香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Transforming our Passion into Perfection

Translating New Gene Regulatory Mechanisms into Effective Cancer Immunotherapy

Alfred Cheng PhD

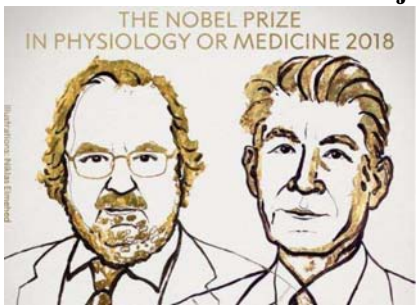
School of Biomedical Sciences
The Chinese University of Hong Kong

Journal Club of the Food and Health Bureau
22 April 2022

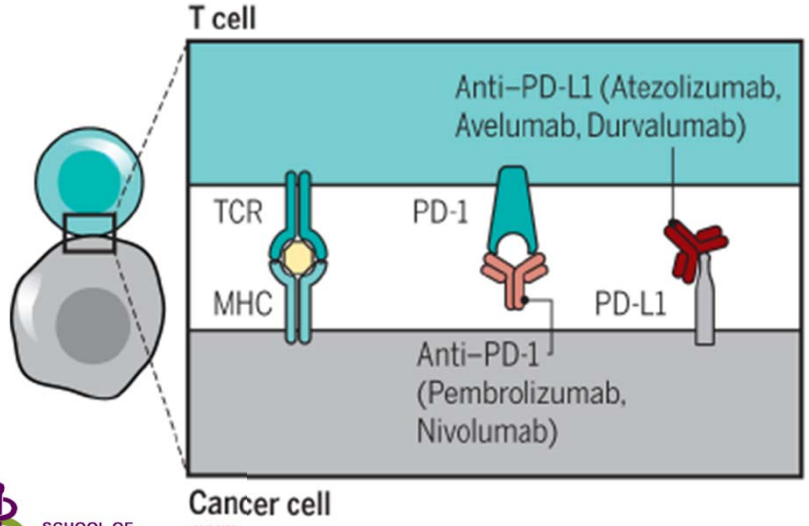
SCHOOL OF BIOMEDICAL SCIENCES CUHK 2010-2020

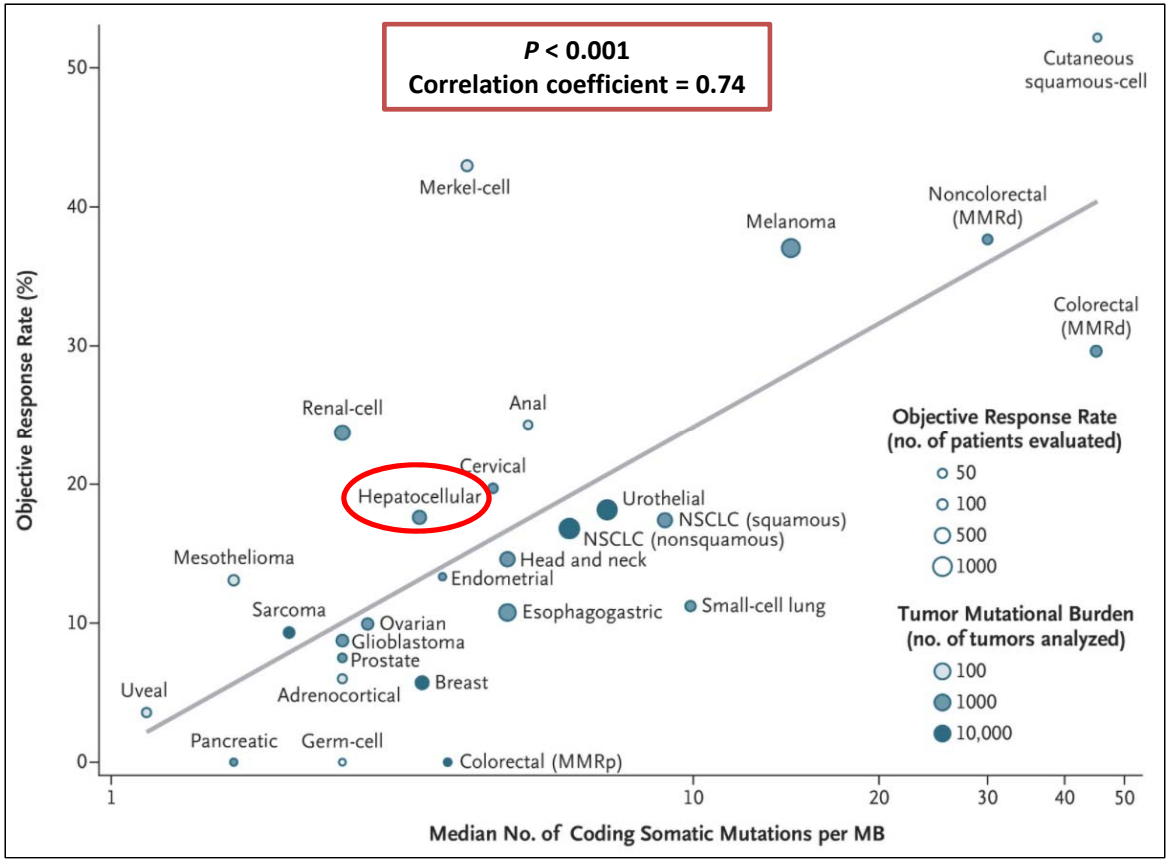
Immune-checkpoint blockade (ICB) therapy

James Allison & Tasuku Honjo



- **Discovery of cancer therapy by inhibition of negative immune regulation**





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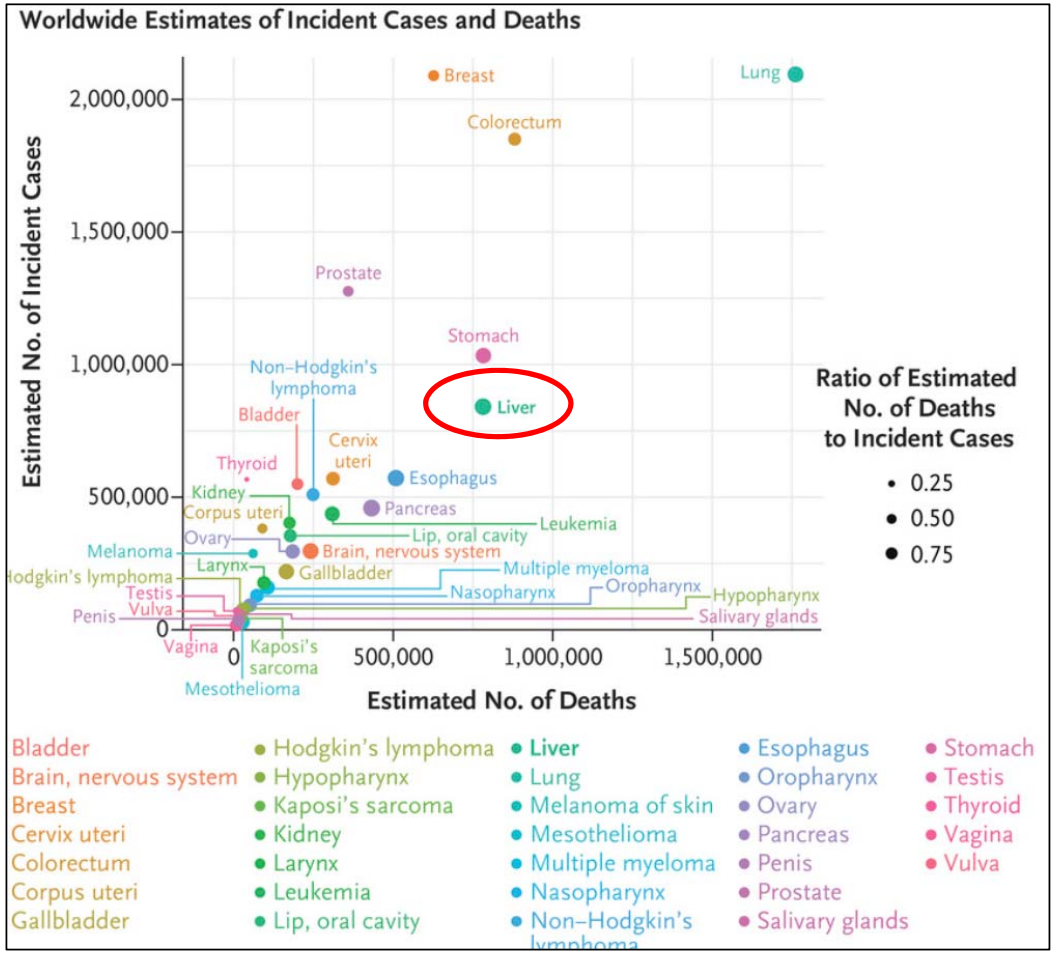
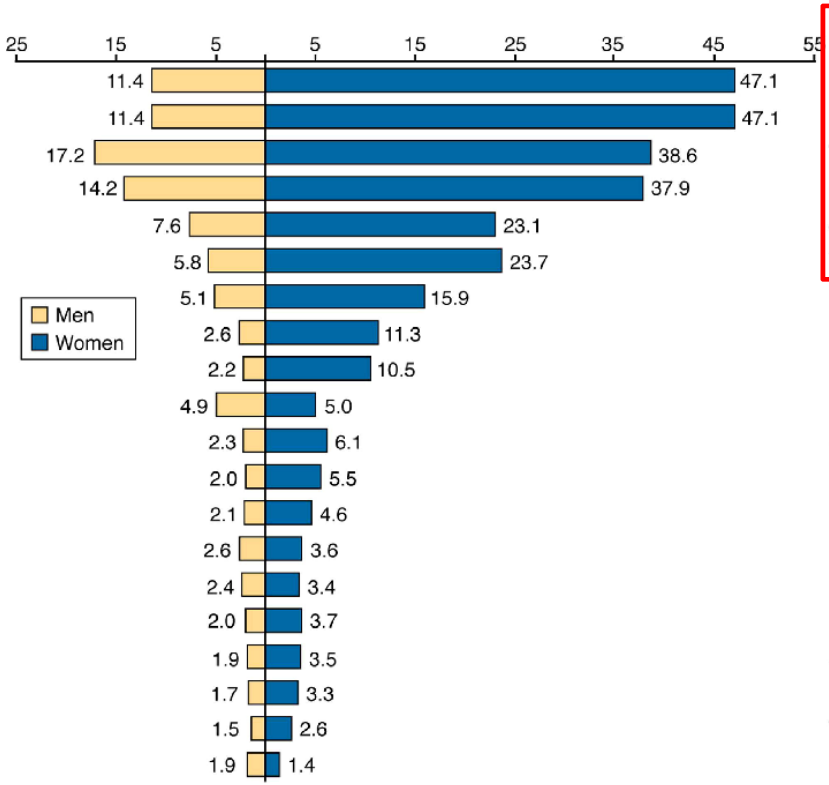
Sharma *et al.*, *Cell* 2017; Yarchoan *et al.*, *New Engl J Med* 2017

