Cancer Genomics: Sequence to Action

Ricardo Brentani Memorial Lecture

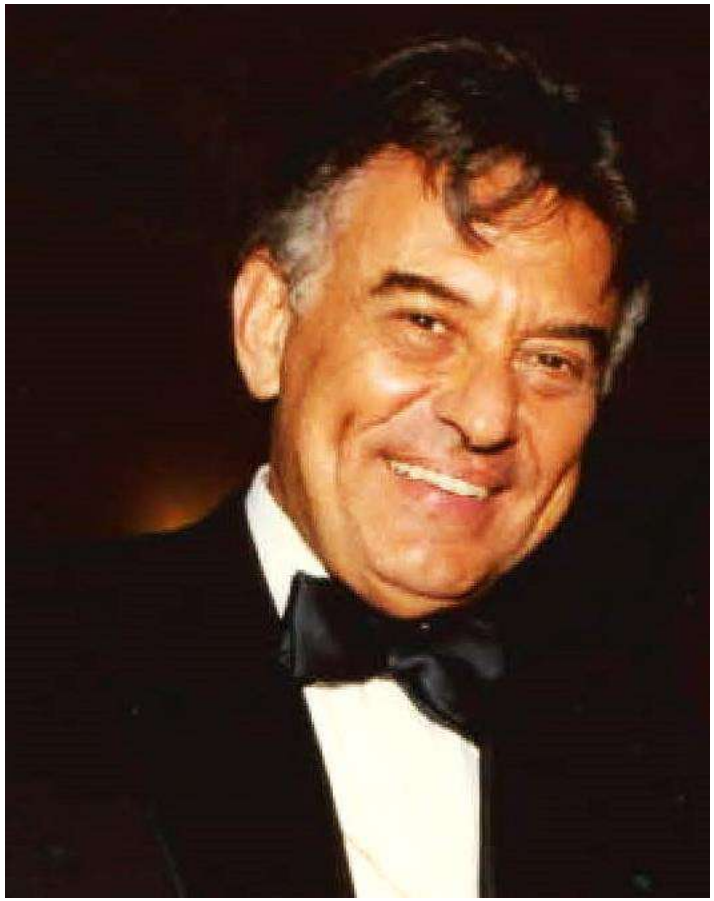
Chi Van Dang

2022

LUDWIG CANCER RESEARCH

JOHNS HOPKINS SCHOOL of MEDICINE

Celebrating Ricardo Brentani

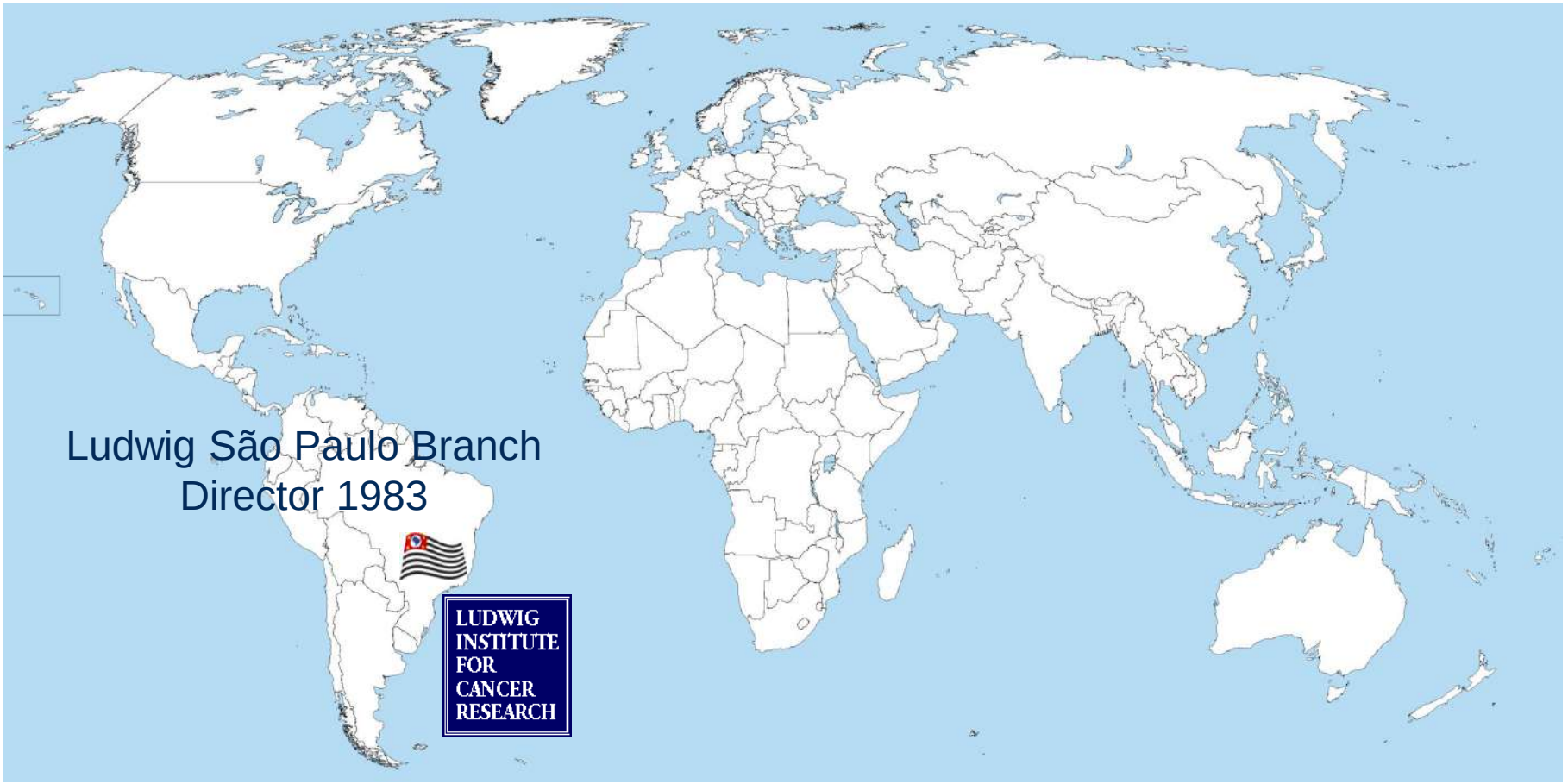


ACADEMIA BRASILEIRA DE CIÊNCIAS
MCMXVI

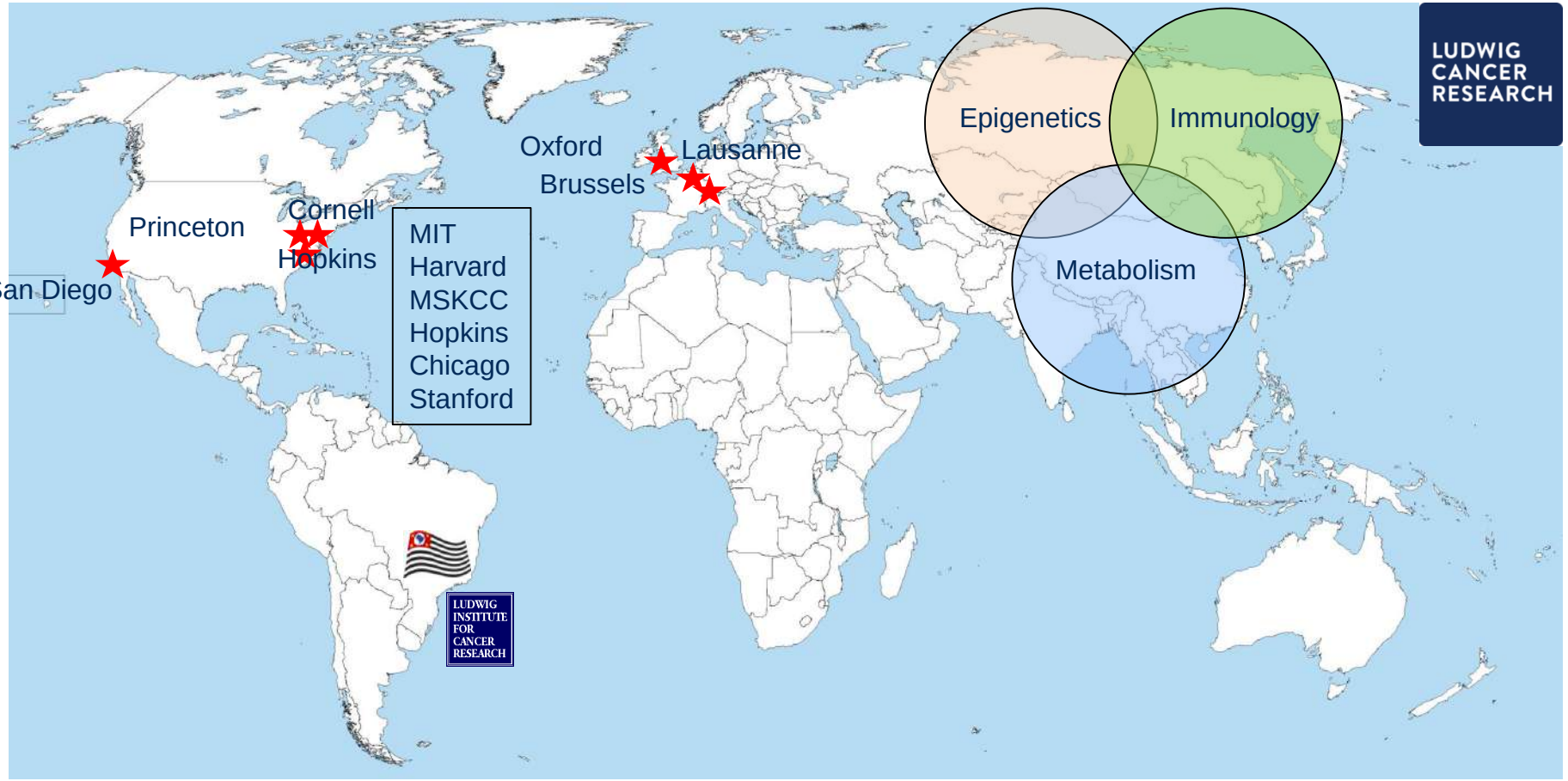
President of the Board of Trustees
FAPESP 2004

Ordem Nacional do Mérito Científico

Ludwig Institute for Cancer Research
Branches, Labs & Centers



Ludwig Institute for Cancer Research
Branches, Labs & Centers

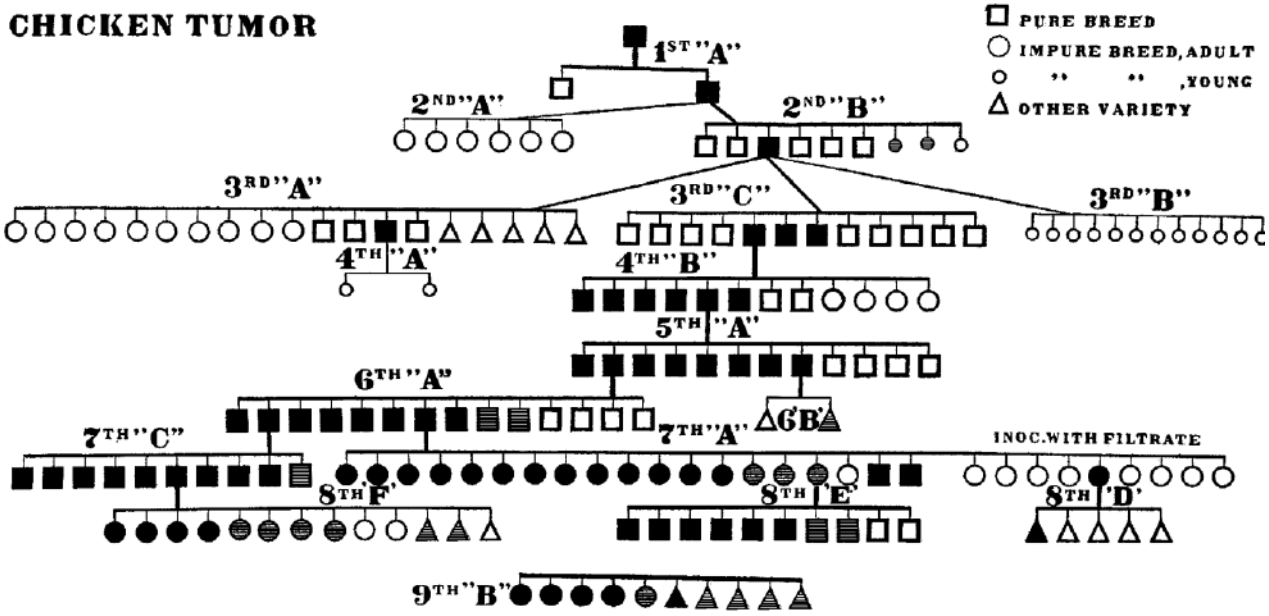


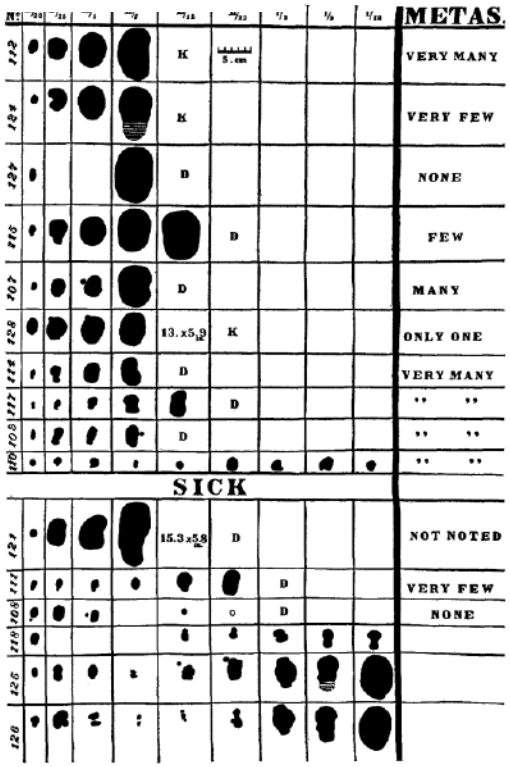
Chickens and Cancer:

A SARCOMA OF THE FOWL TRANSMISSIBLE BY AN AGENT SEPARABLE FROM THE TUMOR CELLS.*

By PEYTON ROUS, M.D.

(*From the Laboratories of the Rockefeller Institute for Medical Research, New York.*)





Rous JEM 1911

Peyton Rous

B.A. (1900) and M.D. (1905) from **Johns Hopkins University**

1909, Rockefeller Institute in New York City

Fig. 1. Peyton Rous at his microscope (1923) at age 44 y in his Rockefeller Institute laboratory. © Van Epps, HL (2005) Originally published in *J Exp Med* 201:320.

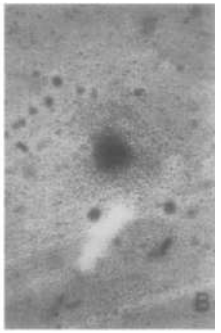
Rubin, PNAS 2011

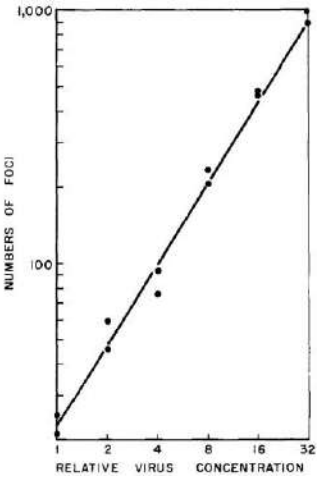
1966

Rous Sarcoma Virus

Transformation in vivo to in vitro

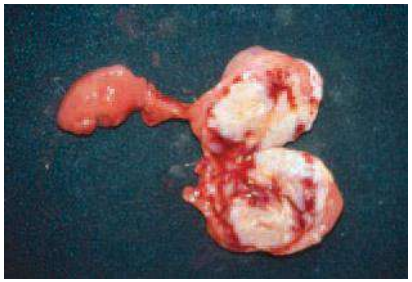
- Partially purified RSV: Bather
  - Br J Cancer 1957
  - Partially purified RSV
  - RNA virus
- Chicken fibroblast transformation: Temin & Rubin
  - Virology 1958; soft agar foci assay
- DNA provirus: Temin
  - PNAS 1964
- Isolation of RSV RNA: Duesberg & Vogt
  - PNAS 1970 v-Src
- Identification of proto-oncogene in normal avian DNA: Stehelin, Varmus, Bishop, Vogt
  - Nature 1976 c-Src





Chickens and Cancer: MYC

carcinosarcoma



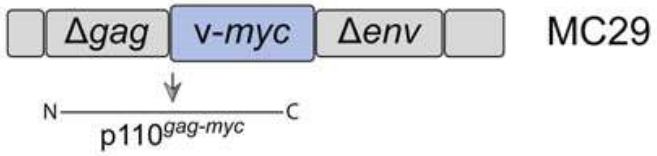
nephroblastoma

Myelocytomatosis

Sheiness & Bishop, J Virol 1979

"The avian carcinoma virus MC29 (MC29V) contains a sequence of approximately1,500 nucleotides which may represent a gene responsible for tumorigenesis by MC29V. We present evidence that MC29V has acquired this nucleotide sequence from the DNA of its host."

MC29 virus: RNA
Duesberg, Bister, Vogt PNAS1977



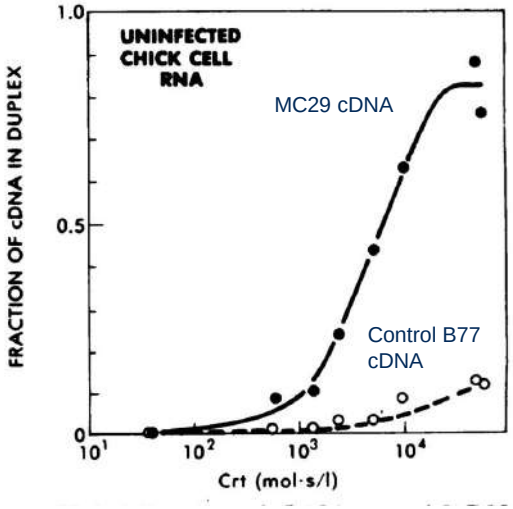


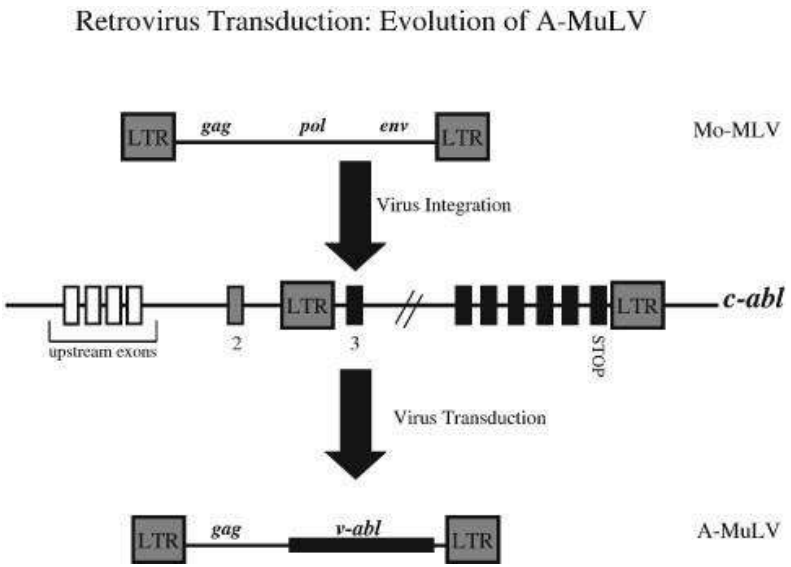
Fig. 3. Hybridization of MC29 cDNA with RNA from chicken embryo fibroblasts.

