医療Innovationと PMDAに期待すること

PMDAフォーラム　2014年2月8日（一ツ橋ホール）

日本医学会長
自治医科大学名誉学長
髙久　史麿

医療Innovation

～日本の医薬品・医療機器産業の国際競争力強化と高い経済成長を実現～

■日本発の革新的医薬品・医療機器の開発と実用化
〇日本発の革新的医薬品・医療機器の研究開発の推進

〇臨床研究の成果等を治験や承認につなげるための基盤整備及び効果的な保険
償還価格の設定
・PMDAによる薬事戦略相談
・PMDA等の体制強化
・実用化を見据えたレギュラトリーサイエンスの推進

■医療上必要な医薬品・医療機器の患者への迅速な提供（ドラッグ・ラグ，デバイス・ラグへの対応）

厚生労働省　第7回社会保障改革に関する集中検討会議「医療イノベーションに関する資料」（H23.5.19)より

Targeted Therapy

- 遺伝子の変化をTarget
- Monoclonal Antibody

Identification of the Transforming *EML4-ALK* Fusion Gene in Non-Small-Cell Lung Cancer

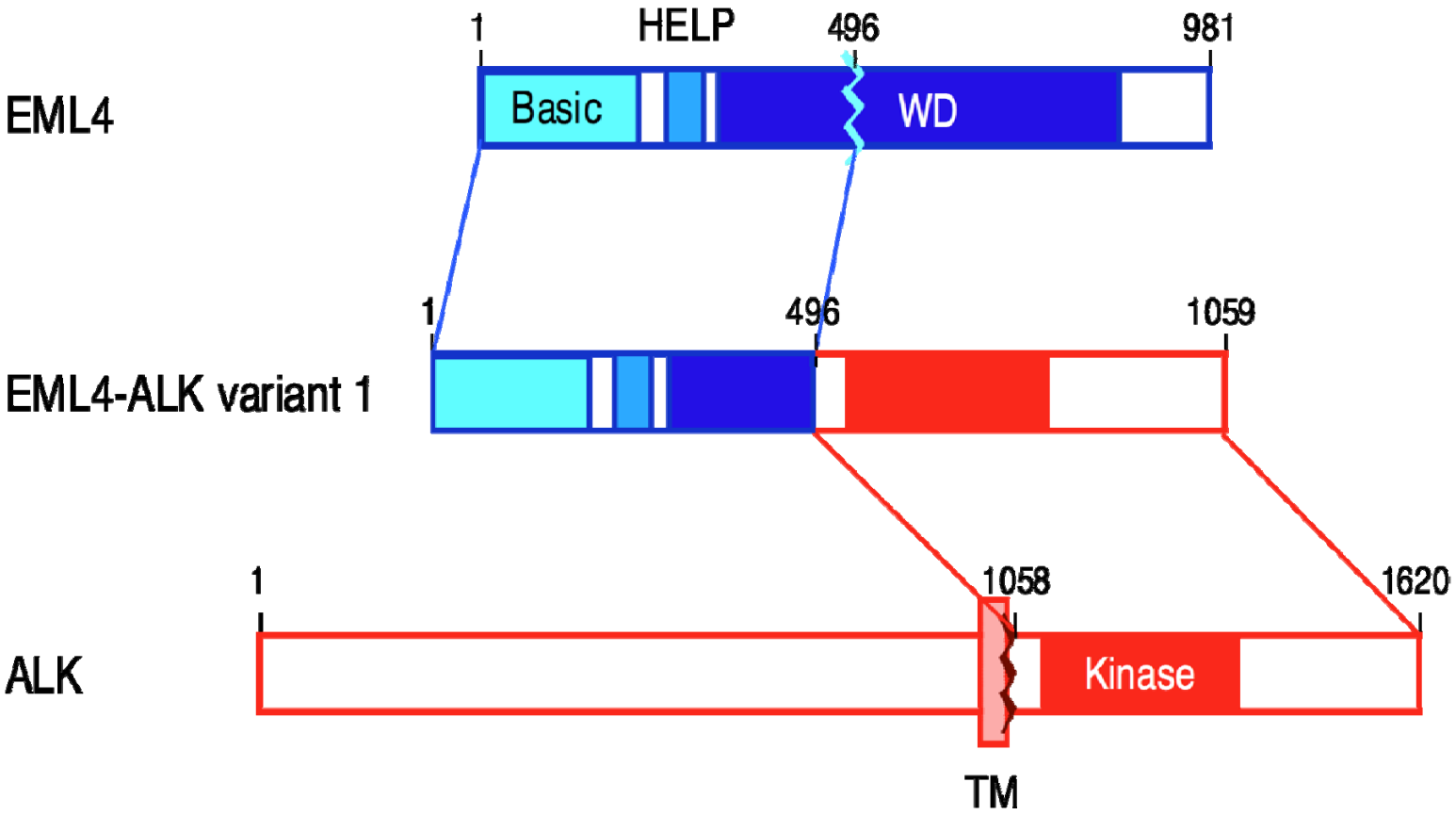
Manabu Soda, Hiroyuki Mano, et al.

Nature Vol.448, Aug. 2, 2007

- **Small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 gene (*EML4*) and the anaplastic lymphoma kinase gene (*ALK*) in non-small-cell lung cancer (NSCLC) cells.**
- **Detected in 6.7％ (5 out of 75) of NSCLC patients.**

非小細胞肺癌におけるEML4-ALK融合遺伝子

EML4-ALKの発見



Soda et al. Nature 448: 561-566, 2007

Nature Medicineが選ぶ2007年の重要な発見10

Nature Medicine 13:1401, 2007

■ Lung cancers, including the poorly understood tumors associated with smoking, may be triggered by the fusion of two genes, Japanese researchers reported in August. Formed by a small chromosomal inversion, the transforming gene fusion generates an activated kinase, and is found in seven percent of tumors from smokers and nonsmokers. Small compounds already known to inhibit the kinase may be able to treat the disease. (*Nature* **448**, 561–566)

Notable advances

Some of the key papers published in 2007

…e old wives' tale that carrots can …n the dark? A cluster of papers …der reason to get your daily dose …may help ward off inflammatory …y promoting the generation of …s, which dampen inflammation. …n the gut are particularly adept at …e vitamin A metabolite retinoic …ong with TGF-β, skews T cells …g regulatory T cells. (*Science* **317**, …*Med.* **204**, 1757–1764; 1765–1774;

…much can lead to increased …in fat tissue and, over time, …In May, researchers showed that …tein in fat cells, controls proper …e while keeping inflammation …increases the levels of STAMP2, …xpression of key cytokines that …nflammation …g the cell's …ng pathway, …s the storage …ents. (*Cell*

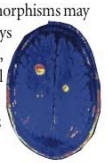
…papers this year unveiled the …microRNAs (miRNAs) in heart …unction and disease. The studies …mechanisms by which specific …regulate heart morphogenesis, …electrical conduction and …Hearts from patients with …y or coronary artery disease …levels of some of these miRNAs, …they could be new therapeutic …t disease. (*Nat. Med.* **13**, 486–491; …, 303–317; *Science* **316**, 575–579)

■ How the heart is put together during embryonic development has been extensively studied, but scientists reported a new twist to this story late last year. Three groups isolated mouse multipotent progenitor cells that can give rise to three major heart cell types—cardiac muscle, smooth muscle and endothelial cells. The findings may help researchers devise treatments for congenital and adult heart disease. (*Dev. Cell* **11**, 723–732; *Cell* **127**, 1137–1150; 1151–1165)

■ Platelets live for only ten days before they are removed from the bloodstream. In March, an Australian team revealed that anuclear apoptosis is the secret to this platelet lifespan. Antagonism between the proapoptotic protein Bak and the antiapoptotic Bcl-x_L protein sets up the ticking clock, and targeting this interaction could extend or limit the life of platelets to maintain healthy platelet counts. (*Cell* **128**, 1173–1186)

■ MiRNAs are key in the battle between viruses and their host cells, as revealed by four papers this year. Host cells produce a battery of miRNAs that shut off HIV gene expression, suppressing replication of the virus and contributing to latent infection. But other viruses can make their own miRNAs to hit back: human cytomegalovirus expresses miRNAs that promote the survival of infected cells. (*Science* **315**, 1579–1582; **317**, 376–381; **316**, 1345–1348; *Nat. Med.* **13**, 1241–1247)

■ The decades-long search for genes associated with multiple sclerosis finally bore fruit this year, as three groups reported a link between polymorphisms in the interleukin-7 receptor gene and the disorder. The polymorphisms may dampen the signaling pathways downstream of interleukin-7, potentially affecting the survival of some inflammatory cells. (*Nat. Genet.* **39**, 1083–1091; 1108–1113; *N. Engl. J. Med.* **357**, 851–862)



Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer

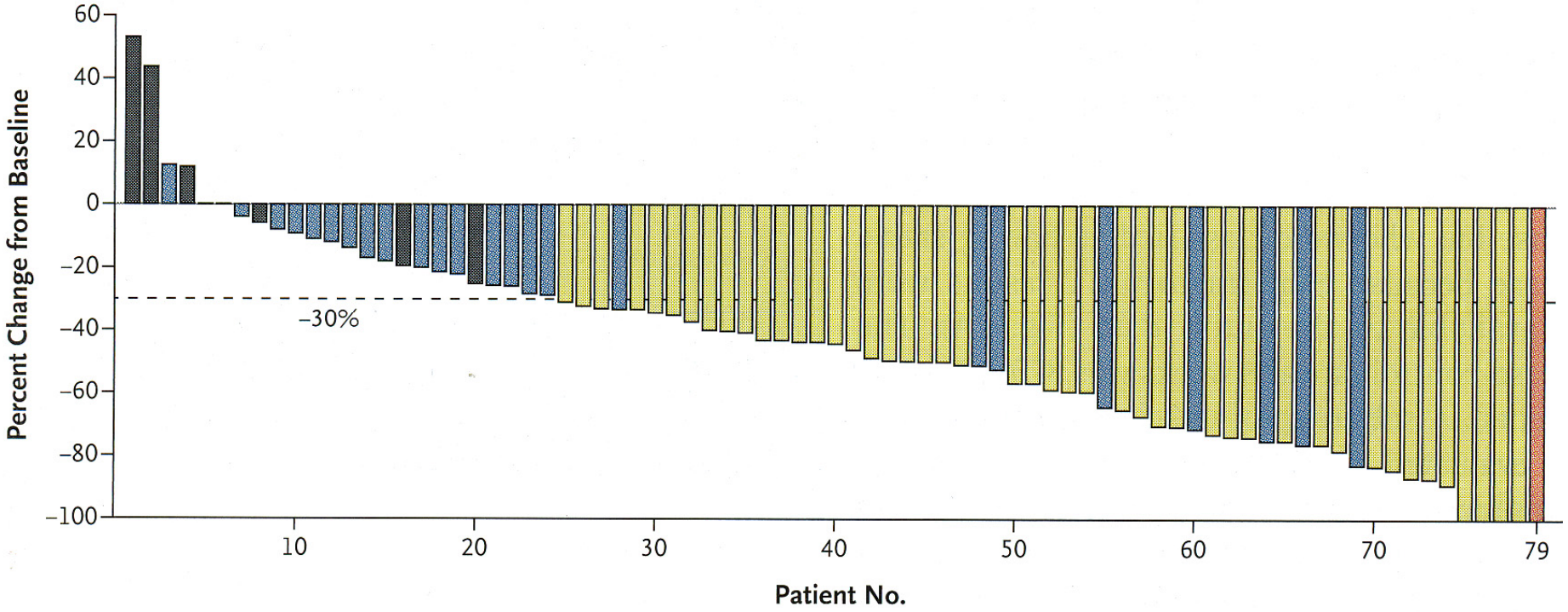
Eunice L. Kwak, et al.

NEJM Vol. 363, Oct.28, 2010.

