(epi)genetics in osteosarcomagenesis

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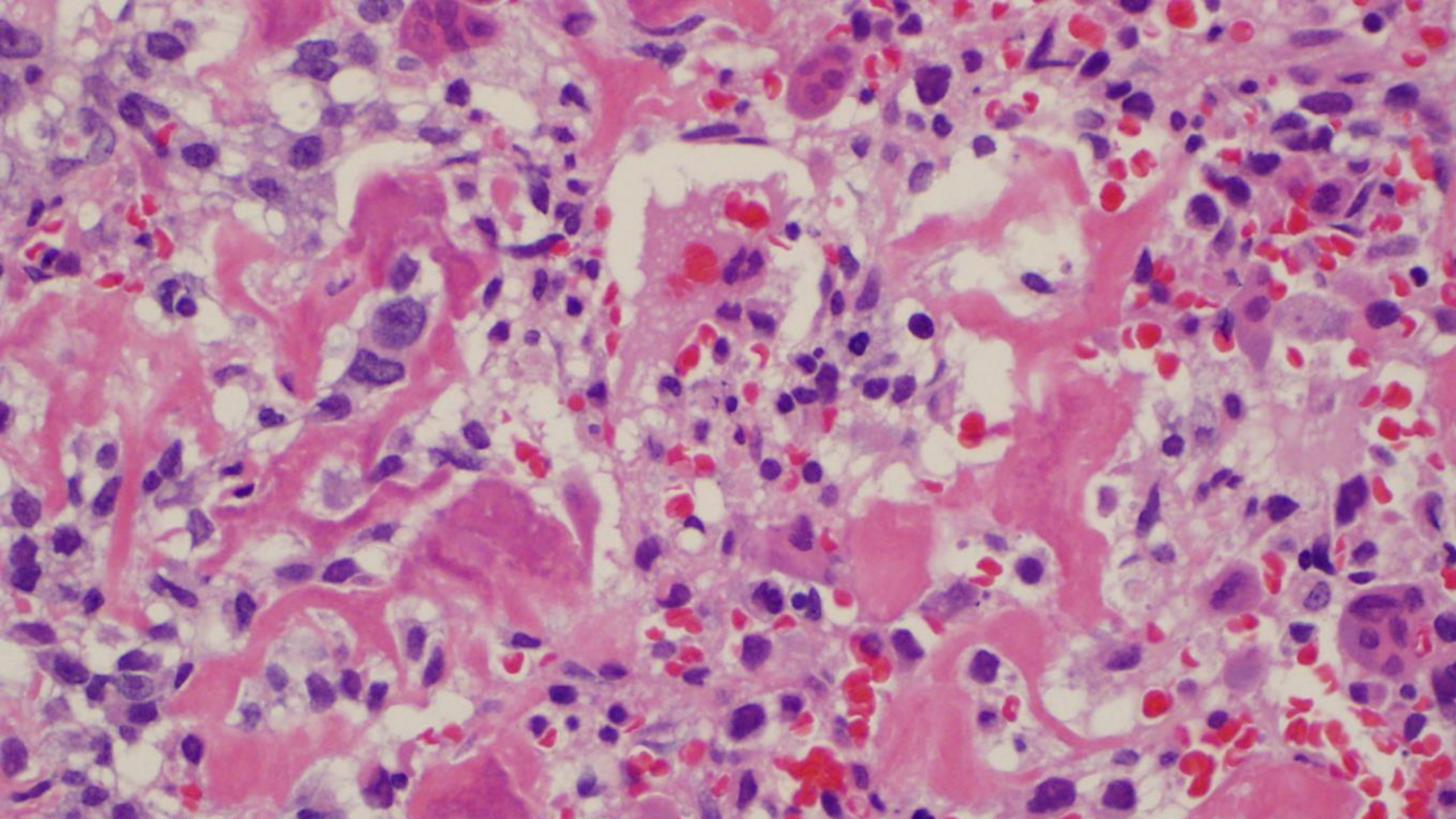
the beginning

osteosarcomagenesis

initiation

creation

osteosarcomagenesis




over
on
upon
epigenetics
at
near
after
around
before

DNA?

genome?

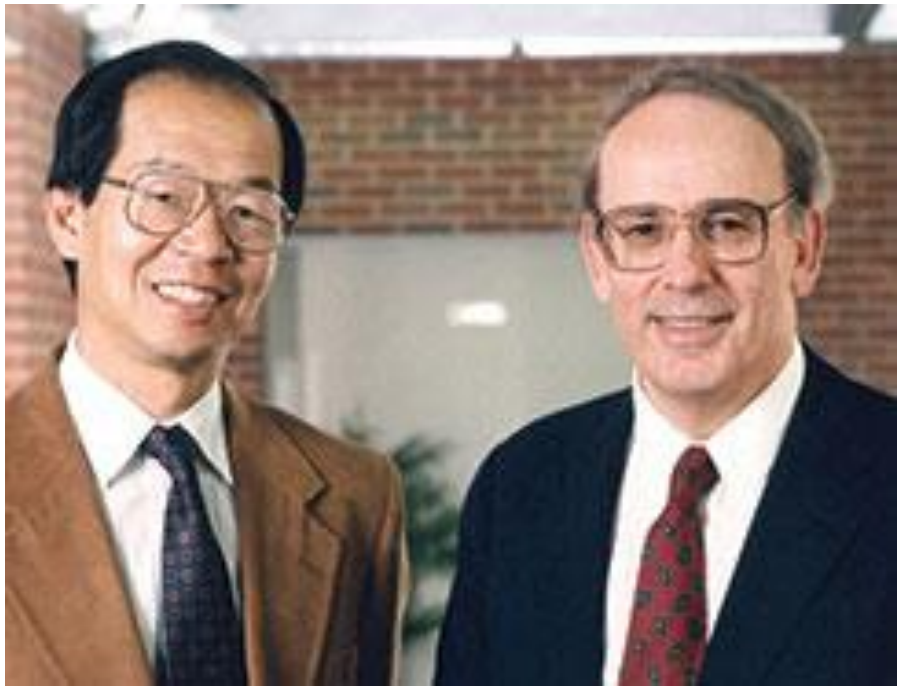
epigenetics

exome?

transcriptome?

genetics

1969



Frederick Li
Joseph Fraumeni, Jr.

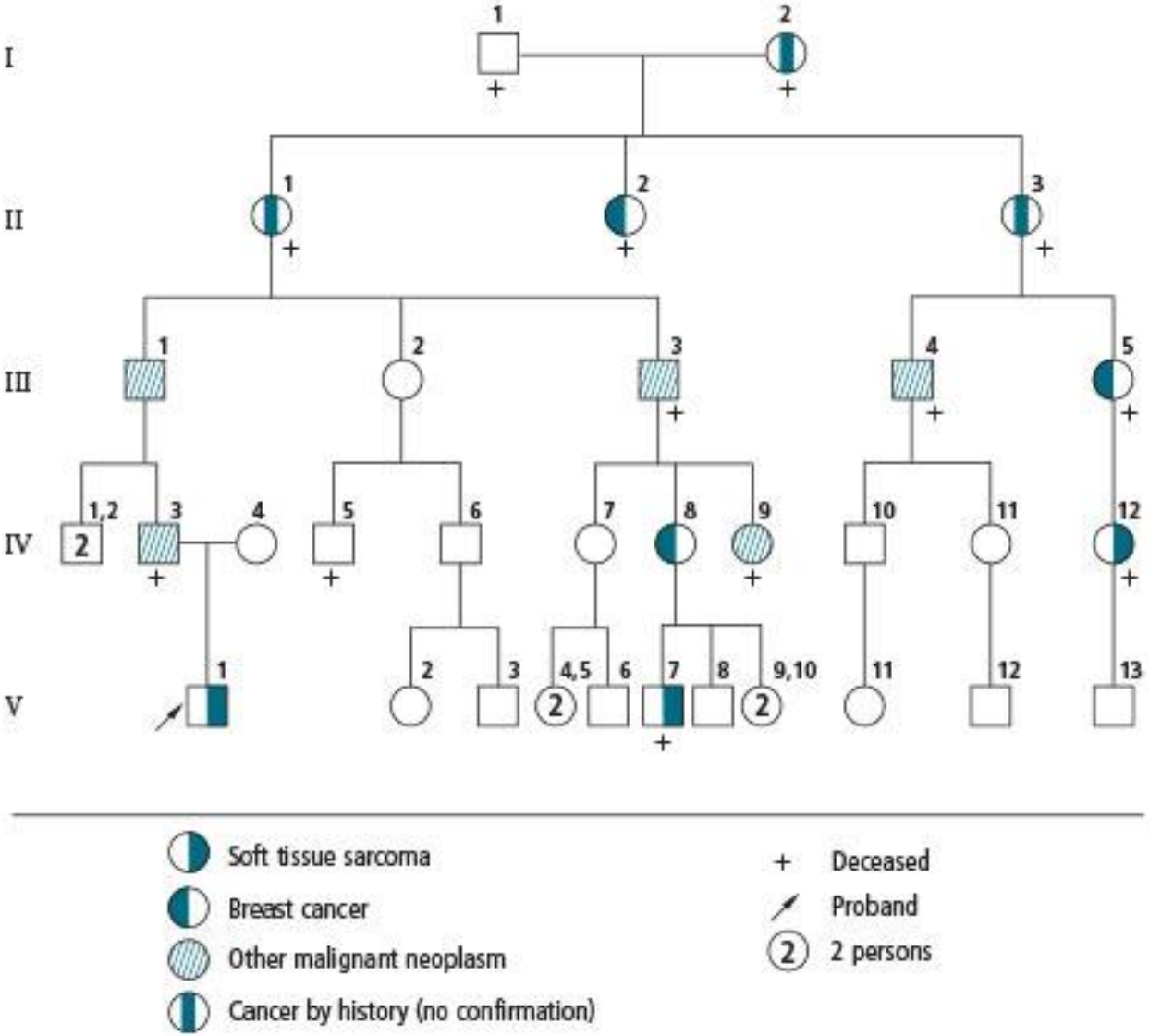


Figure 1. Pedigree of Family A from the first paper documenting the constellation of tumors in what would later be known as Li-Fraumeni syndrome. This family developed a remarkable combination of multiple cancers in children and young adults, including soft tissue sarcomas and breast cancer. The proband, noted by an arrow, was the first affected individual identified in the study. (Li F, Fraumeni JF, Jr. *Ann Intern Med* 1969)

Proc. Nat. Acad. Sci. USA
Vol. 68, No. 4, pp. 820–823, April 1971

Mutation and Cancer: Statistical Study of Retinoblastoma

ALFRED G. KNUDSON, JR.

