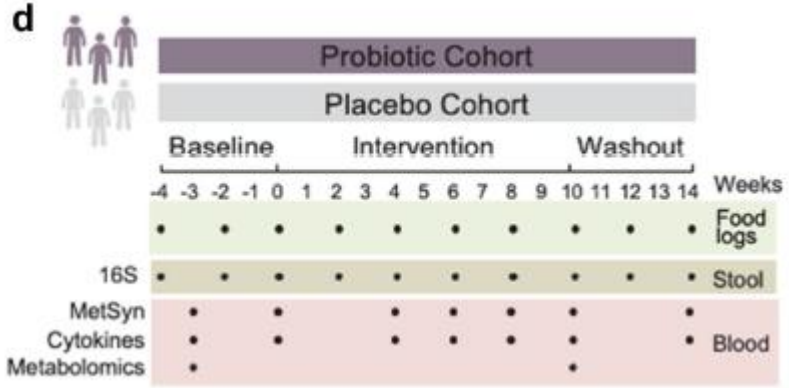
a



b

Inclusion Criteria	IDF Guidelines
Waist Circumference	≥ 94cm (men); ≥90cm (Asian men); ≥80cm (women)
Blood Pressure	≥130 systolic blood pressure; ≥85 diastolic blood pressure; or treatment for hypertension
Triglycerides	≥150mg/dL or treatment for elevated triglycerides
HDL Cholesterol	≤40mg/dL (men); ≤50mg/dL (women) or treatment for low HDL
Fasting Plasma Glucose	≥100mg/dL or treatment for elevated FPG

d



Wastyk et al., Gut microbes, 2023

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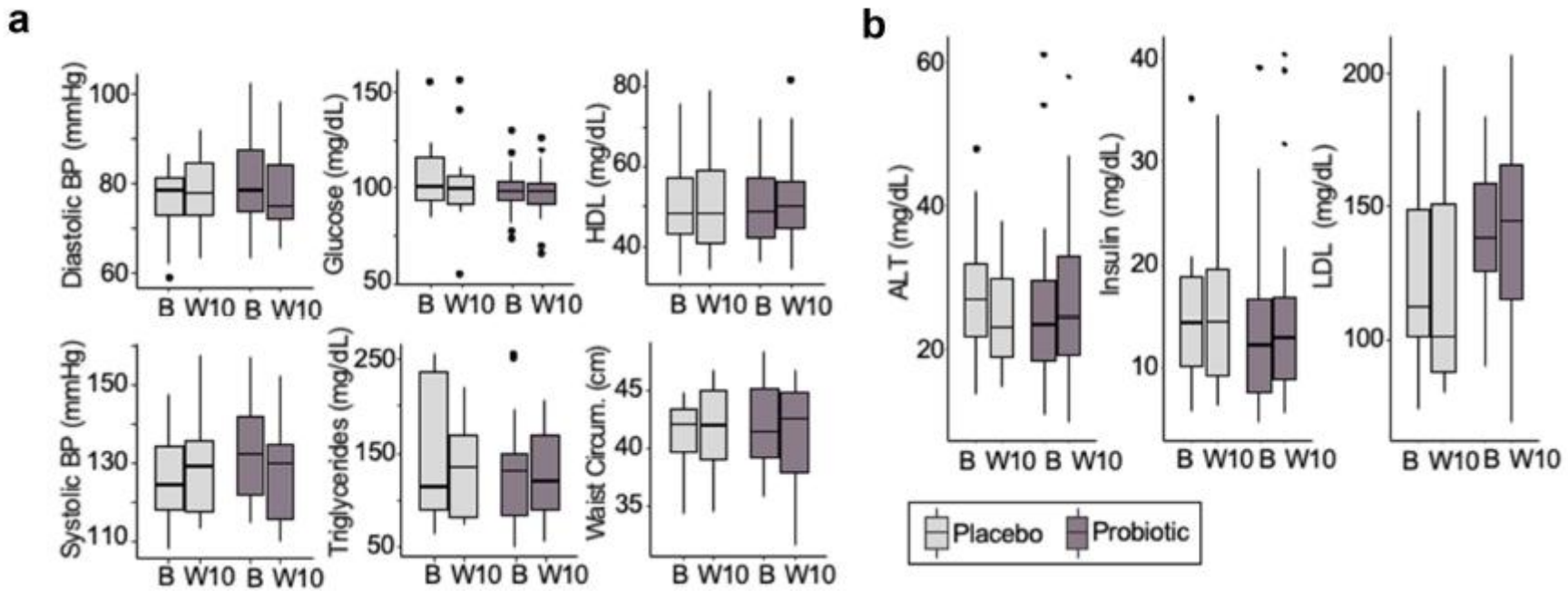