- Most of the patients had little or no exposure to tobacco and had adenocarcinomas.
- The overall response rate was 57% (47 of 82 patients)
- 27 patients (33%) had stable disease.
- A total of 63 of 82 patients (77%) were continuting to receive crizotinib at the time of data cutoff

非小細胞肺癌に対するALK inhibitorの効果

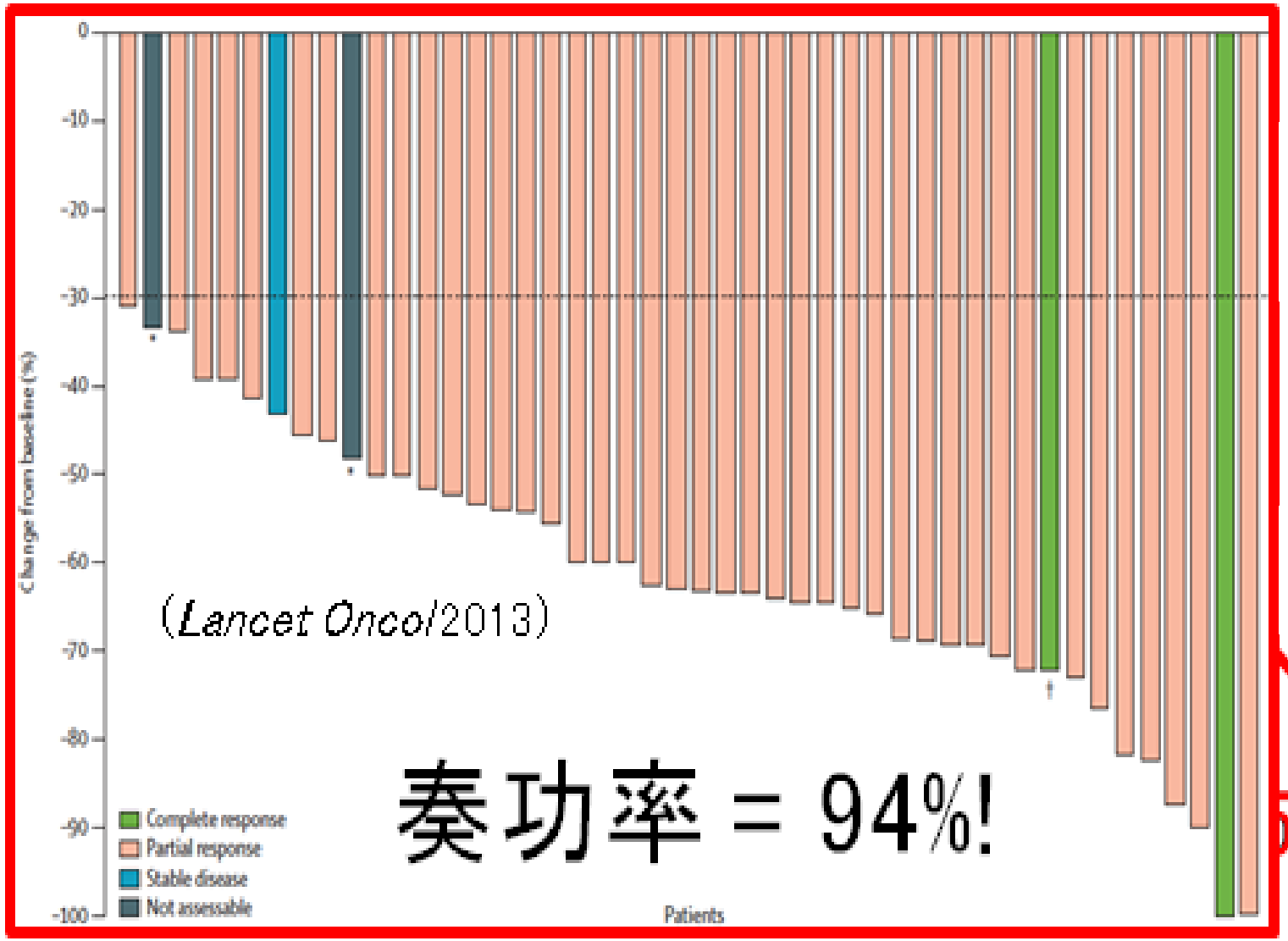
Response to ALK Inhibition
Percent Change in Tumor Burden



Eunice L. Kwak, et al. NEJM Vol. 363, Oct.28, 2010.

ALKチロシンキナーゼ阻害薬

Drug	Company
クリゾチニブ	Pfizer
ASP3026	Astellas
CH5424802	Chugai
LDK378	Novartis
AP26113	Ariad pharmaceuticals


0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Change from baseline (%)
Complete response
Partial response
Stable disease
Not assessable
Patients
(Lancet Onco/2013)
奏功率＝94%!
5424802

CH5424802 (RO5424802) for patients with *ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1—2 study

Seto,T. et al

In the phase 2 portion of the study, 46 patients were treated with the recommended dose, of whom 43 achieved an objective response (93·5%, 95% CI 82·1—98·6) including two complete responses (4·3%, 0·5—14·8) and 41 partial responses (89·1%, 76·4—96·4).

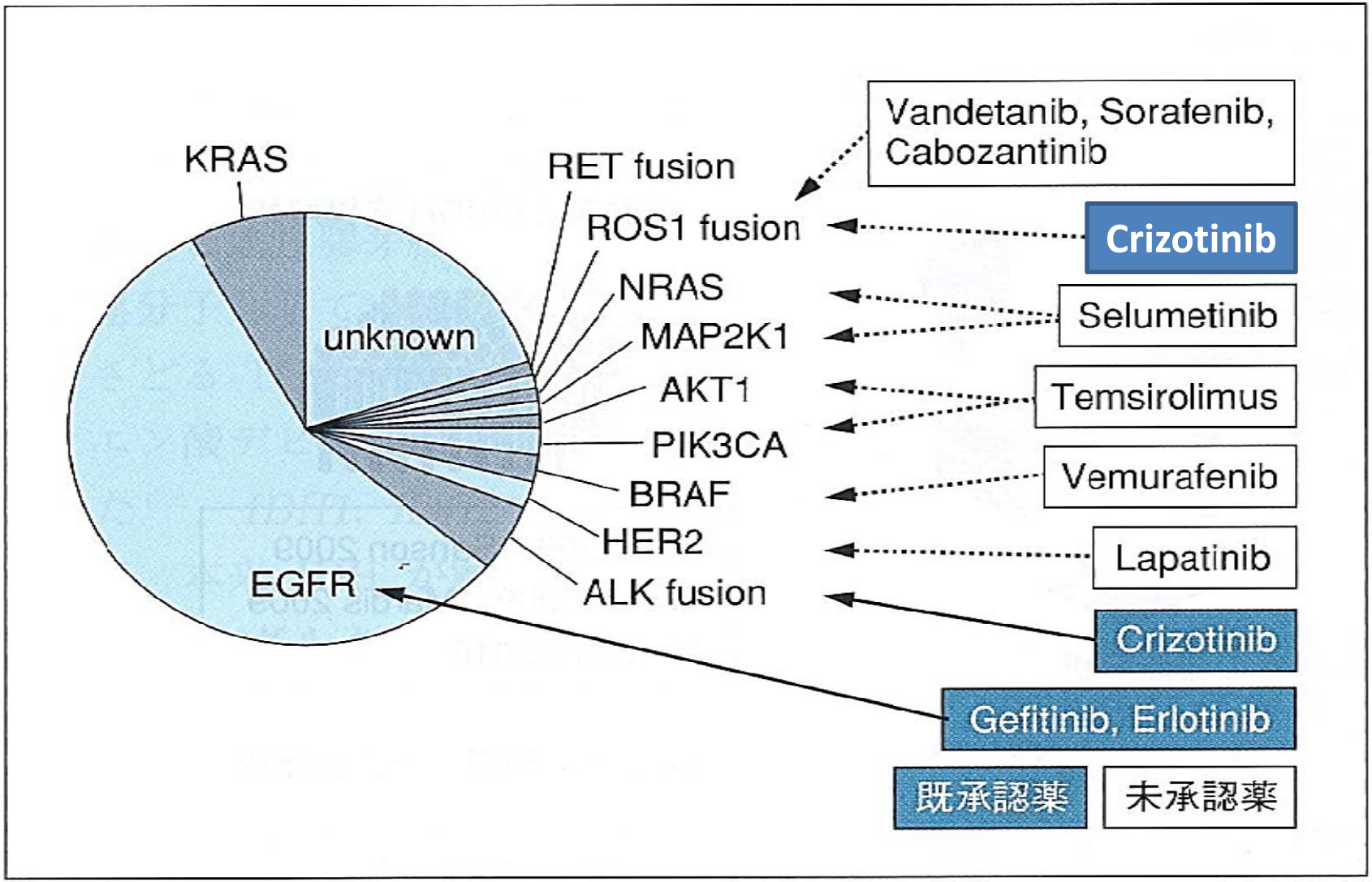
Lancet Oncology 14(7),590-598,2013

Matching Tumor Types to Drugs Boosts Lung Cancer Outcomes

Sunday, Apr.18 (2012)(HealthDay) The number one cancer killer, lung cancer, may be more susceptible to treatment when doctors match up targeted drugs to tumors with key genetic traits, a new study finds.

The study-the first of its kind-found that, overall, **46 percent of patients with stage IV (advanced) non-small cell lung cancer gained control of their disease** (a measure of overall survival) within two months of treatment when doctors matched chemotherapy to tumor ···

日本人肺腺がんにおけるドライバー遺伝子変異の分布と分子標的治療薬



上原一哉　最新医学2012;67(12)95－102:図2より引用

Oncogenic and drug-sensitive *NTRK1* rearrangements in lung cancer

Vaishnavi,A. et al

Both the *MPRIP-NTRK1* and *CD74-NTRK1* fusions lead to constitutive TRKA kinase activity and are oncogenic.

Treatment of cells expressing *NTRK1* fusions with inhibitors of TRKA kinase activity inhibited autophosphorylation of TRKA and cell growth.

肺癌における発癌性並びに薬剤感受性NTRK1融合遺伝子

Nature Med .2013:19(11)1469-1471

Monoclonal　抗体

Monoclonal Antibody

- Infliximab （抗TNF)（マウス, ヒトキメラ抗体）
- Adalimumab （抗TNF)(ヒト抗体）
- Tocilizumab （ヒト化抗IL-6受容体抗体）

→ 関節リウマチ

- Rituximab （抗CD20）
  - → 非ホジキンリンパ腫
  - → 関節リウマチ
- Gemtuzumab Ozogamicin
  (抗CD33＋抗生剤）(Mylotarg)
  - → 急性骨髄性白血病
- Bevacizumab $4400/m (Avastin)(抗VEGF)
  - → 大腸癌
  - → 小細胞癌
  - → 進行乳癌
- Transtuzumab (Herceptin)(抗HER-R)
  - → 進行乳癌
- Eculizumab （抗補体C5）
  - → PNH
- Mogamulizumab（抗CCR4）
  - → ATL

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Topalian,S.L et al .(USA)

Blockade of programmed death 1 (PD-1), an inhibitory receptor expressed by T cells,can overcome immune resistance.

We enrolled patients with advanced melanoma, non–small-cell lung cancer, castrationresistant prostate cancer, or renal-cell or colorectal cancer to receive anti–PD-1 antibody.

Among 236 patients in whom response could be evaluated, objective responses were observed in those with **non–small-cell lung cancer, melanoma, or renal-cell cancer.**

Of 17 patients with PD-L1–negative tumors, none had an objective response; 9 of 25 patients (36%) with PD-L1–positive tumors had an objective response (P = 0.006).

Anti–PD-1 antibody produced objective responses in approximately one in four to one in five patients with non–small-cell lung cancer, melanoma, or renal-cell cancer.

抗PD-1（ programmed death 1 ）抗体の癌に対する安全性と効果

N Eng J Med :2012:366(26)2443-2454

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Brahmer,J.R.et al (USA)

Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models.

