触媒にどこまでできるのか
～有機化学のCREATIVITYを追究して～

2017年4月20日

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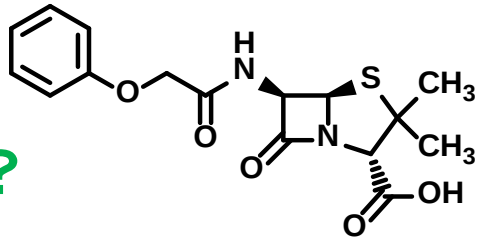
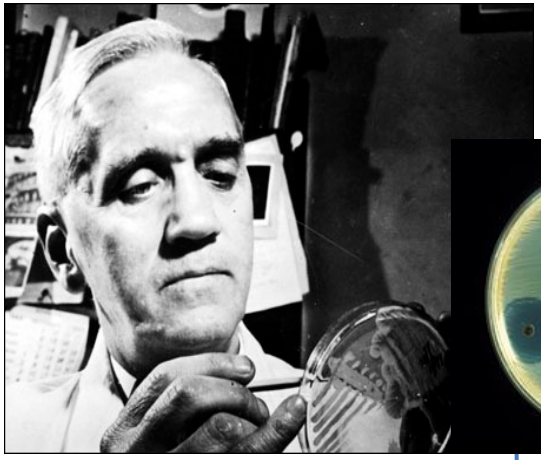
東京大学
THE UNIVERSITY OF TOKYO

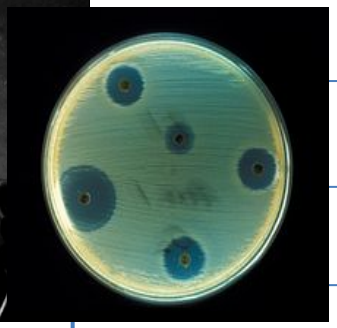
K-LiSCat
ERATO

世界の平均寿命の推移

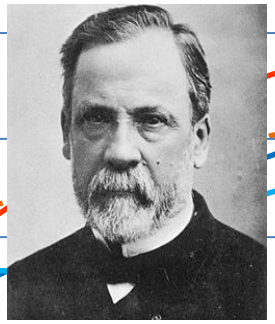


この20年間に何があったのか？

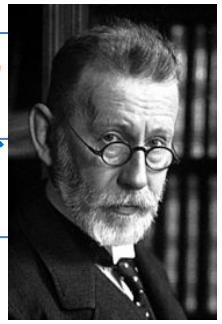




1928年　Alexander Flemingによるペニシリンの発見



Louis Pasteur
（1861年）



Paul Ehrlich
（1904年）

Gerhard Domagk
（1927年）

Nobel医学生理学賞
(1945年）

第二次世界大戦

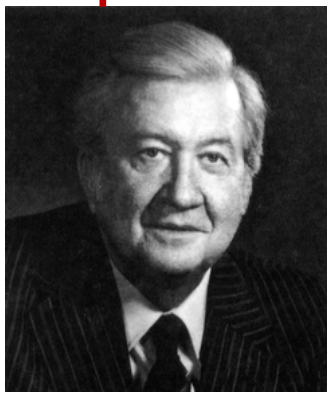
1950

Howard Florey

Ernst Chain

ペニシリンの純粋大量生産（ペニシリンプロジェクト）

Dorothy Hodgkin
1945年ペニシリンの構造決定（1964年Nobel化学賞）



John Sheehan
1957年ペニシリンの化学合成

創薬は総合科学の結晶

資本力の低さを克服する方策

Department of Biology
（生物学のみ）

欧米の製薬会社
研究員

Department of Chemistry
（有機化学のみ）

横断的•総合的能力の高い研究者養成が日本の鍵

日本の製薬会社
研究員

薬学

- 有機化学
- 生物化学
- 物理化学

- 特定分野での深い専門知識とともに、幅広い専門知識を習得させ、横断的•総合的能力を有する創薬研究者を養成
- **グローバル創薬企業において修士はアシスタント、博士をとって初めてリサーチリーダーの資格**

