

Therapeutic targeting neuraminidase-1 in multi-stage of tumorigenesis

Myron R. Szewczuk

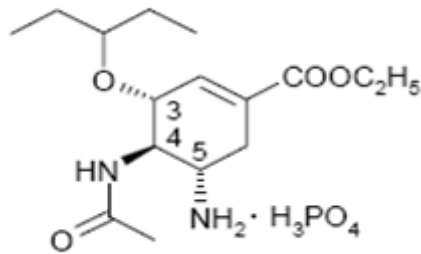
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HIGHLIGHTS....

- **An innovative and promising entirely new targeted therapy for cancer.**
- **Mammalian neuraminidase-1 (Neu1) in complex with matrix metalloproteinase-9 and G-protein coupled receptor tethered to RTKs and TLRs is identified as a major target in the multi-stage of tumorigenesis.**
- **Preclinical studies support an entirely new cancer targeted therapy:**
 - **unaffected by mutations of growth factor receptors,**
 - **blocks tumor neovascularization,**
 - **overcomes chemo-resistance of tumors,**
 - **blocks immune-mediated tumorigenesis,**
 - **blocks tissue invasion and metastasis.**

Therapeutic targeting neuraminidase-1 in multi-stage of tumorigenesis

Oseltamivir phosphate

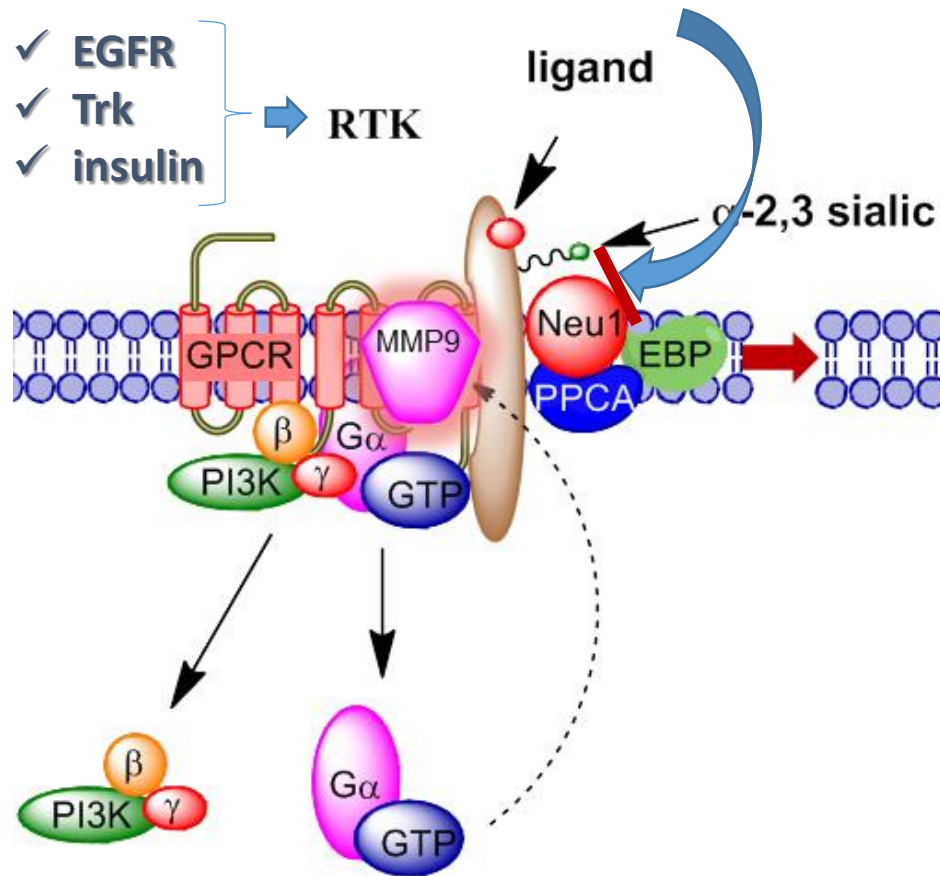


Published:

✓ TLR-4, -7 & -9

✓ EGFR
✓ Trk
✓ insulin

RTK



- Therapeutic efficacy of oseltamivir phosphate alone or in combination with chemotherapeutics
- tumor **growth** and **metastatic spread, tumour neovascularization** and **chemo-resistance**
- **pancreatic, breast and ovarian cancers**
- heterotopic xenograft of tumors growing in RAGxGy double mutant mice

Cellular Signalling 25 (2013) 2587-2603

A novel epidermal growth factor receptor-signaling platform and its targeted translation in pancreatic cancer[☆]



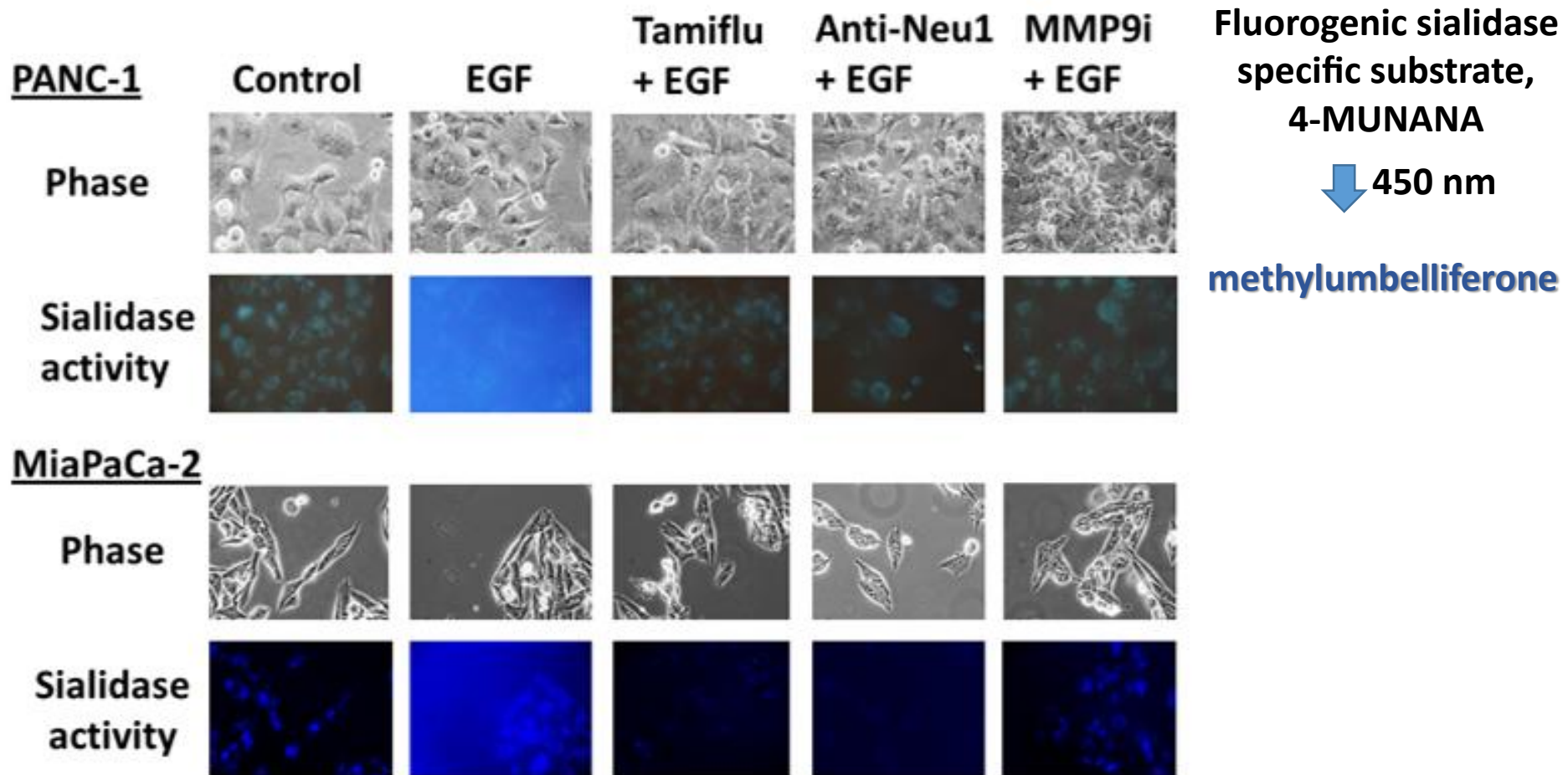
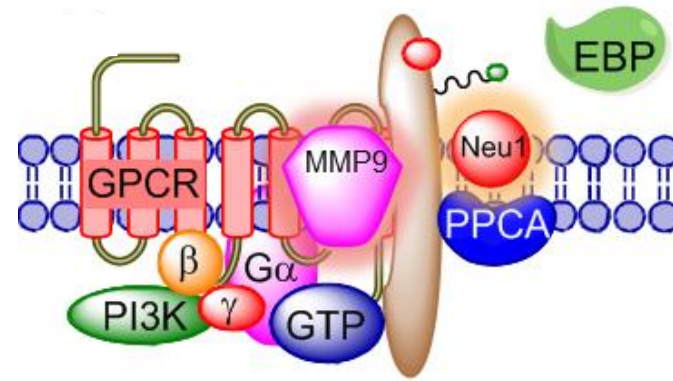
Alanna M. Gilmour¹, Samar Abdulkhalek¹, Timothy S.W. Cheng², Farah Alghamdi, Preethi Jayanth³, Leah K. O'Shea, Olivia Geen, Luis A. Arvizu, Myron R. Szewczuk^{*}