Graduate School of Biomedical Sciences and M. D. Anderson Hospital and Tumor Institute,

The University of Texas at Houston, Houston, Texas 77025

Communicated by James V. Neel, February 8, 1971

1971

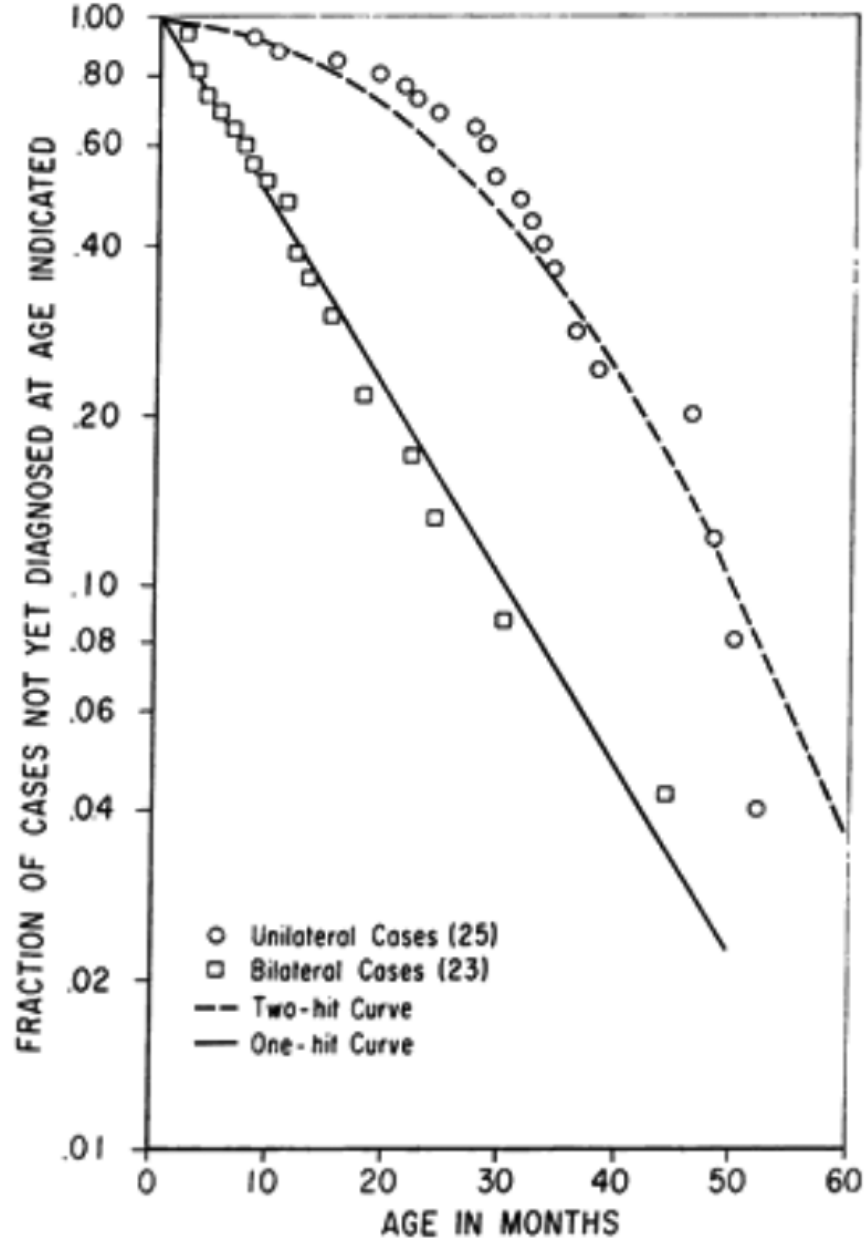


FIG. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -t/30$, the two-hit curve from $\log S = -4 \times 10^{-5} t^2$.

Heritable Clinical Syndromes linked to OS

in 1970s

Bilateral Retinoblastoma
Li-Fraumeni
Rothmund-Thomson

1985

Science

Genetic Origin of Mutations Predisposing to Retinoblastoma

WEBSTER K. CAVENEE, MARC F. HANSEN, MAGNUS NORDENSKJOLD, ERIC KOCK, IRENE MAUMENEE, JEREMY A. SQUIRE, ROBERT A. PHILLIPS, AND BRENDA L. GALLIE

Authors Info & Affiliations

SCIENCE · 26 Apr 1985 · Vol 228, Issue 4698 · pp. 501-503 · DOI: 10.1126/science.3983638

Abstract

Retinoblastoma is one of several human tumors to which predisposition can be inherited. Molecular genetic analysis of several nonheritable cases has led to the hypothesis that this tumor develops after the occurrence of specific mitotic events involving human chromosome 13. These events reveal initial predisposing recessive mutations. Evidence is presented that similar chromosomal events occur in tumors from heritable cases. The chromosome 13 found in the tumors was the one carrying the predisposing germline mutation and not the homolog containing the wild-type allele at the *Rb-1* locus. These results suggest a new approach for identifying recessive mutant genes that lead to cancer and a conceptual basis for accurate prenatal predictions of cancer predisposition.

nature

Letter | Published: 16 October 1986

A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma

Stephen H. Friend, Rene Bernards, Snezna Rogelj, Robert A. Weinberg, Joyce M. Rapaport, Daniel M. Albert & Thaddeus P. Dryja

Nature **323**, 643–646 (1986) | Cite this article

1986

The NEW ENGLAND JOURNAL of MEDICINE

1992

ORIGINAL ARTICLE

Germline Mutations of the p53 Tumor-Suppressor Gene in Children and Young Adults with Second Malignant Neoplasms

Authors: David Malkin, M.D., Kent W. Jolly, M.D., Noële Barbier, M.D., A. Thomas Look, M.D., Stephen H. Friend, M.D., Ph.D., Mark C. Gebhardt, M.D., Tone I. Andersen, M.D., Anne-Lise Børresen, Ph.D., Frederick P. Li, M.D., Judy Garber, M.D., and Louise C. Strong, M.D. Author Info & Affiliations

Published May 14, 1992 | N Engl J Med 1992;326:1309-1315 | DOI: 10.1056/NEJM199205143262002

VOL. 326 NO. 20

by mid 1990s

TP53 and *RB1*

loci linked to OS

nature genetics

1999

Letter | Published: May 1999

Mutations in *RECQL4* cause a subset of cases of Rothmund-Thomson syndrome

Saori Kitao, Akira Shimamoto, Makoto Goto, Robert W. Miller, William A. Smithson, Noralane M. Lindor & Yasuhiro Furuichi ✉

Nature Genetics **22**, 82–84 (1999) | Cite this article

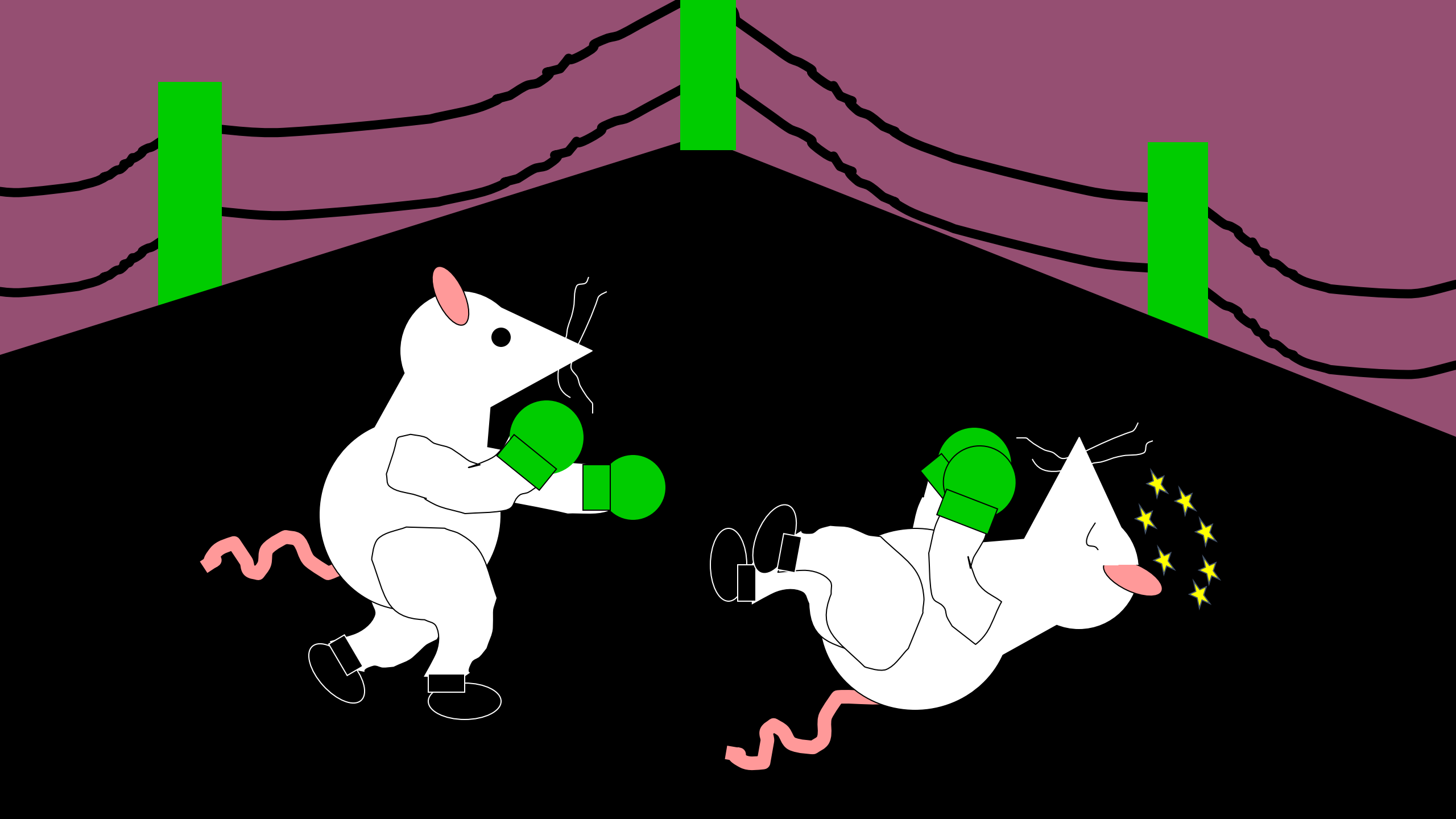
genetics

Were all non-familial cases

epigenetic

osteosarcomagenesis?

