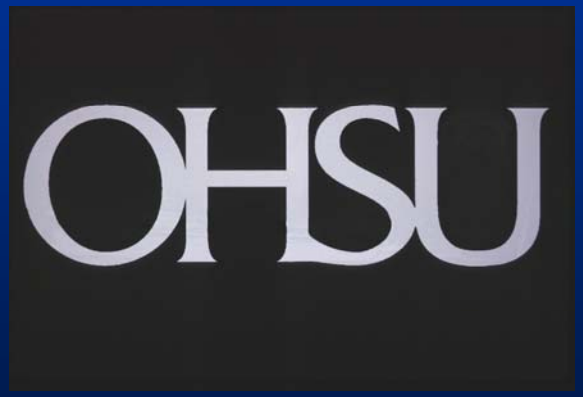
Fanconi Anemia: Diagnosis and Treatment

Markus Grompe, MD

Oregon Health & Science University



What this talk will cover

- History (brief)
- Clinical presentation
- Cellular phenotype
- Genetics/Biochemical function
- Pathogenesis
- Treatment
- Search for new therapies

Fanconi anemia history

- Named after the Swiss Pediatrician Guido Fanconi (1892-1979)
- Guido Fanconi attended the University of Zürich. Before graduating in 1918 he trained in Lausanne, Munich, Zürich, and Bern.
- His main field of interest was in paediatrics, and in 1929 he became director of the Children's Hospital and professor of paediatrics at the University of Zurich
- His name is attached to 17 conditions.

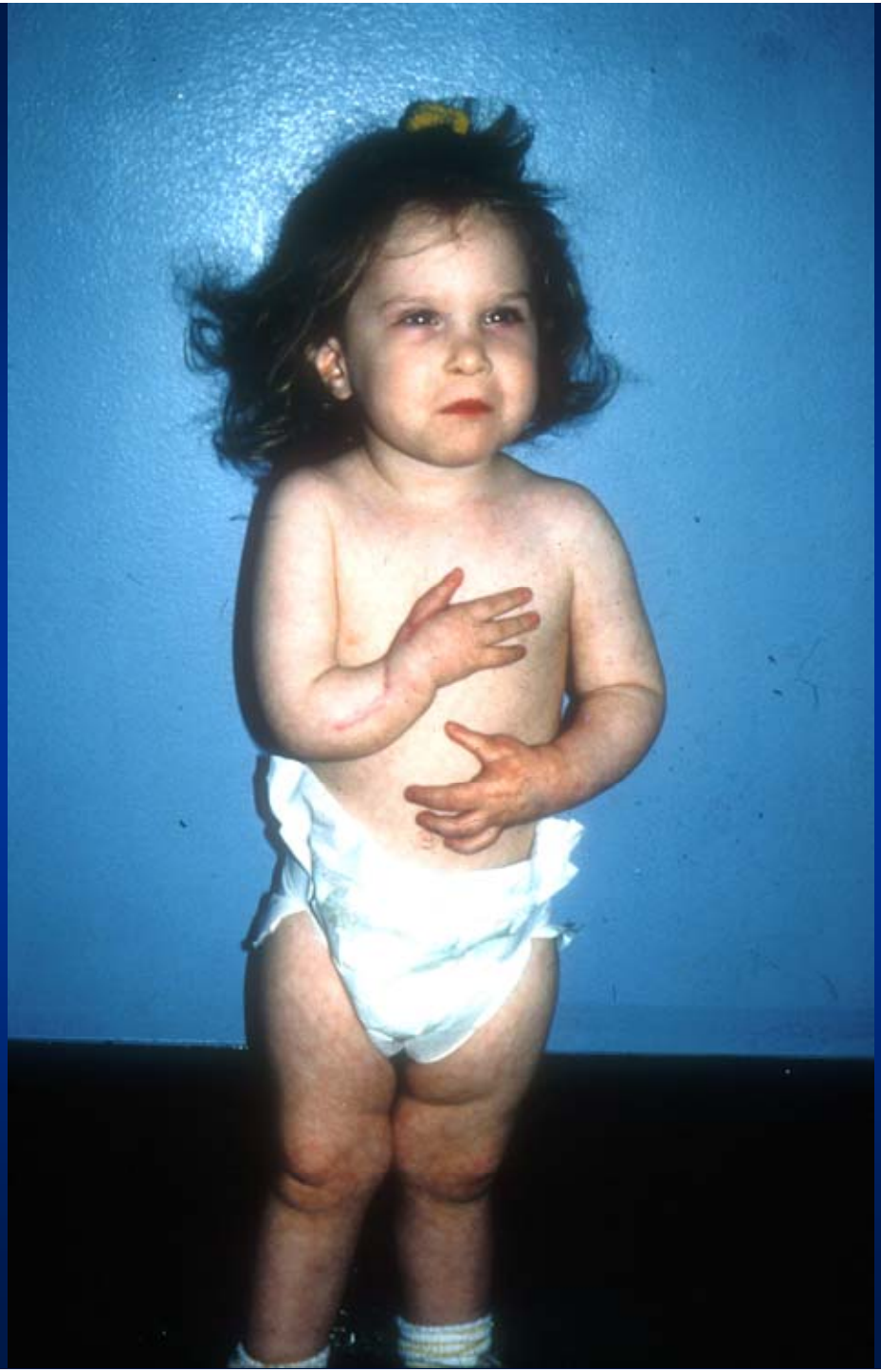
Fanconi Anemia

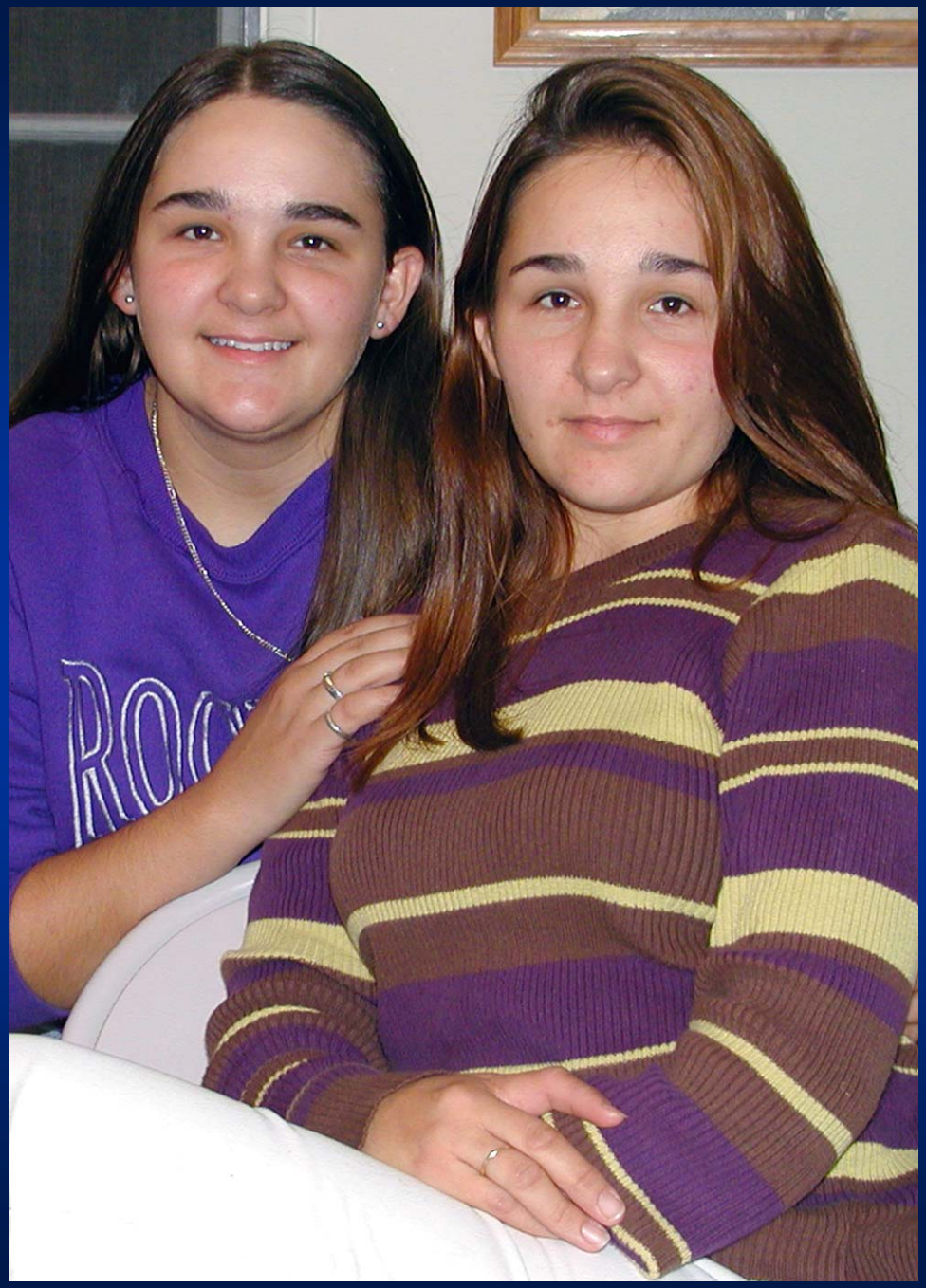
- Two major initial presentations
  - Birth defects
  - Anemia
- Typical birth defects
  - Diagnosis early in life, often before anemia
- Anemia
  - Patients usually have no/minor birth defects
  - Later presentation

Percentage of birth defects

Abnormality	Percent in all FA patients
Radial ray defect	49
Other skeletal	22
Renal and urinary tract	34
Male genital	20
Gastrointestinal	14
Heart defect	13
Hearing loss	11
CNS deformity	8

Image courtesy
Dr Blanche Alter





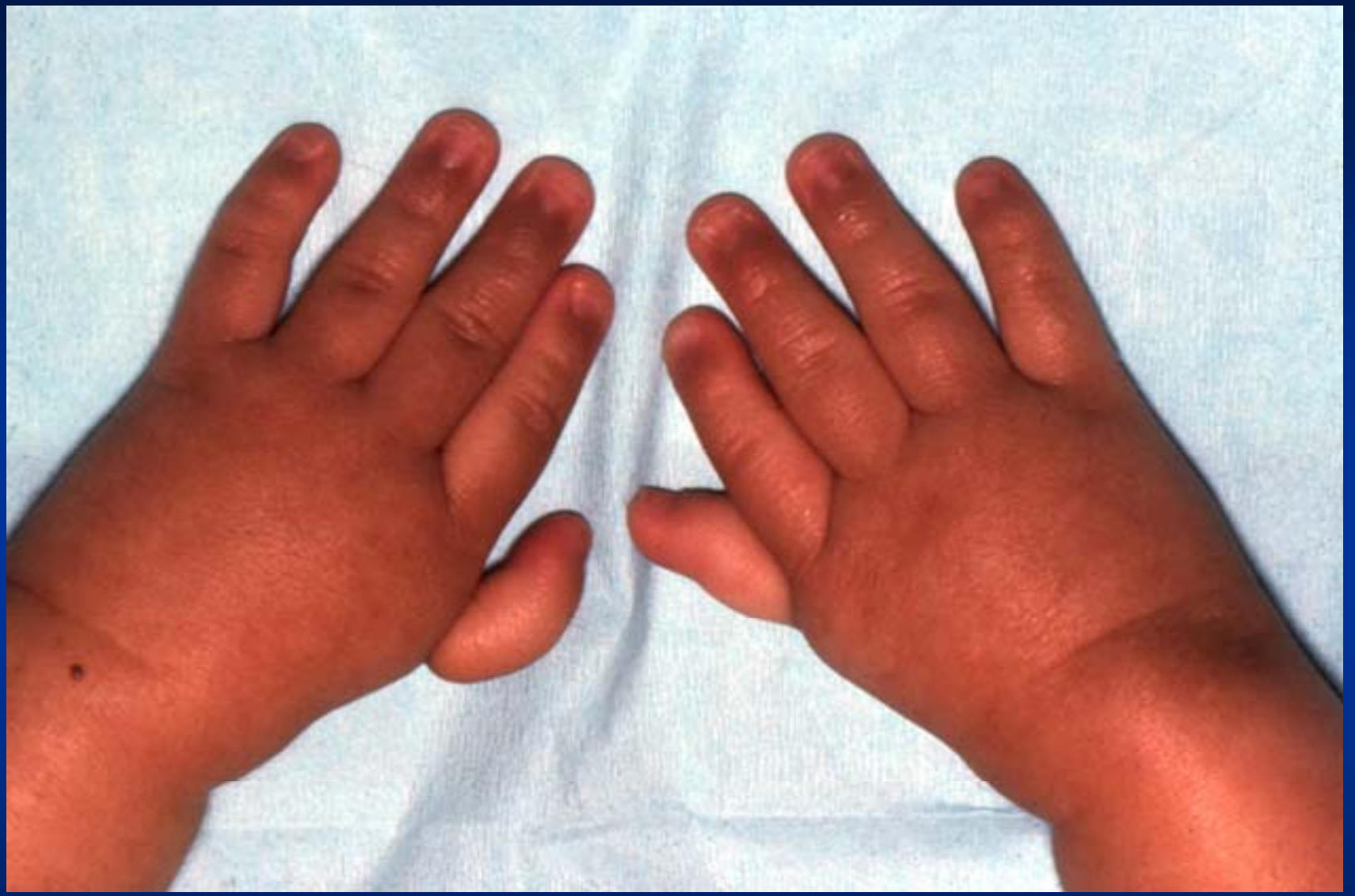
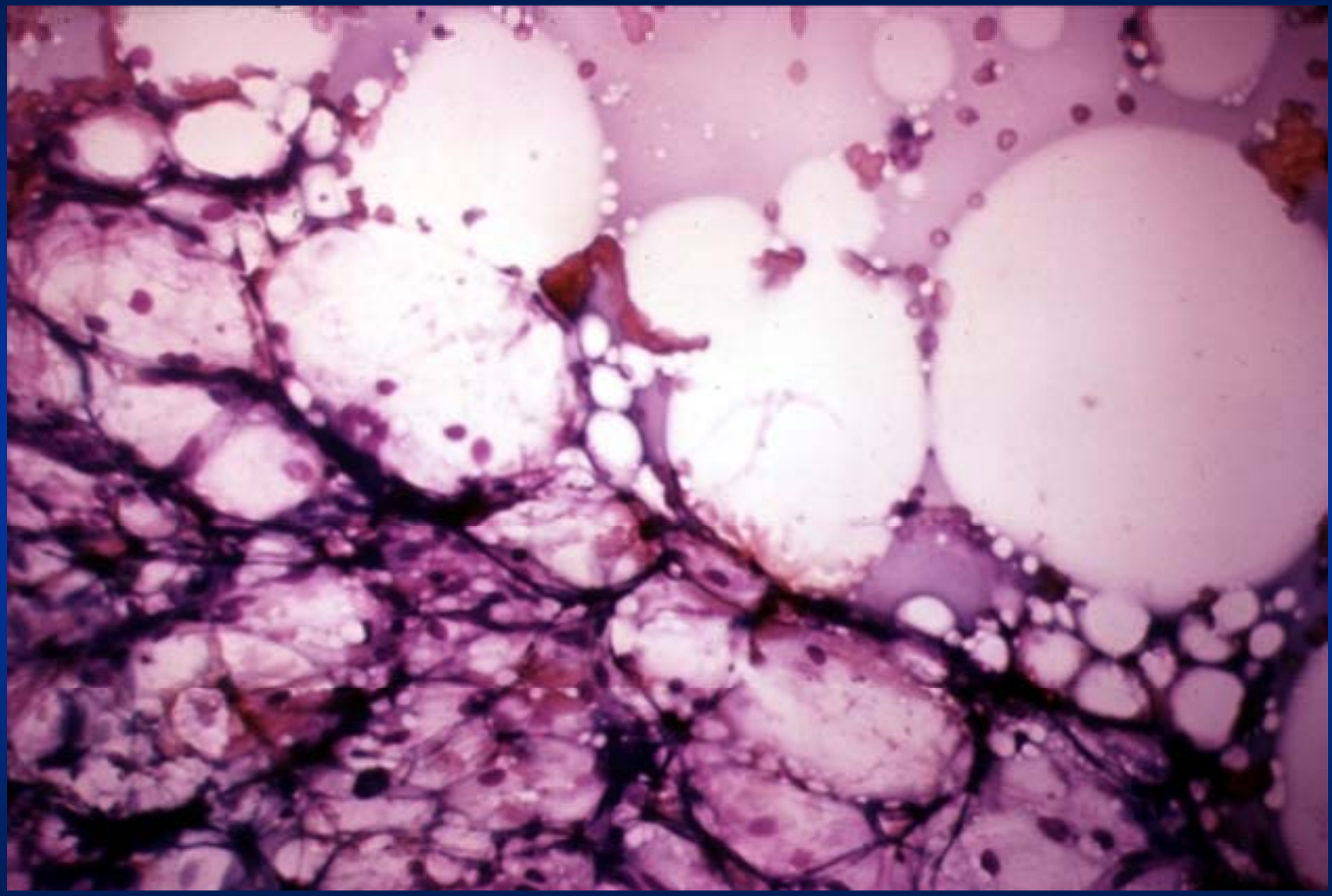


Image courtesy
Dr Blanche Alter

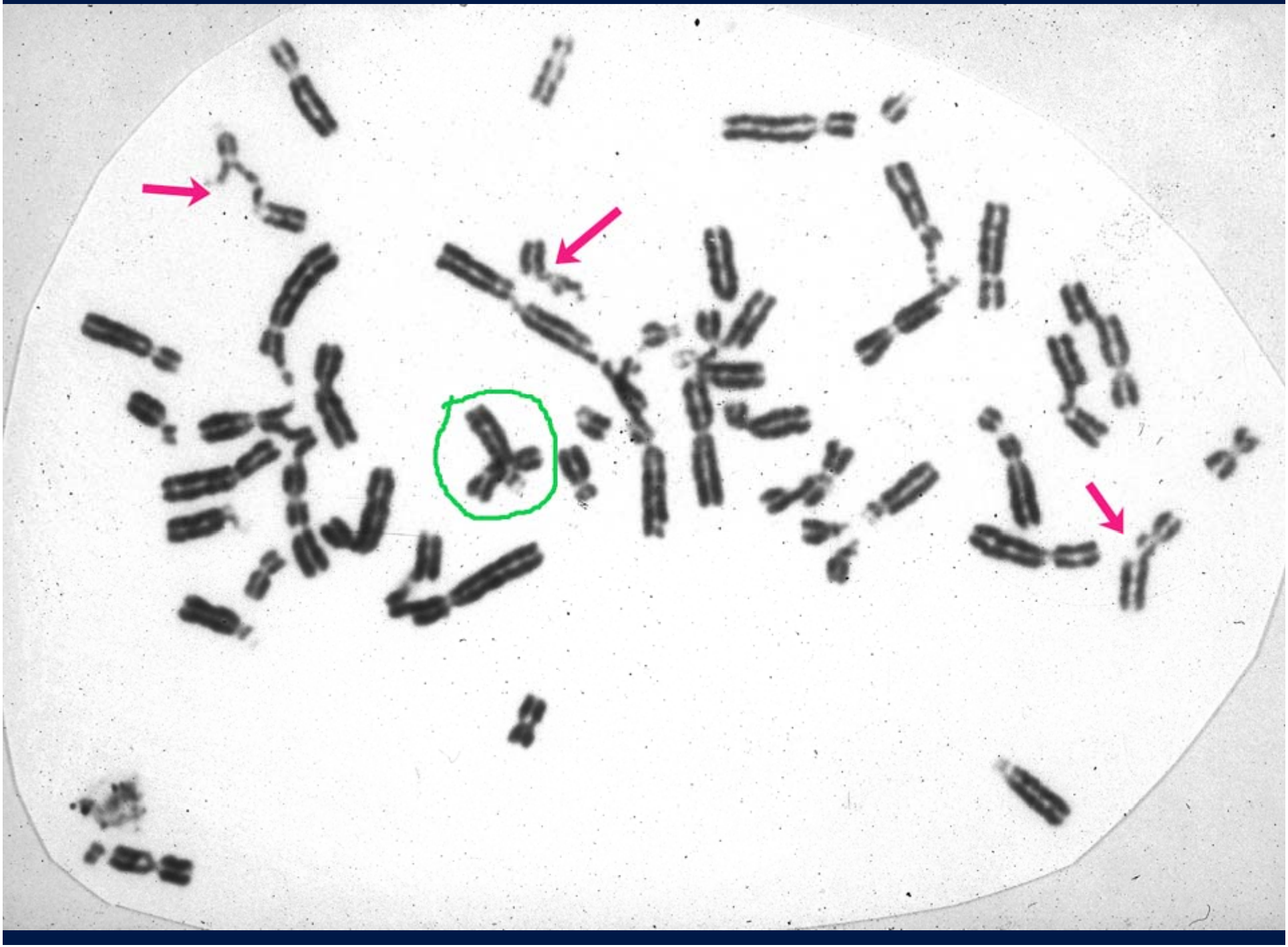
Anemia

- Pancytopenia/progressive bone marrow failure
  - Empty marrow on biopsy
- Initial presentation can be any blood lineage
- Age of onset: 2 -12 years
  - Rarely, if ever, presents in newborn period
- Red blood cell anemia
  - macrocytic
- Neutropenia
- Thrombocytopenia



Fanconi Anemia: Cellular phenotype

- Hypersensitivity to interstrand DNA cross-linking agents
  - Chromosome breakage, radial formation, apoptosis
  - Mitomycin C, diepoxybutane, cytoxan, psoralen + UVA
- Abnormal "G2/M" phase of the cell cycle
  - spontaneously prolonged "G2/M"
  - "G2/M" accumulation after crosslinker treatment
- ? Oxygen sensitivity
- ? Sensitivity to inhibitory cytokines (γ-IFN, TNF-α)



Chromosome breakage read-out

ML#	Ref Lab	Clastogen	Conc	Total # of Cells with the Following Breaks per Cell									#	%	Total
	#		ng/ml	0	1	2	3	4	5	6	7	>8	Radials	Radials	# of Cells
8823	GM02361	None	0	40	8	1	1	0	0	0	0	0	0	0%	50
	p.13	MMC	15	4	1	2	6	5	0	0	0	3	29	58%	50
		DEB	150	7	1	0	5	2	1	1	0	3	30	60%	50

The Fifteen Fanconi Anemia Genes

Gene	FA patients, estimated, %	Chromosome location	Protein product, kD
A	60%	16q24.3	163
B	2%	Xp22.31	95
C	10%	9q22.3	63
D1/BRCA2	4%	13q12.3	380
D2	4%	3p25.3	155
E	10%	6p21-22	60
F	rare	11p15	42
G	10%	9p13	68
I	rare	15q26	150
J/BRIP1	rare	17q23.2	130
L	rare	2p16.1	52
M	rare	14q21.2	250
N/PALB2	rare	16p12	130
O/RAD51C	rare	17q25.1	42
P/SLX4	rare	16p13.3	200