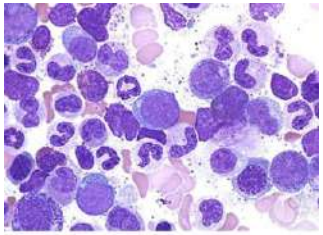
Chickens and Cancer:
Cellular Proto-oncogenes to Viral Oncogenes

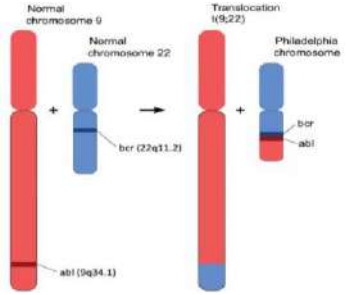
1989

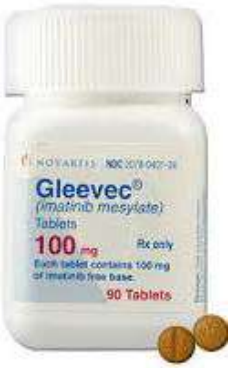
Harold Varmus & J Michael Bishop

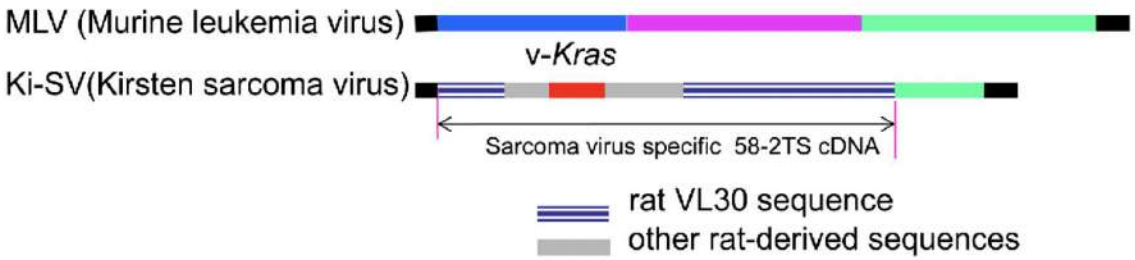
Pre-Cancer Genomics
Genome Science: AMuLV

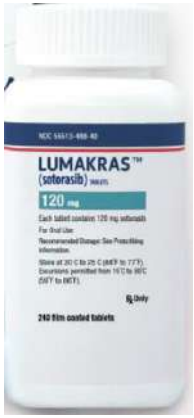






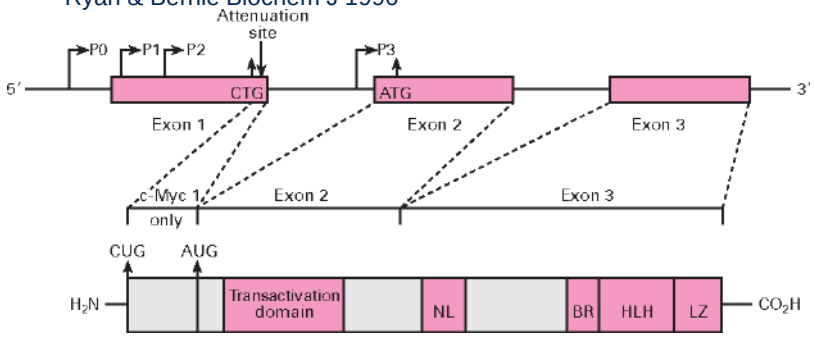


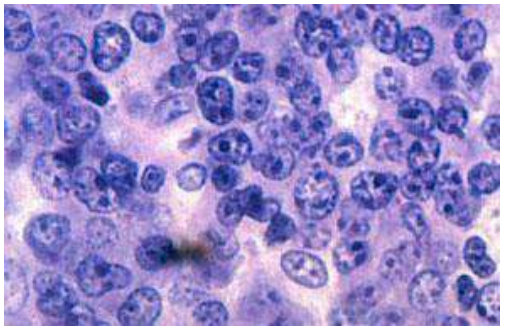


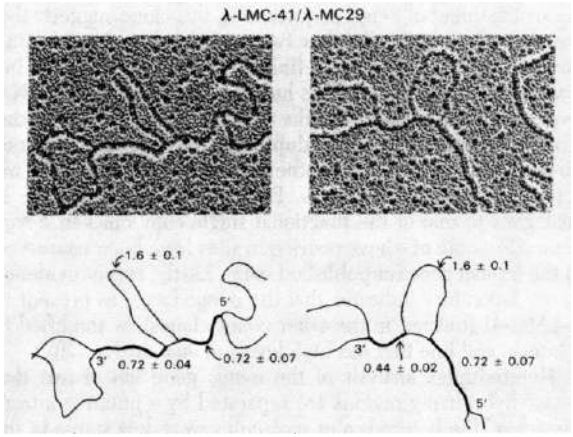


Avian Virus to Human Cancer:
MYC Oncogenes

Ryan & Bernie Biochem J 1996

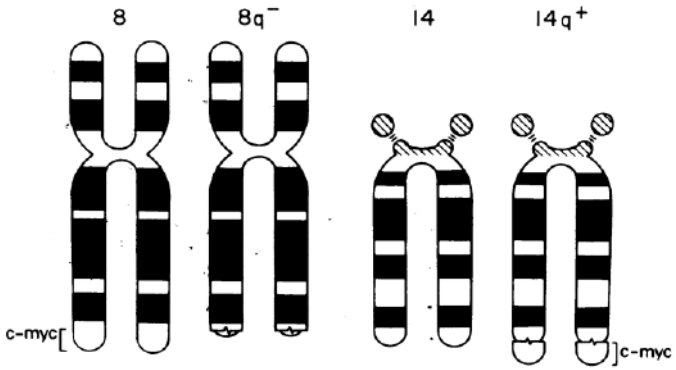






v-Myc and human genomic DNA phage clone
Hybridization EM

Dalla-Favera et al PNAS, Nov & Dec 1982
Taub et al. PNAS, 1982



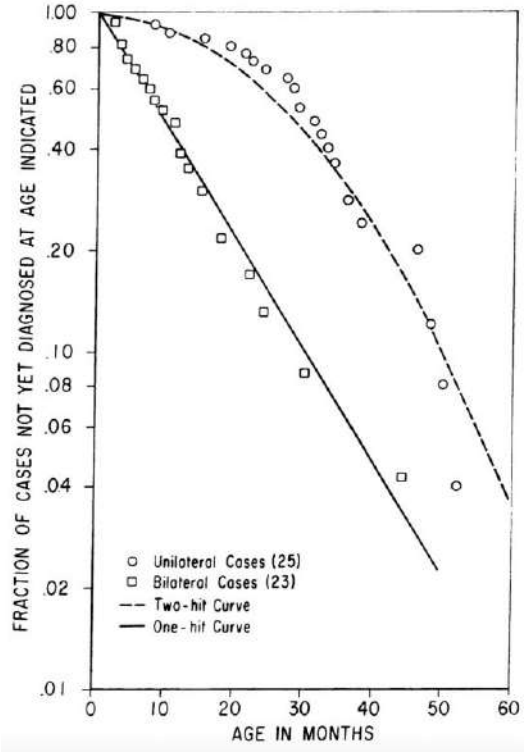
2-Hit Hypothesis: Tumor Suppressor

Knudson PNAS 1971:
"Mutation and Cancer: Statistical Study of Retinoblastoma"

ABSTRACT Based upon observations on 48 cases of retinoblastoma and published reports, the hypothesis is developed that retinoblastoma is a cancer caused by two mutational events. In the dominantly inherited form, one mutation is inherited via the germinal cells and the second occurs in somatic cells. In the nonhereditary form, both mutations occur in somatic cells.

The second mutation produces an average of three retinoblastomas per individual inheriting the first mutation. Using Poisson statistics, one can calculate that this number (three) can explain the occasional gene carrier who gets no tumor, those who develop only unilateral tumors, and those who develop bilateral tumors, as well as explaining instances of multiple tumors in one eye.

This value for the mean number of tumors occurring in genetic carriers may be used to estimate the mutation rate for each mutation. The germinal and somatic rates for the first, and the somatic rate for the second, mutation, are approximately equal. The germinal mutation may arise in some instances from a delayed mutation.



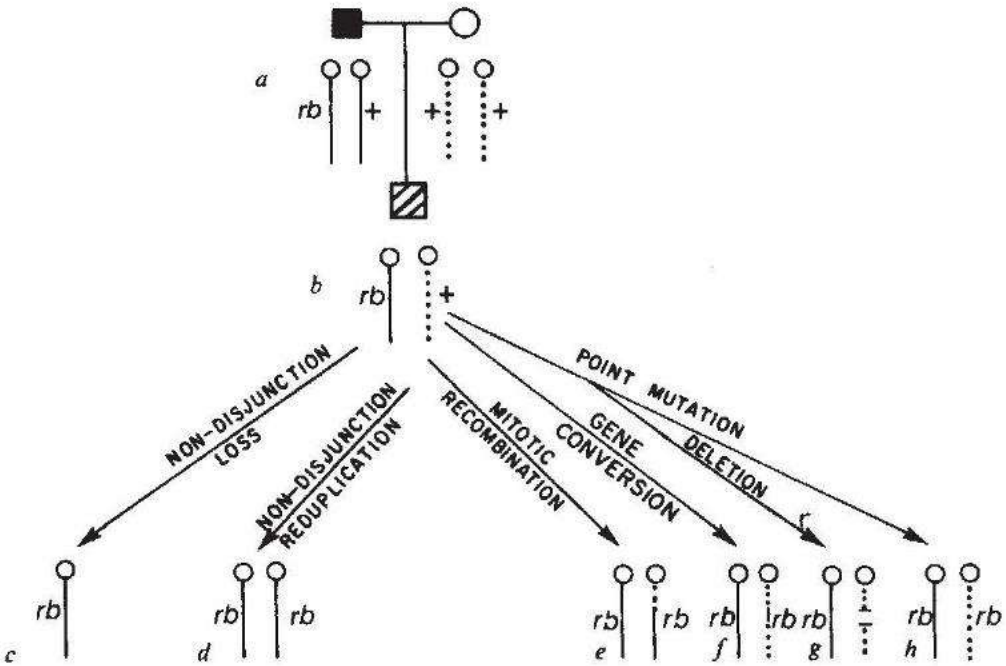
2-Hit Hypothesis: Tumor Suppressor

nature
1983

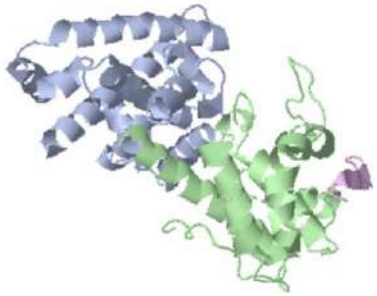
Expression of recessive alleles by chromosomal mechanisms in retinoblastoma

W. K. Cavenee*#, T. P. Dryja†, R. A. Phillips‡, W. F. Benedict§, R. Godbout‡, B. L. Gallie‡, A. L. Murphree‖, L. C. Strong§ & R. L. White*

Cavenee:
Ludwig San Diego
1991-2015

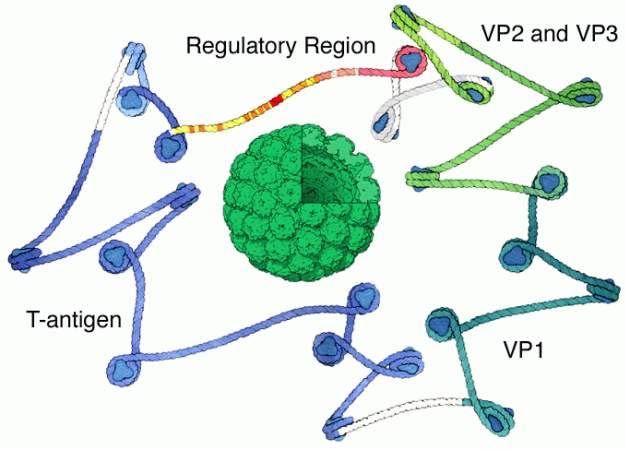


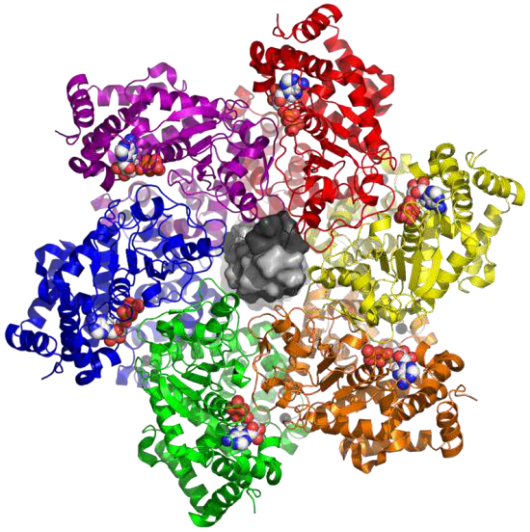
SV40 and Tumor Suppressors



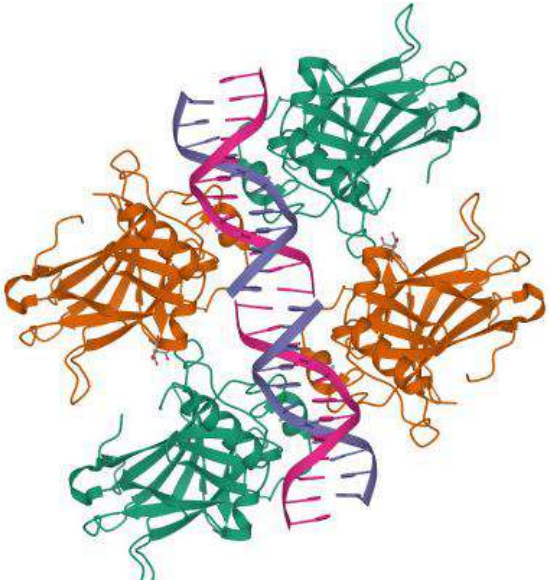
Rb
Livingston
1988

Ludwig Harvard Center





SV40 Large T



p53

1979: Lane, Levine, May

Lane
LICR 2013-2015

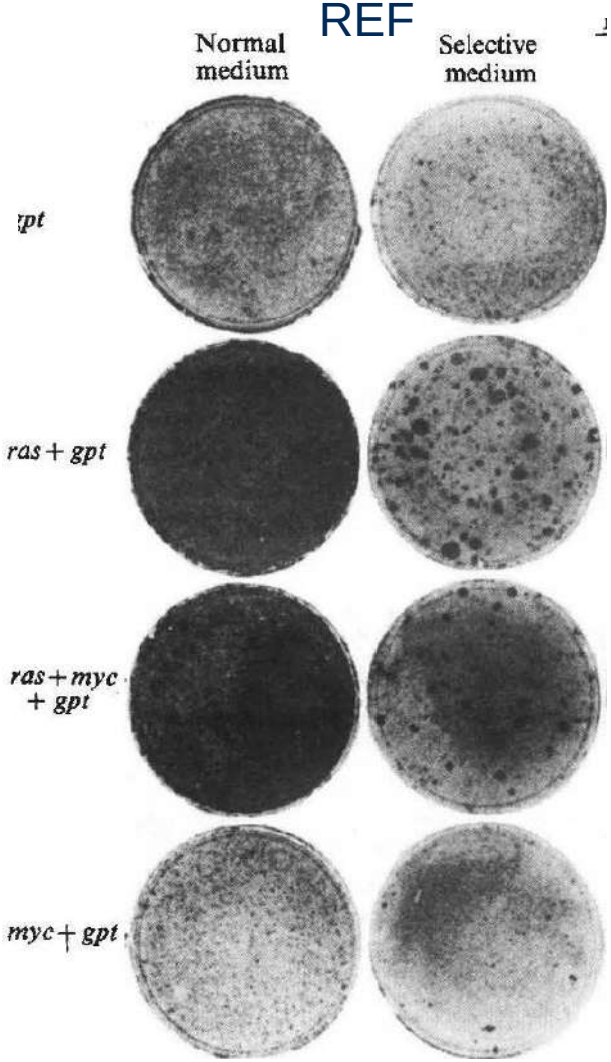
Multi-step Tumorigenesis

nature
1983

Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes

Hartmut Land, Luis F. Parada & Robert A. Weinberg

REF



Weinberg
Ludwig MIT Center

Multi-step Tumorigenesis

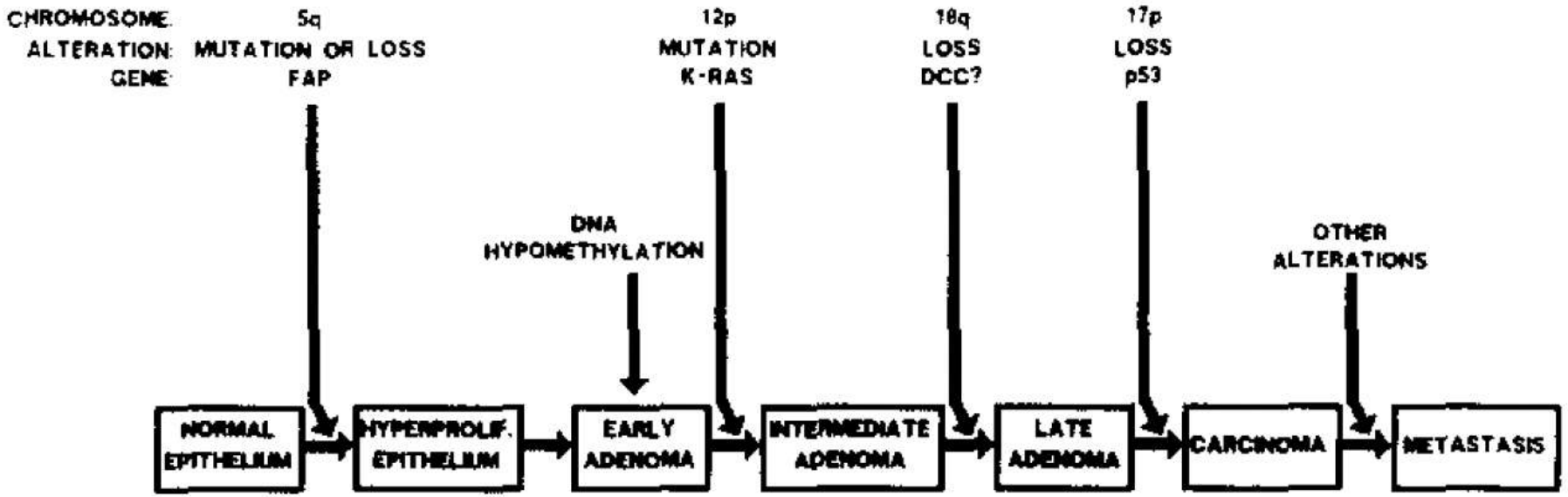


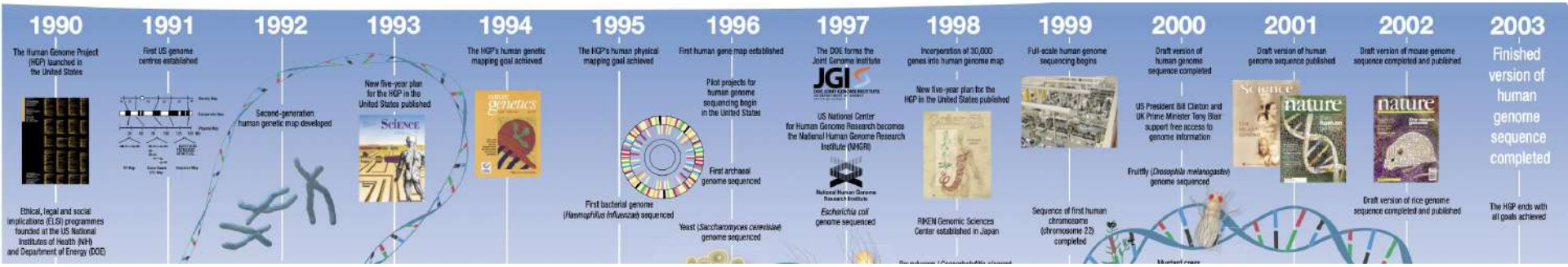
Figure 3. A Genetic Model for Colorectal Tumorigenesis

