Biology of cell-free nucleic acids and its role in initiation and metastasis of cancer

Professor Indraneel (Neel) Mittra
MBBS, FRCS (England), PhD.(London), FASc, FNA

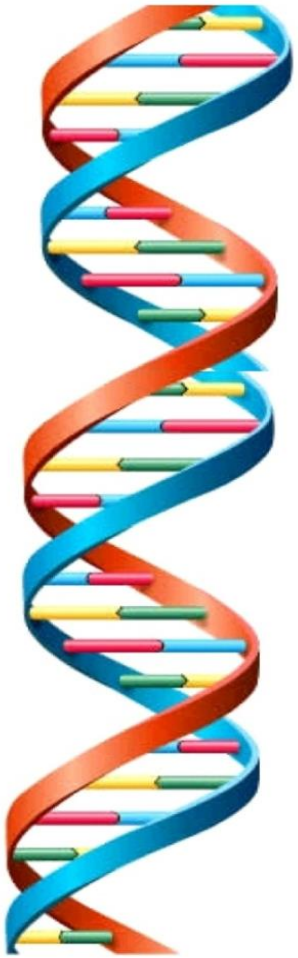
Dr. Ernest Borges Chair in Translational Research
and Professor Emeritus
Department of Surgical Oncology
Tata Memorial Centre, Mumbai

10^9 – 10^{12} cells die in adult human body daily

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Cell - death

DNA



Early apoptosis

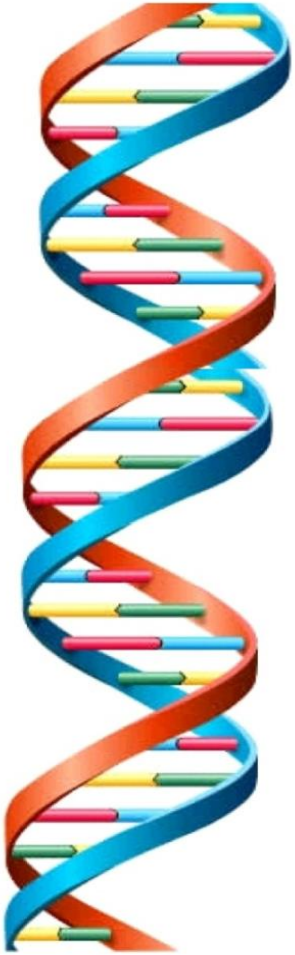


Late apoptosis



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Biologically inactive



Biologically active



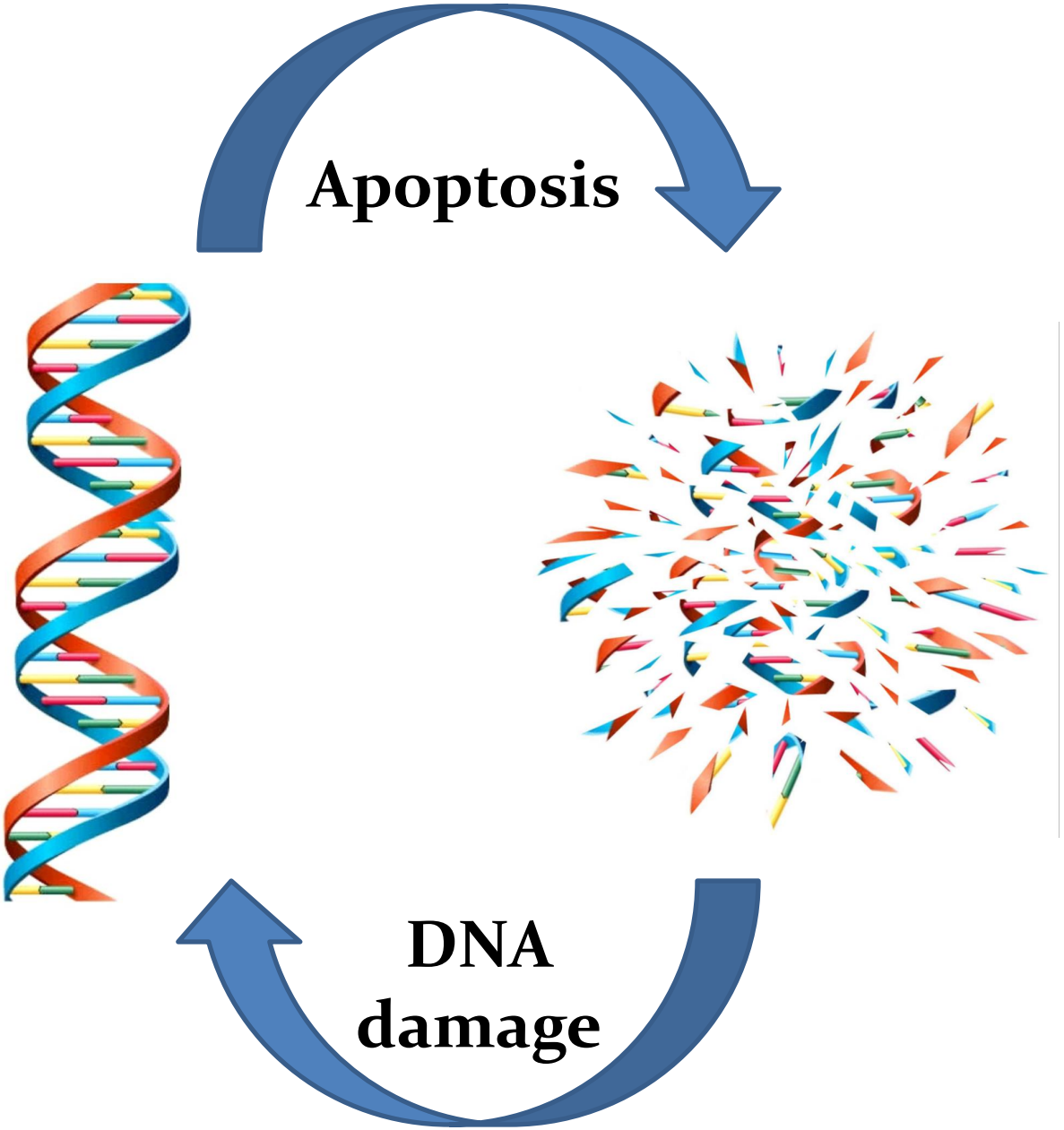
DNA damaging

Mutagenic

Carcinogenic

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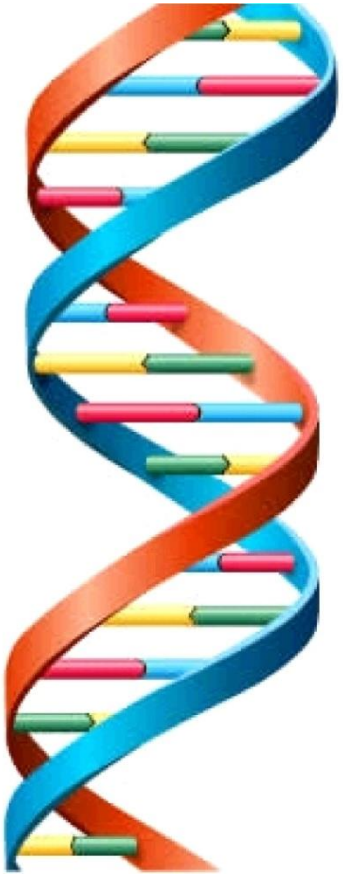
DNA's self-destructive life cycle

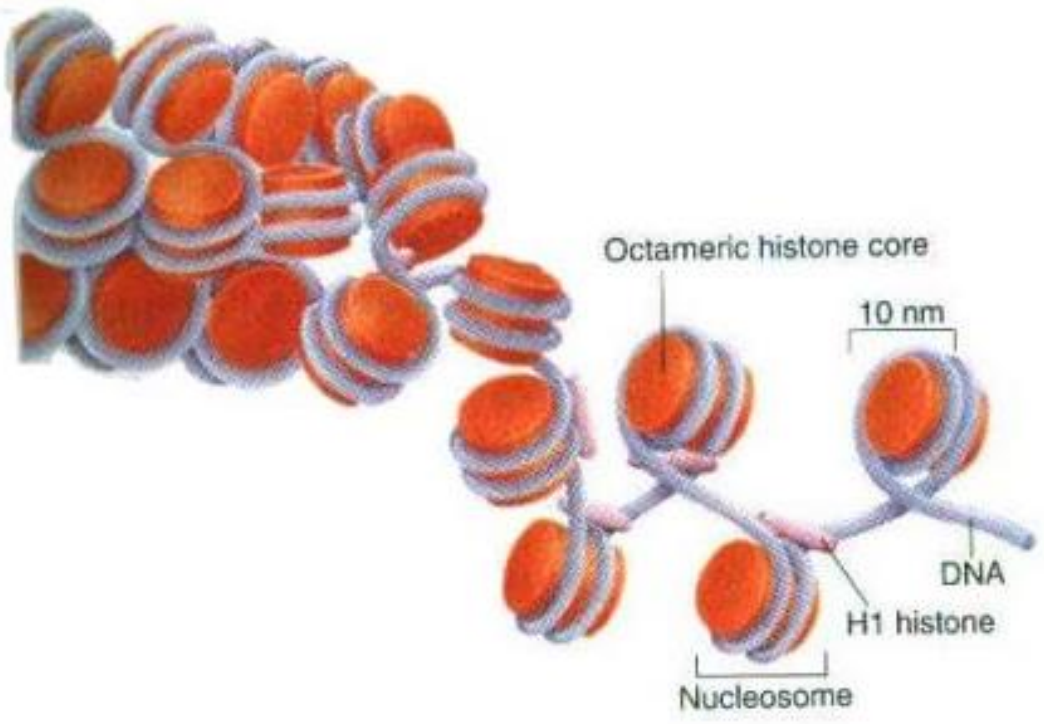


DNA's self destruction and birth of a new biology

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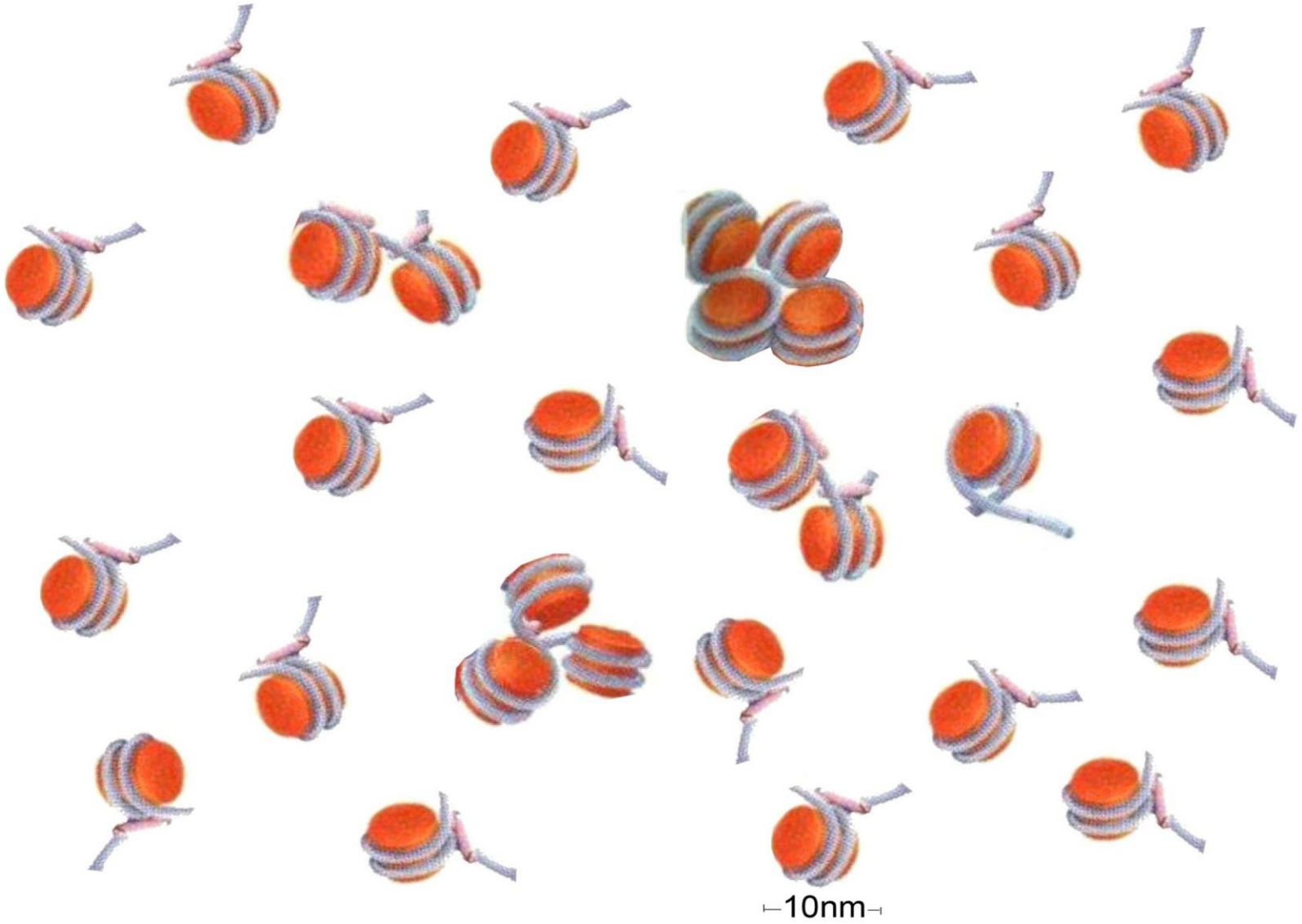
DNA or chromatin?





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Cell-free chromatin



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Cell-free chromatin

=

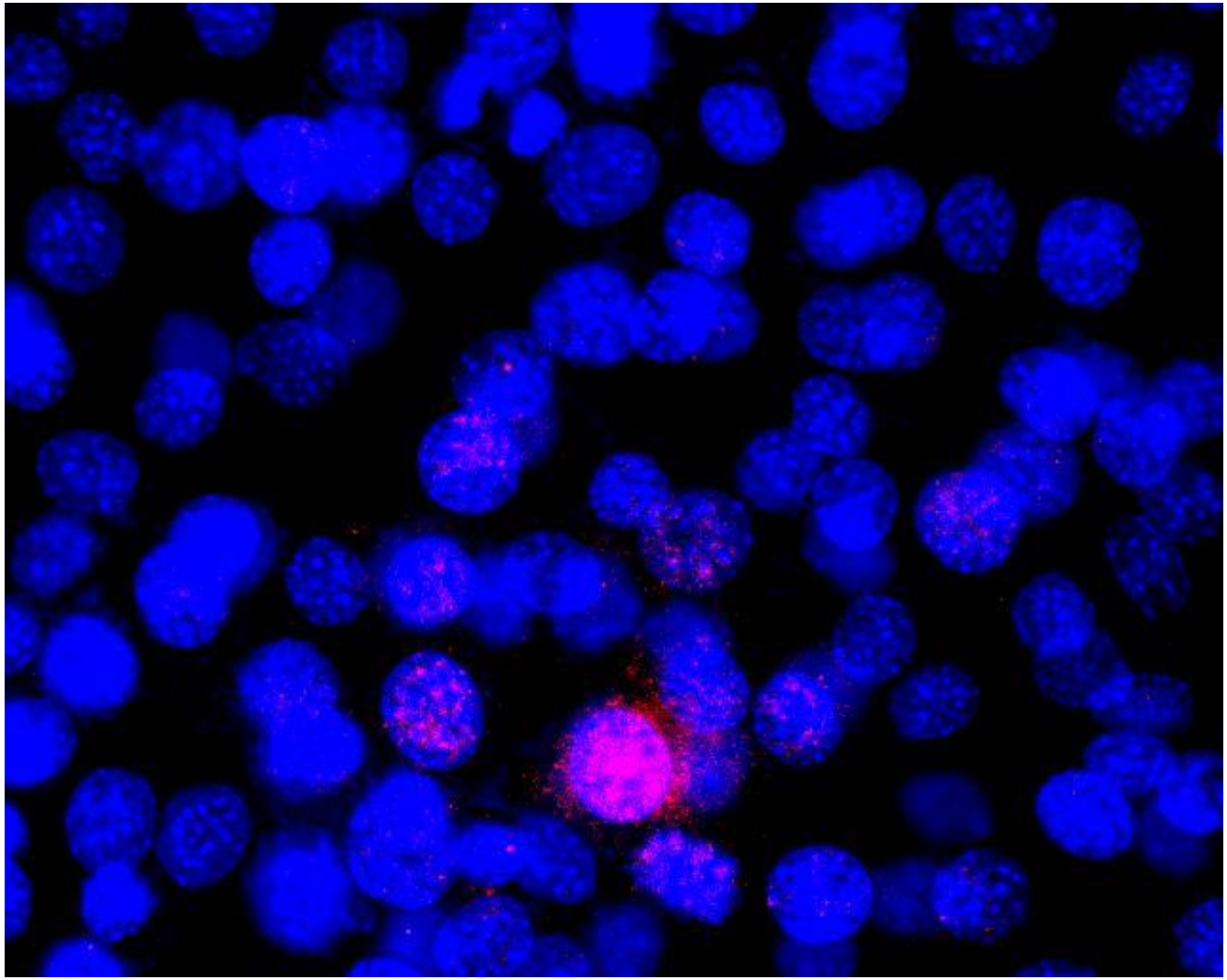
cfCh

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Biology of cfCh from dying cells

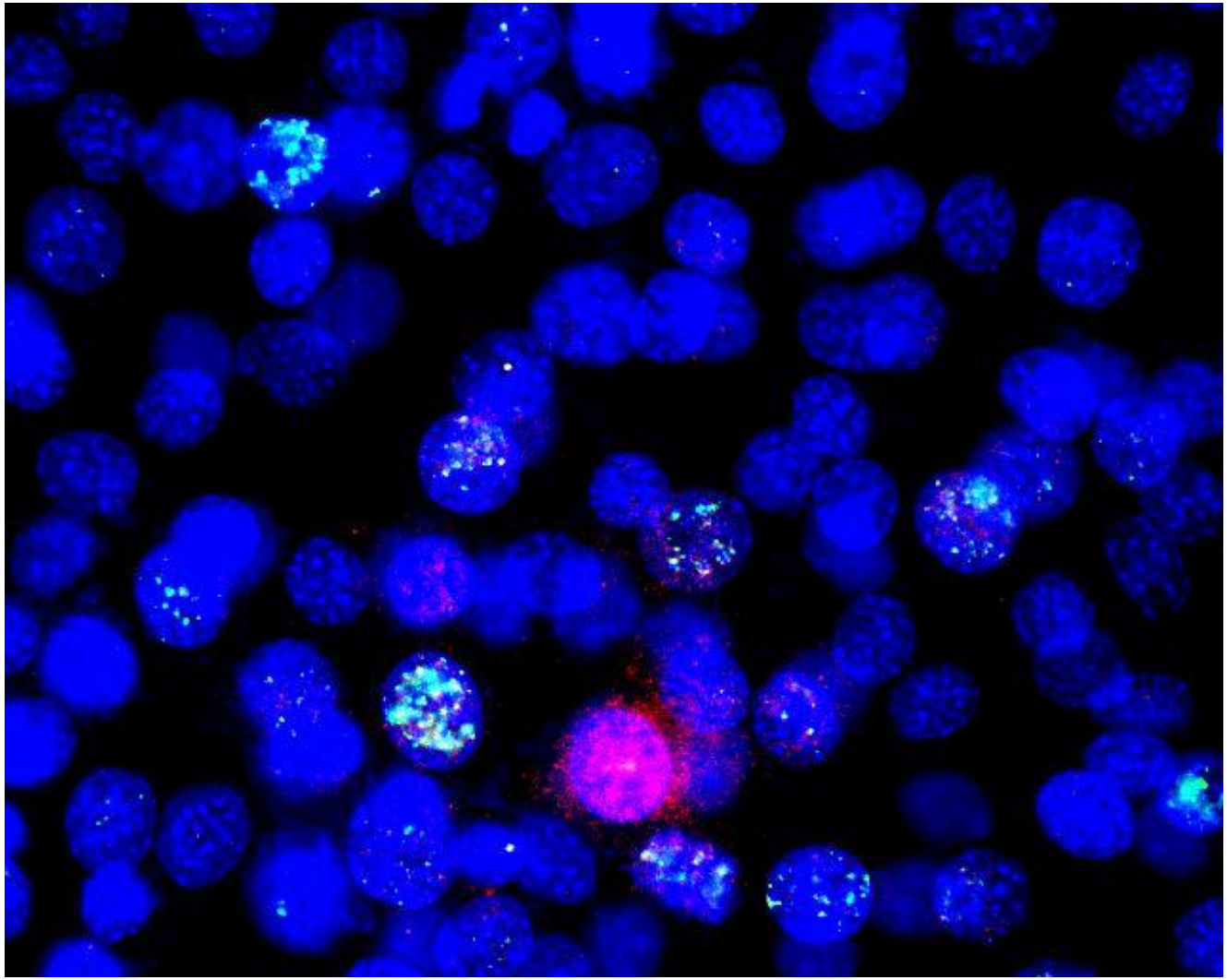
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Bystander effects of cfCh in normal fibroblast microenvironment



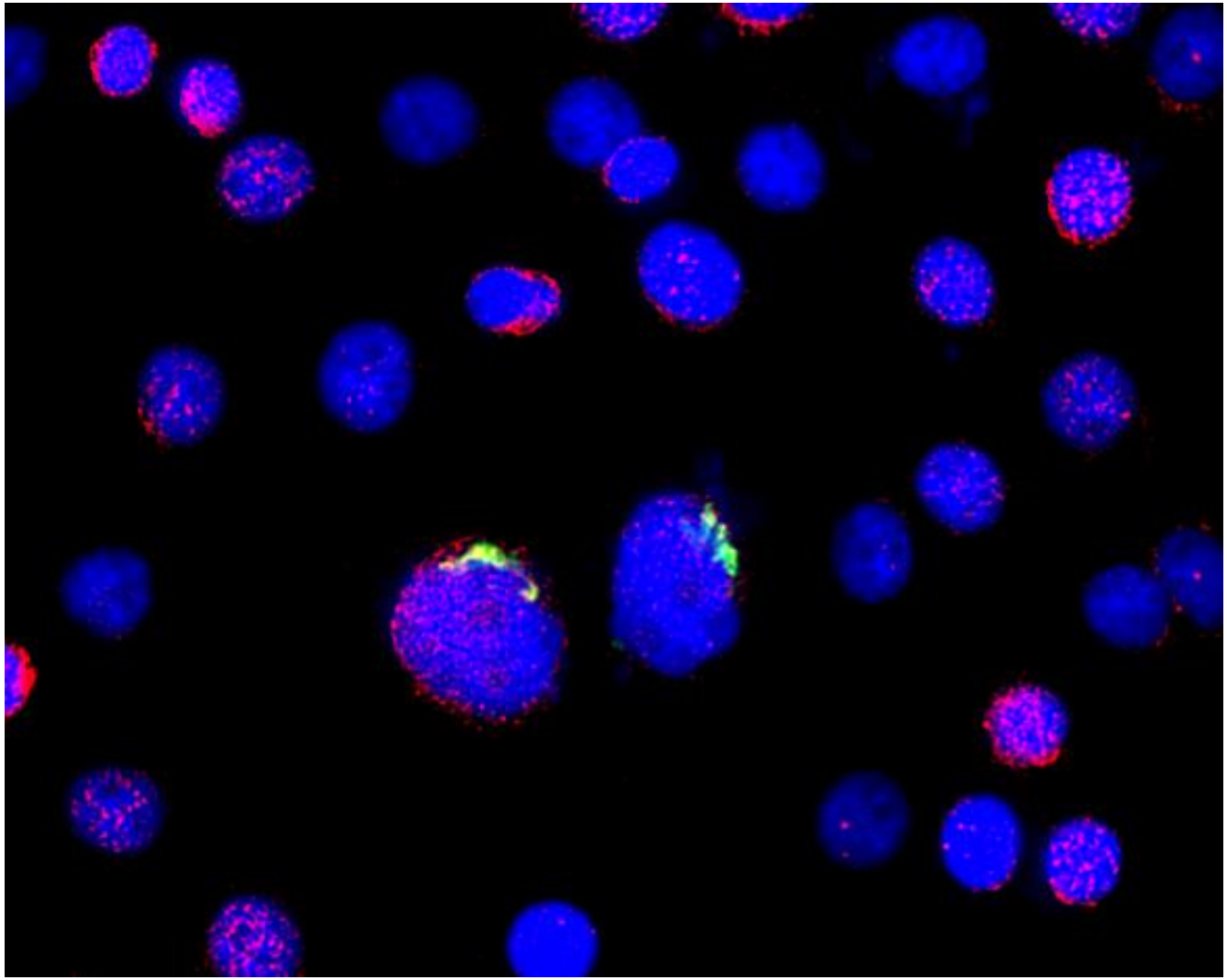
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Bystander DNA damage - γH2AX in normal fibroblast microenvironment



