BIO NEWS

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1．腸内微生物を操作して癌の免疫療法の有効性を高める可能性について -マウス実験

2018 年 4 月 2 日

ペンシルベニア大学医学部ペレルマン校の新しい研究によると、胃腸管における細菌組成が、どの難治性の癌患者が個人化された細胞療法から最も利益を受けるか予測する手がかりを握っている可能性がある、としている。
Journal of Clinical Investigation 誌の報告によると、研究者らは、癌を有するマウスにおける養子 T 細胞療法（ACT - adoptive T cell therapy）の有効性が生来の腸内細菌の構成の相違や抗生物質の治療によって多いに影響を受けることを発見し、更に再発性のクロストリジウム・ディフィシル腸炎の治療で近年益々使用されている糞便移植においても、異なるげっ歯類系統間で ACT の有効性に影響を及ぼすことを発見した。
彼らの実験では、異なる微生物群を保有する異なるベンダーから得たマウス（各グループは遺伝的に同一のマウス）で ACT を行い、その結果は同一ではなかった。このベンダーは Jackson Laboratory と Harlan Laboratories で、Harlan からのマウスは Jackson からのマウスと比較してはるかに強い抗腫瘍効果を示した、としている。
また、腸内細菌と ACT の有効性の関係を更に明らかにするために、Jackson マウスの糞便中の微生物を Harlan マウスに移植したところ、Harlan マウスが Jackson マウスの抗腫瘍応答および腫瘍増殖をコピーすることも発見した。
この知見は、ACT の抗腫瘍効果において、腸内微生物叢が果たす役割を実証するものだ、と結論している。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180402171038.htm

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Potential of manipulating gut microbiome to boost efficacy of cancer immunotherapies

Date:

April 2, 2018

Source:

University of Pennsylvania School of Medicine

Summary:

The composition of bacteria in the gastrointestinal tract may hold clues to help predict which cancer patients are most apt to benefit from the personalized cellular therapies that have shown unprecedented promise in the fight against hard-to-treat cancers.

FULL STORY

The composition of bacteria in the gastrointestinal tract may hold clues to help predict which cancer patients are most apt to benefit from the personalized cellular therapies that have shown unprecedented promise in the fight against hard-to-treat cancers, according to new research from the Perelman School of Medicine at the University of Pennsylvania.

Reporting in the *Journal of Clinical Investigation Insights*, a team led by senior author Andrea Facciabene, PhD, a research assistant professor of Radiation Oncology and Obstetrics/Gynecology, found that the effectiveness of adoptive T cell therapy (ACT) in mice with cancer is significantly affected by differences in the natural makeup of gut bacteria and treatment with antibiotics. The team also found that the use of fecal transplants -- which are increasingly used for treating recurrent C. difficile colitis -- affected the efficacy of ACT between different strains of lab rodents. ACT enlists a patient's own immune system to fight diseases, such as cancer and certain infections. T cells are collected from a patient and grown in the lab to increase the number of tumor-killing T cells. . The pumped-up cells are then given back to the patient as reinforcements to the body's natural anti-tumor immune response.

Experiments performed by coauthor Mireia Uribe-Herranz, PhD, a research associate in Facciabene's lab, demonstrate that when ACT was performed on genetically identical animals obtained from different vendors (Jackson Laboratory or Harlan Laboratories), which carry different microbiota, impact of the therapy was not identical. Animals obtained from Harlan showed a much stronger anti-tumor effect compared to animals from Jackson.

Depletion of gram-positive bacteria within the gut, using an antibiotic called vancomycin, also increased the efficacy of the therapy, improving the anti-tumor response and overall remission rate in less-responsive mice. The beneficial responses were associated with an increase in systemic dendritic cells, which in turn increased the expression of interleukin 12 (IL-12), which sustained expansion and anti-tumor effects of transferred T cells.

To define a relationship between gut bacteria and the efficacy of ACT, the researchers transplanted fecal microbiota from Jackson mice to Harlan mice. They found that Harlan mice transplanted with Jackson microbiota copied the anti-tumor response and tumor growth of Jackson mice.

"This means that the microbiota-dependent response to ACT was successfully transferred between mice, and that modulation with specific antibiotics can be used to increase ACT efficacy," Facciabene said, confirming that this technique could be applied to control gut microbiome populations and improve ACT. Collectively, the findings demonstrate an important role played by the gut microbiota in the antitumor effectiveness of ACT.

This research was supported by Be the Difference Foundation, Teal Tea Foundation, and the Pennsylvania Department of Health.

Story Source:

Materials provided by **University of Pennsylvania School of Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Mireia Uribe-Herranz, Kyle Bittinger, Stavros Rafail, Sonia Guedan, Stefano Pierini, Ceylan Tanes, Alex Ganetsky, Mark A. Morgan, Saar Gill, Janos L. Tanyi, Frederic D. Bushman, Carl H. June, Andrea Facciabene. **Gut microbiota modulates adoptive cell therapy via CD8α dendritic cells and IL-12**. *JCI Insight*, 2018; 3 (4) DOI: 10.1172/jci.insight.94952

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2. 筋肉が酸素消費を調整する方法 -マウス実験

2018 年 4 月 3 日

科学雑誌 *Cell Metabolism* に掲載されているスウェーデンのカロリンスカ研究所による新しい研究で、FIH という酵素が、筋肉がどのように酸素を消費するか決定すること、この酵素がなければ運動中に酸素の必要性が増すこと、が示されている。
運動すると酸素のレベルが特定の範囲の値に下がるまで筋肉が酸素を消費してエネルギーを生成する。引き続き無酸素性代謝プロセスによってエネルギーが生成されるが、これは乳酸の生産をもたらし、疲れや痙攣を引き起こす。この研究で、研究者らは酵素 FIH (Factor Inhibiting HIF) がこの切り替えが起こるためのカギになっていることを、酵素の産生を遮断されたマウスを使用して実証している：筋肉に FIH を欠くマウスは運動時に通常より多くの酸素を必要とした。
FIH は 10 年以上前に発見されたが、今までその正確な機能は理解されていなかった。FIH は身体のどの部分よりも筋肉に 50~100 倍豊富である。この知見は、新陳代謝に影響を及ぼす薬剤に対して新しい道を開くことができる、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180403124046.htm

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How muscles regulate their oxygen consumption

Date:

April 3, 2018

Source:

Karolinska Institutet

Summary:

A new study shows that an enzyme called FIH determines how muscles consume oxygen. Without the enzyme, the need for oxygen increases during physical exercise. The finding is of potential significance to elite athletes, who have been found to have higher levels of FIH in their muscles than others.

FULL STORY

A new study by researchers from Karolinska Institutet in Sweden shows that an enzyme called FIH determines how muscles consume oxygen. Without the enzyme, the need for oxygen increases during physical exercise. The finding is of potential significance to elite athletes, who have been found to have higher levels of FIH in their muscles than others. The study is published in the scientific journal *Cell Metabolism*.

When you exercise, your muscles consume oxygen to produce energy, until the level of oxygen drops below a particular threshold. Subsequently, energy is generated by the process of anaerobic metabolism, which does not require oxygen. However, this leads to the production of lactic acid and eventually exhaustion and cramping. In a new study, researchers demonstrate that the enzyme FIH (Factor Inhibiting HIF) is a key to how this switch-over happens.

"We've discovered that the muscles regulate oxygen consumption in a very precise way using the oxygen-sensitive enzyme FIH," says principle investigator Professor Randall Johnson at the Department of Cell and Molecular Biology, Karolinska Institutet. "The enzyme makes sure that the muscles can use a more effective oxygen-based metabolism for as long as possible and then promotes a very quick transition to anaerobic metabolism."

Using mice in which the production of the enzyme was blocked, the researchers found that mice lacking FIH in their muscles require more oxygen than normal when exercising.

"We were able to show that without FIH, the muscles use much more oxygen than is otherwise the case," says Professor Johnson. "This could be of great significance to elite athletes, who, according to an earlier study of ours, have uncommonly high levels of muscular FIH."

FIH was discovered over ten years ago, but until now no one has understood its exact function. FIH is found in all the body's cells and tissues, but is 50 to 100 times more abundant in the muscles than in any other part of the body. The findings can now open the way for new forms of metabolism-affecting drugs.

"No one's entertained the idea of developing a drug that affects FIH before, but I think our study will lead to greater examination of that possibility," says Professor Johnson. "Here you're able to affect the metabolism itself, perhaps mainly in the muscles, but possibly in other parts of the body too. This can be important in other contexts, such as diabetes and obesity."

Story Source:

Materials provided by **Karolinska Institutet**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Jingwei Sim, Andrew S. Cowburn, Asis Palazon, Basetti Madhu, Petros A. Tyrakis, David Macías, David M. Bargiela, Sandra Pietsch, Michael Gralla, Colin E. Evans, Thaksaon Kittipassorn, Yu C.J. Chey, Cristina M. Branco, Helene Rundqvist, Daniel J. Peet, Randall S. Johnson. **The Factor Inhibiting HIF Asparaginyl Hydroxylase Regulates Oxidative Metabolism and Accelerates Metabolic Adaptation to Hypoxia**. *Cell Metabolism*, 2018; 27 (4): 898 DOI: 10.1016/j.cmet.2018.02.020

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Karolinska Institutet. "How muscles regulate their oxygen consumption." ScienceDaily. ScienceDaily, 3 April 2018. <www.sciencedaily.com/releases/2018/04/180403124046.htm>.