Hepatocellular carcinoma (HCC)





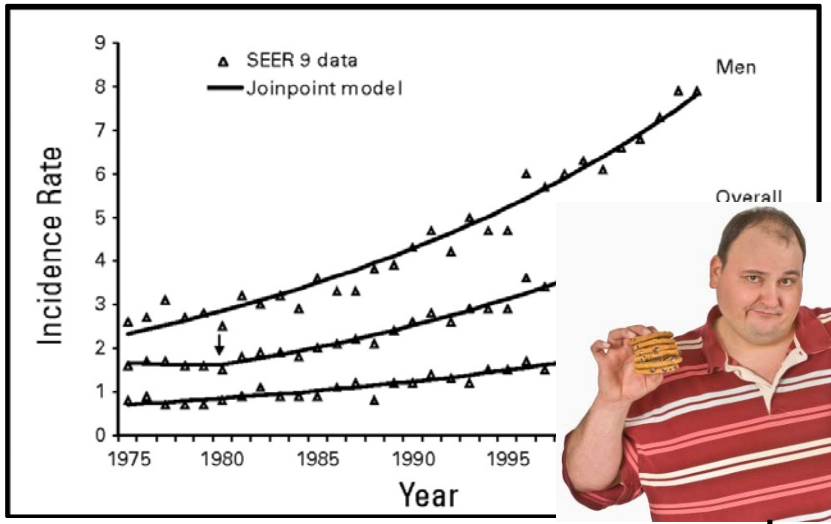
	Male:female ratio
South Korea	4.1
North Korea	4.1
Thailand	2.2
China	2.7
Japan	3.0
Vietnam	4.1
Italy	3.1
Indonesia	4.3
France	4.8
Mexico	1.0
South Africa	2.7
USA	2.8
Russia	2.2
Poland	1.4
Brazil	1.4
Sweden	1.9
Argentina	1.8
United Kingdom	1.9
Turkey	1.7
Iran	0.7

Villanueva, *New Engl J Med* 2019

El-Serag. *Gastroenterology* 2012

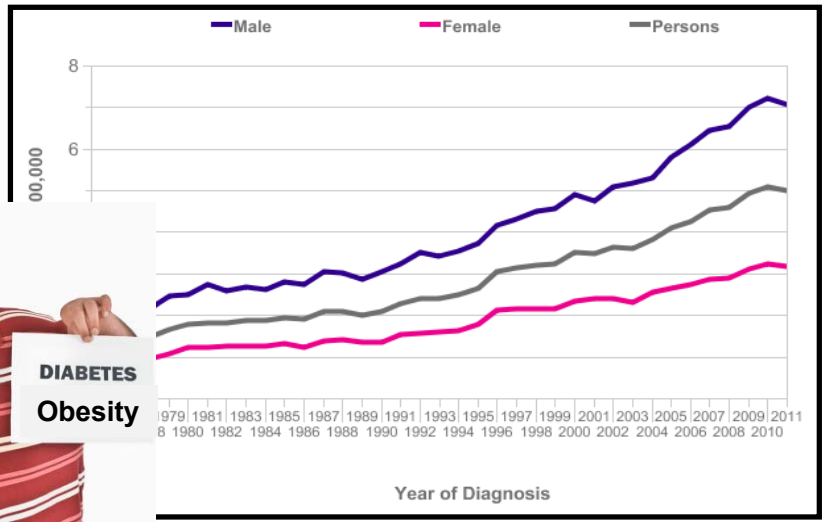
Increasing HCC incidence in Western countries

United States



Altekruse *et al.*, *J Clin Oncol* 2009

United Kingdom



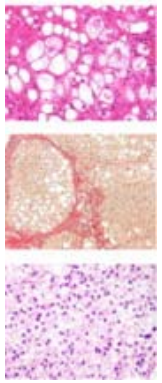
Non-alcoholic fatty liver disease (NAFLD)

↓

Fibrosis/cirrhosis

↓

Hepatocellular carcinoma (HCC; 2-10%)



CANCER RESEARCH UK

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Yu *et al.*, *Semin Cancer Biol* 2014

Grand challenges of HCC immunotherapy

U.S. FOOD & DRUG ADMINISTRATION

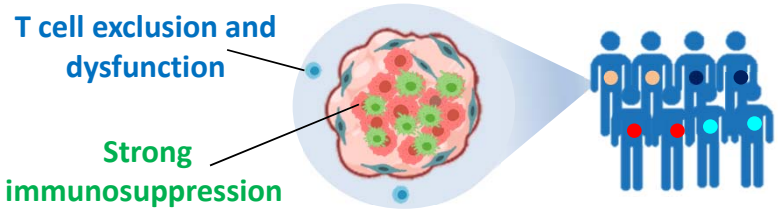
ICB therapy approval for HCC treatment

Objective response rate

2017	2018	2020
Nivolumab	Pembrolizumab	Nivolumab+Ipilimumab
PD-1 (~15%)	PD-1 (~17%)	PD-1+CTLA-4 (~32%)
		Atezolizumab+Bevacizumab
		PD-L1+VEGF (~27%)

Low response rates (15-27%)
No predictive biomarker

'Cold' tumor microenvironment (TME)



Inter- and intra-tumor heterogeneity

Our Overall Goal:

Unraveling the cellular and molecular basis of ICB therapeutic resistance to advance cancer immunotherapy

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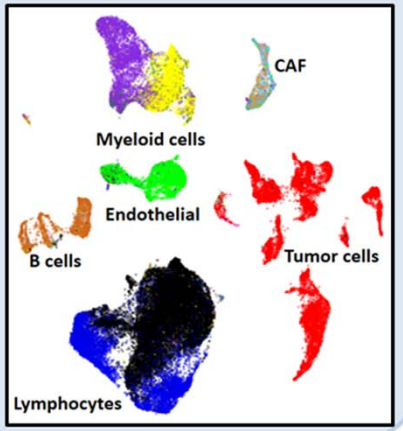
EI-Khoueiry *et al.*, *Lancet* 2017; Zhu *et al.*, *Lancet Oncol* 2018; Yau *et al.*, *JAMA Oncol* 2020; Finn *et al.*, *New Engl J Med* 2020

Our multi-disciplinary approach

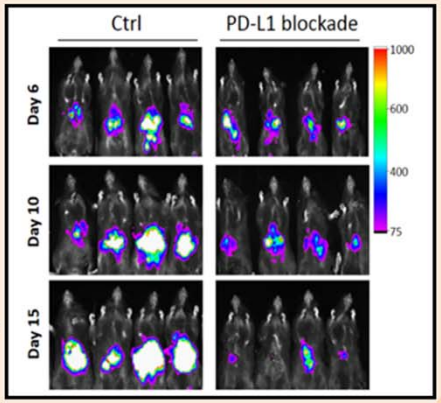
Single-cell multi-omics

- scRNA/ATAC-seq
- CITE-seq
- TCR-seq
- High-parameter flow cytometry
- Spatial transcriptomics
- Hi-C/Hi-ChIP/ChIP-seq



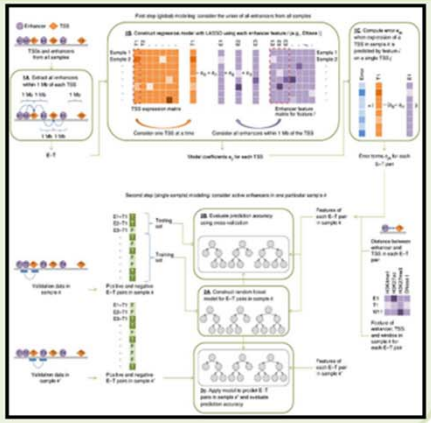
Pre-clinical models

- Orthotopic fibrotic HCC models
- Spontaneous NAFLD-HCC models
- Hydrodynamic injection models
- Humanized PDX models



Computational bioinformatics

- Omics data integration
- Gene regulatory network delineation
- Therapeutic target identification
- Biomarker construction by artificial intelligence



Clinical collaborations

- Collaborates with oncologist/pathologist/hepatologist/endocrinologist/surgeons
- Patient specimens validation
- Phase I/II clinical trials

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Unlocking the Difference between the Sexes in Liver Cancer

Alfred Cheng figured out
Men contract liver cancer far more often than women

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2010-2020

Unlocking the difference between sexes in liver cancer

Impact objectives:

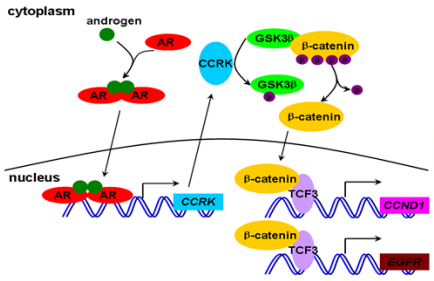
- *Increase our understanding why hepatitis B virus (HBV)-infected men have higher risk of developing HCC than women*
- *Use of integrative genomic and preclinical study to explain the gender disparity in liver cancer*
- *Identify novel druggable targets for treating liver cancer*

Discovery timeline

2011 — 2012 — 2013 — 2014 — 2015 — 2016 — 2017 — 2018 — 2019 — 2020 — 2021

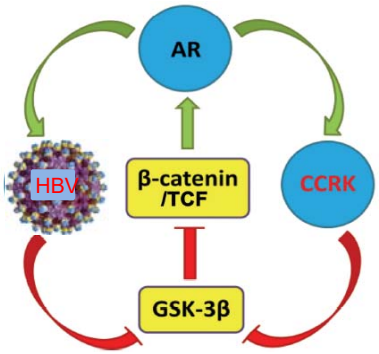
2011 — *Discovery of Cell cycle-related kinase (CCRK) as a direct AR-regulated oncoprotein*

Feng *et al.*, ***J Clin Invest*** 2011



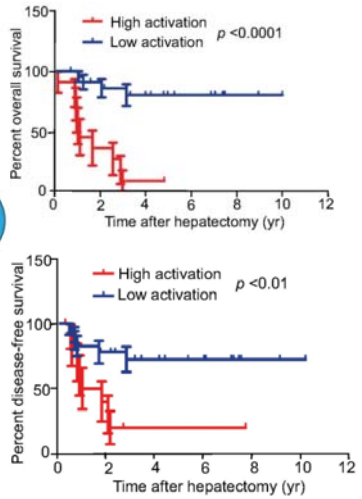
2012 — *CCRK mediates HBV-host circuitry to promote HCC*

