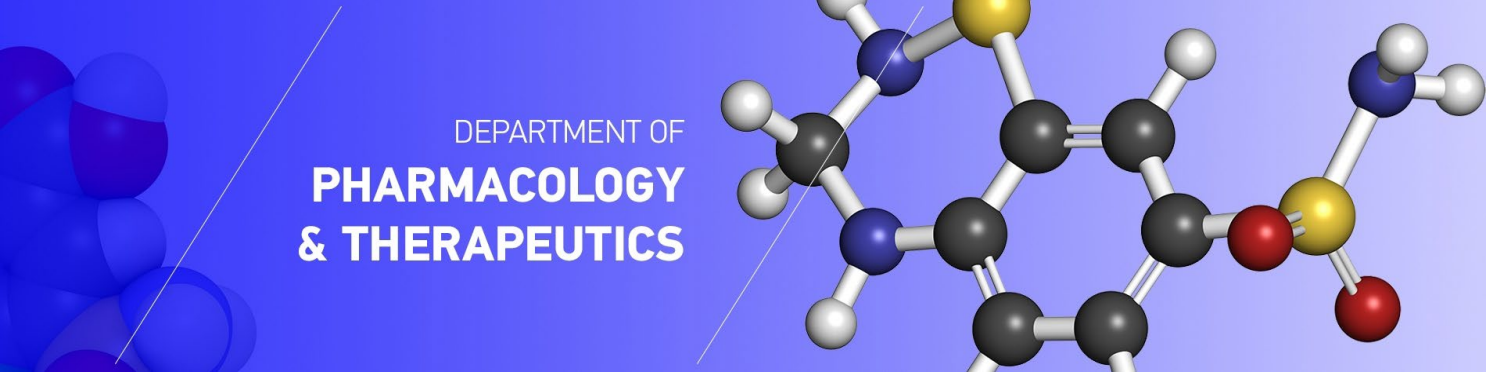


McGill

Department of Pharmacology and Therapeutics

Département de pharmacologie et de thérapeutique

Potential mechanisms of tungsten-induced carcinogenesis

Koren K. Mann

May 4, 2023

Genetic Toxicology Association Annual Meeting

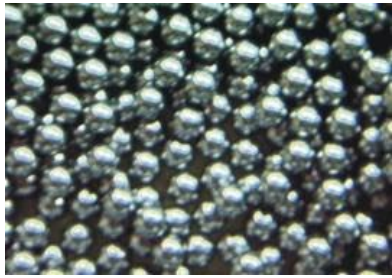
COI

I receive research funding from Recludix for a DLBCL project (unrelated to the current talk).

Tungsten
74

W

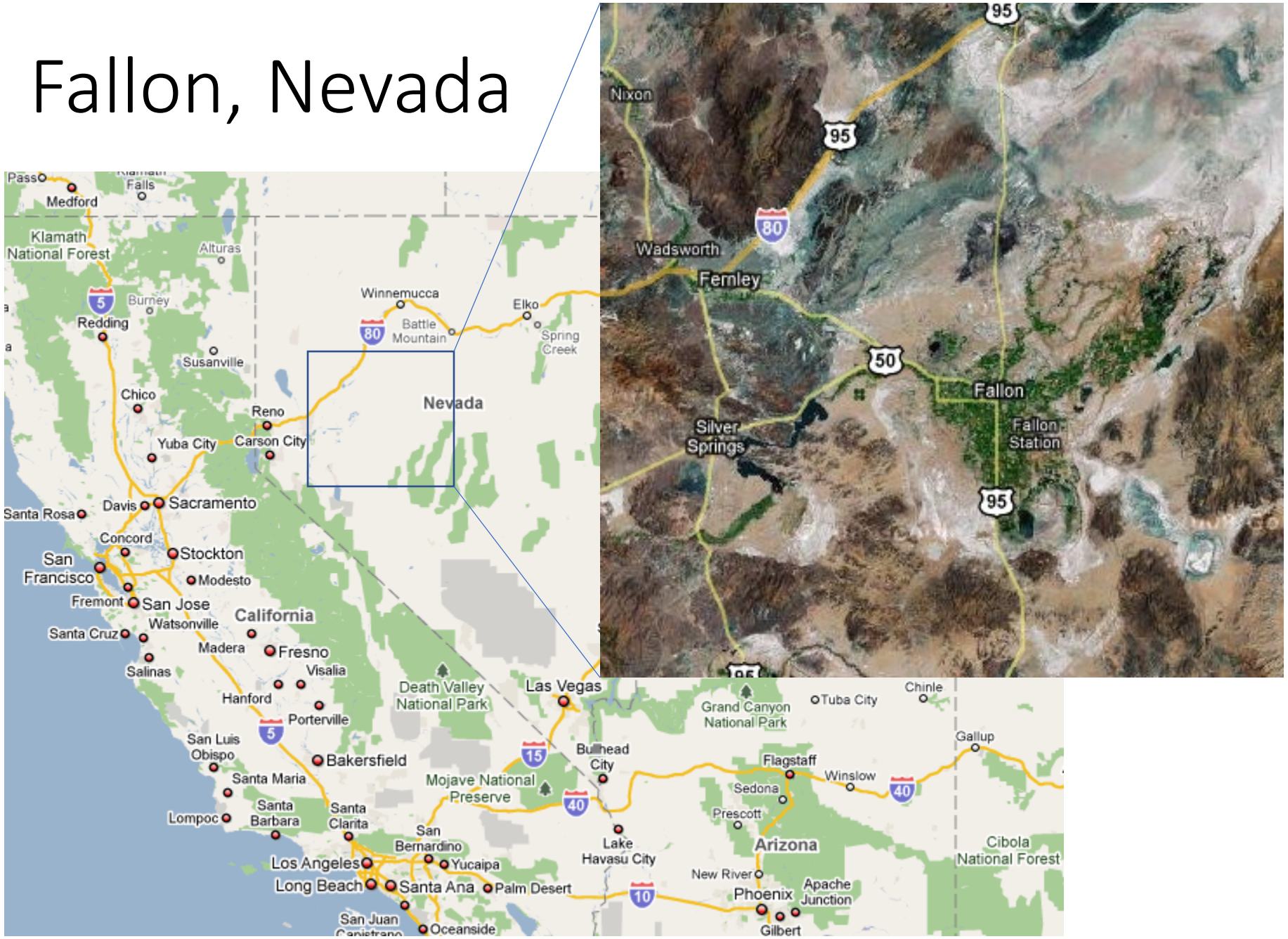
183.84



Tungstates

Bolt and Mann, Curr Env Health Rep 2016

Fallon, Nevada



Fallon, Nevada Leukemia Cluster

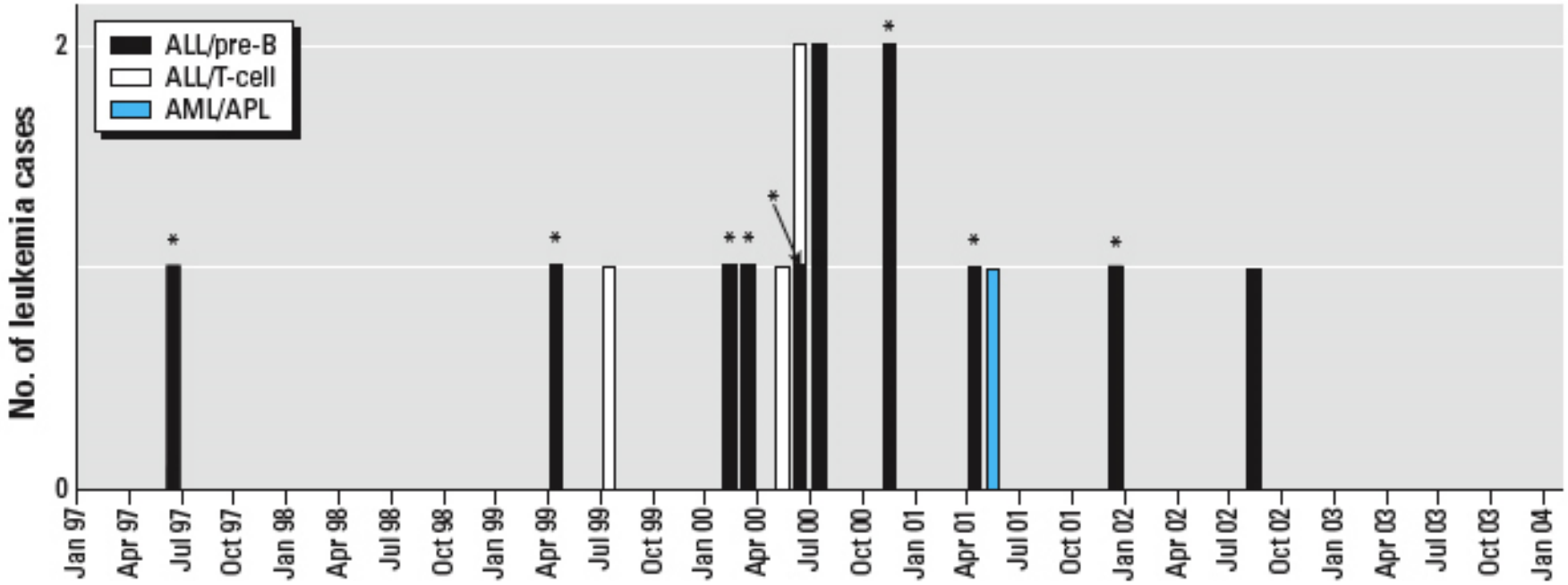
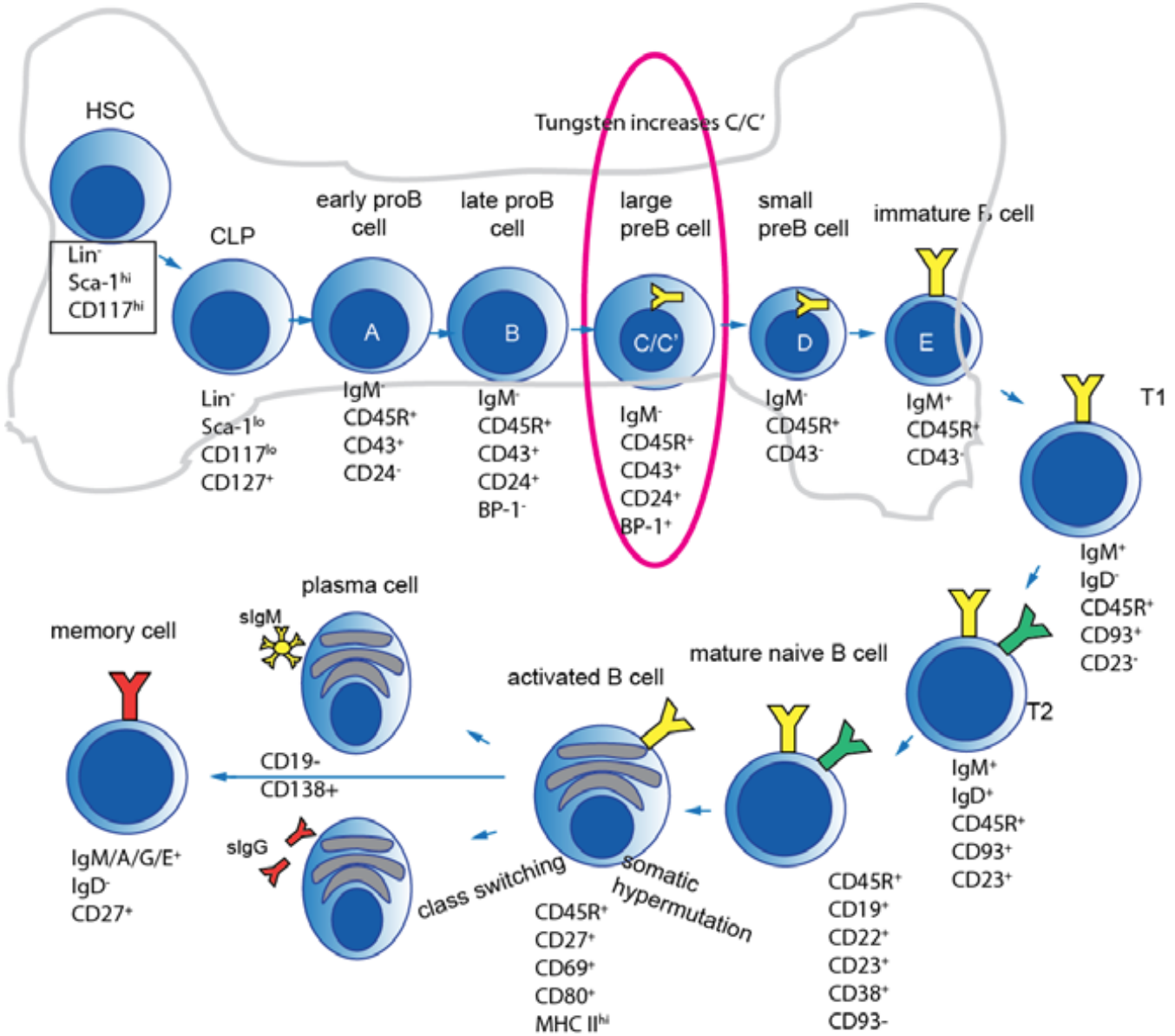


Figure 1. Temporal distribution of the 16 children who had lived in Churchill County, Nevada, and were diagnosed with leukemia between June 1997 and August 2002. Cancer type and cell type are defined. One case declined participation in the study, and one was diagnosed outside the study period. The nine individuals fitting the restricted case definition are indicated by asterisks (*).