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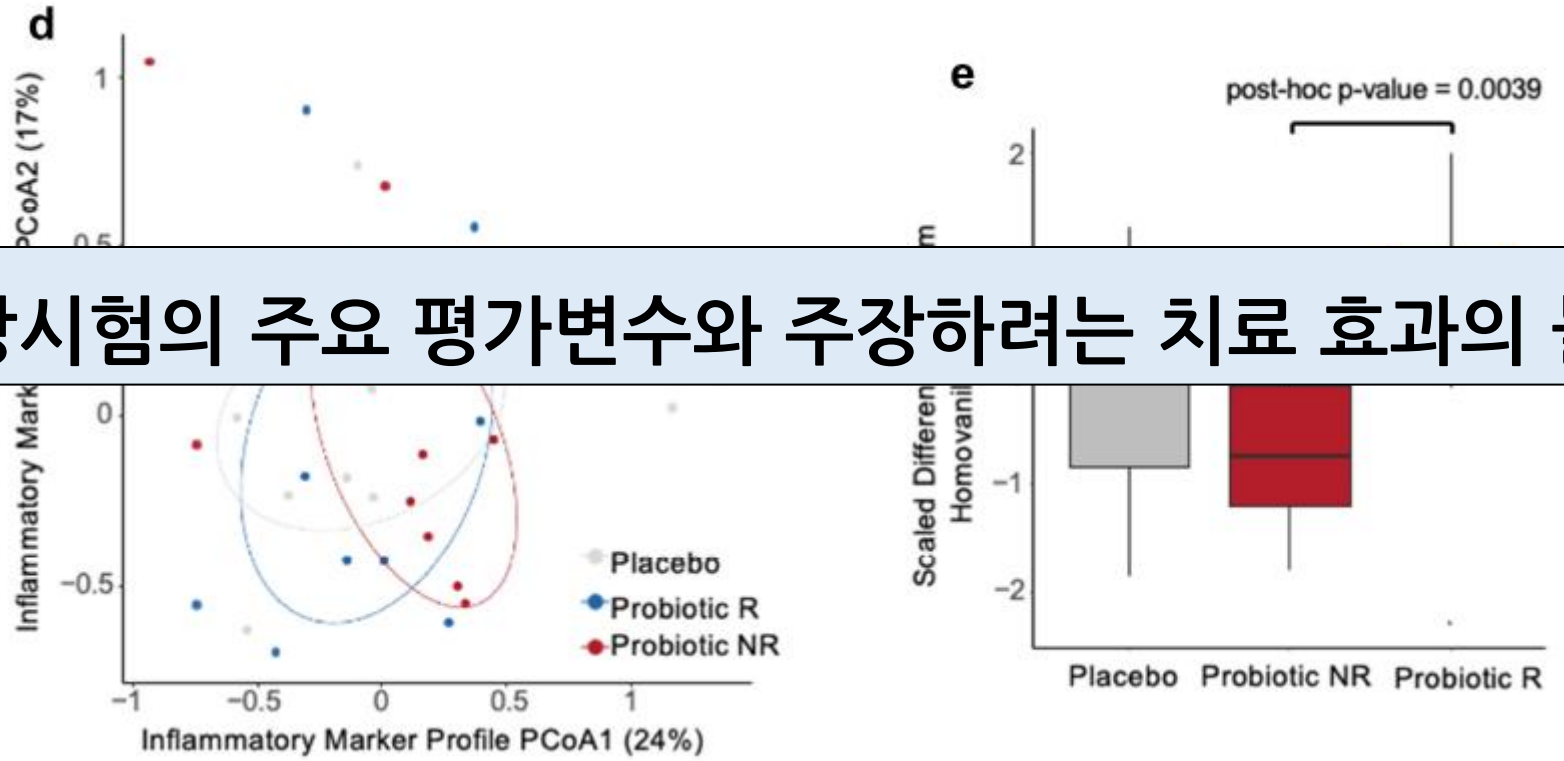
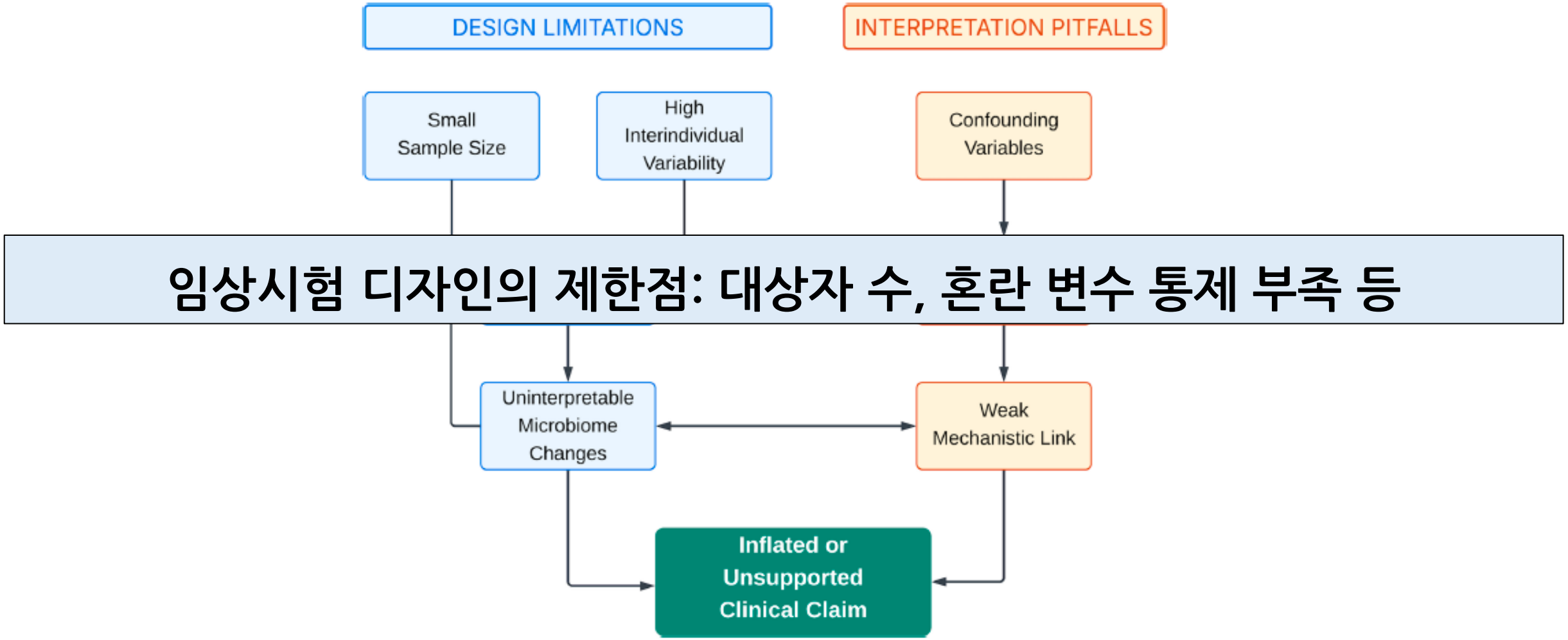


임상시험의 주요 평가변수와 주장하려는 치료 효과의 불일치

Wastyk et al., Gut microbes, 2023

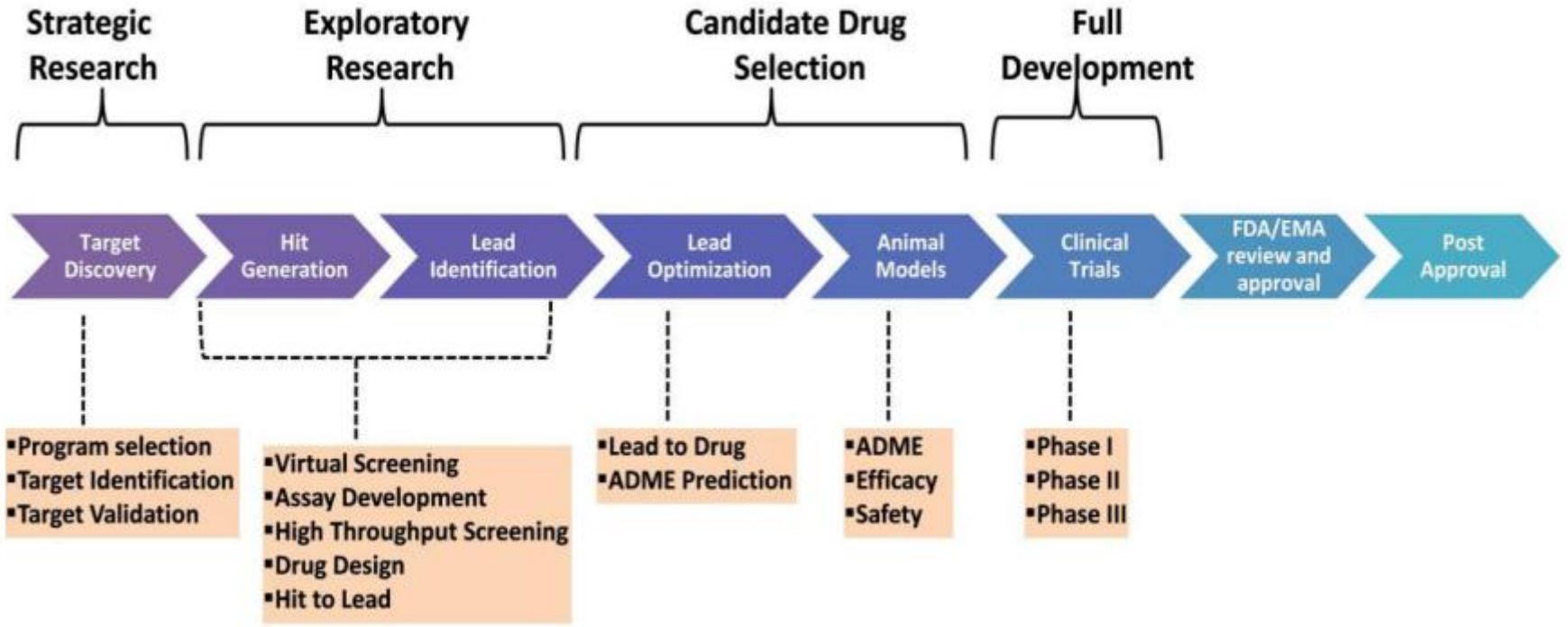
왜 마이크로바이옴 임상시험 대부분이 실패하는가? (3)



RJ Cano and GG Menendez. Microorganisms, 2026

신약, 마이크로바이옴 개발의 특수성

전통적 신약개발 패러다임



Kaur RP. Int J. Life Sci, 2024

성공적인 신약 개발의 뼈대: MoA

유효성 (Efficacy)

질병 경로의 정확한 차단 지점을 파악하여 최적의 바이오마커와 환자군 선별

안전성 (Safety)