Yu *et al.*, ***Gut*** 2014



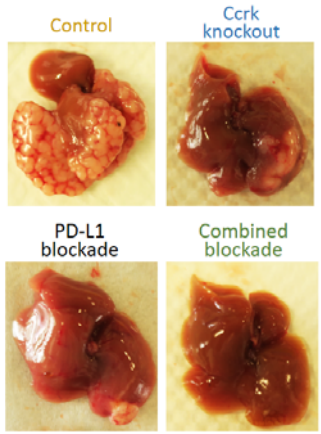
2014 — *CCRK-EZH2 epigenetic circuitry correlates with HCC prognosis*

Feng *et al.*, ***J Hepatol*** 2015



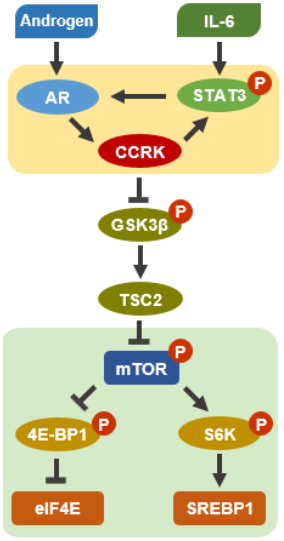
2016 — *CCRK inhibition enhances HCC immunotherapy*

Zhou *et al.*, ***Gut*** 2018



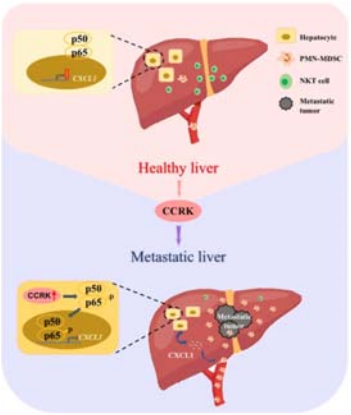
2018 — *CCRK induces immune suppressive TME in obesity-related HCC*

Sun *et al.*, ***Nat Comm*** 2018



2021 — *CCRK signaling sets up a metastasis-prone liver environment*

Zeng, ***Cell Mol Immunol*** 2021



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HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Hepatology Elsewhere

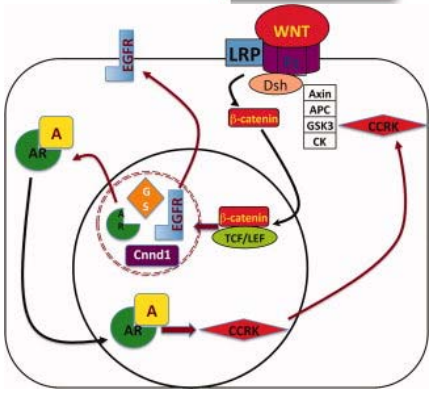
Cell cycle–related kinase links androgen receptor and β-catenin signaling in hepatocellular carcinoma: Why are men at a loss?†

Prince K. Awuah M.D.[1] and Satdarshan P. Monga M.D.[1,2]

Article first published online: 23 FEB 2012
DOI: 10.1002/hep.24774

Issue

Hepatology
Volume 55, Issue 3, pages 970–974, March 2012



- ***"The authors elegantly unveil one of the mechanisms of sex-related disparity of HCC....that may be exploited for therapeutic intervention."***

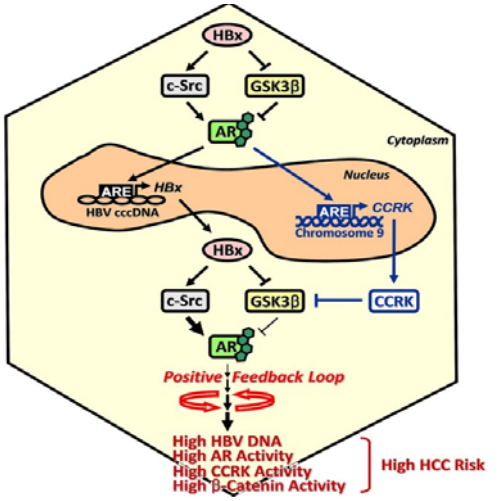
Commentary

GUT

Gut Online First, published on March 5, 2014 as 10

The driving circuit of HBx and androgen receptor in HBV-related hepatocarcinogenesis

Sheng-Han Wang,[1] Shiou-Hwei Yeh,[1,2] Pei-Jer Chen[1,2,3,4]



- ***"This experimental and clinical evidence underscores the crucial role of CCRK....in HBV-infected male hepatocarcinogenesis ..... a specific kinase inhibitor against CCRK could be explored."***

GUT

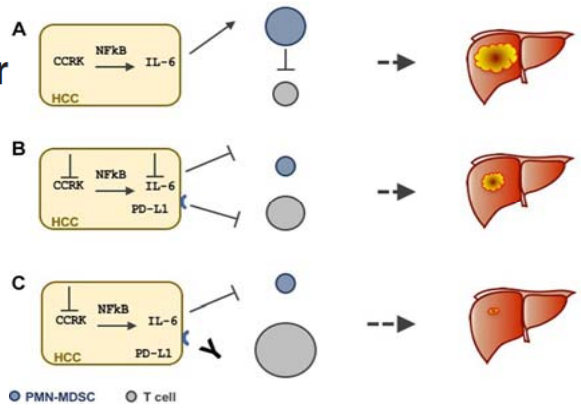
Gut Online First, published on October 24, 2017 as 10.1136/gutjnl-2017-315091

Commentary

CDK20 inhibition and immune checkpoint blockade: bringing cancer biology and tumour immunology together to develop novel treatment options for HCC

Tim F Greten, Firouzeh Korangy

National Cancer Institute, NIH



Combined CCRK and PD-L1 blockade leads to effective T cell-mediated anti-HCC immunity

- ***"In summary, the authors provide convincing evidence from human clinical samples and murine studies.....this is a very interesting and novel study with <u>potentially a very high clinical impact</u>."***

Cellular & Molecular Immunology

COMMENT

CCRK—a hub for liver metastasis and cancer

Jie-Ting Low[1,2], Guan-Ling Lin[1,2] and Michael W. Y. Chan[1,2,3]

Cellular & Molecular Immunology (2021) 18:1341–1342; https://doi.org/10.1038/s41423-020-00569-5

- ***"CCRK acts as a signaling hub that connects carcinogenesis and tumor immunoevasion. <u>Targeting CCRK may be a novel strategy against liver metastasis and cancer.</u>"***

CDK20 (cyclin-dependent kinase 20) = CCRK

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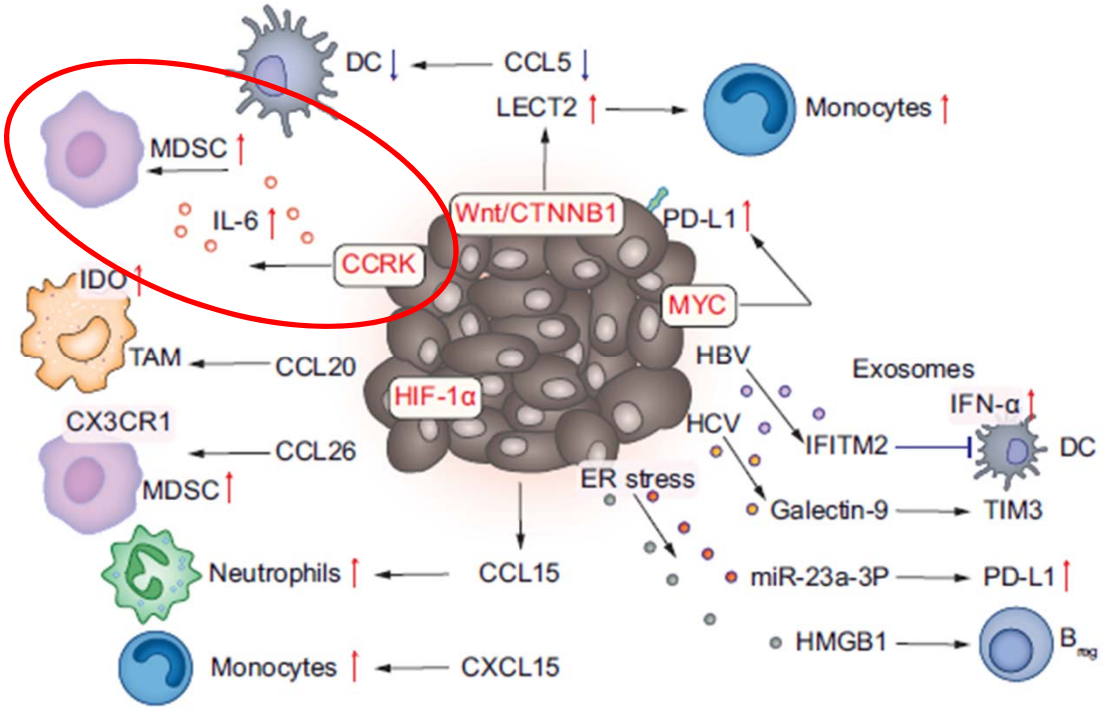
Review

JOURNAL
OF HEPATOLOGY

The immunobiology of hepatocellular carcinoma in humans and mice: Basic concepts and therapeutic implications

Jiajie Hou[1,4,5], Haiyan Zhang[5], Beicheng Sun[1,2,*], Michael Karin[3,*]



