Bio News – November, 2019

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

10/1　ナノ粒子でがん細胞破壊　京大などのグループが新手法開発

https://headlines.yahoo.co.jp/hl?a=20191001-00000000-kyt-sctch

10/1　Sanofi が日本で 200 職の削減を計画しているらしい

Reuters によると、フランスとドイツの 466 職近くの削減を 6 月に発表した Sanofi が日本でおよそ 200 職の削減を計画している。

10/2　Novartis、Microsoft と組んで人工知能を活用した創薬に取り組む

10/3　"vant"会社の一つ、Immunovant が Health Sciences Acquisitions と合併して Nasdaq に上場

10/3　胃薬 790 万錠を自主回収、福井の医薬品メーカー小林化工

https://headlines.yahoo.co.jp/hl?a=20191003-00000171-kyodonews-soci

10/3　ノーベル賞　2年連続の受賞なるか、医学・生理学賞は京大 森和俊氏が有力

https://headlines.yahoo.co.jp/hl?a=20191003-00000577-san-sctch

10/4　Biogen の研究開発長 Michael Ehlers 氏が辞任～投資会社 ATP に転職

10/5　米国妊婦の出産時 C 型肝炎ウイルス(HCV)感染率がここ 15 年間で 5 倍も上昇

10/6　Jim Swanson 氏が Bayer から古巣の J&J に戻って最高情報責任者(CIO)に就任

10/7　2025 年の売り上げ世界一予想の薬は Merck & Co の Keytruda～200 億ドル超え

10/7　ゲノム食品、年内にも食卓へ＝安全審査、表示義務なく－消費者に懸念も

10/8　サリドマイド薬害、仕組み解明 -東京医科大など研究グループ

https://headlines.yahoo.co.jp/hl?a=20191008-00000001-asahi-soci

10/8　Gilead、Roche の Genentech から最高医学責任者引き抜き

10/8　米国の毎年の医療費、その約 4 分の 1 の 7,600～9,350 億ドルは無駄遣い

10/9　今年 1Q の時価総額上位 20 以内に武田薬品が仲間入り

今年 1Q の時価総額上位 20 以内に Shire を買った武田薬品が仲間入りし、アルツハイマー病薬 aducanumab の Ph3 失敗で株価の大幅下落を被った Biogen が圏外となった。

詳しくは以下をクリックして下さい。
2019 年第 1 四半期、製薬会社 時価総額トップ 20 社(GlobalData)

10/10　Bayer、理研と組んで薬の標的を探す

理化学研究所(理研)の研究成果を企業と連携して社会に役立てることを目指すその子会社・理研鼎業と Bayer が手を結んだ。

10/10　米国の大手製薬会社が患者団体に大金を払っている

Bloomberg の調べによると、薬価上昇をなんとかしようとする米国政府の取り組みに反対する勢力を多く含む非営利の意見団体に製薬大手 6 社・AbbVie、Bristol-Myers Squibb、Pfizer, Merck & Co.、AstraZeneca、Johnson & Johnson は昨年 6 億 8,000 万ドル超を支払っている。

10/10　電子タバコ、たばこ、大麻製品が SF ベイエリアの高校に蔓延している現実 -UCSF 研究

https://www.sciencedaily.com/releases/2019/10/191010135706.htm

サンフランシスコベイエリアの高校を調べたところ、学校内外の駐車場や歩道に散らばる何百もの廃棄物（電子タバコ、たばこ、大麻製品関連）が発見された。このことは、これらの製品が十代の若者たちに広く使用されていることを反映しているだけでなく、研究者らは、これらの製品に含まれる可能性のある重金属、プラスチック、ニコチン、リチウムイオン電池、その他の毒素のために環境に有害であると述べている。
この論文は、2019 年 10 月 10 日、連邦疾病管理予防センターの科学雑誌である罹患率と死亡率の週報（Morbidity and Mortality Weekly Report -MMWR）に掲載されている。

10/11　貧血治療薬を生み出したノーベル賞受賞研究

https://headlines.yahoo.co.jp/article?a=20191011-83770093-business-sctch

10/15　Novartis の不正の温床をなんとかするには企業文化の見直しが必要/FiercePharma

トランプ大統領の元弁護士への疑惑の 120 万ドルの支払いや脊髄性筋萎縮症（SMA）遺伝子治療 Zolgensma (onasemnogene abeparvovec) のデータ捏造で Novartis は特定の人物を犯人に仕立てたが、Novartis に蔓延する不正の温床をなんとかするには特定の人物をやりだまに上げるのではなく、企業文化の見直しこそ必要と企業倫理専門家 Hui Chen 氏が製薬ニュース FiercePharma に話している。因みに Novartis は世界で不正に関与しており、欧州や韓国では賄賂、イタリアでは価格強制、日本ではデータ捏造があった。

10/15　ファストフードで体内に「永遠の化学物質」の危険

https://headlines.yahoo.co.jp/article?a=20191015-00010001-nknatiogeo-sctch

10/16　Lilly が英国の Erl Wood アールウッド神経科学研究所を来年末までに閉鎖して米国に移設

10/16　武田薬品、新興市場での 30 製品をスイスの Acino に約 2 億ドルで売却（Shire 買収後の借金減らし）

10/17　Sandoz、Pear の薬物/アルコール乱用治療アプリの共同販売から手を引く

10/18　電子タバコ販売大手 JUUL がメンソールとたばこ味以外の製品の米国販売を中止

10/18　人は健康に 150 歳まで生きられる？ハエの寿命を 1.5 倍に伸ばした新研究 - ロンドン大学

10/18　第 1 回「輝く女性研究者賞」に欧州分子生物学研の戎家氏

https://headlines.yahoo.co.jp/hl?a=20191018-00010000-sportal-sctch

10/18　光合成で酸素生成 過程の一端解明　菅岡山大准教授ら米科学誌に発表

https://headlines.yahoo.co.jp/hl?a=20191018-00010001-sanyo-sctch

10/19　Merck & Co、米国の営業担当と本部販売部門の 500 職を削減

10/19　J&J が否定するアスベスト混入が FDA の検査で認められた

発癌性物質アスベストは混入していないとしてタルク粉製品と癌を関連付ける数々の訴えを否定している Johnson & Johnson だが、米国 FDA の検査でアスベストの一種・クリソタイル繊維が同社の Baby Powder から検出された。
アスベストは発癌性物質であり、FDA はタルク含有品のアスベスト混入を絶えず検査している。

10/21　Sanofi が米国とカナダで店頭販売 Zantac を回収～Teva は英国で後発品回収

発癌性と思しきニトロソアミン不純物 NDMA 混入の恐れは拡大しており、Teva が英国、Sanofi が米国とカナダで ranitidine（ラニチジン）含有薬を回収している。
Sanofi は米国とカナダで Zantac 店頭販売品（Zantac OTC）、Teva は英国で Zantac 後発品・Ranitidine Effervescent 錠 150μg と 300mg を回収。
混入の恐れがあることを受けて両社とも安全を期しての回収で、調査は進行中。

10/22　CRISPR、Bayer との CRISPR 遺伝子編集治療合弁事業を完全掌握する

10/22　Biogen/Eisai、アルツハイマー病薬 aducanumab を来年早々に米国に承認申請

主要目標を達成できそうにないとの今年初めの途中解析結果を受けて中止されたアルツハイマー病薬 aducanumab（アデュカヌマブ）第 3 相試験 2 つを新たなデータを含めてよく解析したところ、その 1 つ EMERGE 試験がなんと主要目標を達成しており（P=0.01）、Biogen/Eisai（エーザイ）は同剤を来年早々に米国 FDA に承認申請する。

