2012年10月24日

第３回JSPS研究開発専門委員会

抗がん剤創薬プラットホームとしてのがん細胞パネル

ＮＣＩ生まれの方法論の日本風アレンジから創薬へ

独立行政法人

医薬品医療機器総合機構 （PMDA）

審査センター長　　矢守隆夫

Cancer Chemotherapy Center, *JFCR*

2012年10月24日

第３回JSPS研究開発専門委員会

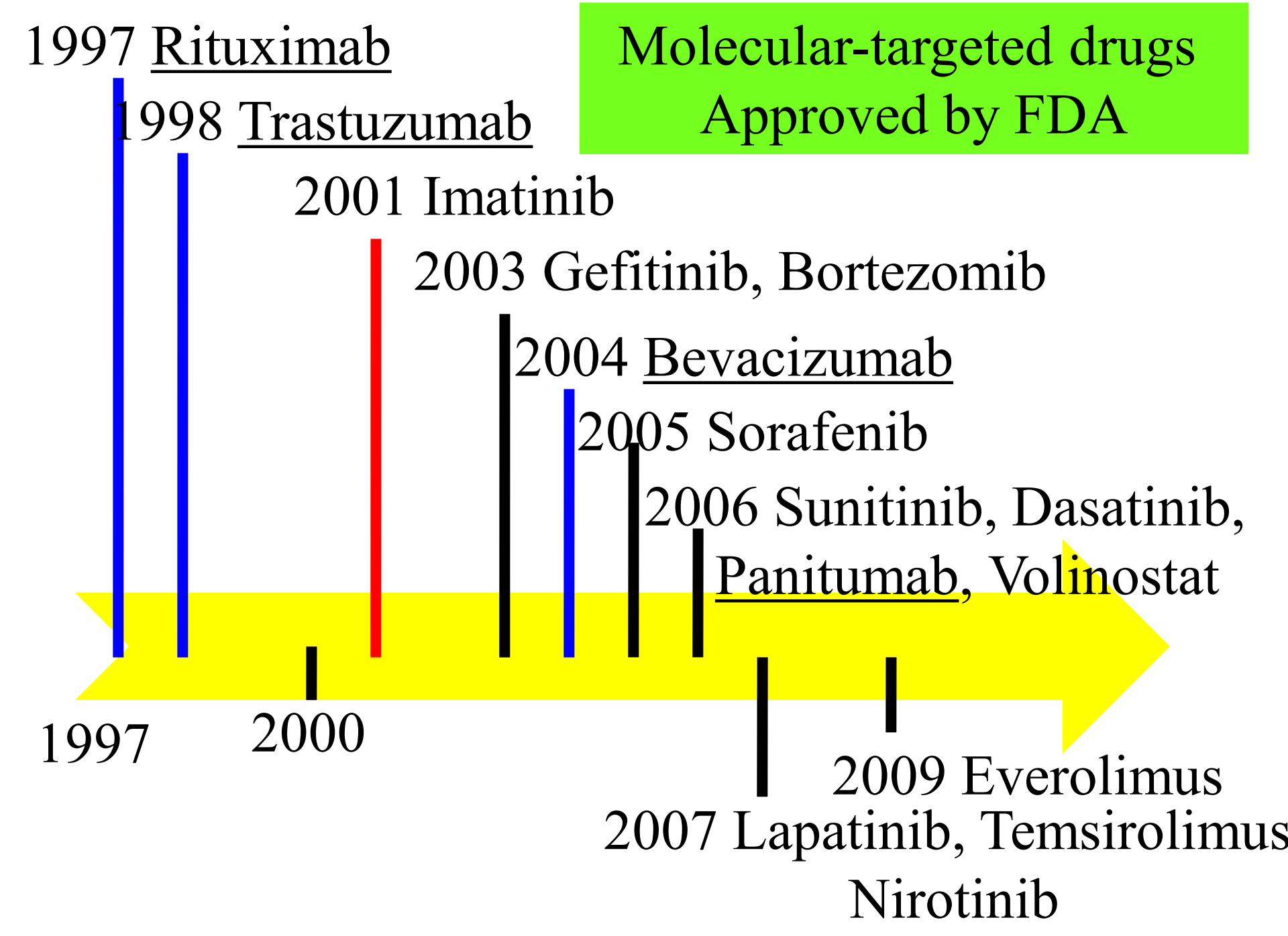
本日の講演は、個人的立場でさせていただきます

独立行政法人

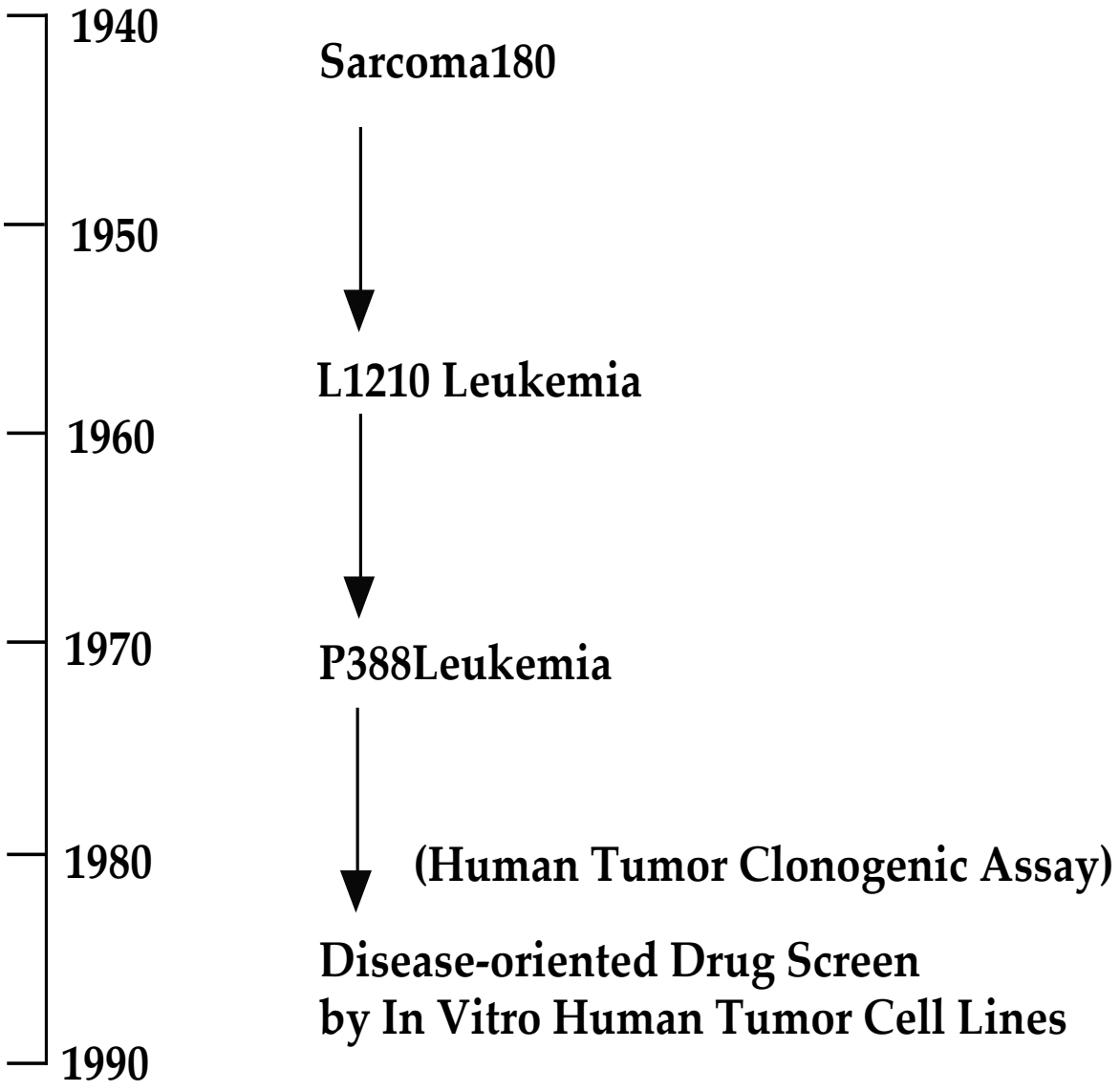
医薬品医療機器総合機構 （PMDA）

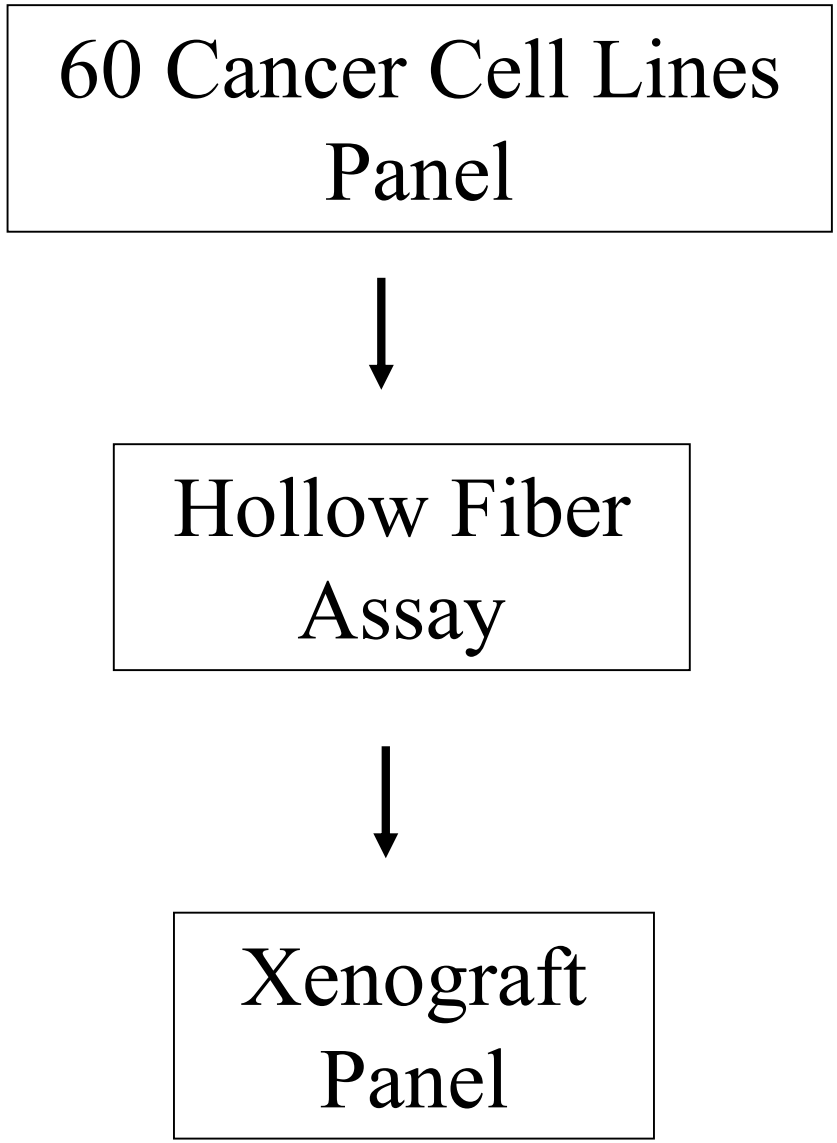
審査センター長　　矢守隆夫

Cancer Chemotherapy Center, *JFCR*


Molecular-targeted drugs
Approved by FDA
1997 Rituximab
1998 Trastuzumab
2001 Imatinib
2003 Gefitinib, Bortezomib
2004 Bevacizumab
2005 Sorafenib
2006 Sunitinib, Dasatinib,
Panitumab, Volinostat
2009 Everolimus
2007 Lapatinib, Temsirolimus
Nirotinib
1997
2000