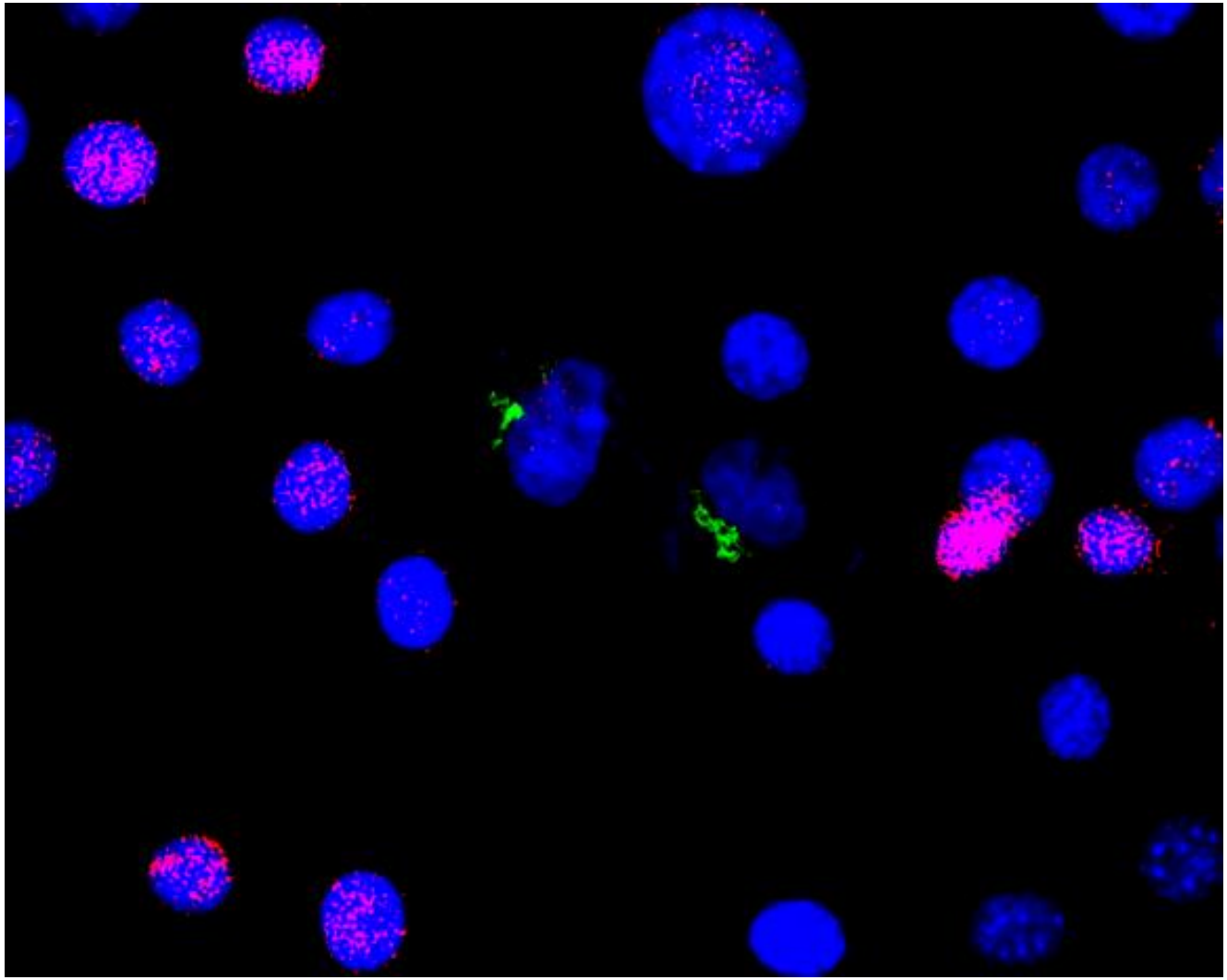
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Bystander DNA damage - γH2AX in tumour microenvironment



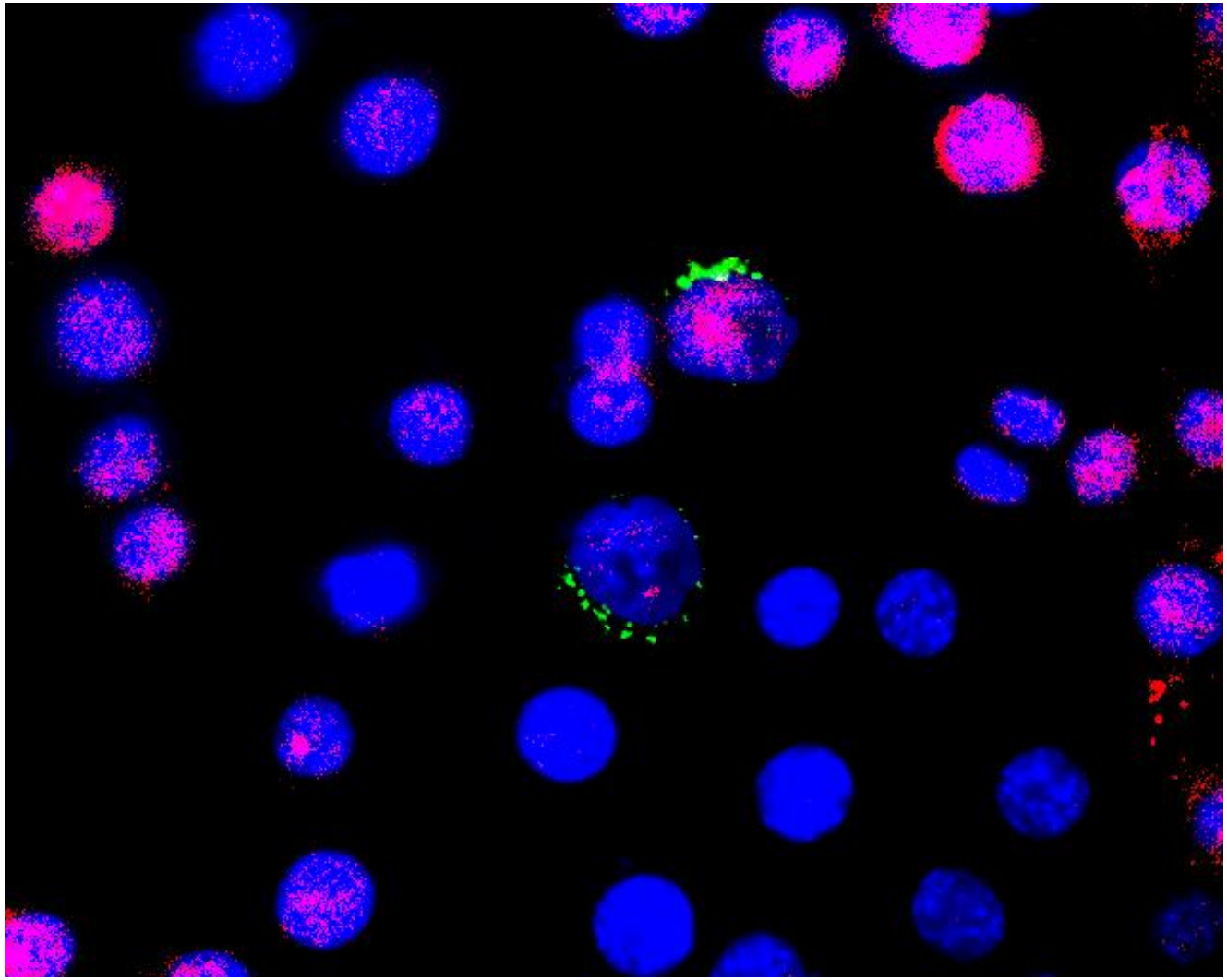
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Bystander DNA damage – ATM in tumour microenvironment



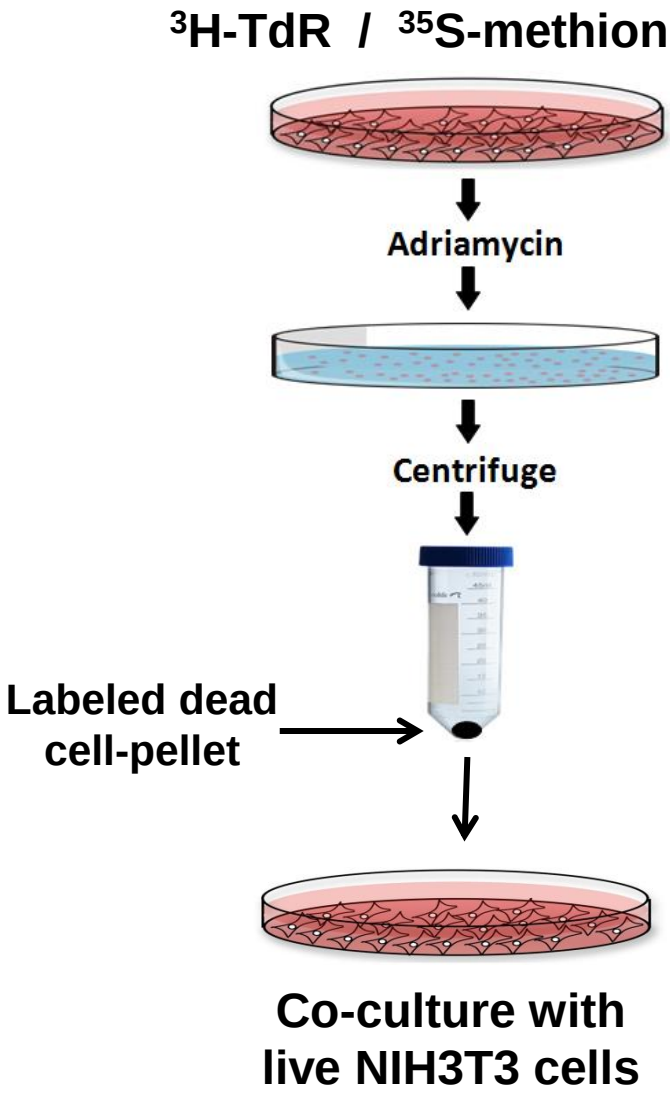
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Bystander inflammation- NFκB in tumour microenvironment



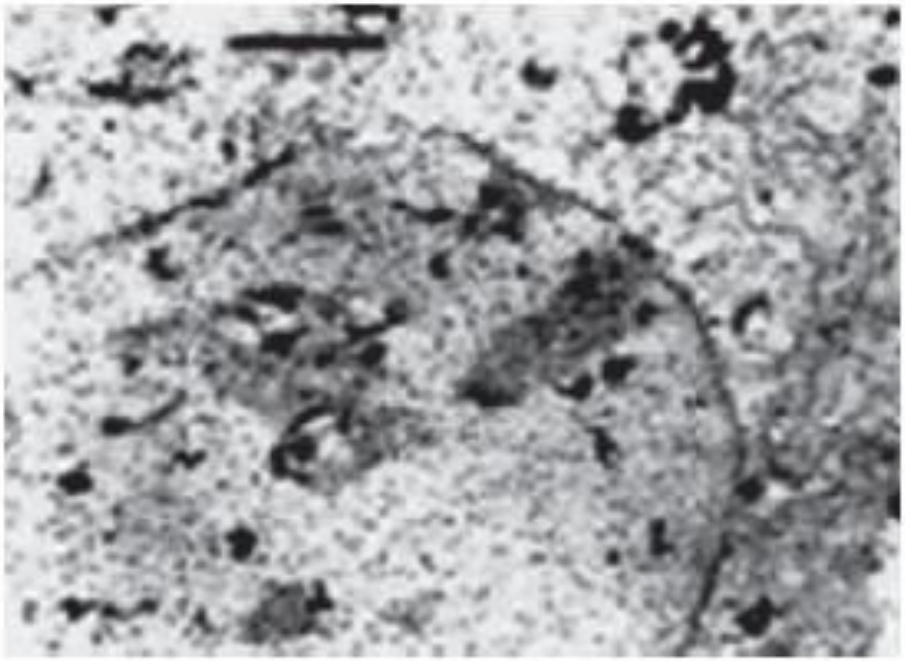
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^{3}H-TdR / ^{35}S-methionine pre-labeled Jurkat cells

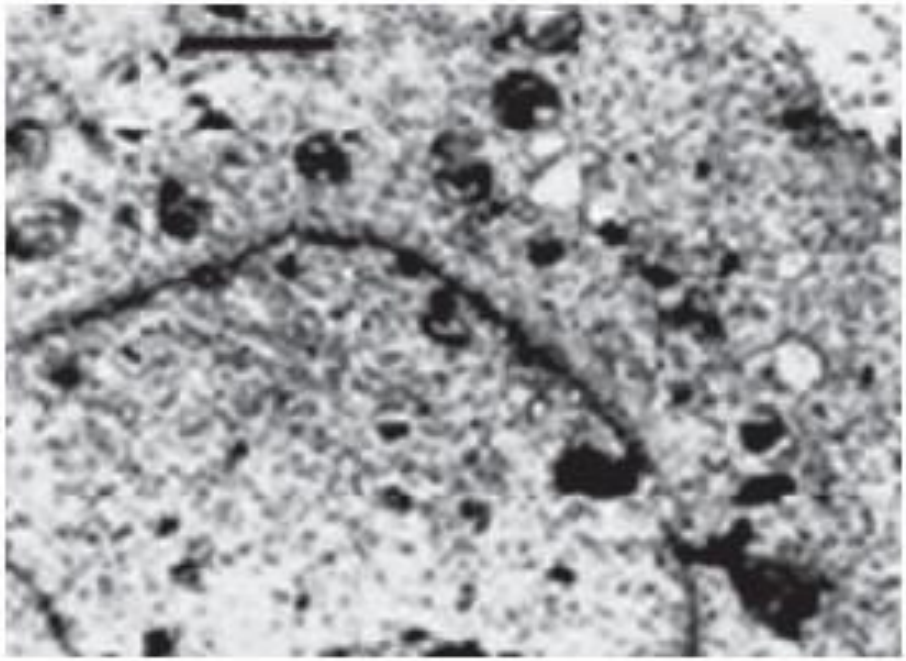


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Nuclear uptake of radio-labelled cfCh from apoptotic B16-F10 cells (48 hr)



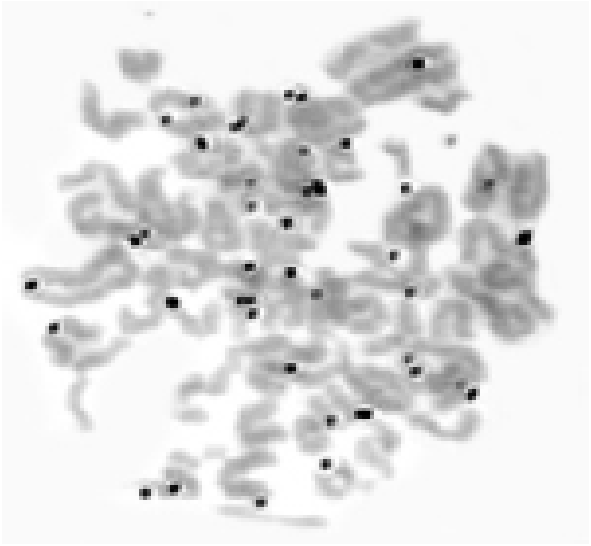
NIH3T3+ P1 (^{3}H-TdR)



NIH3T3+ P1 (^{35}S-methionine)

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Intra-nuclear cfCh associate with host cell chromosomes



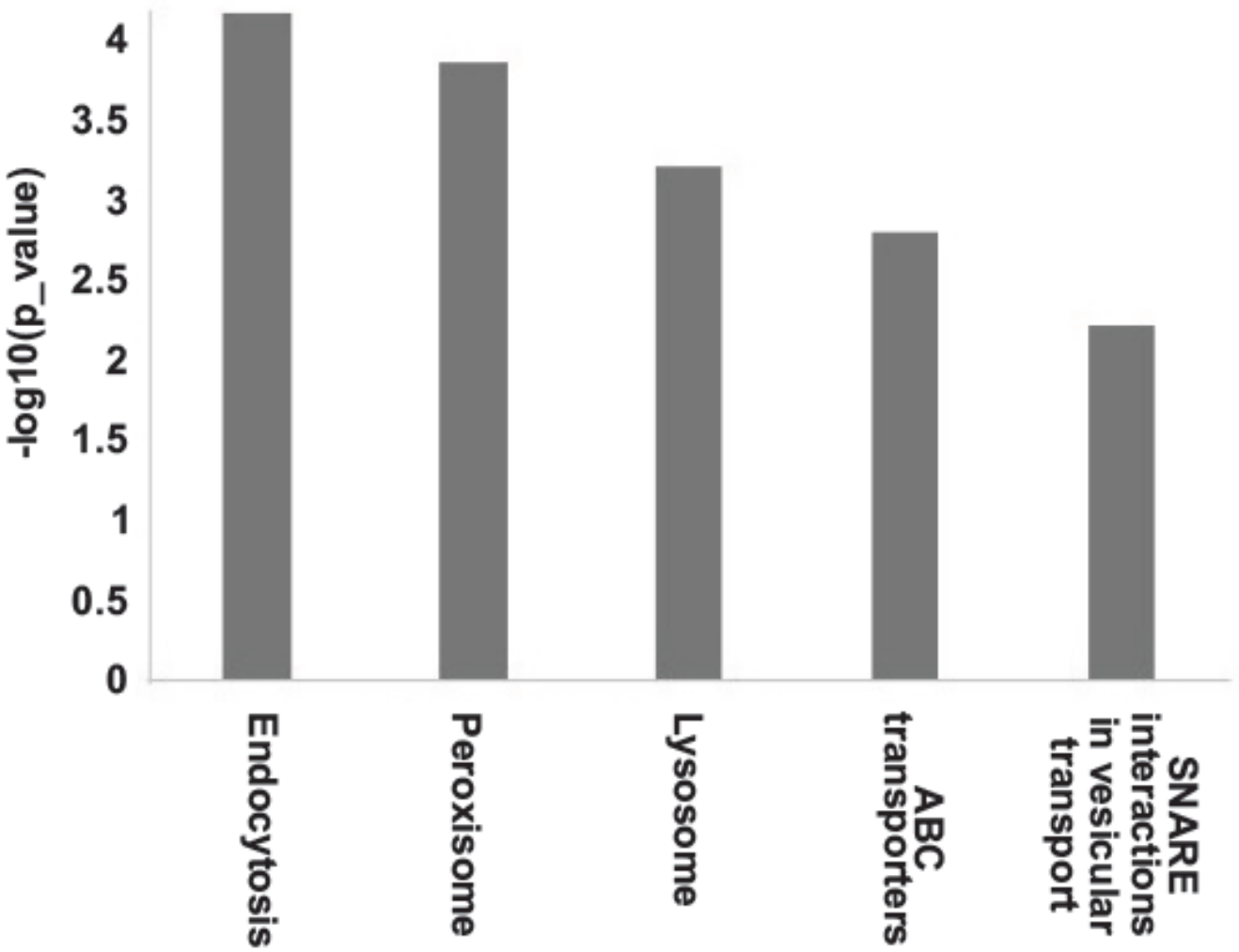
^{3}H-TdR



^{35}S-methionine

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Up-regulation of phagocytosis pathways (6hr)



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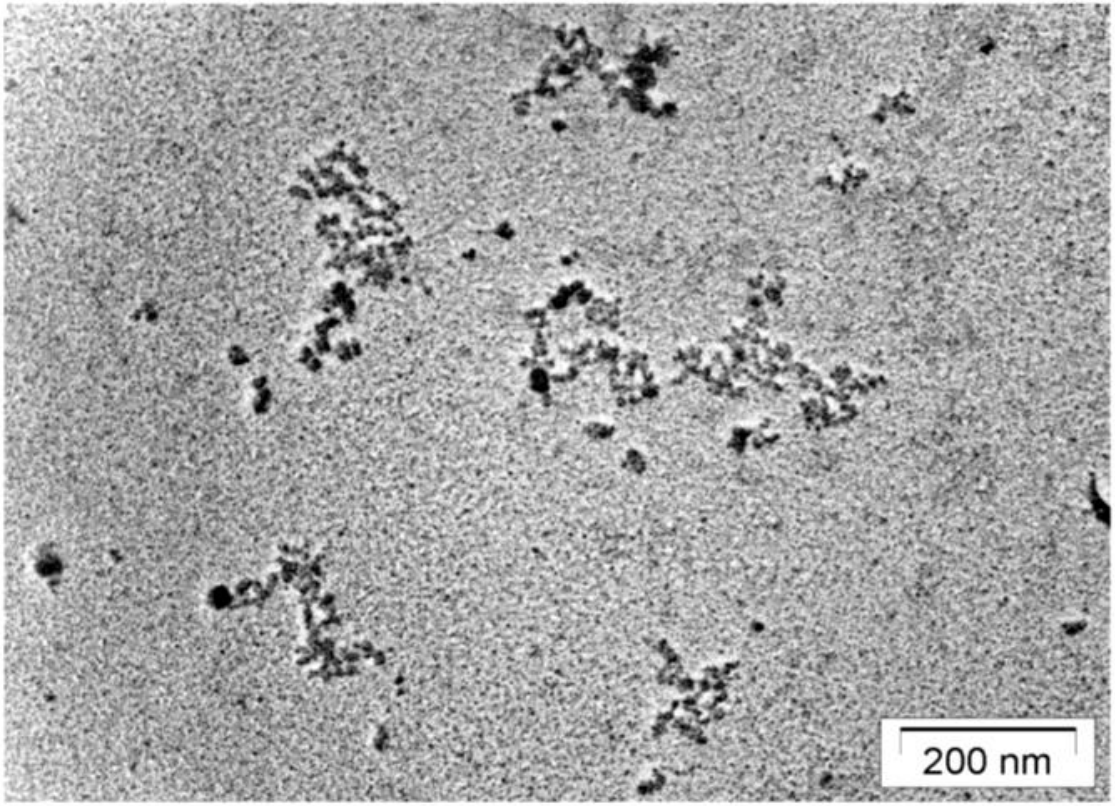
Biology of circulating cfCh

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Circulating nucleic acids damage DNA of healthy cells by integrating into their genomes

INDRANEEL MITTRA[1,*], NAVEEN KUMAR KHARE[1], GORANTLA VENKATA RAGHURAM[1], ROHAN CHAUBAL[2], FATEMA KHAMBATTI[1], DEEPIKA GUPTA[1], ASHWINI GAIKWAD[1], PREETI PRASANNAN[1], AKSHITA SINGH[1] AISHWARYA IYER[1], ANKITA SINGH[2], PAWAN UPADHYAY[2], NAVEEN KUMAR NAIR[1], PRADYUMNA KUMAR MISHRA[1] and AMIT DUTT[2]

[1]Translational Research Laboratory, [2]Integrated Cancer Genomics Laboratory; Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Kharghar, Navi Mumbai 410210, India



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F1000Research F1000Research 2015, 4:924 Last updated: 13 NOV 2015

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OPINION ARTICLE

Circulating nucleic acids: a new class of physiological mobile genetic elements

Indraneel Mittra

Translational Research Laboratory, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi-Mumbai, India

Mutation Research 793 (2016) 15–21

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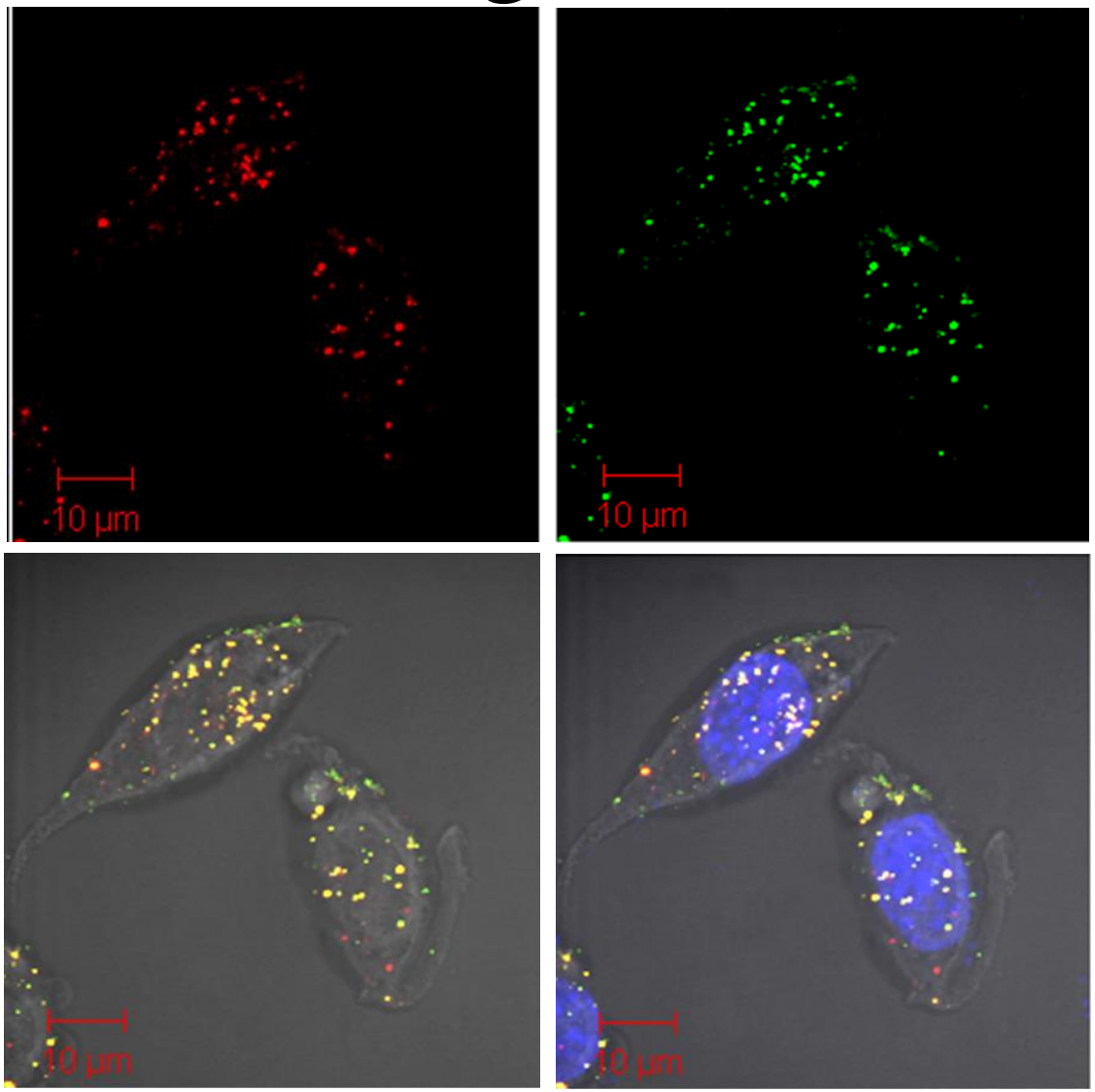
Review

Evidence for cell-free nucleic acids as continuously arising endogenous DNA mutagens

Ranjan Basak, Naveen Kumar Nair, Indraneel Mittra*

Translational Research Laboratory, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai 410210, India