genetics



Cell

Volume 36, Issue 1, January 1984, Pages 51-60

Article

c-fos protein can induce cellular transformation: A novel mechanism of activation of a cellular oncogene

A. Dusty Miller, Tom Curran, Inder M. Verma

Well, transgenic mice

1984

1988

SV40T

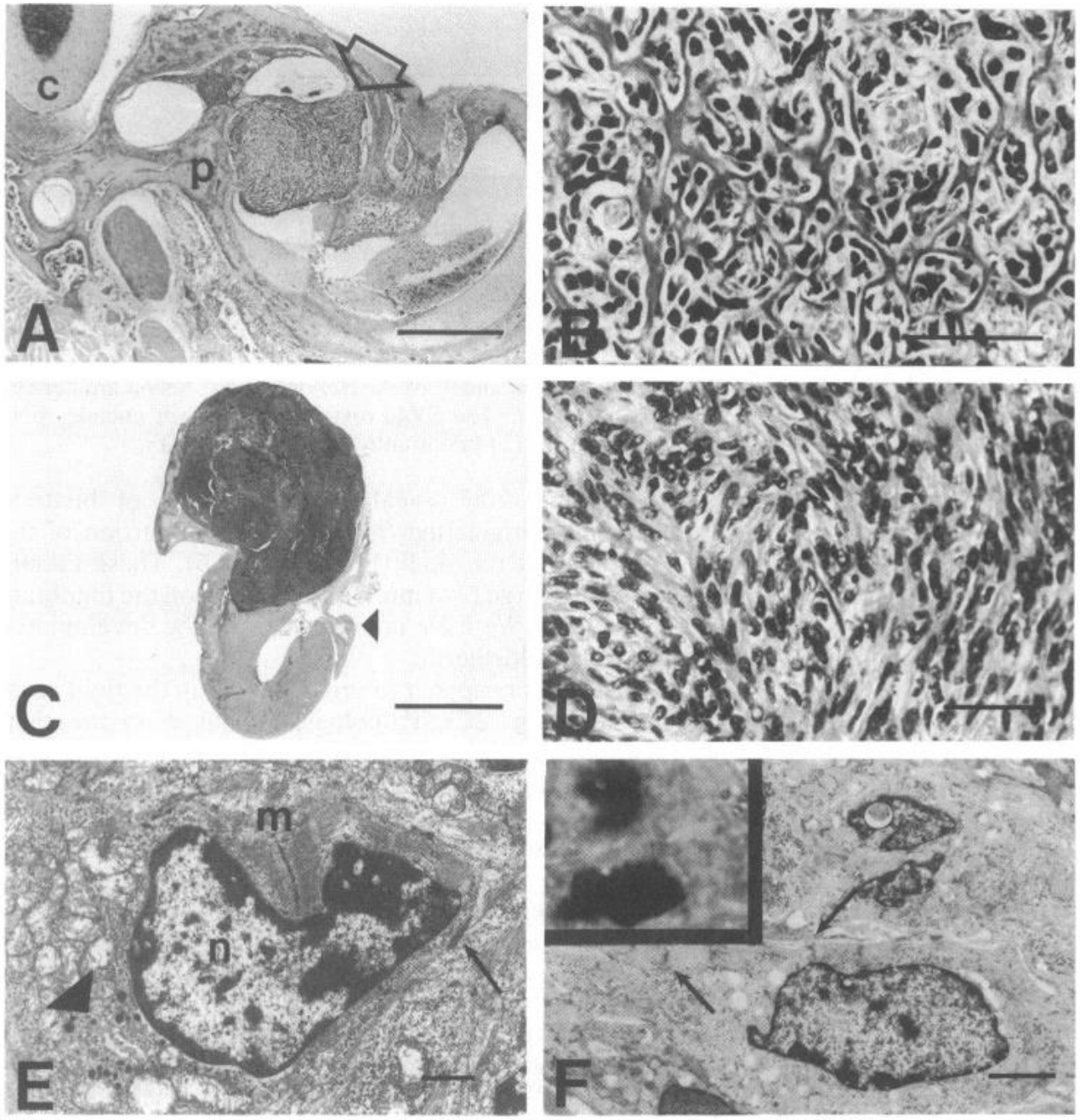


FIG. 2. Heart and temporal bone pathology in mP1–SV40 transgenic mice. (*A–D*) Photomicrographs of hematoxylin/eosin-stained paraffin sections. (*A*) Osteosarcoma of petrous temporal bone of inner ear in a 9-week-old mouse (1736-1 line). Arrow indicates tumor; c, cerebellum; p, petrous temporal bone. (Bar = 500 μm.) (*B*) Osteosarcoma from founder 1736-11 at 20 weeks of age, showing pleomorphic tumor cells surrounded by amorphous osteoid. (Bar = 50 μm.) (*C*) Rhabdomyosarcoma of right atrium of founder 1738-12 at 18 weeks of age. Left atrium (arrowhead) is at right. (Bar = 2 mm.) (*D*) Rhabdomyosarcoma from a 9-week mouse (1736-8 line), showing interweaving arrangements of spindle-shaped tumor cells growing in a fibrillar eosinophilic matrix. Cross-striations were not readily apparent by light microscopy. (Bar = 25 μm.) (*E*) Electron micrograph of neoplastic cell from right atrial tumor in a 19-week mouse (1736-1 line), showing irregularly shaped nucleus with coarse, clumped chromatin (n), thick and thin myofilaments organized around prominent Z-bands (m), electron-dense granules (arrowhead), and junctional complexes between cells (arrow). (Bar = 1 μm.) (*F*) Right atrial tumor from an 18-week mouse (1738-3 line), stained by immunoperoxidase for SV40 T antigen in a 1-μm thick section (*Inset*). Adjacent thin section was then examined in the electron microscope to evaluate ultrastructure of T-antigen-positive

MOLECULAR AND CELLULAR BIOLOGY, Sept. 1989, p. 3982–3991
0270-7306/89/093982-10$02.00/0

Vol. 9, No. 9

1989 mut *TP53*

High Incidence of Lung, Bone, and Lymphoid Tumors in Transgenic Mice Overexpressing Mutant Alleles of the p53 Oncogene

ALAIN LAVIGUEUR,[1,2] VICTOR MALTBY,[1] DAVID MOCK,[3] JANET ROSSANT,[1,2] TONY PAWSON,[1,2] AND ALAN BERNSTEIN[1,2]*

Division of Molecular and Developmental Biology, Mount Sinai Hospital Research Institute, 600 University Avenue, Toronto, Ontario, Canada M5G 1X5,[1] and Department of Medical Genetics, Faculty of Medicine,[2] and Department of Oral Medicine and Pathology, Faculty of Dentistry,[3] University of Toronto, Toronto, Ontario, Canada M5G 1G6

Received 10 April 1989/Accepted 12 June 1989

We have investigated the role of the p53 gene in oncogenesis in vivo by generating transgenic mice carrying murine p53 genomic fragments isolated from a mouse Friend erythroleukemia cell line or BALB/c mouse liver DNA. Elevated levels of p53 mRNA were detected in several tissues of two transgenic lines tested. Increased levels of p53 protein were also detected in most of the tissues analyzed by Western blotting (immunoblotting). Because both transgenes encoded p53 proteins that were antigenically distinct from wild-type p53, it was possible to demonstrate that overexpression of the p53 protein was mostly, if not entirely, due to the expression of the transgenes. Neoplasms developed in 20% of the transgenic mice, with a high incidence of lung adenocarcinomas, osteosarcomas, and lymphomas. Tissues such as ovaries that expressed the transgene at high levels were not at higher risk of malignant transformation than tissues expressing p53 protein at much lower levels. The long latent period and low penetrance suggest that overexpression of p53 alone is not sufficient to

Article | March 13 2006

Osteoblast differentiation and skeletal development are regulated by Mdm2–p53 signaling

Christopher J. Lengner, Heather A. Steinman, James Gagnon, Thomas W. Smith, Janet E. Henderson, Barbara E. Kream, Gary S. Stein, Jane B. Lian, Stephen N. Jones

+ Author and Article Information

Check for updates

J Cell Biol (2006) 172 (6): 909–921. | https://doi.org/10.1083/jcb.200508130 | **Article history**