Rubin et al. EHP 2003

B lymphocyte Development



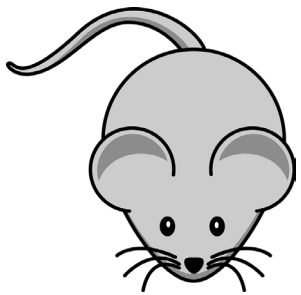
Can tungsten exposure lead to leukemogenesis?

IF….THEN

- B cell development occurs in the bone marrow within the bone after birth. Thus, this compartment should be exposed to tungsten.

- Kids in Fallon, largely had Acute Lymphoblastic Leukemia of the preB subtype. So, tungsten would be predicted to have an effects on developing B cell populations.

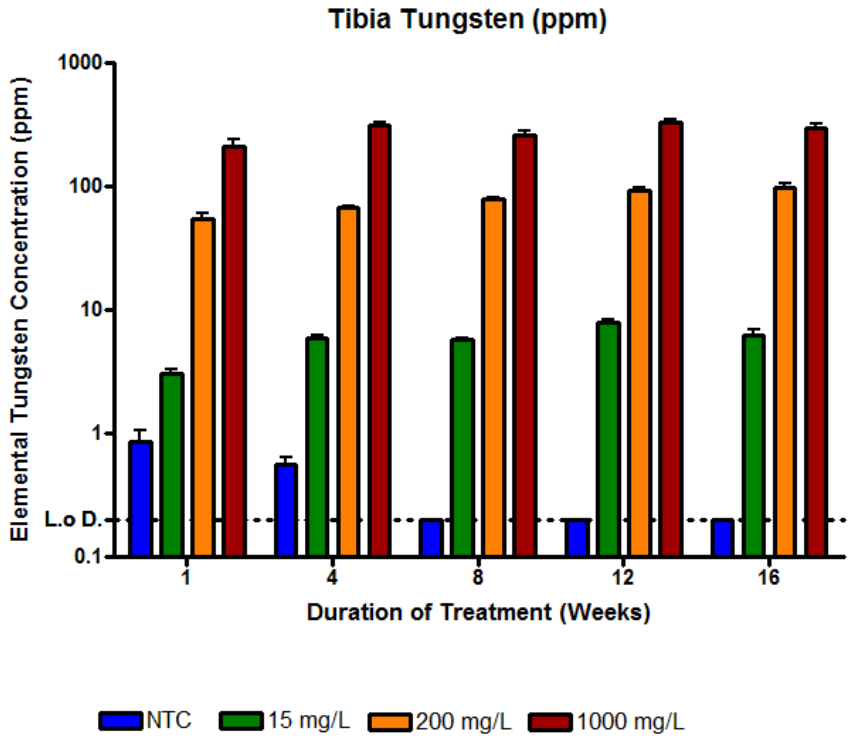
Tungsten Accumulates in the Bone

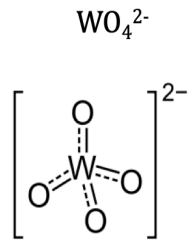


Tap water with or without Sodium tungstate

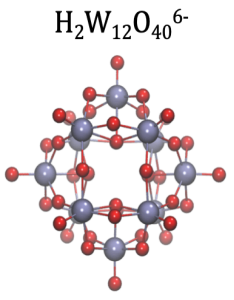
Male C57Bl6/J mice
5 weeks old

ICP-MS

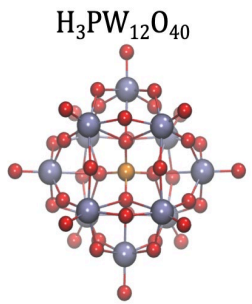




Orthotungstate
(Sodium tungstate)



Metatungstate

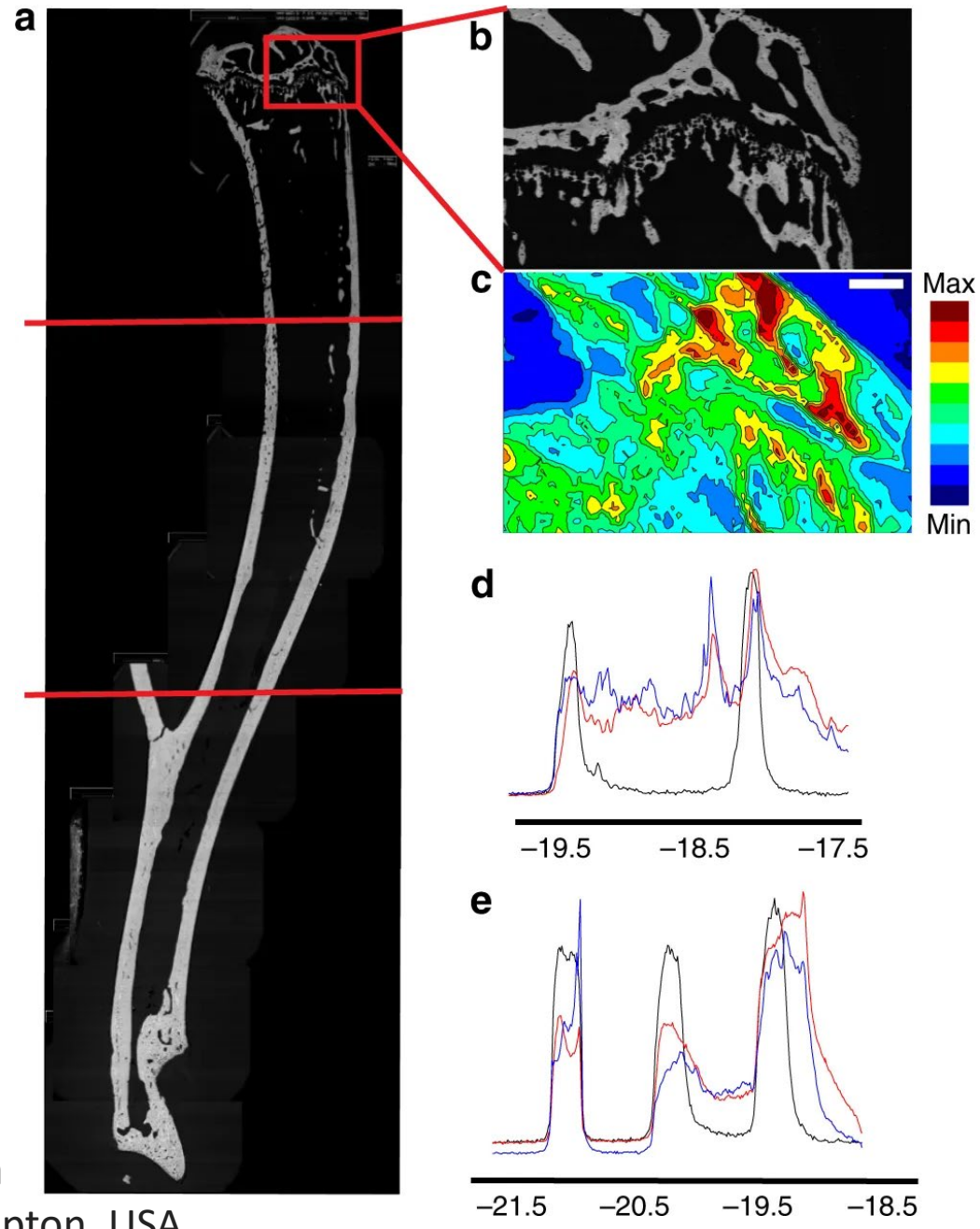


Phosphotungstate

Kelly et al. Tox Sci 2013

VanderSchee et al. Comm Chem 2018

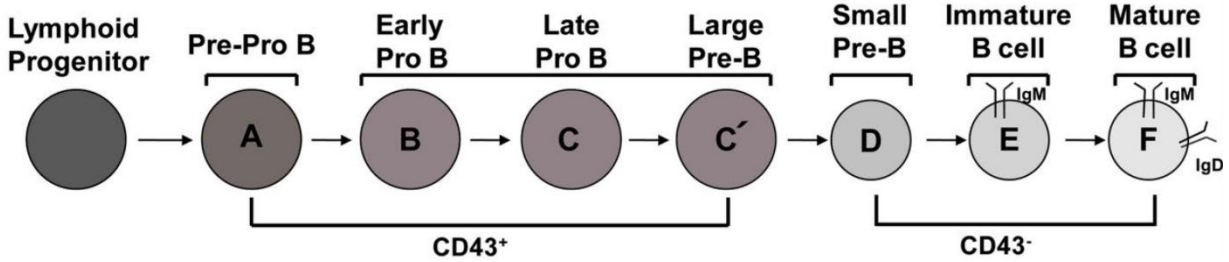
Synchrotron radiation micro X-ray fluorescence (SR-µXRF) shows tungsten in bone



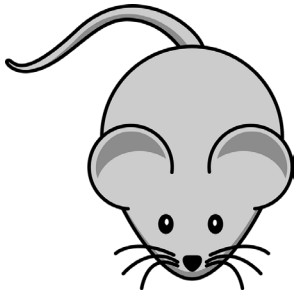
Black = calcium
Red= tungsten
Blue= zinc

VanderSchee et al. Comm Chem 2018
Canadian Light Source (CLS) in Saskatoon, Canada
National Synchrotron Light Source II (NSLS-II) in Upton, USA