➢ ***Oncogenic signals promote evasion of anti-HCC immunity***

Hou *et al.*, *J Hepatol* 2020

Pharmacology & Therapeutics 186 (2018) 138–151

Contents lists available at ScienceDirect

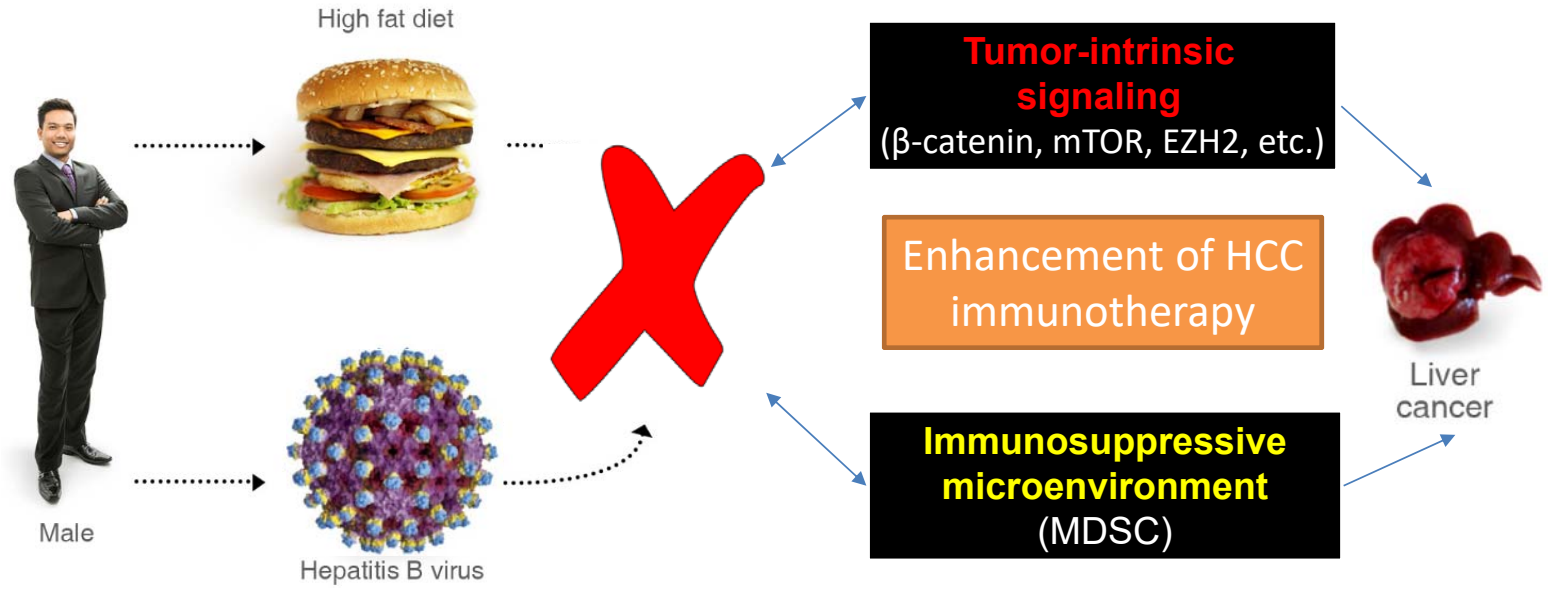
Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

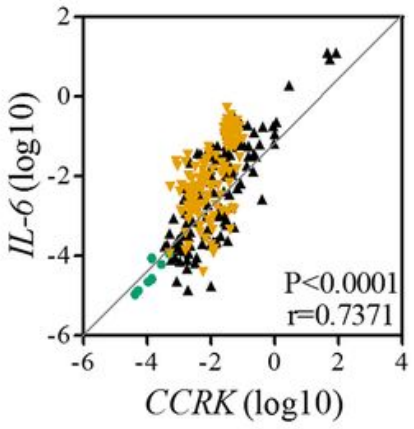
CCRK is a novel signalling hub exploitable in cancer immunotherapy

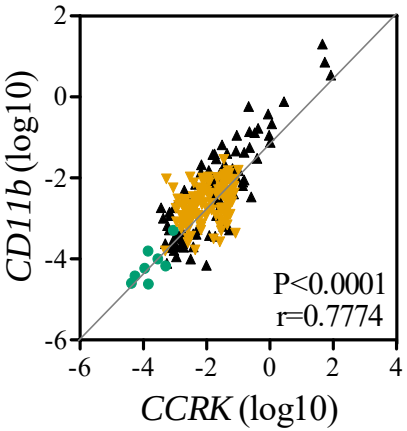
Myth T. Mok [a], Jingying Zhou [a], Wenshu Tang [a], Xuezhen Zeng [a], Antony W. Oliver [c], Simon E. Ward [d], Alfred S. Cheng [a,b,*]

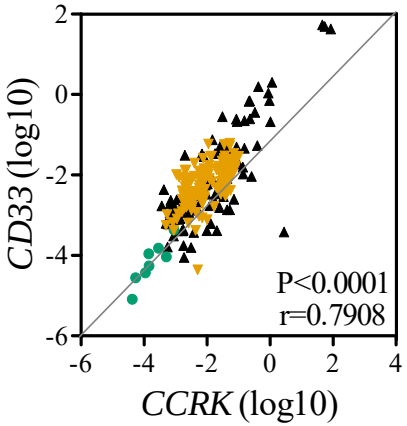
[a] School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China
[b] State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China
[c] Genome Damage and Stability Centre, School of Life Sciences, University of Sussex, Falmer, UK
[d] Medicines Discovery Institute, Cardiff University, Main Building, Cardiff, Wales, CF10 3AT, UK

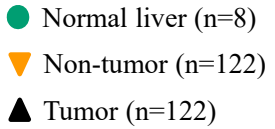


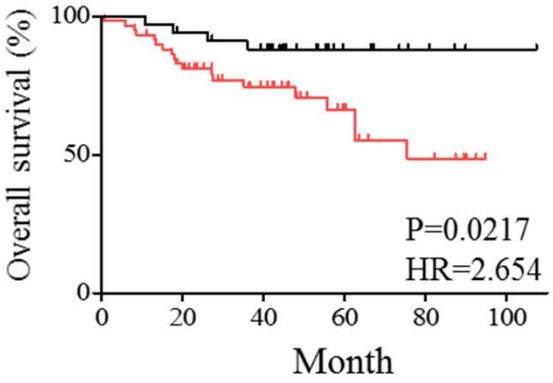
Increased CCRK signaling associates with poor prognosis of HCC patients

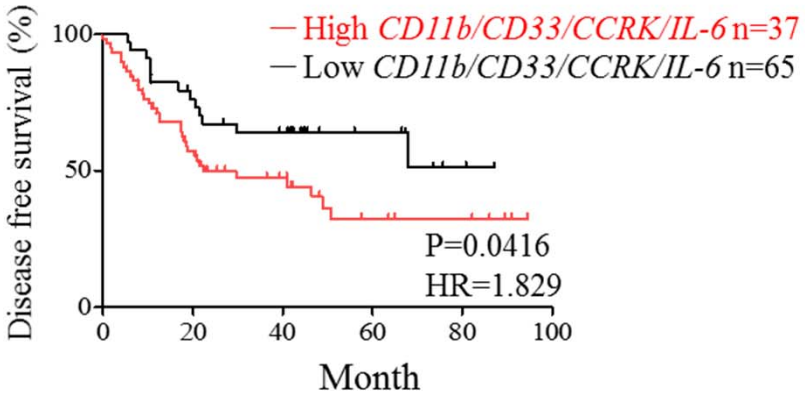


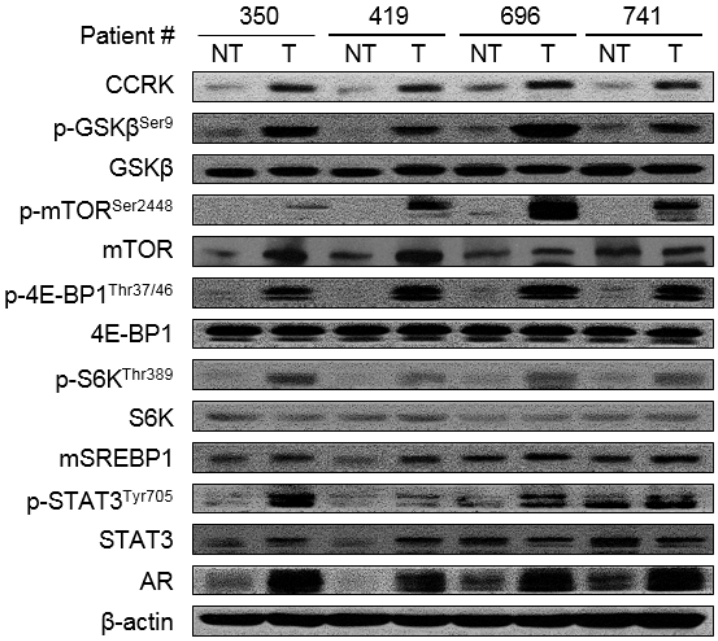












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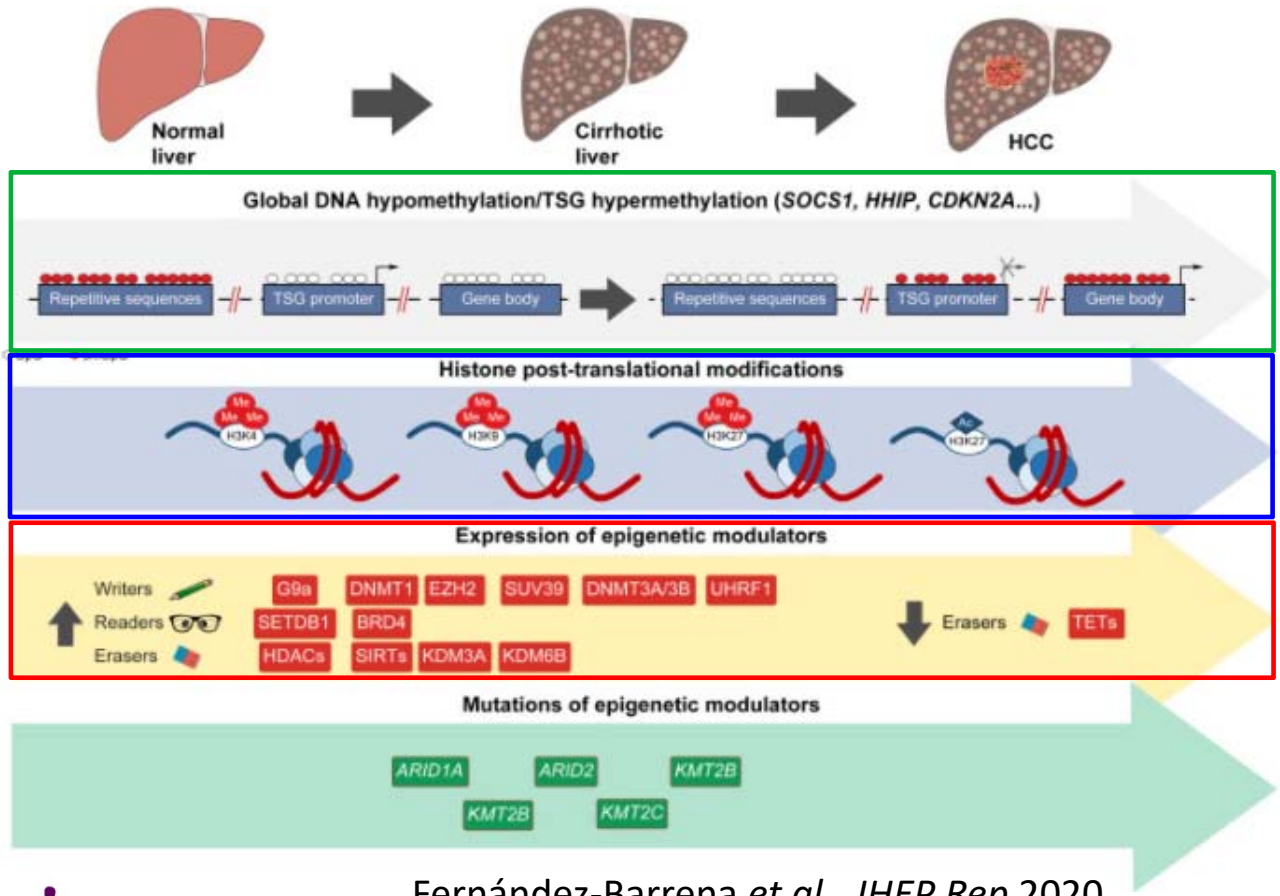
Feng *et al.*, *J Clin Invest* 2011; Yu *et al.*, *Gut* 2014; Feng *et al.*, *J Hepatol* 2015; Zhou *et al.*, *Gut* 2018; Sun *et al.*, *Nat Commun* 2018