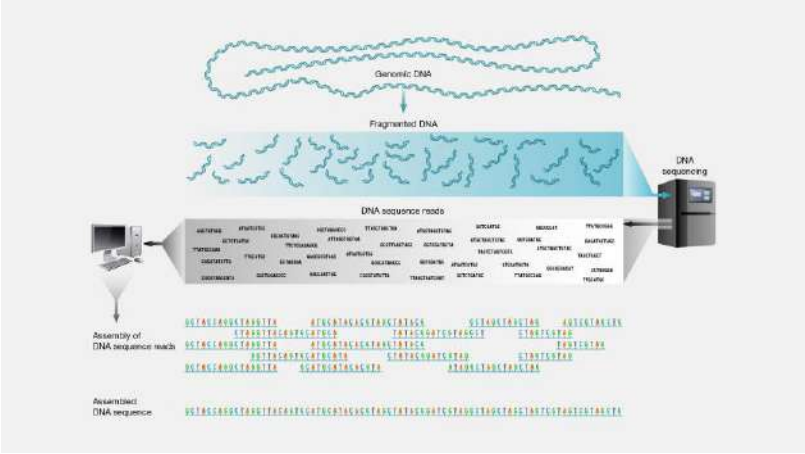
Fearon & Vogelstein Cell 1990

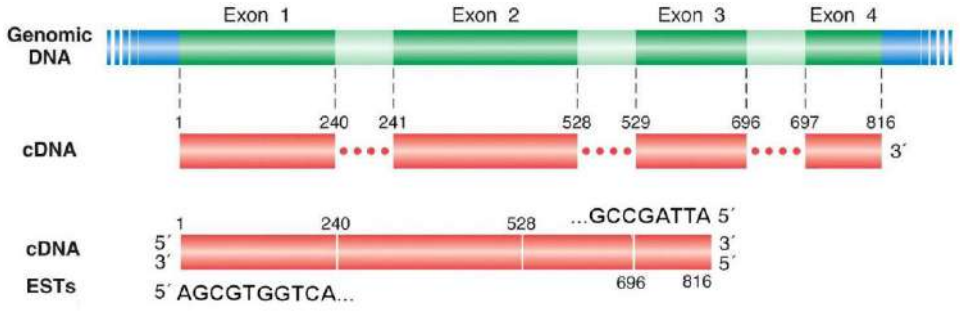
Vogelstein
Ludwig Hopkins Center

Human Genome Project

1990-2003







FAPESP 60 YEARS 1962 - 2022

nature

Vol 398, 8 April 1999

Brazilian scientists team up for cancer genome project

[SÃO PAULO] Brazilian researchers have entered the competitive field of human genome sequencing with the signing of an agreement between the state funding agency of São Paulo (FAPESP) and the US-based Ludwig Institute for Cancer Research.

Each will contribute US$5 million to a two-year Human Cancer Genome Project. According to FAPESP, the programme is "aimed at providing sequences from genes expressed in tumours that are important within the context of public health in the state of São Paulo".

Expressed Sequence Tags (ESTs)

The Economist

July 20, 2000

LUDWIG INSTITUTE FOR CANCER RESEARCH

Brazilian science

Fruits of co-operation

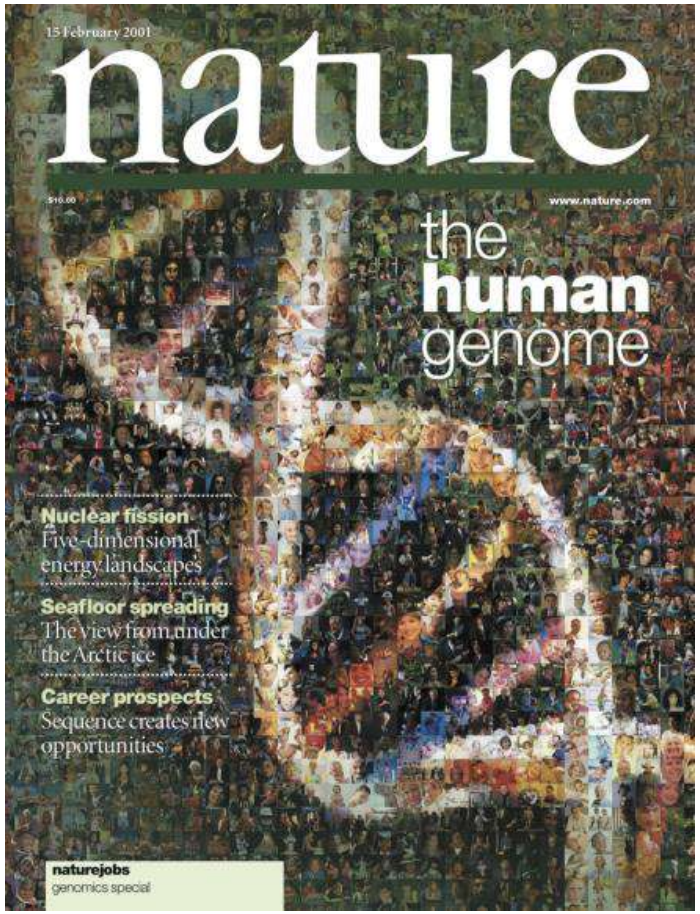
SAO PAULO

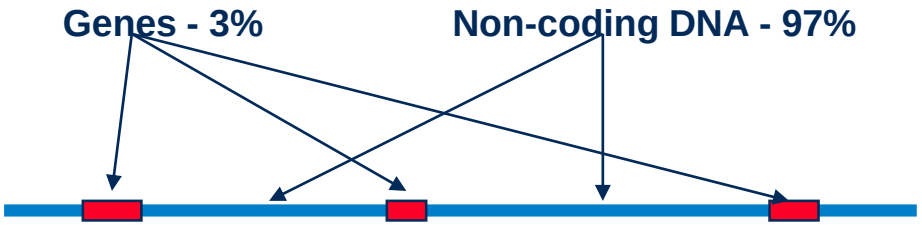
SAMBA, football and...genomics. The list of things for which Brazil is renowned has suddenly got longer. Only a few days after publishing, on July 13th, the first-ever sequence of the genome of a plant pathogen, scientists at Sao Paulo's state research agency, Fapesp, were due to announce, on July 21st, another success—the composition of 279,000 human expressed-sequence tags, small pieces of DNA that allow genes to be located along chromosomes. Only in America and Britain have more than that number of human ESTs been identified.

Courtesy of Andy Simpson

Human Genome Sequencing

15 February 2001





PNAS 2001

The contribution of 700,000 ORF sequence tags to the definition of the human transcriptome

Anamaria A. Carmago, .. , Ricardo R. Brentani, Andrew J.G. Simpson and Sandro J. de Souza

LUDWIG INSTITUTE FOR CANCER RESEARCH

Comparative and Functional Genomics
Comp Funct Genom 2001; **2**: 169–175.
DOI: 10.1002/cfg.81

Review Article

Definition of the gene content of the human genome: the need for deep experimental verification

Andrew J. G. Simpson*, Sandro J. de Souza, Anamaria A. Camargo and Ricardo R. Brentani
The Ludwig Institute for Cancer Research, Rua Professor Antônio Prudente, 109, 4th floor, São Paulo, 01509-010, SP, Brazil

FAPESP 60 YEARS 1962 - 2022

nature

October 16, 1997

Brazil to sequence 'first plant pathogen'

[SÃO PAULO] The creation of a network of laboratories in São Paulo state, Brazil, to sequence the complete genome of a microorganism was announced last week by the Foundation for the Support of Research of the State of São Paulo (FAPESP), the state funding agency.

The Organisation for Nucleotide Sequencing and Analysis will first tackle the bacterium *Xylella fastidiosa*, the causal agent of many economically important plant diseases, particularly citrus variegated chlorosis, which poses a major threat to São Paulo's orange cultivation. This is thought to be the first plant pathogen genome to have been sequenced.

Citrus variegated chlorosis, first

pest, with obvious gains to the state's economy. It will also help to forge links between research centres and the private sector, which is contributing to the cost of the project.

The state says that it is keen to create a network of laboratories that will "significantly increase the number of laboratories in the state capable of using modern molecular biology techniques".

The project will be overseen by a five-member steering committee consisting of three international experts in genome sequencing and two researchers from São Paulo state. Two of the experts, André Goffeau of the University of Louvain in Belgium and Steve Oliver of the University

São Paolo Genome Annotation

February 2000

Courtesy of Andy Simpson

Brasilia
March 25, 2000

FAPESP 60 YEARS 1962 - 2022

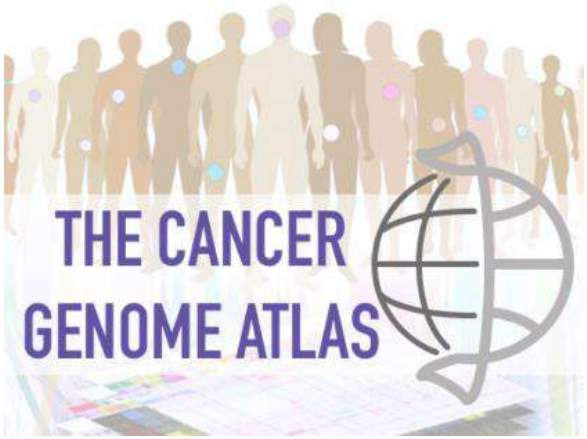
Xylella fastidiosa

July 13, 2000

Simpson
LICR 2007

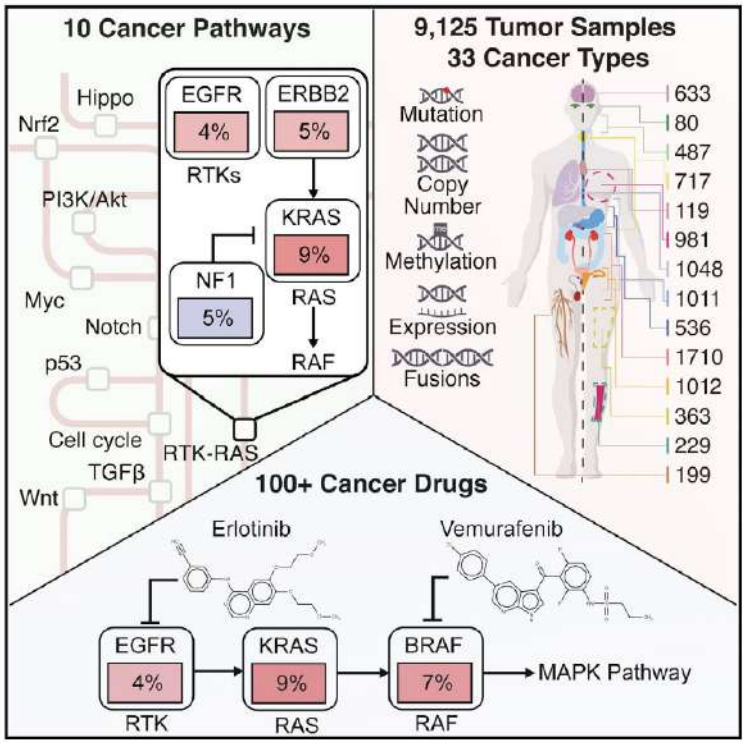
Courtesy of Andy Simpson

Cancer Genome Sequencing



2006: Launch
2010: 20 cancers
2018: Pan-Cancer Atlas
10,000 Tumors
33 Tumor Types

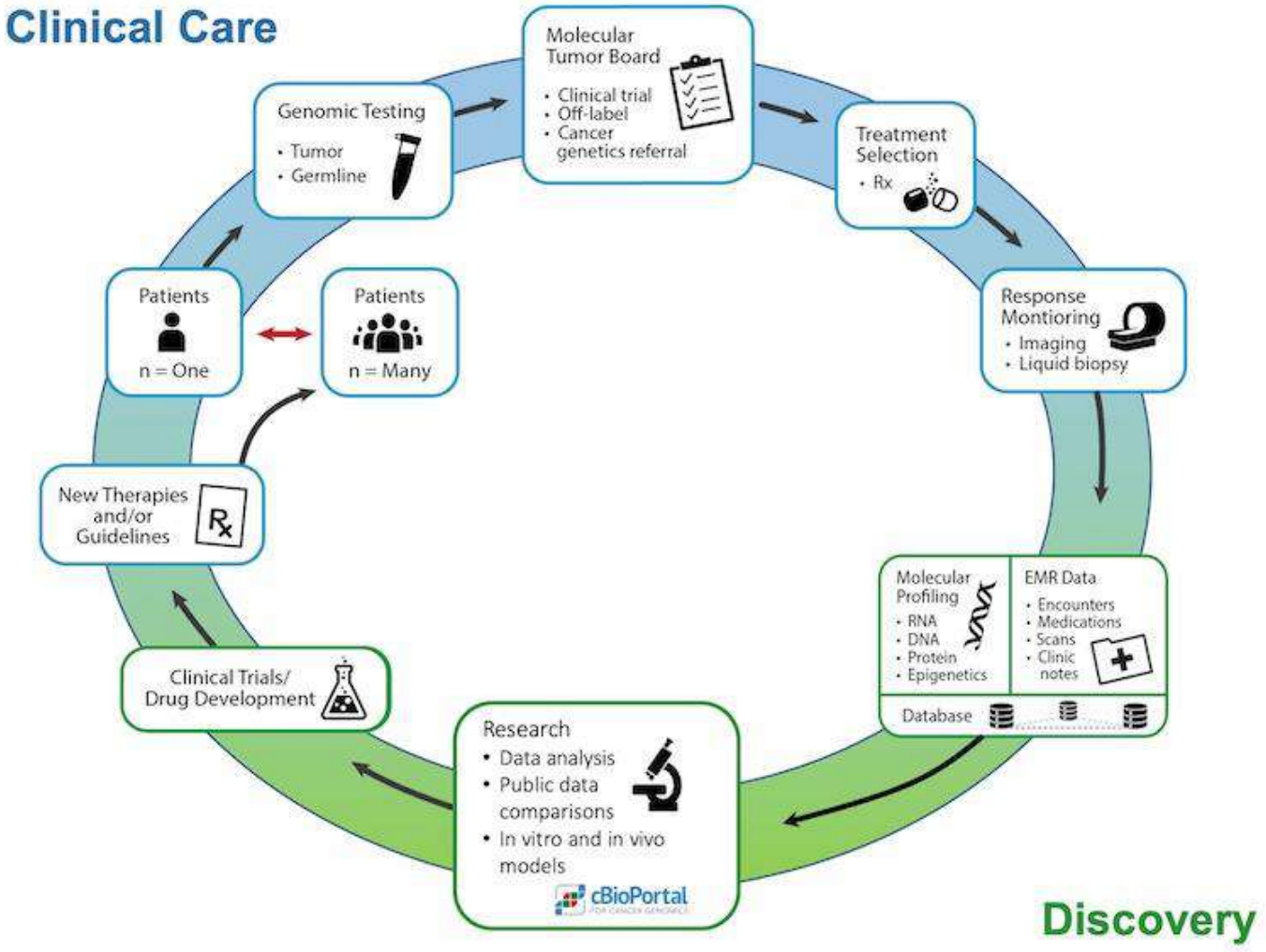
LESSONS:
Oncogenic Signaling Pathways
Mutations of Epigenetic Modifiers
Role of Non-coding RNAs