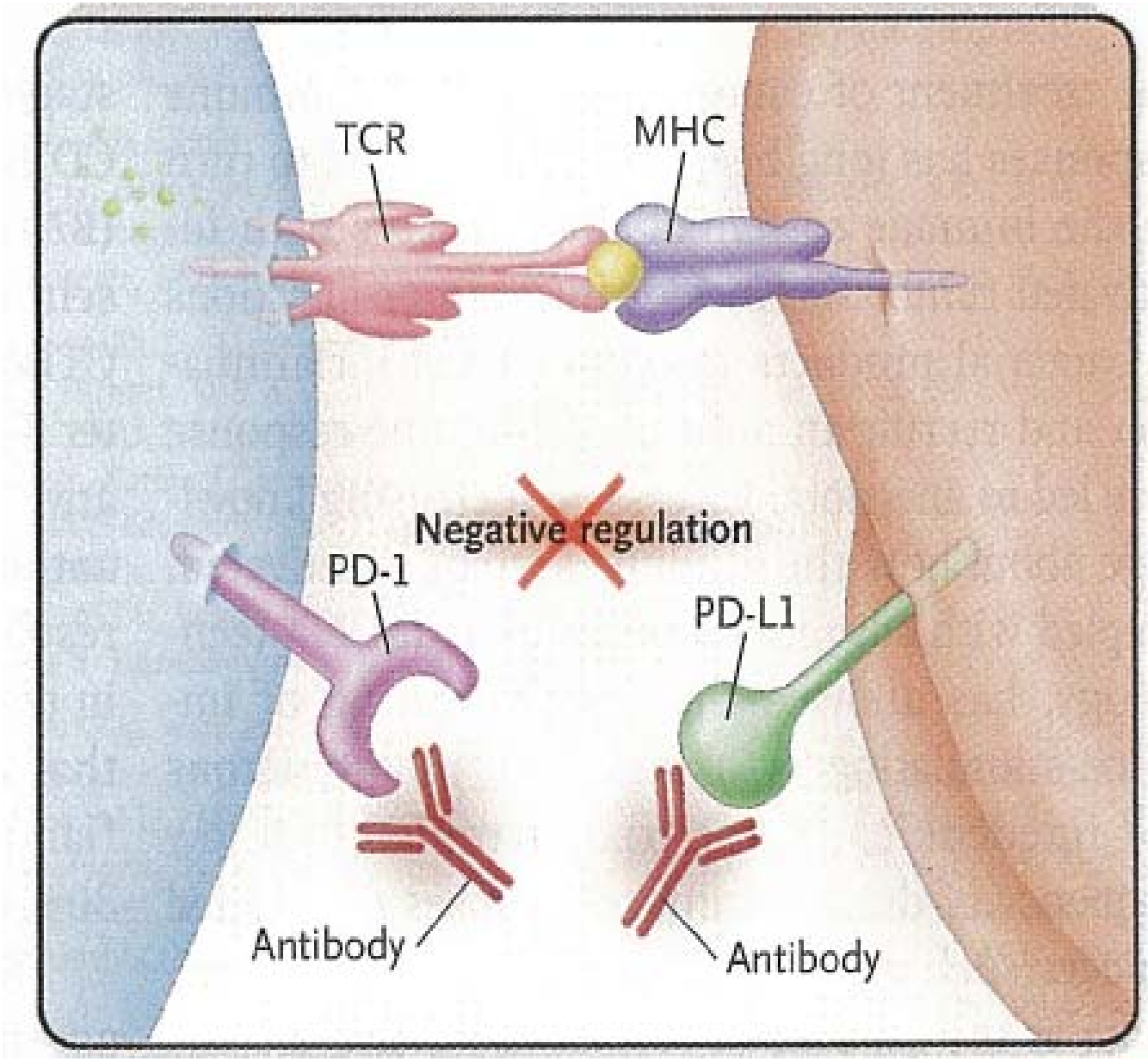
207 patients — 75 with non–small-cell lung cancer, 55 with melanoma, 18 with colorectal cancer, 17 with renal-cell cancer, 17 with ovarian cancer, 14 with pancreatic cancer, 7 with gastric cancer, and 4 with breast cancer — had received anti–PD-L1 antibody.

Antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non–small-cell lung cancer, melanoma, and renal-cell cancer.

進行性癌に対する抗PD-L1抗体の安全性と有効性

N Engl J Med：2012 366(26)2455-2465

Blockade of PD-1 or CTLA-4 Signaling in Tumor immunotherapy



Tumor Immunotherapy Directed at PD-1

Ribas. A et al

N Eng J Med:2012, 366(26),2518,Fig1

Epigenetics

1) DNA methylation

2) Acetylation of Histone

3) Methylation of Histone

4) Non-coding RNA(microRNA)

Micro RNAと癌

Serum miR-21 as a Diagnostic and Prognostic Biomarker in Colorectal Cancer

Y. Toiyama et al.

High *miR-21* expression in serum and tissue was statistically significantly associated with tumor size, distant metastasis, and poor survival.

大腸癌の診断、予後のbiomarkerとしての血清miR-21値

Journal of National Cancer Institute 2013, Jun 19 ;849

Identification of serum microRNA profiles in colon cancer

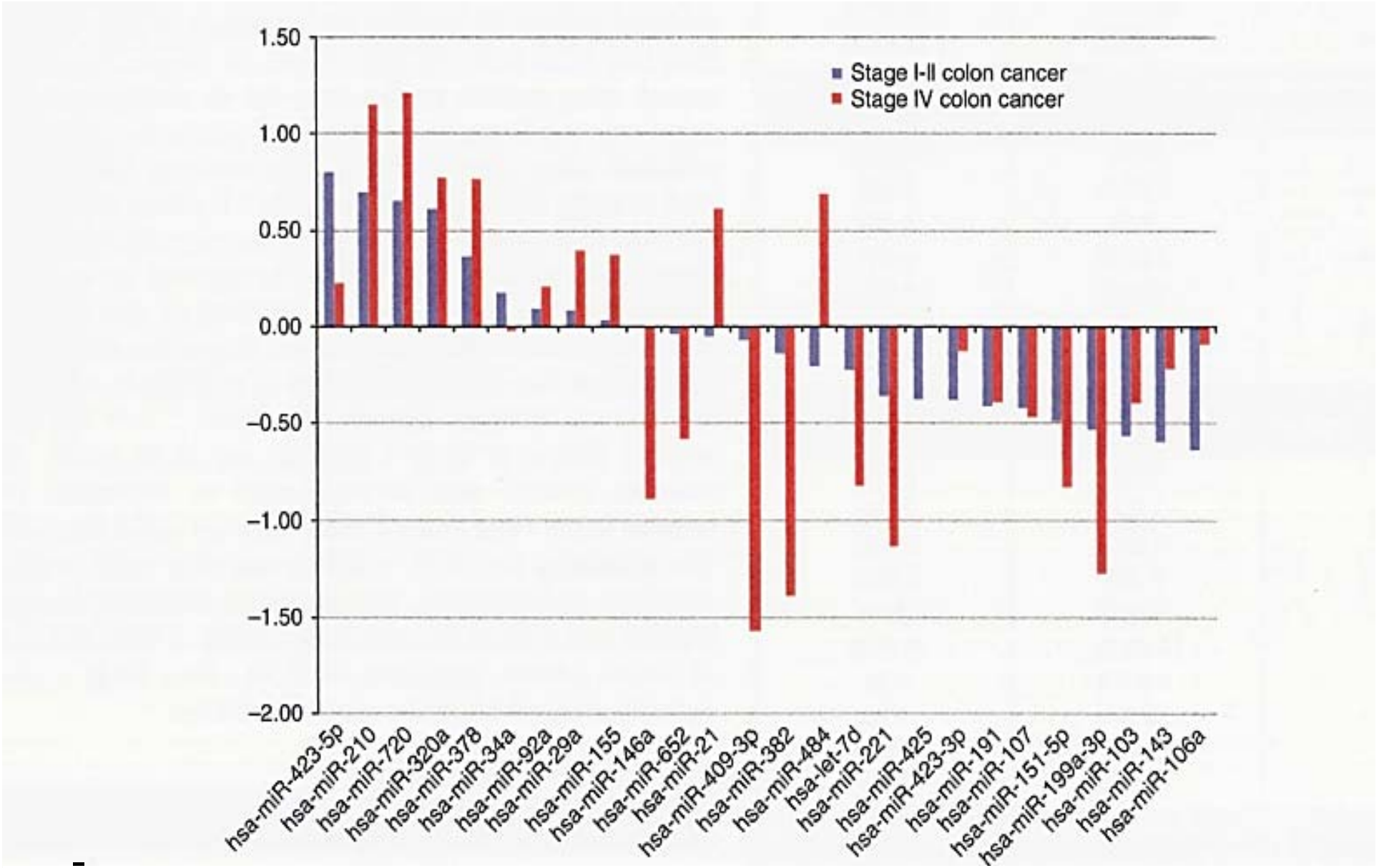
Hofsli E,et al

Twenty miRNAs were differentially expressed in serum from stage IV patients compared with controls ($P<0.01$).

Serum miRNA expression profiling may be utilised in early detection of colon cancer.

大腸癌における血清microRNAのプロファイル

Brtish Journal of Cancer: 2013,108,1712-1719



Differentially expressed miRNAs in stage IV(red bars)vs stage I-II(blue bars) colon cancer.

British Journal of Cancer: 2013,108,1712-1719

乳癌で発現異常をきたしているmiRNA

miRNA	染色体位置	標的遺伝子
乳がんで増加しているmiRNA		
miR-9-1	1q22	
miR-10b	2q31.3	*TIAM, HOXD10, TIAM*
miR-21	17q23.1	*TPM1, PDCD4*
miR-27a	19p13.13	*ZBTB10, MYT1*
miR-29b1	7q32.3	
miR-29c	1q32.2	
miR-93	7q22.1	
miR-155	21p21.3	*FOXO3A, SOCS1, RHOA*
miR-191	3p21.31	
miR-196a1	17q21.32	*ANXA1*
miR-203	14q32.33	
miR-206	6p12.2	
miR-210	11p15.5	*MNT, RAD52*

遺伝子医学MOOK23　柴田龍弘，2012; 第1章6.乳癌におけるmicroRNA診断,55，表1

乳癌で発現異常をきたしているmiRNA

miRNA	染色体位置	標的遺伝子
乳がんで減少しているmiRNA		
let-7		*RAS, HMGA2, MYC*
miR-17	13q31.3	*AIB1, CyclinD1, E2F*
miR-20a	13q31.3	
miR-34	1p36.22	
miR-100	11q24.1	
miR-125a	19q13.41	*ERBB2, ERBB3, BAK, CRAF, MUC1, ERA, RTKN*
miR-125b	11q24.1	*ERA, ERBB3*
miR-141	12p13.31	
miR-143	5q32	
miR-145	5q32	*RTNK, MUC1, ERA*
miR-200a/b	1p36.33	
miR-205	1q32.2	*HER3, VEGFA*
miR-206	6p12.2	*ERA*
miR-429	1p36.33	
miR-497	17p13.1	

遺伝子医学MOOK23　柴田龍弘，2012; 第1章6.乳癌におけるmicroRNA診断,55　表1

胃がん患者における血中バイオマーカーとしてのmiRNA

報告者(発表年)	miRNA
Tujiura M（2010）[8]	miR-17-5p, miR-21, miR-106a, miR-106b（増加）, let-7a（減少）
Liu R（2010）[9]	miR-1, miR-20a, miR-27a, miR-34a, miR-423-5p（増加）
Liu H（2012）[10]	miR-187*, miR-371-5p, miR-378（増加）
Konishi H（2012）[11]	miR-451, miR-486（増加）

*areas under receiver-operating characteristics curve

遺伝子医学MOOK23　阿部浩幸他　2012; 第1章9.胃がんにおけるmiRNA診断,73　表2

患者の予後と相関する胃がん組織中のmiRNA

報告者（発表年）	miRNA
Li X （2010）[4]	miR-10b, miR-21, miR-223, miR-338, let-7a, miR-30a-5
Ueda T （2010）[1]	let-7g, miR-433, miR-214
Nishida N （2011）[2]	miR-125a-5p
Zhang X （2011）[5]	miR-375, miR-142-5p
Kogo R （2011）[3]	miR-146a
Brenner B （2011）[6]	miR-195, miR-199a-3p, miR-451

遺伝子医学MOOK23　阿部浩幸他　2012; 第1章9.胃がんにおけるmicroRNA診断,73　表1

miRNA	膀胱がんでの発現
-129-5p	Up
-21	Up
-221	Up
-1/133a	Down
-1/133a/218	Down
-19a	Down
-30a-3p/133a/199a	Down
-34a	Down
-99a/100	Down
-101	Down
-125b	Down
-133a	Down
-143	Down
-145	Down
-145/133a	Down
-195-5p	Down
-200a/b/c/205	Down
-200c	Down
-203	Down
-218	Down
-493	Down
-517a	Down
-574-3p	Down
-1826	Down

膀胱がんで発現異常が報告されているmiRNA

遺伝子医学MOOK23　竹下文隆他 2012; 第2章5.膀胱がんにおけるmiRNA治療の可能性，147 表1

Identification of microRNAs in the cerebrospinal fluid as biomarker for the diagnosis of glioma

Baraniskin,A.et al. (Germany)

Inclusion of miR-15b and miR-21 in combined expression analyses resulted in an increased diagnostic accuracy with 90% sensitivity and 100% specificity to distinguish patients with glioma from control subjects and patients with primary CNS lymphoma.