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3. ヒト脳細胞におけるアルツハイマー病の遺伝的危険因子を修正

2018 年 4 月 9 日

サンフランシスコのグラッドストーン研究所の研究者らは、ヒトの脳細胞を用いて、アルツハイマー病の主要な遺伝的危険因子とされる apoE4 と呼ばれる遺伝子の原因およびその潜在的解決策を発見し、*Nature Medicine* 誌に発表した。
遺伝子の最も一般的なバージョンである apoE3 遺伝子と比較した場合、apoE4 遺伝子のコピーを 1 つ保有することによって、アルツハイマー病発症の可能性は 2 倍以上に、2 つ保有すればそのリスクは 12 倍増加するとされているが、この apoE4 が脳細胞に与える影響については不明であった。
この研究では、apoE4 がヒト脳細胞においてどのようにアルツハイマー病リスクを与えるのかが明らかにされているばかりではなく、apoE4 を小さな分子で apoE3 様のバージョンに変更することで apoE4 によって引き起こされるダメージを消滅させることができた、としている。
特筆すべきことは、ほとんどのアルツハイマー病の研究および薬物開発は、この病気のマウスモデルで行われているが、最近では、臨床試験の失敗から他のモデルに移行する傾向にある。この研究においても、研究者らはヒト細胞を使って病気をモデル化し、新薬を試験するとしている。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180409112559.htm

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Scientists fix genetic risk factor for Alzheimer's disease in human brain cells

New insights into how a gene causes damage could impact future drug development

Date:

April 9, 2018

Source:

Gladstone Institutes

Summary:

Researchers have revealed how apoE4 confers its risk for Alzheimer's disease in human brain cells. What's more, they were able to erase the damage caused by apoE4 by changing it, with a small molecule, into a harmless apoE3-like version.

FULL STORY

Using human brain cells, scientists at the Gladstone Institutes discovered the cause of -- and a potential solution for -- the primary genetic risk factor for Alzheimer's disease, a gene called apoE4.

Having one copy of the apoE4 gene more than doubles a person's likelihood of developing Alzheimer's disease, and having two copies of the gene increases the risk by 12-fold, as compared to the most common version of the gene, apoE3.

The apoE4 gene creates a protein of the same name. The apoE4 protein differs from the apoE3 protein at only one point, but that single change is enough to alter its main structure and, thus, its function. Scientists have been unclear about why apoE4 is so much more damaging to brain cells than other versions of the protein.

In a new study published in *Nature Medicine*, researchers revealed how apoE4 confers its risk for Alzheimer's disease in human brain cells. What's more, they were able to erase the damage caused by apoE4 by changing it, with a small molecule, into a harmless apoE3-like version.

A Better Model

Most Alzheimer's research and drug development are done in mouse models of the disease. However, a succession of clinical trial failures has spurred scientists to turn to other models.

"Drug development for Alzheimer's disease has been largely a disappointment over the past 10 years," says lead author Yadong Huang, MD, PhD, a senior investigator and director of the Center for Translational Advancement at Gladstone. "Many drugs work beautifully in a mouse model, but so far they've all failed in clinical trials. One concern within the field has been how poorly these mouse models really mimic human disease."

Instead, Huang decided to use human cells to model the disease and test new drugs. Thanks to induced pluripotent stem cell technology, his team was able to examine, for the first time, the effect of apoE4 on human brain cells. To do so, the researchers created neurons from skin cells donated by Alzheimer's patients with two copies of the apoE4 gene, as well as from healthy individuals who had two copies of the apoE3 gene.

The researchers confirmed that, in human neurons, the misshapen apoE4 protein cannot function properly and is broken down into disease-causing fragments in the cells. This process results in a number of problems commonly found in Alzheimer's disease, including the accumulation of the protein tau and of amyloid peptides.

Notably, the presence of apoE4 does not change the production of amyloid beta in mouse neurons. But in human cells, scientists noticed apoE4 has a very clear effect on increasing amyloid beta production, which highlights the species difference in the way apoE4 controls amyloid beta metabolism.

"There's an important species difference in the effect of apoE4 on amyloid beta," says Chengzhong Wang, PhD, the first author on the paper and former research scientist at Gladstone. "Increased amyloid beta production is not seen in mouse neurons and could potentially explain some of the discrepancies between mice and humans regarding drug efficacy. This will be very important information for future drug development."

Fixing a Toxic Protein

Once the scientists confirmed that apoE4 does, indeed, cause damage in human cells related to Alzheimer's disease, a key question remained: how does the presence of apoE4 lead to cell damage? Is the presence of apoE4 resulting in a loss of normal apoE3 function, or does the addition of apoE4 cause the toxic effects?

"It's fundamentally important to address this question because it changes how you treat the problem," explains Huang, who is also a professor of neurology and pathology at UC San Francisco. "If the damage is caused due to the loss of a protein's function, you would want to increase protein

levels to supplement those functions. But if the accumulation of a protein leads to a toxic function, you want to lower production of the protein to block its detrimental effect."

To answer this question, the researchers examined brain cells that did not produce either form of the apoE protein, and the neurons looked and functioned just like cells with apoE3. However, if the researchers added apoE4, the cells became riddled with pathologies related to Alzheimer's disease. This discovery indicates that the presence of apoE4 -- and not the absence of apoE3 -- promotes the disease.

Finally, the researchers looked for ways to repair the abnormalities caused by apoE4. In earlier work, Huang and his collaborators developed a class of compounds that can change the structure of the harmful apoE4 protein so it resembles the innocuous apoE3 protein, referred to as apoE4 "structure correctors."

Treating human apoE4 neurons with a structure corrector eliminated the signs of Alzheimer's disease, restored normal function to the cells, and improved cell survival. Huang is now working with his collaborators in academia and the pharmaceutical industry to improve the compounds so they can be tested in human patients in the future.

Story Source:

Materials provided by **Gladstone Institutes**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Chengzhong Wang, Ramsey Najm, Qin Xu, Dah-eun Jeong, David Walker, Maureen E. Balestra, Seo Yeon Yoon, Heidi Yuan, Gang Li, Zachary A. Miller, Bruce L. Miller, Mary J. Malloy & Yadong Huang. **Gain of toxic Apolipoprotein E4 effects in Human iPSC-Derived Neurons Is Ameliorated by a Small-Molecule Structure Corrector**. *Nature Medicine*, 2018 DOI: 10.1038/s41591-018-0004-z

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- APA
- Chicago

Gladstone Institutes. "Scientists fix genetic risk factor for Alzheimer's disease in human brain cells: New insights into how a gene causes damage could impact future drug development." ScienceDaily. ScienceDaily, 9 April 2018. <www.sciencedaily.com/releases/2018/04/180409112559.htm>.

目次に戻る

４．脂肪組織が癌腫瘍にエネルギーを分流させる方法 -マウス実験

2018 年 4 月 9 日

肥満は癌の大きな原因であり、ヒトの健康に対する最大の脅威の一つとされている。しかし、全身の代謝が癌腫瘍形成にどのように影響しているかははっきりしていない。特に脂肪細胞が腫瘍組織と連携する分子メカニズムは、未だに理解されていない。
Sanford-Burnham Prebys メディカルディスカバリー研究所（SBP）の研究者らは、脂肪細胞における p62 と呼ばれるたんぱく質の不活性化が、マウスの攻撃的な転移性前立腺癌を助長することを明らかにし、*Cancer Cell* 誌に報告した。この発見は、広範囲の癌治療のために現在使用されている mTOR 阻害剤が脂肪組織の代謝を停止させ、腫瘍増殖促進という意図しない結果をもたらしている可能性があることを示唆している。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180409120445.htm

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How fat tissue shunts energy to tumors

The loss of p62 curtails energy-consuming activities in fat cells, leaving more nutrients available for tumor growth

Date:

April 9, 2018

Source:

Sanford-Burnham Prebys Medical Discovery Institute

Summary:

Researchers recently discovered that that inactivation of a protein called p62 in fat cells fuels aggressive, metastatic prostate cancer in mice. The findings suggest that mTOR inhibitors currently used to treat a wide range of cancers may have the unintended consequence of shutting down fat tissue metabolism and fueling tumor growth.

FULL STORY

Obesity is the second-leading preventable cause of cancer and represents one of the greatest threats to global human health. But it has not been clear exactly how whole-body metabolism affects tumor formation. In particular, the molecular mechanisms by which fat cells communicate with tumor tissue remain poorly understood.

Sanford Prebys Medical Discovery Institute (SBP) researchers recently addressed this question, revealing that inactivation of a protein called p62 in fat cells fuels aggressive, metastatic prostate cancer in mice. As reported in *Cancer Cell*, p62 deficiency triggers a shutdown of energy-consuming processes in fat tissue, thereby increasing the availability of nutrients for cancer cells.

"This work could lead to better therapies that consider cancer not just as a genetic or cellular disease, but as a whole-body process where tumors communicate with metabolic organs to maintain their unlimited appetite for nutrients," says co-senior study author Maria Diaz-Meco, Ph.D., a professor in the Cancer Metabolism and Signaling Networks Program at SBP. "This is a vulnerability that can be targeted therapeutically."

Diverting energy

Prostate cancer is the second-leading cause of cancer death among men in the United States, and obesity is a major risk factor for the progression and aggressiveness of this disease. But the underlying molecular mechanisms have remained unclear, in part due to the limitations of mouse models of obesity, which have not allowed researchers to study the specific crosstalk between fat cells and tumor tissue independently of dietary factors.

"Most of the studies addressing the role of adiposity and obesity in cancer use mice fed a high-fat diet," says co-senior study author Jorge Moscat, Ph.D., director and professor of the Cancer Metabolism and Signaling Networks Program at SBP. "Although this mimics some of the situations in patients, it prevents a real understanding of the signaling pathways that control the bidirectional communication between tumors and adipocytes, or fat cells. This is essential if we want to identify therapeutic targets that can be harnessed to prevent the pro-tumorigenic signals emanating from the adipose tissue."

To address this problem, Diaz-Meco and Moscat turned to a mouse model of obesity they previously helped to develop. These mice specifically lack p62 in fat cells, leading to increased adiposity and metabolic problems without altering food intake. In the new study, the researchers reveal a central role of p62 in fat tissue-tumor communication, which supports cancer metabolic fitness.

Specifically, they found that p62 deficiency in fat cells promotes the progression and metastasis of prostate cancer in mice by inhibiting a protein complex called mTORC1. The tumors suppress energy-consuming activities such as fat cell development, a metabolic process called oxidative phosphorylation, and fatty acid metabolism in white fat tissue. As a result, more fatty acids and other nutrients are available to support tumor growth. "This metabolic reprograming orchestrated by the loss of p62 in adipocytes appears to help tumors cope with the high-energy demands of an aggressive cancer," Diaz-Meco says.

Additional experiments showed that p62 deficiency in fat tissue promotes the synthesis of proteins called osteopontin and Cpt1a, which are critical for prostate cancer proliferation, migration and invasion. These findings are clinically relevant because high levels of osteopontin and Cpt1a are associated with aggressive, metastatic castration-resistant prostate cancer in humans. "The significance is huge because we identify a new set of therapeutic targets that, if modulated, should block the ability of activated adipose tissue to promote tumor malignancy," Moscat says.

