# Bio News – February, 2025

In-Vivo Science International, Inc.

# 今月の企業関連ニュース/他

1/2　Lilly が配合 tirzepatide をめぐる法廷闘争で発言権を求める

Eli Lilly は、同社の減量薬と糖尿病薬がもはや不足していないという FDA の最近の決定に異議を唱える訴訟に介入する動きを見せた。

Lilly asks to join lawsuit over compounded versions of its weight-loss drugs | Reuters

Lilly seeks to intervene in compounded tirzepatide lawsuit

1/3　PFAS を可視光で分解、立命館大が開発した技術の効果

フッ素化合物は産業で広く利用されている一方、廃棄物の分解が難しく、環境残留や生体蓄積などの課題がある。立命館大学の小林洋一教授らは、難分解性で知られるパーフルオロアルキル化合物（PFAS）を可視光で温和にリサイクル可能なフッ化物イオンに分解する技術を開発した。持続可能なフッ素のリサイクルにつながる成果として期待される。

1/3　恐竜足跡約 200 個を発見、英国で最大規模

英国中南部オックスフォードシャー州でこのほど、1 億 6600 万年前の恐竜の足跡が約 200 個発掘された。同国で発見されたものとしては最大規模とみられる。

1/3　iBio（本社：カリフォルニア州サンディエゴ）、筋肉量を維持する肥満治療薬の開発で AstralBio（本社：マサチューセッツ州ボストン）と 2,900 万ドルのバイオバックス契約を締結

iBio は、既存のパートナーである AstralBio と、筋肉量を維持しながら減量を誘発できると期待される前臨床段階の抗ミオスタチン抗体に関するバックロード契約を締結。iBio は最新の契約で 75 万ドルのみを前払いしているが、2,800 万ドルに達する可能性のあるマイルストーン支払いを約束している。

iBio pens $29M biobucks deal with AstralBio for obesity med

1/6　WuXi、メルクとの 5 億ドルの取引で欧米資産売却継続

WuXi Biologics は、アイルランドのダンドークにあるワクチン製造施設を Merck & Co.に約 5 億ドルで売却すると発表。米国政府からの圧力が最近緩和された中でのこの取引は、中国企業にとって欧米市場からのもう一つの大きな撤退を意味する。

China's WuXi Biologics to sell Irish vaccine facility to Merck as US curbs loom | Reuters

1/7　PostEra（本社：マサチューセッツ州ボストン）が Pfizer との人工知能（AI）創薬提携を拡大して ADC も含める

PostEra announces expansion to $610M in their AI drug discovery collaboration with Pfizer

1/7　鏡像異性体に液体のり成分を加えて放射線治療、マウスのがんがほぼ消失 -東大など

がんの放射線治療に用いるホウ素化合物で実用性が低いとみなされていた鏡像異性体に液体のりの成分を加えると、臨床に使われる薬よりもがん細胞により集まってとどまりやすいことを東京大学などのグループが発見した。ホウ素中性子捕捉療法（BNCT）でマウスのがんをほぼ消失させたという。今後、ヒトの膵臓がんなど完治が難しいがんへの応用を目指す。

1/8　Roche 傘下の中外製薬がスイスの ADC 専門企業に 7 億 8,000 万ドルの契約を締結

スイスのバイオテクノロジー企業 Araris Biotech は、ロシュ傘下の中外製薬と次世代の抗体薬物複合体（ADC）に焦点を当てた研究協力およびライセンス契約を締結した。契約額は最大 7 億 8,000 万ドルに上る。

Pharma Industry News and Analysis | FirstWord Pharma
**Roche's Chugai bets on Swiss ADC specialist in $780M pact**

1/8　沢井製薬 タミフル後発薬供給停止

インフルエンザの急激な流行拡大にともない、沢井製薬は 7 日、治療薬「タミフル」のジェネリック医薬品について、製造が追いつかないとして、一時的に供給を停止すると発表した。

1/9　淡水生物 4 分の 1 絶滅危機　日本固有の魚は 4 割

川や湖といった淡水に生息する世界の魚やザリガニ、トンボなど約 2 万 3 千種のうち 4 分の 1 が絶滅の危機にあるとの分析結果を国際自然保護連合（IUCN）のチームが 8 日付の英科学誌「ネイチャー」に発表した。

1/9　シカ科外来動物キョンが房総半島で大繁殖　生息域広がる懸念

シカ科の小さな草食獣「キョン」が房総半島を中心に大繁殖している。特定外来生物として対策が進むが、生息域の拡大も懸念されている。

1/10　アステラス製薬、地図状萎縮薬 Izervay の 2 年間の結果の追加承認申請を FDA が受理した、と発表

Astellas Pharma announces US FDA confirms Class 1 resubmission of the sNDA for Izervay for geographic atrophy

1/10　Eli Lilly が Alchemab Therapeutics の技術頼りの筋萎縮性側索硬化症（ALS）治療抗体探しに取り組む

Lilly crafts deal with UK biotech for new ALS antibodies

1/10　AMD が AI 創薬の Absci に 2000 万ドル投資し、技術を提供

チップ設計会社 AMD は水曜日、人工知能を使って新しい薬物療法を開発することを目指しているバンクーバーの企業 Absci に 2,000 万ドルを投資すると発表した。
Absci は人工知能によって、バイオロジクスと呼ばれるタンパク質ベースの医薬品の開発を加速し、コンピューターを導入してその有効性を評価し、有望な医薬品を迅速に市場に投入できるようになることを期待している。

1/11　抗酸化物質、白髪抑制に効果　植物由来、マウスで確認　−名古屋大など

ブロッコリーやセロリに含まれる抗酸化物質「ルテオリン」に白髪の進行抑制効果があることを、名古屋大などの研究チームがマウスを使った実験で確認した。内服でも塗布でも効果があるといい、今後ヒトでも有効性や安全性の検証が進めば、白髪予防・改善薬の開発につながると期待される。論文は 11 日までに、国際学術誌アンチオキシダンツに掲載された。

1/11　肝臓がんの増殖抑制に新治療 -近畿大など国際チーム…専門家「新たな標準治療となる可能性も」

血管の近くにあるなど手術で取り切れない肝臓がんに対し、既存の治療薬 2 剤を投与する手法でがんの増殖を抑える期間を 1.5 倍に延ばせることを確認したと、近畿大などの国際共同研究チームが 10 日、発表した。新たな治療法として有望といい、論文が国際医学誌ランセットに掲載された。

1/13　J&J が Intra-Cellular Therapies（本社：ニューヨーク）を 146 億ドルで買収

Intra-Cellular Therapies は神経精神疾患および神経疾患の治療薬を開発するバイオ製薬会社で、最も注目すべき製品は Caplyta（カプリタ）、これは統合失調症および双極性うつ病の治療に承認されている。
Johnson & Johnson は、約 146 億ドルで この Intra-Cellular Therapies を買収して、精神健康および中枢神経系障害の市場に強力な拠点を築くことができる、とされている。

J&J to buy Intra-Cellular Therapies in deal worth $14.6B

1/14　Eisai/Biogen のアルツハイマー病薬 Leqembi 皮下注射品の承認申請を FDA が受理

1/15　日本新薬が Regenxbio（本社：メリーランド州ロックビル）のムコ多糖症遺伝子の米国とアジアでの販売権利を取得

REGENXBIO and Nippon Shinyaku Announce Exclusive Partnership to Develop and Commercialize RGX-121 and RGX-111 for MPS Diseases

Regenxbio Secures A Partnership With Nippon Shinyaku For RGX-111 & 121 | Seeking Alpha

RegenXBio sells Hunter syndrome gene therapy commercial rights

1/16　Lilly の昨年の売り上げは予想より約 4 億ドル少ない 450 億ドルとなる見込みで、株価下落

1/17　Emergent BioSolutions（本社：メリーランド州）が Hikma（本社：ロンドン）のオピオイドオーバードーズ薬の米国/カナダ販売権利取得

Emergent BioSolutions, Hikma enter partnership for sale of Kloxxado nasal spray | Markets Insider

1/18　世界初の完全にロボットで行う両肺移植手術に成功、従来に比べ術後の痛みも軽減　米

ニューヨークの病院で、世界初の完全にロボットで行う両肺移植手術が行われ、成功した。この手術は治癒プロセスを早め、入院期間を短縮することを目的としている。ロサンゼルスの病院が 2022 年に部分的なロボットによる片肺移植手術を実施したほか、昨年 9 月にはニューヨーク大学ランゴーン・ヘルスセンターで、初の完全にロボットによる片肺移植手術が実施された。今回の手術は、こうした低侵襲（患者の身体への負担が少ない）手術をベースにしている。

1/19　中国で「第 2 のコロナ」が大流行

5 年前の悪夢が再びよみがえるのか――。中国でヒトメタニューモウイルス（HMPV）感染症が大流行している。中国政府は感染者数を公表していないものの、現地の SNS 上では患者であふれかえった病院の動画が公開され、中には処置室に入りきらず待合室で点滴を受けている患者もいるという。
さらにアメリカやインドでも感染者が確認されたことから、「第 2 の新型コロナウイルス」とみてパンデミックを懸念する声も少なくない。

見過ごされてきた「ヒトメタニューモウイルス」、中国で感染拡大。公衆衛生への影響は？ | WIRED.jp

1/20　第一三共/AstraZeneca の乳癌薬 Datroway（ダトロウェイ）を FDA が承認

AstraZeneca And Daiichi Sankyo's Datroway Gets US Approval For Metastatic HR+ Breast Cancer | Markets Insider

1/20　トランプ大統領、世界保健機関からの脱退命令に署名

ドナルド・トランプ大統領は、世界保健機関が COVID-19 パンデミックやその他の国際保健危機への対応を誤ったとして、米国は世界保健機関から脱退すると述べた。また、WHO は「WHO 加盟国の不適切な政治的影響」から独立して行動できず、中国など他の大国が提供する金額とは釣り合いが取れない「不当に重い支払い」を米国に要求したとして、世界保健機構からの脱退命令に署名した。通知から 1 年後の脱退となる。

Trump orders US exit from the World Health Organization | Reuters

1/21　中国、米国脱退後も WHO を支援と表明、WHO は「遺憾に思う」「アメリカが再考すること望む」との声明

1/21　約 600 時間 1,328 回の排尿を観察…チンパンジーが“つられション”することを京都大学の研究チームが発表　世界初の研究結果

1/21　危険な合併症の兆候を解明…京大チーム、悪性リンパ腫の新治療法で

悪性リンパ腫などの新しい治療法として注目される「 CAR カー ― T ティー 細胞療法」について、治療を受けた患者の一部で起きる呼吸困難などの危険な合併症の兆候を突き止めたと、京都大チームが発表した。喉の奥などが腫れて呼吸困難を起こす前に、血液中で炎症を起こす物質が増えるなどの兆候がみられた。論文が国際医学誌に掲載された。

1/22　iPS 細胞由来の精子や卵子で受精卵作製を容認へ　内閣府調査会

内閣府の生命倫理専門調査会は 22 日、ヒトの iPS 細胞（人工多能性幹細胞）などから作った精子や卵子を用いて受精卵（ヒト胚）をつくる基礎研究について、条件付きで容認することを大筋で了承した。現在は国の指針で禁止されているが、2 月にもまとまる報告書を受けて指針が改正され、研究が解禁される。

1/22　武田が支援する中国の癌治療薬開発会社 Ascentage Pharma が、米国上場により 1 億 4,900 万ドルの調達を目指す

Ascentage Pharma は、ナスダックでの IPO で 1 億 4,900 万ドル弱の調達を目指しており、今年米国上場を目指す最初の大手中国企業となる。2019 年に香港で上場したこの会社は、730 万の米国預託株式（ADS）を 1 株 20.34 ドルで売却し、17 億 5,000 万ドルの評価額を目指している。1 株の ADS は普通株 4 株に相当する。

1/22　医療機関の倒産廃業、786 件　24 年、過去最多で 7 割が診療所

1/22　トランプ政権、保健機関の多くの報告書とオンライン投稿を凍結

Trump administration freezes many health agency reports and online posts | AP News

1/23　AbbVie と Neomorph（本社：カリフォルニア州サンディエゴ）が 16 億 4,000 万ドル相当の分子接着剤分解剤パートナーシップを締結

AbbVie and Neomorph seal glue degrader deal | The Pharmaletter

1/24　AstraZeneca が 5 億 7,000 万ドルを投じてカナダでの取り組みを広げる

去年カナダのトロントの Fusion Pharmaceuticals を買った AstraZeneca が 5 億 7,000 万ドルを投じて同国での取り組みを広げる。