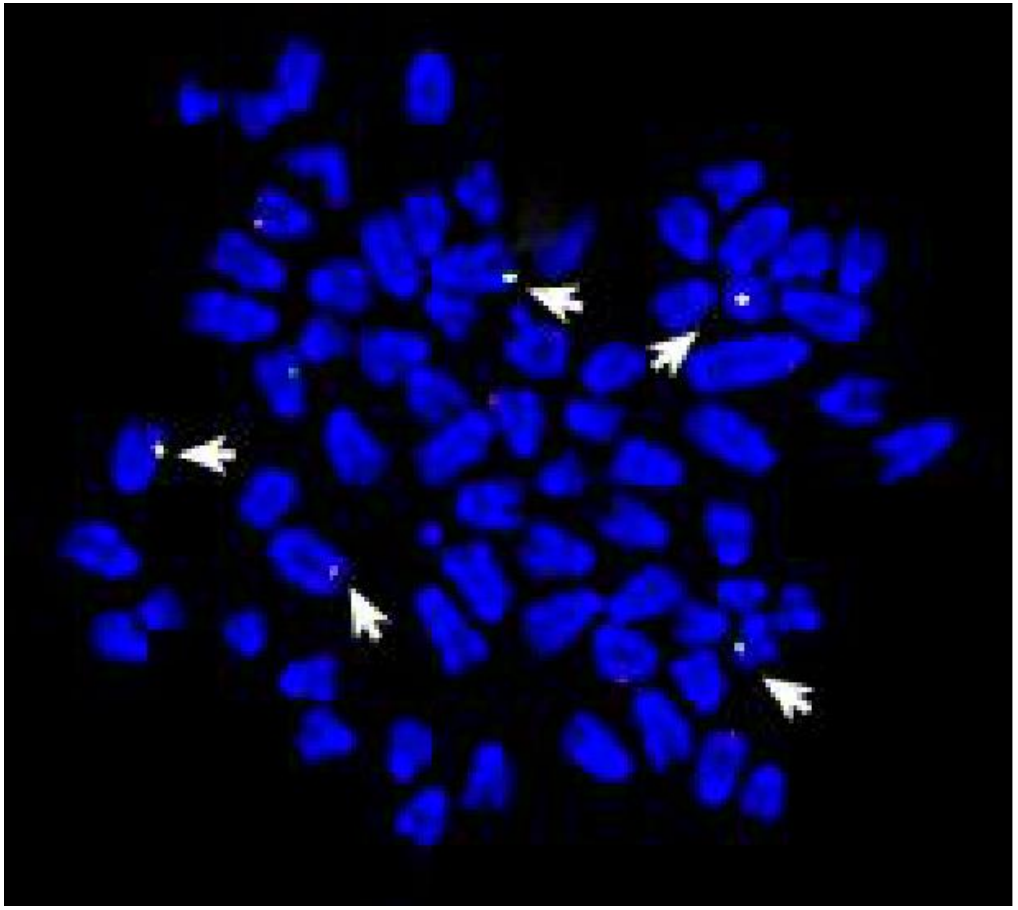
Nuclear uptake of circulating cfCh (6 hr)



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Genomic integration of circulating cfCh

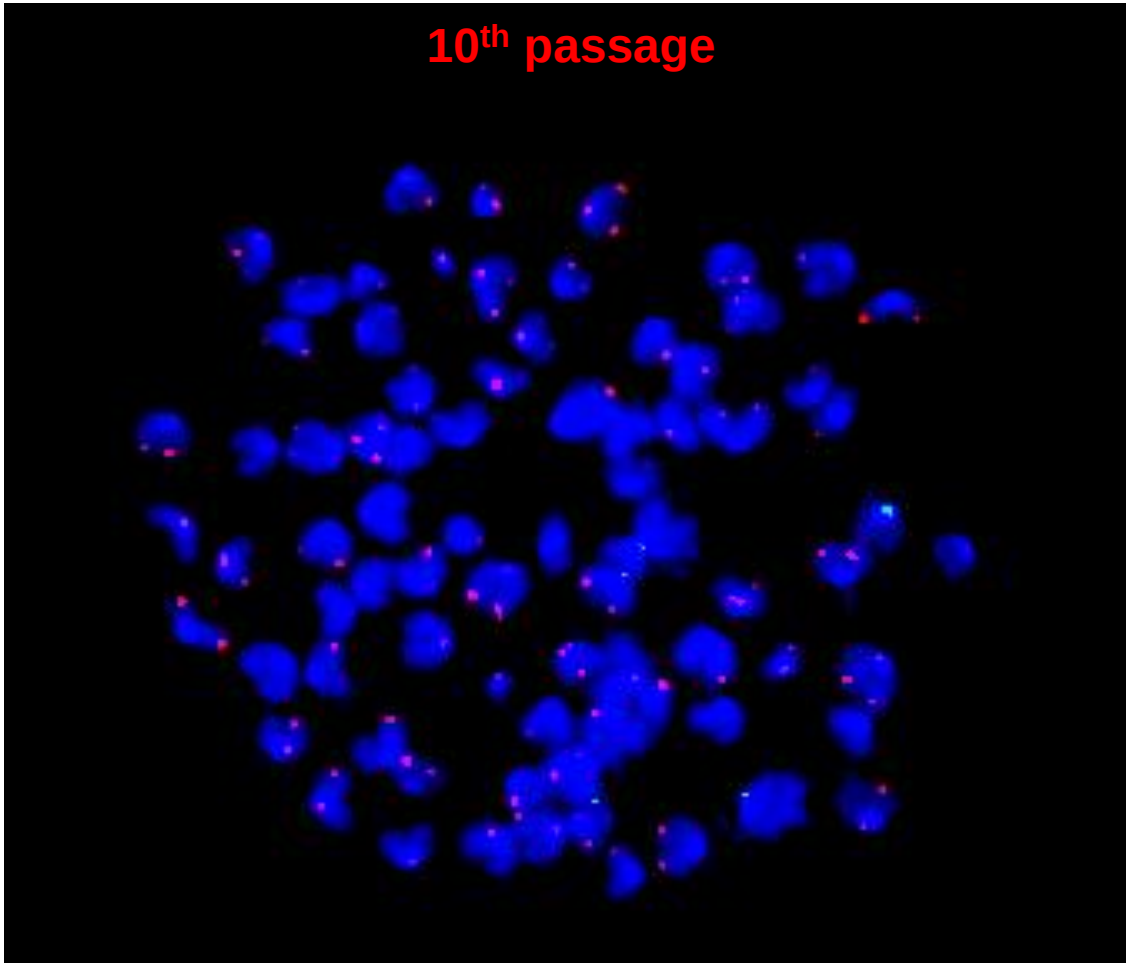
FISH



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Genomic integration of cfCh from dying cells

FISH



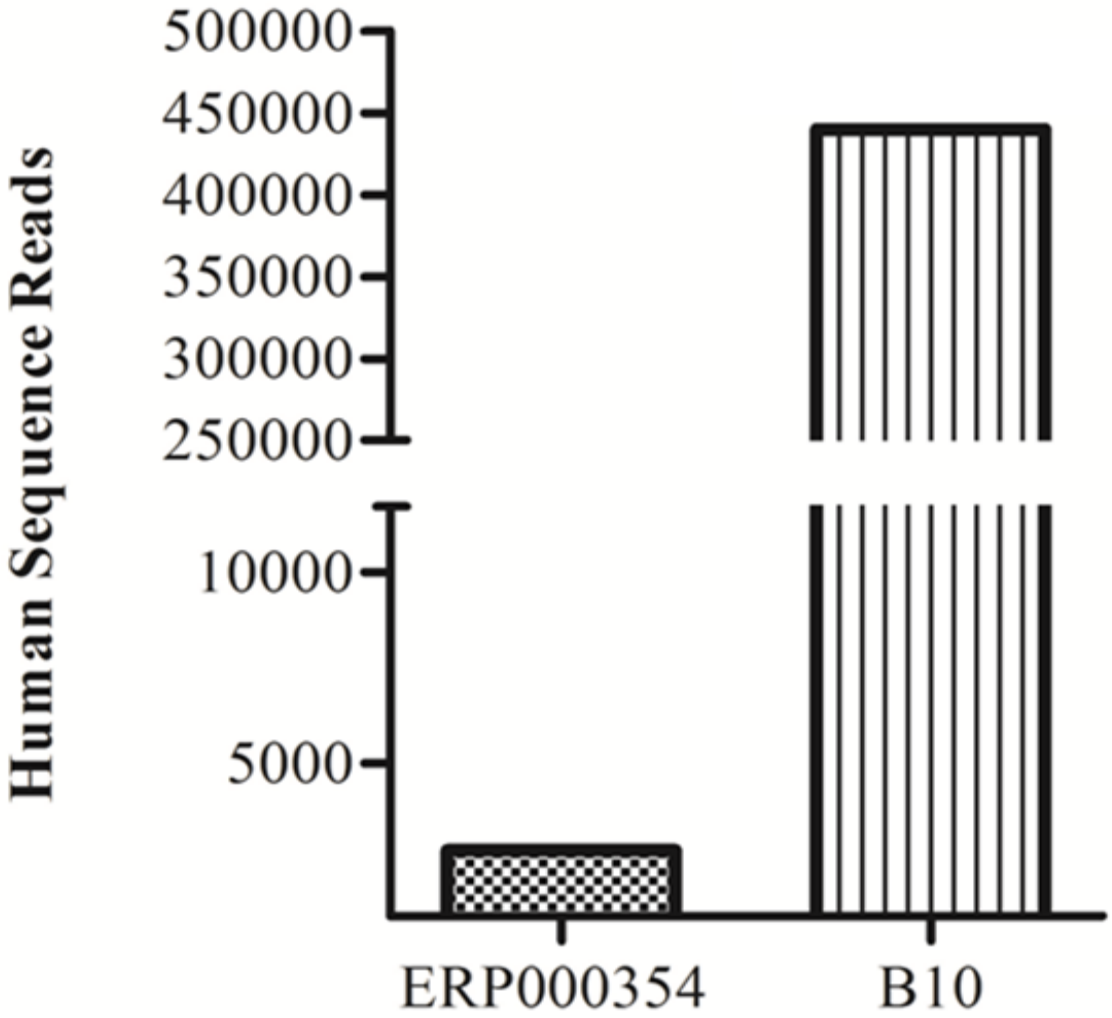
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cfCh derived from dying cells and those in circulation behave in similar manner

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Human DNA in mouse cells

Whole genome sequencing



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Human *Alu* sequences in mouse cells

	Alu-J	Alu-Sx	Alu-Sq	Alu-Sc	Alu-Sp	Alu-FLA	Alu-Sb2	Alu-Sqpx	Alu-Sb
Cfs-derived clone B2	■	■	■	■	■	■	■	■	
Cfs-derived clone D5	■	■	■	■	■	■	■		■
DNAfs-derived clone E10	■	■	■	■	■				
DNAfs-derived clone E12	■	■	■	■	■				
Total	39	28	27	13	9	3	3	1	1

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Integrated Cancer Genomics Laboratory



Dr Amit Dutt



Rohan Chaubal



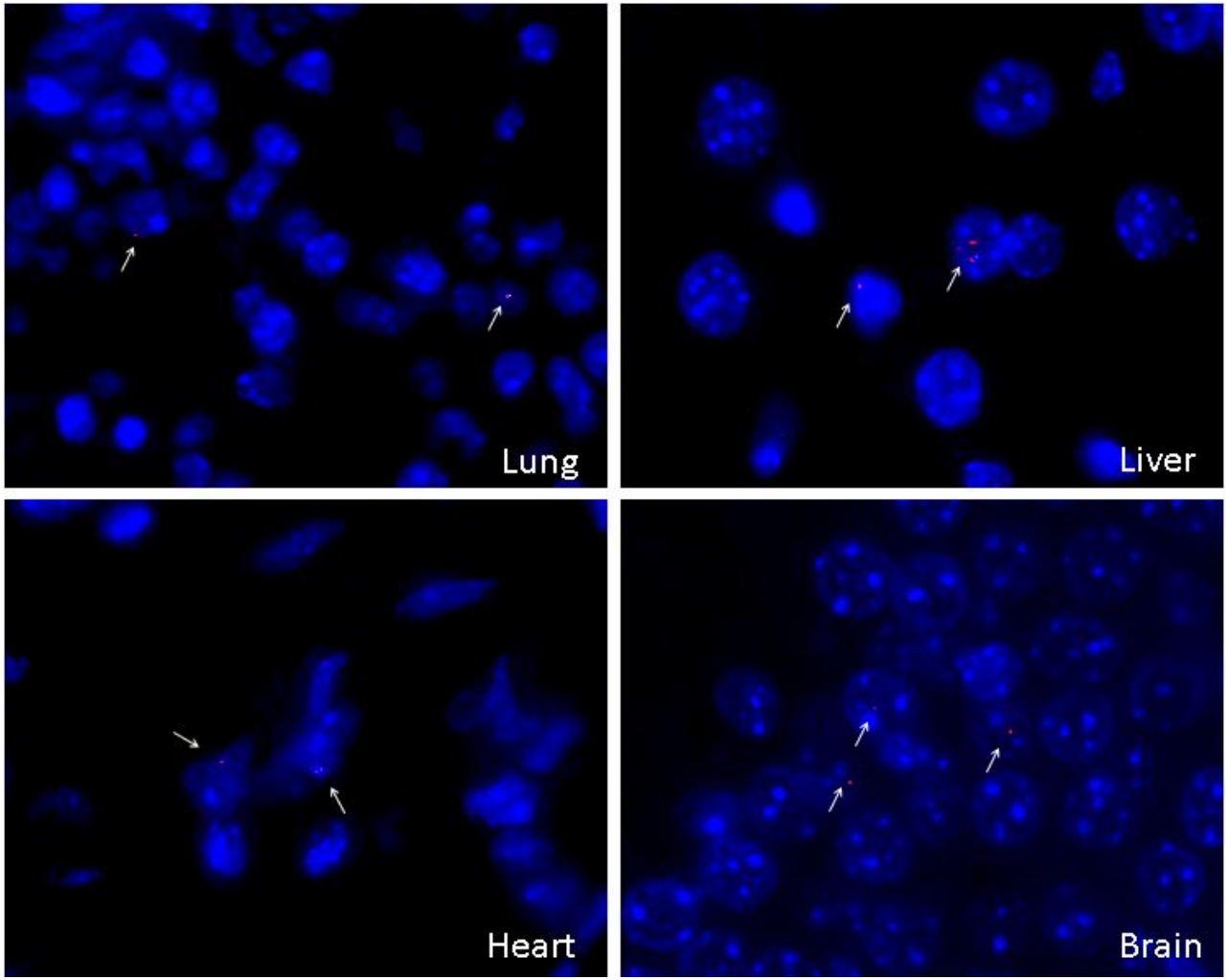
Nilesh Gardi



Pawan Upadhyay

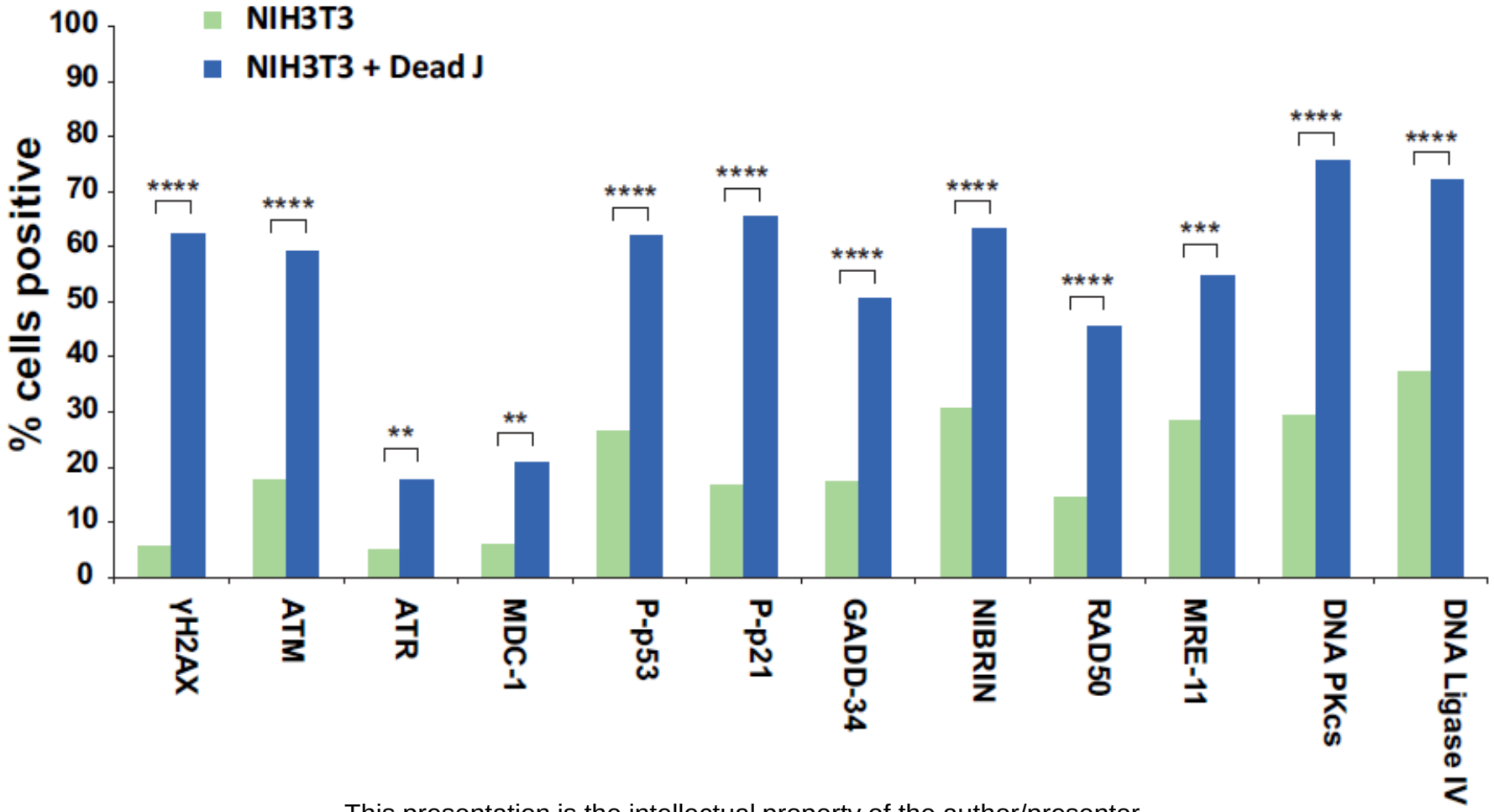
Circulating cfCh integrates into vital organs of mice following i.v. injections

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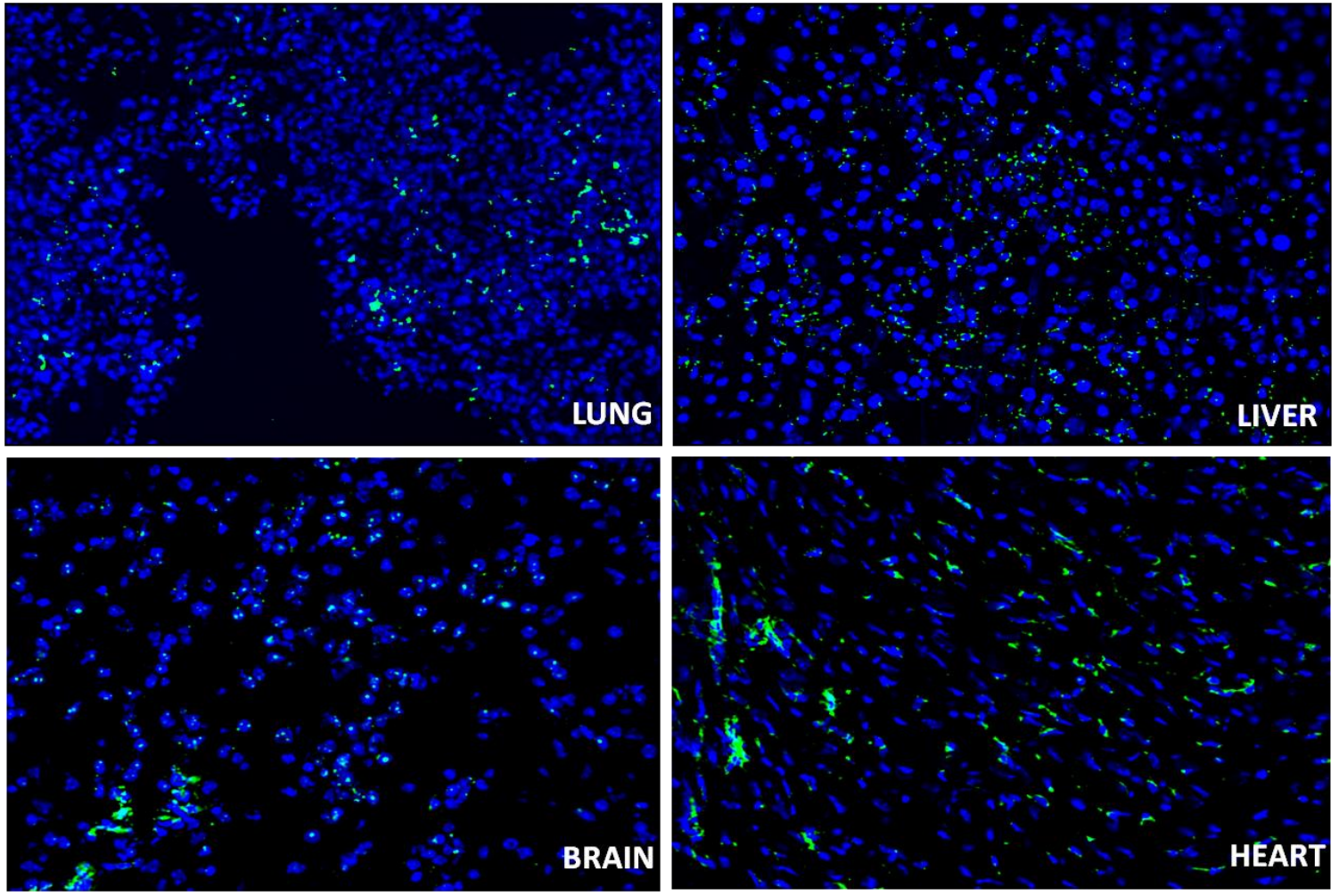
cfCh from dying cells trigger DDR in NIH3T3 cells



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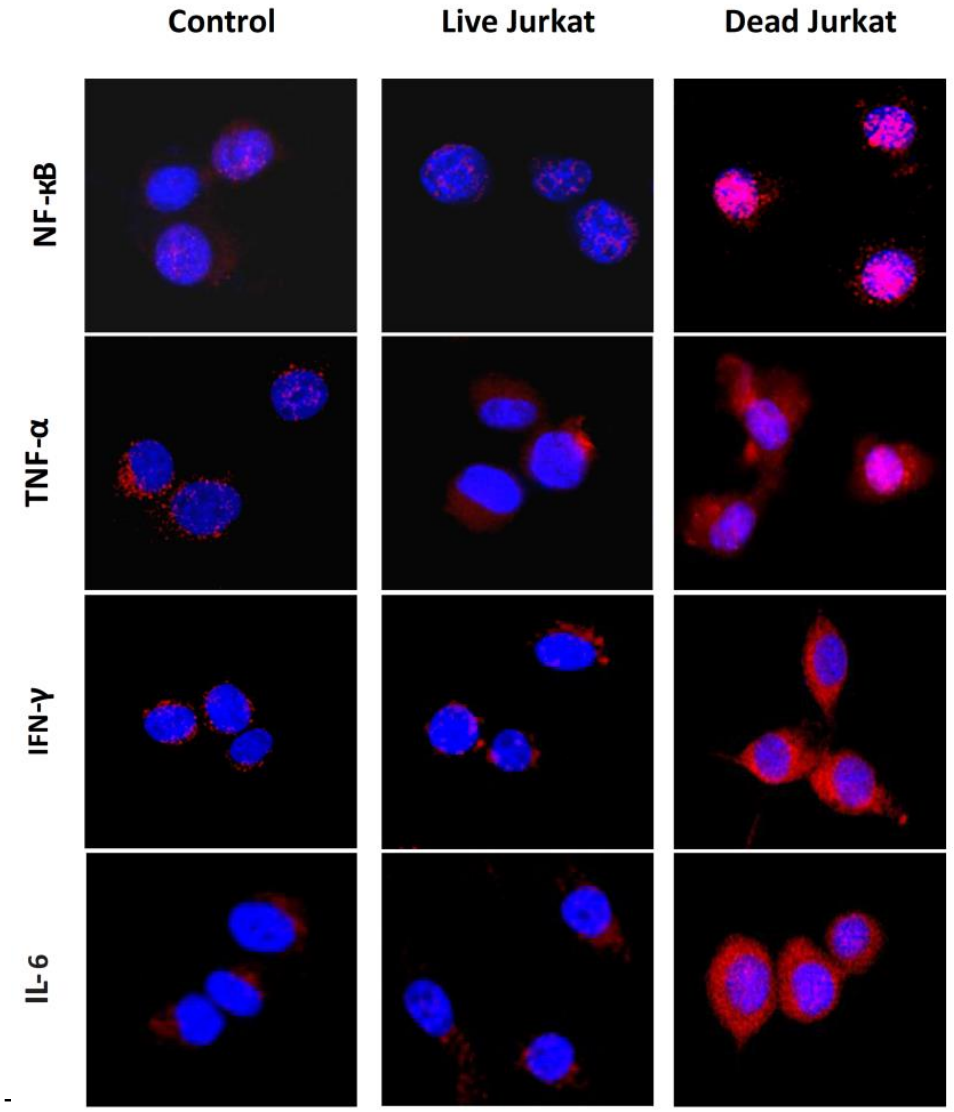
Circulating cfCh induces DNA damage *in vivo*

γH2AX



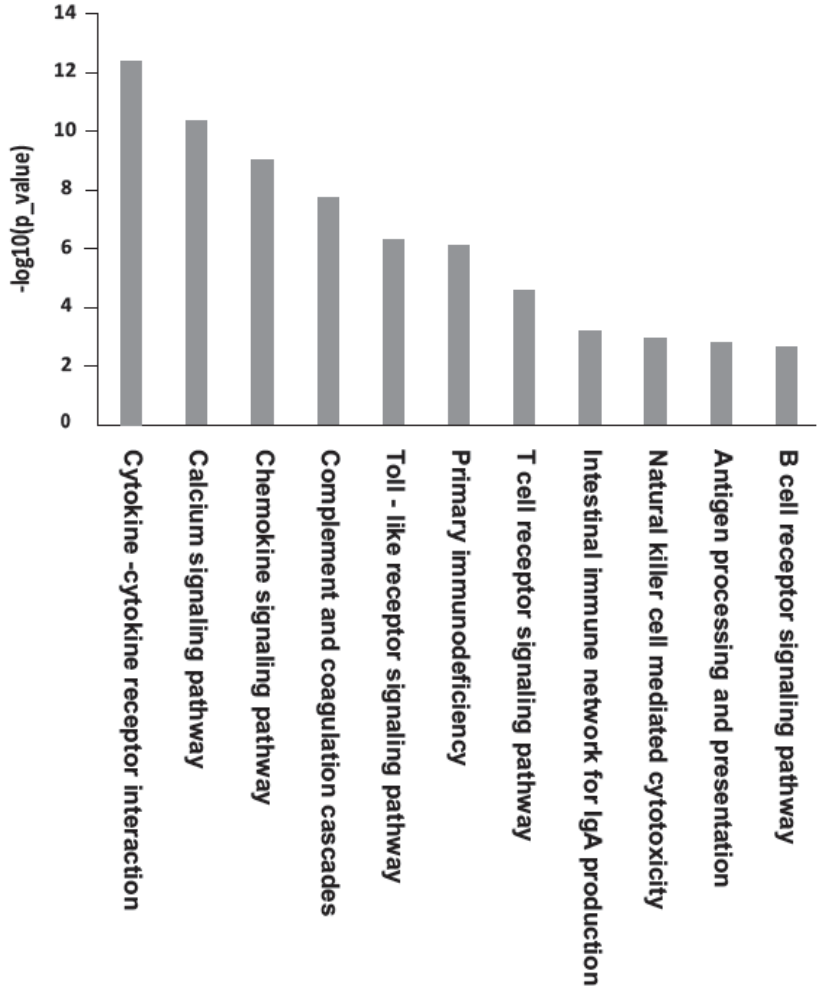
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cfCh from dying cells activate inflammation



