福島県立医科大学　知財資料
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公立大学法人
福島県立医科大学
Fukushima Medical University

再発リスク評価手法権利化と 薬効評価への可能性

Vision: 独自開発手法と抗体による 再発リスク評価と薬効予測へのブレークスルー

福島県立医科大学・医学部・生体物質研究部門
特別研究員　本間 美和子
Fukushima Medical University School of Medicine
Department of Biomolecular Sciences
Email:mkhomma@fmu.ac.jp

共同研究者
橋本優子 福島県立医科大学 医学部 病理病態診断学　教授
鈴木弘行 福島県立医科大学 医学部 呼吸器外科学　教授
野水整 公益財団法人　星総合病院　総長院長

課 題

再発を高確度で予測・診断する方法が無い

初発癌患者

再発するのではないか不安。
どう生活したらよいか決断できない。

担当医

摘出は成功した。あとは
再発や転移しないか定期的に検査するしかない。

メーカー・ディーラー

何を指標に再発予防へ準備をした方が良いのかな。

課 題

・再発による患者の心理的負担
・医療費増大

・治療方針選択における情報不足
・従来の診断手法の限界

・再発予測への検査法が無い

➡ **再発リスク症例を早期に見出す手法を実装する必要がある**

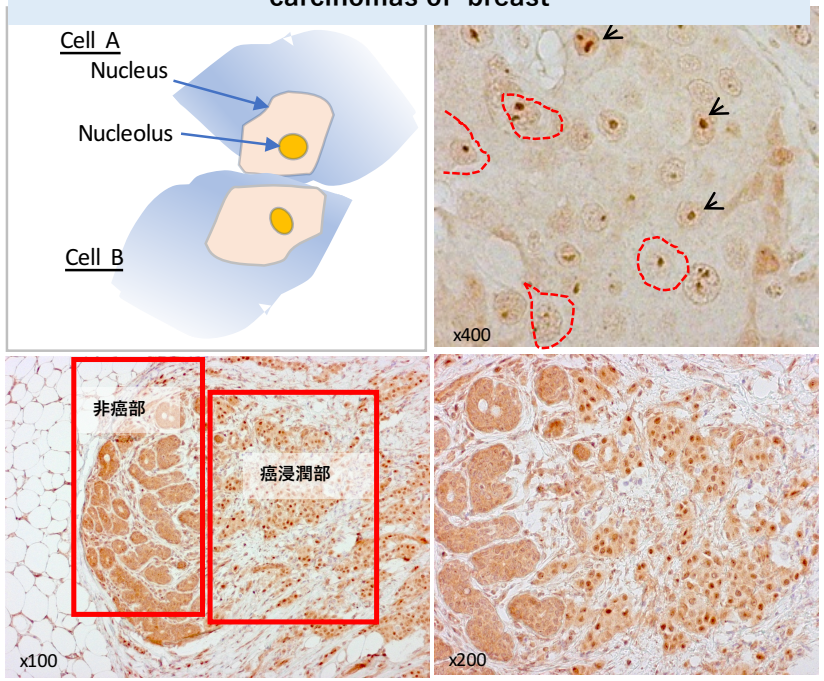
権利化

手法

CK2 核小体染色評価による 癌予後予測指標の有効性　　浸潤性乳管癌, 肺腺癌

癌摘出術時試料の染色評価により将来の再発リスク群を見出せば
再発予防へ資する新たな治療を早期に開始できる

Detection of nuclear protein kinase CK2 α by immunohistochemical analysis of invasive ductal carcinomas of breast