1/24　電子処方箋、病院導入 4% 「ニーズ感じない」 厚労省、目標見直し

国が今年 3 月までに、ほぼ全ての医療機関や薬局で運用をめざすとしていた「電子処方箋（せん）」の普及が進んでいない。医療機関での導入率は 1 割にも満たない状況で、福岡資麿厚生労働相は 22 日、目標を見直すと発表した。対応策を検討し、今年夏をめどに新たな目標を設定する。

1/24　介護休業、子も「対象」と明記　障害児や医療的ケア児

厚生労働省は 24 日、企業などが従業員の介護休業を認めるかどうかの判断基準に、障害児や医療的ケア児も対象として明記する方針を決めた。現行でも子の介護のための休業は認められているが、基準は高齢者を念頭にしており、子の場合は対象なのかが分かりにくいとの指摘があった。4 月から運用する。

1/24　中国の Ascentage は米国デビューで苦戦、Aardvarg も参入

Ascentage Pharma は、新年初のバイオテクノロジー企業として NASDAQ に上場したが、同社の上場は目指していた高みには届かなかった。
Ascentage に加えて、少なくとも 8 つのバイオテクノロジー企業が上場に関心を示しており、その一つ Aardvarg（本社：カリフォルニア州サンディエゴ）も参入。Aardvark は肥満分野で名を馳せたいと考えているが、この分野に資金が流入していた 2024 年初頭のピークから、この市場の勢いは大幅に鈍化しているようだ、とされている。

Pharma Industry News and Analysis | FirstWord Pharma
**Ascentage takes a haircut in US debut as Aardvark throws its hat into the ring**

1/24　AstraZeneca が 5 億 7,000 万ドルを投じてカナダでの取り組みを広げる

Pharma Industry News and Analysis | FirstWord Pharma
**AstraZeneca's $570M investment highlights Canadian life science innovation**

1/25　Merck の Keytruda とエーザイの Lenvima の併用療法 Ph3 試験、胃食道癌の生存目標未達成

Pharma Industry News and Analysis | FirstWord Pharma
**Keytruda, Lenvima duo misses one survival goal, meets another in gastroesophageal cancer**

1/25　欧州医薬品庁（EMA）が X（元 Twitter）から Bluesky に引っ越し

EMA joins mass migration from Twitter to Bluesky

1/25　アステラス製薬が、イゼルベイの EU での将来不透明で、11 億ドルの減損費用を計上

Pharma Industry News and Analysis | FirstWord Pharma
**Izervay's EU future uncertain as Astellas reveals $1.1B impairment charges**

1/27　Biogen/Eisai のアルツハイマー病薬 Leqemb の月 1 回投与を FDA が承認

1/28　日本新薬がスイスの AB2 Bio の NLRC4 変異/XIAP 欠損症薬の米国販売選択権利を取得

Nippon Shinyaku pays $36M for rights to near-approval IL-18 drug

1/28　ガムをかむと食道がんの術後合併症予防に有効 岡山大

食道がん手術後は、口腔機能が低下し、誤嚥（ごえん）や発熱、肺炎といった合併症が起こりやすい。岡山大学の研究グループは、手術前後にガムをかむトレーニングが術後合併症を安全に予防する可能性と有効性があることを確認した。今後は日常で嚥下（えんげ）機能の低下に悩む高齢者などにも応用できるのではないかとしている。

1/29　痛風治療薬の栄光が薄れつつある中、武田薬品の痛風薬 Uloric が米国で販売中止

今週、2009 年に初めて承認されたこの薬は、FDA のオンライン医薬品不足データベースで製造中止としてリストされた。製造中止を緩和するため、武田は 2026 年 3 月 31 日まで米国の卸売業者にウロリックの流通を継続し、年末まで患者に十分な在庫を提供する予定。近年困難に直面していた武田の痛風治療薬ウロリックの旅は、米国で終焉を迎えた。

Takeda discontinues gout med Uloric in US

1/29　「両親とも雄」マウス　遺伝子操作などで誕生、成長　ヒトの難病解明期待・中国科学院

クローンや胚性幹細胞（ES 細胞）、遺伝子操作などの技術を組み合わせ、「両親とも雄」のマウスの子を誕生させたと、中国科学院動物研究所などの研究チームが 28 日付の米科学誌セル・ステムセル電子版に発表した。成体まで成長したものの生殖能力はなく、短命だったという。
ヒトで「両親とも男性」の子を同様の方法で誕生させるのは技術的に困難である上、国際幹細胞学会の指針で禁止されているが、マウスでの研究成果は同疾患のメカニズム解明や治療法の開発に役立つという。

1/29　Ph2 試験で安全性懸念に見舞われた BioAge（本社：カリフォルニア州リッチモンド）の肥満薬 azelaprag の開発中止

BioAge Labs は、一部の患者で特定の肝酵素の高値が観察されたため、実験的肥満薬の中間段階の治験を中止すると発表。これにより、株式はアフターマーケット取引で 73%近く下落し、5.40 ドルとなった。

BioAge axes obesity asset over liver toxicity

1/30　Cullinan（本社：マサチューセッツ州ケンブリッジ）/大鵬薬品の zipalertinib が肺癌 Ph2 奏効目標達成～米国に今年後半承認申請

Cullinan plans approval push for NSCLC drug after ph. 2 win

1/31　武田薬品が米国事業長 Julie Kim 氏を次の CEO に指名、何世紀もの歴史を持つ製薬会社初の女性 CEO

キム氏は 2019 年のシャイアー買収により武田に入社。2022 年 4 月に米国事業の責任者に就任する前は、近年武田の売上の主力である血漿分画療法事業を率いていた。

Takeda Picks First Woman as CEO of Centuries-Old Drugmaker - Bloomberg

1/31　武田薬品が Ph3 試験失敗のてんかん薬 Soticlestat（ソチクレスタット）の開発中止

Takeda axes epilepsy asset after FDA weighs in on data package

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. 雄マウスでは初期の「運」が生涯の競争優位に影響

2. マウスと人間における主要な癌免疫療法ターゲットの驚くべき相違点

3. COVID 出現から 5 年後：多くの人が忘れているパンデミックから学ぶこと

4. 一般的な睡眠補助薬ゾルピデムが睡眠中の脳の洗浄を妨げる可能性 −マウス実験

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8. 体脂肪を減らしながら筋肉を維持する鍵となる分子発見 −マウス実験

9. 遅延する REM 睡眠がアルツハイマー病早期兆候の可能性

## 1. 雄マウスでは初期の「運」が生涯の競争優位に影響

**研究情報**

- **論文タイトル**: Competitive social feedback amplifies the role of early life contingency in male mice
- **発表日**: 2025 年 1 月 3 日
- **ジャーナル**: Science
- DOI: 10.1126/science.adq0579
- **出典**: アメリカ科学振興協会（American Association for the Advancement of Science, AAAS）

**概要**

コーネル大学の Matthew Zipple 氏を筆頭とする研究チームによって行われた新しい研究によると、雄マウスにおいて、初期の「運」が個性や成功に大きく影響を与えることが明らかになった。この研究では、雄マウスにおける社会的競争が、幼少期の些細な違いを増幅させ、生涯にわたる格差を生み出すことが示された。

主な発見：

- 初期の偶然の出来事
  幼少期の微細な環境要因が、発達や行動の分岐を引き起こす可能性がある。この偶然性（「運」）は、特に社会的動物のグループ内では影響が増幅される。
- 「マタイ効果」との類似性
  初期に成功を収めた者が、その後もさらに成功を収める現象である「マタイ効果」が、雄のマウスにおける資源のアクセス、体調、繁殖といった成功指標に関連して観察された。
- 雄と雌の違い
  雄のマウスでは競争的な社会的フィードバックによって、初期の差異が拡大された。一方で、雌は資源を巡る競争を行わないため、このような差異の増幅は見られなかった。

結論と意義：

この研究は、生物学的および社会学的な文献を補完するものであり、予測不可能で制御不可能な経験が、基盤となる才能や質にほとんど違いがなくても、結果に違いを生じさせる可能性を示している。

研究関連ニュース/他のトップページに戻る

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＜英文＞Early life “luck” among competitive male mice | EurekAlert!

**News Release 2-Jan-2025**

# Early life “luck” among competitive male mice leads to competitive advantage overall

**Summary author: Walter Beckwith**

**Peer-Reviewed Publication**

**American Association for the Advancement of Science (AAAS)**

Early life "luck" plays a pivotal role in shaping individuality and success, particularly for males, according to a new study in mice. In male animals, competitive social dynamics amplified small initial differences into lifelong disparities in fitness. The findings highlight parallels between biological competition and societal inequalities and they demonstrate how chance events can drive divergent outcomes even among genetically identical individuals. Contingency (colloquially, "luck") refers to the role of chance in shaping outcomes. It is a critical factor in both biological and social sciences, particularly during early life, when pivotal events can set individuals on diverging trajectories. This is especially pronounced in social animals, where interactions within groups amplify the impact of early contingent events. This often creates self-reinforcing disparities in access to resources and success, akin to the "Matthew effect" discussed in social sciences in which those who achieve early success tend to achieve ever greater success in the future. To date, studying the role of contingency in life outcomes has been challenging due to the difficulty of experimentally isolating and testing the effects of early life circumstances under controlled conditions. Matthew Zipple and colleagues compared the developmental trajectories of genetically identical, free-living mice to better understand how microenvironmental differences during development interact with competitive social processes to shape individuality and behavior over time. Zipple *et al.* found that competition among male mice amplifies minor early life differences, laying the foundation for divergent life paths that affect adult success in areas such as resource access, body condition, and reproduction. In contrast, females – who do not compete for resources – did not show this pattern of contingency amplification. These findings suggest that competitive social dynamics play a critical role in the earlier and more pronounced development of individuality in males compared to females. "Our results add to sociological and biological literature that underscores the potential importance of unpredictable, uncontrollable experiences in generating differences in outcomes even when differences in underlying quality (or "talent") are small or nonexistent," write Zipple *et al*.

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**Journal**

Science

**DOI**

10.1126/science.adq0579

**Article Title**

Competitive social feedback amplifies the role of early life contingency in male mice

**Article Publication Date**

3-Jan-2025

## 2. マウスと人間における主要な癌免疫療法ターゲットの驚くべき相違点

**研究情報**

- **論文タイトル**: Functional differences between rodent and human PD-1 linked to evolutionary divergence
- **発表日**: 2025 年 1 月 3 日
- **ジャーナル**: Science Immunology
- **DOI**: 10.1126/sciimmunol.ads6295
- **出典**: カリフォルニア大学サンディエゴ校（UC サンディエゴ）

**概要**

カリフォルニア大学サンディエゴ校（UC サンディエゴ）の研究チームは、癌免疫療法のターゲットとして注目されてきた「プログラム細胞死タンパク質 1（PD-1）」について、マウスと人間で大きな機能的違いがあることを発見した。この結果は、従来信じられてきたマウスと人間の生物学的類似性という仮定に疑問を投げかけるものとなった。

主な発見：

- PD-1 の種特異的な特徴
  PD-1 は、免疫細胞の活動を制御する「チェックポイント受容体」として知られており、癌治療の重要なターゲットとなっている。しかし、マウスの PD-1 は人間のものよりも著しく弱いことが判明した。これは、PD-1 の特定のアミノ酸配列（モチーフ）がマウスでは欠けているためであり、この特徴は他の哺乳類には見られない。
- 進化的な違い
  PD-1 の人間とマウスの違いは、6,600 万年前の白亜紀末の大量絶滅イベント（K-Pg 境界）の後に生じた可能性がある。この時期に、マウスの祖先は新しい環境への適応を余儀なくされ、免疫受容体の活動が変化したと考えられる。
- マウスモデルの限界
  マウスの PD-1 を人間のものに置き換えた実験では、T 細胞が腫瘍と戦う能力が低下した。この結果は、マウスが PD-1 活性の観点で「例外的」な存在であることを示しており、薬の開発におけるモデルシステムの見直しが必要であることを示唆している。

結論と意義：

この研究は、免疫療法の前臨床モデルとしてのマウスの限界を浮き彫りにし、より正確なモデルシステムの開発が必要であることを強調している。また、進化的視点から免疫チェックポイント受容体の機能的多様性を理解する重要性を示している。

研究関連ニュース/他のトップページに戻る

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＜英文＞Scientists unveil surprising human vs mouse d | EurekAlert!