Epigenetic alterations during liver carcinogenesis



Fernández-Barrena *et al.*, *JHEP Rep* 2020

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-018-08245-z OPEN

Aberrant enhancer hypomethylation contributes to hepatic carcinogenesis through global transcriptional reprogramming

Lei Xiong[1,2], Feng Wu[1,2], Qiong Wu[2], Liangliang Xu[2], Otto K. Cheung[2], Wei Kang[1], Myth T. Mok[2], Lemuel L. M. Szeto[2], Cheuk-Yin Lun[2], Raymond W. Lung[1], Jinglin Zhang[1], Ken H. Yu[1,3], Sau-Dan Lee[3], Guangcun Huang[4], Chiou-Miin Wang[4], Joseph Liu[4], Zhuo Yu[5], Dae-Yeul Yu[6], Jian-Liang Chou[7], Wan-Hong Huang[7], Bo Feng[2], Yue-Sun Cheung[8], Paul B. Lai[8], Patrick Tan[9,10], Nathalie Wong[1], Michael W. Chan[7], Tim H. Huang[4], Kevin Y. Yip[3], Alfred S. Cheng[2] & Ka-Fai To[1,11]

CANCER RESEARCH

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Tumor and Stem Cell Biology

EZH2-Mediated Concordant Repression of Wnt Antagonists Promotes β-Catenin–Dependent Hepatocarcinogenesis

Alfred S.L. Cheng, Suki S. Lau, Yangchao Chen, Yutaka Kondo, May S. Li, Hai Feng, Arthur K. Ching, Kin F. Cheung, Hoi K. Wong, Joanna H. Tong, Hongchuan Jin, Kwong W. Choy, Jun Yu, Ka F. To, Nathalie Wong, Tim H.-M. Huang, and Joseph J.Y. Sung

DOI: 10.1158/0008-5472.CAN-10-3342 Published June 2011

Nucleic Acids Research

Nucleic Acids Research, 2018 1
doi: 10.1093/nar/gky589

Loss of tumor suppressor IGFBP4 drives epigenetic reprogramming in hepatic carcinogenesis

Ying-Ying Lee[1,2,†], Myth T.S. Mok[1,†], Wei Kang[3], Weiqin Yang[1], Wenshu Tang[1], Feng Wu[1,3], Liangliang Xu[1], Mingfei Yan[1], Zhuo Yu[4], Sau-Dan Lee[5], Joanna H.M. Tong[3], Yue-Sun Cheung[6], Paul B.S. Lai[6], Dae-Yeul Yu[7], Qianben Wang[8], Grace L.H. Wong[2], Andrew M. Chan[1], Kevin Y. Yip[5], Ka-Fai To[3,9,10] and Alfred S.L. Cheng[1,10,*]

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➢ *Can we exploit the epigenetic mechanisms to augment immunotherapy?*

Teresa

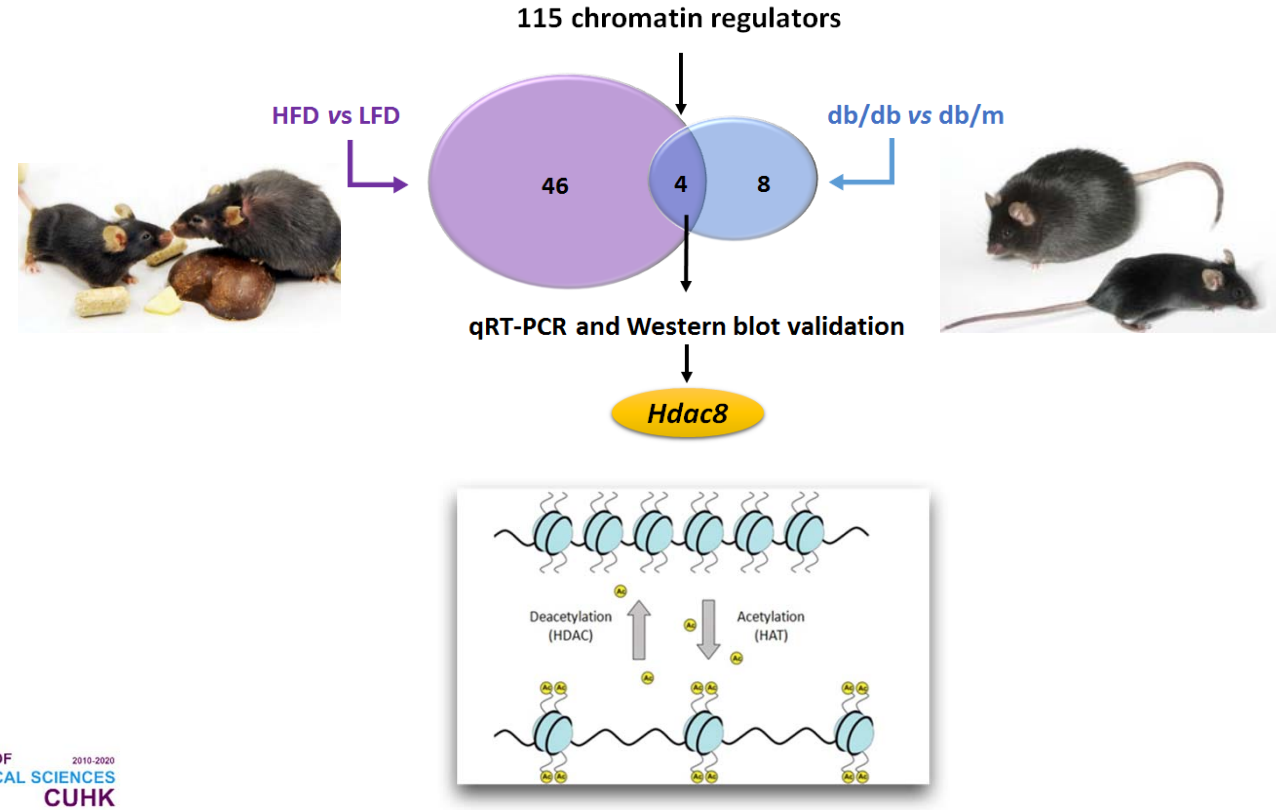
Molecular and Cellular Pathobiology

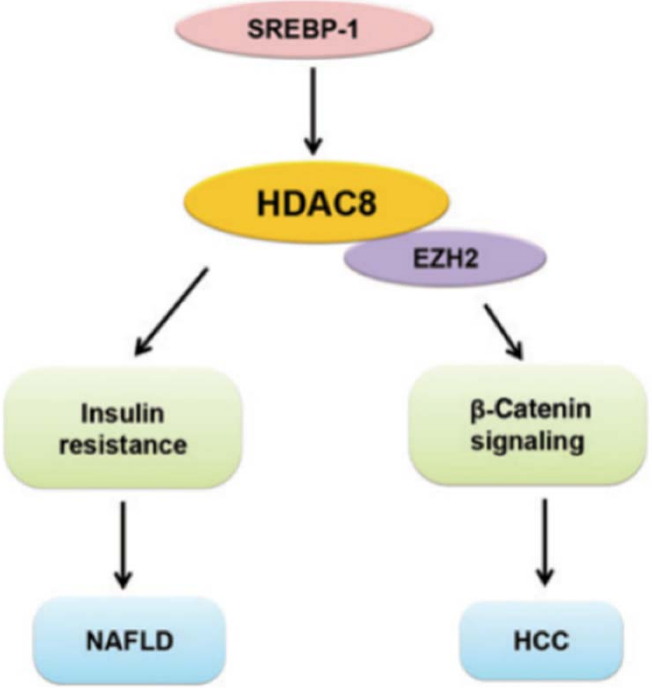
Cancer Research

Histone Deacetylase HDAC8 Promotes Insulin Resistance and β-Catenin Activation in NAFLD-Associated Hepatocellular Carcinoma

Yuan Tian[1,2], Vincent W.S. Wong[1,2], Grace L.H. Wong[1,2], Weiqin Yang[1,2], Hanyong Sun[1,2], Jiayun Shen[1,2], Joanna H.M. Tong[3], Minnie Y.Y. Go[1], Yue S. Cheung[4], Paul B.S. Lai[4], Mingyan Zhou[1], Gang Xu[1], Tim H.M. Huang[5], Jun Yu[1,2], Ka F. To[2,3], Alfred S.L. Cheng[2,6], and Henry L.Y. Chan[1,2]