The Fifteen Fanconi Anemia Genes

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A	60%	16q24.3	163
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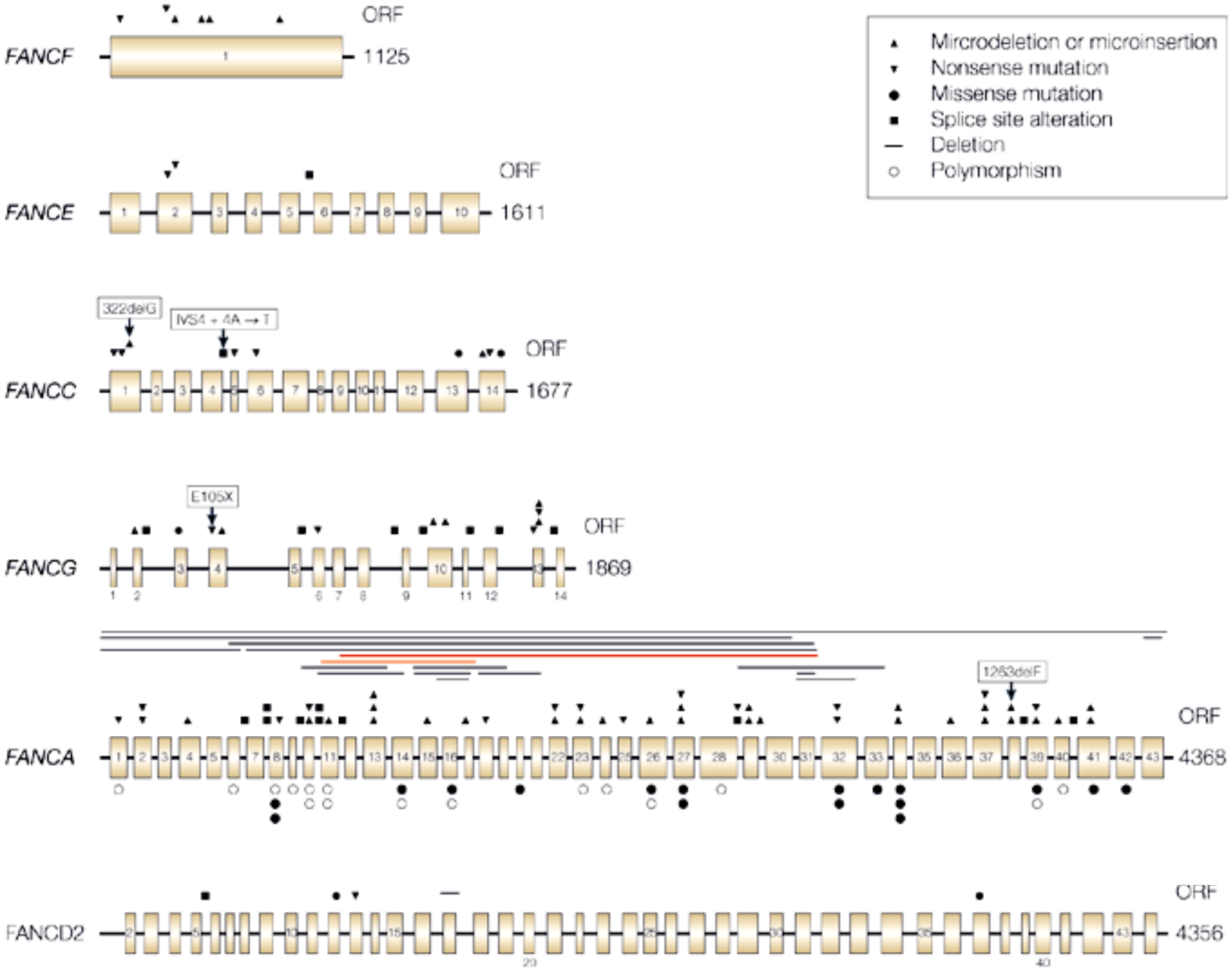
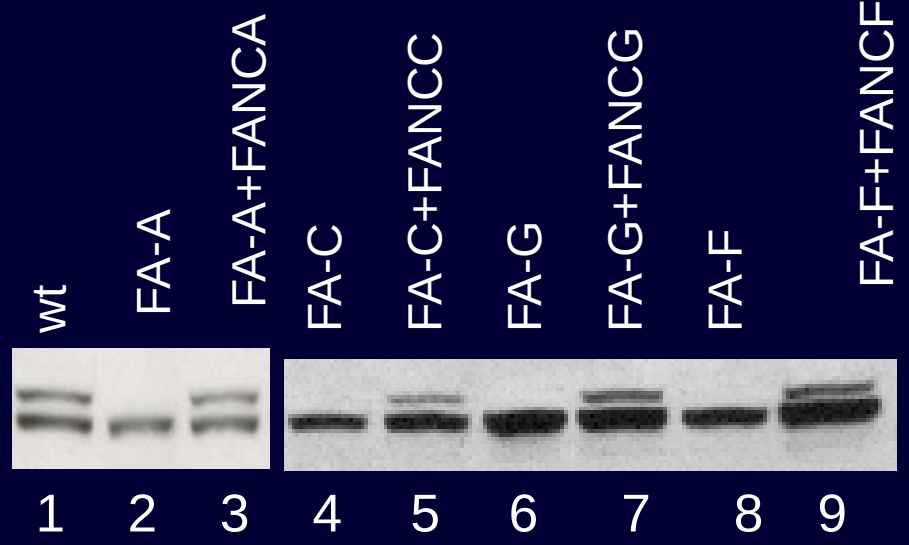

Mircrodeletion or microinsertion
Nonsense mutation
Missense mutation
Splice site alteration
Deletion
Polymorphism
FANCF
ORF
1125
FANCE
ORF
1611
322delG
IVS4 + 4A → T
FANCC
ORF
1677
E105X
FANCG
ORF
1869
1283delF
FANCA
ORF
4368
FANCD2
ORF
4356

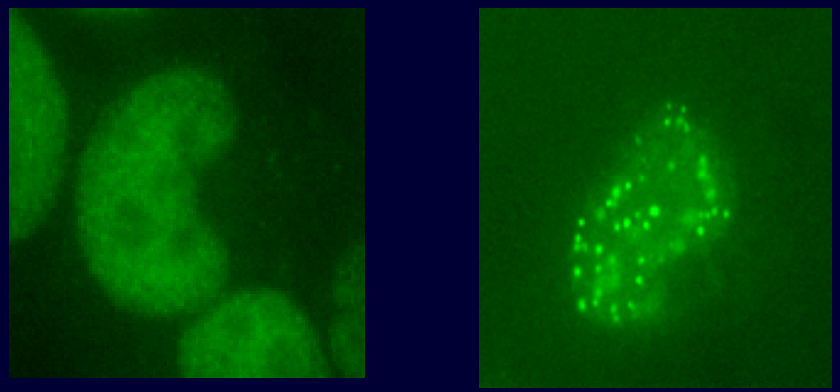
FANCD2 Monoubiquitination is a Critical Event in the FA pathway

Blot- anti-FANCD2

(monoubiquitinated)
FANCD2-L
FANCD2-S

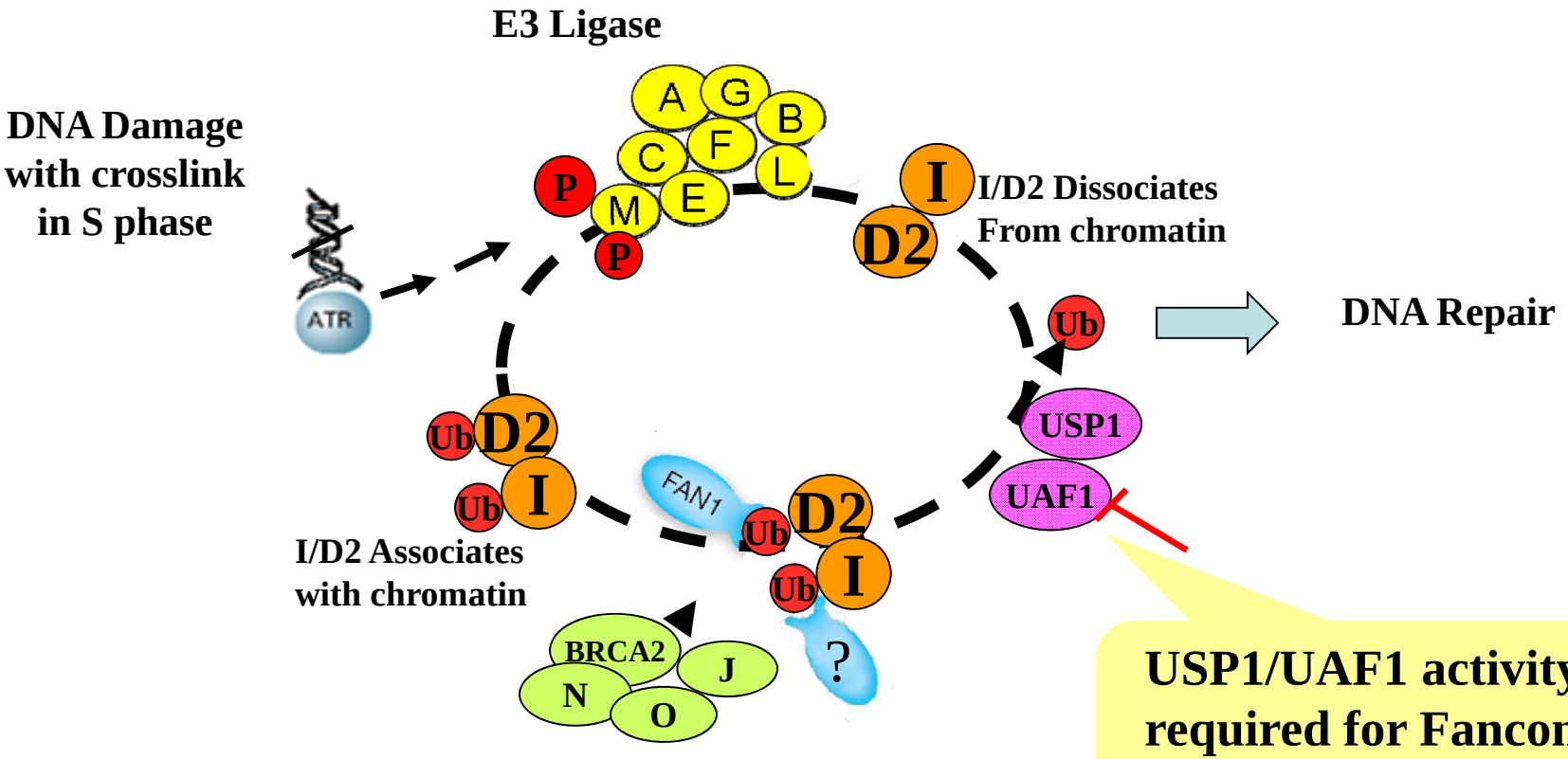


IF-anti-FANCD2



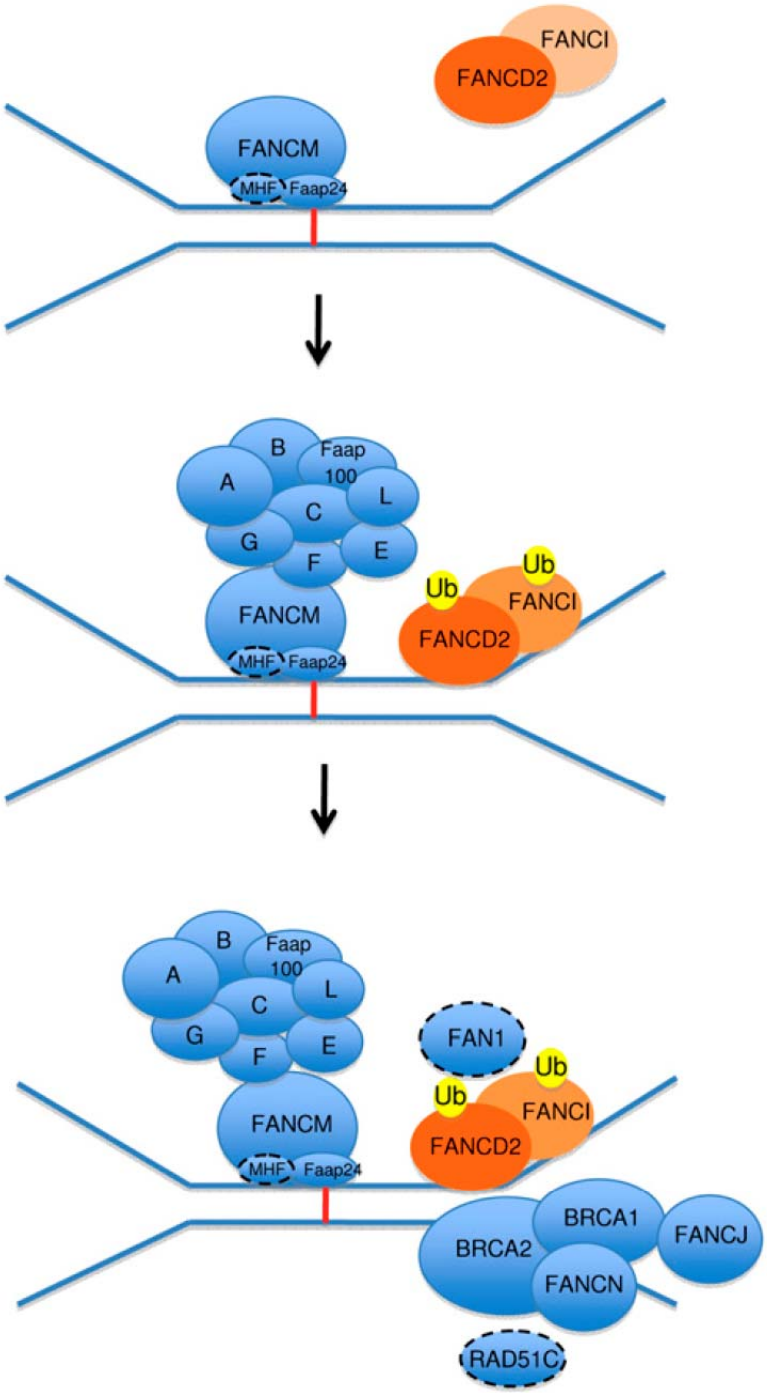
(mutant) (corrected)

The Fifteen FA proteins regulate DNA crosslink repair during S phase



Moldovan and D'Andrea,
Ann Rev Genetics, 2009

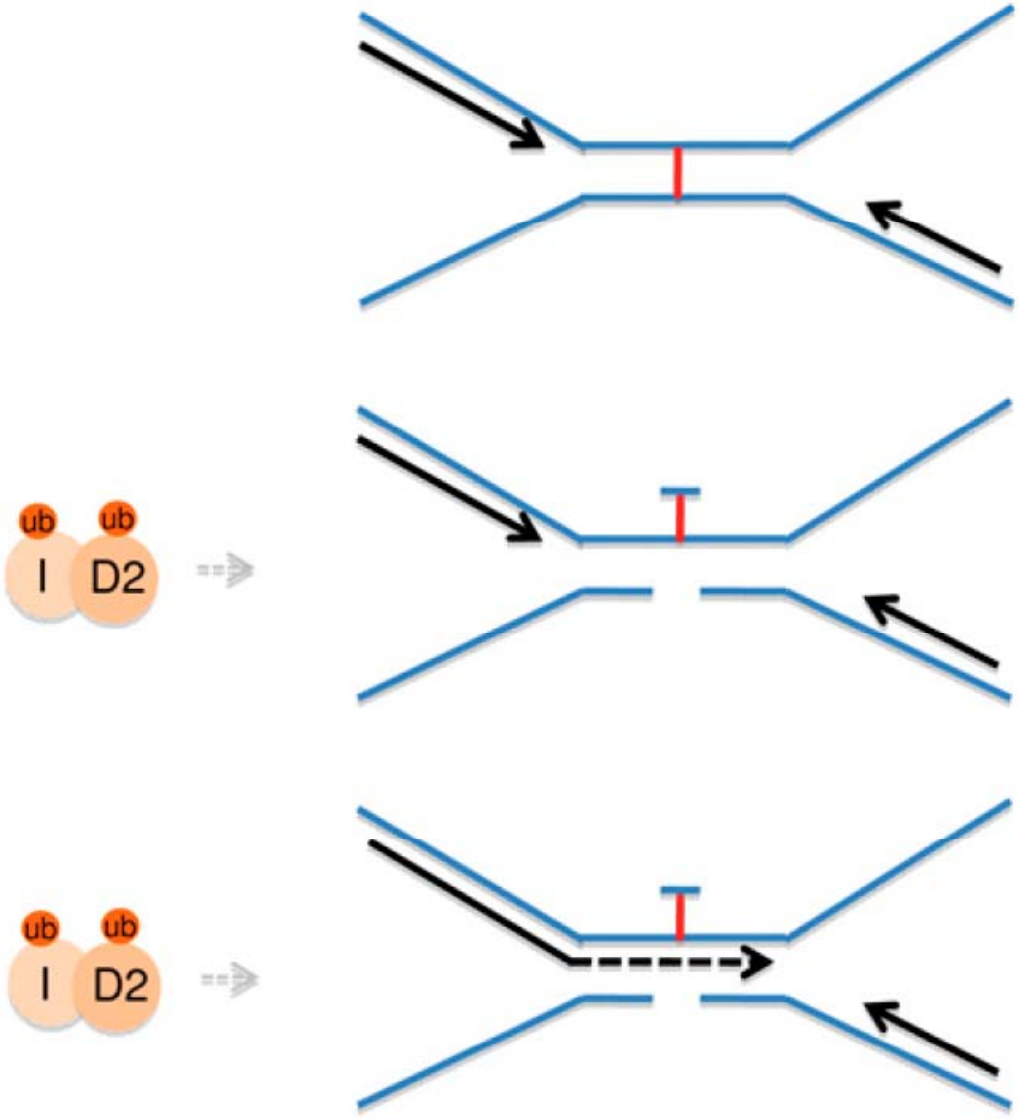
A



Loading of the FA core complex on chromatin induces monoubiquitination of FANCD2/FANCI.

Monoubiquitinated FANCD2/FANCI recruit FAN1 nuclease to the damages sites, and colocalize with downstream FA proteins, possibly including RAD51C, and facilitate DNA repair.

Younghoon Kee and Alan D. D'Andrea[1]



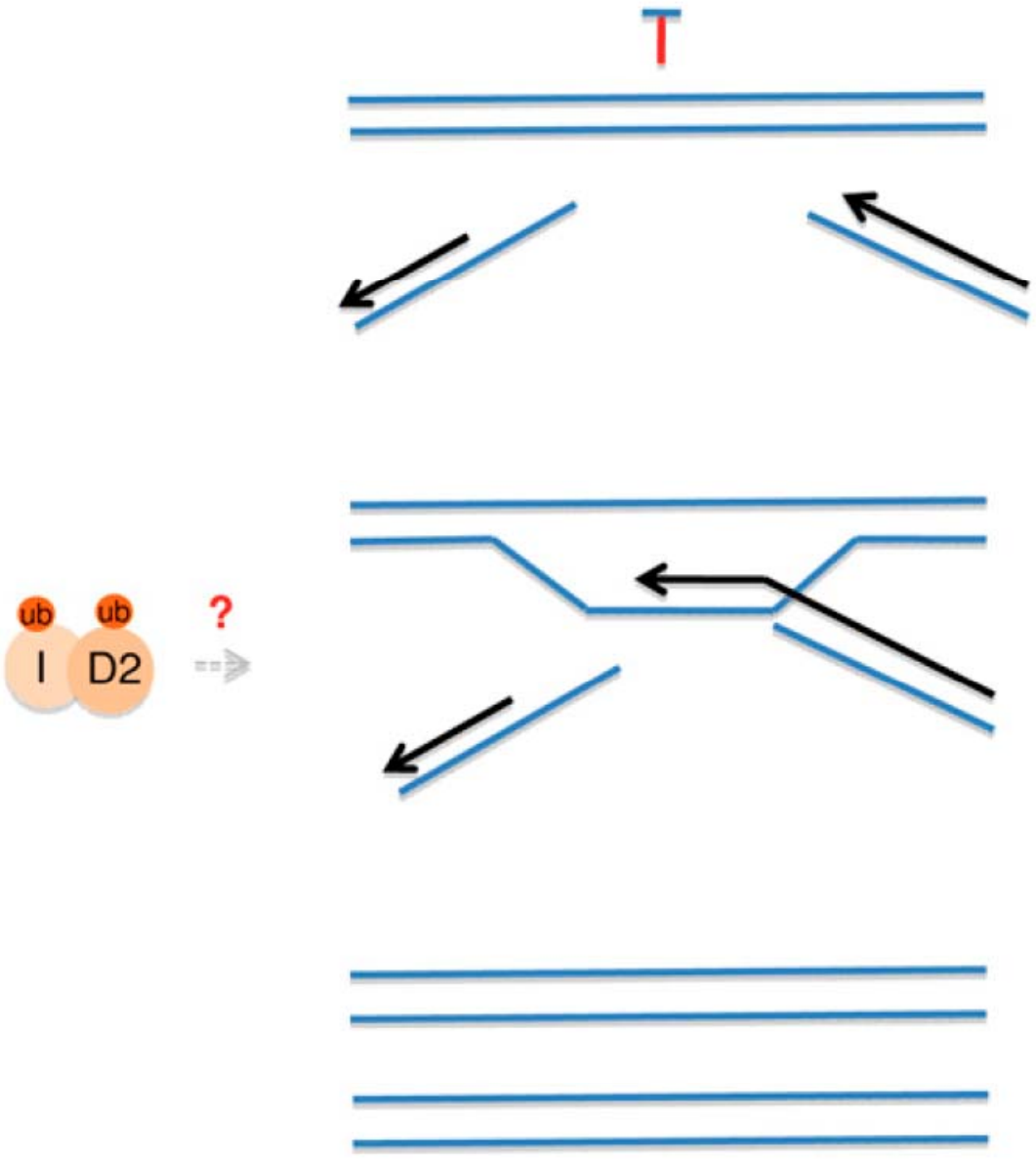
Replication fork is stalled upon collision with ICL

Unhooking of ICL is potentially catalyzed by MUS81-EME1 and XPF-ERCC1, or newly identified FAN1 nuclease.

The unhooked lesion is bypassed by TLS polymerases

Younghoon Kee and Alan D. D'Andrea[1]

GENES & DEVELOPMENT 24:1680–1694 © 2010



NER removes monoadducts and repairs the gap

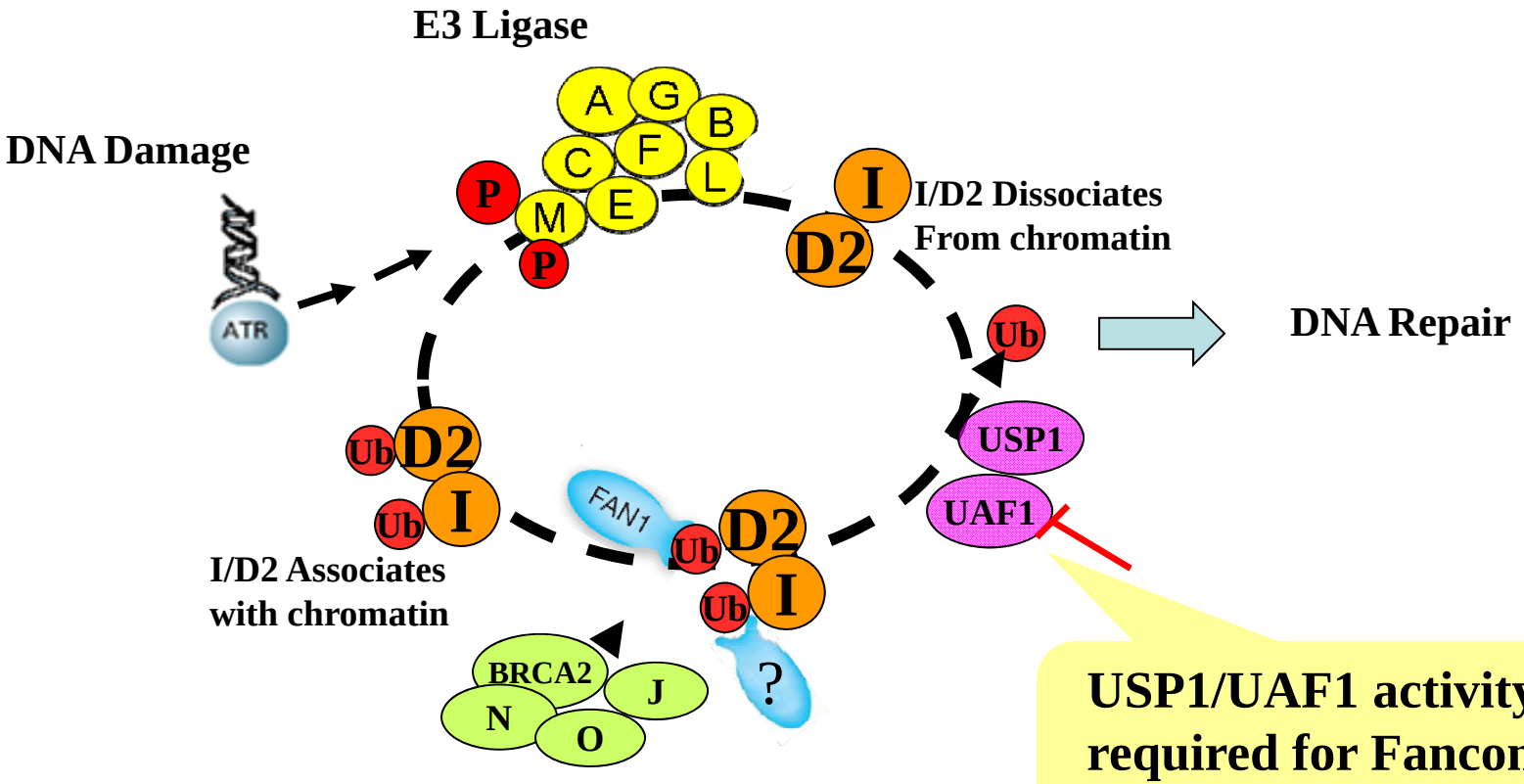
DSB is repaired by HR, initiated by strand invasion