History of Primary Anticancer Drug Screening Models in NCI

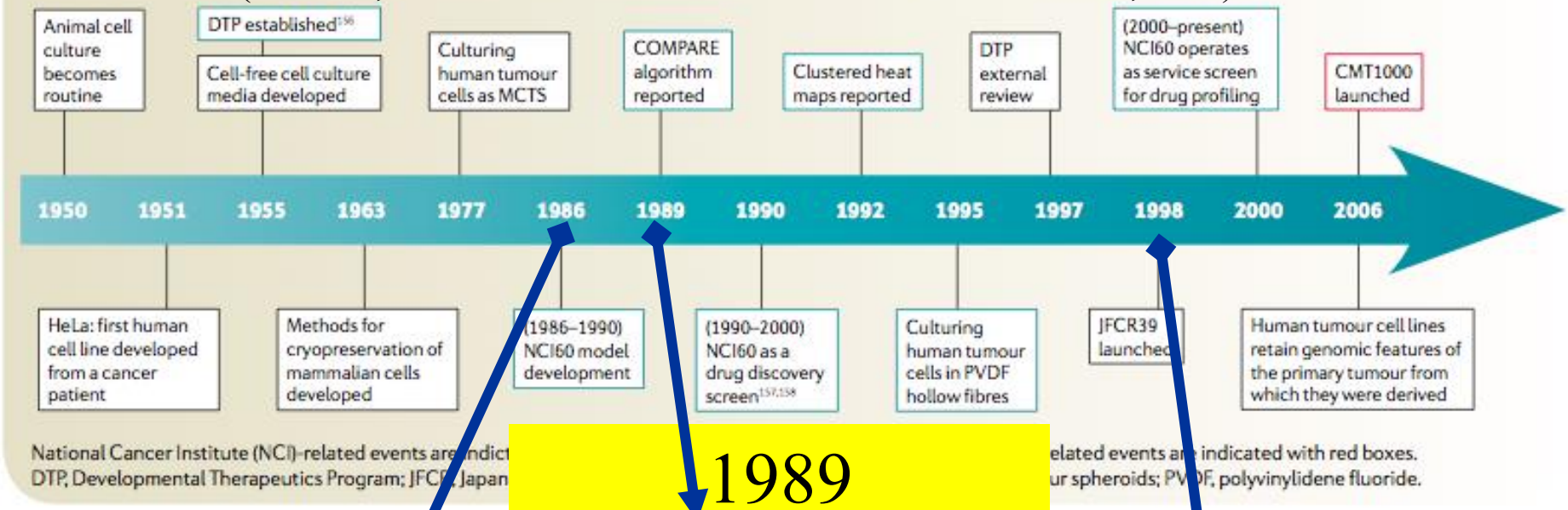




Preclinical Evaluation of Anticancer Compounds in NCI

History of the development of cell-line platforms for evaluating anticancer agents

(Sharma, Settleman et al. Nat Rev Cancer. 10:241-253,2010)



1986–
NCI60

1989
COMPARE
algorithm

1998-
JFCR39

Paull, Shoemaker et al.
J Natl Cancer Inst.81:1088-92.1989.

Yamori et al.
Cancer Res. 59:4042-9, 1999.

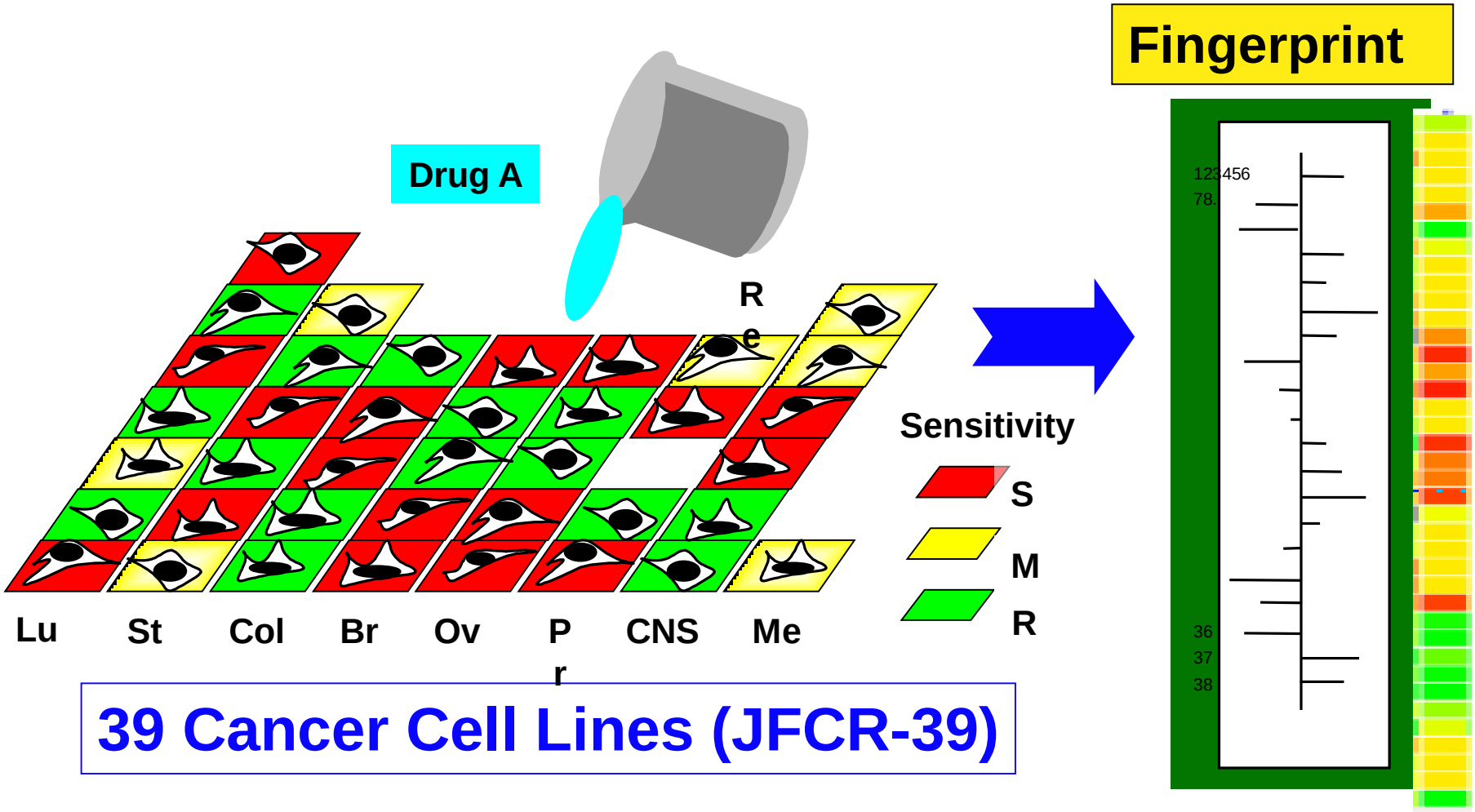
がん細胞パネルとは？

新規化合物の作用機序を評価する系

既存の抗がん剤と比べユニークかどうか？

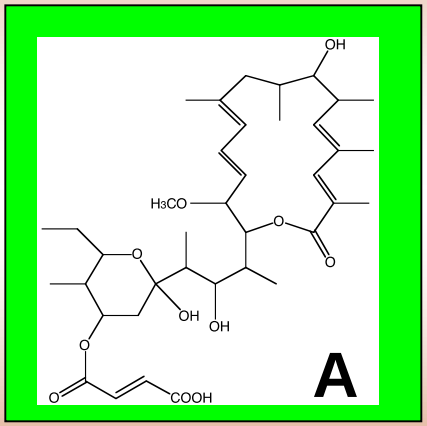
★　分子標的の予測

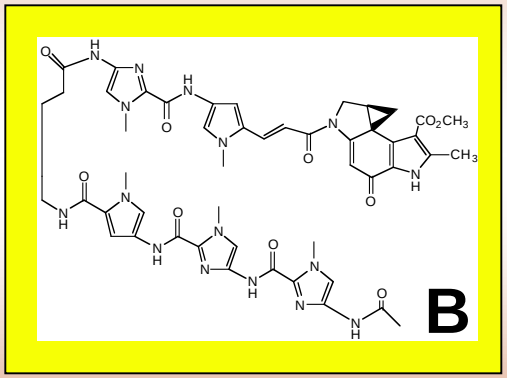
We developed a database of “fingerprints”

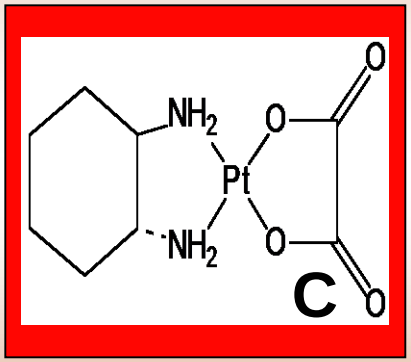


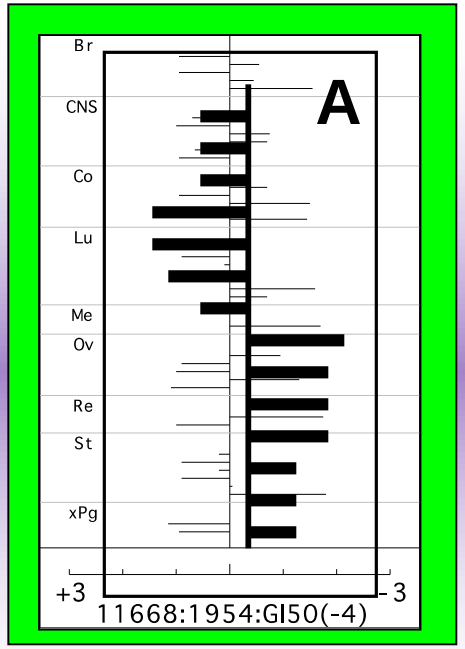
39 Cancer Cell Lines (JFCR-39)

