ADVANCES IN MICROBIAL BIOTECHNOLOGY

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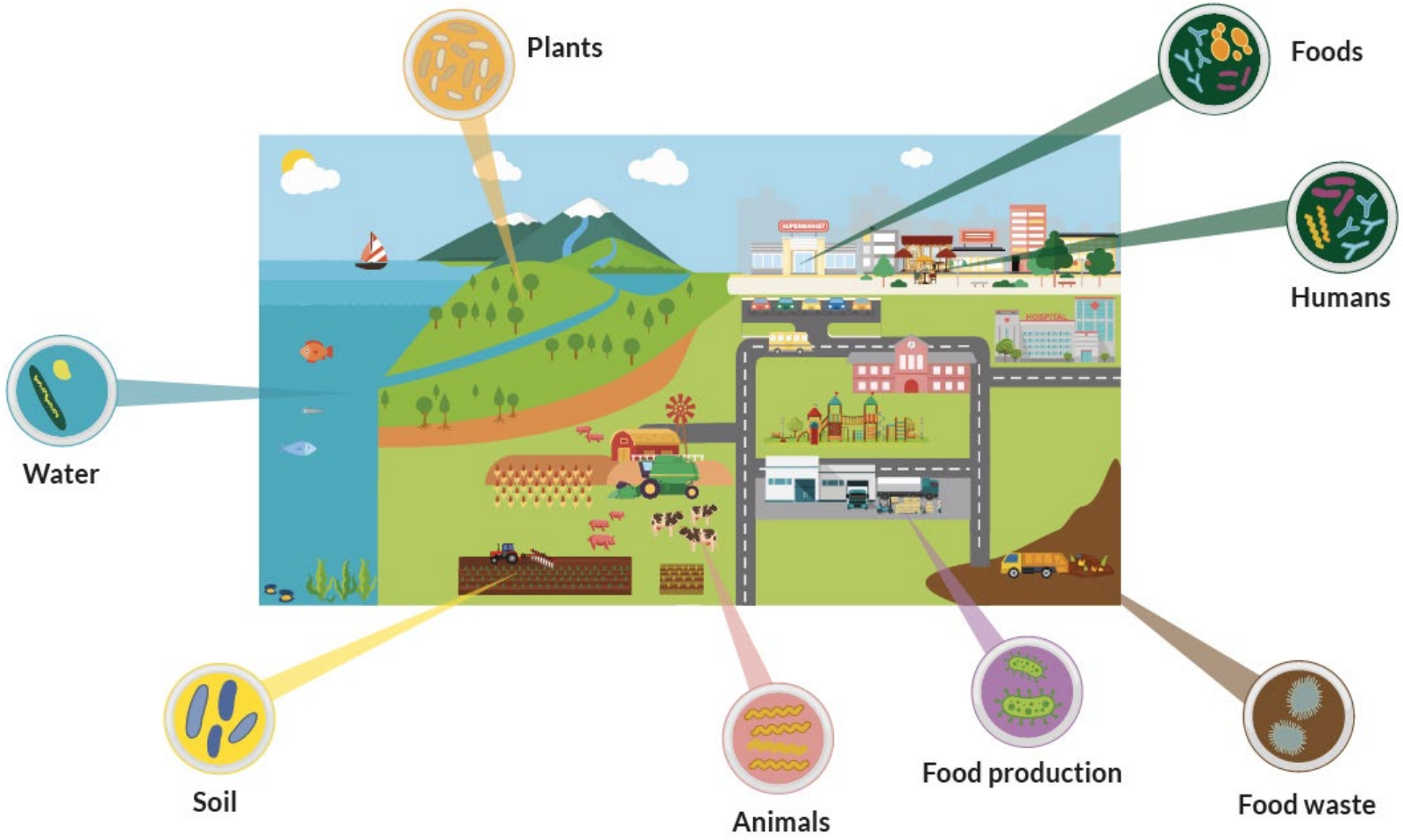
DISCLAIMER