On-target 및 Off-target 독성을 사전에 예측하여 임상 단계의 탈락률(Attrition)을 낮춤

PK/PD 분석

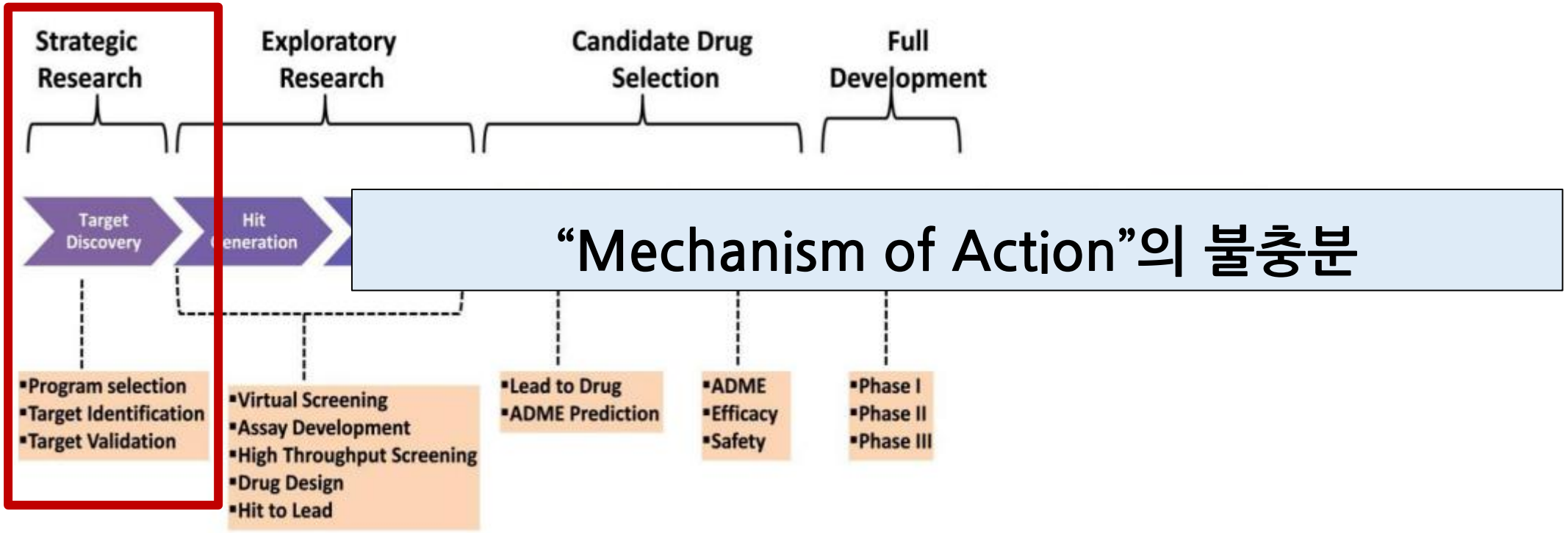
약물 농도와 생리적 반응의 연결 고리를 수학적으로 설계하여 최적의 용량을 결정

Kaur RP. Int J. Life Sci, 2024

PK/PD가 해결하는 개발의 핵심 과제

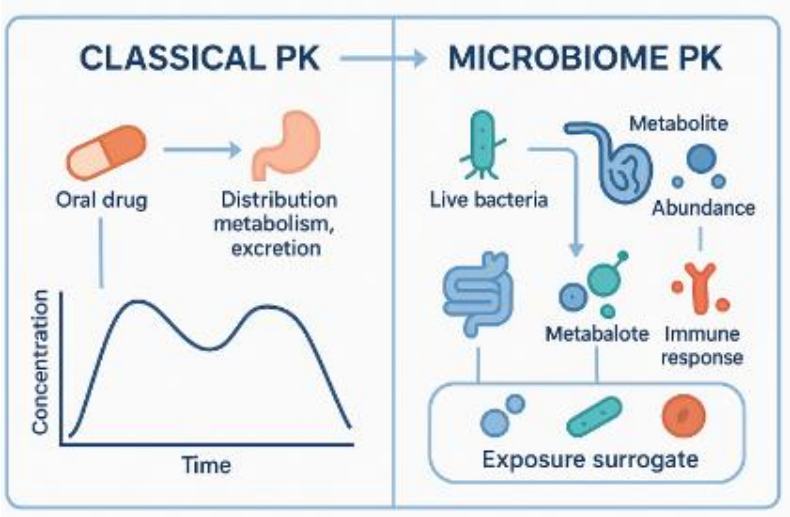
개발 단계별 질문	PK/PD가 제공하는 해답 (Logic)
용량을 어떻게 정할 것인가?	Dose Selection (유효 농도 도달 범위 확인)
투여 간격은 어떻게 설정하나?	Dosing Interval (반감기 및 효과 지속시간)
효과는 왜 나타났는가?	Exposure–Response 또는 Mechanism 확인
이상반응은 노출과 관련 있는가?	Safety Margin (독성 발현 역치 분석)
임상 2상/3상 용량이 타당한가?	Dose Justification (근거 기반의 용량 정당화)

신약, 마이크로바이옴



Kaur RP. Int J. Life Sci, 2024

전통적 약물 vs. 마이크로바이옴의 Pharmacokinetics



구분	전통적 저분자 약물	마이크로바이옴 치료제 (LBP)
측정 지표	혈중 농도 (Plasma Concentration)	장내 생착 및 증식 (Gut Colonization)
평가 요소	흡수, 분포, 대사, 배설 (ADME)	생착, 지속성, 배출 (Shedding)
주요 수치	AUC, Cmax, Tmax	Abundance, Engraftment, Persistence
대사 산물	약물 대사체 (Metabolites)	Microbial Metabolites (SCFA, Bile Acids)

“PK, Exposure”의 재정의 필요

(FDA Live Biotherapeutic Products Guidance, 2016), (VE303 Healthy Volunteer Study, Cell Host Microbe 2022), (Wang et al., Nat Rev Gastroenterol Hepatol 2016)

마이크로바이옴의 Pharmacokinetics

Exposure

투여량 정의

mg 단위가 아닌 CFU (colony forming unit), Spore count, Viable cell count를 통한 투여량 정의가 필수

장내 생착 및 지속

Strain-specific qPCR을 통한 생착 (Engraftment) 여부와 투여 중단 후 지속성을 확인

생태학적 영향

단순 검출을 넘어 미생물 다양성 변화 (Diversity shift) 및 Shedding 양상을 추적

마이크로바이옴 PK/PD

1. 장내 미생물을 직접 타겟하는 경우

VOWST Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VOWST™ safely and effectively. See full prescribing information for VOWST.

VOWST (fecal microbiota spores, live-brpk) capsules, for oral administration
Initial U.S. Approval: YYYY

----------INDICATIONS AND USAGE----------
VOWST is indicated to prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI). (1)

Limitation of Use:
VOWST is not indicated for treatment of CDI.

----------DOSAGE AND ADMINISTRATION----------
For oral administration only. (2)

- Prior to taking the first dose:
  - Complete antibacterial treatment for rCDI 2 to 4 days before initiating treatment with VOWST. (2.1)
  - Drink 296 mL (10 oz) of magnesium citrate on the day before and at least 8 hours prior to taking the first dose of VOWST. In clinical studies, participants with impaired kidney function received polyethylene glycol electrolyte solution (250 mL GoLYTELY, not approved for this use). (2.1)
- The dosage of VOWST is 4 capsules taken orally once daily for 3 consecutive days. (2.2)
- Take each dose (4 capsules) on an empty stomach prior to the first meal of the day. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsule. A single dose is 4 capsules. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Most common adverse reactions (reported in ≥5% of participants) were abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%) and diarrhea (10.0%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics, Inc. at 1-833-246-2566 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Antibacterials should not be administered concurrently with VOWST. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: M/YYYY

1. 장내 미생물을 직접 타겟하는 경우

VOWST Label

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Prior to taking the first dose
  2.2 Dosing regimen
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Transmissible infectious agents
  5.2 Potential presence of food allergens
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.4 Pediatric Use
  8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