10/23　世界初なるか、阪大が iPS 細胞「心筋シート移植」の治験申請へ

https://headlines.yahoo.co.jp/hl?a=20191023-00023601-asahibcv-sctch

10/24　ネズミが車の運転を習得、ストレス軽減効果も 米研究

https://headlines.yahoo.co.jp/hl?a=20191024-00010008-afpbbnewsv-int

10/25　米国でベイピング関連の肺損傷症例数が 1,600 人を超えた

企業関連ニュース/他のトップページに戻る

今月の研究関連ニュース/他

1. アルツハイマー病で脳内にプラークが出現する初期段階

2. マイクロビオームから結腸癌発症を決定する手掛かり

3. 2019 年ノーベル医学生理学賞

4. ロボットは心理学研究の実験用ネズミに取って代われるか？

5. 2019 年第 1 四半期、製薬会社 時価総額トップ 20 社（GlobalData）

6. 免疫系が隠れた癌細胞を見付け出すシステム

7. 雄のマウスと雌のマウスでの脳細胞の相違

8. マウスにおける Cas9 起因の標的外突然変異誘発の定量化

9. PCB 暴露でマウスは脳機能を損なう

10. 研究モデルとしてのマウスは隔離すべきではない

1. アルツハイマー病で脳内にプラークが出現する初期段階

アルツハイマー病では、記憶喪失のような症状が現れるずっと前に、脳内でアミロイドタンパク質プラークの蓄積などアルツハイマー病の根底にある病理が進行している。そして、この分野の長年の目標は、それがどこから始まるのか理解することである。マサチューセッツ工科大学（MIT）の The Picower Institute for Learning and Memory の神経科学者による新しい研究は、この疾患のマウスモデルの脳において、アミロイドが最も初期に出現する領域を特定することによって、この理解への努力を手助けすることである。注目すべきことに、この研究は、ヒトの脳の同じ領域におけるアミロイドの蓄積の程度が疾患の進行と強く相関していることも示している。
近年の多くの研究グループの研究進歩のやり方としては、ポジトロン放出断層撮影などの技術を使用して脳内のアミロイドの経路を追跡し、死後の脳を調べることであったが、この新しい研究では、5XFAD マウスモデルの生後一ヶ月という早い時期に脳全体を見ることによって新たな証拠を追加するというものである。これによって、アミロイドが乳頭体、外側中隔、海馬台などの脳深部領域で行進を始めるように出現し、最終的には記憶の重要な領域である海馬と認知の需要な領域である大脳皮質に至る特定の脳回路に沿って進むことを明らかにした。
チームは、メンバーが開発した SWITCH という技術を使用して、アミロイドプラークにラベルを付け、5XFAD マウスの脳全体を明確にし、さまざまな年齢で細かく画像化できるようにした。チームは一貫して、プラークが最初に脳の深部構造に出現し、Papez 記憶回路などの回路に沿って追跡され、6-12 か月（マウスの寿命は最大 3 年）までには脳全体に広がることを確認した。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-10/piam-spa100319.php

NEWS RELEASE 4-OCT-2019

Study pinpoints Alzheimer's plaque emergence early and deep in the brain

PICOWER INSTITUTE AT MIT

VIDEO: Starting early in the life of an Alzheimer's model (5XFAD) mouse using SWITCH technology, researchers were able to see amyloid plaque buildups (stained white) in deep regions of the brain... view more

Credit: The Picower Institute for Learning and Memory

Long before symptoms like memory loss even emerge, the underlying pathology of Alzheimer's disease, such as an accumulation of amyloid protein plaques, is well underway in the brain. A

longtime goal of the field has been to understand where it starts so that future interventions could begin there. A new study by MIT neuroscientists at The Picower Institute for Learning and Memory could help those efforts by pinpointing the regions with the earliest emergence of amyloid in the brain of a prominent mouse model of the disease. Notably, the study also shows that the degree of amyloid accumulation in one of those same regions of the human brain correlates strongly with the progression of the disease.

"Alzheimer's is a neurodegenerative disease so in the end you can see a lot of neuron loss," said Wen-Chin "Brian" Huang, co-lead author of the study and a postdoc in the lab of co-senior author Li-Huei Tsai, Picower Professor of Neuroscience and director of the Picower Institute. "At that point it would be hard to cure the symptoms. It's really critical to understand what circuits and regions show neuronal dysfunction early in the disease. This will in turn facilitate the development of effective therapeutics."

In addition to Huang, the study's co-lead authors are Rebecca Canter, a former member of the Tsai lab, and Heejin Choi, a former member of the lab of co-senior author Kwanghun Chung, associate professor of chemical engineering and a member of the Picower Institute and the Institute for Medical Engineering and Science.

Tracking plaques

Many research groups have made progress in recent years by tracing amyloid's path in the brain using technologies such as positron emission tomography and by looking at brains post-mortem, but the new study adds substantial new evidence from the 5XFAD mouse model because it presents an unbiased look at the entire brain as early as one month of age. The study reveals that amyloid begins its terrible march in deep brain regions such as the mammillary body, the lateral septum and the subiculum before making its way along specific brain circuits that ultimately lead it to the hippocampus, a key region for memory, and the cortex, a key region for cognition.

The team used SWITCH, a technology developed by Chung, to label amyloid plaques and to clarify the whole brains of 5XFAD mice so that they could be imaged in fine detail at different ages. The team was consistently able to see that plaques first emerged in the deep brain structures and then tracked along circuits such as the Papez memory circuit to spread throughout the brain by 6-12 months (a mouse's lifespan is up to three years).

The findings help to cement an understanding that has been harder to obtain from human brains, Huang said, because post-mortem dissection cannot easily account for how the disease developed over time and PET scans don't offer the kind of resolution the new study provides from the mice.

Key validations

Importantly, the team directly validated a key prediction of their mouse findings in human tissue: If the mammillary body is indeed a very early place that amyloid plaques emerge, then the density of

those plaques should increase in proportion with how far advanced the disease is. Sure enough, when the team used SWITCH to examine the mammillary bodies of post-mortem human brains at different stages of the disease, they saw exactly that relationship: The later the stage, the more densely plaque-packed the mammillary body was.

"This suggests that human brain alterations in Alzheimer's disease look similar to what we observe in mouse," the authors wrote. "Thus we propose that amyloid-beta deposits start in susceptible subcortical structures and spread to increasingly complex memory and cognitive networks with age."

The team also performed experiments to determine whether the accumulation of plaques they observed were of real disease-related consequence for neurons in affected regions. One of the hallmarks of Alzheimer's disease is a vicious cycle in which amyloid makes neurons too easily excited and overexcitement causes neurons to produce more amyloid. The team measured the excitability of neurons in the mammillary body of 5XFAD mice and found they were more excitable than otherwise similar mice that did not harbor the 5XFAD set of genetic alterations.

In a preview of a potential future therapeutic strategy, when the researchers used a genetic approach to silence the neurons in the mammillary body of some 5XFAD mice but left neurons in others unaffected, the mice with silenced neurons produced less amyloid.

While the study findings help explain much about how amyloid spreads in the brain over space and time, they also raise new questions, Huang said. How might the mammillary body affect memory and what types of cells are most affected there?

"This study sets a stage for further investigation of how dysfunction in these brain regions and circuits contributes to the symptoms of Alzheimer's disease," he said.

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In addition to Huang, Canter, Choi, Tsai and Chung, the paper's other authors are Jun Wang, Lauren Ashley Watson, Christine Yao, Fatema Abdurrob, Stephanie Bousleiman, Jennie Young, David Bennett and Ivana Dellalle.

The National Institutes of Health, the JPB Foundation, Norman B. Leventhal and Barbara Weedon fellowships, The Burroughs Wellcome Fund, the Searle Scholars Program, a Packard Award, a NARSAD Young Investigator Award and the NCSOFT Cultural Foundation funded the research.

2. マイクロビオームから結腸癌発症を決定する手掛かり

大腸癌を持つヒトに見られる変異タンパク質は、細胞の増殖と拡大を調節する経路を遮断し、大腸癌発症に関連する細菌種の量を増加させる。これらの発見は、マイクロビオーム中の細菌と結腸癌との関係を示しており、ジョージワシントン大学の研究チームによって、*Gastroenterology* 誌に発表された。
現在のガイドラインでは、結腸癌について 50 歳以上のヒトをスクリーニングすることが推奨されているが、実は結腸癌患者の 15%が 50 歳未満であることが分かっており、若年者の結腸癌数は増加傾向にある。
このマウス研究において発見された結腸腫瘍が発生する前のマイクロビオームの変化は、特に若年層における結腸癌スクリーニング技術へとつながる可能性があり、今後はこれをより詳細により多くのヒトで調査したい、としている。
研究チームは、この微生物プロファイルを *Plos One* 誌内でも公開している。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-10/gwu-mpn100419.php

NEWS RELEASE 4-OCT-2019

Microbiome provides new clues to determining development of colon cancer

A team from the George Washington University published research in the journal Gastroenterology, which found a connection between bacterial species living in the microbiome and development of colon cancer

GEORGE WASHINGTON UNIVERSITY

A mutant protein found in humans with colon cancer blocks a pathway that regulates proliferation and expansion of cells, increasing amounts of bacterial species associated with the development of colon cancer. These findings, showcasing the connection between bacteria in the microbiome and colon cancer, were published by a team of researchers from the George Washington University (GW) in the journal *Gastroenterology*.

"Colon cancer is increasing in young people. Current guidelines recommend screening those over age 50 for colon cancer, but today we are seeing that 15% of those with colon cancer are under the age of 50," said Lopa Mishra, MD, director of the Center for Translational Medicine at the GW Cancer Center and professor of surgery at the GW School of Medicine and Health Sciences. "We hypothesized that diet and its effects on the microbiome may be big players, which is where we focused our study."

Mishra and the research team looked at the interactions among proteins of the carcinoembryonic antigen related cell adhesion molecular (CAECAM) family, which interact with microbes, leading to changes in the growth factor beta (TGFB) signaling pathway. The team collected data on DNA sequences, mRNA expression levels, and patient survival times from 456 colorectal adenocarcinoma cases, and a separate set of 594 samples of colorectal adenocarcinomas, in The Cancer Genome Atlas. The team then used the GW Genomics Core to perform shotgun metagenomic sequencing analysis of feces from mice with defects in TGFB signaling to identify changes in the microbiome before colon tumors developed.

The team found that the expression of CEACAMs and genes that regulate stem cell features of cells are increased in colon cancer and inversely correlated with expression of TGFB pathway genes. They also found colon cancer to express mutant forms of CEACAM5 that inhibit TGFB signaling and increase proliferation and colony formation. This could lead to less invasive screening techniques for colon cancer, particularly for younger patients.