Resolution of recombination intermediates and repair is finished

Younghoon Kee and Alan D. D'Andrea[1]

GENES & DEVELOPMENT 24:1680–1694 © 2010

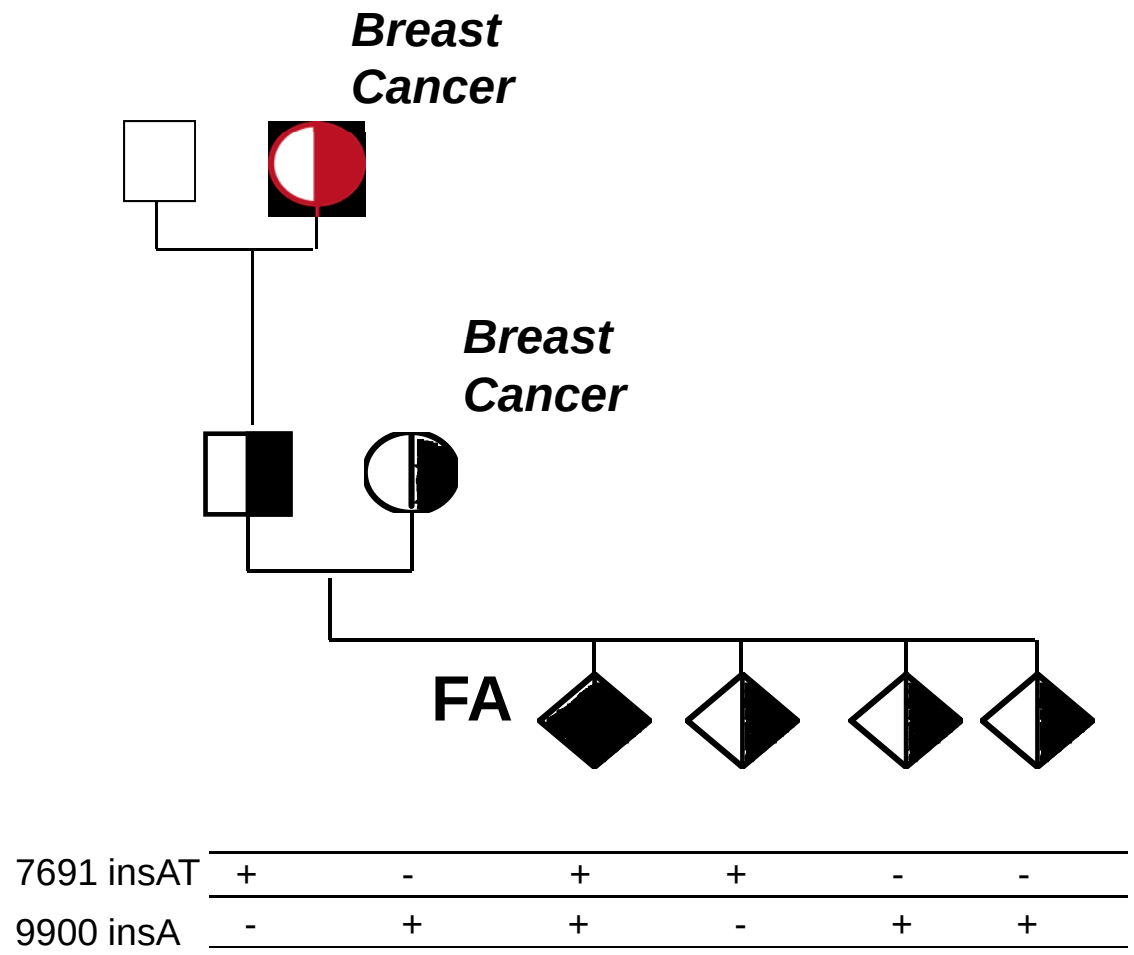
The Fanconi Anemia DNA Repair Pathway



USP1/UAF1 activity is required for Fanconi Anemia pathway

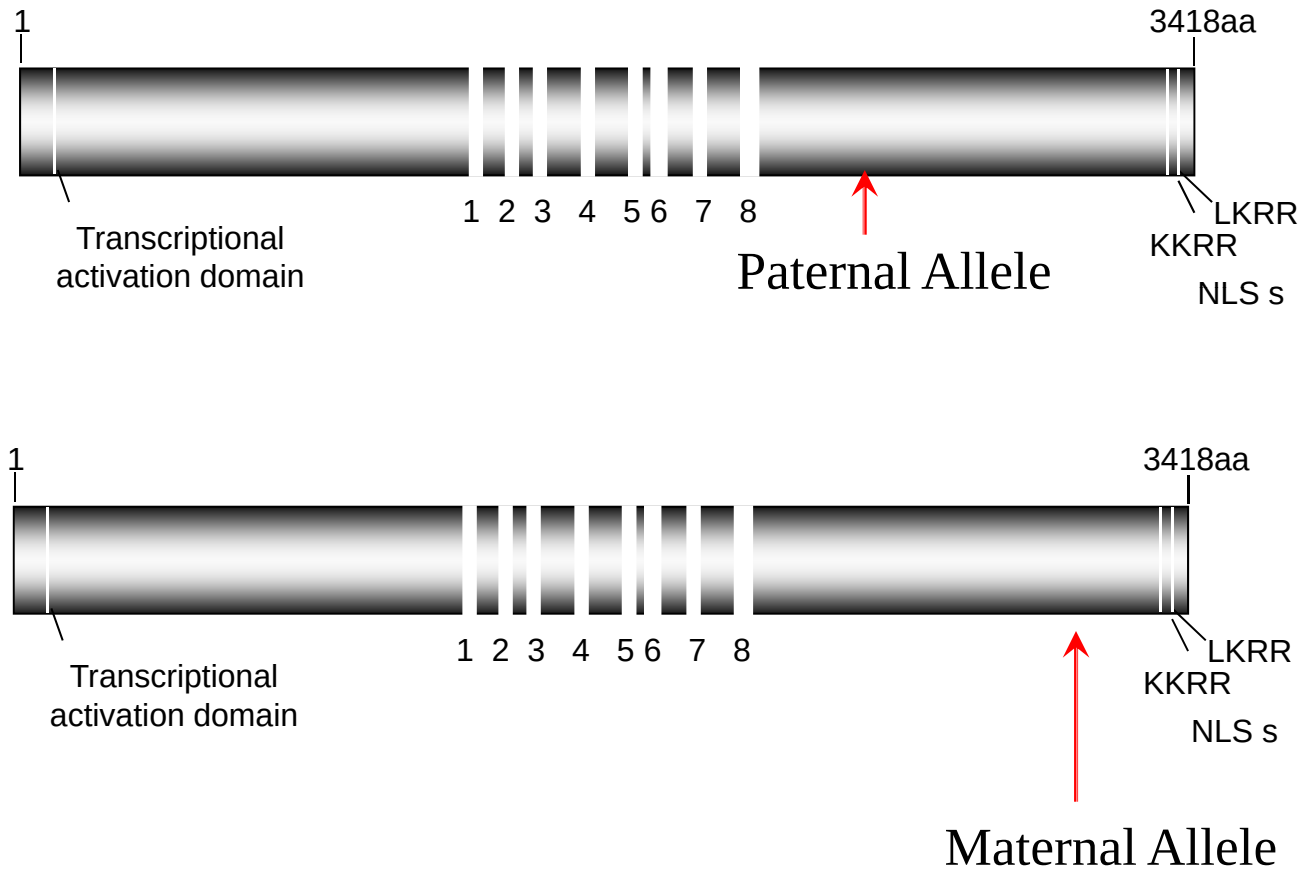
Moldovan and D'Andrea,
Ann Rev Genetics, 2009

BRCA2 is a Fanconi Anemia Gene (D1)



Howlett, N. et al, Science 297: 606, 2002

This Fanconi Anemia (D1) patient has two mutant *BRCA2* alleles



Conclusion: The Breast Cancer Susceptibility Gene, BRCA2, is the Fanconi D1 Gene (> 15 D1 families identified to date)

Paradox

In BRCA2 kindreds:

BRCA2 (+/-) Heterozygous Adult Carriers
Develop Breast, Ovarian, Pancreatic Cancer
(Not AML)

BRCA2(-/-) Children have Fanconi Anemia and
Develop AML, Medulloblastoma, and Wilms
Tumor

Fanconi anemia and somatic mosaicism

- Mosaicism
  - Not all the cells in the patient have the same genetic makeup.
  - In FA, ~ 20% of all patients are mosaic in their peripheral blood.
  - In addition to mutant cells they also have a population of healthy cells

Natural history of FA

BLOOD, 15 FEBRUARY 2003 • VOLUME 101, NUMBER 4

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

A 20-year perspective on the International Fanconi Anemia Registry (IFAR)

David I. Kutler, Bhuvanesh Singh, Jaya Satagopan, Sat Dev Batish, Marianne Berwick, Philip F. Giampietro, Helmut Hanenberg, and Arleen D. Auerbach

- Birth defects
- Pancytopenia
- Leukemia
- Solid tumors

Table 1. Summary of FA cohort reports

Cohort	LIT	IFAR	NAS	*P**
Reporting period or date	1927-2001	1982-2001	2000	—
Total number of subjects	1301	754	145	—
Male-to-female ratio	1.23	1.05	1.10	ns
Age FA diagnosed, median (range)	7 (0-48)	na	5 (0-45)	<.0002
Deceased %, at time of report	38%	38%	30%	ns
Projected median survival age, years	20	24	30	—
Leukemia, no MDS; number (% total cohort)	116 (9%)	47 (6%)	9 (6%)	<.05
Leukemia, cumulative incidence	na	45% by age 50 (includes MDS)	10% by age 24 (no MDS)	—
MDS, number (% total cohort)	89 (7%)	53 (7%)	23 (16%)	.001
Solid tumor, number (% total cohort)	68 (5%)	67 (9%)	13 (9%)	.003
Solid tumor, cumulative incidence	na	36% by age 50	29% by age 48	—
Liver tumor, number (% total cohort)	37 (3%)	18 (2%)	2 (1%)	ns
Hematopoietic stem cell transplant (% total cohort)	220 (17%)	219 (29%)	44 (30%)	<.0001

ns indicates not statistically significant; na, not available; and —, data in rows could not be subjected to test for significance.
**P* value indicates significance of data at the extremes.

B. P. Alter et al Cancer in Fanconi anemia. *Blood 101 (5):2072, 2003.*

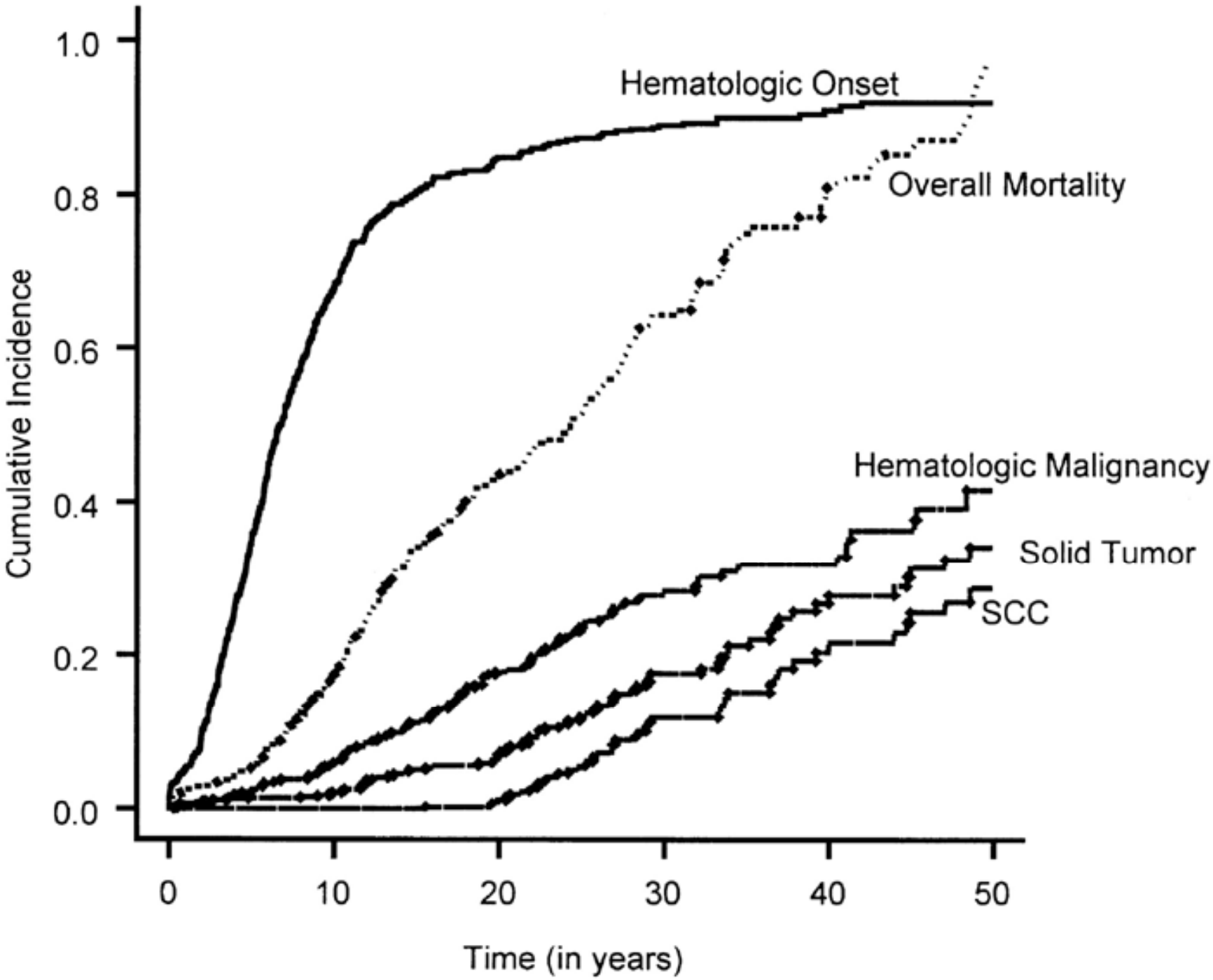

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Incidence
Hematologic Onset
Overall Mortality
Hematologic Malignancy
Solid Tumor
SCC
0
10
20
30
40
50
Time (in years)

Table 2. Neoplasms identified in FA patients

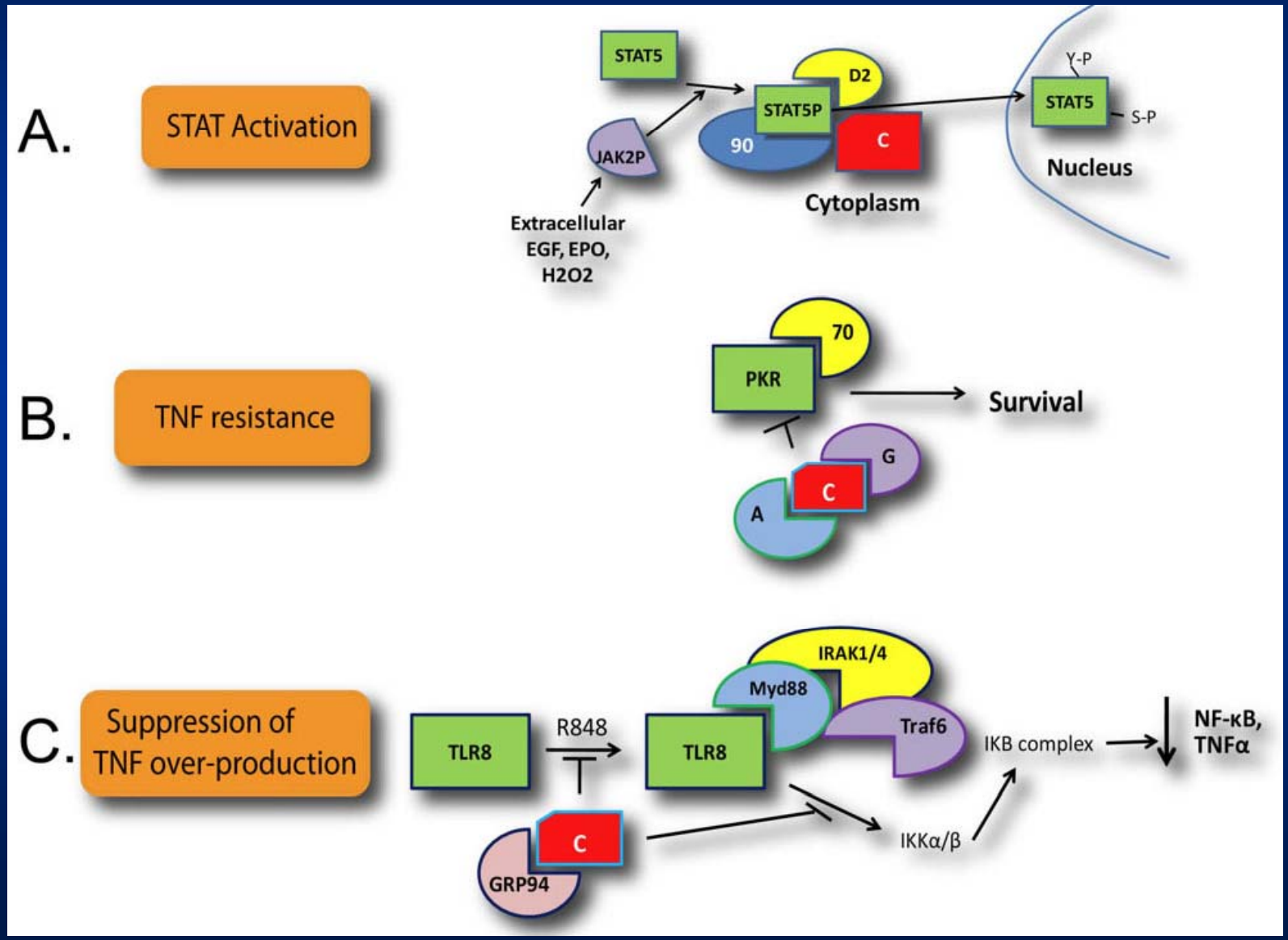
Tumor type	No. cases (%)
Hematologic tumors	120 (60)
AML	60
MDS	53
ALL	5
CMMOL	1
Burkitt lymphoma	1
Nonhematologic tumors	79 (40)
Liver tumors	18 (9)
Liver adenoma	11
Hepatocellular carcinoma	6
Liver adenocarcinoma	1
Brain tumors	5 (2)
Medulloblastoma	4
Astrocytoma	1
Renal tumors	6 (3)
Wilm tumor	4
Renal cell carcinoma	1
Nephroblastoma	1
Squamous cell carcinoma	39 (20)
Head and neck SCC	19
Vulvar	8
Cervix	6
Cutaneous	3
Anus	2
Esophagus	1
Miscellaneous tumors	11 (6)
Breast carcinoma	3
Basal cell carcinoma	2
Neuroblastoma	1
Desmoid tumor	1
Gonadoblastoma	1
Melanoma	1
Neurilemmona	1
Osteogenic sarcoma	1

ALL indicates acute lymphoblastic leukemia; CMMOL, chronic myelomonocytic leukemia; SCC, squamous cell carcinoma.

Pathophysiology

- DNA repair
  - Bone marrow failure: damaged stem cells die
  - Cancer: unrepaired mutations cause cancer
  - Birth defects: damaged cell die
- Signaling defects
  - Bone marrow failure: cytokine hypersensitivity
  - Cancer: Clonal evasion from cytokine hypersensitivity
  - Birth defects: aberrant signaling during development

Non-canonical functions of FA proteins

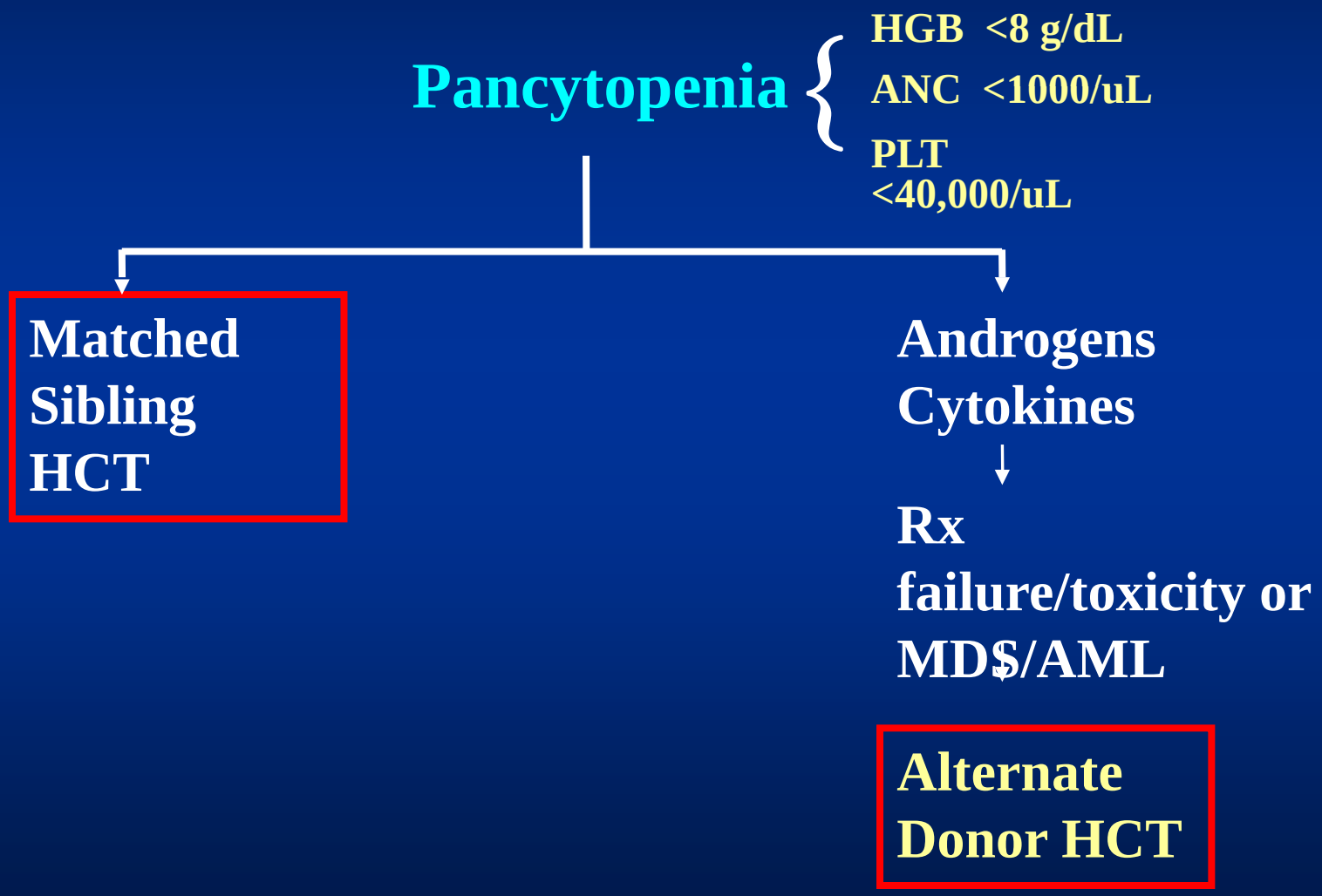


Treatment of Fanconi Anemia

- Androgens
  - Rationale: males have higher hematocrits than females
- G-CSF
- Transfusions/supportive care
  - Red blood cells, platelets
- Bone marrow transplantation