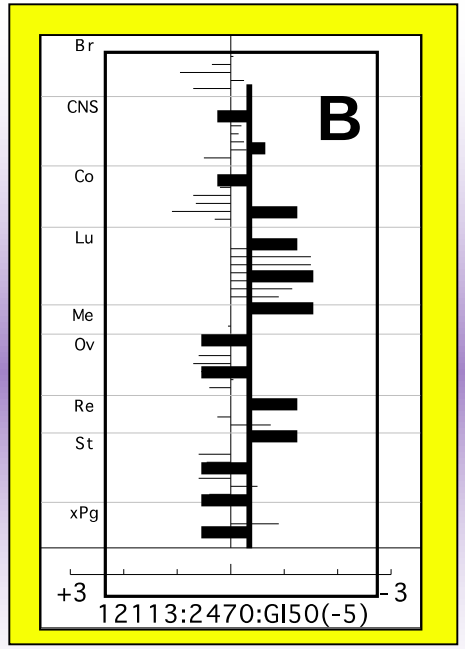
Chemical Structure

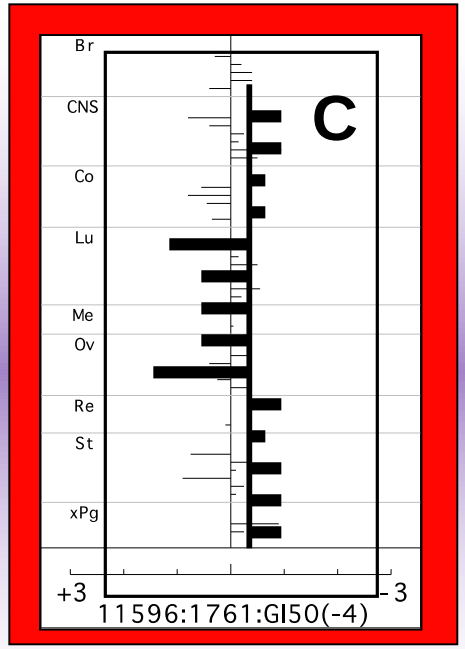








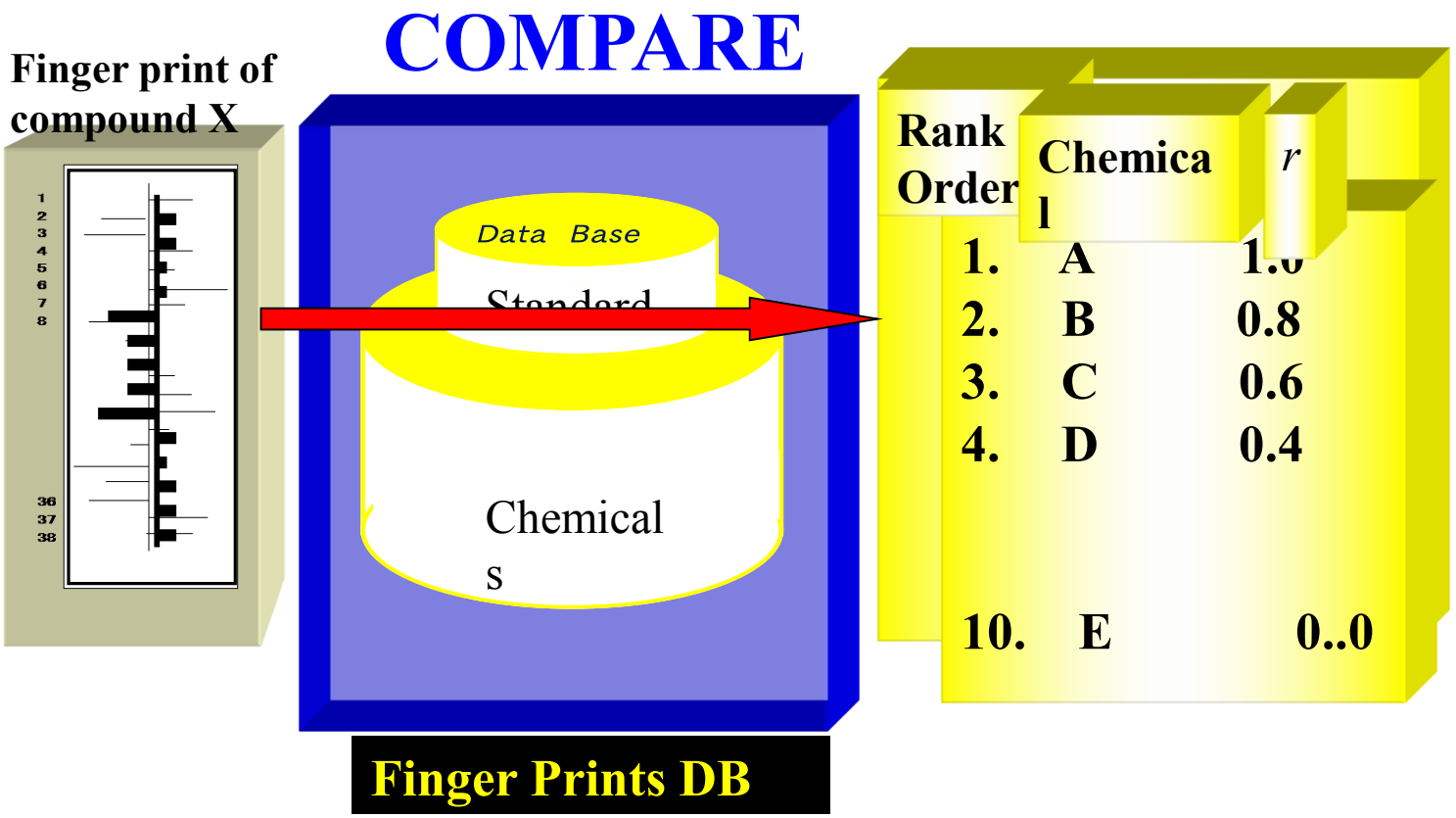




Fingerprint

がん細胞パネルとは？

新規化合物の作用機序を
プロファイリングする系



がん細胞パネルとは？

新規化合物の作用機序を
プロファイリングする系

Step 1　既存の抗がん剤との差別化
（ユニークな作用機序か？）

↓

Step 2　分子標的の予測

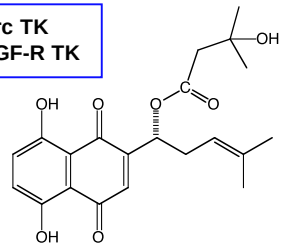
↓

Step 3　検証

New Compounds with Unique Modes of action

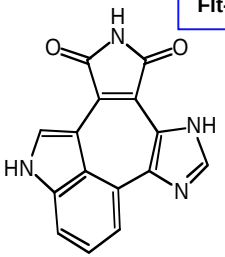
New Tyrosine Kinase Inhibitors

Src TK
EGF-R TK



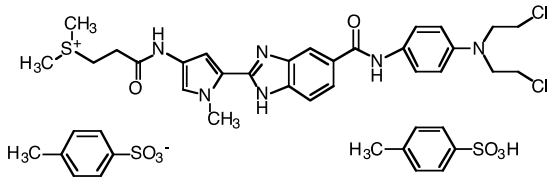
JCI: 11504 β-hydroxyisonalerylshikonin

Src TK
Flt-1/VEGF-R TK



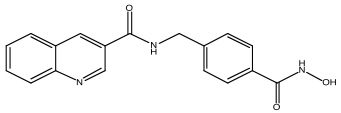
JCI: 12149 1H-imidazo[4",5":4,5] pyrrol-[3,4':6,7]cyclohept[1,2,3-cd]-indole-3,5-dione

New Topo I & II Inhibitor

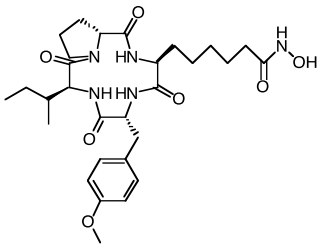


JCI: 11504 MS-247

New HDAC Inhibitors

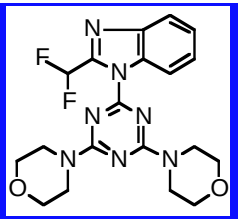


JCI: 12111 K-120



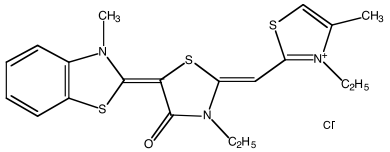
JCI: 10903 CHAP-31

New PI3K Inhibitor



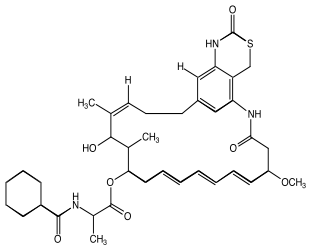
JCI: 2478 ZSTK474

New Telomerase Inhibitor

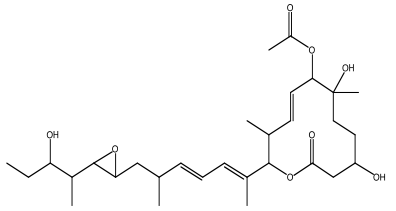


JCI: 10231 FJ-5002

Targets Unknown



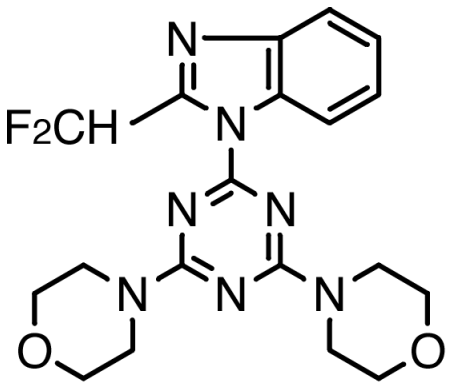
JCI: 10056 Thiazinotrienomycin B



JCI: 12094 Pladienolide B

A New PI3kinase Inhibitor ZSTK474 identified by JFCR Cancer Cell Panel

Target Identification of ZSTK474



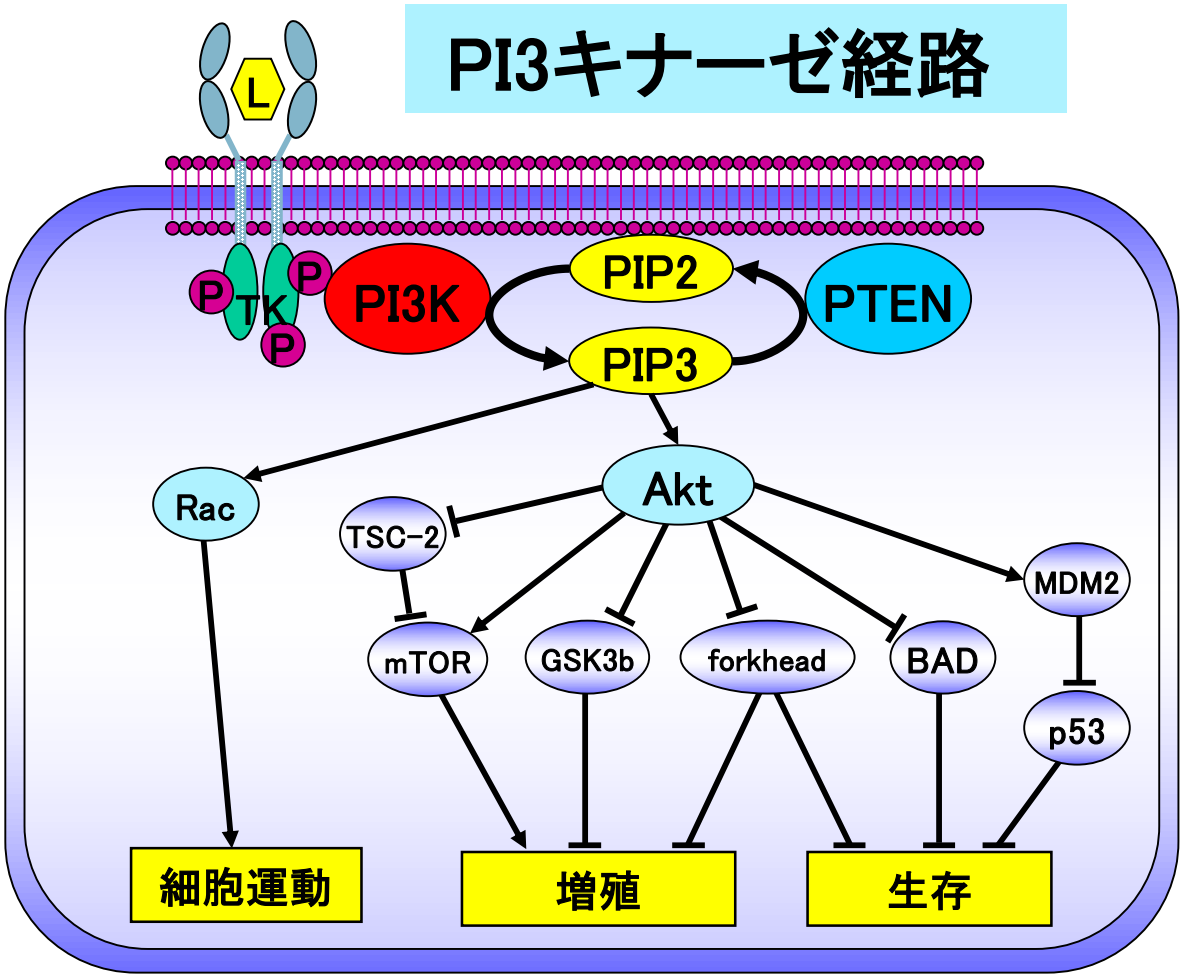
ZSTK474

- selected by cell-based screening by Zenyaku Co.,Ltd.
- has strong antitumor activity
- But,

Its target was unknown.