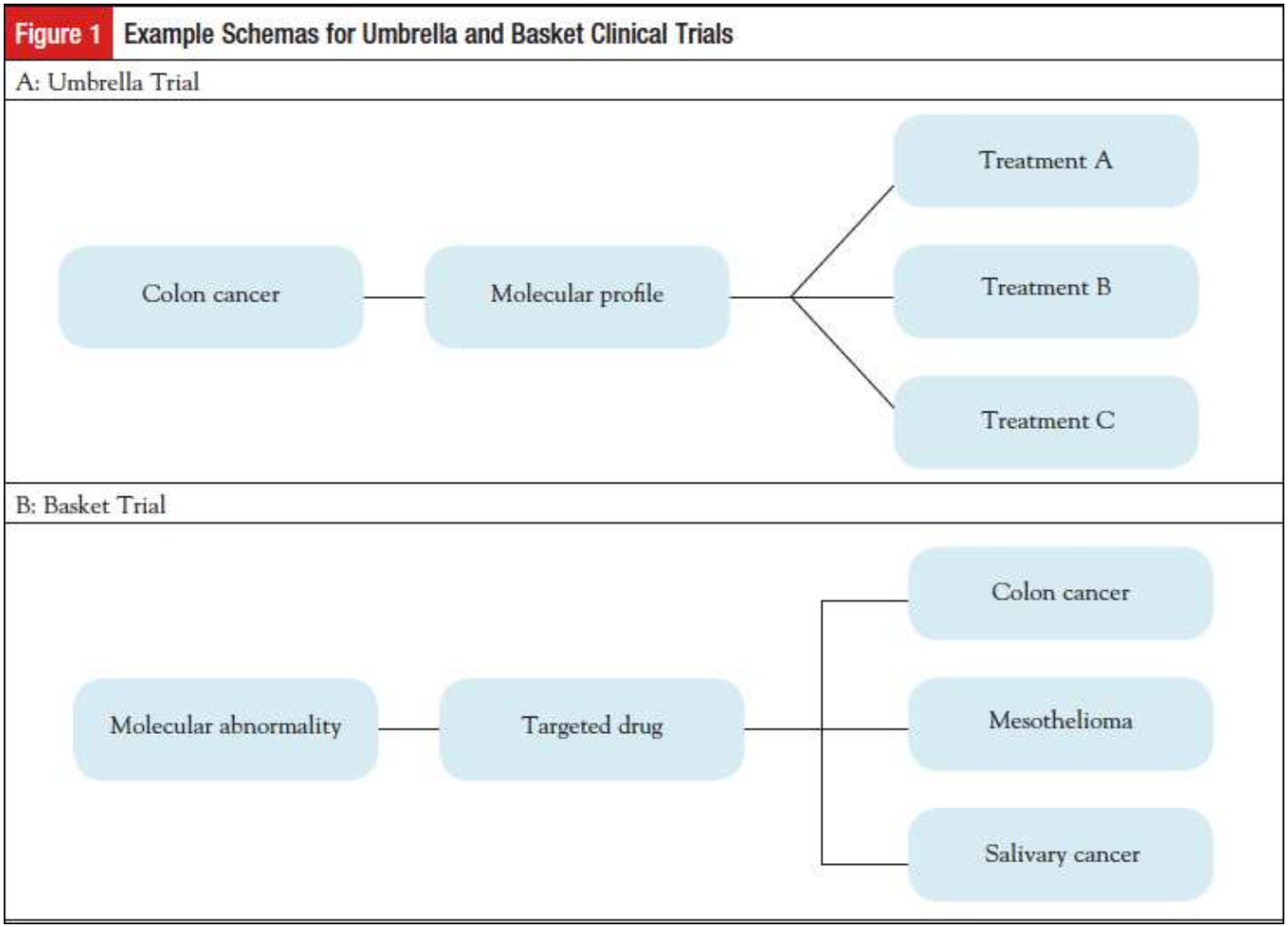
International Cancer Genome Consortium

Sanchez-Vega Cell 2018

Cancer Genome: Tumor Boards



Cancer Genome: Precision Oncology



PMO 2016

Cancer Genome: Germline Risks & Interception

BASSER CENTER FOR BRCA

Penn Medicine

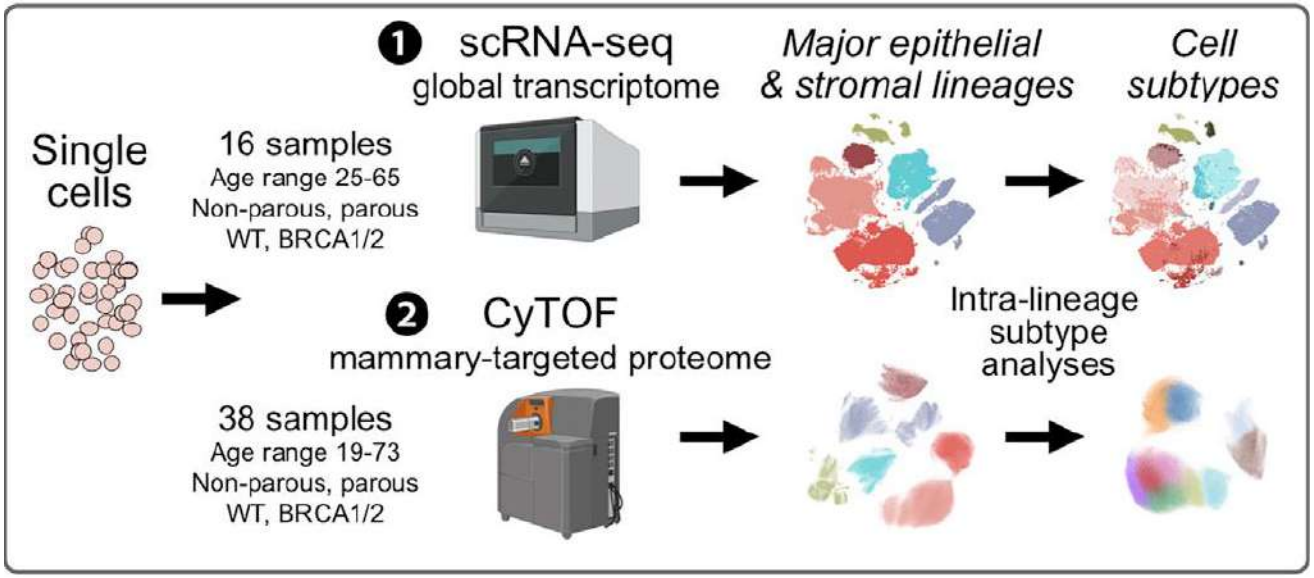
Dev Cell 2022

Resource

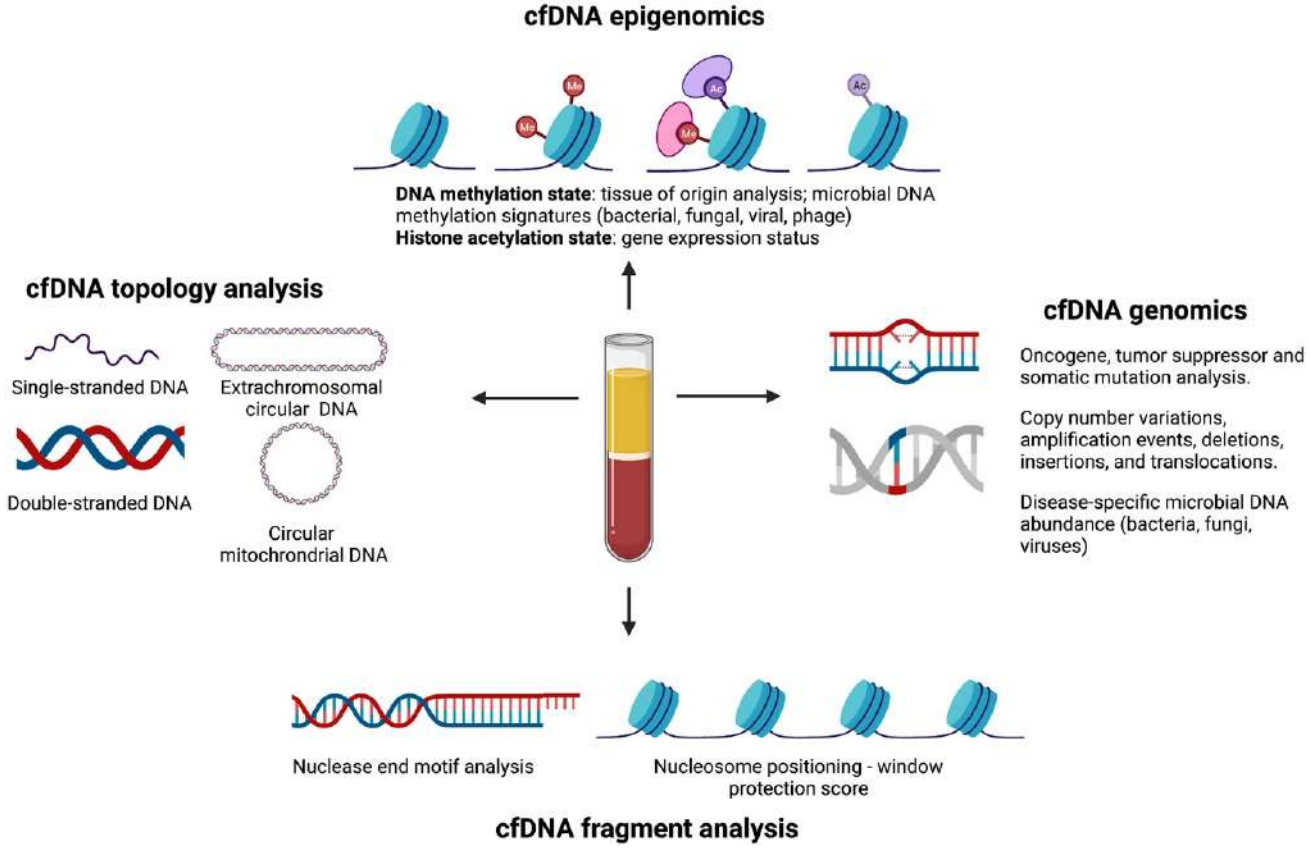
A human breast atlas integrating single-cell proteomics and transcriptomics

G. Kenneth Gray,[1,9] Carman Man-Chung Li,[1,9] Jennifer M. Rosenbluth,[1,2,3,9] Laura M. Selfors,[1,9] Nomeda Girnius,[1,4] Jia-Ren Lin,[4] Ron C.J. Schackmann,[1] Walter L. Goh,[1] Kaitlin Moore,[1] Hana K. Shapiro,[1] Shaolin Mei,[4] Kurt D'Andrea,[5] Katherine L. Nathanson,[5] Peter K. Sorger,[4] Sandro Santagata,[4,6] Aviv Regev,[7,8] Judy E. Garber,[2] Deborah A. Dillon,[6] and Joan S. Brugge[1,10,*]

FOUNDATION gray.



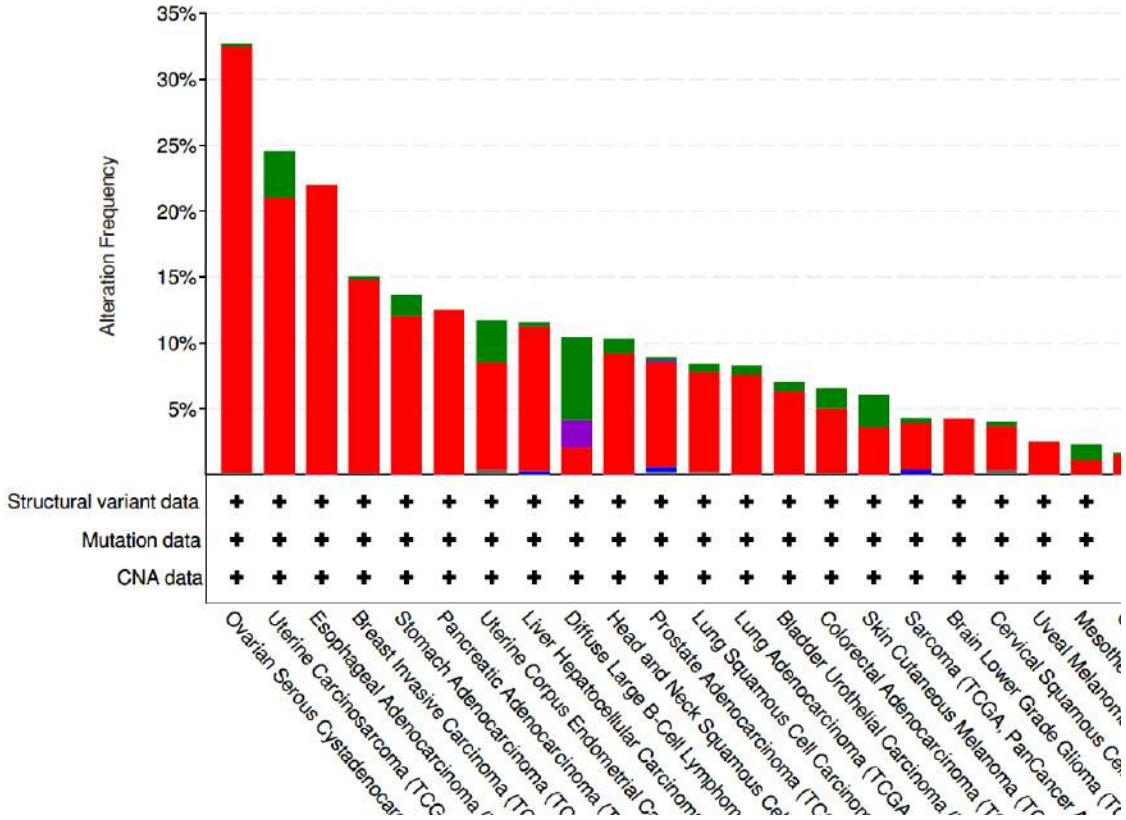
Cancer Genome: Liquid Biopsy

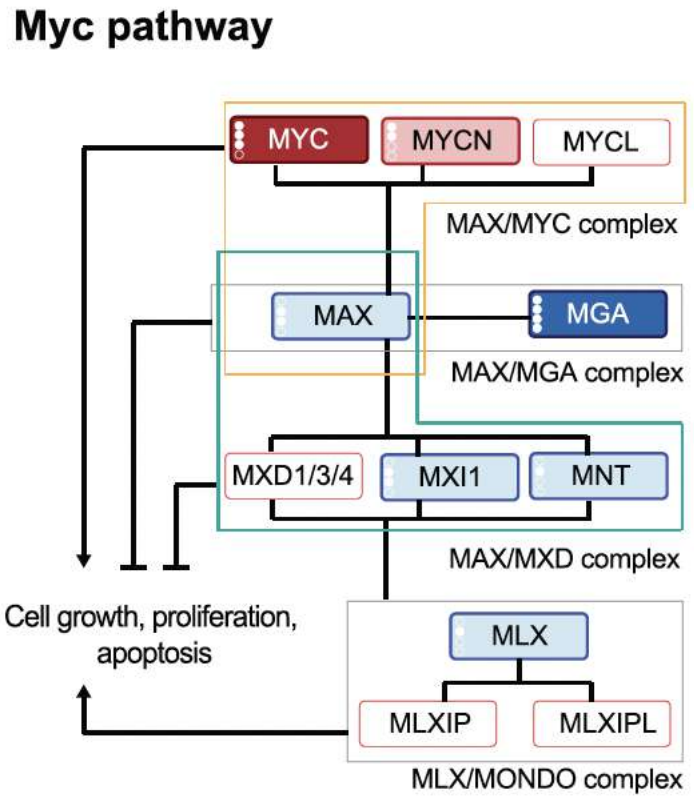


Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions, L858R and T790M*	TAGRISSO® (osimertinib)
	EGFR exon 20 insertions	RYBREVANT™ (amivantamab-vmjw)
	KRAS G12C	LUMAKRAS™ (sotorasib)