本手法の手順と結果

- 浸潤性乳癌摘出FFPE試料(n=112)を対象に抗CK2抗体-IHC染色を実施病変部を5段階(I～V)で染色評価した後 統計解析を実施. 再発例(n=12)は核染色陽性(+) (III, IV,V) のみへ分類された.
- 複数の臨床病理学的指標間でのCox 解析により CK2核小体染色陽性は無再発生存期間について 唯一の独立変数 かつ最も優位性の高い予後マーカー (P = 0.017)であった他, 高いハザード比(Hazard R = 5.26) を示した.
- Luminal type IDC乳癌(n=60), Triple negative type IDC乳癌(n=40)
  肺腺癌(n=120)においても同様の結果を得た.
- CK2染色評価を臨床病理学情報に加えることで, 手術直後に再発リスク群を抽出し,再発予防へ資する適切な治療戦略を検討できる
- CK2, casein kinase 2, は増殖関連キナーゼ.　海外ではその阻害薬(CX-4945)による各種癌を対象とする臨床治験が進行中

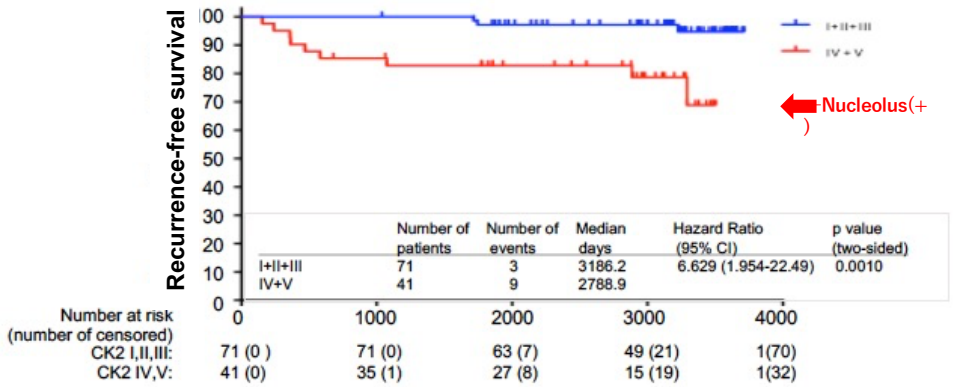
Nucleolar CK2 α status as a precise, new, independent prognostic factor

Cox proportional hazards regression / Multivariate

Factor	Wald	HR	95%-CI	P-value
CK2 Nucleolus (+)	5.711	5.264	1.348-20.553	0.017
Tumor size, >2.0cm	0.639	1.837	0.414-8.152	0.424
p Stage III	0.205	1.356	0.363-5.069	0.651
Nodal lymph, positive	3.616	8.191	0.938-71.56	0.057

Cancer Science (2021) by Homma, et al.
Lancet Oncology (2022 Abstract) by Homma, et al.
Life Science Alliance (2024) by Homma, et al.
Oncology Report (2025) by Mutoo, et al.