- A total of 18 HDAC proteins are grouped into 4 classes
- HDAC8: a Class I HDAC



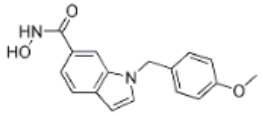


Tian *et al.*, *Cancer Res* 2015

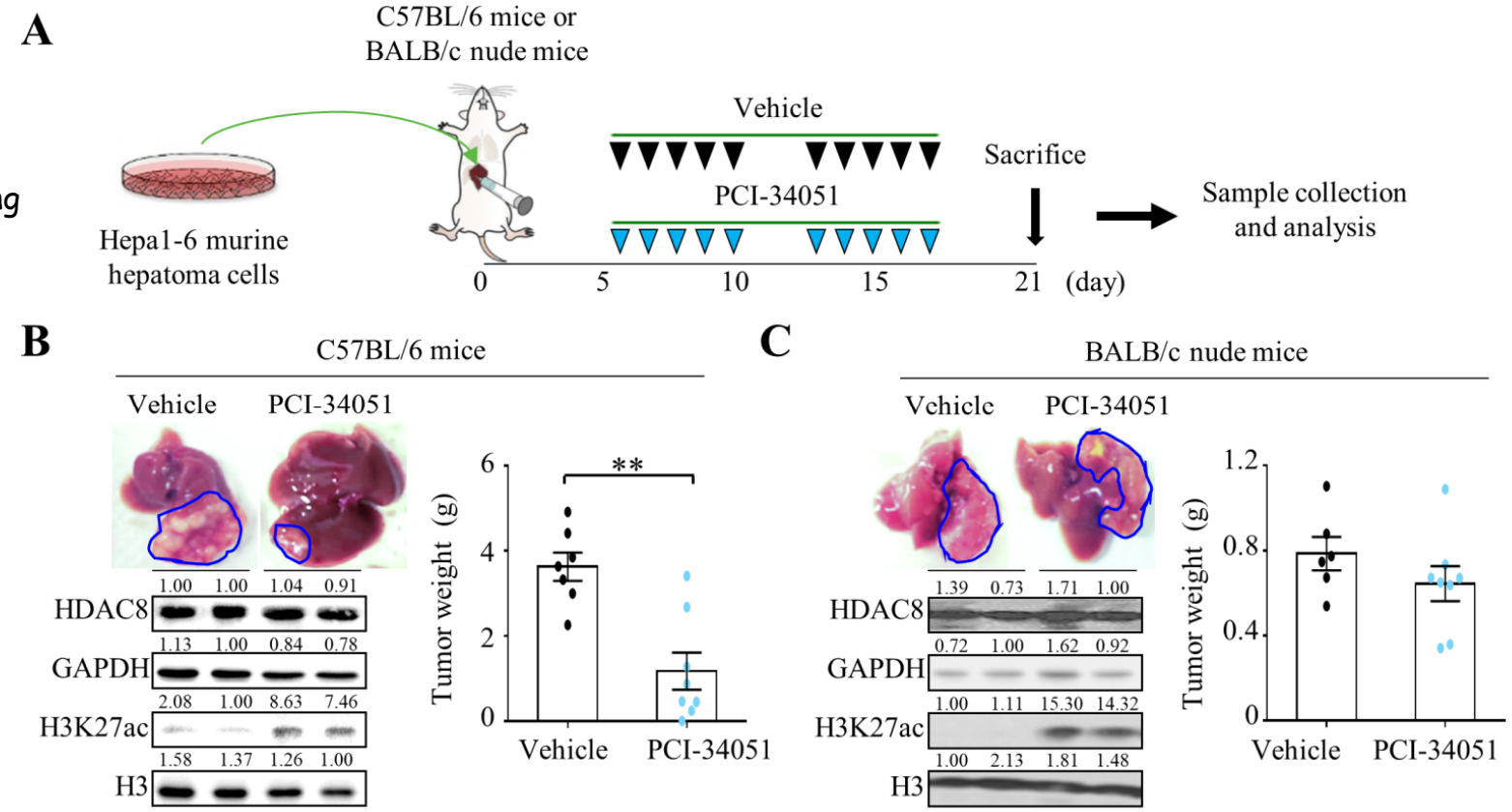
Anti-HCC effect of HDAC8 inhibition depends on adaptive immune response

Weiqin Fengyu Jingying

Selective HDAC8 inhibitor:
PCI-34051



Balasubramanian *et al.*, *Leukemia* 2008



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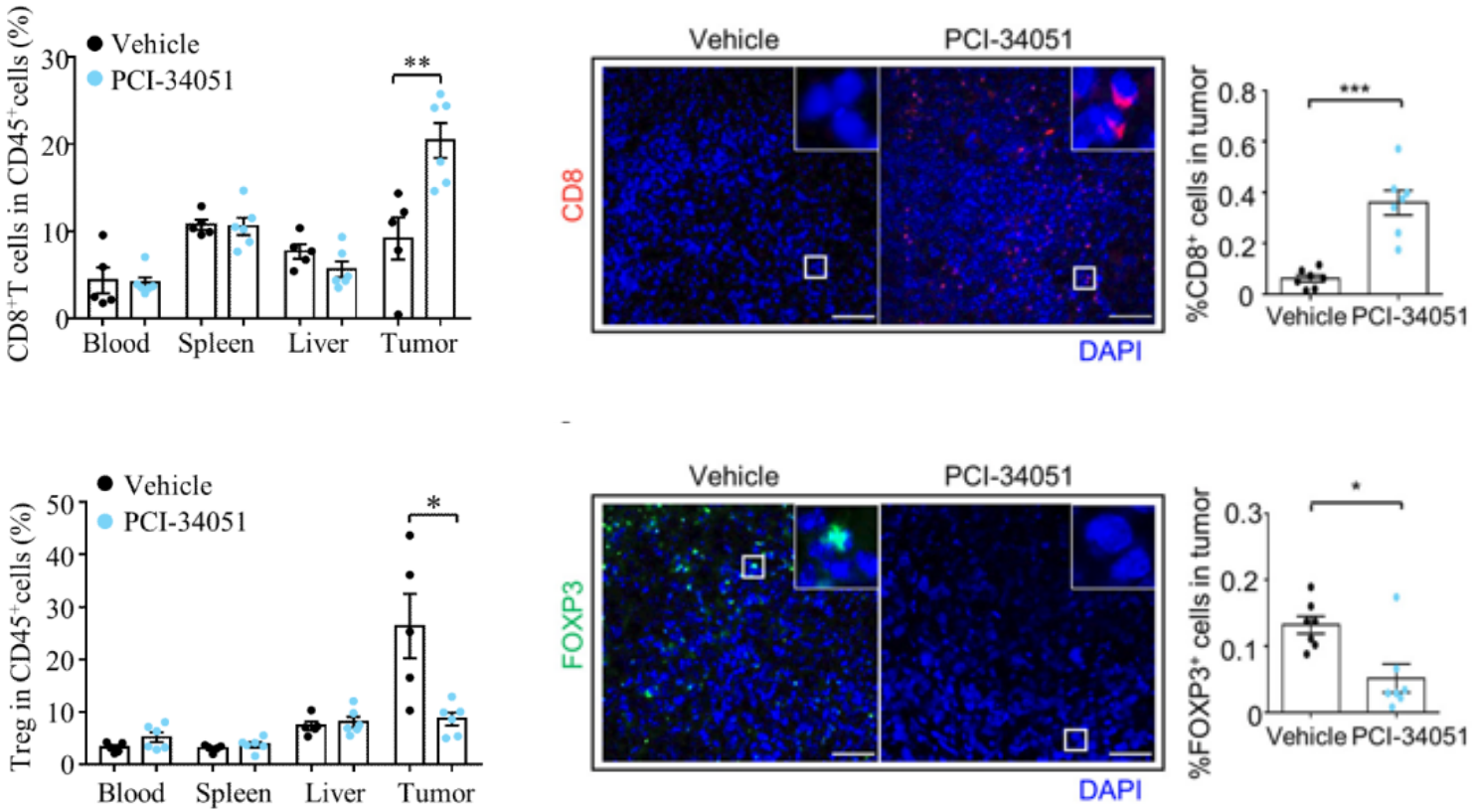
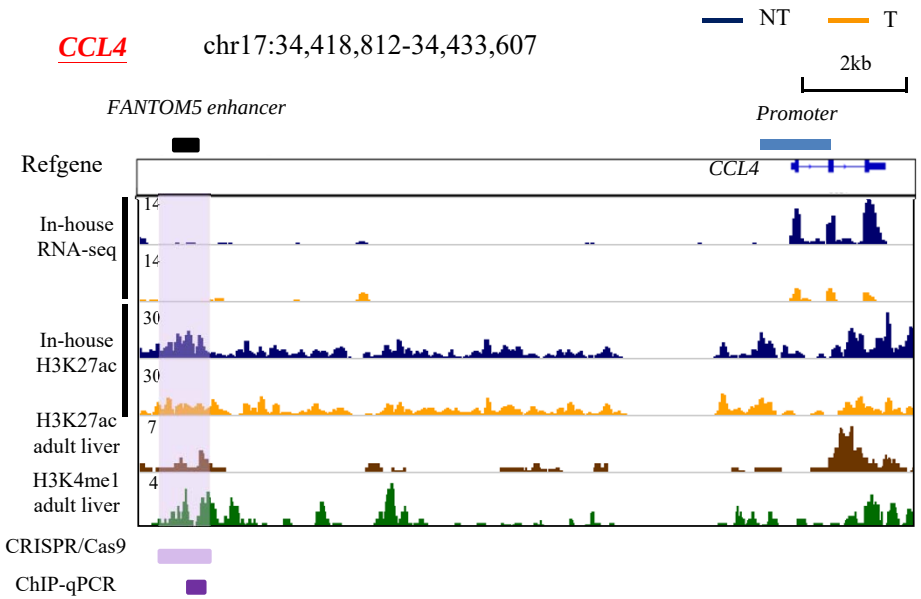
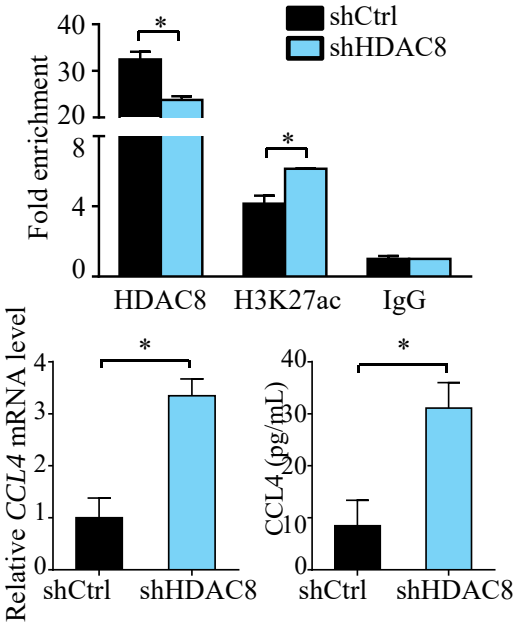
HDAC8 inhibition increases tumor-infiltrating CD8+T but reduces Treg cells

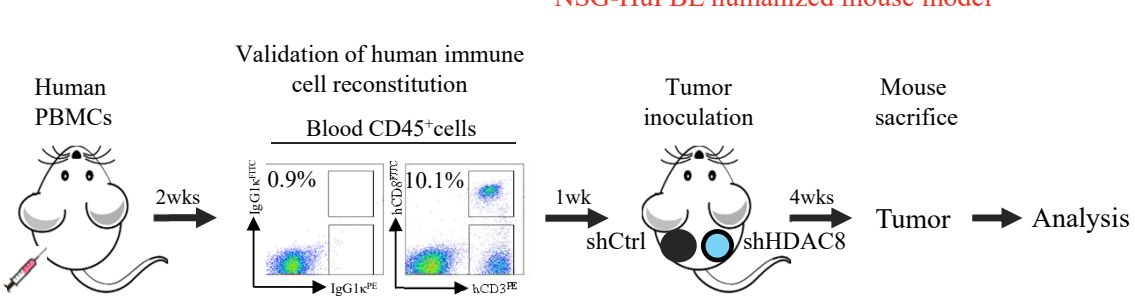


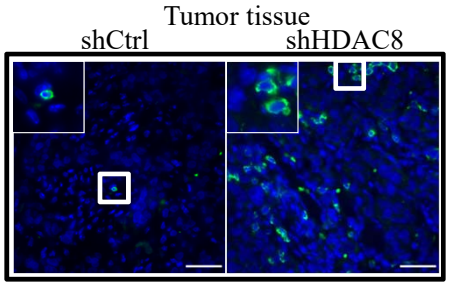
Enhancer reprogramming by HDAC8 inhibition promotes tumor infiltration of CD8⁺ T cells