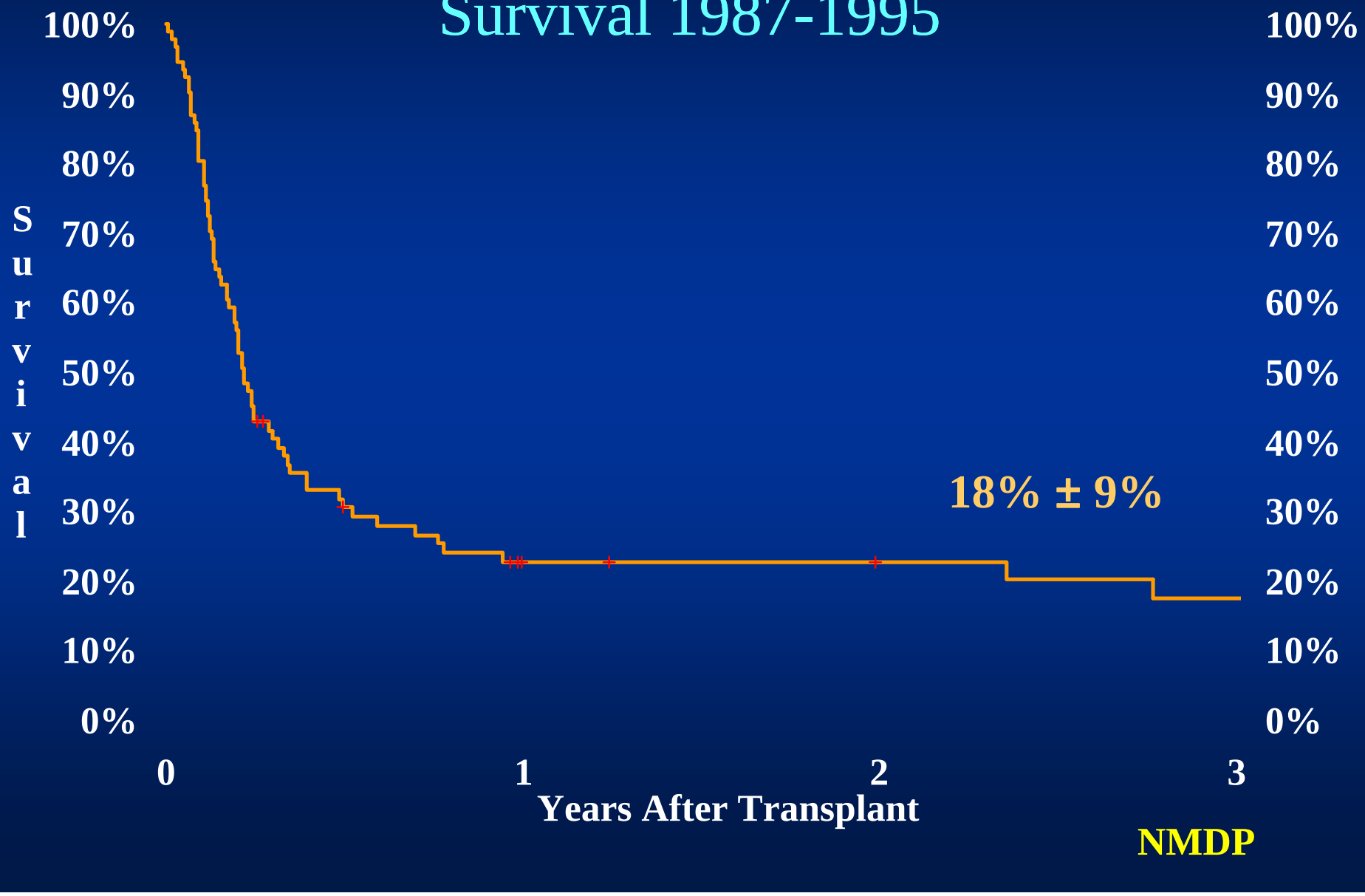
- Most slides are the courtesy of John Wagner, University of Minnesota

HSCT for FA: Standard Guidelines



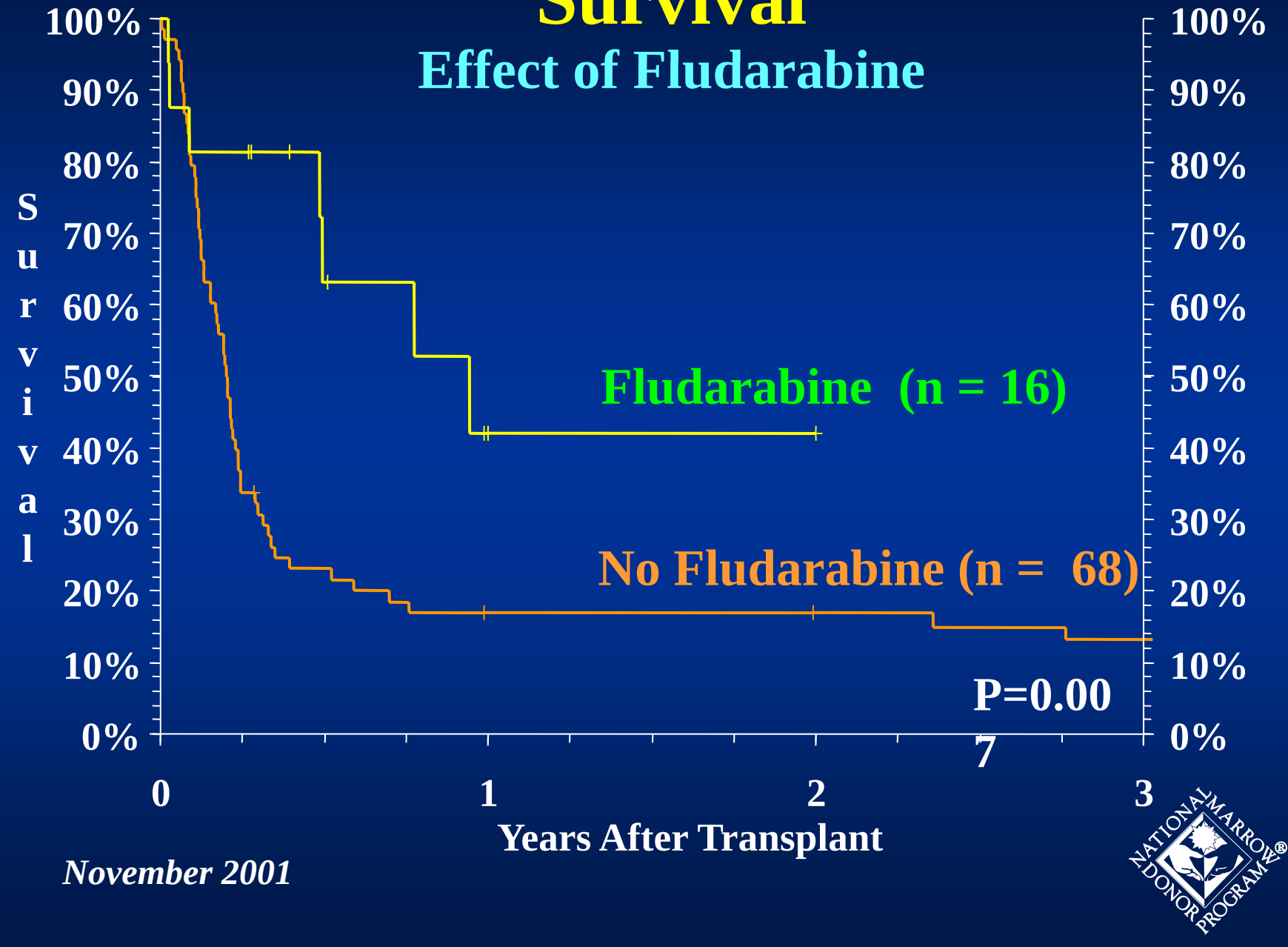
Unrelated Donor BMT for FA

Survival 1987-1995



Survival

Effect of Fludarabine



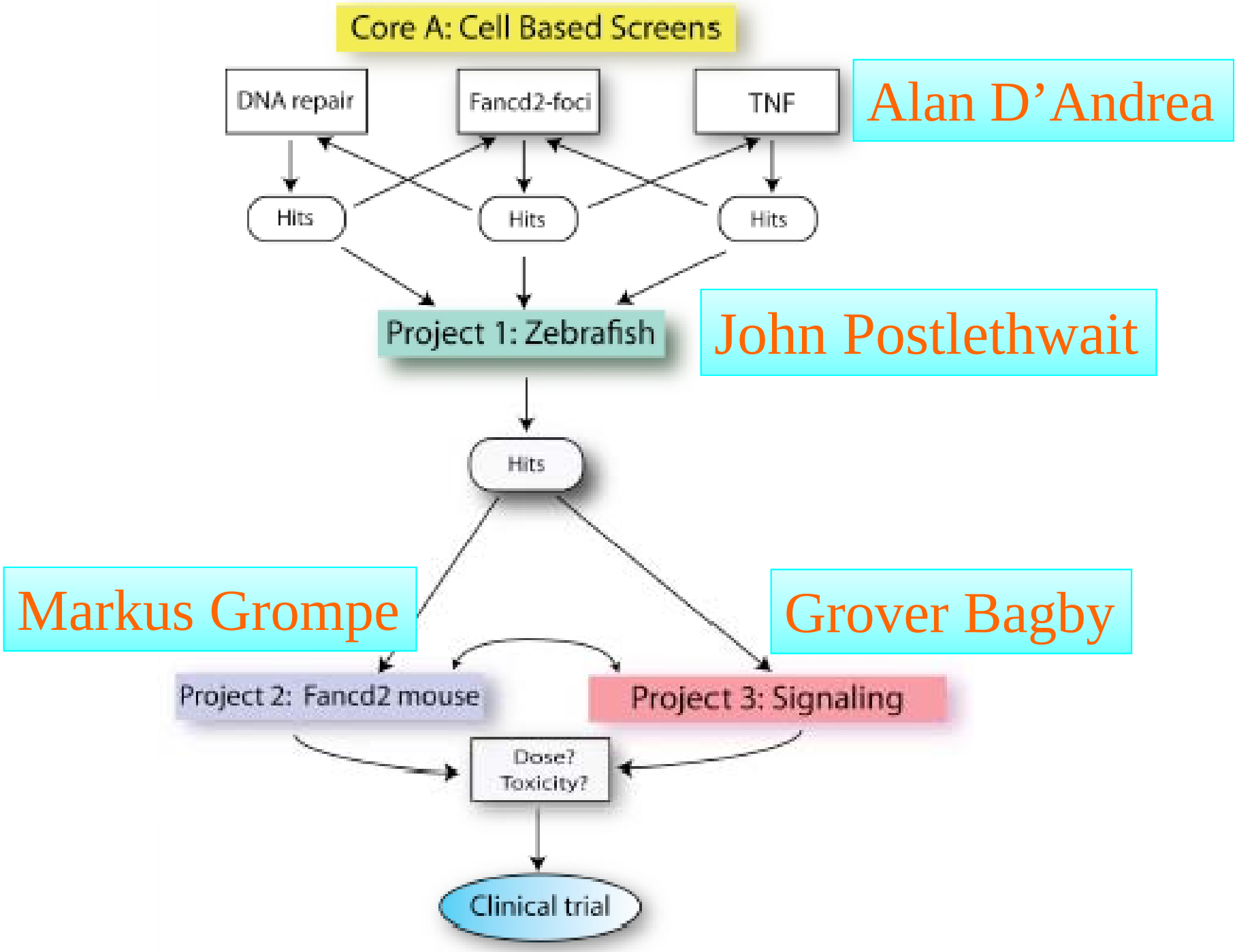
November 2001

New treatments are badly needed

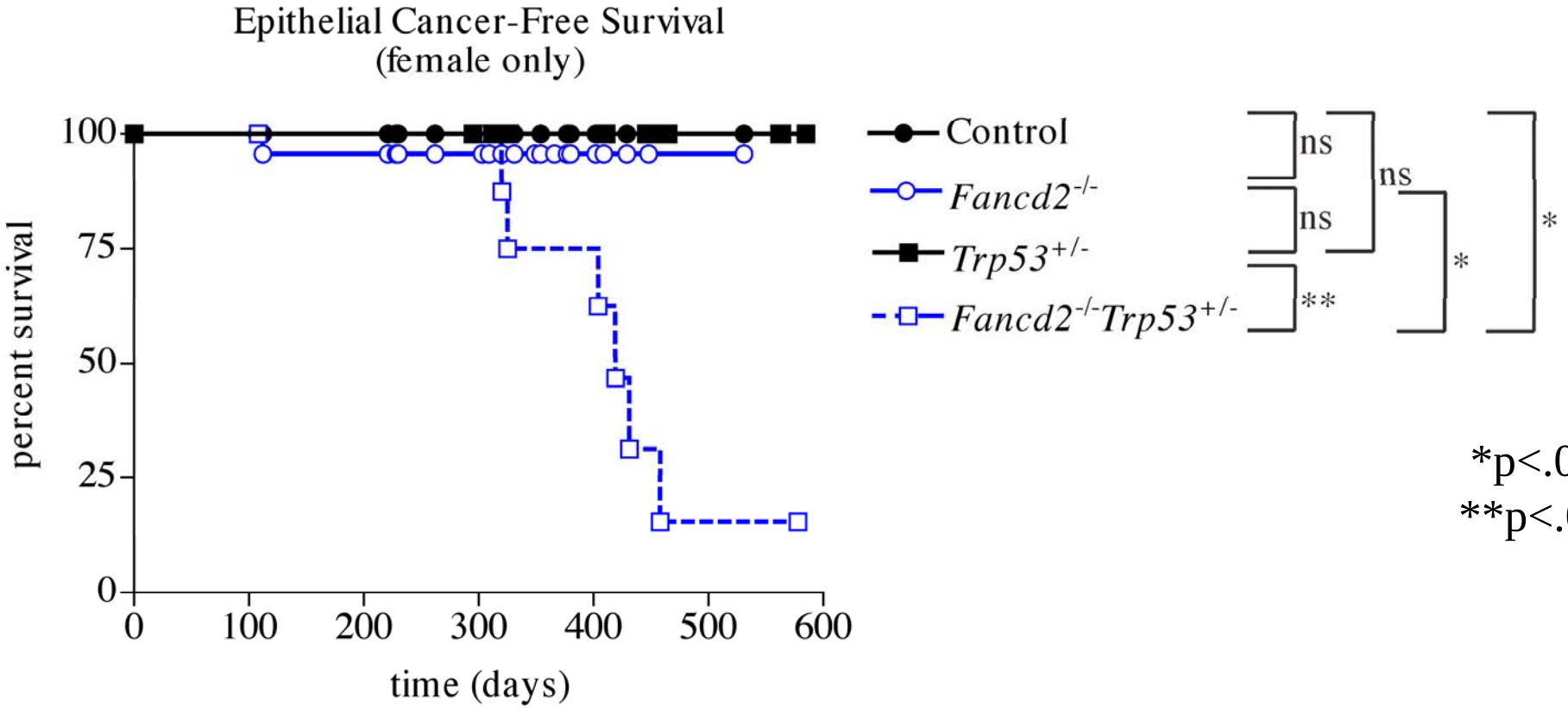
- Gene Therapy
- Cell transplantation
- Small molecule intervention
  - Treatment
  - Prevention
    - Cancer prevention
    - Prevention of bone marrow failure

Is there a small molecule that can be beneficial to both hematopoiesis and cancer prevention?

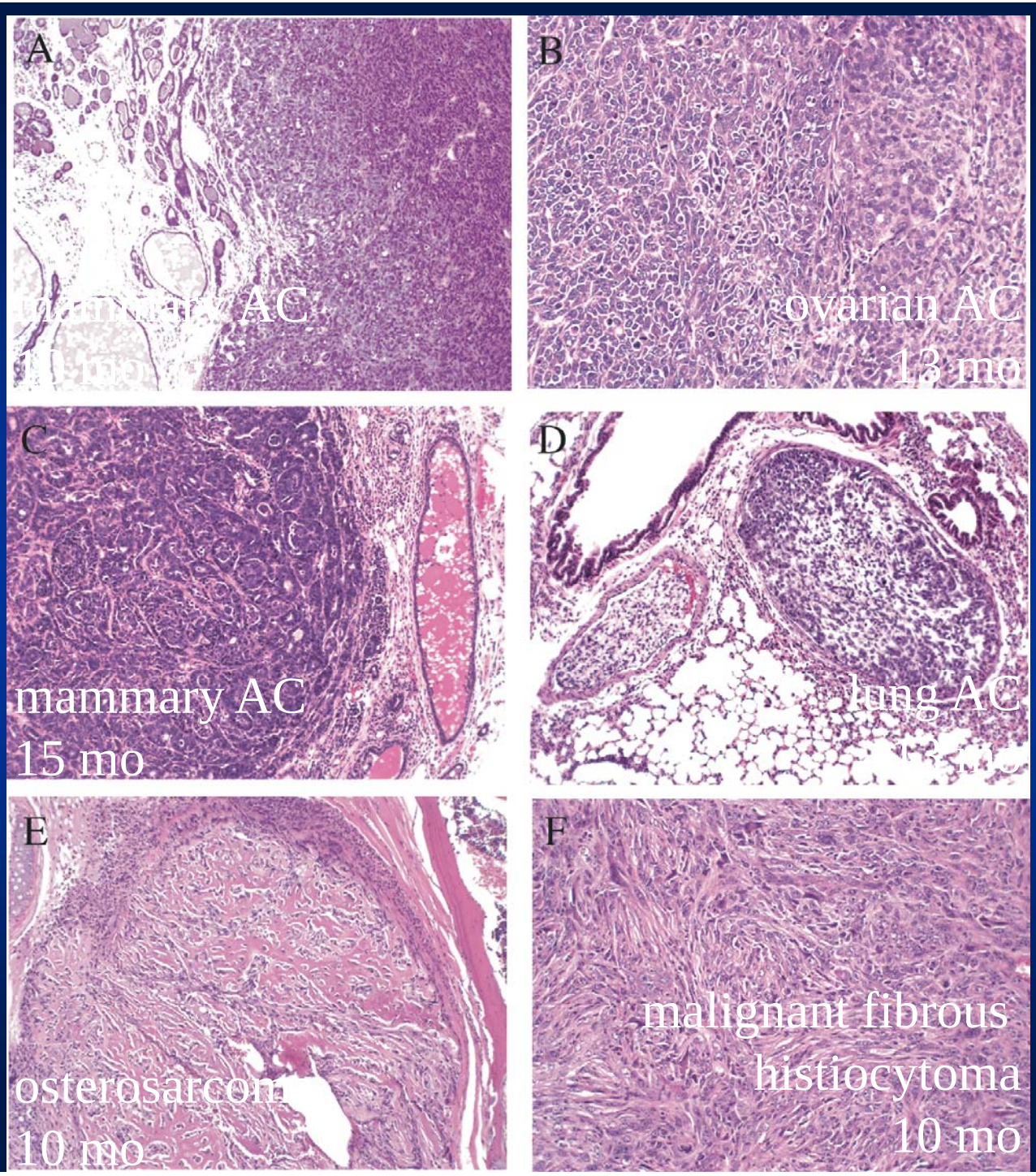
- Cancer prevention
  - Enhance apoptosis of cells with damaged genomes
  - Concern: this could lead to loss of hematopoietic stem cells
- Anemia prevention
  - Enhance survival and growth of HSC
  - Concern: this could stimulate tumor growth
- Best solution
  - Prevent DNA damage or enhance DNA repair


Core A: Cell Based Screens
DNA repair
Fancd2-foci
TNF
Alan D'Andrea
Hits
Hits
Hits
Project 1: Zebrafish
John Postlethwait
Hits
Markus Grompe
Grover Bagby
Project 2: Fancd2 mouse
Project 3: Signaling
Dose?
Toxicity?
Clinical trial

Heterozygosity for *Trp53* accelerates tumors in *Fancd2* KO



*p<.05
**p<.01


A
AC
B
ovarian AC
13 mo
C
mammary AC
15 mo
D
lung AC
E
osterosarcom
10 mo
F
malignant fibrous
histiocytoma
10 mo

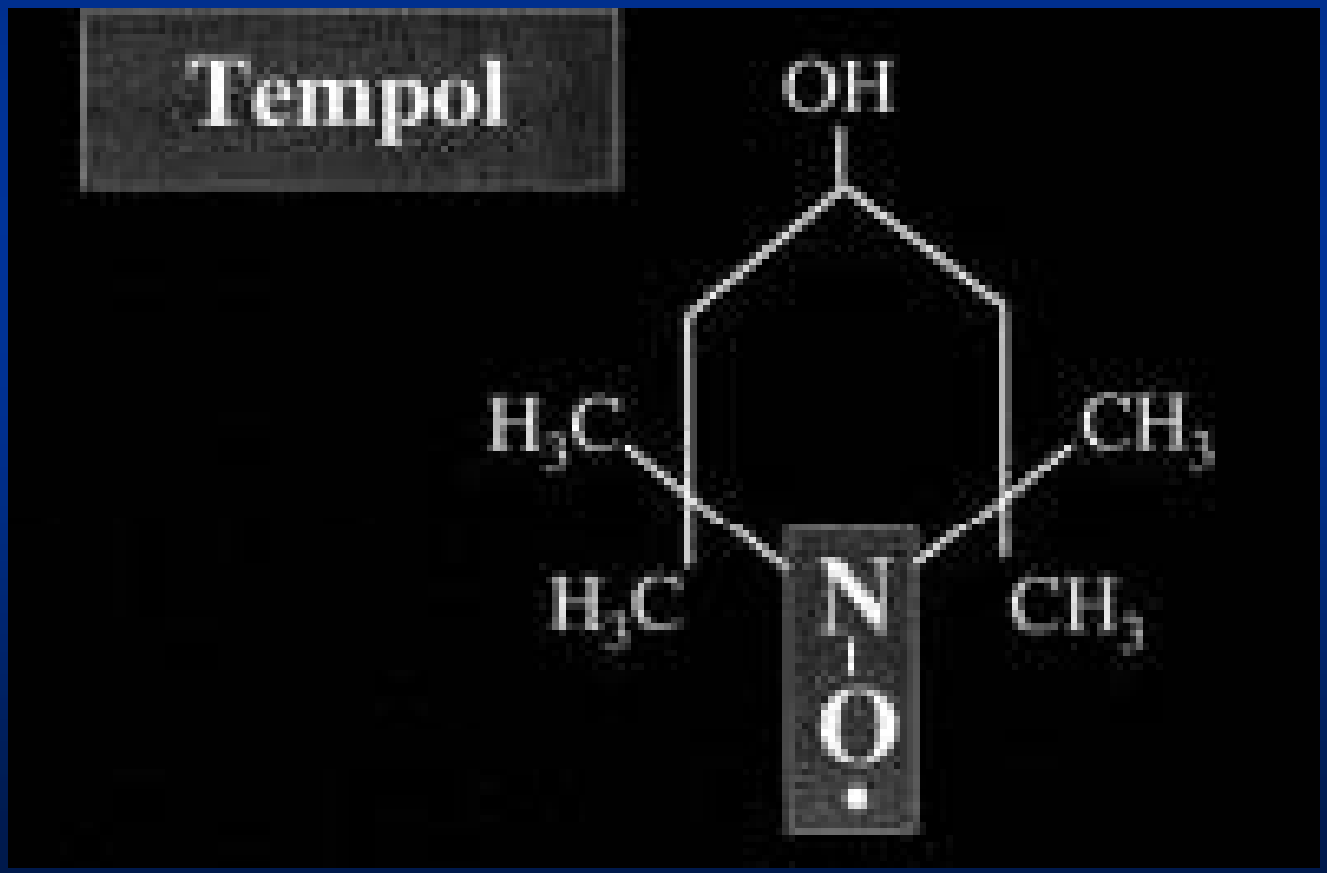
Cancer Res 2008; 68: (5). March 1, 2008

Research Article

Tempol Protects against Oxidative Damage and Delays Epithelial Tumor Onset in Fanconi Anemia Mice