Beyond genetics

According to the authors, the findings suggest that mTOR inhibitors currently used to treat a wide range of cancers may have the unintended consequence of shutting down fat tissue metabolism and fueling tumor growth, at least under certain circumstances. But this possibility needs to be evaluated in future studies. For their own part, the authors plan to further investigate the p62 signaling pathway in patients and identify druggable targets that could be evaluated for their therapeutic potential.

"We need to consider other aspects of cancer therapeutics beyond the better-known genetics," Diaz-Meco says. "That is, we need to invest more in the research of cancer metabolism, which deals with the identification of metabolic vulnerabilities that should be common to all types of cancers.

This will ultimately lead to better therapies that are less susceptible to resistance, which is an all-too-common problem in oncogene-target approaches."

Story Source:

Materials provided by **Sanford-Burnham Prebys Medical Discovery Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Jianfeng Huang, Angeles Duran, Miguel Reina-Campos, Tania Valencia, Elias A. Castilla, Timo D. Müller, Matthias H. Tschöp, Jorge Moscat, Maria T. Diaz-Meco. **Adipocyte p62/SQSTM1 Suppresses Tumorigenesis through Opposite Regulations of Metabolism in Adipose Tissue and Tumor**. *Cancer Cell*, 2018; 33 (4): 770 DOI: 10.1016/j.ccell.2018.03.001

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- MLA
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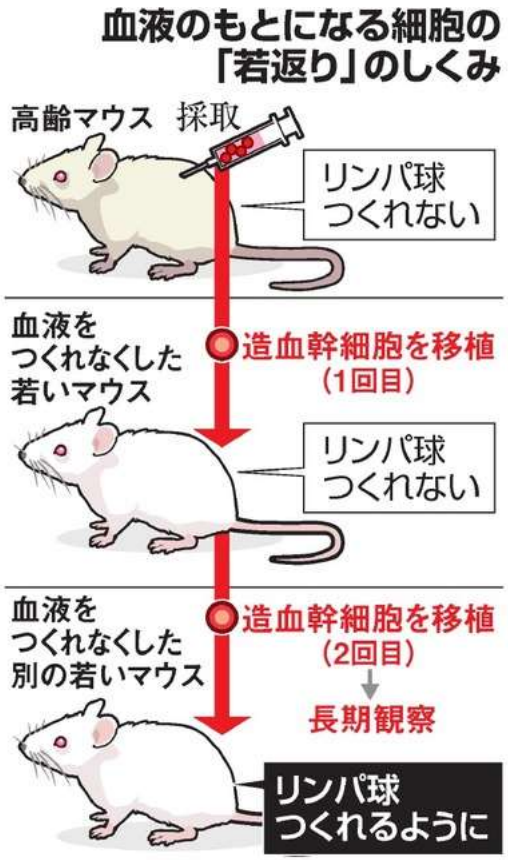
Sanford-Burnham Prebys Medical Discovery Institute. "How fat tissue shunts energy to tumors: The loss of p62 curtails energy-consuming activities in fat cells, leaving more nutrients available for tumor growth." ScienceDaily. ScienceDaily, 9 April 2018. <www.sciencedaily.com/releases/2018/04/180409120445.htm>.

目次に戻る

5．老いた細胞、若いマウス移植後「若返り」

2018 年 4 月 15 日



https://www.asahi.com/articles/photo/AS20180413004216.html

加齢によって白血球の一種になる能力を失った血液のもとになる細胞を、若いマウスに移植すると、その能力を取り戻したとする研究成果を、東京大と米スタンフォード大の共同研究チームが発表した。チームは、仕組みを解明できれば、血液細胞を若返らせ、免疫機能の回復につながる可能性があるとしている。今月、米科学誌セル・ステムセルに掲載された。

血液中の赤血球や白血球などは骨髄にある造血幹細胞から作られる。加齢により、白血球の一部で免疫をつかさどるリンパ球をつくる能力は落ちることが知られてきた。

東京大学幹細胞治療部門の中内啓光特任教授らの研究チームは、生後２０～２４カ月の高齢マウスの骨髄から造血幹細胞を採り、血液をつくれなくした別の若いマウスに移植した。

高齢マウスの造血幹細胞を移植したマウスは、リンパ球をほぼつくれなかった。しかし、そのマウスの造血幹細胞を含む骨髄を別の若いマウスに移植し、観察を続けたところ、造血幹細胞がリンパ球になる能力を持ったことを確認した。

１回目でなく２回目の移植で能力を持った理由は解明されておらず、今後の課題という。研究チームの一員、スタンフォード大の山本玲研究員は「リンパ球になる能力が回復したことは細胞の『若返り』を示唆している。加齢メカニズムの解明につながる」としている。（戸田政考）

記事：

朝日新聞 DIGITAL

https://www.asahi.com/articles/ASL4D4DKBL4DULBJ007.html

目次に戻る

6. 免疫細胞を変化させることによって小児脳腫瘍を消滅 -マウス実験

2018 年 4 月 16 日

4 月 16 日の *Nature Medicine* 誌のオンライン版に掲載されたスタンフォード大学医学部の研究では、エンジニアリングされたヒト免疫細胞によって、マウスモデルで致命的な小児脳腫瘍を消滅させることができることが実証されている。
重度の脳幹癌である脳幹グリオーマ (DIPG –diffuse intrinsic pontine glioma) は、毎年数百人の就学年齢の子供が罹り、その生存期間中央値はわずか 10 か月、その治療法はない、とされている。
この研究では、脳幹にヒト DIPG が移植されたマウスで、キメラ抗原受容体 T 細胞 (CAR-T 細胞) として知られているエンジニアリングされた免疫細胞によって腫瘍を排除でき、残存する癌細胞もほとんど残らなかった、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180416121624.htm

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Altered immune cells clear childhood brain tumor in mice

Date:

April 16, 2018

Source:

Stanford Medicine

Summary:

In mice, a fatal brainstem tumor was cleared by injecting it with engineered T cells that recognized the cancer and targeted it for destruction. The discovery is moving to human trials.

FULL STORY

Engineered human immune cells can vanquish a deadly pediatric brain tumor in a mouse model, a study from the Stanford University School of Medicine has demonstrated.

The study, published online April 16 in *Nature Medicine*, represents the first time a severe brainstem cancer, diffuse intrinsic pontine glioma, has been eradicated in mice with the tumor. DIPG affects a few hundred school-age children across the country each year and has a median survival time of only 10 months; there is no cure. In mice whose brainstems were implanted with human DIPG, engineered immune cells known as chimeric antigen receptor T cells -- or CAR-T cells -- were able to eliminate tumors, leaving very few residual cancer cells.

"I was pleasantly surprised with how well this worked," said Michelle Monje, MD, PhD, assistant professor of neurology and a senior author of the study. "We gave CAR-T cells intravenously, and they tracked to the brain and cleared the tumor. It was a dramatically more marked response than I would have anticipated."

When the brains of the mice were examined via immunostaining after treatment, the animals had, on average, a few dozen cancer cells left, compared with tens of thousands of cancer cells in animals that received a control treatment.

"As a cancer immunotherapist, what gets me really excited is when you take an established tumor and you make it disappear," said Crystal Mackall, MD, professor of pediatrics and of medicine and the study's other senior author. "In animal studies, we can often slow the growth of a tumor, shrink a tumor or prevent tumors from forming. But it isn't so often that we take a tumor that's established and eradicate it -- and that's what you want in the clinic."

However, some mice experienced dangerous levels of brain swelling, a side effect of the immune response triggered by the engineered cells, the researchers said, adding that extreme caution will be needed to introduce the approach in human clinical trials.

'Hiding in plain sight'

To begin the research, the scientists screened human DIPG tumor cultures for surface molecules that could act as targets for CAR-T cells. In CAR-T therapies now used in humans, some of the patient's own immune cells are removed, engineered to attack a surface antigen on the cancer cells, and returned to the patient's body, where they target the cancer cells for destruction. Cell surface antigens are large molecules sticking out from a cell that help the immune system determine whether the cell is harmless or harmful.

Monje's team identified a sugar molecule, GD2, which is abundant on the surface of DIPG tumors in 80 percent of cases. Excess expression of the sugar is caused by the same mutation that drives the growth of most DIPG tumors, known as the H3K27M mutation, the team found. Scientists have known for decades that GD2 levels on some other forms of cancer are very high, but its discovery on this tumor came as a surprise, Mackall said, adding, "It was hiding in plain sight, and we didn't know."

Mackall's team had already designed a way to make CAR-T cells that attack the GD2 sugar; similar anti-GD2 CAR-T cells are now being tested in clinical trials in a few other cancers. In a dish, Mackall's CAR-T cells killed cultured DIPG cells that carry the H3K27M mutation. If the cultured cells were genetically modified to stop expressing the target sugar, the CAR-T cells no longer worked. Other CAR-T cells that were tuned to different molecular targets also did not kill the DIPG cancer cells.

Next, the team tested the GD2 CAR-T cells in mice whose brainstem was implanted with human DIPG tumors, an experimental system that Monje's lab pioneered. Seven to eight weeks after the tumor was established, each mouse received one intravenous injection of GD2 CAR-T cells or, as a control treatment, an injection of CAR-T cells that react to a different target. The cells are able to cross the blood-brain barrier. In the mice that received GD2 CAR-T cells, the DIPG tumors were undetectable after 14 days, while mice receiving the control treatment had no tumor regression. After 50 days, the animals were euthanized and their brains examined. Using immunostaining, the researchers counted the remaining tumor cells; the mice treated with GD2 CAR-T cells had a few dozen remaining cancer cells per animal, while each control mouse had tens of thousands of cancer cells. In the GD2 CAR-T treated animals, the residual cancer cells did not express GD2, suggesting that these remaining cells were not vulnerable to the immune therapy and might be able to cause the cancer to recur.

Risky to use near thalamus

Gliomas occurring in the spinal cord and thalamus of children also exhibit the H3K27M mutation and were found to similarly express very high levels of GD2. The research team also tried the GD2 CAR-T therapy in mice with human spinal cord and thalamic tumors implanted in their respective anatomical locations. Spinal cord tumors were effectively cleared by the GD2 CAR-T cells. However, some animals with thalamic tumors died from the CAR-T treatment. The inflammatory response generated by the immune cells caused brain swelling, which is particularly risky near the thalamus, a structure buried deep inside the brain, the researchers reported.