Cancer Chemotherapy Center, *JFCR*

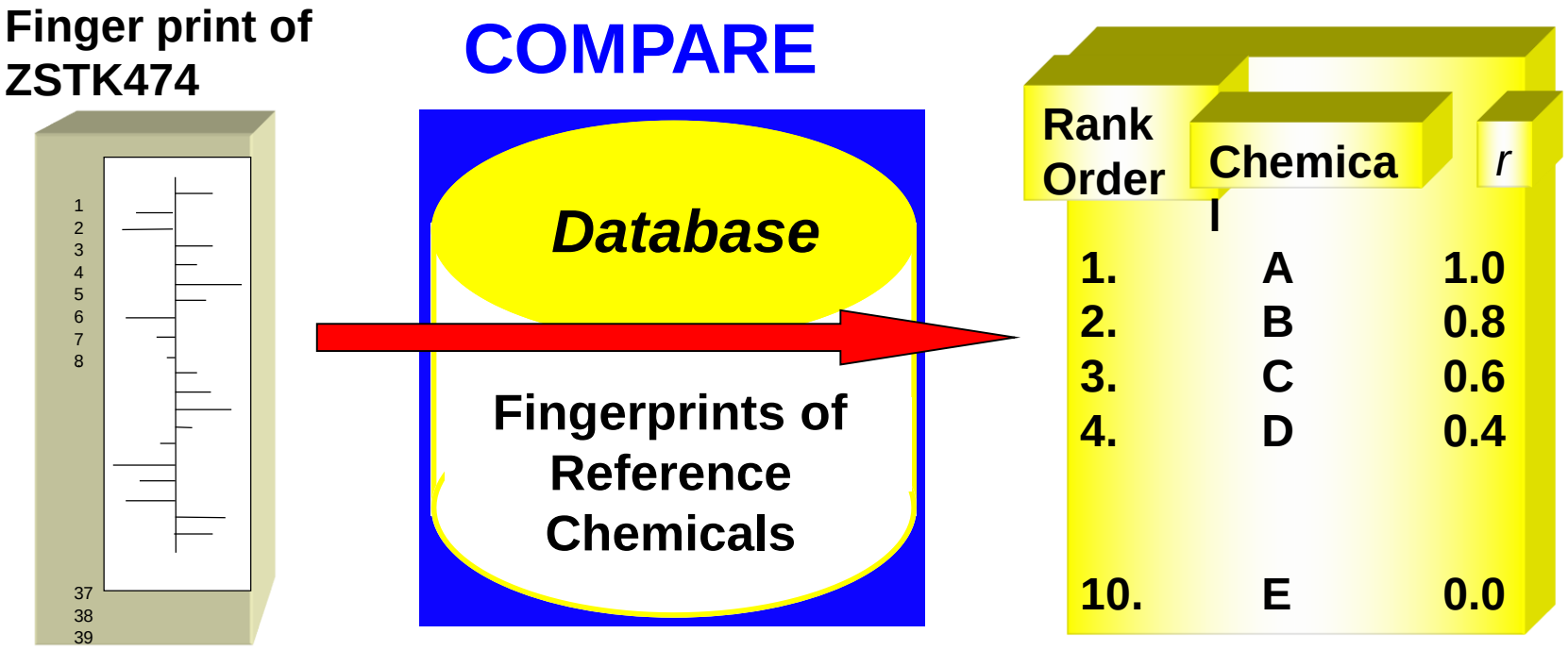
研究の出発点1:



PI3キナーゼは
癌の生存、増殖、転移
に関与する

PI3キナーゼは
有力な分子標的と
考えられる

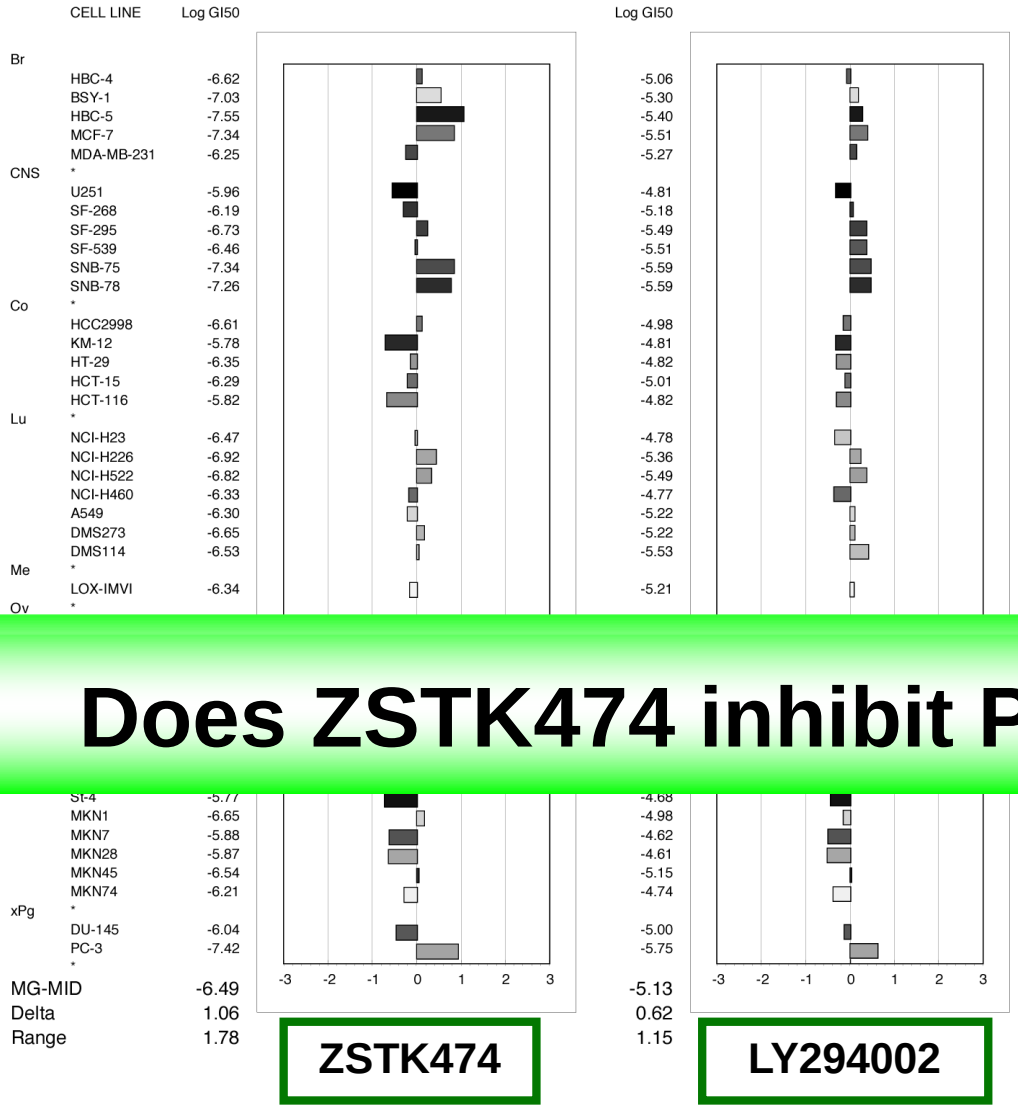
しかし、PI3キナーゼを標的とする
抗がん剤は未開発である！　2004



"COMPARE Algorithm"

1. compares the fingerprint of ZSTK474 with that of each reference chemicals which has a known mode of action.
2. predicts the mode of action of ZSTK474.

The COMPARE analysis indicated that ZSTK474 highly correlated with LY294002 which is a PI3K inhibitor.