News Release 3-Jan-2025

# Scientists unveil surprising human vs mouse differences in a major cancer immunotherapy target

Results of a comprehensive analysis refute assumptions that a key immune checkpoint receptor functions the same in rodents and humans

Peer-Reviewed Publication

University of California - San Diego

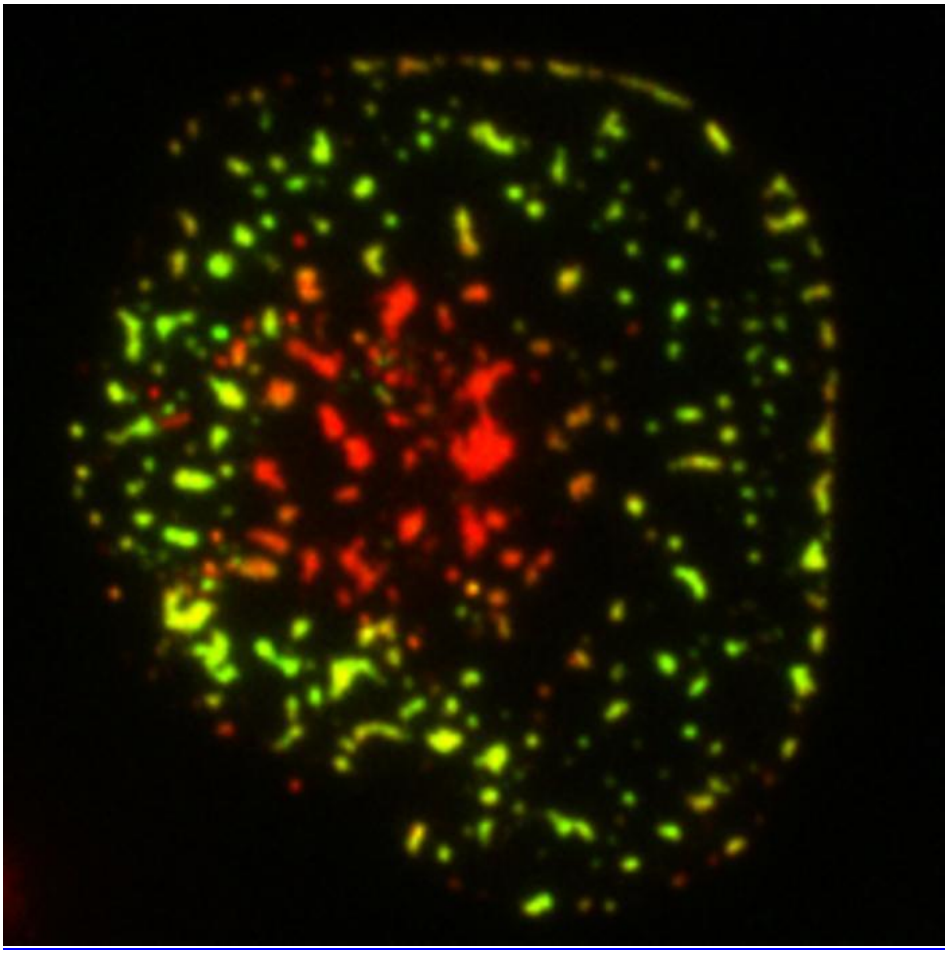

image:

A fluorescent microscope image depicts the spatial pattern of an immunoreceptor (red) and its effector molecules (green) at the plasma membrane of a simulated T cell.

view more

Credit: Hui Lab, UC San Diego

Since its discovery in the 1990s, "programmed cell death protein 1," or PD-1, has been regarded as a leading target in cancer treatments. A "checkpoint" receptor that often resides on the surface of immune system cells, the PD-1 molecule works as a type of off switch that keeps immune cells from attacking other cells.

After its discovery, which revolutionized oncology and earned a 2018 Nobel Prize, researchers developed new drugs to block PD-1 and unleash the body's immune system to fight cancer. Yet treatments leveraging PD-1 are only effective in a small fraction of cancer patients, highlighting the need for a deeper understanding of how PD-1 works. Much of our current knowledge of PD-1's functions comes from studies in mice, grounded on the assumption that rodent and human biology operate similarly.

Researchers in UC San Diego's School of Biological Sciences and School of Medicine have now discovered that this assumption may be flawed. In a comprehensive assessment of PD-1 that featured novel biochemical analyses, animal modeling and a new evolutionary roadmap tracing PD-1 back millions of years, the UC San Diego scientists and their colleagues at the Chinese Academy of Sciences found that PD-1 in mice is significantly weaker than the human version.

The study, led by assistant project scientist Takeya Masubuchi, revealed several previously unknown PD-1 characteristics, including a "motif" — a specific sequence of amino acids — that is vastly different in rodents and humans.

"Our work uncovers unexpected species-specific features of PD-1 with implications for developing better pre-clinical models for PD-1," said Associate Professor Enfu Hui of the School of Biological Sciences, Department of Cell and Developmental Biology, and a senior author of the paper. "We found a motif in PD-1 that's present in most mammals, including humans, but is surprisingly missing in rodents, making rodent PD-1 uniquely weaker."

The results of the study are published January 3, 2025, in the journal *Science Immunology*.

"Although many proteins in mice and humans have similar sequences, receptors in the immune system often show greater differences," said Masubuchi. "Our study shows that these sequence differences can lead to functional variations of immune checkpoint receptors across species."

Furthering their analysis, the researchers tested the impact of PD-1 humanization in mice — replacing mouse PD-1 with the human version — through co-senior author Professor Jack Bui's laboratory in the Department of Pathology. They found that PD-1 humanization disrupted the ability of immune cells (T cells) to combat tumors.

"This study shows that as science progresses we need to have a rigorous understanding of the model systems that we use to develop medicines and drugs," said Bui. "Finding that rodents might be outliers in terms of PD-1 activity forces us to rethink how to deploy medicines to people. If we've been testing medicines in rodents and they're really outliers, we might need better model systems."

To trace the PD-1 human-rodent differences over time, the researchers collaborated with co-senior author Professor Zhengting Zou and his Chinese Academy of Sciences colleagues. They discovered evidence of a major dip in ancestral rodent PD-1 activity around 66 million years ago after the Cretaceous–Paleogene (K–Pg) mass extinction event, which wiped out the (non-avian) dinosaurs. The analysis showed that the rodent PD-1 is uniquely weak among all vertebrates. The weakening

may be attributed to special ecological adaptations to escape the effects of rodent-specific pathogens.

"The rodent ancestors survived the extinction event but their immune receptor activities or landscape might have been altered as a consequence of adaptation to new environmental challenges," said Hui.

Future studies will assess the impact of PD-1 on the anti-tumor activity of T cells in a humanized context across various tumor types.

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**Journal**

Science Immunology

**DOI**

10.1126/sciimmunol.ads6295

**Method of Research**

Experimental study

**Subject of Research**

Animals

**Article Title**

Functional differences between rodent and human PD-1 linked to evolutionary divergence

**Article Publication Date**

3-Jan-2025

**COI Statement**

Enfu Hui consults for Tentarix Biotherapeutics. Jack Bui consults for Valora and DrKumo and serves as chief scientific officer for Paramita Therapeutics and Pathfinder.

## 3. COVID 出現から 5 年後：多くの人が忘れているパンデミックから学ぶこと

**新型コロナウイルス（COVID-19）パンデミックに関する会議の要約：**
2024 年 10 月時点で、COVID-19 による死亡者は毎週約 1,000 人にのぼり、その 75%がアメリカでの死亡者だった。それにもかかわらず、感染症対策への関心が薄れ、パンデミックから得られた教訓が無視されつつある。WHO の疫学者 Maria Van Kerkhove 氏は、「世界はパンデミックが起きなかったかのように振る舞っている」と強調した。
会議の背景と目的：
日本の淡路島で開催されたこの会議には、17 カ国から 140 人の研究者と保健関係者が集まり、パンデミックの起源や新しい治療法、将来の感染症に備えるワクチン戦略について議論した。特に、中国の研究者との国際的な協力を強化することが狙いだった。
主な議論の内容：

- SARS-CoV-2 の進化
  北京大学の免疫学者 Yunlong Cao 氏は、ウイルスの「驚異的な進化速度」によって新しい変異株が再感染を引き起こし、既存の抗体治療やワクチンの効果がすぐに失われる現状を説明した。彼のチームは、少なくとも 2 年間効果を維持すると予測される抗体「SA55」を特定し、それを用いた鼻スプレー型予防薬の臨床試験を進めている。
- AI によるウイルス進化の予測
  コンピュータ生物学者 David Robertson 氏は、AI を使ってウイルスの進化を予測する技術について報告した。この技術によって、より長期間効果を持つワクチンの設計が可能になると期待されている。
- パンデミックの起源について
  武漢市場での動物がパンデミックの起源だとする説を支持する研究者が多い一方で、研究所流出説を支持する研究者もいる。Angela Rasmussen 氏は市場由来説を支持する新たな証拠を提示し、環境サンプルから検出された動物の遺伝子が感染を示す可能性を指摘したが、決定的な証拠には至らなかった。一方、Jesse Bloom 氏は研究所流出説の可能性も排除すべきでないと主張している。
- パンデミック予防への関心の低下
  多くの国がパンデミック予防研究に反感を示し、科学者や研究所への脅威も増している。Maria Van Kerkhove 氏は、新しい病原体に備えるための体制が弱体化している現状を危惧している。

結論と今後の課題：
パンデミックの教訓を忘れず、感染症対策への関心を取り戻す必要がある。特に、動物から人間への感染リスクが高い病原体に対する研究を強化し、効果的なモデルシステムを構築することが求められる。また、ウイルスの進化を予測し、長期的に効果を持つワクチンや治療法を開発することが重要だ。