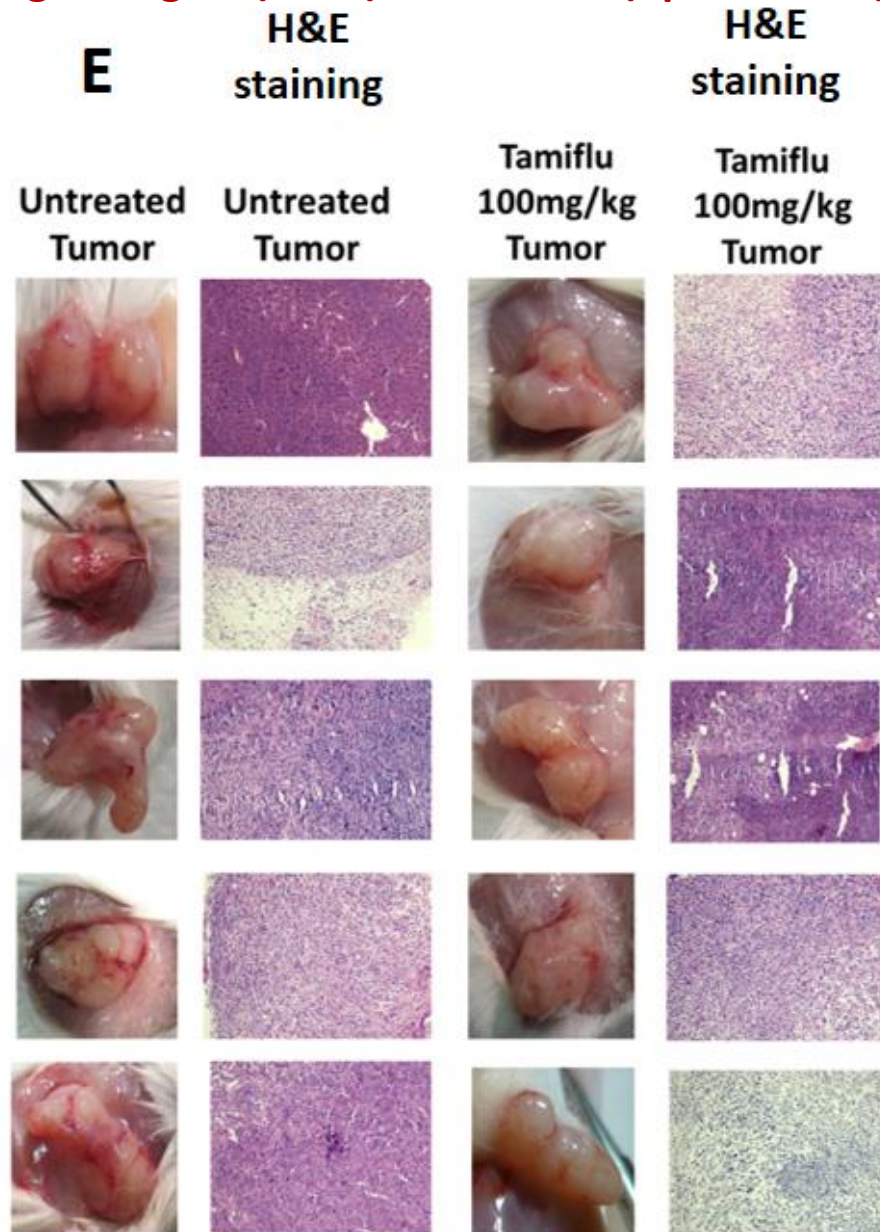
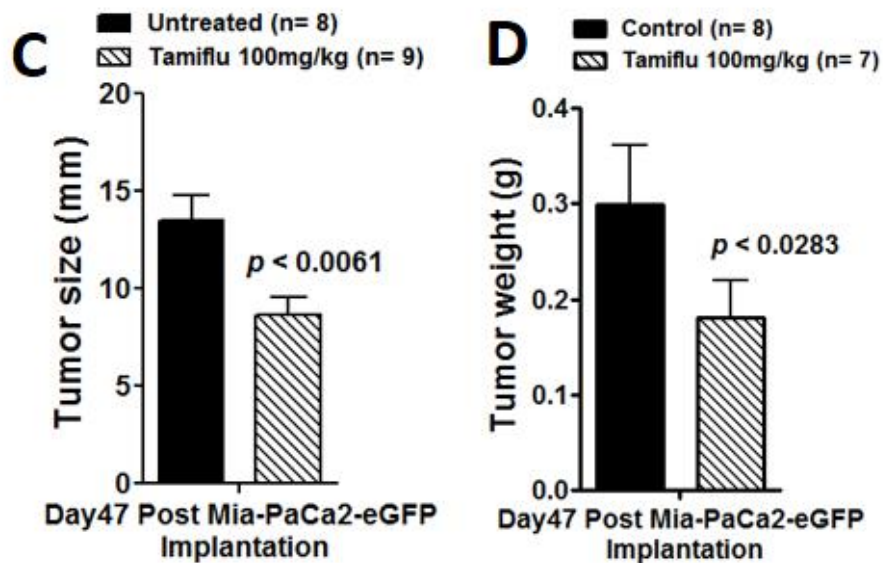
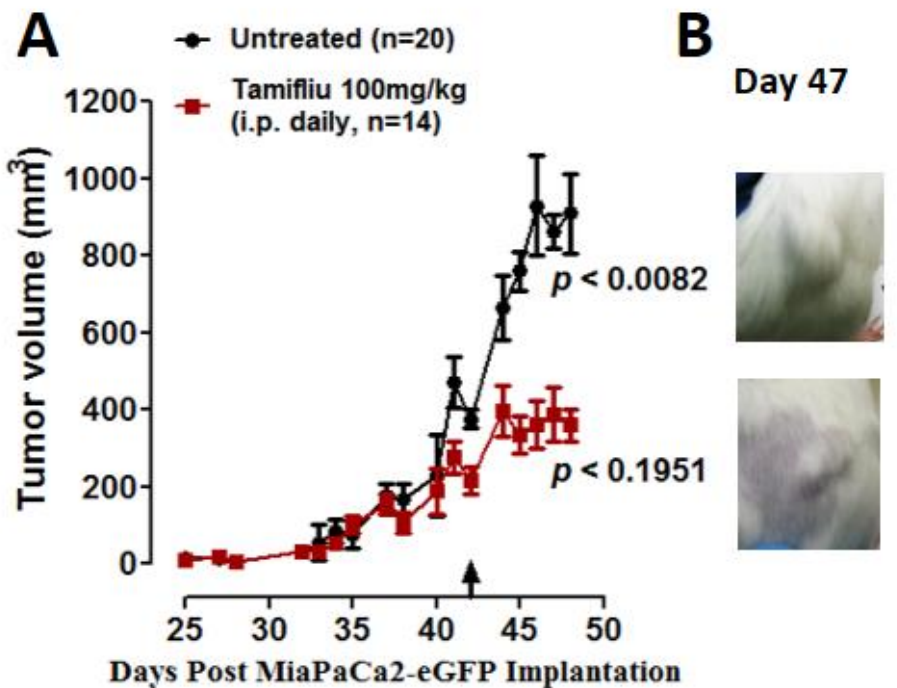
Department of Biomedical & Molecular Sciences, Queen's University, Kingston, ON K7L3N6, Canada