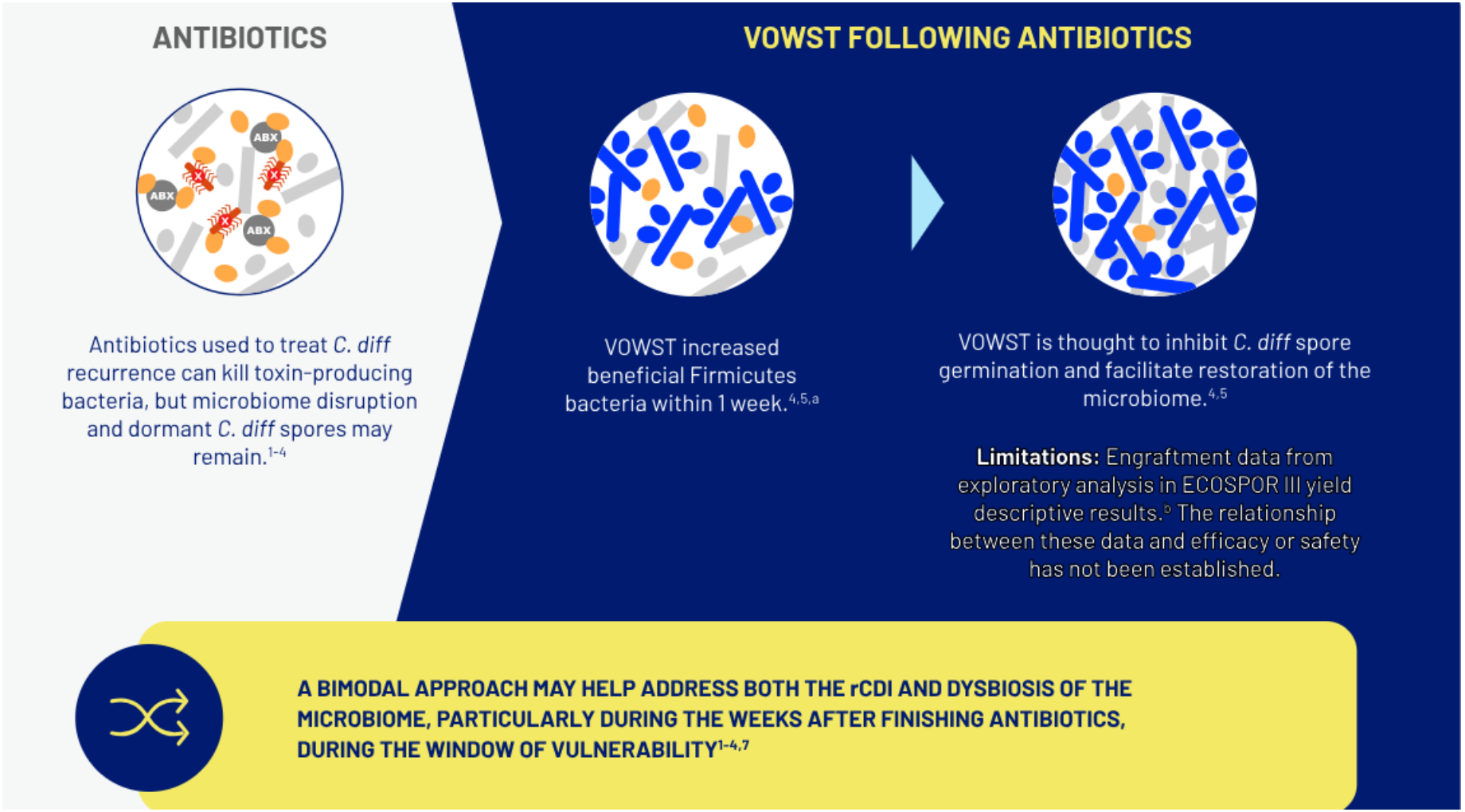
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of VOWST has not been established.

1. 장내 미생물을 직접 타겟하는 경우

VOWST



Vowsthcp.com/moa

1. 장내 미생물을 직접 타겟하는 경우

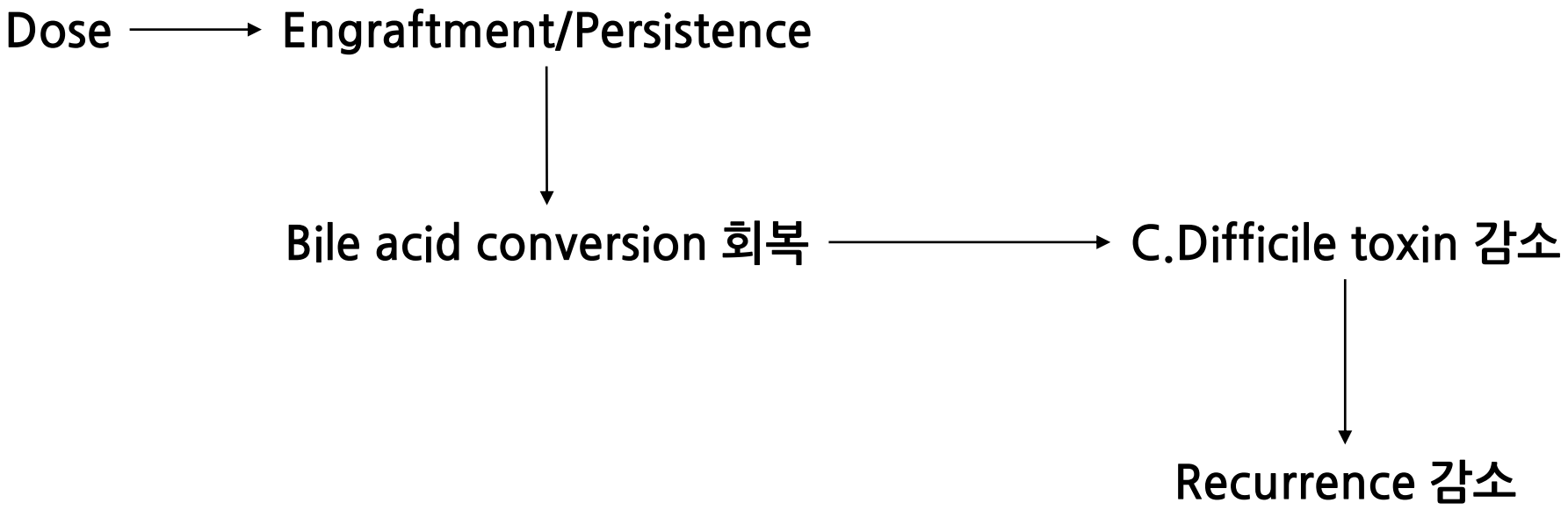
PK-like 지표: 장내 노출과 생착

전통적 PK 개념	장내 미생물 타겟 (예, C.difficile 재발 방지 제제)
Dose	CFU, spore count, viable cell count, 투여 strain 수
Absorption	일반적으로 전신 흡수보다 장내 도달 여부가 중요
Exposure	대변 내 투여 균주 검출량, stratin-specific qPCR, metagenomic strain tracking
Distribution	대장 내 colonization 또는 ecological niche occupation
Persistence	투여 후 1, 2, 4, 8, 12주까지 균주 지속성
Elimination	Fecal shedding 감소 또는 소실 시점
Bioavailability	장내 생착률 또는 기능적 활성 발현 정도

PD-like 지표: 타겟 균의 억제와 장내 기능 회복

PD 측면	장내 미생물 타겟 (예, C.difficile 재발 방지 제제)
Pathogen level PD	C.difficile toxin A/B, toxigenic C.difficile load, spore burden
Microbiome level PD	다양성 회복, donor-like engraftment, C.difficile 저항성 관련 taxa 회복
Functional PD	Bile acid metabolism 회복, SCFA 회복, colonization resistance marker
Host level PD	설사 횟수, 염증 지표, fecal calprotectin, CRP
Clinical endpoint	CDI recurrence-free survival, 8주 또는 12주 재발률, hospitalization