薬は、はじめからそこにあるものでなく、人類が創り出していくものである（創薬）。

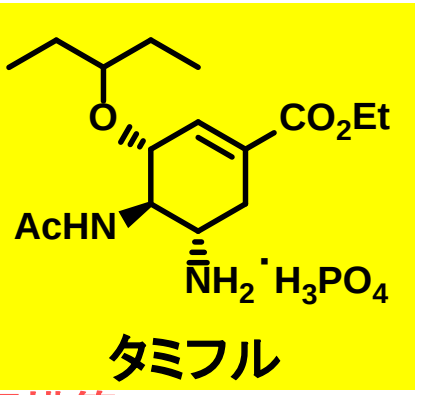
インフルエンザウイルスのライフサイクル

インフルエンザ
ウイルス

80 ~
120 nm

ワクチン

ノイラミニダーゼ阻害剤



タミフル

1. 吸着

2. エンドサイトーシス

3. 脱殻

4. ウイルスRNA
の核移行

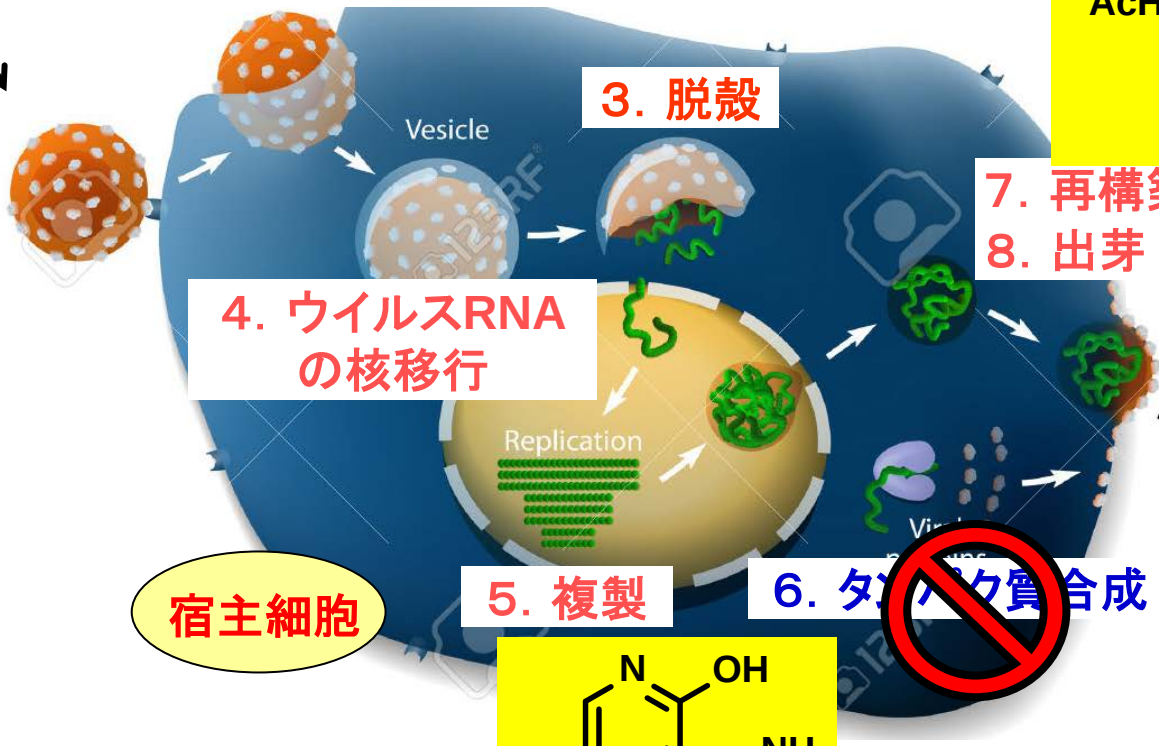
5. 複製

6. タンパク質合成

7. 再構築

8. 出芽

9. 放出

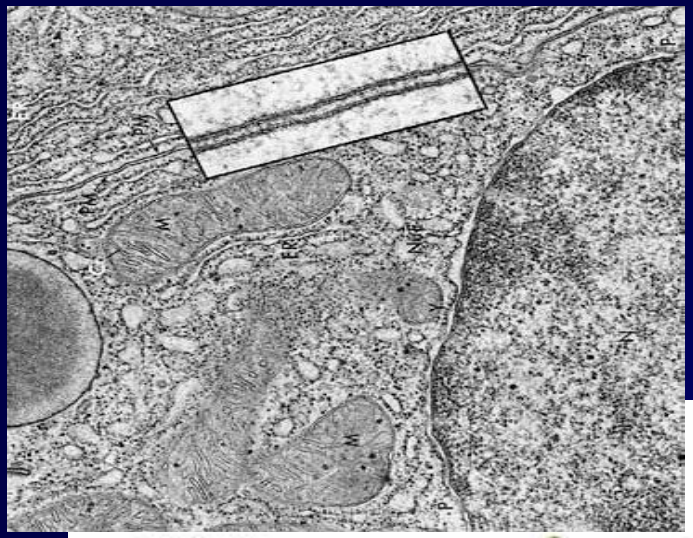


宿主細胞

T-705

感染の拡大へ

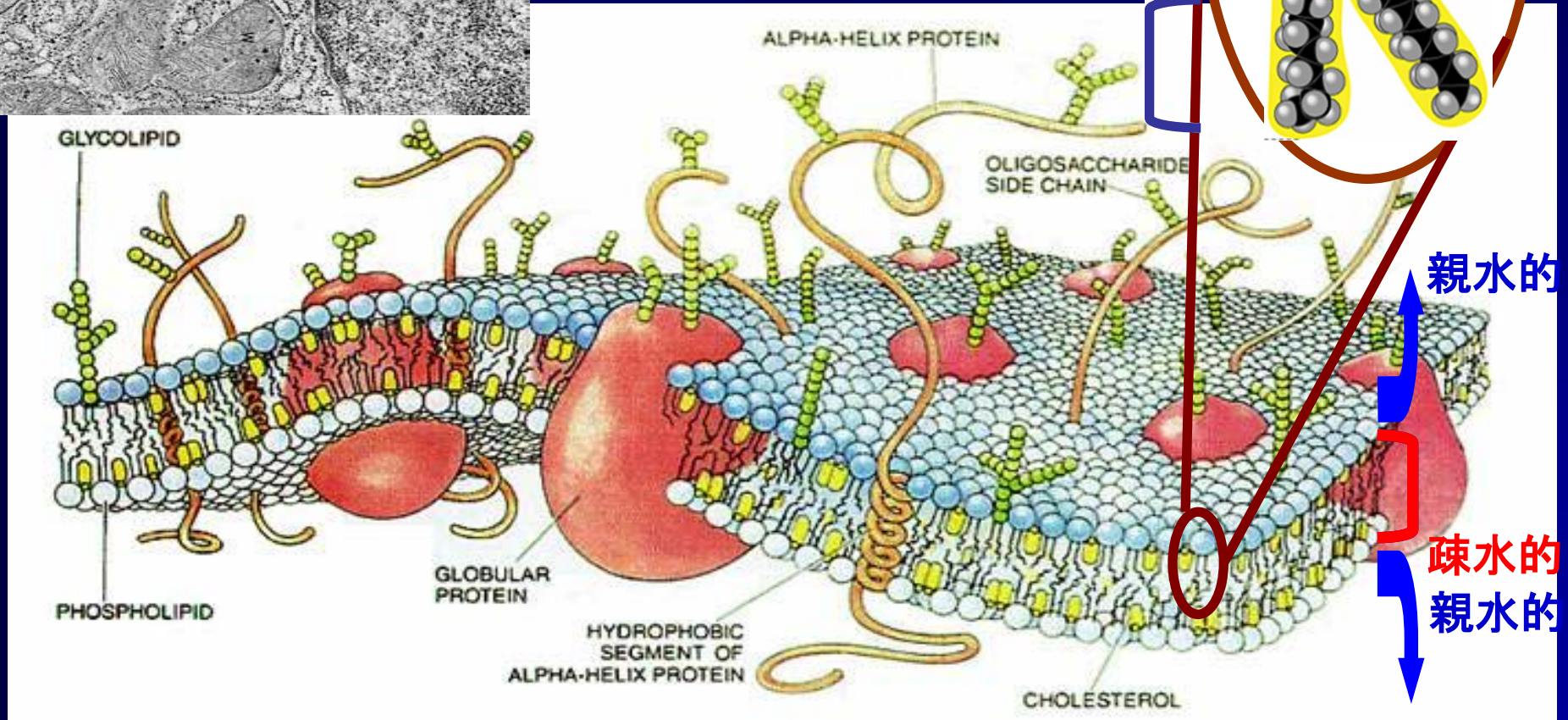
「吸着」・「放出」の起きる場：細胞膜



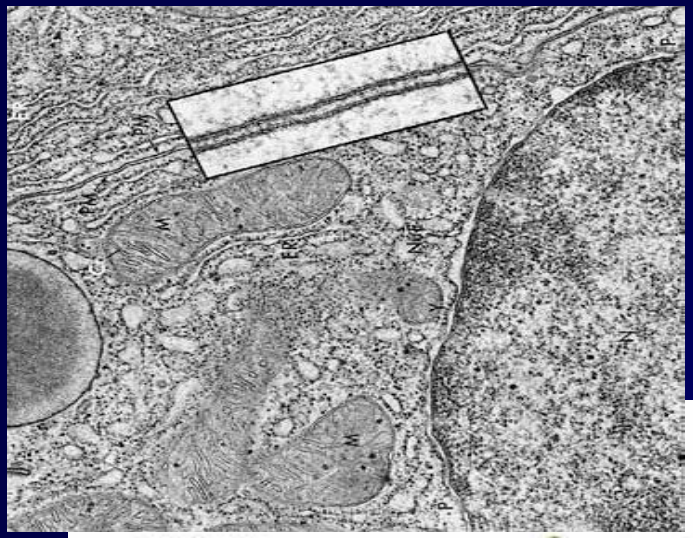
親水性ヘッド

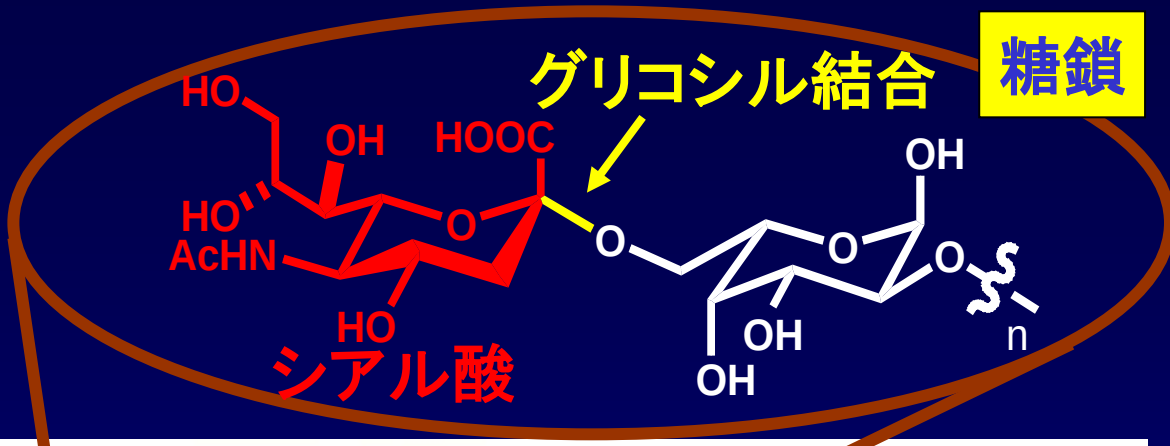
Self-assembly

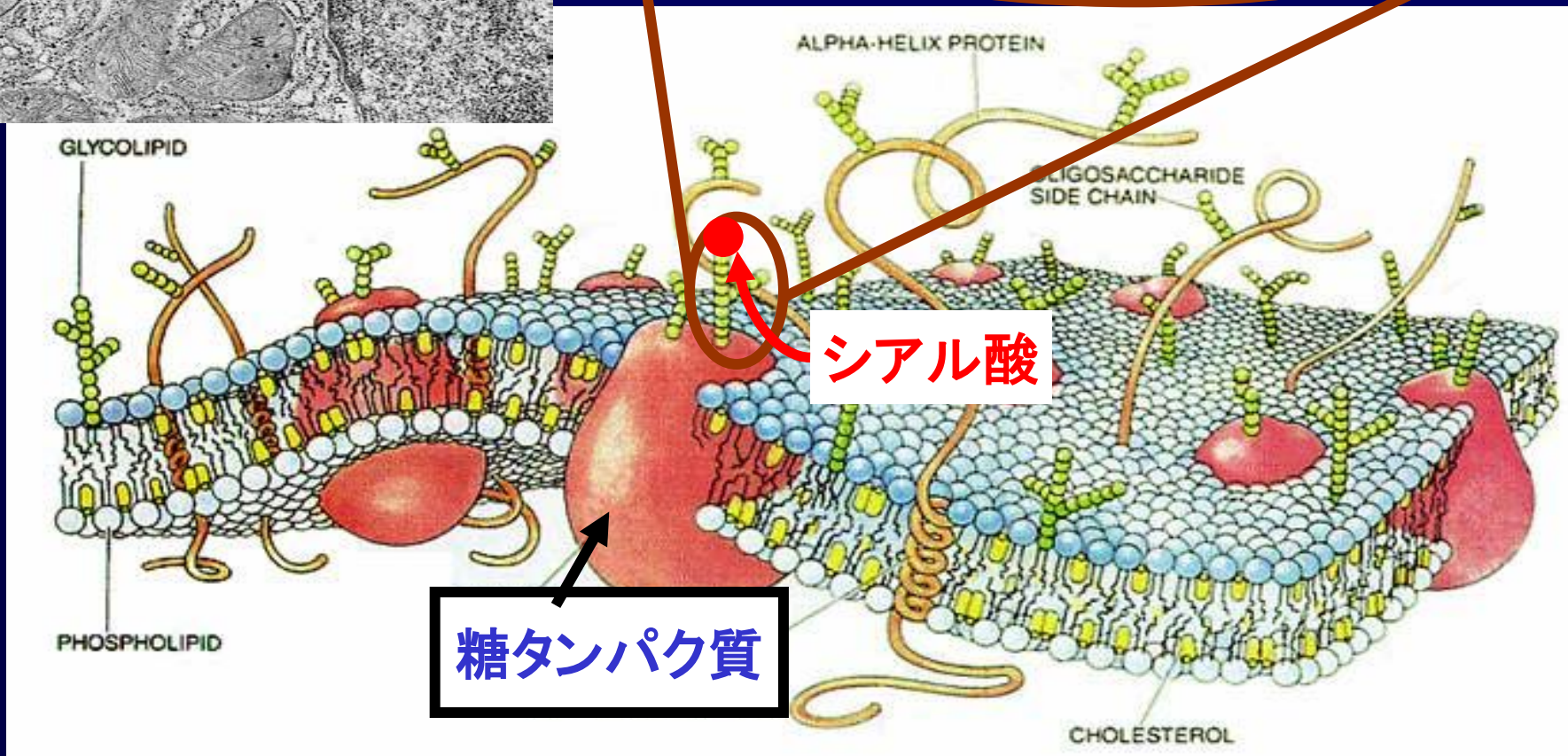
疎水性テール



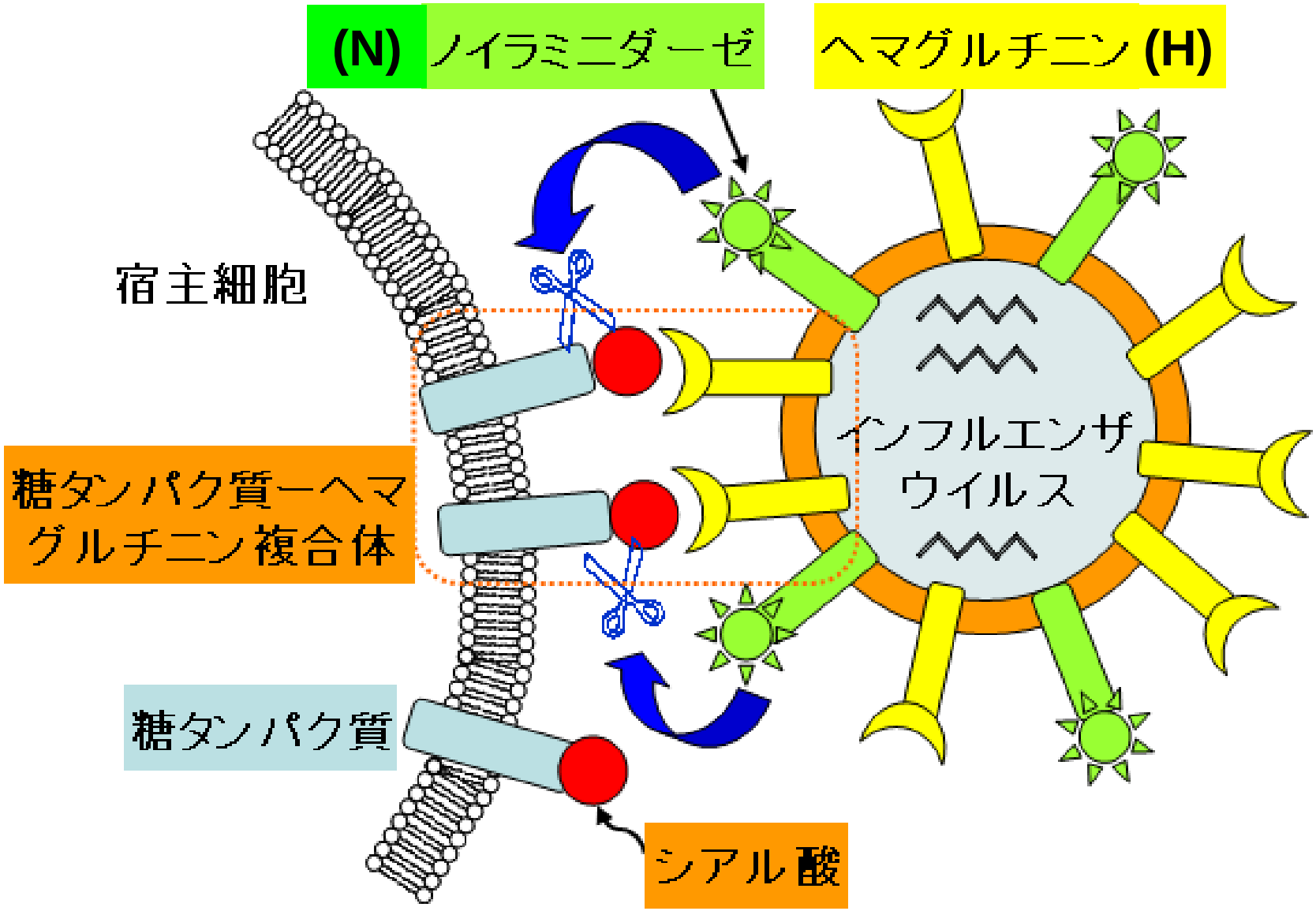
「吸着」・「放出」の起きる場：細胞膜



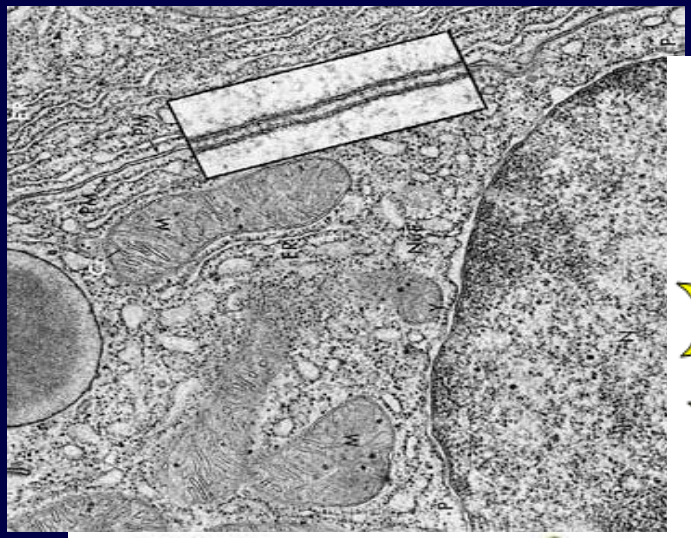


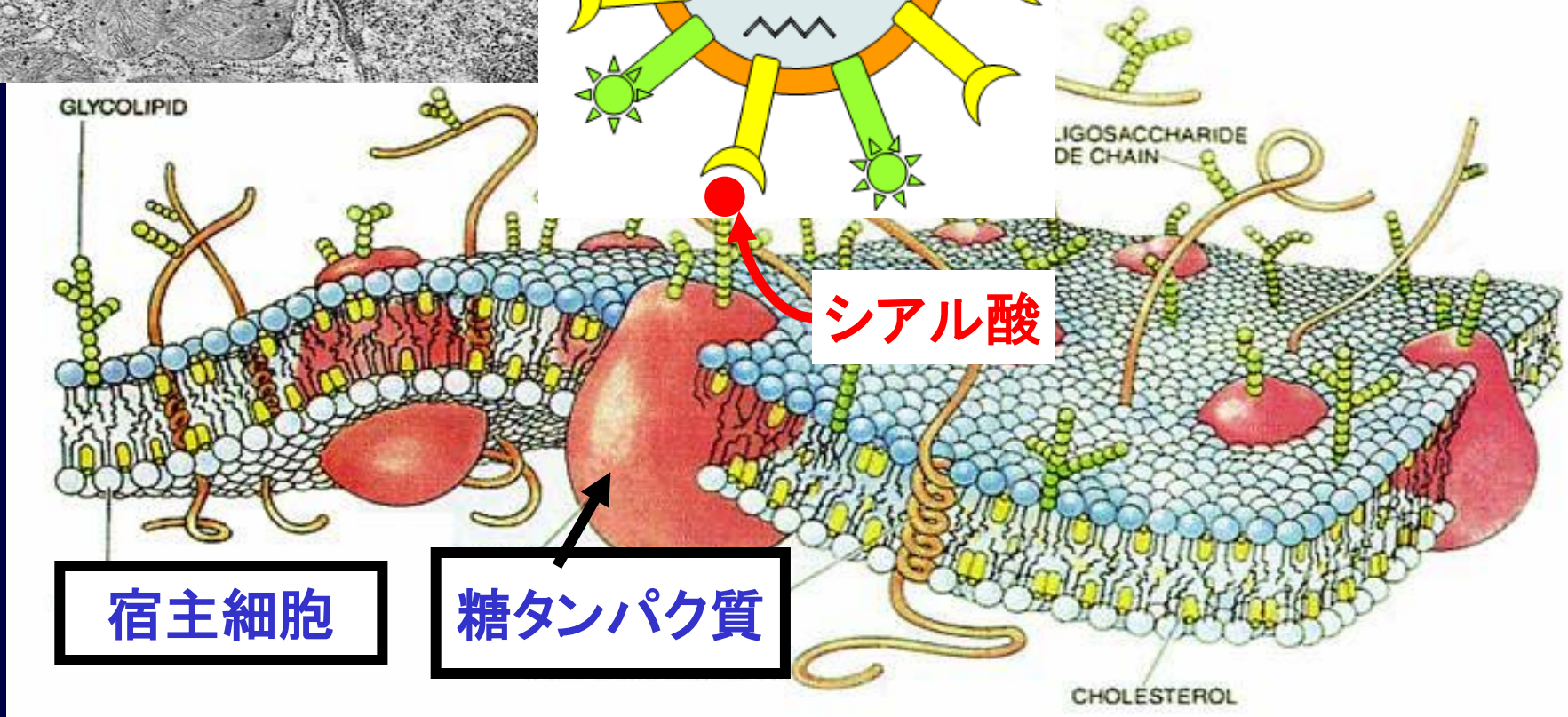


「放出」の分子機構

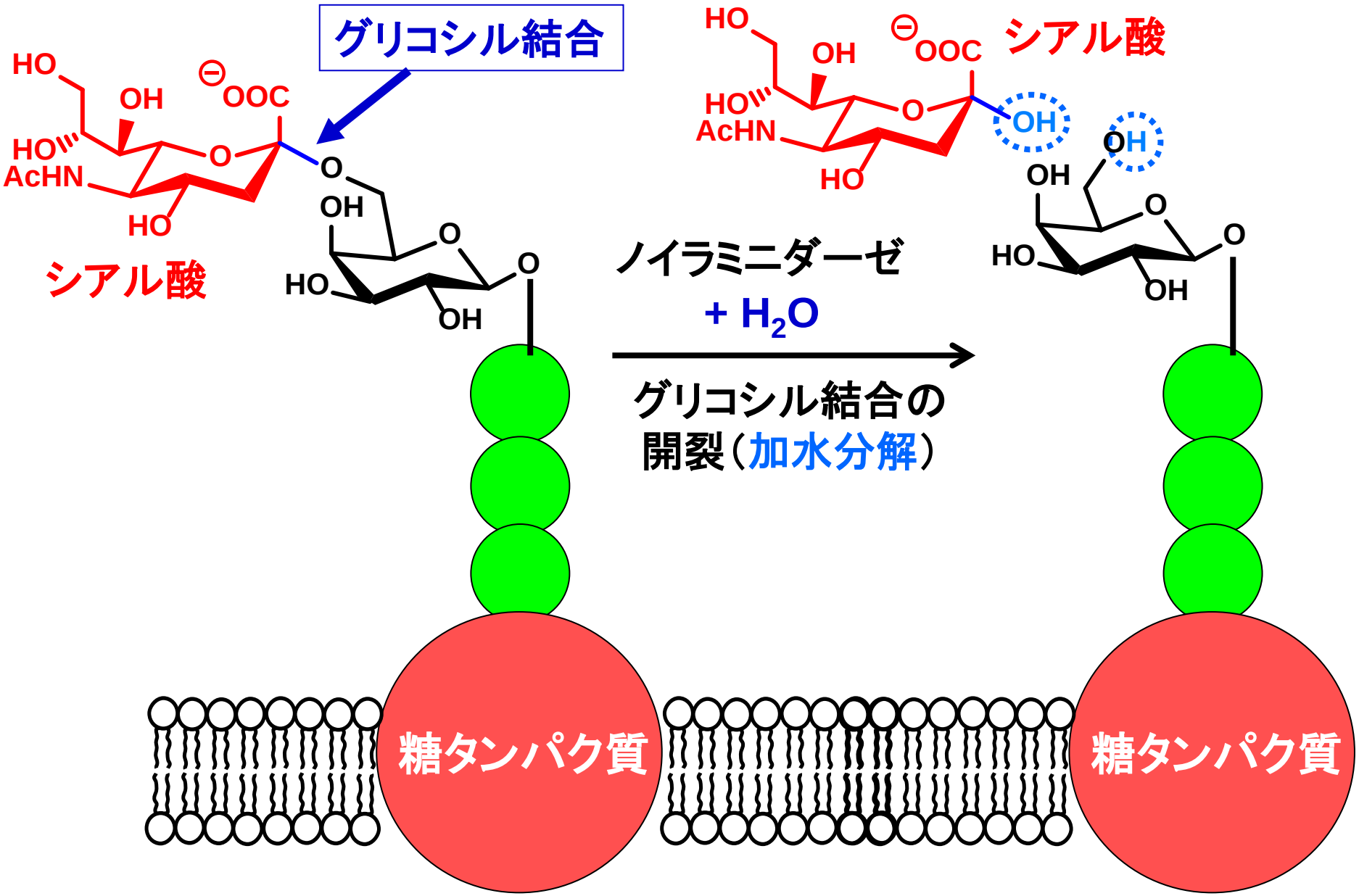

(N) ノイラミニダーゼ
ヘマグルチニン (H)
宿主細胞
糖タンパク質ーヘマグルチニン複合体
糖タンパク質
シアル酸
インフルエンザウイルス

「吸着」・「放出」の起きる場：細胞膜

