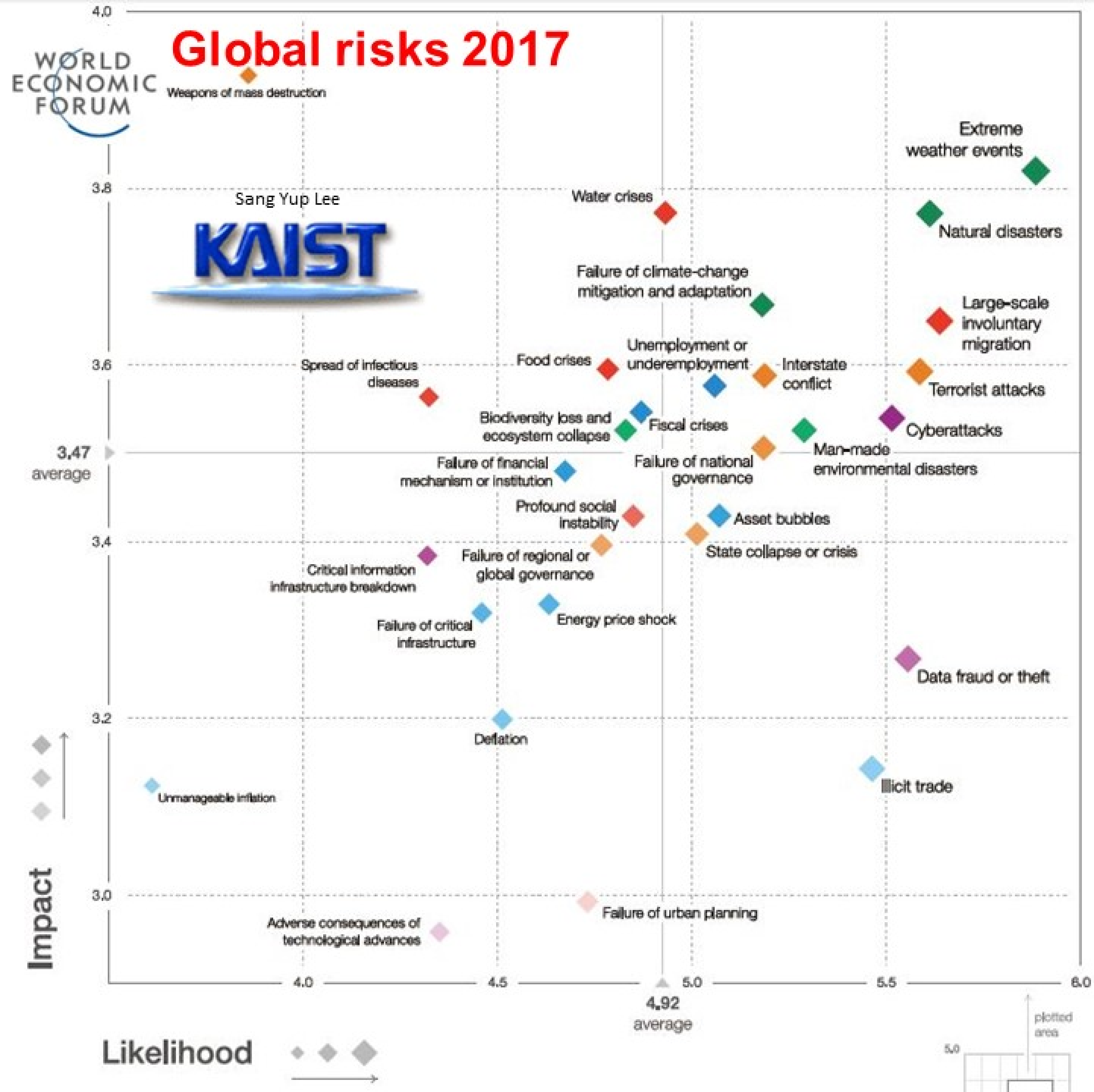
바이오경제와 합성생물학

이상엽
특훈교수
KAIST 연구원장

Global risks 2017



기후변화

대규모 난민

테러

물부족

고령화

고용절벽

감염질환

사이버공격

에너지위기

식량위기

....

바이오테크놀로지

의약/치료/진단

식량/영양/기능성 식품

화학물질/연료/고분자

환경오염 처리/수처리

바이오전자/나노바이오

…

SUSTAINABLE DEVELOPMENT GOALS

17 GOALS TO TRANSFORM OUR WORLD

Sang Yup Lee

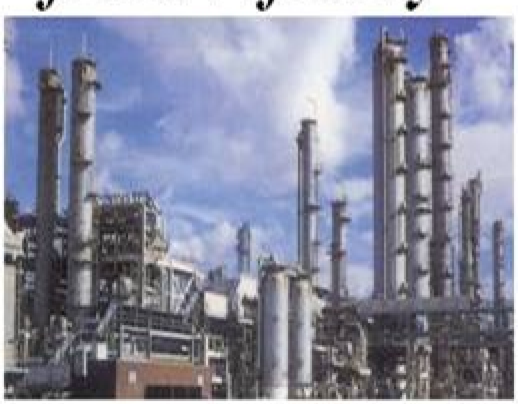
산업바이오로 재생가능한 비식용 바이오매스로부터 화학품, 연료, 물질의 지속가능한 생산

from fossil oil

to renewable biomass

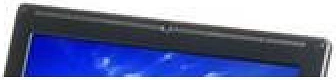
KAIST Institute for the BioCentury
CSSB
Center for Systems & Synthetic Biotechnology

from refinery



to biorefinery




질문:

이 모든 화학물질들을 바이오리파이너리로 생산 가능?



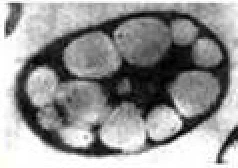


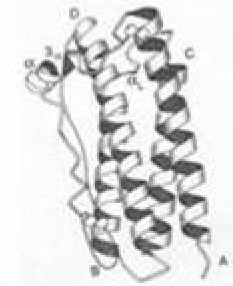

미생물에 의한 화학물질 생산 ?

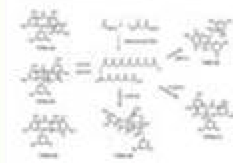
MBEL

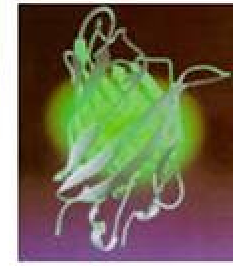
Primary metabolites
Secondary metabolites
Proteins/Peptides
Enzymes
Lipid/Fatty acids
Carbohydrates
Whole cell catalyst

자연계에서 분리시
성능 매우 낮음









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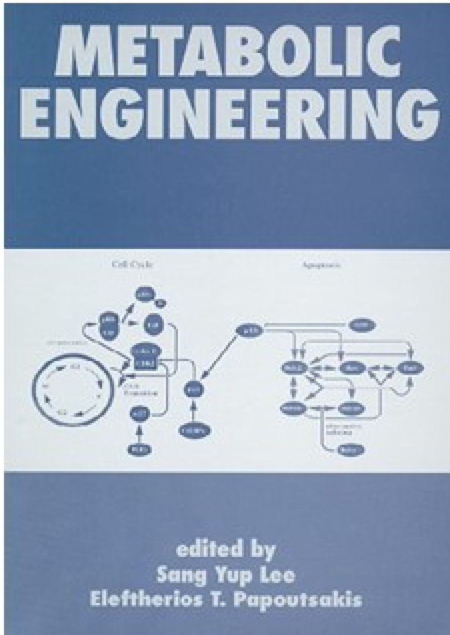
대사공학

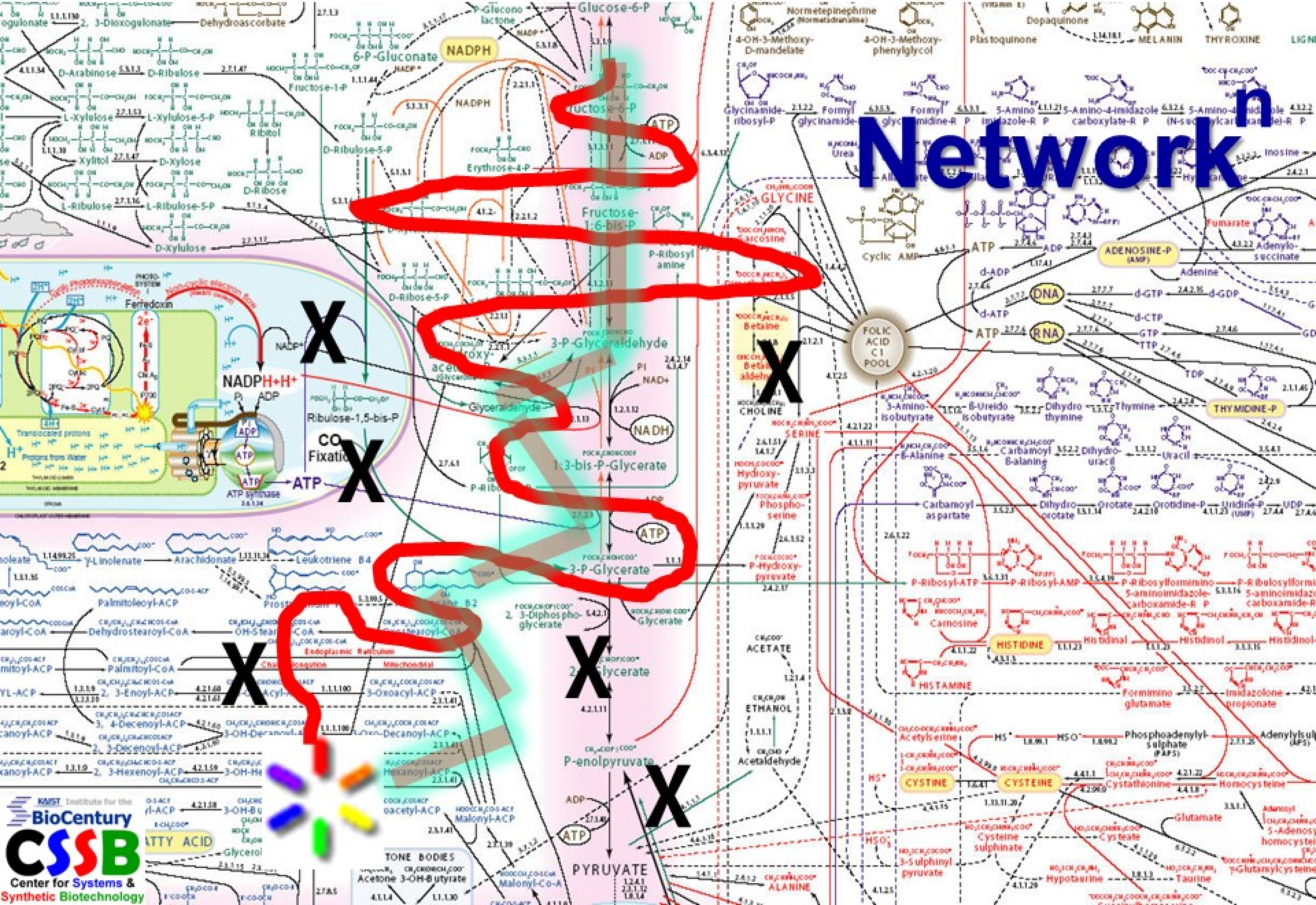
세포의 대사 및 조절 네트워크를 공학적으로 조작하여 다음의 뚜렷한 목적을 달성하는 기술

1. 기 생산 대사산물의 효율적 생산
2. 비 생산 대사산물의 신규 생산
3. 다양한 탄소원 활용
4. 인체 및 환경 유해 화학물질의 분해
5. 생물공정의 효율화



Sang Yup Lee
KAIST

대사공학의 어려움...