研究関連ニュース/他のトップページに戻る

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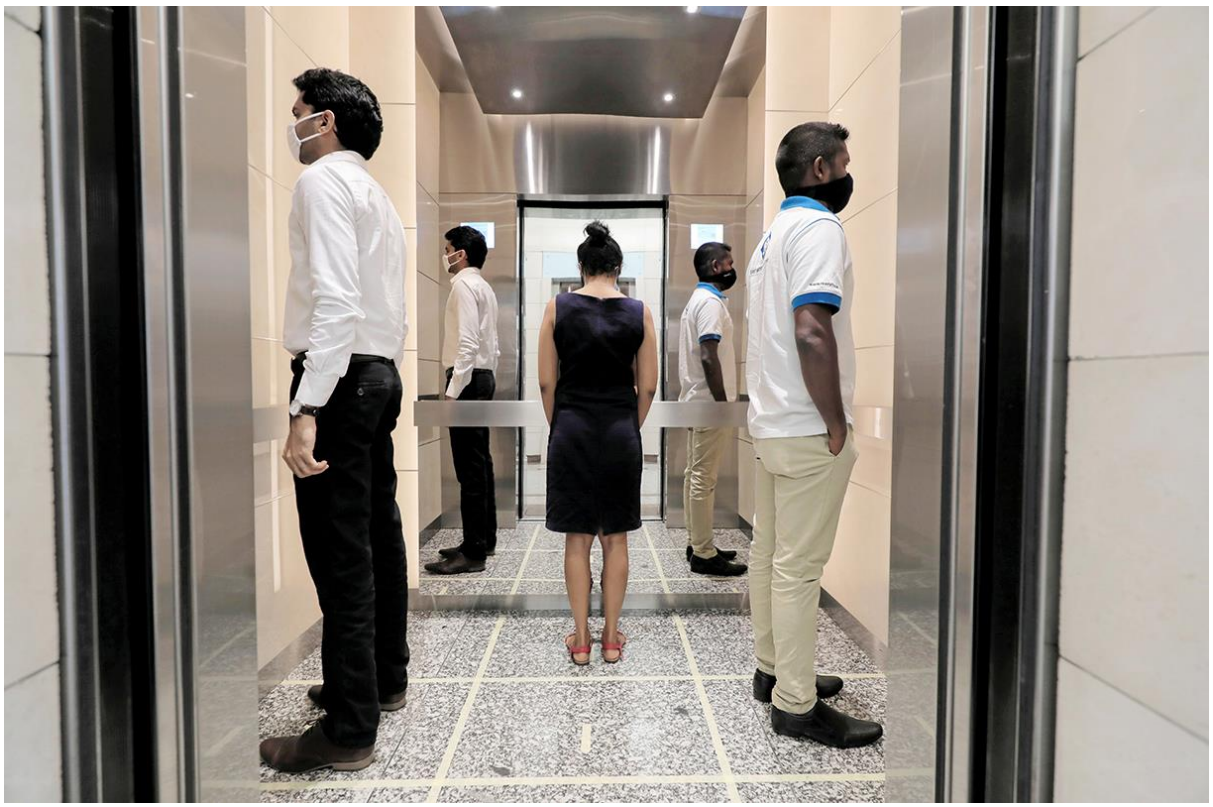
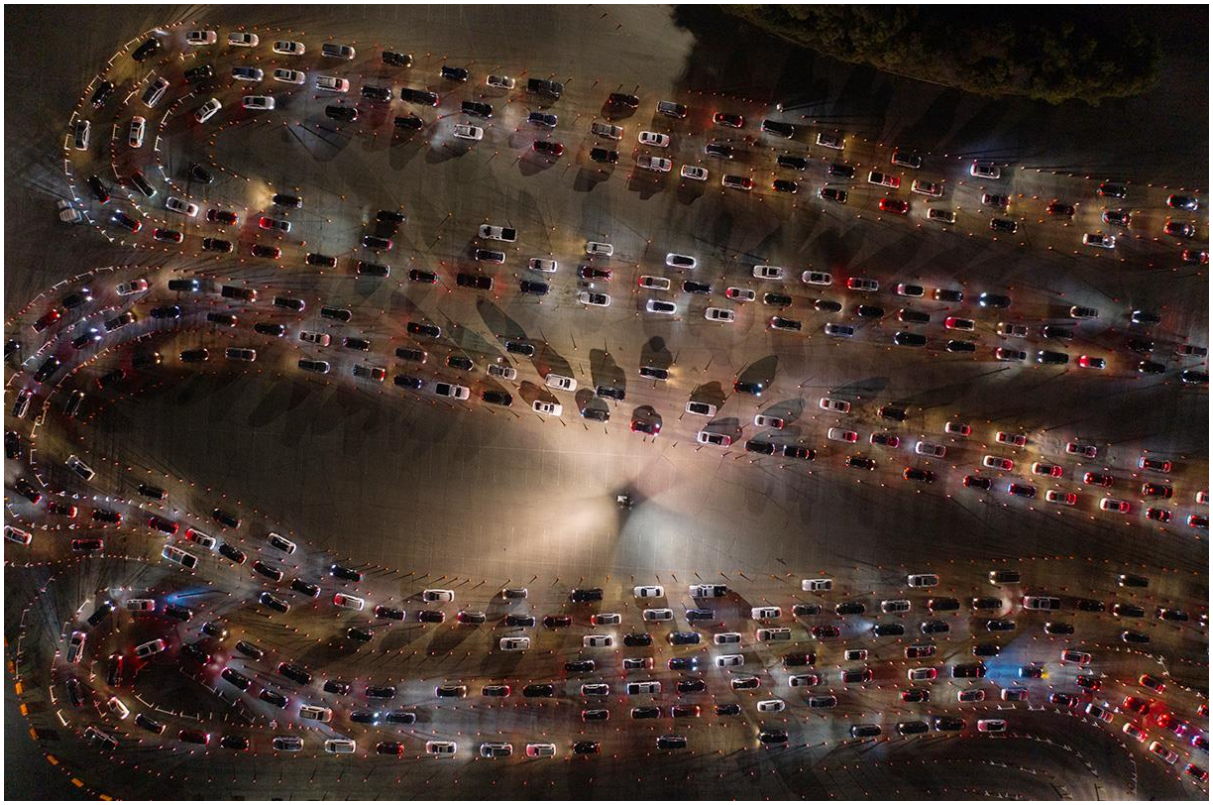
＜英文＞COVID 5 years later: Learning from a pandemic many are forgetting | Science | AAAS

A version of this story appeared in Science, Vol 387, Issue 6729.Download PDF





**COVID-19 overwhelmed hospitals in Wuhan, China, in January 2020.HECTOR RETAMAL/AFP via Getty Images**

AWAJI, JAPAN—The COVID-19 pandemic, as best as we can tell, took more than 20 million lives, cost $16 trillion, kept 1.6 billion children out of school, and pushed some 130 million people into poverty. And it's not over: Figures from October 2024 showed at least 1000 people died from COVID-19 each week, 75% of them in the United States, and that's relying only on data from the 34 countries that still report deaths to the World Health Organization (WHO). Last month, at a 4-day meeting here on preventing future pandemics, WHO epidemiologist Maria Van Kerkhove ticked off those figures with exasperation. "The world I live in right now, no one wants to talk about COVID-19," she told the gathering. "Everyone is acting as though this pandemic didn't really happen."

Yet 5 years after a coronavirus dubbed SARS-CoV-2 first surfaced in Wuhan, China, scientists are still intensively trying to make sense of COVID-19. "We would each have to read over 240 papers every single day to actually keep up with all of the [COVID-19] literature that's come out" in 2024, Cherilyn Sirois, an editor at *Cell*, noted.

Despite the flood of insights into the behavior of the virus and how to prevent it from causing harm, many at the meeting worried the world has turned a blind eye to the lessons learned from the pandemic. "I feel this massive gravitational pull to go back to what we were doing before," Van Kerkhove said. "There's no way we should be going back."

Even more concerning to some at the conference, many countries have actually become hostile toward pandemic prevention research, much of the anger stemming from an unproven assertion that SARS-CoV-2 leaked from a lab. "There's been massive public and political backlash against the virology community and public health in general, so we may be worse off now locally than we were prior to the pandemic," said virologist Ralph Baric of the University of North Carolina at Chapel Hill, who was recently accused by Robert Redfield, former head of the U.S. Centers for Disease Control and Prevention, of being the "scientific mastermind" of a supposed effort to engineer the virus.

The conference, held under the auspices of Cold Spring Harbor Asia, brought together 140 researchers and health officials from 17 countries to discuss everything from the origin of the pandemic to SARS-CoV-2's mutational patterns, new treatments, and creative vaccine strategies to fend off future threats. "One of the big reasons we wanted to hold this conference is because we couldn't meet in person during the pandemic," said virologist Kei Sato of the University of Tokyo, an organizer. He also hoped the location would attract infectious disease scientists from China, who have had limited interactions with the global research community since 2020.

Some 20 scientists from China attended, but two of the country's most prominent COVID-19 researchers were notable no shows. Shi Zhengli, who studied bat coronaviruses at the Wuhan Institute of Virology (WIV) and became the focus of intense criticism by people who suspect SARS-CoV-2 leaked from her lab, only gave a prerecorded video talk—on the sequencing of other coronavirus genomes—despite being a co-organizer of the event. So did Chinese Academy of Sciences virologist George Gao, former head of China's Center for Disease Control and Prevention. Sato suspects the Chinese government would not let either attend. Shi, now with the Guangzhou Laboratory, and Gao both declined to explain their absence to *Science*.

A Chinese scientist did offer one of the most provocative presentations. Immunologist Yunlong Cao of Peking University, another organizer of the meeting, noted the "extraordinary viral evolutionary speed" of SARS-CoV-2 not only means fresh variants are "continuously causing reinfections," but that antibody treatments and vaccines can quickly lose effectiveness. None of the first approved monoclonal antibodies and vaccines work against current circulating strains.

Cao noted that only two of 140 antibodies his lab identified in early 2020 as able to neutralize the first variant of SARS-CoV-2 could protect against the virus in circulation 2 years later. "The only solution to this problem," he said, "is if we can do accurate predictions about viral evolution" to assess which antibodies will retain their powers.

Cao's group recently identified an antibody, dubbed SA55, he predicts will work against whatever SARS-CoV-2 variants evolve for at least two more years. His team began by drawing blood from an unusual cohort of 28 people; nearly 2 decades ago each had recovered from severe acute respiratory syndrome (SARS), a severe illness caused by another coronavirus, and then during the pandemic received vaccines against SARS-CoV-2. The researchers isolated some 13,000 memory B cells and screened the antibodies they made for the ability to neutralize both coronaviruses and several relatives found in bats and other species. SA55 stood out as a superstar.

Sinovac Biotech, one of China's largest pharmaceutical companies, has tested a nasal spray containing SA55 as a preventive. In clinical trials, researchers gave it at least two times each day to participants who came in contact with infected people at home or work. The spray had about 80% efficacy at preventing infections, according to still unpublished work, Cao says. Under "compassionate use" regulations, some 300,000 people in China have already received this spray and Sinovac plans a large phase 3 efficacy study. "We still know very little about nasal antibodies and we are trying hard to advance the knowledge in this field," says Cao, who licensed the antibody to Sinovac.

Accurately predicting how viruses will evolve could also allow vaccinemakers to design more durable products. Computational biologist David Robertson of the University of Glasgow is part of a growing effort to peer into the future of SARS-CoV-2 with artificial intelligence (AI). Specifically, they're using protein language models—which convert genetic sequences of the virus into predicted protein structures—to map "evolutionary landscapes" that indicate how viral proteins might mutate and still retain their ability to infect new hosts and copy themselves. Ultimately, Robertson says, the models present the "exciting" possibility that they could guide design of vaccines that produce antibodies able to thwart a wide range of potential variants.

Many speakers emphasized that Omicron and other SARS-CoV-2 "variants of concern" have evolved in people who have weakened immune systems and cannot quickly clear infections. "A compromised host comes along and a weirdo virus comes out," said University of Sydney evolutionary biologist Edward Holmes. He calls AI prediction of virus evolution an "amazing tool," but cautions it has "a good way to go" in forecasting the variants that will emerge during ever changing pandemic environments.

Presenters also explored how to protect against other threatening coronaviruses. Molecular pharmacologist Gurpreet Brar of the Coalition for Epidemic Preparedness Innovations (CEPI) described how the nonprofit is funding development of vaccines for nine coronaviruses that have been found in mink, pigs, cattle, dogs, camels, and bats. "These are ones that have a high risk of spillover, and if they were to jump into humans we'd have a big problem," Brar said. The project adds to ongoing efforts by CEPI and others to develop pancoronavirus vaccines that potentially work against all SARS-CoV-2 variants as well as unknown relatives in the same viral family.

Everyone is acting as though this pandemic didn't really happen.
Maria Van Kerkhove/World Health Organization

Major mysteries remain about what SARS-CoV-2 is doing today, and where it came from. There's no consensus on how the virus produces Long Covid, the debilitating symptoms that have afflicted millions after their infections have seemingly been cleared, or how to treat or prevent the condition. And efforts to unravel the pandemic's origin have largely stalled.

Meeting organizers, concerned that people angered by the idea SARS-CoV-2 leaked from a lab would crash the gathering and might harm invited scientists, hired extra security guards. But only one scientist, Jonathan Latham, a virologist with the Bioscience Resource Project, made the case publicly for a lab leak, with a poster contending that SARS-CoV-2 came from WIV, which analyzed body samples from copper miners who mysteriously became ill in 2012. Virologist Angela Rasmussen from the University of Saskatchewan challenged Latham during a heated confrontation at his poster, arguing that no evidence supports his theory. She later gave a talk that described her own attempt to find new information in a much-studied set of "environmental samples" collected between January and March 2020 from the Huanan Seafood Wholesale Market in Wuhan, which has been linked to many of the first COVID-19 cases in December 2019. "I'm slicing the salami ever thinner," Rasmussen said.

She is among a large contingent of researchers at the meeting who contend those samples and other evidence supports the theory that animals at the market carried SARS-CoV-2—and sparked the pandemic.

She reported that the market samples held animal genes that had been turned on by interferon, which occurs during viral infections. Rasmussen ultimately concluded that raccoon dogs and greater hog badgers were the two most likely wild animals at the market to have been infected with SARS-CoV-2. But she acknowledged the limits of this analysis: "Spoiler alert: I have not found an infected animal."

Virologist Jesse Bloom of the Fred Hutchinson Cancer Center, who is not convinced the pandemic began at the market and has urged colleagues to remain open to the possibility of a lab leak, wasn't swayed by Rasmussen's new work. "There's still little actual information about the first human cases," Bloom says. "There's just not a lot of knowledge about what was really going on in Wuhan in late 2019."

Christian Drosten, a coronavirus researcher from the Charité Institute of Virology in Berlin who thinks the evidence strongly supports the market theory, decried the politicization of the origin debate. He was particularly exercised by a recent report from a Republican-led House of Representatives panel arguing that U.S. funding may have helped create SARS-CoV-2 at WIV before it leaked. "It's very clear that they are not only ignoring existing evidence, but they are falsifying the evidence that's on the table," Drosten said. "It's really surprising and puzzling that people at this meeting aren't speaking up. Why don't they go public immediately? We will be quiet until we don't have a chance to speak anymore."