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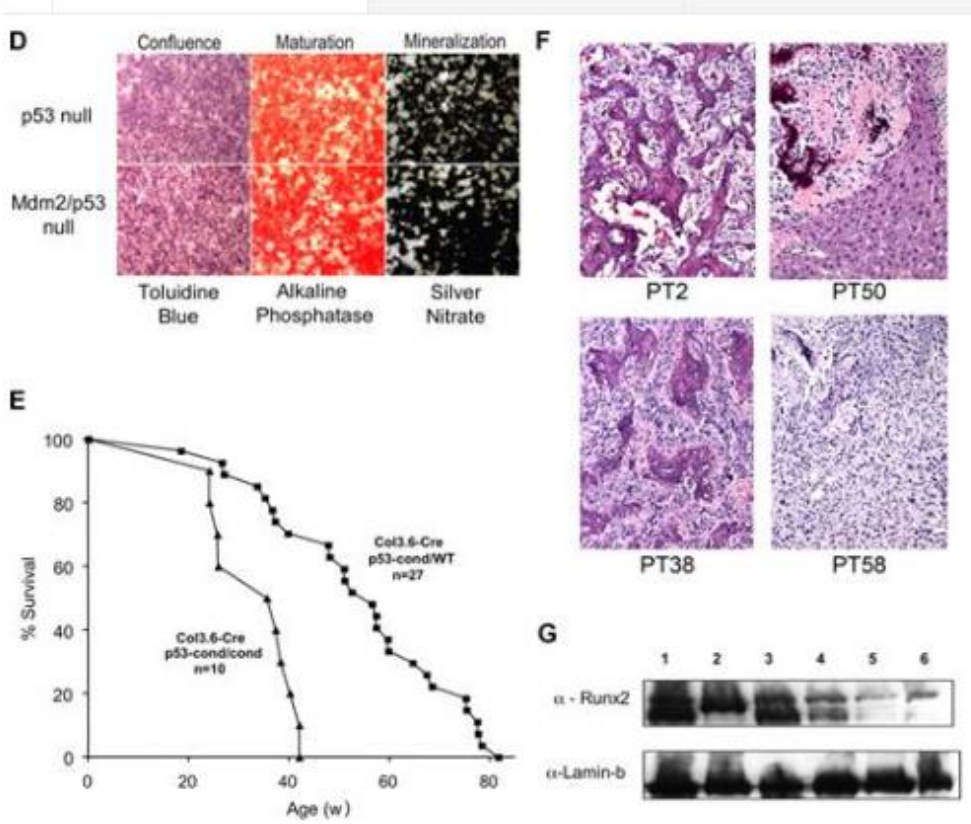
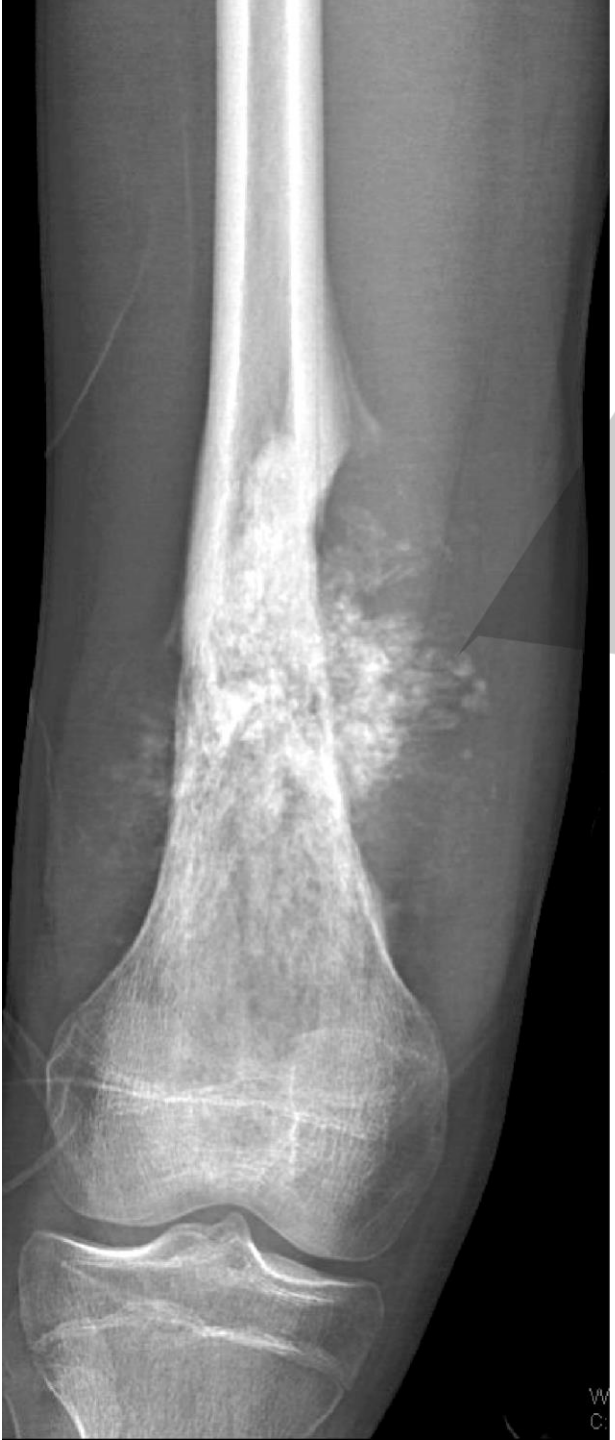
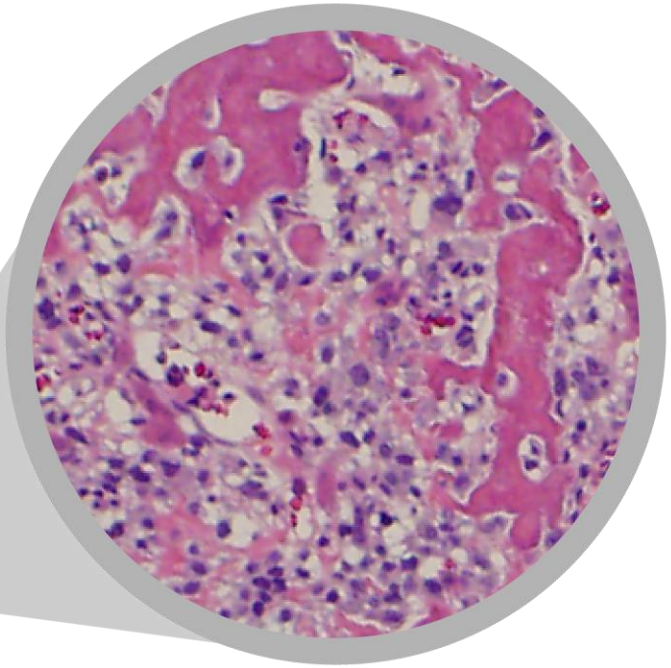
Mdm2 is required to negatively regulate p53 activity at the peri-implantation stage of early mouse development. However, the absolute requirement for Mdm2 throughout embryogenesis and in organogenesis is unknown. To explore Mdm2–p53 signaling in