"While this strategy is very promising for a disease with few therapeutic options, it's crucially important to keep in mind that these tumors are located in precarious neuroanatomical sites that just do not tolerate much swelling -- and those regions are already expanded by tumors," Monje said. "With any effective clearing of a tumor by the immune system, by definition there is inflammation, which means there will be some degree of swelling. It's a dangerous situation."

The team plans to move the CAR-T treatment into human clinical trials, but will build as many safeguards as possible into the trial to minimize risks to people who participate, Monje said. "I think this is something we can bring to the clinic soon, but it needs to be done very carefully," she said.

"These CAR-T cells are extremely potent," Mackall said, noting that a therapy that uses CAR-T cells to treat pediatric leukemia was approved by the Food and Drug Administration in 2017. "In leukemia, that potency is the reason this has been a transformative therapy, but it is also the major cause for toxicity. It's very difficult to find a cancer medicine that works but doesn't have a down side."

Because the CAR-T cells do not eradicate all cancer cells, the researchers think the immune therapy will need to be combined with other treatments. Monje's team is also studying chemotherapy drugs to treat DIPG.

"I don't think one strategy is going to cure this extremely aggressive and deadly cancer," Monje said. "However, I think CAR-T immunotherapy is part of the puzzle of DIPG treatment in a way that I'm quite hopeful about."

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Story Source:

Materials provided by **Stanford Medicine**. Original written by Erin Digitale. *Note: Content may be edited for style and length.*

Journal Reference:

1. Christopher W. Mount, Robbie G. Majzner, Shree Sundaresh, Evan P. Arnold, Meena Kadapakkam, Samuel Haile, Louai Labanieh, Esther Hulleman, Pamelyn J. Woo, Skyler P. Rietberg, Hannes Vogel, Michelle Monje, Crystal L. Mackall. **Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M diffuse midline gliomas**. *Nature Medicine*, 2018; DOI: 10.1038/s41591-018-0006-x

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Stanford Medicine. "Altered immune cells clear childhood brain tumor in mice." ScienceDaily. ScienceDaily, 16 April 2018. <www.sciencedaily.com/releases/2018/04/180416121624.htm>.

目次に戻る

7. 健康な脳に不可欠な不可解な遺伝子 -マウス実験

2018 年 4 月 16 日

ヒトゲノムが 2001 年に初めて配列決定されて以来、科学者らは、明らかに機能が欠如しているにも拘わらず、細胞によってリボ核酸（RNA）内に作られる DNA の謎に悩まされてきた。基本的な生物学的タスクを担うタンパク質を作るために使用されないのに、どうしてその RNA が作られるのか？このいわゆる非コード RNA は、何か決定的な未知のタスクを担っているのではないだろうか？と。
今回、バース、オックスフォード、エジンバラ大学の科学者らは、若いマウスにおいて、脳がどのように発達するかに影響を及ぼす Paupar と呼ばれる非コード RNA を同定した。彼らは、この研究において Paupar が神経発達を制御するたんぱく質を調整することを示し、*The EMBO Journal* に発表した。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180416121550.htm

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Enigmatic gene critical for a healthy brain

New research has shown how an unusual gene is needed for brain development in young mice

Date:

April 16, 2018

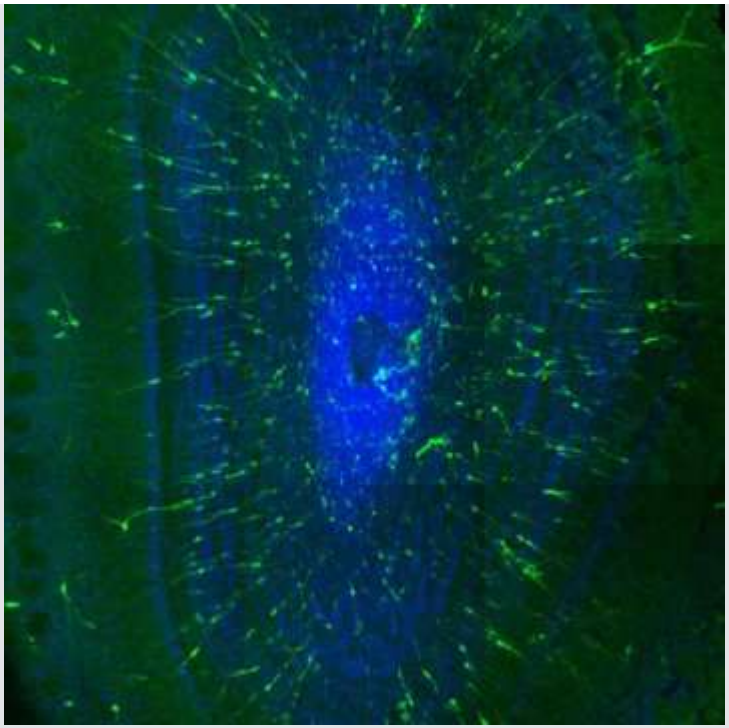
Source:

University of Bath

Summary:

Scientists have identified a non-coding RNA, called Paupar, influences how healthy brains develop during early life. They have shown that Paupar orchestrates proteins that control neurodevelopment.

FULL STORY



A cross section of the mouse olfactory bulb. Green is electroporated neuroblasts born in the sub ventricular zone that migrated into the olfactory bulb. Blue is a DAPI nuclear counterstain.

Credit: Francis Szele

New research has shown how an unusual gene is needed for brain development in young mice.

Since the human genome was first sequenced in 2001, scientists have puzzled over swathes of our DNA that despite apparently lacking function are made into ribonucleic acid (RNA) by the cell. Why make RNA at all when it is not then used to make proteins, which perform fundamental biological tasks? Perhaps these so-called non-coding RNAs perform critical, but as yet unknown, tasks?

Scientists from the Universities of Bath, Oxford and Edinburgh have now identified one such non-coding RNA, called Paupar, which influences how healthy brains develop during early life. They have shown that Paupar orchestrates proteins that control neurodevelopment.

They studied KAP1, a gene that codes for an essential protein associated with several fundamental processes in neurodevelopment. The KAP1 protein acts as a regulator for several other genes which allow the brain to grow healthily and develop several types of brain cell.

Using molecular biology techniques they discovered that Paupar can act as a switch, modulating how KAP1 acts by binding to it- thus influencing the development of healthy brains in mice. It is the first time that a non-coding RNA has been shown to bind to KAP1.

The research is published in *The EMBO Journal*.

Dr Keith Vance, from the University of Bath Department of Biology & Biochemistry led the research. He said: "It is now clear that the genome expresses many non-coding RNAs that are not made into protein. Despite this, there is a lot of controversy regarding their function. Some groups argue that these non-coding RNAs are a result of transcriptional noise with no apparent use whilst others think that the vast majority of them must be doing something important.

"We have shown here good evidence that one of these genes, called Paupar, is important for development of the brain.

"It's a young field, but I think it's clear we have to reassess the central dogma of molecular biology that DNA is transcribed to RNA that codes for a protein. We're now seeing that some RNAs can go off and do something themselves.

"Our findings also help us understand the essential role of KAP1, which is something we're really interested in as we look at the development of the central nervous system."

Story Source:

Materials provided by **University of Bath**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ioanna Pavlaki, Farah Alammari, Bin Sun, Neil Clark, Tamara Sirey, Sheena Lee, Dan J Woodcock, Chris P Ponting, Francis G Szele, Keith W Vance. **The long non-coding RNA Paupar promotes KAP1-dependent chromatin changes and regulates olfactory bulb neurogenesis**. *The EMBO Journal*, 2018; e98219 DOI: 10.15252/embj.201798219

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University of Bath. "Enigmatic gene critical for a healthy brain: New research has shown how an unusual gene is needed for brain development in young mice." ScienceDaily. ScienceDaily, 16 April 2018. <www.sciencedaily.com/releases/2018/04/180416121550.htm>.

目次に戻る

8. 癒えない糖尿病の傷を治療する新たな希望 -マウス研究

2018 年 4 月 22 日

糖尿病の最も不快な合併症の一つは、足あるいは下肢での創傷の発症である。一旦できると数カ月間持続することもあり、痛みを伴う危険な感染症に繋がる。
イェール大学の研究者らによる新しい研究は、糖尿病性傷を維持する特定のタンパク質を同定してその役割を明らかにし、その効果を逆転させることで創傷治癒の助けとなる、と示唆している。
研究者らは、まず糖尿病のマウスモデルにおいて、特定のタンパク質であるトロンボスポンジン 2 (TSP2) が上昇していることを発見、この TSP2 が創傷治癒の遅延に寄与しているかどうか判断するために、マウスモデルから TSP2 を遺伝的に除去し、創傷治癒が改善されたことを観察した。
この研究成果は、4 月 21 - 25 日にサンディエゴで開催される実験生物学会 2018 期間中の米国心臓病学会年次総会で発表される。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180423110825.htm

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New hope for treating diabetic wounds that just won't heal

Mice bred without TSP2 protein heal faster, suggesting a new target for better treatments

Date:

April 23, 2018

Source:

Experimental Biology 2018

Summary:

New research uncovers the role of a particular protein in maintaining diabetic wounds and suggests that reversing its effects could help aid wound healing in patients with diabetes.

FULL STORY

One of the most frustrating and debilitating complications of diabetes is the development of wounds on the foot or lower leg. Once they form, they can persist for months, leading to painful and dangerous infections.

New research uncovers the role of a particular protein in maintaining these wounds and suggests that reversing its effects could help aid wound healing in patients with diabetes.

"We discovered that a specific protein, thrombospondin-2 (TSP2), is elevated in wounds of patients with diabetes as well as in animal models of diabetes," said Britta Kunkemoeller, a doctoral student at Yale University who conducted the study. "To determine whether TSP2 contributes to delayed wound healing, we genetically removed TSP2 from a mouse model of diabetes and observed improved wound healing. Our study shows that TSP2 could be a target for a specific therapy for diabetic wounds."