WHO's Scientific Advisory Group for the Origins of Novel Pathogens is expected to issue its own report in the next few weeks. But no one at the meeting anticipated major revelations. "I fully believe there's much more data that's out there that we don't have access to," says Van Kerkhove, who oversees the group. She knows of a Chinese database that has some 500 viral sequences from January and February 2020 that WHO cannot access. "The biggest question I have are the farms," she says, referring to the possibility that SARS-CoV-2 came from animals being bred to sell at markets for their meat.

As for the future, Van Kerkhove warns that the world is dropping its guard against novel pathogens. Infectious disease is "not a safe space to really be working in," she told *Science*. "Labs have been threatened. People have been threatened. Governments don't necessarily want to be the ones to say, 'Hey, we found something new.'"

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doi: 10.1126/science.zl5utoy

## 4. 一般的な睡眠補助薬ゾルピデムが睡眠中の脳の洗浄を妨げる可能性 –マウス実験

**研究情報**

- **論文タイトル**: Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep
- **発表日**: 2025 年 1 月 8 日
- **ジャーナル**: Cell
- DOI: 10.1016/j.cell.2024.11.027
- **出典**: ロチェスター大学医療センター

**概要**

ロチェスター大学医療センターによる研究で、睡眠中に脳内の老廃物を除去する「グリンパティックシステム」の重要性が明らかになった。特に、非レム睡眠中のノルエピネフリン（神経伝達物質）、脳血流量、脳脊髄液（CSF）の同期した振動が、老廃物の除去を促進する役割を果たしていることが示された。この仕組みは、アルツハイマー病などの神経変性疾患の原因となるアミロイドやタウタンパク質の蓄積を防ぐために重要である。

研究では、一般的な睡眠薬であるゾルピデム（商品名：アンビエン）がグリンパティックシステムを抑制し、老廃物除去を妨げる可能性があることが指摘された。この抑制により、長期的には脳の健康を損なうリスクが高まる可能性がある。

研究のポイント：

- グリンパティックシステムの仕組み
  ノルエピネフリンのゆっくりした波動が「マイクロ覚醒」を引き起こし、血管のリズミカルな収縮（血管運動）を促す。これが脳脊髄液を循環させ、老廃物を除去する。
- 新たな観察方法
  研究者たちは、マウスに自由に動かせた状態で脳活動を記録する新たな技術を用いた。これにより、従来の研究方法では得られなかった、睡眠中の脳内での動態を解明した。具体的には、流量ファイバーフォトメトリーという光学技術を使用し、脳波と筋電図を同時にモニターした。この方法では、マウスが麻酔を使わずに睡眠や覚醒を繰り返す際の脳の活動を観察できた。
- 睡眠薬の影響
  ゾルピデムは睡眠を誘導するものの、ノルエピネフリンの振動を抑制し、グリンパティック機能を阻害することが確認された。この結果は、長期的に使用すると脳の老廃物除去機能に悪影響を及ぼす可能性があることを示唆している。

研究の意義と警告：

この研究は、自然な睡眠構造の重要性を強調しており、特定の睡眠薬が長期的に脳の健康に悪影響を与える可能性があると警告している。また、睡眠の修復機能のメカニズムを深く理解するための重要な手がかりを提供した。

研究関連ニュース/他のトップページに戻る

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＜英文＞Common sleep aid may leave behind a dirty bra | EurekAlert!

News Release 8-Jan-2025

# Common sleep aid may leave behind a dirty brain

Peer-Reviewed Publication

University of Rochester Medical Center

Getting a good night's sleep is a critical part of our daily biological cycle and is associated with improved brain function, a stronger immune system, and a healthier heart. Conversely, sleep disorders like insomnia and sleep apnea can significantly impact health and quality of life. Poor sleep often precedes the onset of neurodegenerative diseases and is a predictor of early dementia.

New research appearing in the journal *Cell* describes for the first time the tightly synchronized oscillations in the neurotransmitter norepinephrine, cerebral blood, and cerebrospinal fluid (CSF) that combine during non-rapid eye movement (non-REM) sleep in mice. These oscillations power the glymphatic system—a brain-wide network responsible for removing protein waste, including amyloid and tau, associated with neurodegenerative diseases.

"As the brain transitions from wakefulness to sleep, processing of external information diminishes while processes such as glymphatic removal of waste products are activated," said Maiken Nedergaard, MD, DMSc, co-director of the University of Rochester Center for Translational Neuromedicine and lead author of the study. "The motivation for this research was to better understand what drives glymphatic flow during sleep, and the insights from this study have broad implications for understanding the components of restorative sleep."

The study also holds a warning for people who use the commonly prescribed sleep aid zolpidem. The drug suppressed the glymphatic system, potentially setting the stage for neurological disorders like Alzheimer's, which are the result of the toxic accumulation of proteins in the brain.

## The "missing link" in the glymphatic system

The research, conducted by a team at the University of Rochester and the University of Copenhagen, employed an optic technique called flow fiber photometry combined with electroencephalogram and electromyography monitors. Unlike previous research techniques, which immobilized the mice and used anesthesia to induce sleep, the new approach allowed researchers to record brain activity during long, uninterrupted periods of wakefulness and sleep while allowing mice to move freely during recordings.

The research highlights the critical role of norepinephrine, a neurotransmitter associated with arousal, attention, and the body's response to stress. The team observed that slow synchronized waves of norepinephrine, cerebral blood volume, and CSF flow characterized non-REM sleep. The norepinephrine triggered "micro-arousals," causing vasomotion, the

rhythmic constriction of blood vessels independent of the heartbeat. This oscillation, in turn, generates the pumping action necessary to move CSF in the glymphatic system during sleep.

"These findings, combined with what we know about the glymphatic system, paint the whole picture of the dynamics inside the brain, and these slow waves, micro-arousals, and the norepinephrine were the missing link," said Natalie Hauglund, PhD, first author of the study and currently a postdoctoral fellow at the University of Oxford.

**The hidden risks of sleep aids**

The study also explored whether sleep aids replicate the natural oscillations necessary for glymphatic function. The team focused on zolpidem, a sedative marketed under the name Ambien, which is frequently prescribed to treat insomnia.

While zolpidem effectively induced sleep in the mice, it also suppressed norepinephrine oscillations, disrupting the glymphatic system and impeding the brain's waste-clearing processes, a finding that raises concerns about its long-term use.

Scientists now have a new tool and potential target to improve sleep. "The research provides a mechanistic link between norepinephrine dynamics, vascular activity, and glymphatic clearance, advancing understanding of sleep's restorative functions," said Nedergaard. "It also calls attention to the potentially detrimental effects of certain pharmacological sleep aids on brain health, highlighting the necessity of preserving natural sleep architecture for optimal brain function."

Additional co-authors include Mie Andersen, Klaudia Torkarska, Tessa Radivanovic, Celia Kjaerby, Frederikke Sorensen, Zuzanna Bojarowska, Verena Untiet, Sheyla Ballestero, Mie Kolmos, Pia Weikop, and Hajime Hirase with the University of Copenhagen. The research was supported with funding the Novo Nordisk Foundation, the National Institutes of Health, the US Army Research Office, the Human Frontier Science Program, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, the Simons Foundation, and the Cure Alzheimer Fund.

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**Journal**

Cell

**DOI**

10.1016/j.cell.2024.11.027

**Article Title**

Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep

**Article Publication Date**

8-Jan-2025

## 5. 赤色光が血栓リスクを低下させる可能性 –マウス実験

**研究情報**

- **論文タイトル**: Alterations in visible light exposure modulate platelet function and regulate thrombus formation
- **発表日**: 2025 年 1 月 10 日
- **ジャーナル**: Journal of Thrombosis and Haemostasis
- **DOI**:
- **出典**: ピッツバーグ大学

**概要**

ピッツバーグ大学医学部と UPMC（ピッツバーグ大学医療センター）の研究によると、赤色光（長波長光）を浴びたヒトやマウスは、心臓発作や肺損傷、脳卒中を引き起こす血栓のリスクが低下することが示された。この研究は、血管や動脈の血栓形成を抑える新しい治療法の可能性を示唆している。

研究内容：

- 実験方法
  マウスを対象に、12 時間赤色光、青色光、または白色光を浴びせた後、12 時間の暗闇に置くサイクルを 72 時間続けた。その結果、赤色光を浴びたマウスは、青色光や白色光を浴びたマウスに比べて血栓が約 5 分の 1 に減少した。行動、睡眠、食事、体重、体温に差は見られなかった。
- 臨床データの分析
  白内障手術を受けた 1 万人以上の患者データを分析した結果、青色光を減少させる特殊なレンズを使用した患者は、従来のレンズを使用した患者より血栓リスクが低いことが判明した。この傾向は特に血栓リスクが高い癌患者で顕著だった。
- 赤色光の効果
  赤色光を浴びることで、炎症や免疫系の活性化が抑制されることが確認された。例えば、赤色光を浴びたマウスでは、免疫細胞が作る「NETs（ニュートロフィル細胞外トラップ）」が減少していた。この構造は微生物を捕捉するが、同時に血小板を捕らえ、血栓形成を促進する。また、赤色光により脂肪酸の生成が増加し、血小板の活性化を抑制することで血栓の形成が減少した。
- メカニズムと次の課題
  赤色光は視覚経路を通じて影響を与えることが示され、盲目のマウスや直接血液に光を当てた場合には効果が見られなかった。次のステップとして、赤色光が血栓リスクを低下させる生物学的メカニズムを解明し、臨床試験での効果を検証することが計画されている。

将来的な応用：

赤色光を浴びる治療法をより便利にするために、光量を制御するゴーグルが開発されており、血栓リスクが高い人々への応用が期待されている。これにより、世界中で血栓による死亡や障害を大幅に減らす可能性がある。

研究関連ニュース/他のトップページに戻る

＜英文＞Red light linked to lowered risk of blood clo | EurekAlert!

**News Release 10-Jan-2025**

# Red light linked to lowered risk of blood clots

Peer-Reviewed Publication

University of Pittsburgh

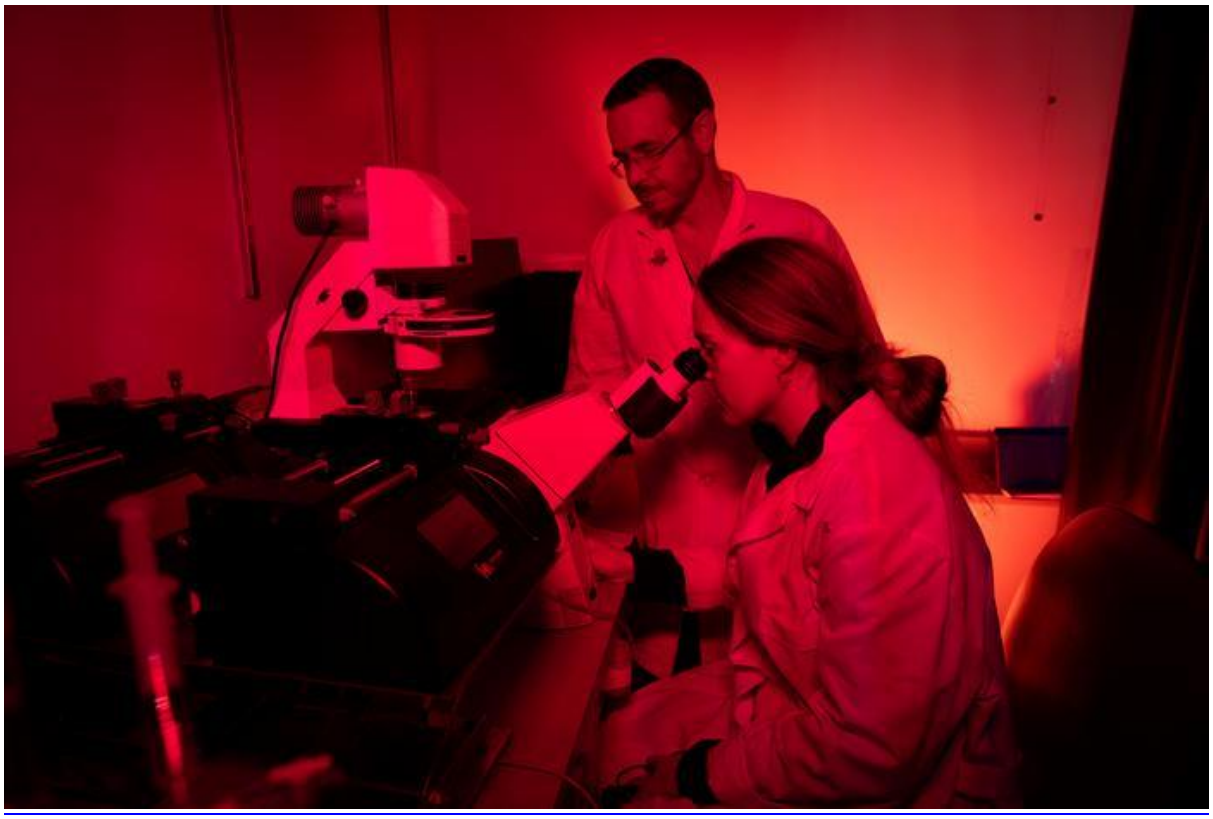

**image:**

**Humans and mice exposed to long-wavelength red light had lower rates of blood clots that can cause heart attacks, lung damage and strokes, according to research led by Elizabeth Andraska, M.D. (seated) and Matthew Neal, M.D., both of the University of Pittsburgh and UPMC.**

view more

**Credit: Tim Betler, UPMC**

Humans and mice exposed to long-wavelength red light had lower rates of blood clots that can cause heart attacks, lung damage and strokes, according to research led by University of Pittsburgh

School of Medicine and UPMC surgeon-scientists and published today in the *Journal of Thrombosis and Haemostasis*.