脳脊髄液中のmicroRNAがglioma（神経膠腫）のbiomarkerになる

Neuro Oncol.2012;14(1)29-33

DNA Methylation Predicts Survival and Response to Therapy in Patients With Myelodysplastic Syndromes

Shen,L. et al

We found that patients with higher levels of methylation, compared with patients with lower levels, had a shorter median overall survival

DNA Methylation からMDS患者の生存率並びに治療に対する反応を予知する事が可能である

J Clin Oncol 2010;28(4),605-613

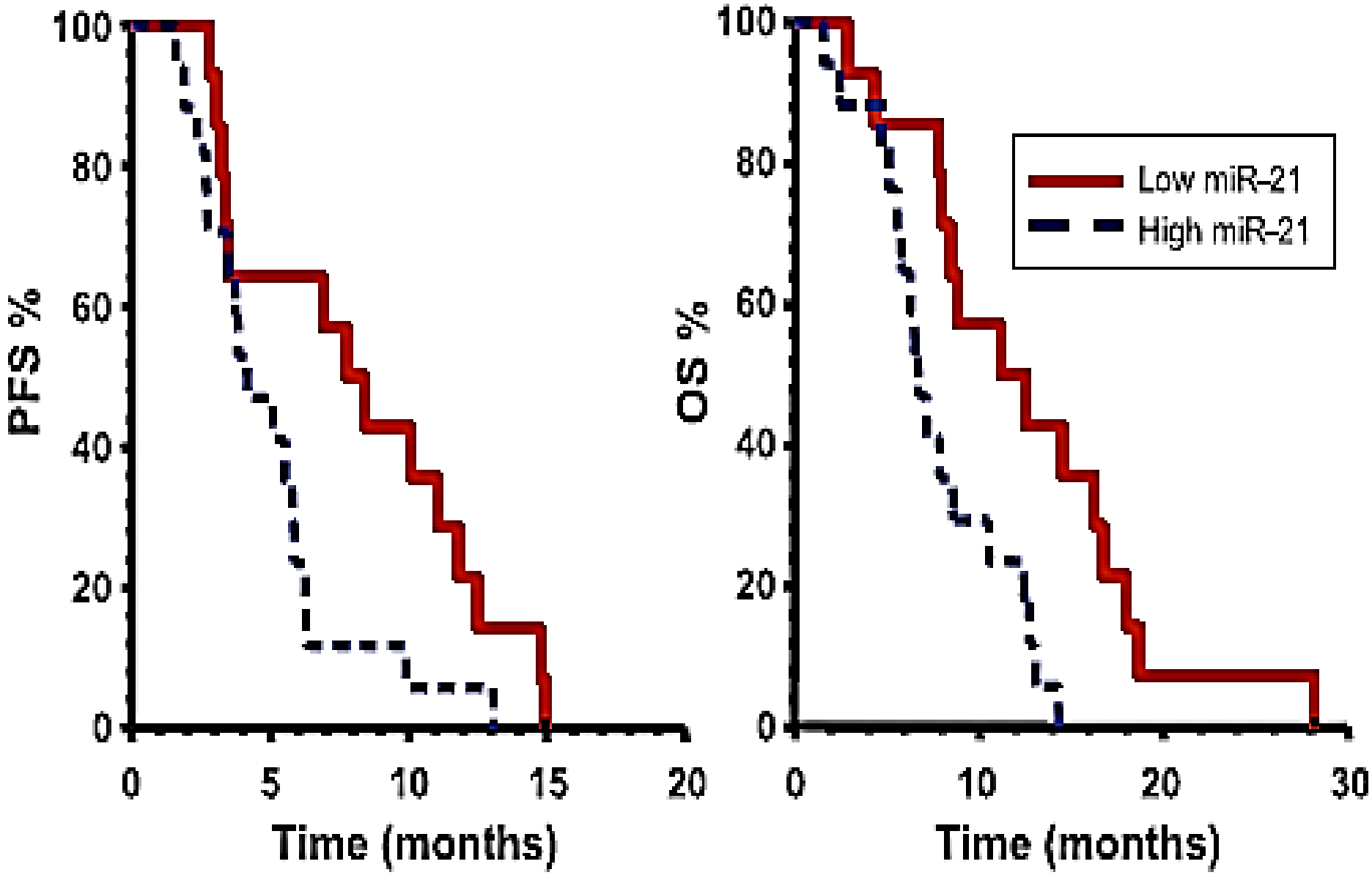
MicroRNA-21 in Pancreatic Cancer: Correlation with Clinical Outcome and Pharmacologic Aspects Underlying Its Role in the Modulation of Gemcitabine Activity

Giobannetti.E et al, (Netherland)

MicroRNA-21 (miR-21) was reported to be overexpressed and contributes to invasion and gemcitabine resistance in pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to evaluate whether miR-21 expression was associated with the overall survival (OS) of PDAC patients treated with gemcitabin.

MicroRNA21の膵癌患者に対するgemcitabineの有効性に及ぼす影響

Cancer Res;2010,70(11),4528-4538



Cancer Res;2010,70(11),4530.Fig1.B Giobannetti.E,(Netherland) et al

Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model

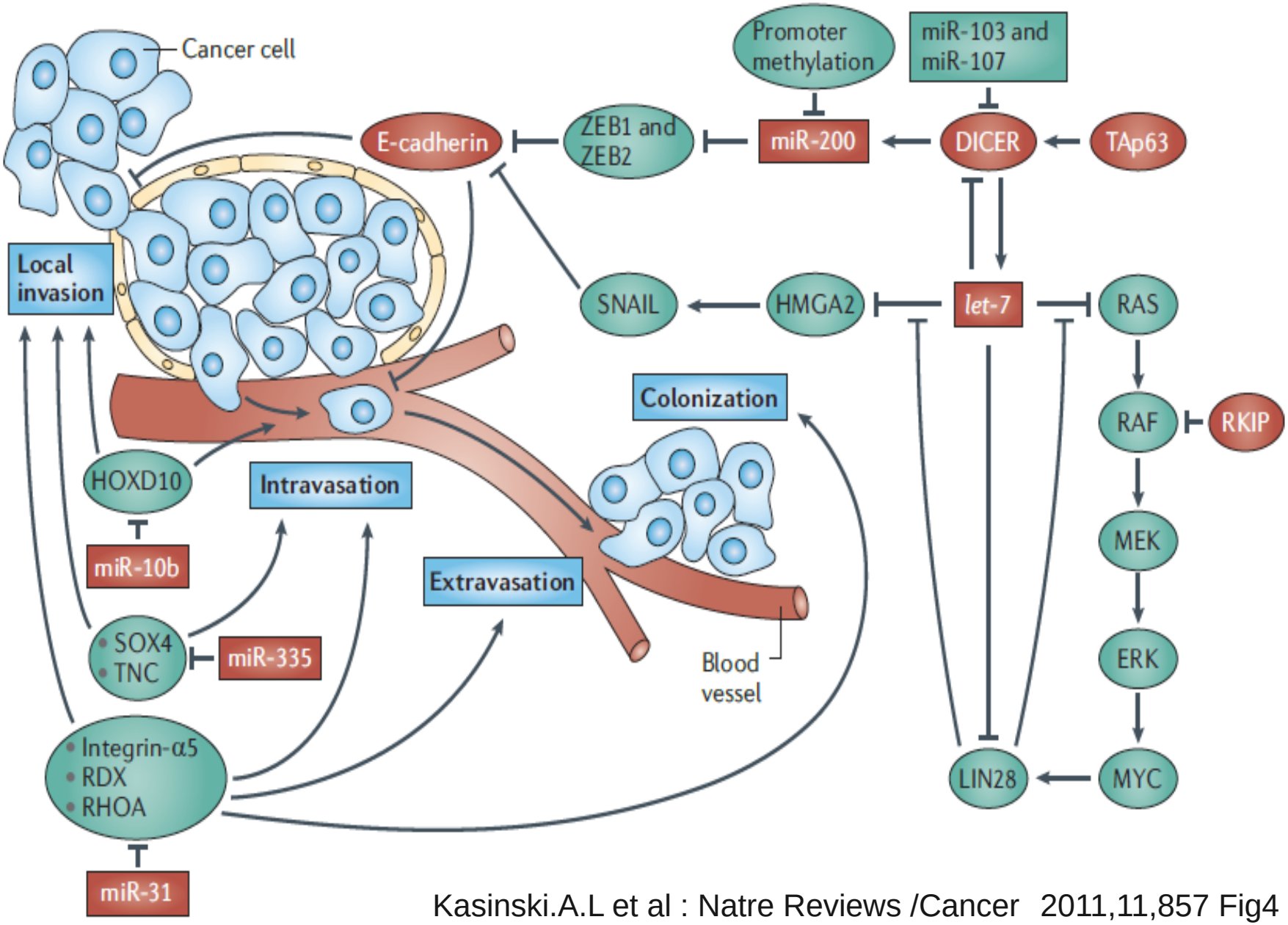
Reinhardt,L.F. et al. (MIT)

Here we show that systemic treatment of tumor-bearing mice with miR-10b antagomirs—a class of chemically modified anti-miRNA oligonucleotide—suppresses breast cancer metastasis both *in vitro* and *in vivo.*

miR-10の活性を抑制すると乳癌の転移を阻害する(マウス)

Nature Biotechnol;2010,28(4),341-348

miRNAs that contribute to metastasis（Mouse）



Kasinski.A.L et al : Natre Reviews /Cancer 2011,11,857 Fig4

Therapeutic microRNA Delivery Suppresses Tumorigenesis in a Murine Liver Cancer Model

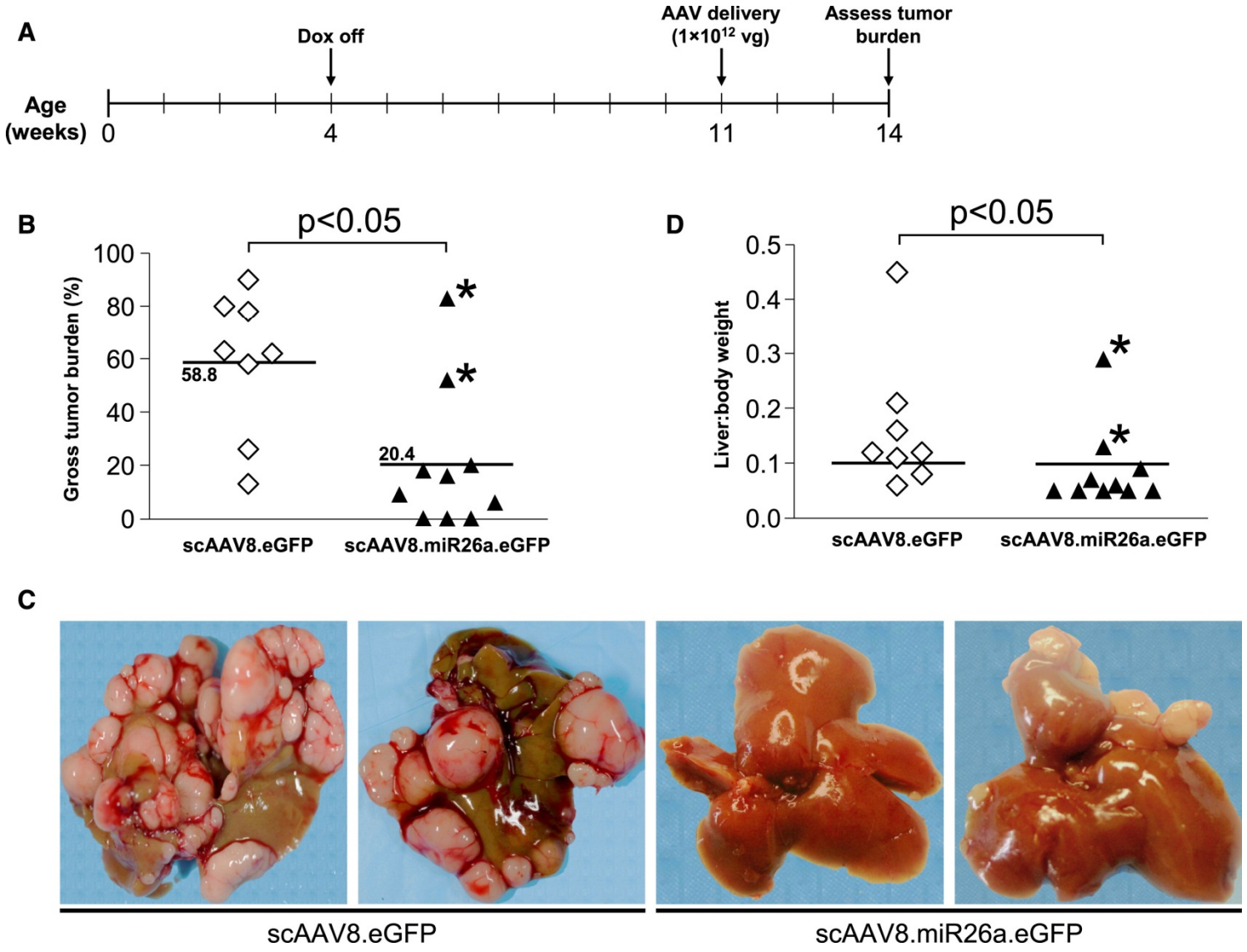
Janaiah Kota, et al.