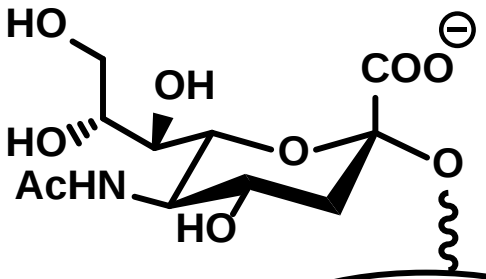




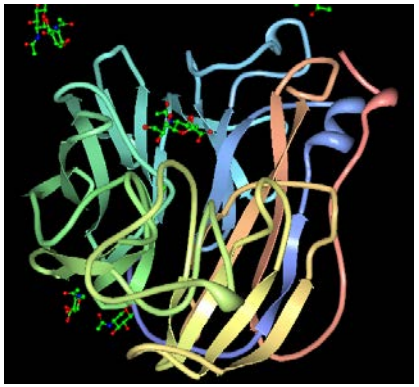
ノイラミニダーゼの働き

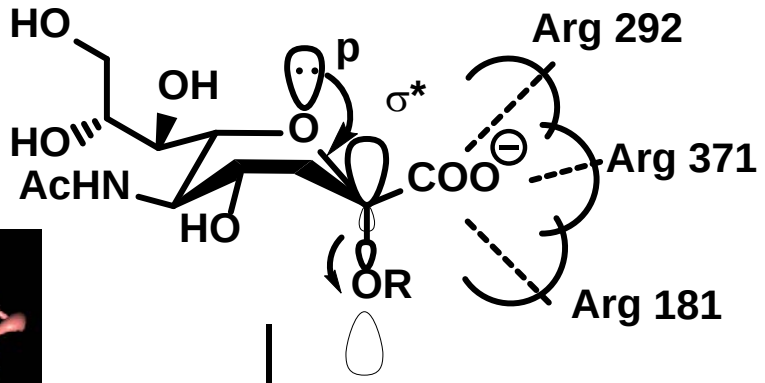


ノイラミニダーゼ阻害薬の分子設計



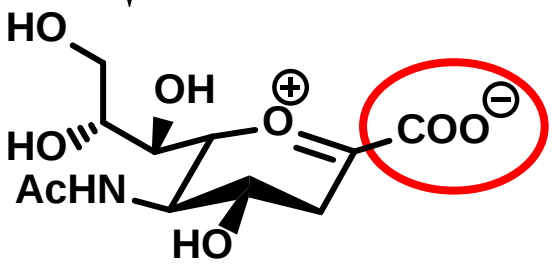
ノイラミニダーゼ





福井、Hoffmann
(1981年Nobel化学賞）

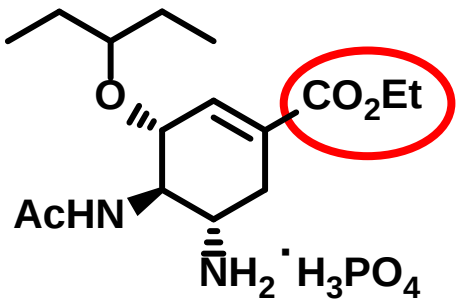
HOR



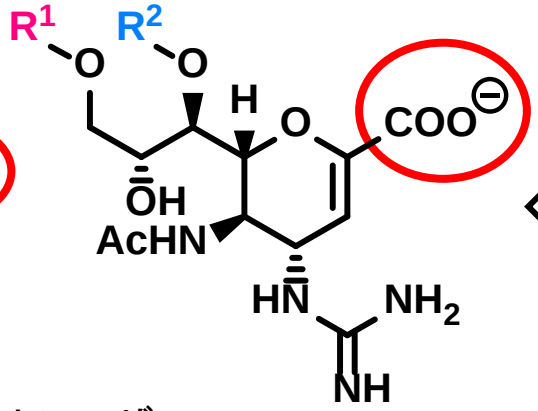
オキソニウム中間体

類似性

Pro-drug



タミフル
(Roche)



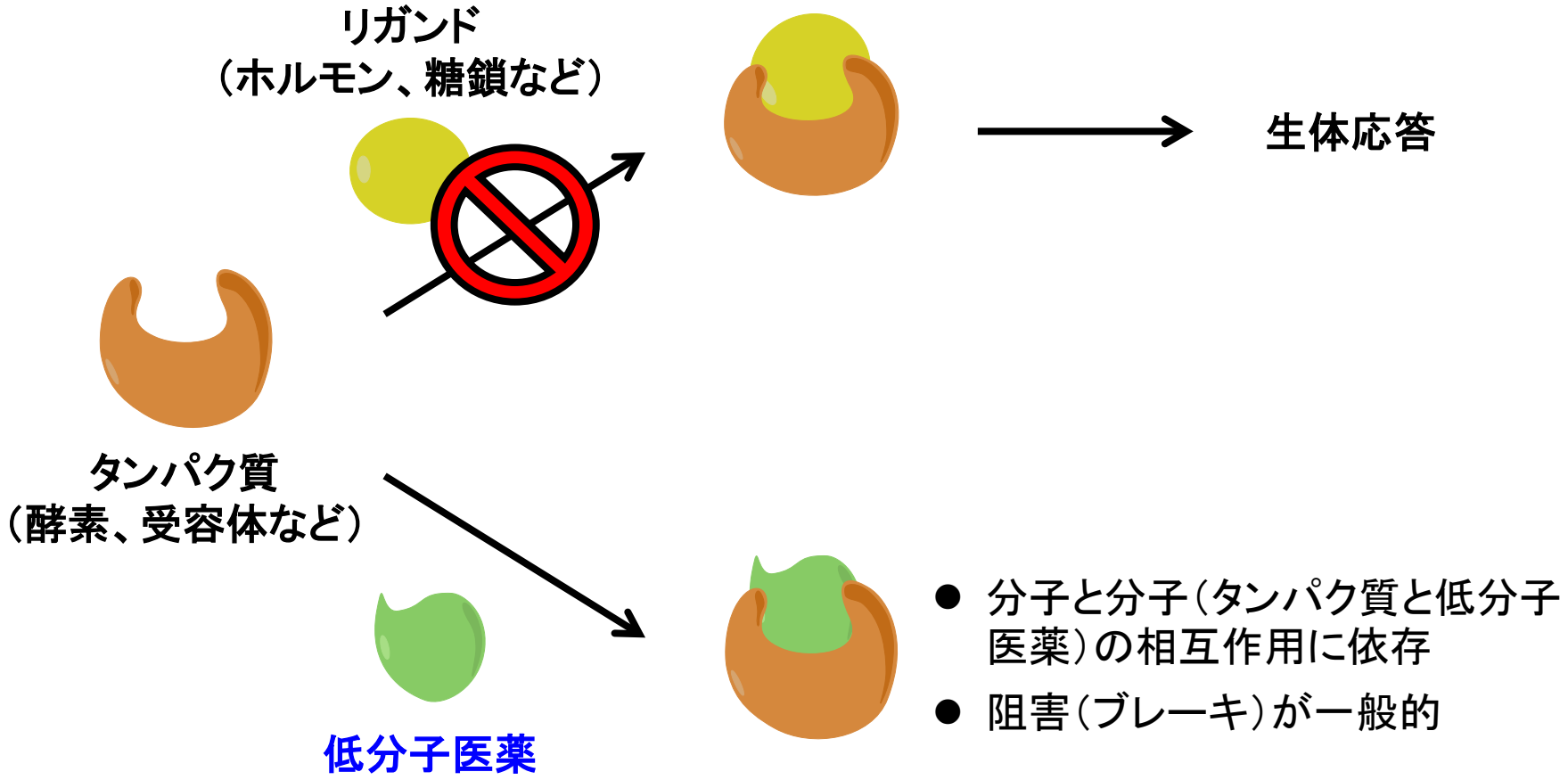
リレンザ (GSK): $R^1 = R^2 = H$

イナビル (Daiichi-Sankyo): $R^1 = C_7H_{15}CO$, $R^2 = CH_3$

経口可

吸入

低分子医薬の基本的な考え方

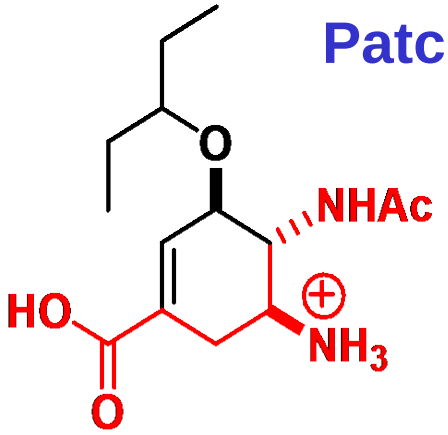


- 分子と分子（タンパク質と低分子医薬）の相互作用に依存
- 阻害（ブレーキ）が一般的

Pharmacologic Action of Oseltamivir on the Nervous System

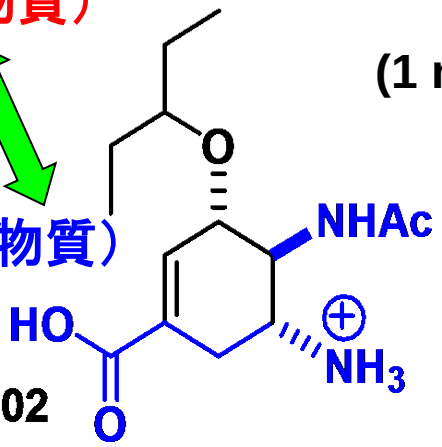
Ishii, K.; Hamamoto, H.; Sasaki, T.; Ikegaya, Y.; Yamatsugu, K.; Kanai, M.; Shibasaki, M.; Sekimizu, K.* *Drug Discov. Ther.* 2008, *2*, 24.