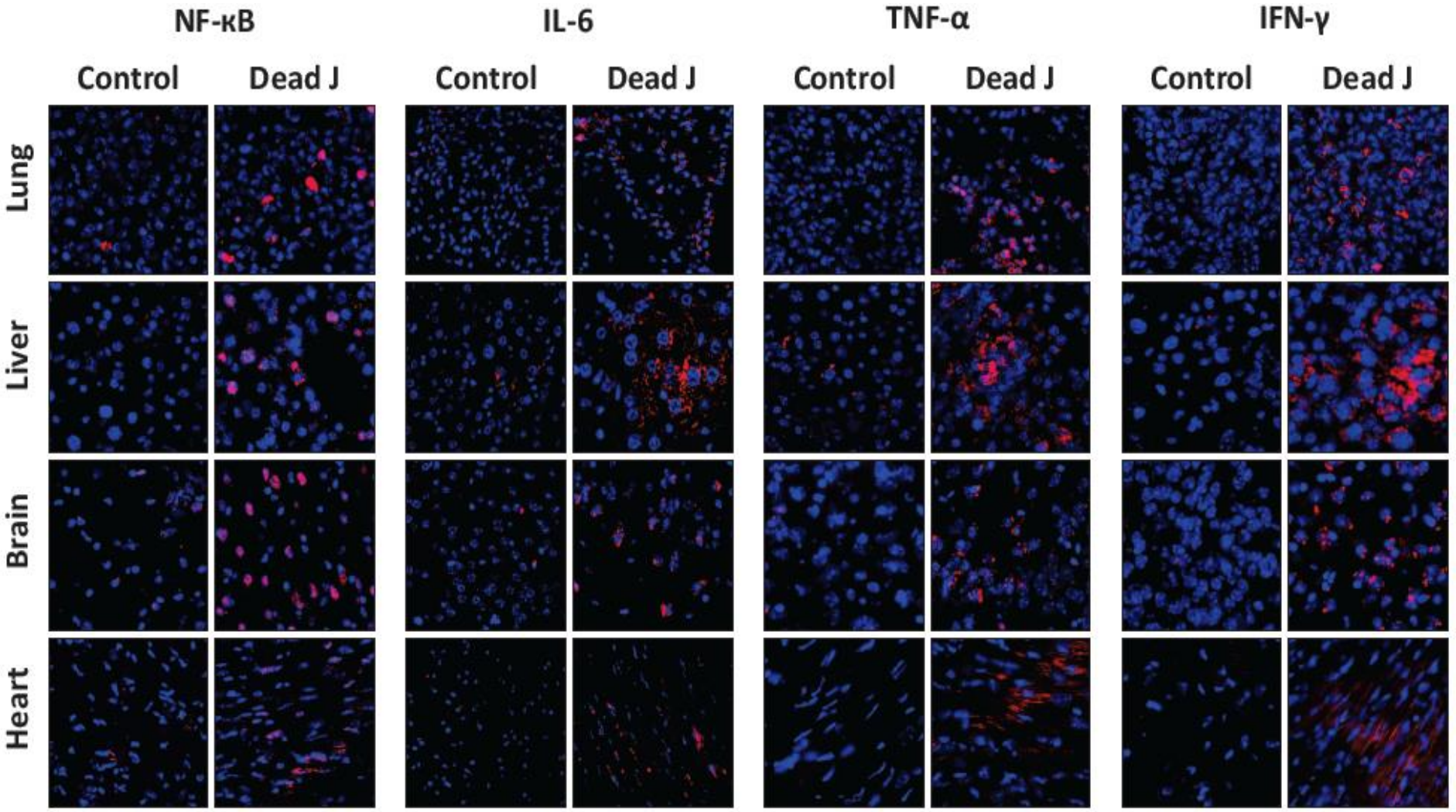
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cfCh from dying cells activate inflammatory pathways



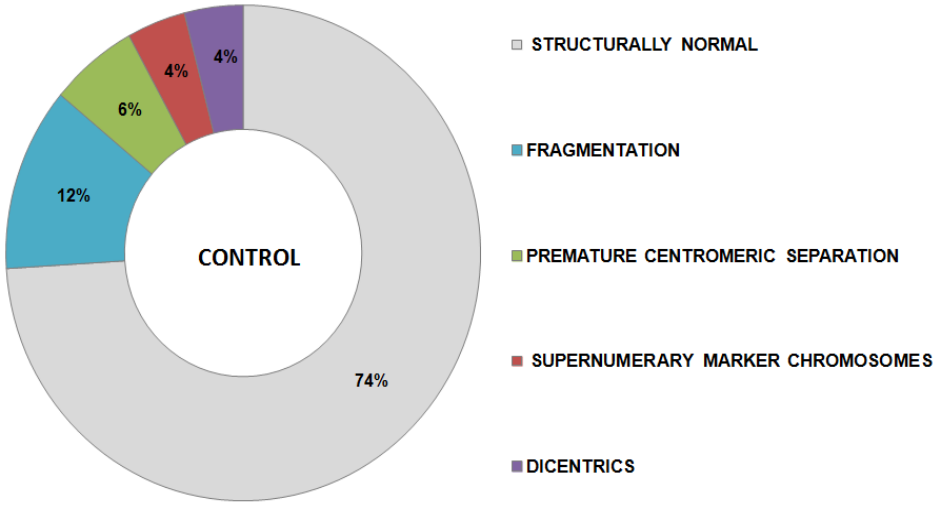
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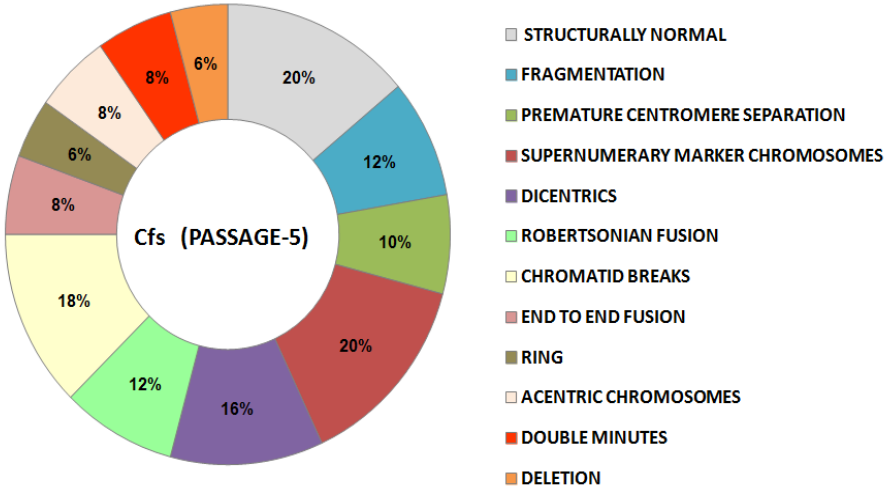
cfCh from dying cells activate systemic inflammation in mice



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cfCh from dying cells induce chromosomal aberrations in NIH3T3 cells

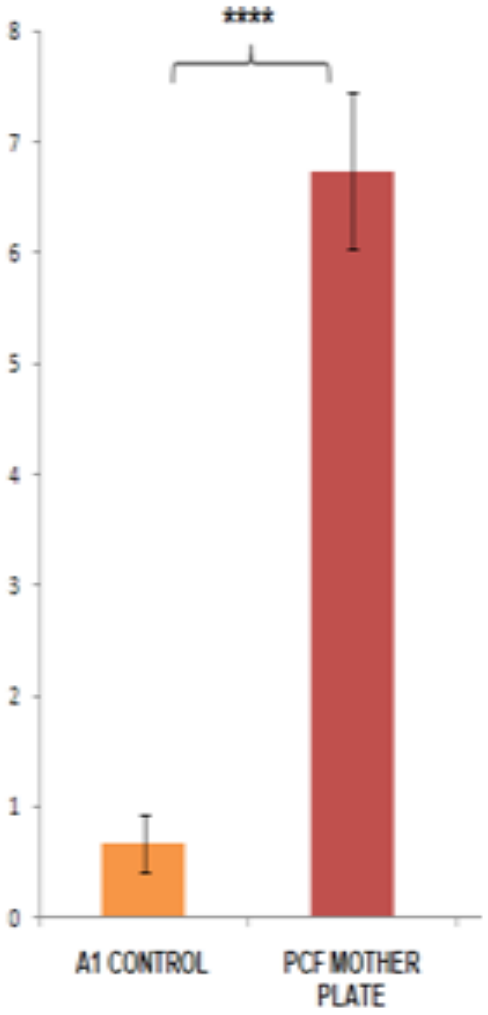




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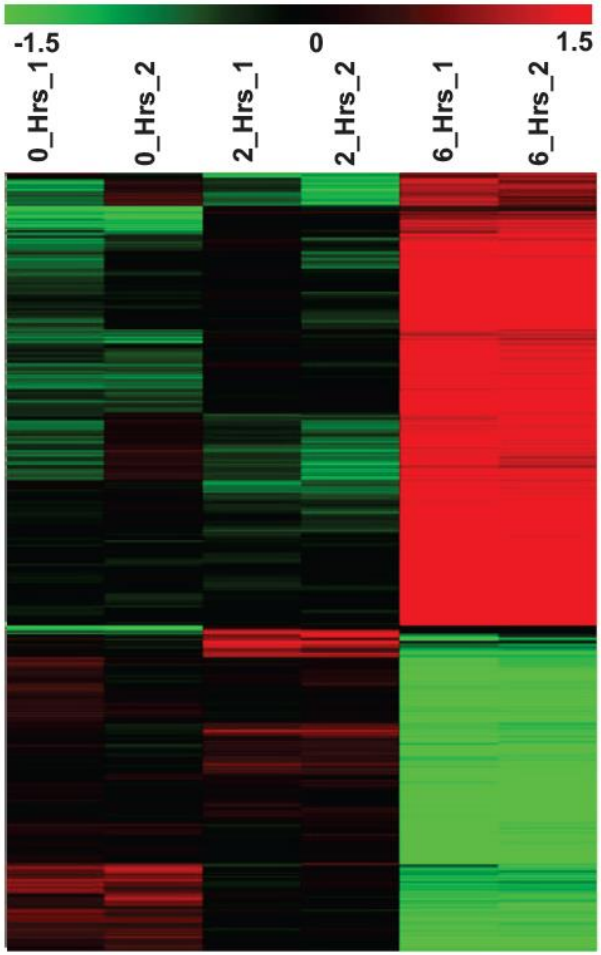
cfCh from dying cell induce chromosomal translocations





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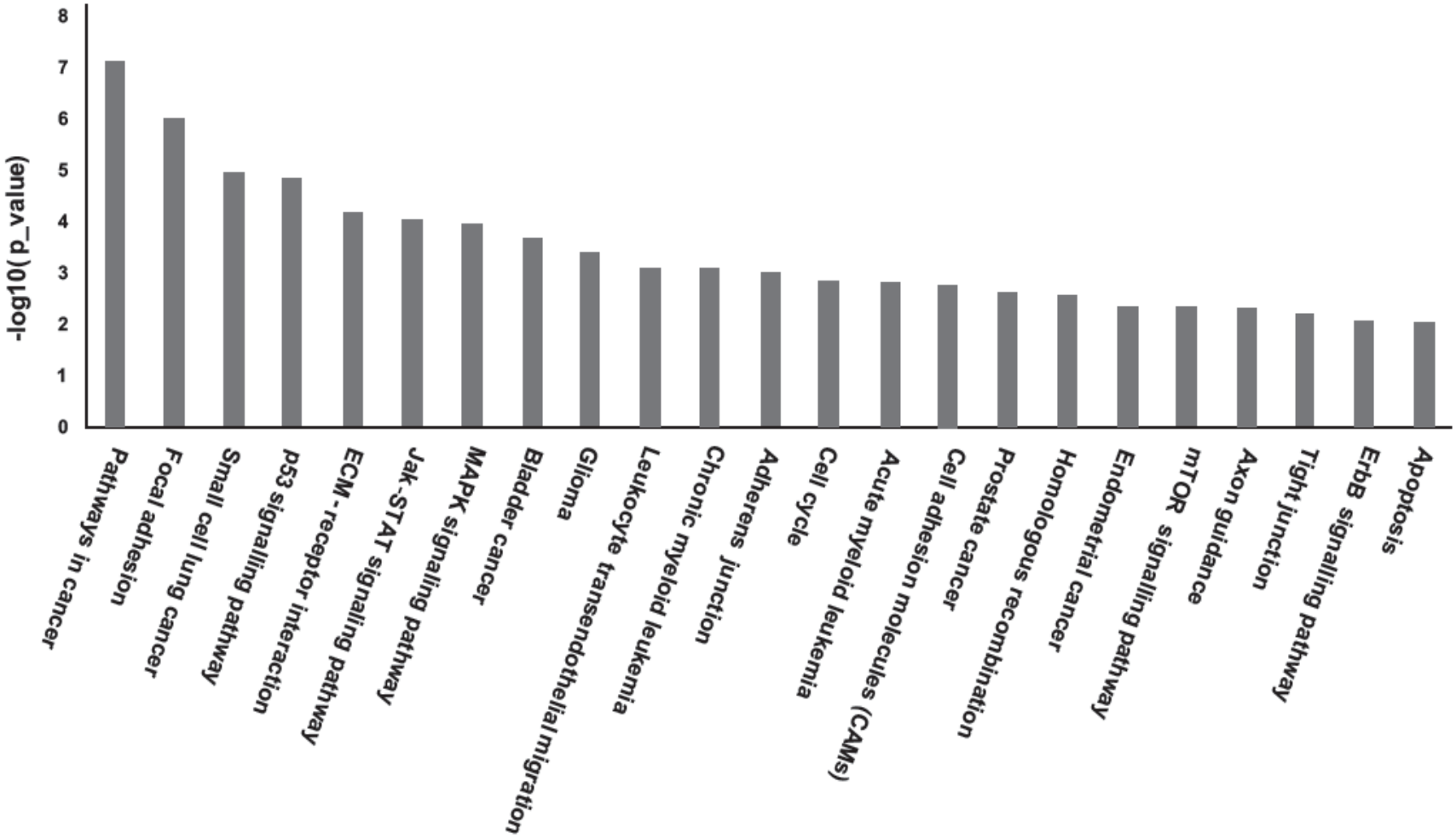
cfCh from dying cells trigger global transcriptional de-regulation in NIH3T3 cells



Total number of de-regulated genes = 1004

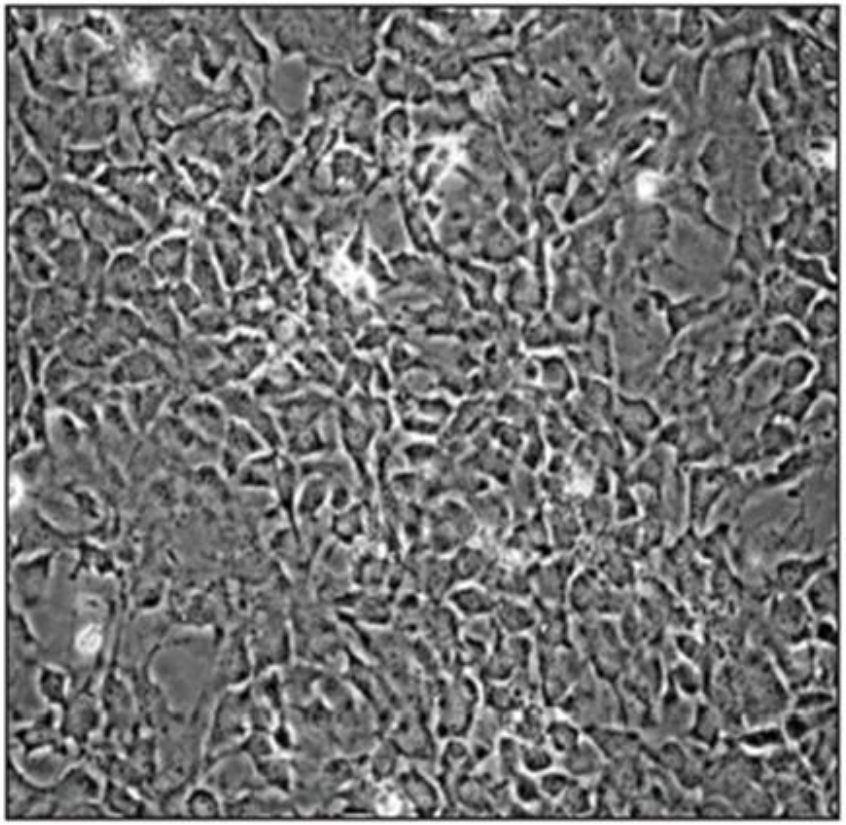
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cfCh from dying cells up-regulate cancer pathways by 6 hr

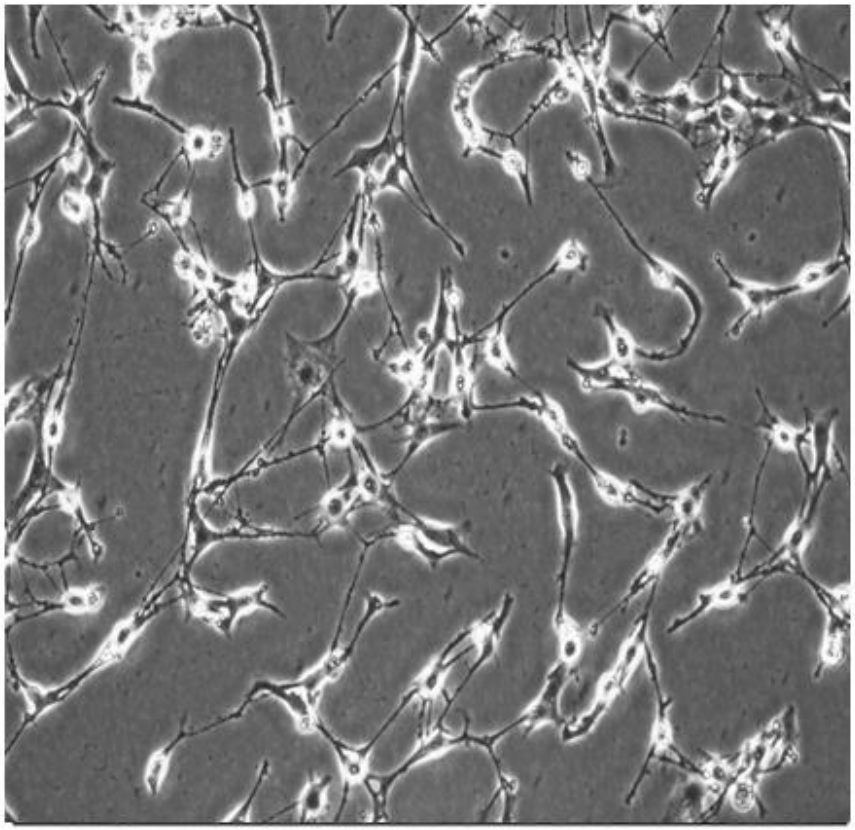


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Circulating cfCh isolated from cancer patients induces oncogenic transformation



NIH3T3



NIH3T3 + Cfs

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Oncogenic transformation

Circulating cfCh

Cancer Patients	26 / 58 (44.83%)

Circulating DNA

Cancer Patients	0 / 40

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cfCh from dying cancer cells induce oncogenic transformation / senescence

Cell lines

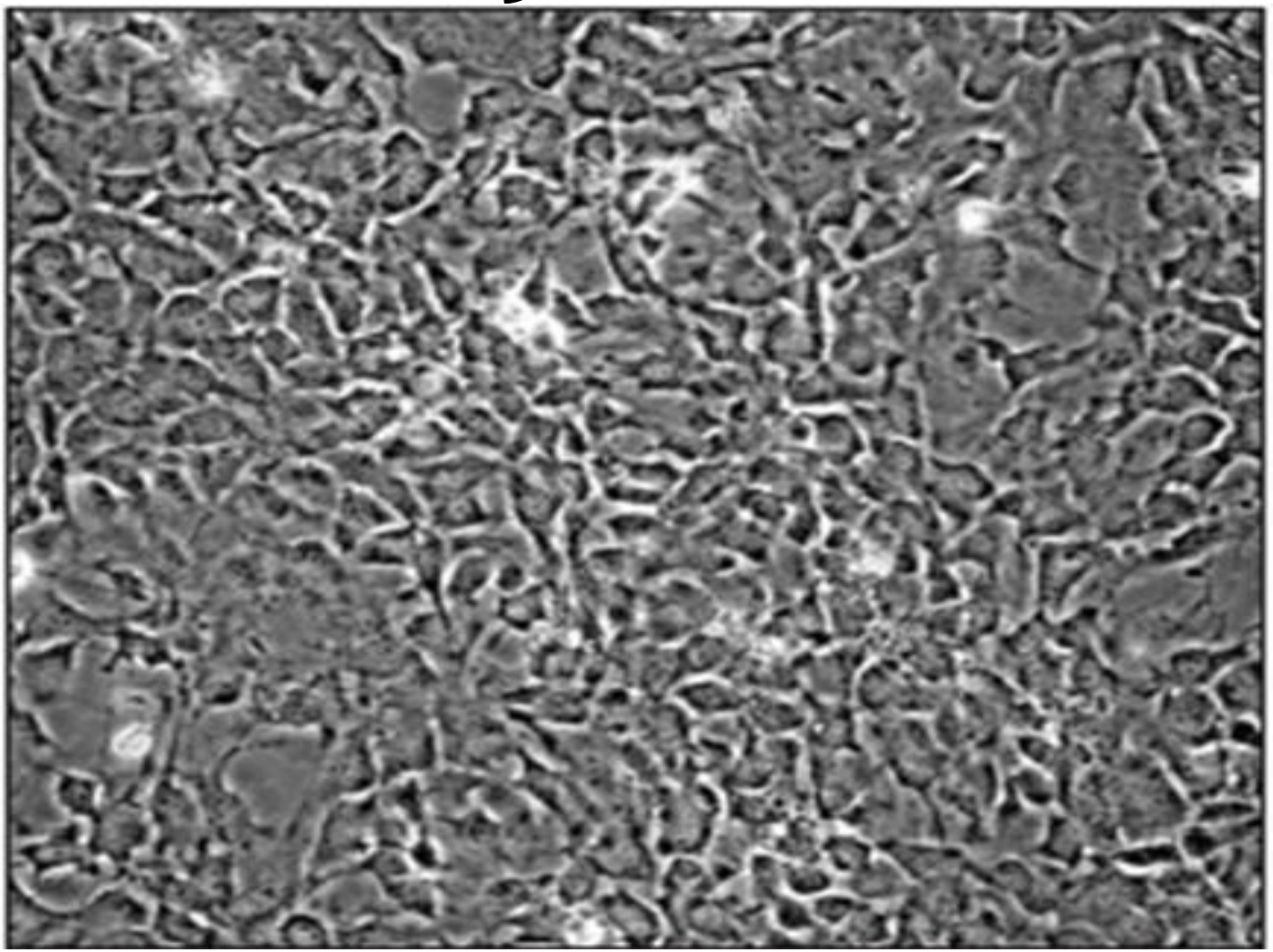
1. Jurkat
2. MDA MB-231
3. B16F10
4. MCF-7
5. A-375
6. HeLa
7. HT-29
8. A-549
9. ZR-75
10. T-24

Treatment

1. FAS-ligand
2. Hypoxia
3. Radiation
4. Adriamcin

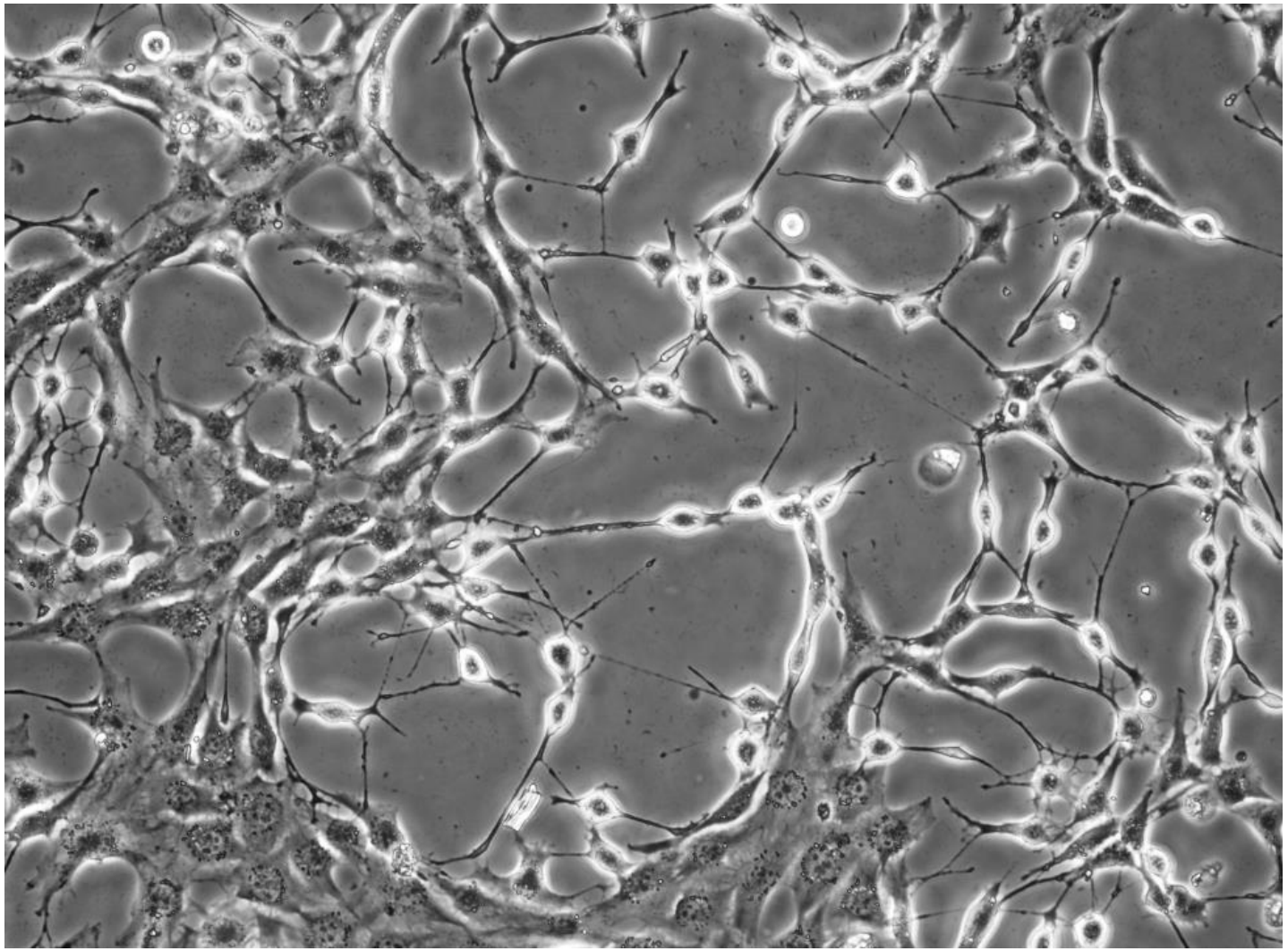
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Morphology of NIH3T3 cells at 96 hours