Tungsten exposure results in increased preB cells

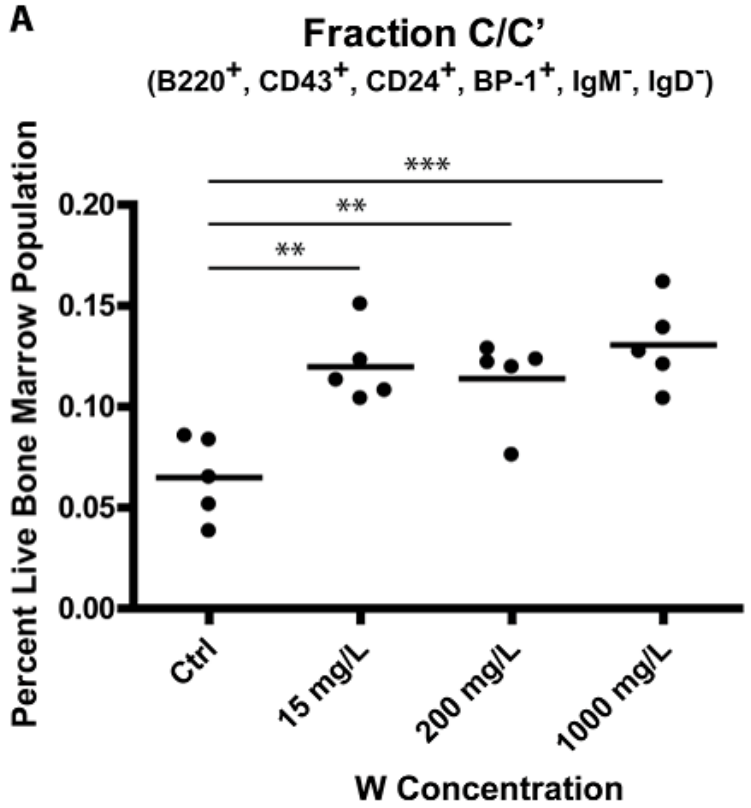


Tap water with or without Sodium tungstate



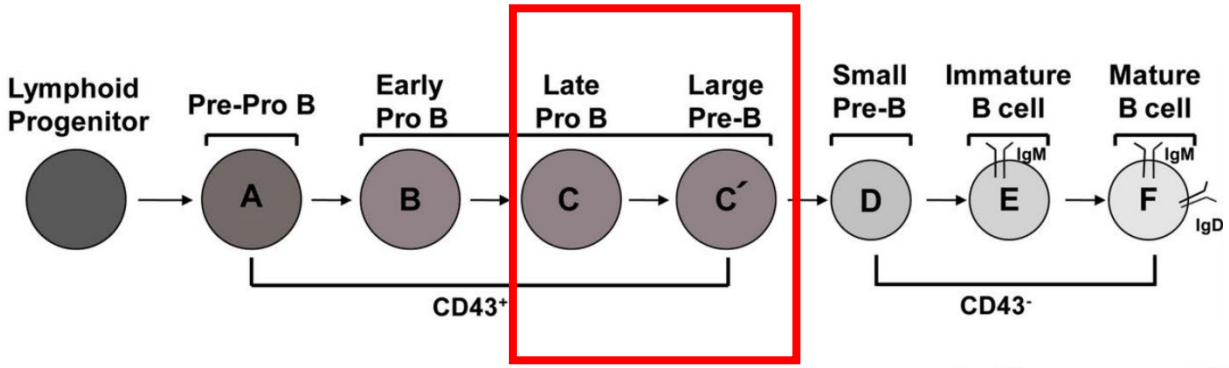
Male C57Bl6/J mice
5 weeks old

Bone Marrow for B cell Immunophenotyping by flow cytometry

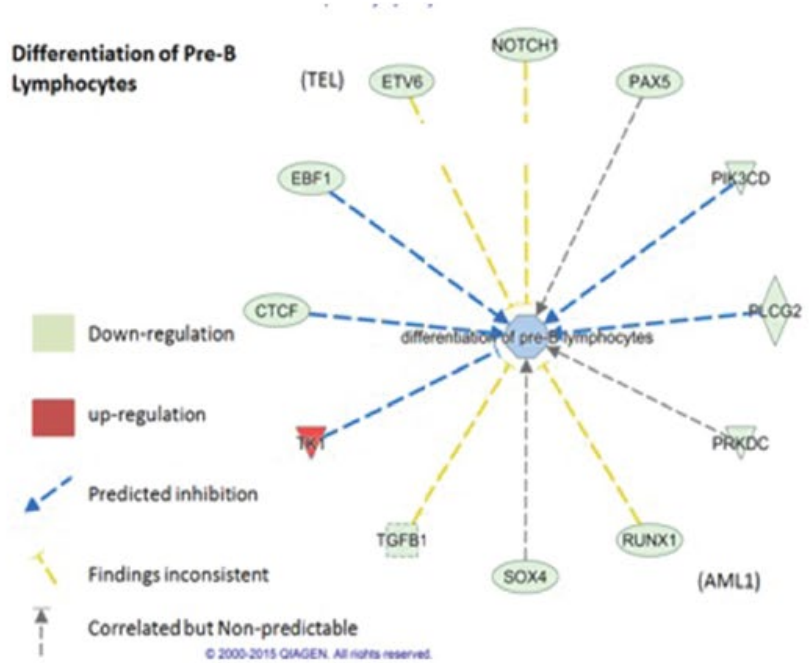


Kelly et al. Tox Sci 2013

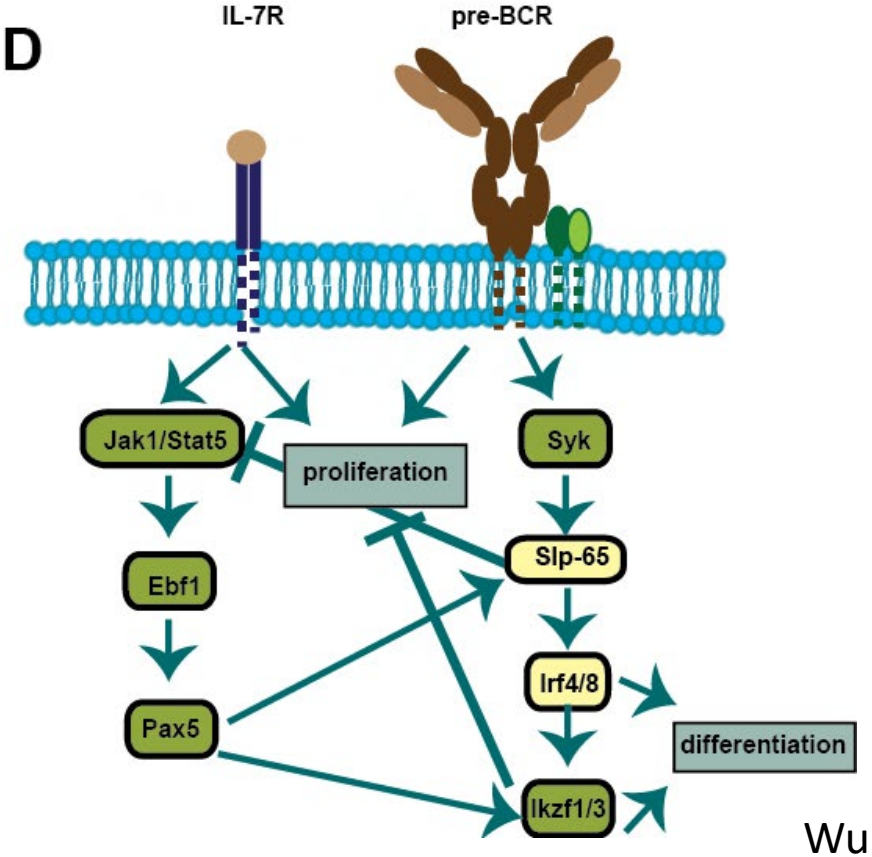
Tungsten-induced changes in preB cells sorted from murine bone marrow



C



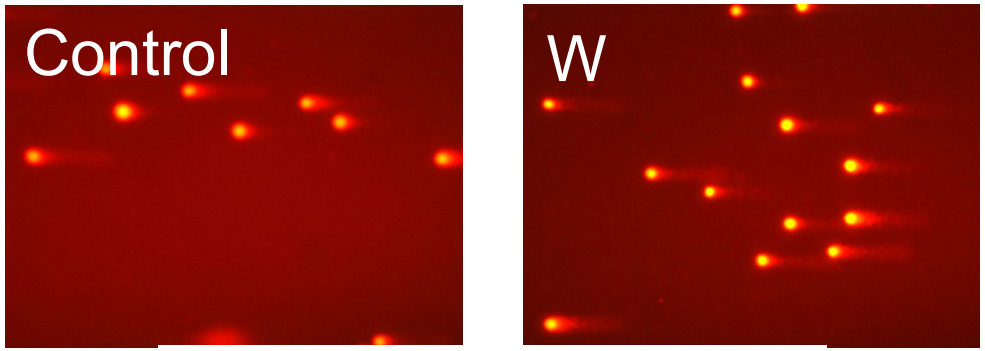
D

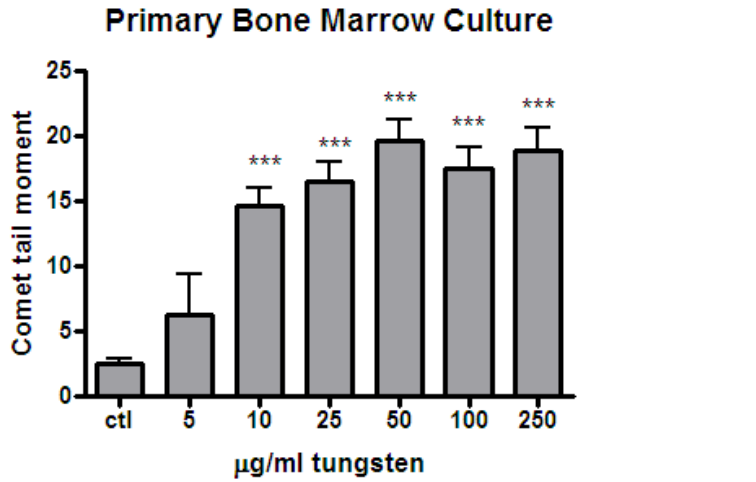


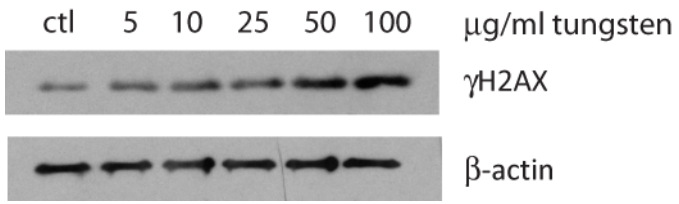
Wu et al. Tox Sci 2019

Tungsten exposure increases DNA damage in Developing B cells

In Vitro Whitlock-Witte Cultures

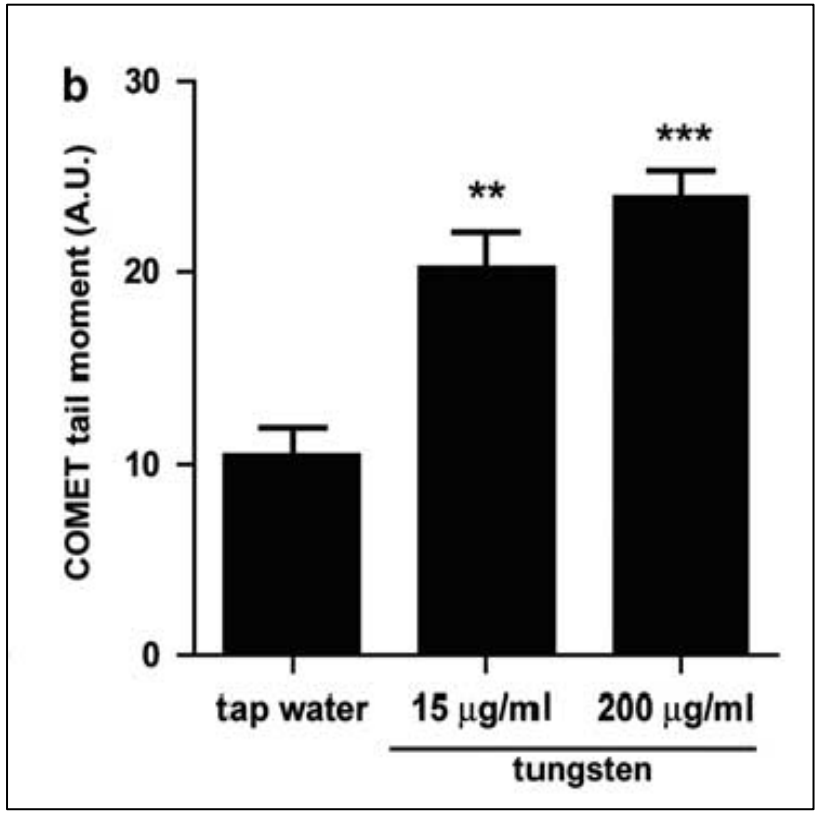






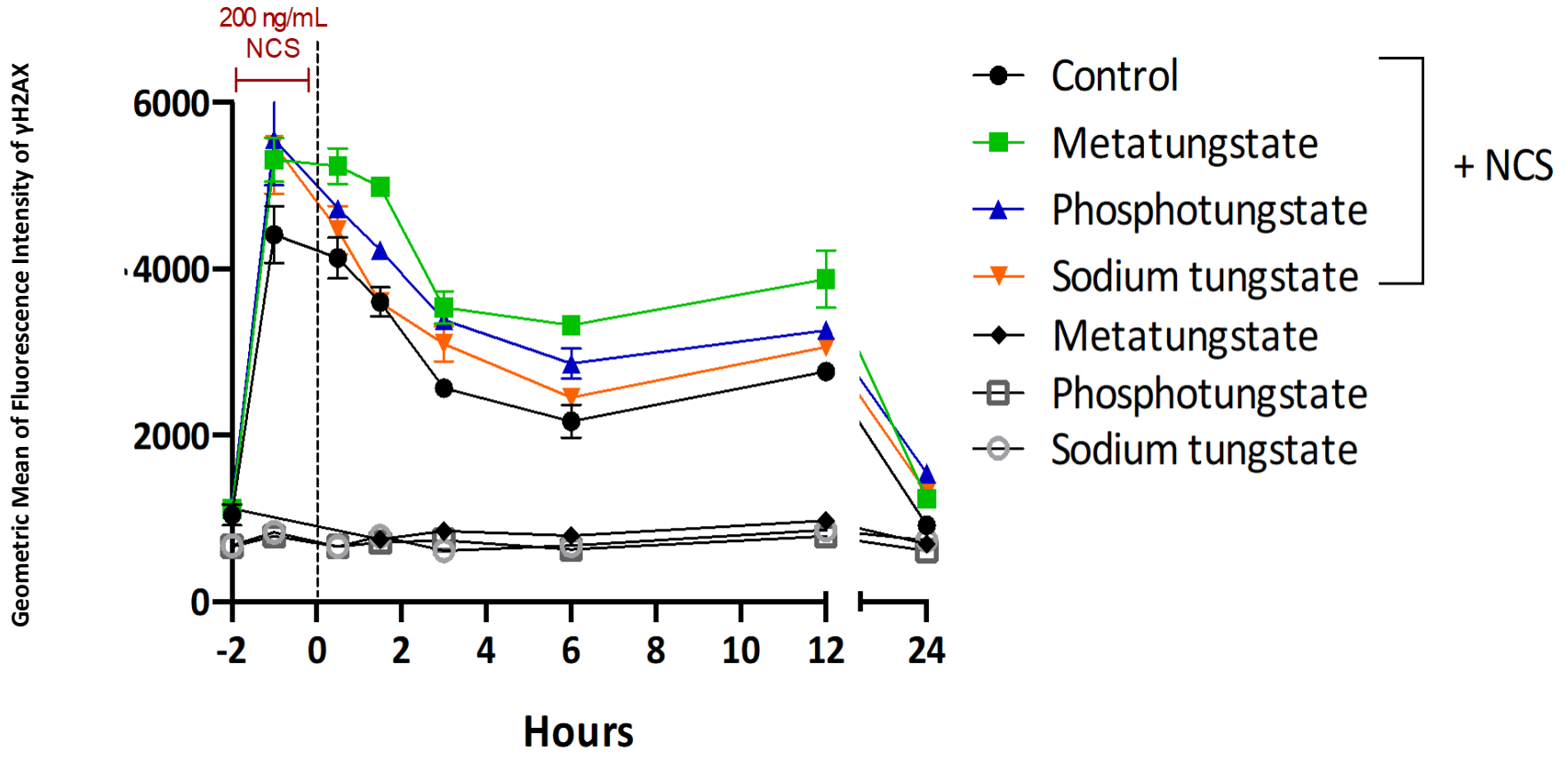
Guilbert et al. Leukemia 2011

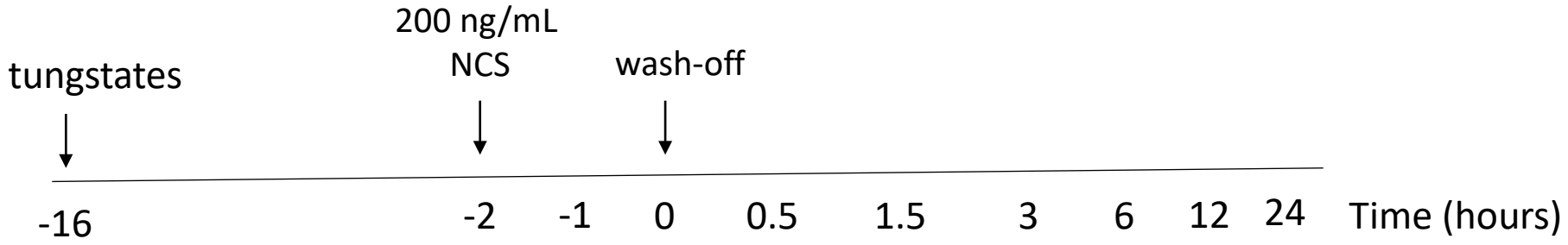
***In Vivo* Tungsten exposed mouse (8 weeks)**