Patch-Clamp Electrophysiologic Responses

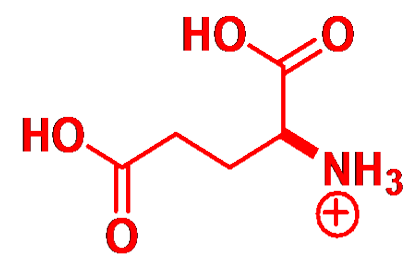


Ro64-0802
(active form of oseltamivir)
（左手物質）

エナンチオマー

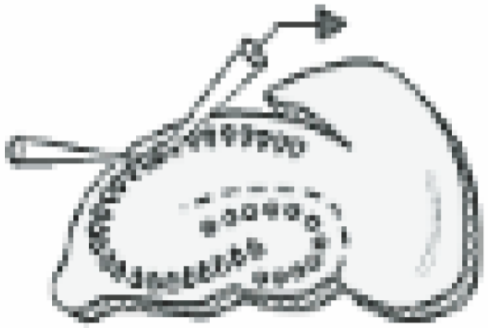


ent-Ro64-0802
（右手物質）



L-Glu

(1 mM)



rat brain
(CA1 pyramidal cells)

active

burst-like action potential (6/13)

inactive

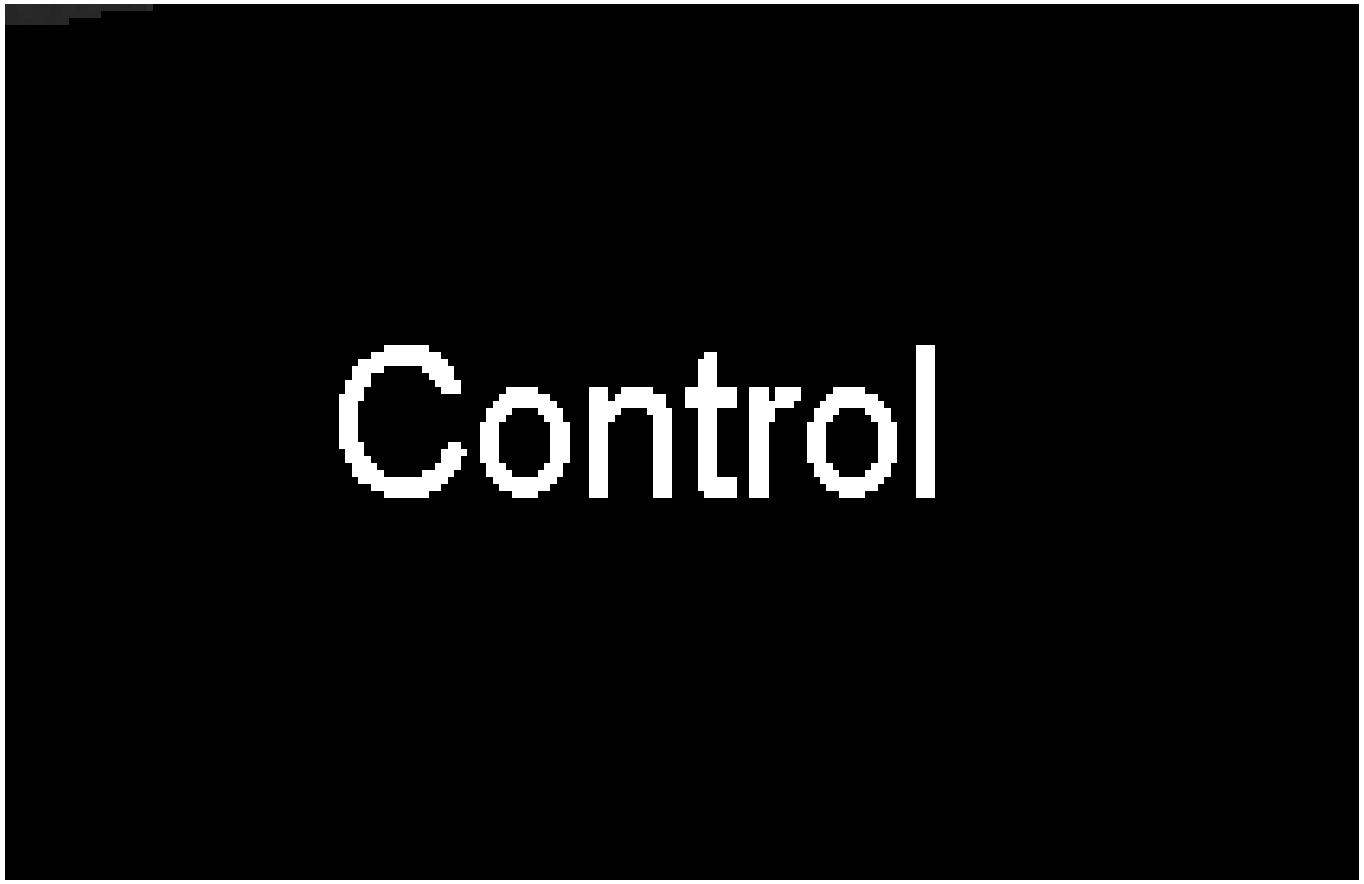
Muscle Relaxation of Silkworm Larvae; Convulsive Seizures of Mice

Related study: Izumi, Y. *et al. Neurosci. Lett.* 2007, *426*, 54.

Oseltamivir Enhances Hippocampal Network Synchronization

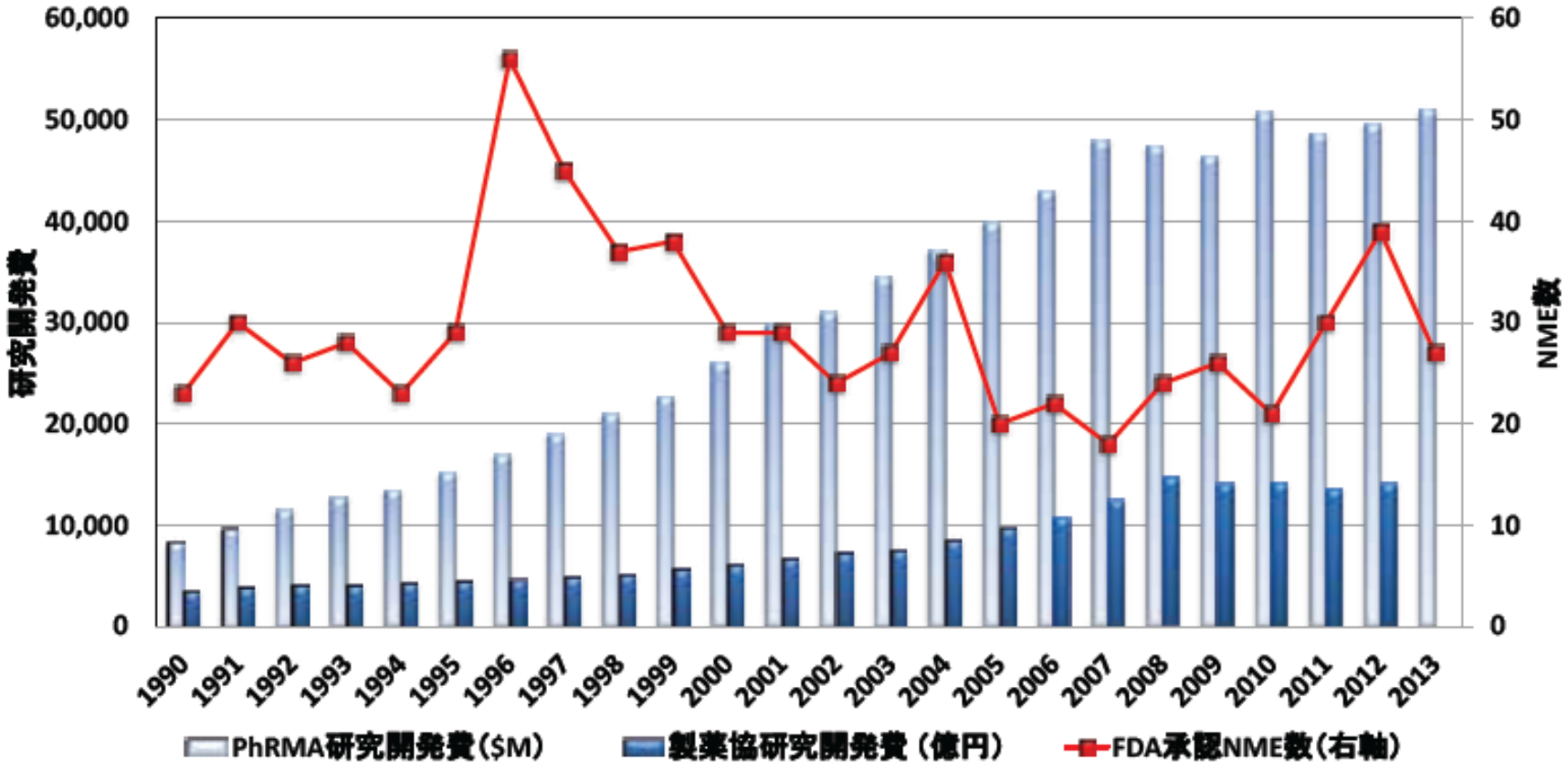
Usami, A.; Sasaki, T.; Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T.; Yamatsugu, K.; Kanai, M.; Shibasaki, M.; Matsuki, N.; Ikegaya, Y.* *J. Pharmacol. Sci.* 2008, *106*, 659.

Functional Multineuron Calcium Imaging



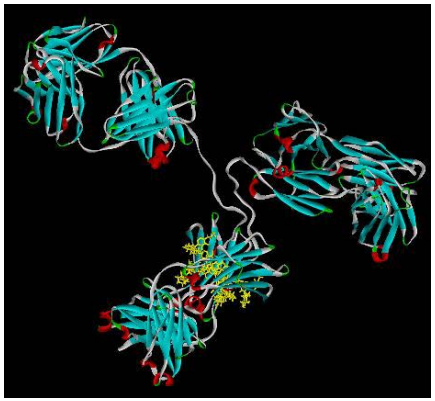
Population burst (44.7 ± 3.4 Hz, n = 234 bursts, 100 μM: **γ oscillations**): Activation of inhibitory interneuron by modulating sialylation-mediated neurite connectivity?

新薬の創出が難しくなってきている

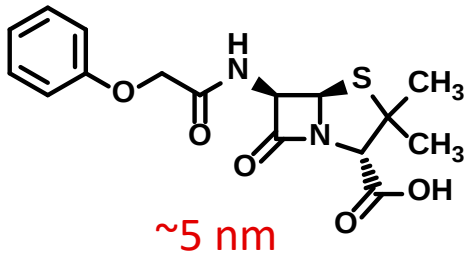


参考：製薬協Data Book、PhRMA Industry Profile、FDAホームページ

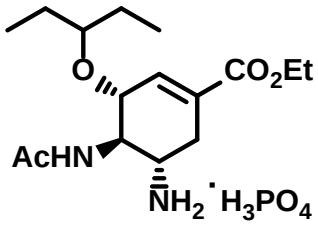
触媒医療：第四の疾病治療パラダイム創出を目指して

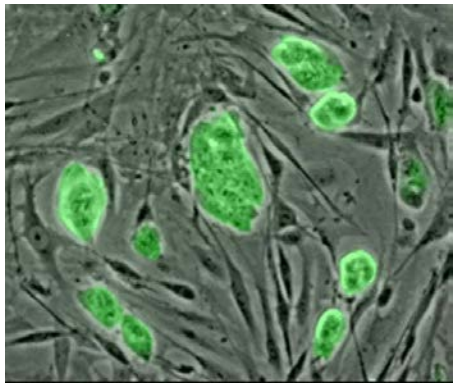


~100 nm



~5 nm





~10000 nm

低分子医薬

- 阻害（ブレーキ）が一般的

生物医薬（抗体等）

再生医療（iPS細胞）

新パラダイム（触媒医療）

~5 nm

- 低分子医薬の利点を維持したまま、生体高分子の化学構造を積極的に変化（＝**化学反応**）させる概念を導入
- 促進（アクセル）も可

Chemistry can make life.

Life is simply a matter of chemistry.----James Watson

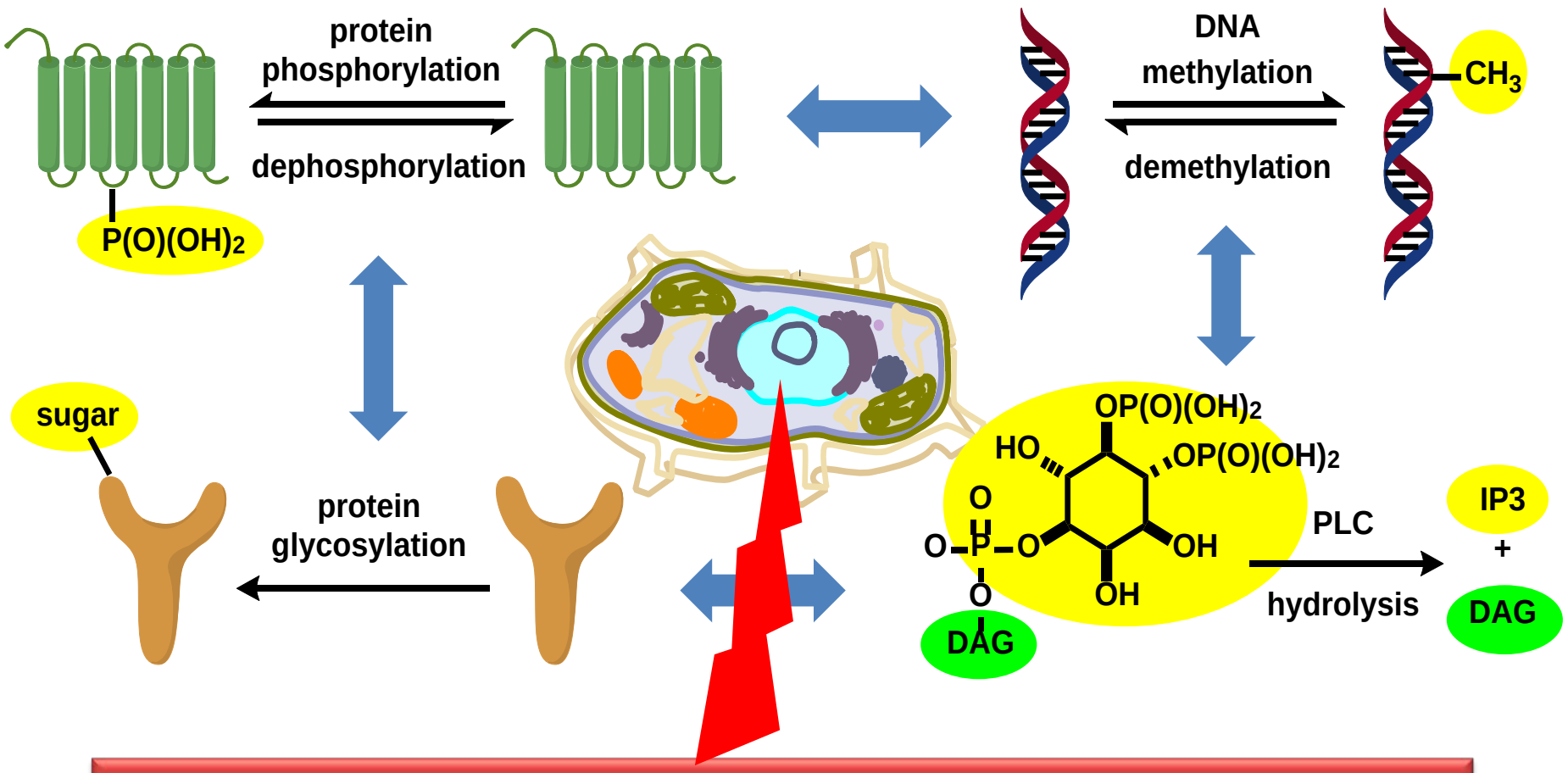
The answers to the questions we have about biology all lie at the level of chemistry.----Roger Kornberg

What I cannot create, I do not understand.