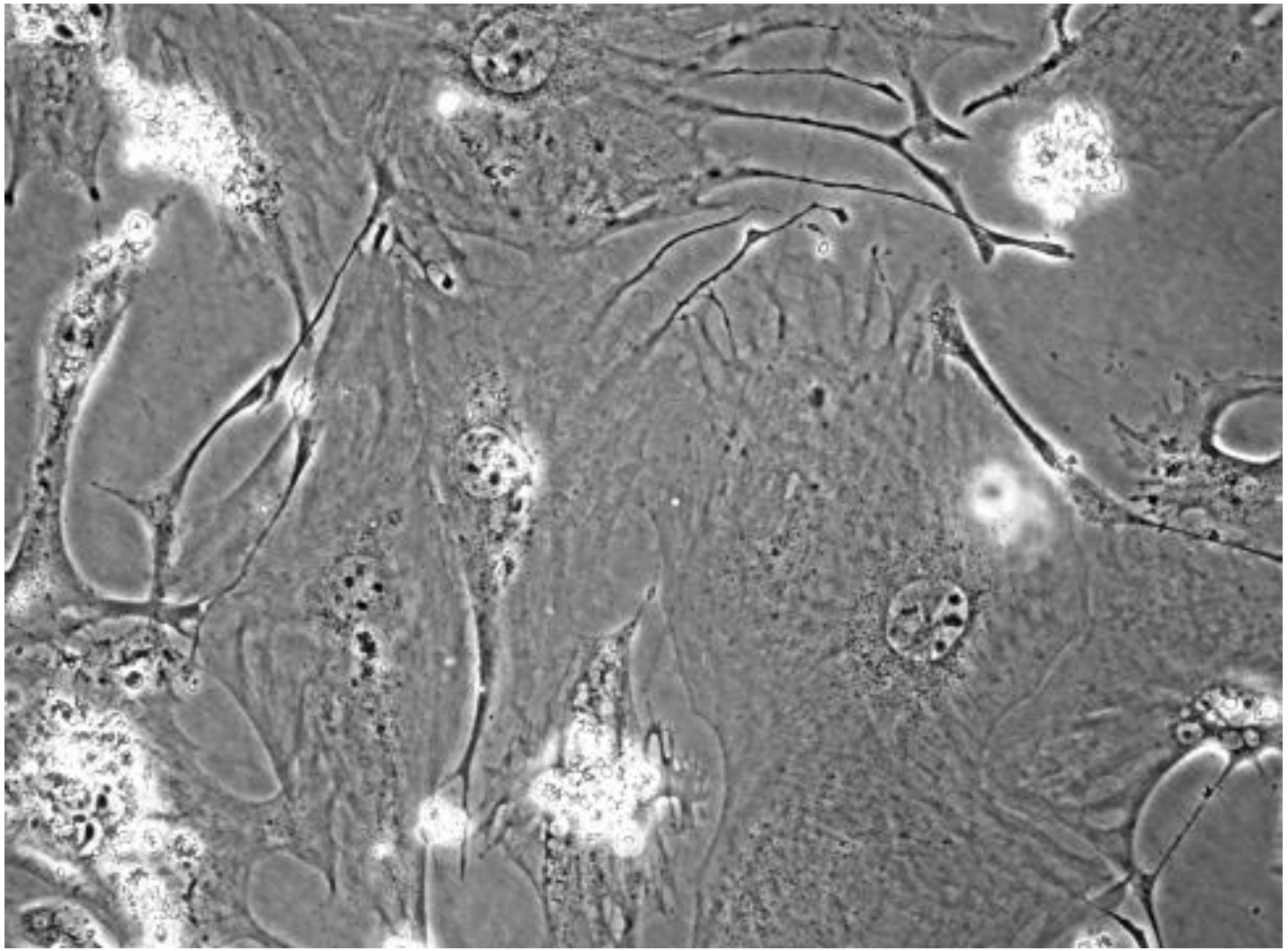
Control NIH3T3

Morphological changes at 96 hours



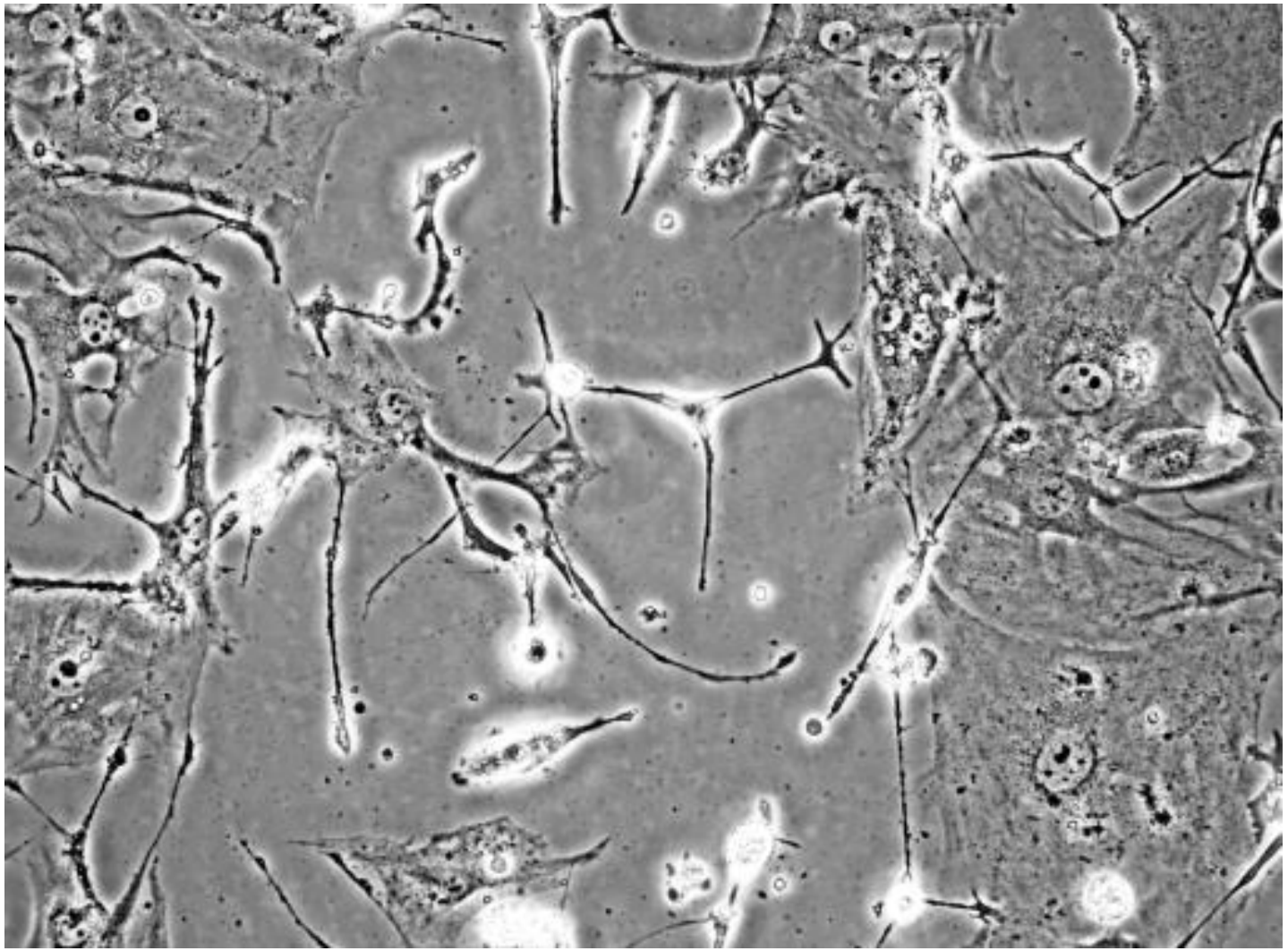
Oncogenic transformation

Morphological changes at 96 hours



Senescence

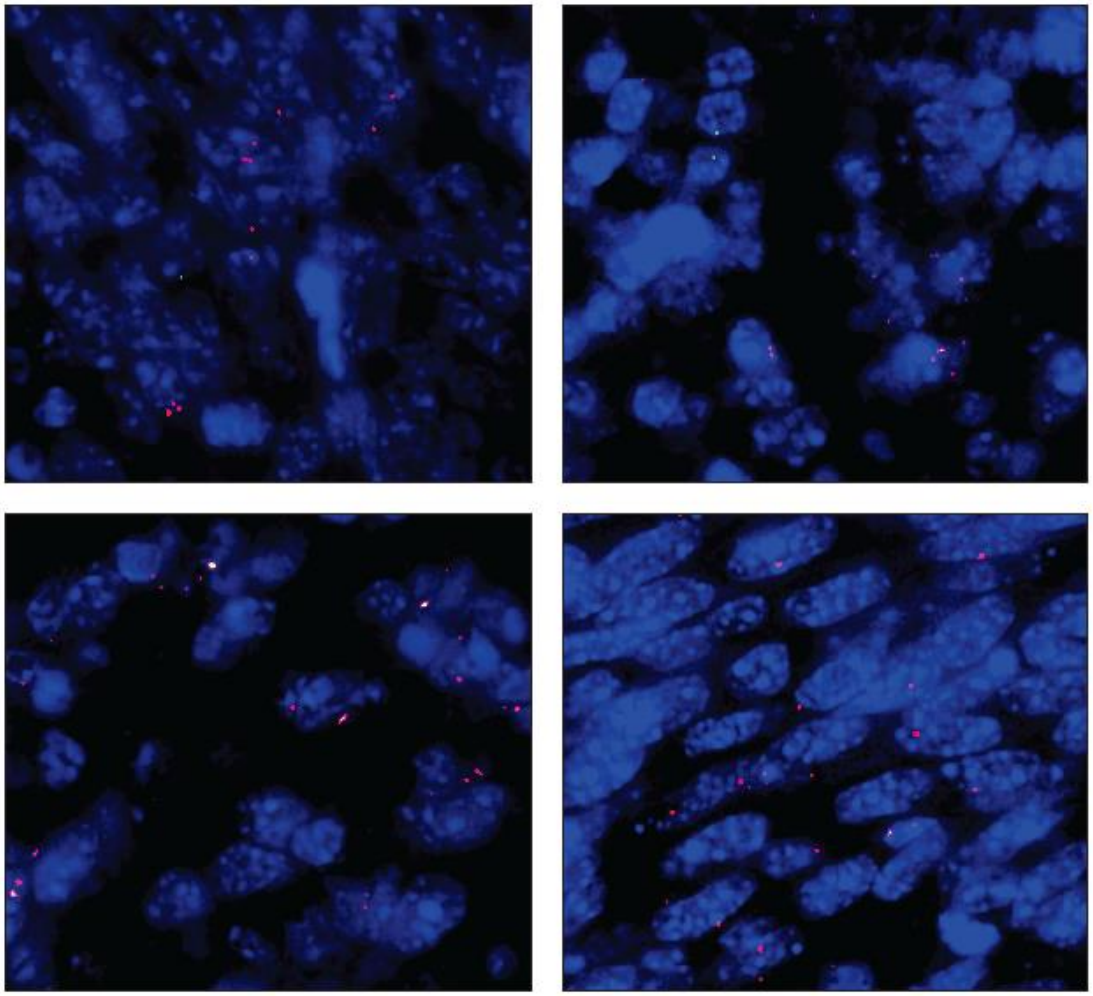
Morphological changes at 96 hours



Mixed Phenotype

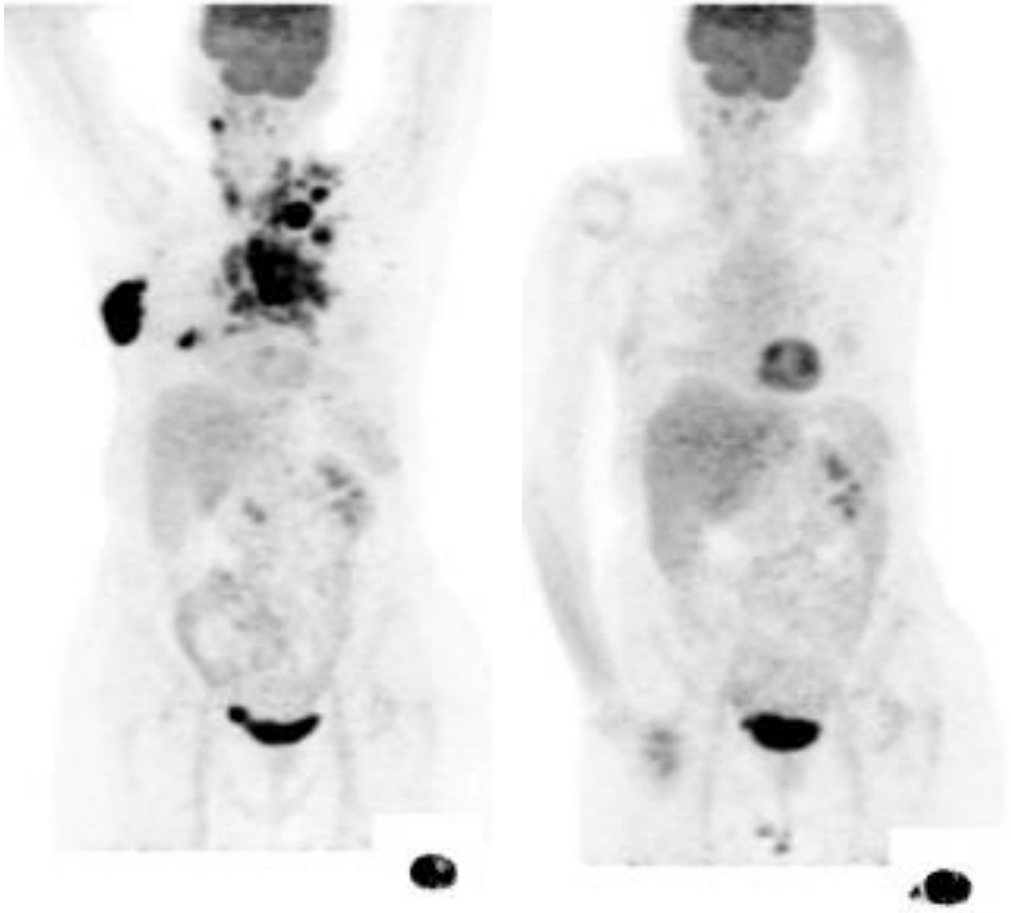
Transformed NIH3T3 cells are tumourigenic in SCID mice

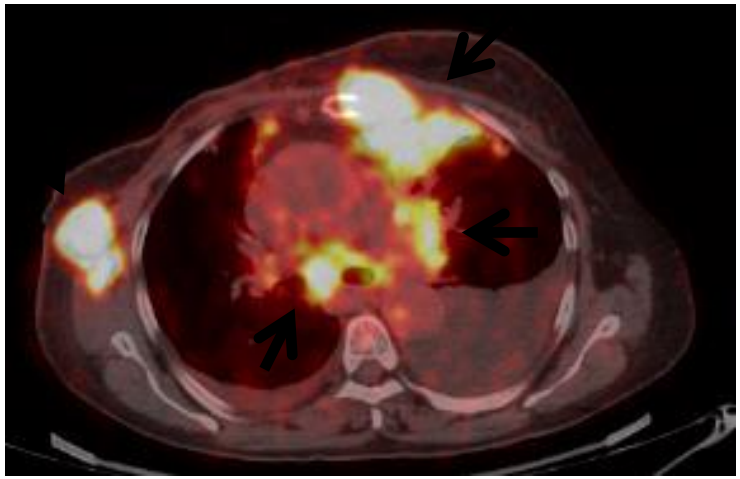


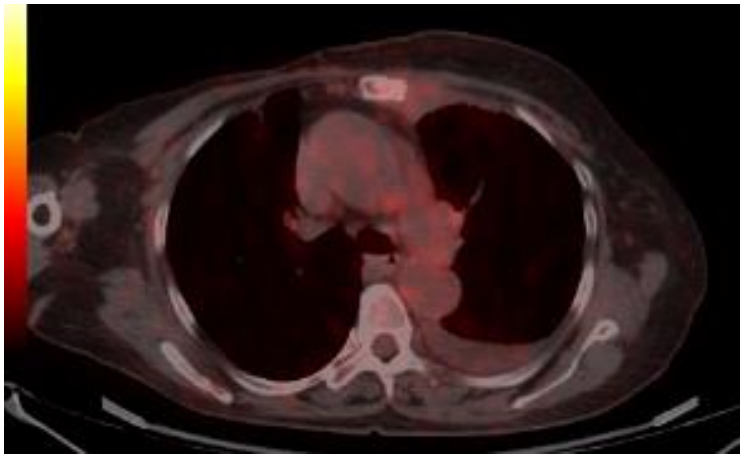


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Why is cancer treatment failing !







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The entrenched theory of cancer metastasis is implausible !

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ARTICLE

doi:10.1038/nature15748

Epithelial–to–mesenchymal transition is not required for lung metastasis but contributes to chemoresistance

Kari R. Fischer[1,2,3,4], Anna Durrans[1,2,3], Sharrell Lee[1,2,3], Jianting Sheng[5], Fuhai Li[5], Stephen T. C. Wong[5,6], Hyejin Choi[1,2,3,4], Tina El Rayes[1,2,3,4], Seongho Ryu[1,3,7], Juliane Troeger[8,9], Robert F. Schwabe[8,9], Linda T. Vahdat[10], Nasser K. Altorki[1,3], Vivek Mittal[1,2,3] & Dingcheng Gao[1,2,3]

LETTER

doi:10.1038/nature16064

Epithelial–to–mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer

Xiaofeng Zheng[1]*, Julienne L. Carstens[1]*, Jiha Kim[1], Matthew Scheible[1], Judith Kaye[1], Hikaru Sugimoto[1], Chia-Chin Wu[2], Valerie S. LeBleu[1] & Raghu Kalluri[1,3,4]

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PLOS ONE

RESEARCH ARTICLE

Expression of Hypoxic Marker Carbonic Anhydrase IX Predicts Poor Prognosis in Resectable Hepatocellular Carcinoma

Wei-Ju Huang[1,2], Yung-Ming Jeng[1,3], Hong-Shiee Lai[4], Iok-U Fong[1], Fang-Yu Bonnie Sheu[5], Po-Lin Lai[3], Ray-Hwang Yuan[4,6]*

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American Journal of Pathology. 2001;159:17-20.

Short Communications

Circulating Breast Cancer Cells Are Frequently Apoptotic

Gábor Méhes*, Armin Witt, Ernst Kubista and Peter F. Ambros*
From the Children's Cancer Research Institute,*
St. Anna Kinderspital, Vienna; and the Department of Special Gynecology,
Vienna General Hospital, Vienna, Austria

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Journal of the National Cancer Institute
jnci.oxfordjournals.org

JNCI J Natl Cancer Inst (1970) 45 (4): 773-782. doi: 10.1093/jnci/45.4.773

Metastasis: Quantitative Analysis of Distribution and Fate of Tumor Emboli Labeled With ^{125}I-5-Iodo-2′-deoxyuridine[2,3]

Isaiah J. Fidler

Summary

^{125}I–5–iodo–2′–deoxyuridine was used to label pure B16 melanoma cells grown in tissue culture. *In vitro* and *in vivo* studies established the optimal, nontoxic labeling dose. C57BL/6J mice were given intravenous injections of labeled cells and killed at various intervals after injection. Blood and organs were collected, processed, and monitored. The label was released only after cell death. It was poorly reutilized and quickly eliminated. Hence, organ radioactivity represented almost exclusively the number of live cells present when the animals were killed. The data permitted the following conclusions: The lung contained most of the tumor cells at all intervals. Some tumor cell emboli recirculated. Tumor cells in the lung decreased in numbers at about 5 minutes post injection and returned to high levels by 10 minutes post injection. Tumor cells died rapidly, and about 1% of cells survived after 24 hours. About 400 melanoma cells were in the lung after 14 days, and those yielded an average of 78 metastases. Apparently very few surviving tumor cells are needed to establish a metastasis.

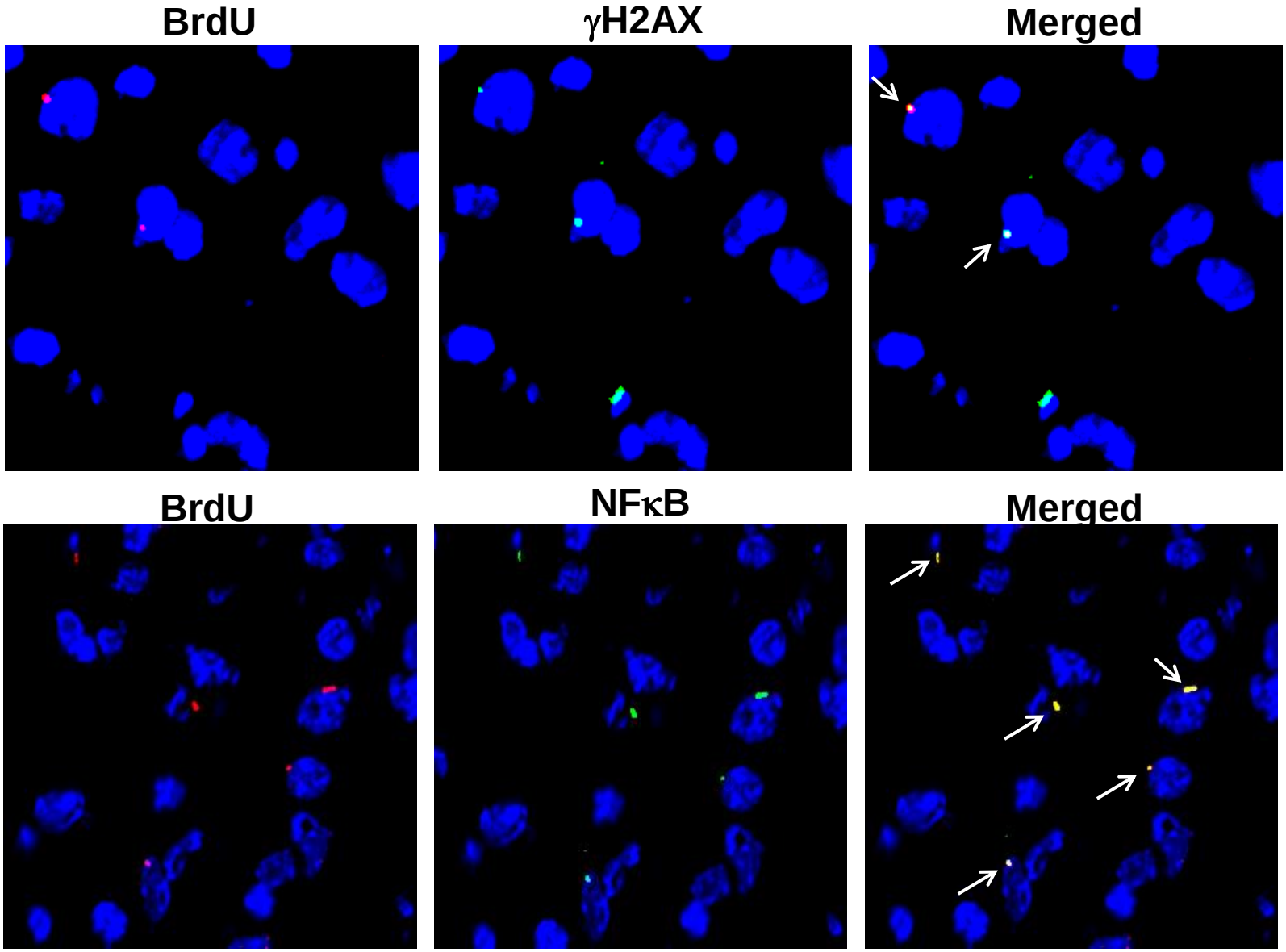
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“Tumor cells died rapidly, and about 1% of cells survived after 24 hours.”