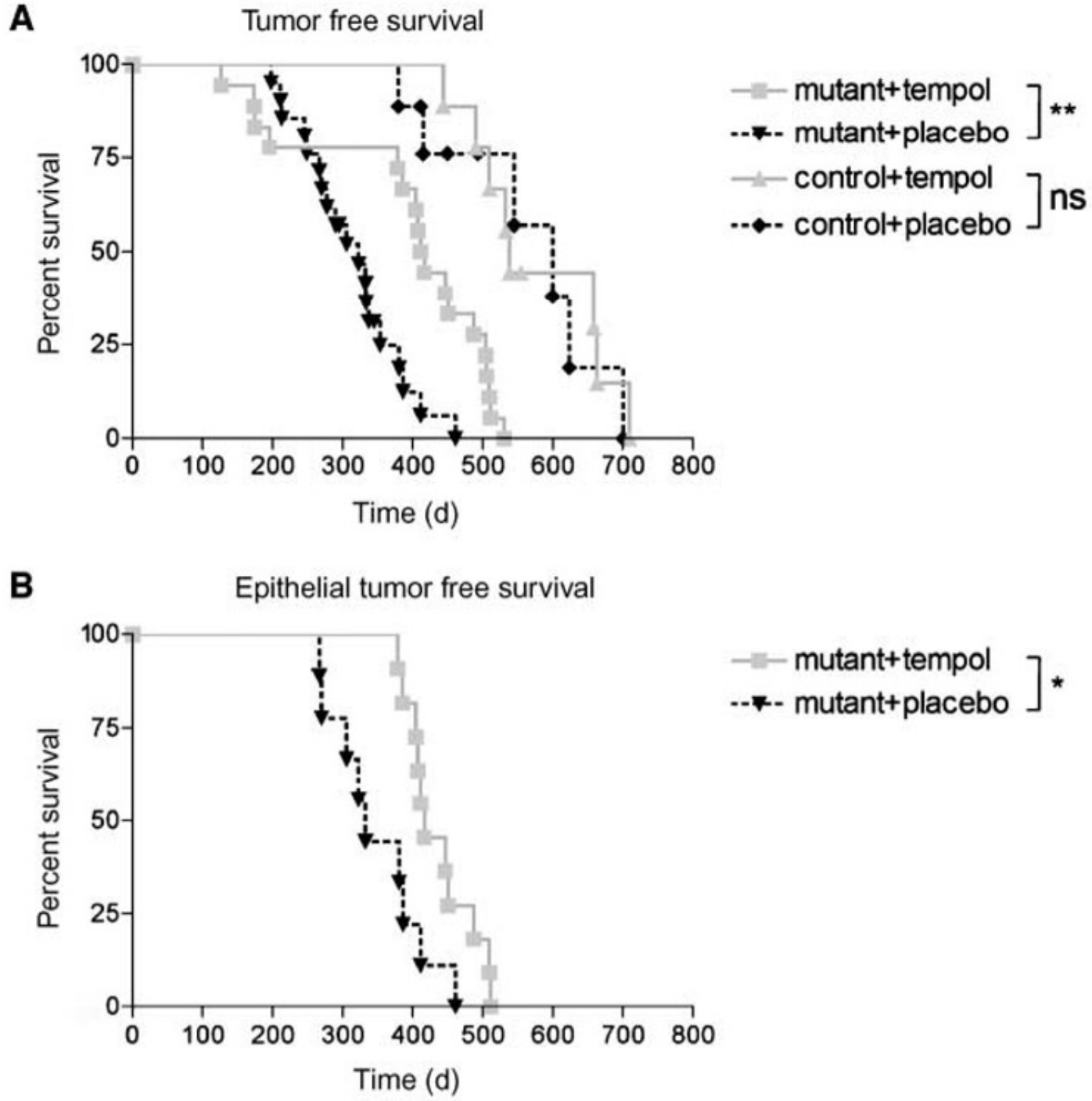
Qing-Shuo Zhang,[1] Laura Eaton,[1] Eric R. Snyder,[2] Scott Houghtaling,[1] James B. Mitchell,[3] Milton Finegold,[4] Carter Van Waes,[2] and Markus Grompe[1]

First small molecule to be tested in *Fancd2* mutant mice

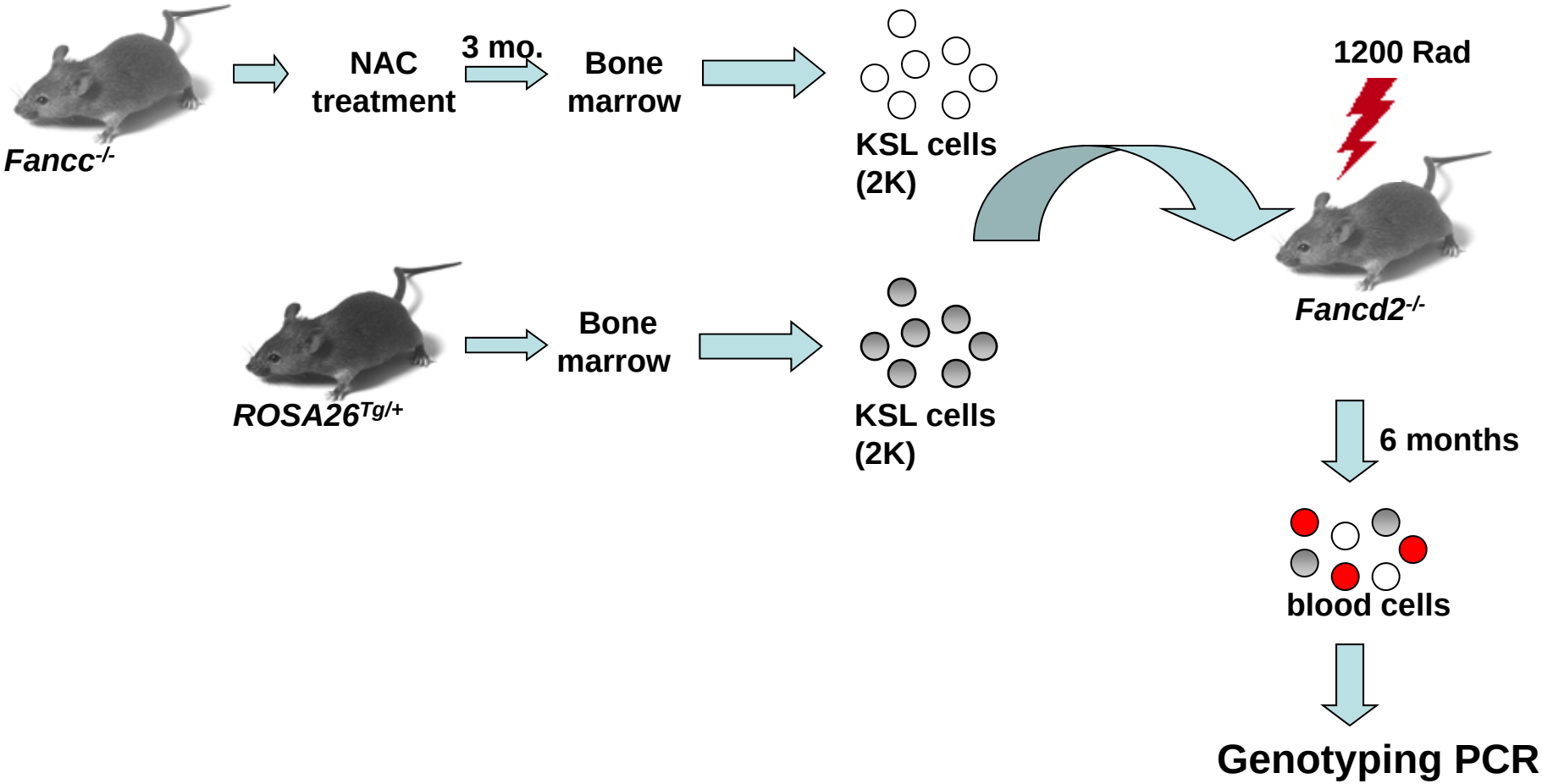


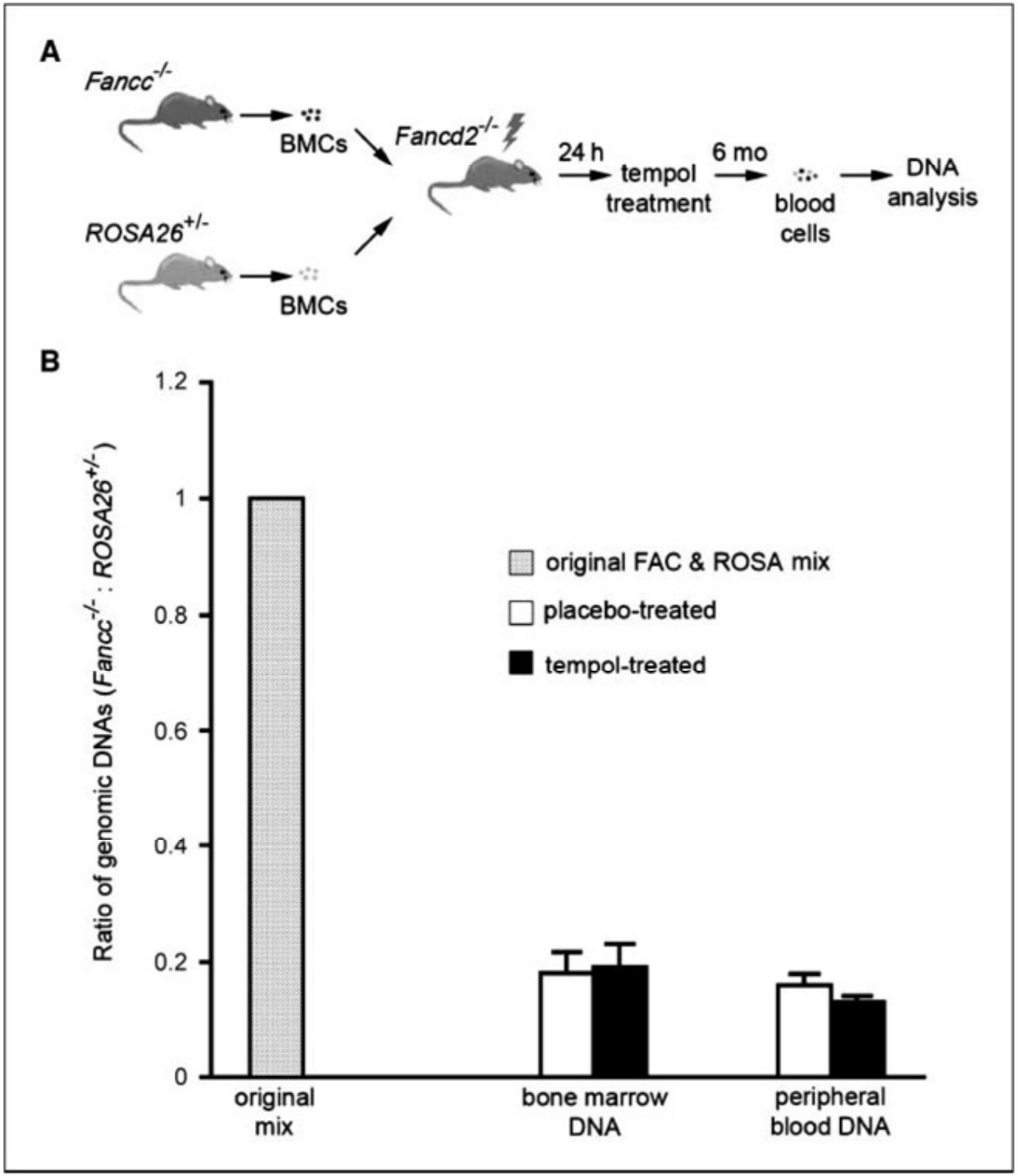
Properties of tempol

- Superoxide dismutase (SOD) mimetic
- Hydroxyradical scavenger
- Effective in animal models of ischemia-reperfusion injury
  - Myocardial infarction
  - Renal ischemia
- Effective in reducing tumor incidence in animal models of cancer


A
Tumor free survival
Percent survival
100
75
50
25
0
0
100
200
300
400
500
600
700
800
Time (d)
mutant+tempol
mutant+placebo
control+tempol
control+placebo
**
ns
B
Epithelial tumor free survival
Percent survival
100
75
50
25
0
0
100
200
300
400
500
600
700
800
Time (d)
mutant+tempol
mutant+placebo
*

In vivo competitive repopulation assay:



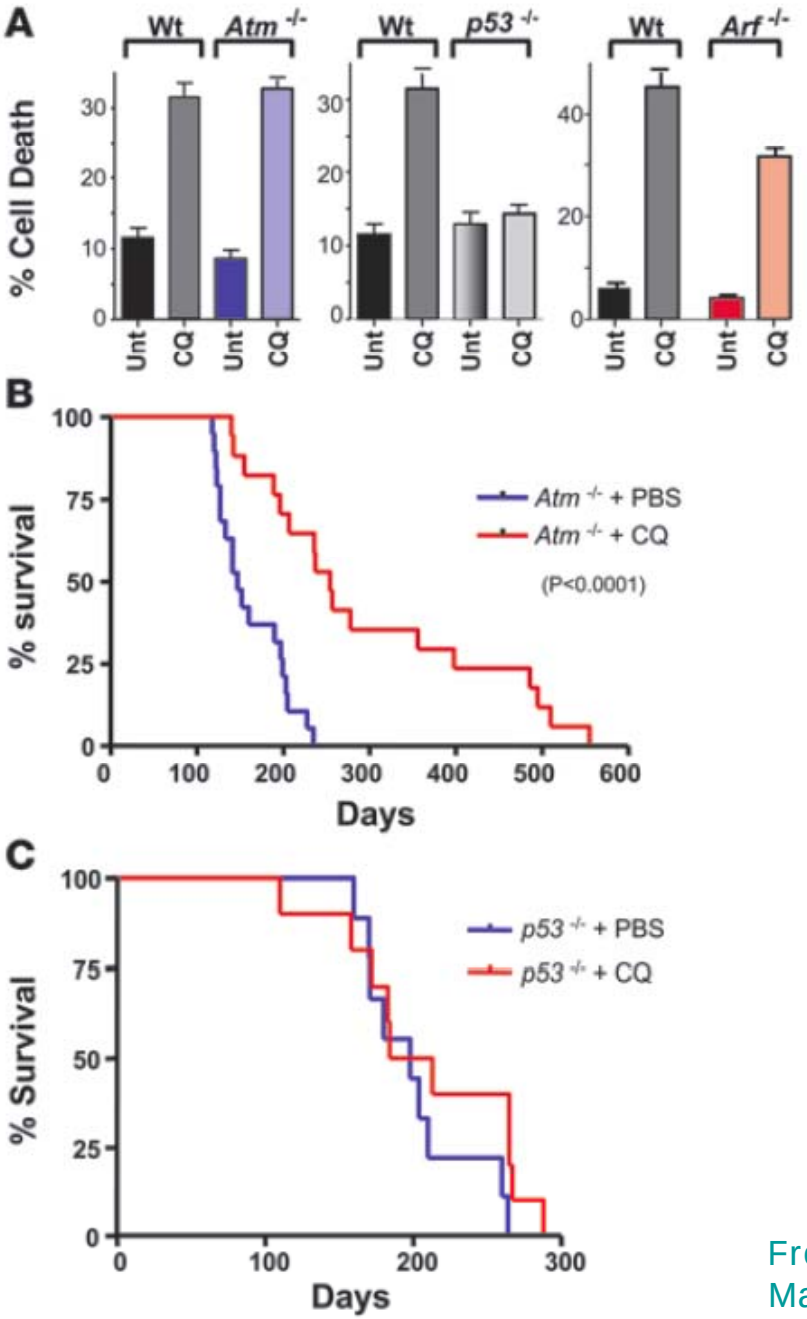

A
Fancc-/-
BMCs
Fancd2-/-
24 h
tempol treatment
6 mo
blood cells
DNA analysis
ROSA26+/-
BMCs
B
Ratio of genomic DNAs (Fancc-/- : ROSA26+/-)
1.2
1
0.8
0.6
0.4
0.2
0
original FAC & ROSA mix
placebo-treated
tempol-treated
original mix
bone marrow DNA
peripheral blood DNA

Conclusions

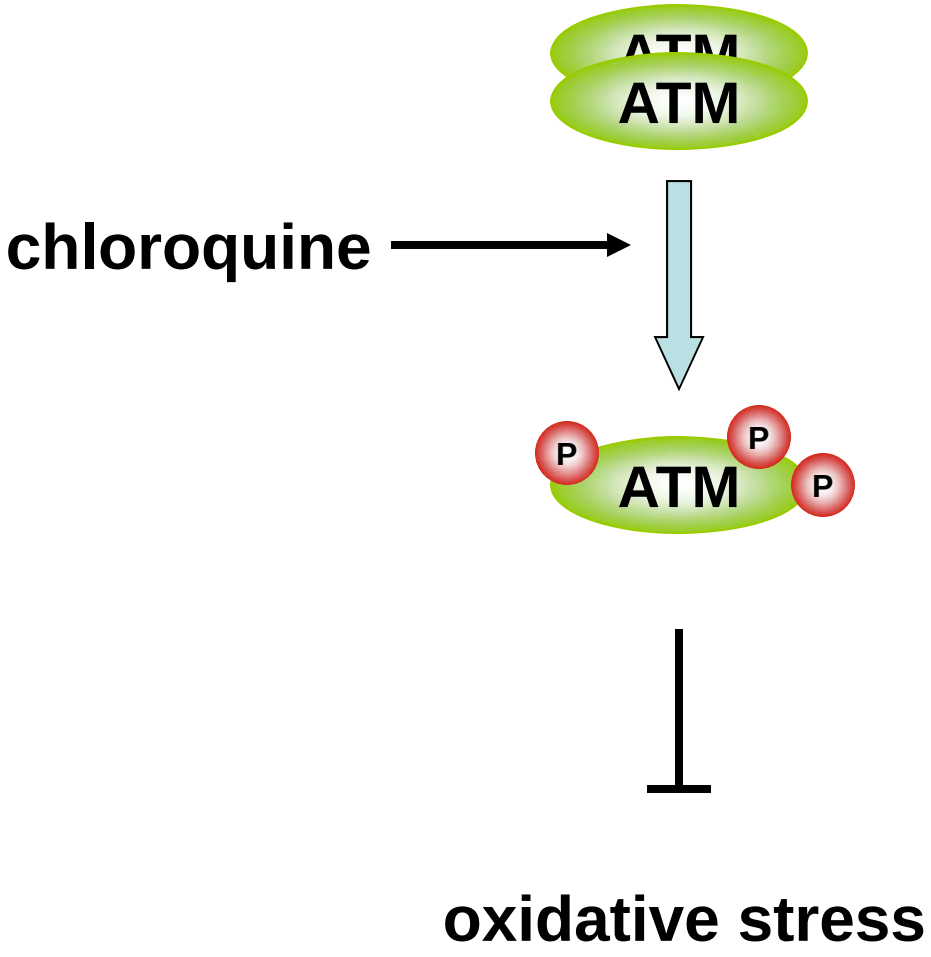
- The SOD mimetic tempol significantly delays tumors in an FA animal model.
- This effect is not specific for FA, but also has been seen in 3 other tumor-prone mouse models.
- Oxidative damage may be the main source of DNA damage in FA, but also other tumor models in mice.
- Tempol does not adversely affect the repopulating ability of FA mutant stem cells.
- Should we have a clinical trial with a) tempol, b) another SOD-mimetic?

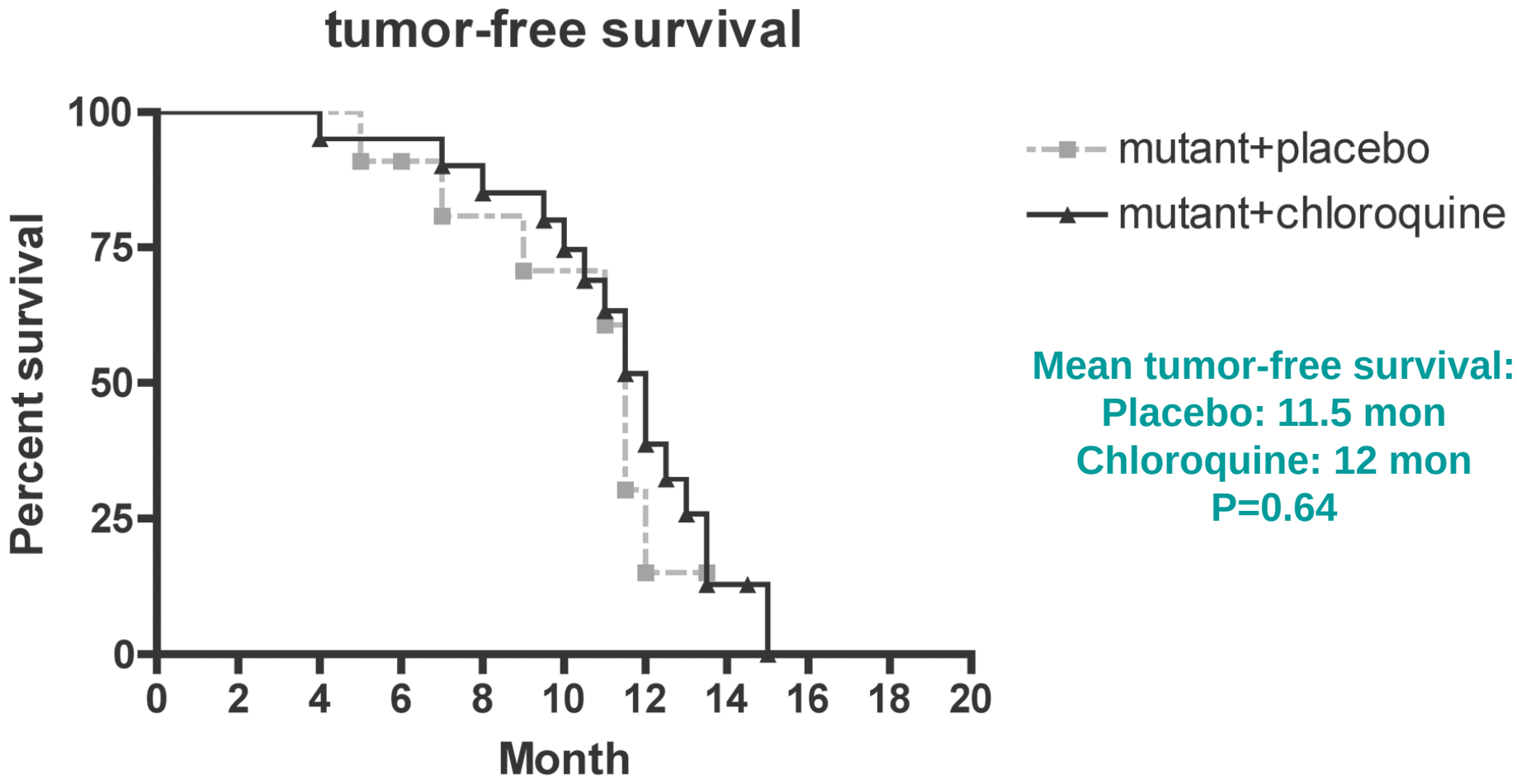
Other compounds that have been tested

- Chloroquine
- N-Acetylcysteine



From:
Maclean KH, Dorsey FC, Cleveland JL, Kastan MB.
J Clin Invest. 2008 Jan 2;118(1):79-88.