Cell Vol.137, June 12, 2009

miRNA-26a in a mouse model of HCC using adeno-associated virus (AAV) results in inhibition of cancer cell proliferation, induction of tumor-specific apoptosis, and dramatic protection from disease progression without toxicity.

miRNAが肝癌を抑える （in vivo マウス）

AAV-Mediated miR-26a Delivery Suppresses Tumorigenesis in tet-o-MYC; LAP-tTA Mice



Janaiah Kota, et al. Cell Vol.137, June 12, 2009

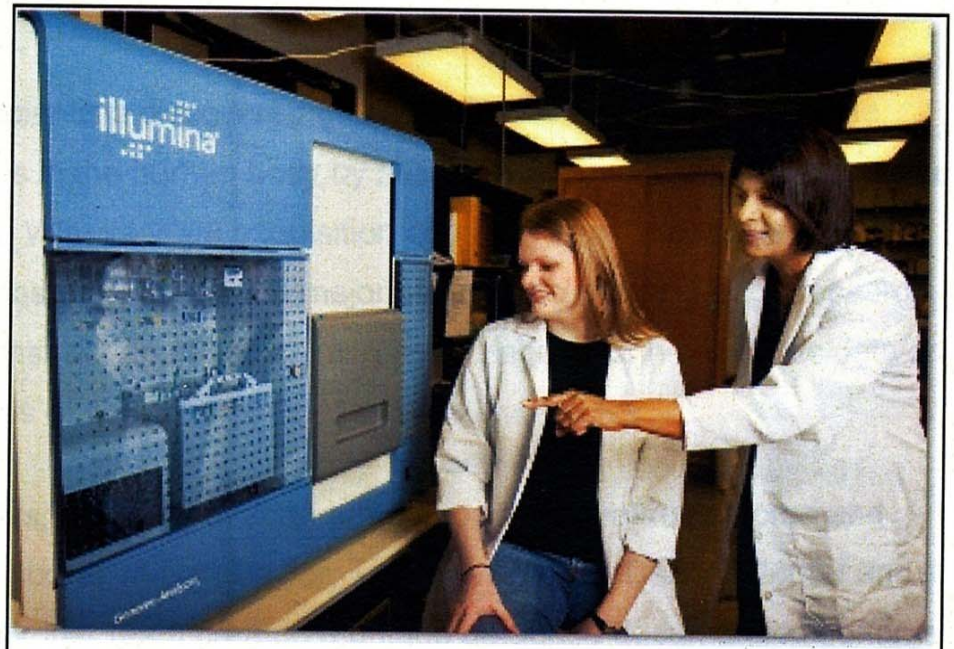
Lisa Merkl
lkmerkl@uh.edu
713-743-8192

UH Biochemist Works to Revolutionize Ovarian Cancer Treatment

Preethi Gunaratne Wins Key Grants to Unleash Body's Natural Cancer-fighting Agents

December 21, **2010-Houston-** **The day** when an ovarian cancer patient can treat her tumor with a single, painless pill instead of a toxic drug cocktail is the ultimate goal of the pioneering research of a University of Houston (UH) scientist.

Preethi Gunaratne, assistant professor in the department of biology and biochemistry, is studying a class of tiny genetic molecules known as microRNAs and pinpointing those that could unleash the body's natural cancer-fighting agents. Additionally, she is developing a novel method to effectively deliver this treatment to the targeted cells by using an unusual carrier – nanoparticles of



A strong proponent of student success, Preethi Gunaratne is pictured with one of the many students from her lab. Here, she points out the Illumina Genome Analyzer, a key piece of equipment used in her research, to graduate student Ashley Benham. (Photo by Thomas Campbell)

Univ.Houstonの研究者がmicroRNA31 (gold particle上)を用いて卵巣癌を治療

MicroRNAの
他の疾患に対する影響

MicroRNAs 103 and 107 Regulate Insulin Sensitivity

Mirko Trajkovski,et al.

Nature doi:10.1038/nature10112

- Here we show that the expression of microRNAs 103 and 107 (miR-103/107) is upregulated in obese mice.
- Silencing of miR-103/107 leads to improved glucose homeostasis and insulin sensitivity.

microRNA 103と107がインスリン感受性を調節（マウス）

MicroRNA-Mediated In Vitro and In Vivo Direct Reprogramming of Cardiac Fibroblasts to Cardiomyocytes

T.M.Jayawardena,et al

We identified a combination of miRNAs 1, 133, 208, and 499 capable of inducing direct cellular reprogramming of fibroblasts to cardiomyocyte-like cells in vitro.

Importantly, administration of miRNAs into ischemic mouse myocardium resulted in evidence of direct conversion of cardiac fibroblasts to cardiomyocytes in situ.

MicroRNAによる心筋線維芽細胞の心筋細胞への　in vitro, in vivo reprogramming（マウス）

Circul Res 2012;110:1465-1473

Plasma microRNA signature as a noninvasive biomarker for acute graft-versus-host disease

Xiao,B.et.al

Here, we show that plasma samples from aGVHD patients have a distinct microRNA (miRNA) expression profile. We found that 6 miRNAs (miR-423, miR-199a-3p, miR-93*, miR-377, miR-155, and miR-30a) were significantly upregulated in the plasma of aGVHD patients (n5116) when compared with non-GVHD patients.

血漿中のmicroRNAのパターンが急性GVHDのbiomarkerになる

Blood .2013:122(19),3365～3375

MicroRNA-140 plays dual roles in Both cartilage development and homeostasis

Miyaki,S. et al. Japan,USA.

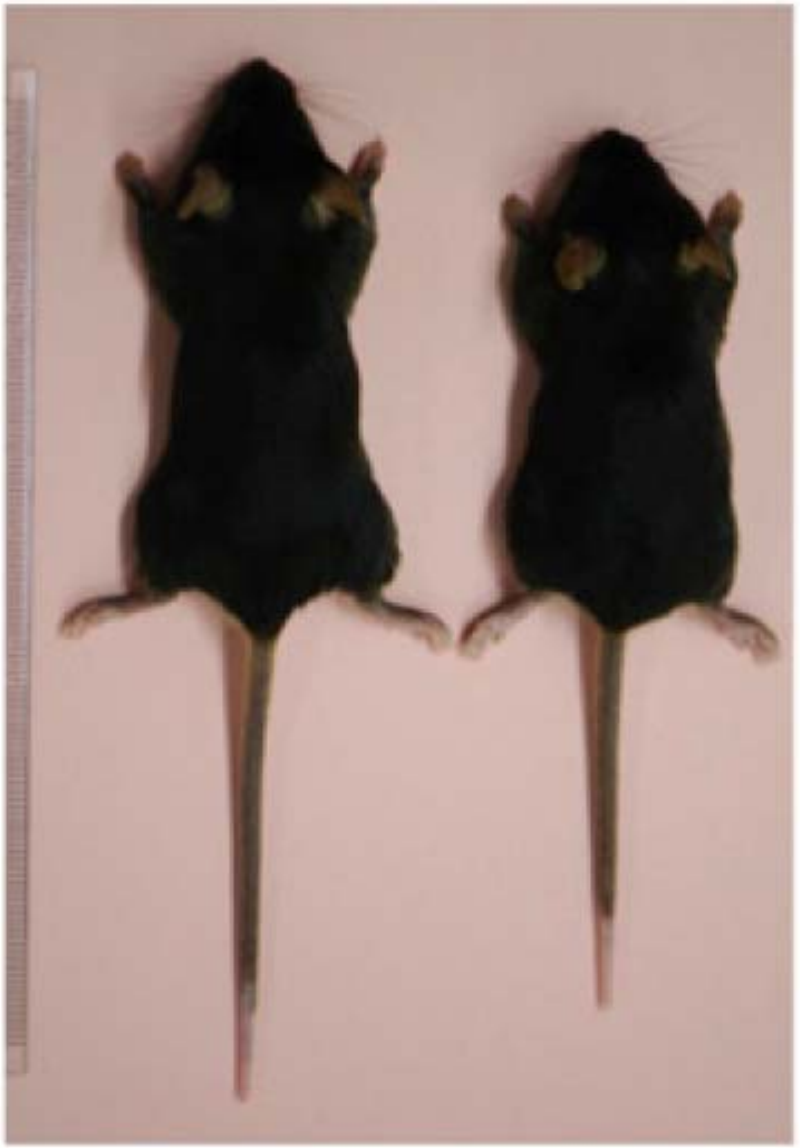
miR-140$^{-/-}$ mice showed age-related OA-like changes overexpressing miR-140 in cartilage were resistant to antigen-induced arthritis.

We show that miR-140 regulates cartilage development and homeostasis, and its loss contributes to the development of age-related OA-like changes.

MicroRNA-140は軟骨の生成と恒常性の維持に必要

Genes & Development 2010;24,1173-1185

Growth retardation in miR-140 $^{-/-}$ mice



Wild miR-140$^{-/-}$

Miyaki,S. et al.
Japan,USA.

Genes &
Development
2010;24,1176
Fig2.B

Clinical trials of antimiR－122 in the Treatment of HCV

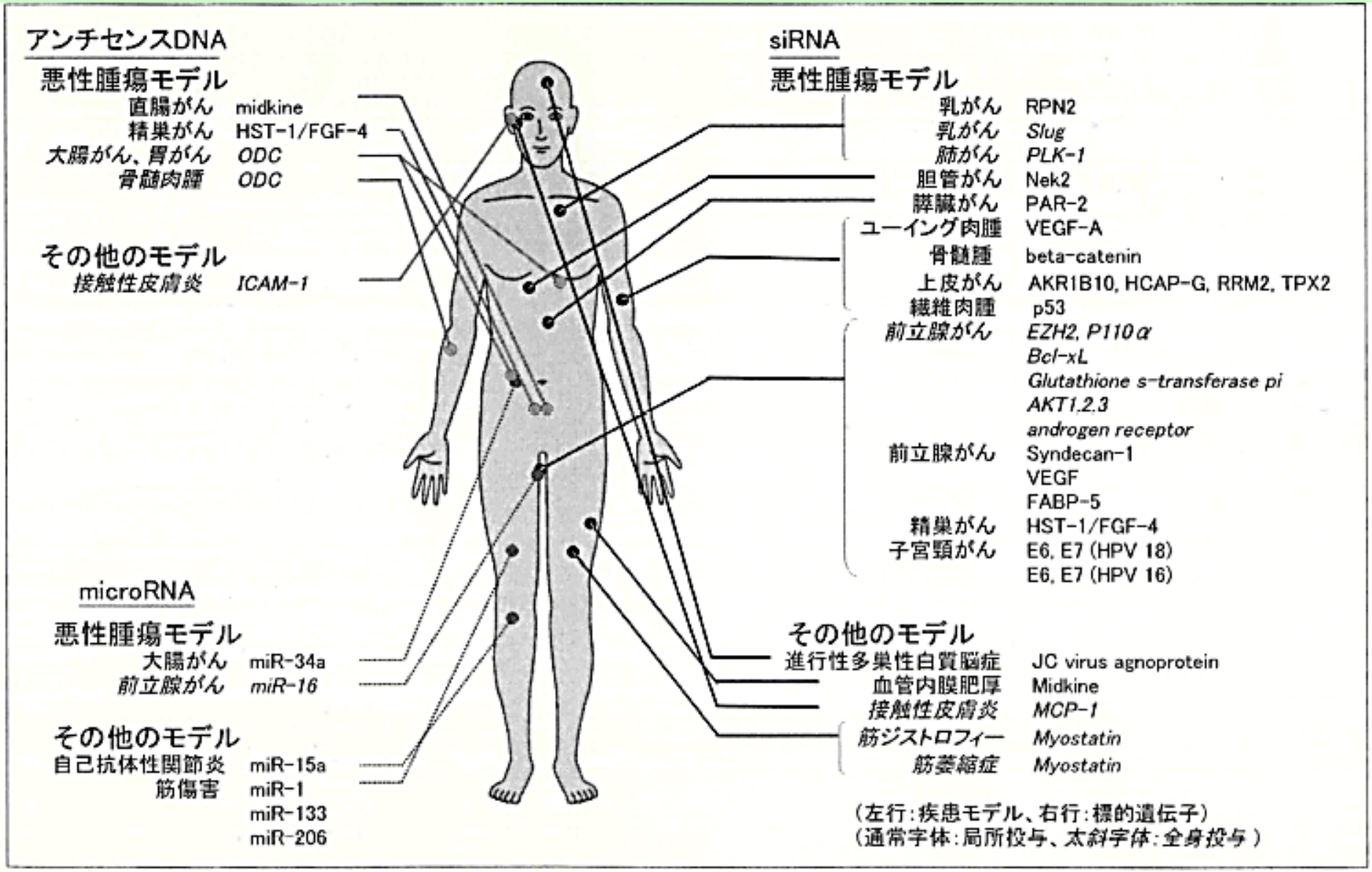
Reviews　Rooji,E. van. and　Olson R.N.