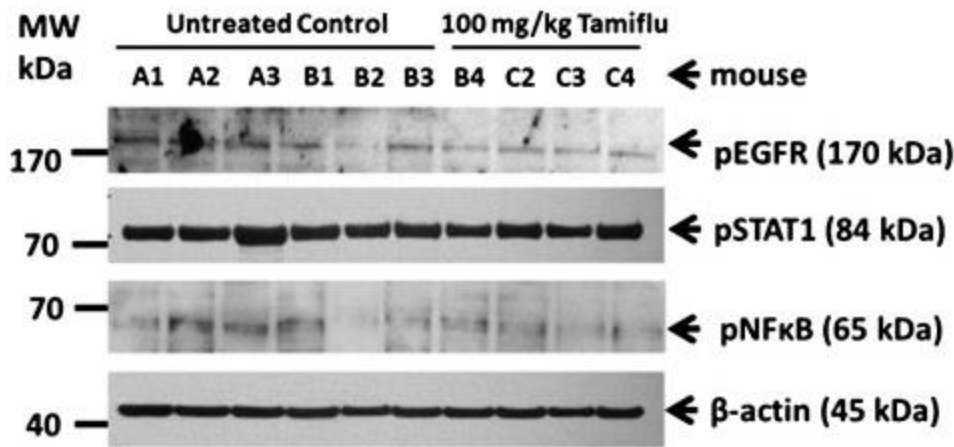
Highlights

- EGFR is fully glycosylated on 8 of the 11 Asn-X-Ser/Thr (X ≠ Pro) canonical N-glycosylation sites; two of the sites are not glycosylated, and one is partially glycosylated.
- The mechanism(s) behind epidermal growth factor (EGF)-induced receptors is unknown.
- The modification of glycosylation on EGF receptors involves the activation of Neu1.
- EGF binding receptor activates neuromedin B receptor (NMBR or BB1) GPCR–Neu1–MMP-9 crosstalk tethered to EGFR at the ectodomain on the cell surface.