Kelly et al. Tox Sci 2011

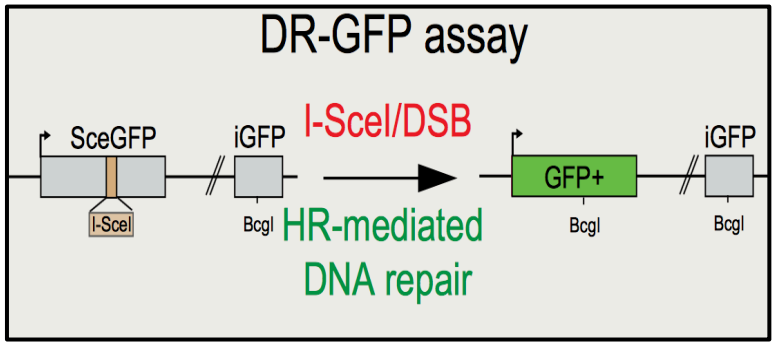
Tungsten Alters DNA Damage Repair

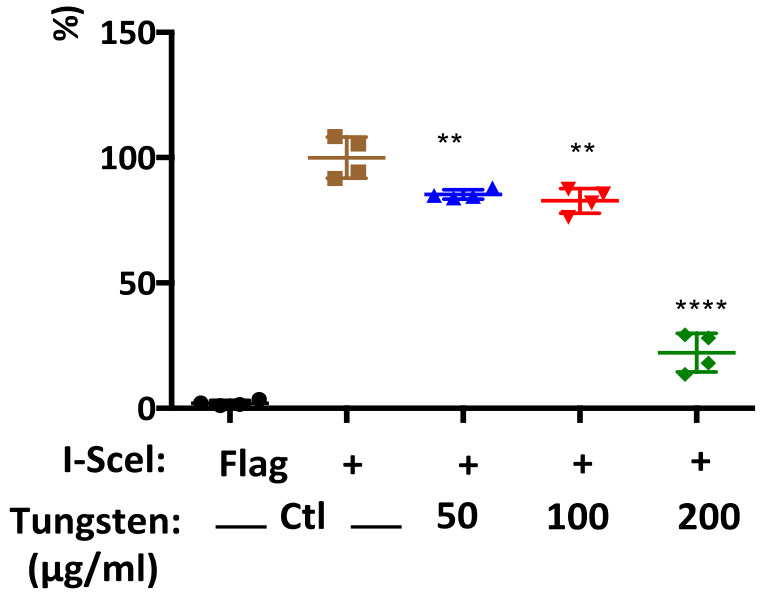


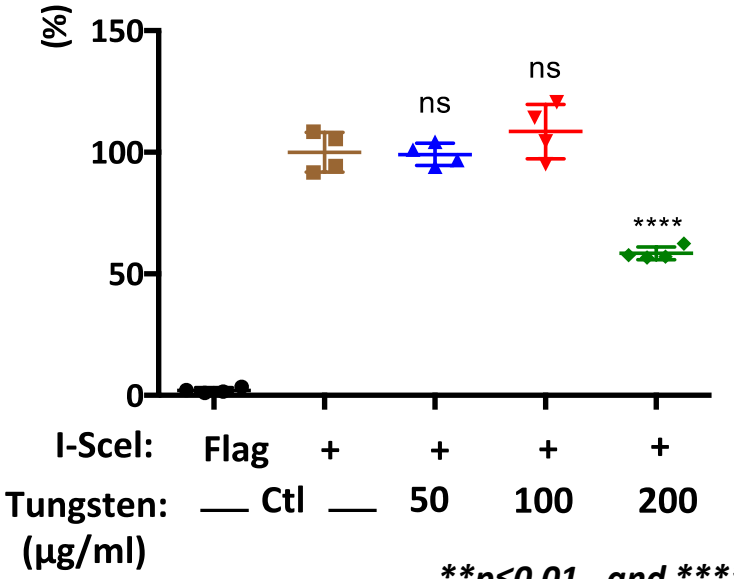


Tungstates Inhibit HR DNA Damage Repair

Homology-mediated GFP-based DNA reporter assay



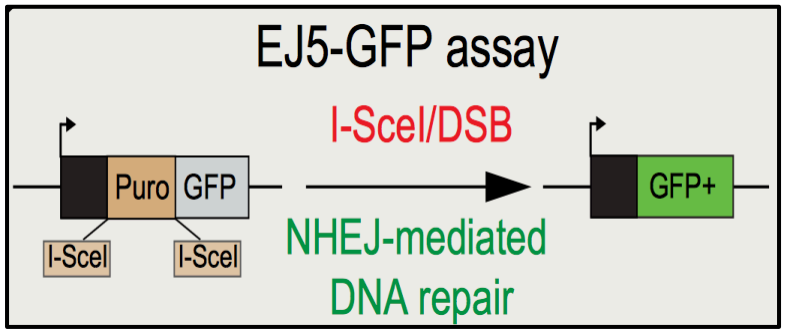


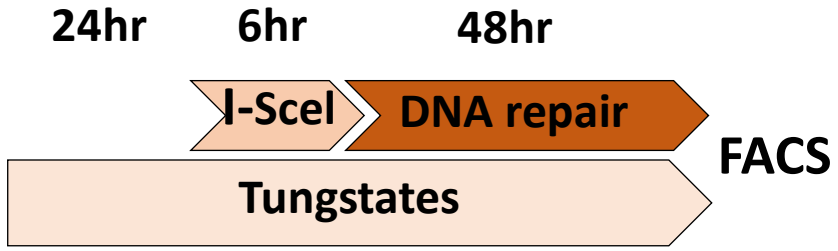


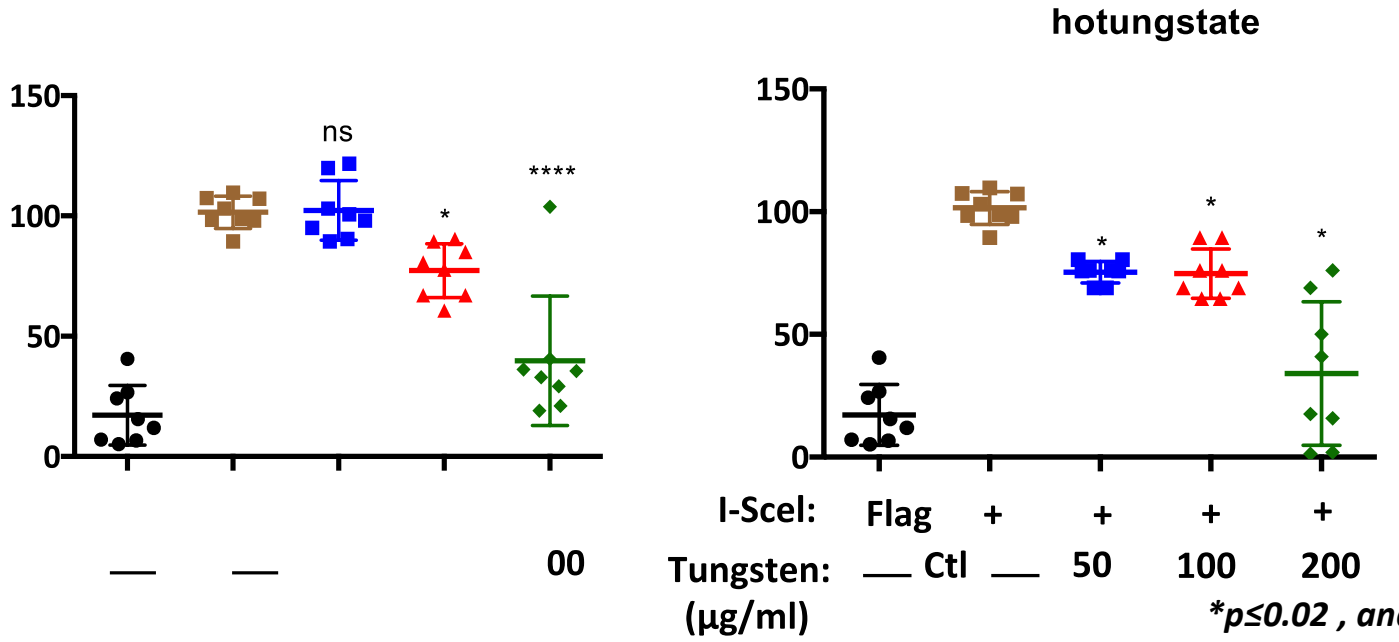
***p≤0.01 , and ****p≤0.0001 to the I-Scel control*

Tungstates Inhibit NHEJ DNA Damage Repair

Non-Homologues End Joining -mediated GFP-based DNA reporter assay

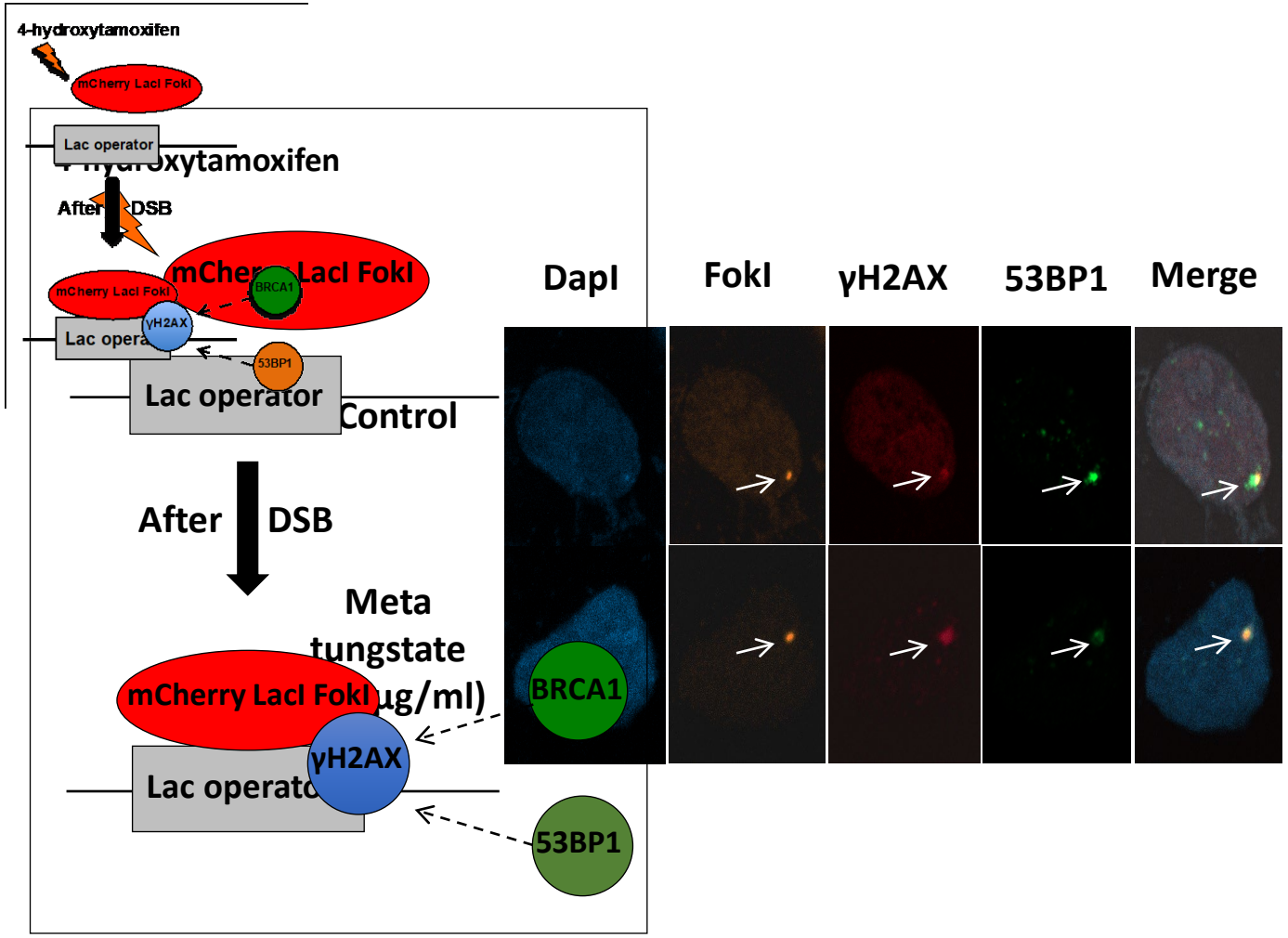


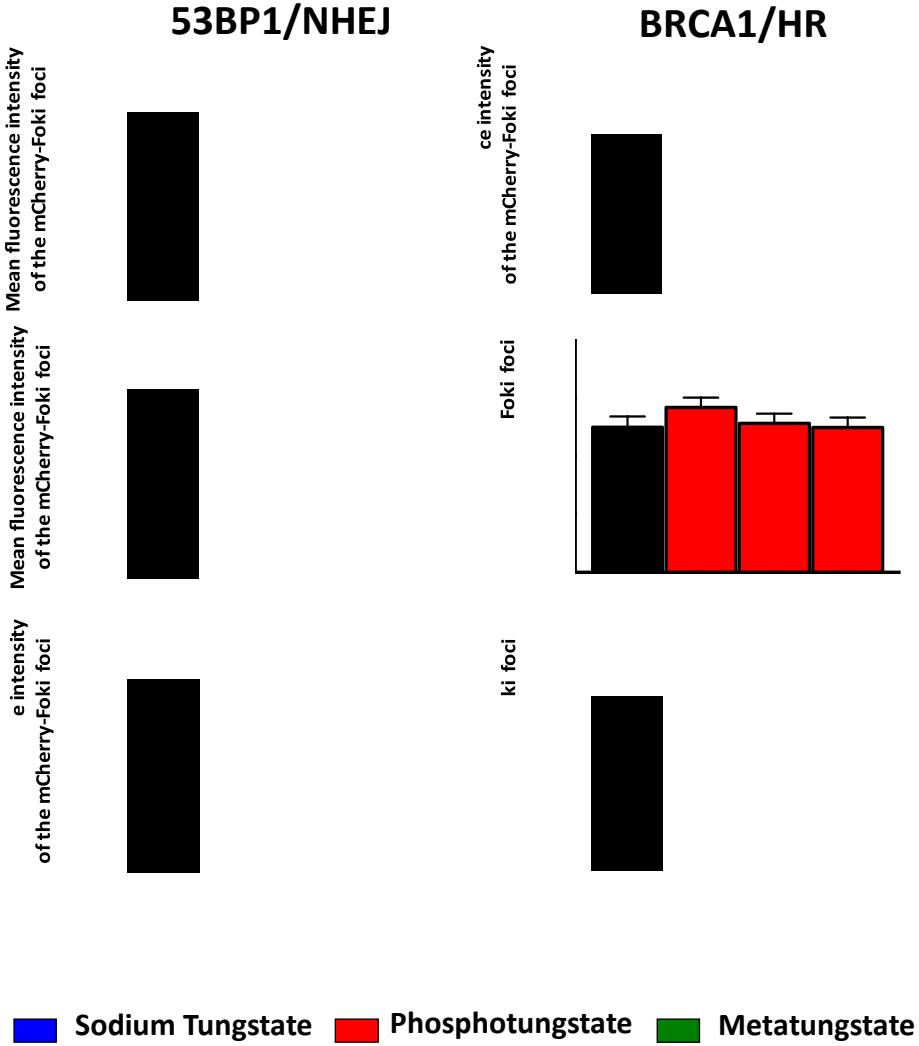




*p≤0.02 , and ****p≤0.0001 to the I-Scel control

Tungstates Modulate the Recruitment of DNA Damage Repair Regulatory Proteins of HR and NHEJ





N=1/ approximately 60-80 foci were counted

Conclusions

Tungsten may contribute to carcinogenesis by:

- Modulating intracellular signaling leading to an inhibition of differentiation

- Acting to increase DNA damage in the context of endogenous or exogenous damage, although not inducing DNA damage itself.