Kunkemoeller will present the research at the American Society for Investigative Pathology annual meeting during the 2018 Experimental Biology meeting, held April 21-25 in San Diego.

Diabetes currently afflicts nearly 26 million Americans, more than 8 percent of the population. Diabetic wounds are one of many complications of the disease.

Treatment for these wounds is mostly limited to standard wound care, such as moist bandages, removal of damaged tissue and footwear that reduces pressure on the wound. Despite these measures, the wounds often persist. In the most severe cases, it becomes necessary to amputate the affected foot or lower leg; diabetic wounds are the leading cause of amputations in the United States.

Most previous work on wound healing in diabetes has focused on the types of cells that are involved in wound healing such as immune cells, skin cells and the cells that form blood vessels. By contrast, Kunkemoeller's research focuses on TSP2, a component of the extracellular matrix. The extracellular matrix is a meshwork that serves as the structural foundation for cells, like the scaffolding used in construction.

In addition to providing structural support, the extracellular matrix regulates processes that are important to wound healing, including the behavior of immune, skin and vessel-forming cells. TSP2 is a component of the extracellular matrix that influences how the matrix is formed, as well as the development and communication of other types of cells that grow within the matrix.

"Our focus on TSP2 therefore allowed us to study a single molecule that influences several wound-healing related processes," explained Kunkemoeller.

The team bred mice that develop type 2 diabetes but cannot produce TSP2. When the researchers induced wounds in these mice, they found that the mice without TSP2 healed significantly better and faster than other mice that had diabetes along with normal levels of TSP2.

They also analyzed the factors that influence how much TSP2 the body produces. That part of the study revealed that TSP2 production increases when blood sugar levels are higher, explaining why people with diabetes have higher levels of TSP2 than people without diabetes.

"Currently, our lab is developing engineered biomaterials derived from extracellular matrix that lacks TSP2," said Kunkemoeller. "Our plan is to apply such materials to diabetic wounds in mouse models in order to evaluate their efficacy. Going forward, additional research will focus on either preventing the production or inhibiting the function of TSP2 in diabetic wounds."

Story Source:

Materials provided by **Experimental Biology 2018**. *Note: Content may be edited for style and length.*

Cite This Page:

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Experimental Biology 2018. "New hope for treating diabetic wounds that just won't heal: Mice bred without TSP2 protein heal faster, suggesting a new target for better treatments." ScienceDaily. ScienceDaily, 23 April 2018. <www.sciencedaily.com/releases/2018/04/180423110825.htm>.

目次に戻る

9. ヒト加速老化症候群の新たな標的を特定 -マウス研究

2018 年 4 月 27 日

ケンブリッジ大学の科学者らは、早期老化を特徴とする致命的な遺伝的疾患 Hutchinson-Gilford Progeria Syndrome (HGPS) において潜在的な治療標的を同定した。
HGSP は稀な疾患で、患者の平均余命は 15 年とされている。低身長、低体重、脱毛、皮膚肥厚、脂肪蓄積問題、骨粗鬆症、心血管疾患など様々な症状を呈し、典型的には心臓発作で死亡する。
科学者らは、この HGSP のマウスモデルにおいて、酵素 N-アセチルトランスフェラーゼ 10 (NAT10) の化学的阻害又は遺伝的脱調節が、有意な健康および延命をもたらすことを示す前臨床データを、今日の *Nature Communications* 誌で示している。

英文記事：
https://www.sciencedaily.com/releases/2018/04/180427085223.htm

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Mouse study identifies new target for human accelerated aging syndrome

Date:

April 27, 2018

Source:

University of Cambridge

Summary:

Scientists have identified a potential therapeutic target in the devastating genetic disease Hutchinson-Gilford Progeria Syndrome (HGPS), which is characterized by premature aging.

FULL STORY

Scientists from the University of Cambridge have identified a potential therapeutic target in the devastating genetic disease Hutchinson-Gilford Progeria Syndrome (HGPS), which is characterised by premature ageing.

In a paper published today in *Nature Communications*, scientists provide preclinical data showing that chemical inhibition or genetic deregulation of the enzyme N-acetyltransferase 10 (NAT10) leads to significant health and lifespan gains in a mouse model of HGPS.

HGPS is a rare condition: patients have an average life expectancy of around 15 years, suffering a variety of symptoms including short stature, low body weight, hair loss, skin thickening, problems with fat storage, osteoporosis, and cardiovascular disease, typically dying of a heart attack.

The disease arises from specific mutations in the gene for the protein Lamin A, which lead to production of a shorter, dysfunctional protein that accumulates in cells, specifically in the membranes surrounding the nucleus. This causes disorganisation of chromatin (the 'packaging' around DNA), deregulated transcription, accumulation of DNA damage and defective cell proliferation.

By screening candidate molecules for an effect on nuclear membranes in human HGPS patient-derived cells in vitro, the authors have previously identified a small molecule called remodelin as an effective ameliorative agent. They then identified which component of the cells was being affected by remodelin: an enzyme with a variety of cell functions, called NAT10.

Their aim in the new study was to take these findings into a mouse model with the same genetic defect as HGPS patients, to see whether inhibiting NAT10 -- either chemically by administration of remodelin or genetically by engineering reduced production of NAT10 -- could ameliorate the

disease. The results show that these approaches indeed significantly improved the health of the diseased mice, increased their lifespan, and reduced the effects of the HGPS mutation across a variety of measures in body tissues and at the cellular level.

The research was led by Dr Gabriel Balmus from the Wellcome Trust/ Cancer Research UK Gurdon Institute and Dr Delphine Larrieu from the Cambridge Institute for Medical Research, University of Cambridge; and Dr David Adams from the Wellcome Sanger Institute.

Senior author Professor Steve Jackson commented: "We're very excited by the possibility that drugs targeting NAT10 may, in future, be tested on people suffering from HGPS. I like to describe this approach as a 're-balancing towards the healthy state'.

"We first studied the cell biology to understand how the disease affects cells, and then used those findings to identify ways to re-balance the defect at the whole-organism level. Our findings in mice suggest a therapeutic approach to HGPS and other premature ageing diseases."

This study was funded by the Wellcome and the Medical Research Council, and core funding to the Gurdon Institute from the Wellcome and Cancer Research UK.

Story Source:

Journal Reference:

1. Gabriel Balmus, Delphine Larrieu, Ana C. Barros, Casey Collins, Monica Abrudan, Mukerrem Demir, Nicola J. Geisler, Christopher J. Lelliott, Jacqueline K. White, Natasha A. Karp, James Atkinson, Andrea Kirton, Matt Jacobsen, Dean Clift, Raphael Rodriguez, David J. Adams, Stephen P. Jackson. **Targeting of NAT10 enhances healthspan in a mouse model of human accelerated aging syndrome**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/S41467-018-03770-3

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- APA
- Chicago

University of Cambridge. "Mouse study identifies new target for human accelerated aging syndrome." ScienceDaily. ScienceDaily, 27 April 2018. <www.sciencedaily.com/releases/2018/04/180427085223.htm>.

目次に戻る

10. PhoenixBio PXB マウス関連研究論文

株式会社 フェニックスバイオ（本社：広島県広島市鏡山三丁目 4 番 1 号）は、米国ニューヨークとカナダに子会社を持ち、2018 年 3 月現在の資本金は 2,245 百万円。
肝臓の 70%以上がヒト肝細胞に置換された PXB マウスおよびそのマウスを用いた研究の受託サービスを提供している。その内容は主に HBV、HCV などの肝炎ウィルス関連の抗ウィルス薬の薬効評価試験、感染防御試験であるが、どんな研究機関が具体的にどんな研究を行っているか、以下ここ数年にわたる論文を表にまとめてみた。

タグ	研究機関	論文タイトル	研究者	学術誌	年月日	doi
HCV	1 Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA. 2 Division of Pre-Clinical Innovations, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, Maryland, USA.	Preclinical Pharmacological Development of Chlorcyclizine Derivatives for the Treatment of Hepatitis C Virus Infection.	Rolt A1, Le D1, Hu Z1, Wang AQ2, Shah P2, Singleton M2, Hughes E2, Dulcey AE2, He S1, Imamura M3, Uchida T3, Chayama K3, Xu X2, Marugan JJ2, Liang TJ1.	The Journal of Infectious Diseases	1/24/2018	10.1093/infdis/jiy039

	3 Department of Medicine and Molecular Sciences, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan.					
HCV	1 Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, 560012, India. 2 Molecular Biophysics Unit, Indian Institute of Science, Bangalore, 560012, India. 3 Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, 560012, India. Electronic address: sdas@iisc.ac.in.	A natural small molecule inhibitor corilagin blocks HCV replication and modulates oxidative stress to reduce liver damage.	Reddy BU1, Mullick R1, Kumar A1, Sharma G1, Bag P1, Roy CL1, Sudha G2, Tandon H2, Dave P1, Shukla A1, Srinivasan P1, Nandhitha M1, Srinivasan N2, Das S3.	Antiviral Research	2/15/2018	10.1016/j.antiviral.2017.12.004
HBV	1 Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan. 2 Research and Development Center, FUSO Pharmaceutical Industries, Osaka, Japan. 3 Department of Microbiology and Cell Biology,	Investigating the hepatitis B virus life cycle using engineered reporter hepatitis B viruses.	Nishitsuji H1, Harada K1, Ujino S1, Zhang J2, Kohara M3, Sugiyama M1, Mizokami M1, Shimotohno K1.	Cancer Science	1/9/2018	10.1111/cas.13440

	Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan.					
HCV	1 GlaxoSmithKline Research and Development , 5 Moore Drive, Research Triangle Park, North Carolina 27709, United States.	Hepatitis C replication inhibitors that target the viral NS4B protein.	Miller JF1, Chong PY, Shotwell JB, Catalano JG, Tai VW, Fang J, Banka AL, Roberts CD, Youngman M, Zhang H, Xiong Z, Mathis A, Pouliot JJ, Hamatake RK, Price DJ, Seal JW 3rd, Stroup LL, Creech KL, Carballo LH, Todd D, Spaltenstein A, Furst S, Hong Z, Peat AJ.	Journal of Medical Chemistry	3/13/2018	10.1021/jm400125h
	1 Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. Electronic address: sanoh@hiroshima-u.ac.jp. 2 Faculty of Pharmaceutical Science, Hiroshima International University, Hiroshma, Japan. 3 Nihon Pharmaceutical University, Saitama, Japan.	Significance of aldehyde oxidase during drug development: Effects on drug metabolism, pharmacokinetics, toxicity, and efficacy.	Sanoh S1, Tayama Y2, Sugihara K2, Kitamura S3, Ohta S4.	Drug Metabolism and Pharmacokinetics	2015 Feb	10.1016/j.dmpk.2014.10.009