MYC & Human Cancers

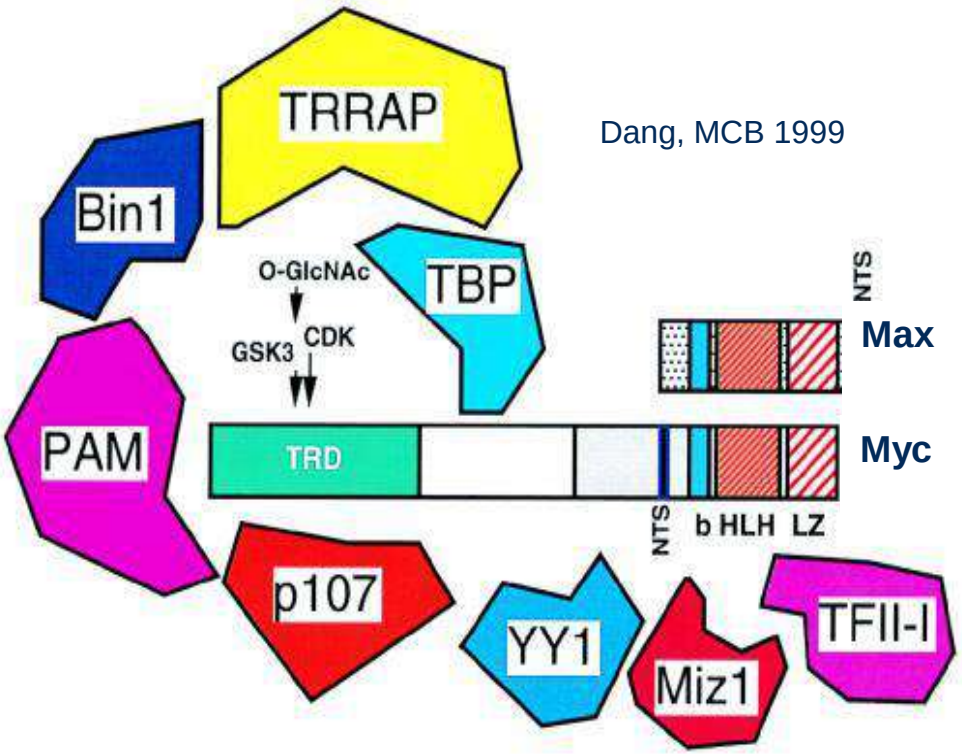
cBioPortal: MYC



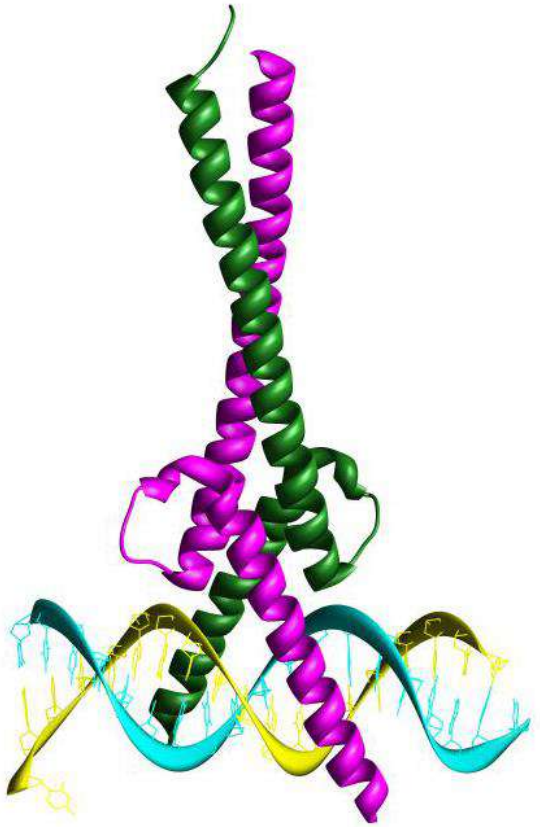


Sanchez-Vega Cell 2018

MYC Function: MYC:MAX

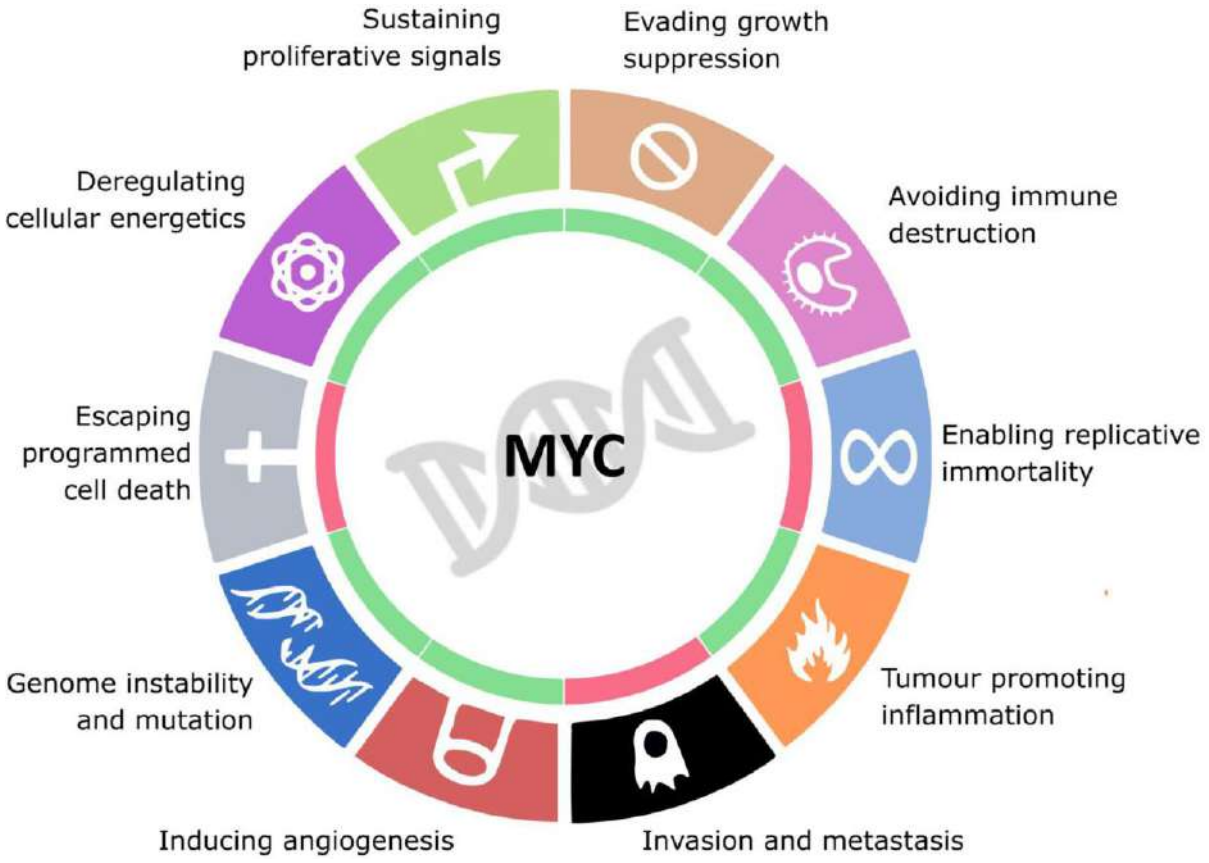


Dang, MCB 1999



Nair & Burley Cell 2003

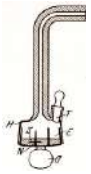
MYC Target Genes



Llombard & Mansour eBioMed 2021

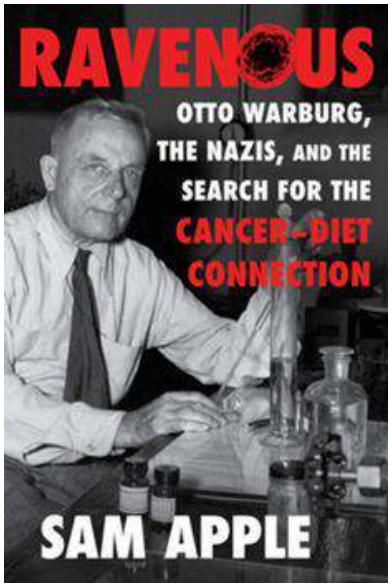
Cancer Metabolism

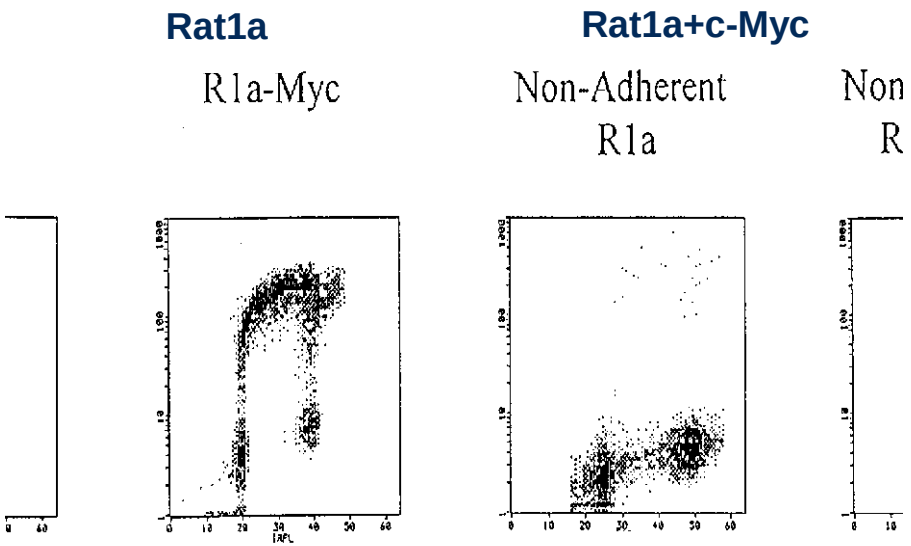
Glucose ⟶ Lactate



Otto Warburg 1920's:
Cancers
1) aerobic glycolysis
2) defective respiration

1970-1980's:
Oncogenes (Myc, Ras),
Tumor Suppressors (p53, Rb)
Cell Cycle





Lewis et al., MCB 1997

MYC and The Warburg Effect

Brian Lewis

MOLECULAR AND CELLULAR BIOLOGY, Sept. 1997, p. 4967–4978
0270-7306/97/$04.00+0

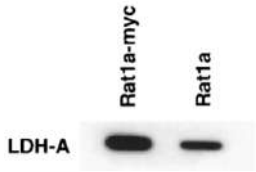
Vol. 17, No. 9

1997

Identification of Putative c-Myc-Responsive Genes: Characterization of *rcl*, a Novel Growth-Related Gene†

BRIAN C. LEWIS,[1,2] HYUNSUK SHIM,[1] QING LI,[3] CHYI SUN WU,[1] LINDA A. LEE,[1] AMIT MAITY,[1] AND CHI V. DANG[1,2,3,4,5]*

Slot-blot amplicons



Professor and George F. Booth Chair in the Basic Sciences, University of Massachusetts

Hyunsuk Shim

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 6658–6663, June 1997
Biochemistry

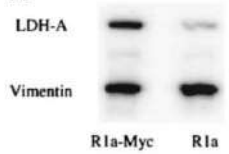
1997

c-Myc transactivation of *LDH-A*: Implications for tumor metabolism and growth

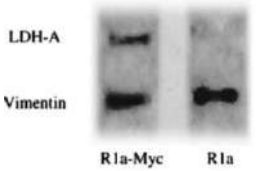
(oncogene/lactate dehydrogenase/hypoxia/tumorigenicity)

HYUNSUK SHIM*, CHRISTINE DOLDE†, BRIAN C. LEWIS†, CHYI-SUN WU*, GERARD DANG*, RICHARD A. JUNGMANN‡, RICCARDO DALLA-FAVERA§, AND CHI V. DANG*†¶‖**

A Rnase protection



B Nuclear Run-on



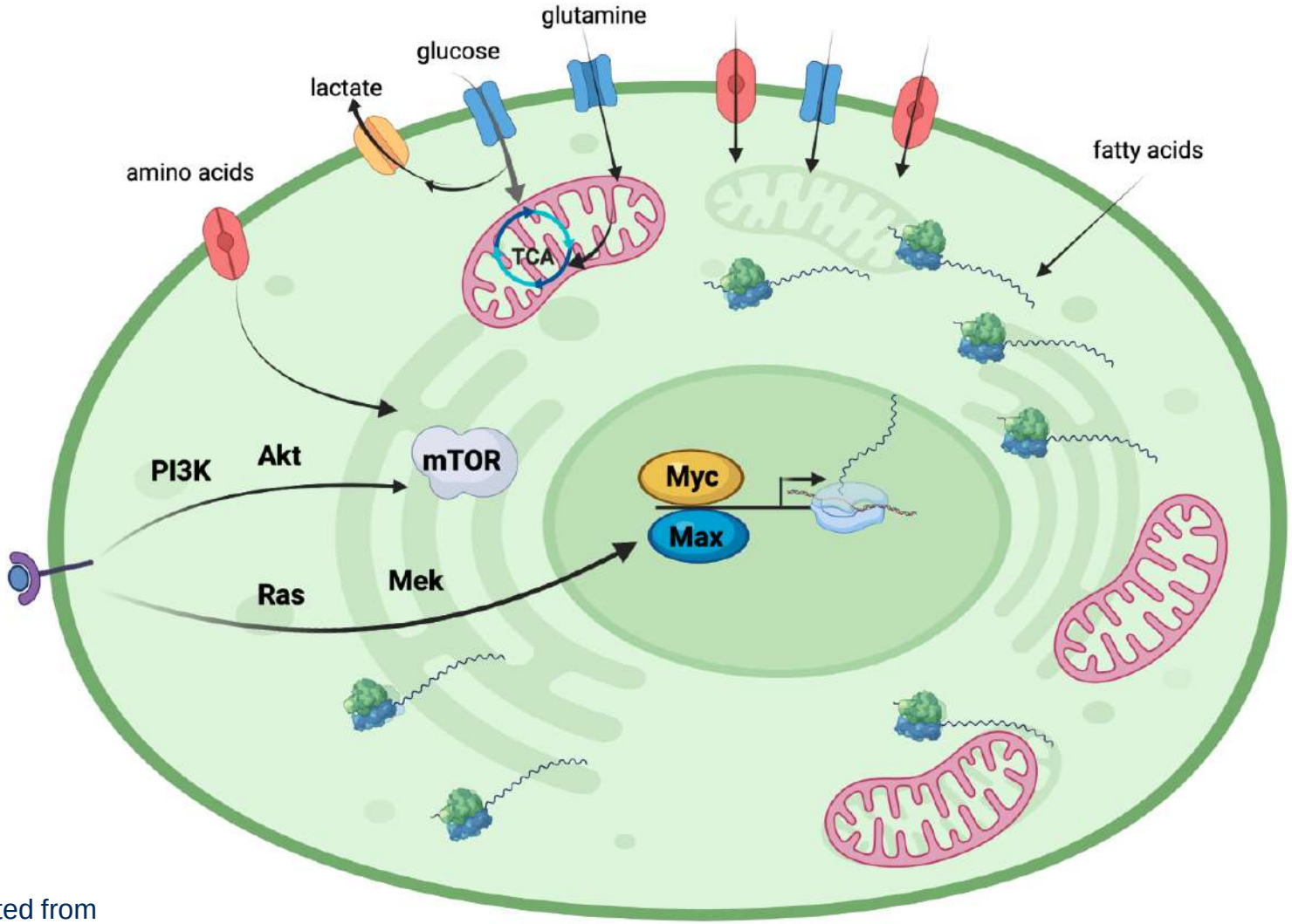
Professor and Crocker Family Chair in Cancer Innovation, Emory University

nature
Milestones in Cancer #6

c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. (Shim, H. et al., 1997)