Nucleolar CK2 α staining is associated with poor outcomes of IDC patients

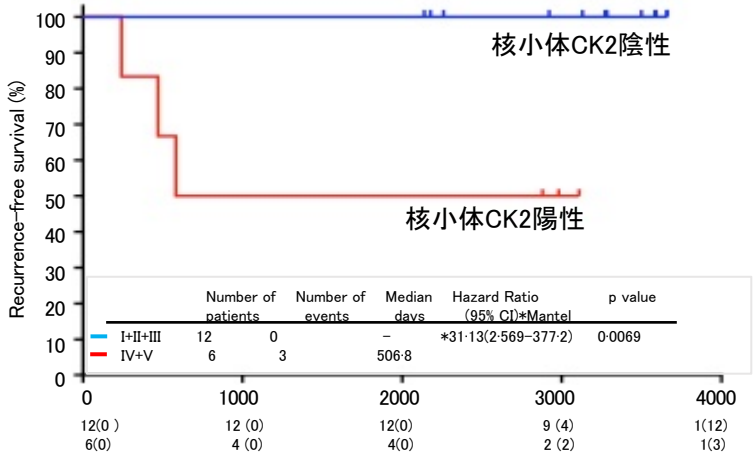


本手法の活用

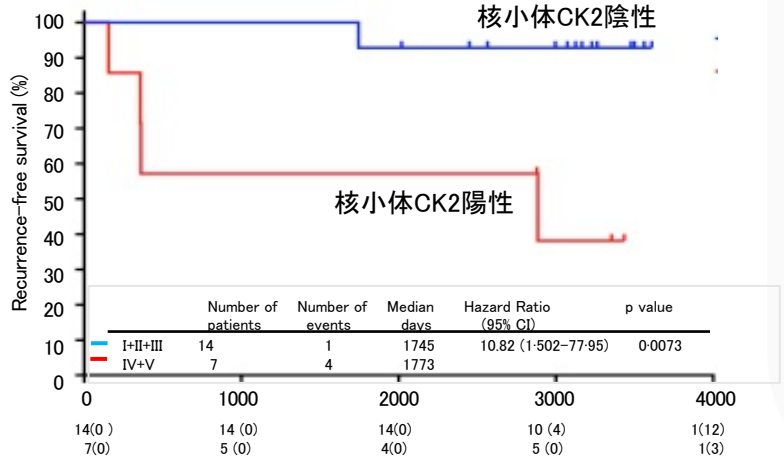
CK2核小体染色による包括的な予後予測診断

より正確に

Triple-negative group



p Stage III group



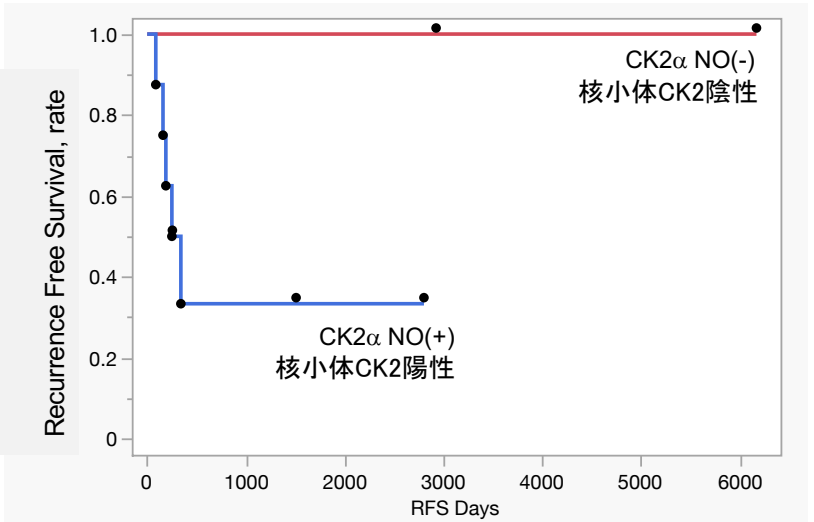
より早い予測を

再発するまで様子をみましょう…という現状から

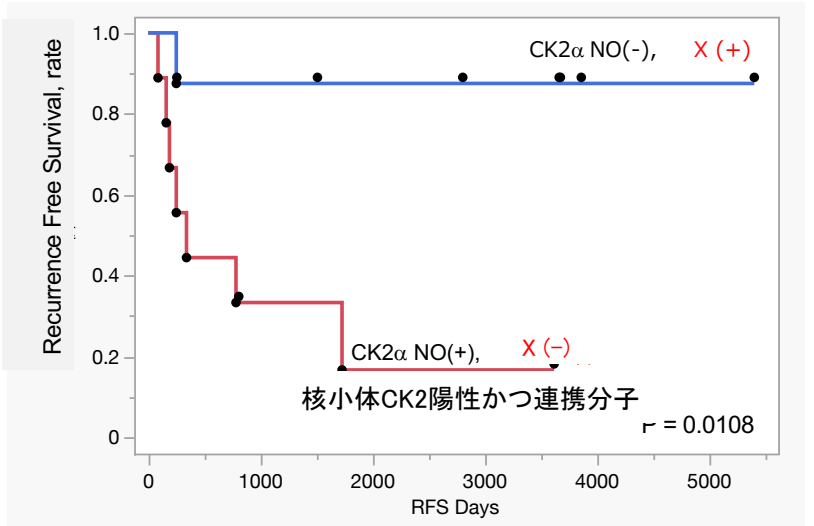
早期ステージからリスク群を見出し 再発予防へ

より精密な医療実現へ

術前化学療法奏功性予測(増悪症例)



