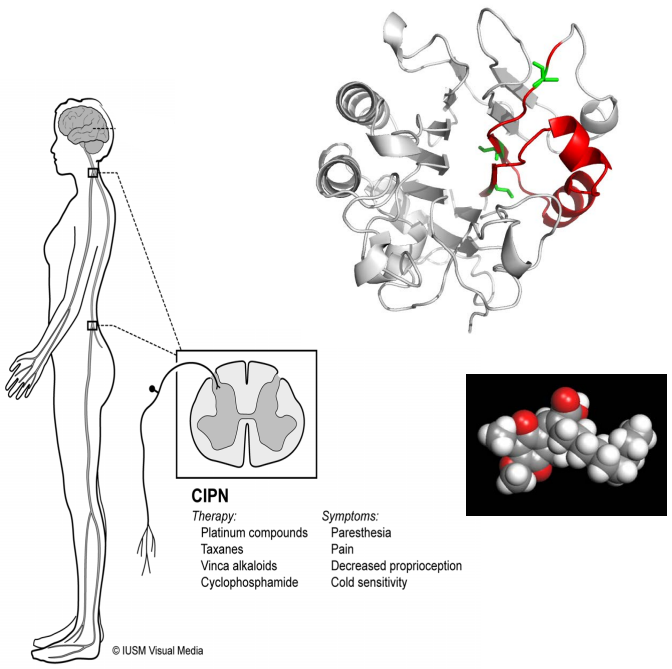
Development of the first clinical drug targeting the DNA repair/redox signaling APE1/Ref-1; Clinical indications for solid tumors and CIPN prevention

Mark Kelley, Ph.D., with Jordan Dew



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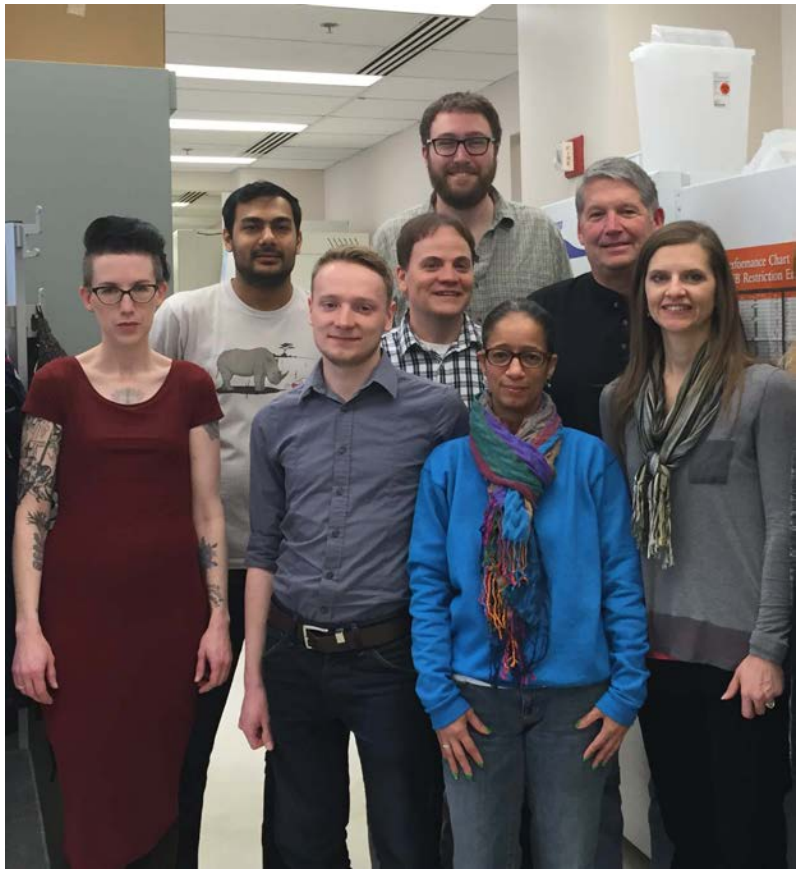
- Professor, Departments of Pediatrics, Biochemistry & Molecular Biology and Pharmacology & Toxicology
- Associate Director, Herman B Wells Center for Pediatric Research
- Associate Director of Basic Science Research, Indiana University Simon Cancer Center
- Director, Program in Pediatric Molecular Oncology & Experimental Therapeutics

Disclosures:

Chief Scientific Officer and Founder, Apexian Pharmaceuticals

Licensing agreements for antibodies and reagents to:

Novus Biologicals
Abcam
Millipore



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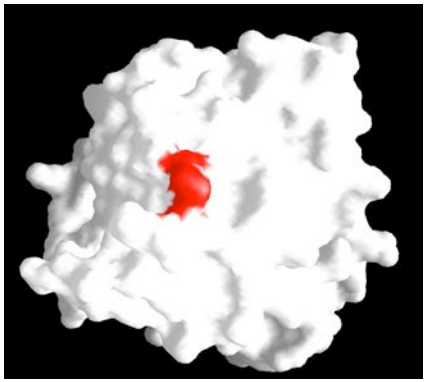
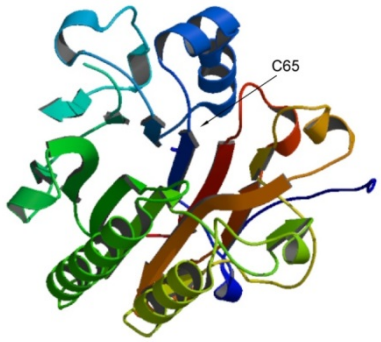
The Target

APE1/Ref-1 Overview

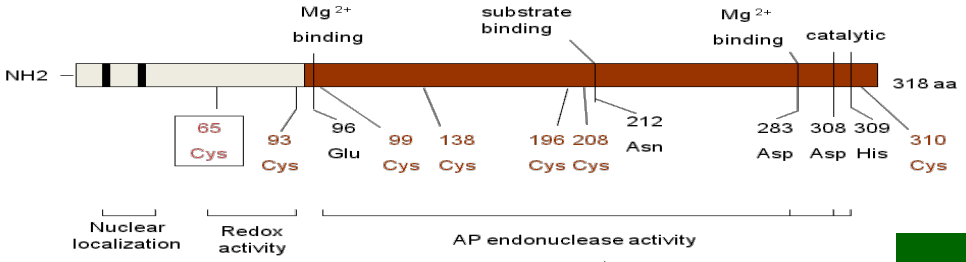
- APE1 (apurinic/apyrimidinic endonuclease), also called Ref-1 (redox effector factor 1), is a multifunctional cellular protein with at least two distinct and separate functions:
  - **APE1 Redox Function**: Redox regulation of transcription factors (TFs) effecting critical aspects of cancer cell survival and growth including HIF-1, STAT3, NF-KB, and others.
  - **DNA Repair Function**: DNA base repair caused by oxidative stress, alkylating agents, and ionizing radiation
  - **RNA Degradation and quality control:** Interaction with NPM1
- Various cancers, including treatment resistant tumors, have shown elevated expression of APE1 suggesting adaptation and unique survival mechanisms through this pathway.

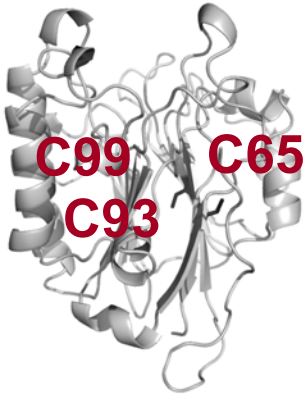




- We can target multiple signaling pathways relevant to various cancers with one protein— as APE1 regulates transcription factors (TFs) HIF1a, STAT3, NFkB and others.
- APX3330 inhibits only the APE1 redox signaling activity.

APE1/Ref-1 functions:
DNA repair and Redox signaling regulation of TFs





Redox Role

(reduced)

Ref-1

(oxidized)

(oxidized)

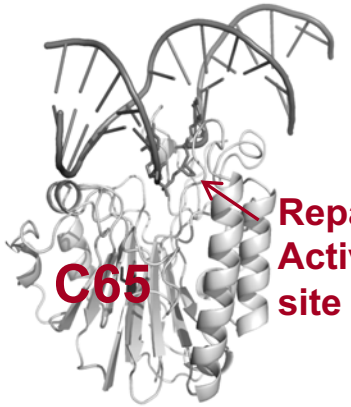
(reduced)

AP-1
p53
NFkB
HIF-1α

CREB
PAX
STAT3

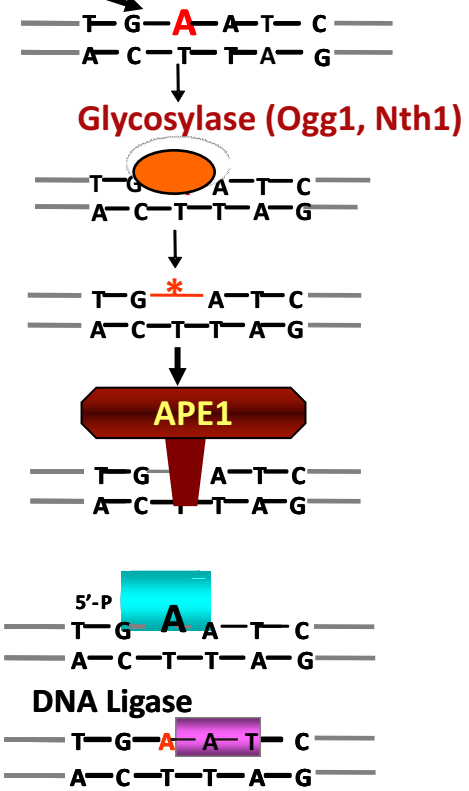
Redox control of Transcription factors

Target gene expression:
Growth
Inflammation
Angiogenesis



DNA damage

DNA Repair

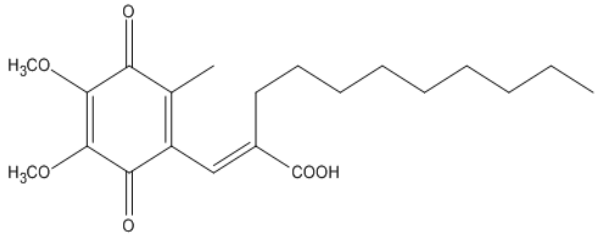


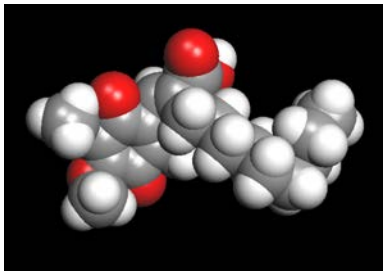
Alteration of APE1/Ref-1 protein expression has been shown to be elevated in:

1. Non-small cell lung cancer
2. Colorectal cancer
3. Breast cancer
4. Prostate cancer
5. Gynecologic cancers (ovarian, cervical)
6. Pancreatic cancer
7. Glioblastoma multiforme, meduloblastoma
8. Renal cancer
9. Gastric cancer
10. Germ cell tumors
11. Head-and-neck cancers
12. Multiple myeloma (hematologic cancer)
13. Osteosarcoma and Rhabdomyosarcoma (pediatric)

The Drug

E3330 = APX3330





- APX3330 was originally developed by Eisai (E3330) as a NFkB-TNFa inhibitor for the treatment of inflammatory liver disease.

- Eisai ended APX3330 development after in-licensing Revovir® (clevudine) for the treatment of hepatitis B and Humira (adalimumab) for treatment of rheumatoid arthritis, IBD and other indications.

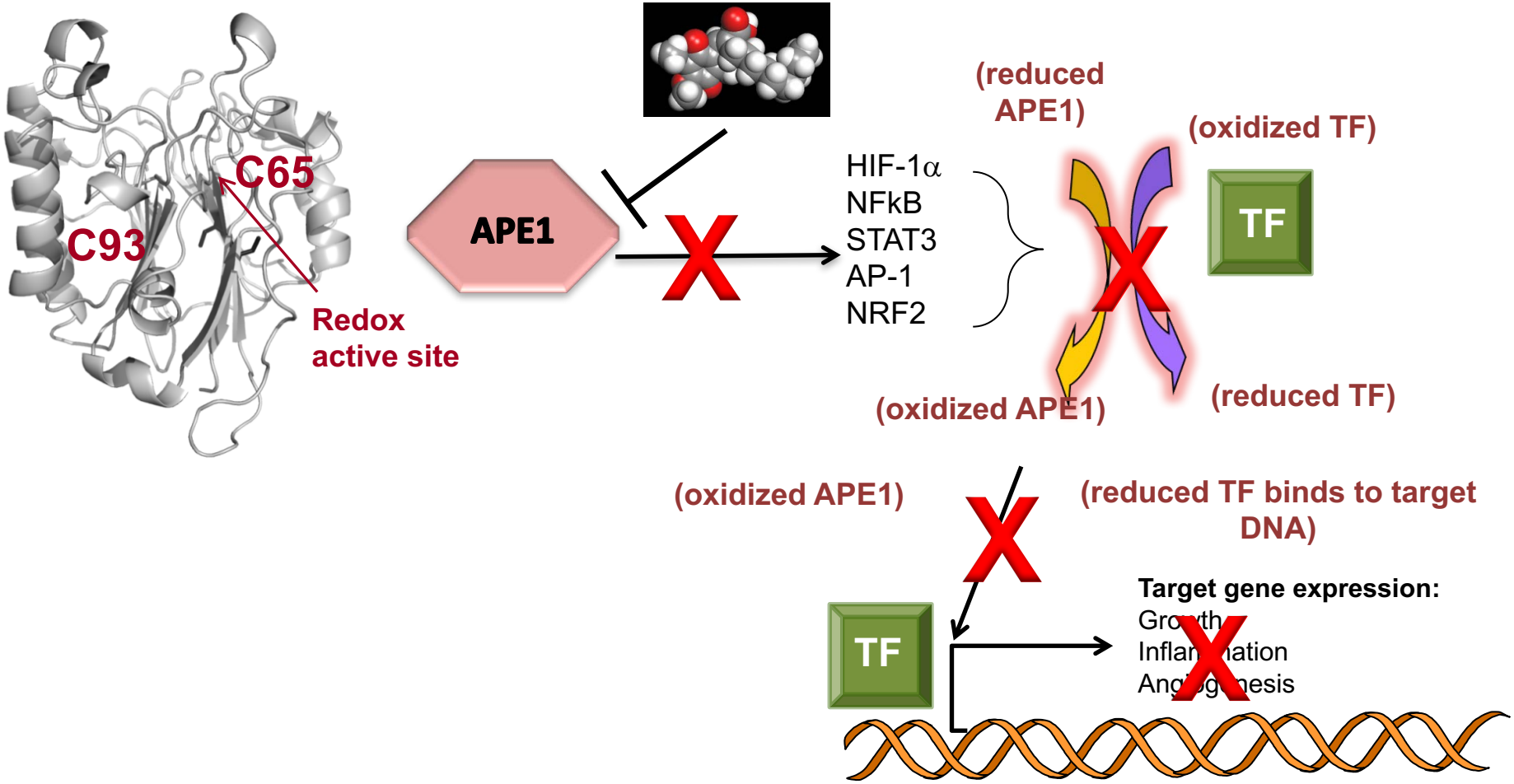
APX3330 Continued

- The drug has a direct and selective interaction with APE1 as demonstrated by chemical footprinting, mass spectrometry, and other biochemical data.

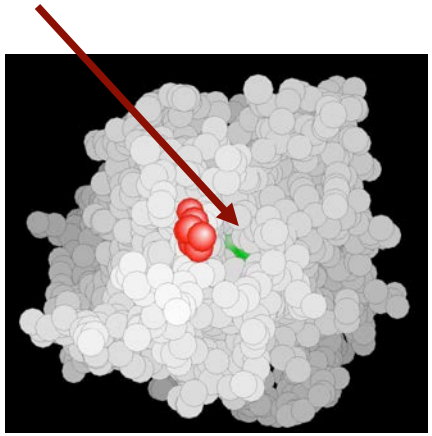
- Although multiple pathways may be modulated, unacceptable toxicity following APE1 inhibition has not been observed in animal or human studies.

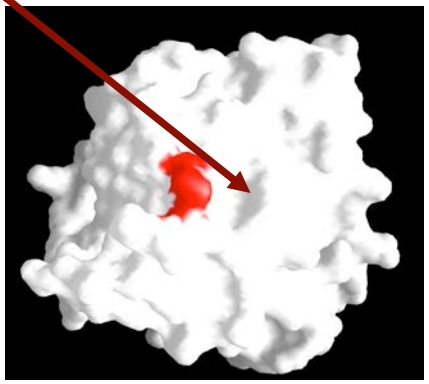
- Preclinical data supports the use of the drug as a single agent; **future directions indicate partnering APX3330 with various clinical agents** such as JAK2 inhibitors (Ruxolitinib, LY3009104. etc), STAT3 inhibitors, gemcitabine and Abraxane (nab-paclitaxel).

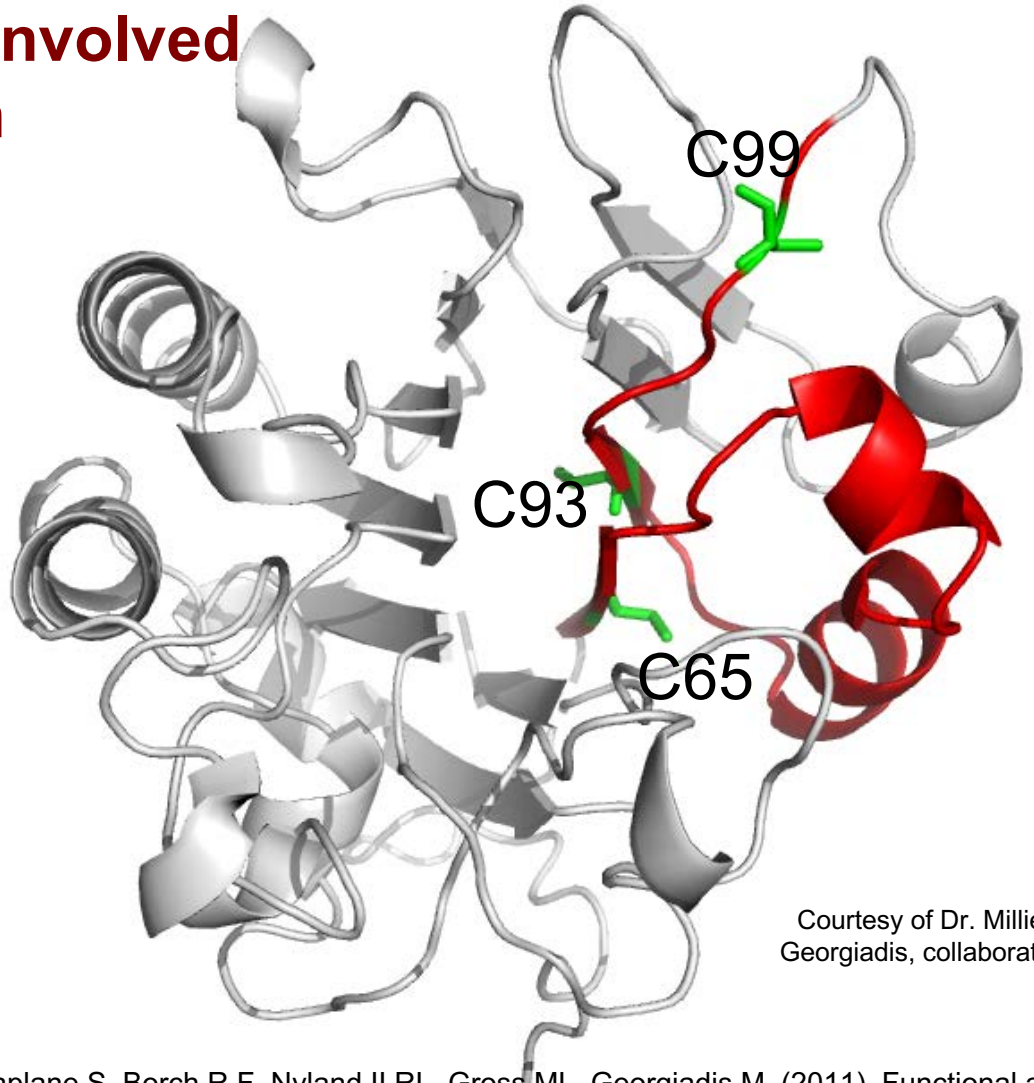
APX3330 inhibits APE1 Redox Function Blocking TF Activity



APE1 cysteines involved in redox function







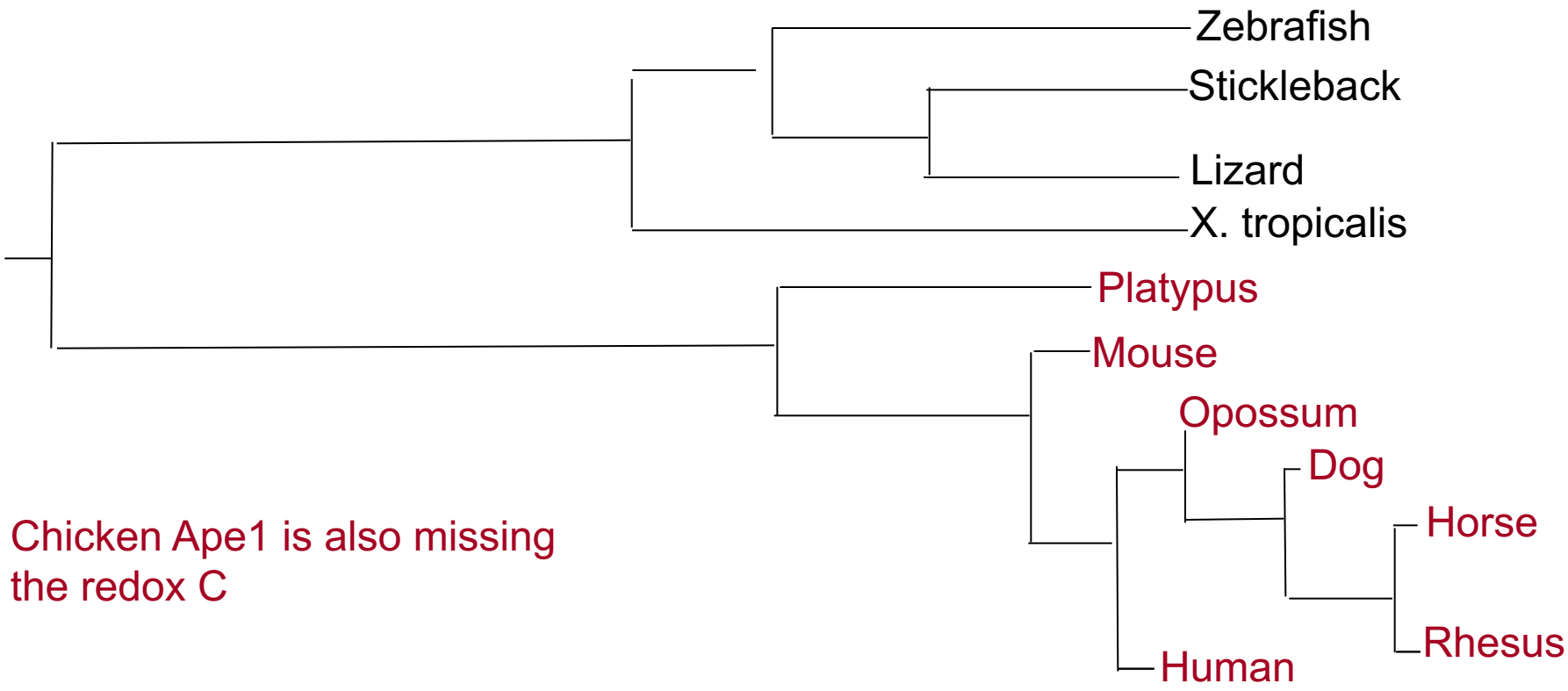
Disulfide bonds

65-93
65-99
93-99

Courtesy of Dr. Millie Georgiadis, collaborator

- **Kelley MR,** Luo M, Reed A, Su D, Delaplane S, Borch R F, Nyland II RL, Gross ML, Georgiadis M. (2011) Functional analysis of new and novel analogs of E3330 that block the redox signaling activity of the multifunctional AP endonuclease/redox signaling enzyme APE1/Ref-1. *Antioxid Redox Signal*. April; 14(8): 1387-1401.
- Su D, Delaplane S, Luo M, Rempel D, Vu B, **Kelley MR,** Gross ML, Georgiadis M. (2011) Interactions of APE1with a redox inhibitor: Evidence for an alternate conformation of the enzyme. *Biochemistry*. 50(1): 82-92.
- Luo M, Zhang J, He H, Su D, Chen Q, Gross M, **Kelley MR**, Georgiadis, M. (2012) Characterization of the Redox Activity and Disulfide Bond Formation in Apurinic / Apyrimidinic Endonuclease. *Biochemistry*. Jan 17; 51(2):695-705.
- Zhang J, Luo M, Marascot D, Logsdon D, LaFavers KA, Chen Q, Reed A, **Kelley MR**, Gross ML, Georgiadis MM. (2013) Inhibition of Apurinic/apyrimidinic endonuclease I's redox activity revisited. *Biochemistry.* Apr 30;52(17):2955-66