Network^n
Glucose-6-P
Fructose-6-P
Fructose-1,6-bis-P
3-P-Glyceraldehyde
1,3-bis-P-Glycerate
3-P-Glycerate
P-enolpyruvate
PYRUVATE
NADPH
ATP
NADH
DNA
RNA
FOLIC ACID C1 POOL
GLYCINE
SERINE
HISTIDINE
CYSTEINE
CYSTINE
X
X
X
X
X
X
BioCentury
CSSB
Center for Systems & Synthetic Biotechnology

합성생물학의 정의

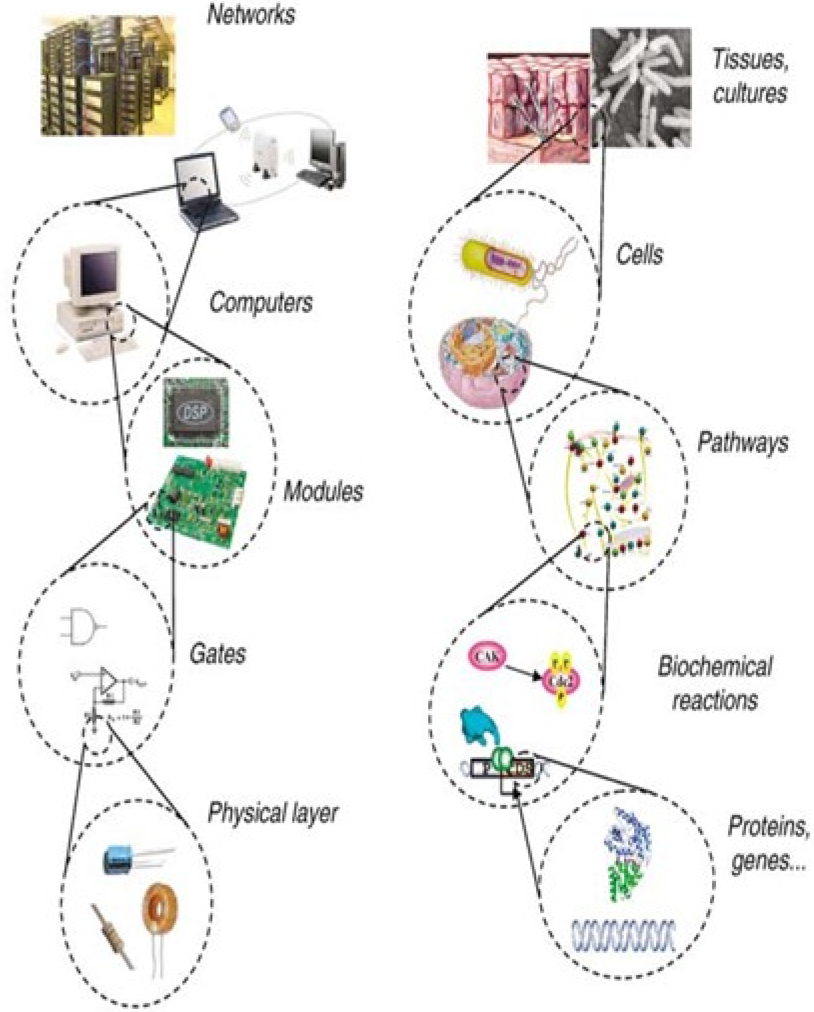
생물학적 부품, 모듈, 디바이스, 시스템의 디자인과 제작 및 응용

기존 생물시스템의 재디자인 및 응용

새로운 생물시스템의 디자인, 제작 및 응용

Sang Yup Lee

Hierarchy for synthetic biology inspired by computer engineering

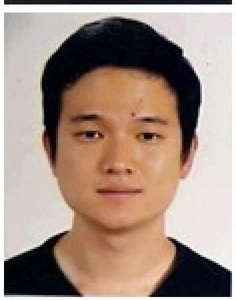


Andrianantoandro et al 2006 Mol Sys Biol msb4100073

Choi et al., EcoSal Plus 2016;
doi:10.1128/ecosalplus.ESP-0010-2015

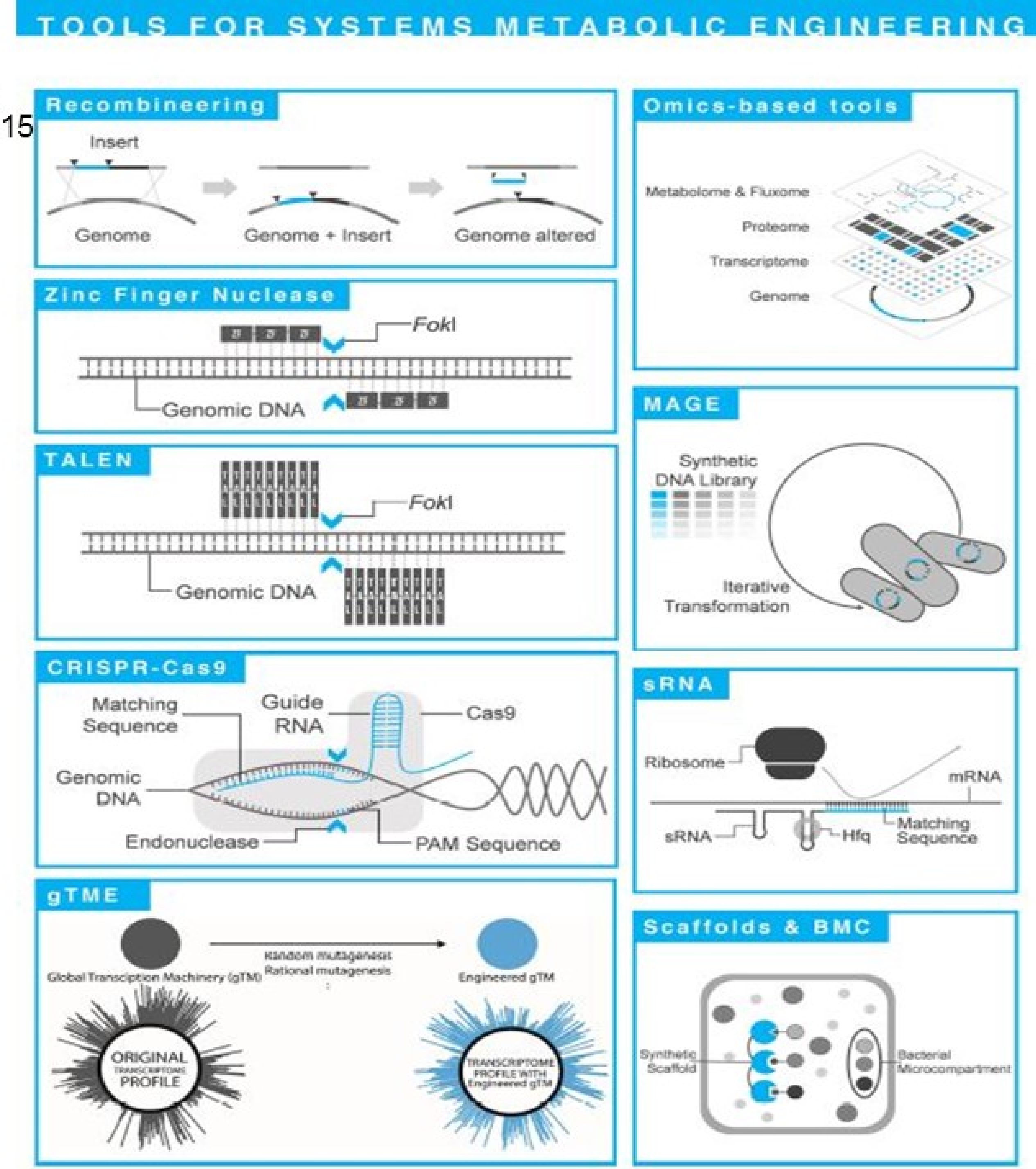
Kyeong Rok Choi

Jae Ho Shin

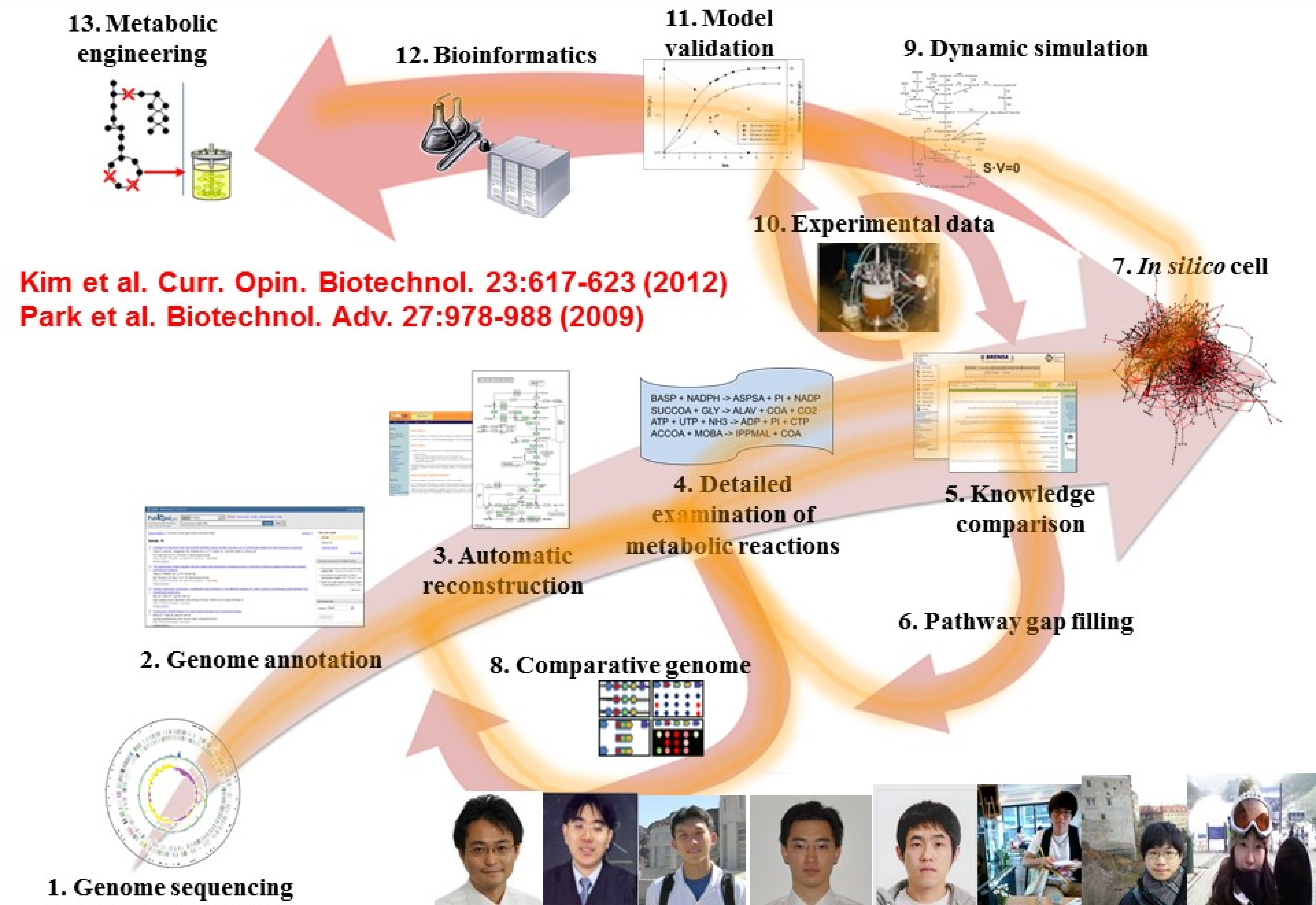


Jae Sung Cho

Dong Soo Yang



Reconstruction of *in silico* genome-scale model



Systems metabolic engineering

Metabolic Engineering

+

Systems Biology

+

Synthetic Biology

+

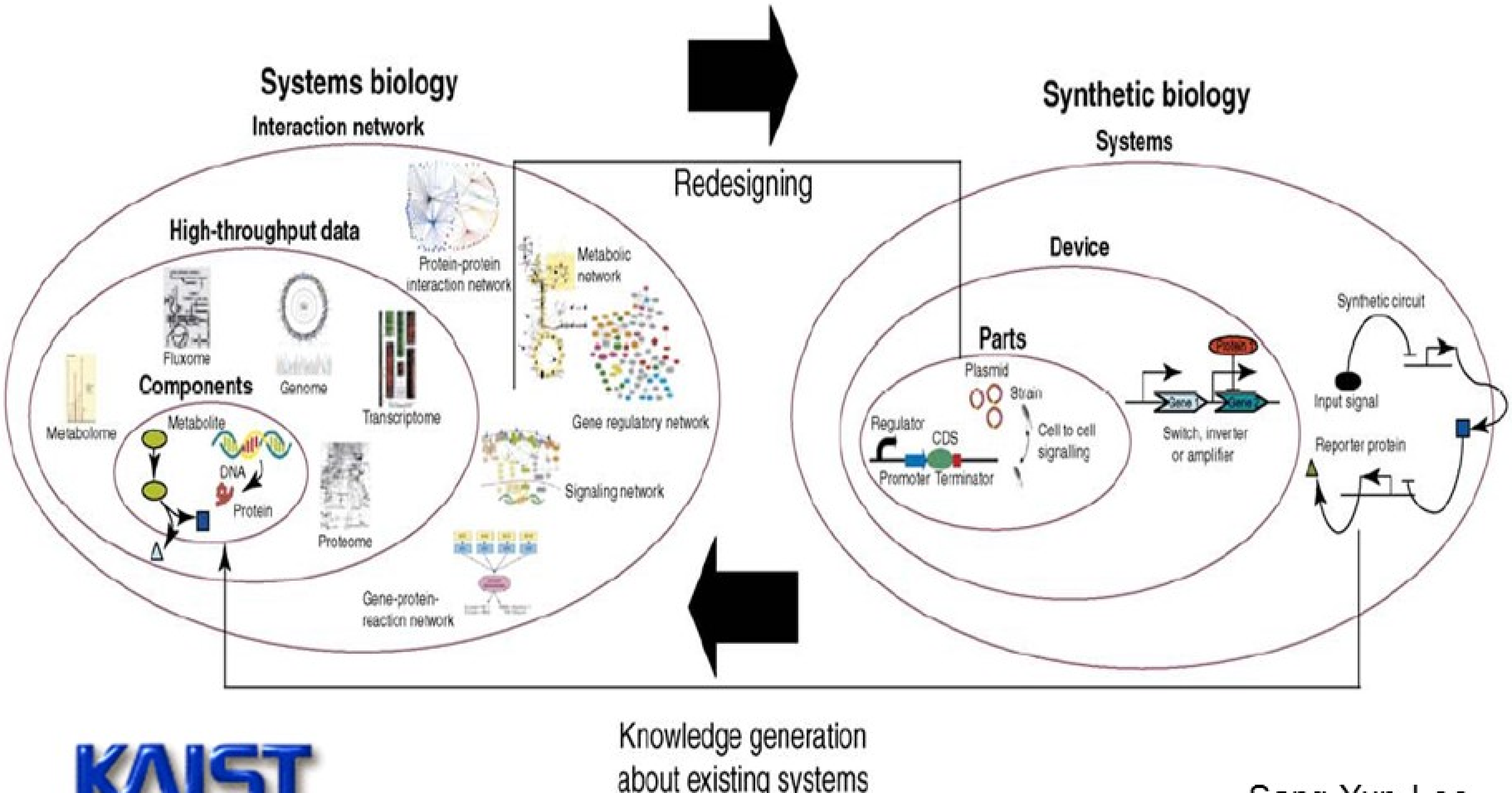
Evolutionary Engineering

Systems biotechnology

Lee et al. *Trends Biotechnol*. 23: 349-358 (2005)