- Inhibiting DNA damage repair mechanisms, potentially through common NHEJ/HR DDR molecule.

Get peace of mind for today and to

Open your RSP or TFSA and we'll get you started with a $25 Bonus.

Open an

Riddled With Metal by Mistake in a Study

Ann Johansson for The New Y

QUANDARY One woman is considering a disfiguring operation to remove tungsten.

By DENISE GRADY
Published: March 21, 2011

Women participating in a study of patients with breast cancer have been inadvertently left with hundreds of tiny particles of the heavy metal tungsten in their breast tissue and chest muscles. The particles came from a device used during surgery. The device has since been recalled.

RECOMME
TWITTER
LINKEDIN
SIGN IN TO MAIL

Get peace of mind for today and tomorr

Open your RSP or TFSA and we'll get you started with a $25 Bonus.

Open an Accou

Breast Device Recall Made Most Severe

By DENISE GRADY
Published: April 14, 2011

The recall of a medical device that left particles of tungsten in women's breasts has been classified as the most serious type of recall, one involving "situations in which there is a reasonable probability that use of these products will cause serious adverse health consequences or death," the Food and Drug Administration said on Wednesday.

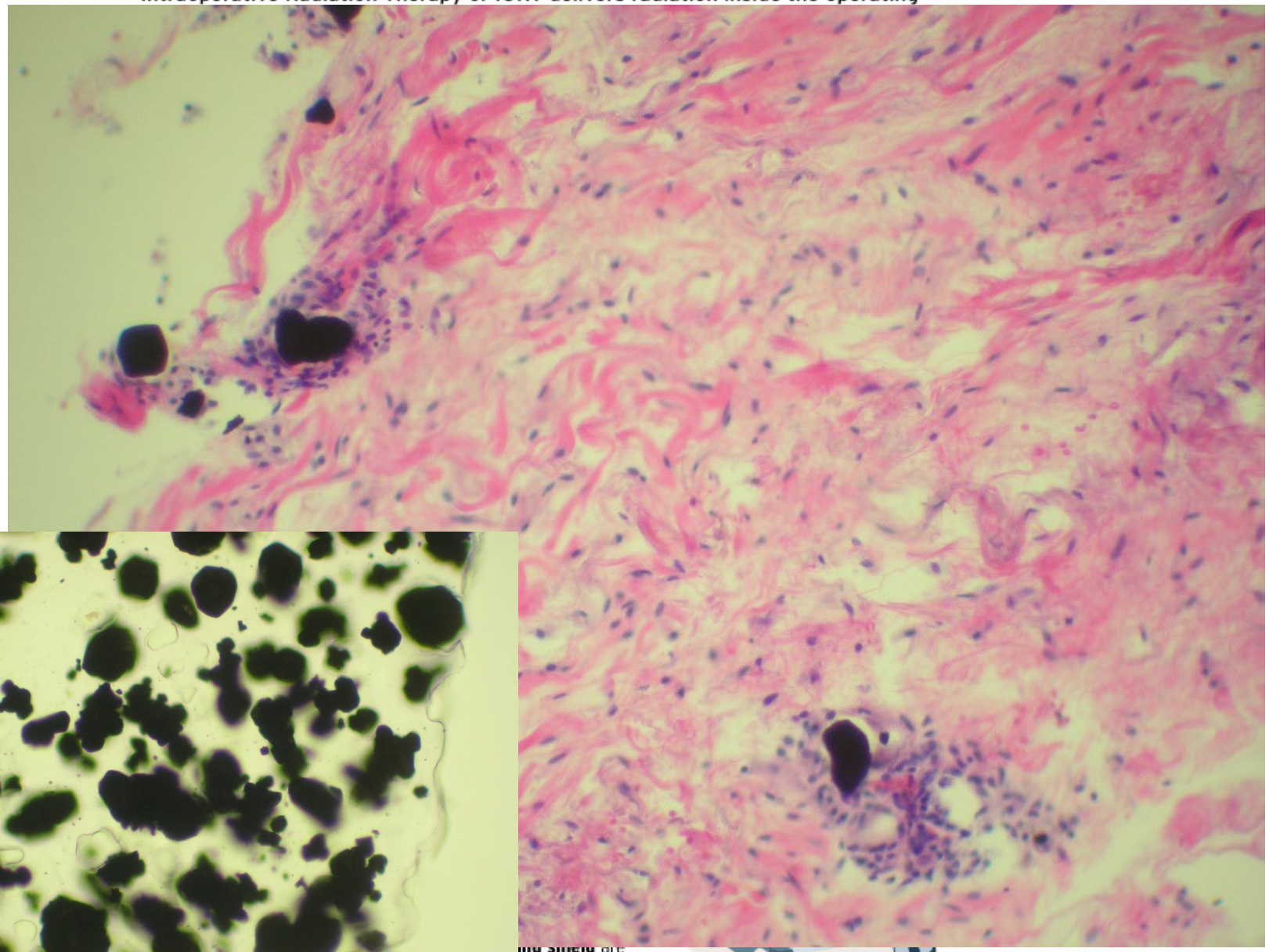
The device, the Axxent FlexiShield Mini, was a pad made of tungsten and silicone rubber that was temporarily placed inside breast incisions

RECOMMEND
TWITTER
LINKEDIN
SIGN IN TO E-MAIL
PRINT
REPRINTS
SHARE

501 (k) expedited approval!!!

How IORT works

Intraoperative Radiation Therapy or IORT delivers radiation inside the operating

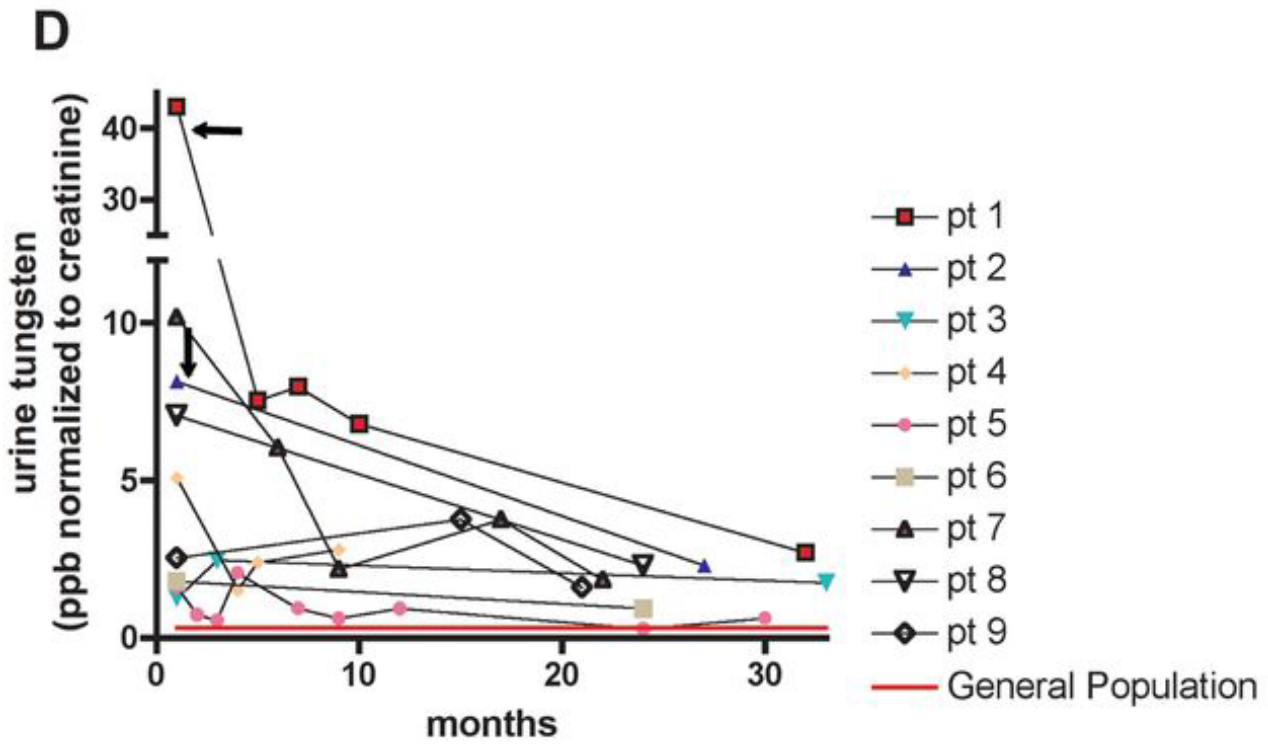


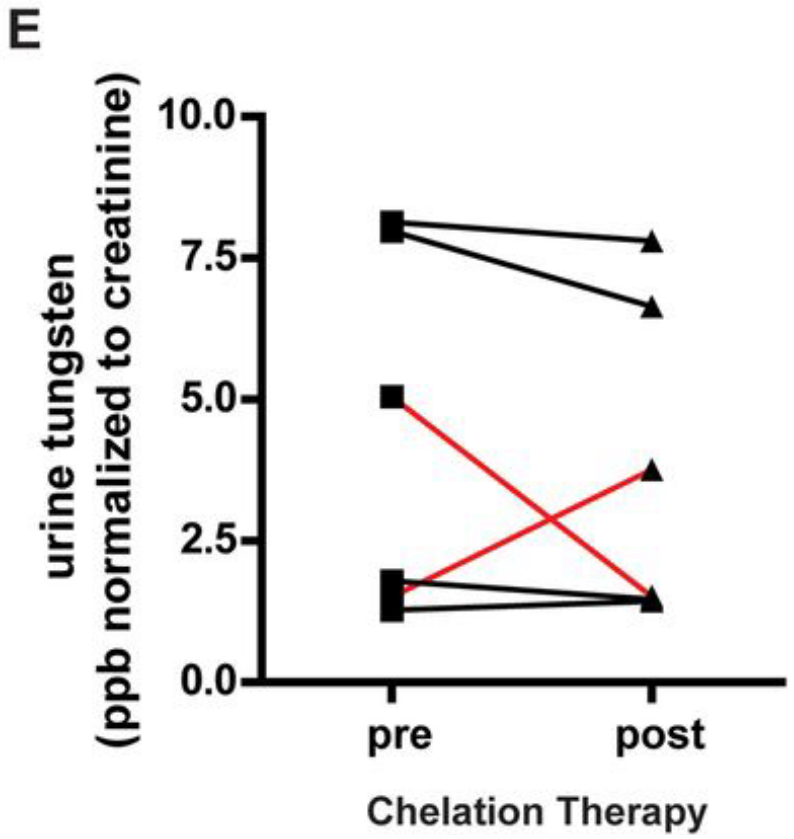
incision is
outine procedure.

Source: **www.xoftinc.com**

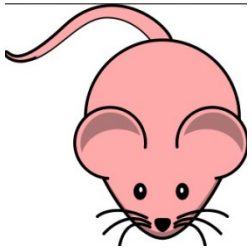
Molly Zisk / The Register

Breast cancer patients were exposed to tungsten during a recent clinical trial.