Evolution of the C65 redox center in APE1



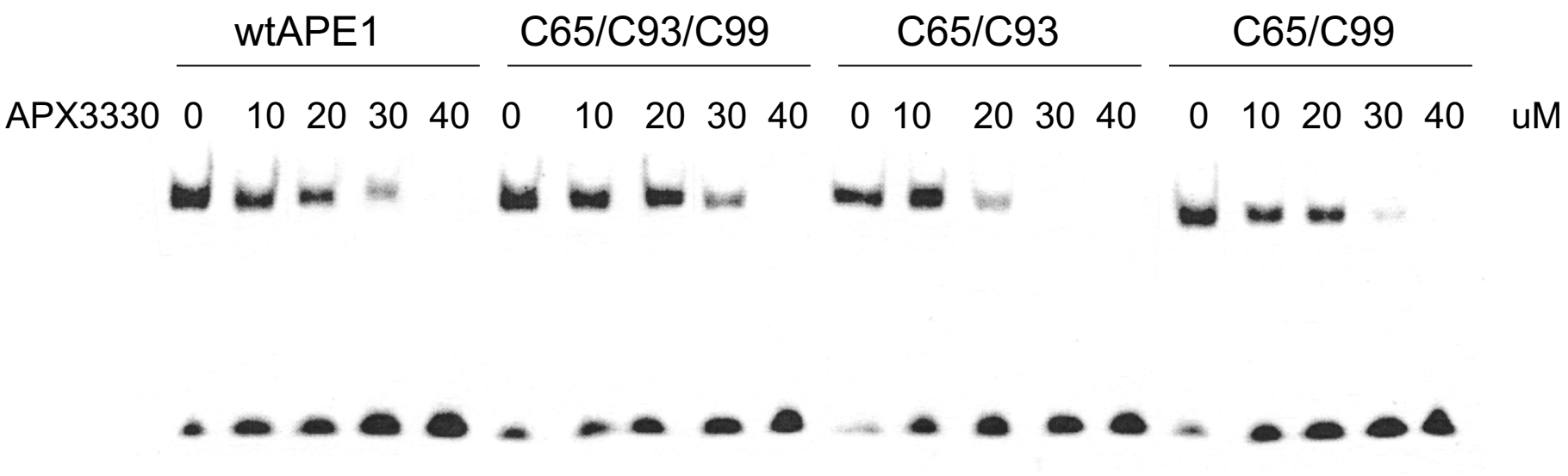
Chicken Ape1 is also missing the redox C

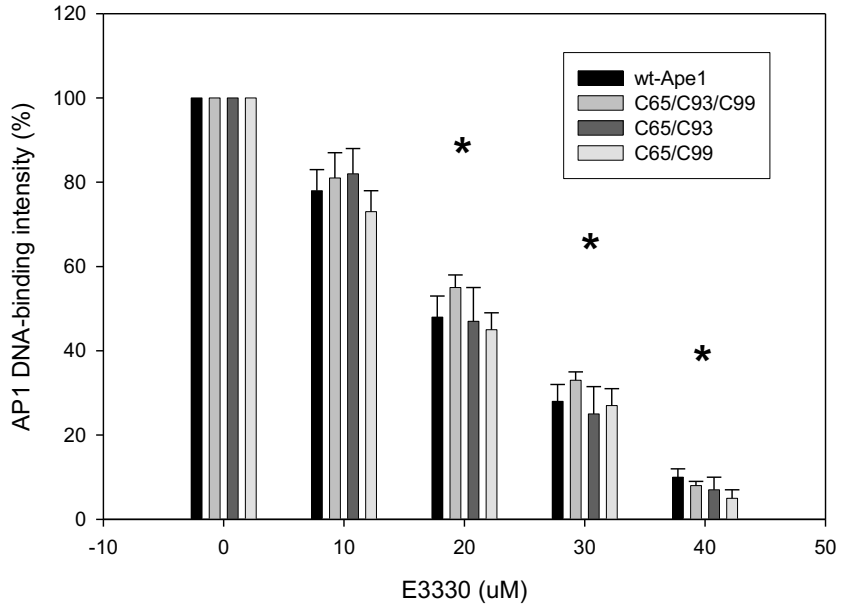
Human	CCCCCCC
Rhesus	CCCCCCC
Mouse	CCCCCCC
Dog	CCCCCCC

Horse	CCCCCCC
Opossum	CCCCCCC
Platypus	CCCRCCC
Lizard	TCCKCCC

X. tropicalis	SCCKCCC
Stickleback	TCCECCC
Zebrafish	TCCECCC

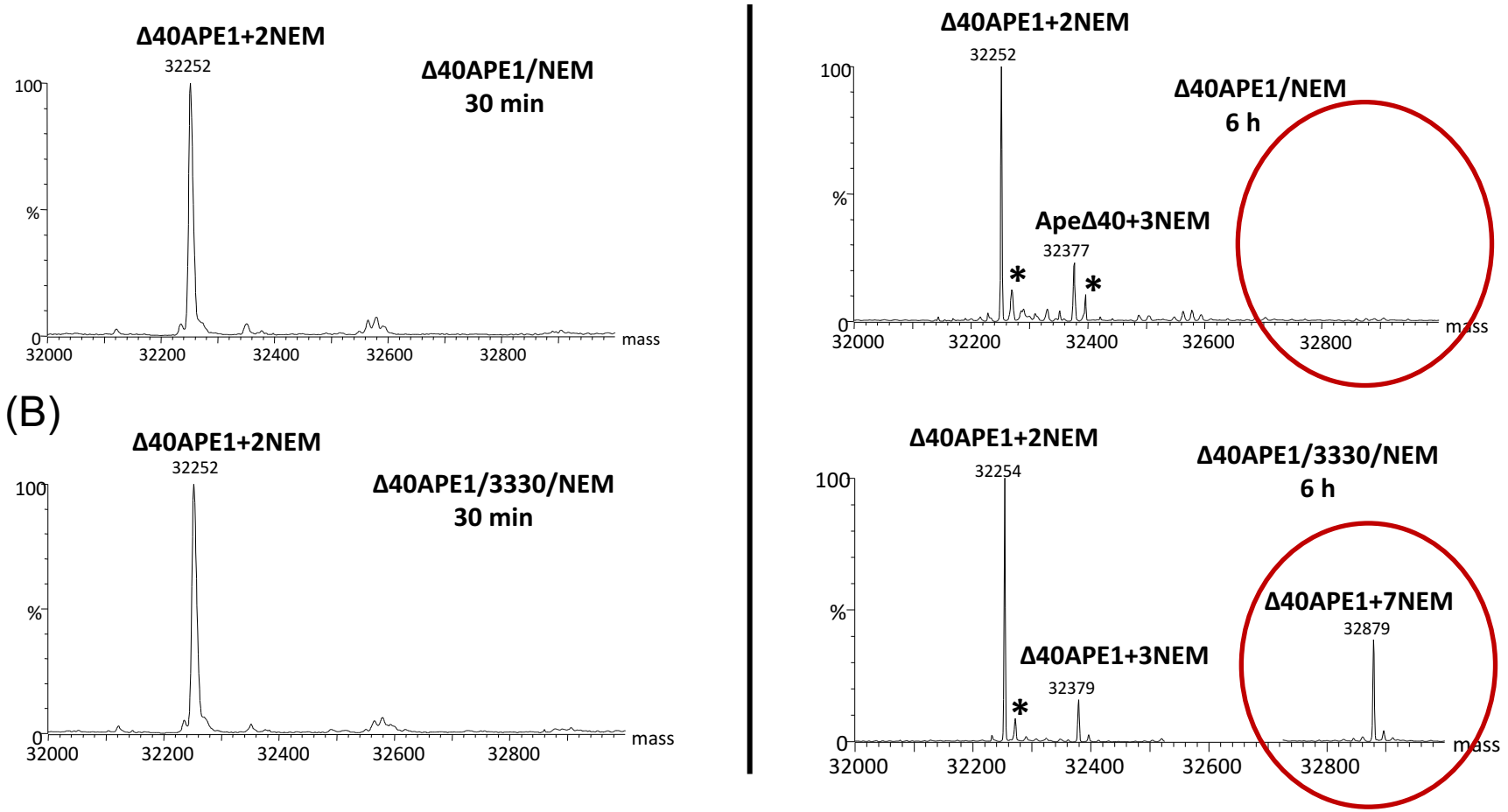
APX3330 blocks the activity of primary Cys residues required for APE1 redox function





Labeling indicates only the Cys present

Mass spectra of APE1 after incubation without (A) and with APX3330 (B) in the presence of NEM for 30 min (left panel) and 6 h (right panel).

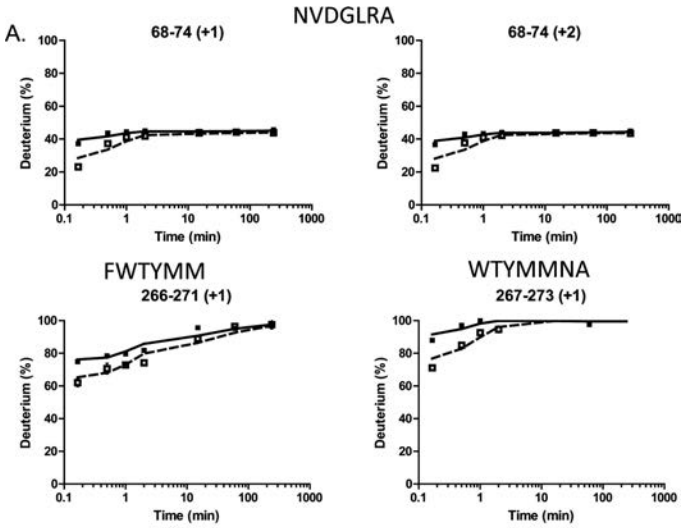


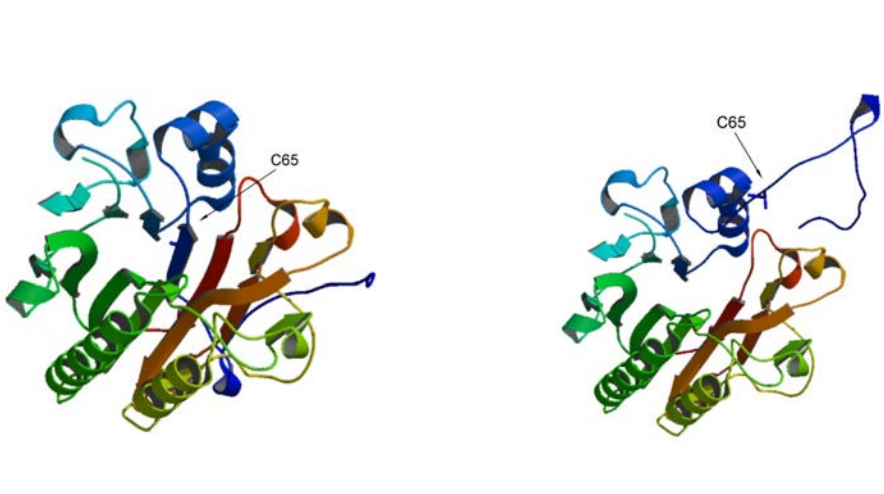
No 3330, NEM specifically modifies APE1 resulting in the formation of a +2 NEM = C99 C138 (solvent accessible). +3330 = 7NEM appearance = all cys now accessible

Su D, Delaplane S, Luo M, Rempel D, Vu B, Kelley MR, Gross ML, Georgiadis M. (2011) Interactions of APE1with a redox inhibitor: Evidence for an alternate conformation of the enzyme. *Biochemistry*. In Press

Using HDX mass spectrometry, APX3330 interacts with and inhibits the redox activity of APE1 at two regions.

These results suggest that APX3330 destabilizes APE1's structure rather than stabilizing it.

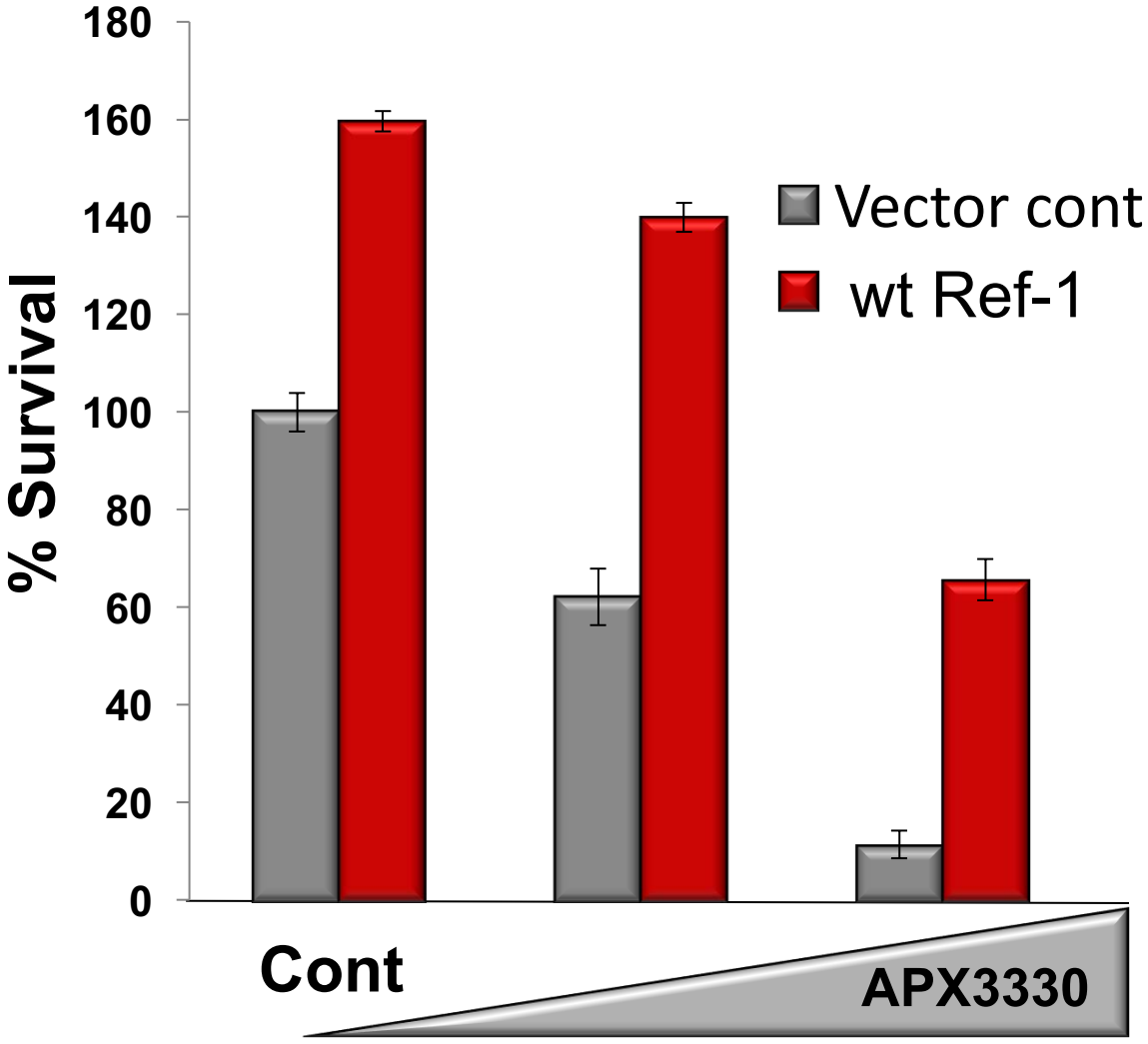




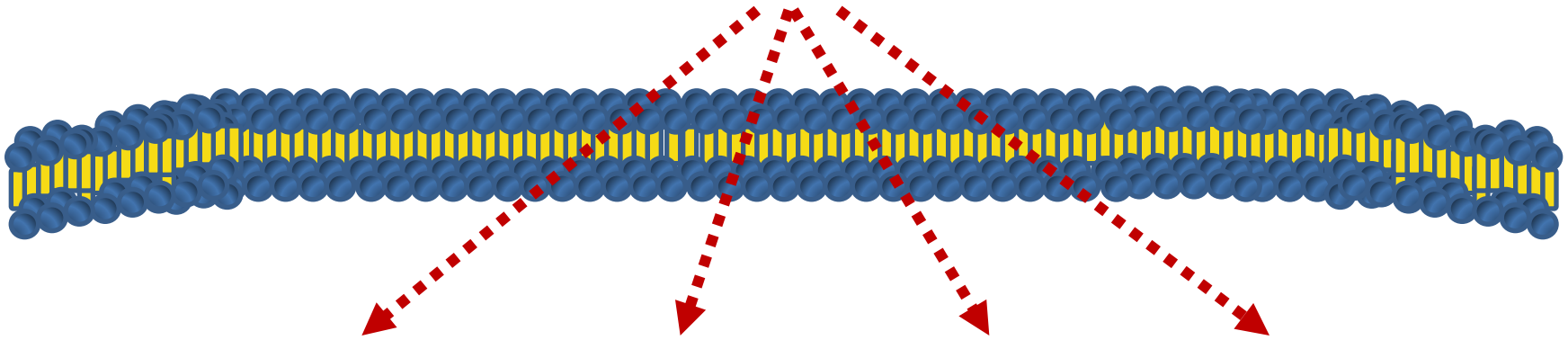
Interaction of APX3330 with APE1 as detected by HDX mass spectrometry. (A) HDX data are shown for peptides with slower exchange rates in the presence of 1.6 mM E3330 (☐) as compared to the exchange rates in the absence of compound (■). (B) The peptides that showed protection from deuterium exchange are shown highlighted on the structure of APE1. Residues 68–74 are colored orange and residues 266–273 magenta. Shown as stick models are R73 (orange) and R177 (blue), two Arg residues in the proximity of the regions of interaction identified by HDX mass spectrometry.

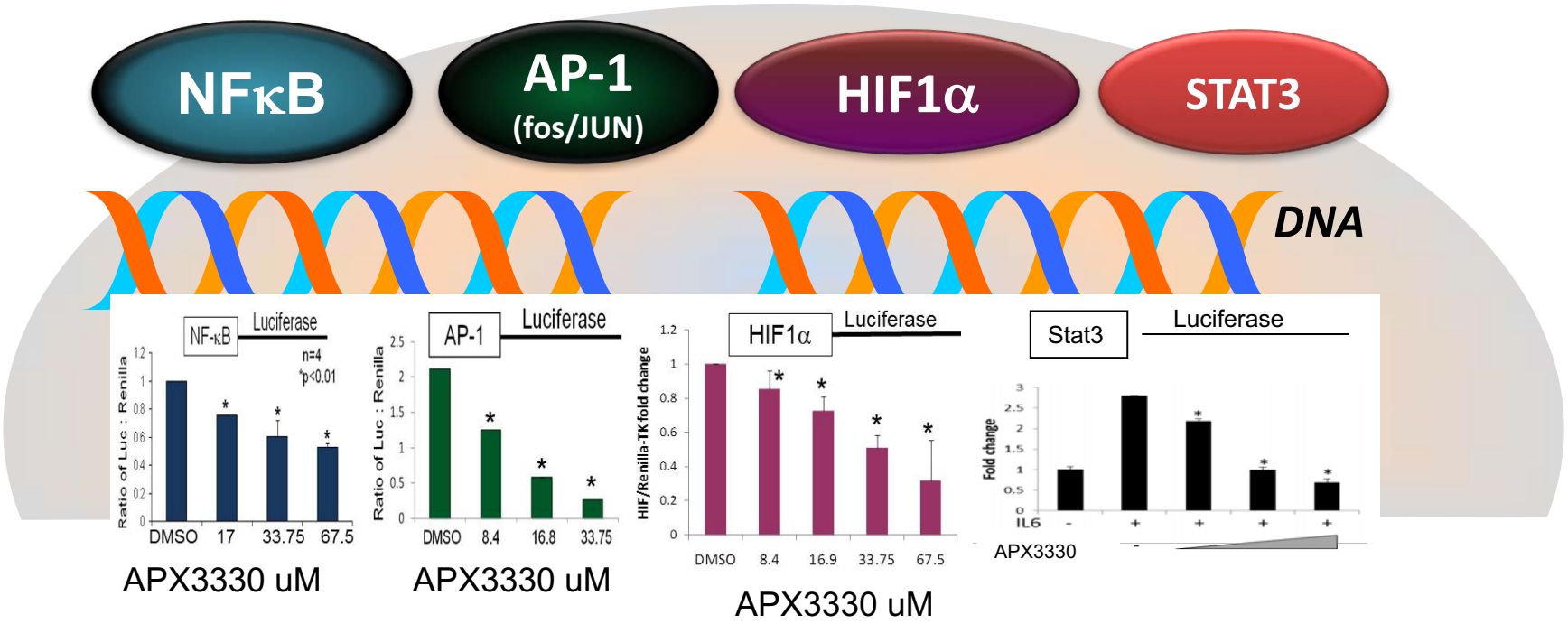
Published in: Jun Zhang; Meihua Luo; Daniela Marasco; Derek Logsdon; Kaice A. LaFavers; Qiujia Chen; April Reed; Mark R. Kelley; Michael L. Gross; Millie M. Georgiadis; *Biochemistry* **2013,** 52, 2955-2966.

Supporting Drug Selectivity Data



Inhibition of APE1/Ref-1 with APX3330 Blocks TF Function and Downstream Factors





High Unmet Clinical Need for Pancreatic Cancer

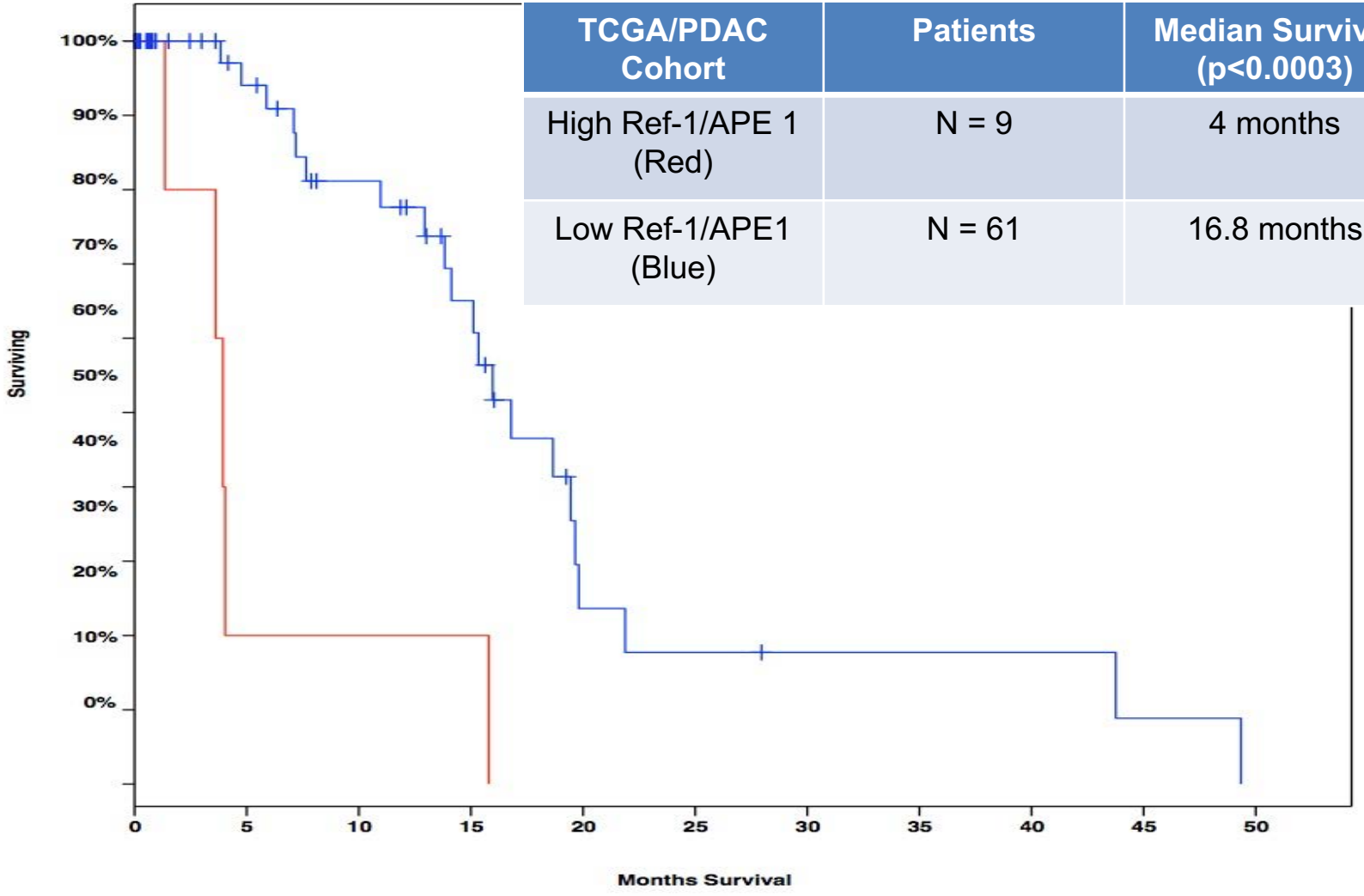
- In 2015, 48,960 Americans will be diagnosed with pancreatic cancer and more than 40,560 will die from the disease. Pancreatic cancer 1-year survival rates are ~25% and 5-year survival rates are ~7%.
- Pancreatic cancer thrives in an **inflammatory, hypoxic**, and dense/stromal microenvironment making it hard to treat. Few patients are diagnosed at an early stage leading to an average life expectancy following diagnosis of 3 to 6 months.
- Currently approved chemotherapeutic treatments include combination and single-agent use of paclitaxel, cisplatin, gemcitabine (Gemzar®), and 5-flurouracil. Other approved treatments (Abraxane, FOLFIRINOX) have high toxicities limiting use to patients that can tolerate the side effects.
- Pancreatic cancer represents an area of high unmet clinical need with Breakthrough Therapy regulatory approval potential for even modest improvements in survival.