他分子と組合せによる精度向上



知　財

網羅的な特許戦略

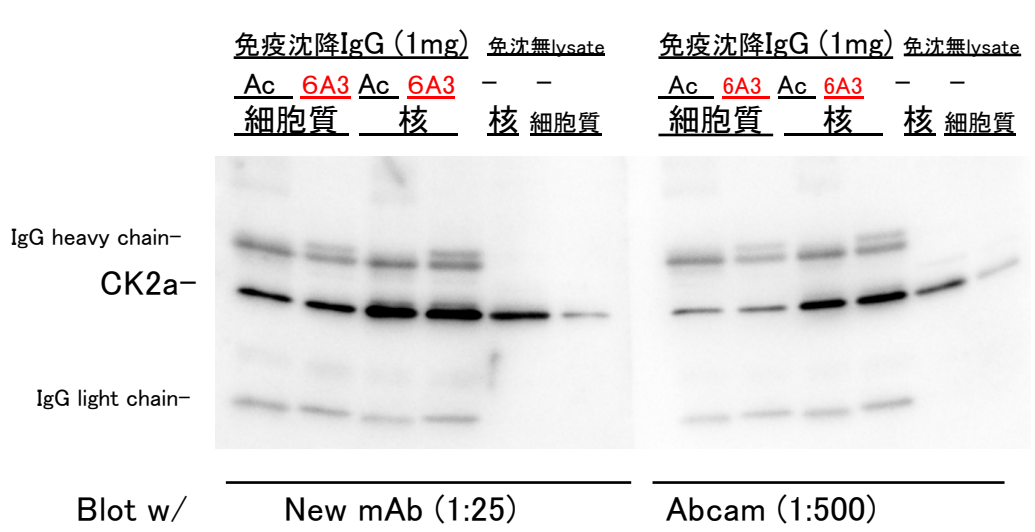
一部の癌細胞で見出される 細胞核小体内での分子集積を検出する

2025年権利化

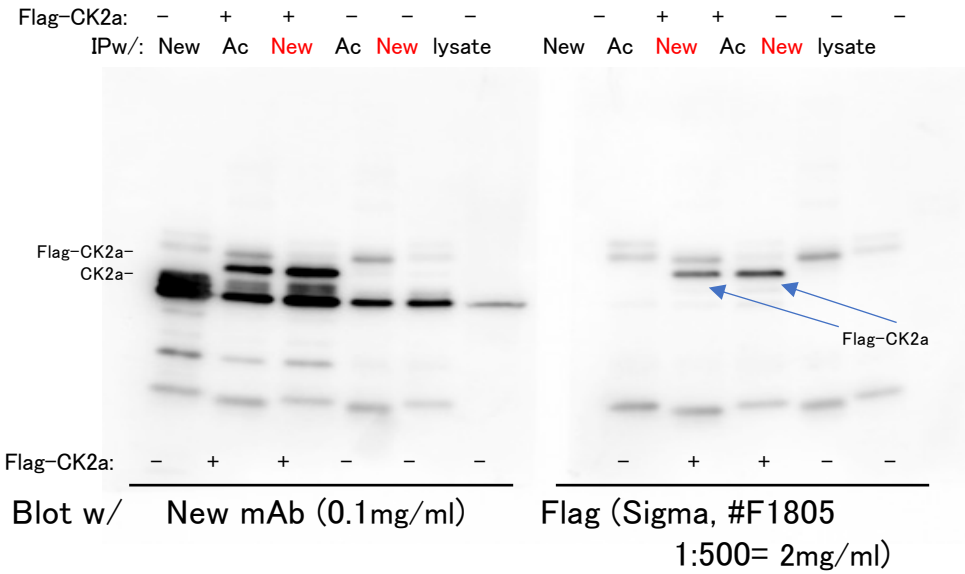
手法	01 乳癌のバイオマーカー（国内/手法）	02 癌のバイオマーカー PROGNOSTIC BIOMARKER OF CANCER（国際）	03 癌のバイオマーカー PROGNOSTIC BIOMARKER OF CANCER（USA，EU）
	No.2019-234099 (25Dec2019)	No.PTC/JP2020/048650 (25Dec2020)	wo2021/132544A1 (5July2021)
物質	04 モノクローナル抗体（国内/物質）	05 モノクローナル抗体 ANTI-CK2 ALPHA ANTIBODY OR FRAGMENT THEREOF（国際）	06 モノクローナル抗体 ANTI-CK2 ALPHA ANTIBODY OR FRAGMENT THEREOF（ USA, EU ）
	No.2022-55606 (30Mar2022)	No.PCT/JP2023/01069 (30Mar2023)	wo2023/190820A1 (5October2023)