Systems metabolic engineering

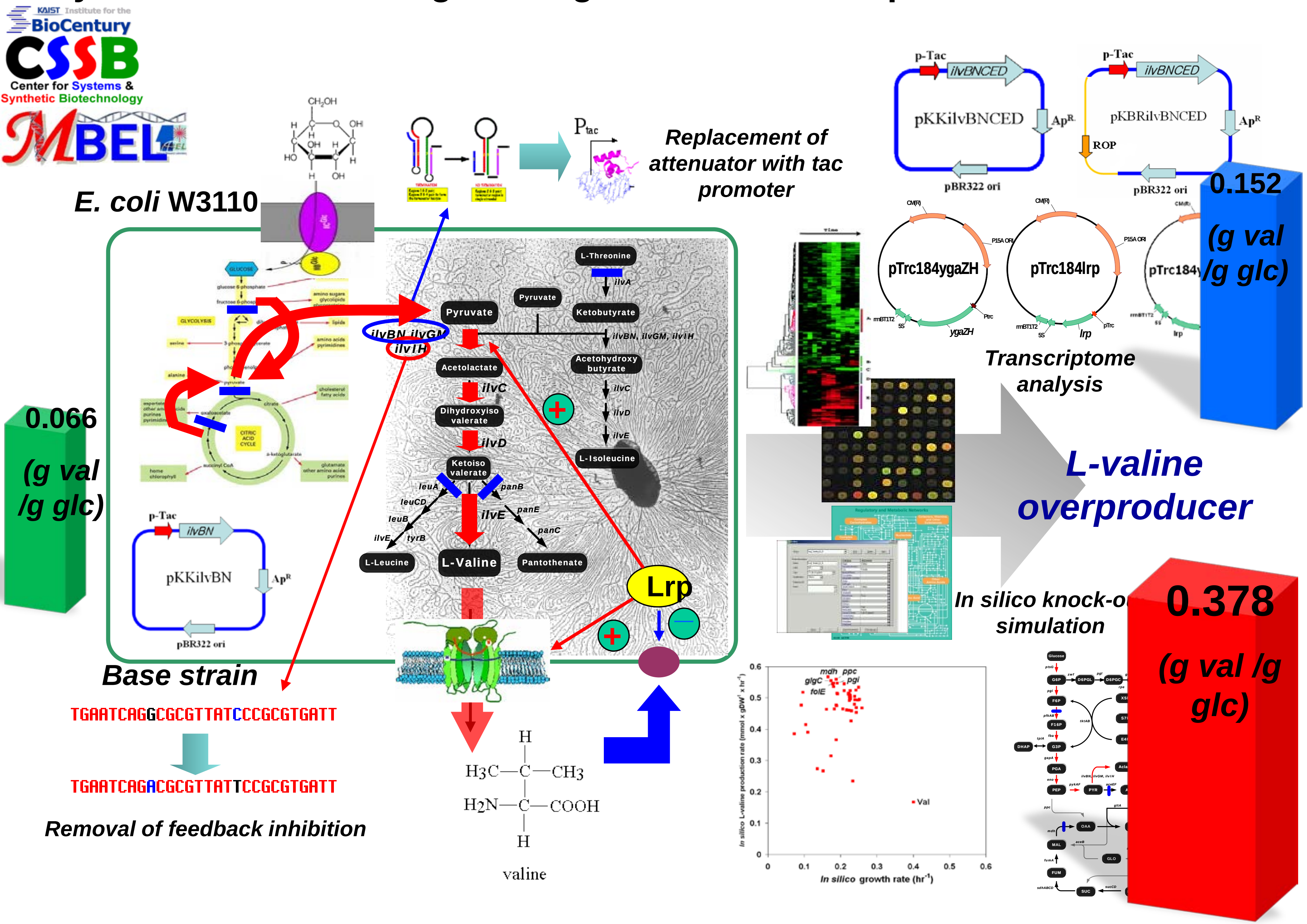
Lee et al. *Mol Sys Biol*. 3:1-8 (2007), Lee & Kim, *Nature Biotechnol*., 33:1061–1072 (2015)



Sang Yup Lee

Current Opinion in Biotechnology

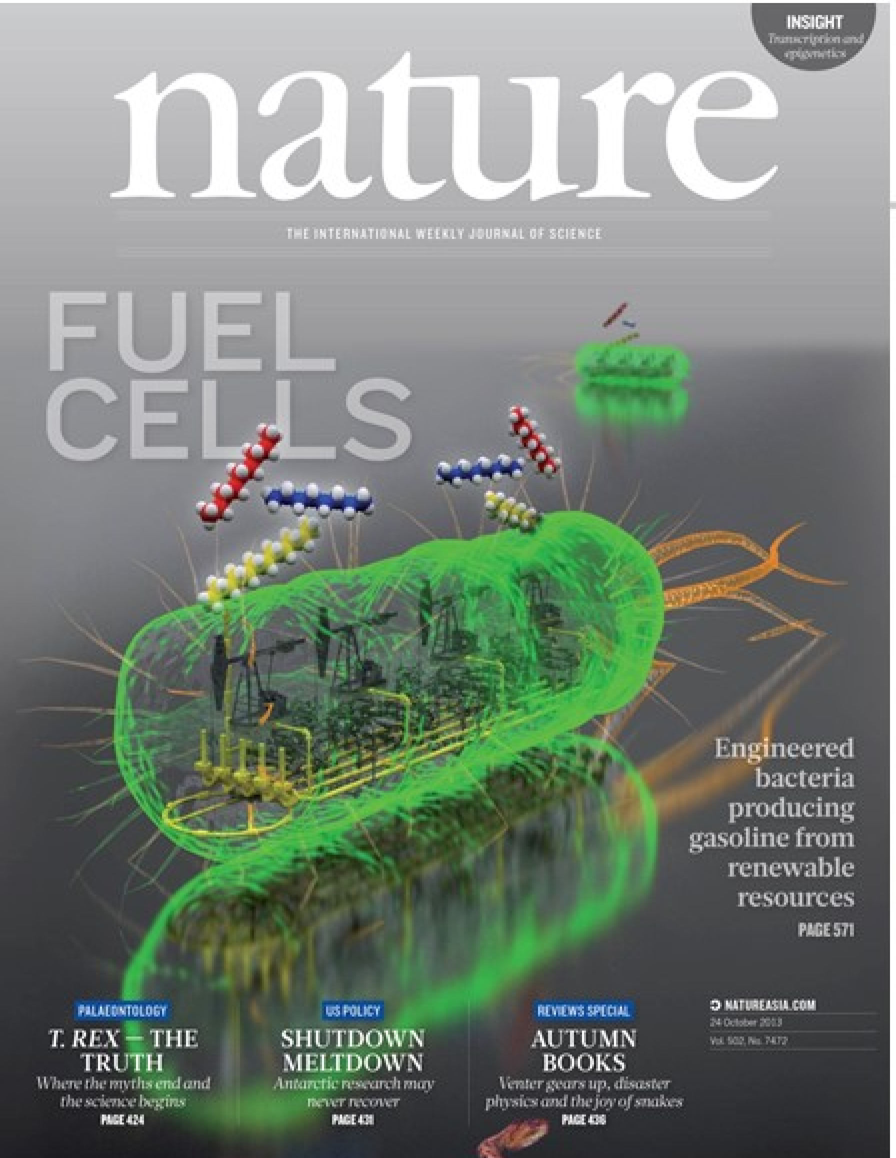
Systems metabolic engineering of *E. coli* for the production of L-valine



nature

Microbial production of short-chain alkanes

Yong Jun Choi[1] & Sang Yup Lee[1,2]



Monday, September 30, 2013 8:38:40 GMT

THE WALL STREET JOURNAL.

South Korean Scientists Use E. Coli to Make Gasoline

Article | Comments

Email | Print

By In-Soo Nam

Korea Advanced Institute of Science and Technology

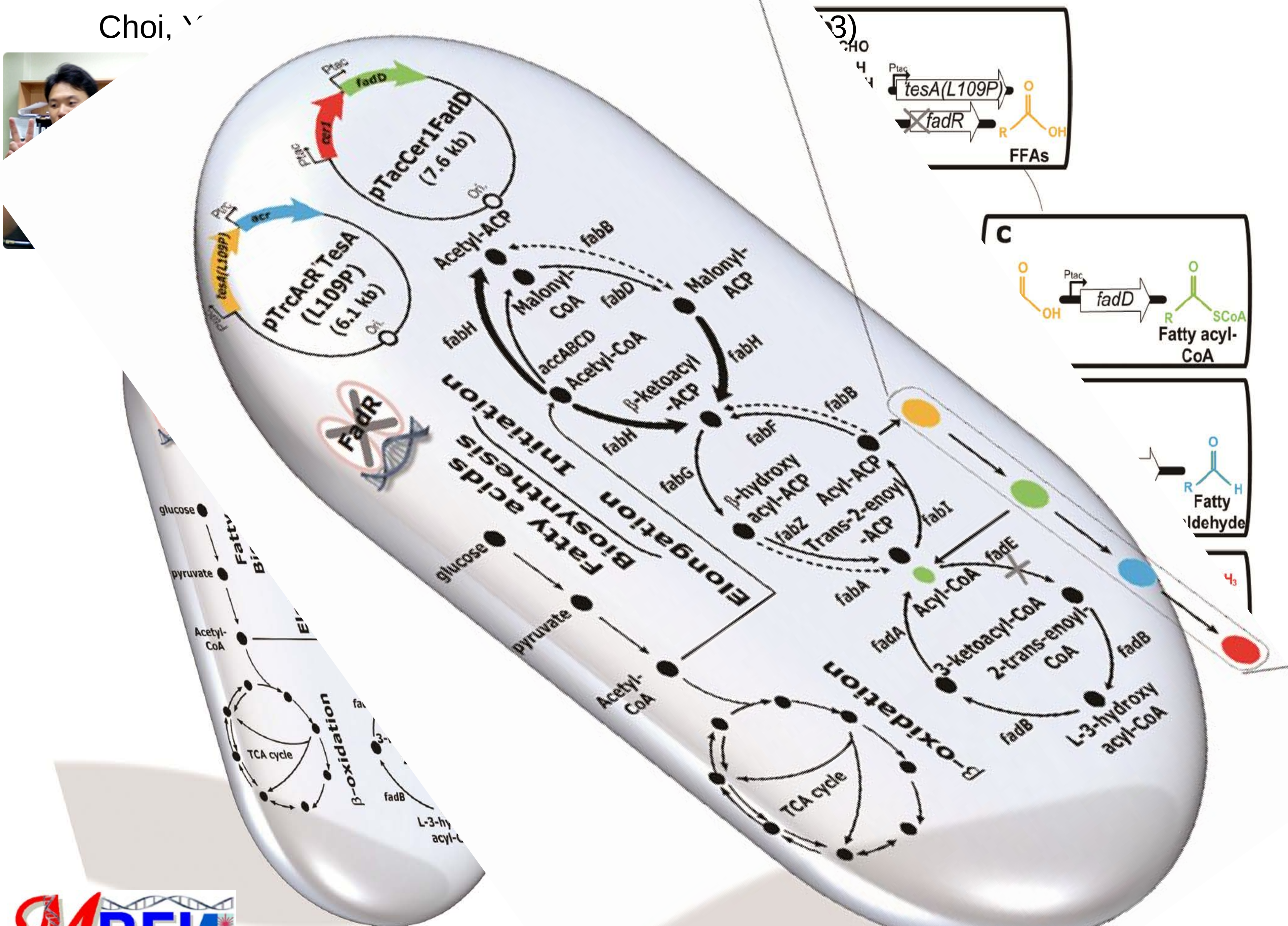
Researchers at Korea Advanced Institute of Science and Technology have tapped into E. coli to reprogram the bacteria to produce gasoline.

Escherichia coli can cause serious food poisoning but Korean scientists have come up with a more helpful use for the sometimes-deadly bacteria: producing gasoline.