AntimiR therapeutics（inhibitors of microRNAs）recently　became　a　reatity when Santaris Pharma　reported　both　the safety and efficacy　of　its　antimiR against the microRNA　miR－122, miravirsen, in humans.

HCV肝炎に対するantimiR-122の治療効果（ヒト）

Natre Reviews Drug Discover :2012,11 ,860-872

様々なモデルにおける核酸／アテロコラーゲンの応用例



遺伝子医学MOOK23　牧田尚樹他　2012; 第3章1. アテロコラーゲンによる核酸医薬デリバリー開発，203　図1

miRNA医薬品の開発状況

企業	標的 miRNA	疾患	開発ステージ (提携先)
Santaris 社	miR-122	HCV 感染症	Phase2
Regulus 社	miR-33	アテローム性動脈硬化	Pre-clinical
	miR-21	肝臓がんなど	Pre-clinical
	miR-21	線維症	Pre-clinical (Sanofi-Aventis)
	miR-122	HCV 感染症	Pre-clinical (GlaxoSmithKline)
	miR-155	免疫・炎症領域	Pre-clinical (GlaxoSmithKline)
Mirna 社	miR-34	肺がん，前立腺がんなど	Pre-clinical
	miR-16	前立腺がんなど	Pre-clinical
	let-7	肺がんなど	Pre-clinical
Miragen 社	miR-208/499	慢性心不全	Pre-clinical
	miR-15/195	心筋リモデリング	Pre-clinical
	miR-451	真性多血症	Pre-clinical
	miR-29	心線維化	Pre-clinical

遺伝子医学MOOK23　山田陽史他　2012; 第3章2. miRNA医薬開発の現状と展望，212　表1

読売新聞

（第3種郵便物認可）　2014年(平成26年)1月7日（火曜日）

唾液・血でがん発見

遺伝情報分析、健康診断で

経産省が開発支援

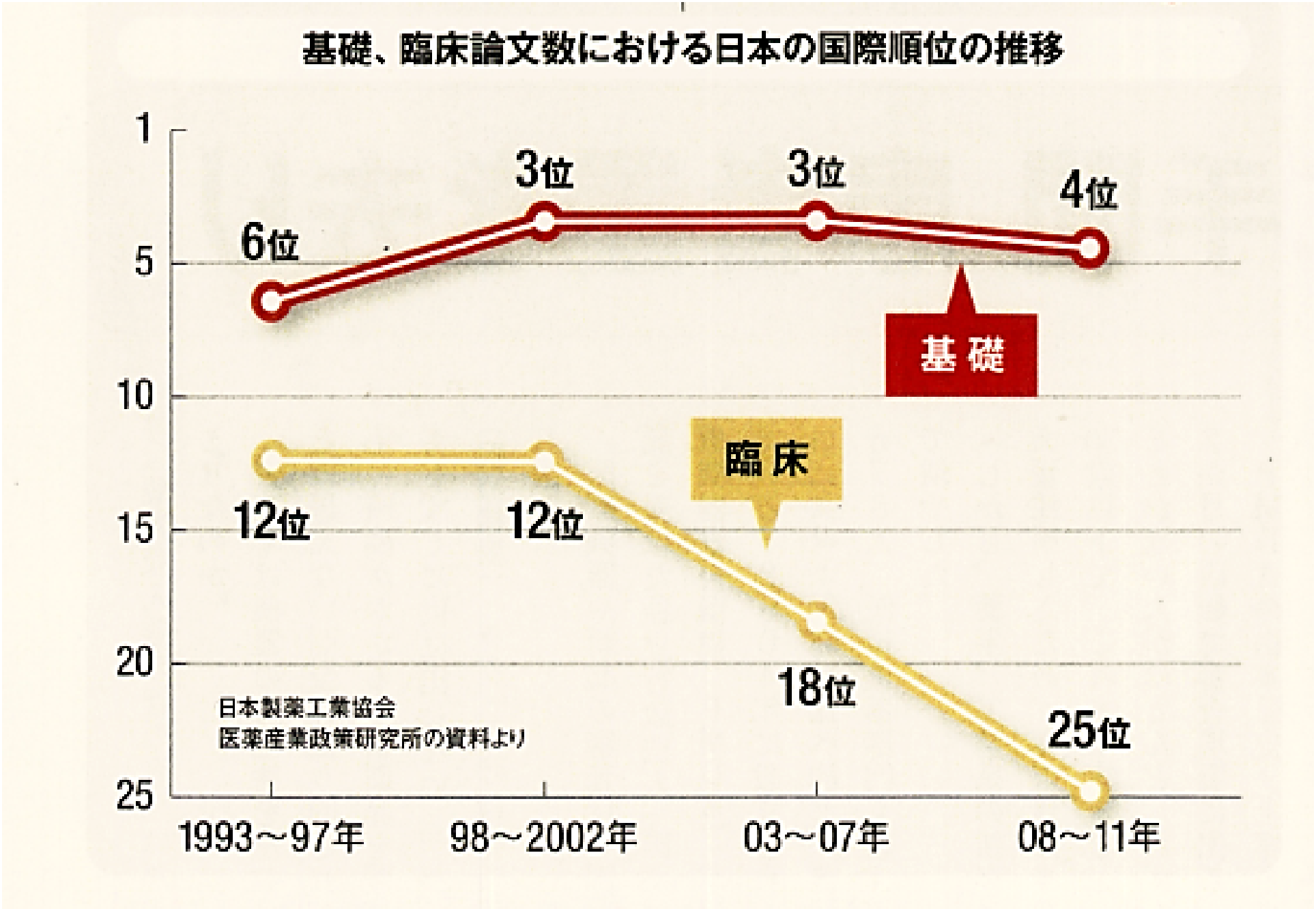
健康診断で血液や唾液から、がんを早期発見する――。こうした新技術の開発に向け、経済産業省は研究機関や医療機器メーカーを5年がかりで支援することを決めた。「がんになりたての細胞を見つけ、治療する『先制医療』の技術を確立させたい」と話している。

国立がん研究センターなどの研究によると、体内の細胞は「マイクロRNA」と呼ばれる、非常に小さな遺伝情報を脂質の袋にくるんで血液の中に放出し、ごく一部は唾液にも含まれる。細胞の種類や状態によって、袋に入る情報は様々で、中にはがんの手がかりになる情報も含まれているという。

そこで、血液や唾液からこの袋を集めて遺伝情報を分析し、体内のどこで、どんながんが生まれているかを早期診断する研究が世界的に進んでいるが、実用化に成功した例はまだない。

このため、経産省生物化学産業課は「がんの情報を効率的に見つける技術を確立すれば、多くのがんを一度に診断する健康診断用の検査キットなどの開発につながる」とみて、新年度予算案に15億7000万円を計上した。今後、国内のがんの研究機関や医療機器メーカーなどを公募し、がん患者の血液に含まれる遺伝情報の配列から、どうすればがんと診断できるかの研究を支援する。