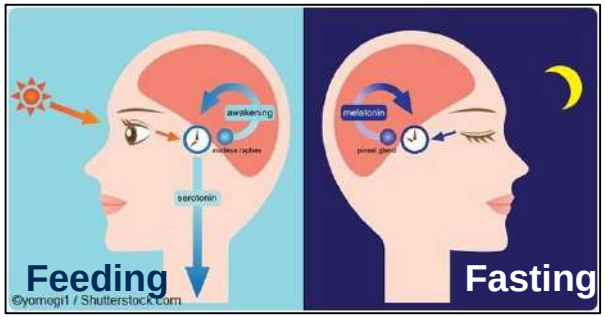
MILESTONE STUDY

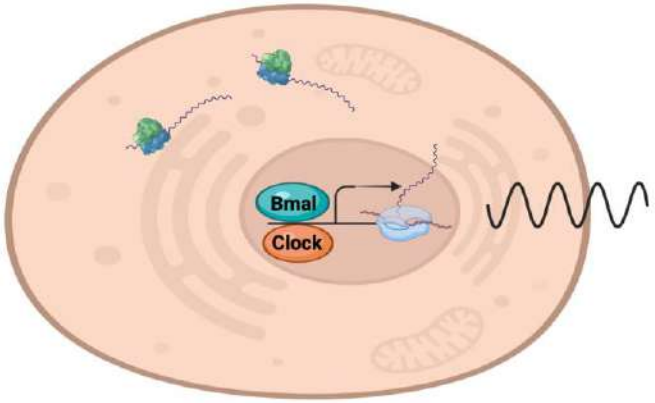
Proliferative metabolism



Adapted from
Dang, ***CSHL Quant Biol Symp*** 2013

Circadian Maintenance Metabolism

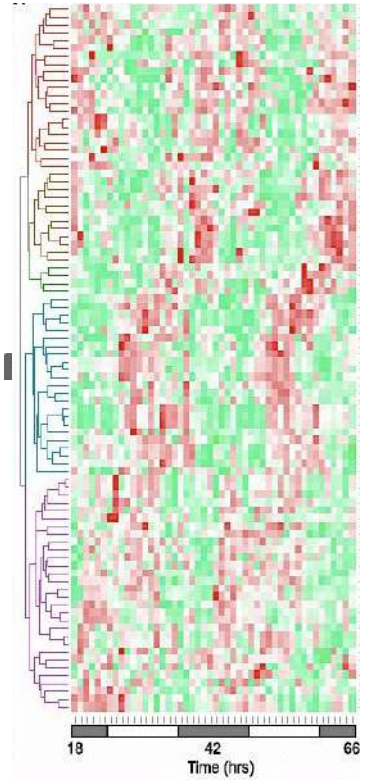




Wake

Sleep

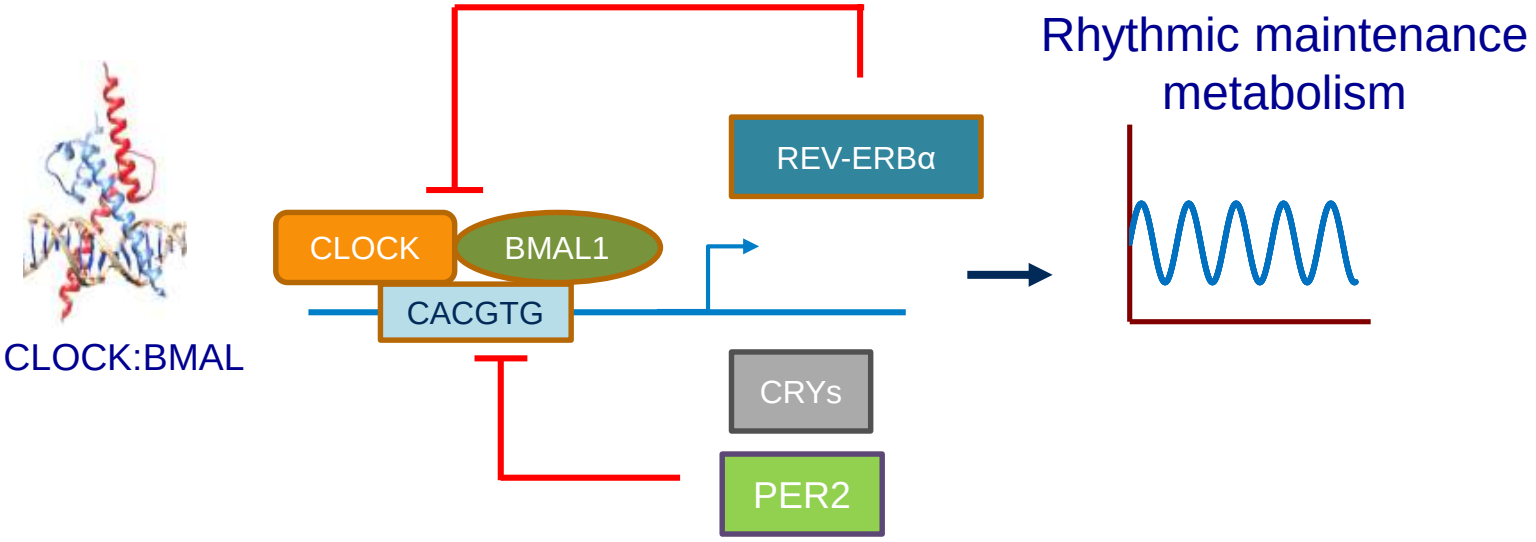
Liver circadian metabolome



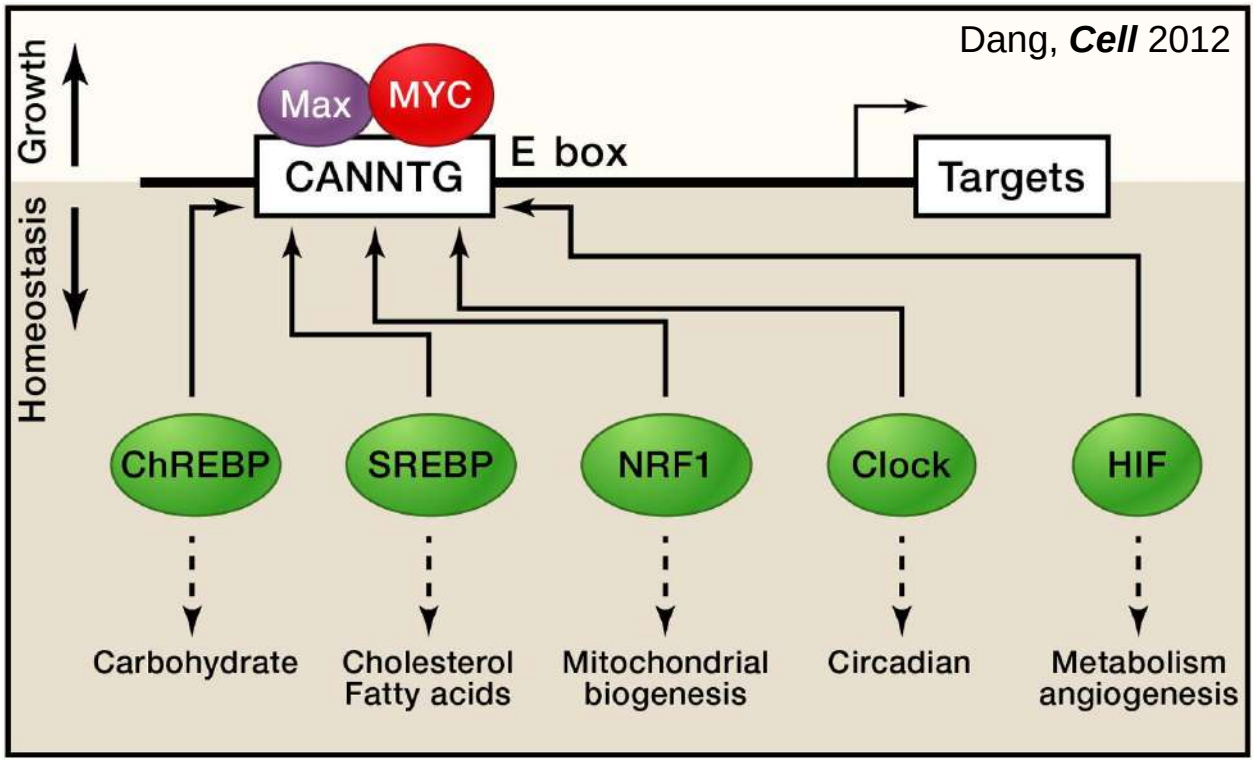
Krishnaia et al. ***Cell Metab*** 2017

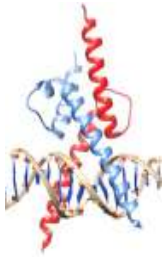
Weijie & Hogenesch

Mammalian cell intrinsic circadian clock

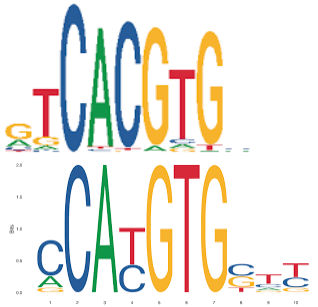


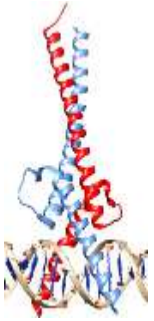
Circadian to Proliferative Metabolism





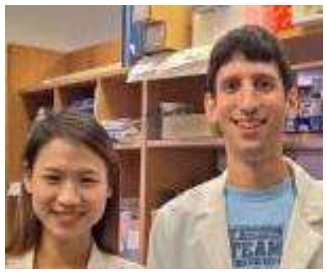
CLOCK:BMAL





MYC:MAX

Oncogenic MYC & the molecular clock

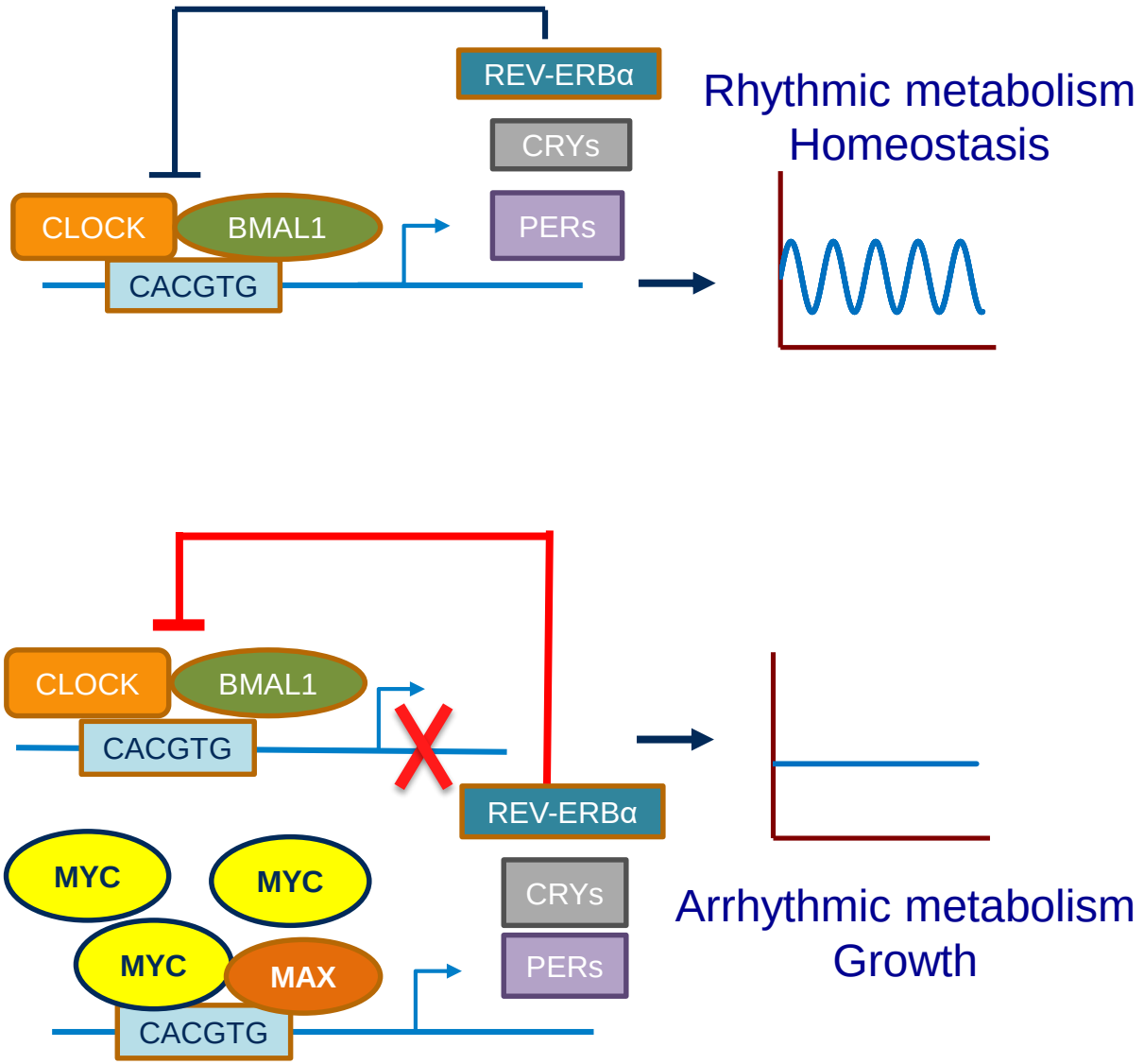


Brian Altman
Annie Hsieh

Aalim Weljie

Sai Krishnaiah

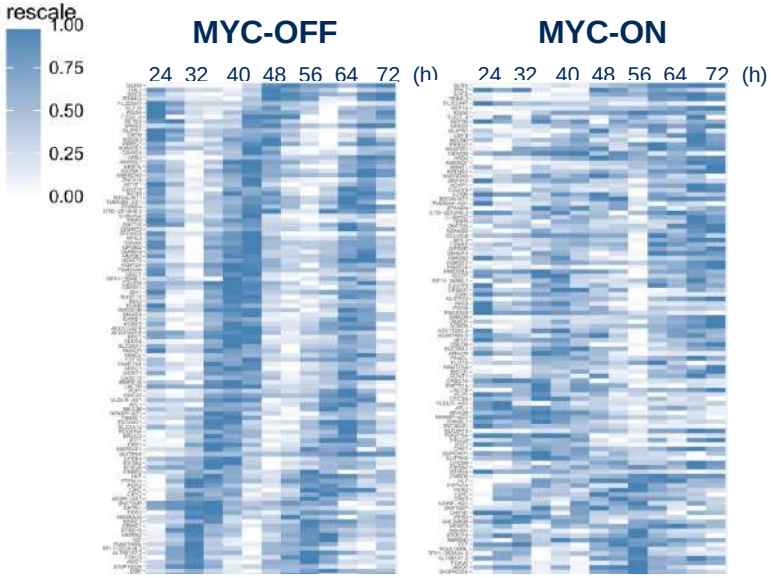
John Hogenesch



Altman & Hsieh et al. ***Cell Metabolism*** 2015

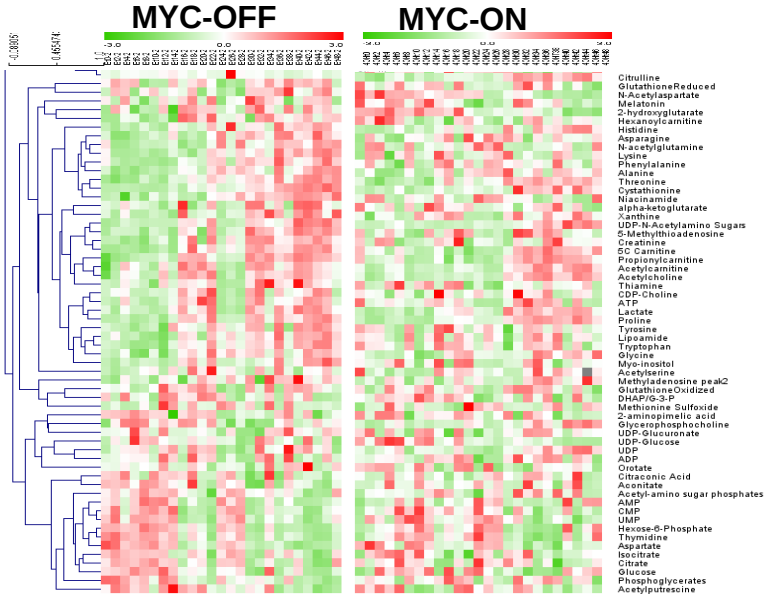
Myc alters circadian transcriptome & metabolome

RNAseq (*unpublished*)

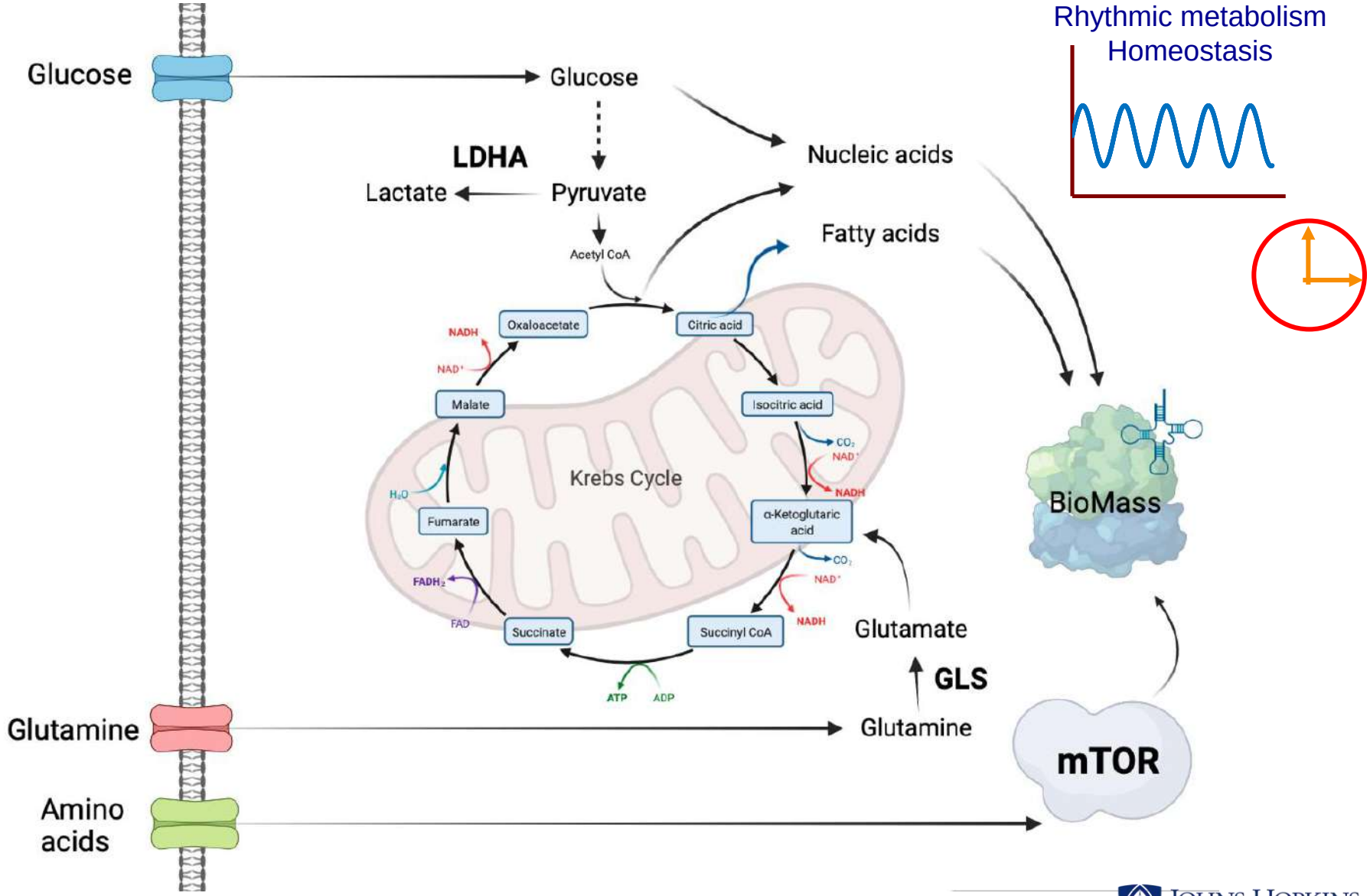


Altman, unpublished

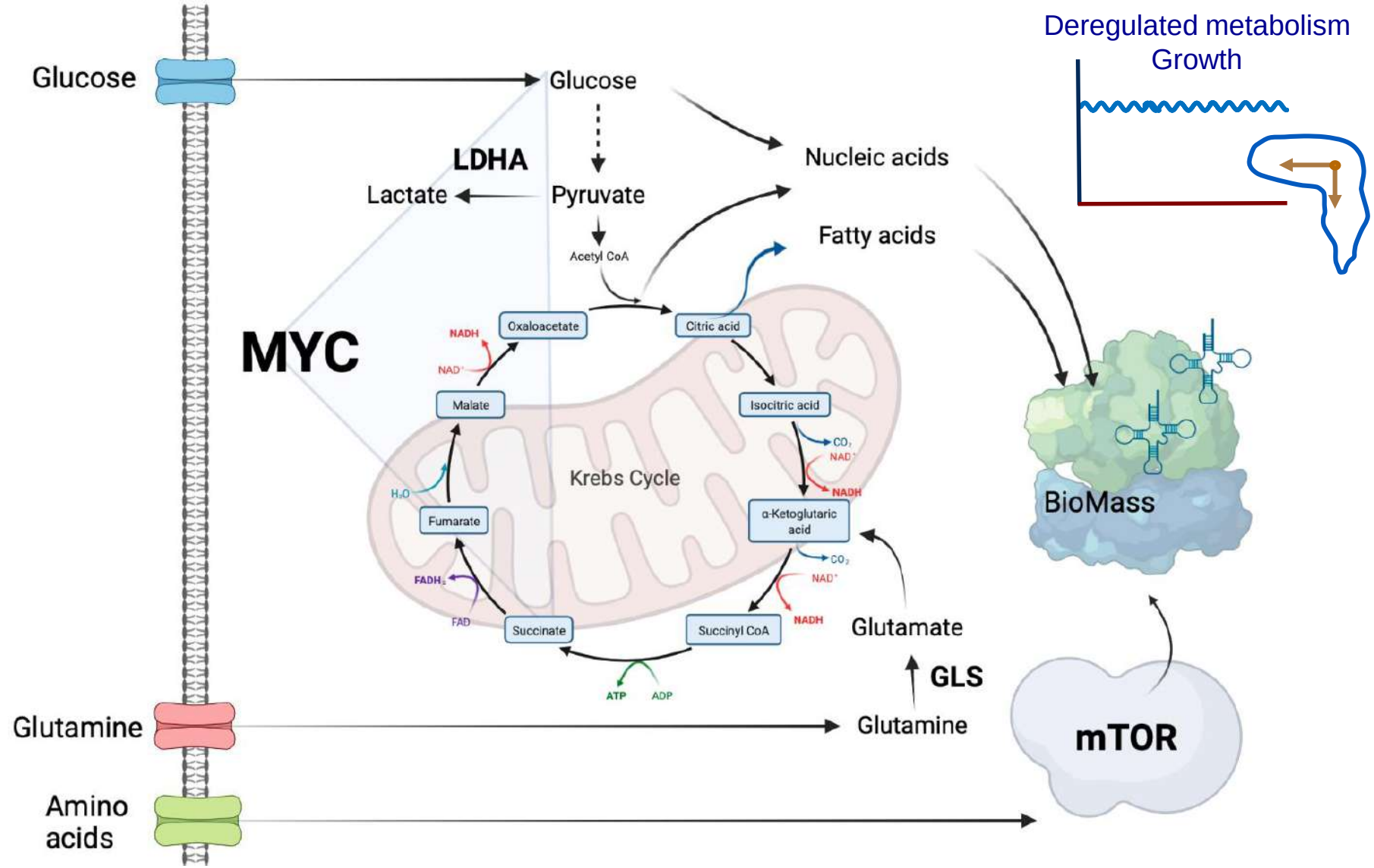
Mass spec (*unpublished*)