"We found four microbiome species profoundly altered in our mouse study," said Shuyun Rao, PhD, assistant research professor of surgery at the GW School of Medicine and Health Sciences. "Our next steps are to explore this in greater detail and in a much larger population - in the future, younger patients can simply have their stool tested for these altered microbiomes and look for risk for colon cancer, preventing its development."

In addition to Mishra and Rao, the research team consisted of Shoujun Gu, PhD, bioinformatics scientist at the National Institutes of Health, and Sobia Zaidi, PhD, postdoctoral scientist at the GW School of Medicine and Health Sciences. There were also significant contributions made by Raja Mazumder, PhD, co-author and professor of biochemistry and molecular medicine at the GW School of Medicine and Health Sciences and Keith A. Crandall, PhD, director of the Computational Biology Institute at Milken Institute School of Public Health at GW, and their research teams, who just published a microbial profile in the journal *PLOS ONE*.

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"Mutated CEACAMs Disrupt Transforming Growth Factor beta Signaling and Alter the Intestinal Microbiome to Promote Colorectal Carcinogenesis" was published in *Gastroenterology* and is available at https://www.gastrojournal.org/article/S0016-5085(19)41365-6/fulltext.

3. 2019 年ノーベル医学生理学賞

http://scienceportal.jst.go.jp/news/newsflash_review/newsflash/2019/10/20191007_01.html

今年のノーベル医学生理学賞は米英の 3 人に 授賞理由は「細胞の低酸素応答の仕組みの発見」

掲載日:2019 年 10 月 7 日

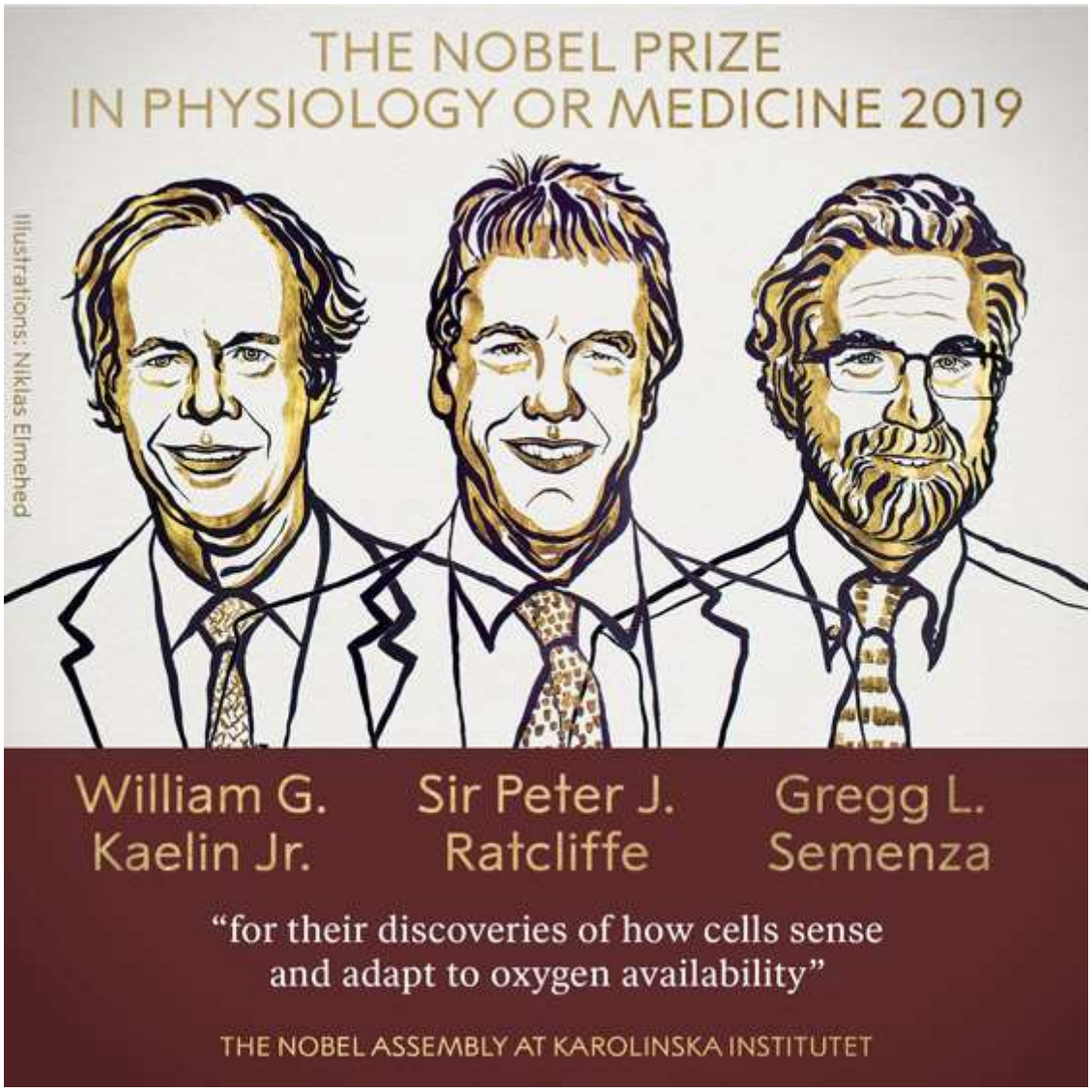
スウェーデンのカロリンスカ研究所は 7 日、2019 年のノーベル医学生理学賞を、細胞が酸素不足の環境でも応答する仕組みを解明した米国と英国の 3 人の研究者に授与する、と発表した。授賞理由は「細胞の低酸素応答の仕組みの発見」。同賞は昨年、本庶佑氏が免疫反応にブレーキをかけるタンパク質を見つけ、画期的ながん治療薬の開発に道を開いた業績で受賞したが、2 年連続の同賞日本人受賞にはならなかった。

ノーベル医学生理学賞に選ばれたのは、米国ジョンズホプキンズ大学のグレッグ・セメンザ氏、英国オックスフォード大学のピーター・ラトクリフ氏、米国ハーバード大学のウィリアム・ケーリン氏。

授賞式は 12 月 10 日にストックホルムで開かれ、賞金 900 万スウェーデン・クローナ(約 9700 万円)が 3 氏に贈られる。

低酸素応答とは、酸素濃度が低い環境下でも細胞が恒常的に働く機構のこと。3 人は、低酸素状態になると体内で「HIF」と呼ばれる特別なタンパク質が大量に作られ、酸素を取り込んでその状態に適応することなどを解明した。低酸素応答は、がんや虚血性の疾患、免疫疾患などの病気でも見られ、こうした病気と密接に関係している。これは生命活動の基本で、今回これらの病気の研究や治療法に道を開いたことが評価された。

セメンザ氏は科学技術振興機構(JST)の戦略的創造研究推進事業(ERATO)で、末松誠慶応大学客員教授(現・日本医療研究開発機構理事長)と共同で 2009～2014 年、新たな代謝システムを探索する国際プロジェクトの研究総括を務めた。



医学生理学受賞者のイラスト。左からウィリアム・ケーリン氏、ピーター・ラトクリフ氏、グレッグ・セメンザ氏（ノーベル財団提供）

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.nobelprize.org/uploads/2019/10/press-medicine2019.pdf

The Nobel Assembly at Karolinska Institutet
has today decided to award
the 2019 Nobel Prize in Physiology or Medicine
jointly to
William G. Kaelin, Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza.
for their discoveries of how cells sense and adapt to oxygen availability

SUMMARY

Animals need oxygen for the conversion of food into useful energy. The fundamental importance of oxygen has been understood for centuries, but how cells adapt to changes in levels of oxygen has long been unknown.

William G. Kaelin Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza discovered how cells can sense and adapt to changing oxygen availability. They identified molecular machinery that regulates the activity of genes in response to varying levels of oxygen.

The seminal discoveries by this year's Nobel Laureates revealed the mechanism for one of life's most essential adaptive processes. They established the basis for our understanding of how oxygen levels affect cellular metabolism and physiological function. Their discoveries have also paved the way for promising new strategies to fight anemia, cancer and many other diseases.

Oxygen at center stage

Oxygen, with the formula O2, makes up about one fifth of Earth's atmosphere. Oxygen is essential for animal life: it is used by the mitochondria present in virtually all animal cells in order to convert food into useful energy. Otto Warburg, the recipient of the 1931 Nobel Prize in Physiology or Medicine, revealed that this conversion is an enzymatic process.

During evolution, mechanisms developed to ensure a sufficient supply of oxygen to tissues and cells. The carotid body, adjacent to large blood vessels on both sides of the neck, contains specialized cells that sense the blood's oxygen levels. The 1938 Nobel Prize in Physiology or Medicine to Corneille Heymans awarded discoveries showing how blood oxygen sensing via the carotid body controls our respiratory rate by communicating directly with the brain.

HIF enters the scene

In addition to the carotid body-controlled rapid adaptation to low oxygen levels (hypoxia), there are other fundamental physiological adaptations. A key physiological response to hypoxia is the rise in levels of the hormone erythropoietin (EPO), which leads to increased production of red blood cells (erythropoiesis). The importance of hormonal control of erythropoiesis was already known at the beginning of the 20th century, but how this process was itself controlled by O2 remained a mystery.