- **Employee of Société des Produits Nestlé SA (Switzerland)**
  Senior R&D specialist in Biotransformation; Nestle Culture Collection coordinator
  Expertise in beneficial microbes, their metabolism and genetics (probiotics and fermentation)

- **PhD in Microbiology from Wageningen University (The Netherlands)**
  Host & Microbe Interactomics group; Prof. M. Kleerebezem

Research and Development

MICROBES ARE EVERYWHERE…



Extremophiles

Hot springs, fumaroles

Hypersaline lakes

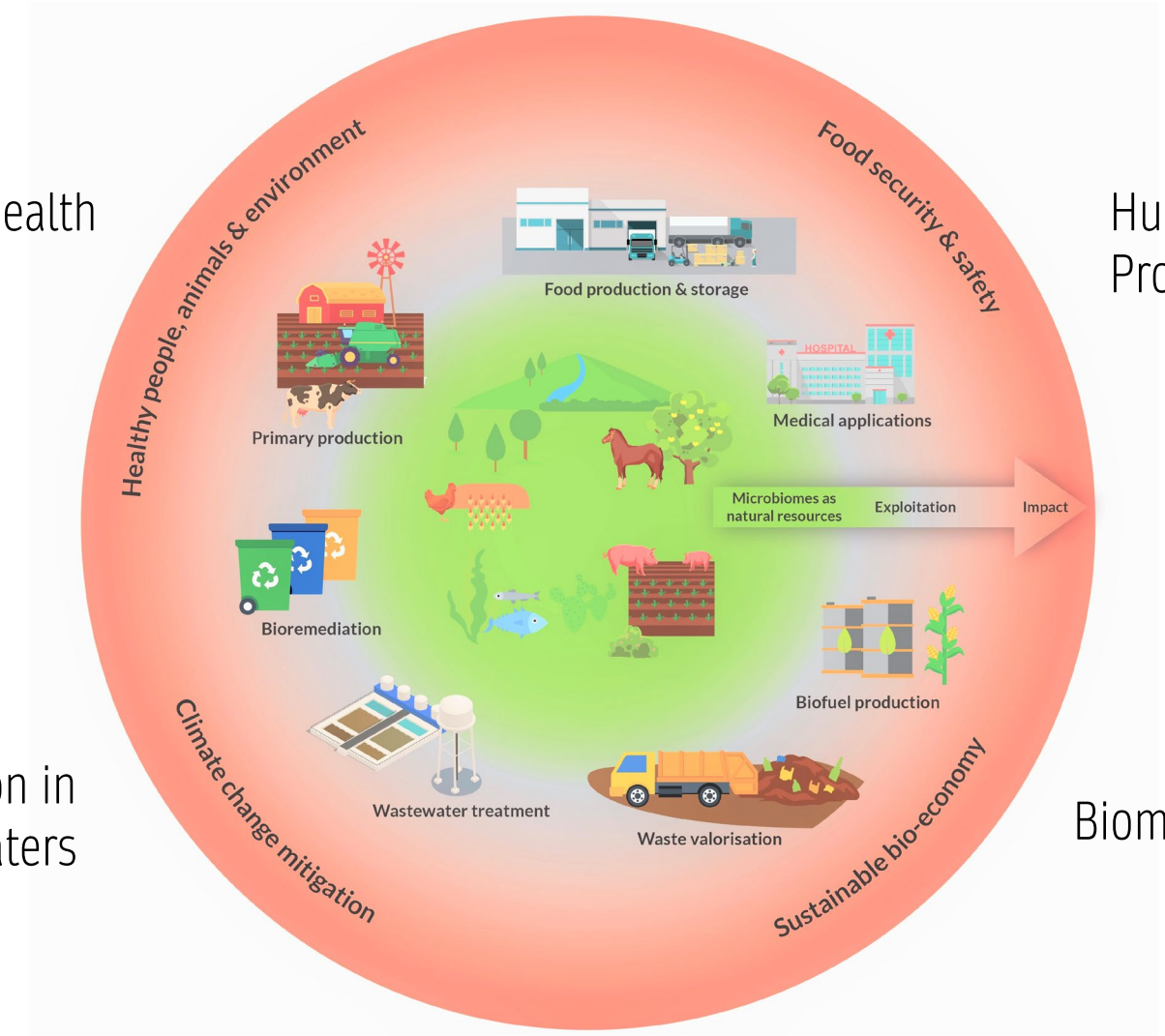
The project MicrobiomeSupport (www.microbiomsupport.eu) has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 818116.