NSG-HuPBL humanized mouse model





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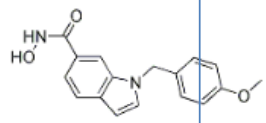
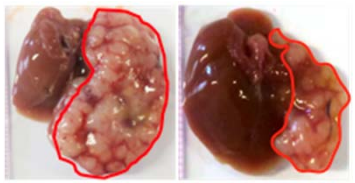
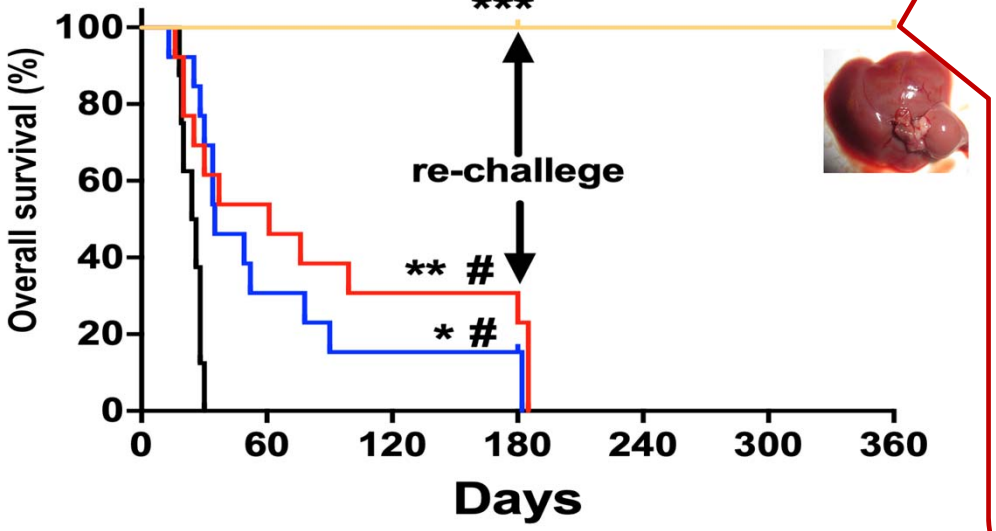
Effective and durable anti-tumor response by HDAC8/PD-L1 co-blockade

Selective HDAC8 inhibitor:
PCI-34051

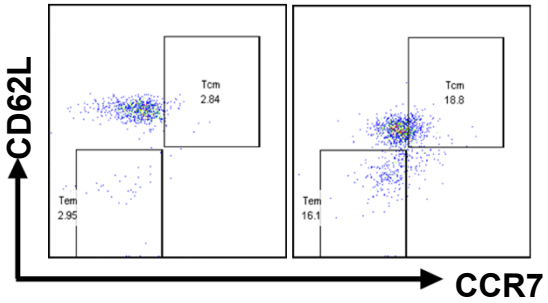


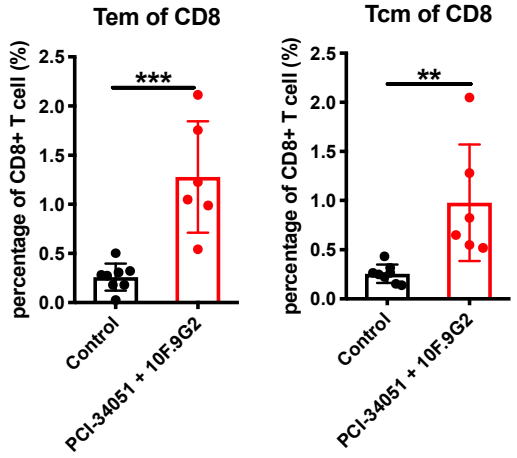




N = 6-12 per group

Strong memory induction





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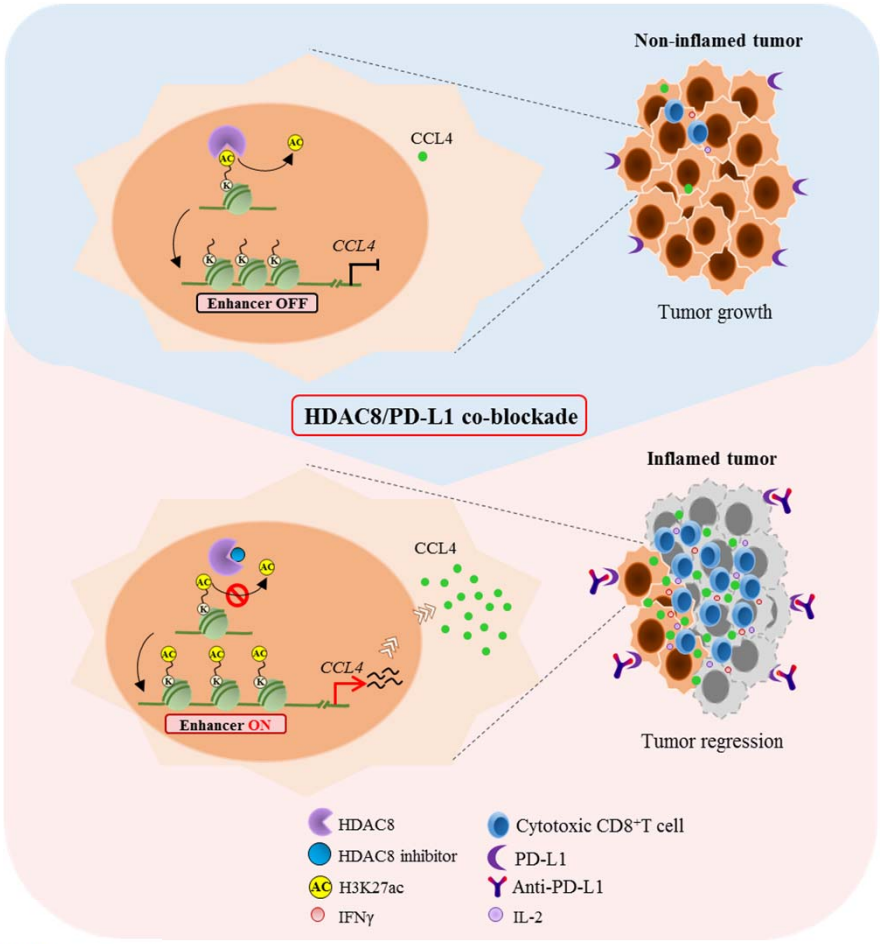
A selective HDAC8 inhibitor potentiates anti-tumor immunity and efficacy of immune checkpoint blockade in HCC



Science Translational Medicine
AAAS

A new isozyme-specific epigenetic immunotherapy

- Our study identified a HDAC8-regulated enhancer landscape that promotes tumor immune evasion through T cell exclusion
- Targeted HDAC8 inhibition yielded an immunostimulatory TME with a high CD8+ T cell/Treg to potentiate tumor remission and long-term survival benefits by PD-L1 blockade with no evidence of toxicity
- Our findings may be of great value for future clinical development of selective HDAC8 inhibitors in HCC and other HDAC8-expressing malignancies.

Yang, Feng, Zhou *et al.*, *Sci Transl Med* 2021

SCHOOL OF BIOMEDICAL SCIENCES CUHK 2010-2020

← Tweet

CUHK Medicine ✓
@CUHKMedicine

Turning “cold” #LiverTumour “hot” can lead to an effective and durable combined #immunotherapy. Our study in @ScienceTM shows that the new treatment brings at least a 15-month tumour-free period with no evidence of side effects in mice model: bit.ly/2PwgB2k

LinkedIn Jobs | CUHK Medicine | Hong Kong SAR

CUHK Medicine’s Post

CUHK Medicine
1,074 followers
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Our recent study uncovers a new strategy to turn “cold” Liver Tumour “hot” leading to an effective and durable combined immunotherapy. Immunotherapy is a major pillar of cancer therapy. Immune checkpoint inhibitors activate the cancer-killing T cells that had been suppressed by the cancer cells, leading to tumour shrinkage and improved survival rates. Most of the liver cancers (hepatocellular carcinoma or HCC) are “cold” or T cell-exc...

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大公報 | 2021-04-29
報刊 | A06 | 要聞 |
圖片頁數: 1/1

中大研究發現 激活免疫細胞治肝癌

中大研究發現 激活免疫細胞治肝癌

【大公報訊】免疫療法是治療癌症其中一個主要方案，惟過往的臨床研究顯示，該療法對肝細胞癌患者的有效率僅10%至20%。香港中文大學（中大）醫學院研究團隊研究發現，將肝腫瘤由「冷」轉「熱」激活免疫T細胞滅癌，使帶有肝細胞癌小鼠的腫瘤消失最少15個月。研究結果將有望提升免疫療法的功效，並已於《科學轉化醫學》期刊發表。

免疫檢查點抑制劑（immune checkpoint inhibitor）可激活免疫T細胞，恢復其殺滅癌細胞的功能，令腫瘤縮小並提高患者存活率。然而，大部分肝癌（即肝細胞癌）屬於「冷腫瘤」，會排斥T細胞。中大發現，一種名為HDAC8的促癌基因是導致癌腫瘤排斥免疫細胞的關鍵。抑制HDAC8有助重新編程腫瘤細胞的「表觀遺傳基因組」，增加T細胞在腫瘤中的浸潤。

團隊的研究亦顯示，使用HDAC8和免疫檢查點抑制劑的新型合併免疫療法，可以令帶有肝細胞癌小鼠的腫瘤消失最少15個月，而且暫未有證據顯示有關療法存在副作用。

中大醫學院生物醫學學院教授鄭詩樂教授表示，是次研究對開發治療肝細胞癌的HDAC8抑制劑具有重要價值。由於其他同樣會排斥T細胞的癌症，例如卵巢癌和胰臟癌等，亦有HDAC8蛋白過度表達的情況，期望日後有進一步研究進行驗證，為癌症患者帶來有效的免疫治療。