Gregg Semenza studied the EPO gene and how it is regulated by varying oxygen levels. By using gene-modified mice, specific DNA segments located next to the EPO gene were shown to mediate the response to hypoxia. Sir Peter Ratcliffe also studied O2-dependent regulation of the EPO gene, and both research groups found that the oxygen sensing mechanism was present in virtually all tissues, not only in the kidney cells where EPO is normally produced. These were important findings showing that the mechanism was general and functional in many different cell types.

Semenza wished to identify the cellular components mediating this response. In cultured liver cells he discovered a protein complex that binds to the identified DNA segment in an oxygendependent manner. He called this complex the hypoxia-inducible factor (HIF) . Extensive efforts to purify the HIF complex began, and in 1995, Semenza was able to publish some of his key findings, including identification of the genes encoding HIF. HIF was found to consist of two different DNA-binding proteins, so called transcription factors, now named HIF-1a and ARNT. Now the researchers could begin solving the puzzle, allowing them to understand which additional components were involved and how the machinery works.

VHL: an unexpected partner

When oxygen levels are high, cells contain very little HIF-1a. However, when oxygen levels are low, the amount of HIF-1a increases so that it can bind to and thus regulate the EPO gene as well as other genes with HIF-binding DNA segments (Figure 1). Several research groups showed that HIF-1a, which is normally rapidly degraded, is protected from degradation in hypoxia. At normal oxygen levels, a cellular machine called the proteasome, recognized by the 2004 Nobel Prize in Chemistry to Aaron Ciechanover, Avram Hershko and Irwin Rose, degrades HIF-1a. Under such conditions a small peptide, ubiquitin, is added to the HIF-1a protein. Ubiquitin functions as a tag for proteins destined for degradation in the proteasome. How ubiquitin binds to HIF-1a in an oxygen-dependent manner remained a central question.

The answer came from an unexpected direction. At about the same time as Semenza and

Ratcliffe were exploring the regulation of the EPO gene, cancer researcher William Kaelin, Jr. was researching an inherited syndrome, von Hippel-Lindau's disease (VHL disease). This genetic disease leads to dramatically increased risk of certain cancers in families with inherited VHL mutations. Kaelin showed that the VHL gene encodes a protein that prevents the onset of cancer. Kaelin also showed that cancer cells lacking a functional VHL gene express abnormally high levels of hypoxia-regulated genes; but that when the VHL gene was reintroduced into cancer cells, normal levels were restored. This was an important clue showing that VHL was somehow involved in controlling responses to hypoxia. Additional clues came from several research groups showing that VHL is part of a complex that labels proteins with ubiquitin, marking them for degradation in the proteasome. Ratcliffe and his research group then made a key discovery: demonstrating that VHL can physically interact with HIF-1a and is required for its degradation at normal oxygen levels. This conclusively linked VHL to HIF-1a.

Oxygen sHIFts the balance

Many pieces had fallen into place, but what was still lacking was an understanding of how O2 levels regulate the interaction between VHL and HIF-1a. The search focused on a specific portion of the HIF-1a protein known to be important for VHL-dependent degradation, and both Kaelin and Ratcliffe suspected that the key to O2-sensing resided somewhere in this protein domain. In 2001, in two simultaneously published articles they showed that under normal oxygen levels, hydroxyl groups are added at two specific positions in HIF-1a (Figure 1). This protein modification, called prolyl

hydroxylation, allows VHL to recognize and bind to HIF-1a and thus explained how normal oxygen levels control rapid HIF-1a degradation with the help of oxygen-sensitive enzymes (so-called prolyl hydroxylases). Further research by Ratcliffe and others identified the responsible prolyl hydroxylases. It was also shown that the gene activating function of HIF-1a was regulated by oxygen-dependent hydroxylation. The Nobel Laureates had now elucidated the oxygen sensing mechanism and had shown how it works.

Figure 1 When oxygen levels are low (hypoxia), HIF-1a is protected from degradation and accumulates in the nucleus, where it associates with ARNT and binds to specific DNA sequences (HRE) in hypoxia-regulated genes (1). At normal oxygen levels, HIF-1a is rapidly degraded by the proteasome (2). Oxygen regulates the degradation process by the addition of hydroxyl groups (OH) to HIF-1a (3). The VHL protein can then recognize and form a complex with HIF-1a leading to its degradation in an oxygen-dependent manner (4).

Oxygen shapes physiology and pathology

Thanks to the groundbreaking work of these Nobel Laureates, we know much more about how different oxygen levels regulate fundamental physiological processes. Oxygen sensing allows cells to adapt their metabolism to low oxygen levels: for example, in our muscles during intense exercise. Other examples of adaptive processes controlled by oxygen sensing include the generation of new blood vessels and the production of red blood cells. Our immune system and many other physiological functions are also fine-tuned by the O2sensing machinery. Oxygen sensing has even been shown to be essential during fetal development for controlling normal blood vessel formation and placenta development.

Oxygen sensing is central to a large number of diseases (Figure 2). For example, patients with chronic renal failure often suffer from severe anemia due to decreased EPO expression. EPO is produced by cells in the kidney and is essential for controlling the formation of red blood cells, as explained above. Moreover, the oxygen-regulated machinery has an important role in cancer. In tumors, the oxygen-regulated machinery is utilized to stimulate blood vessel formation and reshape metabolism for effective proliferation of cancer cells. Intense ongoing efforts in academic laboratories and pharmaceutical companies are now focused on developing drugs that can interfere with different disease states by either activating, or blocking, the oxygen-sensing machinery.

Figure 2 The awarded mechanism for oxygen sensing has fundamental importance in physiology, for example for our metabolism, immune response and ability to adapt to exercise. Many pathological processes are also affected. Intensive efforts are ongoing to develop new drugs that can either inhibit or activate the oxygenregulated machinery for treatment of anemia, cancer and other diseases.

Key publications:

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Jakkola, P., Mole, D.R., Tian, Y.-M., Wilson, M.I., Gielbert, J., Gaskell, S.J., von Kriegsheim, A., Heberstreit, H.F., Mukherji, M., Schofield, C.J., Maxwell, P.H., Pugh, C.W. & Ratcliffe, P.J. (2001). Targeting of HIF-a to the von Hippel-Lindau ubiquitylation complex by O2regulated prolyl hydroxylation. Science, 292, 468-472

William G. Kaelin, Jr. was born in 1957 in New York. He obtained an M.D. from Duke University, Durham. He did his specialist training in internal medicine and oncology at Johns Hopkins University, Baltimore, and at the Dana-Farber Cancer Institute, Boston. He established his own research lab at the Dana-Farber Cancer Institute and became a full professor at Harvard Medical School in 2002. He is an Investigator of the Howard Hughes Medical Institute since 1998.

Sir Peter J. Ratcliffe was born in 1954 in Lancashire, United Kingdom. He studied medicine at Gonville and Caius College at Cambridge University and did his specialist training in nephrology at Oxford. He established an independent research group at Oxford University and became a full professor in 1996. He is the Director of Clinical Research at Francis Crick Institute, London, Director for Target Discovery Institute in Oxford and Member of the Ludwig Institute for Cancer Research.

Gregg L. Semenza was born in 1956 in New York. He obtained his B.A. in Biology from Harvard University, Boston. He received an MD/PhD degree from the University of Pennsylvania, School of Medicine, Philadelphia in 1984 and trained as a specialist in pediatrics at Duke University, Durham. He did postdoctoral training at Johns Hopkins University, Baltimore where he also established an independent research group. He became a full professor at the Johns Hopkins University in 1999 and since 2003 is the Director of the Vascular Research Program at the Johns Hopkins Institute for Cell Engineering.

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4. ロボットは心理学研究の実験用ネズミに取って代われるか？

マウスを迷路に送ると、その小さな脳がどのように学習するか、多くのことを知ることができる。では、様々な行動パターンについて研究するために、脳のサイズや構造を自由に変えることができるとしたら、どうだろうか？
フロリダアトランティック大学の研究者らは、人工知能を搭載したロボットで心理学実験を行っている。彼らのラップトップサイズのロボットローバーは、カメラを介して環境を移動・感知できる。また、ニューラルネットワークを実行するコンピュータによって導かれる。これは人間の脳に類似したモデルだとして、先週のアメリカ心理学会の Technology Mind & Society Conference でこの「ロボット心理学」アプローチが発表された。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencemag.org/news/2019/10/could-robots-be-psychology-s-new-lab-rats?utm_campaign=news_daily_2019-10-07&et_rid=375979900&et_cid=3020218

Artificial intelligence–equipped rovers could offer psychologists a new—and highly malleable—model of the brain.

WILLIAM HAHN/FLORIDA ATLANTIC UNIVERSITY

Could robots be psychology's new lab rats?

By Kelly ServickOct. 7, 2019 , 4:15 PM

WASHINGTON, D.C.—Sending a mouse through a maze can tell you a lot about how its little brain learns. But what if you could change the size and structure of its brain at will to study what makes different behaviors possible? That's what Elan Barenholtz and William Hahn are proposing. The cognitive psychologist and computer scientist, both at Florida Atlantic University in Boca Raton, are running versions of classic psychology experiments on robots equipped with artificial intelligence. Their laptop–size robotic rovers can move and sense the environment through a camera. And they're guided by computers running neural networks—models that bear some resemblance to the human brain.