Bolt A M et al. Toxicol. Sci. 2015;143:165-177



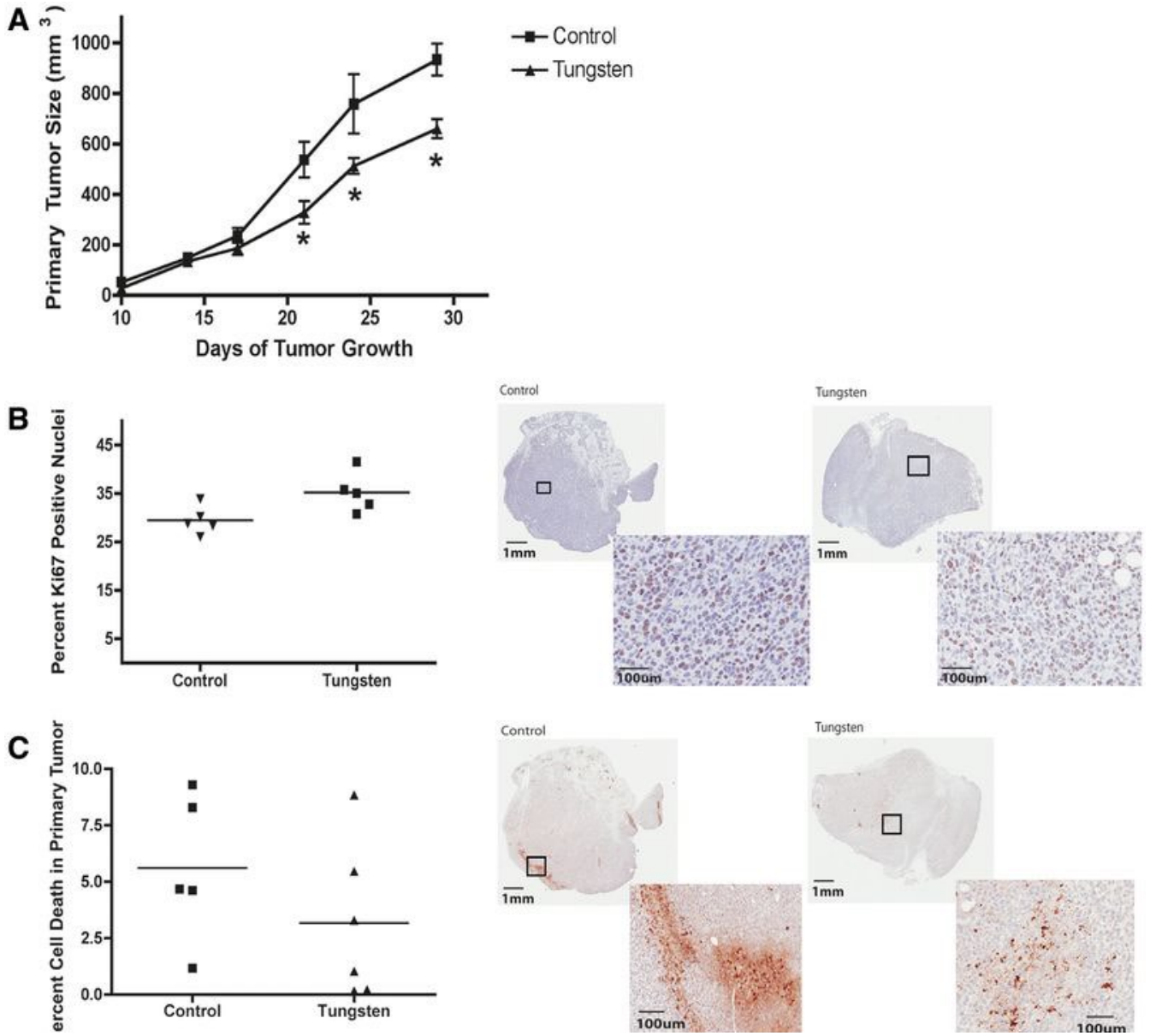
tungsten for
one month

Implant 66Cl4
breast tumor

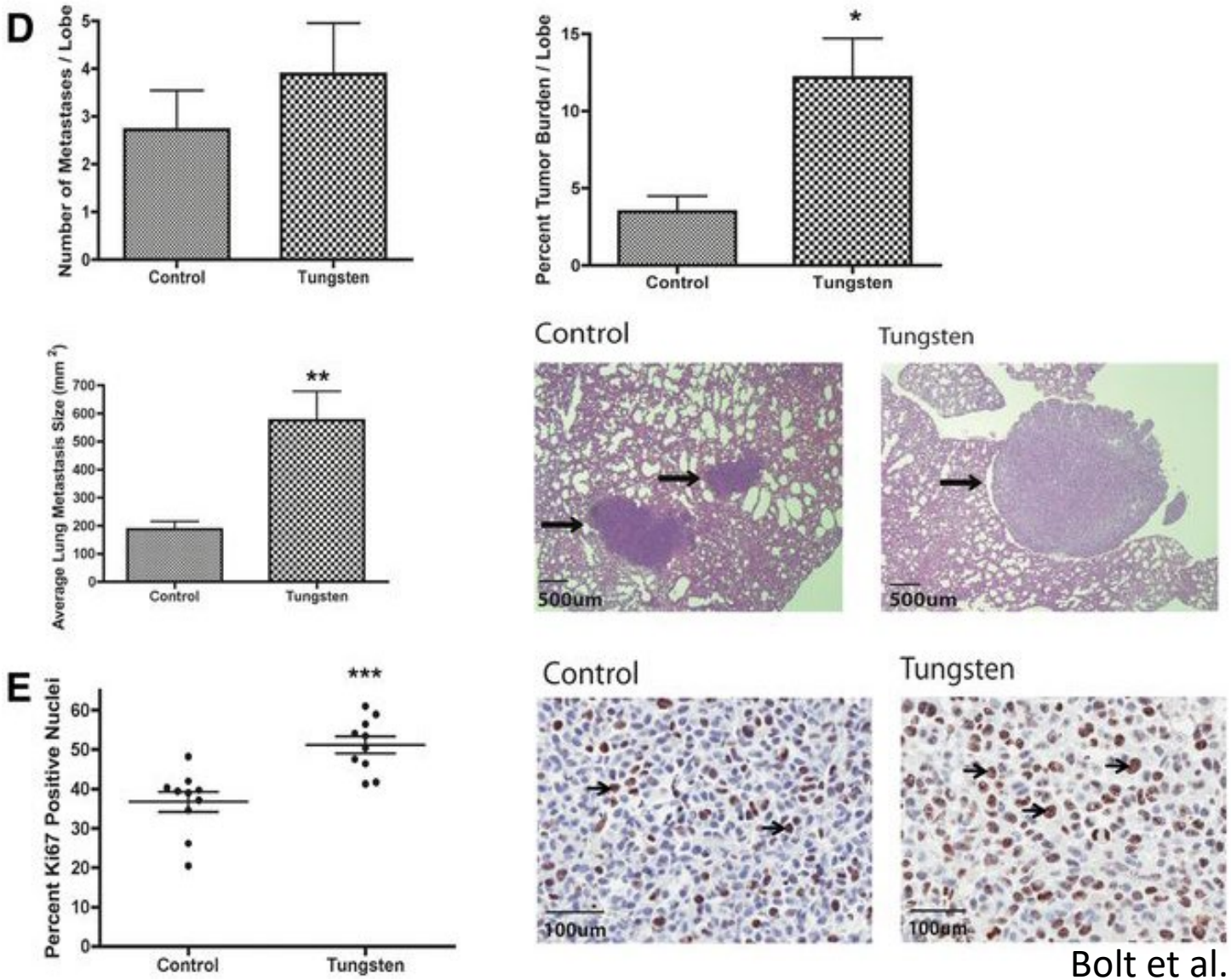
Measure primary
tumor growth and
metastases
in lung

Bolt et al. Tox Sci 2015

Tungsten does not enhance primary tumor growth

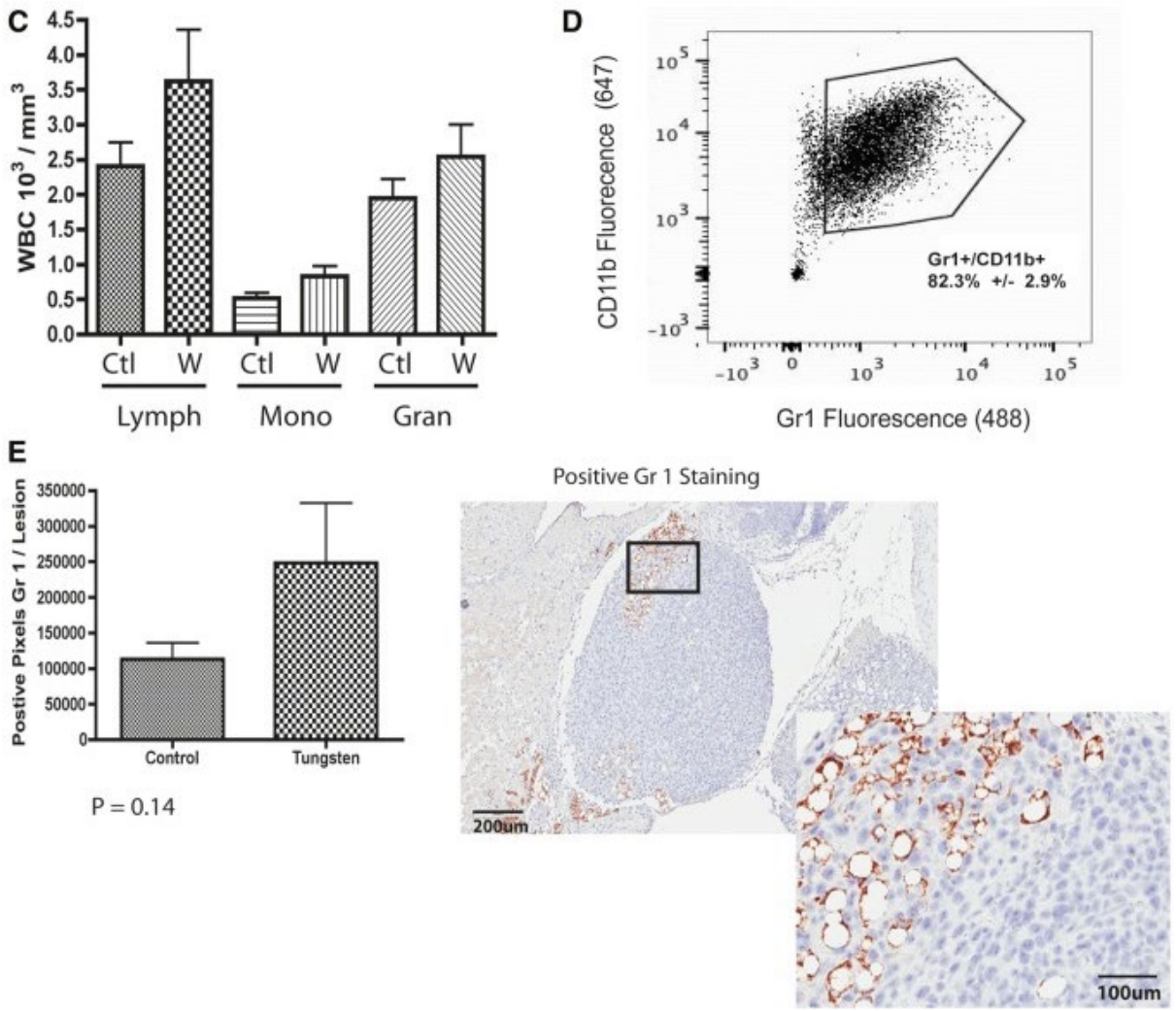


Tungsten does enhance lung metastases



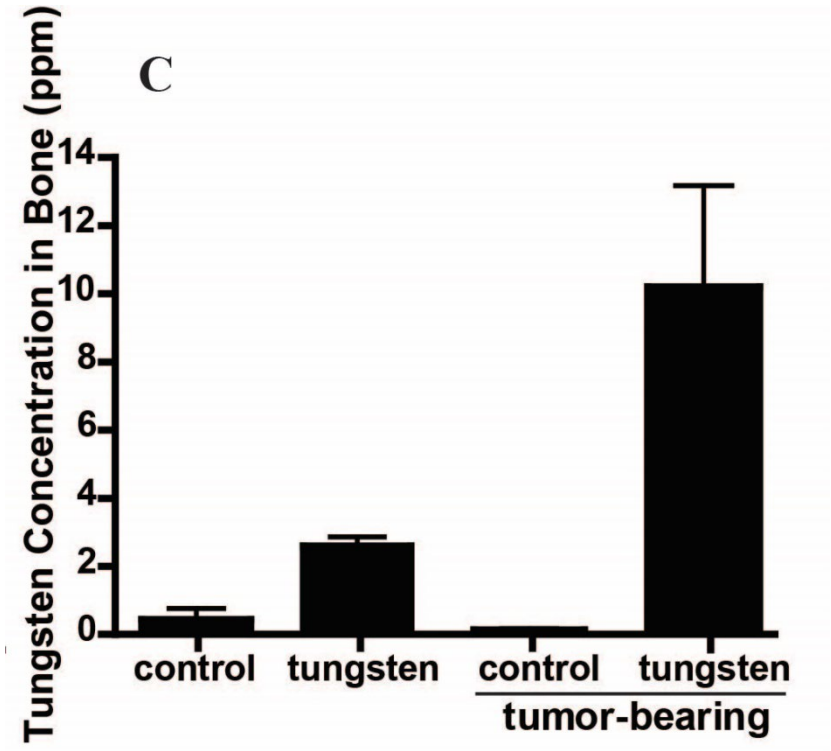
Bolt et al. Tox Sci 2015

Tungsten increases myeloid-derived suppressor cell number



Bolt et al. Tox Sci 2015

Tungsten content of the bone is increased in tumor-bearing mice



Conclusions II

Tungsten may contribute to carcinogenesis by:

- Modulating intracellular signaling leading to an inhibition of differentiation
- Acting to increase DNA damage in the context of endogenous or exogenous damage, although not inducing DNA damage itself.
- Inhibiting DNA damage repair mechanisms, potentially through common NHEJ/HR DDR molecule.
- **Modulating the metastatic niche and recruiting repressive immune components.**

Lab Alumni

- Alex Benoit
- **Alicia Bolt**
- Chris Chiavatti
- **Hsiang Chou**
- Sara Ghandour
- **Alex Kelly**
- Maryse Lemaire
- **Sheen Li**
- Fernando Negro Silva
- Alessandra Padovani
- Dany Plourde
- **Joshua Wu**