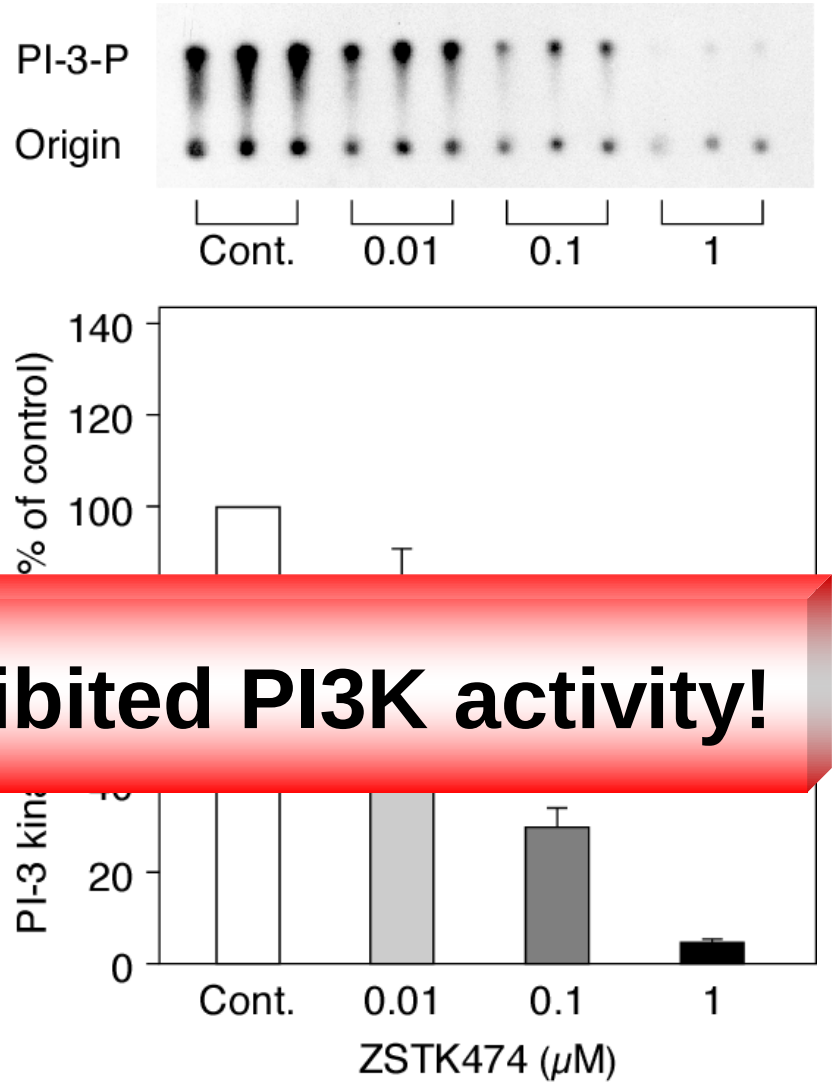


$r = 0.766$

$P = 1.3 \times 10^{-8}$

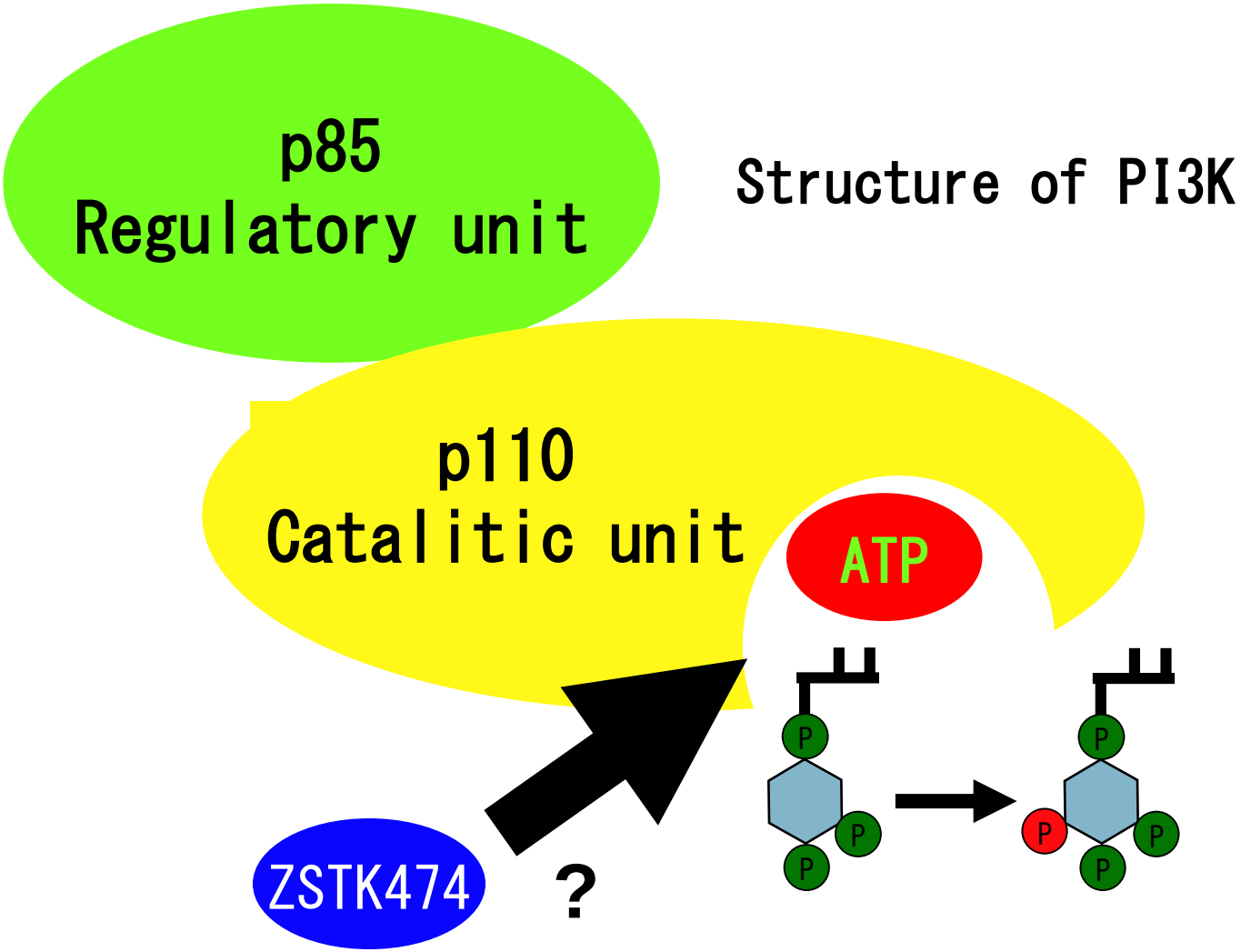
Does ZSTK474 inhibit PI3K?

The effect of ZSTK474 on PI3K activity.



ZSTK474 actually inhibited PI3K activity!

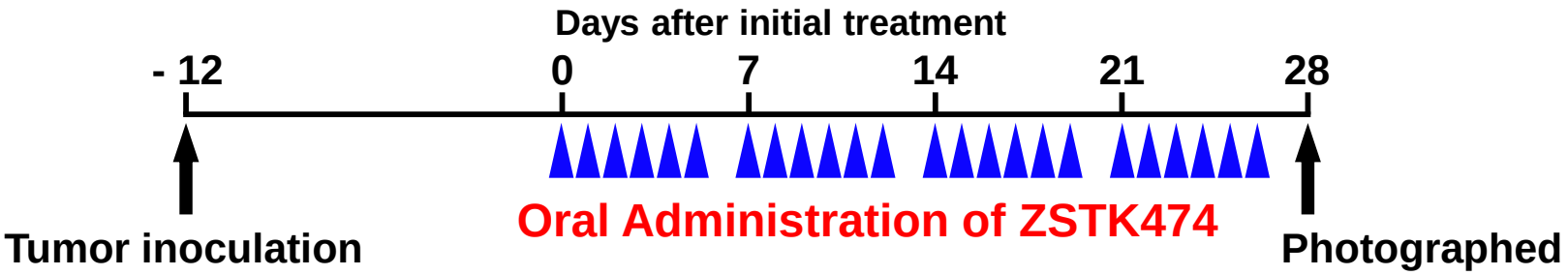
Mode of action of ZSTK474 to PI3K



Growth inhibition of human colon cancer xenograft WiDr by ZSTK474

Control

ZSTK474



Visualization of cell cycle distribution in live cells *in vivo*

Cell transplantation

ZSTK474 administration

Day 0 Day 1 Day 2 Day 3 Day 4 Day 5 Day 6

Observation with OV100 *in vivo* imaging system

IX81

Fluorescence microscope

G_0/G_1 cells $S/G_2/M$ cells Merge

Day 0

micro

macro

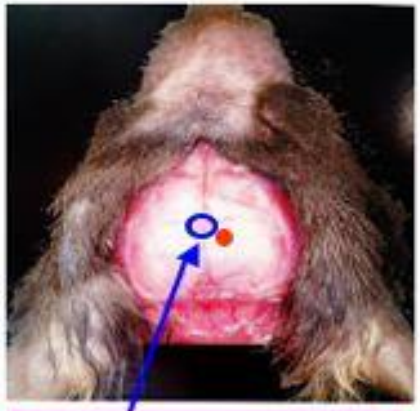
Day X

micro

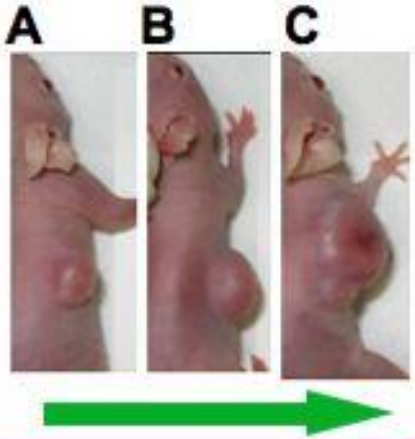
macro

Efficacy in various xenogrft models using JFCR-39

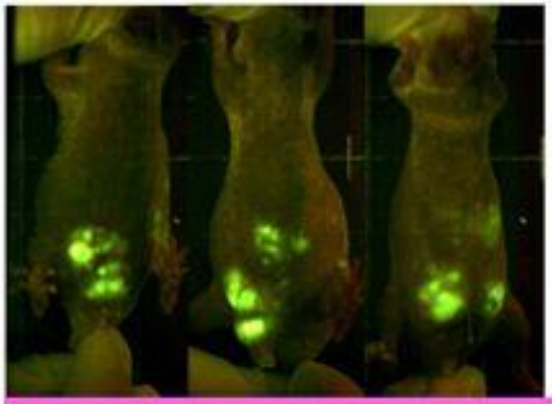
Various xenografts



Orthotopic Brain Tumor

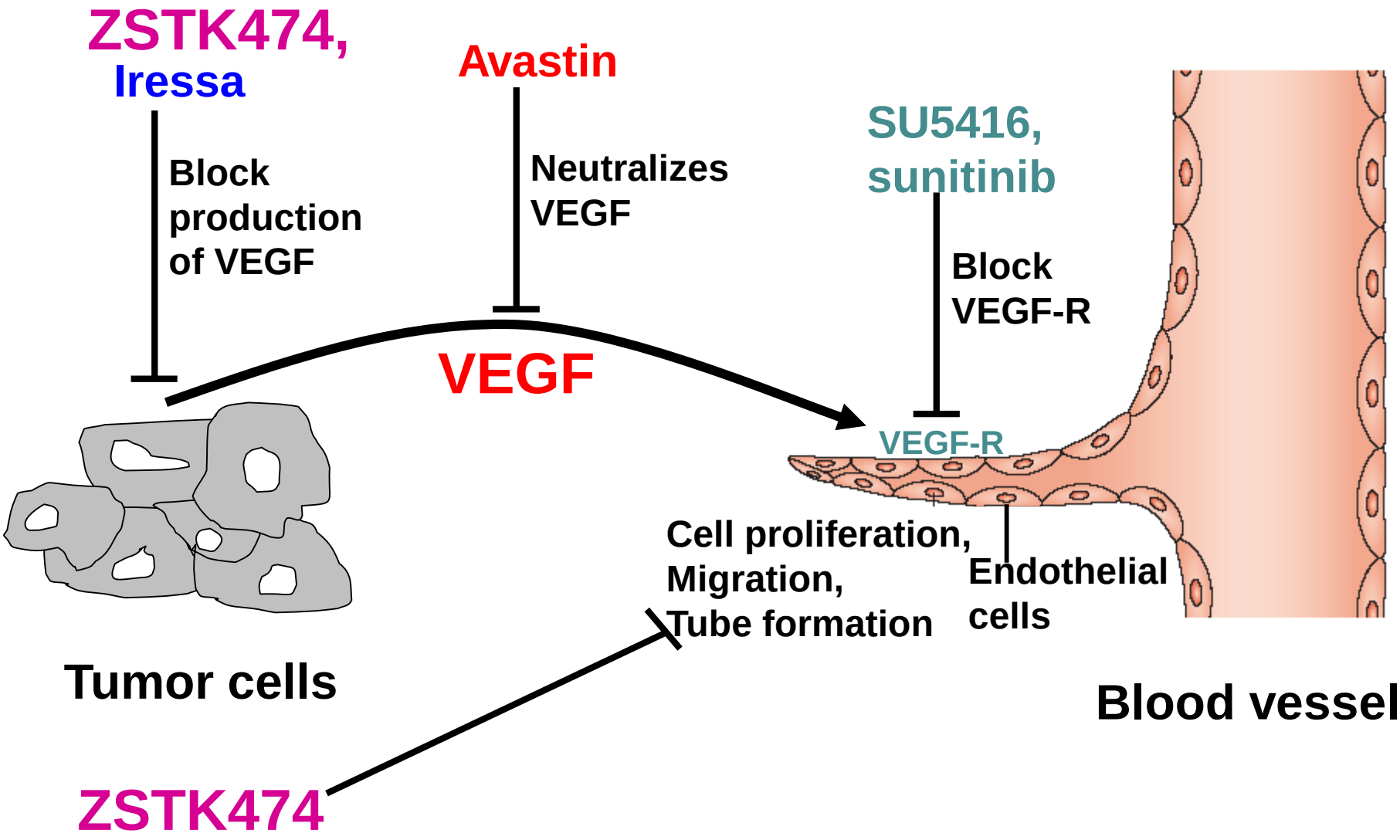


Advanced Cancer



Orthotopic Prostate Ca.