---Richard Feynman

触媒医療（Catalysis Medicine）

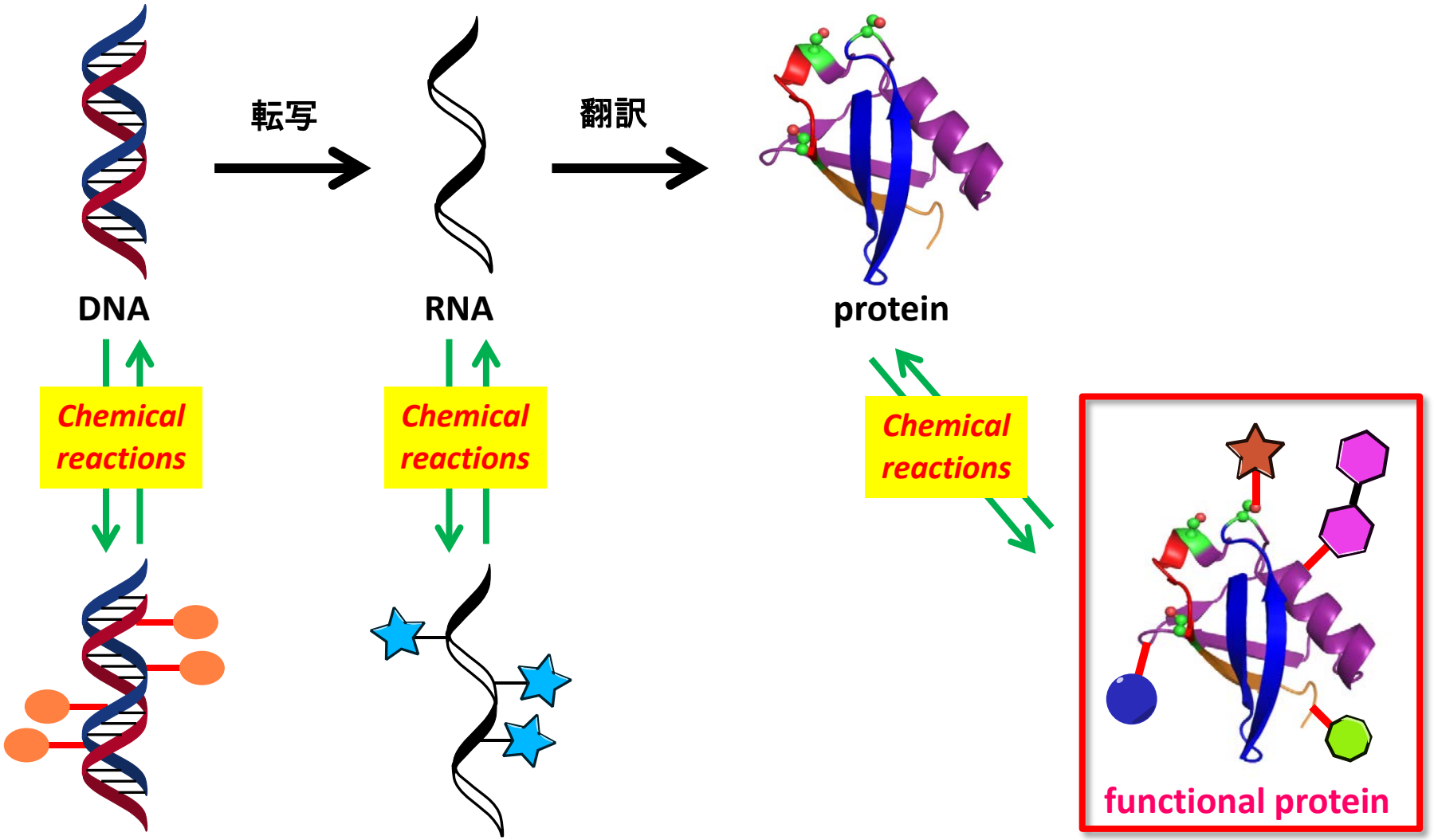
生命は触媒が媒介する化学反応システム



人工触媒によって媒介される化学反応を薬にできないか？

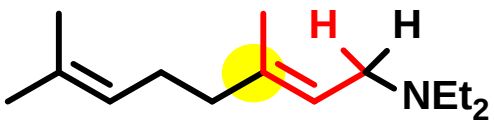
分子 & 化学反応

Central dogma



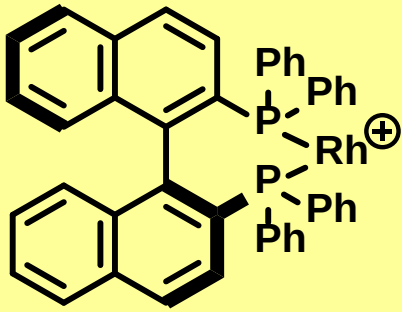
Epigenetics

触媒って何だ？



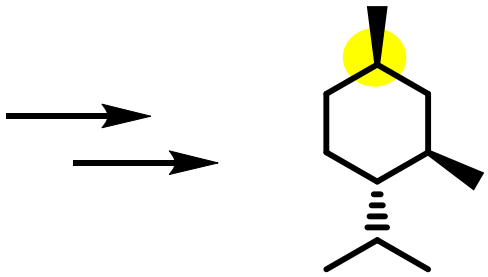
原料

野依触媒



低分子触媒
in 工場

生成物



（－）－メントール

数十～数百万トン/年

R. Noyori, "Synthesizing our future" *Nature Chemistry* 2009,

synthesis must pursue 'practical elegance'[1] — that is, it must be logically elegant but must at the same time lead to practical applications. Many of the stoichiometric reactions used at present, although useful, can and should be replaced by more efficient catalytic processes.

Catalysis has been, and will remain, one of the most important research subjects, because this is the only rational means of producing useful compounds in an economical, energy-saving and environmentally benign way. According to a promotional brochure from the renowned German chemical company BASF, more than 80% of globally produced chemicals are made using catalytic processes. The importance of efficient heterogeneous, homogeneous and biological catalysts[2] is continually increasing. Practical catalysts must enable reactions that are rapid, capable of being scaled up, and selective in the products formed. Molecular catalysts displaying chiral efficiency that rivals or exceeds that of enzymes are highly desirable[3–5].

lower activation energy, however, it does not improve the ability to conduct endothermic processes, which require the investment of extra energy or the use of special product-separation technology to shift chemical equilibria to favour the formation of a desired product.

There are many reactions that do not work under thermal conditions. To enhance the power of synthetic chemistry, photosynthetic catalysis enabling otherwise energetically forbidden transformations needs to be explored in greater depth. Similarly, current step-by-step organic syntheses must be a combination of all thermodynamically downhill reactions, limiting the overall efficacy. Therefore, cascade syntheses[6], or those that combine multiple components in a single step[7], are particularly appealing. An intricately designed device that can integrate multiple catalysts along with suitable cofactors to achieve this without the necessity of human intervention is a worthy goal.

Ideally, we should aim at synthesizing target compounds with a 100% yield and

technology has brought with it a range of global issues. Scientists' efforts should be directed towards solving a range of existing or predicted social and global issues associated with energy, materials, the environment, natural disasters, water, food and health. Chemists have an immense responsibility to tackle these problems; however, the prevalent over-specialization in science tends to make it difficult to find solutions because there are usually multiple causes. To remedy this situation, we need a more broadly based science education, which will better equip future chemists to tackle the issues outlined above.

Science is, in principle, objective. But it is human intelligence and endeavour that discover and create scientific knowledge. The scientific world should be borderless; scientists from both advanced and emerging nations — with different backgrounds and values — must cooperate for the survival of our species within the confines of our planet. This is the greatest challenge facing chemists in conducting their research. ❐

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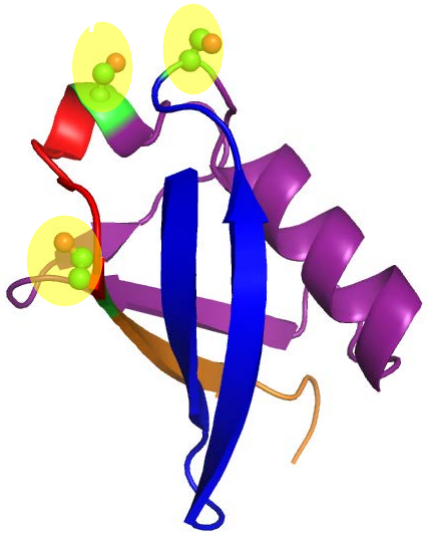
e-mail: noyori@riken.jp

References

1. Noyori, R. *Chem. Commun.* 1807–1811 (2005).
2. Schmid, A. *et al. Nature* **409**, 258–268 (2001).
3. Knowles, W. S. *Angew. Chem. Int. Ed.* **41**, 1998–2007 (2002).

Serine-Selective Aerobic Oxidative Cleavage of Protein

Ubiquitin: UQ(1-76) 1 mM

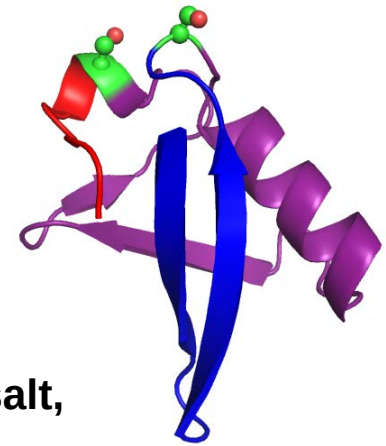


A : CuI (500 mol %)
bathophen salt (500 mol %)
ketoABNO (500 mol %)
$NaNO_2$ (1500 mol %)

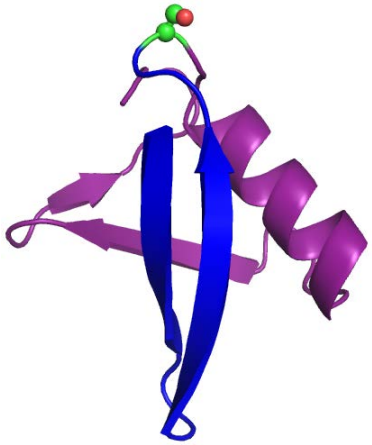
$CH_3CN/H_2O/$ AcOH (9/9/2)
rt, O_2 (1 atm), ~20 h

B : without ketoABNO
C : without CuI, bathophen salt, ketoABNO

UQ(1-64)
Band 1

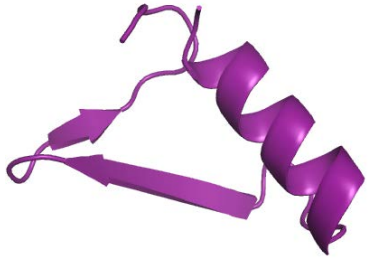


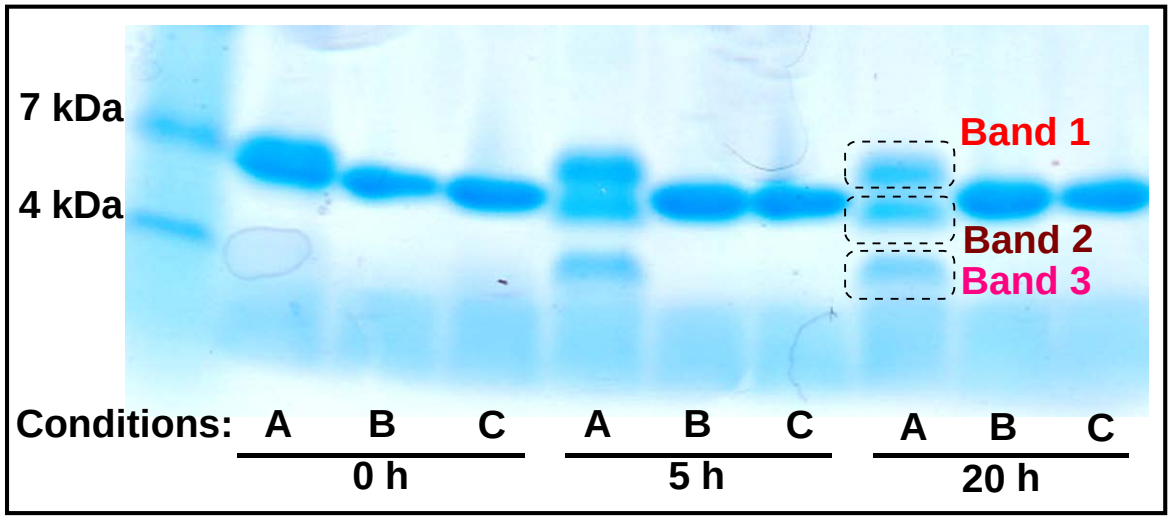
UQ(1-56)
Band 2



UQ(1-19)
Band 3

UQ(21-56)
Band 3

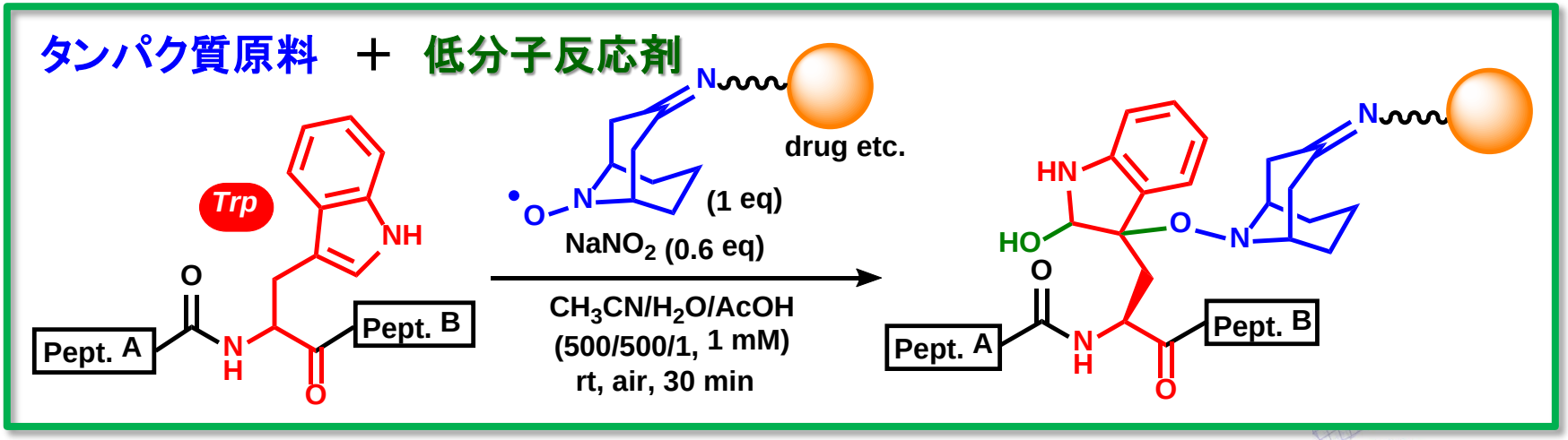




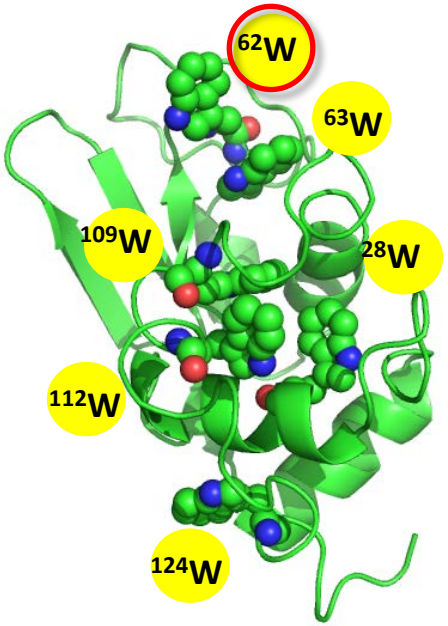
Seki, Tanabe, Sasaki, Sohma, Oisaki, Kanai, *ACIE*, 2014, 53, 6501.