ATM
ATM
chloroquine
P
P
P
ATM
oxidative stress

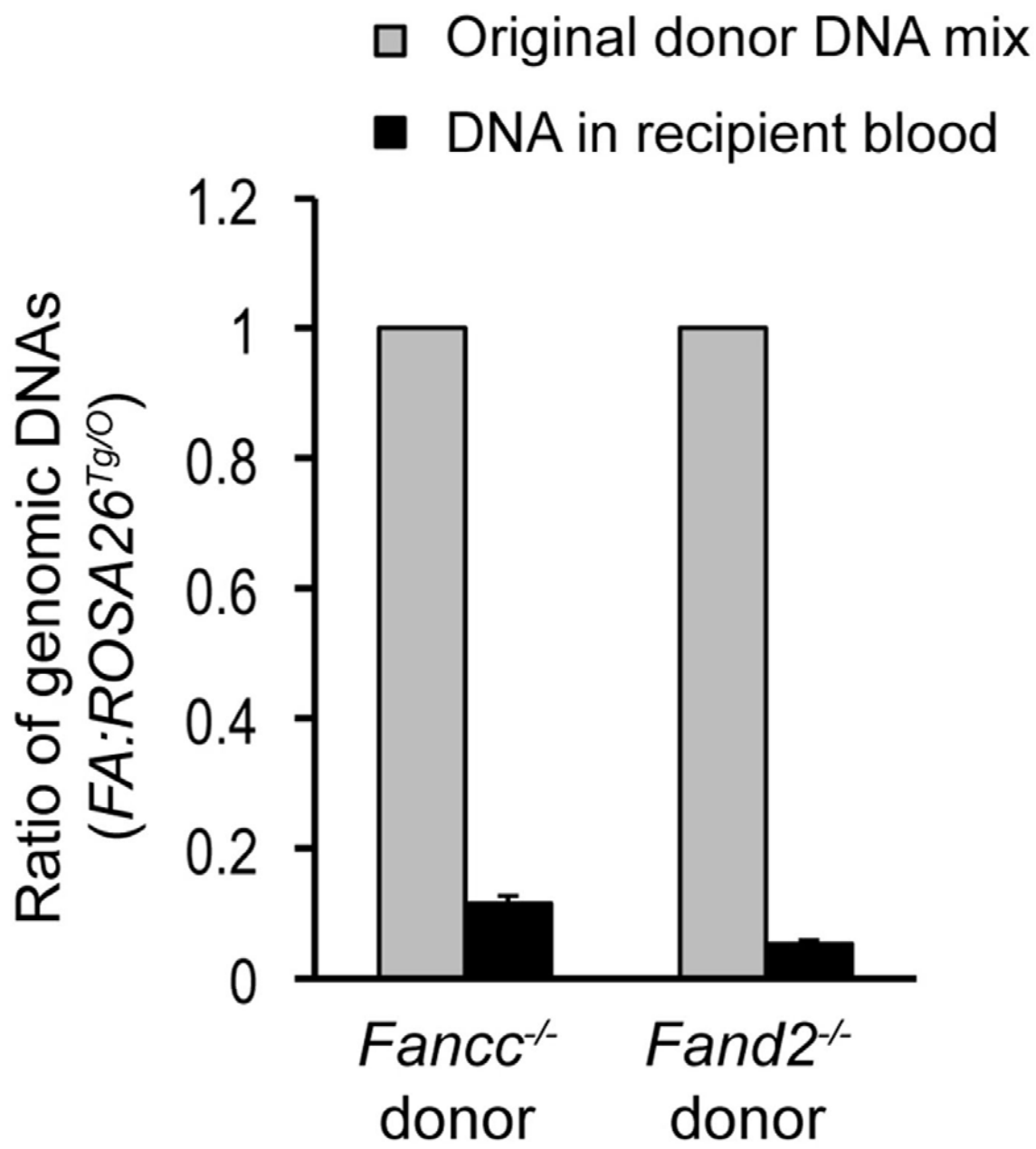


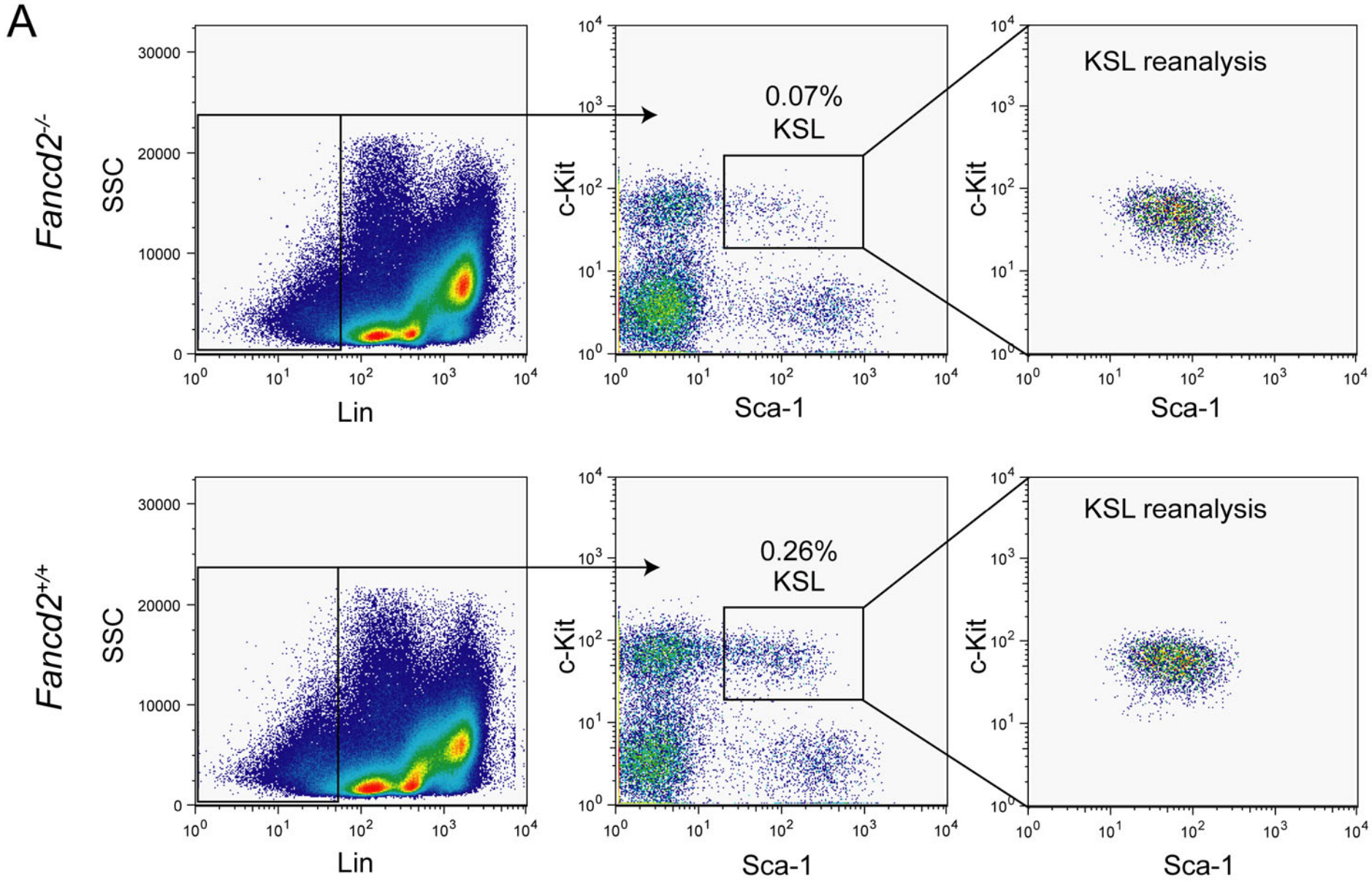
Mean tumor-free survival:
Placebo: 11.5 mon
Chloroquine: 12 mon
P=0.64

Models for hematopoietic defects in Fanconi Anemia

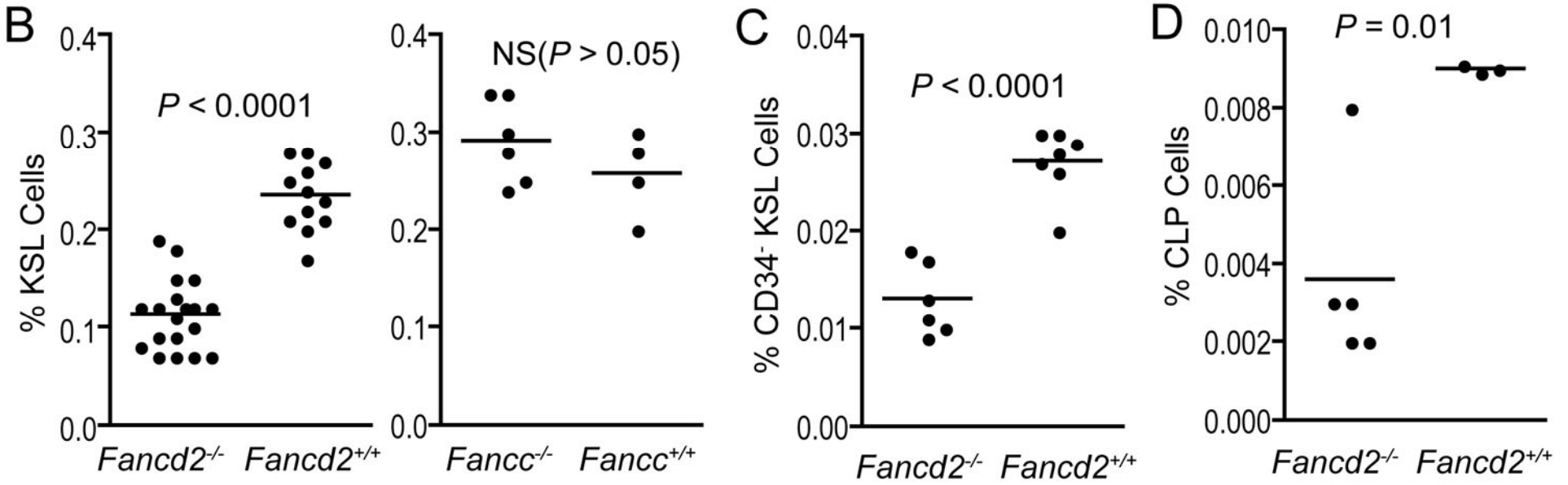
Is it really true that FA knockout mice are not a model for the anemia?

A

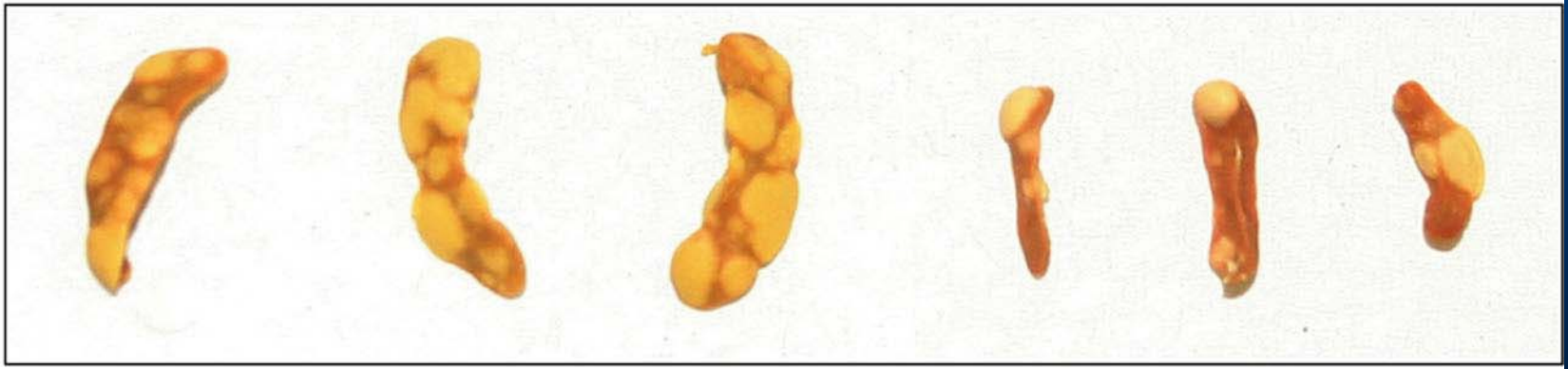

Original donor DNA mix
DNA in recipient blood
Ratio of genomic DNAs
(FA:ROSA26Tg/O)
1.2
1
0.8
0.6
0.4
0.2
0
Fancc-/-
donor
Fand2-/-
donor


A
Fancd2-/-
SSC
Lin
0.07%
KSL
c-Kit
Sca-1
KSL reanalysis
Fancd2+/+
SSC
Lin
0.26%
KSL
c-Kit
Sca-1
KSL reanalysis

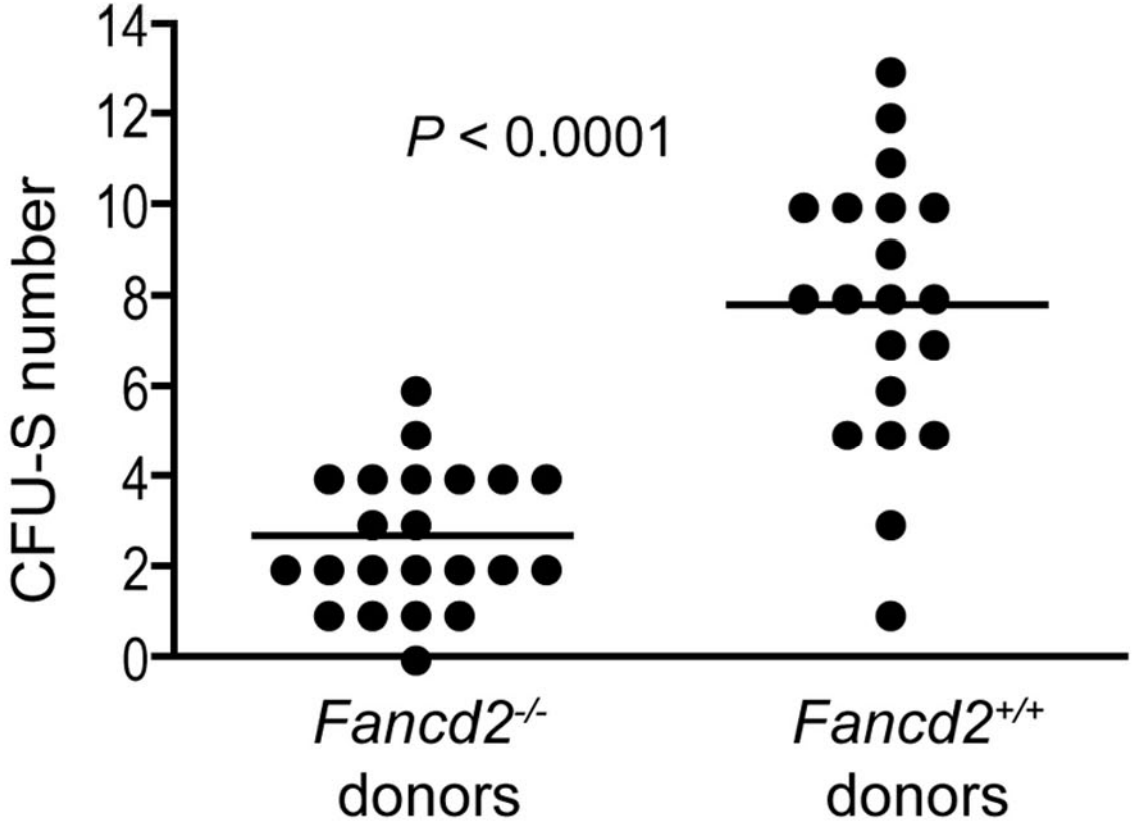
Reduced numbers of stem cells



B

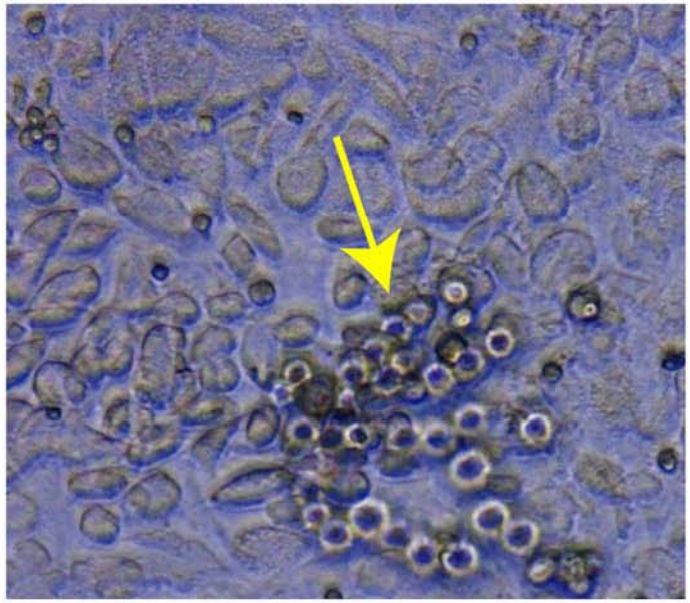

Fancd2$^{+/+}$ donor
Fancd2$^{-/-}$ donor

C

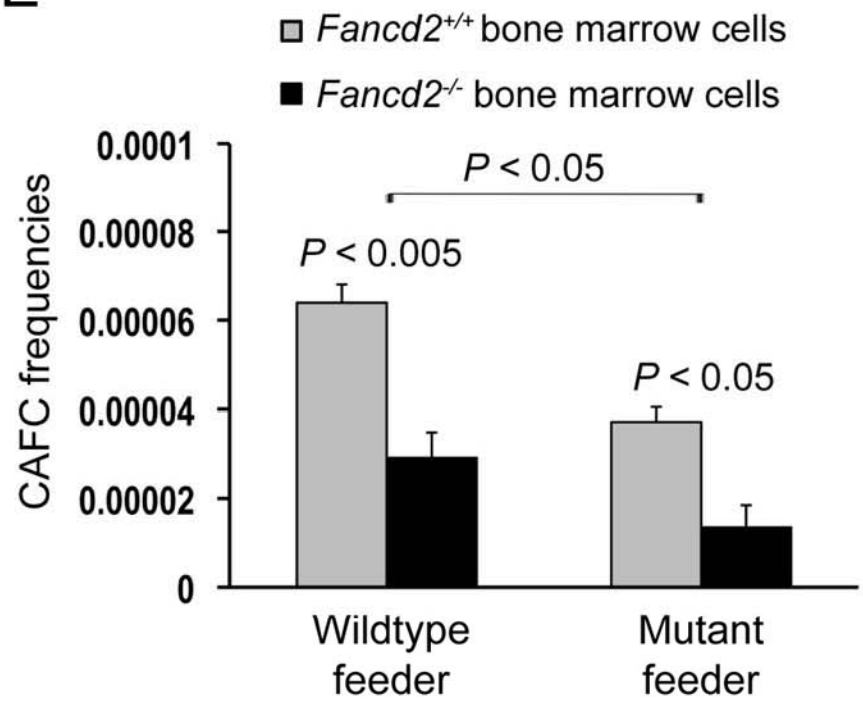

CFU-S number
14
12
10
8
6
4
2
0
P < 0.0001
Fancd2$^{-/-}$ donors
Fancd2$^{+/+}$ donors

Reduced colony forming ability

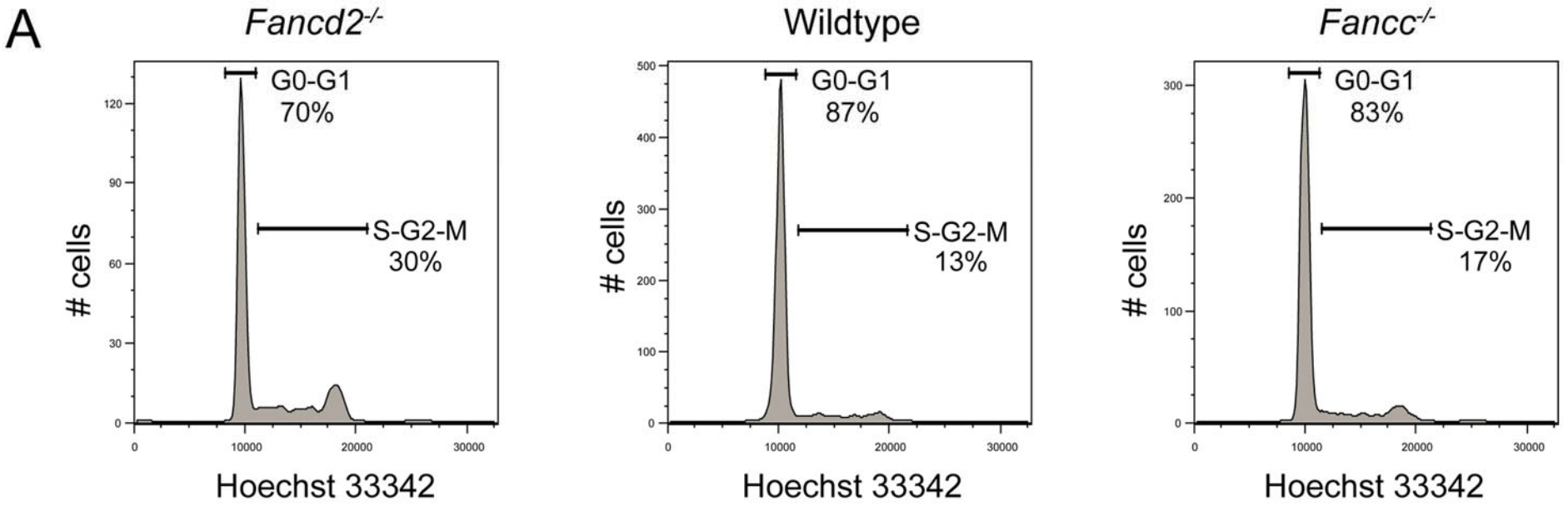
D

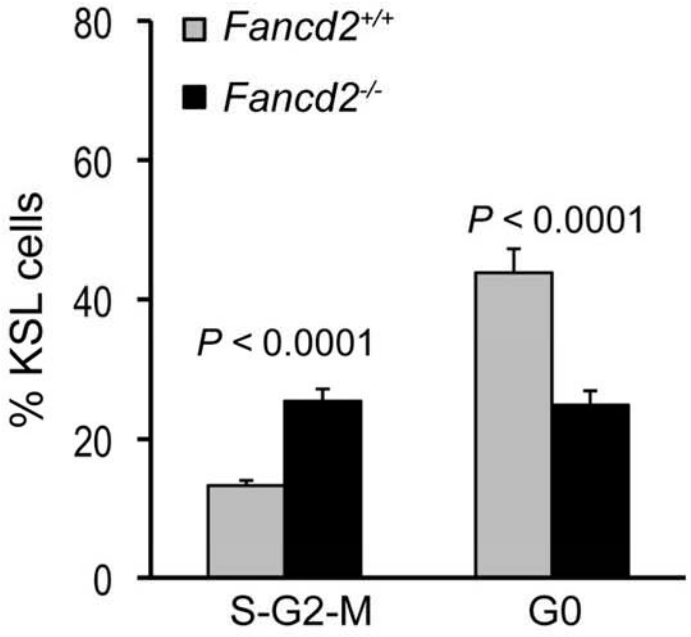


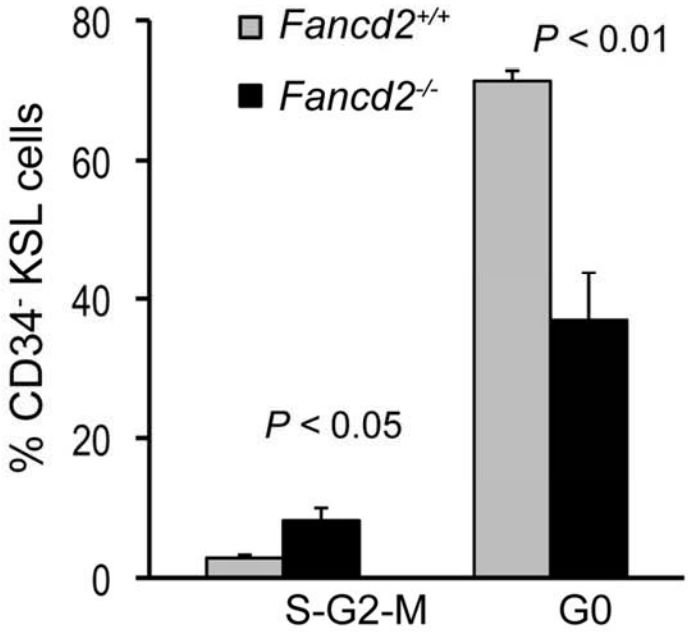
E



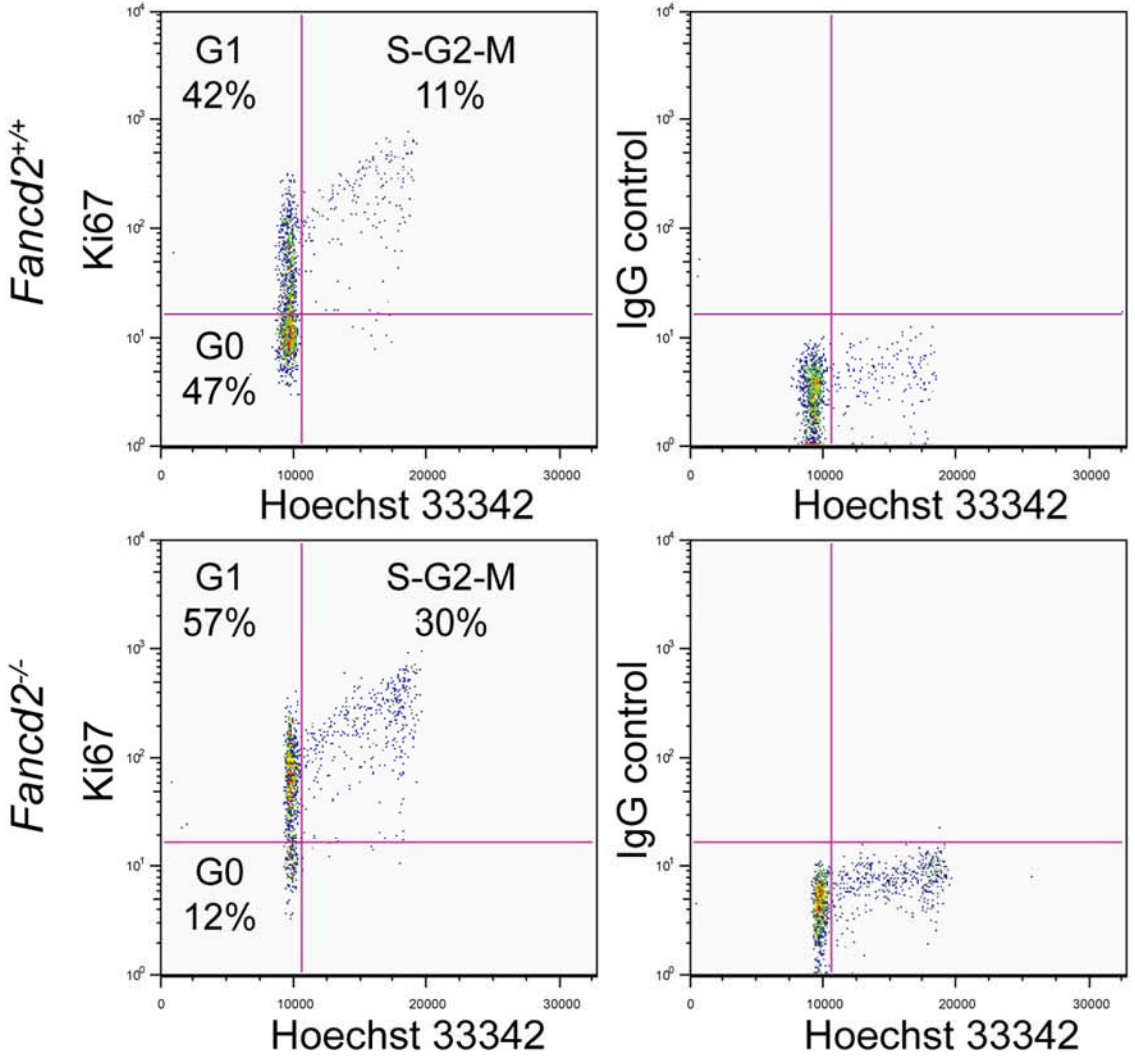
Changes in cell cycle status of stem cells