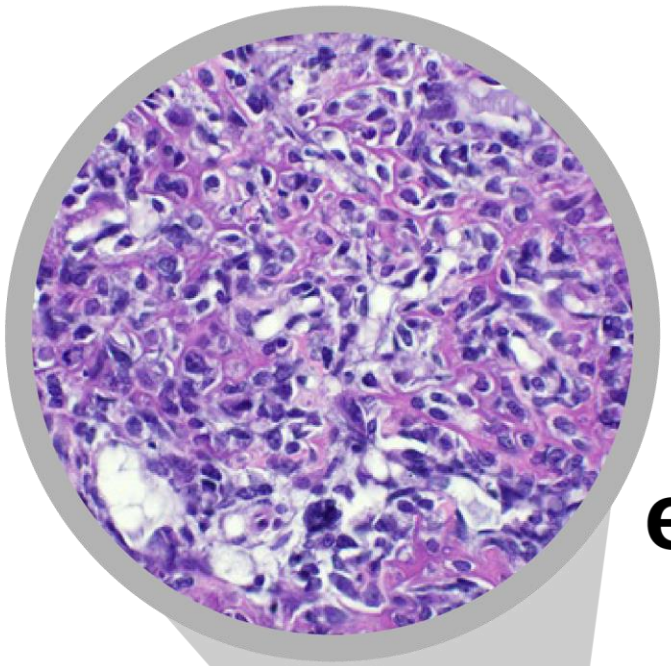


2006 1st appropriate context



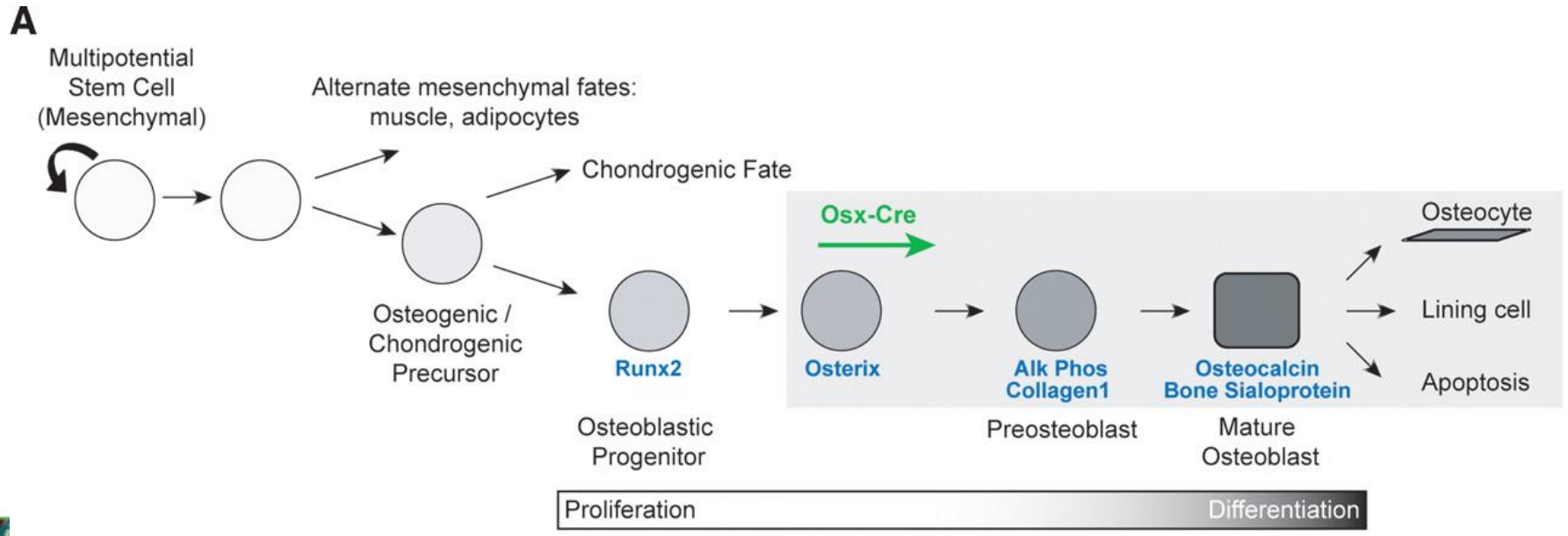


TP53 -/-
observed



Trp53 -/-
mouse
experiment

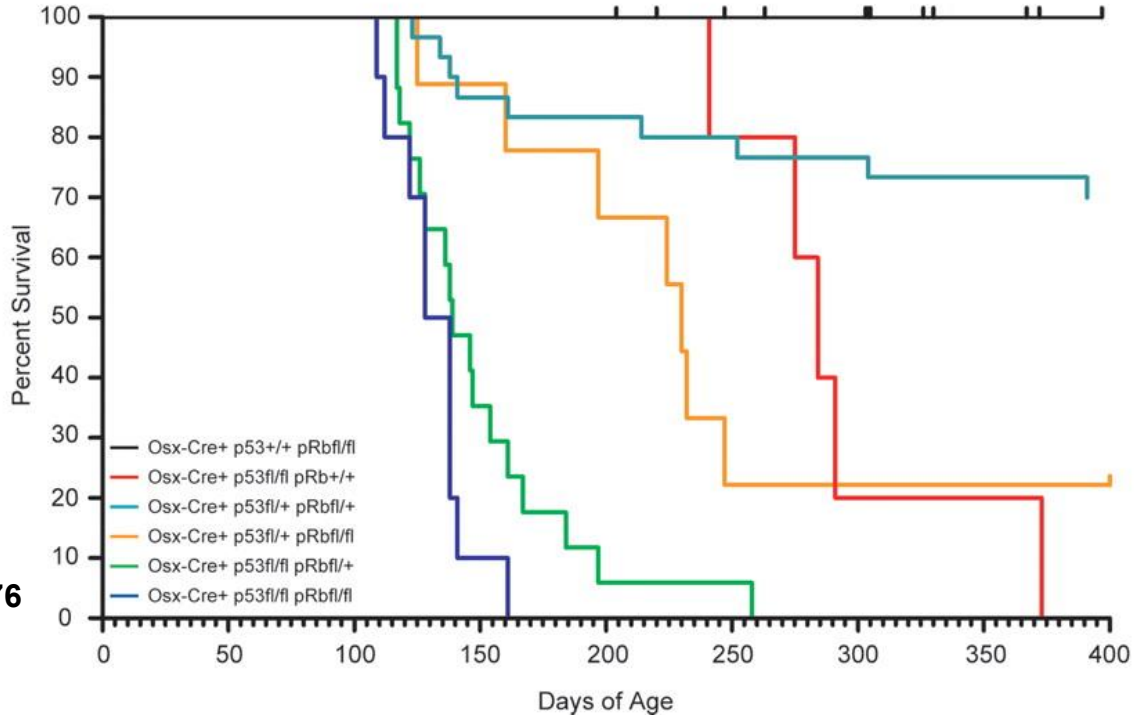
2008

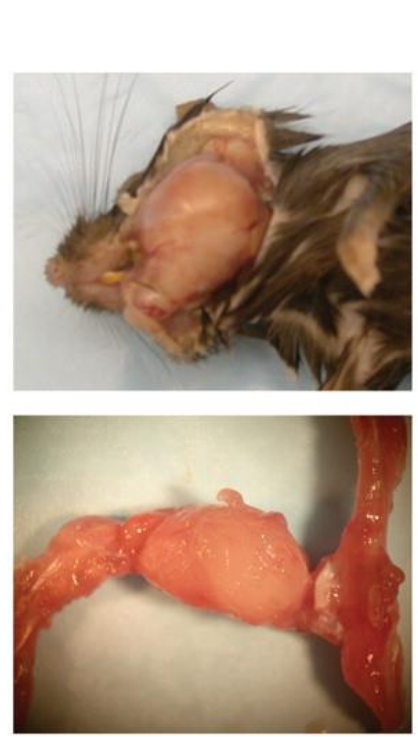


Conditional mouse osteosarcoma, dependent on p53 loss and potentiated by loss of Rb, mimics the human disease

Carl R. Walkley[1,8], Rameez Qudsi[1], Vijay G. Sankaran[1], Jennifer A. Perry[1], Monica Gostissa[2], Sanford I. Roth[3], Stephen J. Rodda[4], Erin Snay[5], Patricia Dunning[6], Frederic H. Fahey[5], Frederick W. Alt[2], Andrew P. McMahon[4], and Stuart H. Orkin[1,7,9]

Carl R. Walkley et al. Genes Dev. 2008;22:1662-1676





PNAS | NOW READING:

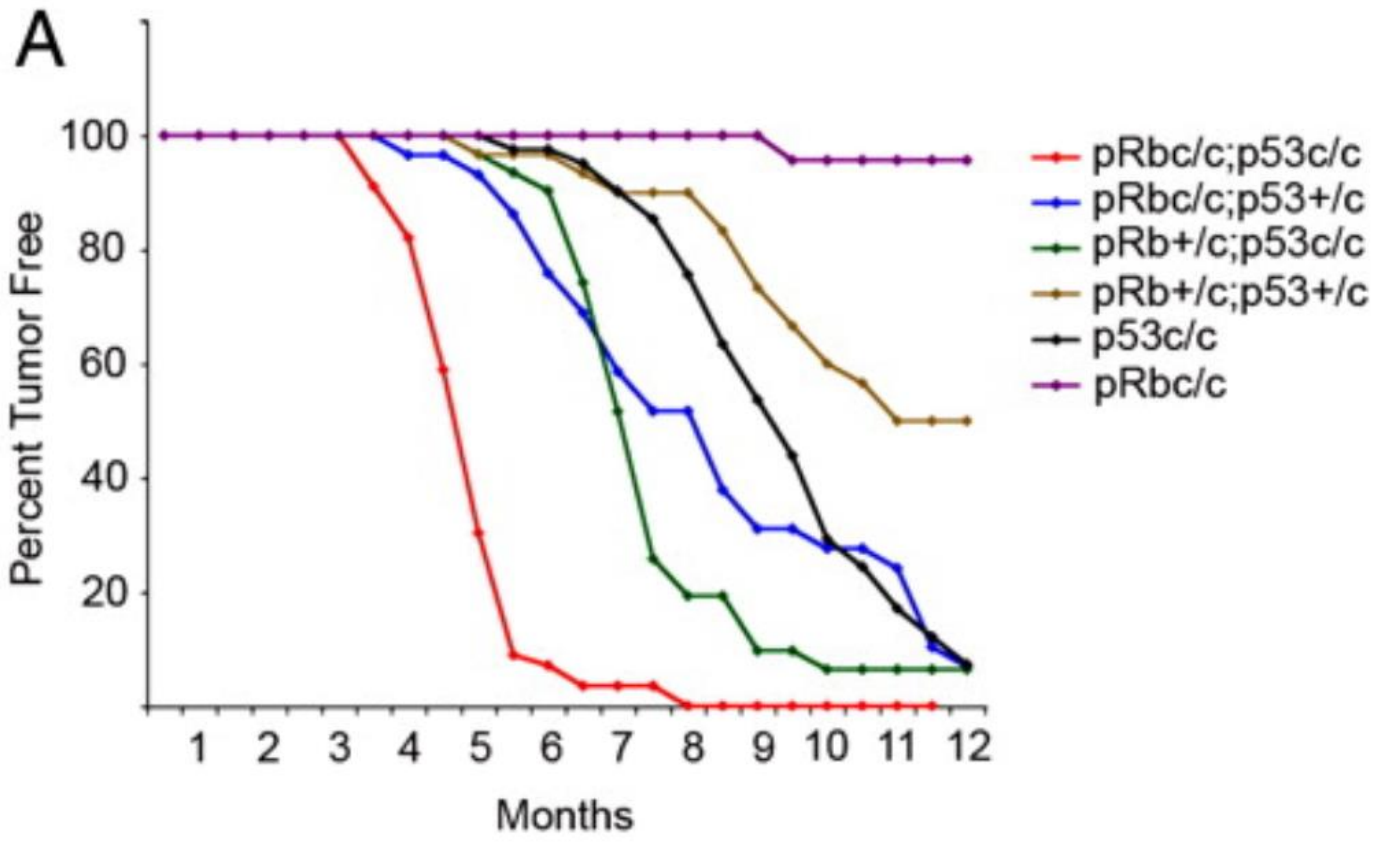
Metastatic osteosarcoma induced by inactivation of *Rb* and *p53* in the osteoblast lineage

Seth D. Berman, Eliezer Calo, Allison S. Landman, Paul S. Danielian, Emily S. Miller, Julie C. West, Borel Djouedjong Fonhoue, Alicia Caron, Roderick Bronson, Mary L. Bouxsein, Siddhartha Mukherjee, and Jacqueline A. Lees

August 19, 2008
105 (33) 11851-11856

2008

Fig. 1.



May we conclude that osteosarcomagenesis is driven genetically by *Trp53* and *Rb1* loss?

What about *RECQL4*?