Mechanism of ZSTK474 to inhibit angiogenesis

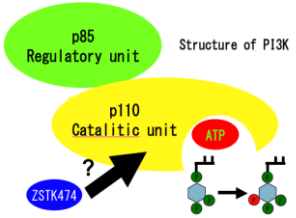


(ID05-13)「PI3キナーゼ(ホスファチジルイノシトール3キナーゼ)を標的とする分子標的薬の創製 」

目標は、1)新しいPI3K阻害剤ZSTK474を医薬品化するべくその有効性と安全性の科学的根拠を示し、この新薬候補が効きやすい癌のタイプを予測する。2)PI3Kによる癌悪性化の分子機序を明らかにし、これを阻止する新しい分子標的薬の開発を行う。

酵素阻害様式を決定

ZSTK474のPI3K酵素阻害の様式を決定



ZSTK474の毒性分子機序を解析

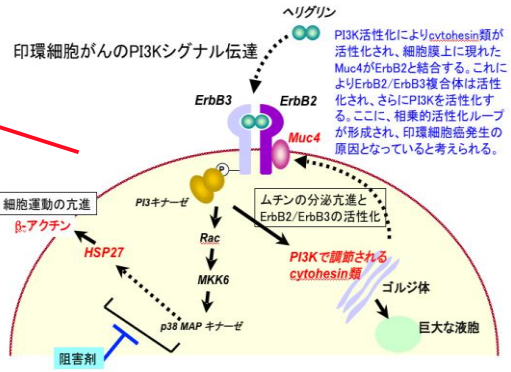
薬物代謝酵素を同定

新しい創薬シーズ開発へ

研究の全体構想

矢守	石川	矢口	福井
ZSTK474の抗癌作用、分子機序、感受性因子の解析	臨床癌におけるPI3K/PTEN系の異常と臨床病理的特徴	ZSTK474の薬物動態と毒性の分子機序の解析	癌の悪性化におけるPI3Kの意義の解明
有効性	臨床病理	安全性	PI3K

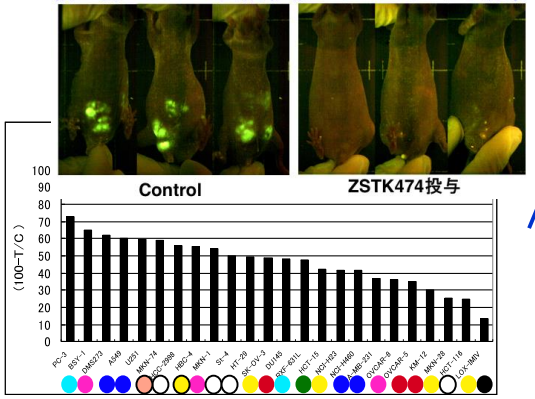
ZSTK474の医薬品化に向けたトランスレーショナルリサーチの推進



PI3Kによる悪性化の機序を解析

ZSTK474による癌抑制の分子機序を解析

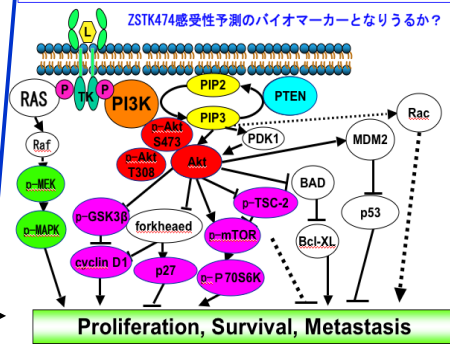
前立腺がんPC3同所移植モデルにおける効果



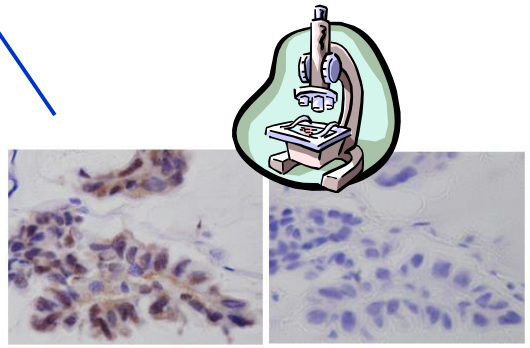
ZSTK474の有効性を証明

PI3K下流因子の発現

ZSTK474感受性予測のバイオマーカーとなりうるか？



感受性予測バイオマーカーを探索同定



臨床がんにおけるバイオマーカーの発現を確認

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

List Results | Refine Search | Results by Topic | Results on Map

Found 1 study with search of: ZSTK474

Hide studies that are not seeking new volunteers.

Rank	Status	Study
1	Recruiting	A Safety Study of Oral ZSTK474 in Patients With Cancer Condition: Neoplasms Intervention: Drug: ZSTK474

Save this search by bookmarking this page.
When you use your bookmark, the search will be performed again on the most recent collection of studies.

RSS Feeds for studies found by your search that were:

First received in the last 14 days, Last updated (includes received) in the last 30 days

Download Options

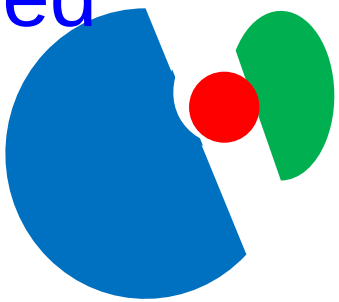
国内の治験開始　2012年9月

基本情報 (Basic information)		
項目(Item)	日本語(Japanese)	英語(English)
試験名 (Official scientific title of the study)	進行性固形癌患者を対象としたZSTK474の安全性、忍容性、薬物動態および有効性を検討する臨床第Ｉ相非盲検用量漸増試験	A Phase 1, Multi-Center, Open Label, Uncontrolled, Serial Cohort, Dose Escalation Study of the Safety, Tolerability, Pharmacokinetics and Efficacy of ZSTK474 in Japanese Patients with Advanced Solid Malignancies
試験簡略名 (Title of the study (Brief title))	進行性固形癌患者を対象にしたZSTK474の第I相試験	A Phase 1 study of ZSTK474 in Japanese Patients with Advanced Solid Malignancies
試験実施地域 (Region)	日本/Japan	

UMIN CTR 臨床試験登録情報より

A novel Golgi disruptor AMF-26

Brefeldin A (BFA) was developed toward anticancer drug, but it was stopped because of low bioavailability.

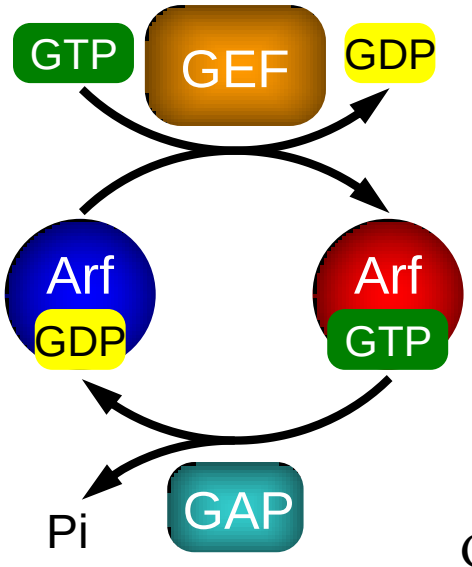


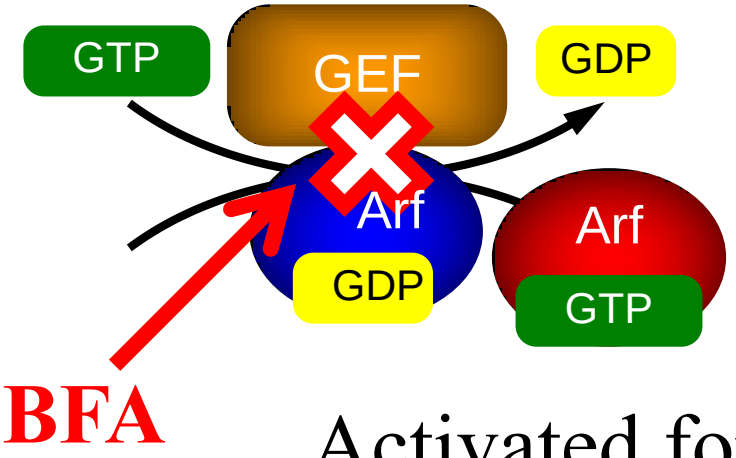
PPI inhibitor	Target	References
Brefeldin A	Arf1-Arf1GEF	*Nature,* 426:525, 2003
Nutlin 3	p53-MDM2	*Science,* 303:844, 2004
ABT-737	BCL2	*Science,* 305:1466, 2004
SP304	TNF-α	*Science*, 310:1022, 2004
ICG-001	β-Catenin-CBP	*PNAS,* 101:12682, 2004
FJ9	FRZ-7–DVL	*Cancer Res.,* 67:573, 2007

Brefeldin A (BFA)

1. is an PPI inhibitor
2. inhibits the activation of small G protein Arf
3. disrupts golgi apparatus

GDP-GTP Exchange by Arf- GEF interaction





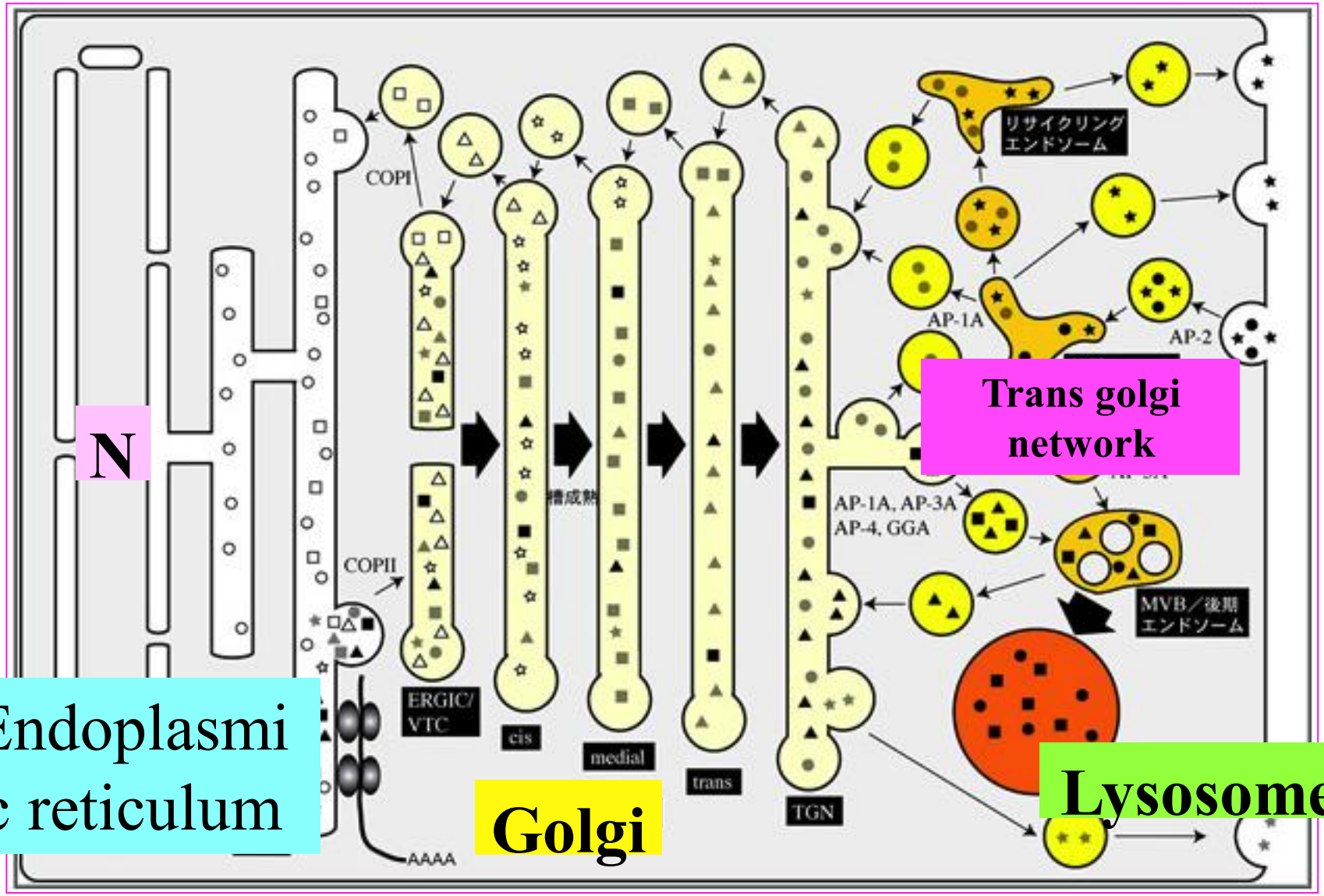
Activated form

ARF: ADP ribosylation factor guanine-nuceotide exchanging factor

GEF: Guanine Nucleotide Exchange Factors

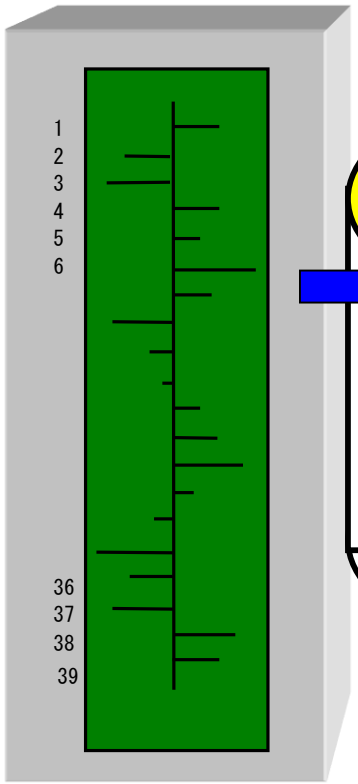
J Biochem 136:761, 2004

Memrane Traffic



Dr. H Nakayama (Kyoto Univ) （http://www.pharm.kyoto-u.ac.jp/physchem/nakayama’%20s%20work.html）