Fancd2+/+
Fancd2-/-
% KSL cells
80
60
40
20
0
P < 0.0001
P < 0.0001
S-G2-M
G0


Fancd2+/+
Fancd2-/-
% CD34- KSL cells
80
60
40
20
0
P < 0.01
P < 0.05
S-G2-M
G0

D


Fancd2+/+
Fancd2-/-
Ki67
IgG control
G1
42%
S-G2-M
11%
G0
47%
G1
57%
S-G2-M
30%
G0
12%
Hoechst 33342
Hoechst 33342
Hoechst 33342
Hoechst 33342

Hematopoietic defects in Fancd2-/- mice

- Reduced numbers of KLS stem cells
- Reduced repopulation ability
- Reduced CFU-S
- Reduced colony forming ability (cobblestone assay)
- Decreased pool of quiescent (G0) stem cells

Cell

Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT1 and PGC-1α

Marie Lagouge,[8,1] Carmen Argmann,[8,1] Zachary Gerhart-Hines,[2] Hamid Meziane,[3] Carles Lerin,[2] Frederic Daussin,[4] Nadia Messadeq,[3] Jill Milne,[5] Philip Lambert,[5] Peter Elliott,[5] Bernard Geny,[4] Markku Laakso,[6] Pere Puigserver,[2] and Johan Auwerx[1,3,7,*]

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[2] Department of Cell Biology, John Hopkins University School of Medicine, Baltimore, MD 21205, USA
[3] Institut Clinique de la Souris, BP10142, 67404, Illkirch, France
[4] Department of Respiratory, Cardiocirculatory and Exercise Physiology, Hôpitaux Universitaires, 67000 Strasbourg, France
[5] Sirtris Pharmaceutical, Cambridge, MA 02139, USA
[6] Department of Medicine, University of Kuopio, 70211 Kuopio, Finland
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DOI 10.1016/j.cell.2006.11.013

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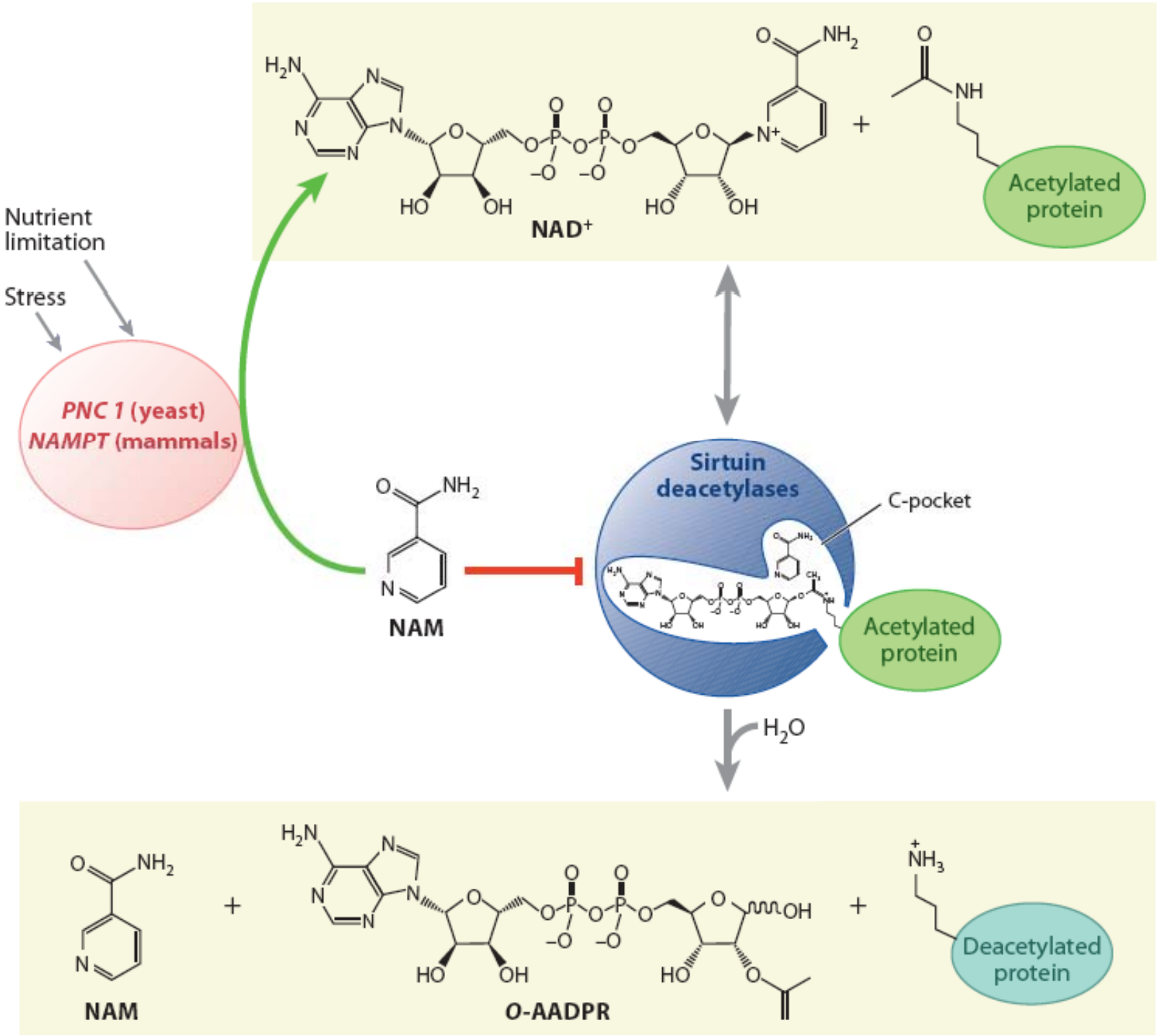
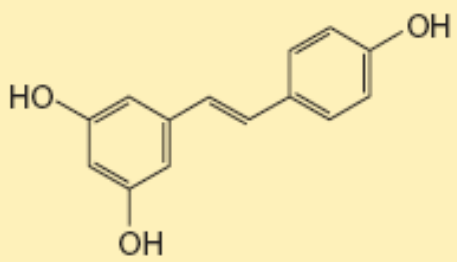
PLoS one

The SIRT1 Deacetylase Suppresses Intestinal Tumorigenesis and Colon Cancer Growth

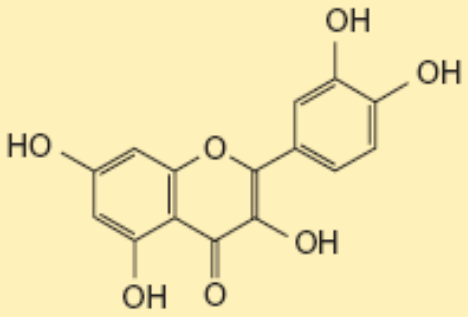
Ron Firestein[1,3,4,6☯], Gil Blander[2☯¤b], Shaday Michan[1☯], Philipp Oberdoerffer[1], Shuji Ogino[3,4], Jennifer Campbell[1], Anupama Bhimavarapu[2], Sandra Luikenhuis[1¤a], Rafael de Cabo[5], Charles Fuchs[6], William C. Hahn[6], Leonard P. Guarente[2], David A. Sinclair[1*]


Nutrient limitation
Stress
PNC 1 (yeast)
NAMPT (mammals)
NAD+
Acetylated protein
NAM
Sirtuin deacetylases
C-pocket
Acetylated protein
H2O
NAM
O-AADPR
Deacetylated protein

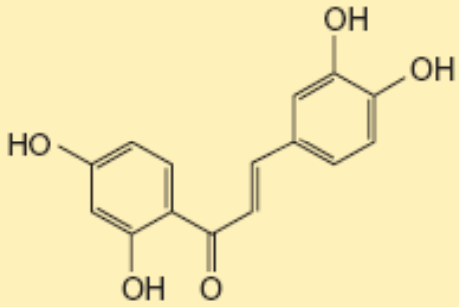
Activators



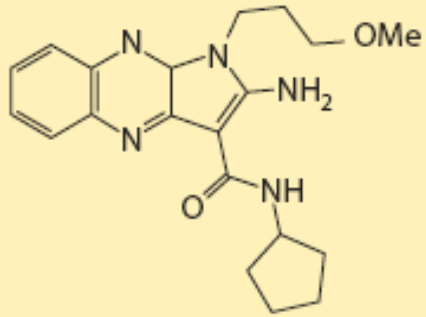
Resveratrol (46 μM)



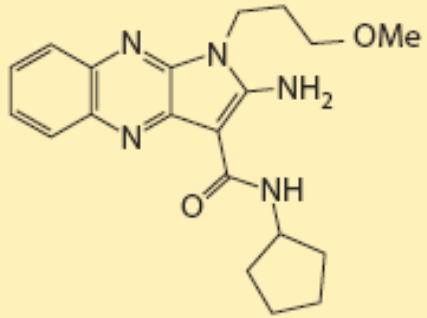
Quercetin



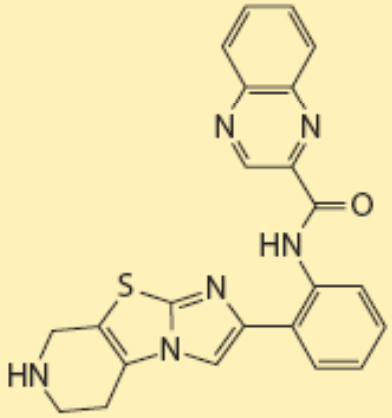
Butein



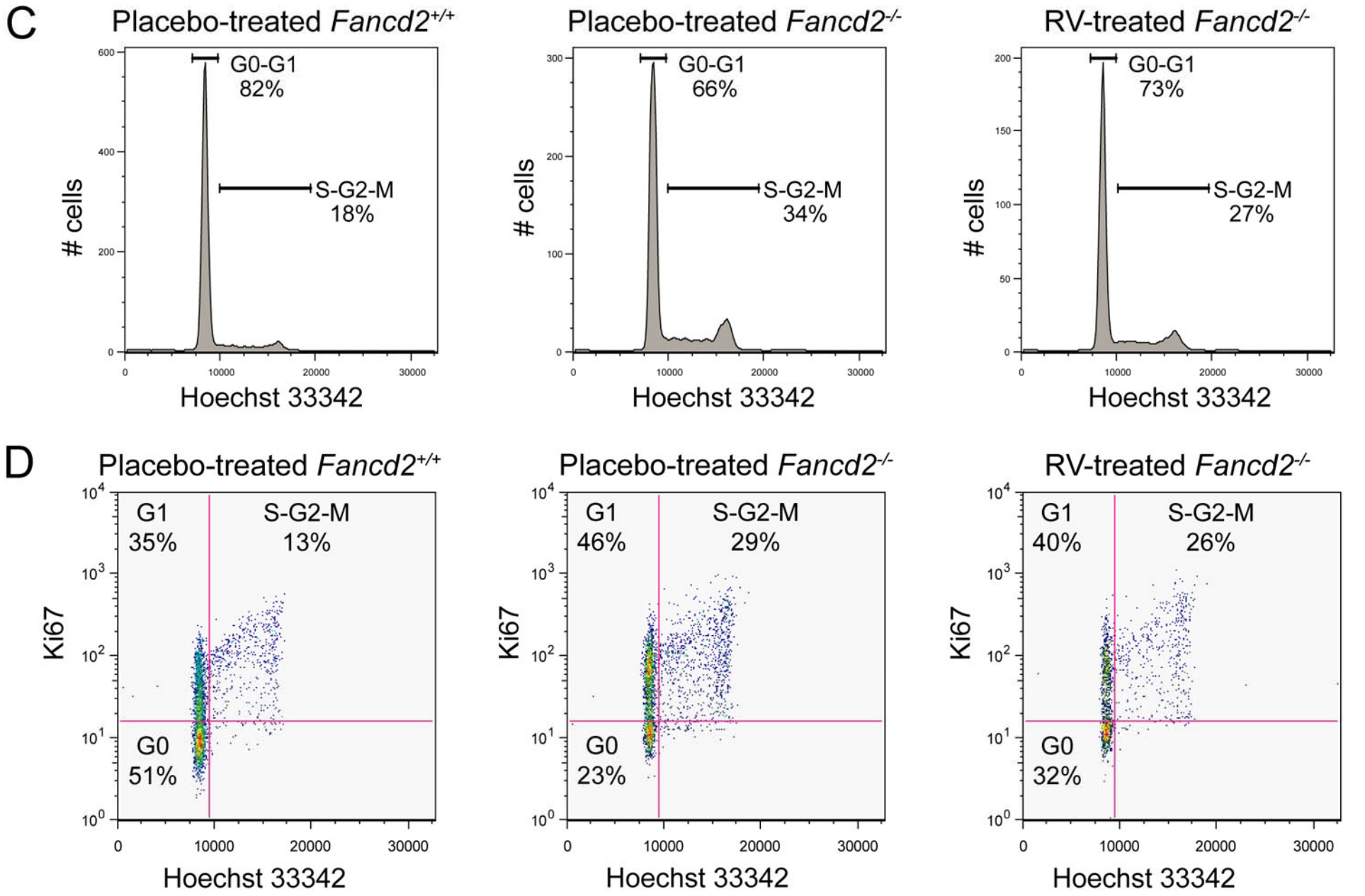
Pyrroloquinoxaline (233% at 10 μM)

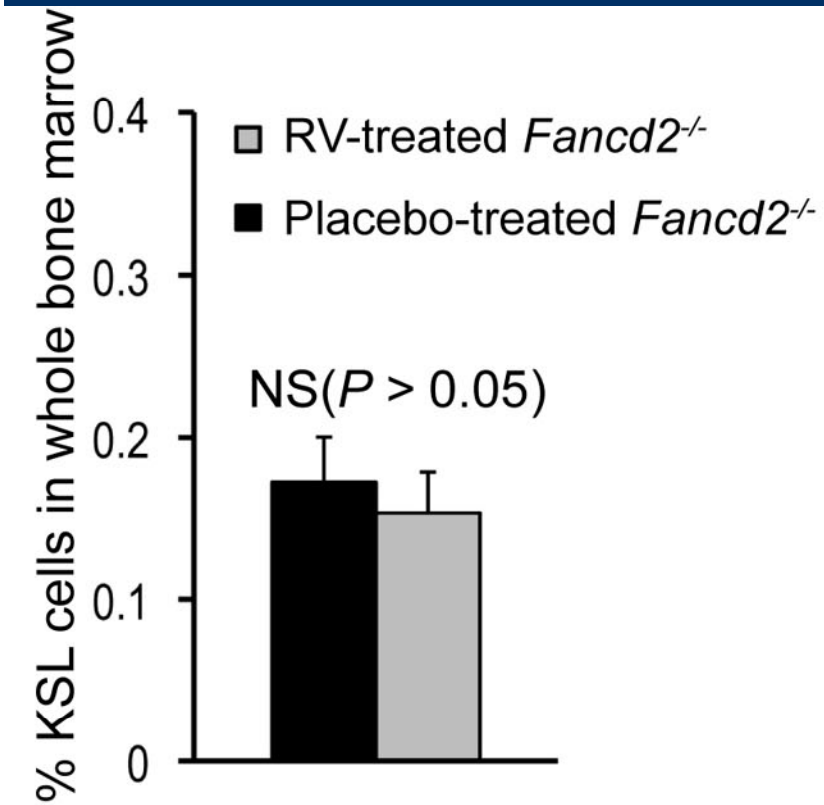


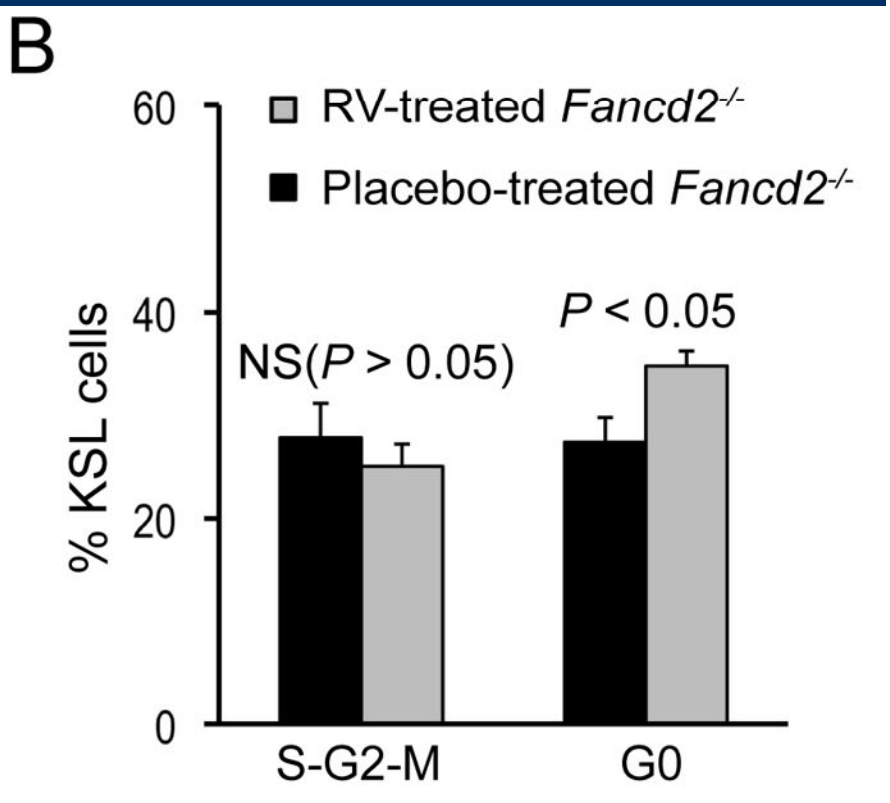
Oxazolopyridine (0.09 μM)

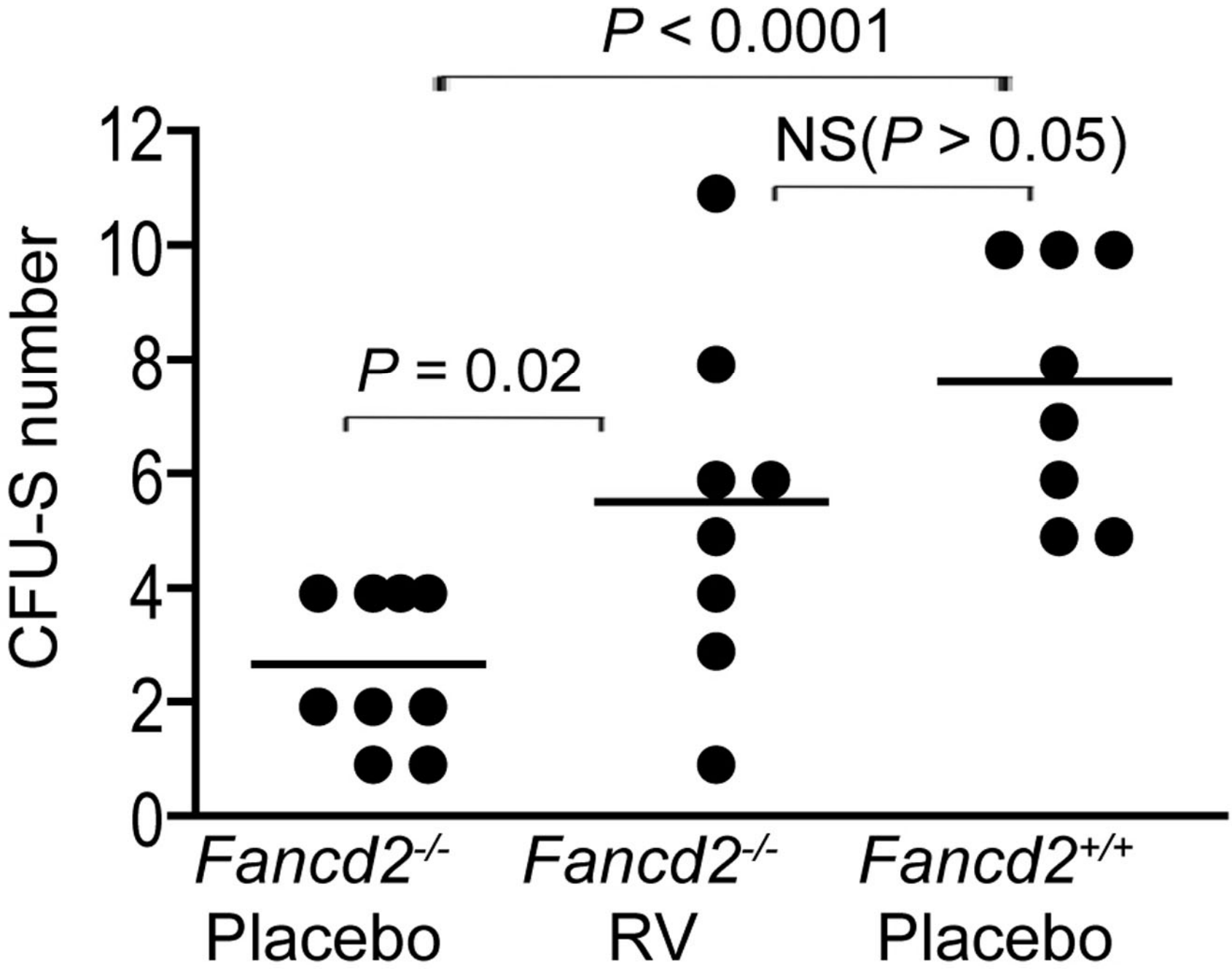


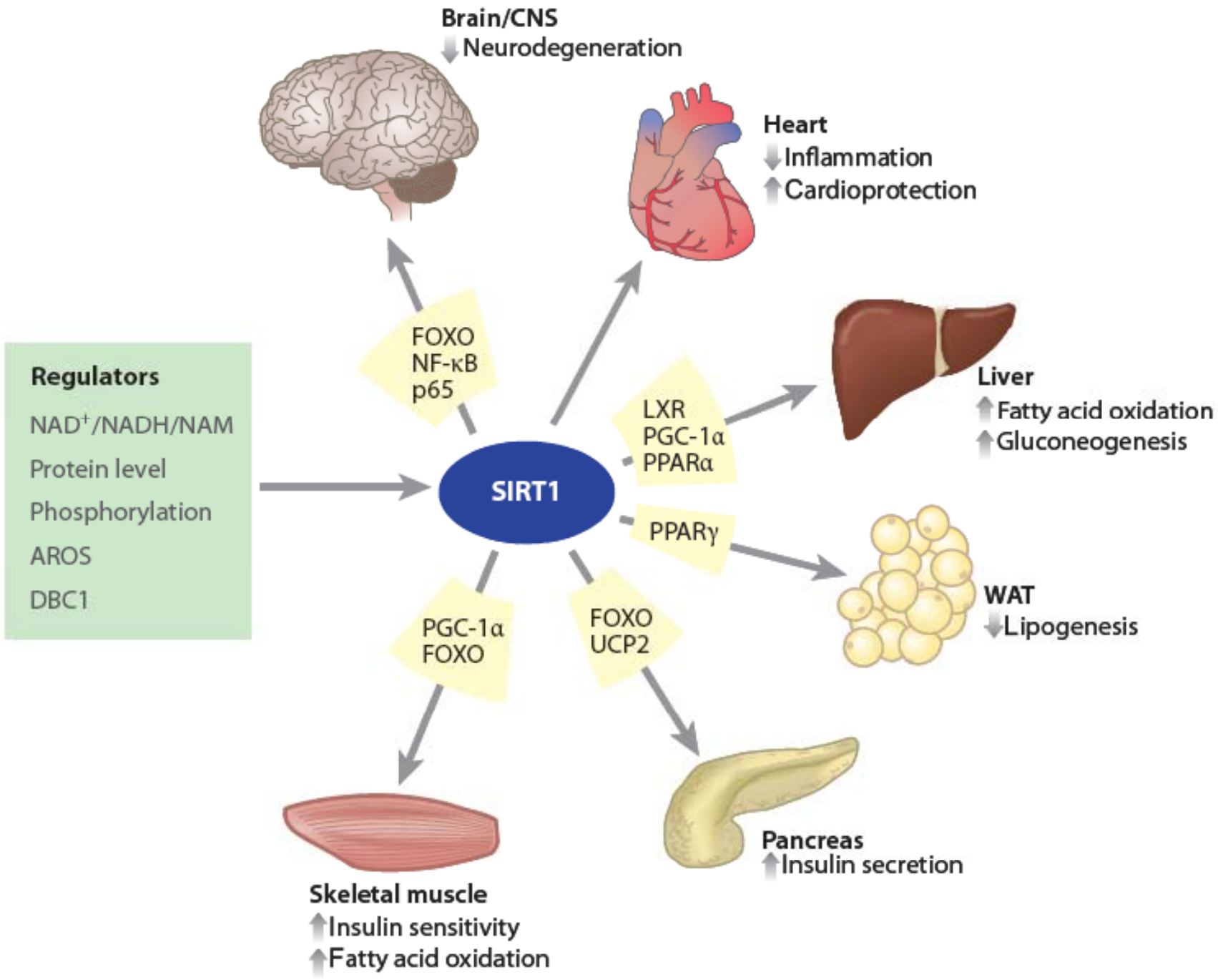
SRT1720 (0.16 μM)