SOURCE: American Cancer Society website

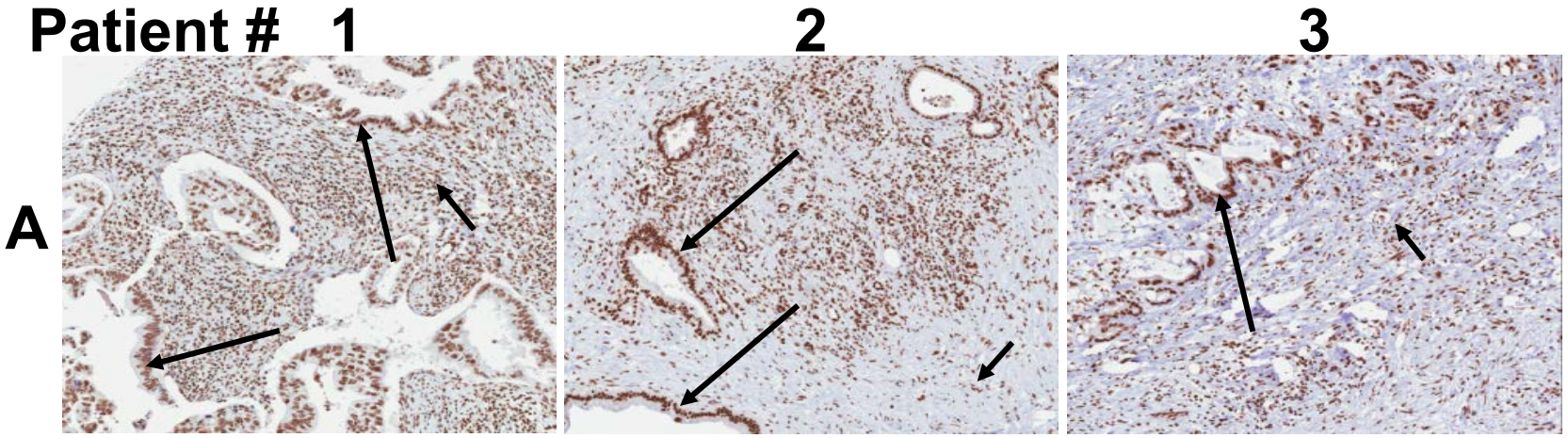
APE1 Expression is Linked to Poor Survival in Pancreatic Patients

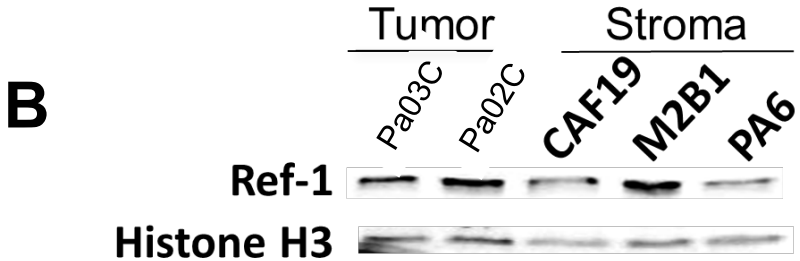
Early stage patients undergoing Whipple procedure

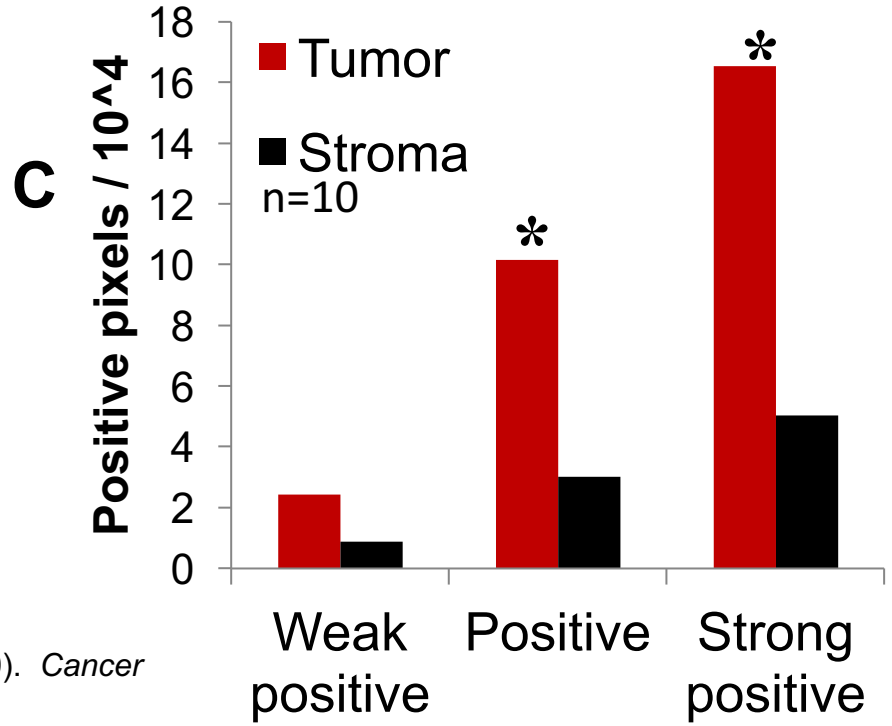
TCGA/PDAC Cohort	Patients	Median Survival (p<0.0003)
High Ref-1/APE 1 (Red)	N = 9	4 months
Low Ref-1/APE1 (Blue)	N = 61	16.8 months



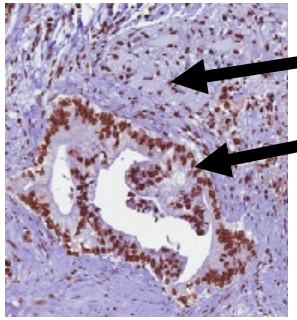
Pancreatic cancer patient tumors express APE1/Ref-1 in both tumor and stroma



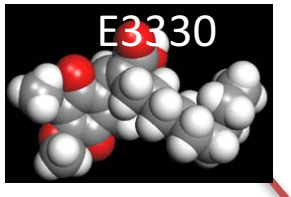




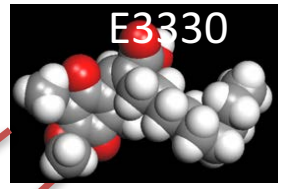
Jiang Y, Zhou S, Sandusky GE, Kelley MR, and Fishel ML. (2010). *Cancer Investigation* 28 (9): 885-895



Ref-1 expression in panc patient sample



Signaling



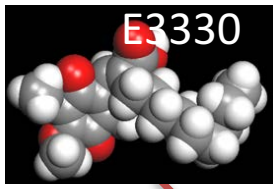
Ref-1

HIF-1α

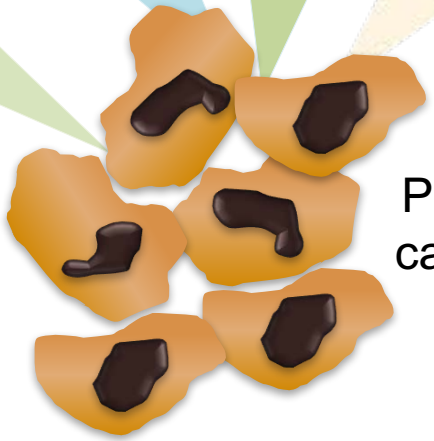
AP-1

NFκB

Pro-Angiogenic Factors
VEGF
IL8

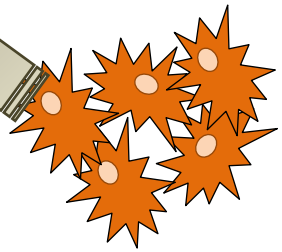


Angiogenesis / Invasion / Metastases



Pancreatic cancer cells

NFκB

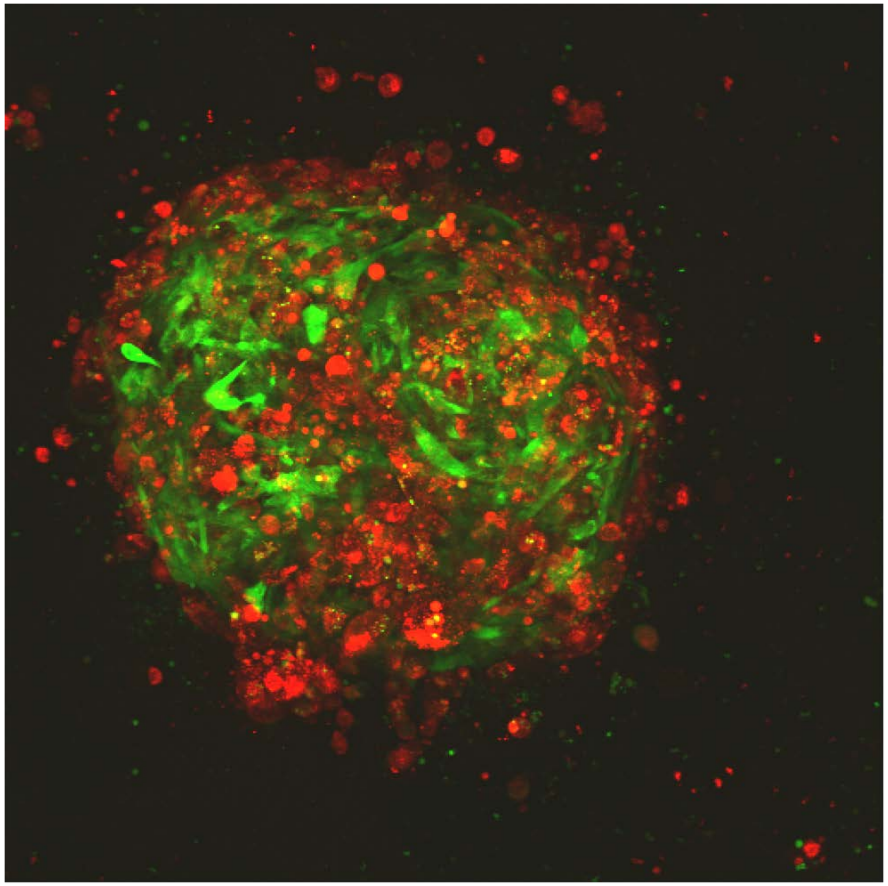


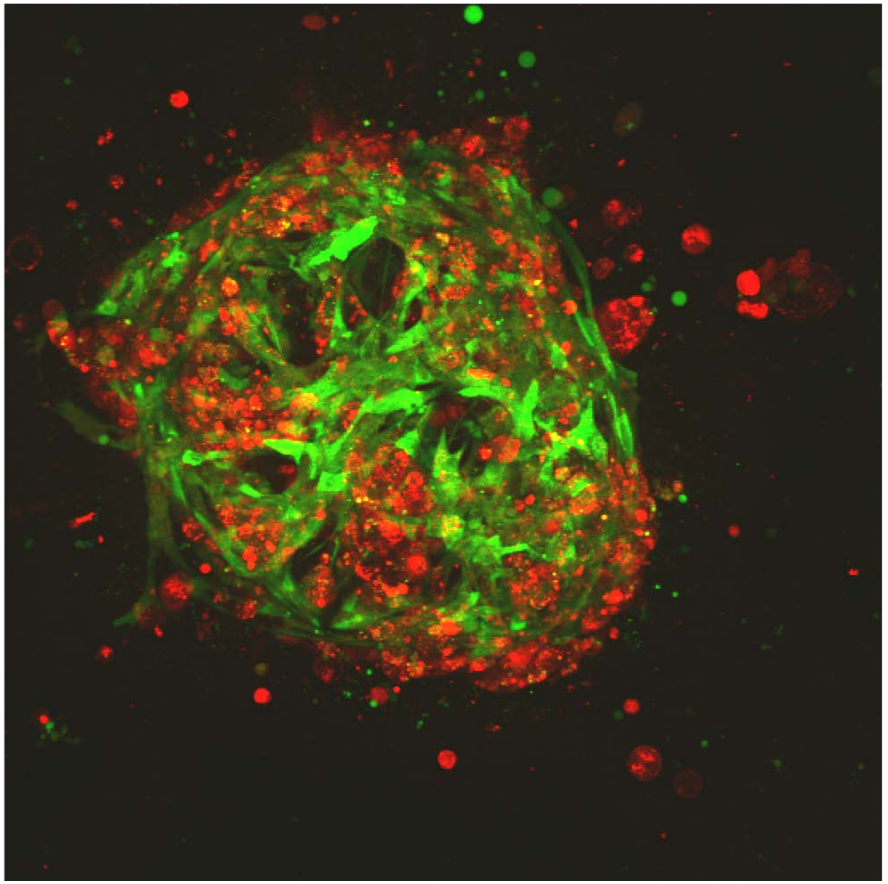
Tumor-assoc. macrophages
Stellate Cells
Cancer Associated Fibroblasts (CAFs)

Tumor Microenvironment (Angiogenesis/Invasion/ Metastases)

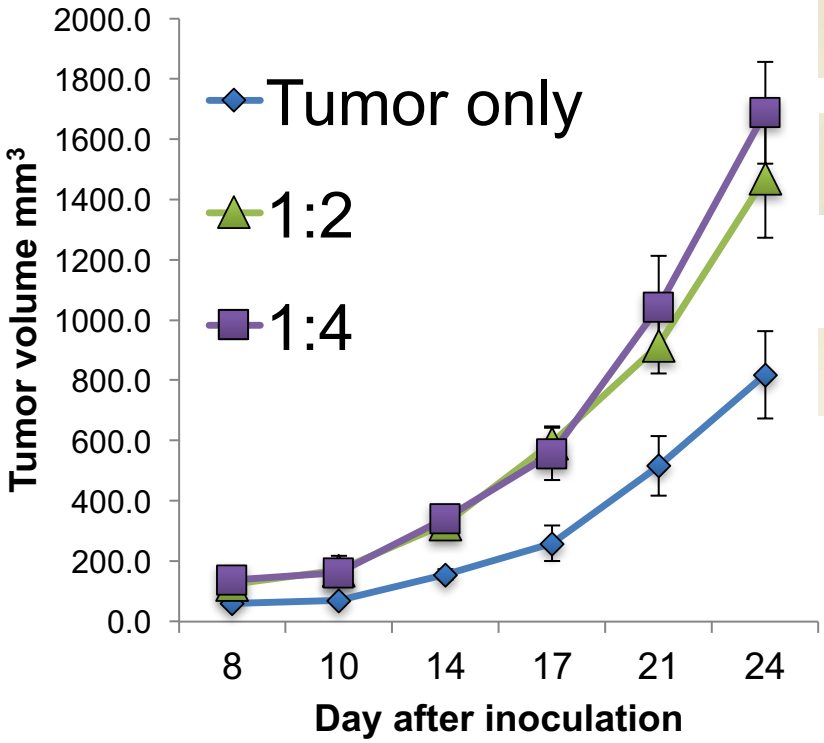
Tumor + CAFs (1:4)

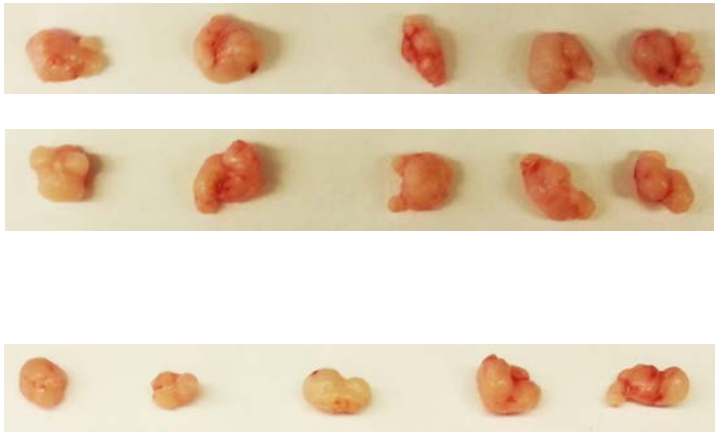
(Pa03C & 1301-63 hTERT-GFP)