Barenholtz presented this "robopsychology" approach here last week at the American Psychological Association's Technology Mind & Society Conference. He and Hahn told *Science* how they're using their unusual new test subjects. The interview has been edited for clarity and length.

Q: Why put neural networks in robots instead of just studying them on a computer?

Elan Barenholtz: There are a number of groups trying to build models to simulate certain functions of the brain. But they're not making a robot walk around and recognize stuff and carry out complex cognitive functions.

William Hahn: What we want is the organism itself to guide its own behavior and get rewards. One way to think about it would be to try to build the simplest possible models. What is the minimum complexity you need to put in one of these agents so that it acts like a squirrel or it acts like a cat?

Q: What kind of experiments can you run with these machines?

E.B.: We actually have a preliminary result with our little rover car, in what we jokingly call a Skinner box. [In B. F. Skinner's classic experiments on animal learning], a pigeon wanders around the cage, and then it maybe walks over to a certain location, and maybe that's electrified. It gets a shock, so it learns very quickly not to go there. Or maybe the pigeon pecks at a little button and it gets a food reward.

We put [the rover] in a box with colors on the various sides of the wall, and we just reward it for facing the correct direction. We were asking whether we could get this kind of robot to engage in a behavior just based on reinforcement. We're never telling it, "This is the right thing to do." Instead, we're just allowing it to explore, given, "Here's my camera input, here's my behavior, is there an outcome—do I get rewarded?"

Q: And its "reward" is just being told it's correct?

E.B.: [Yes,] right now, this is what it's trying to optimize. And that brings up a very interesting question—a psychological question: What's the nature of reward that really best simulates the way it works in organisms? There isn't a score in our heads. There's

endorphins and there's serotonin, and there's all this stuff that happens that we call reward.

Q: So did the robot learn to face the right wall?

E.B.: Yes, it was able to solve it.

Q: And what did that tell you?

E.B.: One is, OK, these systems are capable, in a real-world situation, of solving this kind of problem. On the flip side, we also realized, through the course of trial and error, how incredibly difficult even that simple task was.

Q: Are there more complex questions you'd eventually like to ask in this type of experiment?

E.B.: [We want to] extend the rover's capability beyond rotating on its axis in a little box to be able to have, say, multistep kinds of processes to get the reward. It first has to go to location A, and then location B. Even something as simple as that, in a small space, is extraordinarily difficult.

Q: In your talk, you mentioned that you're testing whether some computational units in these networks evolve properties of place cells—the neurons that fire when an animal is at a particular location, no matter which way its head is facing. Can you tell me more about that?

E.B.: We give [the robot] the current frame, and we say, "What do you think the world would look like a second from now if you were to take a right?" To be able to do that, it has to know where it is. It has to build, in its own mind, a map of, "I am here, and then there's another world over there, and if I turn, I'll now be at that world."

W.H.: [We want to know,] do we have to put place cells in there explicitly? Or if we just [give] reinforcement, do place cells just show up because that makes it easier to find reward?

Q: Do you encounter people who are skeptical that these robots are good models to study the brain?

W.H.: We get pushback from both directions. People are like, "This doesn't look like regular engineering robotics," and then other people are like "This doesn't look like psychology research. Why would you think this has anything to do with the brain?"

E.B.: [To those] who say, "This can't be the brain, the brain is much too complex," … my response is: Let's see how far this can go. Let's see what it can't account for.

Q: Do you think these robot experiments could ever replace certain kinds of animal research?

W.H.: That's been one of our motivations. If you imagine 100 years from now, are we still going to be running mice in mazes? Probably not.

Posted in:

- Social Sciences
- Technology

doi:10.1126/science.aaz7641

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5. 2019 年第 1 四半期、製薬会社 時価総額トップ 20 社（GlobalData）

武田薬品工業株式会社は、2019 年 3 月 31 日に終了した第 1 四半期時価総額に基づいて、上場しているグローバル製薬企業上位 20 位のリストに加わった（23 位から 16 位に）。アイルランドの製薬会社 Shire の買収を背景に 634 億米ドルに成長。GlobalData の専門家は「武田が Biogen に代わって 20 位以内に入った。Shire との合併に加えて、アジルバ（アジルサルタン）の第 1 四半期売上高は 2018 年第 4 四半期からその収益がほぼ倍増したことが理由」としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.globaldata.com/globaldata-presents-top-20-global-innovative-pharma-companies-by-market-capitalization-in-q1-2019/

09 OCT 2019

GlobalData presents top 20 global innovative pharma companies by market capitalization in Q1 2019

Posted in Business Fundamentals

Takeda Pharmaceutical Co Ltd broke into the list of top 20 publicly traded innovative global pharmaceutical companies based on market capitalization (Market Cap) during the first quarter (Q1) ended 31 March 2019, according to GlobalData, a leading data and analytics company.

Takeda's Market Cap during Q1 2019 grew to US$63.4bn, at the back of its takeover of Irish pharmaceuticals firm Shire Plc.

Quentin Horgan, Pharmaceutical Data and Analytics at GlobalData, comments: "Takeda is the new entrant in the list, replacing Biogen Inc. Takeda's merger with Shire coupled with strong growth in drugs such as Azilva (Azilsartan), which reported a 36% increase in sales in Q1 2019, saw its revenues almost double from the fourth quarter (Q4) 2018 to Q1 2019."

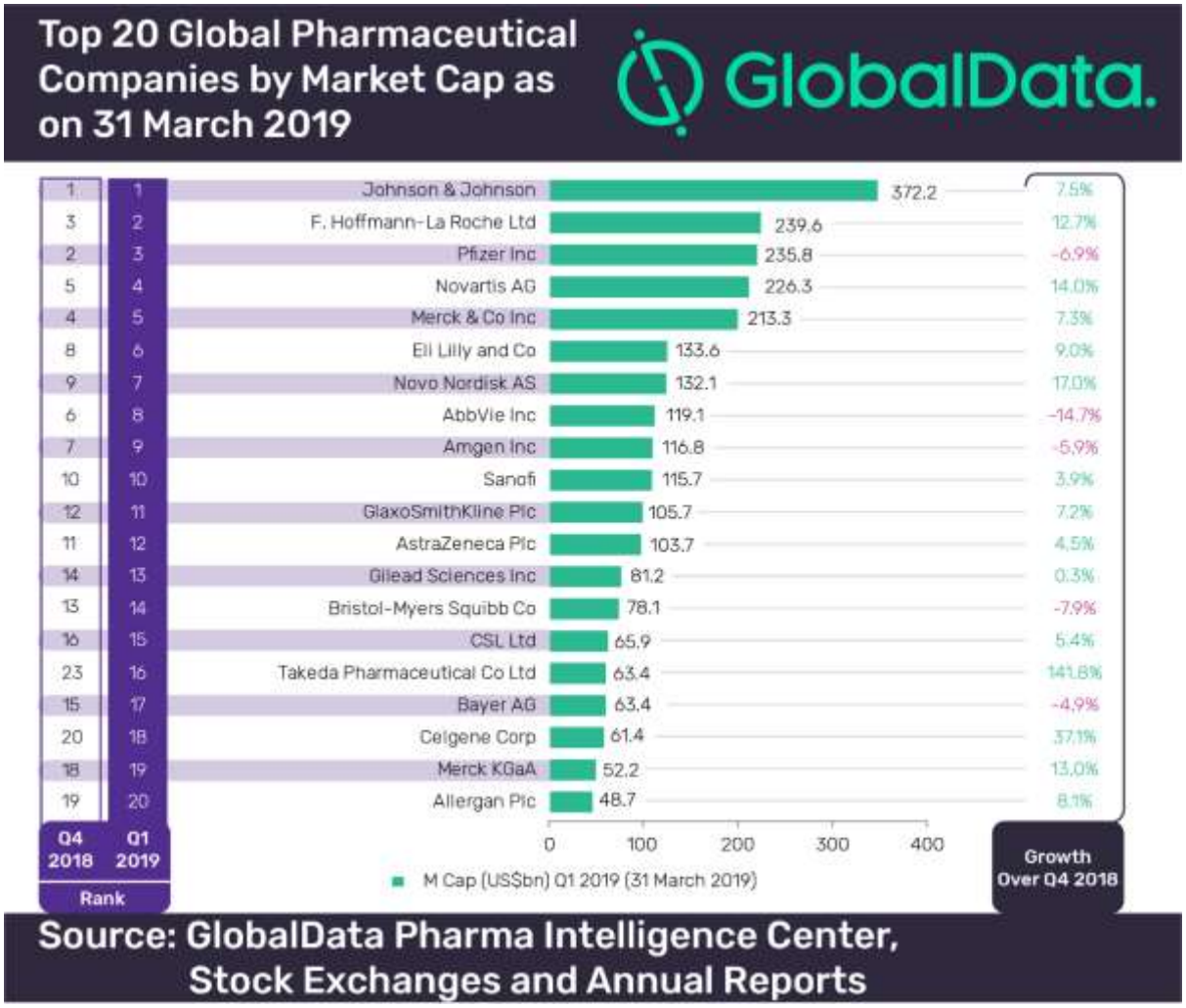

IMAGE FOR PUBLICATION – Please click this link for the chart

The top 20 pharma companies reported an aggregated Maket Cap of US$2.63 trillion in Q1 2019, a growth of 6.2% compared to US$2.47 trillion as on 31 December 2018 (Q4 2018).