Sang Yup Lee

KAIST

Choi, Y 3)



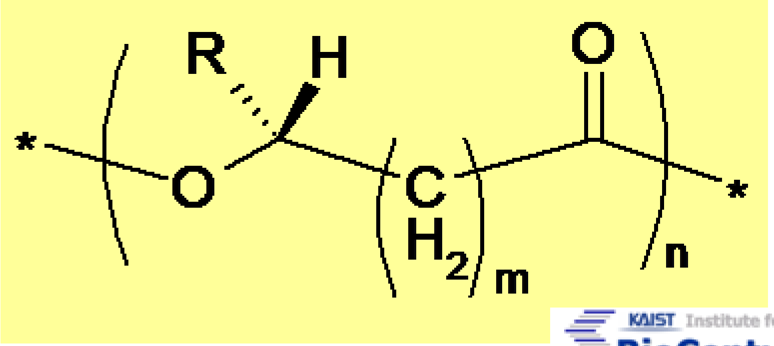
Ptac
fadD
cer1
pTacCer1FadD
(7.6 kb)
Ori.
acr
tesA(L109P)
pTrcAcR'TesA
(L109P)
(6.1 kb)
FadR
Acetyl-ACP
fabB
Malonyl-CoA
fabD
Malonyl-ACP
fabH
accABCD
Acetyl-CoA
β-ketoacyl-ACP
Initiation
fabF
fabG
β-hydroxy acyl-ACP
Acyl-ACP
Trans-2-enoyl-ACP
fabZ
fabI
fabA
Elongation
Fatty acids Biosynthesis
glucose
pyruvate
Acetyl-CoA
Acyl-CoA
fadE
3-ketoacyl-CoA
2-trans-enoyl-CoA
fadA
fadB
L-3-hydroxy acyl-CoA
β-oxidation
TCA cycle
tesA(L109P)
fadR
FFAs
C
Fatty acyl-CoA
Fatty
ldehyde

MBEL

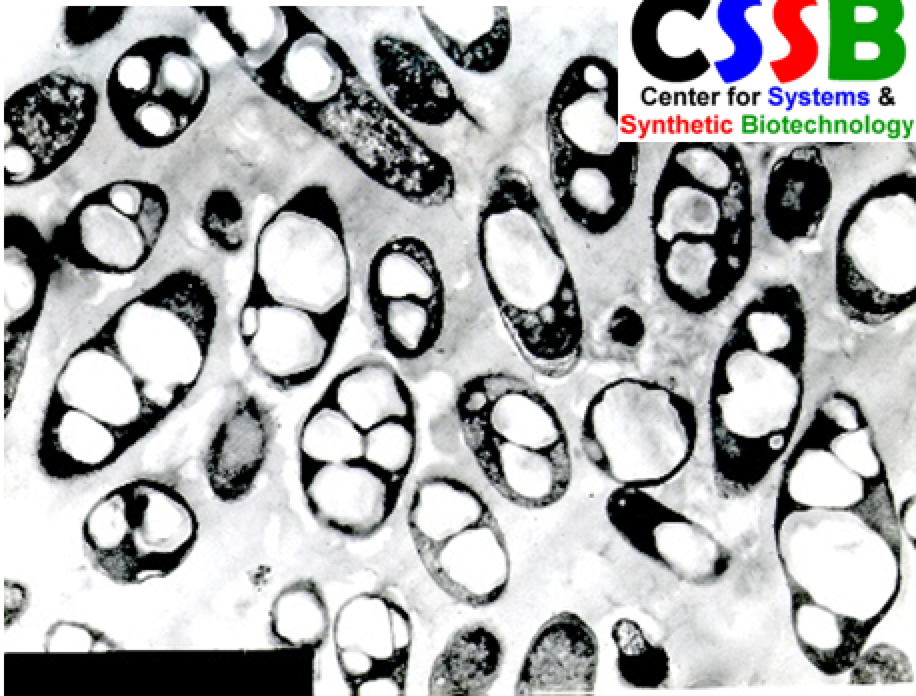
Polyhydroxyalkanoates (PHAs)

Lee, S.Y. (1996) Trends Biotechnol. 14, 431
Lee, S.Y. (1996) Biotechnol. Bioeng. 49, 1
Lee, S.Y. (1997) Nature Biotechnol. 15, 17

Also see reviews by Doi, Steinbuchel, Sinskey



- Energy/carbon/reducing power storage material
- Intracellularly accumulated as distinct granules by numerous microorganisms
- Synthesized usually when an essential nutritional component is limiting in the presence of excess carbon source



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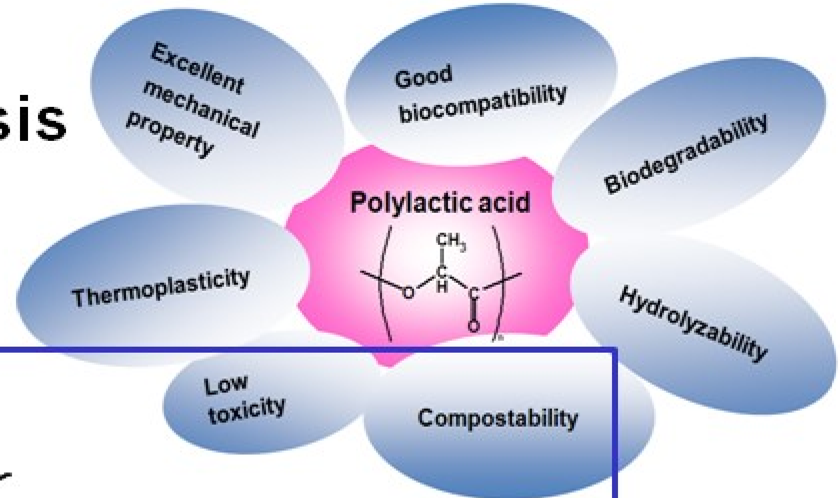
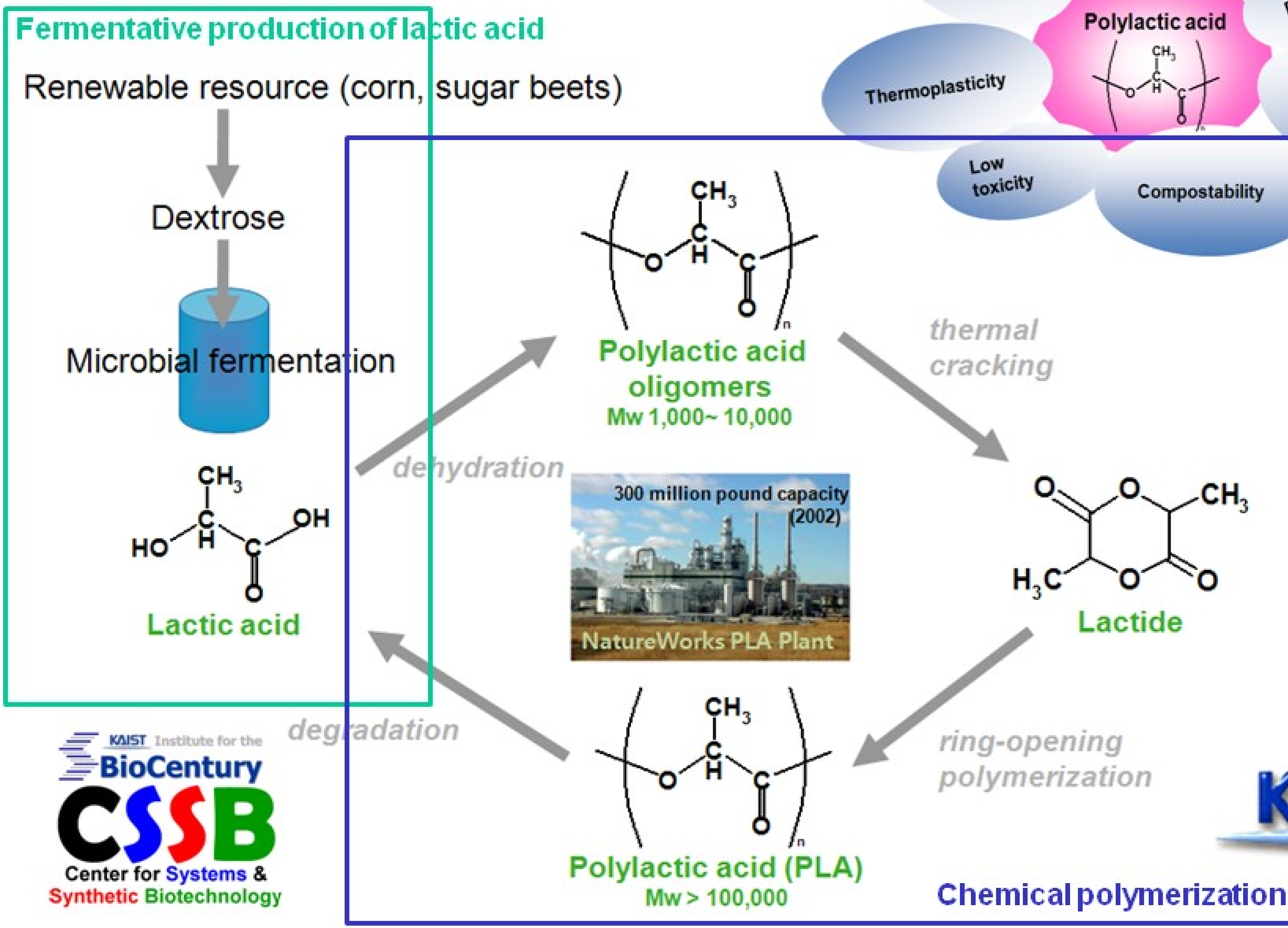
Polylactic acid (PLA)

-Two-step process for PLA synthesis





Part of complete coverage on
Eco Solutions

Eco Solutions

Koreans make plastics without fossil fuel chemicals

November 23, 2009 2:25 a.m. EST

Bioengineered plastics would be more environmentally-friendly than those from fossil fuel-based chemicals.

(CNN) -- A team of South Korean scientists have produced the polymers used for everyday plastics through bioengineering, rather than through the use of fossil fuel-based chemicals.

It is believed that the technique may now allow for the production of environmentally-friendly plastic that is biodegradable and low in toxicity.

STORY HIGHLIGHTS

- Korean scientists develop a plastic not derived from fossil fuel chemicals
- Bio-based polymers make the plastics biodegradable and less toxic
- Research team is from KAIST

The research focused on Polylactic Acid (PLA), a bio-based polymer which holds the key to producing plastics through natural and renewable resources. Polymers are molecules found in everyday life in the form of plastics and rubbers.

"The polyesters and other polymers we use everyday are mostly derived from fossil oils made through the refinery or chemical process," Professor Sang Yup Lee, who lead the research, said in a press statement

Breakthrough: Bioengineers Produce Plastic Without Fossil Fuels

Posted: November 24, 2009

Content provided by
National Science Foundation
WHERE DISCOVERIES BEGIN

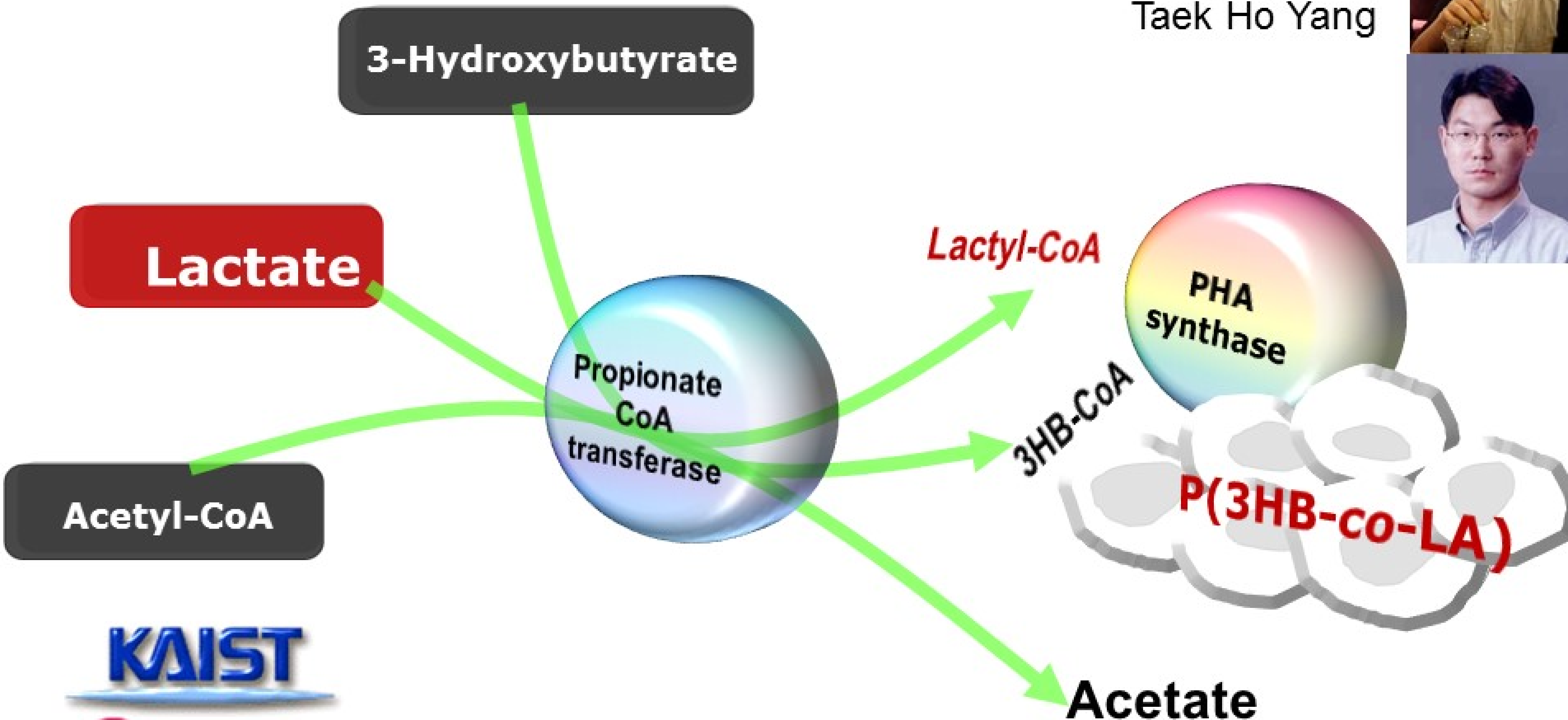
A team of pioneering South Korean scientists have succeeded in produc
for everyday plastics through bioengineering, rather than through the us
chemicals. This groundbreaking research, which may now allow for the p
environmentally conscious plastics, is published in two papers in the jour
and Bioengineering to mark the journal's 50th anniversary.