	4 Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.					
HBV	1 Roche Pharma Research and Early Development, Roche Innovation Center Basel, 4070 Basel, Switzerland. 2 Roche Pharma Research and Early Development, Roche Innovation Center Shanghai, Shanghai 201203, China. 3 Department of Internal Medicine and Institute of Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany. 4 Roche Pharma Research and Early Development, Roche Innovation Center Basel, 4070 Basel, Switzerland. Electronic address: john.young.jy3@roche.com. 5 Roche Pharma Research and Early Development, Roche Innovation Center Basel,	A novel orally available small molecule that inhibits hepatitis B virus expression.	Mueller H1, Wildum S1, Luangsay S1, Walther J1, Lopez A1, Tropberger P1, Ottaviani G2, Lu W2, Parrott NJ1, Zhang JD1, Schmucki R1, Racek T1, Hoflack JC1, Kueng E1, Point F1, Zhou X2, Steiner G1, Lütgehetmann M3, Rapp G3, Volz T3, Dandri M3, Yang S2, Young JAT4, Javanbakht H5.	Journal of Hepatology	2018 March	10.1016/j.jhep.2017.10.014

	4070 Basel, Switzerland. Electronic address: ajbakht@gmail.com.					
HBV	1 Novira Therapeutics Inc, part of the Janssen Pharmaceutical Companies, Doylestown, Pennsylvania. Electronic address: klausgklumpp@gmail.com. 2 PhoenixBio Co., Ltd., Higashi-Hiroshima, Japan. 3 I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. 4 I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Institute of Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. 5 Novira Therapeutics Inc, part of the Janssen Pharmaceutical Companies, Doylestown, Pennsylvania. 6	Efficacy of NVR 3-778, Alone and In Combination With Pegylated Interferon, vs Entecavir In uPA/SCID Mice With Humanized Livers and HBV Infection.	Klumpp K1, Shimada T2, Allweiss L3, Volz T3, Lütgehetmann M4, Hartman G5, Flores OA5, Lam AM5, Dandri M6.	Gastroenterology	2018 Feb	10.1053/j.gastro.2017.10.017

	I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; German Center for Infection Research, Hamburg-Lübeck-Borstel Partner Site, Germany.					
DMPK	a Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., 1-98, 3-Chome, Kasugade-Naka, Konohana-ku, Osaka 554-8558, Japan.	Candidate genes responsible for early key events of phenobarbital-promoted mouse hepatocellular tumorigenesis based on differentiation of regulating genes between wild type mice and humanized chimeric mice.	Ayako Ohara,a Yasuhiko Takahashi,a Miwa Kondo,a Yu Okuda,a Shuji Takeda,a Masahiko Kushida,a Kentaro Kobayashi,a Kayo Sumidaa and Tomoya Yamada*a	Toxicology Research	2017	Issue 6
DMPK	1 Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd. 2 Graduate School of Environmental and Life Science, Okayama University. 3	Evaluation of the human relevance of the constitutive androstane receptor-mediated mode of action for rat hepatocellular	Okuda Y1,2, Kushida M1, Kikumoto H1, Nakamura Y2, Higuchi H1, Kawamura S1, Cohen SM3, Lake BG4, Yamada T1.	The Journal of Toxicology Sciences	2017	10.2131/jts.42.773

	Department of Pathology and Microbiology, University of Nebraska Medical Canter, USA. 4 Centre for Toxicology, Faculty of Health and Medical Sciences, University of Surrey, United Kingdom.	tumor formation by the synthetic pyrethroid momfluorothrin.				
HBV	1 Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12 Nishi 6, Kita-ku, Sapporo 060-0812, Japan. 2 Department of Microbiology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Tokyo 156-8506, Japan. 3 Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12 Nishi 6, Kita-ku, Sapporo 060-0812, Japan. Electronic address: harasima@pharm.hokudai.ac.jp.	Highly specific delivery of siRNA to hepatocytes circumvents endothelial cell-mediated lipid nanoparticle-associated toxicity leading to the safe and efficacious decrease in the hepatitis B virus.	Sato Y1, Matsui H1, Yamamoto N2, Sato R1, Munakata T2, Kohara M2, Harashima H3	Journal of Controlled Release	2017 Nov 28	10.1016/j.jconrel.2017.09.044
DMPK	1 Pharmaceutical Research Laboratories, Toray Industries, Inc., Kamakura, Kanagawa, Japan (M.U., Y.T., E.S., R.H.); and PhoenixBio Co., Ltd., Higashihiroshima, Hiroshima, Japan (M.K., Y.K., T.O., C.T.) masashi_uchida@nts.toray.co.jp	Organic Anion-Transporting Polypeptide (OATP)-Mediated Drug-Drug Interaction Study between	Uchida M1, Tajima Y2, Kakuni M2, Kageyama Y2, Okada T2, Sakurada E2, Tateno C2, Hayashi R2	Drug Metabolism and Disposition	2018 Jan	10.1124/dmd.117.075994

	masashi.uchida@bonac.co.jp. 2 Pharmaceutical Research Laboratories, Toray Industries, Inc., Kamakura, Kanagawa, Japan (M.U., Y.T., E.S., R.H.); and PhoenixBio Co., Ltd., Higashihiroshima, Hiroshima, Japan (M.K., Y.K., T.O., C.T.).	Rosuvastatin and Cyclosporine A in Chimeric Mice with Humanized Liver.				
DMPK, Toxicology	1 Graduate School of Biomedical and Health Sciences, Hiroshima University. 2 R&D Dept., PhoenixBio, Co., Ltd. 3 Liver Research Project Center, Hiroshima University.	Assessment of amiodarone-induced phospholipidosis in chimeric mice with a humanized liver.	Sanoh S1, Yamachika Y1, Tamura Y1, Kotake Y1, Yoshizane Y2, Ishida Y2,3, Tateno C2,3, Ohta S1	The Journal of Toxicology Sciences	2017	10.2131/jts.42.589
HCV	1 Department of Biopharmaceutics and Drug Metabolism, Graduate School of Pharmaceutical Sciences, Kyoto University, Japan. 2 Department of Biopharmaceutics and Drug Metabolism, Graduate School of Pharmaceutical Sciences, Kyoto University, Japan. Electronic address: ytakahashi@pharm.kyoto-u.ac.jp.	Evaluation of antiviral effect of type I, II, and III interferons on direct-acting antiviral-resistant hepatitis C virus.	Hamana A1, Takahashi Y2, Uchida T3, Nishikawa M1, Imamura M3, Chayama K3, Takakura Y1	Antiviral Research	2017 Oct	10.1016/j.antiviral.2017.08.017

	3 Department of Gastroenterology and Metabolism, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, Japan.					
HBV	1 Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD. 2 Department of Gastroenterology and Metabolism, Hiroshima University, Hiroshima, Japan.	Hepatitis B virus evades innate immunity of hepatocytes but activates cytokine production by macrophages.	Cheng X1, Xia Y1, Serti E1, Block PD1, Chung M1, Chayama K2, Rehermann B1, Liang TJ1	Hepatology	2017 Dec	10.1002/hep.29348
HBV	1 Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. 2 Natural Science Center for Basic Research and Development, Hiroshima University, Hiroshima, Japan. 3 Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 4	Development of a Novel Site-Specific Pegylated Interferon Beta for Antiviral Therapy of Chronic Hepatitis B Virus.	Tsuge M1,2,3, Uchida T1,3, Hiraga N1,3, Kan H1,3, Makokha GN1,3, Abe-Chayama H1,3,4, Miki D1,3,5, Imamura M1,3, Ochi H1,3,5, Hayes CN1,3, Shimozono R6, Iwamura T6, Narumi H6, Suzuki T6, Kainoh M6, Taniguchi T7, Chayama K8,3,5	Antimicrobial Agents and Chemotherapy	2017 May 24	10.1128/AAC.00183-17

	Center for Medical Specialist Graduate Education and Research, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. 5 Laboratory for Digestive Diseases, RIKEN Center for Integrative Medical Sciences, Hiroshima, Japan. 6 Pharmaceutical Research Laboratories, Toray Industries. Inc., Kanagawa, Japan. 7 Department of Molecular Immunology, Institute of Industrial Science, The University of Tokyo, Tokyo, Japan. 8 Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan chayama@hiroshima-u.ac.jp.					
HCV	1 Department of Virology & Parasitology, Laboratory Animal Facilites & Services, Hamamatsu University School of Medicine, Hamamatsu, Japan.	Critical role of CREBH-mediated induction of transforming growth factor β2	Chida T1,2, Ito M1, Nakashima K1, Kanegae Y3, Aoshima T4, Takabayashi S4, Kawata K2, Nakagawa Y5,	Hepatology	2017 Nov	10.1002/hep.29319

	2 2nd Department of Internal Medicine, Laboratory Animal Facilites & Services, Hamamatsu University School of Medicine, Hamamatsu, Japan. 3 Core Research Facilities of Basic Science (Molecular Genetics), Research Center for Medical Science, Tokyo, Japan. 4 Preeminent Medical Photonics Education & Resarch Center, Laboratory Animal Facilites & Services, Hamamatsu University School of Medicine, Hamamatsu, Japan. 5 Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine, University of Tsukuba, Tsukuba, Japan. 6 Research Institute for Microbial Diseases, Osaka University, Osaka, Japan. 7 Department of Laboratory Medicine, The Jikei University School of Medicine, Tokyo, Japan.	by hepatitis C virus infection in fibrogenic responses in hepatic stellate cells.	Yamamoto M6, Shimano H5, Matsuura T7, Kobayashi Y2, Suda T2, Suzuki T1			