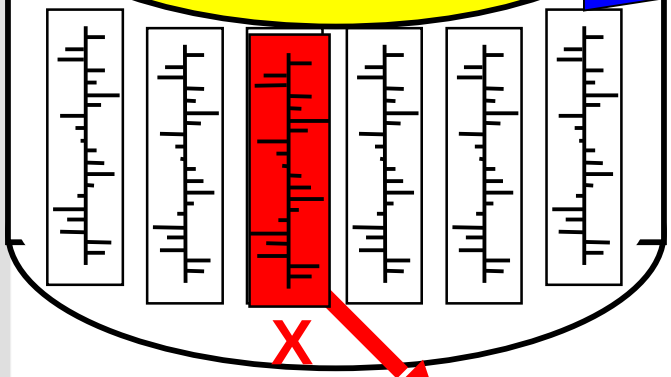
Screening of BFA-like compounds by COMPARE



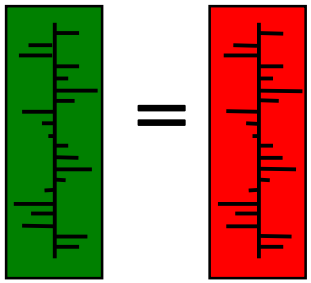
Fingerprint of BFA

COMPARE

Undefined New Chemicals



Rank Order	Chmical	*r*
1.	X	1.0
2.	Y	0.8
3.	Z	0.6
4.	•	0.4
10.	•	0.0



X can be a novel inhibitor of Golgi!

Prediction

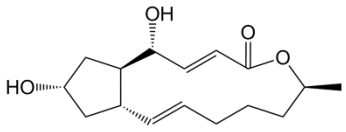
Screening of BFA-like compounds by COMPARE

Brefeldin A Median vs ANY

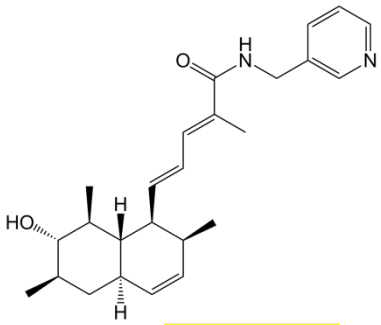
SEED	Brefeldin A
Data base:	GI50
Numeric type of data:	LOG
TARGET:	ANY

Positive correlation

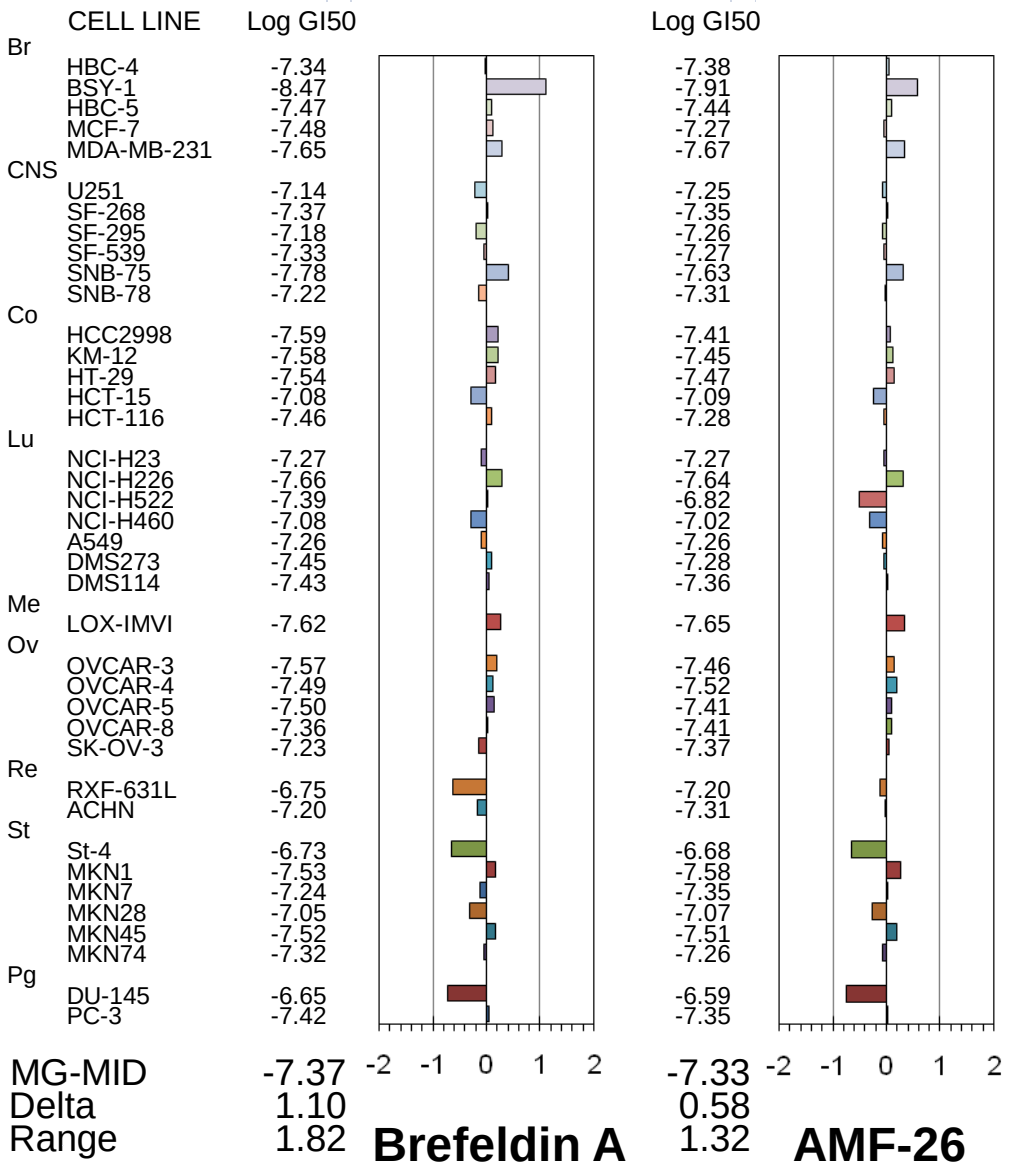
1	0.913	Brefeldin A
2	0.909	Brefeldin A
3	0.895	Brefeldin A
4	0.831	AMF-26
5	0.783	AMF-26
6	0.778	AMF-59
7	0.776	AMF-26
8	0.767	AMF-26