One-step direct fermentative production of PLA & copolymers

a series of ~25 patents since 2005

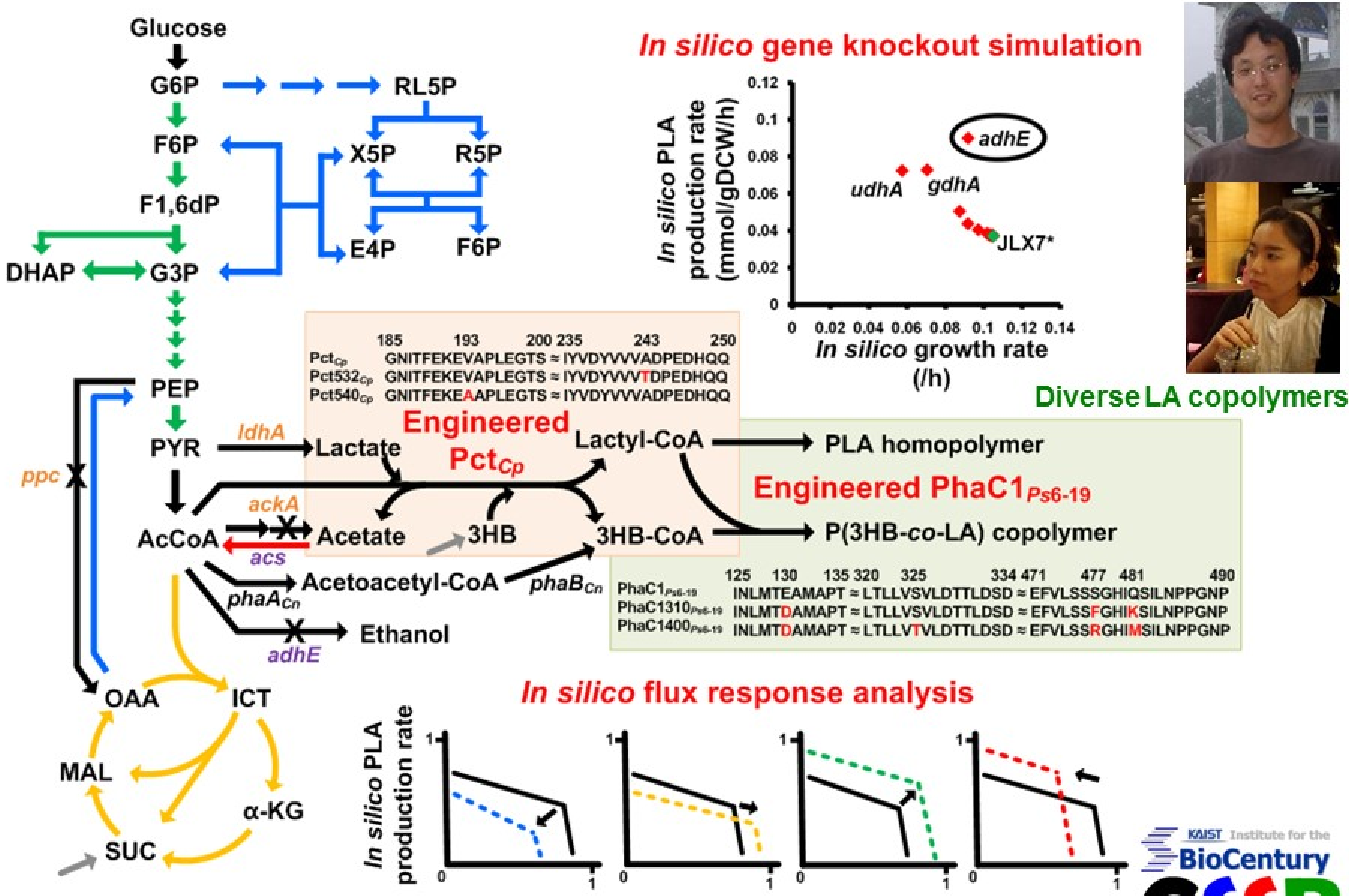
Si Jae Park
Yu Kyung Jung
Taek Ho Yang

Biosynthesis of PLA or P(3HB-*co*-LA)



KAIST
LG Chem

Synthetic metabolic network for one-step production of PLA polymers



Yang et al., (2010) Biotechnol. Bioeng. 105: 150-160
Jung et al., (2010) Biotechnol. Bioeng., 105: 161- 171

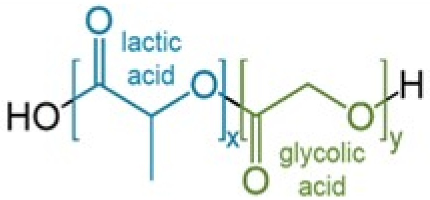
Jung and Lee (2011) J. Biotechnol. 151(1): 94-101

Choi et al. *Nature Biotechnology* 34(4): 435-440 (2016. 4)

Poly(lactate-*co*-glycolate) [PLGA]

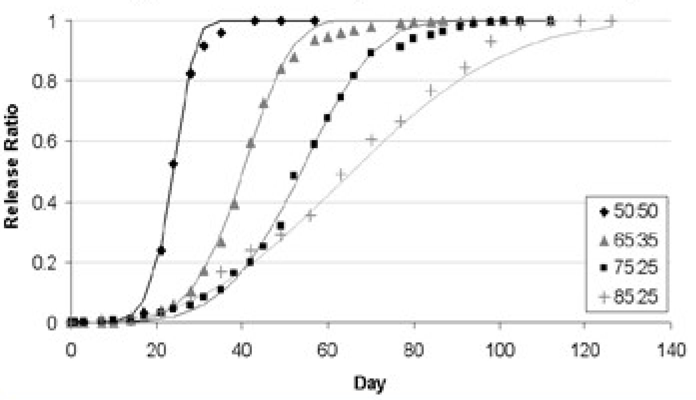
Representative synthetic biomedical polymer

So Young Choi

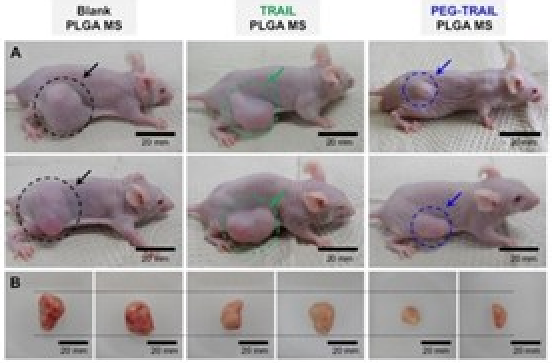


- Random copolymers of lactic and glycolic acids
- Representative **synthetic biopolymer**
- Biodegrades within **1 – 6** months
- Biocompatible & low toxicity
- **FDA-approved** biopolymer

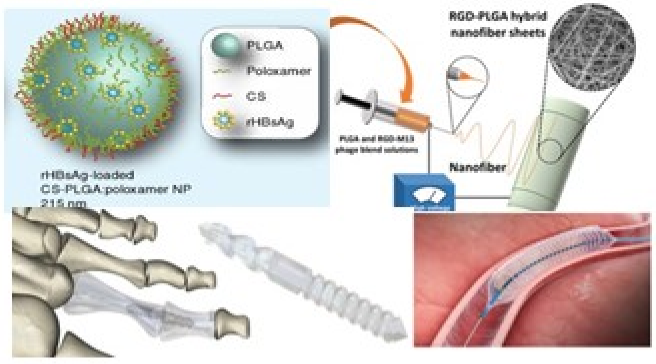
Degradation rate (controlled release)



Many clinical trials



Various types of PLGAs



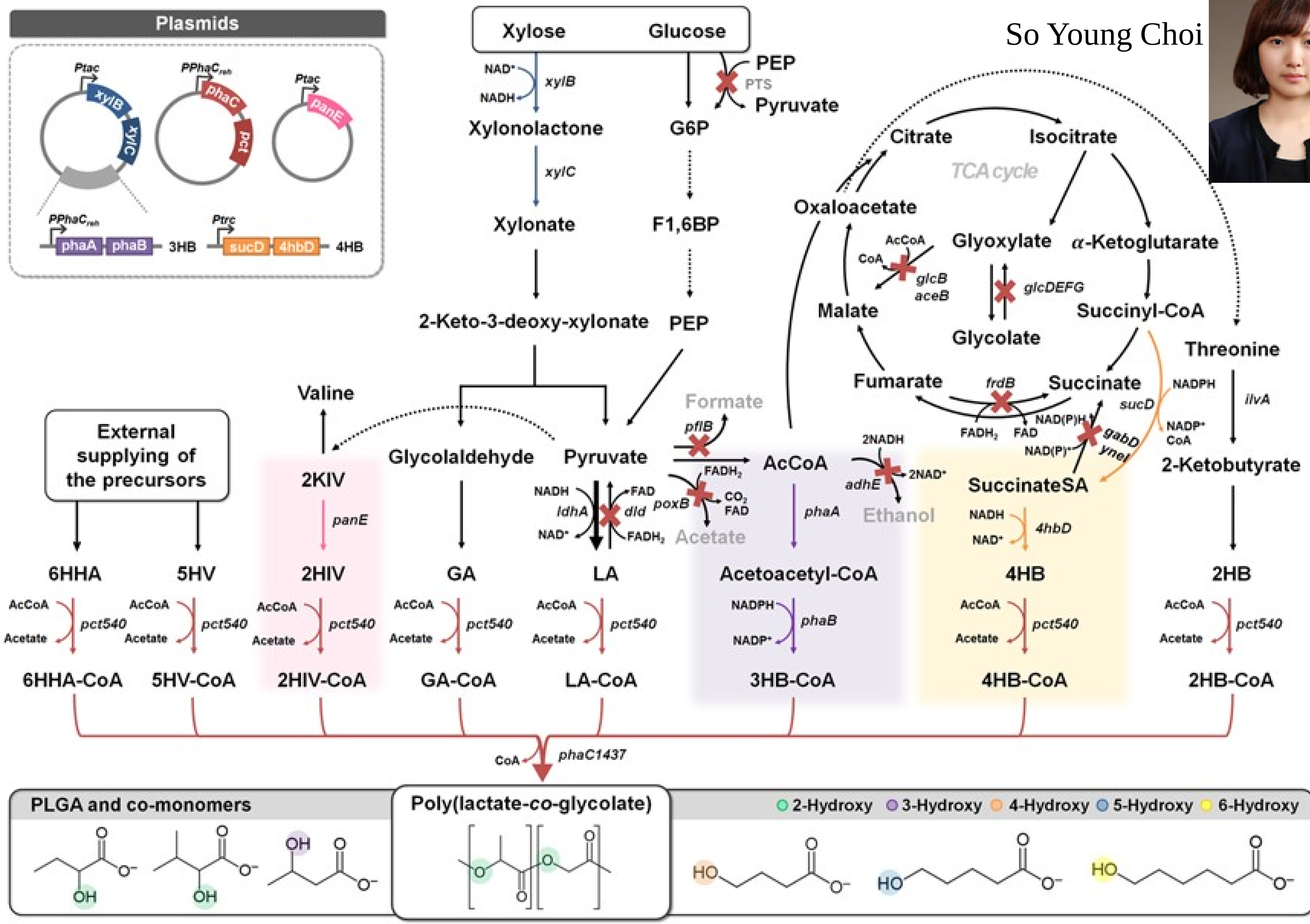
Nanosphere, nanofiber, microsphere, implants.....

Sang Yup Lee

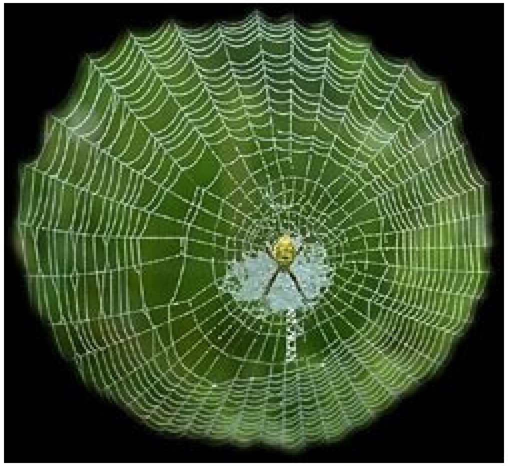
Choi et al. *Nature Biotechnology* 34(4): 435-440 (2016. 4)

Systems metabolic engineering for biopolymer production

So Young Choi



거미실크단백질: 미래의 첨단 소재?



바이오강철

- 가장 가벼운 섬유
- 가장 질긴 섬유
- 탄성 매우 우수
- 케블라에 버금가는 강도

Material	Strength (N m^{-2})	Elongation (%)	Energy to break (J kg^{-1})
Major ampullate silk	4×10^9	35	4×10^5
Minor ampullate silk	1×10^9	5	3×10^4
Flagelliform silk	1×10^9	>200	4×10^5
Kevlar	4×10^9	5	30
Rubber	1×10^6	600	8×10^4
Tendon	1×10^6	5	5×10^3

MBEL

Teule et al., *Nature protocols.* **2009**, *4(3)*, 341

대장균의 대사공학과 합성생물학에 의한 초고분자량 거미실크 단백질의 생산

PNAS

Native-sized recombinant spider silk protein produced in metabolically engineered *Escherichia coli* results in a strong fiber

PNAS in press (2010)

Xiao-Xia Xia[a,1], Zhi-Gang Qian[a,1], Chang Seok Ki[b], Young Hwan Park[b], David L. Kaplan[c], and Sang Yup Lee[a,d,e,2]

Gene design & synthesis

[SGRGGLGGQGAGMAAAAM GGAGQGGYGGLGSQGT]

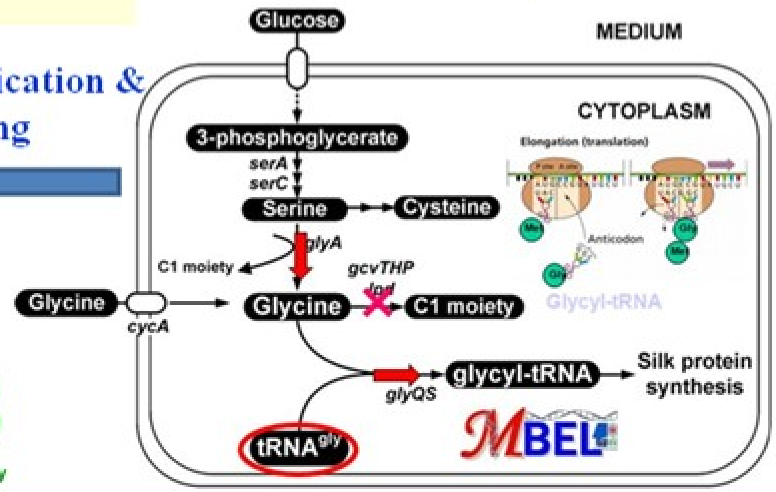
Repeating unit: 32, 48, 64, 80, 96 copies

Synthetic redesign of *E. coli* metabolism

High Mw (285 kDa) spider silk protein results in Kevlar strength spider silk !!!