Isaiah J Fidler

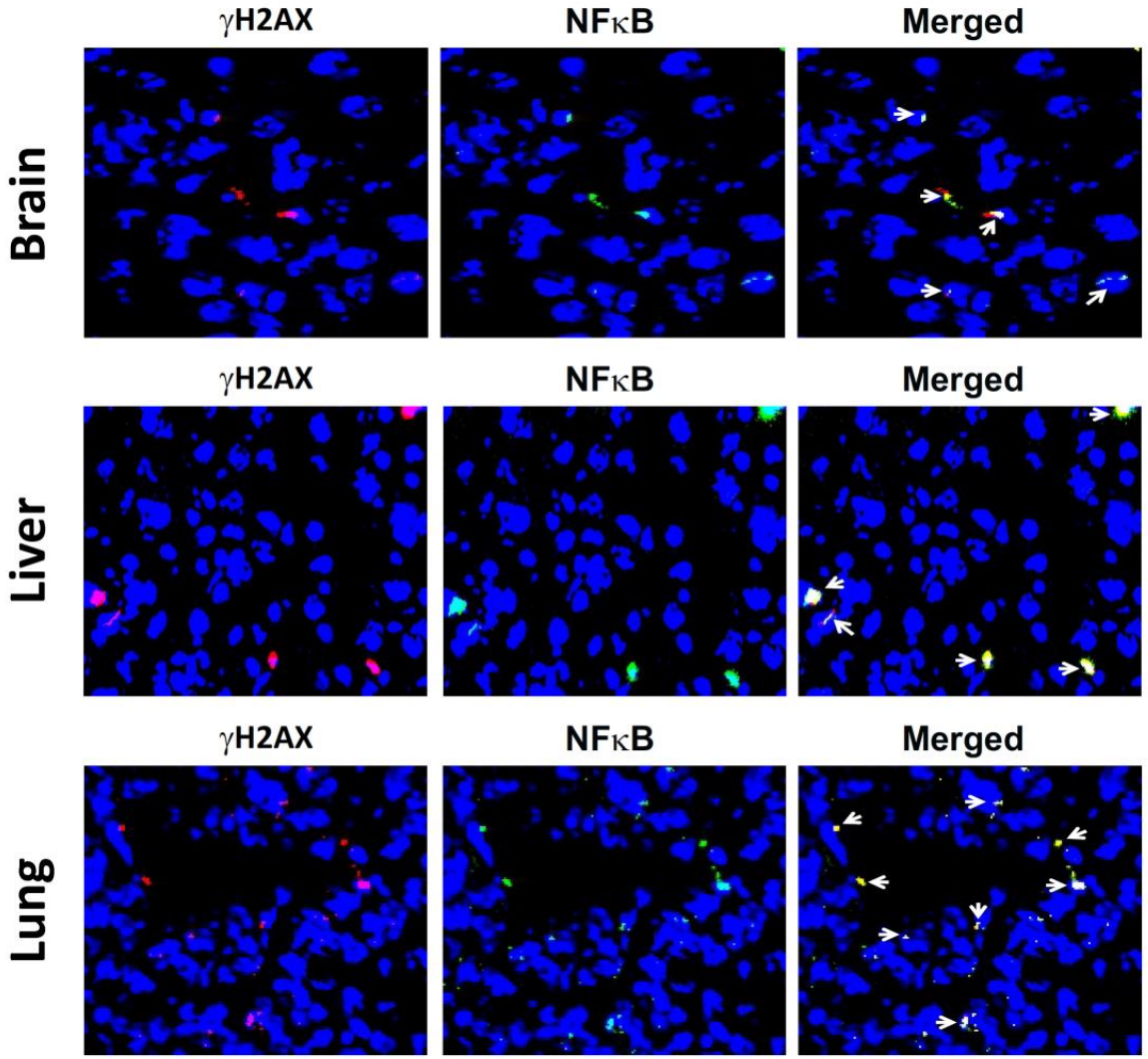
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cfCh from dying cells can enter mouse brain and trigger DNA damage and inflammation



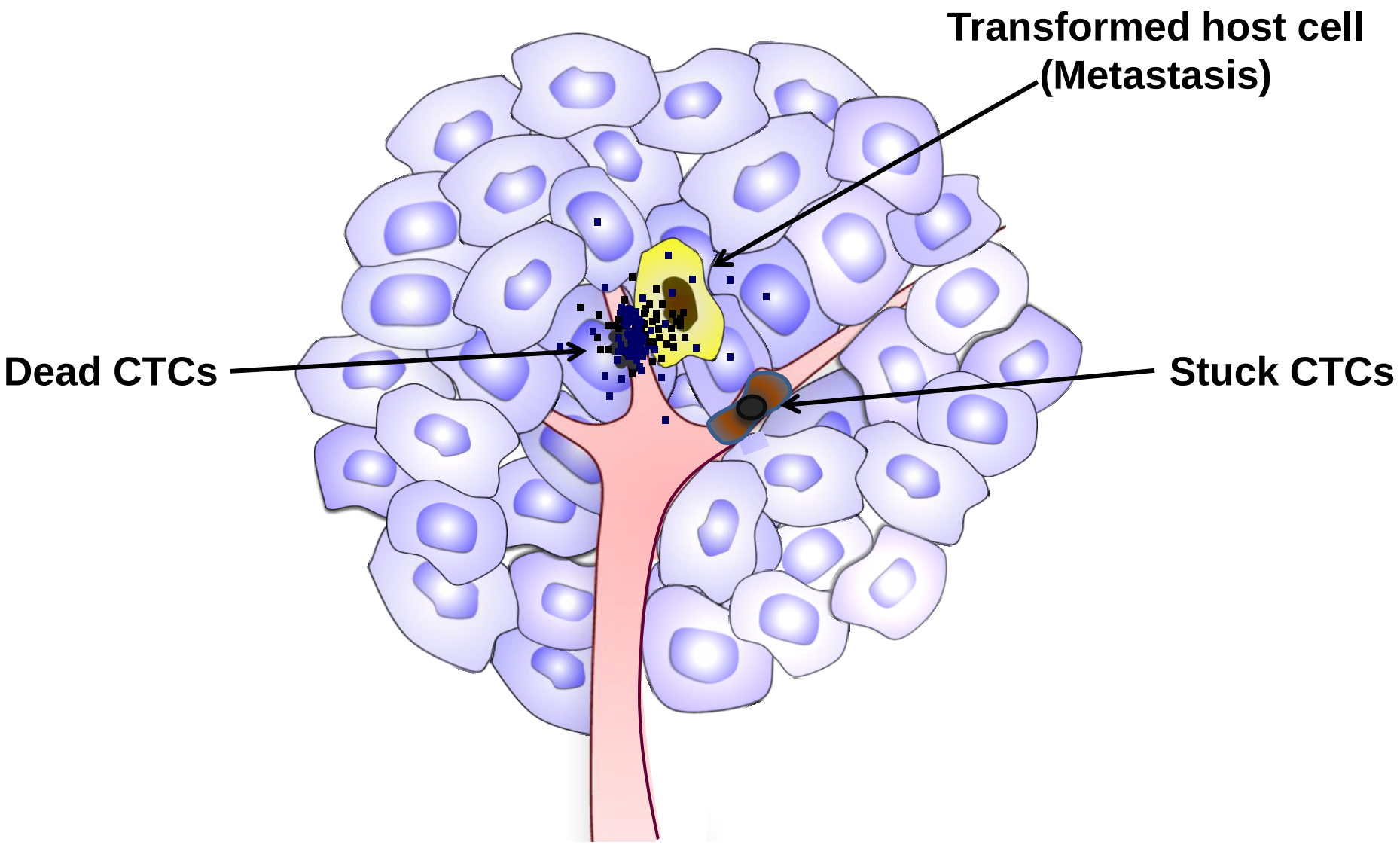
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cfCh from dying cells induce a pro-oncogenic milieu



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The new theory of cancer metastasis



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MOLECULAR ONCOLOGY 7 (2013) 680–692

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Monitoring apoptosis and Bcl-2 on circulating tumor cells in patients with metastatic breast cancer☆

Jeffrey B. Smerage[a], *G. Thomas Budd*[b], *Gerald V. Doyle*[c], *Marty Brown*[a], *Costanza Paoletti*[a], *Maria Muniz*[a], *M. Craig Miller*[c], *Madeline I. Repollet*[c], *David A. Chianese*[c], *Mark C. Connelly*[c], *Leon W.W.M. Terstappen*[d], *Daniel F. Hayes*[a,*]

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[b]*Taussig Cancer Center, Cleveland Clinic Foundation, Cleveland, OH 44195, United States*
[c]*Veridex LLC, Raritan, NJ, USA*
[d]*Department of Medical Cell BioPhysics, University of Twente, Enschede, The Netherlands*

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Breast cancer
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ABSTRACT

Background: Enumeration of circulating tumor cells (CTC) from whole blood permits monitoring of patients with breast carcinoma. Analysis of apoptosis & Bcl-2 expression in CTC might add additional prognostic and predictive information. We estimated the degree of these markers in CTC from patients being treated for metastatic breast cancer.
Methods: Eighty-three evaluable patients initiating a new therapy for metastatic breast cancer were enrolled. Whole blood was collected at baseline, at one of three short term time windows (24, 48, or 72 h) after initiating treatment, and at first follow-up (3–5 weeks). CTC were isolated, enumerated, and expression of M30 and Bcl2 was determined using the CellSearch® System.
Results: At baseline, window, and 3–5 weeks post-treatment, 41/80 (51%), 40/80 (50%) and 21/75 (28%) patients had ≥5 CTC, respectively. At baseline, the proportion of CTC-apoptosis (M30) was inversely correlated with CTC number, and modestly inversely correlated with CTC-Bcl-2. As expected, higher CTC levels at baseline or first follow-up were associated with worse prognosis. Surprisingly, in patients with elevated CTC, higher levels of CTC-apoptosis were associated with worse prognosis, while higher CTC-Bcl-2 levels correlated with better outcomes.
Conclusions: CTC apoptosis and expression of Bcl-2 can be analytically determined in patients with metastatic breast cancer and may have biological and clinical implications.

“Surprisingly, in patients with elevated CTC, higher levels of CTC-apoptosis were associated with worse prognosis,”

Smerage *et al*., 2013

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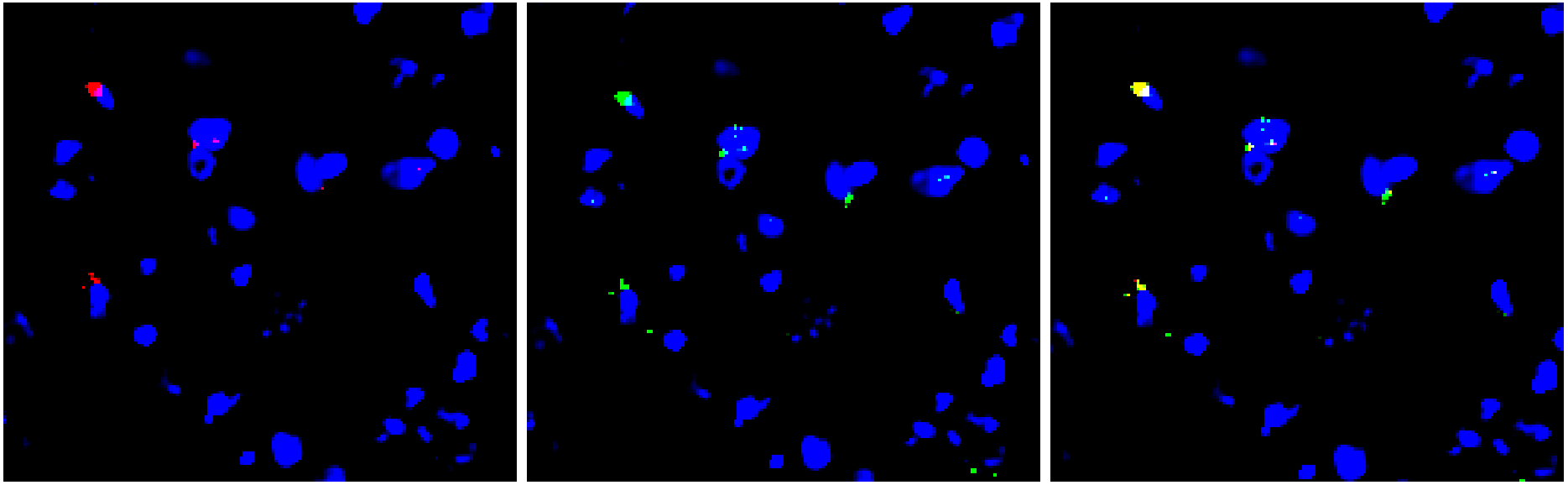
Apoptotic circulating tumor cells (CTCs) in the peripheral blood of metastatic colorectal cancer patients are associated with liver metastasis but not CTCs

Joshua E. Allen[1], Bikramajit Singh Saroya[1], Miriam Kunkel[1], David T. Dicker[1], Avisnata Das[1], Kristi L. Peters[1], Jamal Joudeh[1], Junjia Zhu[1], and Wafik S. El-Deiry[1]

[1] Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey, PA

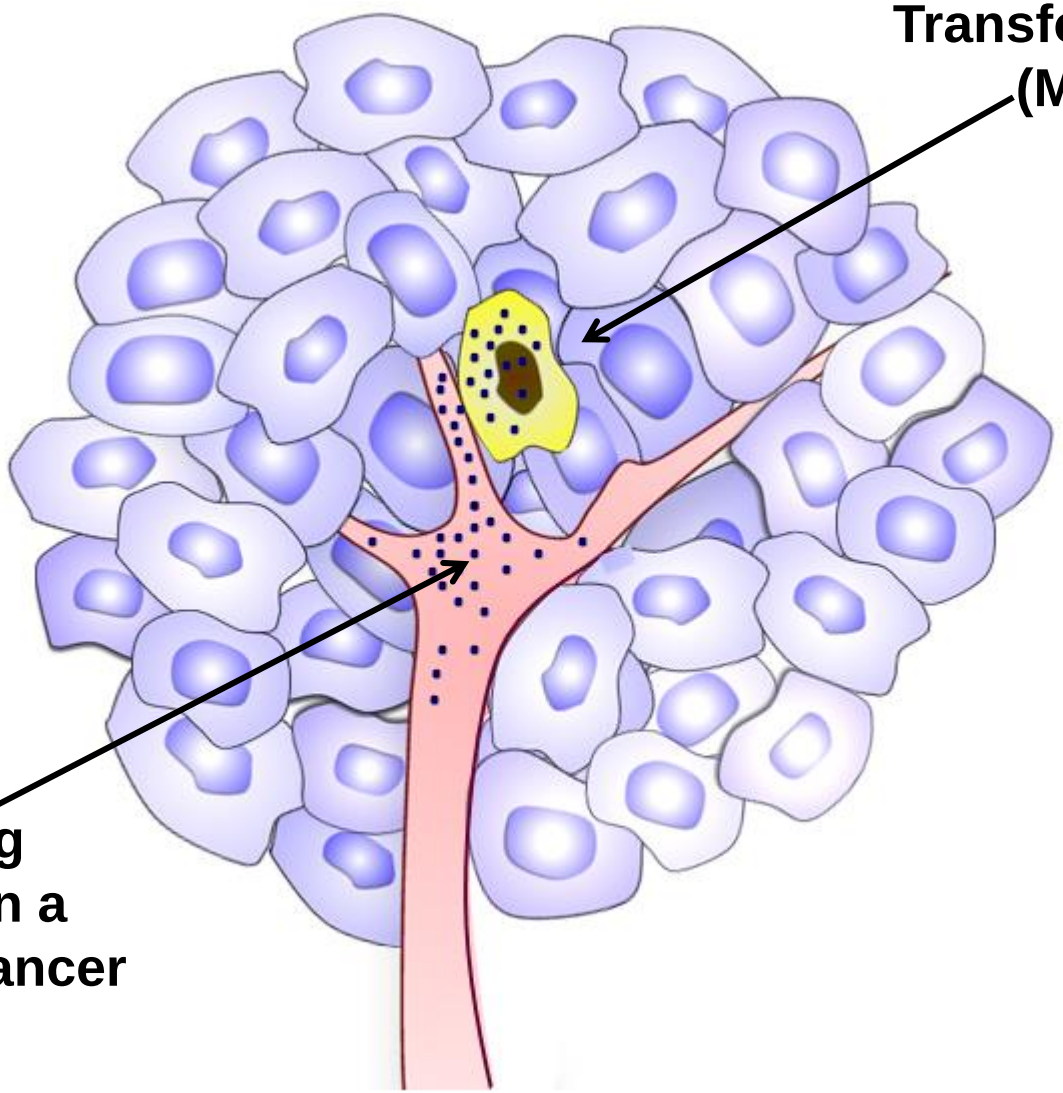
Circulating cfCh from cancer patients can cross blood-brain barrier

Brain



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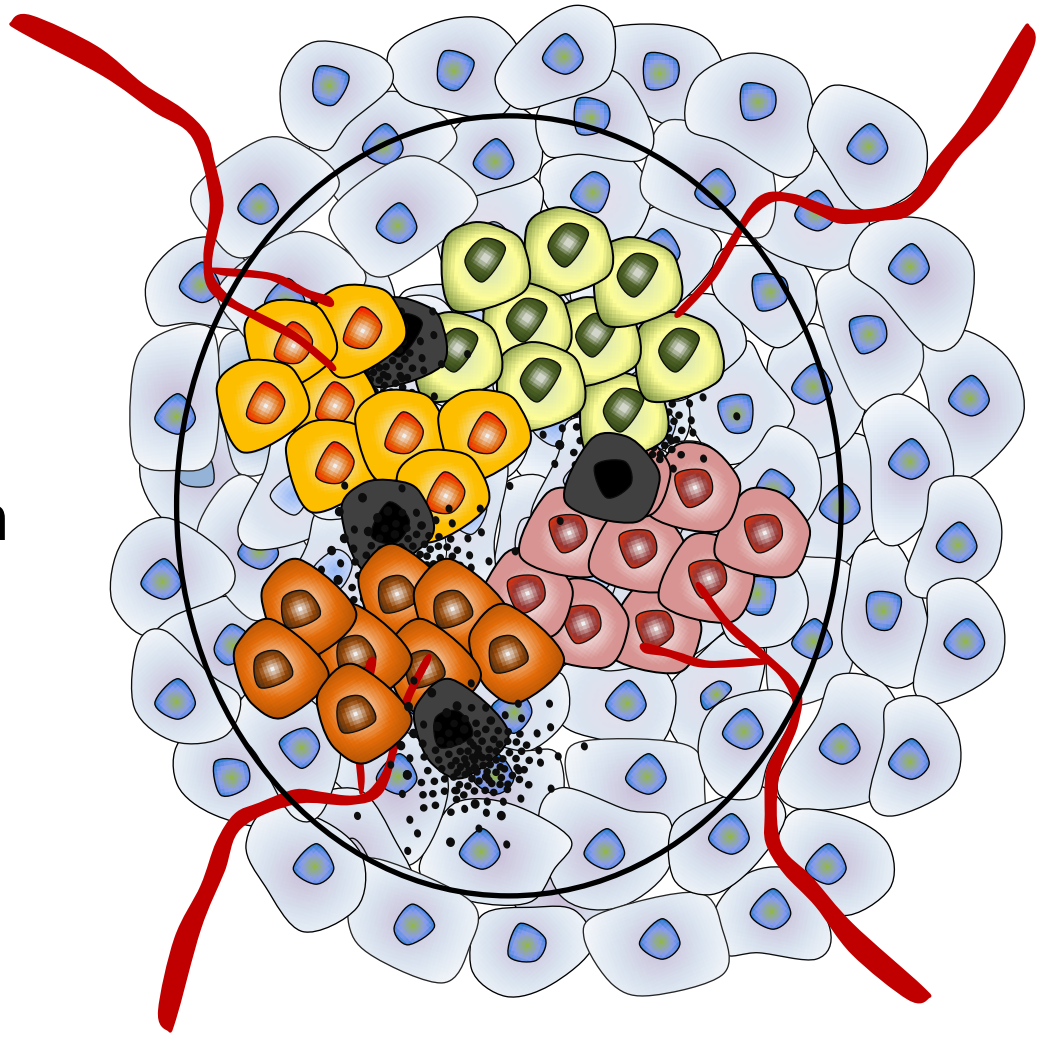
The new theory of cancer metastasis



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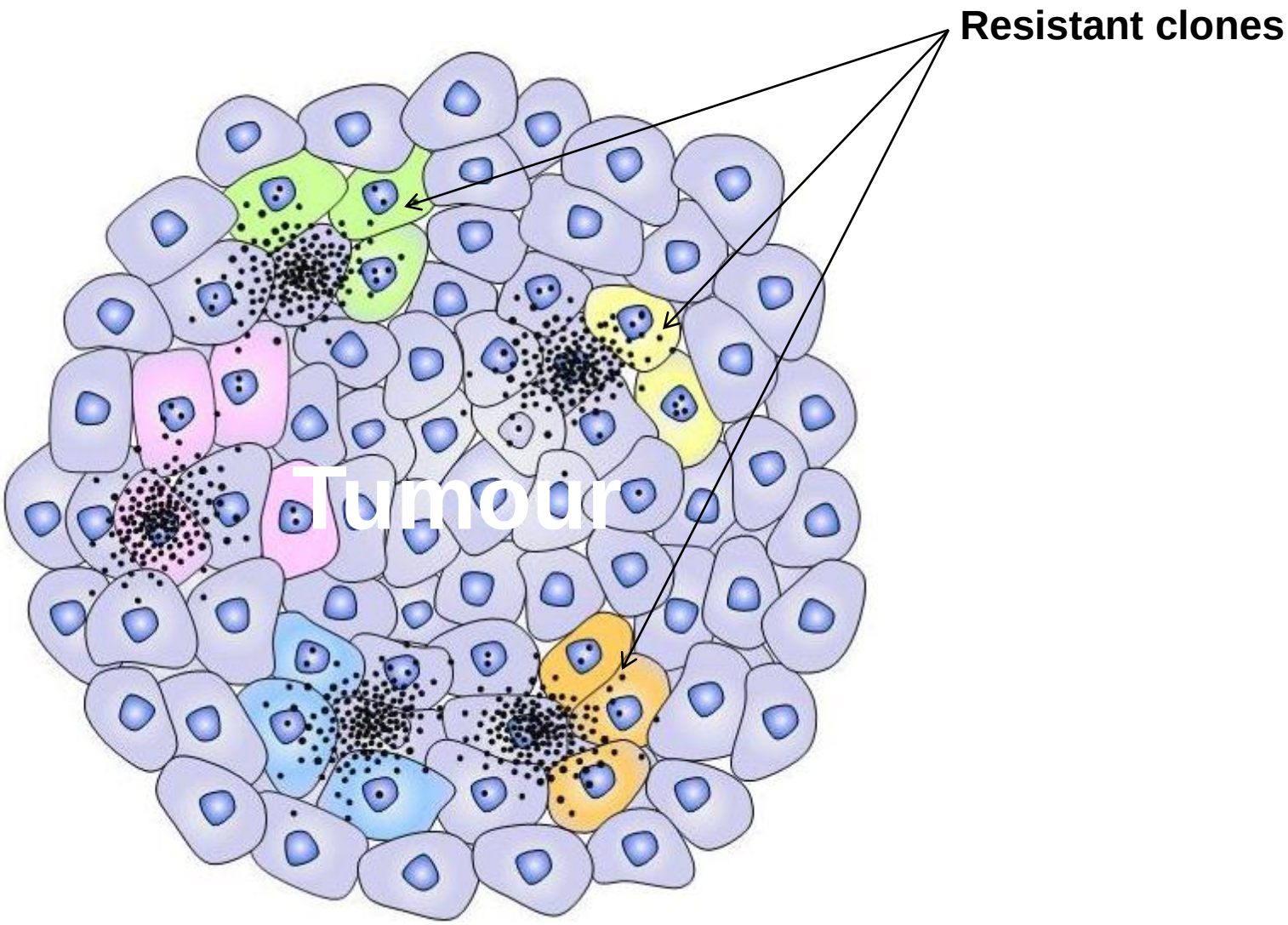
A new theory of cancer evolution

Breast epithelium



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A new theory of chemo- / radio-resistance



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How can we eliminate cfCh from circulation or from dying cells?