HBV	1 Gilead Sciences, Foster City, California, United States of America. 2 Department of Microbiology and Molecular Medicine, University Medical Center (C.M.U.), Geneva, Switzerland.	The Smc5/6 Complex Restricts HBV when Localized to ND10 without Inducing an Innate Immune Response and Is Counteracted by the HBV X Protein Shortly after Infection.	Niu C1, Livingston CM1, Li L1, Beran RK1, Daffis S1, Ramakrishnan D1, Burdette D1, Peiser L1, Salas E1, Ramos H1, Yu M1, Cheng G1, Strubin M2, Delaney WE IV1, Fletcher SP1	Plos One	2017 Jan	10.1371/journal.pone.0169648
HBV	1 Department of Microbiology and Molecular Medicine, University Medical Centre (C.M.U.), Rue Michel-Servet 1, 1211 Geneva 4, Switzerland. 2 CRCL, INSERM U1052, CNRS 5286, Université de Lyon, 151, Cours A Thomas, 69424 Lyon Cedex, France. 3 Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404, USA.	Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor.	Decorsière A1, Mueller H1, van Breugel PC1, Abdul F1, Gerossier L2, Beran RK3, Livingston CM3, Niu C3, Fletcher SP3, Hantz O2, Strubin M1	Nature	2016 May	10.1038/nature17170

HBV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan. 2 Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 3 Natural Science Center for Basic Research and Development, Hiroshima University, Hiroshima, Japan. 4 Center for Medical Specialist Graduate Education and Research, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. 5 Laboratory for Digestive Diseases, RIKEN Center for Integrative Medical Sciences, Hiroshima, Japan. 6 PhoenixBio Co., Ltd., Higashihiroshima, Japan. 7 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of	Persistent Loss of Hepatitis B Virus Markers in Serum without Cellular Immunity by Combination of Peginterferon and Entecavir Therapy in Humanized Mice.	Uchida T1,2, Imamura M1,2, Hayes CN1,2, Hiraga N1,2, Kan H1,2, Tsuge M1,2,3, Abe-Chayama H1,2,4, Zhang Y1,2, Makokha GN1,2, Aikata H1,2, Miki D2,5, Ochi H2,5, Ishida Y2,6, Tateno C2,6, Chayama K7,2,5	Antimicrobial Agents and Chemotherapy	2017 Aug	10.1128/AAC.00725-17

	Biomedical & Health Science, Hiroshima University, Hiroshima, Japan chayama@hiroshima-u.ac.jp.					
DMPK	1 Resverlogix Corp., Suite 300, 4820 Richard Road SW, Calgary, AB, T3E 6L1, Canada. 2 Resverlogix Inc., San Francisco, CA, USA. 3 Resverlogix Corp., Suite 300, 4820 Richard Road SW, Calgary, AB, T3E 6L1, Canada. Ewelina@resverlogix.com.	Downregulation of the Complement Cascade In Vitro, in Mice and in Patients with Cardiovascular Disease by the BET Protein Inhibitor Apabetalone (RVX-208).	Wasiak S1, Gilham D1, Tsujikawa LM1, Halliday C1, Calosing C1, Jahagirdar R1, Johansson J2, Sweeney M2, Wong NC1, Kulikowski E3	Journal of Cardiovascular Translational Research	2017 Aug	10.1007/s12265-017-9755-z
HCV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan. 2 Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 3 Laboratory for Digestive Diseases, Center for Genomic Medicine, The Institute of Physical	Interferon alpha treatment stimulates interferon gamma expression in type I NKT cells and enhances their antiviral effect against hepatitis C virus.	Miyaki E1,2, Hiraga N1,2, Imamura M1,2, Uchida T1,2, Kan H1,2, Tsuge M1,2, Abe-Chayama H1,2, Hayes CN1,2, Makokha GN1,2, Serikawa M1,2, Aikata H1,2, Ochi H2,3, Ishida Y2,4, Tateno C2,4, Ohdan H2,5, Chayama K1,2,3	Plos One	2017 Mar	10.1371/journal.pone.0172412

	and Chemical Research (RIKEN), Hiroshima, Japan. 4 PhoenixBio Co., Ltd., Higashihiroshima, Japan. 5 Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, Hiroshima, Japan.					
HBV	1 Department of Microbiology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan. 2 Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Chuo-ku, Tokyo, Japan. 3 Mammalian Genetics Project, Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan. 4 PhoenixBio Co, Ltd, Higashi-Hiroshima, Hiroshima, Japan.	Transmission of HBV DNA Mediated by Ceramide-Triggered Extracellular Vesicles.	Sanada T1, Hirata Y1, Naito Y2, Yamamoto N1, Kikkawa Y3, Ishida Y4, Yamasaki C4, Tateno C4, Ochiya T2, Kohara M1	Cellular and molecular Gastroenterology and Hepatology	2016 Oct	10.1016/j.jcmgh.2016.10.003

HCV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan. 2 Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 3 Laboratory for Digestive Diseases, Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Hiroshima, Japan. 4 PhoenixBio Co., Ltd, Higashihiroshima, Japan.	Usefulness of humanized cDNA-uPA/SCID mice for the study of hepatitis B virus and hepatitis C virus virology.	Uchida T1, Imamura M1, Kan H1, Hiraga N1, Hayes CN1, Tsuge M1, Abe-Chayama H1, Aikata H1, Makokha GN1, Miki D2, Ochi H2, Ishida Y3, Tateno C3, Chayama K4	The Journal of General Virology	2017 May	10.1099/jgv.0.000726
DMPK	1 Analysis & Pharmacokinetics Research Laboratories, Drug Discovery Research, Astellas Pharma Inc., Miyukigaoka 21, Tsukuba-shi, Ibaraki, 305-8585, Japan. naoyuki.nakada@astellas.com.	Evaluation of the Utility of Chimeric Mice with Humanized Livers for the Characterization and Profiling of the Metabolites of a Selective Inhibitor (YM543) of the	Nakada N1	Pharmaceutical Research	2017 Apr	10.1007/s11095-017-2116-4

		Sodium-Glucose Cotransporter 2.				
DMPK	1 a Drug Metabolism and Pharmacokinetics Research Laboratories, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited , Fujisawa , Japan.	Comparison of predictability for human pharmacokinetics parameters among monkeys, rats, and chimeric mice with humanised liver.	Miyamoto M1, Iwasaki S1, Chisaki I1, Nakagawa S1, Amano N1, Hirabayashi H1	Xenobiotica ; the Fate of Foreign Compounds in Biological Systems	2017 Dec	10.1080/00498254.2016.1265160
HBV	1 Department of Virology II, National Institute of Infectious Diseases, Tokyo 162-8640, Japan; SCYNEXIS, Inc., Durham, NC 27713, USA. 2 Department of Virology II, National Institute of Infectious Diseases, Tokyo 162-8640, Japan; Department of Applied Biological Science, Tokyo University of Sciences, Noda 278-8510, Japan; CREST, Japan Science and Technology Agency (J.S.T.), Saitama 332-0012, Japan. Electronic address: kwatashi@nih.go.jp. 3 Department of Virology II, National Institute of Infectious Diseases, Tokyo 162-8640, Japan;	Cyclosporin derivatives inhibit hepatitis B virus entry without interfering with NTCP transporter activity.	Shimura S1, Watashi K2, Fukano K3, Peel M4, Sluder A4, Kawai F5, Iwamoto M6, Tsukuda S7, Takeuchi JS8, Miyake T9, Sugiyama M10, Ogasawara Y11, Park SY5, Tanaka Y12, Kusuhara H9, Mizokami M10, Sureau C13, Wakita T8	Journal of Hepatology	2017 Apr	10.1016/j.jhep.2016.11.009

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	Pharmaceutical Sciences, Tokyo 113-0033, Japan. 10 The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa 272-8516, Japan. 11 Department of Analytical Biochemistry, Meiji Pharmaceutical University, Kiyose 204-8588, Japan. 12 Department of Virology and Liver Unit, Nagoya City University Graduate School of Medicinal Sciences, Nagoya 467-8601, Japan. 13 Laboratoire de Virologie Moléculaire, Institut National de la Transfusion Sanguine (INTS), Paris, France.					
HBV	1 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan. 2 Micro-Signaling Regulation Technology Unit, RIKEN CLST, Wako, Japan. 3 Department of Applied Biological Science,	A new class of hepatitis B and D virus entry inhibitors, proanthocyanidin and its analogs, that directly act on	Tsukuda S1,2, Watashi K1,3,4, Hojima T5, Isogawa M6, Iwamoto M1,3, Omagari K6, Suzuki R1, Aizaki H1, Kojima S2, Sugiyama M7, Saito A5, Tanaka Y6,	Hepatology	2017 Apr	10.1002/hep.28952

	Tokyo University of Science, Noda, Japan. 4 CREST, Japan Science and Technology Agency (JST), Saitama, Japan. 5 Department of Advanced Science and Engineering, Graduate School of Engineering, Osaka Electro-Communication University, Neyagawa, Japan. 6 Department of Virology and Liver Unit, Nagoya City University Graduate School of Medicinal Sciences, Nagoya, Japan. 7 Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan. 8 Laboratoire de Virologie Moléculaire, Institut National de la Transfusion Sanguine, Paris, France.	the viral large surface proteins.	Mizokami M7, Sureau C8, Wakita T1			

DMPK	1 Drug ADME Research (K.G.J., M.J.), Department of Drug Metabolism (A.J.), Discovery DMPK (C.B.), Clinical Pharmacology (D.Ø.N.), and Department of Bioanalysis (Z.T.), H. Lundbeck A/S, Valby Denmark; and Discovery Chemistry & DMPK, Lundbeck Research, New Jersey (G.C.) kgj@lundbeck.com. 2 Drug ADME Research (K.G.J., M.J.), Department of Drug Metabolism (A.J.), Discovery DMPK (C.B.), Clinical Pharmacology (D.Ø.N.), and Department of Bioanalysis (Z.T.), H. Lundbeck A/S, Valby Denmark; and Discovery Chemistry & DMPK, Lundbeck Research, New Jersey (G.C.).	Lack of Exposure in a First-in-Man Study Due to Aldehyde Oxidase Metabolism: Investigated by Use of 14C-microdose, Humanized Mice, Monkey Pharmacokinetics, and In Vitro Methods.	Jensen KG1, Jacobsen AM2, Bundgaard C2, Nilausen DØ2, Thale Z2, Chandrasena G2, Jørgensen M2	Drug Metabolism and Disposition	2017 Jan	10.1124/dmd.116.072793
HCV	1 Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical and Health Sciences. 2 Liver Research Project Center, Hiroshima University. 3 Laboratory for Digestive Diseases, Center for	Protease Inhibitor Resistance Remains Even After Mutant Strains Become Undetectable by Deep Sequencing.	Kan H1,2, Imamura M1,2, Uchida T1,2, Hiraga N1,2, Hayes CN1,2, Tsuge M1,2, Abe H1,2, Aikata H1,2, Makokha GN1,2, Chowdhury S1,2, Miki D2,3, Ochi H2,3, Ishida Y2,4, Tateno C2,4, Chayama K1,2,3	The Journal of Infectious Diseases	2016 Dec	10.1093/infdis/jiw437