X.-X. Xia

Production, purification & material processing



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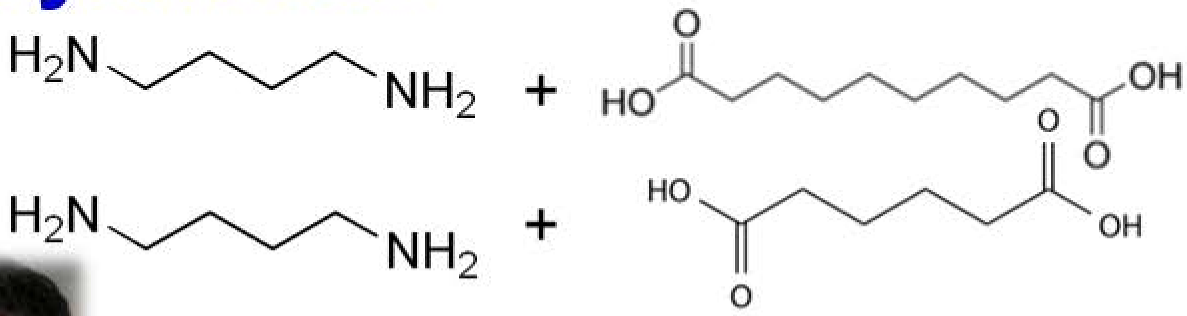
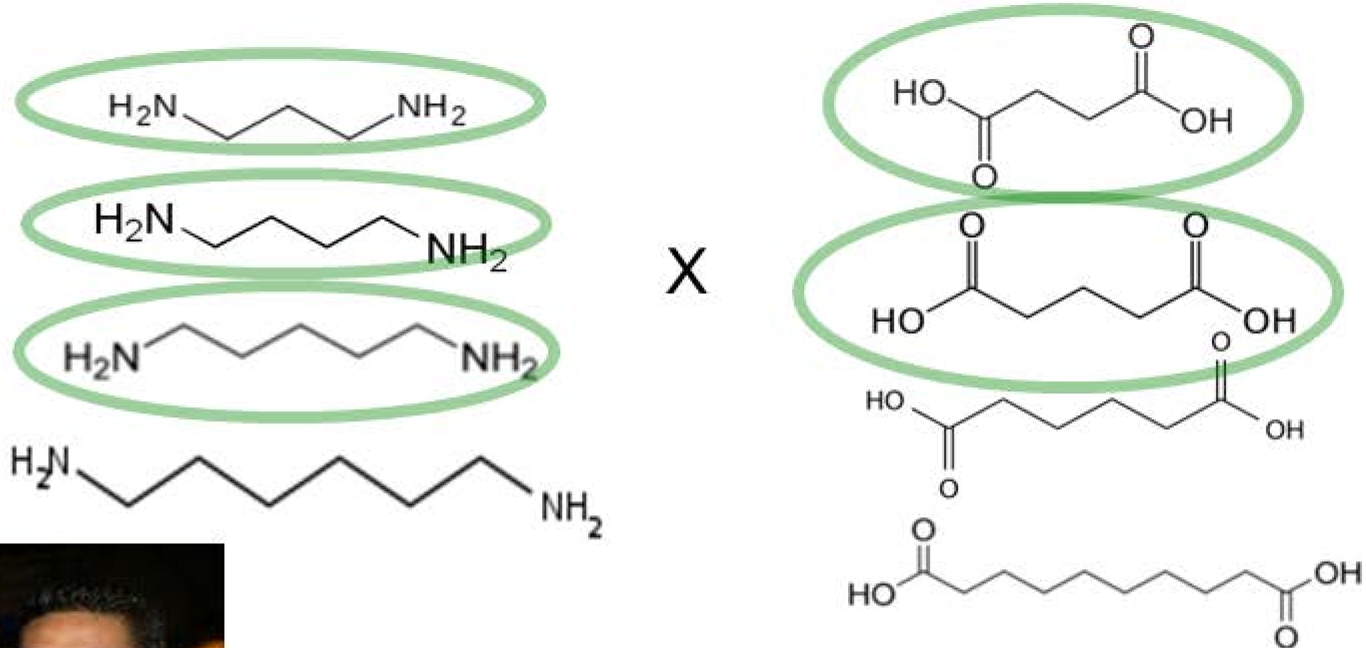
Polyamides



= EcoPaXX (nylon 4,10)

= Stanyl (nylon 4,6)

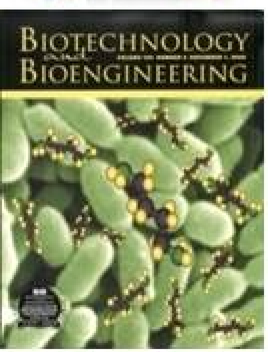


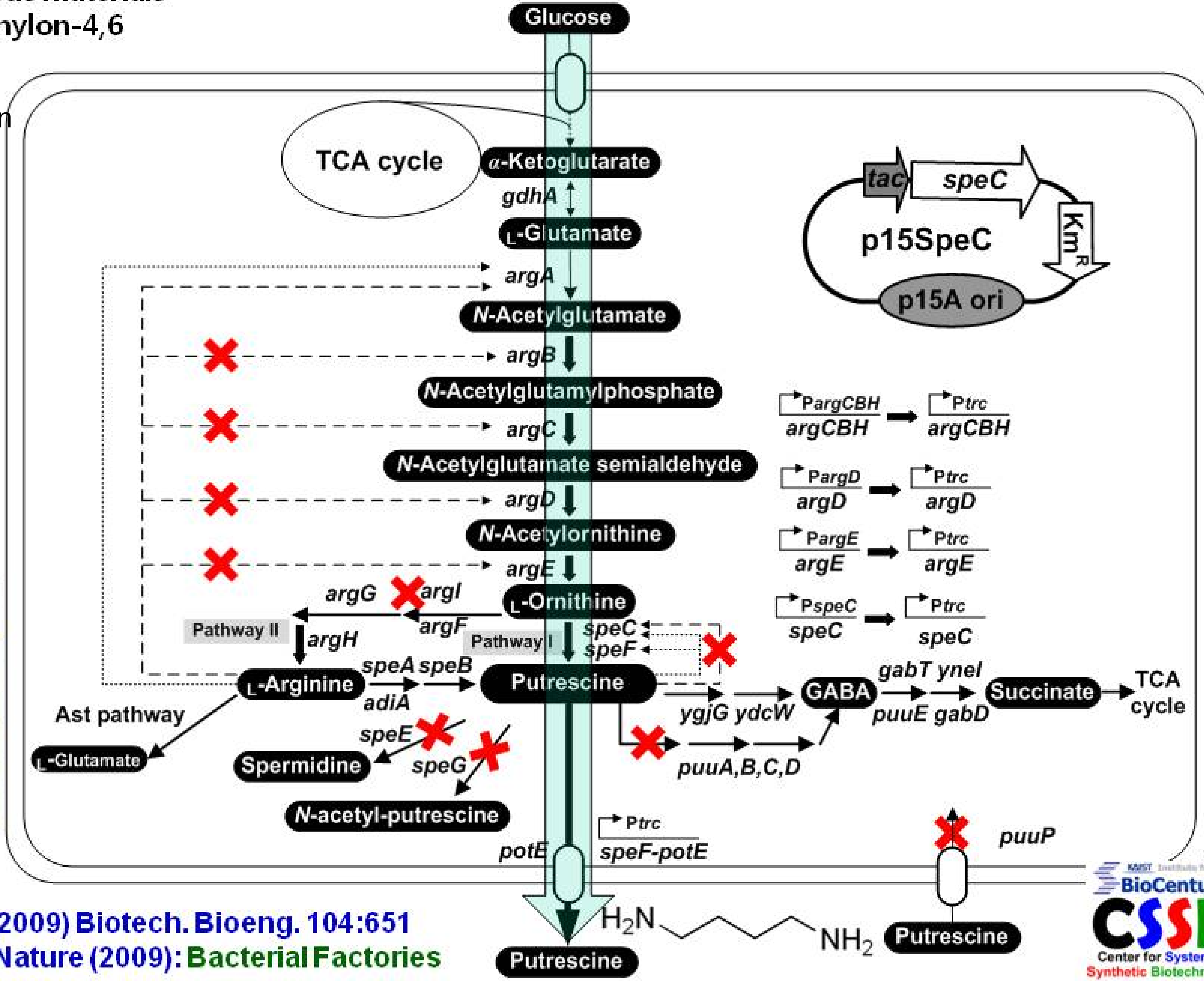
Putrescine
(1,4-diaminobutane)
used for various materials
Including nylon-4,6

Met Eng for nylon precursor I

Dr. Zhigang Qian

Dr. XiaoXia Xia





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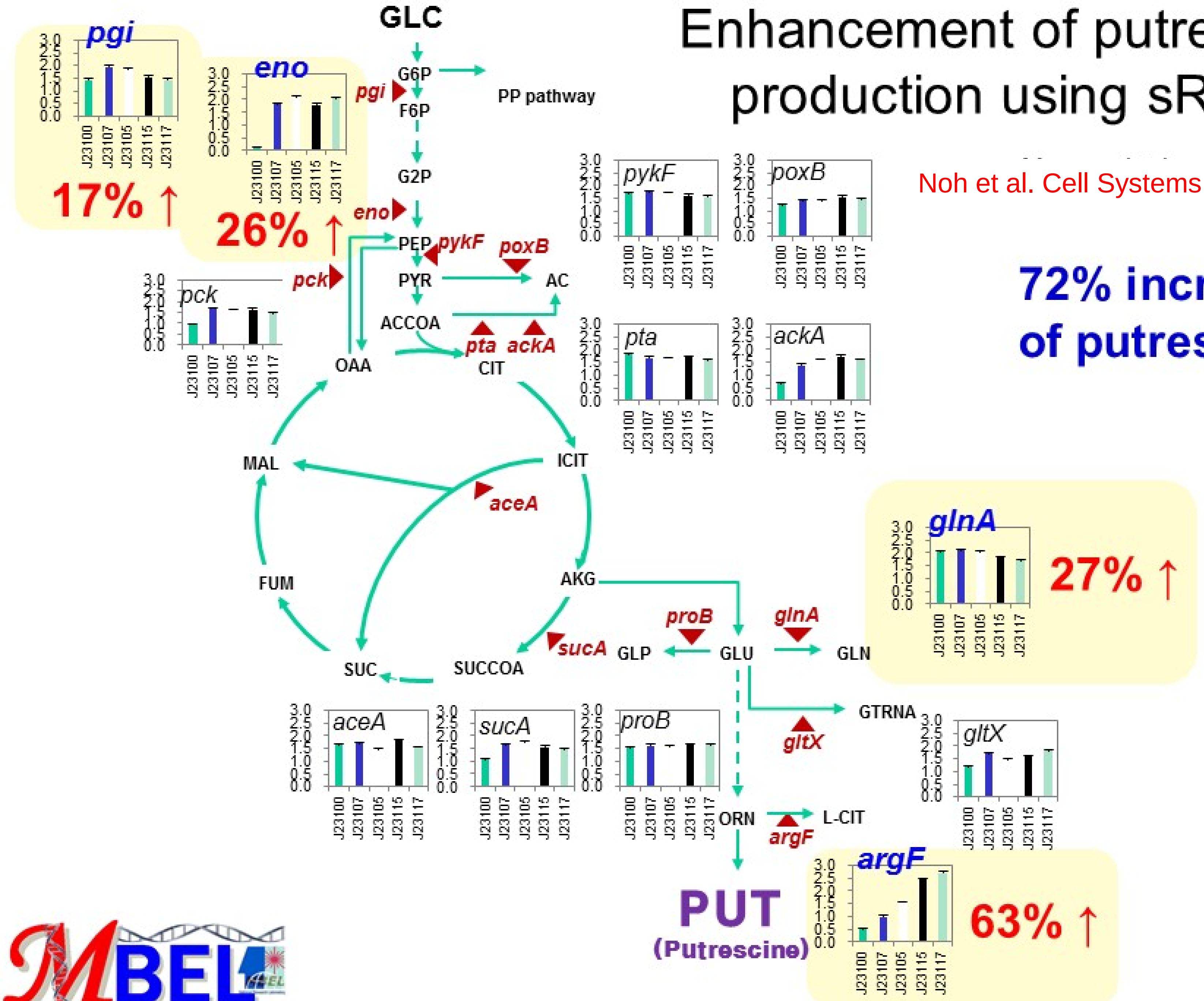
Qian et al. (2009) Biotech. Bioeng. 104:651
Highlights in Nature (2009): Bacterial Factories