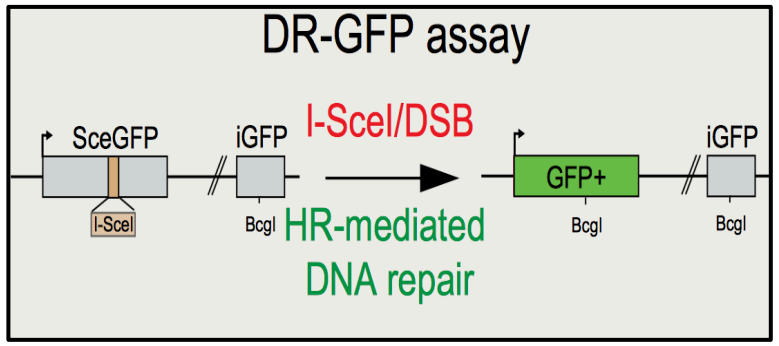
Collaborators

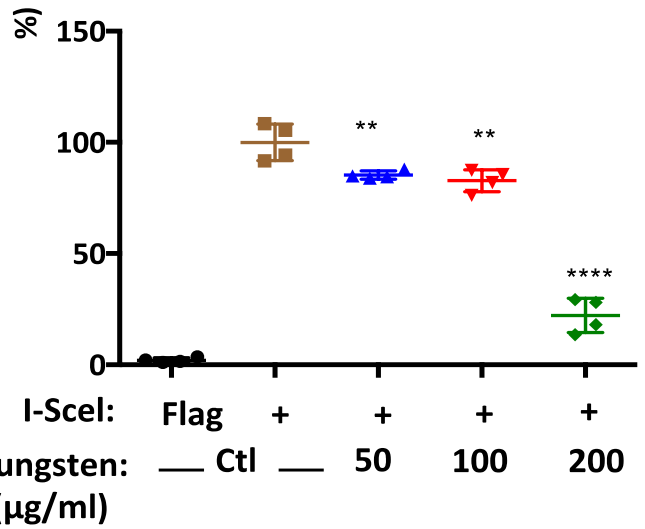
- Dr. Fackson Mwale and Dr. Michael Grant (LDI)
- Dr. Scott Bohle and Cassidy VanderSchee (McGill University)
- Dr. Mike Tyers and Caroline Huard (IRIC)
- Dr. Barbara Hales and Lama Iskandarani (McGill University)
- Dr. Brian P. Jackson, Dartmouth College

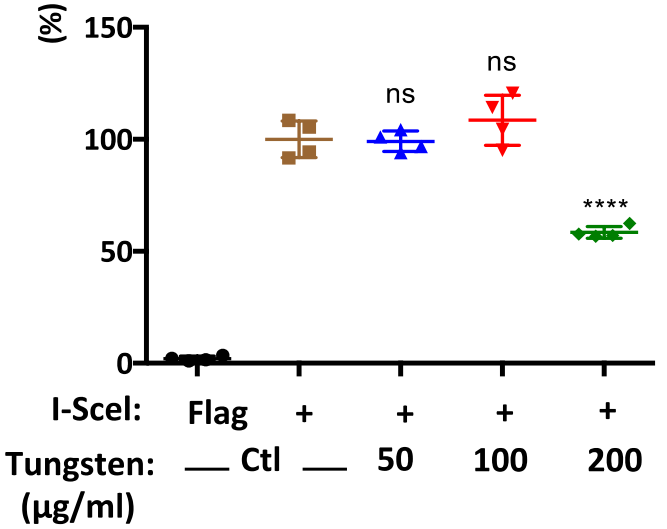
Fonds de recherche Santé Québec
CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada
NSERC CRSNG
Cancer Research Society
100% research since 1945

Tungstates Inhibit DNA Damage HR Response

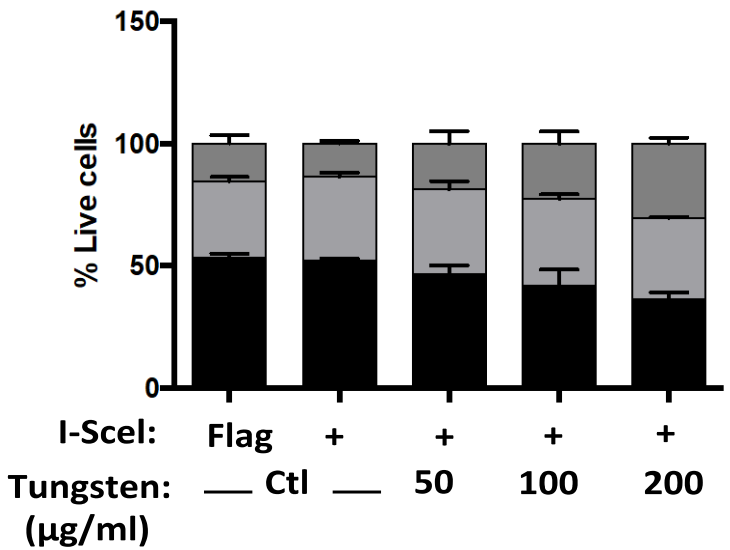
Homology-mediated GFP-based DNA reporter assay

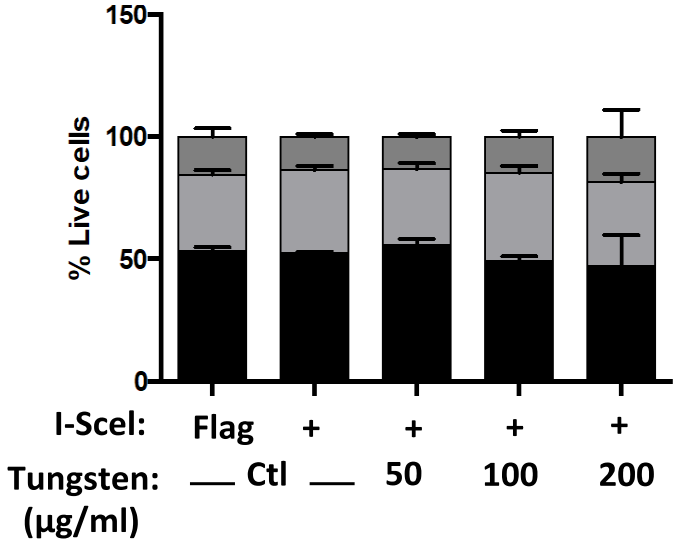


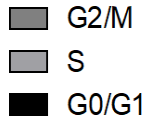




HeLa cells





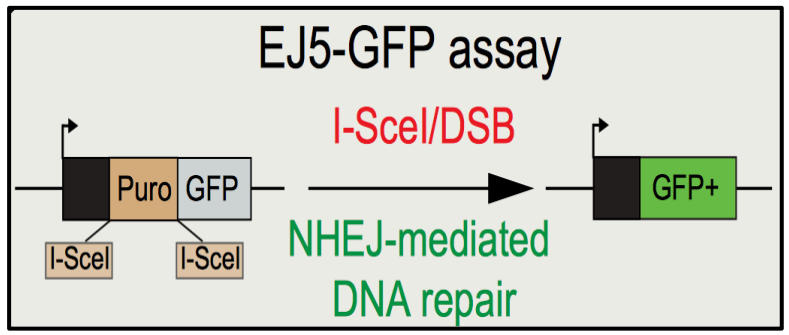


N=3

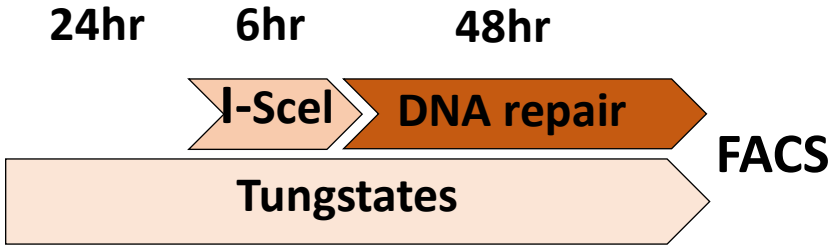
**p≤0.02 , and ****p≤0.0001 to the I-Scel control*

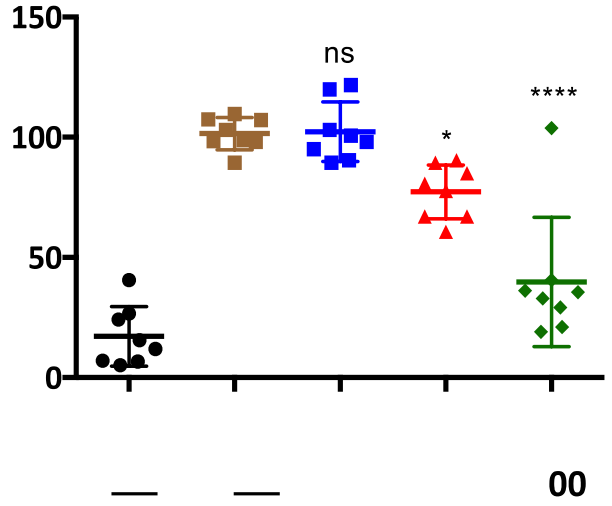
Tungstates Inhibit DNA damage NHEJ Response

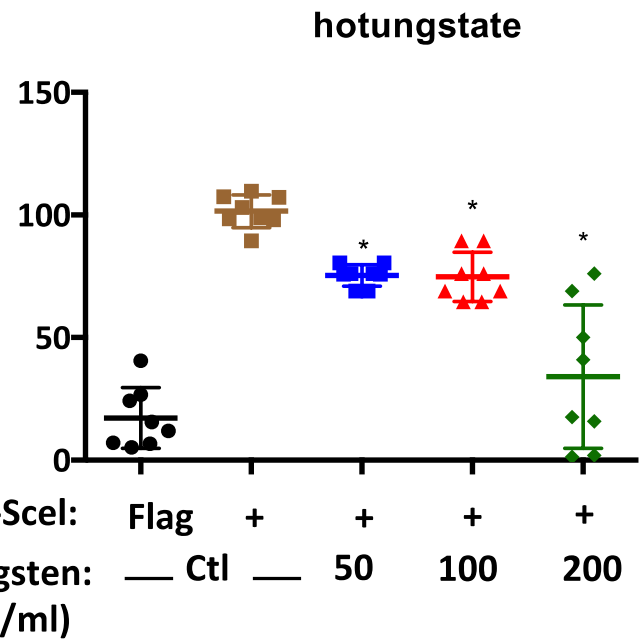
Non-Homologues End Joining -mediated GFP-based DNA reporter assay