C
Placebo-treated Fancd2+/+
G0-G1
82%
S-G2-M
18%
cells
Hoechst 33342
Placebo-treated Fancd2-/-
G0-G1
66%
S-G2-M
34%
cells
Hoechst 33342
RV-treated Fancd2-/-
G0-G1
73%
S-G2-M
27%
cells
Hoechst 33342
D
Placebo-treated Fancd2+/+
G1
35%
S-G2-M
13%
G0
51%
Ki67
Hoechst 33342
Placebo-treated Fancd2-/-
G1
46%
S-G2-M
29%
G0
23%
Ki67
Hoechst 33342
RV-treated Fancd2-/-
G1
40%
S-G2-M
26%
G0
32%
Ki67
Hoechst 33342

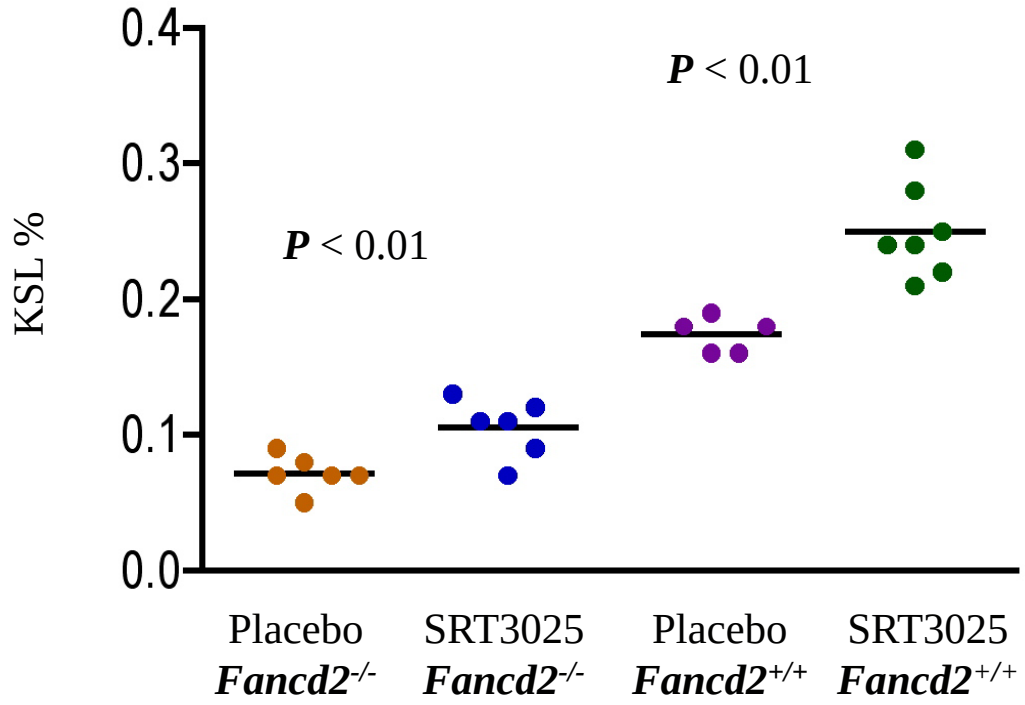

% KSL cells in whole bone marrow
0.4
0.3
0.2
0.1
0
RV-treated Fancd2-/-
Placebo-treated Fancd2-/-
NS(P > 0.05)


B
% KSL cells
60
40
20
0
RV-treated Fancd2-/-
Placebo-treated Fancd2-/-
NS(P > 0.05)
P < 0.05
S-G2-M
G0


P < 0.0001
NS(P > 0.05)
P = 0.02
CFU-S number
12
10
8
6
4
2
0
Fancd2-/-
Placebo
Fancd2-/-
RV
Fancd2+/+
Placebo


Brain/CNS
Neurodegeneration
Heart
Inflammation
Cardioprotection
Liver
Fatty acid oxidation
Gluconeogenesis
WAT
Lipogenesis
Pancreas
Insulin secretion
Skeletal muscle
Insulin sensitivity
Fatty acid oxidation
Regulators
NAD+/NADH/NAM
Protein level
Phosphorylation
AROS
DBC1
SIRT1
FOXO
NF-κB
p65
LXR
PGC-1α
PPARα
PPARγ
FOXO
UCP2
PGC-1α
FOXO

SRT3025 (“SirT Diet”) treatment increased the frequencies of KSL cells in both D2 mutant and wildtype mice

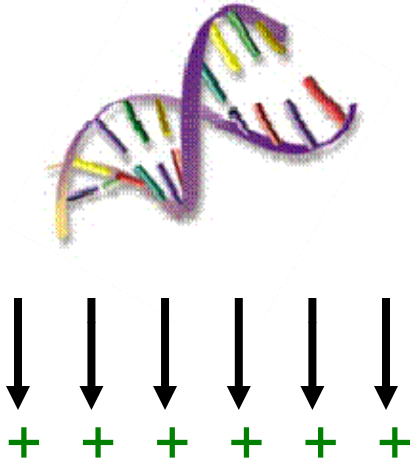


Conclusions

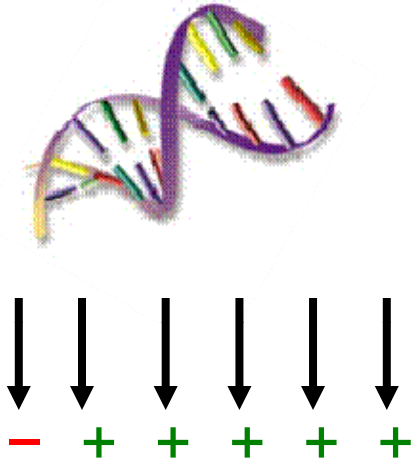
- Fancd2 mutant mice have several hematopoietic defects, which can be used to test drugs for their potential to ameliorate the defect
- The FA defects affects the stem cells themselves as well as the stroma
- The Sirt1 mimetic resveratrol ameliorates some of these hematopoietic defects
- Srt3025 significantly increases the number of stem cells in both wild-type and FA mutant mice

Cancer Cells are often defective in one DNA Repair Pathway

Normal cells



Cancer cells



BRCA1 mutation

Predicts PARPi sensitivity of breast cancer

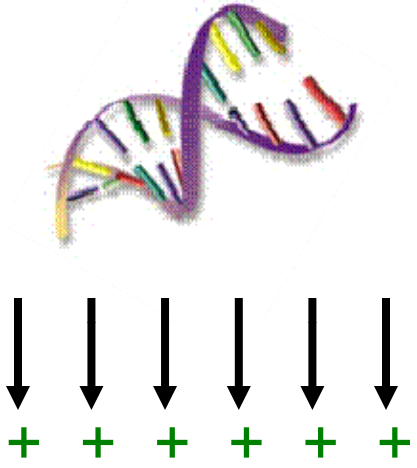
Six normal DNA repair pathways

The specific pathway lost may determine the best course of chemotherapy and radiation (personalized medicine)

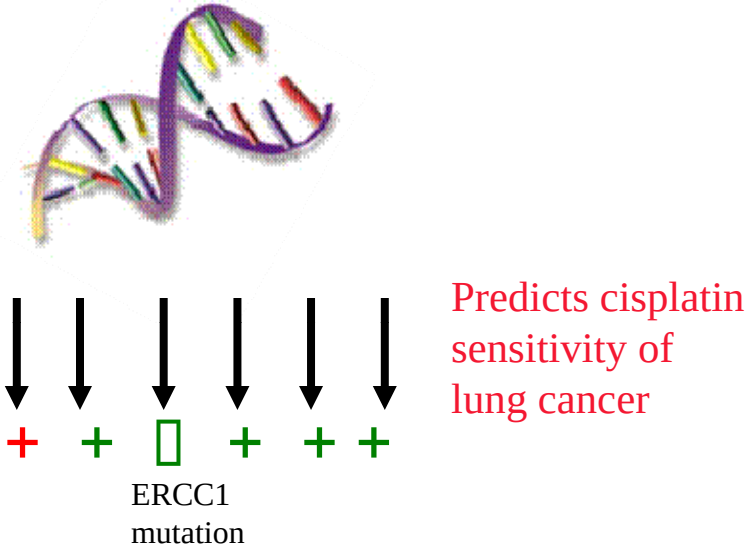
Kennedy and D'Andrea, J.C.O. 24: 3799, 2006

Cancer Cells are often defective in one DNA Repair Pathway

Normal cells



Cancer cells



Six normal DNA repair pathways

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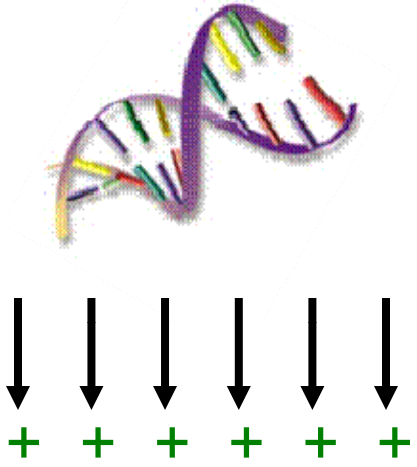
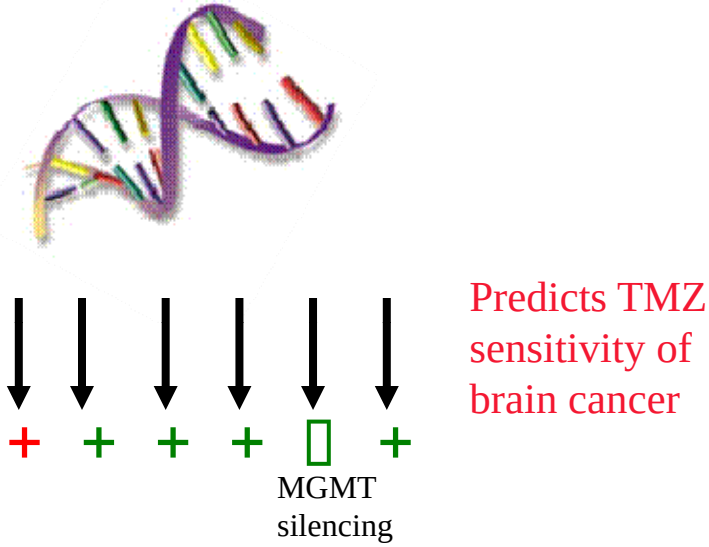
Cancer Cells are often defective in one DNA Repair Pathway

Normal cells



Cancer cells



Six normal DNA repair pathways

The specific pathway lost may determine the best course of chemotherapy and radiation (personalized medicine)

Kennedy and D'Andrea, J.C.O. 24: 3799, 2006

Using Synthetic Lethality to treat tumors with Underlying defects in the Fanconi Anemia Pathway

Since 5-20 % of solid tumors in the general population have a defect in the FA pathway, we would like to find targeted therapies for these tumors.

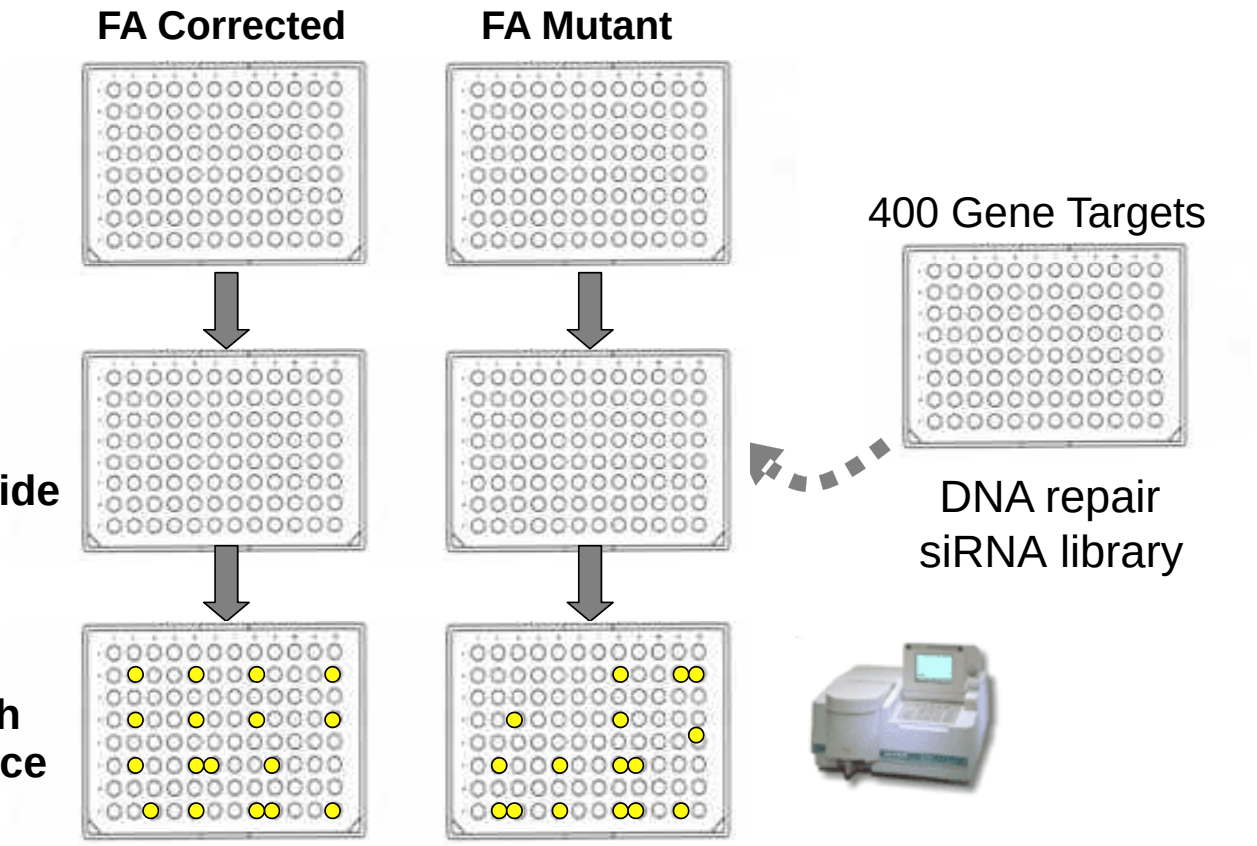
Used the principle of “Synthetic Lethality”

Screening Approach to Identify Gene Targets in FA Cells.

Day 1
Cells seeded

Day 2
Each well transfected with siRNA oligonucleotide

Day 6
Measure Cell viability with ATP-activated luminiscence (quantitative measure)



siRNA Targets Specifically Toxic to FA Pathway Deficient Cells

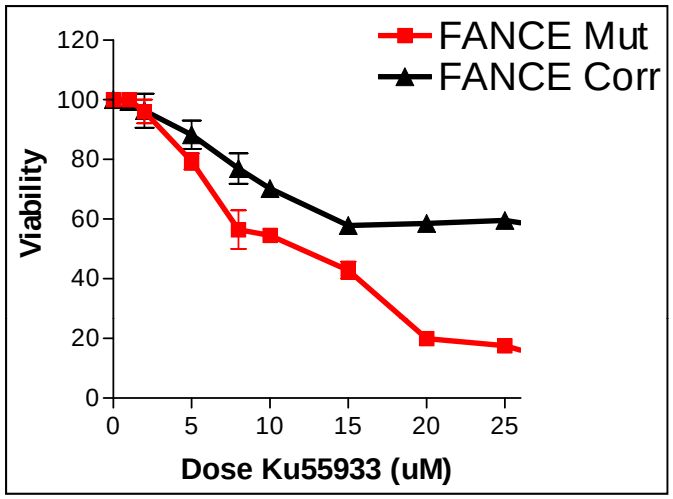
Gene	Function
PARP1	BER
NEIL1	BER
LIG1	BER/DNA replication
LIG3	BER
NBS1	MRN complex-DSB response
RAD50	MRN complex-DSB response
ATM	DSB signaling

siRNA Targets Specifically Toxic to FA Pathway Deficient Cells

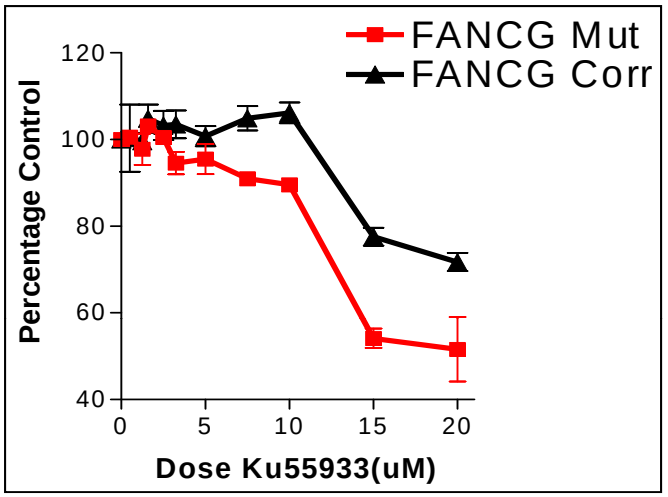
Gene	Function	
PARP1	BER	←
NEIL1	BER	
LIG1	BER/DNA replication	Small Molecule Inhibitors Available
LIG3	BER	
NBS1	MRN complex-DSB response	
RAD50	MRN complex-DSB response	
ATM	DSB signaling	←

FA Cell Lines Are Hypersensitive to the ATM Inhibitor, Ku55933

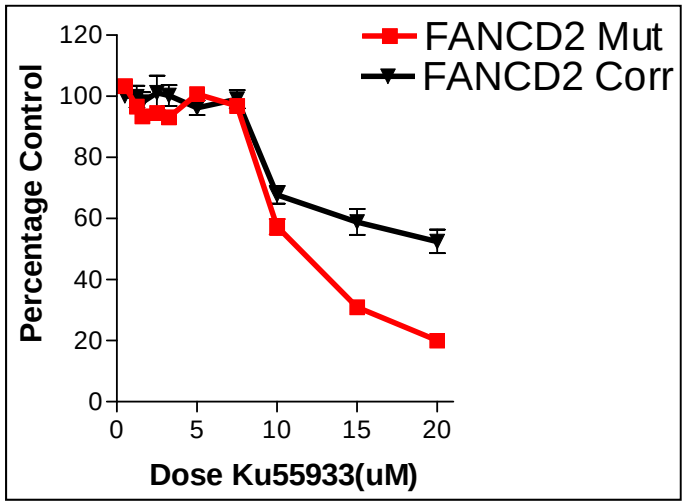
FA-E Cells



FA-G Cells

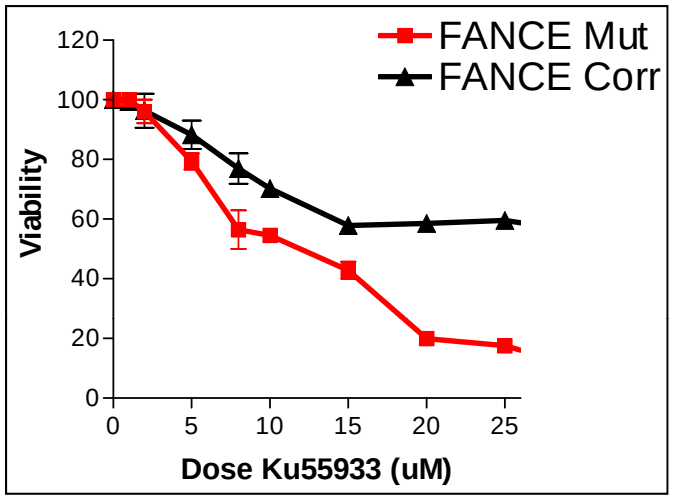


FA-D2 Cells

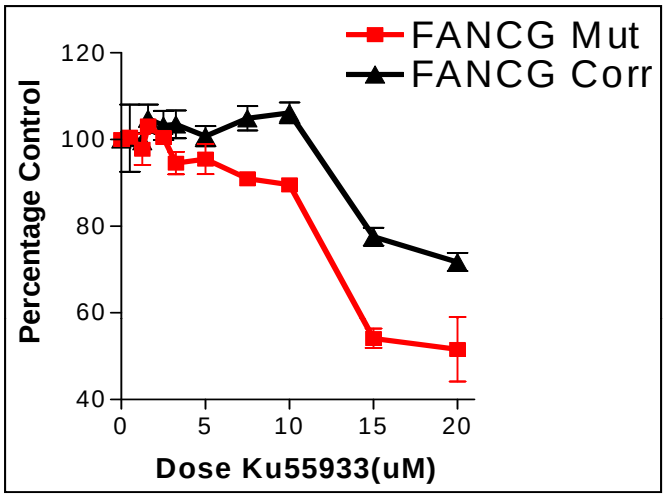


FA Cell Lines Are Hypersensitive to the ATM Inhibitor, Ku55933

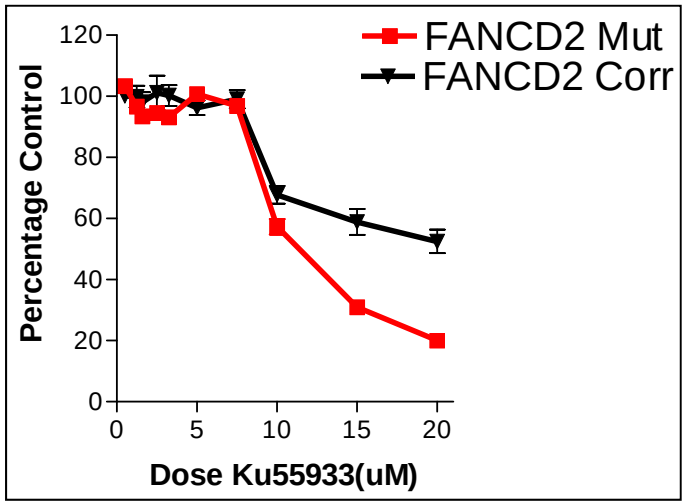
FA-E Cells



FA-G Cells



FA-D2 Cells



Synthetic Lethal Relationships of DNA repair pathways are reciprocal

Conclusions:

1) Conventional cancer treatments (Radiation and Chemotherapy) kill tumors by causing DNA damage.

2) There are six major DNA Repair pathways, and each pathway has suitable biomarkers and druggable targets

3) There is an emerging class of DNA repair inhibitors which may be useful in cancer chemotherapy as sensitizers of conventional treatments.

4) Based on the principle of Synthetic Lethality, DNA repair inhibitors, such as Parp or Atm inhibitors, may be useful as Monotherapy for some cancers with underlying DNA repair defects.

5) Biomarkers of the FA pathway provide a convenient predictor of subsets of human tumors which are sensitive to Parp and Atm inhibitors.