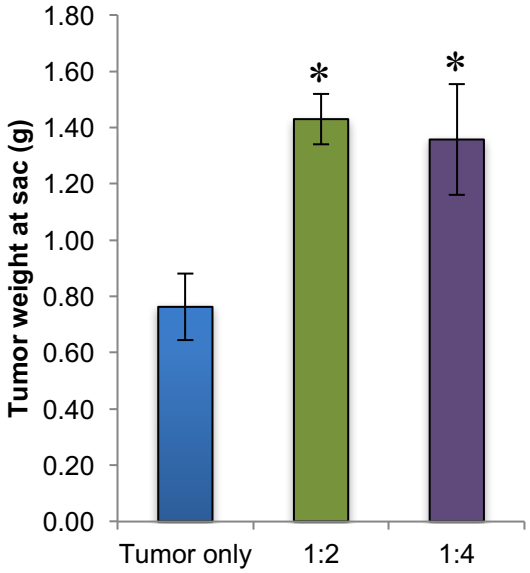


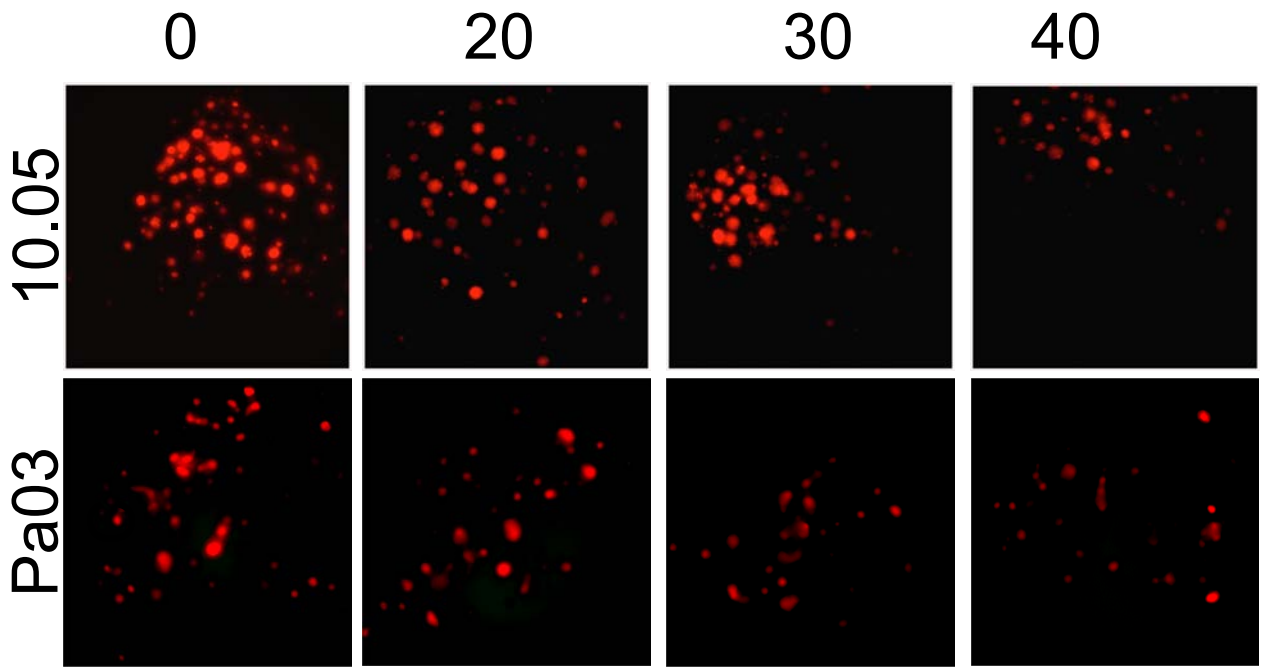


Addition of CAFs to tumors accelerates tumor growth rate *in vivo*



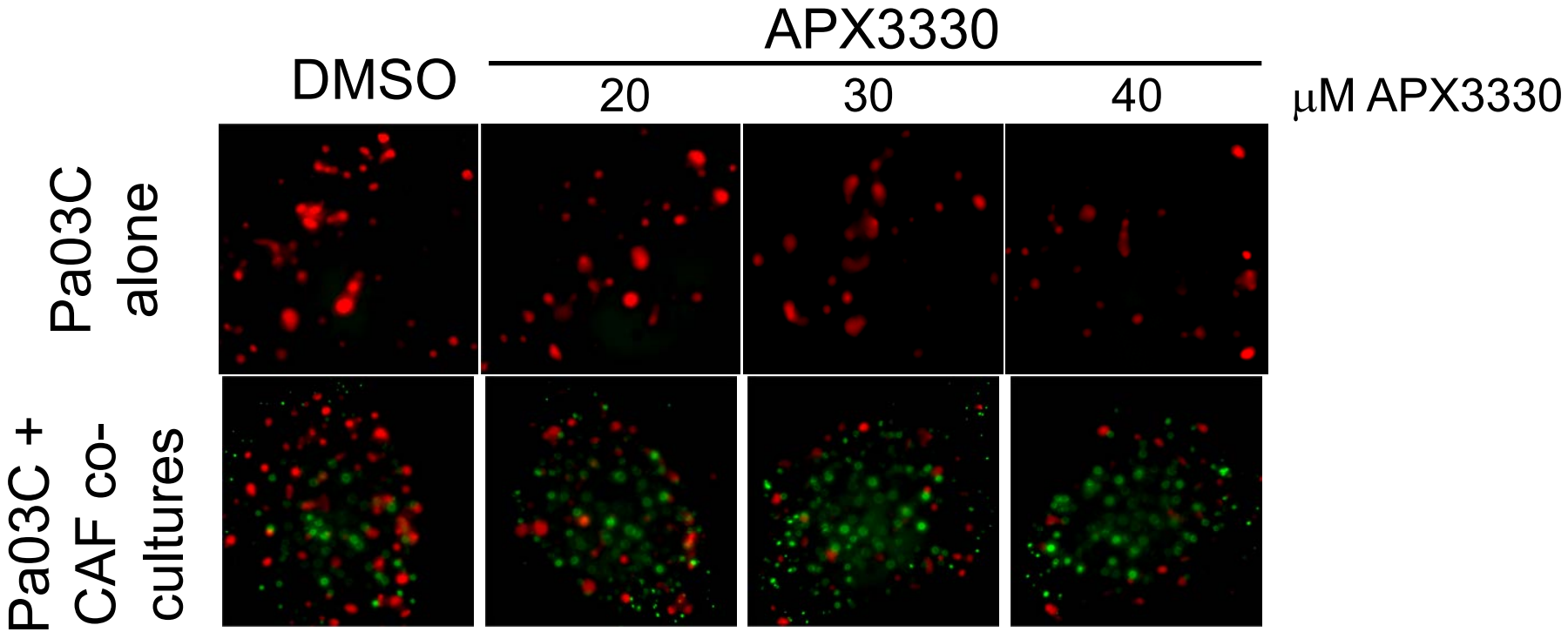






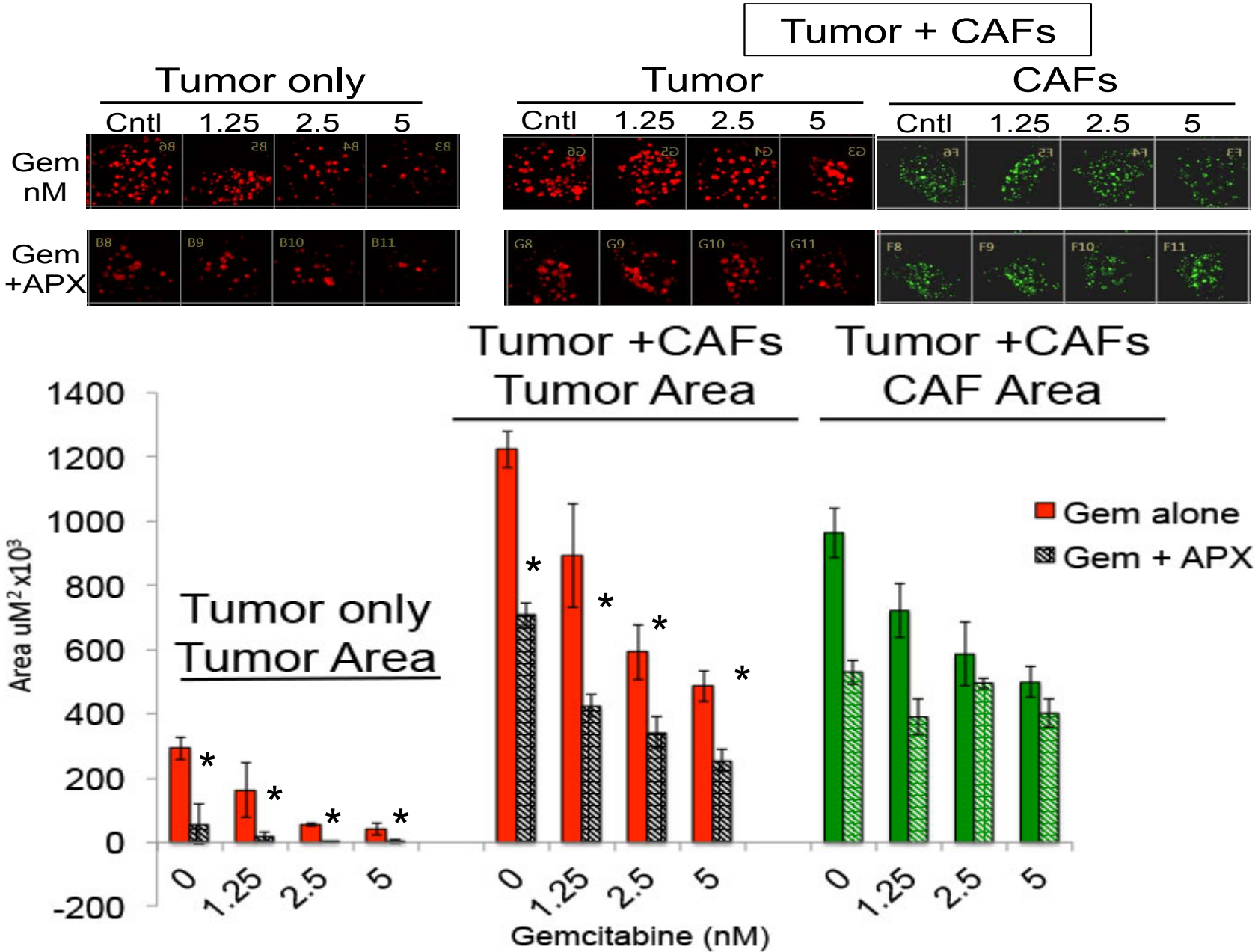
PDAC (Tumor) Cells

Pa03C



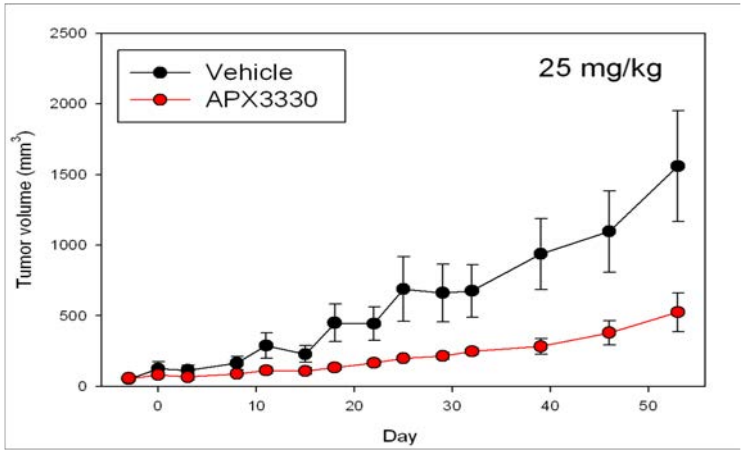
PDAC Cells + CAFs

Gem + APX3330 in 3D model

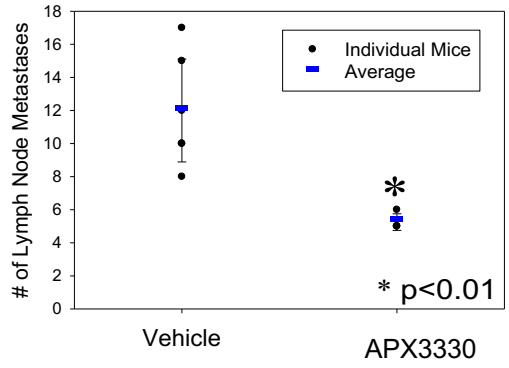


APX3330 Reduces Tumor Growth and Metastasis

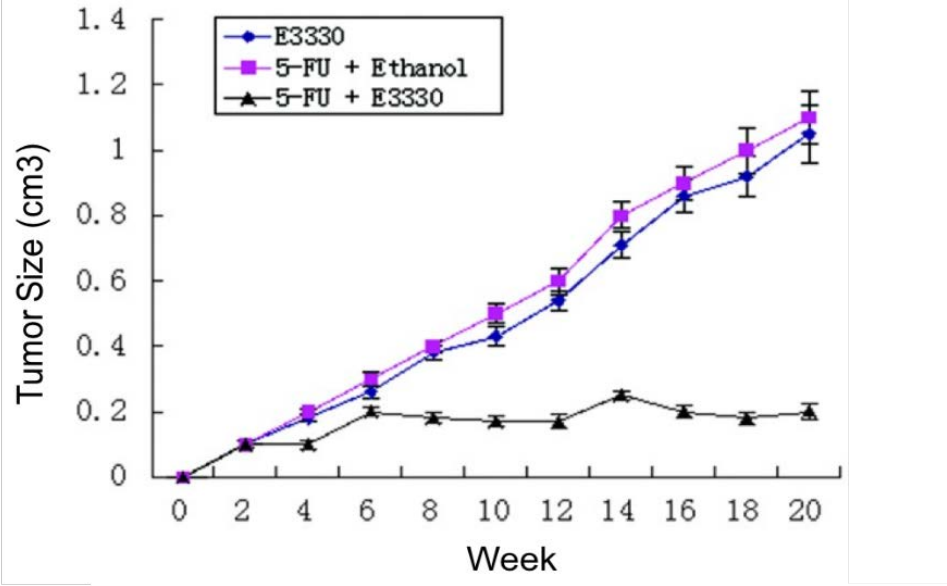
PaCa-2



Human PDAC Metastasis



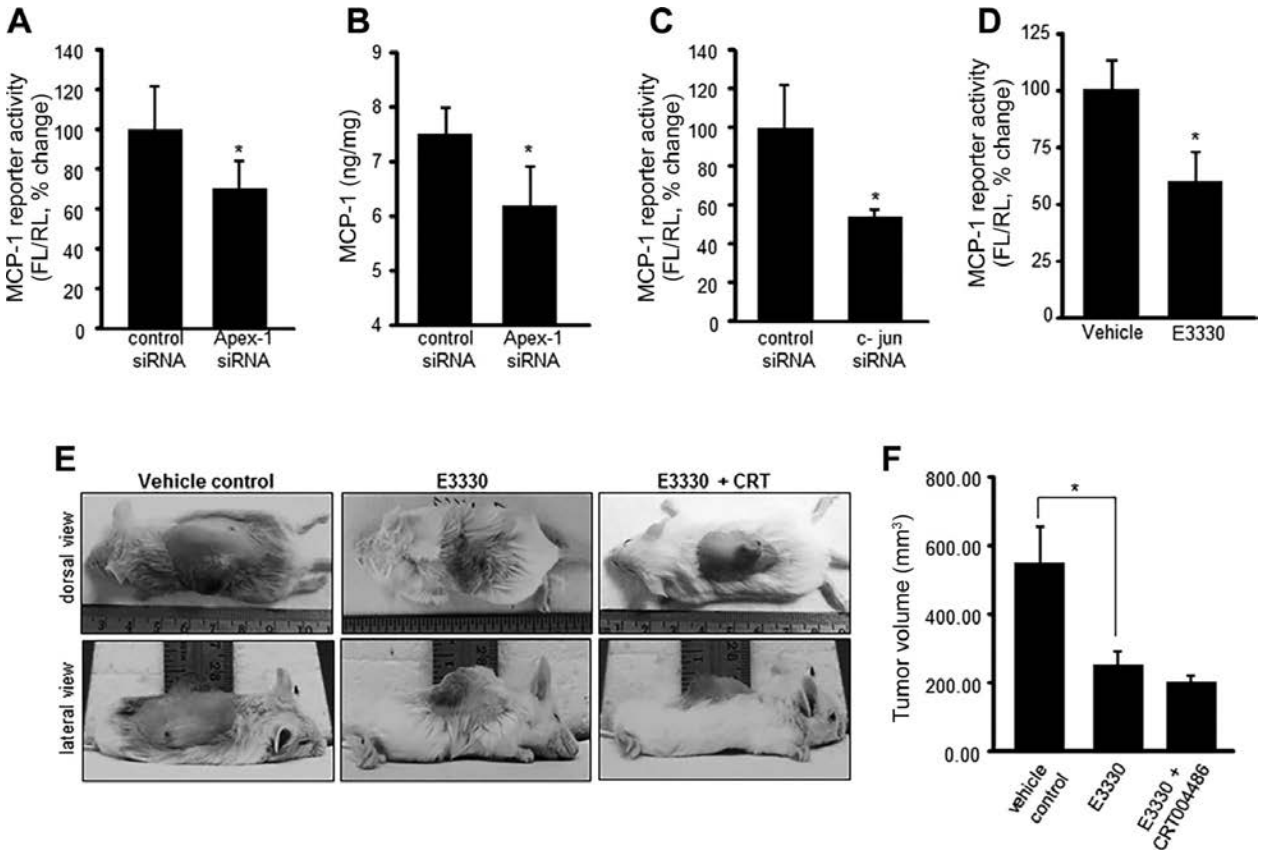
APX3330 in combination with 5-FU enhanced tumor growth suppression of CD133+/ESA+ colon cancer stem cells (CCSC) in vivo



5-FU: 15 mg/kg/day, 5d/wk, x2 wks; APX3330: 1.5 mg/kg/day, 5d/wk, x 2 weeks; 5-FU+APX3330: 5-FU 15 mg/kg/day +APX3330 1.5 mg/kg/day, 5d/wk, x2 wks

[1]**SOURCE**: Fishel ML, Jiang Y, Rajeshkumar NV, Scandura G, Sinn AL, He Y, Shen C, Jones DR, Pollok KE, Ivan M, Maitra A, **Kelley MR.** (2011). Impact of APE1/Ref-1 Redox Inhibition on Pancreatic Tumor Growth. *Molecular Cancer Therapeutics*. Sep;10(9):1698-708.

Endothelial cell tumor growth is Ape/ref-1 dependent



Redox function of Apex-1 is required for MCP-1 activation and EC tumor growth in vivo. *Apex-1* knockdown in EOMA cells resulted in significant decrease in MCP-1 reporter activity (*A*), and MCP-1 release in the media was measured by ELISA (*B*). *C*: MCP-1 reporter activity was significantly decreased in *c-Jun* knockdown EOMA cells and in E3330 (50 μM, 5 h)-treated cells (*D*). Redox changes of Apex-1 influences HE outcome in vivo. *E*: tumor growth rates were evaluated after 7 days of E3330 treatment (25 mg/kg ip twice daily) alone and in combination with CRT0044876 (10 mg/kg ip twice daily). *F*: tumor volume was quantified using calipers (length × width × height). Results are expressed as means ± SD; **P* < 0.05.

Clinical Plans for APX3330

- Apexian will complete a two-part phase I oncology study:
  - Increasing doses in patients with treatment-refractory solid tumors
  - 20-40 patients
- Study endpoint:
  - Identify the RP2 dose of APX3330
  - Based upon
    - tolerability of the agent
    - evidence of anti-tumor effect
    - pharmacokinetic and pharmacodynamic
- IND accepted by the FDA:
  - All study documents are ready and sites identified
  - Contracts pending completion of the funding round
- Additional safety, tolerability and efficacy POC

Academic – Industry / Biotech Partnership

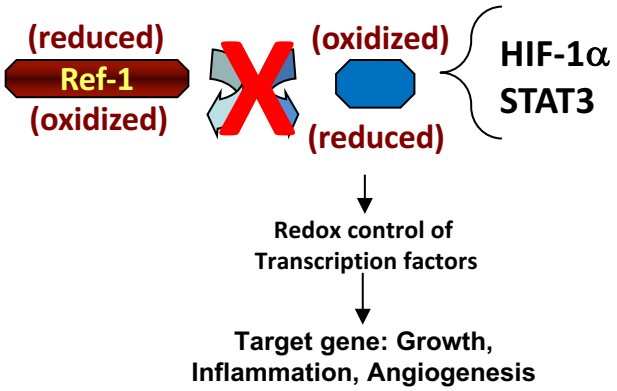
MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

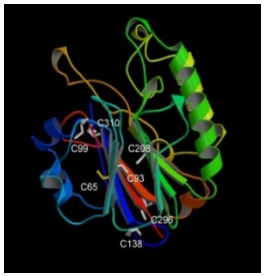
HERMAN B WELLS CENTER FOR PEDIATRIC RESEARCH
INDIANA UNIVERSITY
Department of Pediatrics

Apexian Pharmaceuticals

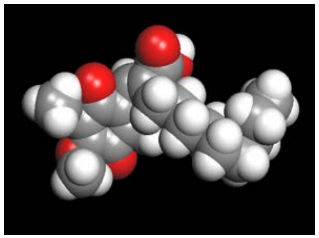
Bench to Bedside

Bench Findings:
Inhibition of Ref-1 via APX3330 reduces tumor burden in mice



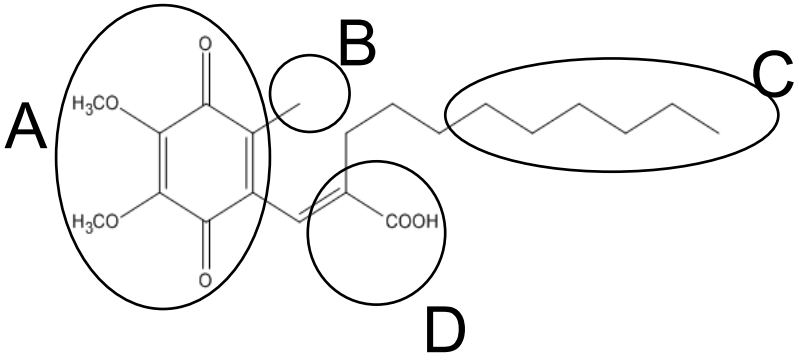


Target APE1/Ref-1


Inhibitor:
APX3330

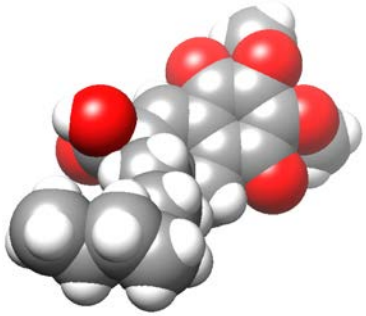
A <u>Phase I Clinical Trial</u>
Open-Label Dose Escalation Study of Oral APX3330 in Subjects with Advanced Solid Tumors

IND approved July 16, 2016
IU IRB approved Aug 22, 2016

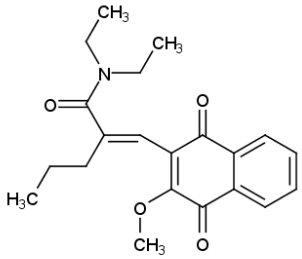


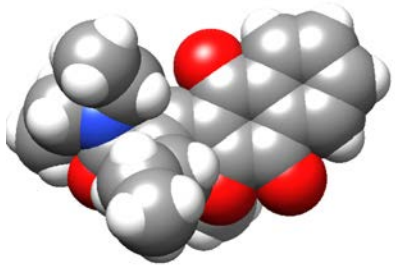
Schematic of APX3330. Groups to be further investigated include the

(A) Quinone series,
(B) 3-Position series,
(C) Alkyl Sidechain series and
(D) Carboxylic Acid/Amide series.



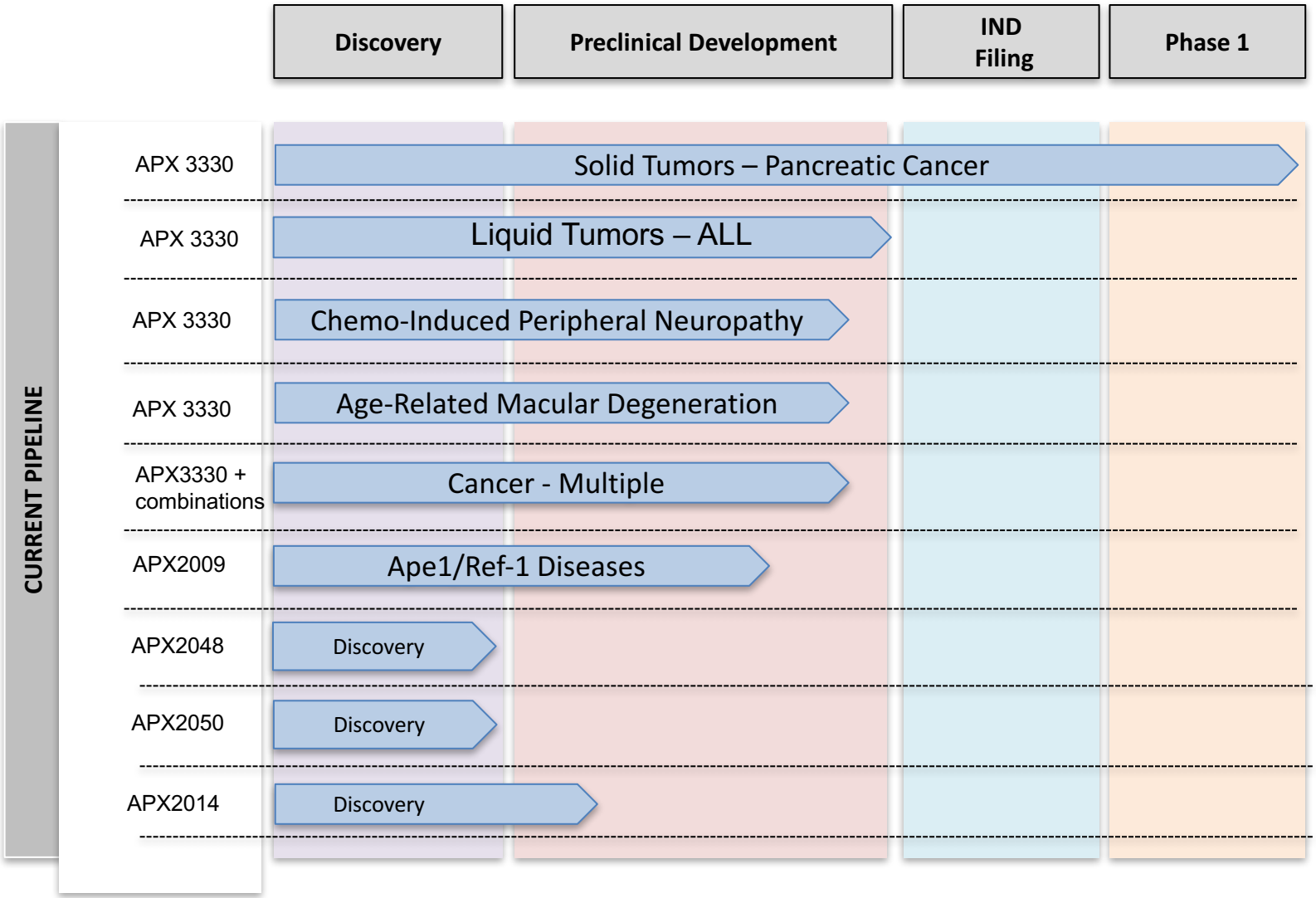
APX3330



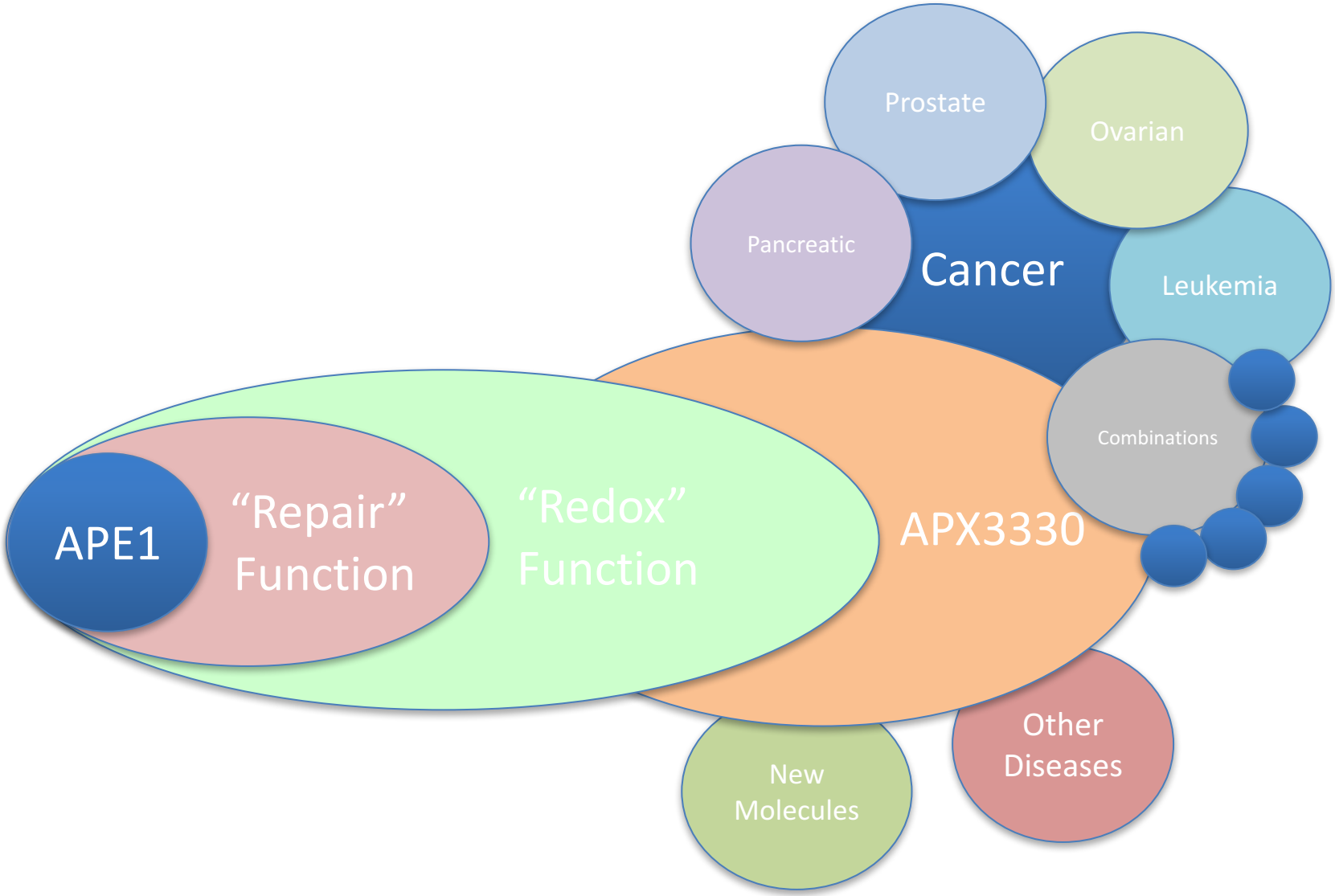


APX2009

Pipeline and Indications



Continuing to Follow the Science



Example pathways that are altered in low passage patient derived PDAC cells following APE1 knockdown and Fluidigm C1 single cell sorting-RNA seq analysis.

Table 1. Pathway affected by Ref-1 knockdown	# of genes affected	p-value
STAT3 Pathway	9	0.006
HIF1 Signaling	17	0.002
ERK/MAPK Signaling	25	0.003

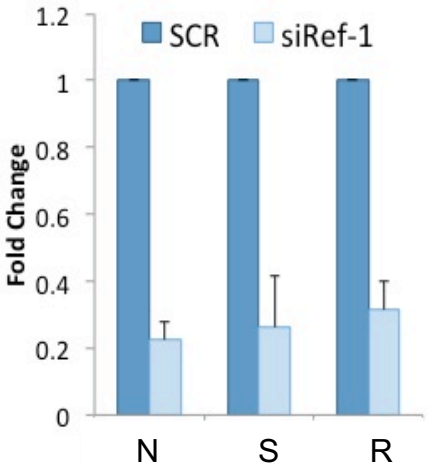
Validation of Single Cell KD
&
Potential Use for Drug Development/Specificity

A. Identification of Ref-1 biomarkers using Single Cell RNAseq:

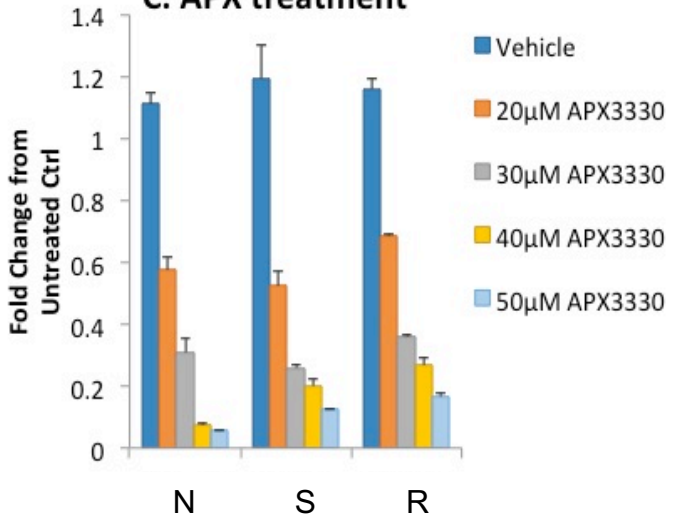
sc RNAseq	N	S	R
Fold change from SCR	0.06	0.01	0.10
p value	4.3×10^{-8}	2.78×10^{-6}	8.14×10^{-7}

Validation by :