What about the many prior models?

bone-targeting radio-isotopes?
bone injected chemical carcinogens?
osteosarcomas following ionizing radiation?

nature genetics

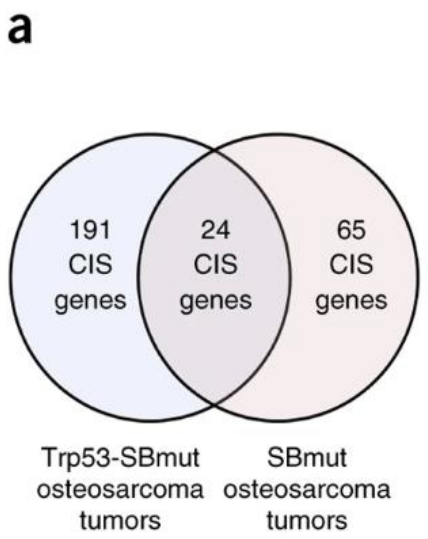
Article | Published: 11 May 2015

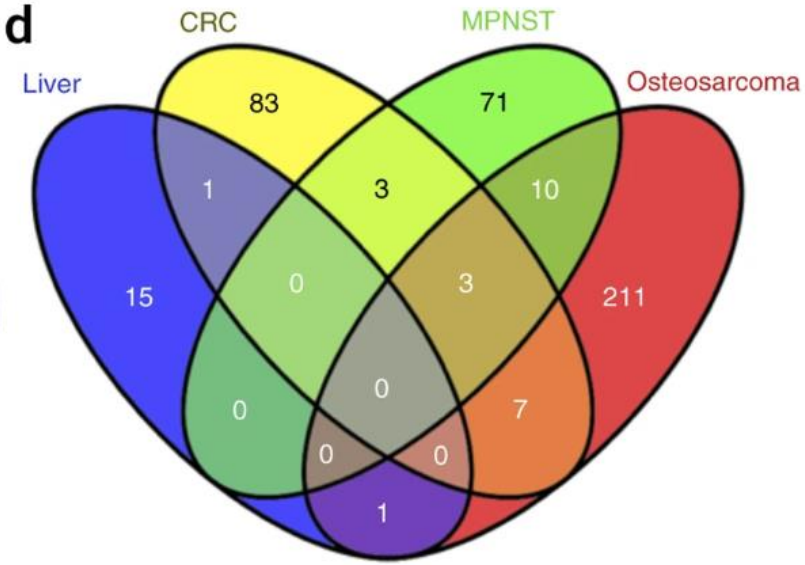
A *Sleeping Beauty* forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis

Branden S Moriarity, George M Otto, Eric P Rahrmann, Susan K Rathe, Natalie K Wolf, Madison T Weg, Luke A Manlove, Rebecca S LaRue, Nuri A Temiz, Sam D Molyneux, Kwangmin Choi, Kevin J Holly, Aaron L Sarver, Milcah C Scott, Colleen L Forster, Jaime F Modiano, Chand Khanna, Stephen M Hewitt, Rama Khokha, Yi Yang, Richard Gorlick, Michael A Dyer & David A Largaespada