… AND POSSESS TREMENDEOUS VALUE

Fermented foods

Soil & plant health

Humans & animals:
Probiotics & biotherapeutics



Bioremediation in soil & waters

Biomass valorization

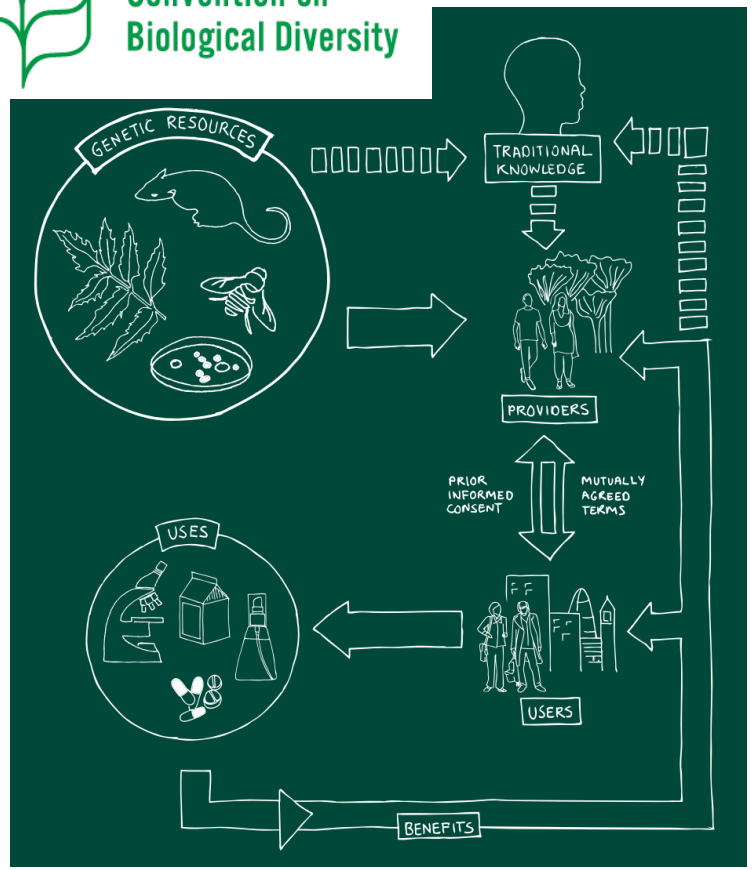
The project MicrobiomeSupport (www.microbiomsupport.eu) has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 818116.

COMPLIANT EXPLOITATION OF MICROBES

Environmental isolates
(soil, water, plants, etc..)

Human isolates

Convention on Biological Diversity



International Ethical Guidelines for Health-related Research Involving Humans

CIOMS

WMA Declaration Of Helsinki :
Ethical Principles For Medical Research Involving Human Subjects