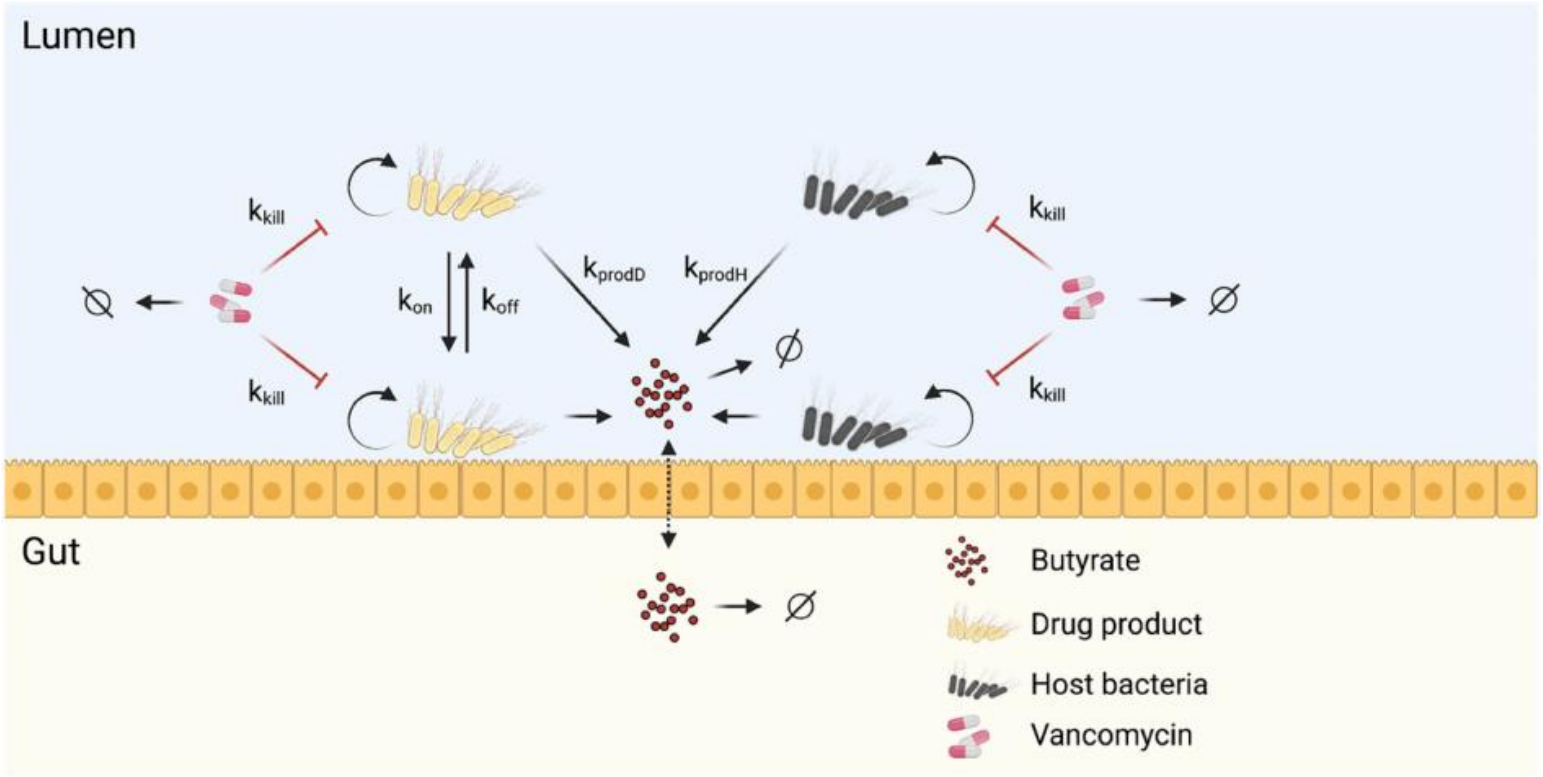
1. 장내 미생물을 직접 타겟하는 경우



1. 장내 미생물을 직접 타겟하는 경우

- **건강 성인 대상: 적정 용량 용법 결정**

Dose ⟶ Engraftment/Persistence ⟶ Butyrate 증가



Renardy et al., CPT 2023

Cellular kinetics

$$\frac{dH_L}{dt} = k_{growH}\left(1 - \frac{H_L}{CC_{otherL}}\right)H_L - k_{kill}VH_L$$

$$\frac{dH_S}{dt} = k_{growH}\left(1 - \frac{H_S}{CC_{otherS}}\right)H_S - k_{kill}VH_S$$

$$\frac{dQ_L}{dt} = k_{growH}Q_L\left(1 - \frac{Q_L + D_L}{CC_L}\right) - k_{kill}VQ_L$$

$$\frac{dQ_S}{dt} = k_{growH}Q_S\left(1 - \frac{Q_S + D_S}{CC_S}\right) - k_{kill}VQ_S$$

Vancomycin

$$\frac{dV}{dt} = -k_{clear}V$$

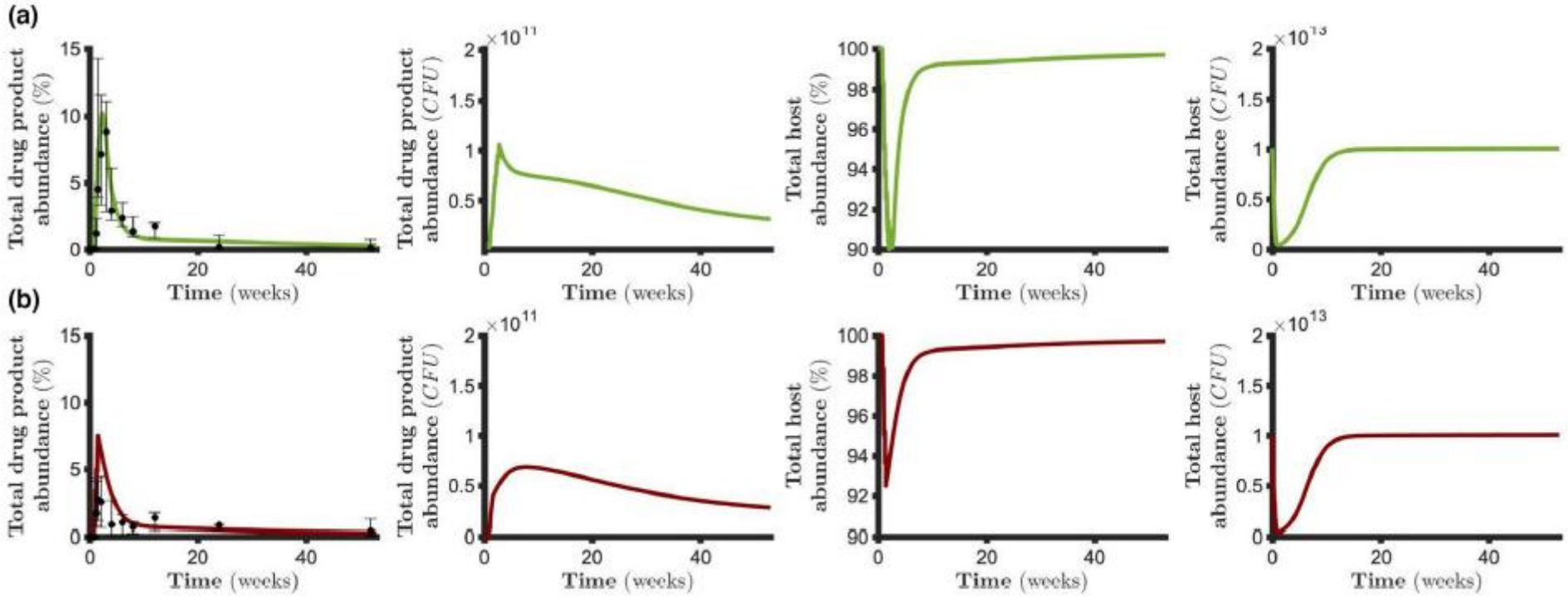
Butyrate dynamics

$$\frac{dB_L}{dt} = k_{prodH}\left[\left(1 - \frac{1}{1 + \frac{0.5*CC_{Ltot}}{H_{Ltot}}}\right)H_{Ltot} + \left(1 - \frac{1}{1 + \frac{0.5*CC_{Stot}}{H_{Stot}}}\right)H_{Stot}\right] + k_{prodD}(D_L + D_S) - \left(SA*\frac{D}{r}\right)\left(10^{-15}\frac{L}{um^3}\right)\left(\frac{B_L}{V_L} - \frac{B_G}{V_G}\right) - (k_{out} + k_{decay})B_L$$

$$\frac{dB_G}{dt} = \left(SA*\frac{D}{r}\right)\left(10^{-15}\frac{L}{um^3}\right)\left(\frac{B_L}{V_L} - \frac{B_G}{V_G}\right) - k_{decay}B_G$$