知　財（物質）
品質の検証

免疫沈降物に対するウェスタンブロット
内在性 intact CK2a → *SDS*-denatured

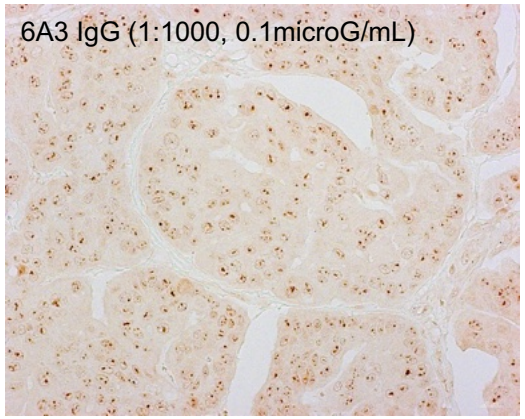


ウェスタンブロット法による検証
SDS-denatured Flag-tagged CK2a

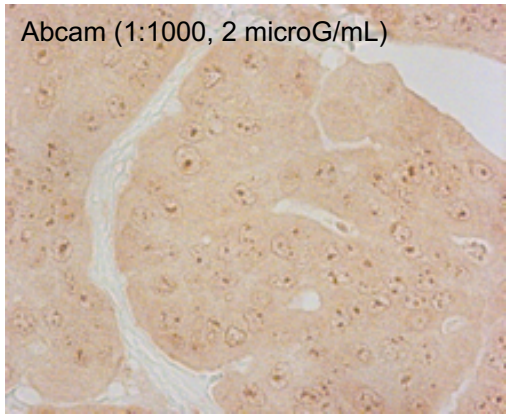


組織化学染色

独自抗体IgG



市販品IgG



CK2抗体は 多くの用途で感度と特異性に優れる

- ELISA
- Western blot
- IP
- ChIP-Seq
- IHC

- **病理の限界を克服できる**

CK2抗体はHE染色による2次元病理では反映されない小さなリンパ管/静脈侵襲を効率よく抽出出来ると考えられる

未来構想

Vision: 独自の抗体と手法により再発リスクを早期に見出す体外診断薬の開発

実装により達成される事

- 癌の核小体におけるCK2α陽性が、数年後の再発および患者の予後不良と強く関連していることを検証し、重要なブレークスルーを達成した。
- 癌再発マーカーとしてCK2核小体分子集積を感度高く判定する体外診断薬の開発と実装は「再発を待つ」現状から「再発予防」へ貢献できる。
- 染色機器自動化により標準化された染色評価が可能となる。さらにICT技術/AI活用による高度化が達成できる。

Summary

We have achieved a significant breakthrough by demonstrating that positive immune-staining of a protein kinase, CK2α, in nucleoli of invasive breast carcinomas and lung adenocarcinoma is strongly associated with tumor recurrence and poor patient outcomes.