The findings, which need to be verified through clinical trials, have the potential to reduce blood clots in veins and arteries, which are leading causes of preventable death worldwide.

"The light we're exposed to can change our biological processes and change our health," said lead author Elizabeth Andraska, M.D., assistant professor of surgery in Pitt's Trauma and Transfusion Medicine Research Center and vascular surgery resident at UPMC. "Our findings could lead to a relatively inexpensive therapy that would benefit millions of people."

Scientists have long connected light exposure to health outcomes. The rising and setting of the sun underlies metabolism, hormone secretion, even the flow of blood, and heart attacks and stroke are more likely to happen in the morning hours than at night. Andraska and her colleagues wondered if light could have an impact on the blood clots that lead to these conditions.

To test this idea, the team exposed mice to 12 hours of either red, blue or white light, followed by 12 hours of darkness, in a 72-hour cycle. They then looked for differences in blood clots between the groups. The mice exposed to red light had nearly five times fewer clots than the mice exposed to blue or white light. Activity, sleep, eating, weight and body temperature remained the same between the groups.

The team also analyzed existing data on more than 10,000 patients who had cataract surgery and received either conventional lenses that transmit the entire visible spectrum of light, or blue light-filtering lenses, which transmit about 50% less blue light. They discovered that cancer patients who received blue light-filtering lenses had lower risk of blood clots compared to their counterparts with conventional lenses. This is especially notable because cancer patients have nine times the risk of blood clots of non-cancer patients.

"These results are unraveling a fascinating mystery about how the light to which we're exposed on a daily basis influences our body's response to injury," said senior author Matthew Neal, M.D., professor of surgery, Watson Fund in Surgery Chair and co-director of the Trauma and Transfusion Medicine Research Center at Pitt, and trauma surgeon at UPMC. "Our next steps are to figure out why, biologically, this is happening, and to test if exposing people at high risk for blood clots to more red light lowers that risk. Getting to the bottom of our discovery has the potential to massively reduce the number of deaths and disabilities caused by blood clots worldwide."

The recently published study indicates that the optic pathway is key – light wavelength didn't have any impact on blind mice, and shining light directly on blood also didn't cause a change in clotting.

The team observed that red light exposure is associated with less inflammation and activation of the immune system. For example, red light-exposed mice had fewer neutrophil extracellular traps – aptly abbreviated as "NETs" – which are web-like structures made by immune cells to trap invading microorganisms. They also trap platelets, which can lead to clots.

The mice exposed to red light also had increased fatty acid production, which reduces platelet activation. Since platelets are essential to forming clots, this naturally leads to less clot formation.

Understanding how the red light is triggering changes that lower clotting risk could also put scientists on the track of better medications or therapies that could be more potent and convenient for patients than continuous red light exposure.

In preparation for clinical trials, the team is developing red light goggles to control the amount of light exposure study participants receive and investigating who may most benefit from red light

Additional authors on this research are Frederik Denorme, Ph.D., Robert Campbell, Ph.D., and Matthew R. Rosengart, M.D., all of Washington University in St. Louis; Christof Kaltenmeier, M.D., Aishwarrya Arivudainabi, Emily P. Mihalko, Ph.D., Mitchell Dyer, M.D., Gowtham K. Annarapu, Ph.D., Mohammadreza Zarisfi, M.D., Patricia Loughran, Ph.D., Mehves Ozel, M.D., Kelly Williamson, Ph.D., Roberto Mota-Alvidrez, M.D., Sruti Shiva, Ph.D., Susan Shea, Ph.D., and Richard A. Steinman, M.D., Ph.D., all of Pitt; and Kimberly Thomas, Ph.D., of Vitalant Research Institute.

This research was supported by National Institutes of Health grants R35GM119526, K01AG059892, R01HL163019, R01GM147121, R01GM145674, T32HL98036 and S10OD028483, the University of Pittsburgh Center for Research Computing, National Center for Research Resources Shared Instrumentation grants 1S10OD016232-01, 1S10OD018210-01A1 and 1S10OD021505-01, American Heart Association 2021Post830138 award, and a Physician-Scientist Institutional Award from the Burroughs Wellcome Fund.

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**Journal**

Journal of Thrombosis and Haemostasis

**Article Title**

Alterations in visible light exposure modulate platelet function and regulate thrombus formation

**Article Publication Date**

10-Jan-2025

## 6. 雄マウスの不妊症に関連するタンパク質「TLE6」を特定

**研究情報**

- **論文タイトル:** *Tle6* deficiency in male mice led to abnormal sperm morphology and reduced sperm motility
- **発表日: 2025 年 1 月 16 日**
- **ジャーナル:** Frontiers in Cell and Developmental Biology
- **DOI:** https://doi.org/10.3389/fcell.2024.1481659
- **出典: 金沢医科大学**

**概要**

金沢医科大学の研究者たちは、雄マウスの不妊症における TLE6（Transducin-like enhancer of split 6）タンパク質の役割を解明するために、新しい Tle6 遺伝子ヘテロノックアウトマウスモデルを開発した。この研究では、TLE6 欠損が異常な精子構造、精子数の減少、運動性精子の低下につながることを明らかにした。

研究チームは CRISPR-Cas9 技術を使って Tle6 ヘテロノックアウトマウスを作成。このモデルを用いた実験では、交配頻度や子孫の数には違いが見られなかったが、Tle6 欠損マウスの精子の約 57%が異常な頭部構造を持ち、運動性が著しく低下していた。また、テストステロン値が上昇しており、TLE6 が精子のエネルギー産生や構造形成に関与している可能性が示唆された。

この研究は、TLE6 欠損がマウスの雄の不妊に及ぼす影響を初めて明らかにしたものであり、ヒトの不妊治療への応用に向けたさらなる研究の基盤となると期待されている。

**参考**

https://www.kanazawa-med.ac.jp/research/assets/press%20release20241121.pdf

研究関連ニュース/他のトップページに戻る

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＜英文＞TLE6 identified as a protein associated with | EurekAlert!

News Release 16-Jan-2025

# TLE6 identified as a protein associated with infertility in male mice

A deficiency of TLE6 protein, which affects female fertility, was also associated with infertility in male mice

Peer-Reviewed Publication

Kanazawa Medical University

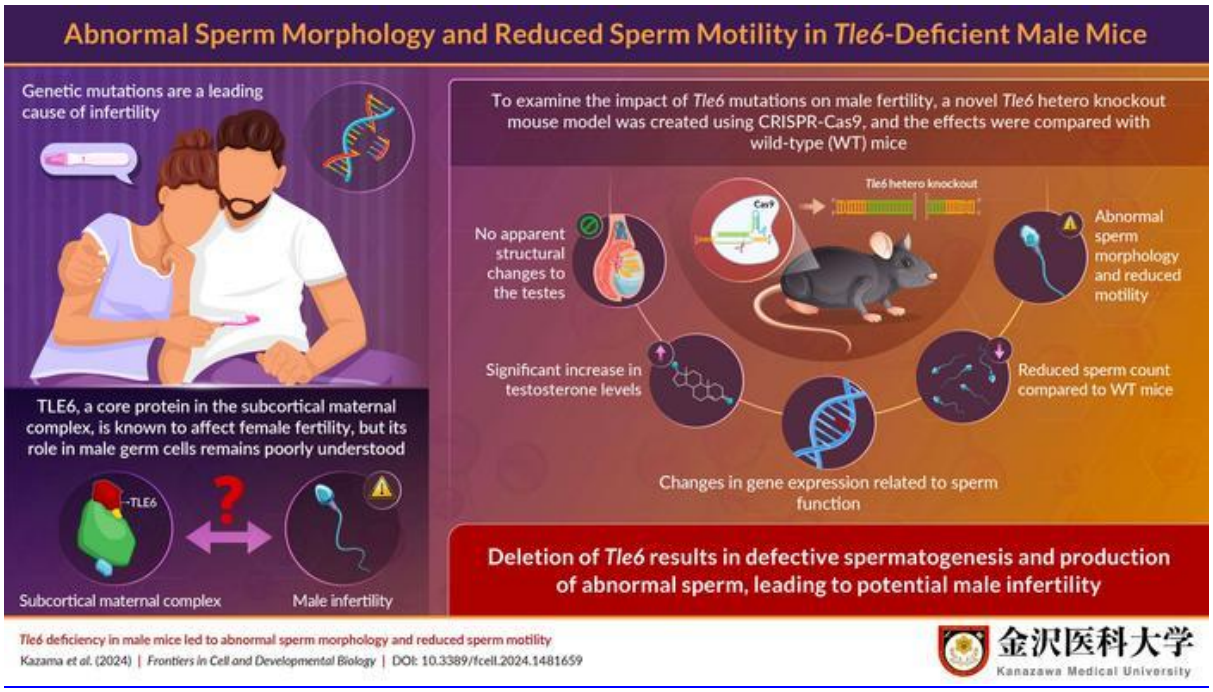


**image:**

**Researchers develop a novel *Tle6* gene hetero knockout mice model to understand the role of this gene in male fertility and find that its deficiency results in abnormal sperm structure, reduced sperm count, and a low number of motile sperm.**

**view more**

**Credit: Kousuke Kazama from Kanazawa Medical University**

Infertility is a major global challenge associated with physiological and psychological impact. Genetic mutations that affect early embryonic development, oocyte (egg cell) maturation, and fertilization have recently been studied as causes of infertility. One of the most well-studied causes of early embryonic infertility is mutations in the subcortical maternal complex (SCMC)-related genes.

SCMC participates in embryo development and cleavage by maintaining the structure of the egg cytoplasm and recruiting proteins that assist proper embryo formation. SCMC is composed of multiple proteins, of which the transducin-like enhancer of split 6 (TLE6) is the most crucial member. In the absence of TLE6, the structural integrity of SCMC is compromised, and consequently cell division in the embryo fails after the two-cell stage, resulting in embryo fragmentation and death. There is ample evidence supporting the role of TLE6 in female infertility, but its role in male germ cells remains unexplored.

To address this gap, Mr. Kousuke Kazama, a Research Associate, from the Research Support Center, Medical Research Institute, Kanazawa Medical University, Japan, along with Dr. Hirofumi Nishizono and Ms. Yuki Miyagoshi, also from Kanazawa Medical University, attempted to understand the effects of *Tle6* gene deficiency on male fertility using the *Tle6* deficient mouse model. They developed a novel *Tle6* gene hetero knockout male mouse model using a technique called CRISPR-Cas9 that enables the editing of genes. Their findings were published in Volume 12 of *Frontiers in Cell and Developmental Biology* on October 24, 2024.

"*We generated Tle6 hetero knockout mice to investigate the effects of Tle6 deficiency in male mice. We performed genome editing of the embryos using the CRISPR-Cas9 system and electroporation to generate the Tle6 hetero*

*knockout mice,*" states Kazama, explaining the main methodology used in the study. To investigate whether *Tle6* deficiency leads to erratic mating behavior, *Tle6*-deficient and wild-type (WT) male mice were mated with WT female mice. The mating frequency and the number of offspring did not differ between *Tle6*-deficient and WT mice. Additionally, embryos derived from the sperm of *Tle6*-deficient male mice showed similar developmental rates as those derived from WT male mouse sperm.