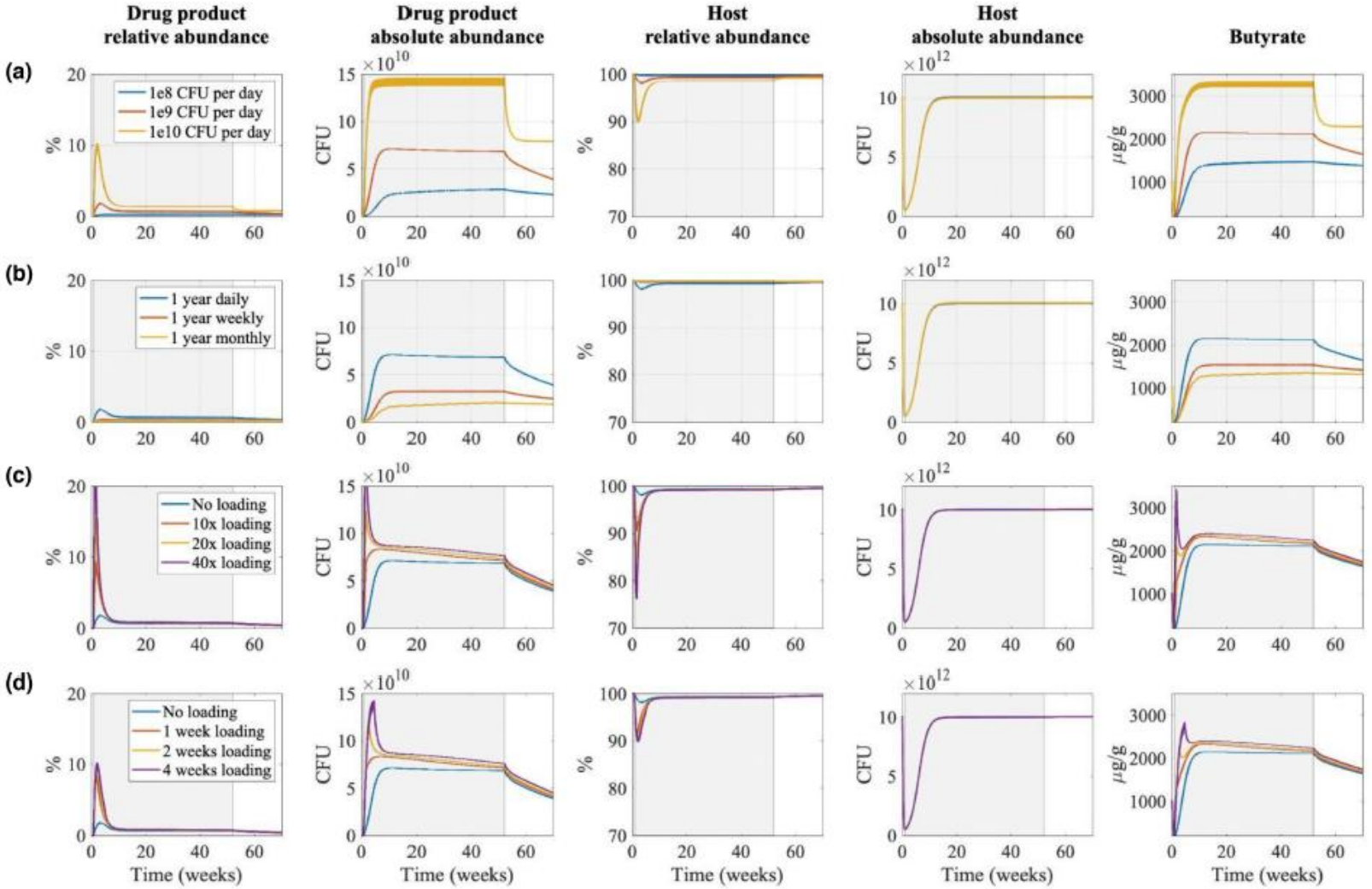
1. 장내 미생물을 직접 타겟하는 경우

Cellular kinetics



Renardy et al., CPT 2023

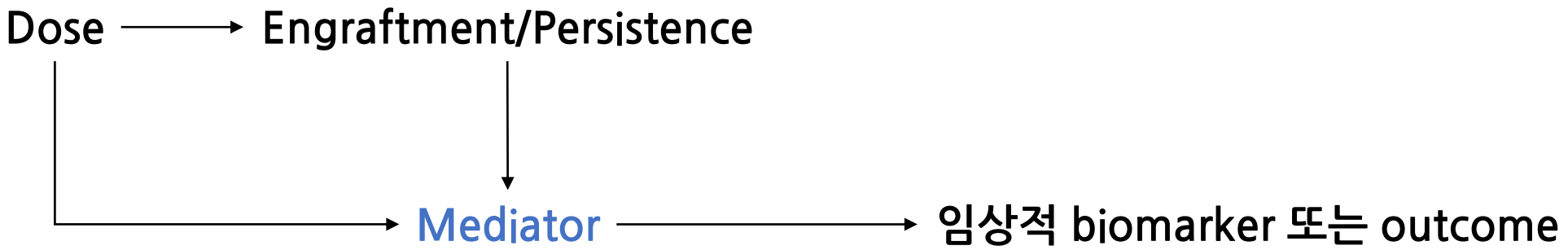
1. 장내 미생물을 직접 타겟하는 경우



Renardy et al., CPT 2023

2. 전신 질환의 예방, 치료, 증상 완화를 목적으로 하는 경우

Dose → Engraftment/Persistence → C.Difficile toxin 감소 → Recurrence 감소



PK-like 지표: biological exposure를 다층적으로 정의

투여한 균 또는 microbiome 변화가 숙주가 감지할 수 있는 기능적 신호를 만들었는가?

PK 측면	측정 지표
Product exposure	CFU, viable count
Gut ecological exposure	Strain persistence, engraftment, baseline microbiome-dependent colonization
Functional exposure	Microbial gene/pathway activation, metatranscriptomics, metaproteomics
Metabolite exposure	Plasma/fefcal/urine metabolomics
Host exposure to microbial products	Circulating SCFA, bile acid derivatives, tryptophan metabolites, LPS-related markers

PD-like 지표: disease biology와 직접 연결

적응증	Microbiome function	후보 PD/biomarker
대사질환/비만	SCFA, bile acid, incretin axis, insulin sensitivity	Fasting glucose, insulin, HOMA-IR, OGTT, GLP-1, lipid profile
염증/면역질환	Barrier function, immune modulation	CRP, IL-6, TNF-alpha, fecal calprotectin, Treg/Th 17 balance
암 보조치료	Immune response, checkpoint response modulation	Immune cell phenotype, cytokines, tumor immune markers, treatment response
신경계/정신건강	Gut-brain metabolites, tryptophan pathway	Kynurenine/tryptophan ratio, inflammatory cytokines, validated symptom scales
심혈관질환	TMAO, bile acid, inflammation	TMAO, LDL-C, hsCRP, BP, endothelial function

신약, 마이크로바이옴

항목	장내 미생물 타겟 (C.difficile)	전신 질환 타겟
작용 부위	장내 국소 작용	장내 → 전신 host response
PK-like exposure	생착, persistence, pathogen suppression	기능적 대사체 노출, host biomarker 변화
PD	C.Difficile toxin/load 감소, bile acid 회복	질환 관련 host pathway 변화
임상 endpoint	CDI recurrence 감소	질환 별 임상 outcome 또는 biomarker
난이도	상대적으로 낮음	매우 높음
주요 위험	재발 endpoint와 microbiome marker 연결 부족	Microbiome 변화와 systemic benefit 사이의 인과성 부족
핵심 분석	Strain tracking + toxin + bile acid	Multi-omics + plasma metabolomics + host biomarker

마이크로바이옴-Drug Interaction

Pharmacomicrobiomics

VOWST Label

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Prior to taking the first dose
  2.2 Dosing regimen
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Transmissible infectious agents
  5.2 Potential presence of food allergens
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.4 Pediatric Use
  8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of VOWST has not been established.