B. Knockdown, n=2

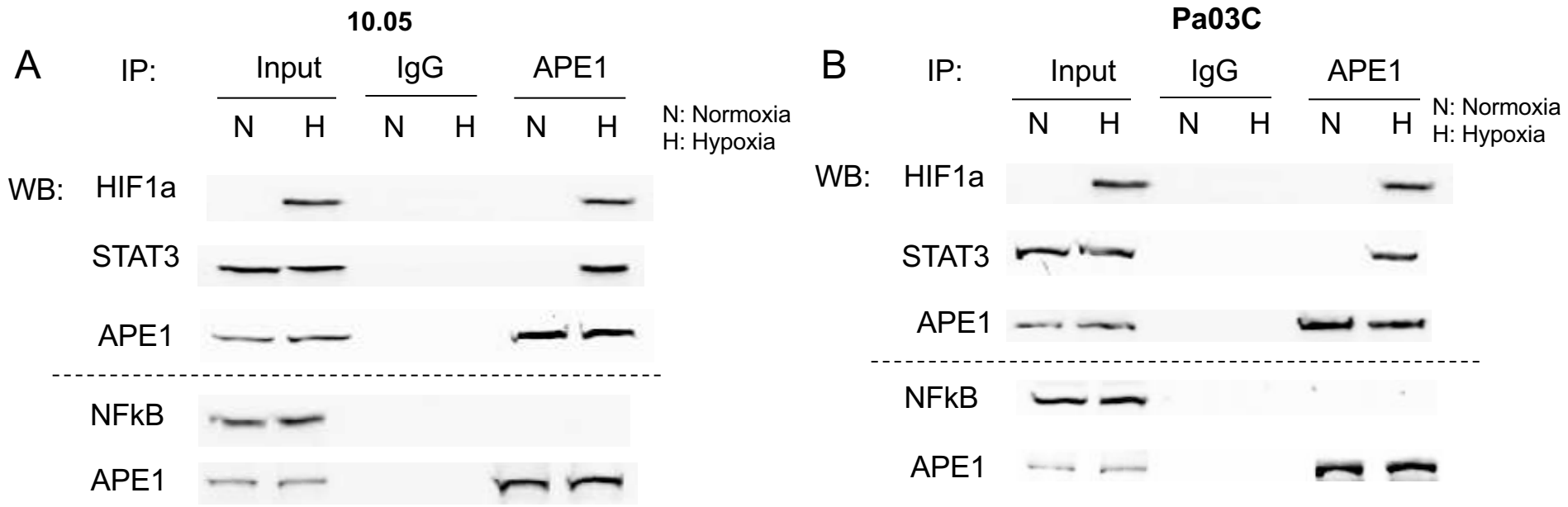


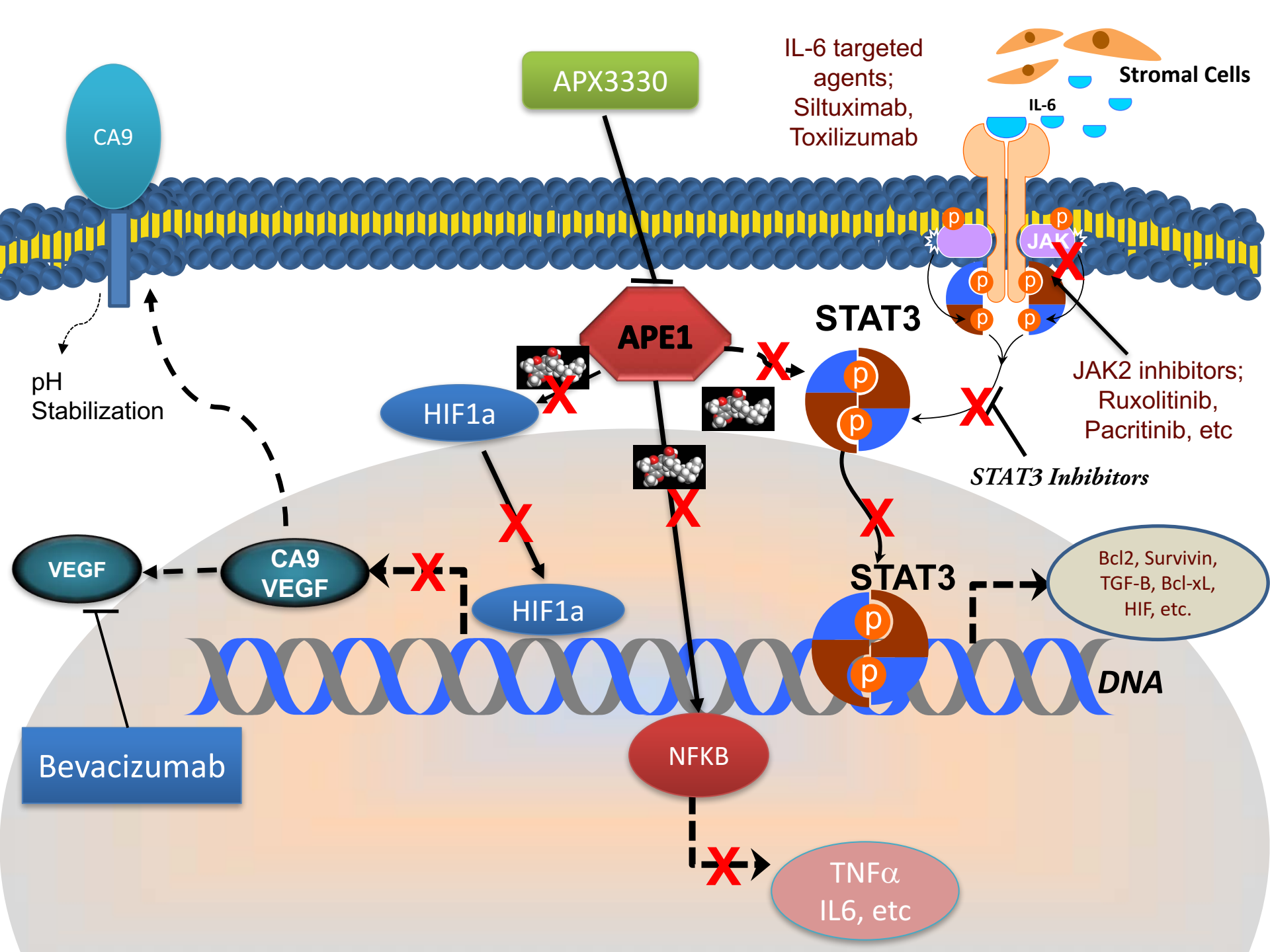
C. APX treatment

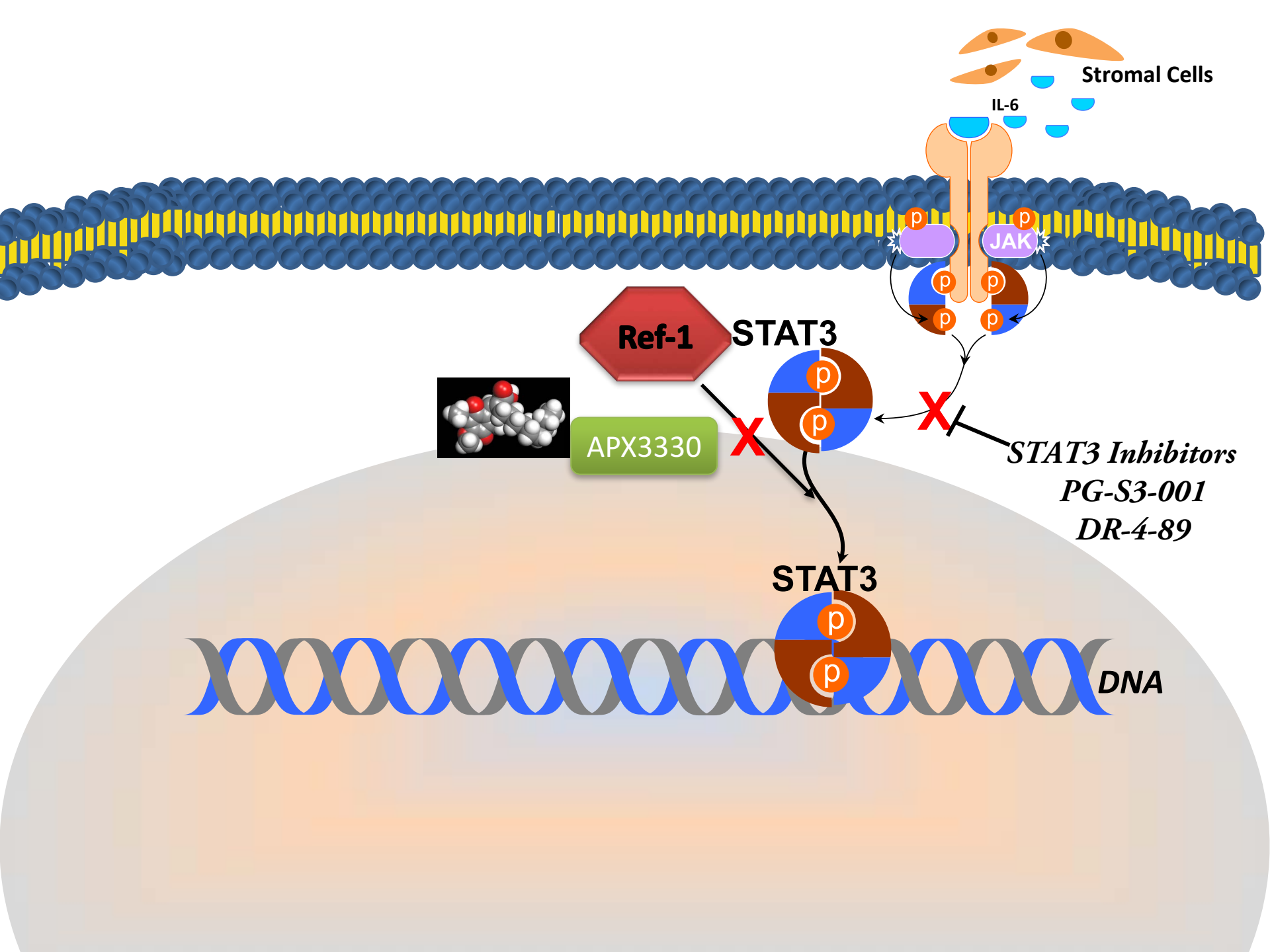


APE1 Complexes with HIF1α & STAT3 under Hypoxia

Endogenous APE1

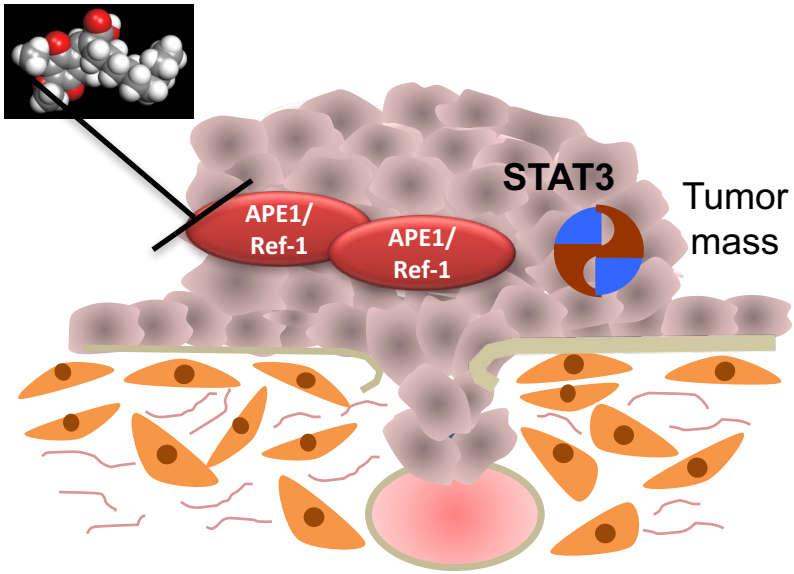


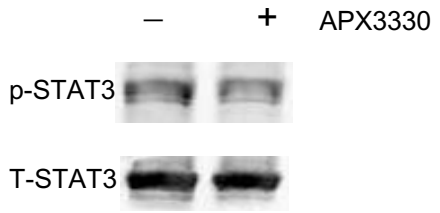

IL-6 targeted agents; Siltuximab, Toxilizumab
Stromal Cells
IL-6
APX3330
CA9
pH Stabilization
APE1
HIF1a
STAT3
JAK2 inhibitors; Ruxolitinib, Pacritinib, etc
STAT3 Inhibitors
VEGF
CA9 VEGF
HIF1a
STAT3
Bcl2, Survivin, TGF-B, Bcl-xL, HIF, etc.
DNA
Bevacizumab
NFKB
TNFα IL6, etc

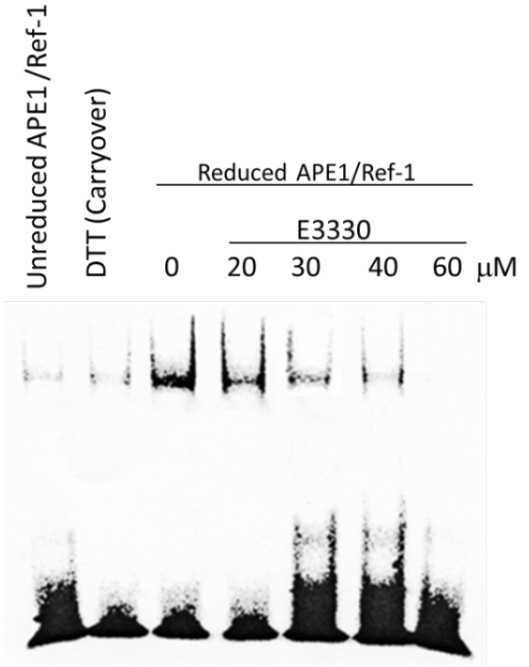

Stromal Cells
IL-6
JAK
p
Ref-1
STAT3
APX3330
X
X
STAT3 Inhibitors
PG-S3-001
DR-4-89
STAT3
DNA

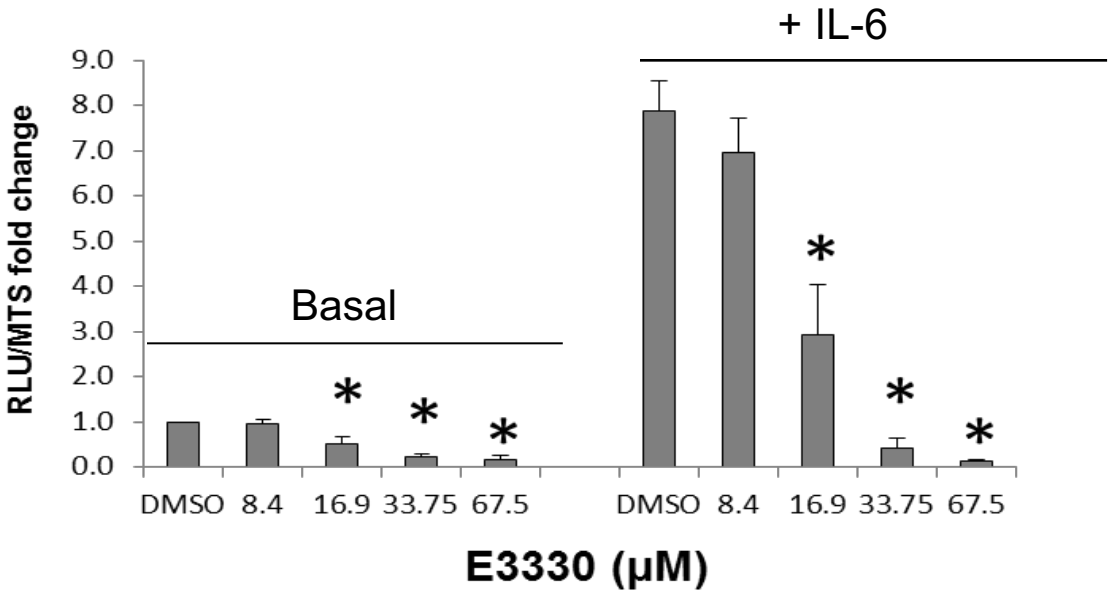
STAT3 DNA binding is redox sensitive and can be stimulated by APE1/Ref-1….and inhibited by APX3330

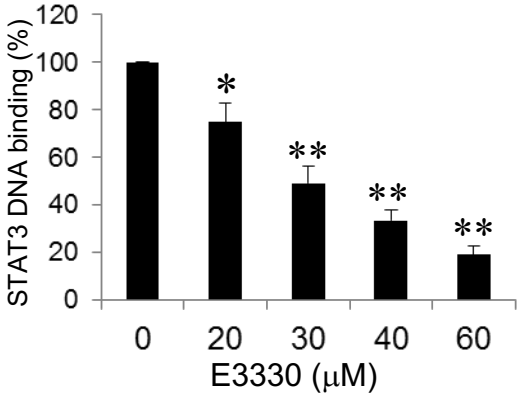
APX3330

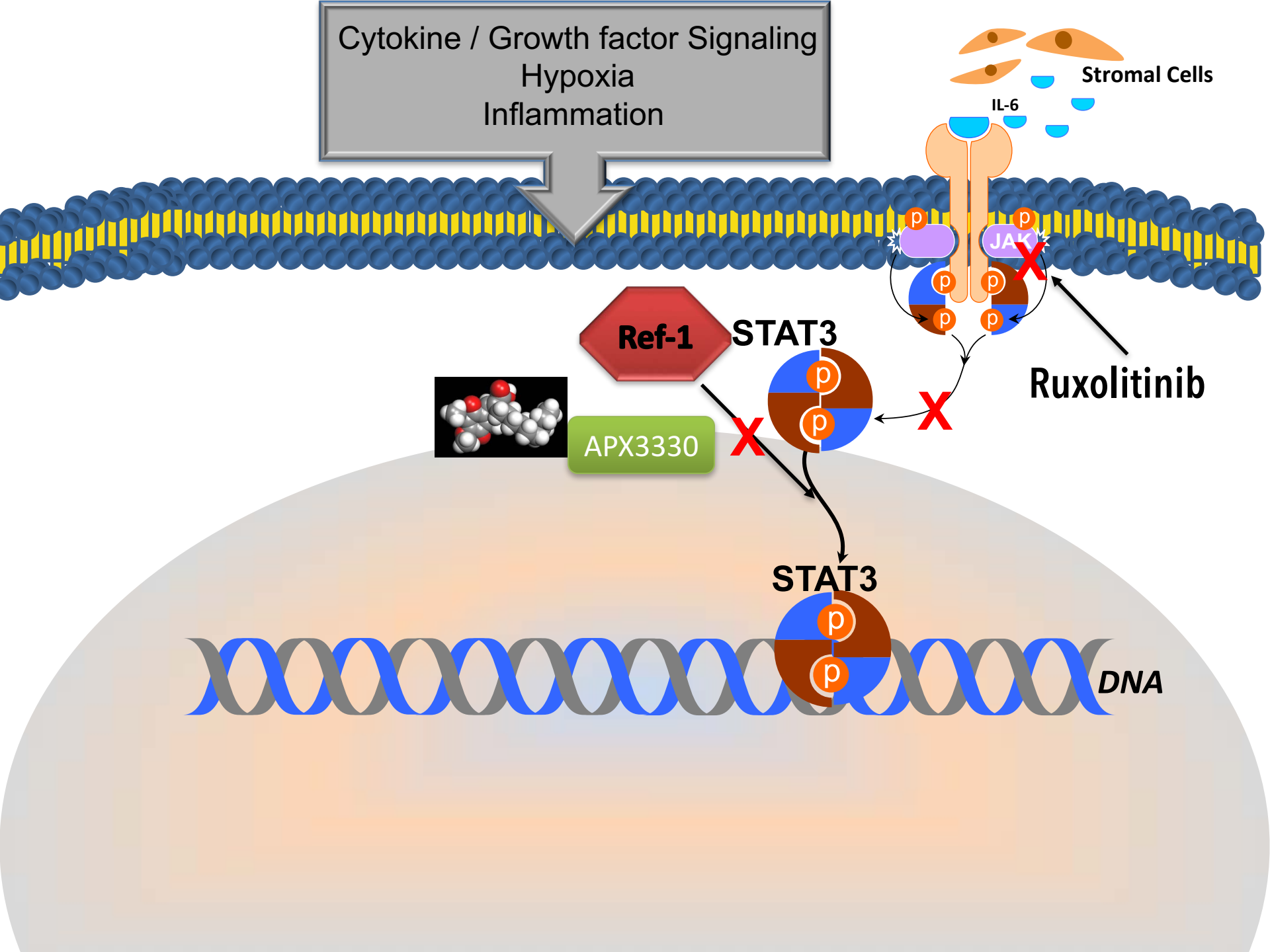






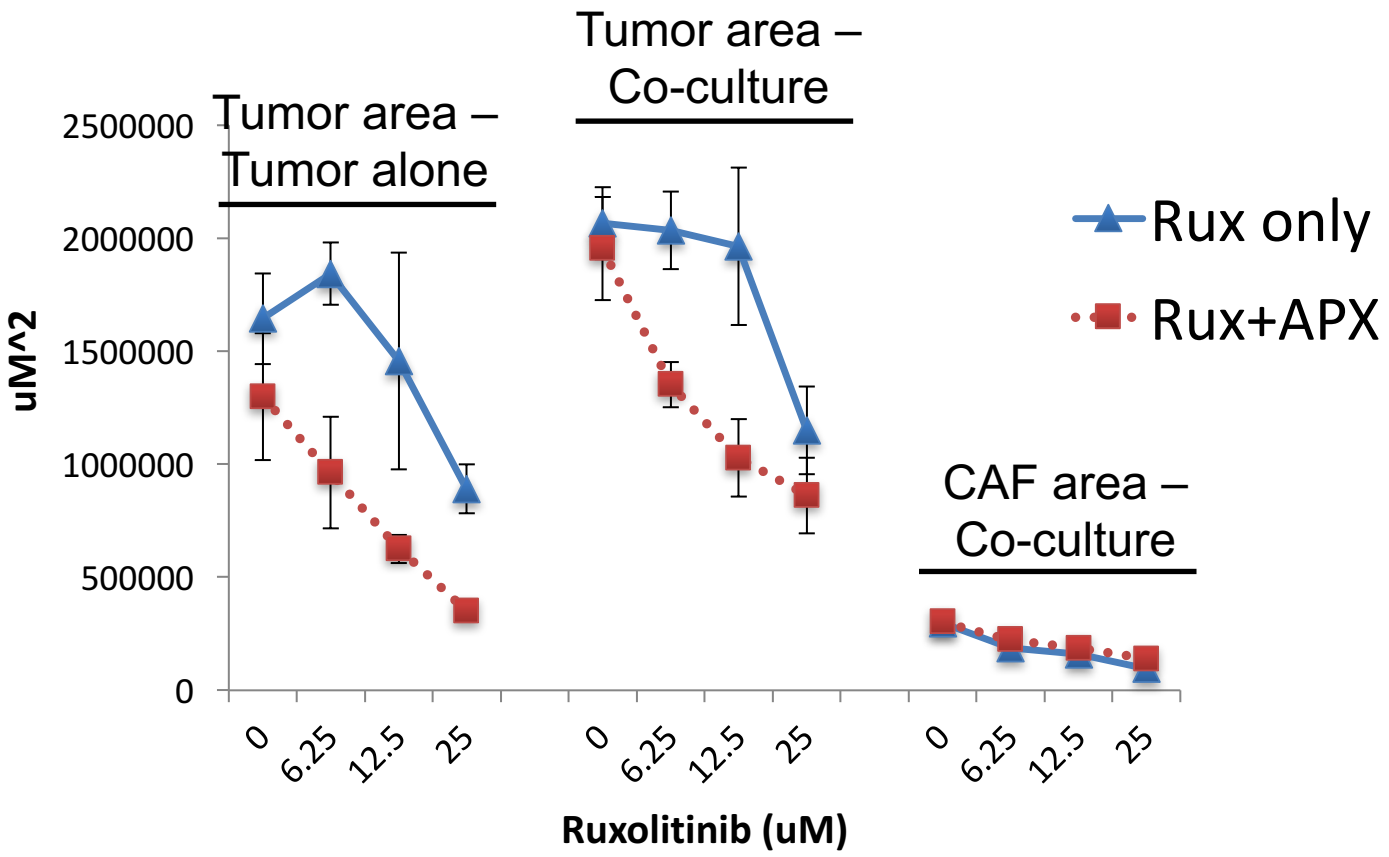


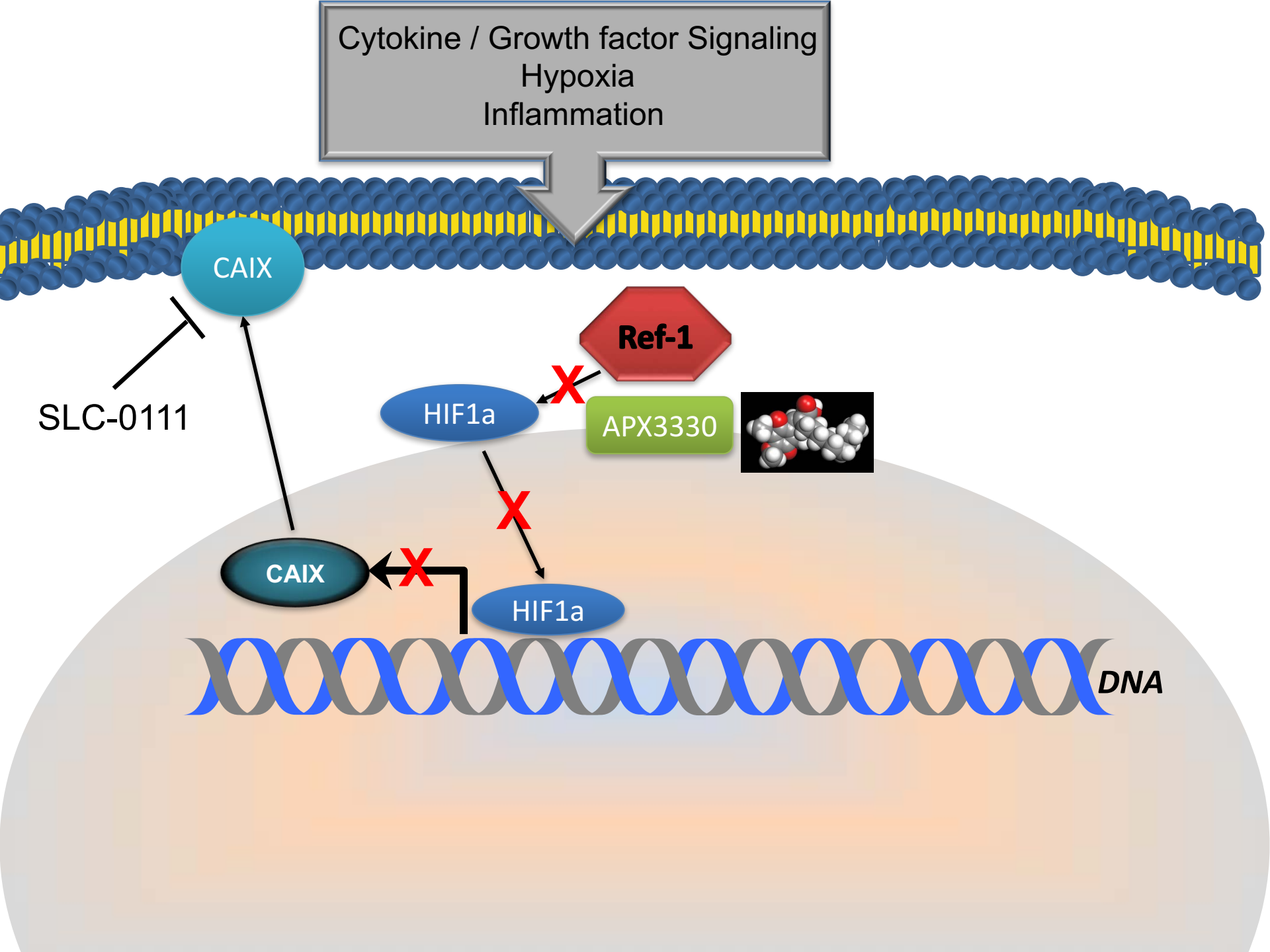



Cytokine / Growth factor Signaling
Hypoxia
Inflammation
Stromal Cells
IL-6
JAK
Ruxolitinib
Ref-1
STAT3
APX3330
STAT3
DNA