The development and implementation of in vitro diagnostics for sensitive detection of CK2 nucleolar accumulation as a marker of cancer recurrence will contribute to “prevention of recurrence” instead of “waiting for recurrence.

Standardized staining evaluation will become possible through automation of staining equipment. Further advancement will be achieved through the use of AI.

CK2 学術

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Original Publications

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2. Homma,M.K., Nakato R, Niida A, Bando M, Fujiki K, Yokota N, Yamamoto S, Shibata T, Takagi M, Yamaki J, Kozuka-Hata H, Oyama M, Shirahige K, Homma Y. Cell cycle-dependent gene networks for cell proliferation activated by nuclear CK2α complexes *Life Science Alliance* 7: e202302077 (2023) doi:10.26508/lsa.202302077
4. Homma, M.K., Hashimoto Y, Homma Y, Nomizu T. CK2α as a prognostic factor in invasive ductal carcinomas of the breast: cancer recurrence prognosis by surgical sampling. *The Lancet Oncology* 23: S25 (Abstract) (2022) doi:10.1016/ s1470-2045(22)00424-7
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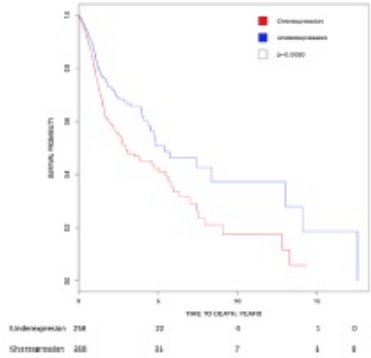
8. Homma, M.K., Li D, Edwin G. Krebs EG, and Homma Y. Association and regulation of casein kinase 2 activity by adenomatous polyposis coli protein. *Proc. Natl. Acad. Sci. USA* 99(9): 5959-5964 (2002).
9. Lu SL, Kawabata M, Imamura T, Akiyama Y, Nomizu T, Miyazono K, Yuasa Y. HNPCC associated with germline mutation in the TGF-β type II receptor gene. *Nature Genetics,* May;19(1):17-8 (1998).

和文総説

1. 本間美和子「総説：プロテインキナーゼCK2核内機能について」*生化学* 日本生化学会,vol 96, no.5, pp662-675,2024
2. 山元想、本間美和子「核小体への分子集積を基盤とする癌予後マーカーの開発」*細胞* ニューサイエンス社, vol 56, no.11, pp.822-824, 2024.
3. 山元想、本間美和子「癌予後マーカーの開発と高感度化へ資する独自抗体について」月刊*BioIndustry* シーエムシー出版 Vol.41, No.7, 2024.
4. 来住野ひなた、松嵜正太郎、加藤遼、福田みちる、本間美和子「癌予後マーカーの開発と高感度化へ資する独自抗体について」月刊JETI vol.73, no.2, pp26-29 (2025) 他

増殖関連酵素 プロテインキナーゼ CK2α
Biological significance of protein kinase CK2 in human cancer



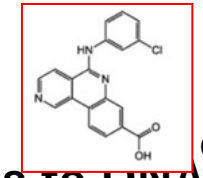
✓ 様々な癌種類においてCK2発現量増加が報告
Increased in the ratio of nuclear to cytosolic content of CK2α,
comparing with those in normal tissue
in **head and neck carcinomas, lymphomas**

✓ CK2阻害薬による臨床治験
A candidate for targeted therapy, with CK2 inhibitors in ongoing clinical trials
- **CX-4945**: small molecule ATP-competitive inhibitor targeting its active site
- **CIGB-300**: cyclic peptide that prevents phosphorylation of the E7 of HPV16
- Both exhibit antitumor efficacy
- In combination with cisplatin or gemcitabine, either CX-4945 or CIGB promote synergistic induction of apoptosis.