Brefeldin A

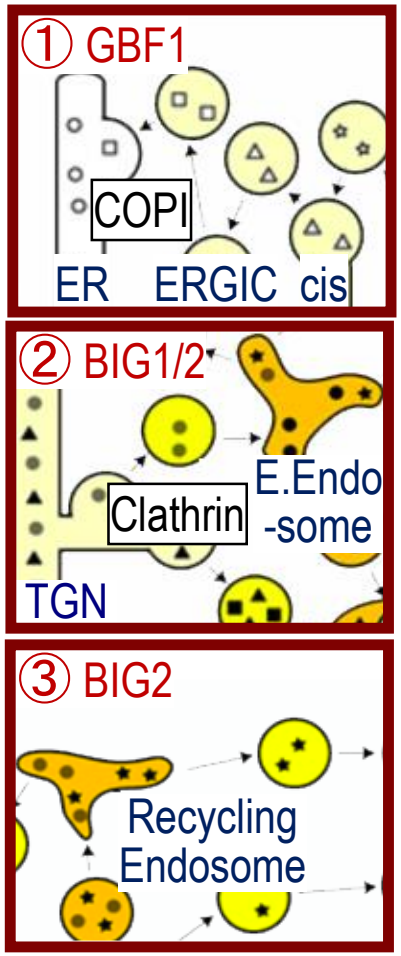


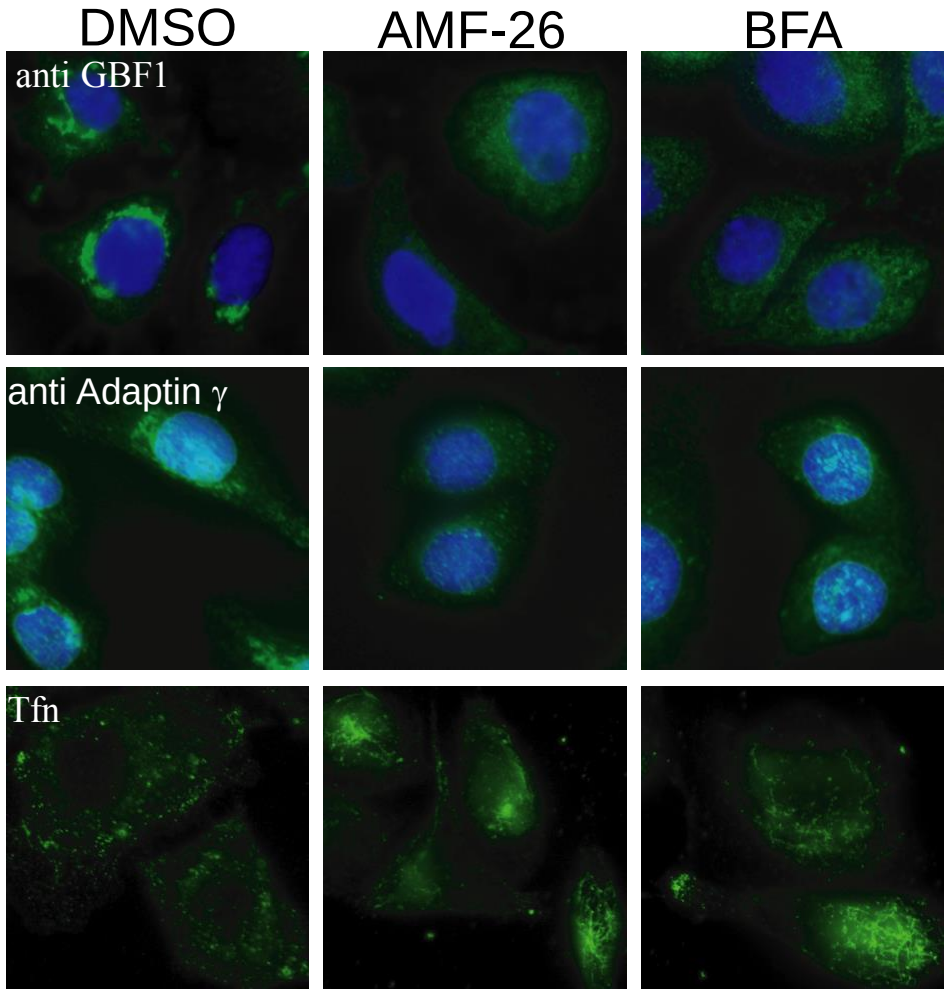
AMF-26



Ohashi Y.,Yamori T *et al., J Biol Chem 2012*

AMF-26 inhibits membrane traffics as BFA



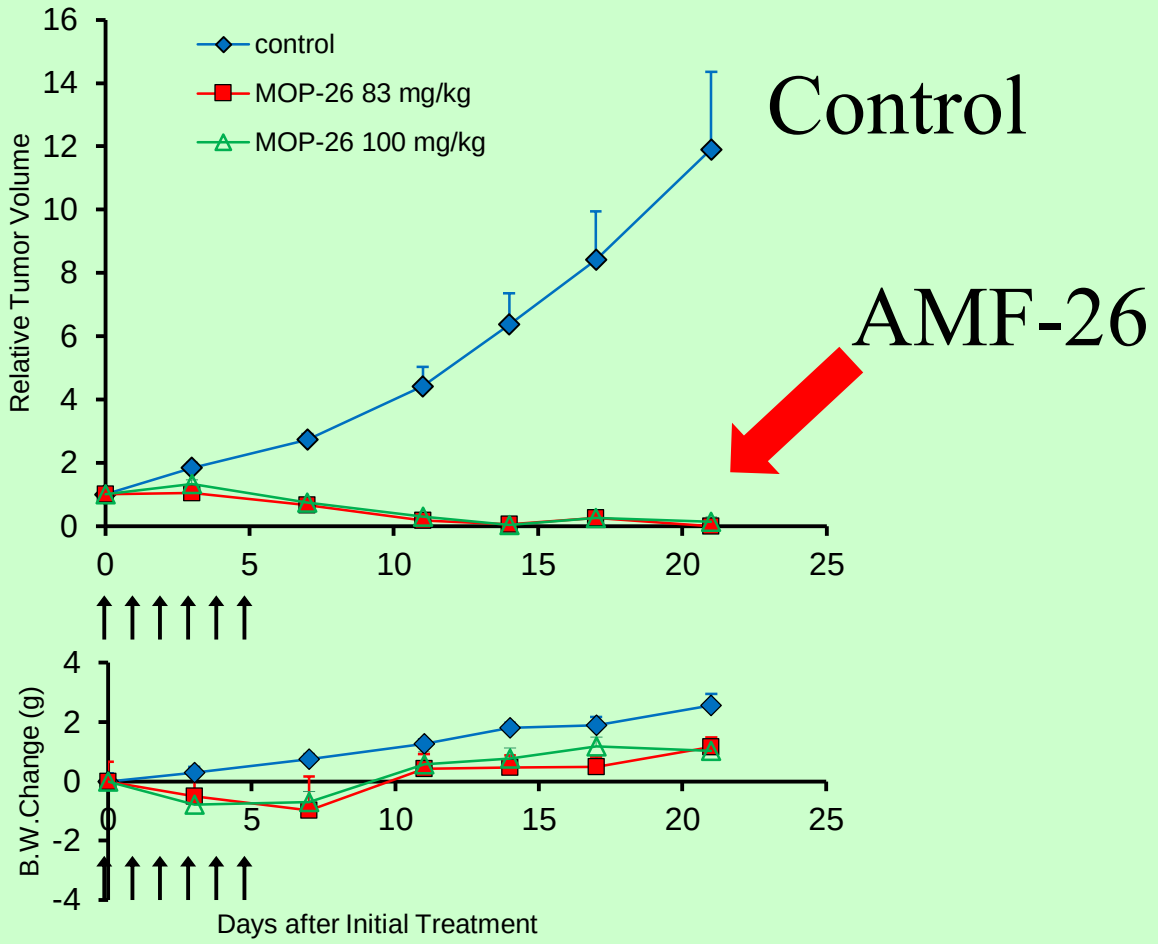


(BSY1 Cells , Drug treatment: 1 uM, 1hr)

Ohashi Y.,Yamori T *et al., J Biol Chem 2012*

Potent antitumor activity of AMF-26

（BSY-1 xenograft model）



Ohashi Y.,Yamori T *et al., J Biol Chem 2012*

2012年10月24日

第３回JSPS研究開発専門委員会

抗がん剤創薬プラットホームとしてのがん細胞パネル

ＮＣＩ生まれの方法論の日本風アレンジから創薬へ

独立行政法人

医薬品医療機器総合機構 （PMDA）

審査センター長　　矢守隆夫

Cancer Chemotherapy Center, *JFCR*

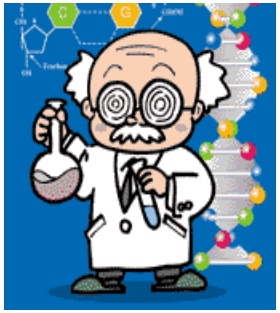
文部科学省がん特定領域研究・統合がん

化学療法基盤情報支援班

活動内容

化療支援活動

研究者による新抗がん物質発見を支援



研究者

情報提供

新薬開発情報

バイオインフォーマティクス

化合物評価サービス

化合物提供

がん細胞パネル評価

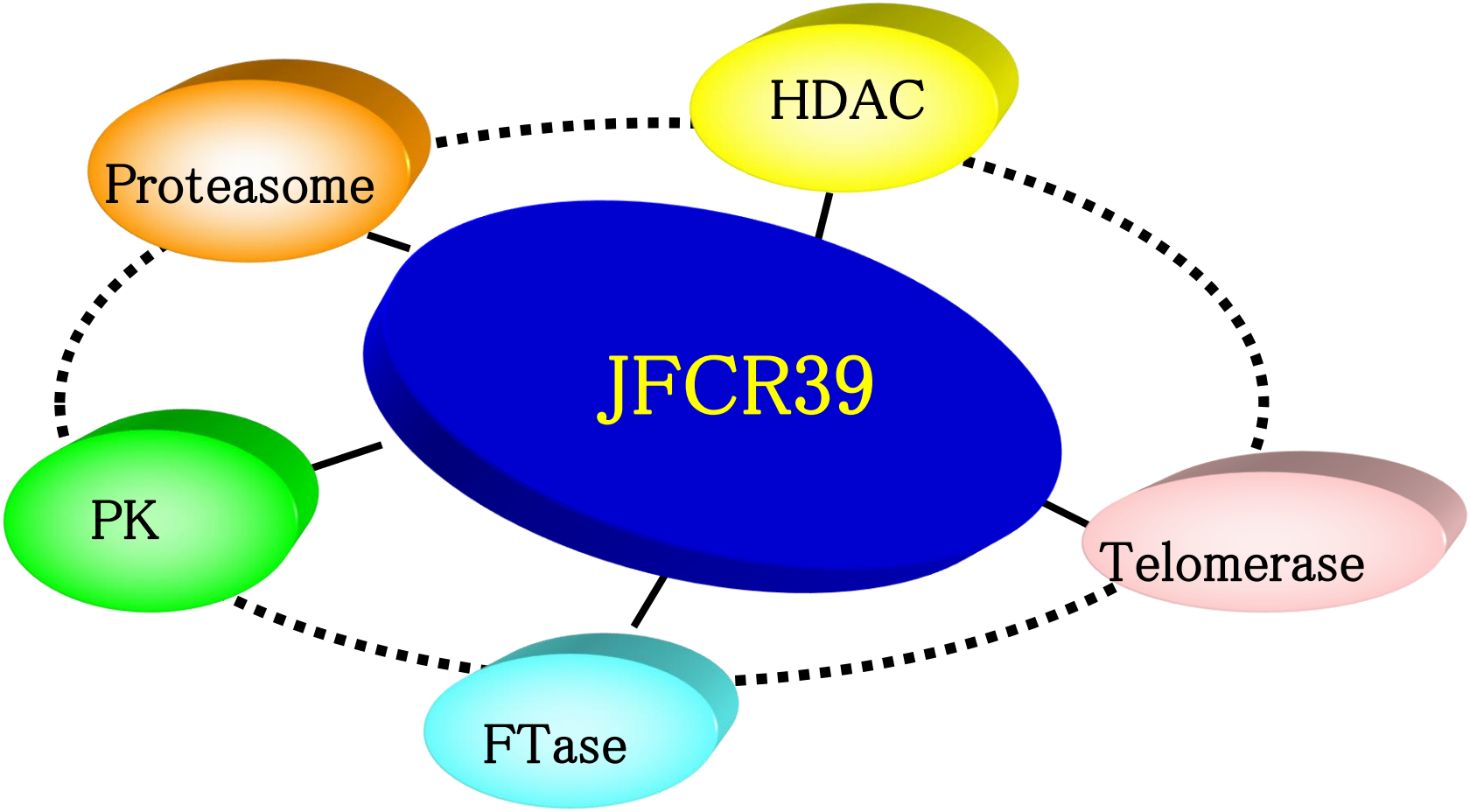
分子標的スクリーニング

阻害剤キット

化合物ライブラリー

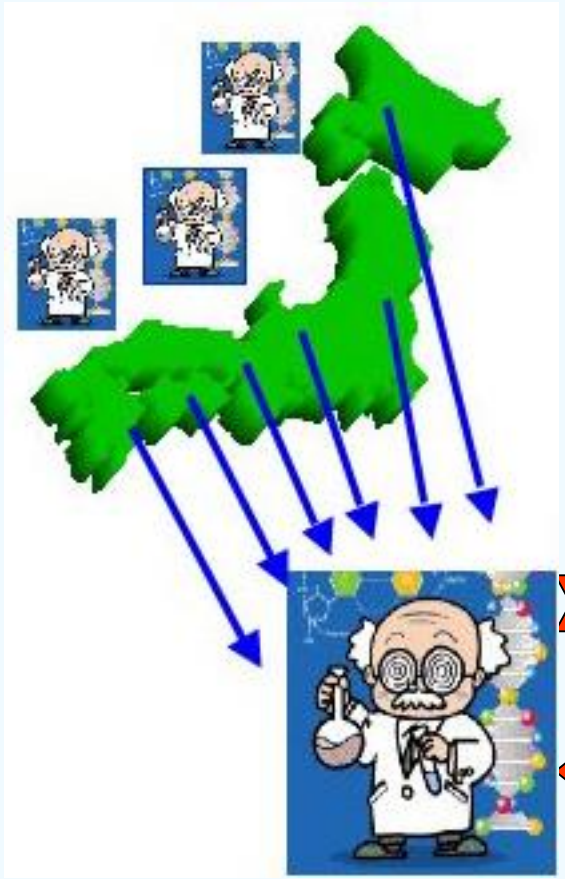
Molecular Target Screening Combined with JFCR39

by Committee of Anticancer Drug Screening



MEXT

Committee of Anticancer Drug Screening



Chemicals

Database

Evaluation

database

Report

Chemists

Structure & Activity

Stimulate Drug Development


癌と化学療法
Japanese Journal of Cancer and Chemotherapy
特集
制がん剤の分子標的スクリーニング成績
わが国における制がん補補物質のスクリーニング成績・第10報
癌と化学療法
Japanese Journal of Cancer and Chemotherapy
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癌と化学療法
Japanese Journal of Cancer and Chemotherapy
Vol.34
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Supplement
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癌と化
特集・制がん剤の分子標的スクリーニング成績
II
特集・制がん剤の分子標的スクリーニング成績
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II
3月
Supplement
特集・わが国における制がん補補物質のスクリーニング成績・第7報