7 DRUG INTERACTIONS

VOWST contains bacterial spores; therefore, antibacterials should not be administered concurrently with VOWST.

Pharmacomicrobiomics

- Definition
  - The study of how intra- and inter-individual differences in the microbiome affect drug response, including bioavailability, efficacy, and toxicity.

- Mechanism focus
  - It examines both direct (microbial metabolism) and indirect (immune modulation, competition for enzymes) interactions between microbes and drugs.

Gronich et al., CPT 2025

Pharmacomicrobiomics

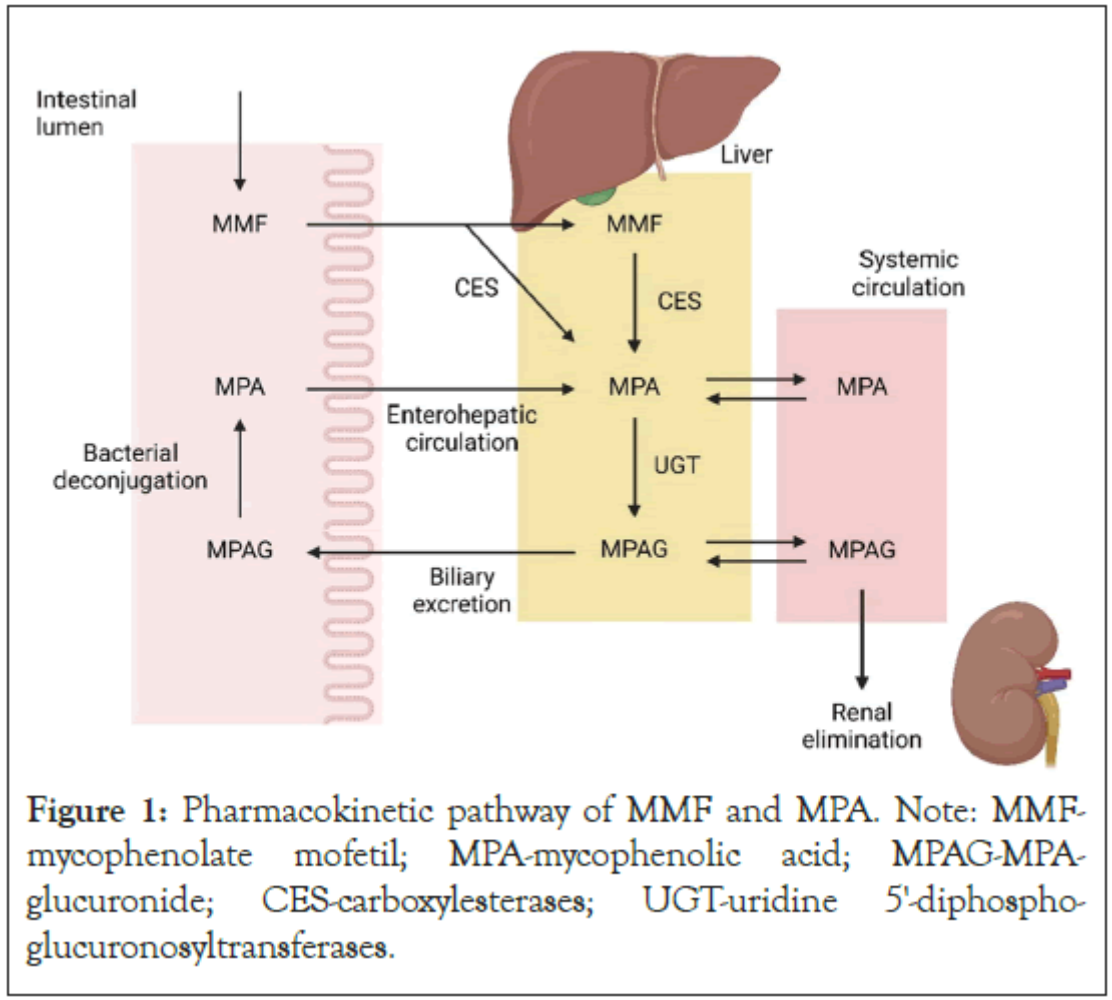
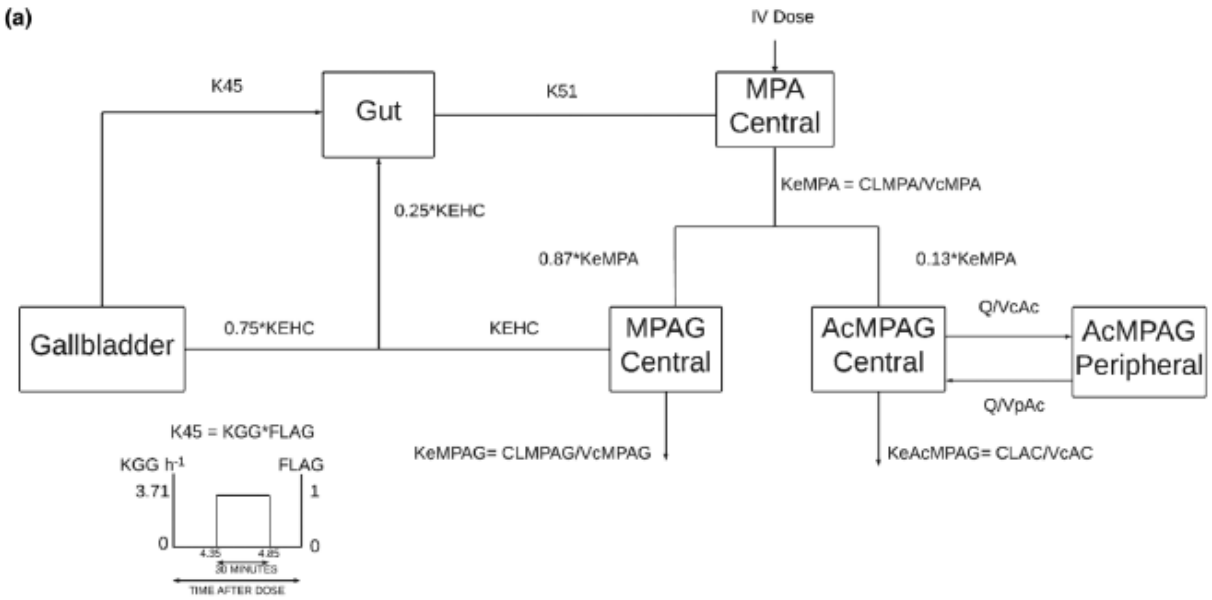
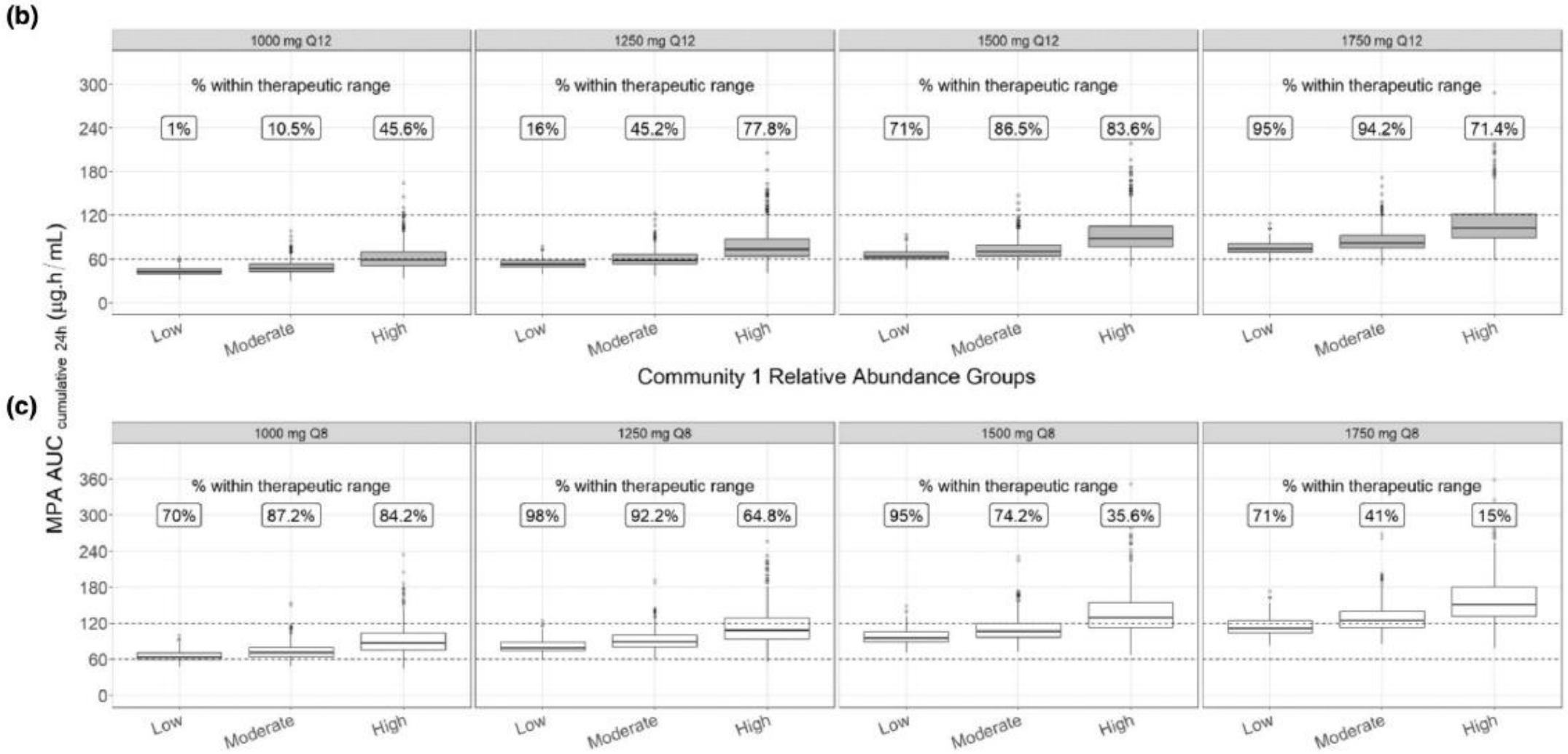