As new CK2i: **APL-5125, SGC-CK2-1, AB668**

GRKKRRQRRRPPQ β-ala CWMSPRHLGTC

CIGB-300



CX-4945

✓ CK2阻害薬による生理機能の検証
Potential of CK2 inhibitors to interfere:
- **caspase action**
- **enhance the susceptibility of cancer cells to DNA damage**

Clin Cancer Res 22(12) 2840-7 2016

CK2α阻害薬による癌臨床治験　Clinical Trials for cancer treatment with CK2α inhibitors

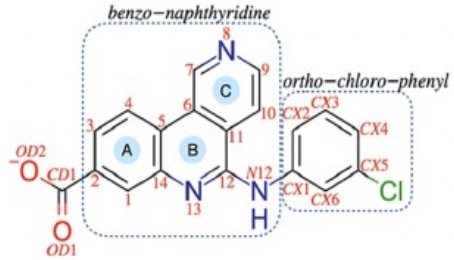
Status	Study Title	Conditions	Interventions	Locations
Active, not recruiting	**Treatment Duration Increment and Pharmacodynamic Study of CX-4945 in Patients With Basal Cell Carcinoma (BCC)**	•**Carcinoma, Basal Cell**	•Drug: **CX-4945**	•University of Colorado Anschutz Medical Campus Aurora, Colorado, United States •H. Lee Moffitt Cancer Center & Research Institute, Inc. Tampa, Florida, United States •University of Texas MD Anderson Cancer Center Houston, Texas, United States •Inova Schar Cancer Institute Fairfax, Virginia, United States
Recruiting	**Testing the Safety and Tolerability of CX-4945 in Patients With Recurrent Medulloblastoma Who May or May Not Have Surgery**	•**Medulloblastoma, Childhood**	•Drug: **CX 4945**	•Children's Hospital of Los Angeles Los Angeles, California, United States •Stanford University and Lucile Packard Children's Hospital Palo Alto, California, United States •Children's National Medical Center Washington, District of Columbia, United States •(and 9 more...)
Unknown	**Study of CX-4945 in Patients With Relapsed or Refractory Multiple Myeloma**	•**Multiple Myeloma**	•Drug: **CX-4945**	•Kettering, Ohio, United States •Oregon Health Science University Portland, Oregon, United States •Springfield, Oregon, United States •(and 3 more...)
Completed	**Study of CX-4945 in Combination With Gemcitabine and Cisplatin for Frontline Treatment of Cholangiocarcinoma**	•**Cholangiocarcinoma**	•Drug: **CX-4945** •Drug: Cisplatin •Drug: Gemcitabine	•Mayo Clinic Scottsdale, Arizona, United States •University of Colorado- Denver Aurora, Colorado, United States •Mayo Clinic Jacksonville, Florida, United States •(and 13 more...)
Uknown	**Dose-escalation Study of Oral CX-4945**	•**Advanced Solid Tumors** •**Breast Cancer** •**Inflammatory Breast Cancer** •**(and 2 more...)**	•Drug: **CX-4945** oral formulation	•Mayo Clinic Arizona Scottsdale, Arizona, United States •Front Range Cancer Specialists Fort Collins, Colorado, United States •Front Range Cancer Specialists Loveland, Colorado, United States •U T M D Anderson Cancer Center Houston, Texas, United States
Recruiting	**Evaluation of a Promising New Combination of Protein Kinase Inhibitors on Organotypic Cultures of Human Renal Tumors**	**Kidney Cancer**	•Combination Product: CK2 and ATM inhibitors serine/ threonin Kinase combination •Drug: Sunitinib •Drug: Pazopanib •Drug: Temsirolimus	•Grenoble Alps Hospital Grenoble, France

https://clinicaltrials.gov/ct2/results?cond=&term=CX-4945&cntry=&state=&city=&dist=

CK2α阻害薬によるCOVID-19臨床治験

Clinical Trials for COVID-19 with CK2α inhibitors

CX-4945
(Silmitasertib)