Of the top 20,15 pharma companies reported quarter-on-quarter (QoQ) Market Cap growth, with six of them, Takeda (grew by 141.8%), Celgene Corp (37.1%), Novo Nordisk AS (17%), Novartis AG (14%) Merck KGaA (13%) and F. Hoffmann-La Roche Ltd (12.7%), registering double digit growth.

This data can be found in GlobalData's Pharmaceutical Intelligence Center Financials Database. Celgene Corp's share price grew from US$64.09 in Q4 2018 to US$87.45 at the end of Q1 2019, following its impending merger with Bristol-Myers Squibb Co.

Novo Nordisk AS too reported significant improvement in its share price, which closed at DKK348.4 as on Q1 2019, against DKK 297.9 at the end of Q4 2018. The rally in share price was due to its strong performance in diabetes care and obesity markets, and positive regulatory approvals helped Novartis AG to expand its Market Cap.

Horgan explains: "For Novartis the Zolgensma launch has been successful with predicted sales for 2019 reaching US$332mn and is predicted to cross the billion dollar mark in 2020, whilst the recently launched Mayzent's predicted sales are less impressive but is still predicted to reach over a billion by the year 2023."

Other notable movements include Roche moving up a place to second in the ranking, with Pfizer slipping a place to third.

Horgan continues: "Lyrica, Pfizer's biggest selling drug in 2018, showed a 10% drop in Q1 2019 sales against its Q4 2018 sales due to its encroaching US Drug Expiry in June 2019 and its recent patent disputes which it lost in the UK at the end of 2018. This was compounded by Enbrel, another Pfizer blockbuster, reporting a 14% drop in sales between Q1 2019 and Q4 2018."

Roche was favorably benefited from key blockbuster drugs such as Ocrevus (Ocrelizumab), which registered 23% growth; and others such as Kadcyla (Trastuzumab Emtansine) and Hemlibra (emicizumab-kxwh), which saw 16% and 96% growth, respectively, during the period.

Among the five pharma companies which suffered Market Cap decline in Q1, AbbVie registered more than 10% QoQ decline as a result of the weakening European sales of its arthritis medication Humira following the introduction of biosimilar competition.

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6. 免疫系が隠れた癌細胞を見付け出すシステム

癌細胞は検出から身を隠す天才であるが、10 月 14 日の *Nature Immunology* 誌に掲載された、Yale 大学の科学者によって開発された新システムは、群衆からそれらを目立つようにし、免疫システムが他の免疫療法が見逃してしまう可能性のある腫瘍を見付けて排除する手助けをする、としている。
この新システムが減少させたり排除したものは、マウスのメラノーマとトリプルネガティブ乳房および膵臓腫瘍、それも腫瘍の元々の発生源から遠く離れた場所にあるものまでが含まれる、と報告されている。
これは、ウイルス遺伝子治療と CRISPR 遺伝子編集技術を結びつける新システムで、DNA の断片を見つけて編集し新しい遺伝子を挿入する代わりに、免疫療法としての内因性遺伝子の多重活性化（MAEGI）と呼ばれる新システムは、数万の癌関連遺伝子の大規模な狩りを開始し、GPS のように動作し、それらの位置をマークし、信号を増幅させる。MAEGI は腫瘍細胞に免疫破壊の印を付け、冷たい腫瘍（免疫細胞を欠く）を熱い腫瘍（免疫細胞を含む）に変える。それは、腫瘍細胞をオレンジ色のジャンプスーツで包むことと分子的に同等であり、免疫系警察が致命的な細胞を迅速に見つけて根絶することを可能にする、としている。又、理論上、この新システムは、現在免疫療法に耐性があるものを含む多くの種類の癌に対して効果的である、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/10/191014111747.htm

Scientists help immune system find hidden cancer cells

Date:

October 14, 2019

Source:

Yale University

Summary:

Cancer cells are masters at avoiding detection, but a new system can make them stand out from the crowd and help the immune system spot and eliminate tumors that other forms of immunotherapies might miss.

FULL STORY

Cancer cells are masters at avoiding detection, but a new system developed by Yale scientists can make them stand out from the crowd and help the immune system spot and eliminate tumors that other forms of immunotherapies might miss, the researchers report Oct. 14 in the journal *Nature Immunology*.

The new system reduced or eliminated melanoma and triple-negative breast and pancreatic tumors in mice, even those located far from the primary tumor source, the researchers report.

"This is an entirely new form of immunotherapy," said Sidi Chen, assistant professor of genetics and senior author of the study.

Immunotherapy has revolutionized the treatment of cancer but existing therapies don't work on all patients or not at all against some cancers. Existing therapies sometimes fail to recognize all molecular disguises of cancer cells, rendering them less effective.

To address those shortcomings, Chen's lab developed a new system that weds viral gene therapy and CRISPR gene-editing technology. Instead of finding and editing pieces of DNA and inserting new genes, the new system -- called Multiplexed Activation of Endogenous Genes as Immunotherapy (MAEGI) -- launches a massive hunt of tens of thousands of cancer-related genes and then acts like a GPS to mark their location and amplify the signals.

MAEGI marks the tumor cells for immune destruction, which turns a cold tumor (lacking immune cells) into a hot tumor (with immune cells). It is the molecular equivalent of dressing tumor cells in orange jump suits, allowing the immune system police to quickly find and eradicate the deadly cells, Chen said.

"And once those cells are identified, the immune system immediately recognizes them if they show up in the future," Chen said.

The new system in theory should be effective against many cancer types, including those currently resistant to immunotherapy, he said.

Upcoming studies will optimize the system for simpler manufacturing and prepare for clinical trials in cancer patients.

Story Source:

Materials provided by **Yale University**. Original written by Bill Hathaway. *Note: Content may be edited for style and length.*

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7. 雄のマウスと雌のマウスでの脳細胞の相違

カリフォルニア工科大学（CALTECH）の研究者らは、雄のマウスと雌のマウスにそれぞれ特有の稀なタイプの脳細胞を発見、これらの性特異的細胞は、攻撃行動と交尾行動の両方を支配する脳の領域で見付かった、として 10 月 17 日に *Cell* 誌で発表している。
脳内には、信号を伝達するニューロンや神経機能をサポートするグリア細胞など、様々なタイプの細胞がある。これらの細胞は全て同じ遺伝子セットまたはゲノムを含んでいるが、細胞の種類はそれらの遺伝子の発現方法において異なる。類推として、ゲノムは各細胞の 88 鍵ピアノのようなものである。つまり、各細胞は 88 のキー全てを使用するわけではない。従って、細胞が「再生」するキーのサブセットによって、細胞のタイプが決定される。
視床下部はヒトを含む全ての脊椎動物に見られる脳の基本領域であるが、以前の研究では、視床下部の特定の解剖学的一区分 –視床下部腹内側核の腹側外側の一区分– には攻撃性と交尾行動を制御する細胞が含まれていることが示されており、これらの研究では、雄および雌のマウスでこれらのニューロンを強く刺激すると脅威がなくてもすぐに攻撃的になり、弱い刺激では交尾行動を始めた、としている。
今回の新しい研究で、研究者らはこの視床下部腹内側核の個々の細胞における遺伝子発現を調べた。これは、細胞に含まれる RNA 転写物を列挙および識別することが可能なトランスクリプトーム技術によって可能になった。研究チームは、この小さな領域だけでも 17 種類の脳細胞があることを発見、遺伝子発現のパターンについては、17 種類のいくつかは、雌よりも雄のマウスではるかに豊富であり、雌でのみ見られるものもあることが明らかになった。今後は、これらの異なるタイプの細胞の機能を決定したい、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/10/191017142809.htm

Male and female mice have different brain cells

Rare sex-specific neurons are present in the brains of male and female mice

Date:

October 17, 2019

Source:

California Institute of Technology

Summary:

Scientists discover that a brain region known to control sex and violence contains rare cell types that differ in male versus female mice.

Caltech researchers have discovered rare brain cell types that are unique to male mice and other types that are unique to female mice. These sex-specific cells were found in a region of the brain that governs both aggression and mating behaviors.

The study was done as a collaboration between the laboratory of David Anderson, Seymour Benzer Professor of Biology, Tianqiao and Chrissy Chen Institute for Neuroscience Leadership Chair, Howard Hughes Medical Institute Investigator, and director of the Tianqiao and Chrissy Chen Institute for Neuroscience; and a team at the Allen Institute for Brain Sciences in Seattle, Washington. A paper describing the research appears online on October 17 in the journal *Cell*.

"The results show that there are differences between male and female mammalian brains at the level of cellular composition as well as gene expression but that those differences are subtle, and their functional significance remains to be explained," says Anderson.