Enhancement of putrescine production using sRNA

Noh et al. Cell Systems, Aug 2017

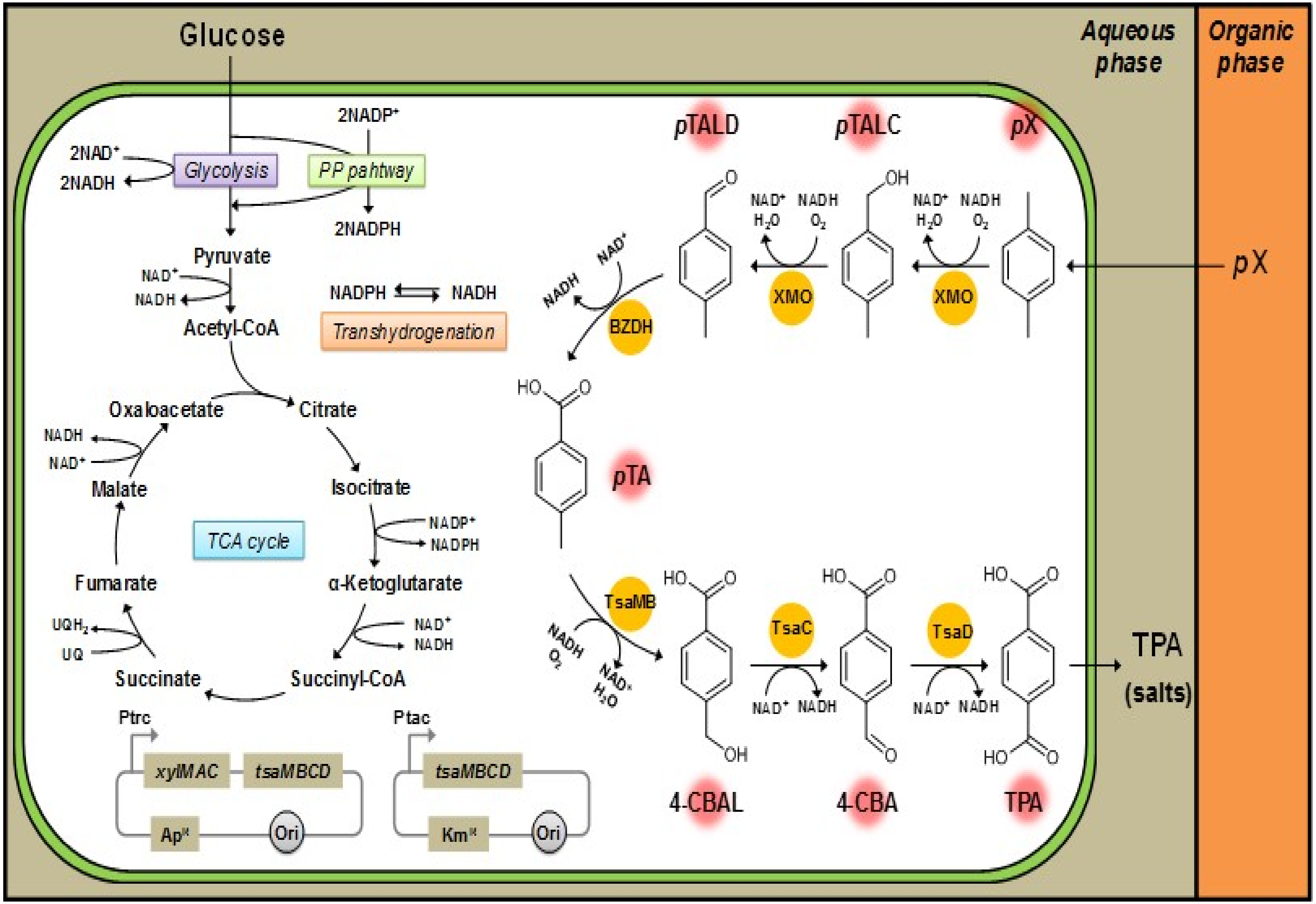
72% increase of putrescine



~19 mt

Strategies for bio-based renewable TPA production

Luo & Lee, *Nature Comm.* 8:15689 | DOI: 10.1038/ncomms15689 (May 31, 2017)

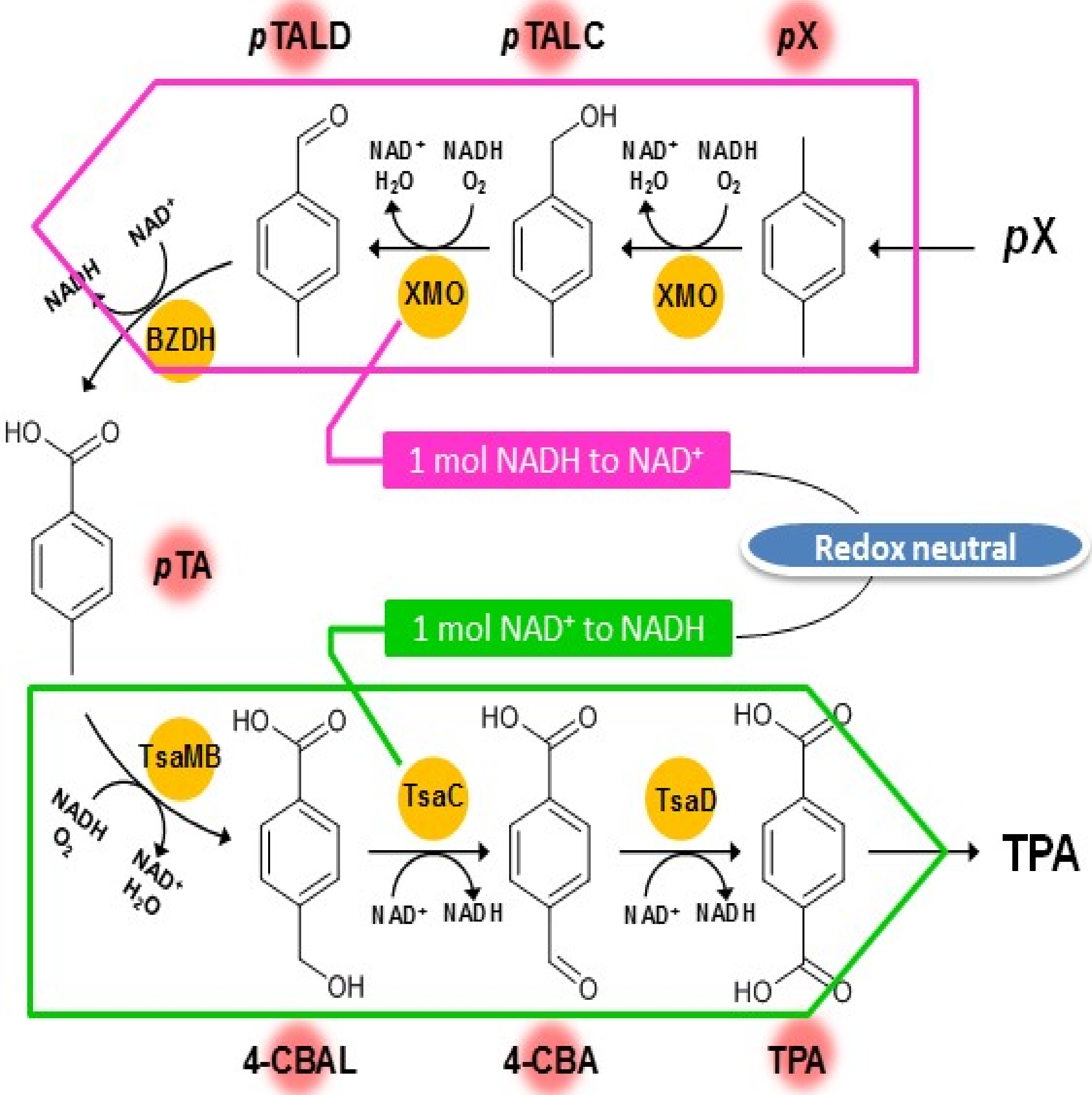


Ziwei Jeff Luo

Sang Yup Lee

Designing the *p*X to TPA synthetic biotransformation pathway

Sang Yup Lee
KAIST

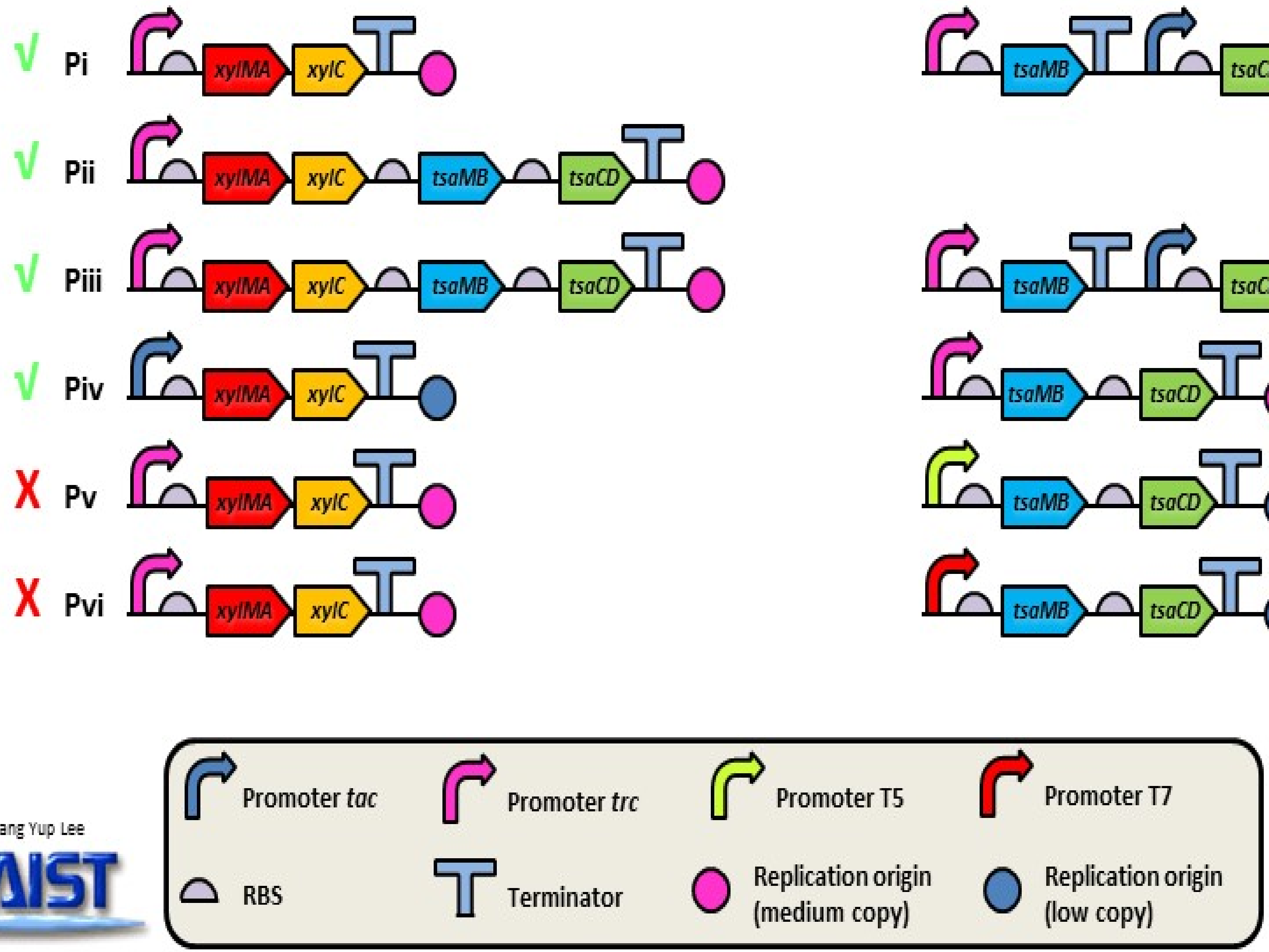


- **Upstream pathway**: *p*X to *p*TA recruited from *p*X degradation in *Pseudomonas putida*
- **Downstream pathway**: *p*TA to TPA recruited from *p*TA degradation in *Comamonas testosteroni* T-2
- Use of the multi-functional XMO allows the overall pathway **redox neutral**

Luo & Lee, *Nature Comm.* 8:15689
DOI: 10.1038/ncomms15689 (May 31, 2017)

Whole pathway assembly & optimization

Luo & Lee, *Nature Comm.* 8:15689 | DOI: 10.1038/ncomms15689 (May 31, 2017)