Nature Genetics **47**, 615–624 (2015) | Cite this article

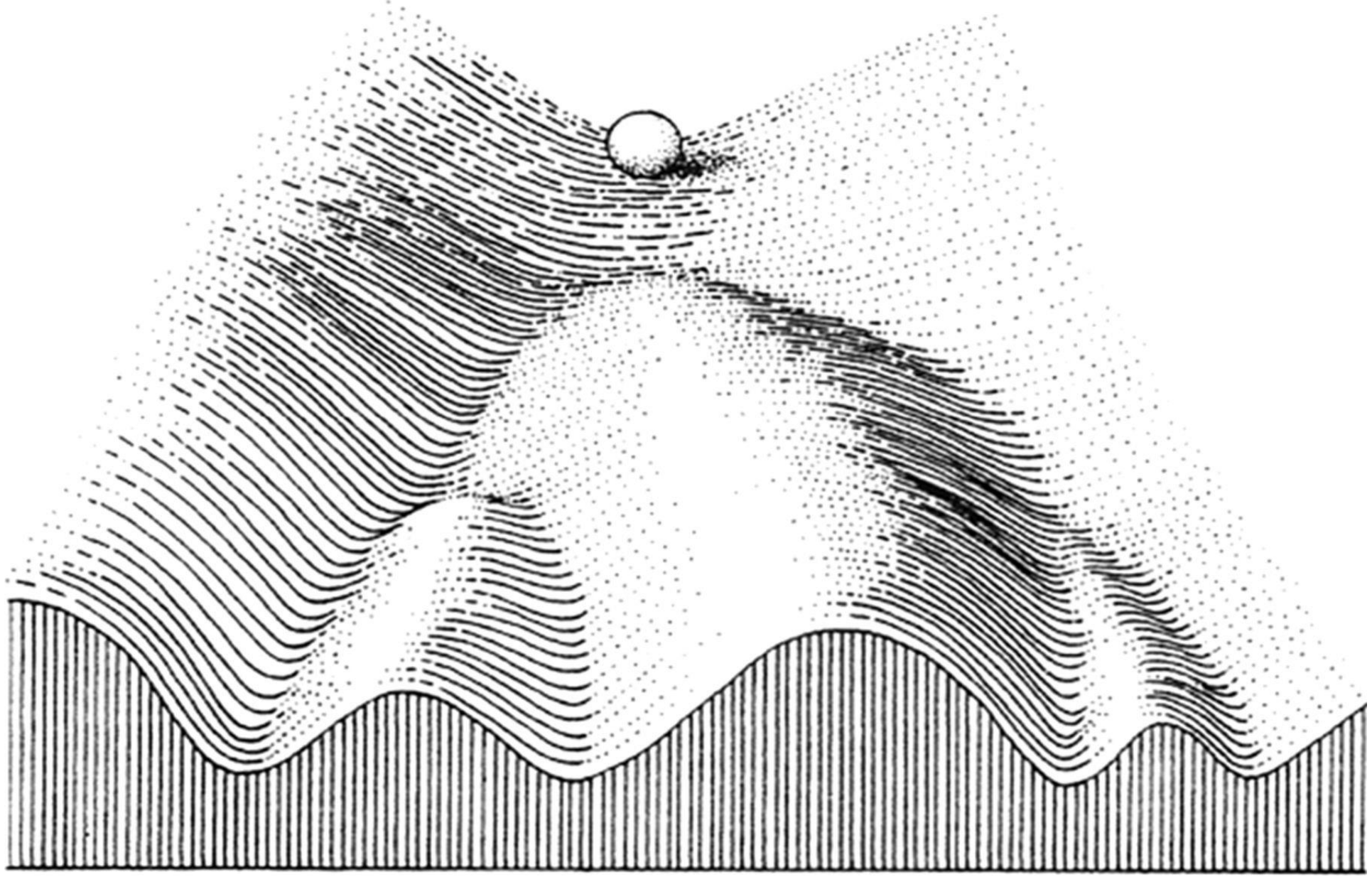
2015



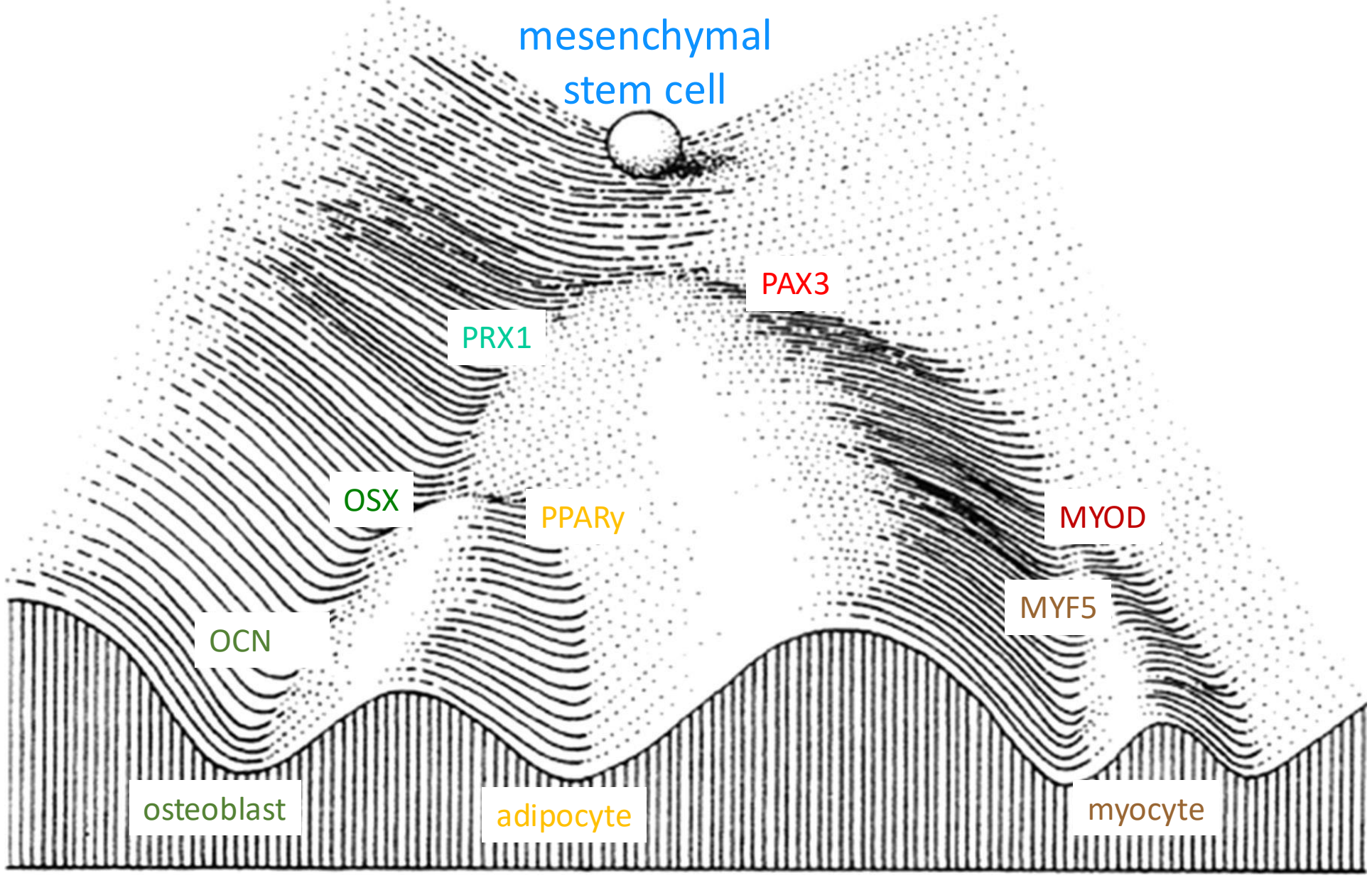


Trp53 and *Rb1* loss

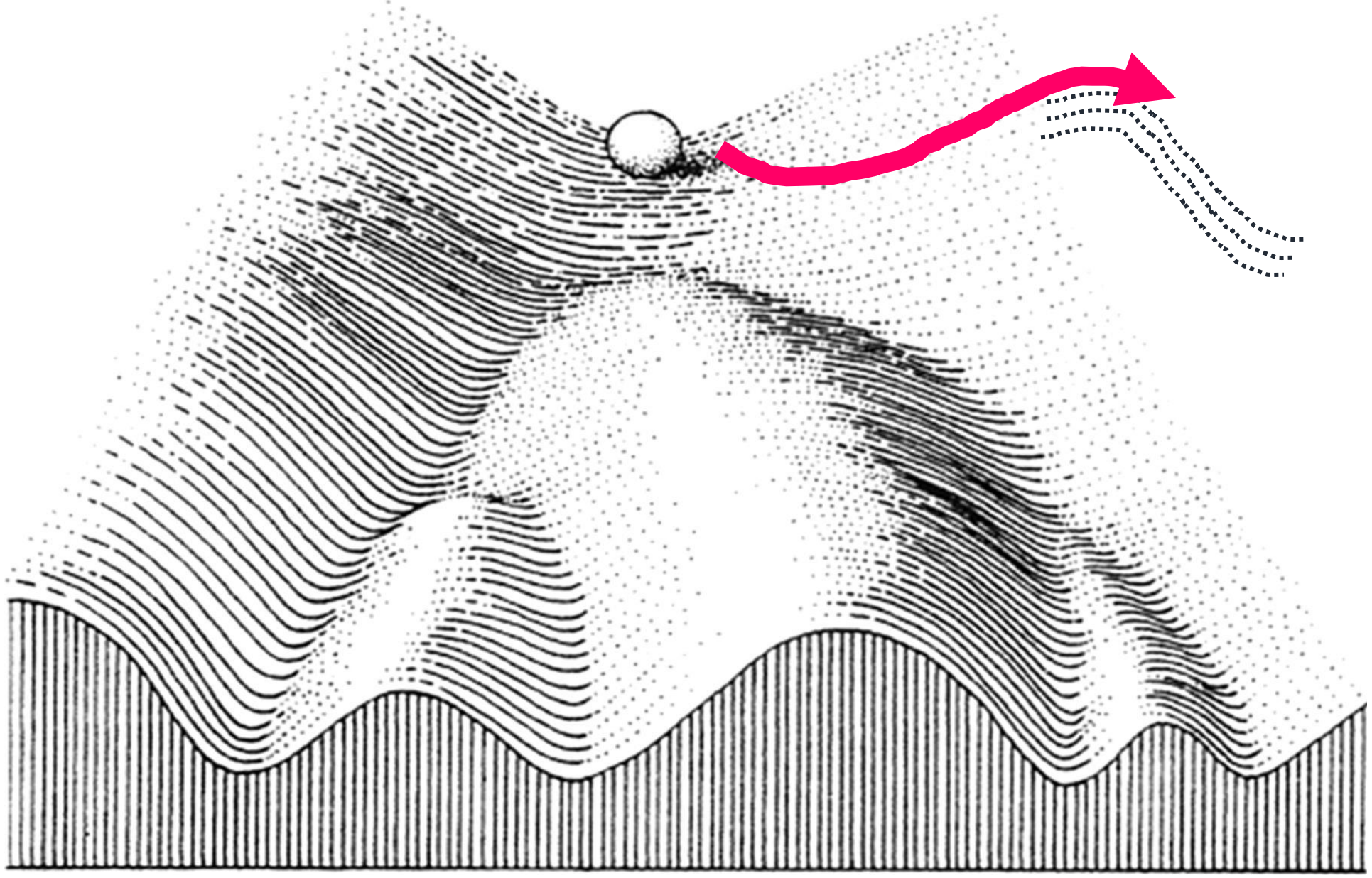
drive?
permit?