There are many different types of cells within the brain, such as neurons that transmit signals and glial cells that support neural functions. Although all of these cells contain the same set of genes, or genome, the types of cells differ in how they express those genes. As an analogy, one can imagine the genome as an 88-key piano in each cell. Each cell does not use all 88 keys. Therefore, the subset of keys that the cell "plays" determines the type of cell it is.

The hypothalamus is a fundamental region of the brain found in all vertebrates including humans. Previous studies have shown that a specific anatomic subdivision in the hypothalamus, called the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl), contains cells that control aggression and mating behaviors. In these studies, strong stimulation of these neurons in male and female mice immediately caused the animals to become aggressive, even in the absence of any threat. However, weak stimulation caused the mice to begin mating behaviors.

In this new work, led by Caltech graduate student Dong-Wook Kim, the researchers examined gene expression in individual cells in the VMHvl. This was made possible by advanced transcriptomic techniques that can enumerate and identify the RNA transcripts that a cell contains; this information can then be used to classify different cell types. Previous studies were only able to examine 10 percent of the transcripts in each cell, whereas this study looked at a larger proportion of transcripts. The team discovered that there are 17 different types of brain cells in this tiny region alone. What is more, an examination of the patterns of gene expression revealed that some of these 17 cell types are much more abundant in male mice than in females, while others are found only in females.

It was known that different genes are expressed in the two mouse sexes -- indeed, a genetic test can tell you whether a mouse is male or female -- but this is the first discovery of types of cells that are sex-specific in a mammalian brain. Cells are considered to be distinct types when the expression of large clusters of genes varies from cell to cell.

Future work will try to determine the functions of these differing cell types.

Story Source:

Materials provided by **California Institute of Technology**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Dong-Wook Kim, Zizhen Yao, Lucas T. Graybuck, Tae Kyung Kim, Thuc Nghi Nguyen, Kimberly A. Smith, Olivia Fong, Lynn Yi, Noushin Koulena, Nico Pierson, Sheel Shah, Liching Lo, Allan-Hermann Pool, Yuki Oka, Lior Pachter, Long Cai, Bosiljka Tasic, Hongkui Zeng, David J. Anderson. **Multimodal Analysis of Cell Types in a Hypothalamic Node Controlling Social Behavior**. *Cell*, 2019; 179 (3): 713 DOI: 10.1016/j.cell.2019.09.020

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8. マウスにおける Cas9 起因の標的外突然変異誘発の定量化

トロントの SickKids 病院のフェノゲノミクスセンター科学技術開発のシニアディレクター Lauryl Nutter 博士を含む研究チームは、CRISPR 酵素 Cas9 の使用を改善し、実験マウスの標的外変異の可能性を減らす新しい方法を見付けている。
Nutter 博士、および複数機関のノックアウトマウスフェノタイピングプロジェクトの共同研究者らは、Cas9 と遺伝子編集を定期的に使用して、特定の変異を持つ実験用マウスの系統を作っている。この作業において、彼らは Cas9 ベースの遺伝子編集の精度を改善する新しい方法を生み出すことに取り組んできたが、今回その成果について、ヒューストンで行われた American Society of Human Genetics 2019 年年次総会で発表した。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/10/191019154003.htm

Researchers quantify Cas9-caused off-target mutagenesis in mice

Date:

October 19, 2019

Source:

American Society of Human Genetics

Summary:

Scientists are finding new ways to improve the use of the CRISPR enzyme Cas9 and reduce the chances of off-target mutations in laboratory mice, according to new results. The findings will help scientists contextualize a common concern related to gene editing and identify new strategies to improve its precision.

FULL STORY

Scientists are finding new ways to improve the use of the CRISPR enzyme Cas9 and reduce the chances of off-target mutations in laboratory mice, according to new results from a research collaboration including Lauryl Nutter, PhD, Senior Director, Science and Technology Development at The Centre for Phenogenomics at The Hospital for Sick Children (SickKids) in Toronto. The findings, which help scientists contextualize a common concern related to gene editing and identify new strategies to improve its precision,

were presented as a featured plenary abstract at the American Society of Human Genetics 2019 Annual Meeting in Houston.

Dr. Nutter and her collaborators from the multi-institution Knockout Mouse Phenotyping Project (KOMP2) regularly use Cas9 and gene editing to produce lines of laboratory mice with specific mutations. In this work, they often encounter questions about the likelihood of off-target mutagenesis -- unintended genetic mutations introduced by the gene editing process -- in their mouse lines.

"We wanted to know: to what extent do we need to worry about off-target mutagenesis?" Dr. Nutter explained. By demonstrating the degree of the problem in mice, the researchers hoped to be better able to evaluate it in human cell lines being studied in the laboratory, as well as generate new ways to improve the precision of Cas9-based gene editing.

To answer these questions, Dr. Nutter's team performed 58 genome editing experiments in mouse embryos with Cas9 and guide RNAs configured to induce a specific, targeted mutation in a different gene, which would be passed down to its descendants. Two to four guides were used for each experiment for a total of 175 different guide RNAs. They then sequenced each mouse's whole genome to search for any additional mutations that may have resulted. To get a baseline rate of mutation, the whole genomes of Cas9-treated mouse lines were compared to those of 25 untreated control mice.

In 31 of the Cas9-treated mouse lines, the researchers found zero off-target mutations, and in the remaining 20 lines, they found an average of 2.3 off-target mutations. In comparison, among both the treated and untreated mouse lines, they found an average of 3,500 naturally occurring, unique mutations in each animal.

"Surprisingly, these results show that the number of naturally-occurring mutations far exceeded those introduced by Cas9," Dr. Nutter said. "They also show that when guide RNAs are properly designed, off-target mutagenesis is quite rare."

The results also add context to the use of inbred laboratory mouse lines in genetics research and the assumptions that scientists make when using them.

"Historically, we have used inbred mouse lines to study genetics in mice because their genomes differed only at certain, defined places, and we've assumed that any difference between the mice is due to those differences," Dr. Nutter explained. "However, we found that even among mice in the same litter, there could be thousands of naturally-occurring genetic differences."

"Our results highlight the need to be cognizant of using Cas9 and other tools in a genome that may not be as well defined as we think," she added.

As next steps, Dr. Nutter and her collaborators plan to explore whether enzymes that inhibit or enhance DNA repair can affect the rate at which new mutations arise. They also plan to examine the tradeoff between improving the efficiency of Cas9 mutagenesis and improving its precision. Given their focus on the production of laboratory mouse lines, the researchers hope their findings will inform the development of better guide RNAs, the short pieces of RNA that enable Cas9 to bind to its intended target and induce the intended mutation.

More broadly, they hope their findings will lead to better use of control groups and a more informed perspective on experimental design. They noted that this knowledge will be particularly important in gene editing research with potential therapeutic applications, including studies of the safety and efficacy of genetics-based therapies.

Reference: L Nutter *et al*. (2019 Oct 18). Abstract: Whole genome sequencing puts Cas9 off-target mutagenesis into the context of genetic drift. Presented at the American Society of Human Genetics 2019 Annual Meeting. Houston, Texas.

Story Source:

Materials provided by **American Society of Human Genetics**. *Note: Content may be edited for style and length.*

Cite This Page:

- MLA
- APA
- Chicago

American Society of Human Genetics. "Researchers quantify Cas9-caused off-target mutagenesis in mice." ScienceDaily. ScienceDaily, 19 October 2019. <www.sciencedaily.com/releases/2019/10/191019154003.htm>.

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9. PCB 暴露でマウスは脳機能を損なう

ジョージタウン大学医療センターの神経科学者らの研究によると、人間が作った環境中に無期限に残留する有害化学物質は、マウスの脳の重要なヘルパー細胞の性能を破壊し、長期の曝露では機能障害を引き起こすとして、シカゴで行われた神経科学学会の年次総会で報告している。
ポリ塩化ビフェニル（PCB）は、癌を引き起こし、免疫系を抑制し、ホルモンシグナルを破壊し生殖機能を損なうことで知られている。また、死後研究では、パーキンソン病患者のドーパミン産生細胞の死に関連している。PCB は化学物質として安定しており、耐熱性があり、電気絶縁性であるため、冷却材、難燃剤、潤滑剤、塗料、接着剤、その他多くの工業製品での使用に最適で、20 世紀に世界的に広く製造および使用された。1970 から 1980 年代には、その毒性のため、一部の国で使用禁止され始め、2001 年に世界的な生産が終了している。しかし、これらの毒素の影響は今も継続している、と発表された。
マウス脳細胞の実験室試験で行われたこの研究は、かつて広く使用されていた PCB の混合物が、毒素を中和しようとする星状細胞の経路をどのように変化させるかを示している。