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Ways to eliminate extra-cellular chromatin

- **DNase I**
- **CNPs (anti-histone -antibody complexed nanoparticles)**
- **Resveratrol -Cu**

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Biomaterials 34 (2013) 6328–6338

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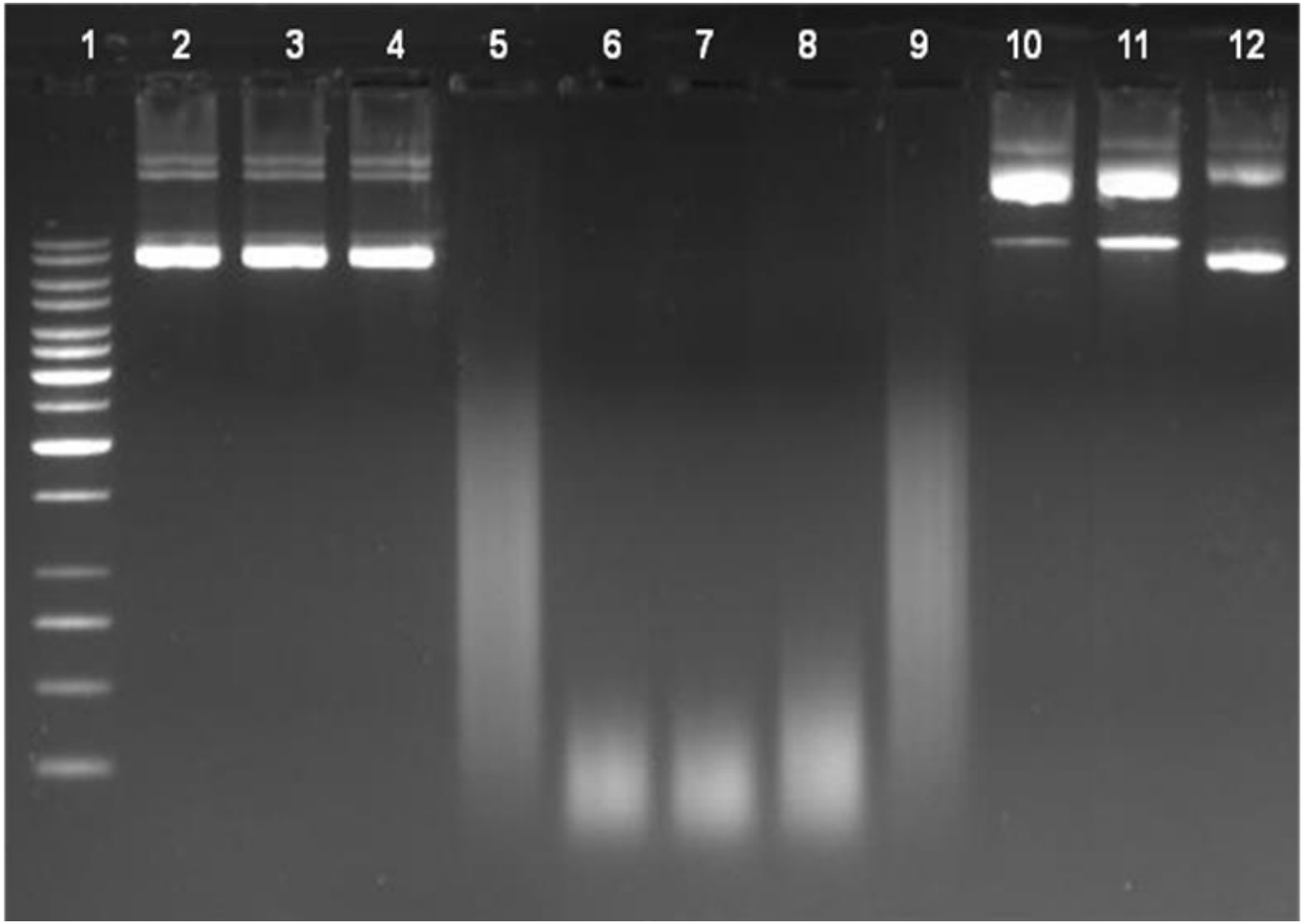
Pullulan-histone antibody nanoconjugates for the removal of chromatin fragments from systemic circulation

M.R. Rekha [a], Kavita Pal [c,1], Preetam Bala [c], Mihir Shetty [c], Indraneel Mittra [c], G.S. Bhuvaneshwar [b,2], Chandra P. Sharma [a,*]

[a] Biosurface Technology Division, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Poojappura, Thiruvananthapuram 695012, Kerala, India
[b] Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Poojappura, Thiruvananthapuram 695012, India
[c] Translational Research Laboratory, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Kharghar, Navi-Mumbai 410210, India

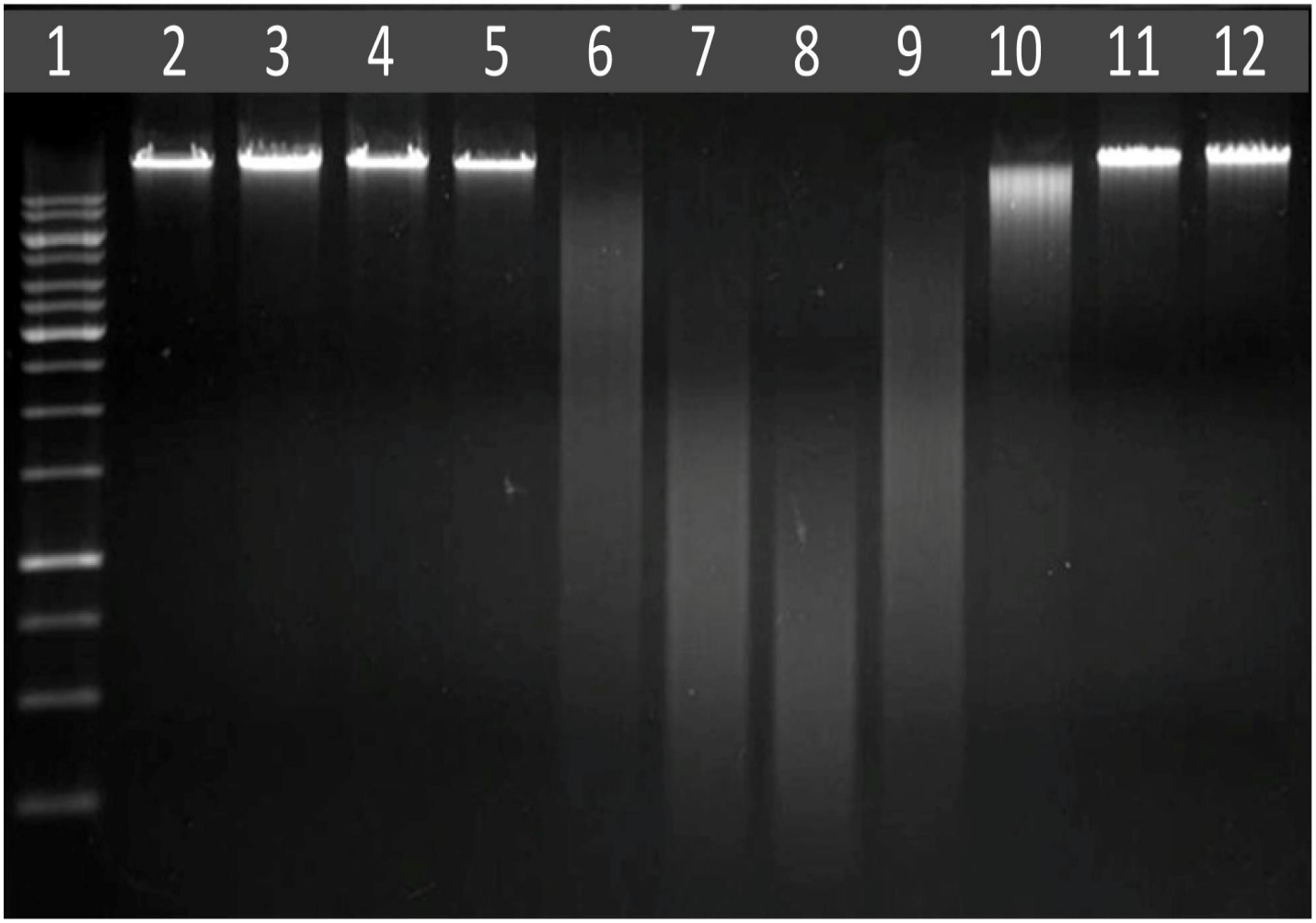
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Resveratrol – Cu^{2+} degrades plasmid DNA



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Resveratrol – Cu^{2+} degrades genomic DNA

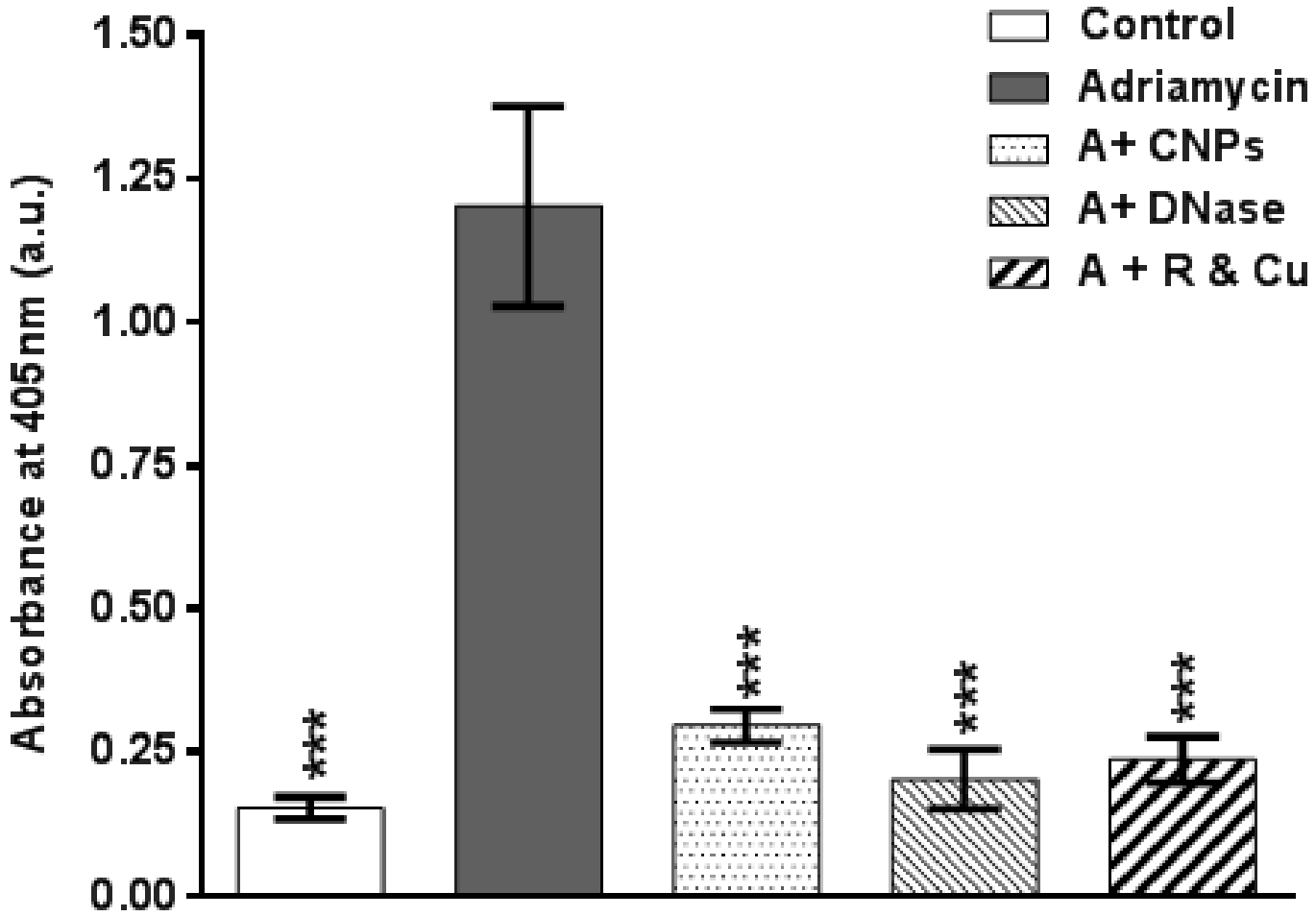


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Prevention of adriamycin toxicity by eliminating cfCh

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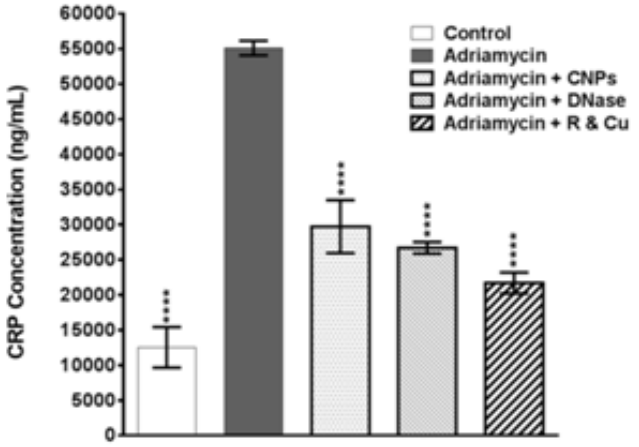
Prevention of adriamycin-induced cfCh surge in blood



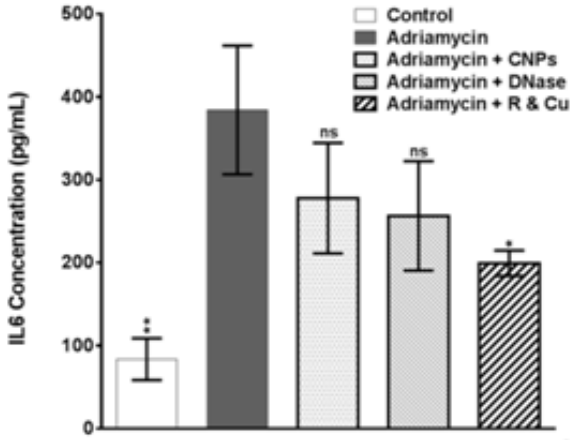
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Prevention of adriamycin-induced inflammatory cytokine surge in blood

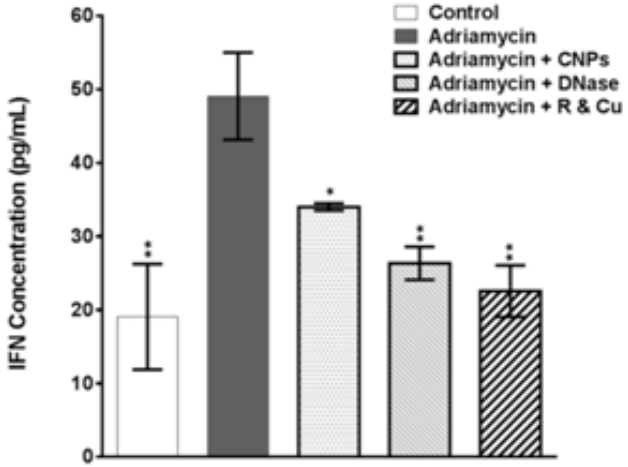
CRP



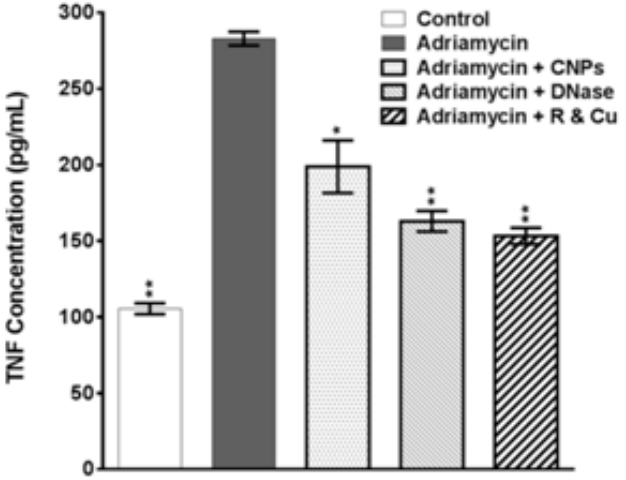
IL-6



IFNγ

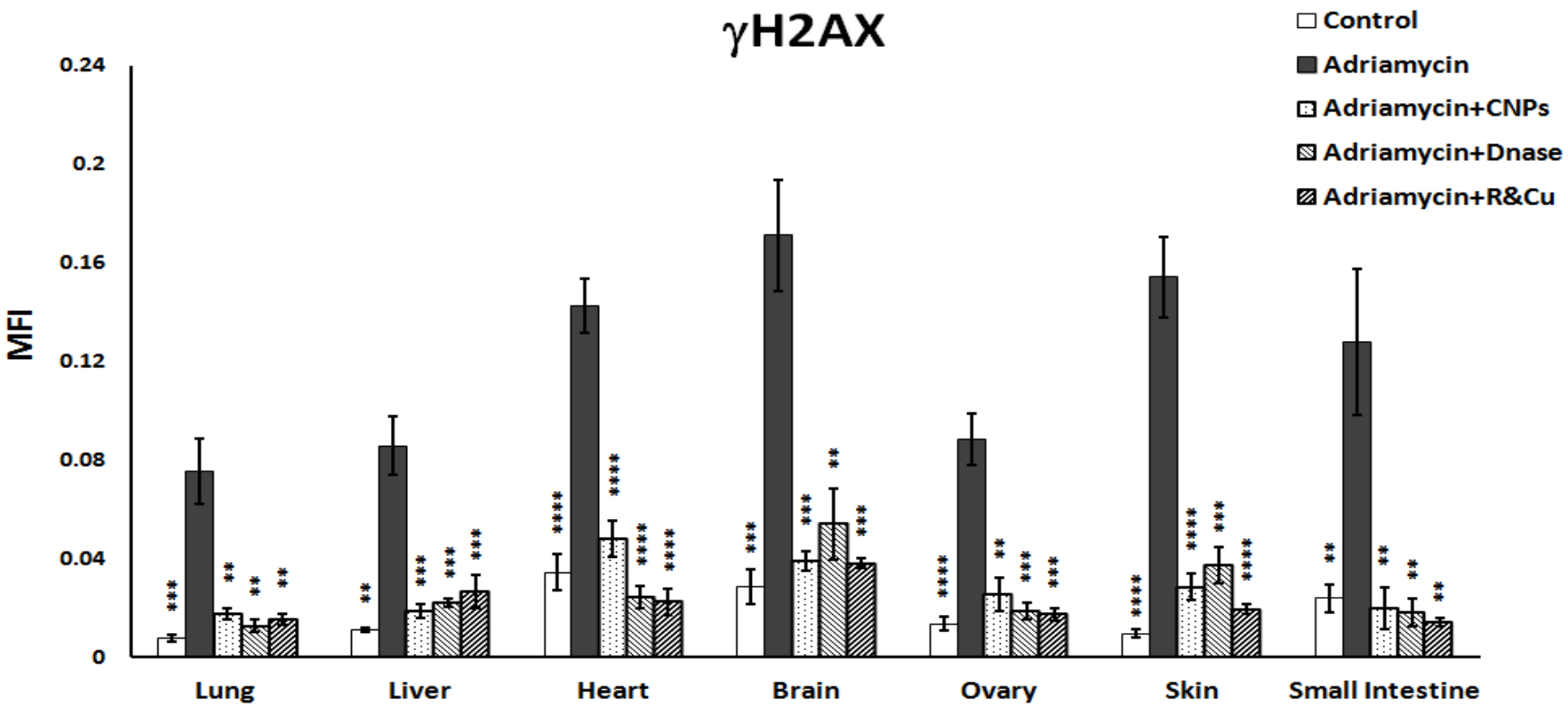


TNFα



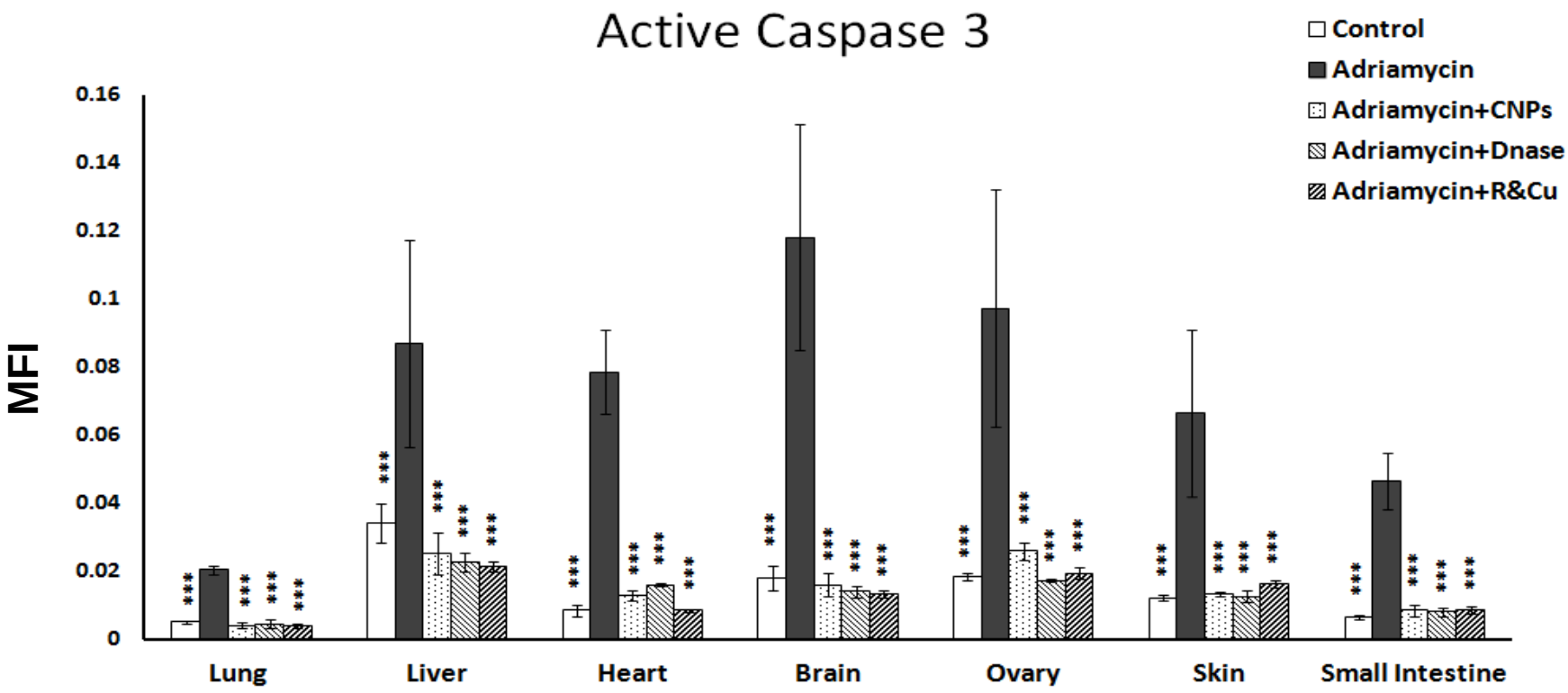
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Prevention of adriamycin-induced tissue damage



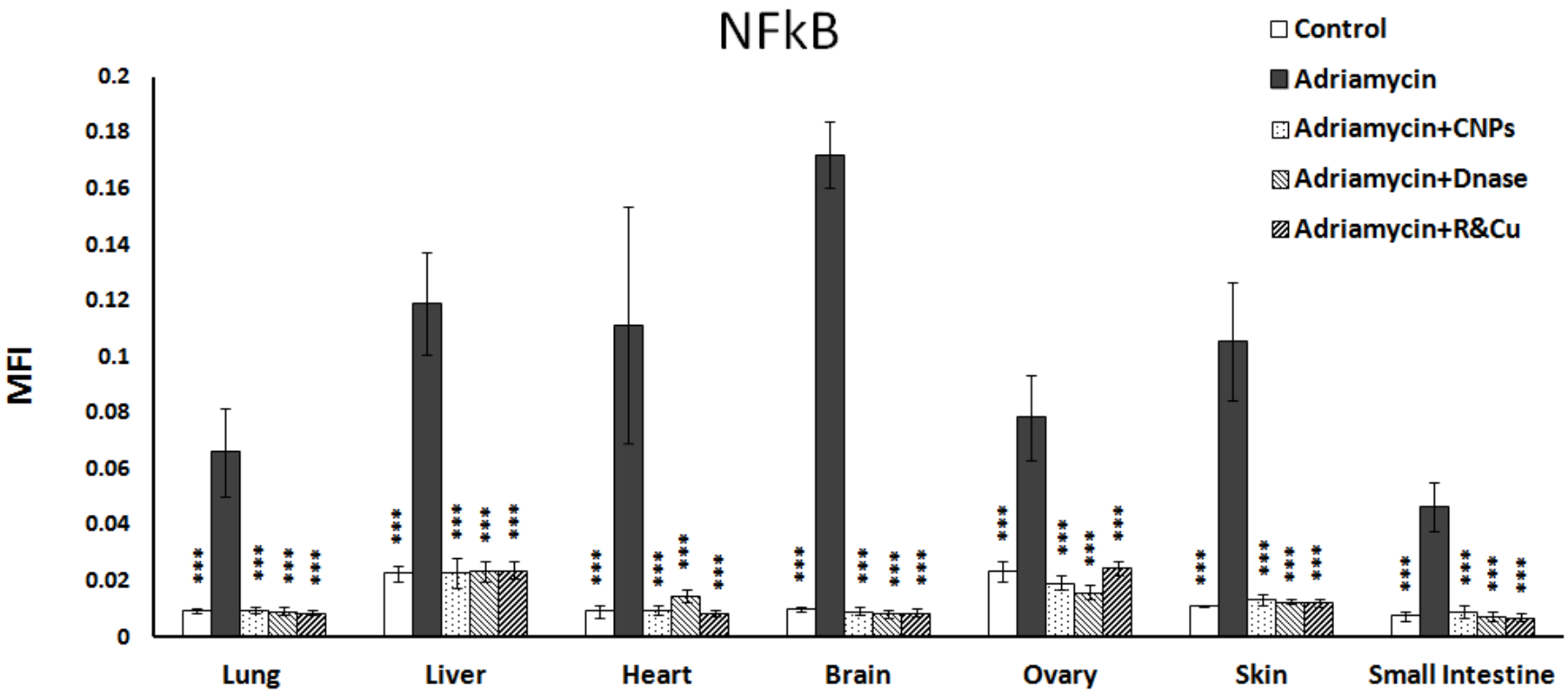
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Prevention of adriamycin-induced tissue damage



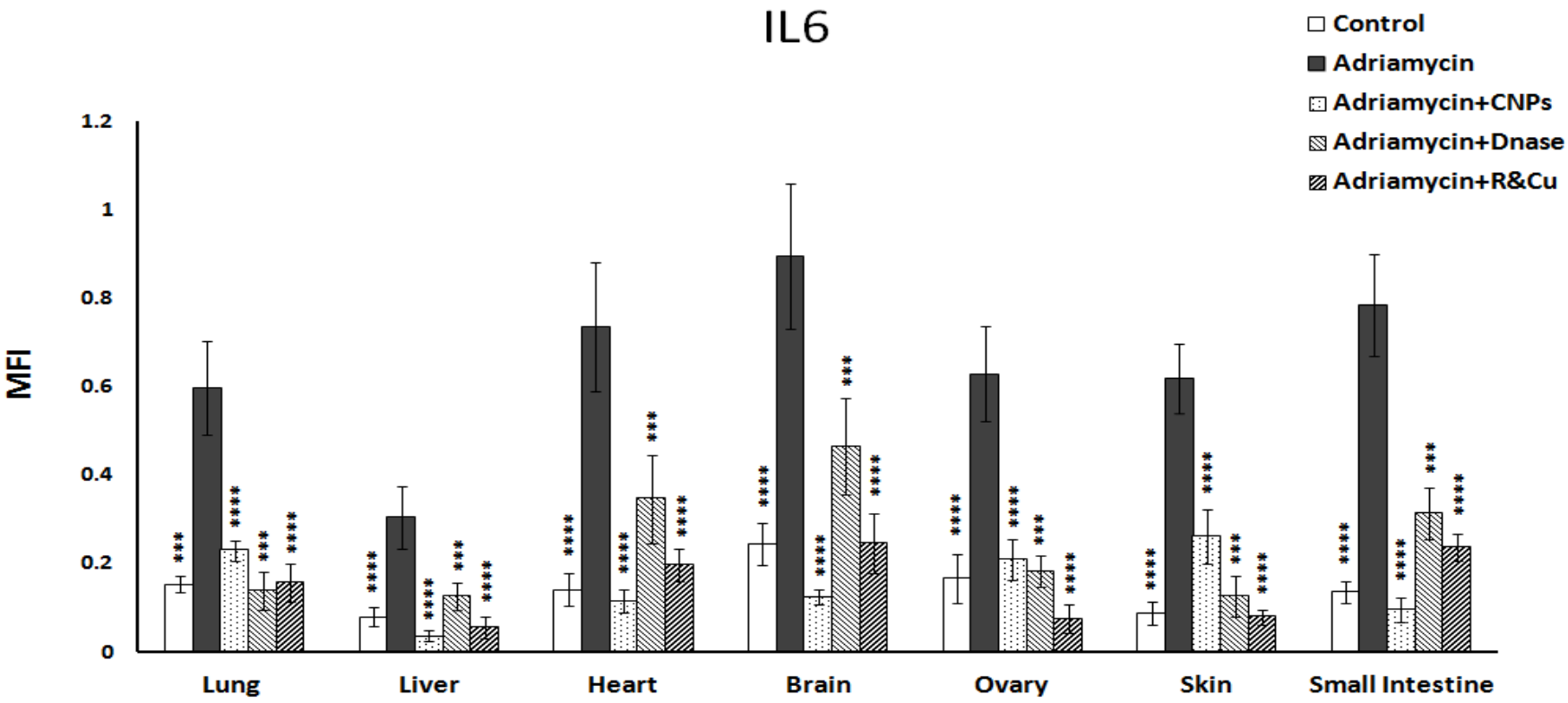
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Prevention of adriamycin-induced inflammation