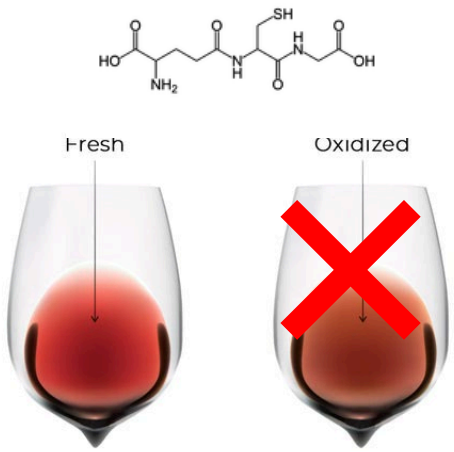
WMA WORLD MEDICAL ASSOCIATION

ICH -Guidelines for good clinical practices

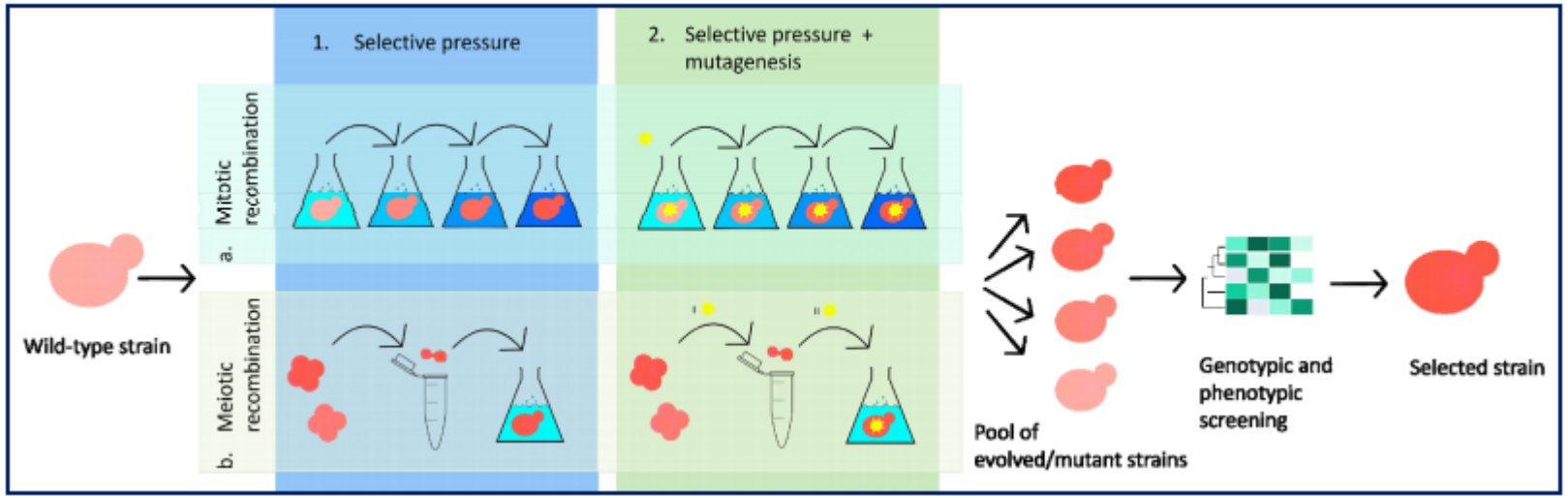
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENHANCE NATURE'S CAPACITIES ADAPTIVE EVOLUTION