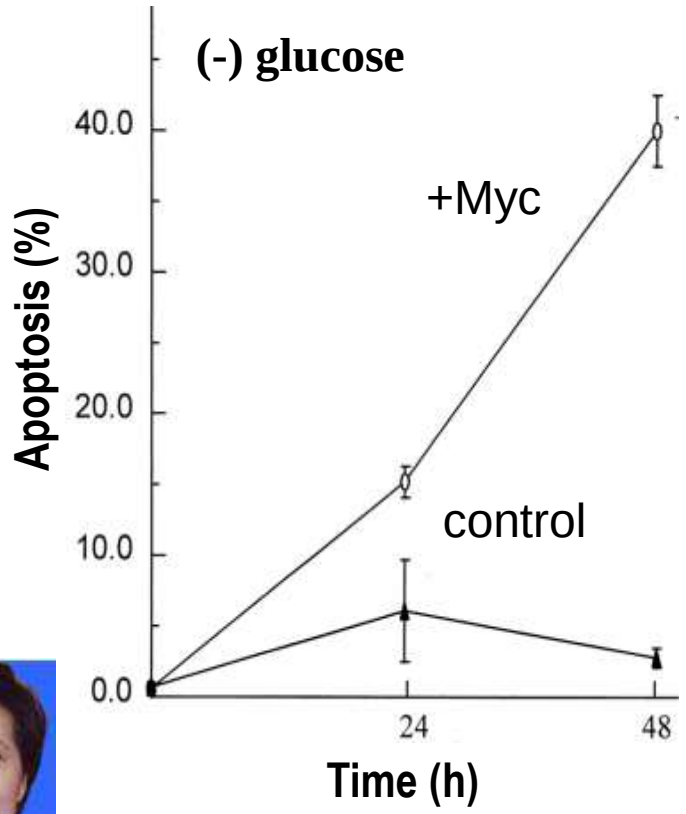
Maintenance metabolism



MYC-induced proliferative metabolism

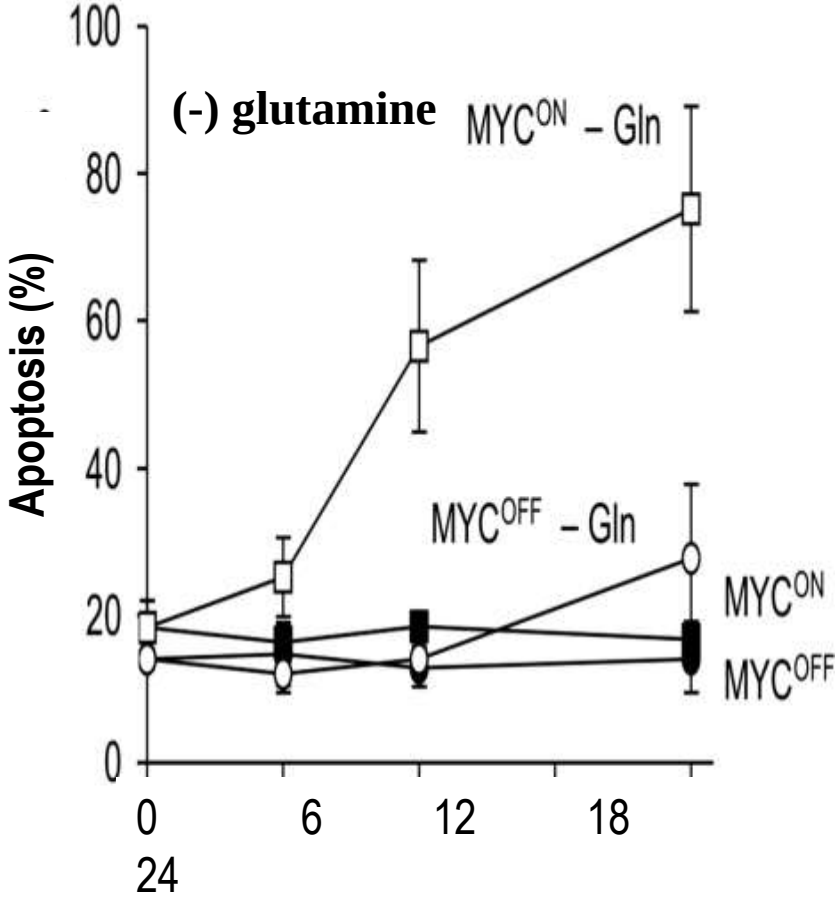


Myc-induced glucose and glutamine dependency



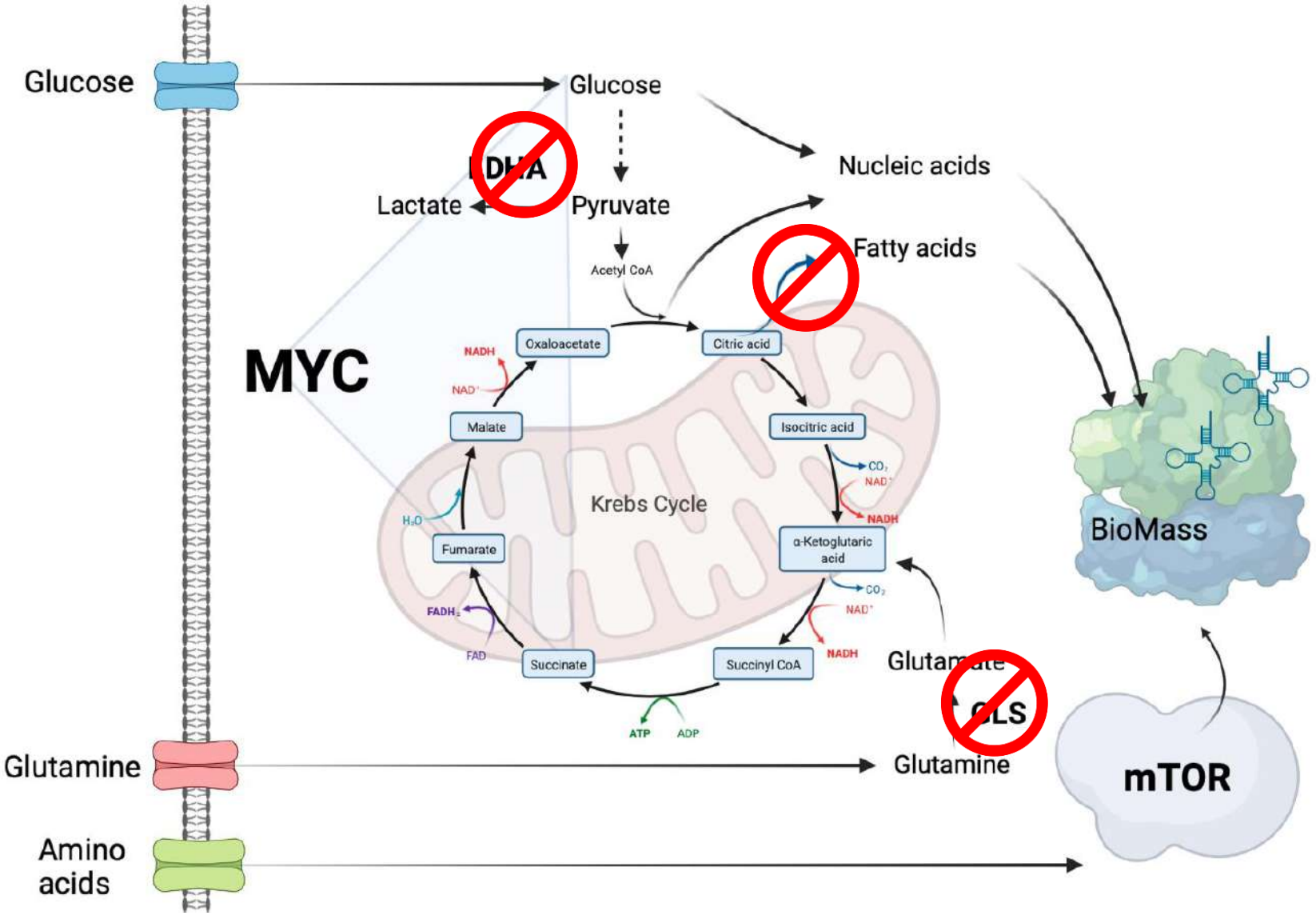
Hyunsuk Shim

Shim H et al. PNAS 1998;95:1511-1516



Yuneva M et al. J Cell Biol 2007;178:93-105

Myc-driven Metabolic Vulnerabilities



Tumor-specific Metabolic Vulnerability

IDH1 and IDH2

Science

2008

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,[1,2]* Siân Jones,[1]* Xiaosong Zhang,[1]* Jimmy Cheng-Ho Lin,[2]* Rebecca J. Leary,[1]* Philipp Angenendt,[1]* Parminder Mankoo,[3] Hannah Carter,[3] I-Mei Siu,[4] Gary L. Gallia,[4] Alessandro Olivi,[4] Roger McLendon,[5] B. Ahmed Rasheed,[5] Stephen Keir,[5] Tatiana Nikolskaya,[6] Yuri Nikolsky,[7] Dana A. Busam,[8] Hanna Tekleab,[8] Luis A. Diaz Jr.,[1] James Hartigan,[9] Doug R. Smith,[9] Robert L. Strausberg,[8] Suely Kazue Nagahashi Marie,[10] Sueli Mieko Oba Shinjo,[10] Hai Yan,[5] Gregory J. Riggins,[4] Darell D. Bigner,[5] Rachel Karchin,[3] Nick Papadopoulos,[1] Giovanni Parmigiani,[1] Bert Vogelstein,[1]† Victor E. Velculescu,[1]† Kenneth W. Kinzler[1]†

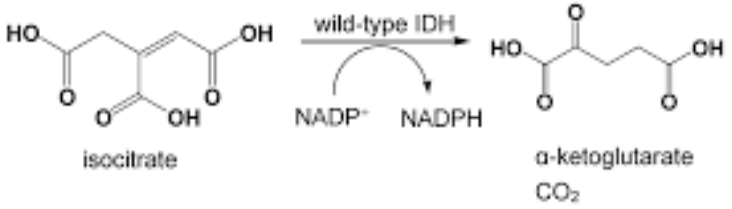
nature

2009

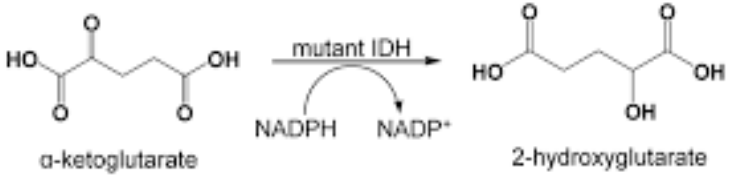
Cancer-associated IDH1 mutations produce 2-hydroxyglutarate

Lenny Dang[1], David W. White[1], Stefan Gross[1], Bryson D. Bennett[2], Mark A. Bittinger[1], Edward M. Drigge[1], Valeria R. Fantin[1], Hyun Gyung Jang[1], Shengfang Jin[1], Marie C. Keenan[1], Kevin M. Marks[1], Robert M. Pri[1], Patrick S. Ward[4], Katharine E. Yen[1], Linda M. Liau[3], Joshua D. Rabinowitz[2], Lewis C. Cantley[5], Craig B. Thompson[1], Matthew G. Vander Heiden[1]† & Shinsan M. Su[1]

Normal reaction:



Neomorphic reaction:



The NEW ENGLAND JOURNAL of MEDICINE 2009

IDH1 mutation

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

Elaine R. Mardis, Ph.D., Li Ding, Ph.D., David J. Dooling, Ph.D., David E. Larson, Ph.D., Michael D. McLellan, B.S., Ken Chen, Ph.D., Daniel C. Koboldt, M.S., Robert S. Fulton, M.S., Kim D. Delehaunty, B.A., Sean D. McGrath, M.S., Lucinda A. Fulton, M.S., Devin P. Locke, Ph.D., Vincent J. Magrini, Ph.D., Rachel M. Abbott, B.S., Tammi L. Vickery, B.S., Jerry S. Reed, M.S., Jody S. Robinson, M.S., Todd Wylie, B.S., Scott M. Smith, Lynn Carmichael, B.S., James M. Eldred, Christopher C. Harris, B.S., Jason Walker, B.A., B.S., Joshua B. Peck, M.B.A., Feiyu Du, M.S., Adam F. Dukes, B.A., Gabriel E. Sanderson, B.S., Anthony M. Brummett, Eric Clark, Joshua F. McMichael, B.S., Rick J. Meyer, M.S., Jonathan K. Schindler, B.S., B.A., Craig S. Pohl, M.S., John W. Wallis, Ph.D., Xiaoqi Shi, M.S., Ling Lin, M.S., Heather Schmidt, B.S., Yuzhu Tang, M.D., Carrie Haipek, M.S., Madeline E. Wiechert, M.S., Jolynda V. Ivy, M.B.A., Joelle Kalicki, B.S., Glendoria Elliott, Rhonda E. Ries, M.A., Jacqueline E. Payton, M.D., Ph.D., Peter Westervelt, M.D., Ph.D., Michael H. Tomasson, M.D., Mark A. Watson, M.D., Ph.D., Jack Baty, B.A., Sharon Heath, William D. Shannon, Ph.D., Rakesh Nagarajan, M.D., Ph.D., Daniel C. Link, M.D., Matthew J. Walter, M.D., Timothy A. Graubert, M.D., John F. DiPersio, M.D., Ph.D., Richard K. Wilson, Ph.D., and Timothy J. Ley, M.D.

MYC, ncRNAs & Cancer

nature

2005

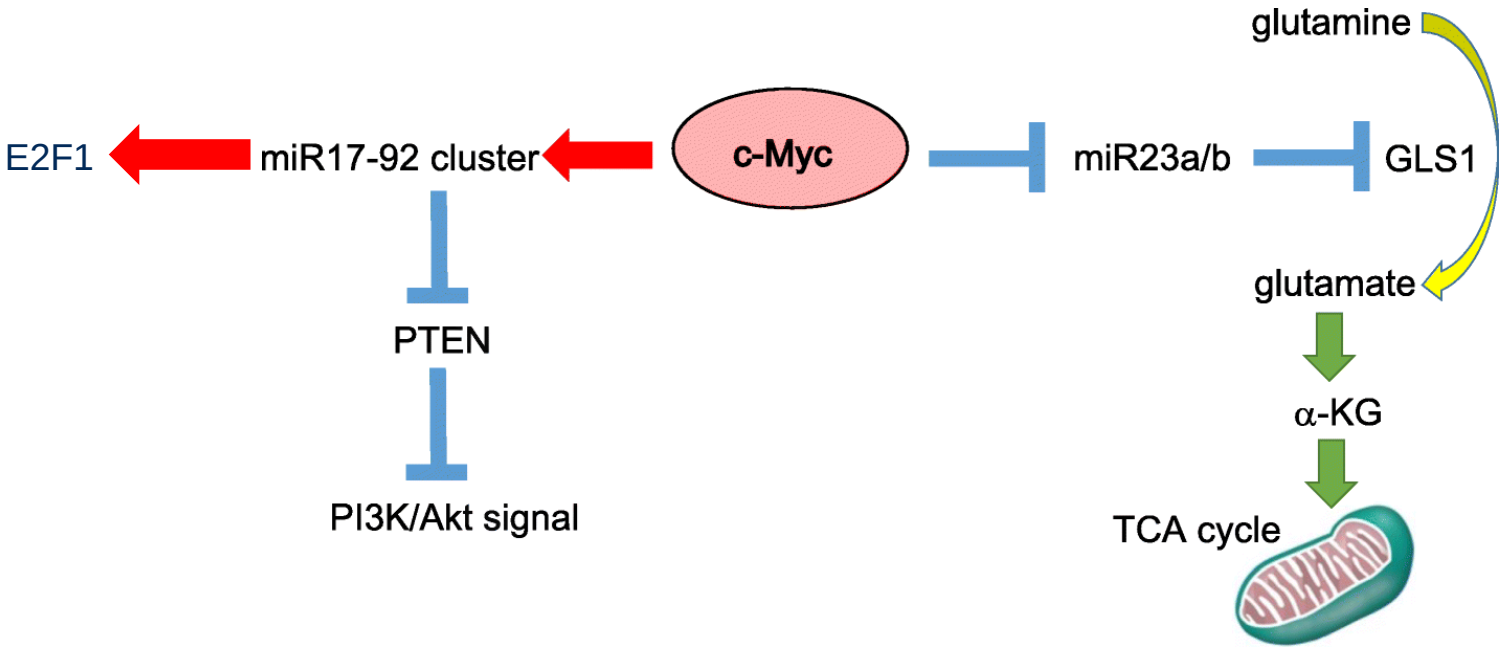
c-Myc-regulated microRNAs modulate E2F1 expression

Kathryn A. O'Donnell[1,2], Erik A. Wentzel[2], Karen I. Zeller[3], Chi V. Dang[1,2,3,5] & Joshua T. Mendell[1,2,4]

2009

c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism

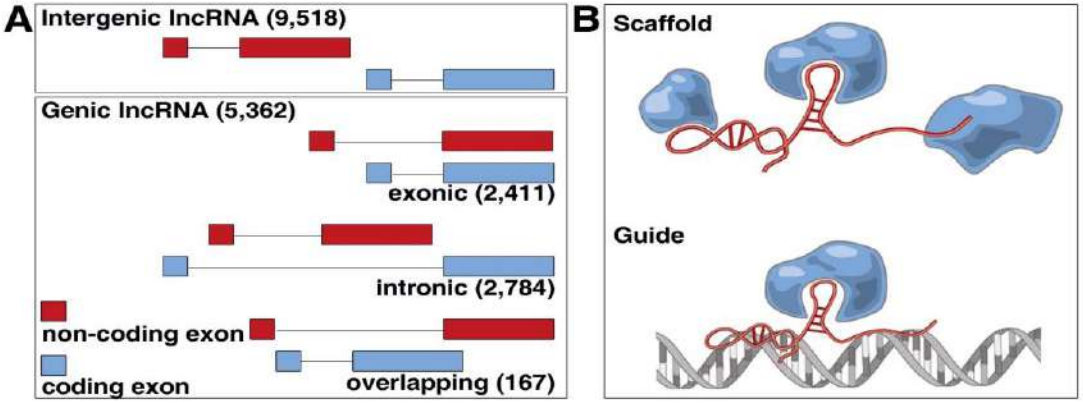
Ping Gao[1], Irina Tchernyshyov[2], Tsung-Cheng Chang[3], Yun-Sil Lee[3], Kayoko Kita[11], Takafumi Ochi[11], Karen I. Zeller[1], Angelo M. De Marzo[6,7,8], Jennifer E. Van Eyk[2,9], Joshua T. Mendell[3,4,5] & Chi V. Dang[1,3,5,6,7,10]



Yoshida J Exp Clin Can Res 2018

ncRNAs & Cancer

Genome ‘dark matter’ = lncRNA

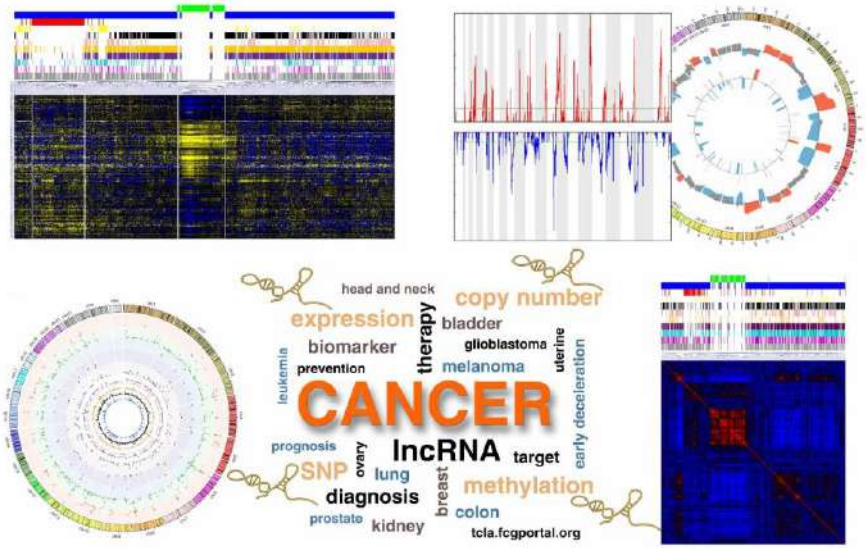


Cancer Research 2018

Molecular Cell Biology

MYC Targeted Long Noncoding RNA DANCR Promotes Cancer in Part by Reducing p21 Levels