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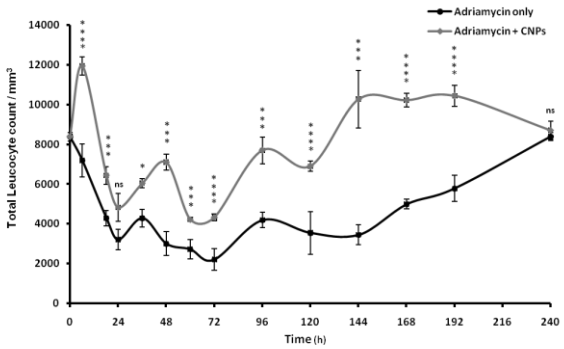
Prevention of adriamycin-induced inflammation



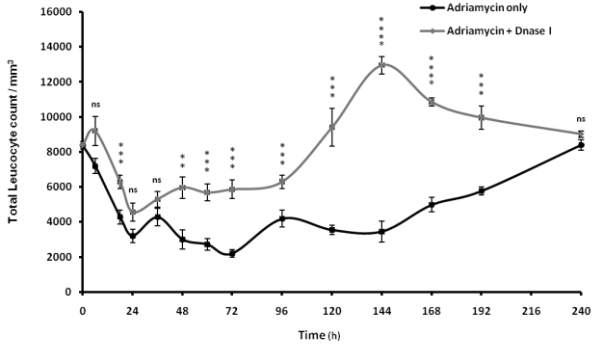
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Prevention of adriamycin-induced neutropenia

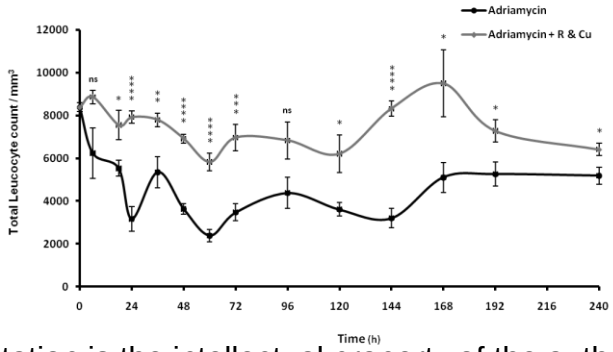
CNPs



DNase I

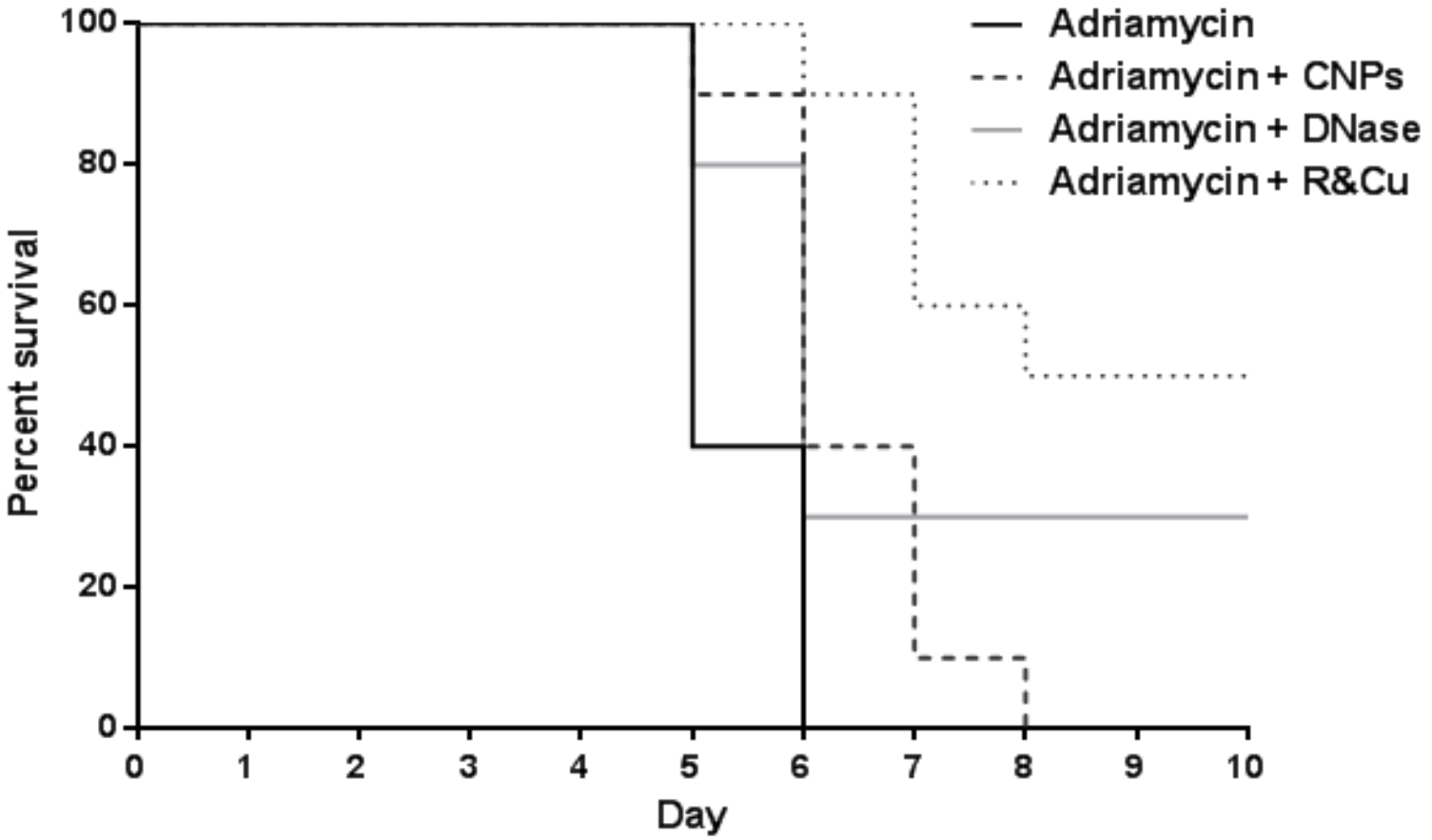


R-Cu



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Prevention of adriamycin-induced lethality



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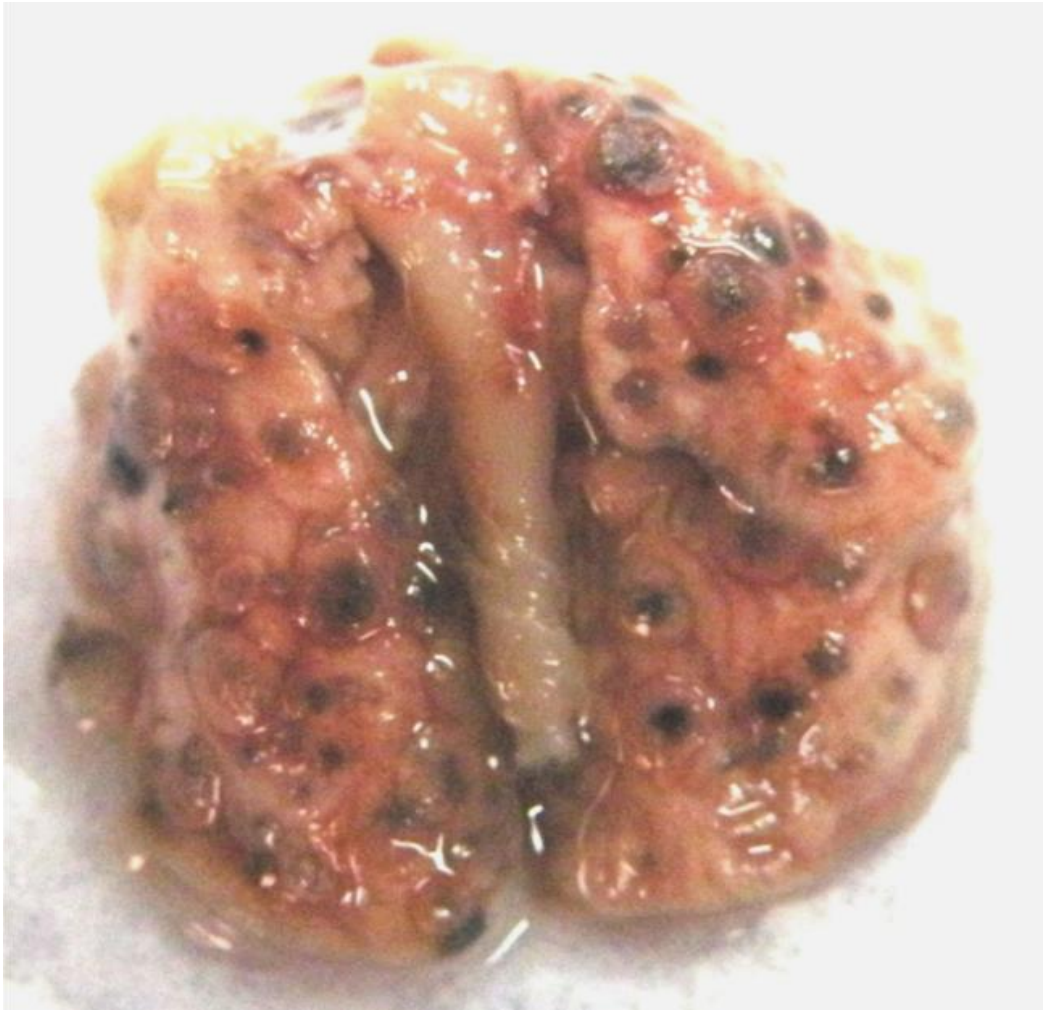
Removal of extra-cellular chromatin in treatment of cancer

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Prevention of metastasis by Resveratrol – Cu^{2+}

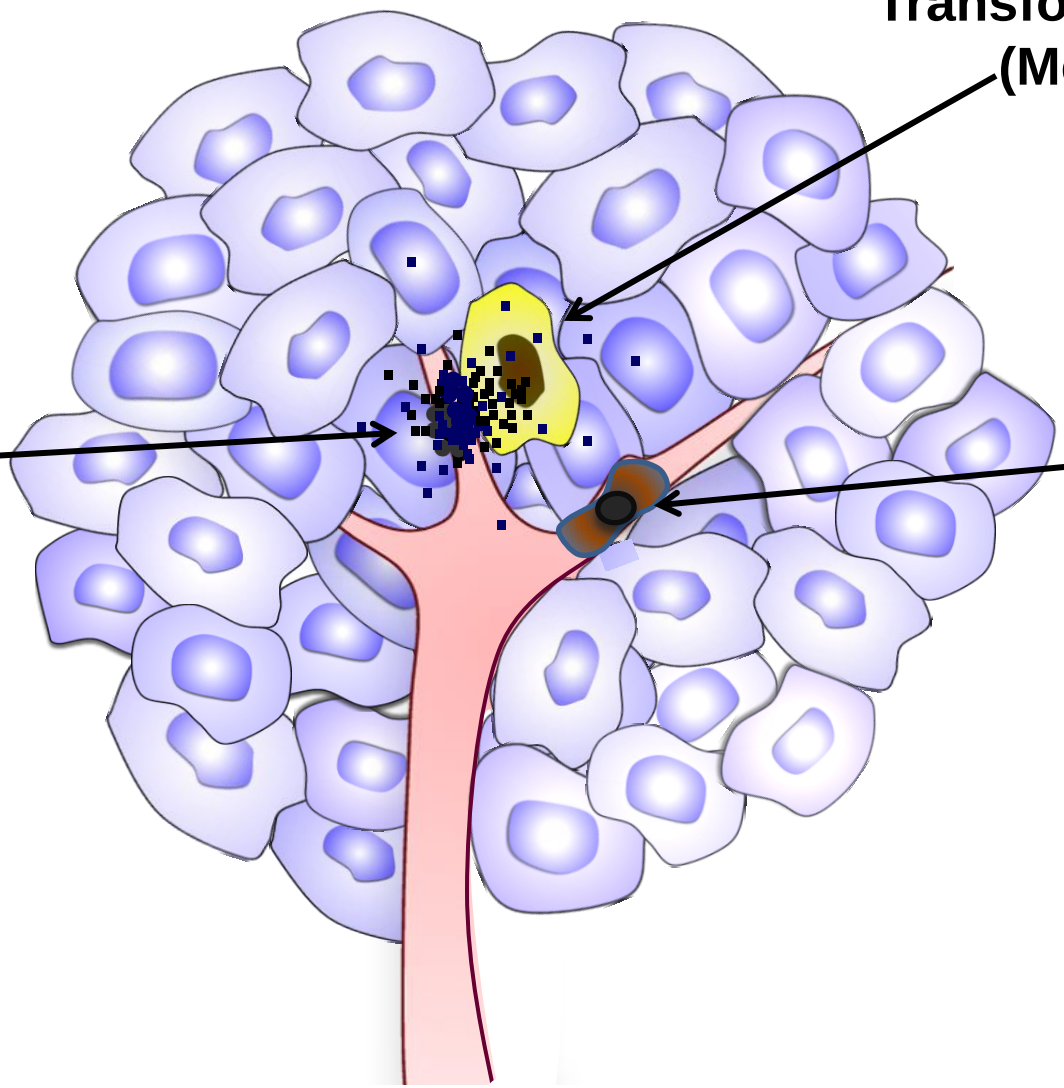
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B16-F10 mouse melanoma model of cancer metastasis



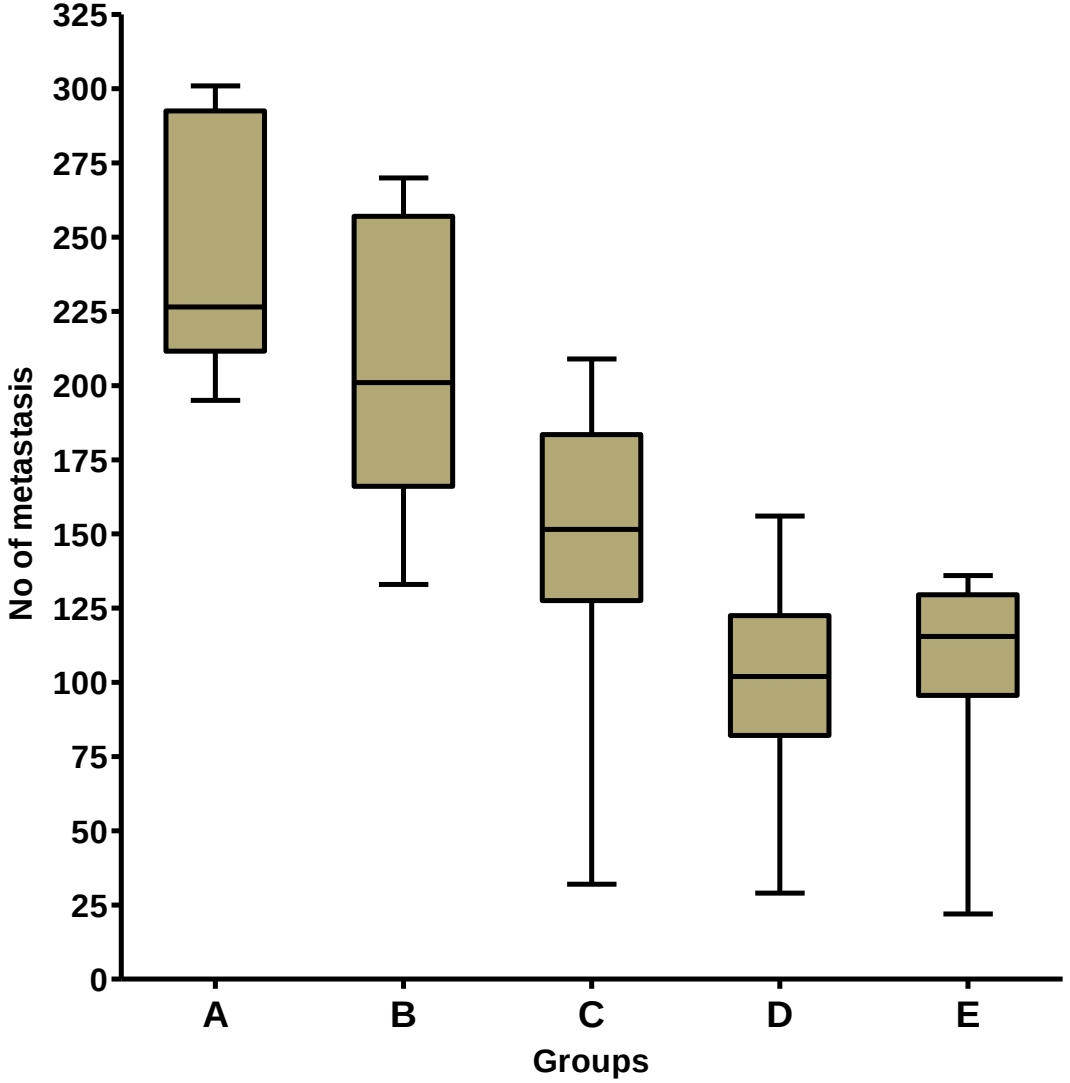
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The new theory of cancer metastasis



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Degrading chromatin with R-Cu prevents cancer metastasis

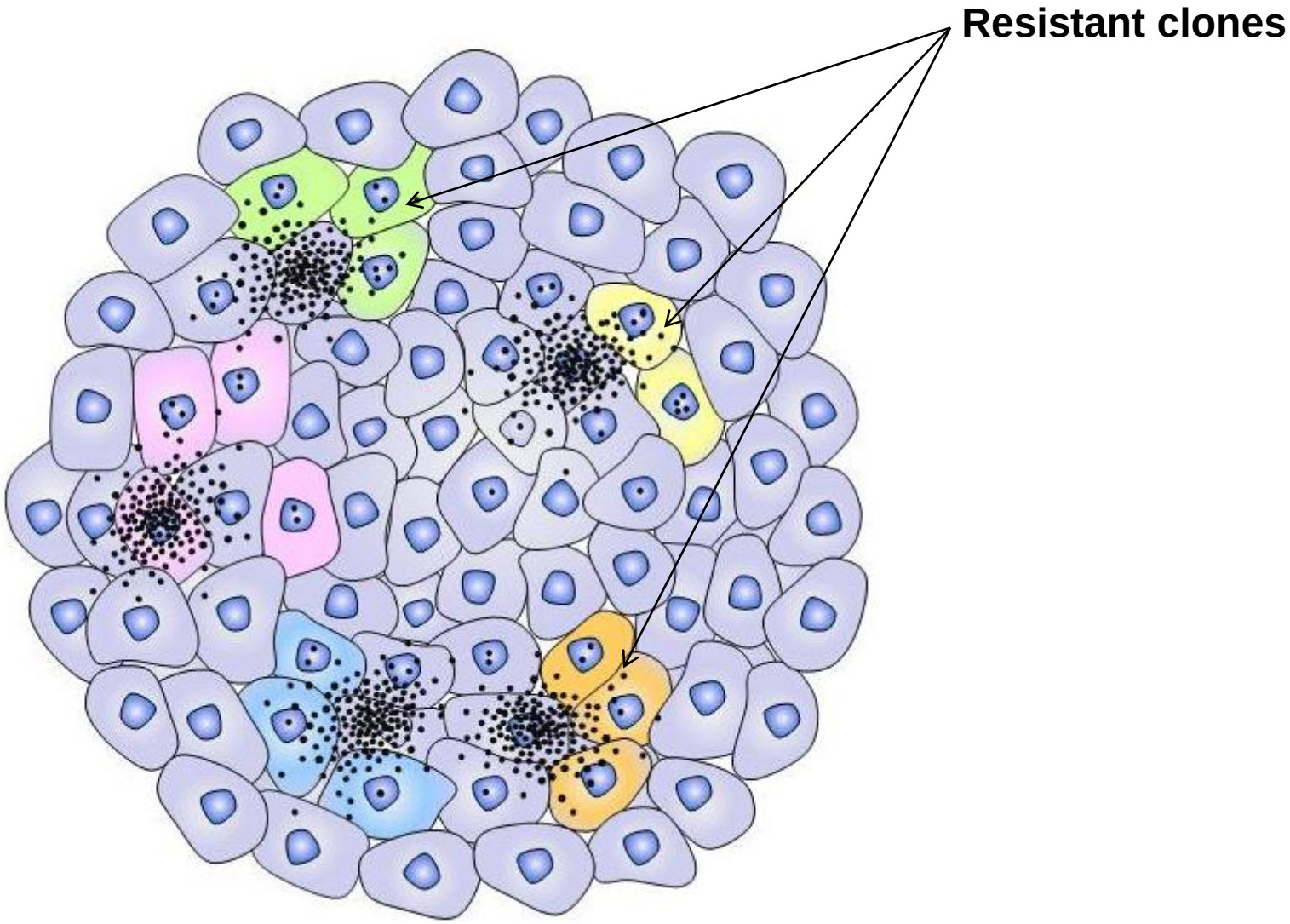


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Enhancing chemosensitivity of adriamycin by Resveratrol-Cu^{2+}

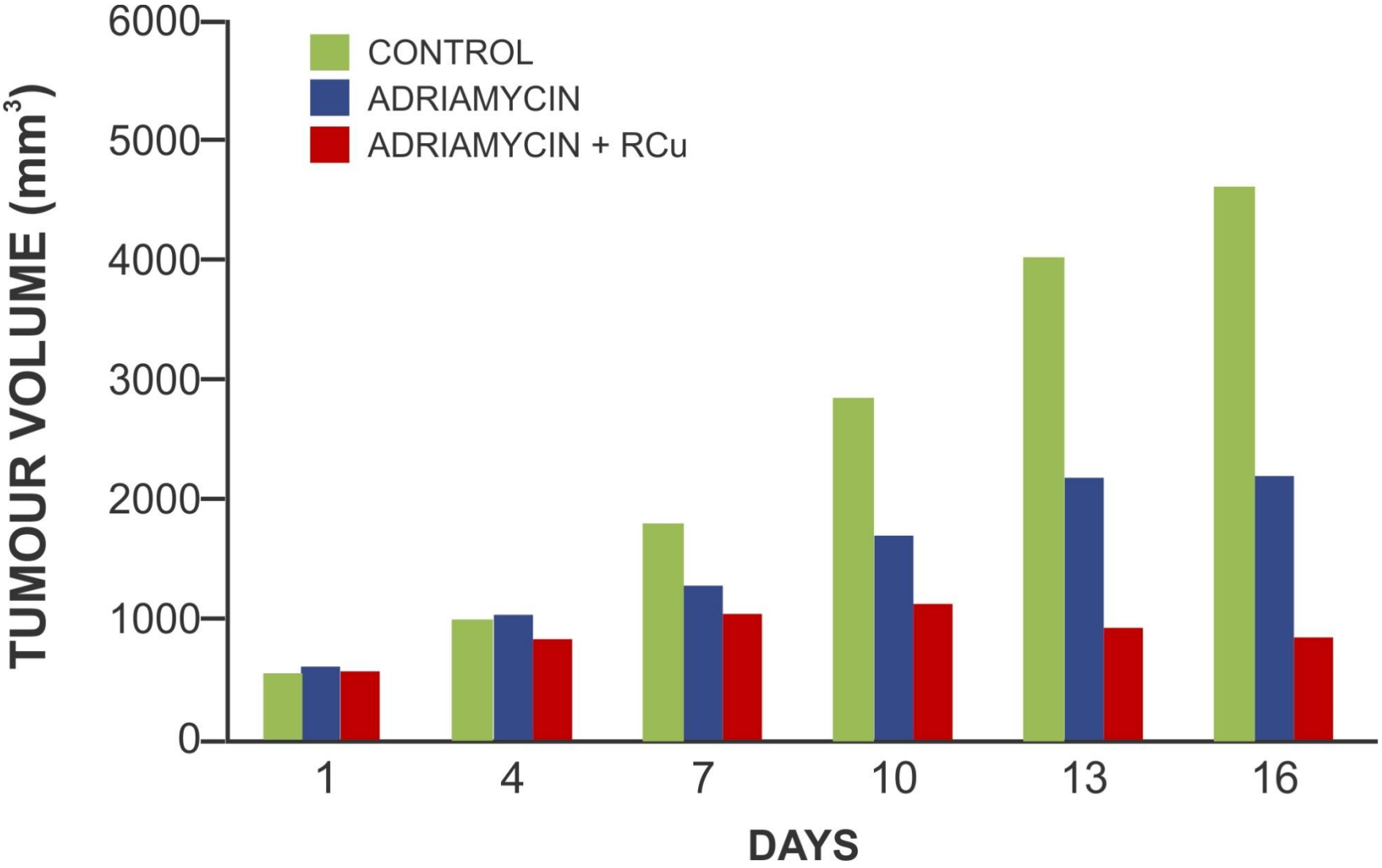
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A new theory of chemo- / radio-resistance



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Resveratrol-Cu^{2+} enhances adriamycin chemosensitivity

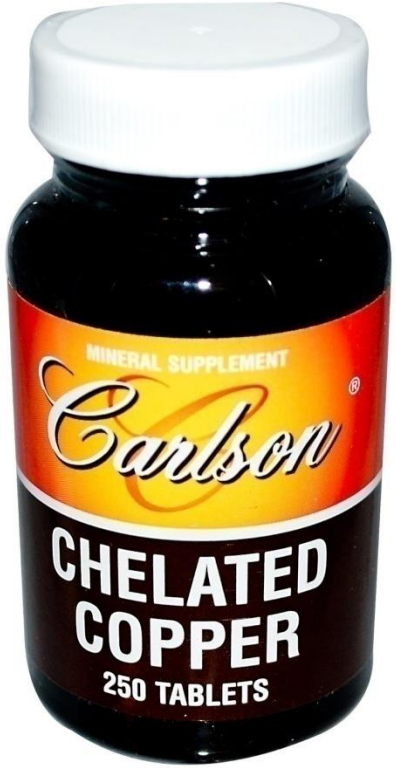


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Onward to clinical trial



Biotivia, TransmaxTR Trans-Resveratrol



Carlson Labs Chelated Copper

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Therapeutic potentials of Resveratrol-Cu

- **May retard ageing and allied conditions**
- **May prevent occurrence of cancer**
- **May reduce chemo-toxicity – permitting higher doses to be delivered**
- **May stall tumour growth when given alone**
- **May eradicate cancer if given with CT or RT**
- **May prevent metastasis**

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Futility of current strategies of cancer therapy

- Chemotherapy
- Hormone therapy
- Radiotherapy
- Targeted therapy
- Immunotherapy
- Nanotherapy

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The future of cancer treatment

Kill cancer cells by all means

..... but please clean up the debris !

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The TRL team



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Thank you for your attention

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