Glutathione



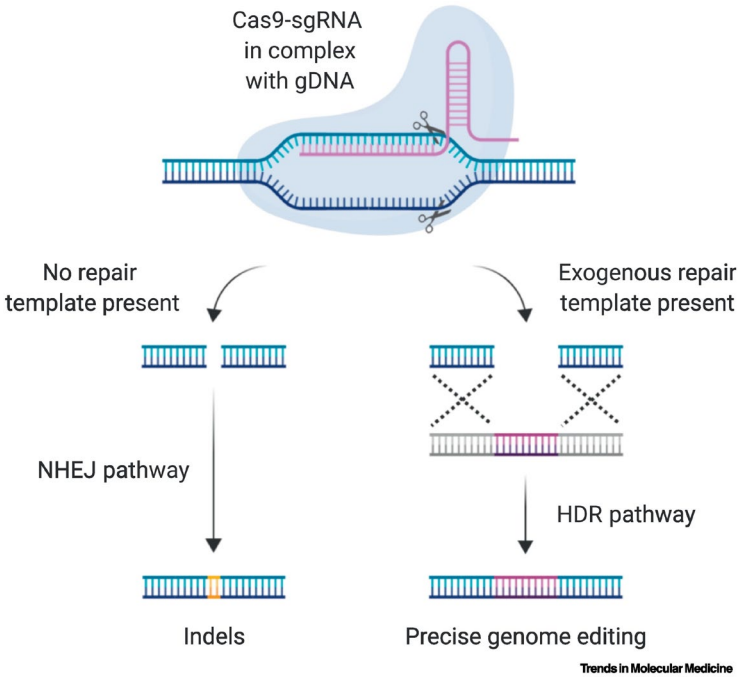
"Adaptive evolution results from the propagation of **advantageous mutations through positive selection**"



De Vero et al. AIMS Microbiology, 2017, 3(2): 155-170

ENHANCE NATURE'S CAPACITIES
TARGETED GENOME EDITING

CRISPR-Cas9

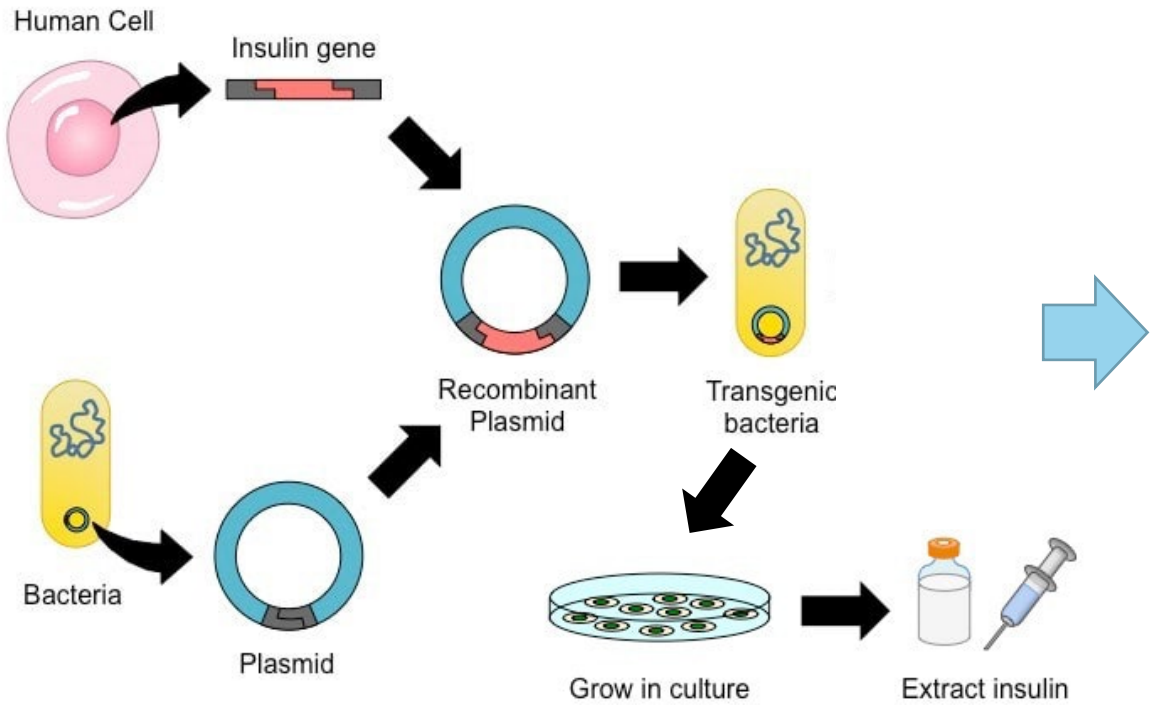


von Kampen and van Rooij, Trends in Molecular Medicine, September 2019, Vol. 25, No