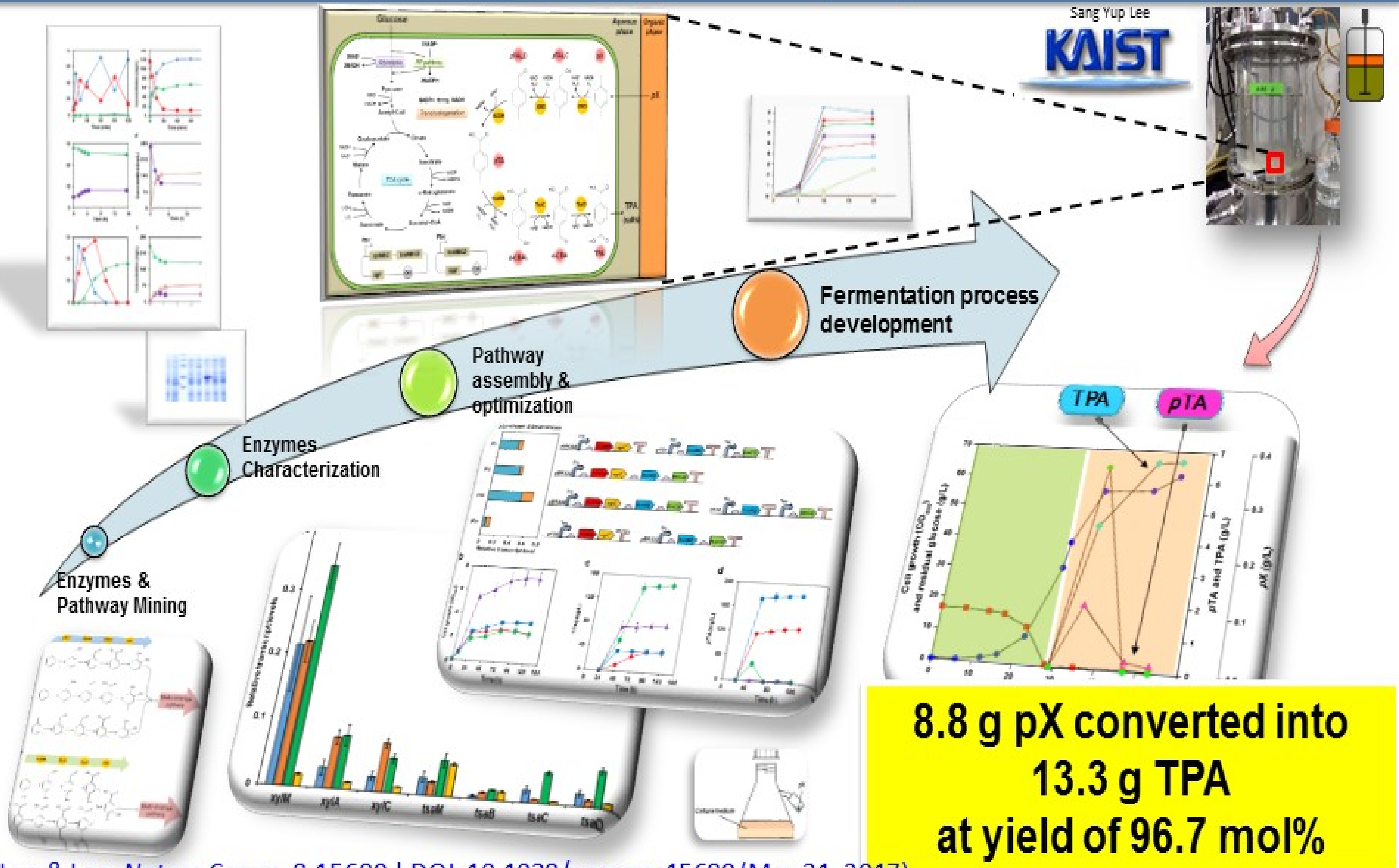


Sang Yup Lee

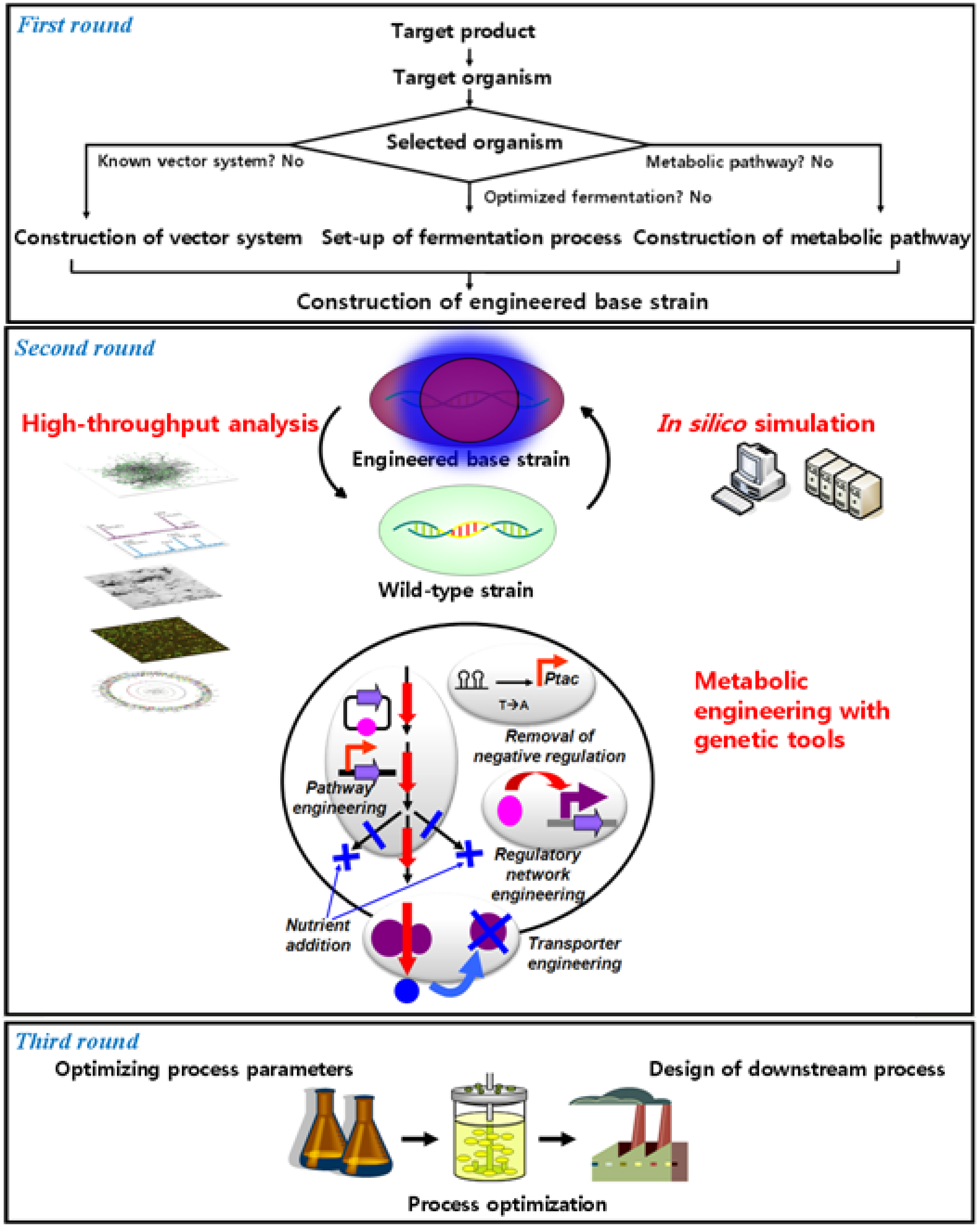
KAIST

Ziwei Jeff Luo

Biotransformation of *pX* into TPA by engineered *E. coli*



Luo & Lee, *Nature Comm.* 8:15689 | DOI: 10.1038/ncomms15689 (May 31, 2017)



Sang Yup Lee

General strategy for Systems biotechnology

Lee et al. Trends Biotechnol. 29:370-378 (2011)
Park et al. Trends Biotechnol. 26:404-412 (2008)

WEF's Top Ten Emerging Technologies 2016

Released on June 23, 2016

1. Nanosensors and the Internet of Nanothings
2. Next Generation Batteries
3. The Blockchain
4. 2D Materials
5. Autonomous Vehicles
6. Organs-on-chips
7. Perovskite Solar Cells
8. Open AI Ecosystem
9. Optogenetics
10. Systems Metabolic Engineering

WORLD ECONOMIC FORUM

Sang Yup Lee

KAIST

합성생물학의 미래

보다 많은 생물 조절 도구들의 개발 및 응용 확대

인공지능과 빅데이터 기반 생물 시스템 설계

자동화 (로봇)에 의한 공장형 산업 균주 제작 시스템

환경친화적인 화학물질의 생산 가속화

신규 고부가가치 의약용/기능성 영양물질 생산 확대

치료용, 예방용 등 의료에의 적용 가능성 확대

Sang Yup Lee
KAIST

3,500,000,000,000,000,000

유가가 50불 혹은 그 이하이면?

우리나라가 지속가능한 화학강국이 되기 위한 제언:

(1) 국책과제로서 바이오기반 화학물질 생산 기술 개발 사업 확대 추진 (합성생물학, 시스템대사공학 등 원천기술 개발 사업 포함): 특허권 선점 등 필요

(2) 산업바이오텍 인력양성 사업 추진

(3) 바이오리파이너리 실증 파일롯/데모 플랜트 건설 및 운영

(4) "그린 케미칼" 인증제도 도입 온실가스 감축제도와 연계 및 적극 운용

(5) 석유화학산업의 바이오화학산업 재편 지원제도 도입

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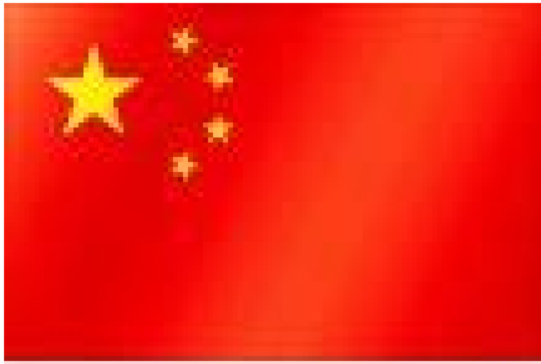
중국 제 13차 5개년 계획(2016-2020)



National Labs
Fundamental Scientific Infrastructure
National Center for Technology Innovation

“National Center for Technology Innovation in Synthetic Biology”

8 billion RMB in 3~5 years + 0.2 billion RMB/yr for operation

2500+ researchers

우리나라가 지속가능한 화학강국이 되기 위한 제언:

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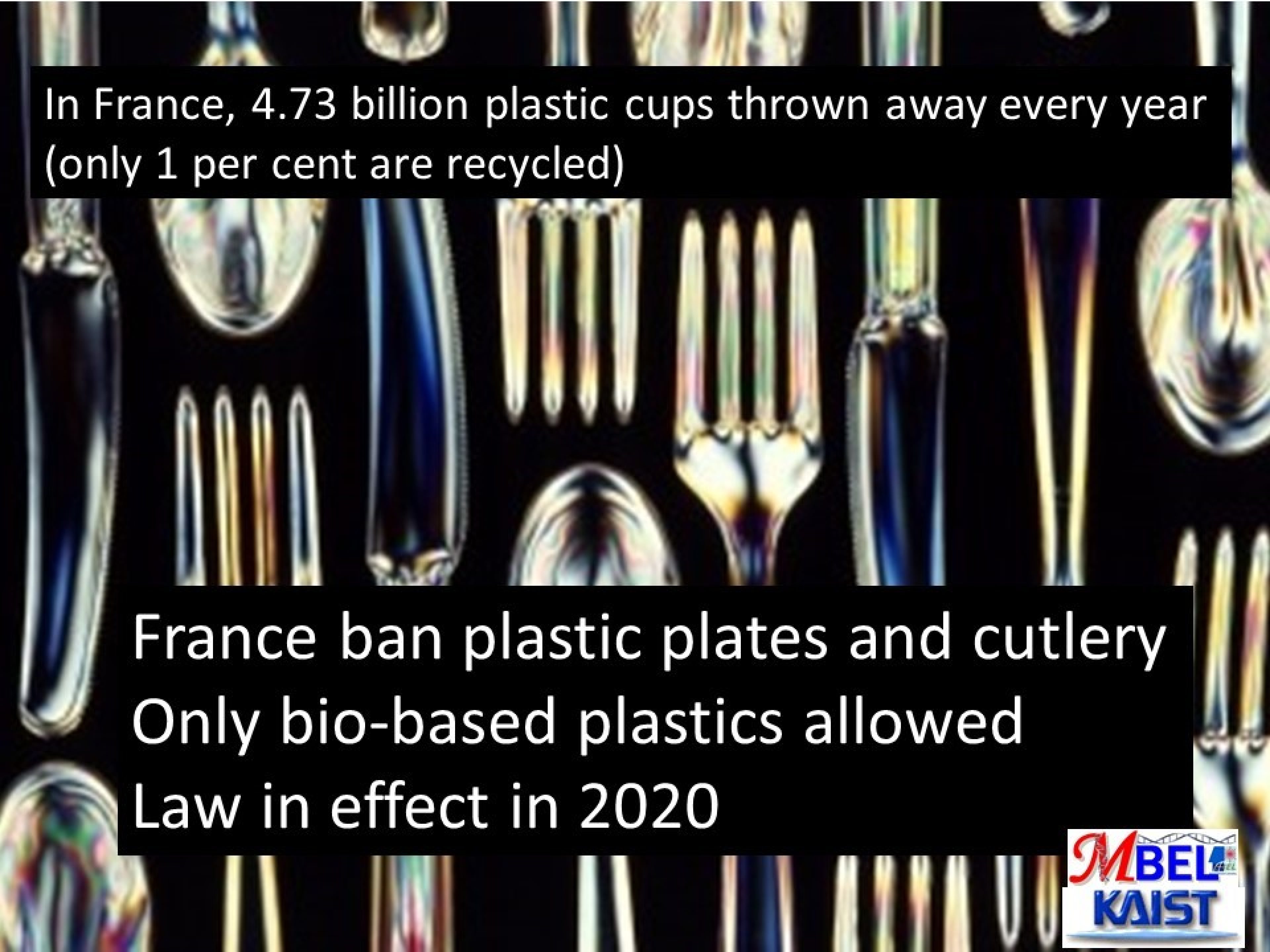

In France, 4.73 billion plastic cups thrown away every year (only 1 per cent are recycled)

France ban plastic plates and cutlery
Only bio-based plastics allowed
Law in effect in 2020

대사공학/합성생물학 – 미래 산업의 핵심

화학/물질

의약/치료

식품/영양

환경

…

감사합니다