6. 中大新型
7. 中大醫學
8. 中大研究
9. 中大發明

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Health Matters - Immunotherapy to Tackle Liver Cancer

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International Sessions

Room 5 | Oct. 3 (Sat.) 13:45-16:15 | E

IS11 Epigenetic therapeutic targets in cancer microenvironment
がん微小環境を標的としたエピジェネティクス治療

Chairpersons: Yutaka Kondo (Div. Cancer Biol., Nagoya Univ. Grad. Sch. of Med.)
Alfred Sze-Lok Cheng (Sch. of Biomed. Sci., The Chinese Univ. of Hong Kong)
座長：近藤 豊（名古屋大・院医・腫瘍生物学）
Alfred Sze-Lok Cheng (Sch. of Biomed. Sci., The Chinese Univ. of Hong Kong)

The 79th Annual Meeting of the Japanese Cancer Association

JCA 2020

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- Information for Participants
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- Presentation Slide (PowerPoint with Audio) NEW
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Confronting the solid truth of cancer and working together

广东省医学会 第六次肝癌学术会议

2021年12月17-18日 中国·广州

邀请函

尊敬的 **Alfred Cheng** 教授：

您好！

广东省医学会肝癌分会承办，广东省医学会肝癌分会承办，中山大学附属第一医院协办的

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于2021年12月17-18 日在广州天河希尔顿酒店

Hong Kong Immunology Forum 2021

- HKSI Annual General Meeting and Scientific Meeting

香港中文大學 The Chinese University of Hong Kong | Faculty of Medicine | Croucher Foundation 裘槎基金會

e: **4th December 2021 (Saturday)**
e: **12:00 – 17:00 pm**
ue: **Pacific Room, 9/F, Royal Pacific Hotel, China Hong Kong City, Tsim Sha Tsui**
(registered participants only)

Online registration by QR c

The conference will also be conducted via

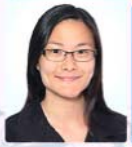
Invited Speakers:

Neuroimmunology / Immunotherapy
Prof. Tak Wah MAK
Department of Medical Biophysics, University of Toronto
Department of Pathology, The University of Hong Kong

Diverse origins of macrophages in lung injury and repair
Prof. Bin ZHOU
Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Science

Molecular control of Treg cell function by the transcription factor Foxp3 and T cell receptor signals
Prof. Shohei HORI
Laboratory of Immunology and Microbiology, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Translating epigenetic mechanism discoveries into cancer immunotherapies
Prof. Alfred Sze Lok CHENG
School of Biomedical Sciences, The Chinese University of Hong Kong



Mechanisms of immune modulation in the tumor microenvironment
Dr. Kwan Ting CHOW
Department of Biomedical Sciences, City University of Hong Kong

ALL ARE WELCOME!

EpiHK

THE HONG KONG EPIGENOMICS PROJECT WINTER 2021 VIRTUAL SYMPOSIUM

TUESDAY, DECEMBER 14th 2021 9:00 AM – 1:30 PM
WEDNESDAY, DECEMBER 15th 2021 1:30 PM – 5:30 PM

Invited Speakers:

Prof Ting Wang
Washington University

Dr Michael Pazin
National Human Genome Research Institute

Prof Melissa Fullwood
National University of Singapore

Prof Louis Lefevre
University of British Columbia

Prof Becki Kuang
HKUST

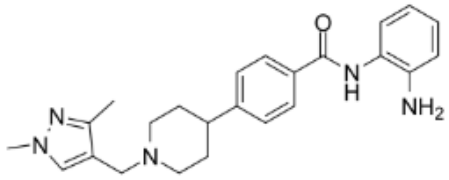
Prof Alfred Cheng
CUHK

Prof Ho Ko
CUHK

Dr Poonam Bheda
Nature Communications

Prof Gonçalo Castelo-Branco
Karolinska Institutet

CXD101: a novel class I HDAC inhibitor



CXD101 Chemical Structure

IC50 & Target[1]	HDAC1	HDAC3	HDAC2
	63 nM (IC_{50})	550 nM (IC_{50})	570 nM (IC_{50})

Product Name	HDAC	HDAC1	HDAC2	HDAC3	HDAC4	HDAC5	HDAC6	HDAC7	HDAC8	HDAC9	HDAC10	HDAC11
CXD101		✔	✔	✔								
Trichostatin A	✔											
PCI-34051									✔			

1. Encouraging and durable clinical activity in patients with hematological malignancies
2. Favorable safety profile
3. Under Phase II clinical trials

CELLERON THERAPEUTICS

A Phase I Study to Assess the Safety, Tolerability, and Pharmacokinetics of CXD101 in Patients With Advanced Cancer

Toby A. Eyre, MD[1,2]; Graham P. Collins, PhD[2]; Avinash Gupta, MD[3]; Nicholas Coupe, MD[1]; Semira Sheikh, PhD[2,4]; John Whittaker[5]; Lai Mun Wang, MD[6]; Leticia Campo[7]; Elizabeth Soilleux, PhD[6]; Finn Tysoe[1]; Richard Cousins[1]; Nick La Thangue, PhD[4,5]; Lisa K. Folkes, PhD[8]; Michael R. L. Stratford, PhD[8]; David Kerr, PhD[5,9]; and Mark R. Middleton, PhD[1,10]

BACKGROUND: In the current study, the authors sought to determine the maximum tolerated dose (MTD) of the novel class 1 selective histone deacetylase inhibitor CXD101 in a dose escalation study in patients with advanced solid tumors or recurrent/refractory lymphoma. **METHODS**: The authors escalated the dose of CXD101 from 1 mg twice daily orally for 5 days in a 21-day cycle (3+3 design). **RESULTS**: A total of 39 patients were enrolled, 36 of whom received CXD101. Of the 30 patients in the escalation cohort, 29 were evaluable for determination of the dose-limiting toxicity (DLT). DLTs were noted at doses of 16 mg twice daily (1 of 6 patients), 20 mg twice daily (1 of 6 patients), and 24/25 mg twice daily (2 of 5 patients, both of whom developed neutropenic fever). The MTD was 20 mg twice daily, which achieved maximal plasma concentrations (±standard deviation) of 231 ± 76 nM to 342 ± 126 nM, which was within the biologically active range. Six patients received 20 mg twice daily in an expansion cohort. The most frequent adverse events were fatigue, nausea, and reversible cytopenia. Key grade 3 to 4 adverse events (according to Common Terminology Criteria for Adverse Events criteria [version 4.03]) included thrombocytopenia (11%), neutropenia (17%), and neutropenic fever (2%) across the 133 CXD101 cycles given. The toxicity profile was similar to that of licensing studies with other histone deacetylase inhibitors. In 22 evaluable patients receiving a dose of ≥16 mg twice daily (17 of whom had lymphoma and 5 of whom had solid tumors), 3 partial responses (2 in patients with classic Hodgkin lymphoma after allogenic stem cell transplantation and 1 in a patient with angioimmunoblastic T-cell lymphoma) and 1 complete response (in a patient with follicular lymphoma) were noted (overall response rate of 18%) in addition to 9 patients who achieved durable stable disease. Responses were noted predominantly among patients with lymphoma (tumor reduction noted in 63% of patients on standard computed tomography). **CONCLUSIONS**: The MTD in the current study was found to be 20 mg twice daily. Encouraging and durable activity was observed in patients with Hodgkin lymphoma, T-cell lymphoma, and follicular lymphoma. ***Cancer* 2019;125:99-108**. *© 2018 American Cancer Society.*

KEYWORDS: biomarker, demethylation, CXD101, histone deacetylase (HDAC), HR23B, phase 1 trial.

A new phase II clinical study for HCC patients resisting to ICB therapy: CXD101 (class I HDAC inhibitor) plus Geptanolimab (anti-PD-1 antibody)

Stephen Chan, M.D.
Clinical oncologist, CUHK

Nick La Thangue, Ph.D
Cancer biologist, Oxford U
CEO, Celleron Therapeutics

Alfred Cheng, Ph.D
Cancer biologist, CUHK

Feng Guo, Ph.D
CEO, Genor Biopharma

CXD101: a novel class I HDAC inhibitor

Geptanolimab: a novel anti-PD-1 antibody

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UNIVERSITY OF OXFORD

CELLERON THERAPEUTICS

嘉和 GENOR BIOPHARMA

Conclusion: Enhancing immunotherapy through molecular discoveries

- Transcriptional and epigenetic reprogramming convert the immunosuppressive and T cell-excluded TME to T cell-inflamed milieu
- Selective epigenetic drugs used in combination with anti-PD-(L)1 therapy may be a promising approach for treating immunologically cold tumors
- The discoveries on tumor ecosystem at single-cell resolution hold the key to the development of biomarker-based precision immunotherapy

Our Multidisciplinary Immuno-Oncology Team

HCC/Epigenetics

Alfred CHENG

PhD

HCC/Immunotherapy

Stephen CHAN

MD

Immunology/Therapeutics

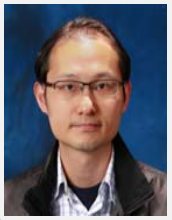
Zhiwei CHEN

PhD

Molecular diagnostics

Ka-Fai TO

MD

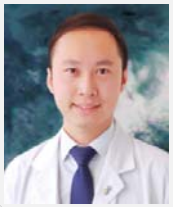


Bioinformatics/Omics

Kevin YIP

PhD

Sanford Burnham Prebys



Medicinal chemistry

Billy NG

PhD

➢ *With complementary basic, clinical, computational and pharmacological expertise for HCC translational research*

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The Government of the Hong Kong Special Administrative Region
Health Research Symposium 2021
23 November 2021
Implementing evidence-based research
in the era of COVID-19 and
other global health challenges
The 10th Anniversary of the Establishment
of the Health and Medical Research Fund

Collaborators:

Zhiwei Chen ***HKU Hong Kong***
Paul Klenerman ***Oxford UK***
Yutaka Kondo ***Nagoya U Japan***
Jason Kim ***MedPACTO Korea***
Nick La Thangue ***Oxford UK***
Danny Leung ***HKUST Hong Kong***
Rihe Liu ***UNC USA***
Wolfgang Sippl ***MLUHW Germany***
Joseph Sung ***NTU Singapore***
Patrick Tan ***Duke-NUS Singapore***
Kevin Yip ***SBPMDI USA***

CUHK:

Hon Fai Chan ***SBS***
Stephen Chan ***Oncology***
Jonathan Choi ***BME***
Alice Kwong ***MED***
Howard Leung ***ACP***
Billy Ng ***Pharmacy***
Kelvin Ng ***Surgery***
KF To ***ACP***
Vincent Wong ***MED***
William Wu ***AIC***
Jun Yu ***MED***
Jingying Zhou ***SBS***