Industrial strains	product
Synechococcus elongatu	succinic acid
Saccharomyces cerevisiae	free fatty acid
E.coli	n-butanol
Corynebacterium glutamicum	glutamic acid
Saccharomyces cerevisiae	β-carotene
Bacillus subtilis	BLA
Clostridium tyrobutyricum	n-butanol
Corynebacterium glutamicum	γ-amino-butyric acid
E.coli	fatty acids
E.coli	5-amino-levulinicacid
E.coli	isopropanol
E.coli	β-carotene
Bacillus subtilis	riboflavin
Myceliophthora thermophile	cellulase
Filamentous fungus	mucic acid
Aspergillus niger	galactaric acid

Zhao et al. 2020, Synthetic and Systems Biotechnology 5 (2020) 269–276

«COPYING» NATURE CAPACITY
RECOMBINANT DNA TECHNOLOGY



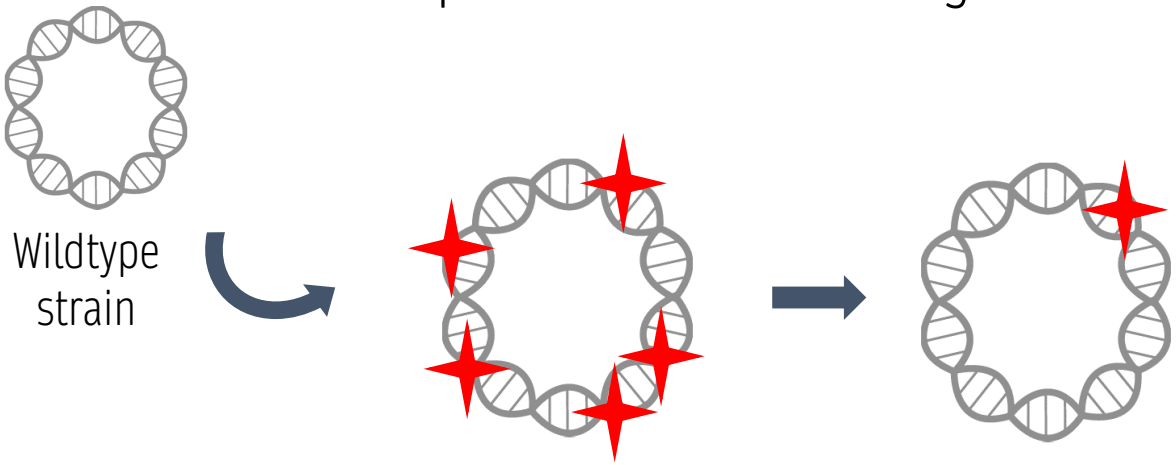
https://mysciencesquad.weebly.com/

Chassis cells	Therapeutic payload	Diseases	Development stages
Lactobacillus	IL-10	IBD	Mice
Lactobacillus	IL-4	IBD	Mice
E. coli	IL-35	IBD	Mice
EcN	Trefoil factor	IBD	Mice
Bacillus thermophilus	Superoxide dismutase	IBD	Mice
Bifidobacterium	RhMnSOD	IBD	Mice
Lactobacillus	Elafin	IBD	Mice
Lactobacillus NZ9001	Recombinant mouse heme oxygenase-1	IBD	Mice
Lactobacillus	Pancreatitis-related protein	Intestinal mucositis	Mice
EcN	Butyrate	Colon cancer HT29	Mice
Salmonella, Typhimurium	IL-1β	Colon cancer CT26	Mice
E. coli	B-glucuronidase	Colon cancer	Mice
Salmonella Typhimurium,	Autoinducer	Colorectal cancer MC26	Mice
EcN	Tum-5	Melanoma	Mice
Salmonella VNP20009	Sox2	Lung cancer	Mice
Salmonella	Transforming growth factor alpha-*pseudomonas* exotoxinTGFa-PE38	Colon cancer CT26 & Breast cancer 4 T-1	Mice
Salmonella SL7207	Diaminopimelate DAP	Hepatocellular carcinoma	Mice
Lactobacillus	GLP-1	Diabetes	Mice
Lactobacillus	Heat shock protein 65HSP65, IA2P2	Diabetes	Mice
Lactobacillus	GLP-1	Obesity	Mice
Bacillus subtilis SCK6	Butyric acid	Obesity	Mice
Bacillus subtilis SCK6	BA	Obesity	Mice
EcN SYNB1020	I-argininel-arg	HyperammonemiaHA	Stop
EcN SYNB1618	Insert phenylalanine ammonia lyase and L-amino acid deaminase gene	PhenylketonuriaPKU	Phase 1/2a
Lactobacillus plantarum	Angiotensin-converting enzyme inhibitory peptidesACEIPS	Hypertensive	Mice
Vibrio cholerae strain Haiti V	Delete CTXF, CTXA, RECA genes	Cholera	Infant rabbit
Meningitis MenB YH102， YH103	Delete rfaF, metH, siaD	Meningitis	Mice
EcN	Insert Phl p1 and Phl p5 gene, control the level of IgE	Allergic poly-sensitization	Mice

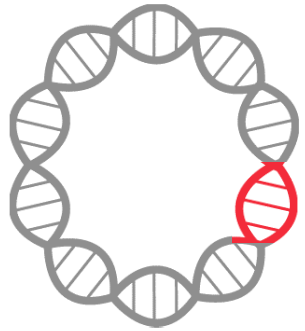
Liu et al., 2022, Front. Microbiol. 13:997587