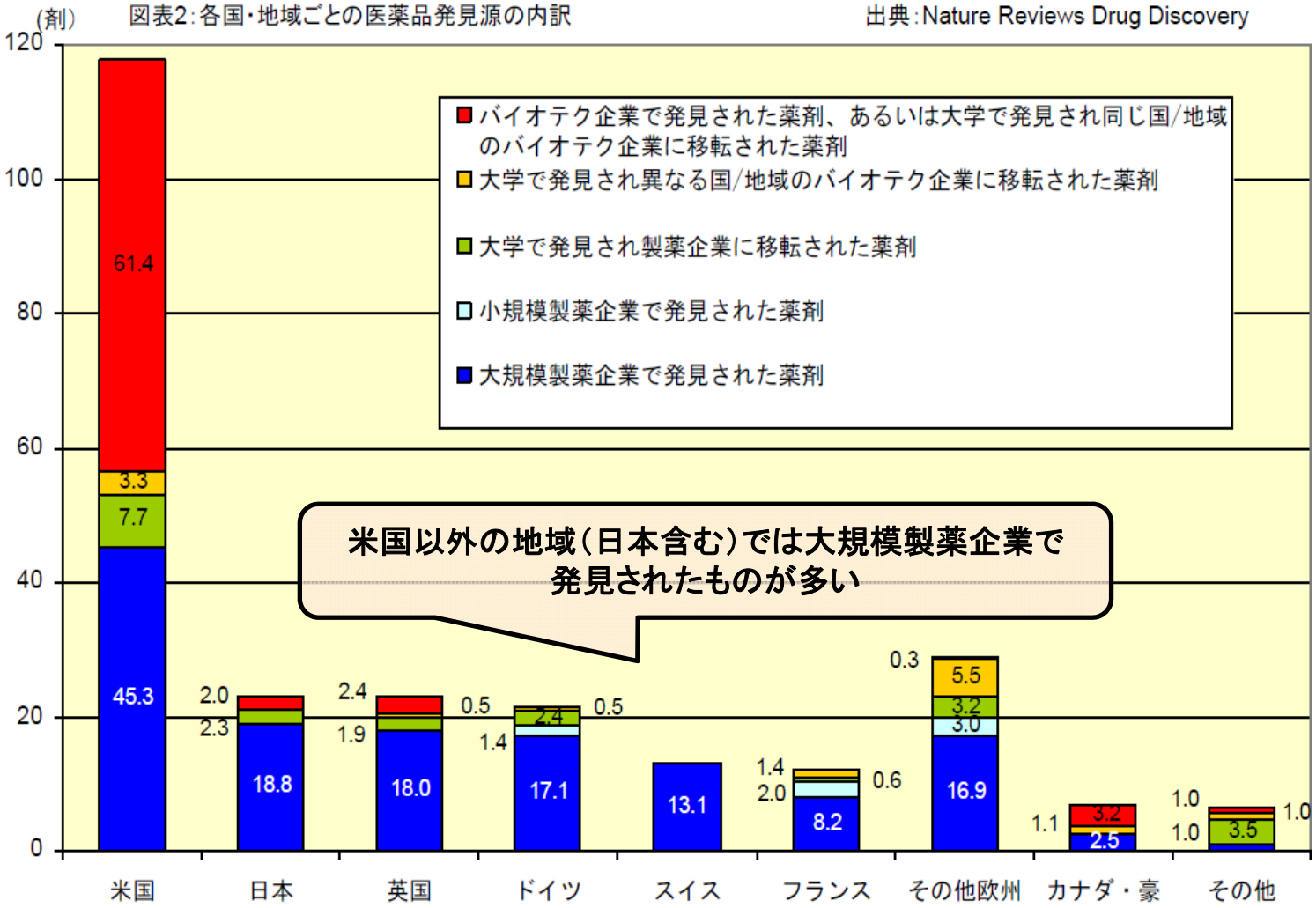
医療Innovation
＝Translational Research



YOMIPACK 2013 : 医療改革2より引用

FDA承認医薬品 発見の源（国別）

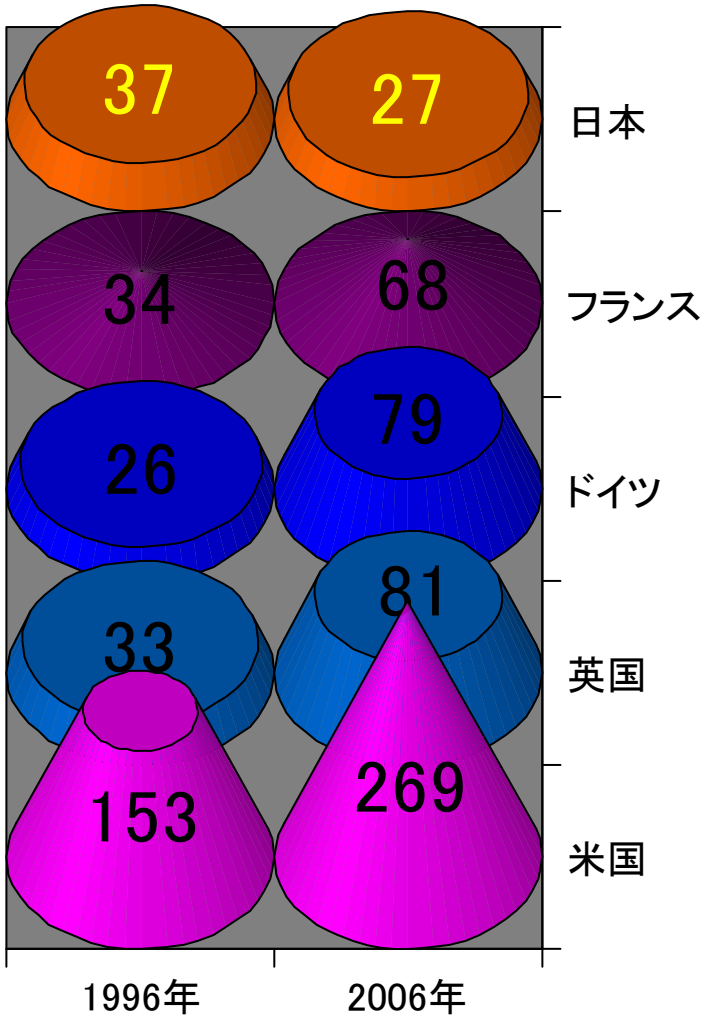
FDAが新規化合物あるいは生物製剤として 1998年から2007年に承認した新薬（252剤）の発見源＜国別・地域別内訳＞



Robert Kneller, Nature Reviews Drug Discovery 9, 867–882, 2010

バイオ医薬品の研究開発の成果が減少傾向

各国のバイオ医薬開発品目数

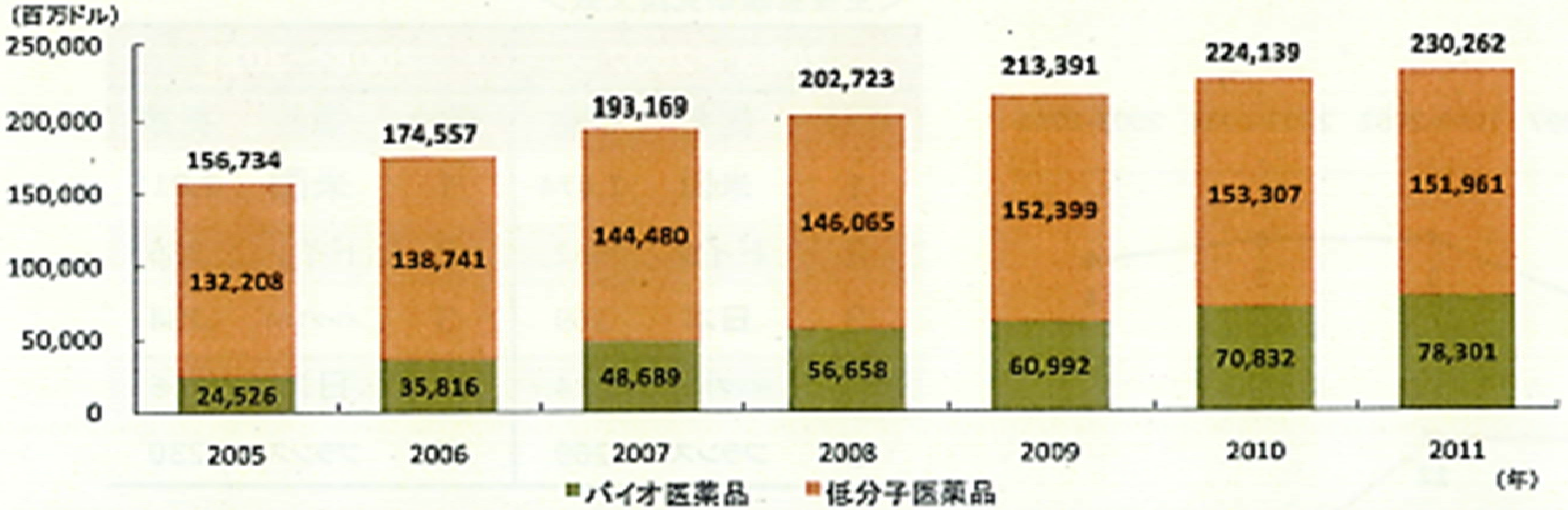


日本製薬医学会

Pharmaprojects,PJB,2007

- **バイオ医薬品の開発目数が減少しており、研究成果を実用化する基盤の強化が必要**

世界の大型医薬品50品目の推移

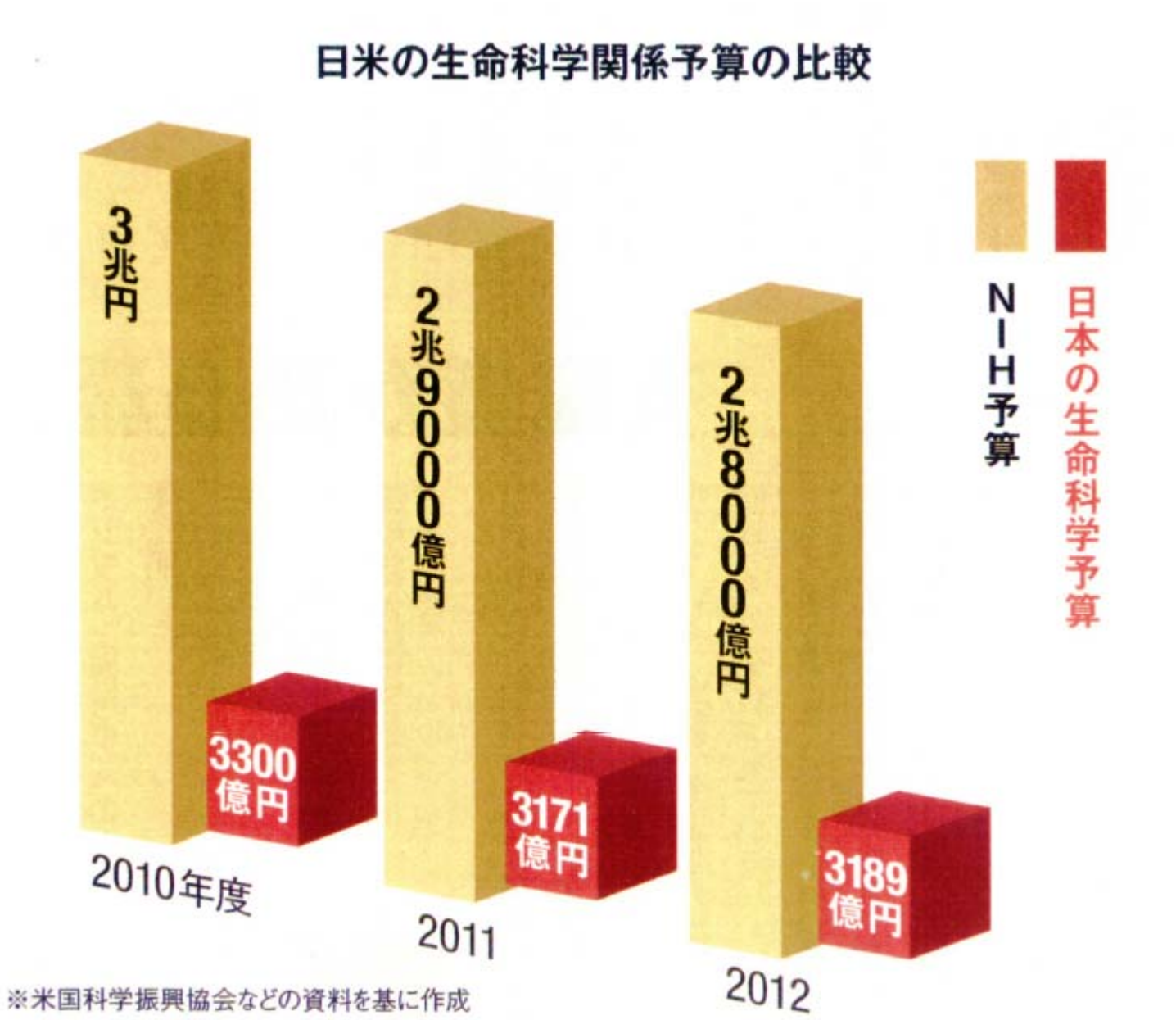


	2005年	2006年	2007年	2008年	2009年	2010年	2011年
バイオ医薬品比率	15.6%	20.5%	25.2%	27.9%	28.6%	31.6%	34.0%
低分子医薬品比率	84.4%	79.5%	74.8%	72.1%	71.4%	68.4%	66.0%
50品目前期比	2.7%	11.4%	10.7%	4.9%	5.3%	5.0%	2.7%
バイオ医薬品前期比率	12.0%	46.0%	35.9%	16.4%	7.6%	16.1%	10.5%
低分子医薬品前期比率	1.2%	4.9%	4.1%	1.1%	4.3%	0.6%	▲0.9%

出典：セジデム・ストラテジックデータ(株)ユート・ブレーン事業部刊「Pharma Future」
（出典：医薬品産業ビジョン2013）

Japan Gets Serious About Creating Its Own NIH

SCIENCE
2013:341,1053



YOMIPACK 2013：医療改革2,32Pより引用

Accelerating Medicines Partnership(NIH)

National Institutes of Health has partnered with 10 drug companies and several nonprofit groups to speed development of biological ways of diagnosing and treating common chronic diseases.

The first diseases targeted by the Accelerating Medicines Partnership are Alzheimer's, type 2 diabetes and two autoimmune disorders, rheumatoid arthritis and lupus.

The partnership will invest more than $230 million over five years on these initial projects. The data and analyses that result will be made available to all biomedical researchers.

SOURCE: U.S. National Institutes of Health, news release, Feb. 4, 2014

日本版NIH-PMDA Collaboration on Regulatory and Translational Science

革新的な医薬品・医療機器等の実用化促進を支援するための共同イニシアチブ

Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation

Sherman,R.E et al

New Engl J Med 2013:369(20),1877-1880

FDA Safety and Innovation Act of 2012 (FDASIA)

1. **This designation can be applied only within the context of a serious or life-threatening disease or condition.**

2. It must be predicated on "preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints".

3. Data from studies in animals or conducted in vitro showing that a drug has promise are not sufficient to justify this designation. Data from clinical trials in humans are needed.