MQIFVKTLTGKTITLEVEP-^{20}S-DTIENVKAKIQDKEGIPPDQQRLIFAGKQLEDGRTL-^{57}S-DYNIQKE-^{65}S-TLHLVLRLRGG

タンパク質の特定のアミノ酸を認識する人工化学反応



- *Lysozyme (1-129)*

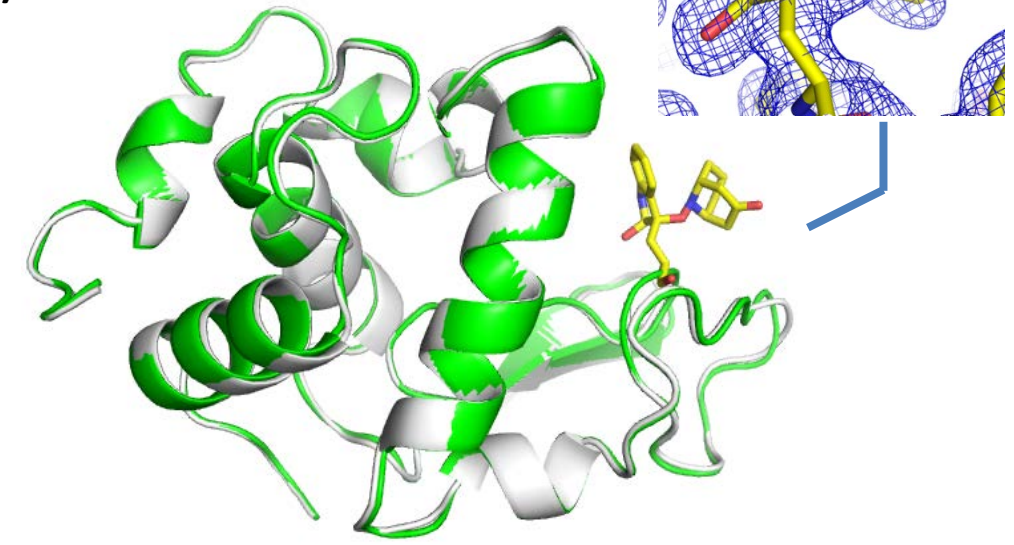


試薬メーカーから市販

keto-ABNO (1 eq)
$NaNO_2$ (0.6 eq)
H_2O/AcOH
(1000/1, 1 mM)
rt, air, 30 min

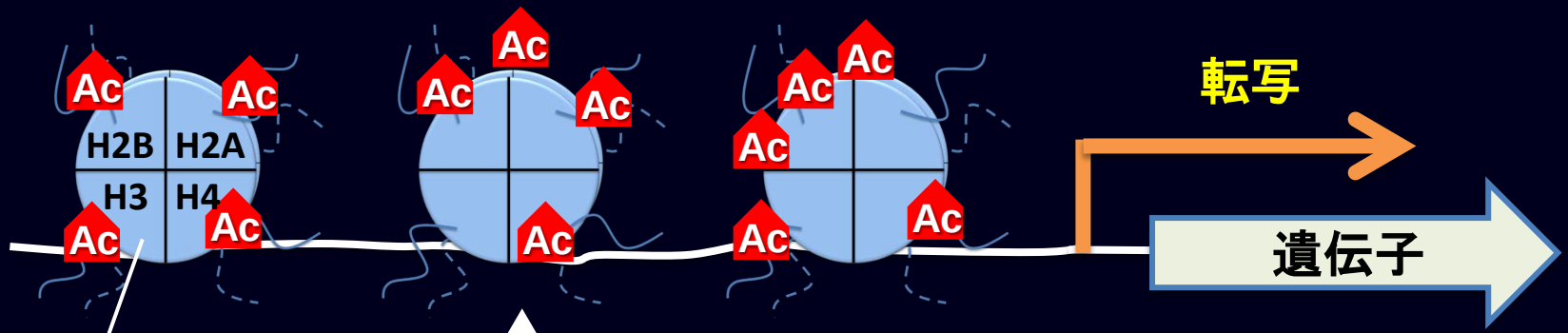
64%

white = modified
green = native



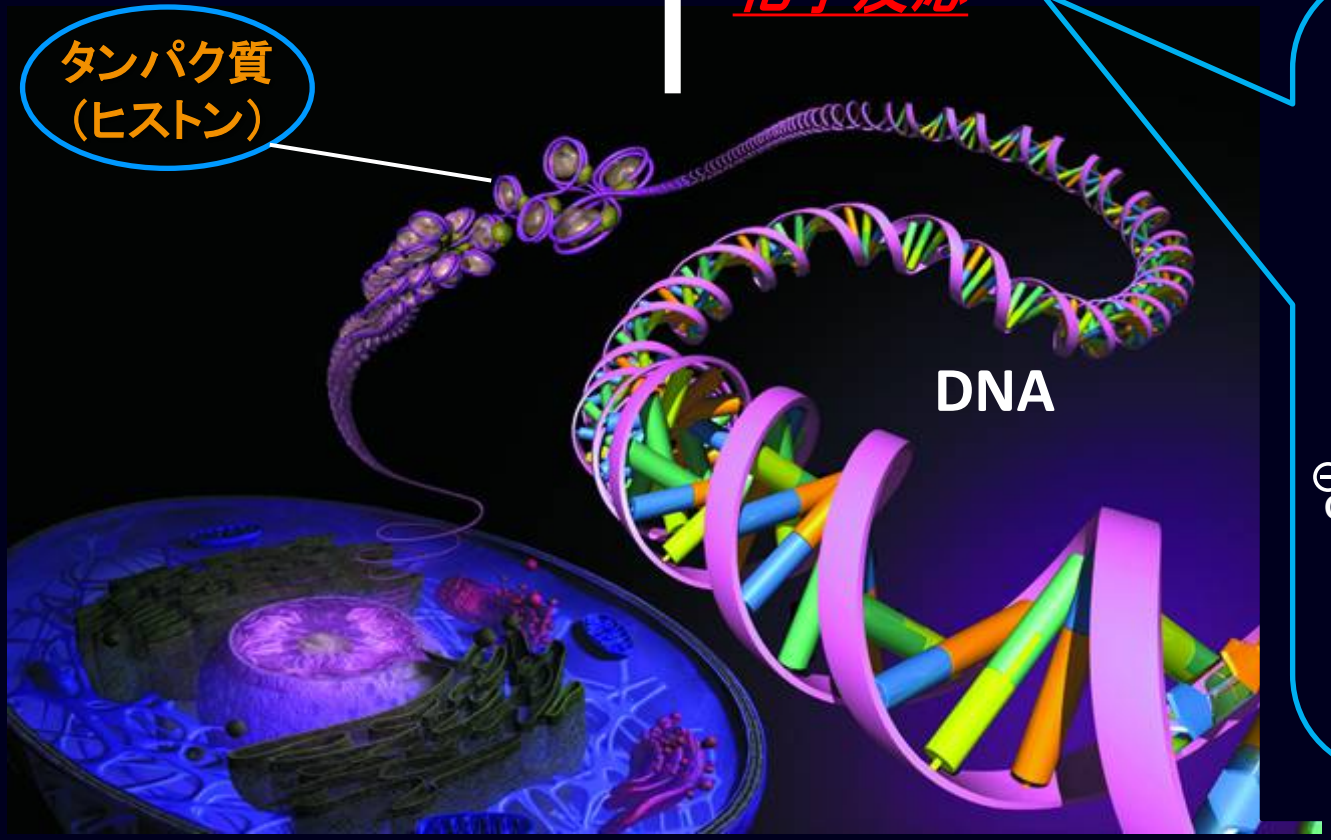
Seki, Ishiyama, Sasaki, Abe, Sohma, Oisaki, Kanai, *JACS* **2016**, *138*, 10798.

タンパク質の化学反応が遺伝子発現を制御



化学反応

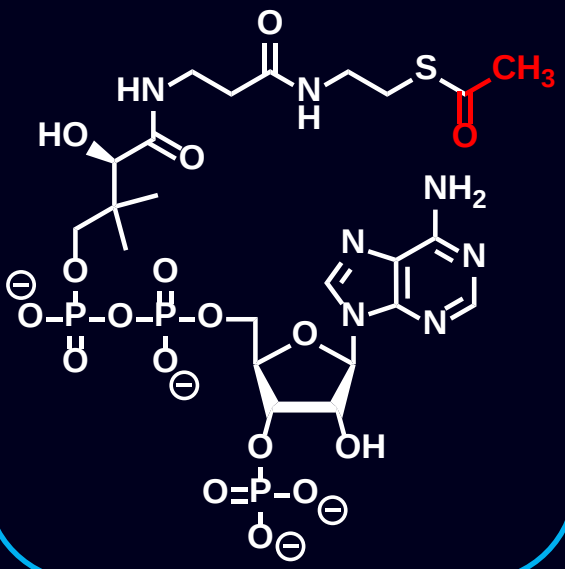
タンパク質
（ヒストン）



触媒＝酵素 (HAT)

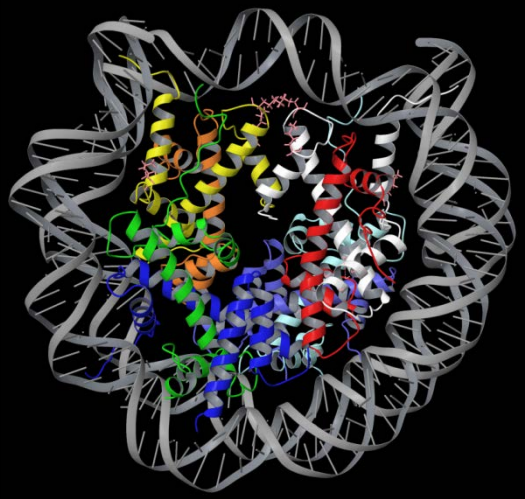
＋

反応剤

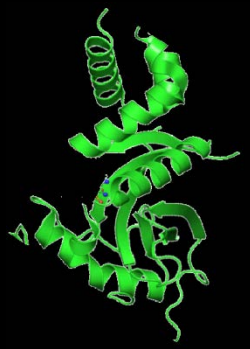


生体内で進行する化学反応は酵素（タンパク質）が触媒する

原料
（クロマチン＝タンパク質＋DNA）

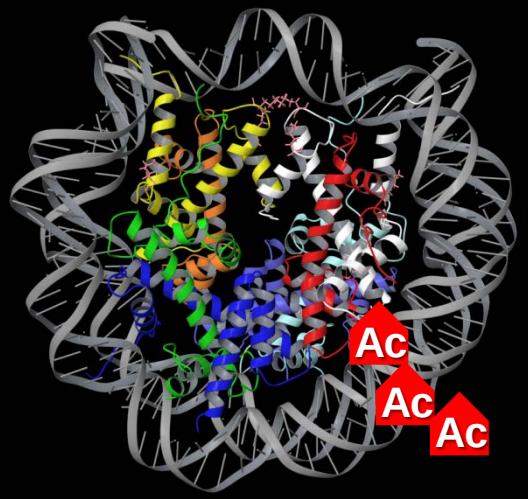


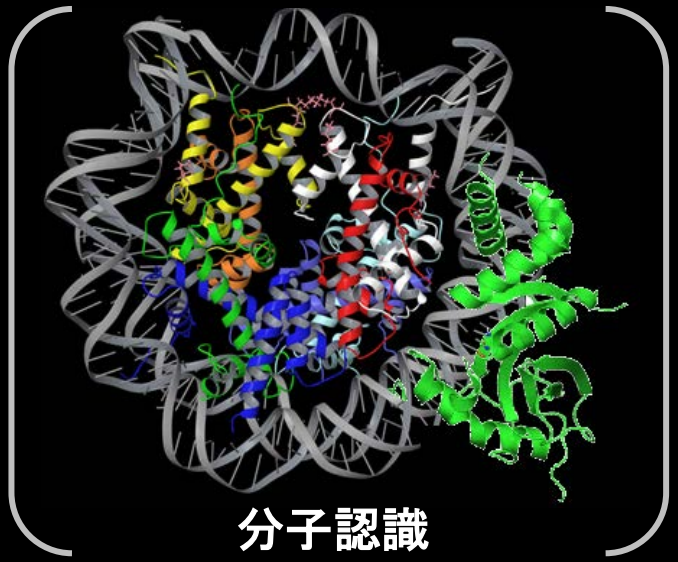
触媒＝酵素 (HAT)



タンパク質触媒
in 細胞

生成物



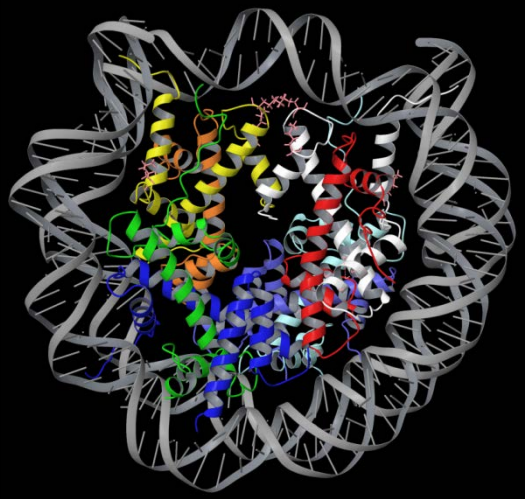


分子認識

生体応答
（がん抑制遺伝子の発現など）

酵素を人工触媒で代替できないか？

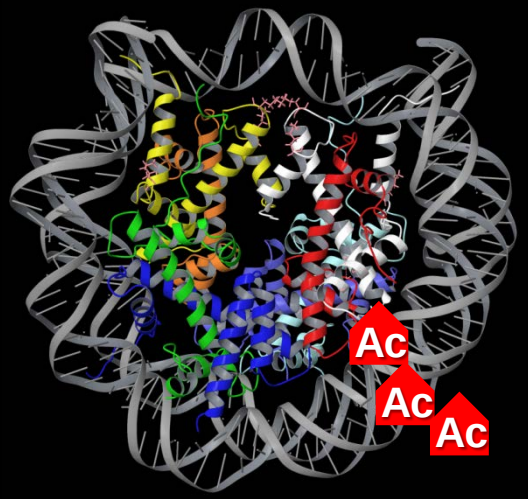
原料
（クロマチン＝タンパク質＋DNA）

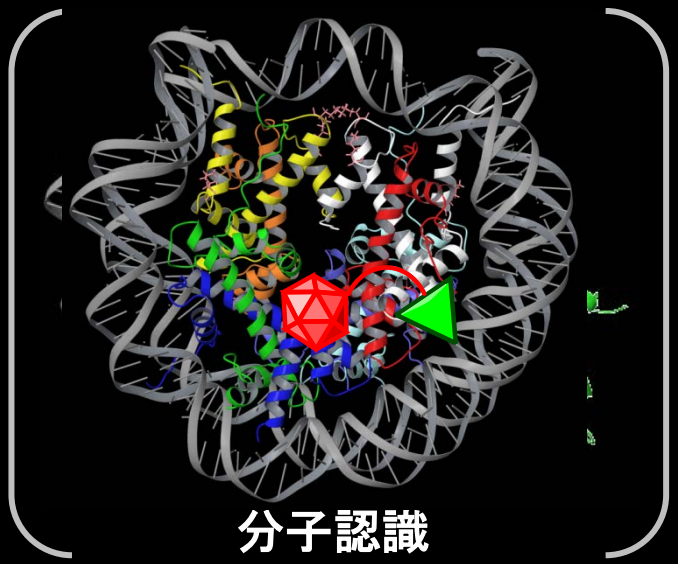


触媒＝酵素 (HAT)