Yunqi Lu[1], Zhongyi Hu[2], Lingegowda S. Mangala[3], Zachary E. Stine[1], Xiaowen Hu[2], Dahai Jiang[3], Yan Xiang[1], Youyou Zhang[2], Sunila Pradeep[3], Cristian Rodriguez-Aguayo[4], Gabriel Lopez-Berestein[4], Angelo M. DeMarzo[5], Anil K. Sood[3], Lin Zhang[2], and Chi V. Dang[1,6,7]



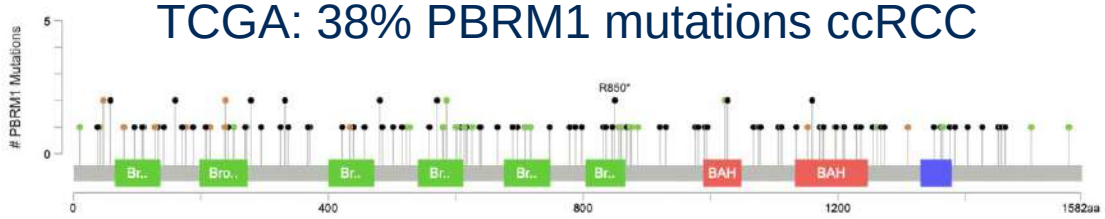
Cancer Cell 2015

Comprehensive Genomic Characterization of Long Non-coding RNAs across Human Cancers

Xiaohui Yan,[1,9,20] Zhongyi Hu,[1,20] Yi Feng,[1,2,20] Xiaowen Hu,[1] Jiao Yuan,[1] Sihai D. Zhao,[10] Youyou Zhang,[1] Lu Yang,[1,12] Weiwei Shan,[1,9] Qun He,[1] Lingling Fan,[1,9] Lana E. Kandalaft,[1,16] Janos L. Tanyi,[3] Chunsheng Li,[1,3] Chao-Xing Yuan,[4] Dongmei Zhang,[1,12] Huiqing Yuan,[11] Keqin Hua,[9] Yiling Lu,[19] Dionyssios Katsaros,[13] Qihong Huang,[14] Kathleen Montone,[5] Yi Fan,[5] George Coukos,[15] Jeff Boyd,[16] Anil K. Sood,[17,18] Timothy Rebbeck,[7] Gordon B. Mills,[19] Chi V. Dang,[2,8,*] and Lin Zhang[1,3,*]

ncRNAs & Cancer

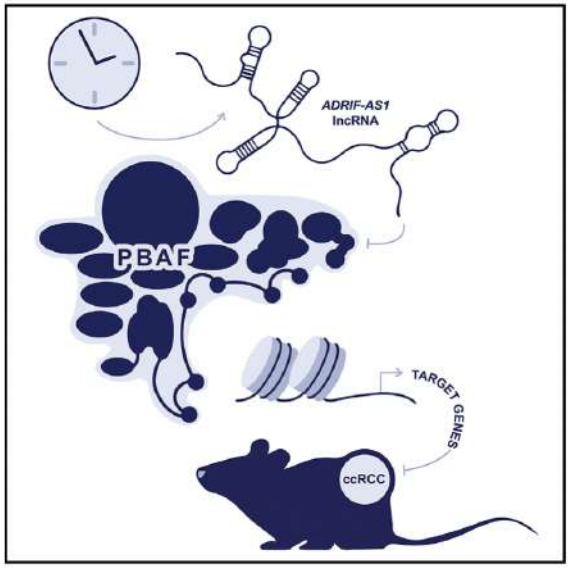
TCGA: 38% PBRM1 mutations ccRCC



Cell Reports 2022

Circadian lncRNA *ADIRF-AS1* binds PBAF and regulates renal clear cell tumorigenesis

Graphical abstract



Authors

Rebekah Brooks, Judith Monzy, Bailey Aaron, ..., David W. Speicher, Lin Zhang, Chi V. Dang

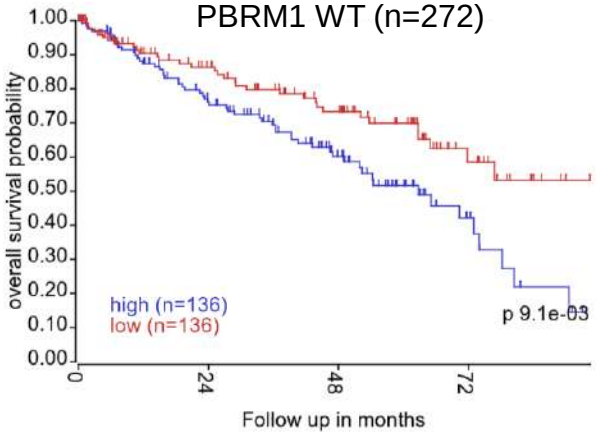
Correspondence

cdang@lcr.org

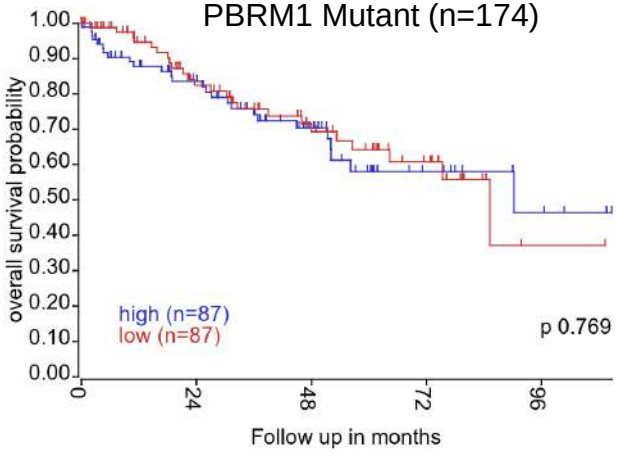
In brief

Brooks et al. identify a circadian lncRNA, *ADIRF-AS1*, that interacts with the PBAF (PBRM1/BRG1) complex. Loss of *ADIRF-AS1* eliminates tumorigenesis of 786-O ccRCC tumor xenografts. High expression of *ADIRF-AS1* portends poor prognosis only in ccRCC cases with wild-type PBRM1, suggesting its role as an oncogenic lncRNA.

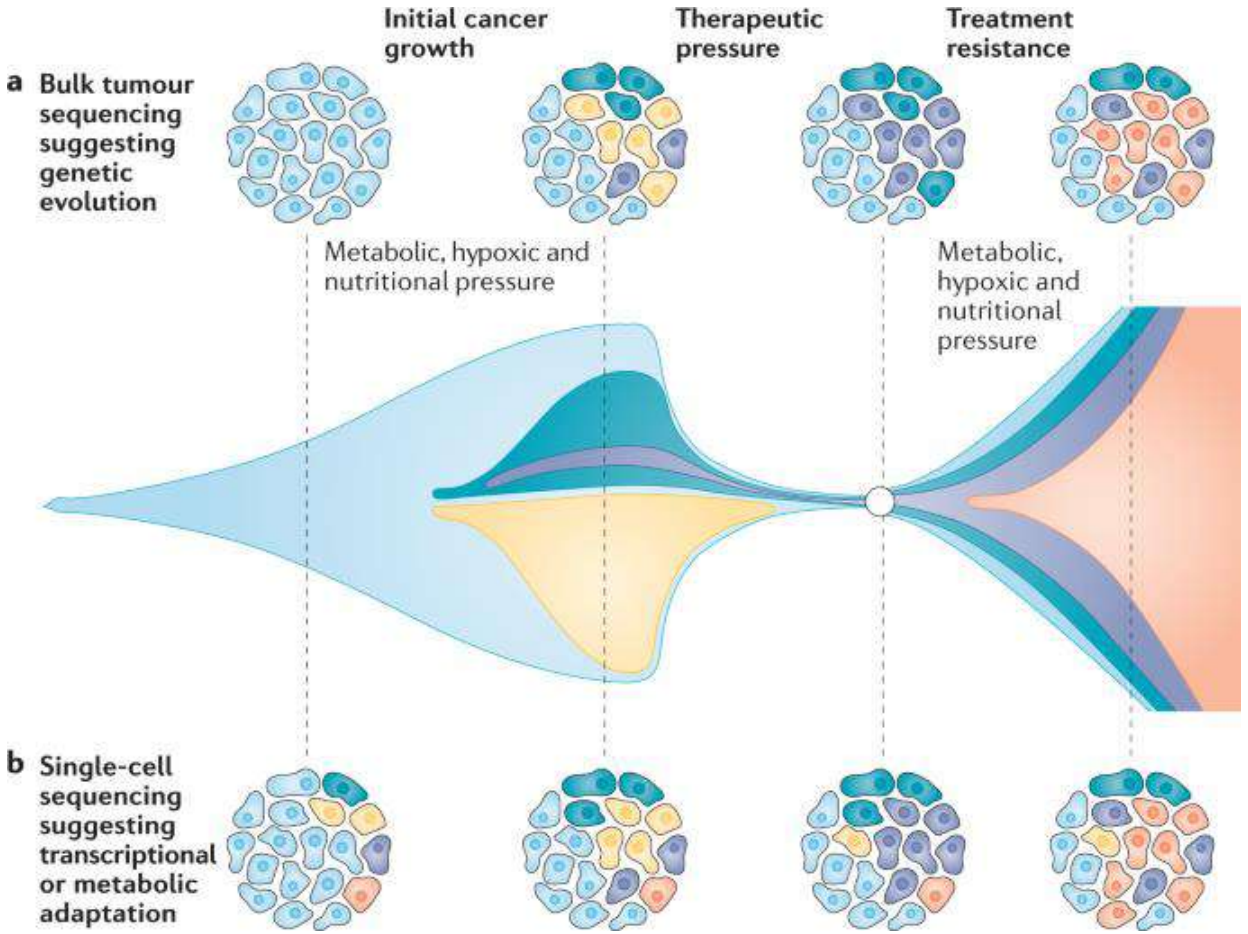
ADIRF-AS1
PBRM1 WT (n=272)



ADIRF-AS1
PBRM1 Mutant (n=174)

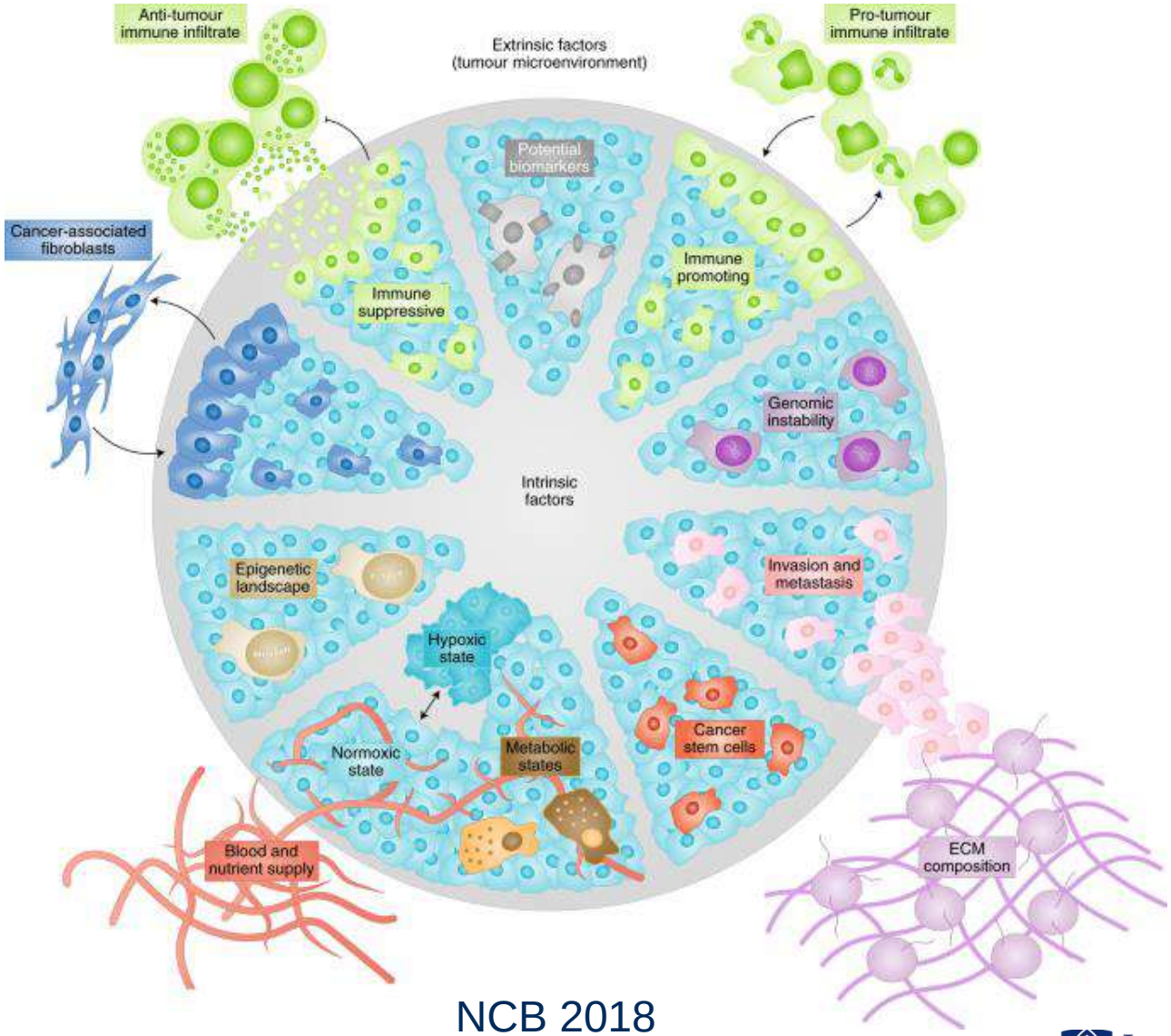


Cancer Functional Genomics: Rx Resistance



Nat Rev Cancer 2020

Cancer Genomics: scHeterogeneity



NCB 2018

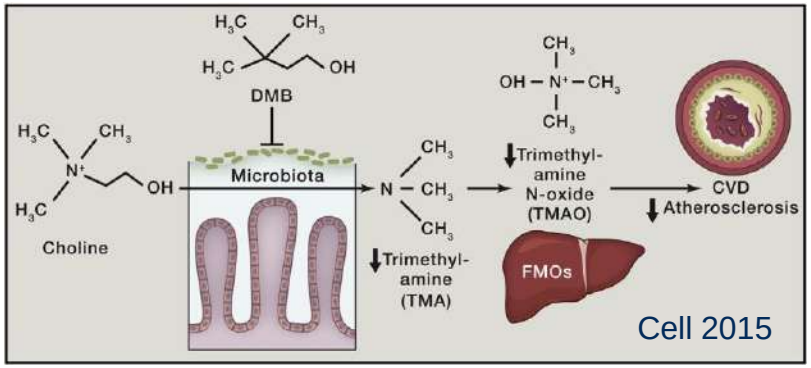
Cancer Meta-Genomics

nature medicine 2019 ARTICLES
https://doi.org/10.1038/s41591-019-0405-7
Corrected: Author Correction

Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation

Andrew Maltez Thomas[1,2,3,32], Paolo Manghi[1,32], Francesco Asnicar[1], Edoardo Pasolli[1], Federica Armanini[1], Moreno Zolfo[1], Francesco Beghini[1], Serena Manara[1], Nicolai Karcher[1], Chiara Pozzi[4], Sara Gandini[4], Davide Serrano[4], Sonia Tarallo[5], Antonio Francavilla[5], Gaetano Gallo[6,7], Mario Trompetto[7], Giulio Ferrero[8], Sayaka Mizutani[9,10], Hirotsugu Shiroma[9], Satoshi Shiba[11], Tatsuhiro Shibata[11,12], Shinichi Yachida[11,13], Takuji Yamada[9,14], Jakob Wirbel[15], Petra Schrotz-King[16], Cornelia M. Ulrich[17], Hermann Brenner[16,18,19], Manimozhiyan Arumugam[20,21], Peer Bork[15,22,23,24], Georg Zeller[15], Francesca Cordero[8], Emmanuel Dias-Neto[3,25], João Carlos Setubal[2,26], Adrian Tett[1], Barbara Pardini[5,27], Maria Rescigno[28], Levi Waldron[29,30,33], Alessio Naccarati[5,31,33] and Nicola Segata[1,33]*

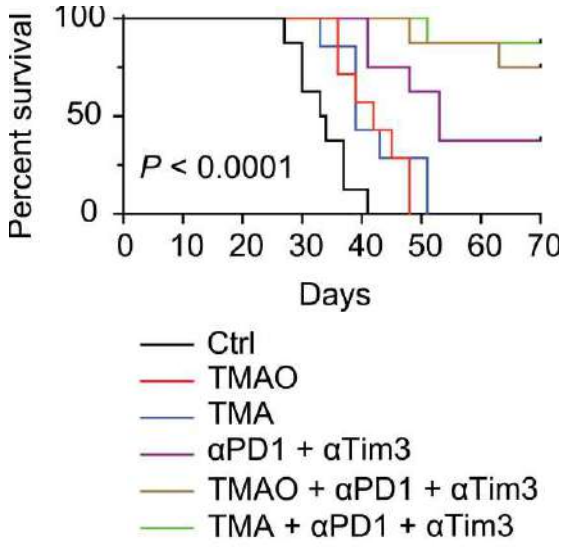
CutC TMA lyase: cancer > control



TRANSPLANTATION BLOOD 2020

The gut microbial metabolite trimethylamine *N*-oxide aggravates GVHD by inducing M1 macrophage polarization in mice

Kunpeng Wu,[1] Yan Yuan,[1] Huihui Yu,[1] Xin Dai,[1] Shu Wang,[1] Zhengxu Sun,[1] Fen Wang,[1] He Fei,[2] Qiwang Lin,[2] Hua Jiang,[2] and Tong Chen[1]



SCIENCE IMMUNOLOGY | RESEARCH ARTICLE 2022

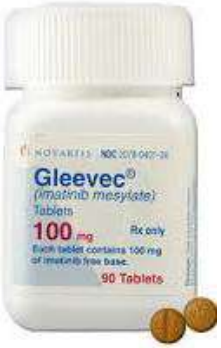
TUMOR IMMUNOLOGY

The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer

Gauri Mirji[1], Alison Worth[1], Sajad Ahmad Bhat[1], Mohamed El Sayed[1], Toshitha Kannan[2], Aaron R. Goldman[3], Hsin-Yao Tang[3], Qin Liu[4], Noam Auslander[4], Chi V. Dang[4,5], Mohamed Abdel-Mohsen[1,6], Andrew Kossenkov[2], Ben Z. Stanger[7,8,9,10], Rahul S. Shinde[1]*

Cancer Genome: Sequence to Action

- ctDNA: early detection
- Germline alterations
  - BRCA interception
  - Pre-cancer to Cancer
- BCR-ABL
- IDHmut
- Mutant RAS to RAS drugs
- Epigenetic modifier mutations
  - Epigenetic drugs
- Genomic instability MSI – immunotherapy
- Genome → Proteome → Metabolome
  - New opportunities: cancer microbiome



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