CORRESPONDING GENETIC SIGNATURES

Adaptive evolution → targeted editing

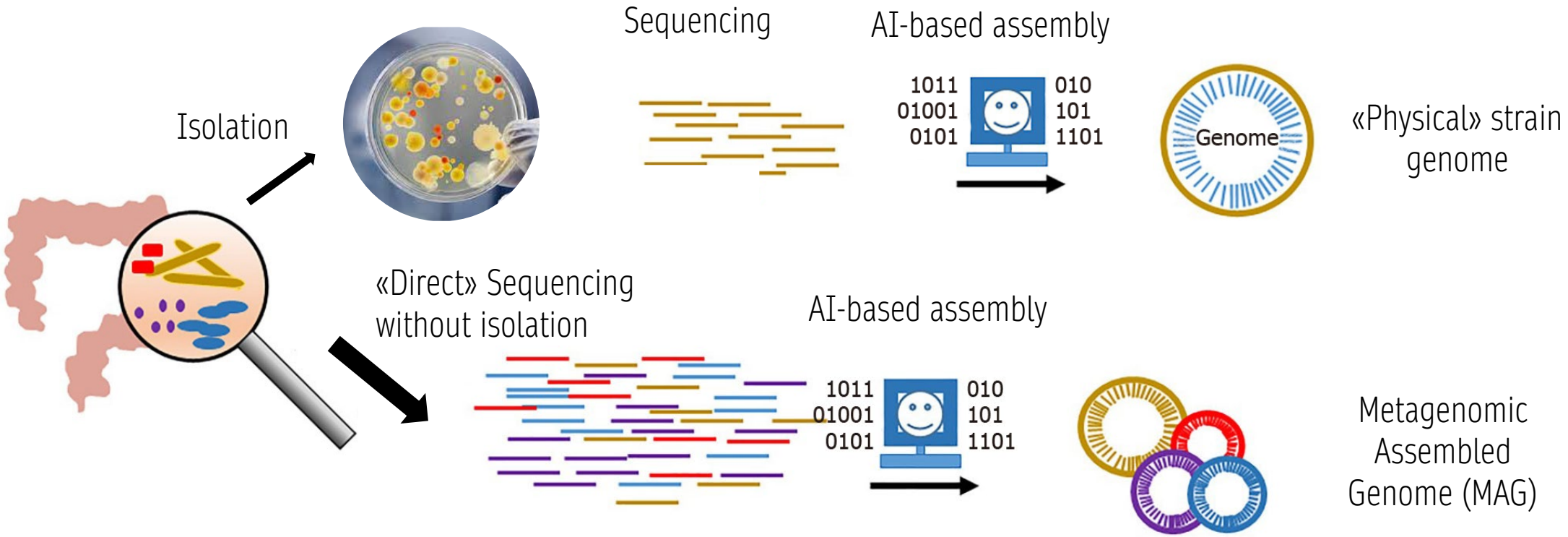


Recombinant DNA technology



Addition of foreign DNA

DO WE NEED «PHYSICAL» STRAINS ? METAGENOMIC ASSEMBLED GENOMES



Modified from Wan, Artif Intell Cancer. Oct 28, 2021; 2(5): 69-78

DO WE NEED «PHYSICAL» STRAINS ? E.G. IN SILICO ENZYME DISCOVERY

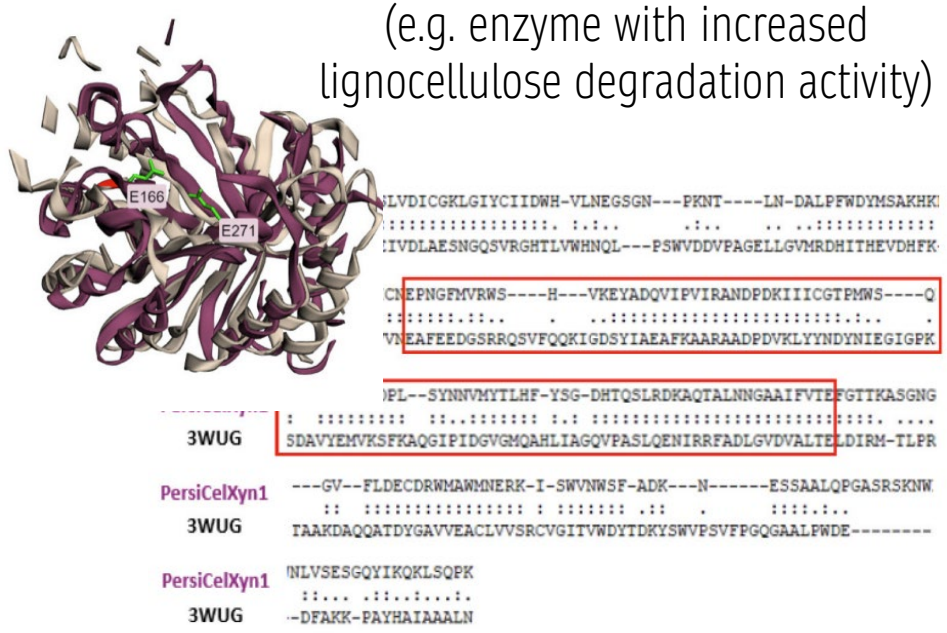
«Physical» strain genome

Metagenomic Assembled Genome (MAG)

AI-base prediction of function

[NCBI Prokaryotic Genome Annotation Pipeline (nih.gov)]

In silico functional prediction (e.g. enzyme with increased lignocellulose degradation activity)



Ariaeenejad et al. International Journal of Biological Macromolecules 177 (2021) 211–220

SUMMARY

- Microbes are everywhere, but their exploitation should be compliant with National/International reglementation
- Beyond recombinant DNA technology, new «non-GMO» technics can be used to improve/inhibit specific strain capacities
    - Depending on the technology used, the extend of genetic changes can vary a lot
- With the advancement of sequencing and artifical intelligence, it is today possible to discover new strains / functions, without going through «physical» isolation

THANK YOU

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