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HCV	1 The Program for Experimental & Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA. 2 Department of Mathematics and Computational Science, University of South Carolina-Beaufort, Bluffton, SC, USA. 3 Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical & Health Sciences, Hiroshima	Hepatitis C virus dynamics and cellular gene expression in uPA-SCID chimeric mice with humanized livers during intravenous silibinin monotherapy.	DebRoy S1,2, Hiraga N3, Imamura M3, Hayes CN3, Akamatsu S3, Canini L1,4, Perelson AS5, Pohl RT6, Persiani S7, Uprichard SL1, Tateno C8, Dahari H1, Chayama K3	Journal of Viral Hepatitus	2016 Sep	10.1111/jvh.12551

	University, Hiroshima, Japan. 4 Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, UK. 5 Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, NM, USA. 6 German Association of Phytotherapy, Speyer, Germany. 7 Rottapharm Biotech SRL, Monza (MB), Italy. 8 PhoenixBio Co. Ltd., Higashi-Hiroshima, Japan.					
DMPK, Toxicology	1 Department of Pharmacy, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.	Halogenated hydrocarbon solvent-related cholangiocarcinoma risk: biliary excretion of glutathione conjugates of 1,2-dichloropropane evidenced by	Toyoda Y1, Takada T1, Suzuki H1	Scientific Reports	2016 Apr	10.1038/srep24586

		untargeted metabolomics analysis.				
HBV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical and Health Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan. 2 Natural Science Center for Basic Research and Development, Hiroshima University, Hiroshima, Japan. 3 Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 4 Laboratory for Liver Diseases, SNP Research Center, Institute of Physical and Chemical Research (RIKEN), Hiroshima, Japan. 5 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical and Health Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan.	Antiviral effects of anti-HBs immunoglobulin and vaccine on HBs antigen seroclearance for chronic hepatitis B infection.	Tsuge M1,2,3, Hiraga N1,3, Uchida T1,3, Kan H1,3, Miyaki E1,3, Masaki K1,3, Ono A1,3, Nakahara T1,3, Abe-Chayama H1,3, Zhang Y1,3, Naswa MG1,3, Kawaoka T1,3, Miki D1,3,4, Imamura M1,3, Kawakami Y1,3, Aikata H1,3, Ochi H1,3, Hayes CN1,3, Chayama K5,6,7	Journal of Gastroenterology	2016 Nov	10.1007/s00535-016-1189-x

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HBV	1 Department of Gastroenterology and Nephrology, Chiba University, Graduate School of Medicine, Chiba, 260-8670, Japan. 2 Department of Molecular Virology, Chiba University, Graduate School of Medicine, Chiba, 260-8670, Japan.	Possible Involvement of Hepatitis B Virus Infection of Hepatocytes in the Attenuation of Apoptosis in Hepatic Stellate Cells.	Sasaki R1, Kanda T1, Nakamura M1, Nakamoto S1,2, Haga Y1, Wu S1, Shirasawa H2, Yokosuka O1	Plos One	2016 Jan	10.1371/journal.pone.0146314

HBV	1 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan Department of Applied Biological Science, Tokyo University of Science, Noda, Japan. 2 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan Department of Applied Biological Science, Tokyo University of Science, Noda, Japan kwatashi@nih.go.jp. 3 Department of Applied Biological Science, Tokyo University of Science, Noda, Japan. 4 Protein Design Laboratory, Yokohama City University, Yokohama, Japan. 5 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan Micro-Signaling Regulation Technology Unit, RIKEN Center for Life Science Technologies, Wako, Japan. 6 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan Scynexis, Inc., Durham, North Carolina, USA.	A Novel Tricyclic Polyketide, Vanitaracin A, Specifically Inhibits the Entry of Hepatitis B and D Viruses by Targeting Sodium Taurocholate Cotransporting Polypeptide.	Kaneko M1, Watashi K2, Kamisuki S3, Matsunaga H3, Iwamoto M1, Kawai F4, Ohashi H1, Tsukuda S5, Shimura S6, Suzuki R7, Aizaki H7, Sugiyama M8, Park SY4, Ito T9, Ohtani N3, Sugawara F3, Tanaka Y10, Mizokami M8, Sureau C11, Wakita T7	Journal of Virology	2015 Dec	10.1128/JVI.01855-15

	7 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan. 8 Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan. 9 Digestive Diseases Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan. 10 Department of Virology and Liver Unit, Nagoya City University Graduate School of Medicinal Sciences, Nagoya, Japan. 11 Laboratoire de Virologie Moléculaire, Institut National de la Transfusion Sanguine, Paris, France.					

	1 a ADME & Tox. Research Institute, Sekisui Medical Co., Ltd. , Chuo-ku , Tokyo , Japan.	Assessment of chimeric mice with humanized livers in new drug development: generation of pharmacokinetics, metabolism and toxicity data for selecting the final candidate compound.	Kamimura H1, Ito S1	Xenobiotica ; the Fate of Foreign Compounds in Biological Systems	2016	10.3109/00498254.2015.1091113

HBV, TX-NOG	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan Liver Research Project Center, Hiroshima University, Hiroshima, Japan Department of Gastroenterology, Faculty Of Medicine, Oita University, Yufu, Japan. 2 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 3 Liver Research Project Center, Hiroshima University, Hiroshima, Japan PhoenixBio Co., Ltd., Higashihiroshima, Japan. 4 Liver Research Project Center, Hiroshima University, Hiroshima, Japan Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima	Human Cytotoxic T Lymphocyte-Mediated Acute Liver Failure and Rescue by Immunoglobulin in Human Hepatocyte Transplant TK-NOG Mice.	Uchida T1, Hiraga N2, Imamura M2, Tsuge M2, Abe H2, Hayes CN2, Aikata H2, Ishida Y3, Tateno C3, Yoshizato K3, Ohdan H4, Murakami K5, Chayama K6	Journal of Virology	2015 Oct	10.1128/JVI.01126-15

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HBV	1 Department of Microbiology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Tokyo 156-8506, Japan. 2 Laboratory of Innovative Nanomedicine, Faculty of Pharmaceutical Sciences, Hokkaido University, Hokkaido 060-0812, Japan. 3 PhoenixBio Co., Ltd., 3-4-1, Kagamiyama, Hiroshima 739-0046, Japan.	Novel pH-sensitive multifunctional envelope-type nanodevice for siRNA-based treatments for chronic HBV infection.	Yamamoto N1, Sato Y2, Munakata T1, Kakuni M3, Tateno C3, Sanada T1, Hirata Y1, Murakami S4, Tanaka Y4, Chayama K5, Hatakeyama H2, Hyodo M2, Harashima H2, Kohara M6	Journal of Hepatology	2016 Mar	10.1016/j.jhep.2015.10.014

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HCV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan; Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 2 Liver Research Project Center, Hiroshima University, Hiroshima, Japan; PhoenixBio Co.,	Elimination of HCV via a non-ISG-mediated mechanism by vaniprevir and BMS-788329 combination therapy in human hepatocyte chimeric mice.	Uchida T1, Hiraga N1, Imamura M1, Yoshimi S1, Kan H1, Miyaki E1, Tsuge M1, Abe H1, Hayes CN1, Aikata H1, Ishida Y2, Tateno C2, Ellis JD3, Chayama K4	Virus Research	2016 Feb	10.1016/j.virusres.2015.11.010

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HCV	1 Department of Gastroenterology and Metabolism, Applied Life Sciences, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan.	Combination therapies with daclatasvir and asunaprevir on NS3-D168 mutated HCV in human hepatocyte chimeric mice.	Kan H1, Hiraga N, Imamura M, Hayes CN, Uchida T, Miyaki E, Tsuge M, Abe H, Aikata H, Miki D, Ochi H, Ishida Y, Tateno C, Chayama K	Antiviral Therapy	2016	10.3851/IMP3009

HBV	1 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan; Liver Research Project Center, Hiroshima University, Hiroshima, Japan. 2 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan; Liver Research Project Center, Hiroshima University, Hiroshima, Japan; Natural Science Center for Basic Research and Development, Hiroshima University, Hiroshima, Japan. 3 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan; Liver Research Project Center, Hiroshima University, Hiroshima, Japan; Laboratory for Digestive Diseases, Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Hiroshima, Japan.	Effect of tenofovir disoproxil fumarate on drug-resistant HBV clones.	Murakami E1, Tsuge M2, Hiraga N1, Kan H1, Uchida T1, Masaki K1, Nakahara T1, Ono A1, Miki D3, Kawaoka T1, Abe H1, Imamura M1, Aikata H1, Ochi H3, Hayes CN1, Akita T4, Tanaka J5, Chayama K6	The Journal of Infection	2016 Jan	10.1016/j.jinf.2015.09.038

	4 Department of Epidemiology, Infectious Disease Control and Prevention, Integrated Health Sciences, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan. 5 Liver Research Project Center, Hiroshima University, Hiroshima, Japan; Department of Epidemiology, Infectious Disease Control and Prevention, Integrated Health Sciences, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan. 6 Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan; Liver Research Project Center, Hiroshima University, Hiroshima, Japan; Laboratory for Digestive Diseases, Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Hiroshima, Japan. Electronic address: chayama@hiroshima-u.ac.jp.					

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HBV	1 Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan. 2 Central Pharmaceutical Research Institute, Japan Tobacco Inc., Osaka, Japan. 3	Novel reporter system to monitor early stages of the hepatitis B virus life cycle.	Nishitsuji H1, Ujino S1, Shimizu Y1, Harada K1,2, Zhang J3, Sugiyama M1, Mizokami M1, Shimotohno K1	Cancer Science	2015 Nov	10.1111/cas.12799

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