低分子触媒
in 細胞

生成物





分子認識

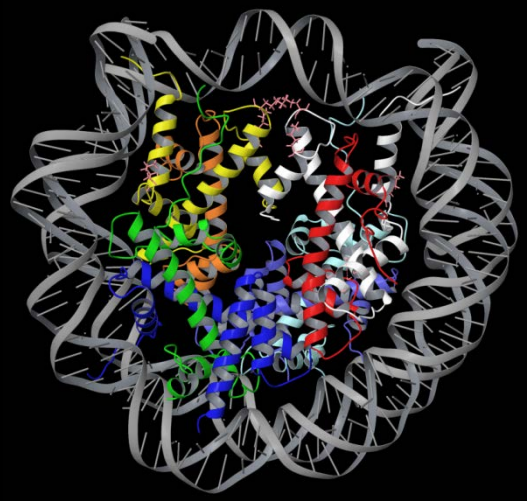
生体応答
（がん抑制遺伝子の発現など）

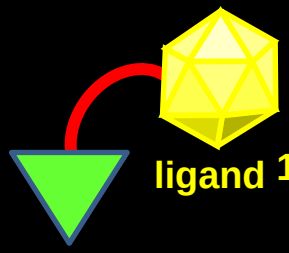
酵素を代替する人工触媒

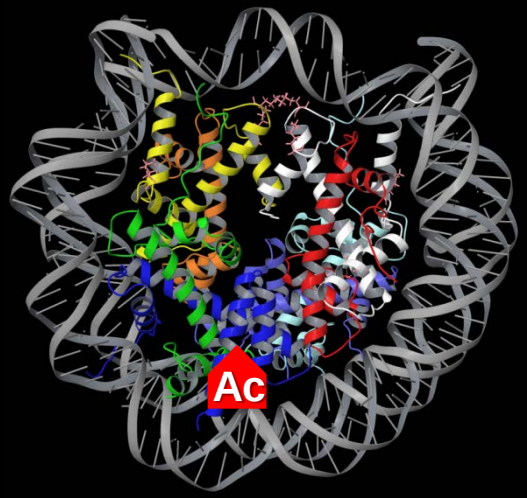
生体高分子原料
（クロマチン＝タンパク質＋DNA）

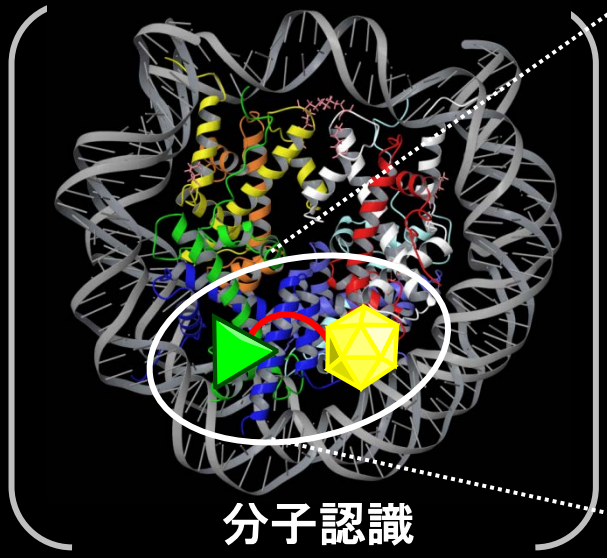
人工低分子触媒1

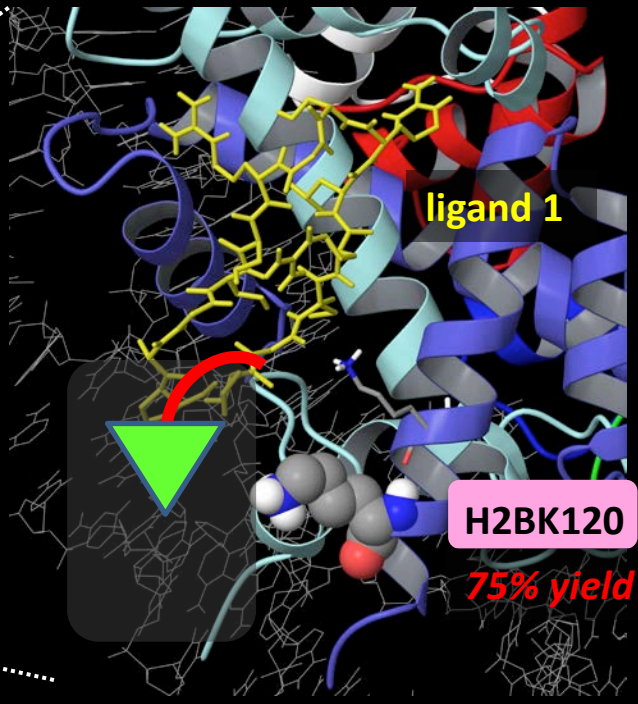
生成物



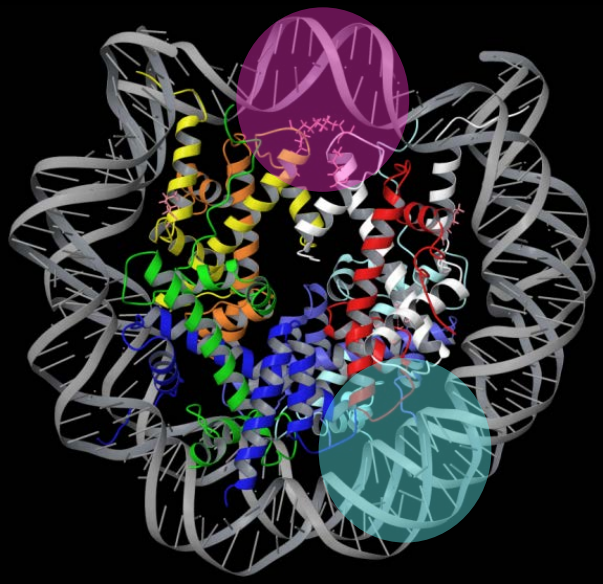




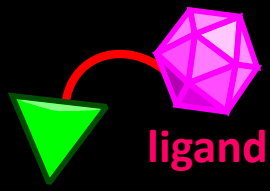


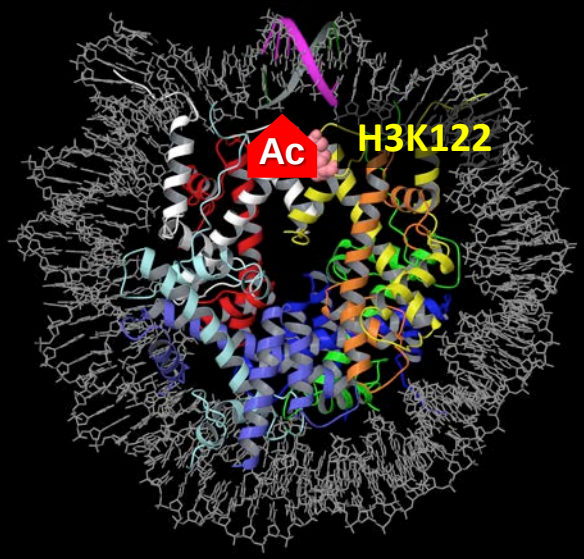


人工触媒のリガンドの選択により反応位置を自在に制御

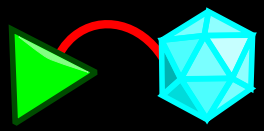


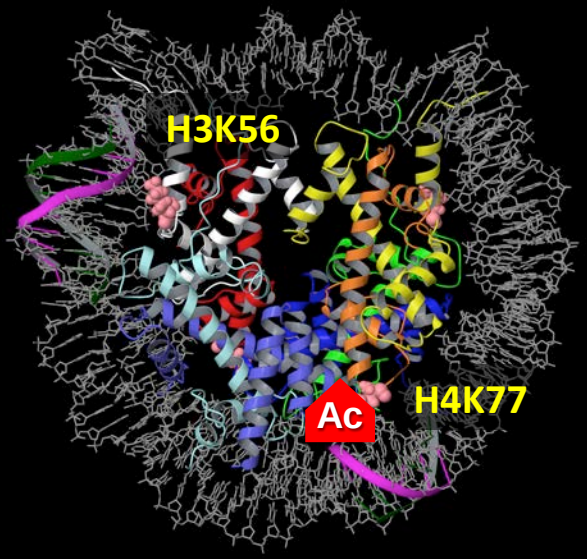
人工低分子触媒2

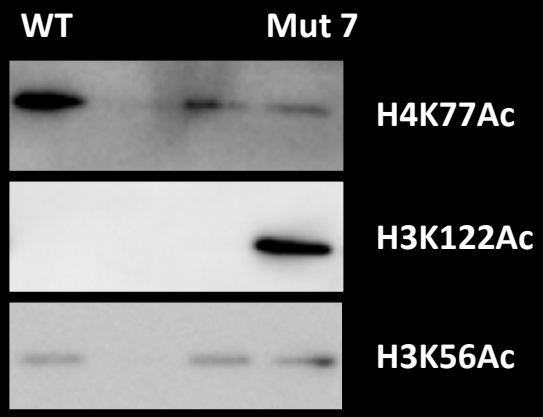




人工低分子触媒3

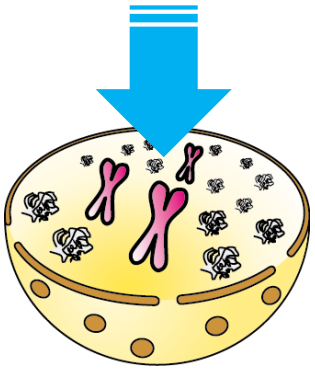


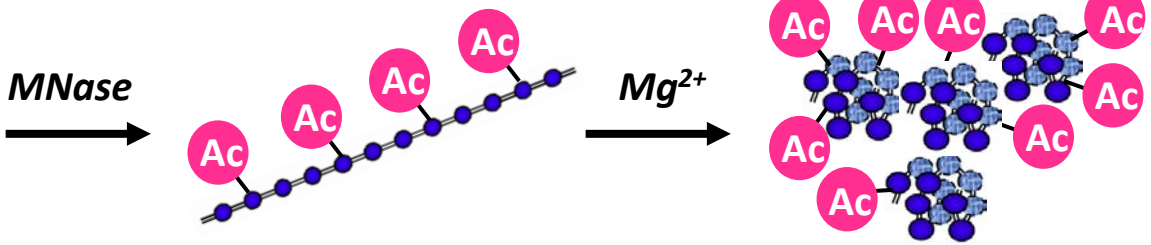




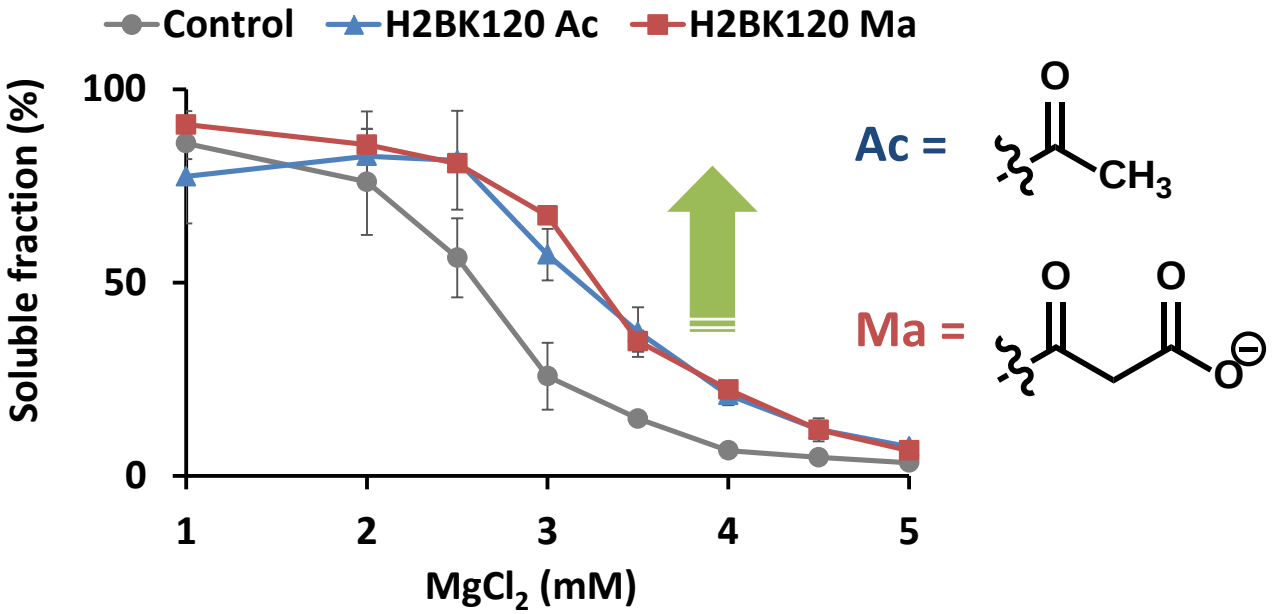
人工触媒反応によって
クロマチンを転写されやすい性質に変えることができた

人工触媒反応



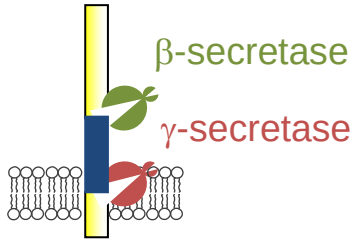


人工エピジェネティクス
分野創出と医療応用へ



Amamoto, Aoi, Nagashima, Suto, Yoshidome, Arimura, Osakabe, Kato, Kurumizaka,
Kawashima, Yamatsugu, Kanai, *submitted*