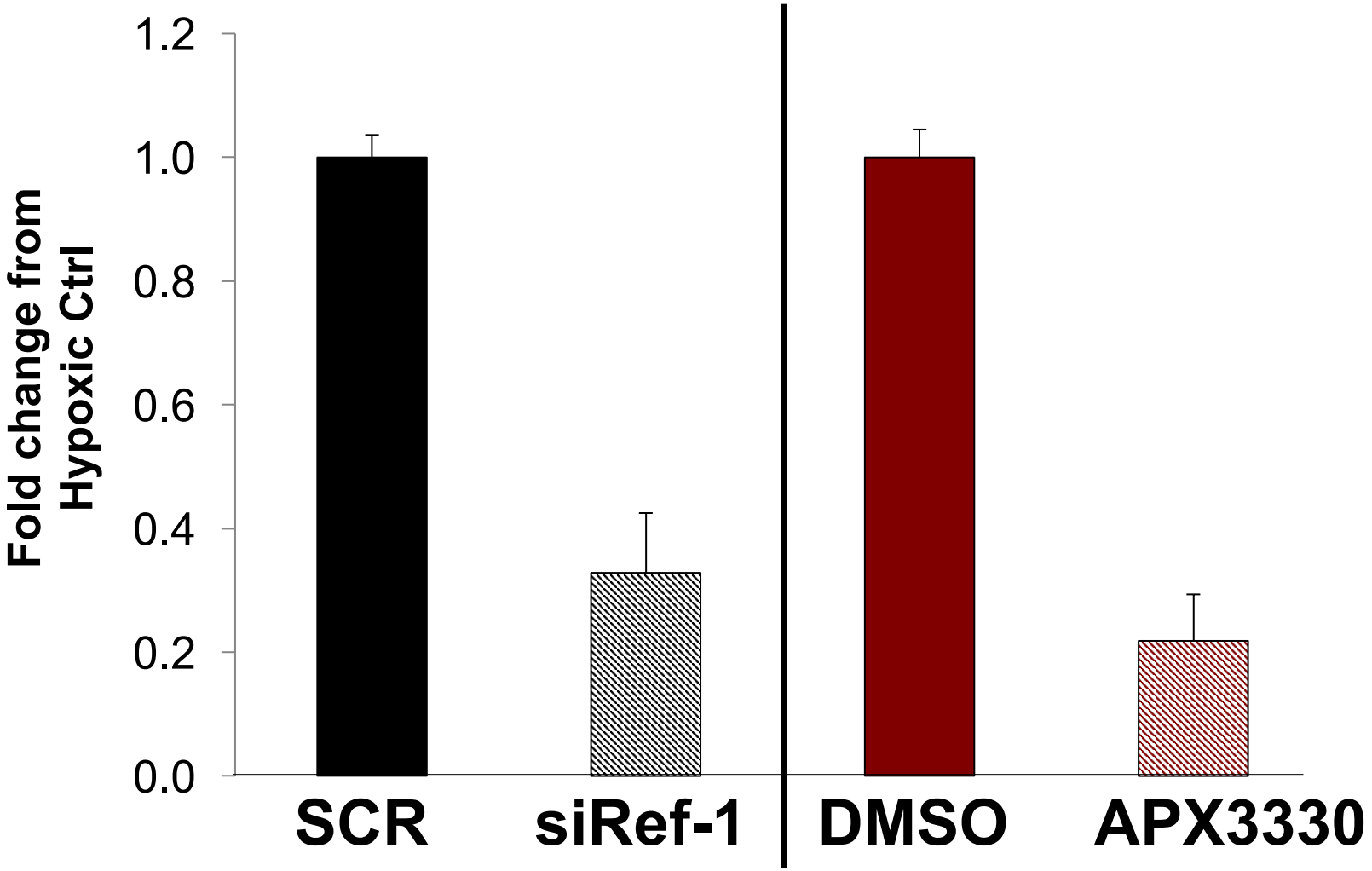
Pa03C cells in 3D:

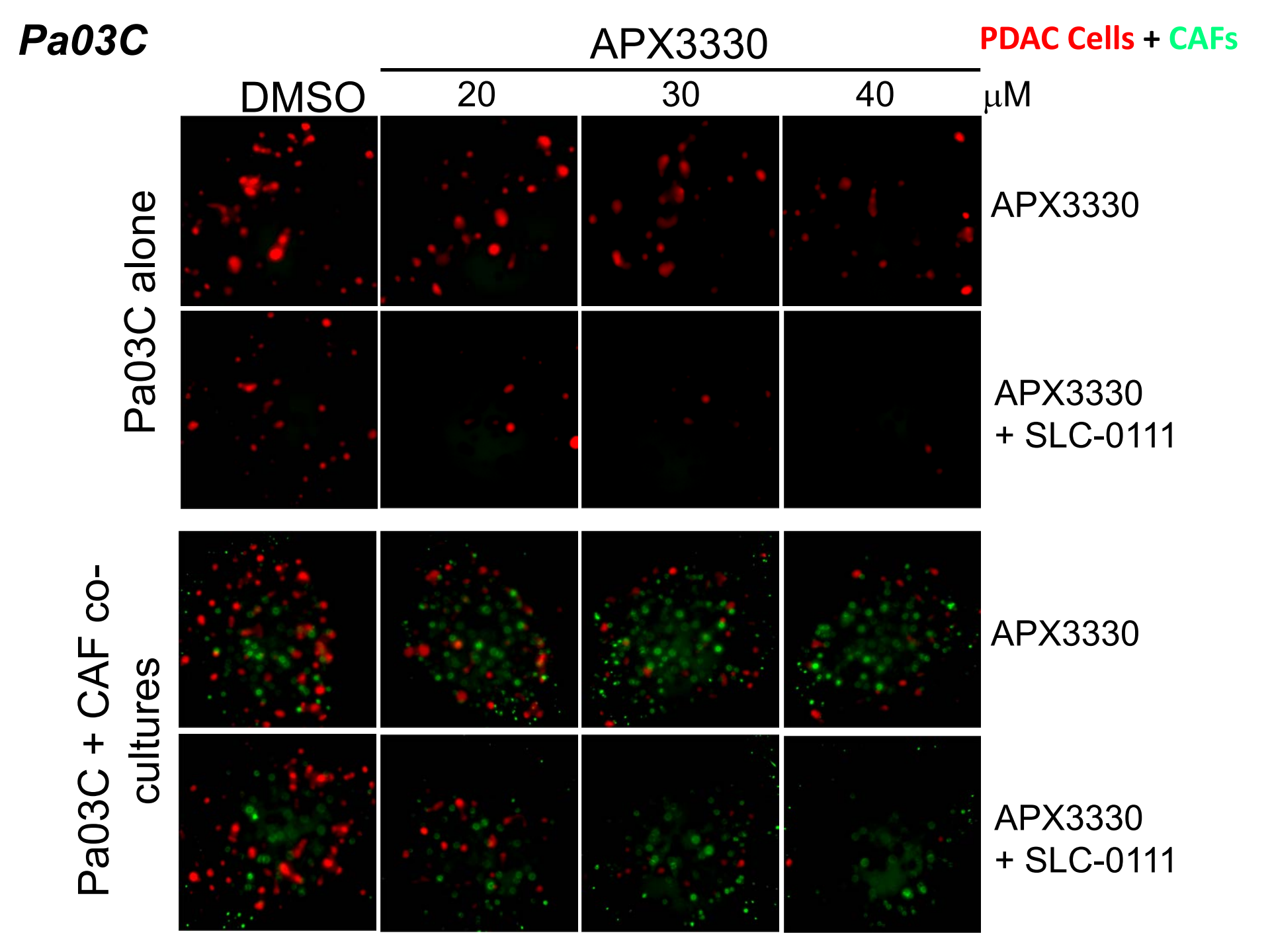
Combo Ref-1 inhibition + Jak2 inhibition




Cytokine / Growth factor Signaling
Hypoxia
Inflammation
CAIX
SLC-0111
Ref-1
HIF1a
APX3330
CAIX
HIF1a
DNA

Hypoxia-Induced CA9 mRNA: Inhibiton by Ref-1 KD and APX3330

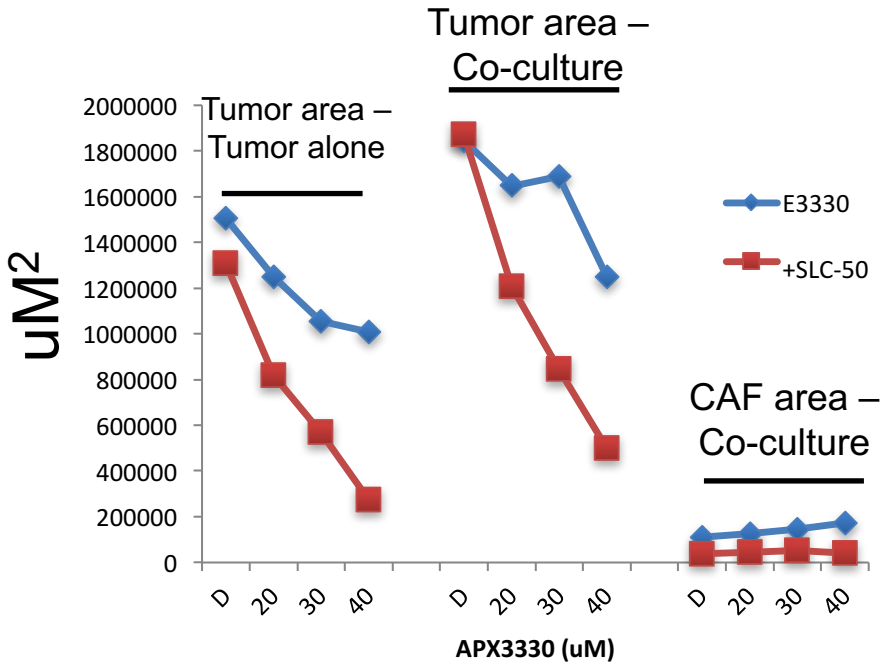



Pa03C
APX3330
PDAC Cells + CAFs
DMSO
20
30
40
μM
Pa03C alone
APX3330
APX3330
+ SLC-0111
Pa03C + CAF co-cultures
APX3330
APX3330
+ SLC-0111

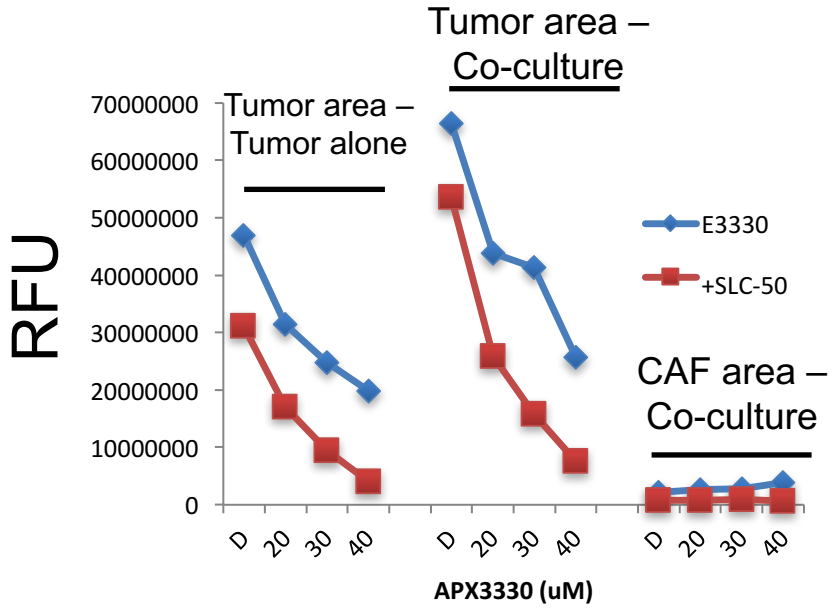
Pa03C cells in 3D:

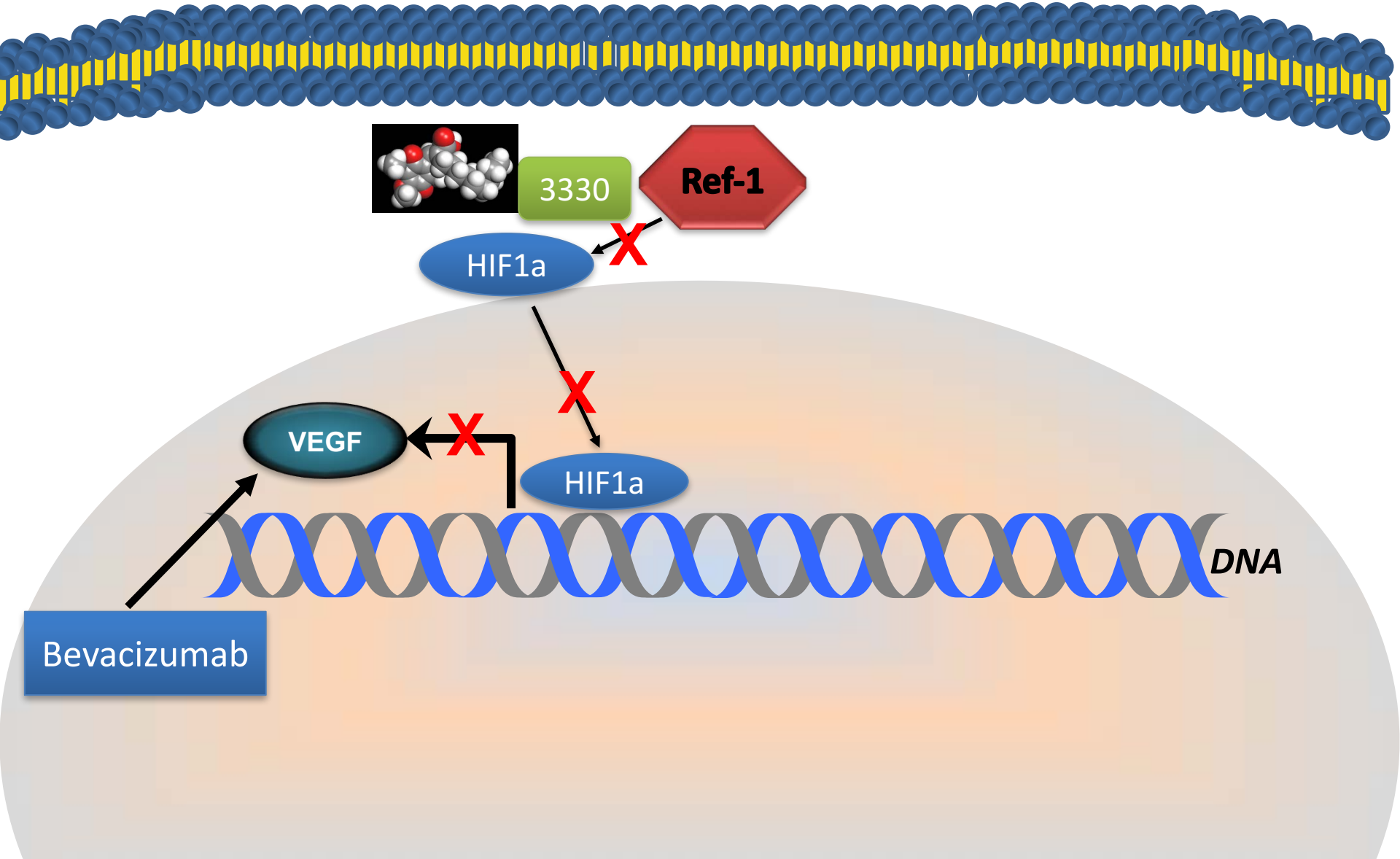
Combo Ref-1 inhibition + CA9/12 inhibition

Area

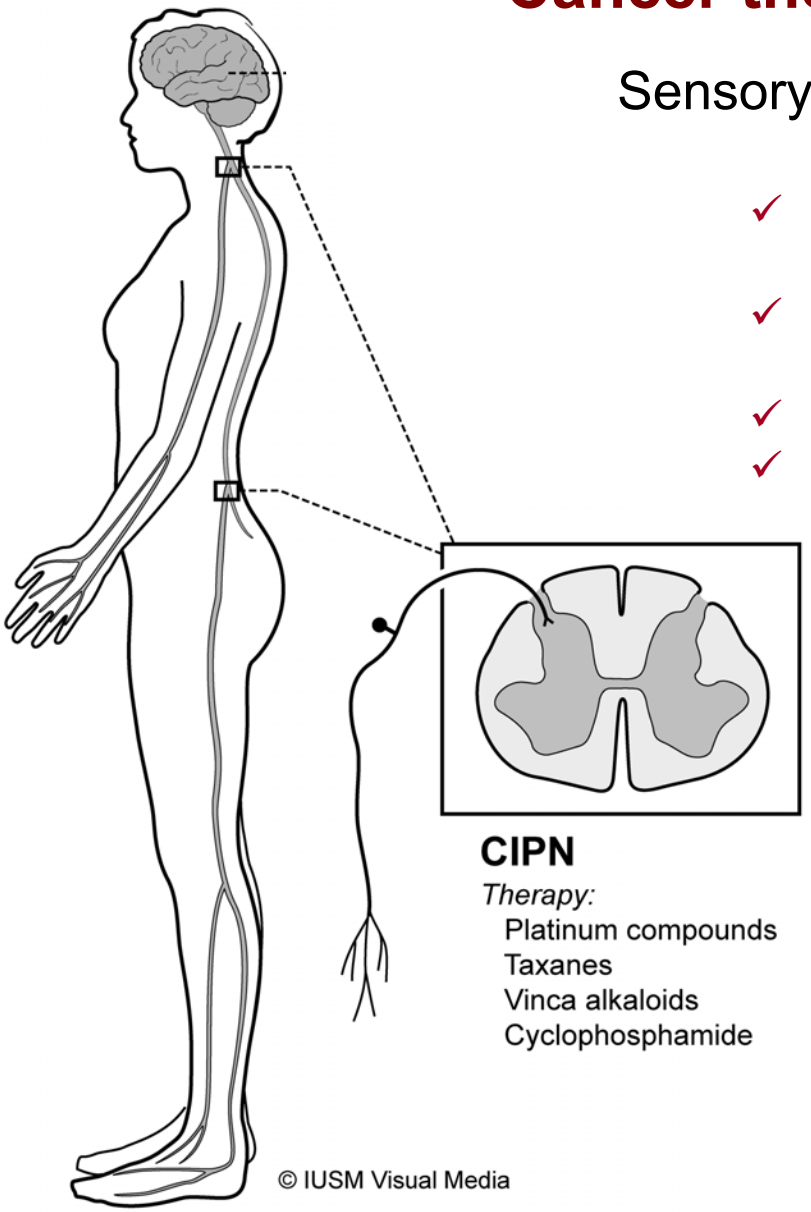


Intensity




3330
Ref-1
HIF1a
VEGF
HIF1a
DNA
Bevacizumab

Cancer therapies that produce CIPN



Sensory neuropathy with symptoms such as:

- ✓ distal parasthesias (tingling, numbness, burning sensations)
- ✓ altered proprioception (awareness of position of one's body)
- ✓ coldness in extremities
- ✓ acute/chronic pain

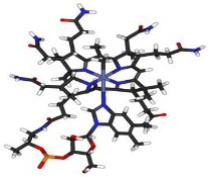
Chemotherapy effects motor neurons less frequently than sensory neurons

Autonomic nervous system dysfunction (palpitations, orthostatic hypotension, impotence) is rarely seen

CIPN

Therapy:	*Symptoms:*
Platinum compounds	Paresthesia
Taxanes	Pain
Vinca alkaloids	Decreased proprioception
Cyclophosphamide	Cold sensitivity

M. Vasko et al. "The Role of DNA Damage and Repair in Neurotoxicity caused by Cancer Therapies" in *DNA Repair in Cancer Therapy: Molecular Targets and Clinical Applications*. (2012) Kelley, M., Ed. Academic Press/Elsevier



Chemotherapy Induced Peripheral Neuropathy (CIPN)

Drugs Associated with CIPN

- Platinum compounds (cisplatin, carboplatin, oxaliplatin)
- Vincristine
- Taxanes (docetaxel, paclitaxel)
- Epothilones (ixabepilone)
- Bortezomib (CIPN occurs in 37%–44% of patients with multiple myeloma)
- Thalidomide (CIPN develops in 20%–40% of patients)
- Lenalidomide

Overall, 40% of patients receiving cisplatin and taxol develop CIPN!

A cross-sectional study of patients with testicular cancer re-evaluated **23–33 years** after finishing treatment showed that CIPN remains detectable in up to 20% of patients, being symptomatic in 10% of them.

The combination of 5-FU and oxaliplatin is frequently used in patients with gastrointestinal cancer, and 92% of patients develop sensory CIPN.

Moya del Pino, Brittany. A Closer Look: Chemotherapy-induced Peripheral Neuropathy. NCI Cancer Bulletin, February 23, 2010. http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2010/022310/page6

Patients used analogies to describe symptoms (Tanay *et al*. 2016)

- ‘Severe buring in fingertips’, ‘Like putting them (fingers) on hot stove’,
- ‘A strip of numbness across fingers’ (Boehmke & Dickerson 2005)

- ‘Like fingernails on a chalkboard’, ‘Pain like needle stuck in my toes’
- (Bakitas 2007)

- ‘Walking on hot coals’, ‘Walking on a rock on the bottom of your feet’, ‘Sandpaper at the bottom of your feet’, ‘Something crawling’
- (Tofthagen 2010b)

- ‘Walking in mud’, ‘Bunched up socks’, ‘Walking on sandpaper’,
- ‘Getting a cast off’, ‘Blob of numbness’, ‘Feet are asleep’
- (Speck *et al*. 2012)

Uses of platinum agents in **pediatric oncology:**

Cisplatin and Carboplatin are used in:

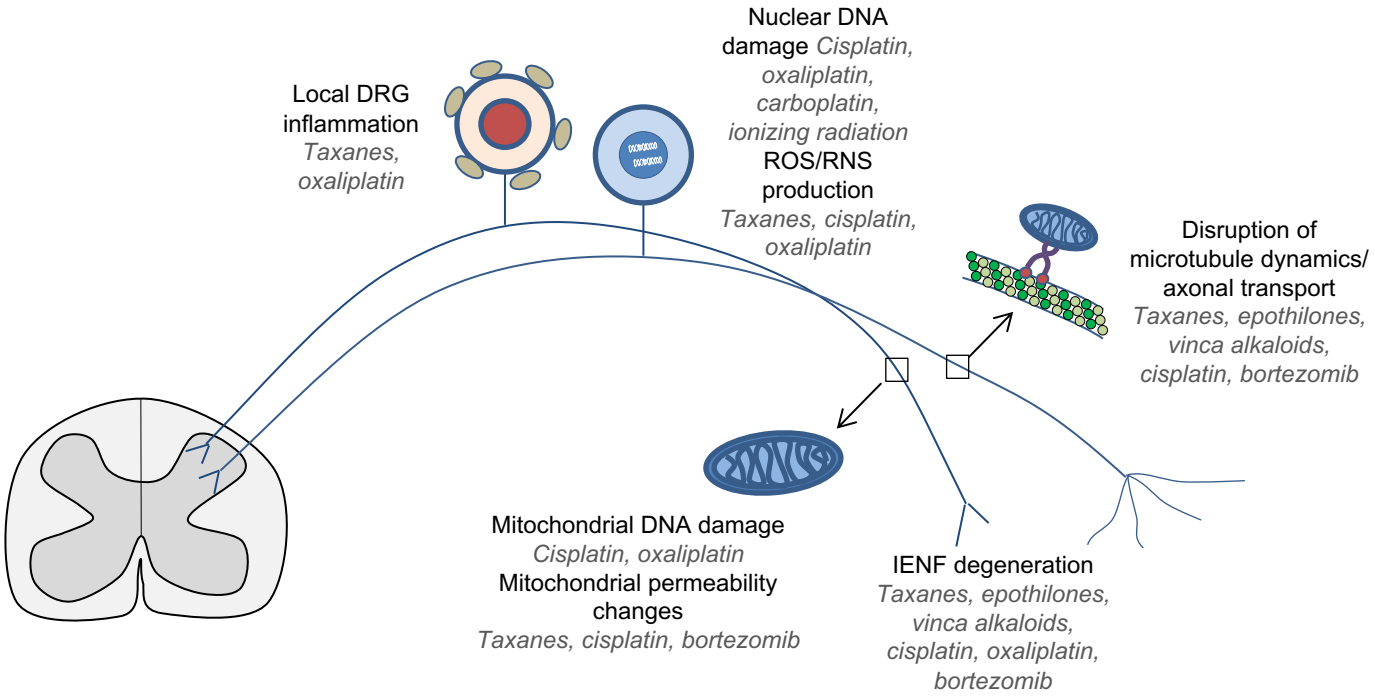
Neuroblastoma
Germ cell tumors
Osteosarcoma
Hepatoblastoma
Brain tumors
Retinoblastoma

Oxaliplatin is not used.