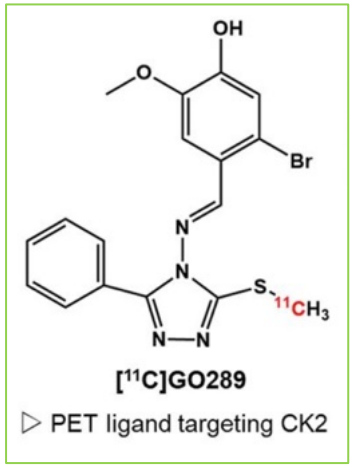
Status	Study Title	Conditions	Interventions	Locations
Completed	Silmitasertib (**CX-4945**) in Patients With Severe Coronavirus Disease 2019 (COVID-19)	Coronavirus	Drug: Silmitasertib	•Banner University Medical Center Phoenix Phoenix, Arizona, United States •Banner University Medical Center Tucson Tucson, Arizona, United States
Active, not recruiting	A Study of Silmitasertib (**CX-4945**) in Healthy Subject	COVID-19	Drug: **CX-4945**	Taipei Medical University Hospital Taipei, Taiwan
Completed	Evaluating Safety, Pharmacokinetics and Clinical Benefit of Silmitasertib (**CX-4945**) in Subjects With Moderate COVID-19	Covid19	Drug: Silmitasertib Drug: SOC	Center for Advanced Research and Education Gainesville, Georgia, United States

https://clinicaltrials.gov/ct2/results?cond=&term=CX-4945&cntry=&state=&city=&dist=

Alzheimer’s disease脳イメージングバイオマーカーとしてCK2iラベル体を活用

Development of a novel PET ligand, [11C]GO289 targeting CK2 expressed in the brain

Abstract
Positron emission tomography (PET) is a powerful imaging tool that enables early in vivo detection of Alzheimer's disease (AD). For this purpose, various PET ligands have been developed to image β-amyloid and tau protein aggregates characteristically found in the brain of AD patients. In this study, we initiated to develop another type of PET ligand that targets protein kinase CK2 (formerly termed as casein kinase II), because its expression level is known to be altered in postmortem AD brains. CK2 is a serine/threonine protein kinase, an important component of cellular signaling pathways that control cellular degeneration. In AD, the CK2 level in the brain is thought to be elevated by its involvement in both phosphorylation of proteins such as tau and neuroinflammation. Decreased CK2 activity and expression levels lead to β-amyloid accumulation. In addition, since CK2 also contributes to the phosphorylation of tau protein, the expression level and activity of CK2 is expected to undergo significant changes during the progression of AD pathology. Furthermore, CK2 could act as a potential target for modulating the inflammatory response in AD. Therefore, PET imaging targeting CK2 expressed in the brain could be a useful another imaging biomarker for AD. We synthesized and radiolabeled a CK2 inhibitor, [^{11}C]GO289, in high yields from its precursor and [^{11}C]methyl iodide under basic conditions. On autoradiography, [^{11}C]GO289 specifically bound to CK2 in both rat and human brain sections. On baseline PET imaging, this ligand entered and rapidly washed out of the rat brain with its peak activity rather being small (SUV < 1.0). However, on blocking, there was no detectable CK2 specific binding signal. Thus, [^{11}C]GO289 may be useful in vitro but not so in vivo in its current formulation. The lack of detectable specific binding signal in the latter may be due to a relatively high component of nonspecific binding signal in the overall rather weak PET signal, or it may also be related to the known fact that ATP can competitively binds to subunits of CK2, reducing its availability for this ligand. In the future, it will be necessary for PET imaging of CK2 to try out different non-ATP competitive formulations of CK2 inhibitor that can also provide significantly higher in vivo brain penetration.
Keywords: Alzheimer’s disease; CK2; positron emission tomography (PET).



Bioorg Med Chem Lett (2023) Jun 15:90:129327.
国立長寿医療センター, 岐阜大学