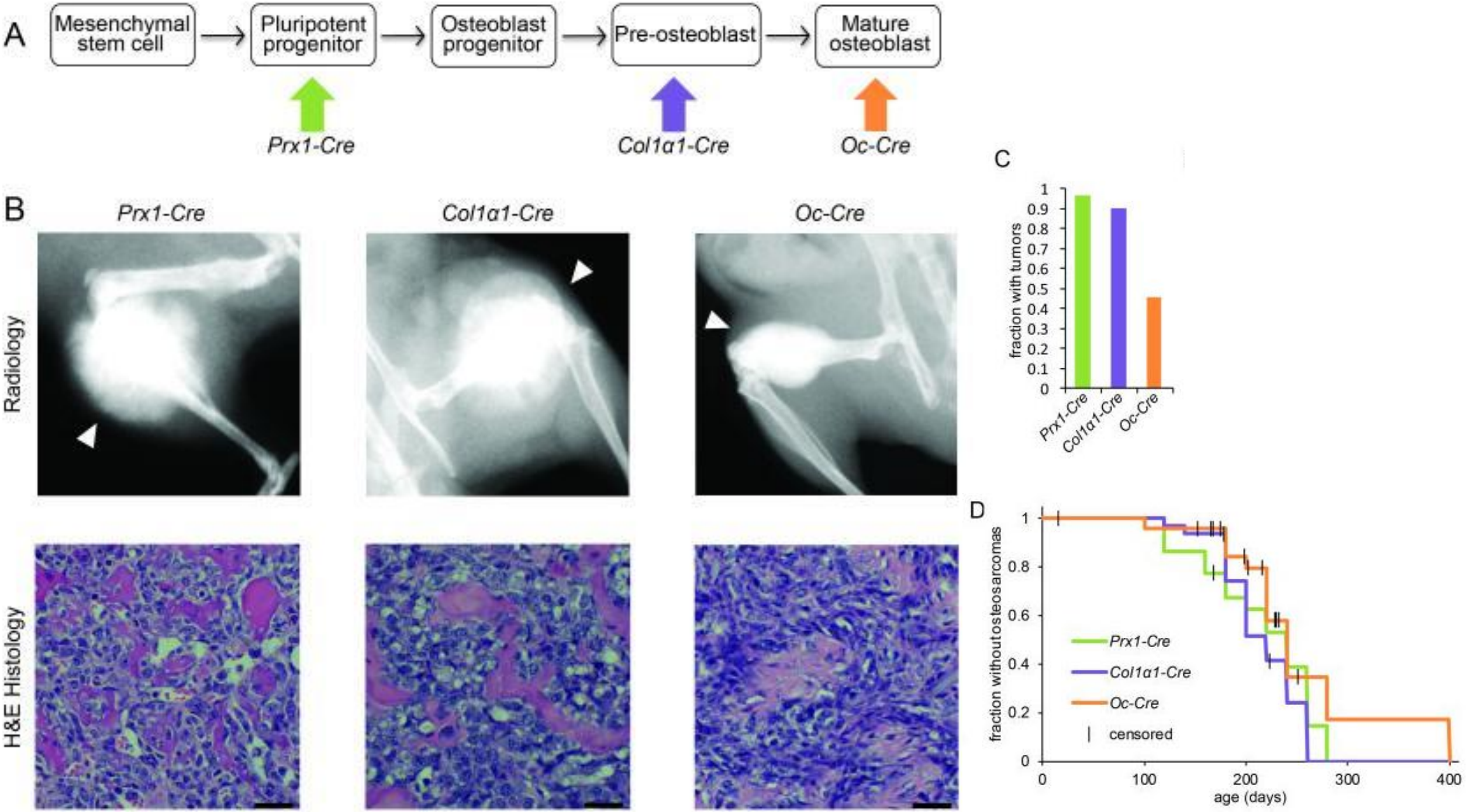
Waddington’s epigenetic landscape

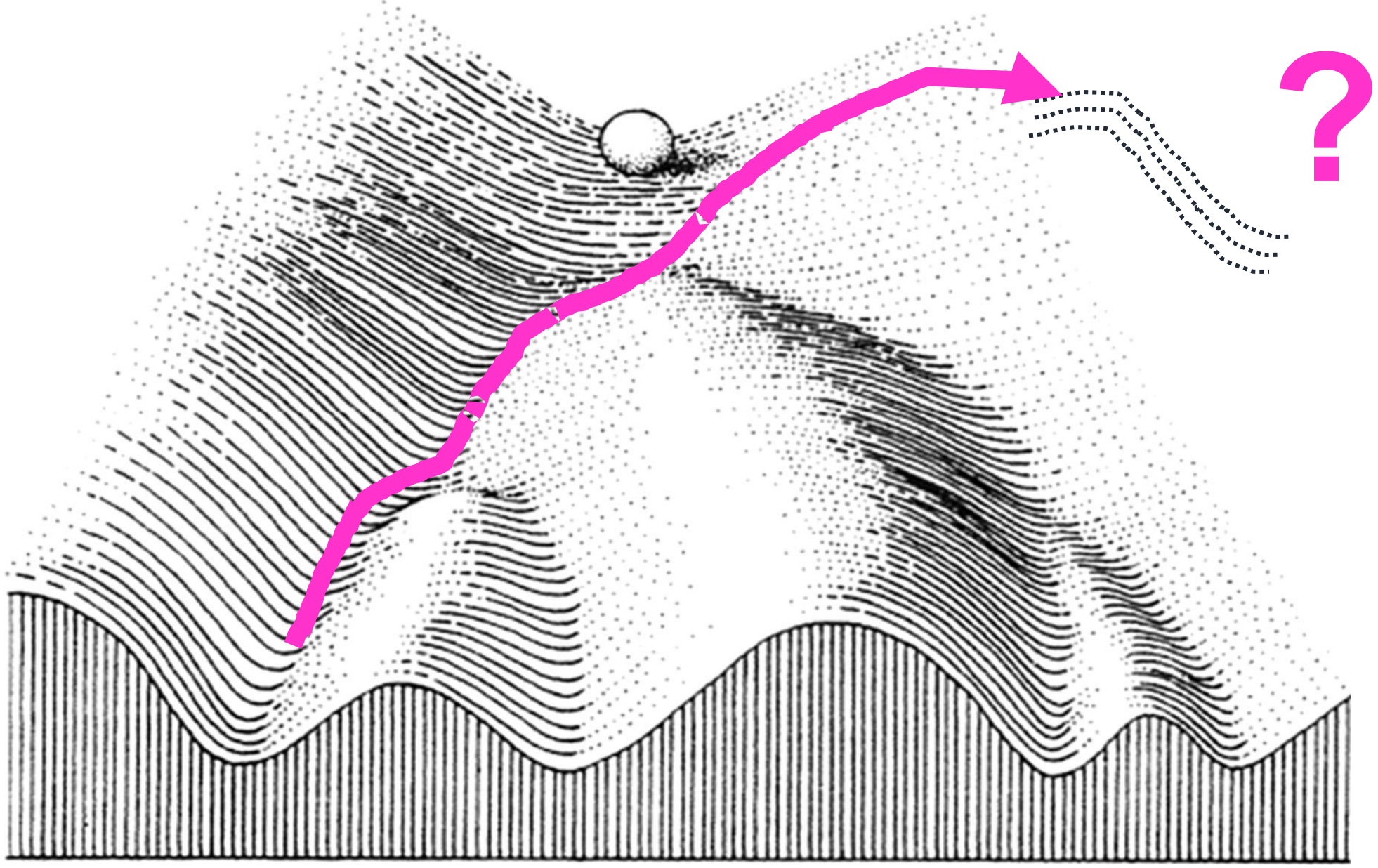


mesenchymal differentiation

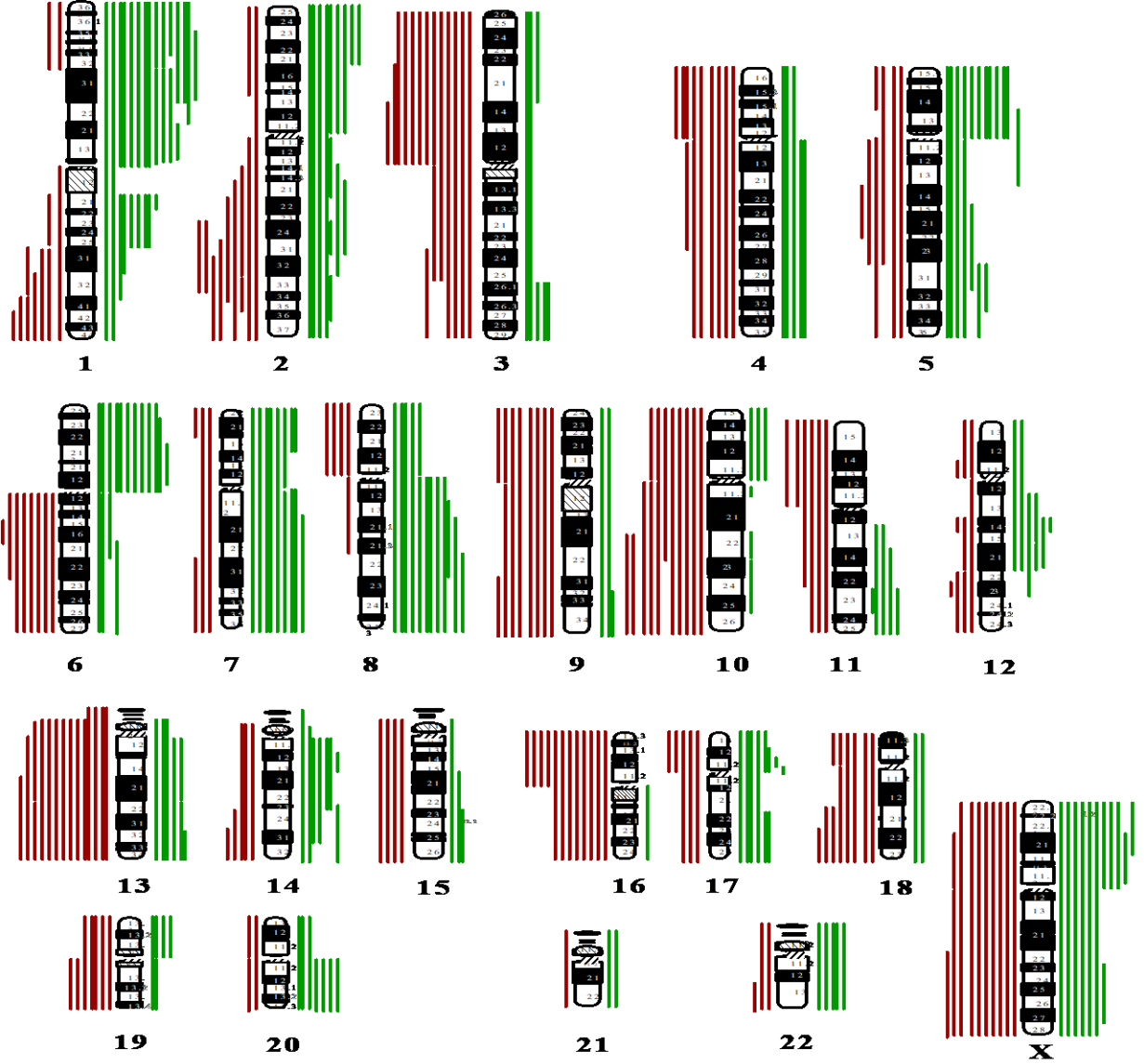


Sarcomagenesis

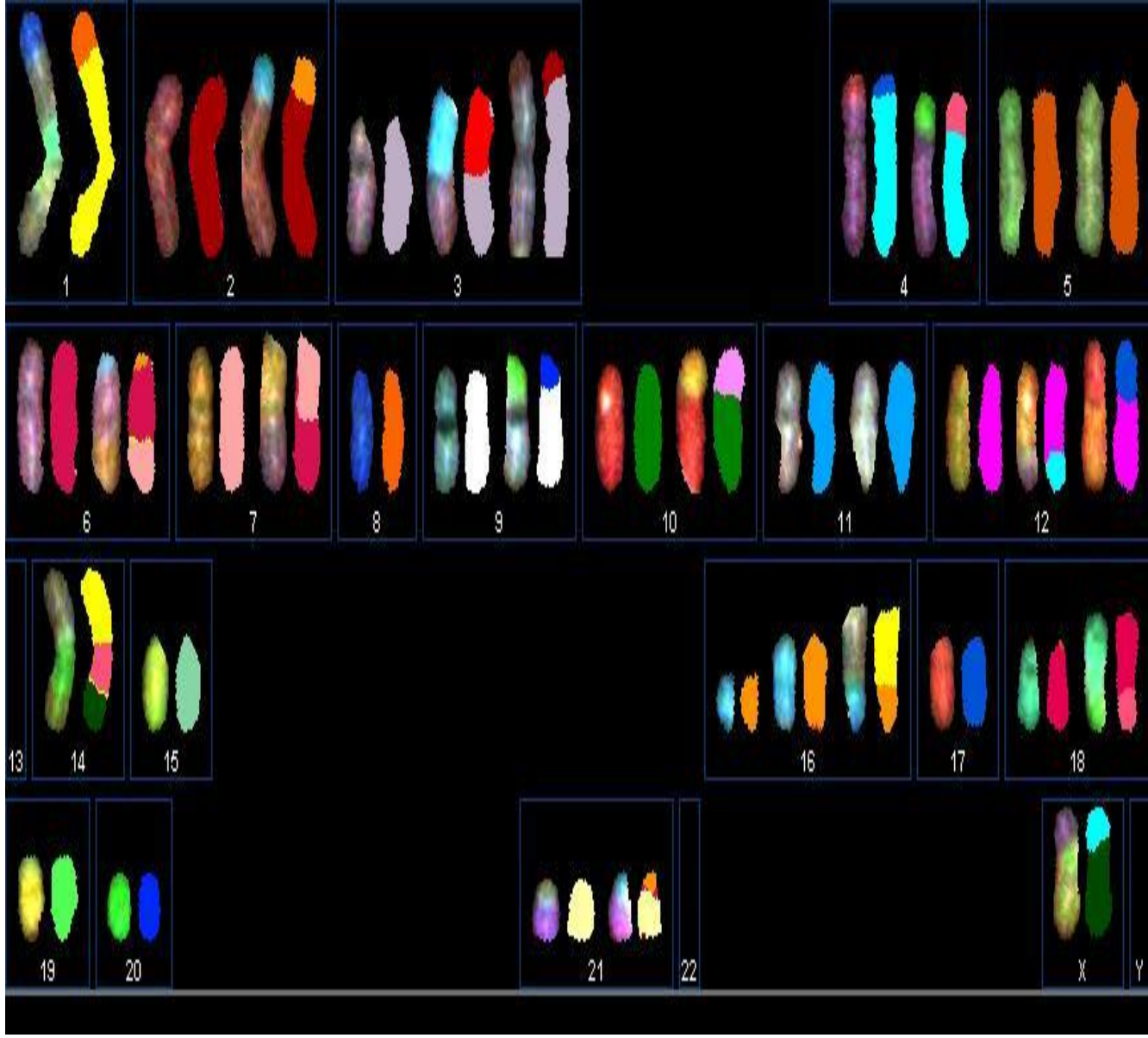

A
Mesenchymal stem cell
Pluripotent progenitor
Osteoblast progenitor
Pre-osteoblast
Mature osteoblast
Prx1-Cre
Col1α1-Cre
Oc-Cre
B
Prx1-Cre
Col1α1-Cre
Oc-Cre
Radiology
H&E Histology
C
fraction with tumors
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Prx1-Cre
Col1α1-Cre
Oc-Cre
D
fraction without osteosarcomas
1
0.8
0.6
0.4
0.2
0
Prx1-Cre
Col1α1-Cre
Oc-Cre
censored
0
100
200
300
400
age (days)



osteosarcomagenesis



- CGH array from 30 osteosarcomas



- Spectral karyotyping of an osteosarcoma