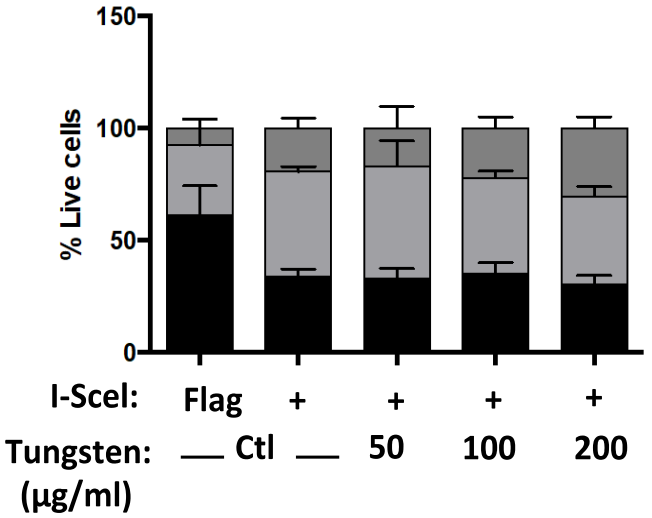


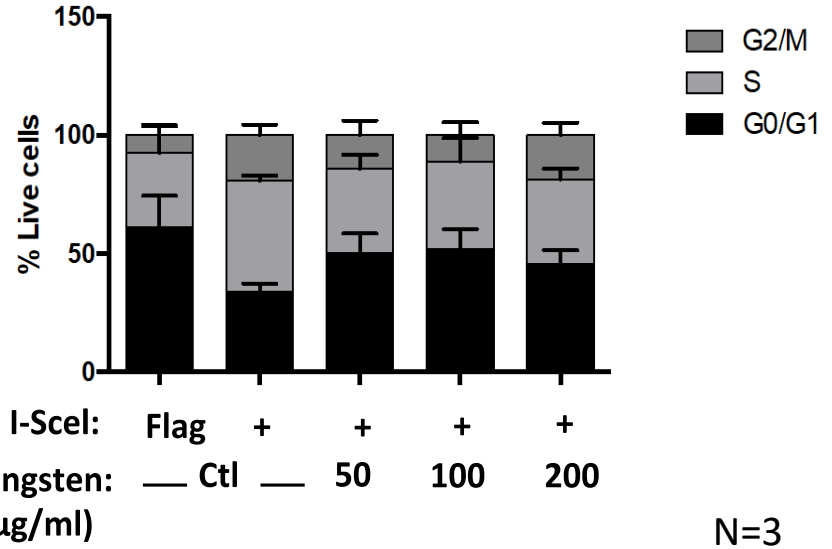
U2OS cells







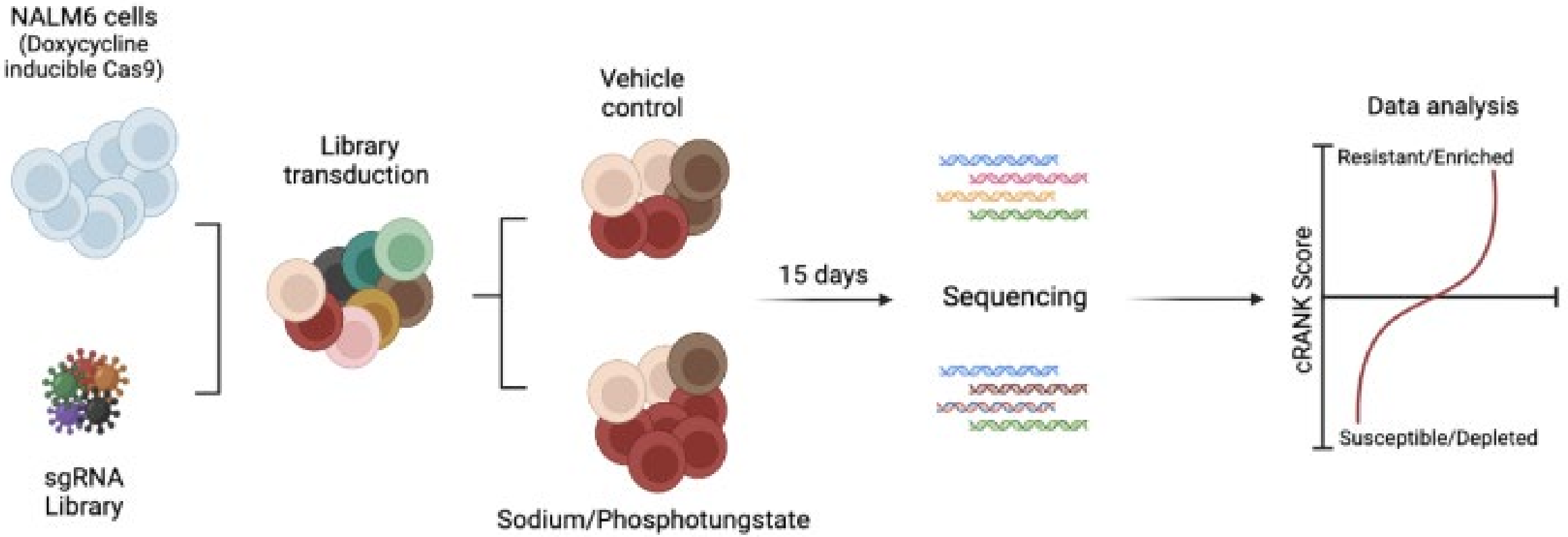




**p≤0.02 , and ****p≤0.0001 to the I-Scel control*

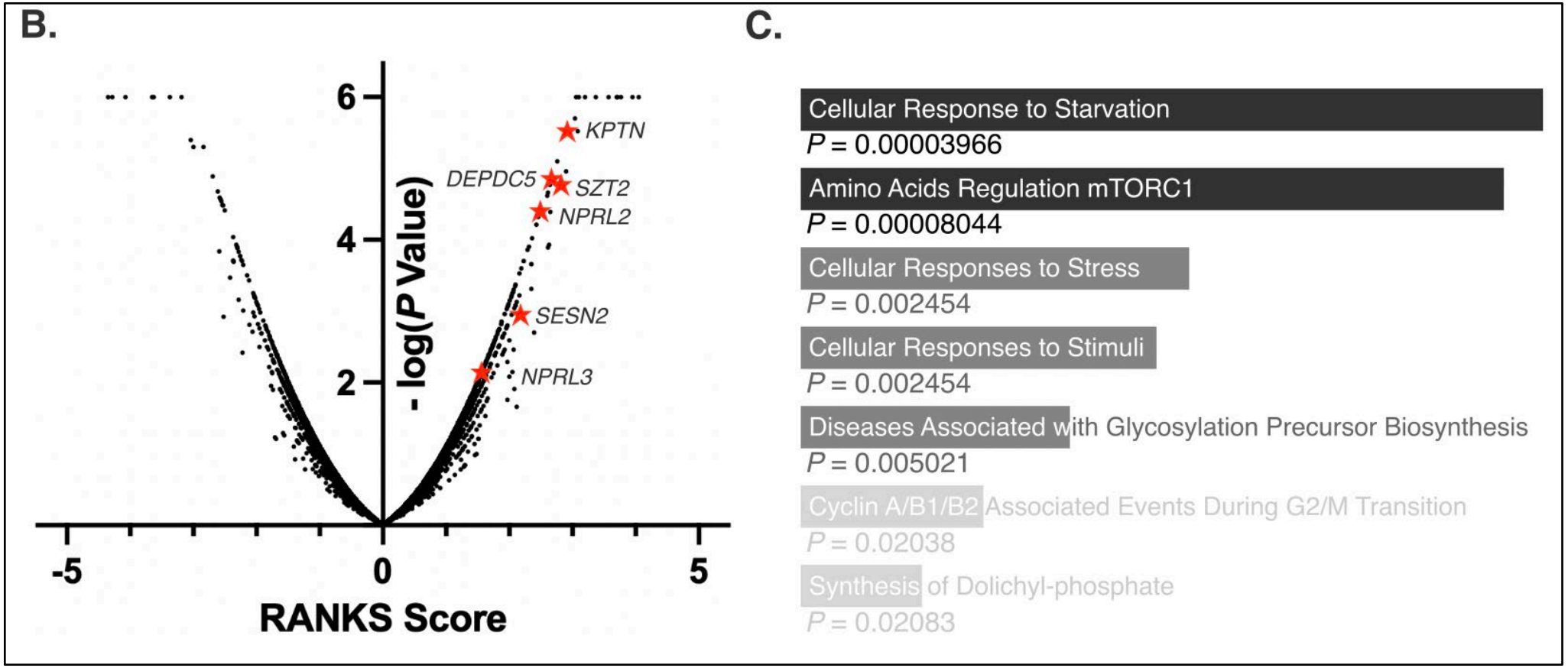
N=3

Genome-wide CRISPR/Cas9 Screen in PreB ALL Cells

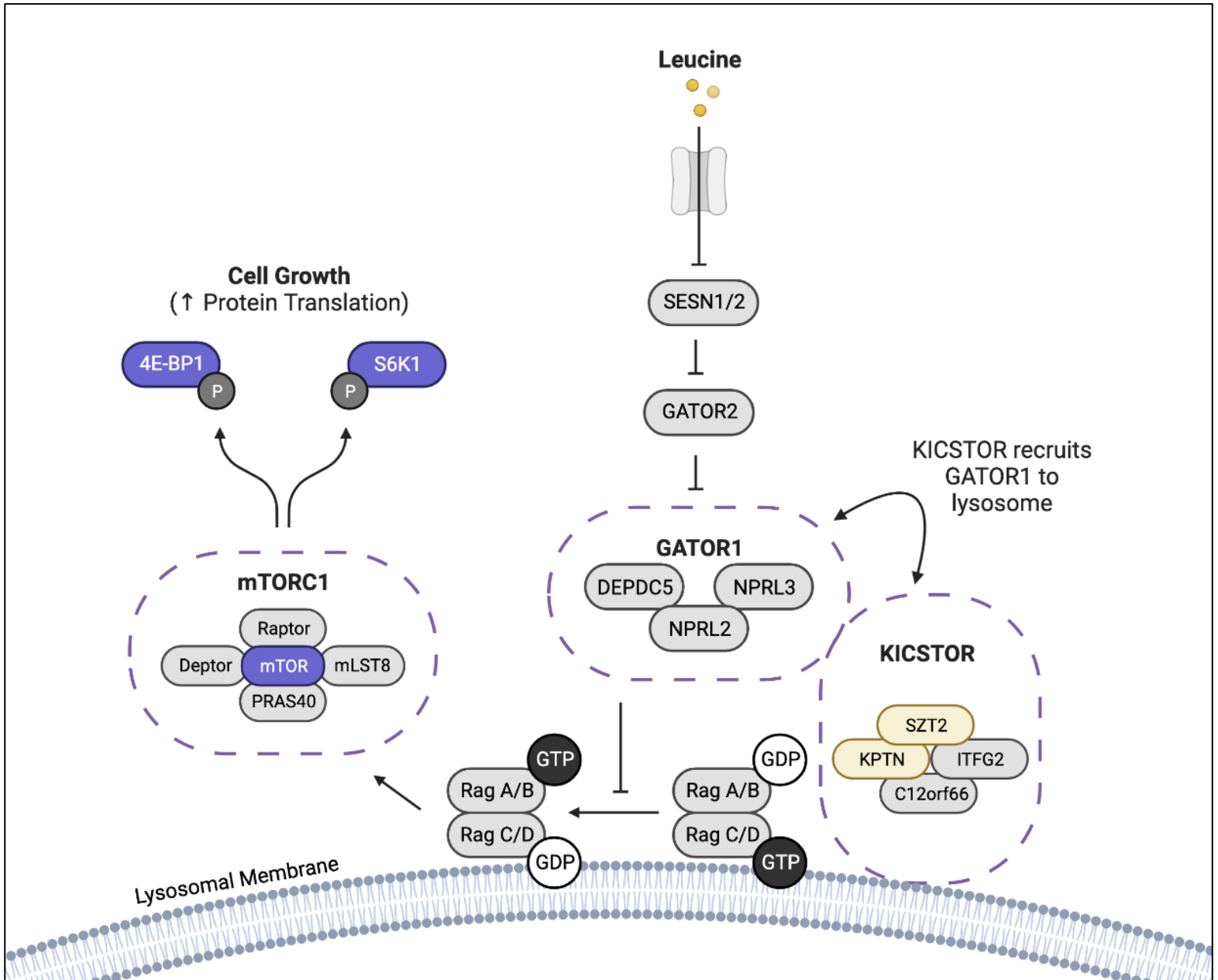


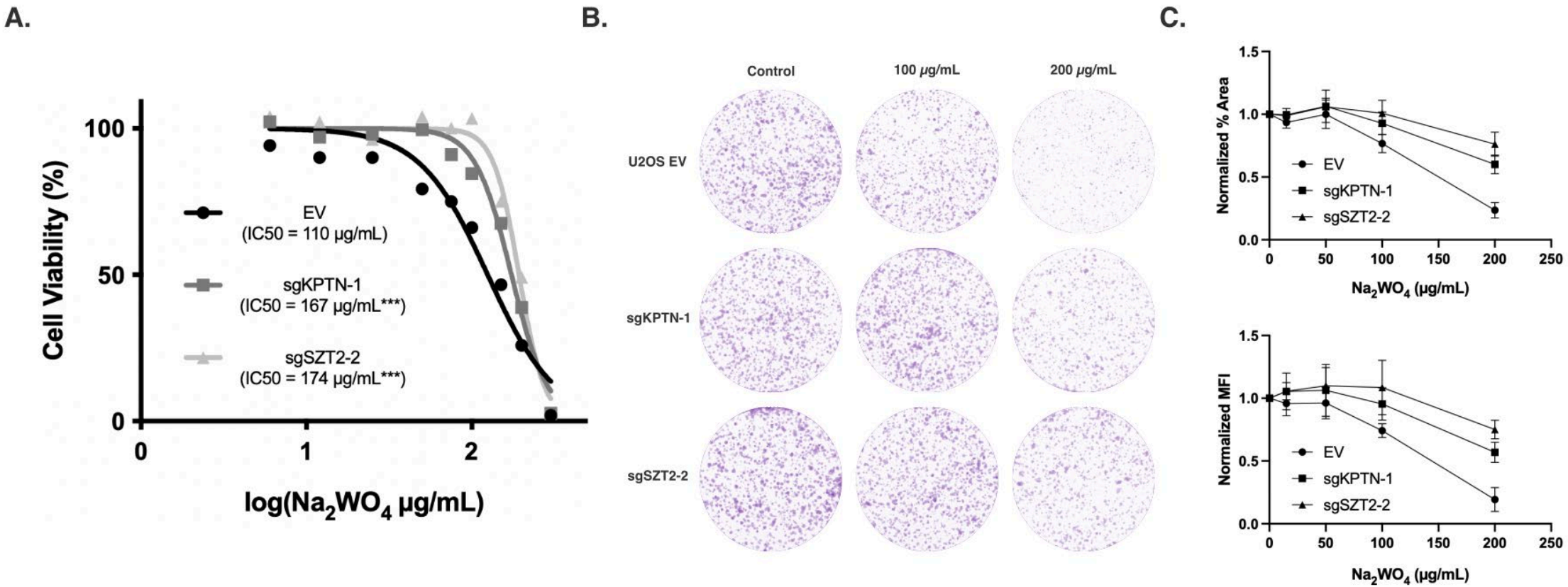
Dr. Mike Tyers: IRIC/U de MTL

CRISPR Screen Revealed Novel Modulators of Tungstate Exposure



Dr. Mike Tyer, University of Montreal


Leucine
SESN1/2
GATOR2
Cell Growth
(↑ Protein Translation)
4E-BP1
P
S6K1
P
KICSTOR recruits
GATOR1 to
lysosome
GATOR1
DEPDC5
NPRL3
NPRL2
mTORC1
Raptor
Deptor
mTOR
mLST8
PRAS40
KICSTOR
SZT2
KPTN
ITFG2
C12orf66
GTP
Rag A/B
Rag C/D
GDP
GDP
Rag A/B
Rag C/D
GTP
Lysosomal Membrane


A.
Cell Viability (%)
100
50
0
0
1
2
log(Na2WO4 µg/mL)
EV
(IC50 = 110 µg/mL)
sgKPTN-1
(IC50 = 167 µg/mL***)
sgSZT2-2
(IC50 = 174 µg/mL***)
B.
Control
100 µg/mL
200 µg/mL
U2OS EV
sgKPTN-1
sgSZT2-2
C.
Normalized % Area
1.5
1.0
0.5
0.0
0
50
100
150
200
250
Na2WO4 (µg/mL)
EV
sgKPTN-1
sgSZT2-2
Normalized MFI
1.5
1.0
0.5
0.0
0
50
100
150
200
250
Na2WO4 (µg/mL)
EV
sgKPTN-1
sgSZT2-2