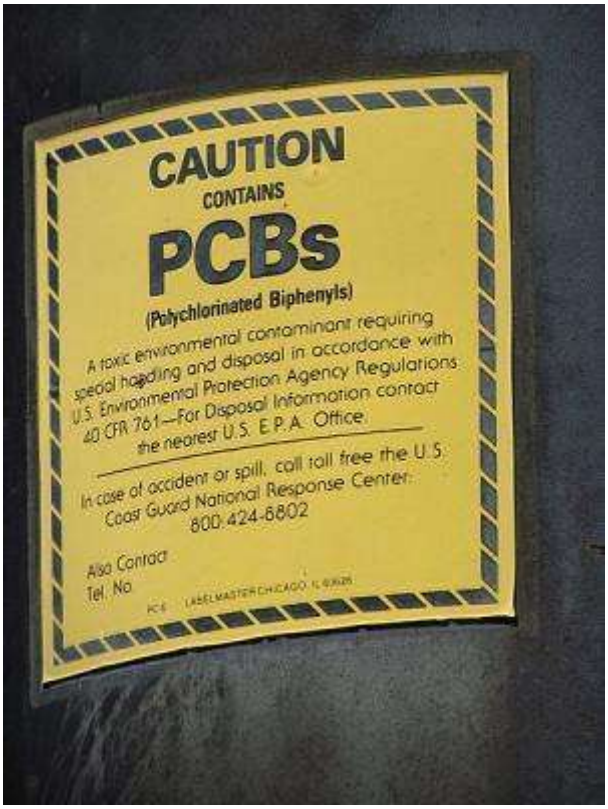
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-10-exposure-environmental-pcbs-impairs-brain.html

OCTOBER 22, 2019

Exposure to environmental PCBs impairs brain function in mice

by Georgetown University Medical Center



PCB warning label affixed to a railroad signal power supply transformer dating from the 1930's at CP-SLOPE interlocking, west of Altoona, PA on the Norfolk Southern Pittsburgh Line. Credit: Sturmovik/Wikipedia

Human-made toxic chemicals that linger indefinitely in the environment disrupt the performance of critical helper cells in the mouse brain, leading to impaired function over long-term exposures, say neuroscientists at Georgetown University Medical Center.

Their study, believed to be the first to test polychlorinated biphenyls (PCBs) in astrocytes—cells that support neurons and are critical for homeostasis throughout the central nervous system—suggests that this persistent environmental toxicant could be a contributing factor in the development of neurodegenerative disorders. They report their findings at the annual meeting of the Society for Neuroscience in Chicago.

The research, conducted in laboratory tests of mouse brain cells, shows how a once widely used mixture of PCBs turns on pathways in astrocytes that attempt to neutralize the toxins. Many antioxidant genes known to be relevant to neurodegeneration in humans are aberrantly activated in the mice cells, says the study's lead researcher, Mondona McCann, a Ph.D. candidate in Georgetown's Interdisciplinary Program in Neuroscience.

"Our findings to date show strong connections between these toxins and the health of astrocytes. They also contribute to our understanding of how crucial these astrocytes are to maintaining brain functioning," says McCann, who is conducting her research in the lab of Kathleen Maguire-Zeiss, Ph.D., chair of Georgetown's Department of Neuroscience.

These star-shaped cells maintain the blood-brain barrier, support neurons, regulate communication between neurons, and repair nervous tissue following injury, among many other supportive tasks. "If astrocytes fail, neurons die. They are key to maintaining homeostasis—physiological stability—throughout the brain," she says.

PCBs are known to cause cancer, suppress the immune system, disrupt hormonal signals and impair reproduction. In postmortem studies, they have also been correlated with death of nigral brain cells—dopamine-producing cells—in patients with Parkinson's disease.

PCBs were globally manufactured and widely used in the 20th century because the chemicals are stable, heat-resistant and electrically insulating, which made them ideal for use in coolants, flame retardants, lubricants, paints, adhesives and many other industrial products. Because of their toxicity, some countries began banning their use in the 1970s and 1980s, but worldwide production only ended in 2001.

The effect of these toxins continues, McCann says. "The same stability that made PCBs so useful also made them persist in the environment."

In addition to several human diseases, PCBs have recently been linked to the decline in the killer whale population; McCann suspects that a combination of environmental stressors such as PCBs and genetic predispositions are linked to neurodegeneration.

"People in certain regions are constantly exposed to a low dose of PCBs and other similar compounds for a long time over their lives," McCann says. "Our lab findings suggest that such an accumulation can lead to oxidative stress in astrocytes, which could not, then, support the neurons they maintain."

It is unlikely that we will ever be able to remove accumulated PCBs from a person, but if research in humans uncovers the specific pathways affected in the brain, "it maybe possible to compensate, clinically, for the deficits seen in functioning of astrocytes. We might be able to engage compensatory mechanisms to increase the cells' capacity to buffer these toxicants and promote survival," she says.

"This concept that environmental stressors impinge on astrocyte health is a fairly understudied area," says Maguire-Zeiss.

Explore further

Study focuses on repair and reversal of damage caused by Huntington's disease

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Provided by Georgetown University Medical Center

10.　研究モデルとしてのマウスは隔離すべきではない

動物モデルは多くのヒトのコミュニケーション障害を理解する上でのゲートウェイとして機能するが、そのような目的の為にマウスを社会的に隔離する今の慣行が、実はヒトに対して貧弱な研究モデルにしている可能性があり、より現実的な社会環境へ移行することで将来の研究の有用性を大幅に改善できる可能性がある、とバッファロー大学の研究者らが *eNeuro* 誌で指摘している。
自閉症や統合失調症などの状態の原因である可能性のある遺伝的経路の洞察は、多くの場合、マウスの音響行動を研究することから始まる。ただ、社会的に隔離されたマウスは通常のマウスよりも超音波発生における区別を学ぶのにより多くの時間を要する。
研究者らは「行動研究からどのような神経効果が起こっているのか未だ分かっていないが、言えることは、マウスを隔離するべきではないということだ」と、結論している。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/10/191024122632.htm

For better research results, let mice be mice

Knowing how to raise and care for animals can improve research on human communication

Date:

October 24, 2019

Source:

University at Buffalo

Summary:

Animal models can serve as gateways for understanding many human communication disorders, but a new study suggests that the established practice of socially isolating mice for such purposes might actually make them poor research models for humans, and a simple shift to a more realistic social environment could greatly improve the utility of the future studies.

FULL STORY

Animal models can serve as gateways for understanding many human communication disorders. Insights into the genetic paths possibly responsible

for conditions such as autism and schizophrenia often begin by studying acoustic behavior in mice.

But a new study from the University at Buffalo suggests that the established practice of socially isolating mice for such purposes might actually make them poor research models for humans, and a simple shift to a more realistic social environment could greatly improve the utility of the future studies.

That's because how mice are raised affects how they hear in the real world, according to Micheal Dent, a professor in UB's Department of Psychology and coauthor of the paper with Laurel Screven, a postdoctoral research fellow at Johns Hopkins, who was a UB graduate student when the research was conducted.

Socialization is critical, according to Dent. "We need to raise our animals in more naturalistic situations since it turns out that it has an effect on their acoustic communication, including how they hear and how long it takes to train them on a behavioral task," says Dent, an expert in the perception of complex auditory stimuli in birds and mammals.

"Normally when we do these studies, we isolate the animals for their entire lives. This is not a good model for humans because we're creating these odd worlds for the mice. It's not natural. Having the mice live together changes their perception of vocalizations, so clearly it is important."

The findings of the new paper, which appear in the journal *eNeuro*, began as a curiosity Screven expressed to Dent, her dissertation adviser at UB.

Screven was interested in the effects of social experience on acoustic communication in mice. Previous research demonstrated that when female mice have babies, their neural responses to calls, or ultrasonic vocalizations, change. Their response depended on whether or not the mice had pups. Screven wondered if the social experience of vocalizations somehow changes the composition of the brain, and changes the composition of the auditory areas of the brain..

It was a possibility that had not been previously studied.

"We can't tell what kind of neural effects are taking place from our behavioral research, but what we can say is that we should not be isolating mice," Dent says. "We should put them together in order to create a more realistic situation, one that's more applicable to human communication.

"Knowing how to raise and care for these animals can improve research on human communication," says Dent.

For their study, Dent and Screven first trained mice to poke their noses through one hole to start a repeating vocalization and then to poke their noses through a different hole when they heard a different vocalization. Mice emit ultrasonic vocalizations (USVs), which vary in frequency, duration and intensity.

The collective differences in these characteristics is the call's "shape." The shapes perceived by the mice are similar to how humans hear different words.

The socially isolated mice required significantly more time to learn to discriminate between the USVs than the socially housed mice, and they used different aspects of the USVs to do it.

"The goal of the research in our lab is to first establish the baseline acoustic communication behavior of the mice so in the future we can start understanding communication in mice with genetic manipulations," says Dent. "If we look at the genes found in humans who stutter, for instance, or have high frequency hearing loss, or accelerated age-related hearing loss, we can see what happens when we knock out those same genes in the mice.

"Eventually, we can attempt to 'fix' the disorders in mice, leading to possible treatments for humans."

For Dent, the findings are immediately applicable and she says the next step in her research will be to house mice together in future experiments.

"Just the finding that the mice train faster when they live together is important for anyone in my line of research wanting to get the data out faster," says Dent. "But I also think that creating a more natural living situation for the mice will make the results of these laboratory experiments more relevant for human communication and studying how humans process vocalizations."

Story Source:

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

Journal Reference:

1. Laurel A. Screven, Micheal L. Dent. **Perception of Ultrasonic Vocalizations by Socially Housed and Isolated Mice**. *eneuro*, 2019; 6 (5): ENEURO.0049-19.2019 DOI: 10.1523/ENEURO.0049-19.2019

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