Drugs with Breakthrough-Therapy Designations Announced as of September 30, 2013	
Investigational Drug Designated as Breakthrough Therapy	**Indication**
Ivacaftor	Cystic fibrosis
Ivacaftor–lumacaftor combination	Cystic fibrosis
LDK378	Metastatic non–small-cell lung cancer
Ibrutinib	Mantle-cell lymphoma, Waldenström's macro-globulinemia,chronic lymphocytic leukemia, small lymphocytic lymphoma
Palbociclib	Breast cancer
Lambrolizumab	Advanced melanoma
Daclatasvir–asunaprevir–BMS-791325 triple combination	Chronic hepatitis C
SD-101	Epidermolysis bullosa
Daratumumab	Multiple myeloma

Sherman,R.E et al

New Engl J Med 2013:369(20),1878 Table-1

Drugs with Breakthrough-Therapy Designations Announced as of September 30, 2013.	
Investigational Drug Designated as Breakthrough Therapy	**Indication**
ABT-450/r–ABT-267–ABT-333 triple Combination	Genotype 1 hepatitis C
Obinutuzumab	Chronic lymphocytic leukemia
Sebelipase alfa	Lysosomal acid lipase deficiency
Asfotase alfa	Hypophosphatasia
Serelaxin	Acute heart failure
Drisapersen	Duchenne's muscular dystrophy
Sofosbuvir–ledipasvir combination	Hepatitis C
Bimagrumab	Sporadic inclusion-body myositis
Amifampridine phosphate	Lambert–Eaton myasthenic syndrome
Entinostat	Advanced breast cancer
Ofatumumab	Chronic lymphocytic leukemia
Volasertib	Acute myeloid leukemia
Alectinib	Advanced non–small-cell lung cancer

Sherman,R.E et al New Engl J Med 2013:369(20),1878 Table-1

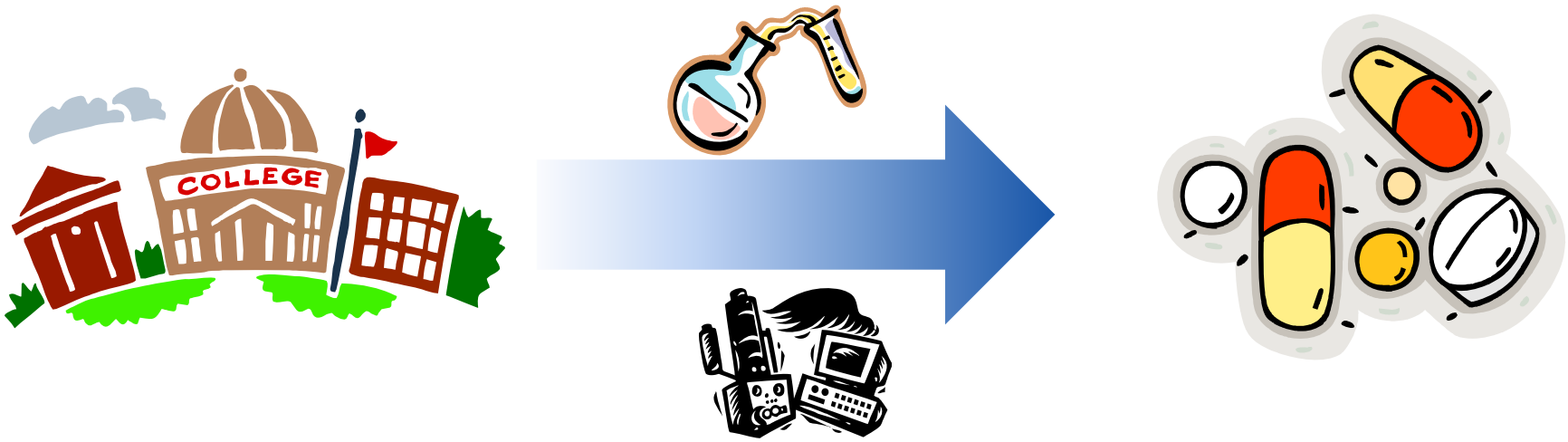
Once a drug is designated as a breakthrough therapy,
the FDA commits to working particularly closely with the drug sponsor to devise the most efficient pathway for generating additional evidence needed about safety and efficacy.

Sherman,R.E et al New Engl J Med 2013:369(20),1878


December13,2013
東京大学トランスレーショナル・
リサーチ・イニシアティブ
第４回シンポジウム

トランスレーショナル・リサーチに関して今後大学に期待すること

- 革新的なシーズを生み出すための医学、薬学、工学等の分野融合の取組の一層の促進
- 適切なタイミング、適切な範囲の知的財産の確保
- 革新的なシーズを継続的に実用化するための質の高い臨床研究・治験体制の整備



臨床研究中核病院整備事業等の選定施設について

早期・探索的臨床試験拠点

（平成23年度から5か所を整備）

＊ヒトに初めて新規薬物・機器を投与・使用する臨床研究を世界に先駆けて行う拠点

- ●国立がん研究センター
  （医薬品/がん分野）
- ●大阪大学医学部附属病院
  （医薬品/脳・心血管分野）
- ●国立循環器病研究センター
  （医療機器/脳・心血管分野）
- ●東京大学医学部附属病院
  （医薬品/精神・神経分野）
- ●慶應義塾大学病院
  （医薬品/免疫難病分野）

（平成23年7月採択）

臨床研究中核病院

（平成24年度から5か所・平成25年度から5か所を整備）

＊国際水準（ＩＣＨ-ＧＣＰ準拠）の臨床研究や医師主導治験の中心的役割を担う拠点

（平成24年度選定施設）

- ● 北海道大学病院
- ● 千葉大学医学部附属病院
- ● 名古屋大学医学部附属病院
- ● 京都大学医学部附属病院
- ● 九州大学病院

（平成24年5月採択）

（平成25年度選定施設）

- ● 東北大学病院
- ● 群馬大学医学部附属病院
- ● 国立成育医療研究センター
- ● 国立病院機構 名古屋医療センター
- ● 岡山大学病院

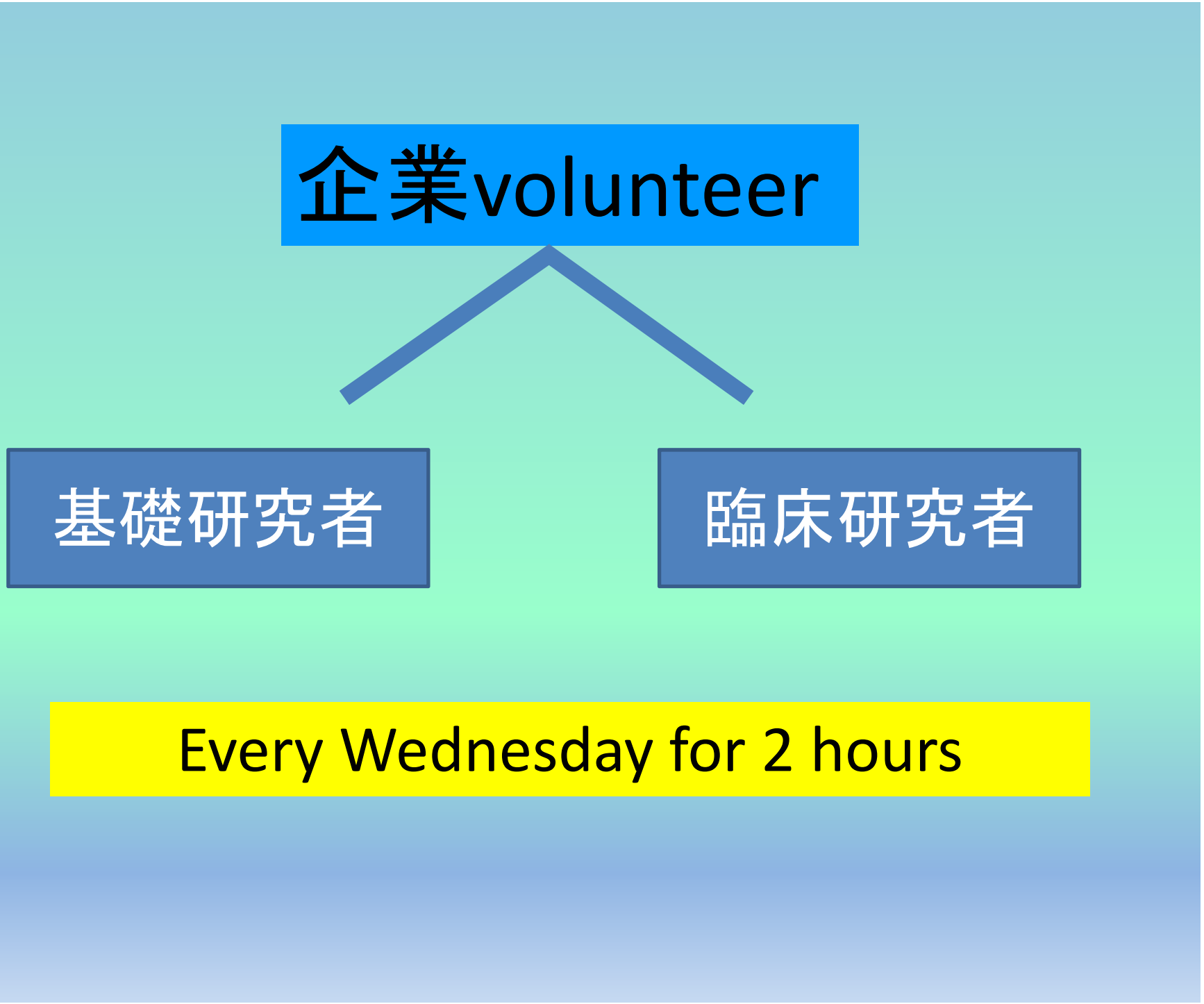
（平成25年4月採択）

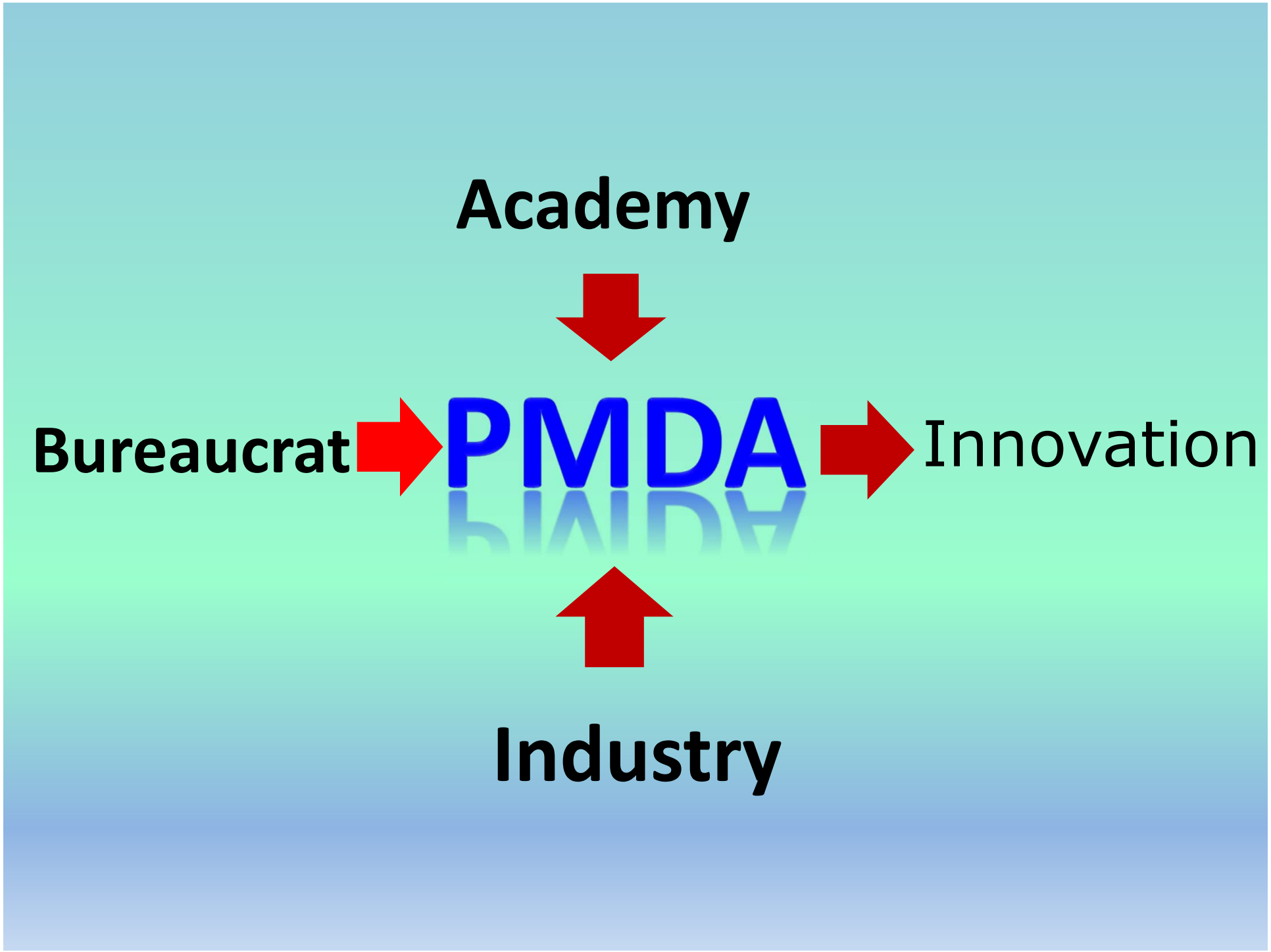
SPARK

AT STANFORD

Daria Mochly-Rosen
Department of Chemical & Systems Biology

An Expanded Role for Drug Development in Academia


企業volunteer
基礎研究者
臨床研究者
Every Wednesday for 2 hours


Academy
Bureaucrat
PMDA
Innovation
Industry

以上で講演を終わらせていただきます。
御静聴ありがとうございました。

日本医学会　会長
自治医科大学 名誉学長　　髙　久　史　麿

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