アミロイドβ（Aβ）の化学的酸素化による代謝・除去



amyloid precursor protein (APP)

inhibition / modulation

production

Aβ

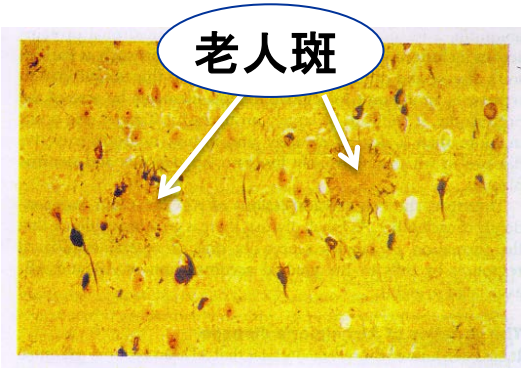
monomer

promotion / immunotherapy

degradation / clearance

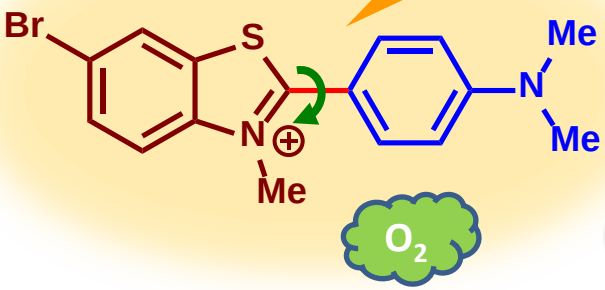
凝集

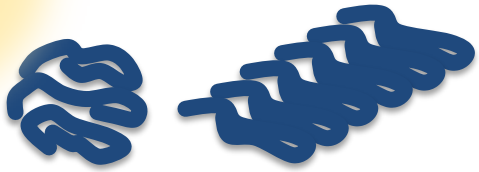
inhibition / modulation



アミロイド除去触媒

hν (500 nm)





oligomer fibril

(cross-β sheet)

神経毒性あり

アルツハイマー病

酸素化Aβ

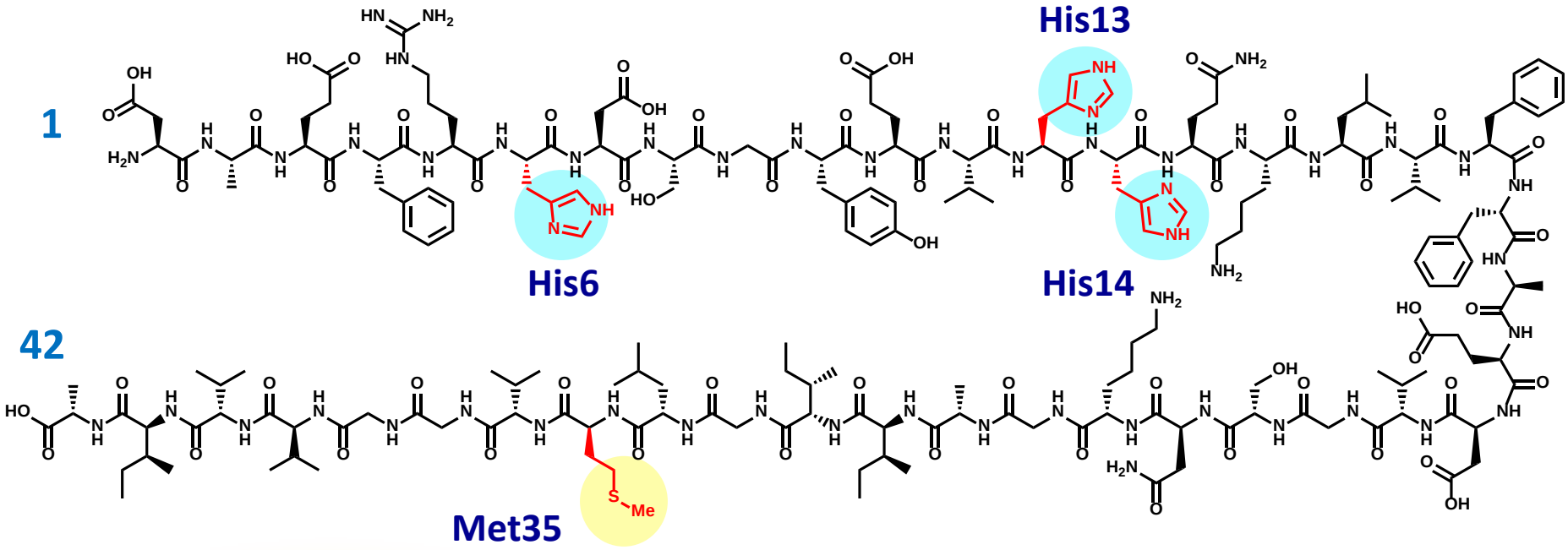
神経毒性なし

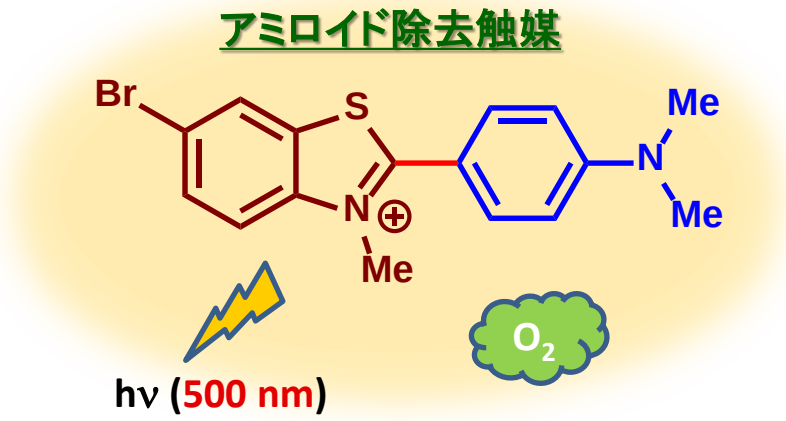
触媒的酸素化反応

毒性タンパク質の化学的代謝・除去

Taniguchi, Shimizu, Oisaki, Sohma, Kanai, *Nat. Chem.* **2016**, *8*, 974.

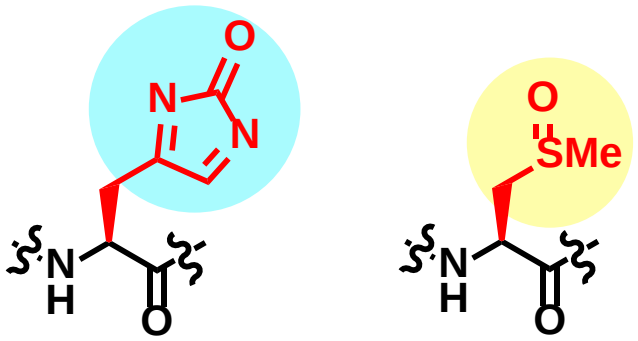
Aβ凝集体の化学的酸素化の反応式





Phosphate buffer (pH 7.4), 37 ˚C
1.5 h, ~75%

酸素化 Aβ



アルツハイマー病を標的とする触媒医療

アミロイド除去触媒
（進化型）

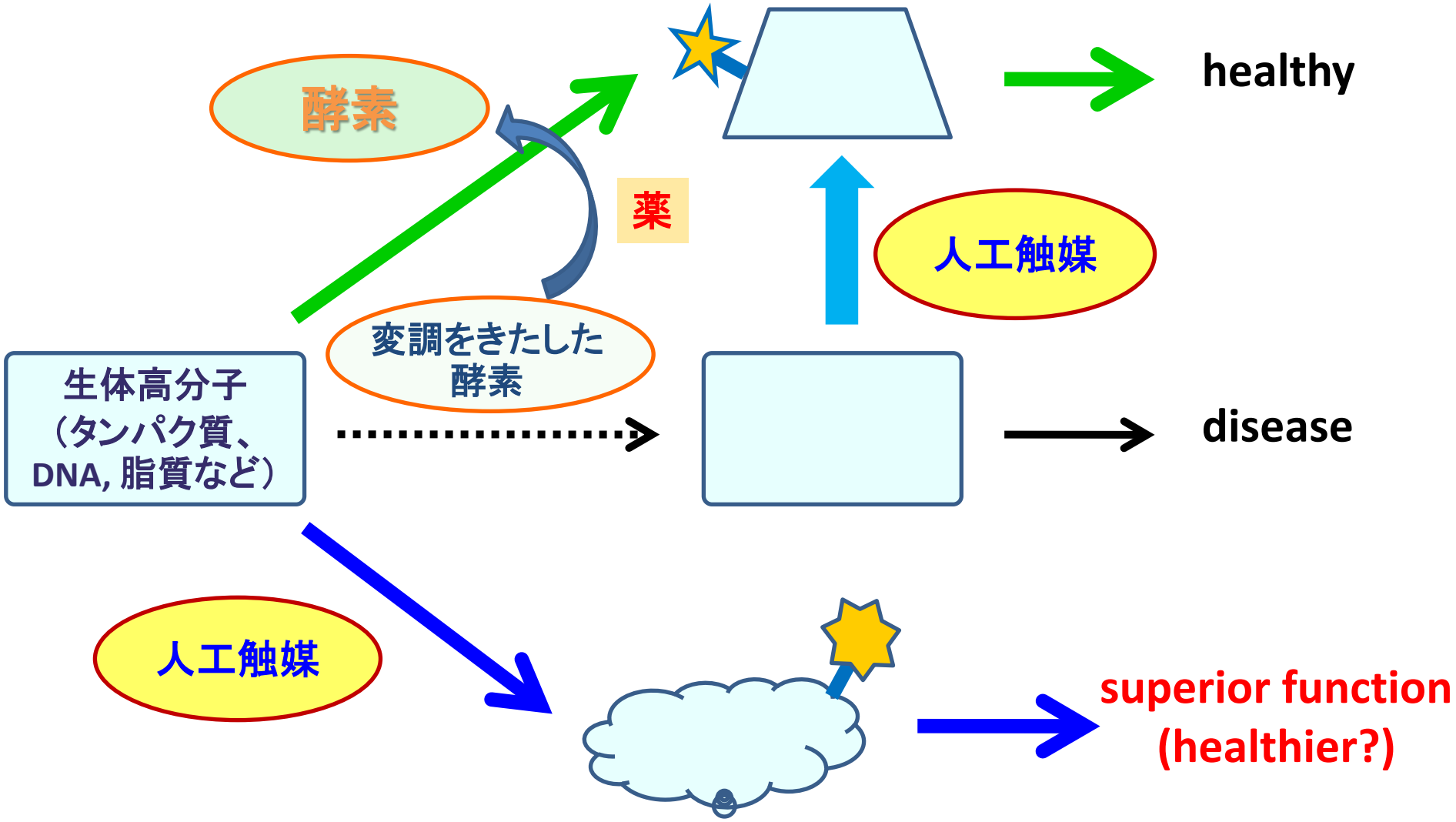
LED
(λ 780 nm)

動物実験が進行中

- 水中反応に適した構造
- 高い安定性
- 低毒性
- 高選択性

Collabo. w/ Prof. Tomita’s lab in UTokyo

触媒医療の将来展望


酵素
薬
人工触媒
変調をきたした
酵素
生体高分子
（タンパク質、
DNA, 脂質など）
healthy
disease
人工触媒
superior function
(healthier?)

革新的触媒がつなぐ物質科学と生命科学

物質科学

Synthesizing molecules
(Hardware of Life)
効率的医薬合成

生命科学

Synthesizing chemical order
(Software of Life)
触媒医療、人工分子生命

- 化学反応性
- 選択性
- 低毒性
- ネットワーク(システム)

新合成法
+ 分子設計

触媒から生命へ

触媒

- 安定分子の活性化
- 生体高分子の化学修飾

- 人工エピゲノム
- 病因タンパク質の除去

Nature 2011, *478*, S4

Aaron Ciechanover

On the wings of imagination

Biochemist at Technion, the Israeli Institute of Technology in Haifa. Shared the 2004 Nobel Prize in Chemistry for the discovery of the ubiquitin system, which mediates protein degradation in all plant and animal cells by destroying proteins that are denatured, misfolded or no longer needed. Family moved from Poland in the 1920s, and he was born in Haifa in 1947. The following year the state of Israel was established.

You won a share of the Nobel prize for your discovery of the cell's protein degradation process. How has the field changed since those early days?

The field has changed dramatically. The ubiquitin proteolytic system is now known to regulate many basic cellular processes, such as cell division, differentiation, transcription and quality control. Altogether, components of the system comprise 6–7% of all genes in the human genome: well above what was expected for just a 'protein scavenger system'. Consequently, it is no surprise to find that aberrations in this system are implicated in the pathogenesis of many

protein accumulation, such as Alzheimer's disease, will be treatable?

There are diseases that involve gain of function and diseases that involve loss of function. With the former, one can be more optimistic because the solution is to develop inhibitors and antagonists, which are easier to develop than agonists or stimulants. In pharmacology, it is easier to slow down a system than to speed it up, so it depends which side of the ubiquitin system you are talking about. On the cancer side — as it involves a gain of function — progress will come faster; on the neurodegenerative side, such as Alzheimer's or Parkinson's disease, it may take longer.

tists, or carry out disease- and drug-oriented research. Curiosity-driven research in the last century brought tremendous development in biomedicine — novel drugs and sophisticated devices — and I strongly believe this is the way to go. If we shift mostly to translational research, the springs of knowledge will dry up, and there will be nothing left to translate. Perhaps the public and our political leaders think that things are going too slowly, but that's a dangerous perspective.

Do you have any advice for graduate students trying to pick a research topic?

Choose a good mentor who asks original questions. Be patient, do not give up: work hard and persevere. Be passionate and excited about what you are doing: think of your scientific profession as if it were your hobby. Luck is important too, but remember, very often luck is not blind: it hits those who are ready. ■

レポート課題

今、自分の人生を通じて取り組んでみたいと興味をもっていること（サイエンティフィックでのノンサイエンティフィックでもよい）について、A4、1枚にまとめよ。

その興味の対象に対して今の自分はどこまでたどり着いているか（興味対象に対する自分の立ち位置）、を含めること。