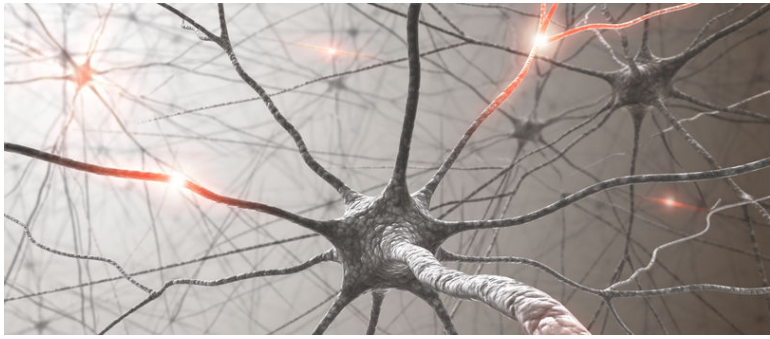
Estimates of the number of **adult** patients treated annually with either **cisplatin, oxaliplatin or carboplatin** are approximately > **200,000** a year:

- ✓ 50,000 patients with metastatic colorectal cancer
- ✓ 20,000 with stage III colon cancer
- ✓ 12,000 with pancreatic cancer
- ✓ 25,000 with gastroesophogeal, and
- ✓ 10,000 with head and neck cancer.
- ✓ 4,000 with ovarian cancer
- ✓ etc

Putative sites of neuronal dysfunction following specific anticancer drug treatments, indicated in italics.



DNA Repair in Neurons



DNA damage in neurons is repaired using these pathways:

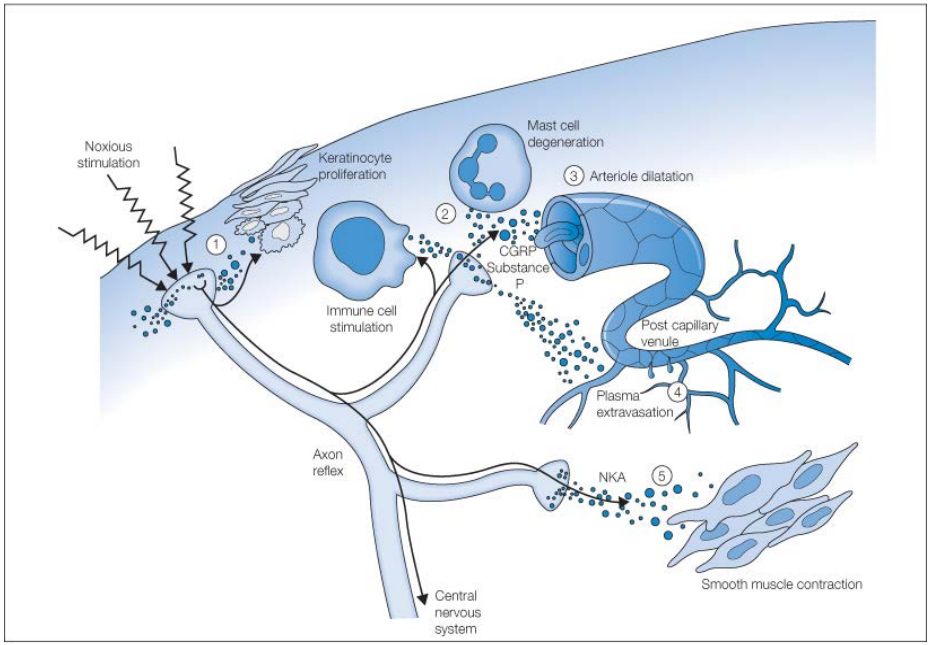
	Nucleus	Mitochondria
Direct Repair		?????
BER	BER	BER
NER	NER	NER
MMR	MMR	MMR
HR / NHEJ	?????	

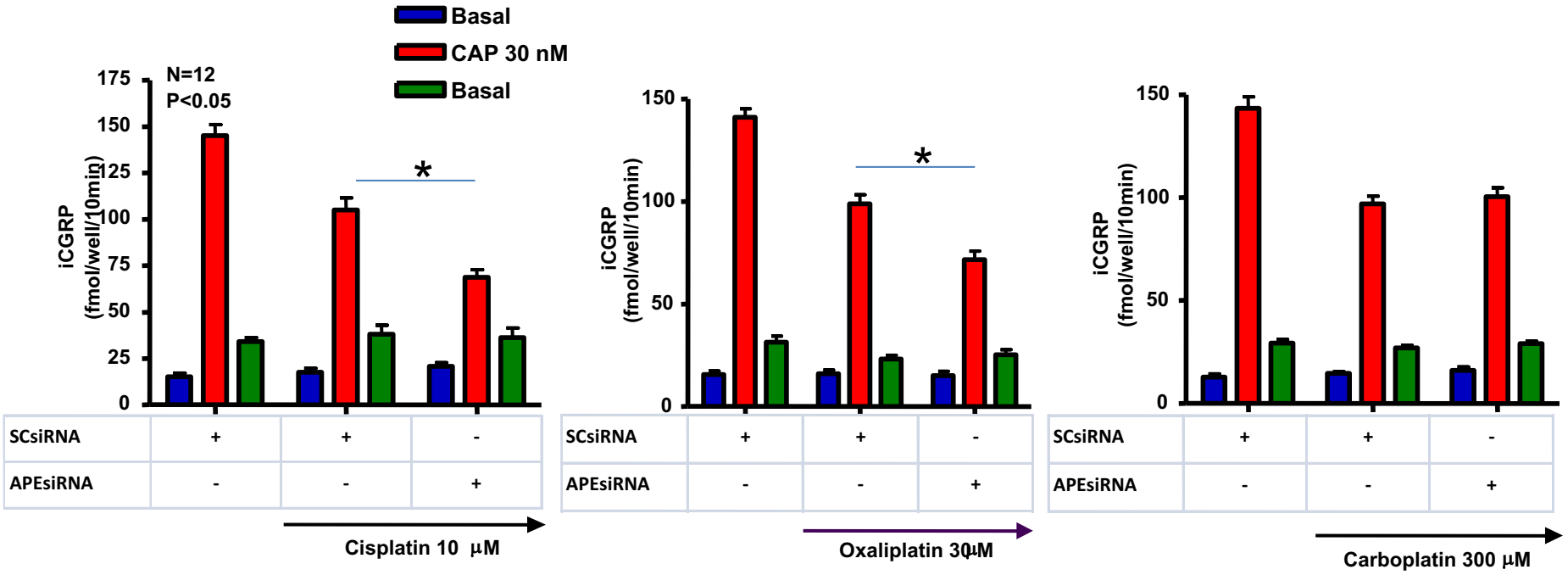
Fishel, ML., Vasko, MR. and Kelley, MR. (2006) DNA repair in neurons: So if they don't divide what's to repair? Invited and peer-reviewed review. *Mutation Research* 614(1-2); 24-36.

Oxidative DNA damage and crosslinks induced by the platinum drugs

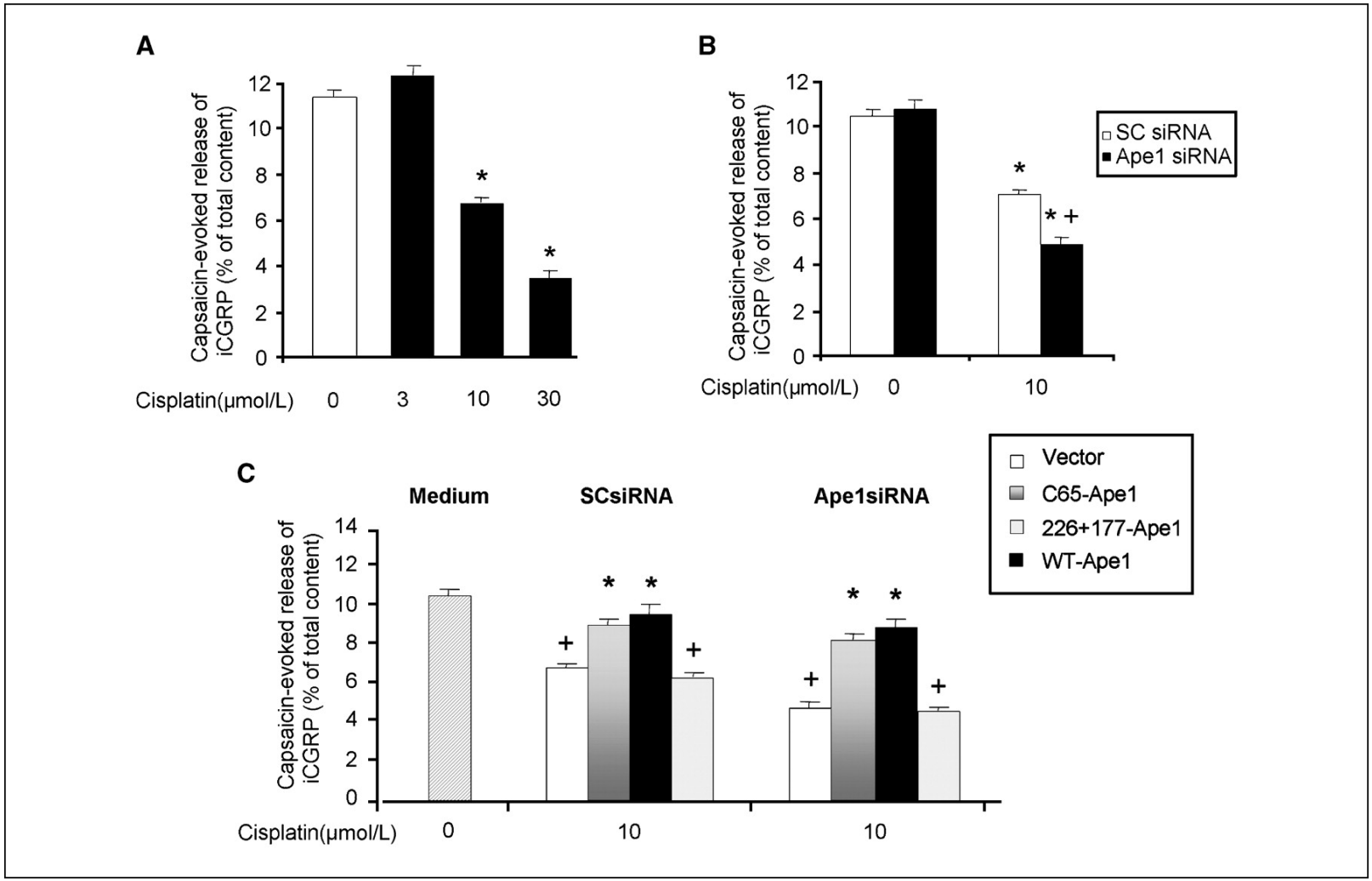
	Cisplatin	**Oxaliplatin**	**Carboplatin**
Oxidative DNA Damage	Yes High	Yes Moderate	No
Type of Crosslink	**Intra**-strand predominant **Pt-d(GpG) (1,2-intrastand) >90%** Pt-d(ApG) (1, 2-interstrand crosslink)	**Inter**-strand predominant Pt-d(GpG) (1,2-intrastand) **Pt-d(ApG) (1,2-interstrand crosslink) >90%**	**Intra**-strand predominant **Pt-d(GpG) (1,2-intrastand) >90%** Pt-d(ApG) (1,2-interstrand crosslink)

APE1 knockdown effect on cisplatin, oxaliplatin and carboplatin-induced iCGRP release in DRG cells





Effect of altered Ape1 levels on cisplatin-induced iCGRP release from sensory neuronal cells.

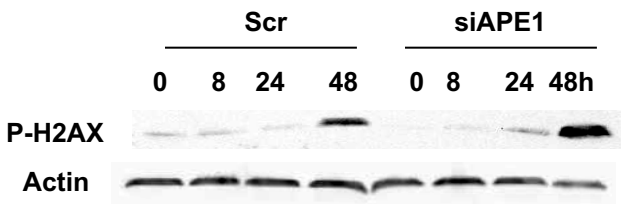


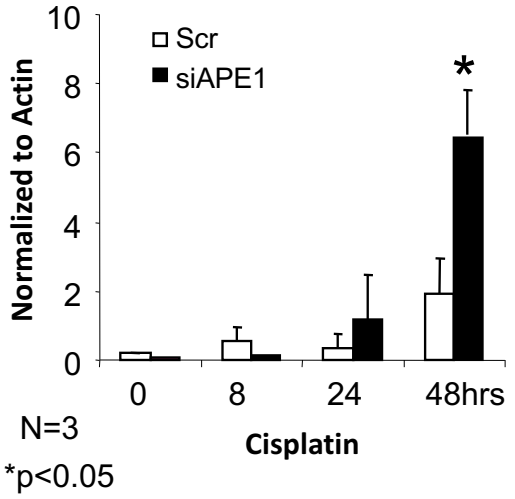
Yanlin Jiang et al. Cancer Res 2008;68:6425-6434

AACR American Association for Cancer Research
Cancer Research

Effect of knocking Ape1 down on cisplatin, oxaliplatin and carboplatin-induced DNA damage (p-H2AX) in DRG cells

A. Cisplatin(50uM)

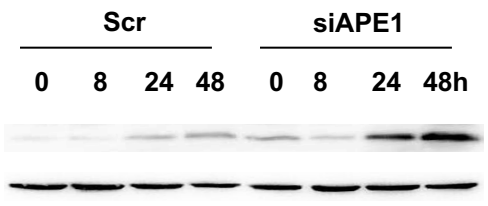


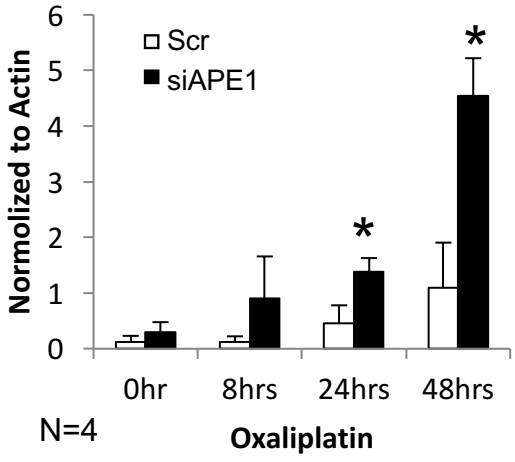


N=3

*p<0.05

B. Oxaliplatin(300uM)

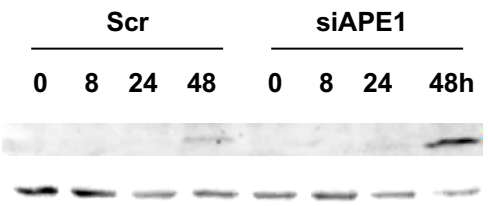


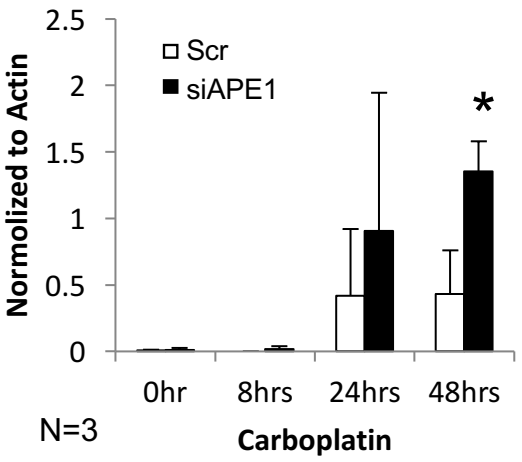


N=4

*p<0.05

C. Carboplatin(500uM)

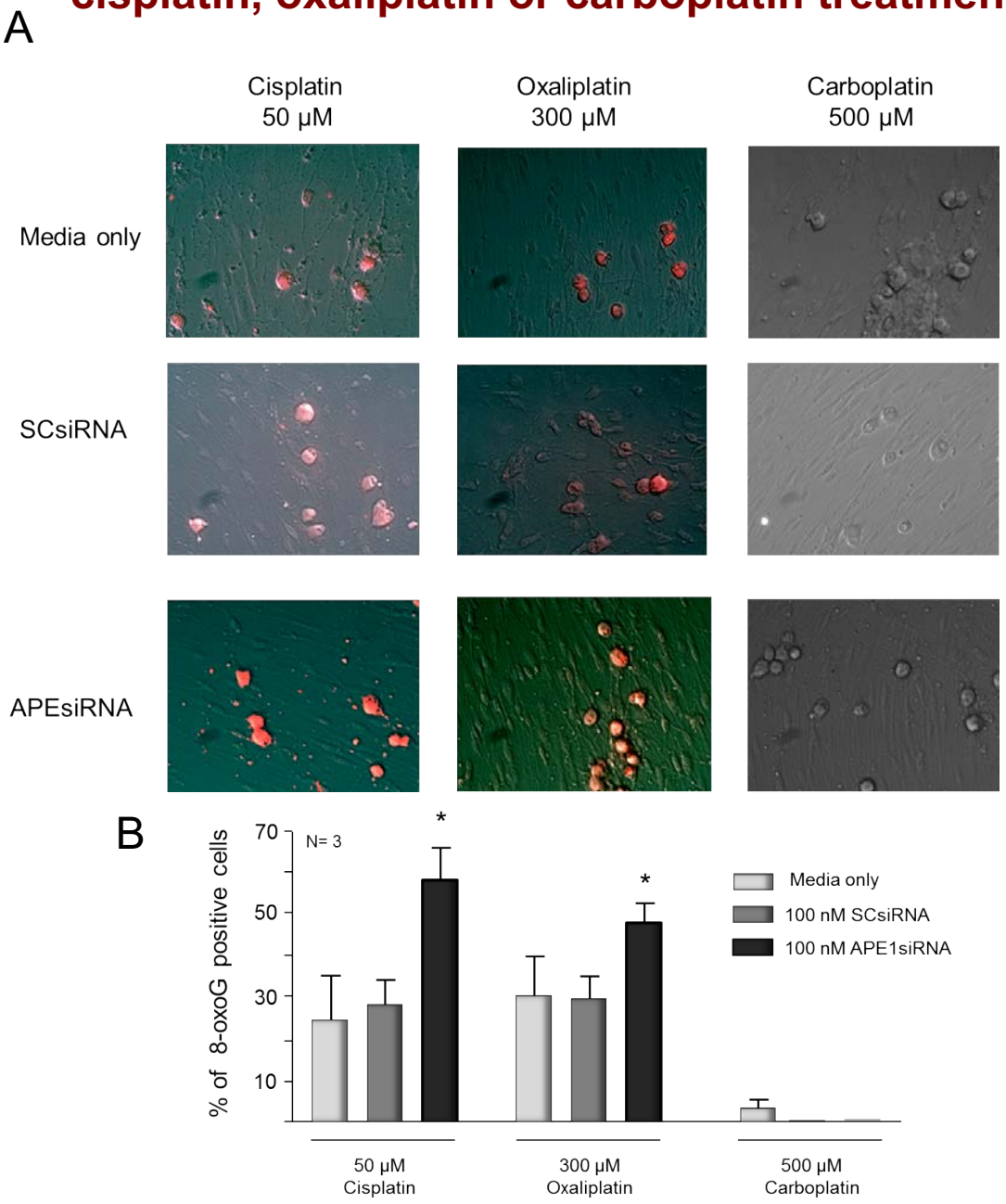




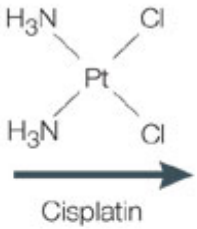
N=3

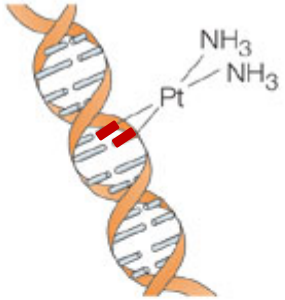
*p<0.05

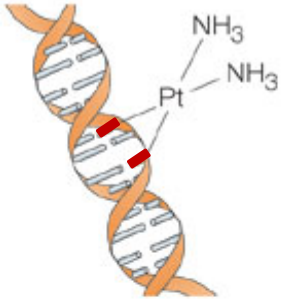
8oxoG levels in DRG Neuronal Cultures following APE1 KD and cisplatin, oxaliplatin or carboplatin treatments

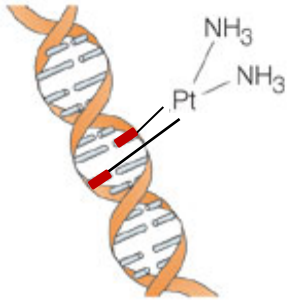


Assessment of Cisplatin-Induced DNA damage









Pt-GpG (1, 2-intrastrand crosslink) **>90%**

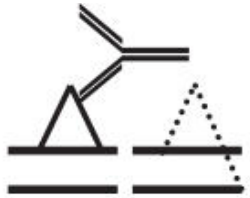
Pt-GpG (1,3-intrastrand crosslink) **<5%**

Pt-GpG (interstrand crosslink) **<5%**

DNA Fragmentation

mAb specific to 1,2-Pt-GG

DNA slot blot

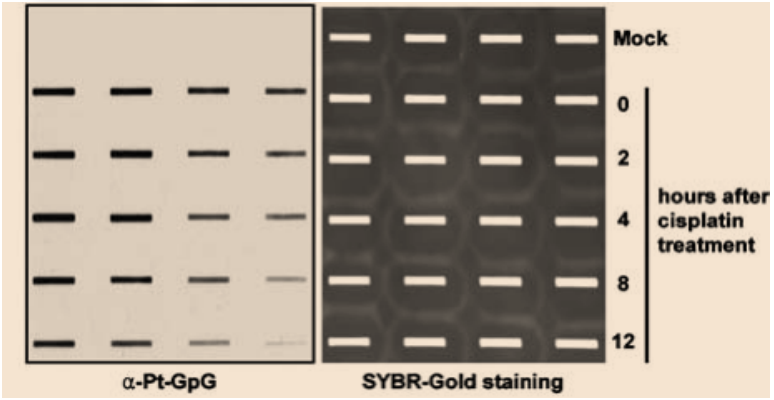


1,2-Pt-GG G-Pt-G

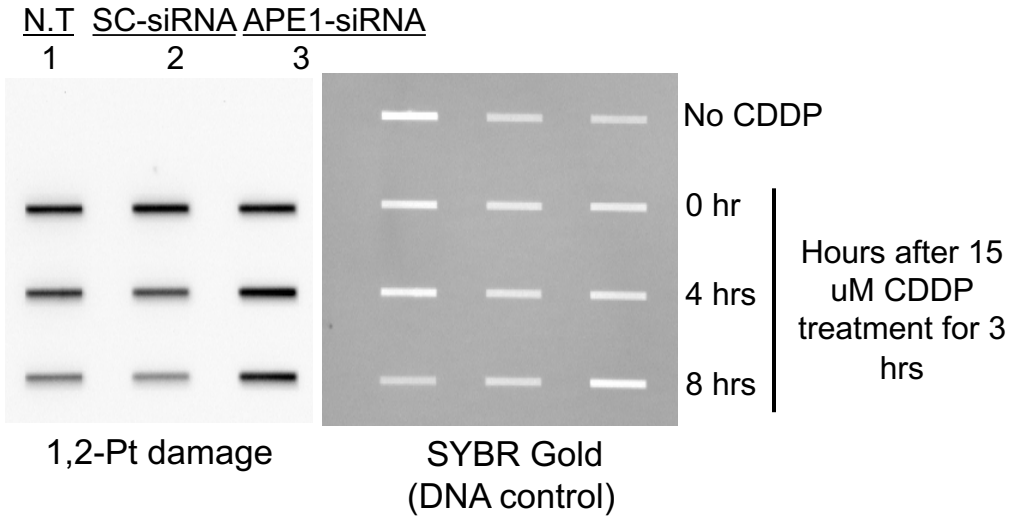
1,3-Pt-GG

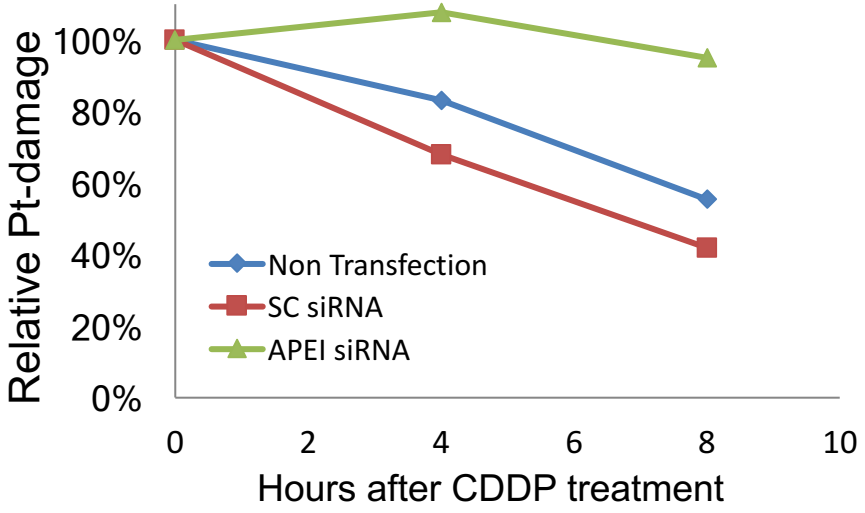
cisplatin conc.