Figure 1: Pharmacokinetic pathway of MMF and MPA. Note: MMF-mycophenolate mofetil; MPA-mycophenolic acid; MPAG-MPA-glucuronide; CES-carboxylesterases; UGT-uridine 5'-diphospho-glucuronosyltransferases.



Saqr et al., Clinical pharmacology & therapeutics 2024
Sagcal-Gironella, et al., Journal of clinical trials 2024

Pharmacomicrobiomics



Saqr et al., Clinical pharmacology & therapeutics 2024

Pharmacomicrobiomics

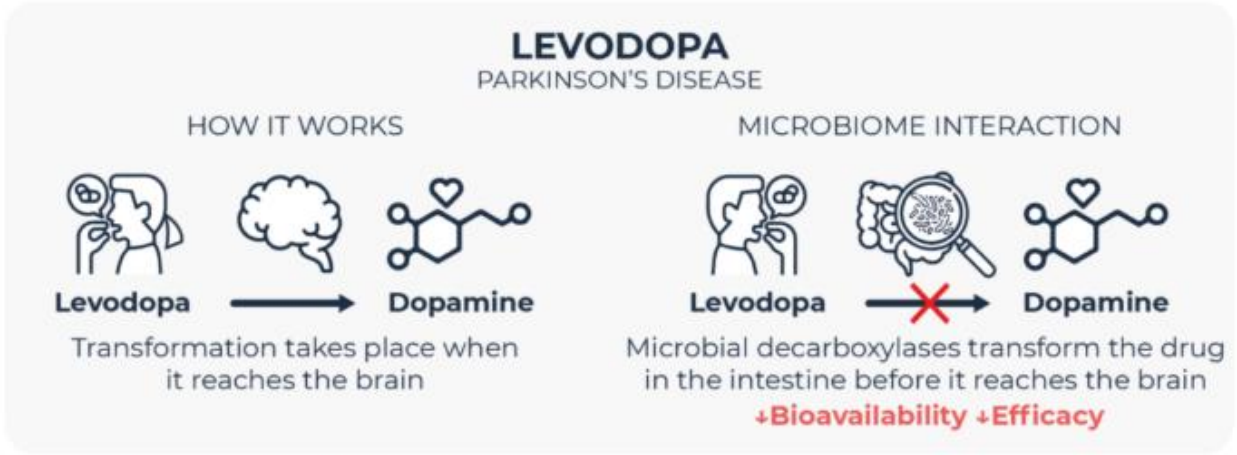


Figure 1. Gut microbiome-Levodopa biotransformation.

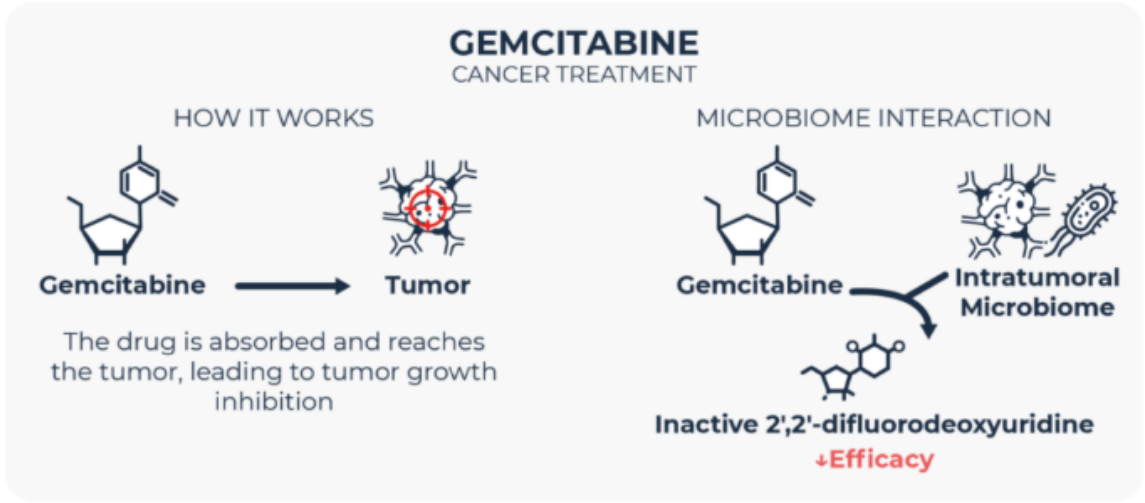


Figure 2 – Intratumoral microbiome-Gemcitabine biotransformation

https://www.microbiometimes.com/pharmacomicrobiomics-the-universe-of-microbiome-drug-interactions/

맺음말

결론

PK/PD 개념의 재정의

- 기존 저분자 약물의 **ADME** 패러다임에서 **마이크로바이옴 특화 지표**(생착, 유전체 변화, 분포, 적응)로 전환 필수
- 단순 혈중 농도 측정이 아닌 **'Functional Exposure** (대사체, 면역 반응, 유전자 발현)'를 통한 다층적 노출 정의

GEN-001 임상 데이터의 함의

- Colonization vs. Function: 장내 직접 생착(Colonization)이 일어나지 않더라도 기능적 대사 작용을 통해 치료 효과 발현 가능 확인
- Surrogate Marker: 혈중 대사체 패턴 변화를 통해 장내 마이크로바이옴 노출(Exposure)을 간접적으로 측정하는 Surrogate Biomarker 가능성 확인

https://www.microbiometimes.com/pharmacomicrobiomics-the-universe-of-microbiome-drug-interactions/

YONSEI UNIVERSITY

KONECT 국가임상시험지원재단 Korea National Enterprise for Clinical Trials

SCRC 스마트임상시험신기술개발연구사업단 SmartTech Clinical Research Center

감사합니다

Severance