The question of why *Tle6* deficiency-related traits were not transmitted to the next generation prompted the researchers to further explore the gene's role in sperm function. Kazama elaborates, "*We hypothesized that the difficulty in transmitting genetic traits from Tle6-deficient male mice could be due to reduced sperm count and motility*." To test this hypothesis, they analyzed the testes and sperm of *Tle6*-deficient male mice. While the structure of the testes was not affected due to *Tle6* deficiency, they found a significant reduction in sperm count and a marked decrease in the number of motile sperm. Moreover, 57% of the sperm from *Tle6*-deficient mice had an abnormal head structure, and 7% were double-headed. The researchers suspected dysregulated hormone levels in these mice and consequently found elevated levels of testosterone (an important sex hormone) in *Tle6* hetero knockout male mice.

Visualization of sperm from WT and *Tle6* knockout mice using immunofluorescence staining revealed that TLE6 protein in deficient mice was localized in the sperm midpiece. This region overlapped with the location of mitochondria, which are important for energy production, suggesting that TLE6 might play a role in energy production in the sperm. Gene expression related to fertilization, sperm motility, and sperm structure in the testes of *Tle6*-deficient mice showed an overall increase.

Together, the findings of this study highlighted the impact of *Tle6* deficiency in male mice and its role in potential male infertility. "*The role of TLE6 in the development of sperm cells may vary between humans and mice. Therefore, further research is necessary to clarify the mechanisms by which Tle6 deficiency causes sperm abnormalities in Tle6 hetero knockout mice and to explore its clinical relevance in humans,*" concludes Kazama.

In summary, this study sheds further light on male infertility and paves the way for more advanced research and the development of new assisted reproductive technologies.

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Reference

Title of original paper: *Tle6* deficiency in male mice led to abnormal sperm morphology and reduced sperm motility

Journal: *Frontiers in Cell and Developmental Biology*

DOI: https://doi.org/10.3389/fcell.2024.1481659

About Kanazawa Medical University (KMU), Japan

Kanazawa Medical University (KMU) is a reputed medical school located in Ishikawa, Japan. Established in 1972 with Albert Schweitzer's idea of "Ehrfurcht vor dem Leben (respect for life) and five "S" keywords: Spirit, Science, Skill, Speed, and Safety, KMU is pledged to the development of high-quality medical professionals. KMU continues to grow by engaging nearly 4,500 graduates from the School of Medicine in medical care globally. Furthermore, KMU sends over 2,500 nurses, public health nurses, and midwives to gain practical exposure in the medical field. By following the motto and five "S" elements along with sustainable development goals, KMU strives to contribute to the creation of innovative medical science technologies and the supply of healthcare workforce, promoting holistic societal development.

Website: https://www.kanazawa-med.ac.jp/English/public_html/

About Mr. Kousuke Kazama from Kanazawa Medical University, Japan

Mr. Kousuke Kazama is a Research Associate at the Research Support Center, Medical Research Institute, Kanazawa Medical University, Japan. His main research interests include the mechanisms of infertility and intracellular structure and epigenetics in sperm, oocyte and embryo. Mr. Kazama has over six publications in this field, with around 48 citations and over 950 reads.

Funding information

This work was supported by the Takeda Science Foundation (Grant No. 2022048848), Lotte Research Promotion Grant (Grant No. LF001353) and a Grant for Promoted Research from Kanazawa Medical University (S2023-1).

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**Journal**

Frontiers in Cell and Developmental Biology

**DOI**

10.3389/fcell.2024.1481659

**Method of Research**

Experimental study

**Subject of Research**

Animals

**Article Title**

Tle6 deficiency in male mice led to abnormal sperm morphology and reduced sperm motility

**Article Publication Date**

24-Oct-2024

**COI Statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## 7. 雄マウスにおけるＹ染色体遺伝子が生殖能力に果たす役割を解明

**研究情報**

- **論文タイトル**: Systematic identification of Y-chromosome gene functions in mouse spermatogenesis
- **発表日**: 2025 年 1 月 24 日
- **ジャーナル**: Science
- DOI: 10.1126/science.ads6495
- **出典**: フランシス・クリック研究所

**概要**

フランシス・クリック研究所の研究者たちは、マウスの Y 染色体上の遺伝子が精子の形成や生殖能力にどのように関与しているかを解明した。この研究は、なぜ一部の男性が十分な精子を生成できず不妊になるのかを理解する手助けとなる可能性がある。
Y 染色体には限られた数の遺伝子しか含まれていないが、雄の生殖能力には不可欠とされている。今回の研究では、Y 染色体の異なる遺伝子を削除した 13 種類のマウスモデルを作成し、精子の数や形態、運動性、繁殖能力を調査した。

主な発見：

- 一部の Y 染色体遺伝子が繁殖に重要であり、これらが欠損すると精子が生成されなくなる、または数が減少し、精子幹細胞が形成されない、あるいは精子の形や運動が異常になることが判明。
- 他の遺伝子は個別に削除しても影響がなかったが、複数を同時に削除すると異常な精子が生成されることが確認された。
- 特に、ヒトの AZFa 領域に相当する 3 つの遺伝子を削除した場合、異常な精子が生成されることが分かった。AZFa 領域の欠失は、男性不妊の中でも最も重篤なケースの一般的な原因であるが、この研究でそのメカニズムの一端が解明された。

その他の発見と今後の研究：

- 一部の Y 染色体遺伝子は、心臓や脳など他の器官にも影響を与える可能性があることが示唆された。
- 年齢を重ねると細胞分裂のエラーにより血液中の Y 染色体が失われることがあり、これがアルツハイマー病や癌と関連する可能性も指摘された。

研究者のコメント：

- Y 染色体は長い間誤解されており、成人においては不要だと考えられていたが、今回の研究でそれが誤りであることが明らかになった。
- 将来的には、Y 染色体の詳細な解析を進めることで、男性不妊の未解明の原因を解明し、体外受精（IVF）などの生殖補助技術を通じて欠失した遺伝子を補うことが可能になるかもしれない。

この研究は、Y 染色体と不妊症の関係に新たな光を当て、さらなる研究の基盤を築く重要な成果となる。

研究関連ニュース/他のトップページに戻る

＜英文＞Uncovering the role of Y chromosome genes in | EurekAlert!

**News Release 23-Jan-2025**

# Uncovering the role of Y chromosome genes in male fertility in mice

**Peer-Reviewed Publication**

**The Francis Crick Institute**




**image:**

**Humans have 23 pairs of chromosomes, including a pair of sex chromosomes (typically XX for females, and XY for males). Chromosomes contain hundreds to thousands of genes, which are sections of DNA located at specific points on a chromosome. The Y chromosome is an exception, only containing a few dozen genes. DNA is the material carrying all the information about the development and functioning of the individual – the blueprint to make proteins.**

view more

**Credit: Jeremie Subrini**

Researchers at the Crick have uncovered which genes on the Y chromosome regulate the development of sperm and impact fertility in male mice. This research could help us understand why some men don't produce enough sperm and are infertile.

Males typically have one copy of the Y chromosome and one copy of the X chromosome, whereas females typically have two X chromosomes. Scientists know that the Y chromosome is essential for male fertility, but which genes are the most important and how they work is less clear.

In research published today in *Science*, a research team at the Crick resolved this question by generating thirteen different mouse models, each with different Y genes removed, and investigated their fertility.

The researchers studied the ability of these adult mice to reproduce, including looking at the number of offspring, number of sperm produced and the appearance and motility of the sperm.

They found that several Y genes were critical for reproduction. If these genes were removed, the mice couldn't produce young, due to absence or reduced number of sperm, failure to produce a reservoir of sperm stem cells or abnormal sperm shape or movement.

Interestingly, some other genes had no impact when removed individually, but did lead to the production of abnormal sperm when removed together.

This was the case for a group of three genes which model a region of the chromosome called AZFa in humans. AZFa deletions are a common cause of the most severe cases of male infertility, but it has been hard to tell which genes in the region are responsible.

The results suggest that many Y genes play a role in fertility and can compensate for each other if one gene is lost. This also means that some cases of infertility likely result from multiple genes being deleted at the same time.

As well as regulating sperm generation, some Y genes are also active in other organs, like the heart and the brain, where they may be very important. Also, as they age, some men can lose their Y chromosomes in blood due to errors in cell division. This loss is associated with conditions like Alzheimer's disease or cancer, so the lab is now aiming to understand what happens in other organs in the mice with Y gene deletions.

Jeremie Subrini, Postdoctoral Research Assistant in the Sex Chromosome Biology Laboratory at the Crick, and first author, said: "Our research has shown that more Y genes are required for mouse fertility than first thought. We saw that some genes are crucial, but others have a cumulative effect. Historically, the Y chromosome has been misunderstood. For a long time, it wasn't thought to be essential in adults, and some even hypothesised that it was going to disappear altogether. We now know that this is clearly not the case!"

James Turner, Principal Group Leader of the Sex Chromosome Biology Laboratory at the Crick, and senior author, said: "Infertility is a big problem, with 1 in 6 couples struggling to conceive. In a significant proportion of cases, genetic factors, particularly those involving the Y chromosome, are the cause. However, the details have been difficult to pinpoint, partly because sequencing and studying the Y chromosome has been technically challenging.

"Now that we've shed light on the Y genes, it will be important to start sequencing the Y chromosome in more individuals, to potentially uncover unexplained causes of male infertility. With more research, we may be able to one day replace missing genes in the cells that make sperm to help couples have children through IVF."

*Peer reviewed*

*Experimental study*

*Animals*

For further information, contact: press@crick.ac.uk or +44 (0)20 3796 5252

**Notes to Editors**

Reference: Subrini, J. *et al*. (2025). Systematic identification of Y-chromosome gene functions in mouse spermatogenesis. *Science*. 10.1126/science.ads6495.

**The Francis Crick Institute** is a biomedical discovery institute dedicated to understanding the fundamental biology underlying health and disease. Its work is helping to understand why disease develops and to translate discoveries into new ways to prevent, diagnose and treat illnesses such as cancer, heart disease, stroke, infections, and neurodegenerative diseases.

An independent organisation, its founding partners are the Medical Research Council (MRC), Cancer Research UK, Wellcome, UCL (University College London), Imperial College London and King's College London.

The Crick was formed in 2015, and in 2016 it moved into a brand new state-of-the-art building in central London which brings together 1500 scientists and support staff working collaboratively across disciplines, making it the biggest biomedical research facility under a single roof in Europe.

http://crick.ac.uk/

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**Journal**

Science

**DOI**

10.1126/science.ads6495

**Article Title**

Systematic identification of Y-chromosome gene functions in mouse spermatogenesis

**Article Publication Date**

24-Jan-2025

## 8. 体脂肪を減らしながら筋肉を維持する鍵となる分子発見 –マウス実験

**研究情報**

- **論文タイトル: BCL6 coordinates muscle mass homeostasis with nutritional states**
- **発表日: 2025 年 1 月 22 日**
- **ジャーナル: Proceedings of the National Academy of Sciences**
- **DOI: 10.1073/pnas.2408896122**
- **出典: ソーク研究所**

**概要**

アメリカでは成人の約 8 人に 1 人が GLP-1 薬を使っており、そのうち約 25%は体重減少を主な目的にしている。ただし、GLP-1 薬による体重減少は、脂肪だけでなく筋肉も減少させることが多い。この問題に対処するため、研究者たちは BCL6 というタンパク質が筋肉の維持に関与していることを突き止めた。

研究結果：

BCL6 を欠損させたマウスは、筋肉量が 40%減少し、筋力も大きく低下した。しかし、BCL6 の発現を増やすと、筋肉量と筋力の低下が回復した。また、絶食したマウスでは BCL6 のレベルが低下することがわかり、これが筋肉維持に悪影響を及ぼすことが示された。

メカニズム：

BCL6 は、成長ホルモンと IGF1（インスリン様成長因子 1）を調節するタンパク質ネットワークの一部として機能する。BCL6 が不足すると SOCS2 というタンパク質の調整が効かなくなり、IGF1 の産生が減少することで筋肉が弱くなり、縮小してしまう。

応用と今後の展望：

この発見は、GLP-1 薬を使う人が筋肉を維持しながら体重を減らすための治療法を開発する道を開く。また、高齢者や疾患による筋肉減少を防ぐ治療法にも応用できる可能性がある。研究チームはさらに、長期的な絶食が BCL6 や筋肉維持に与える影響を詳しく調べる予定だ、としている。

研究関連ニュース/他のトップページに戻る

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＜英文＞Boosting this molecule could help retain muscle while losing fat | ScienceDaily

# Boosting this molecule could help retain muscle while losing fat

*Date:* January 23, 2025

*Source:* Salk Institute

*Summary:*

With the recent surge in popularity of weight loss drugs like Ozempic, altogether called GLP-1s, there has been renewed scientific interest in understanding how our bodies regulate muscle growth. Scientists have linked the protein BCL6 to the maintenance of muscle mass and further suggested that BCL6-boosting therapeutics could help GLP-1 users retain muscle while losing fat. Similar therapies could also be used to treat other populations prone to muscle loss, such as older adults and patients with systemic diseases like sepsis or cancer.