30 uM 10 uM

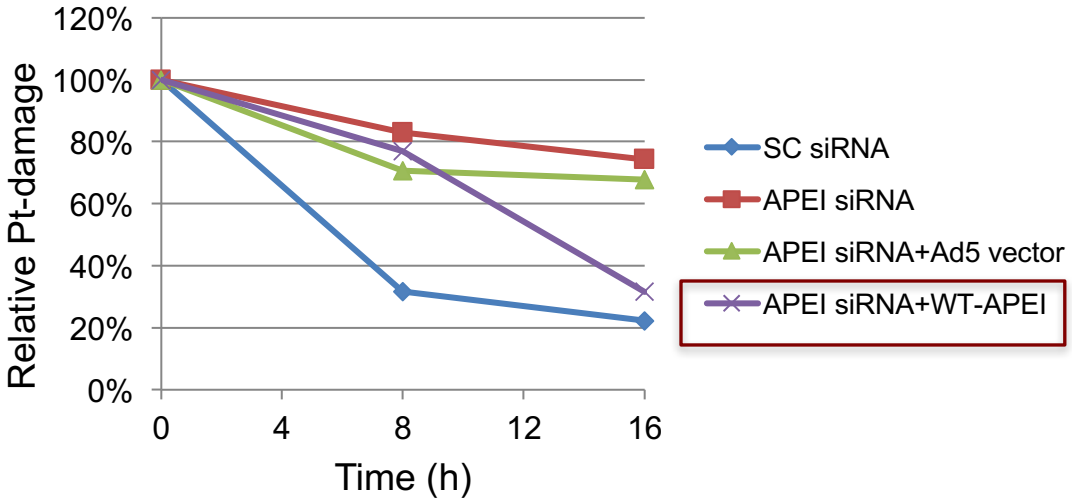


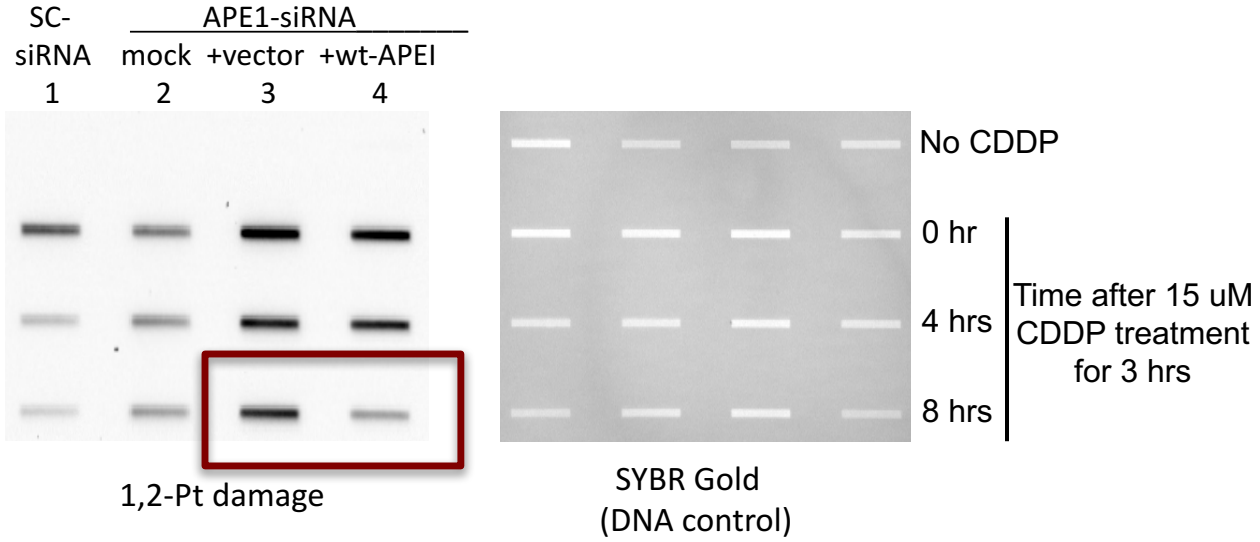
Targeted inhibition of APE1 expression in rat neuronal cells significantly reduces removal of Pt-damage



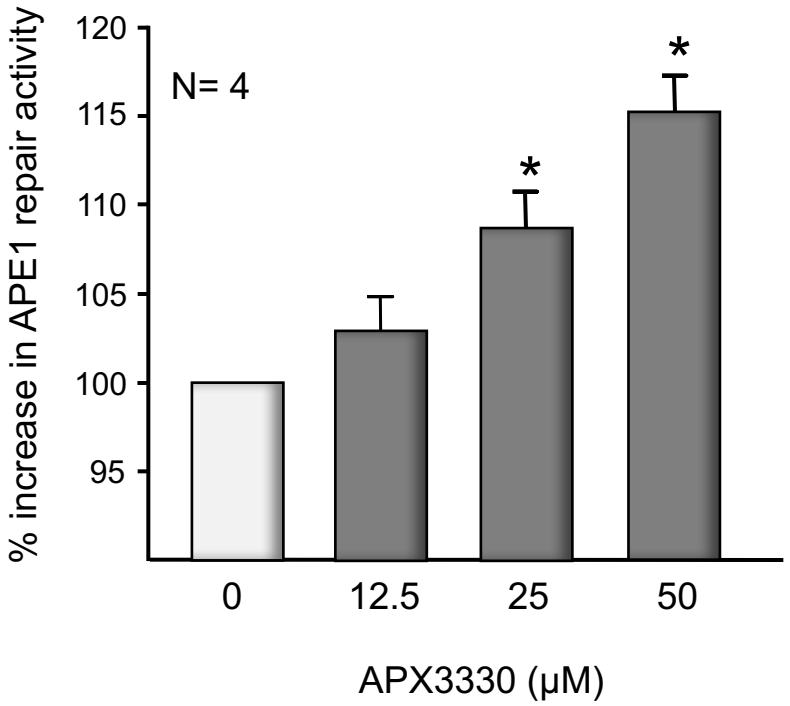


Add-back of wt-APE1 restores repair of 1,2-Pt-GpG damage in DRG cells treated with Ape1-siRNA





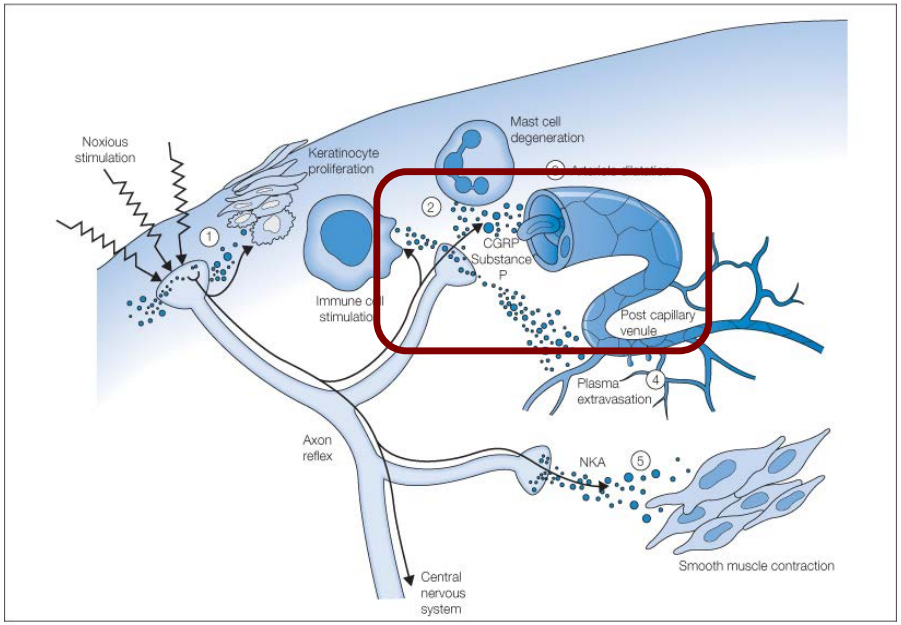
APX3330 enhances APE1 endonuclease DNA repair activity in DRG cells

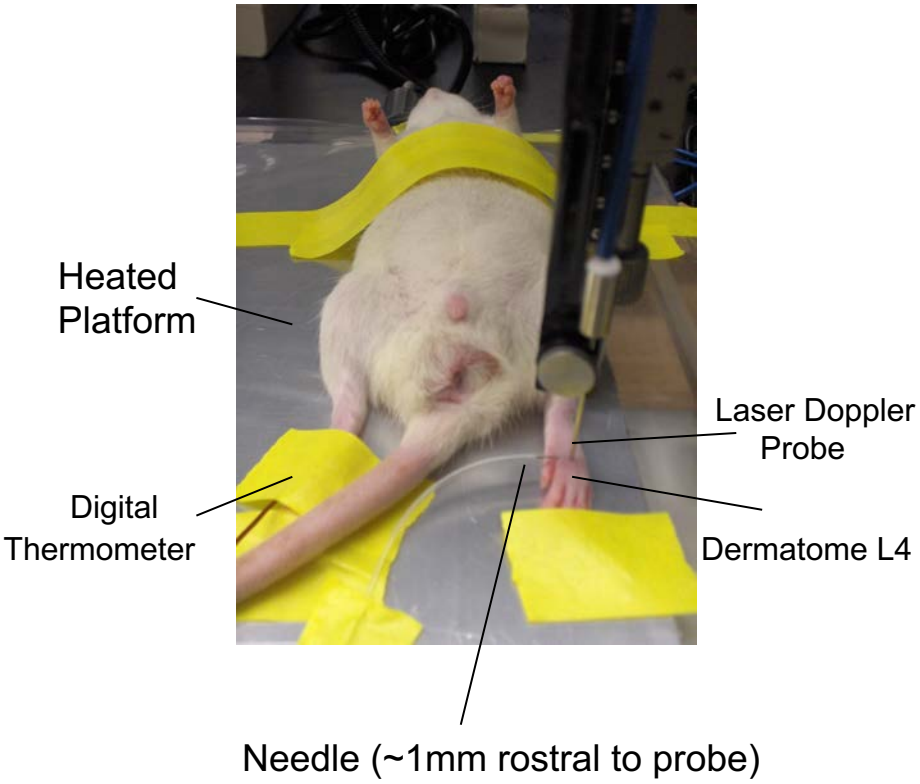


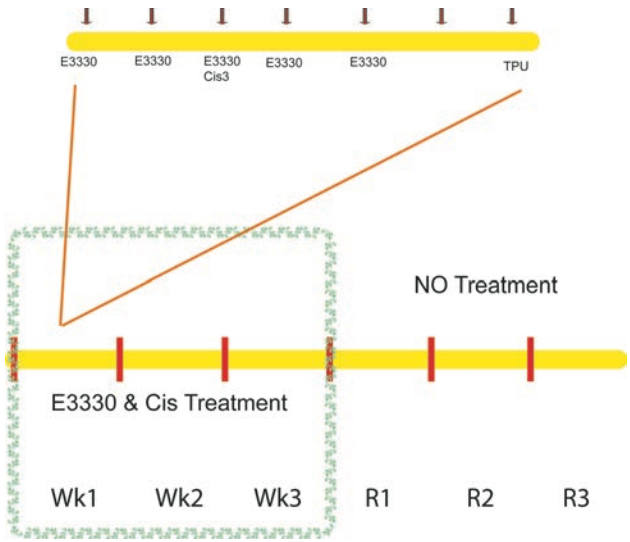
Each column is the mean ± SEM of the percent increase in APE1 endonuclease activity using the established AP endonuclease assay. An asterisk indicates a statistically significant difference between cultures treated with vehicle and those treated with E3330 using Student's *t*-test.

Kelley MR, Jiang Y, Guo C, Reed A, Meng H, Vasko MR. (2014) Role of the DNA base excision repair protein, APE1 in cisplatin, oxaliplatin, or carboplatin induced sensory neuropathy. *PlosOne.* Sept4;9(9):e106485. DOI: 10.1371/journal.pone.0106485. PMCID: PMC4154694

Peripheral blood flow is regulated by CGRP; i.e. measuring iCGRP release *in vitro* or blood flow *in vivo* is indicator of DRG function



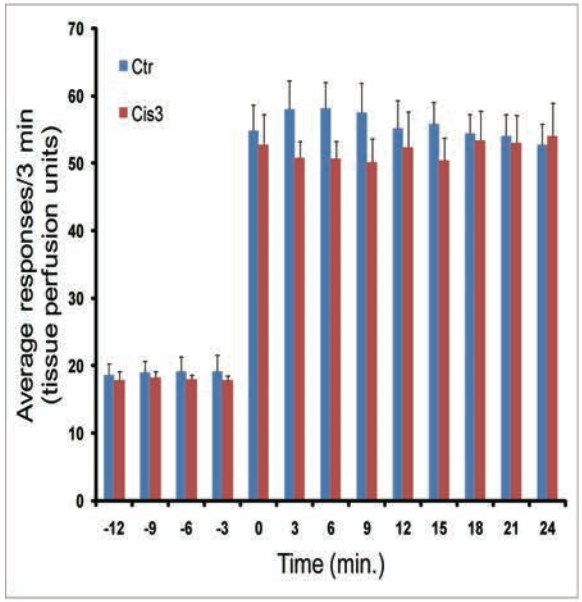




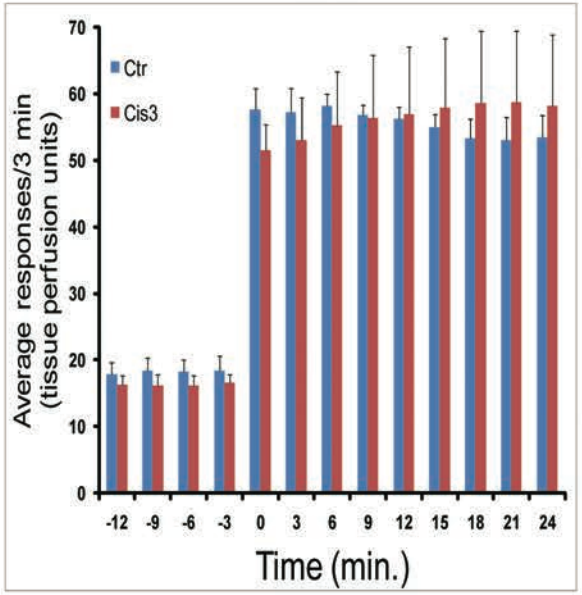
Chemoprotective experiment using APX3330 and cisplatin

Cisplatin 3mg/kg

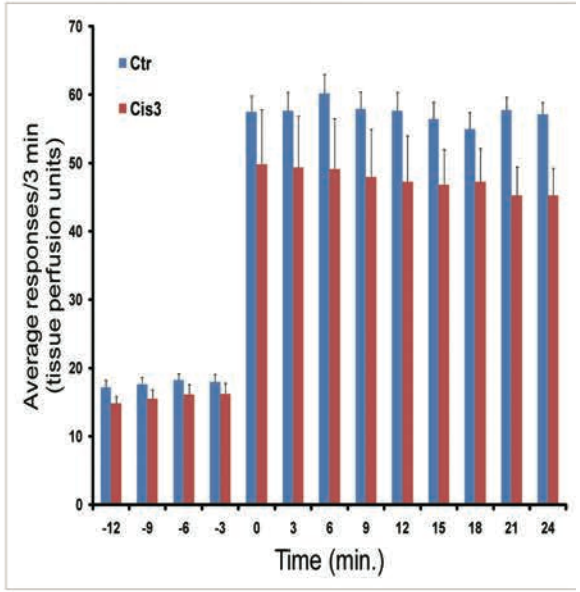
WK1



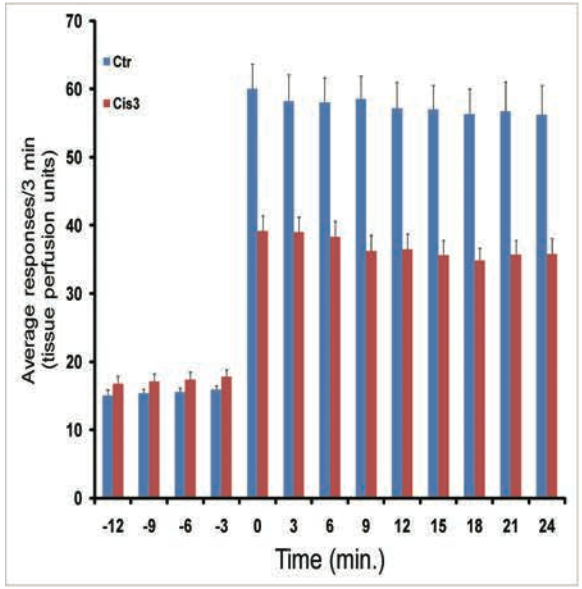
WK2



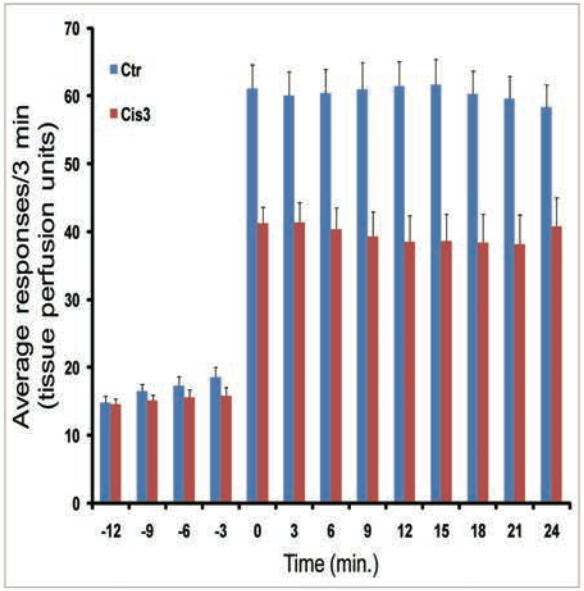
WK3



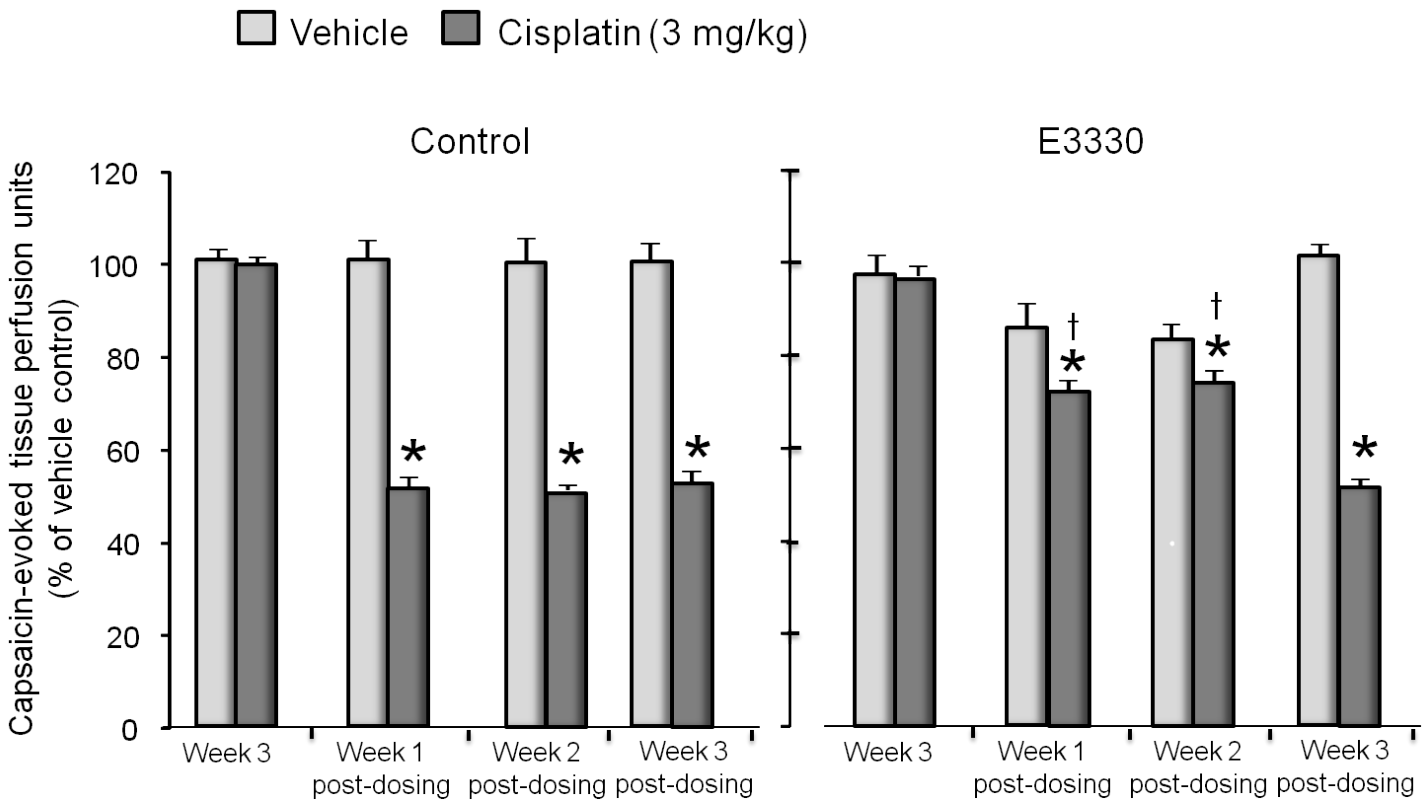
R1

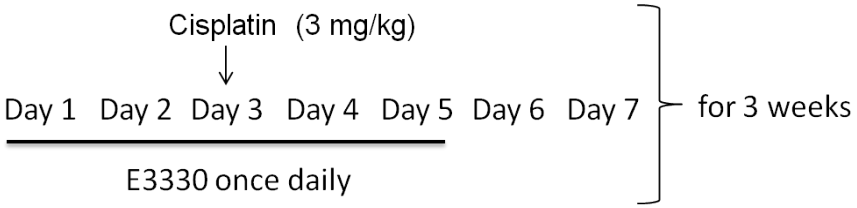


R2

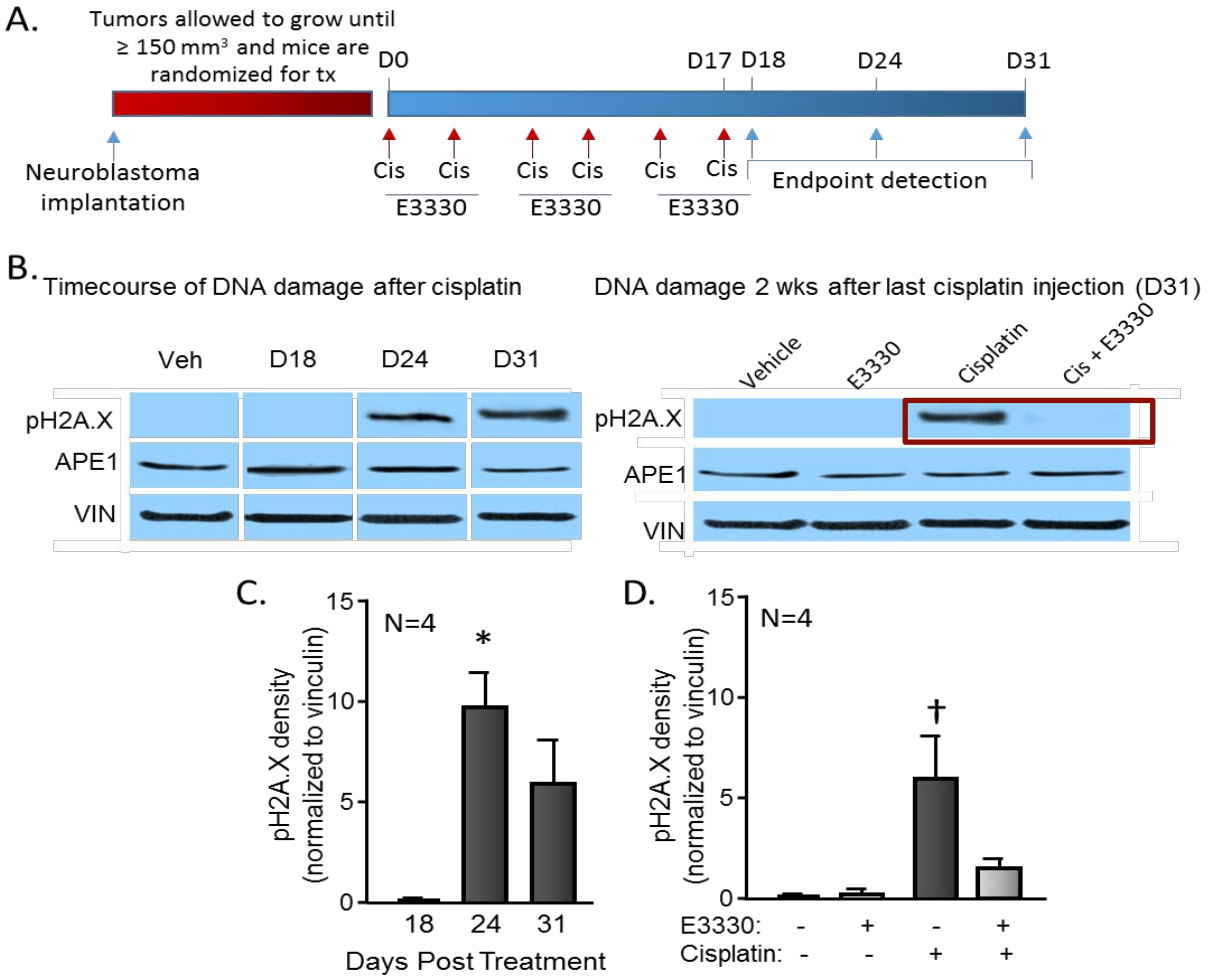


APX3330 treatment (25 mg/kg) can reverse cisplatin neurotoxicity in R1 and R2





APX3330 attenuates neurotoxicity induced by systemic administration of cisplatin to neuroblastoma tumor-bearing mice



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- *Emery T. Goossens (PU-Stats)*
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