**FULL STORY**

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About one in eight adults in the United States has tried or currently uses a GLP-1 medication, and a quarter of those users cite weight loss as their main goal. But weight loss doesn't discriminate between fat and muscle. Patients using GLP-1 drugs can experience rapid and substantial muscle loss, accounting for as much as 40% of their total weight loss. So how can we lose weight without also losing critical muscle?

A new study from the Salk Institute has revealed that a protein called BCL6 is key to maintaining healthy muscle mass. The experiments showed that mice with lower levels of BCL6 had significantly reduced muscle mass and strength, but increasing BCL6 successfully reversed those losses. The results suggest that pairing GLP-1 medications with a BCL6-boosting drug may help counteract unwanted muscle loss. Similar therapies could also be used to treat other populations prone to muscle loss, such as older adults and patients with systemic diseases like sepsis or cancer.

The findings were published in *Proceedings of the National Academy of Sciences* on January 22, 2025.

"Muscle is the most abundant tissue in the human body, so its maintenance is critical to our health and quality of life," says Ronald Evans, professor and director of the Gene Expression Laboratory at Salk. "Our study reveals how our bodies coordinate the upkeep of all this muscle with our nutrition and energy levels, and with this new insight, we can develop therapeutic interventions for patients losing muscle as a side effect of weight loss, age, or illness."

Going too long without eating puts your body in a fasted state. When this happens, your empty stomach sends a hormone called ghrelin to your brain to say, "I'm hungry!"The brain responds by releasing growth hormone into the rest of your body, where it regulates growth and metabolism in your many cells, tissues, and organs. As it travels through your body, growth hormone latches on to cells and directs them to make another protein called insulin-like growth factor 1 (IGF1), which then does the important work of controlling muscle growth.

In the time between growth hormone's arrival and IGF1 synthesis, there is a complex web of proteins that determine how much IGF1 is made. One such protein is SOCS2, which slows down IGF1 production. Without SOCS2, IFG1 production runs out of control and causes gigantism. On the other hand, too much SOCS2 means not enough IFG1, leading to losses in body size and strength.

Still, SOCS2 is only one player in the path between growth hormone and IGF1. To protect people from rapid muscle loss, Salk scientists needed to get a clearer picture of the mechanisms underlying muscle maintenance. In search of other potential players, the researchers scoured a national database of human tissue samples and noticed an abundance of BCL6 in muscle cells -- a clue that it may play an important role in this process.

To determine whether BCL6 was involved in muscle maintenance, the team compared mice with and without functional BCL6 proteins. Mice lacking BCL6 had 40% less muscle mass than their healthy counterparts, and the muscle they *did* have was compromised both in structure and function. However, when the researchers increased the expression of BCL6 in the animals' muscles, this successfully reversed the losses in muscle mass and strength. And when they compared normal mice and those that had fasted overnight, they found fasting mice had less BCL6 in their muscles.

Clearly, BCL6 was controlling muscle maintenance -- but how?

Through a series of subsequent experiments, the steps along the path became clear. Fasting promotes the secretion of growth hormone, which reduces BCL6 levels in muscle cells. BCL6 is a regulator of SOCS2, so less BCL6 leads to less SOCS2. At normal levels, this allows BCL6 to control how much SOCS2 is expressed and therefore how much IGF1 is made. In animals *without* BCL6, the lack of control over SOCS2 slowed IGF1 production *so much* that muscles became weaker and smaller.

"We are excited to reveal BCL6's important role in maintaining muscle mass," says first author of the study Hunter Wang, a postdoctoral researcher in Evans' lab. "These were very surprising and special findings that open the door for a lot of new discoveries and potential therapeutic innovations."

For GLP-1 patients hoping to lose weight while retaining muscle mass, it's possible that a BCL6-boosting injectable could hit the market one day. In the meantime, the researchers plan to investigate what effects longer-term fasting has on BCL6 and muscle maintenance. Wang also notes that hormones tend to operate in cycles and that BCL6 naturally rises and falls with a strong circadian rhythm. A better understanding of this pattern may help further elucidate BCL6's relationship with growth hormone and muscle growth.

Other authors include Hui Wang, Weiwei Fan, Sihao Liu, Kyeongkyu Kim, Satoshi Ogawa, Hyun Gyu Kang, Jonathan Zhu, Gabreila Estepa, Mingxiao He, Lillian Crossley, Morgan Truitt, Ruth Yu, Annette Atkins, and Michael Downes of Salk; Ayami Matsushima of Kyushu University; Christopher Liddle of University of Sydney; and Minseok Kim of Daegu Gyeongbuk Institute of Science and Technology.

The work was supported by the National Institutes of Health (P01 HL147835, DK057978, DK120515, CCSG P30 CA23100, CCSG P30 CA014195, CCSG P30 CA014195, P30 AG068635), Department of the Navy Office of Naval Research (N00014-16-1-3159), Larry Hillblom Foundation (2021-D-001-NET), Wu Tsai Human Performance Alliance, American Heart Association (916787), Salk GT3 (RRID:SCR_014847) and Waitt Advanced Biophotonics (RRID:SCR_014838) Core Facilities, San Diego Nathan Shock Center, Henry L. Guenther Foundation, and Waitt Foundation.

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Story Source:

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

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Journal Reference:

Hui J. Wang, Weiwei Fan, Sihao Liu, Kyeongkyu Kim, Ayami Matsushima, Satoshi Ogawa, Hyun Gyu Kang, Jonathan Zhu, Gabriela Estepa, Mingxiao He, Lillian Crossley, Christopher Liddle, Minseok S. Kim, Morgan L. Truitt, Ruth T. Yu, Annette R. Atkins, Michael Downes, Ronald M. Evans. BCL6 coordinates muscle mass homeostasis with nutritional states. *Proceedings of the National Academy of Sciences*, 2025; 122 (4) DOI: 10.1073/pnas.2408896122

## 9. 遅延する REM 睡眠がアルツハイマー病早期兆候の可能性

**研究情報**

- **論文タイトル**: Association of rapid eye movement sleep latency with multimodal biomarkers of Alzheimer's disease
- **発表日**: 2025 年 1 月 27 日
- **ジャーナル**: Alzheimer's & Dementia
- DOI: 10.1002/alz.14495
- **出典**: カリフォルニア大学サンフランシスコ校

**概要**

夢を見る段階である REM 睡眠に入るまでの時間が大幅に遅れることが、アルツハイマー病の初期兆候である可能性が新たな研究で示された。
REM 睡眠は記憶や感情の整理に重要であり、その遅延は記憶中枢である海馬に悪影響を及ぼし、ストレスホルモンであるコルチゾールの増加を引き起こす可能性がある。
中国で行われた研究では、70 歳を平均年齢とする 128 名を対象に、睡眠中の脳波、眼球運動、心拍などを測定した。その結果、アルツハイマー病患者や軽度認知障害を持つ人では、REM 睡眠への移行が遅れ、脳内の有害なアミロイド β やタウタンパク質が高濃度で蓄積していることが確認された。また、健康なタンパク質 BDNF（brain derived neurotrophic factor）のレベルが低下していた。
注目すべき点として、メラトニンが REM 睡眠を促進し、マウス実験ではタウやアミロイド β の蓄積を減少させる効果が確認されている。他にも、不眠症治療薬がタウやアミロイド β の減少に寄与する可能性が示されている。
アルツハイマー病のリスクを減らすためには、健康的な睡眠習慣を維持することが重要とされている。特に、睡眠時無呼吸の治療や過度な飲酒の回避が推奨される。また、REM 睡眠を抑制する抗うつ薬や鎮静薬を使用中の患者は、医師に相談することが望ましいとされる。
この研究は、睡眠の質がアルツハイマー病の発症に与える影響を明らかにする新たな一歩となった。

研究関連ニュース/他のトップページに戻る

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＜英文＞Delayed REM sleep could be an early sign of Alzheimer's | ScienceDaily

# Delayed REM sleep could be an early sign of Alzheimer's

Taking longer to enter the dream phase can disrupt the ability to consolidate memories and interfere with emotion regulation

*Date:* January 27, 2025

*Source:* University of California - San Francisco

*Summary:* Scientists have recently shown that both the quality and the amount of sleep we get may influence our risk of developing Alzheimer's disease.

**FULL STORY**

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Scientists have recently shown that both the quality and the amount of sleep we get may influence our risk of developing Alzheimer's disease.

Now, a study suggests that people who take significantly longer to start the dream phase of sleep, known as rapid eye movement (REM), may be experiencing an early symptom of the disease.

REM follows three phases of non-REM sleep, each deeper than the last. The four phases take 90 minutes or more to complete, depending on age, and a person may cycle through them four or five times in a typical night. Older people take longer to reach REM.

During REM sleep the brain processes memories, especially those that are emotionally charged, and puts them into long-term storage.

"The delay in REM sleep disrupts the brain's ability to consolidate memories by interfering with the process that contributes to learning and memory," said Yue Leng, PhD, an associate professor in the Department of Psychiatry and Behavioral Sciences at UCSF.

"If it is insufficient or delayed, it may increase the stress hormone cortisol," said Leng, who is part of the UCSF Weill Institute for Neurosciences. "This can impair the brain's hippocampus, a critical structure for memory consolidation."

Leng is a senior author of the paper, which appears Jan. 27 in *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*.

**Higher levels of amyloid, tau**

Researchers followed 128 people with an average age of 70 from the neurology unit of the China-Japan Friendship Hospital in Beijing. Half had Alzheimer's, and about one-third had mild cognitive impairment, a frequent precursor to Alzheimer's. The rest had normal cognition.

The participants in the study slept overnight in the clinic, so researchers could measure their brainwave activity, eye movement, heartrate and breathing. Fitness trackers can capture some of this information, but it is less precise.

The researchers divided the participants into early and delayed REM sleep. On average, the early group reached REM less than 98 minutes after falling asleep, while the late group reached it more than 193 minutes after falling asleep.

Those with Alzheimer's were more likely to have delayed REM sleep, and they also tended to have higher levels of the two toxic proteins, amyloid and tau, found in people with the condition.

Those with delayed REM sleep had 16% more amyloid and 29% more tau than those with early REM sleep. They also had 39% less of a healthy protein called brain derived neurotrophic factor (BDNF), which drops in Alzheimer's.

"Future research should study the effects of certain medications that influence sleep patterns, as these may modify disease progression," Leng said.

Melatonin can boost REM sleep, and studies in mice have shown that it decreases tau and amyloid accumulation. Other drugs that treat insomnia by blocking a chemical that suppresses REM sleep also have been shown to decrease tau and amyloid.

People who are concerned about their risk for Alzheimer's should practice healthy sleep habits that facilitate the transition from light sleep to REM sleep. "This includes treating conditions like sleep apnea and avoiding heavy drinking, since both can interfere with a healthy sleep cycle," said Dantao Peng, MD, of the Department of Neurology at the China-Japan Friendship Hospital in Beijing, who is also a senior author of the paper.

"Patients taking certain antidepressants and sedatives that reduce REM sleep should discuss their concerns with their doctor, if they are worried about Alzheimer's."

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**Story Source:**

Materials provided by **University of California - San Francisco**. Original written by Suzanne Leigh. *Note: Content may be edited for style and length.*

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**Journal Reference**:

Jiangli Jin, Jiong Chen, Clémence Cavaillès, Kristine Yaffe, Joseph Winer, Laura Stankeviciute, Brendan P. Lucey, Xiao Zhou, Song Gao, Dantao Peng, Yue Leng. **Association of rapid eye movement sleep latency with multimodal biomarkers of Alzheimer's disease**. *Alzheimer's & Dementia*, 2025; DOI: 10.1002/alz.14495