Sialidase Assay on Live Pancreatic Cancer Cells

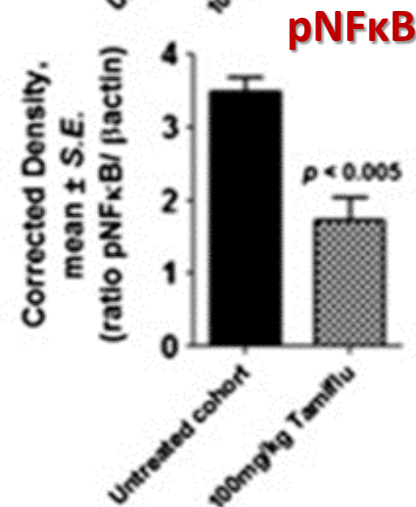
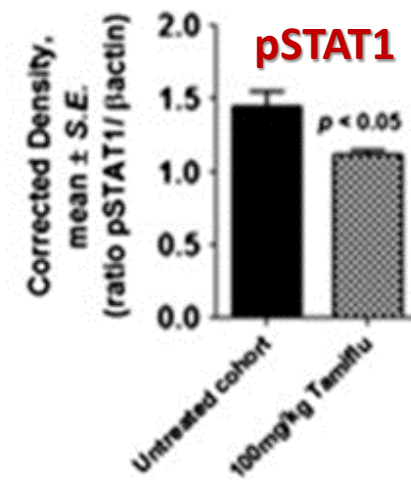
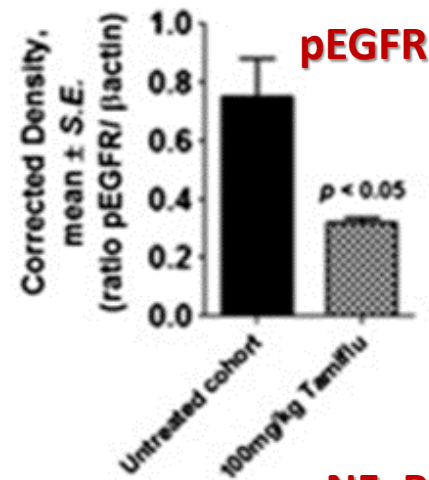






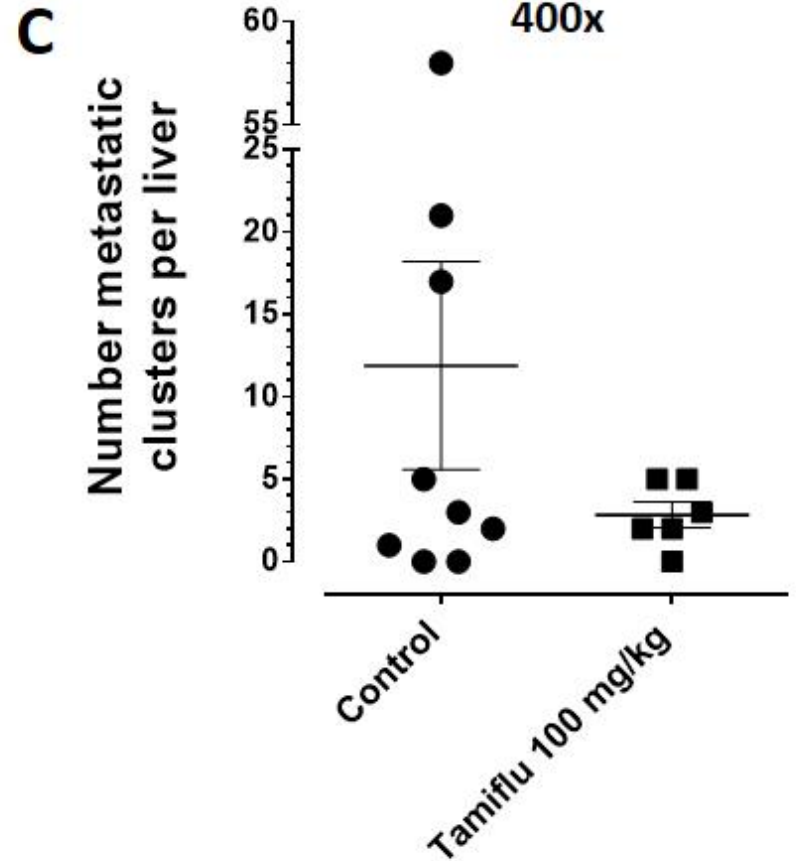
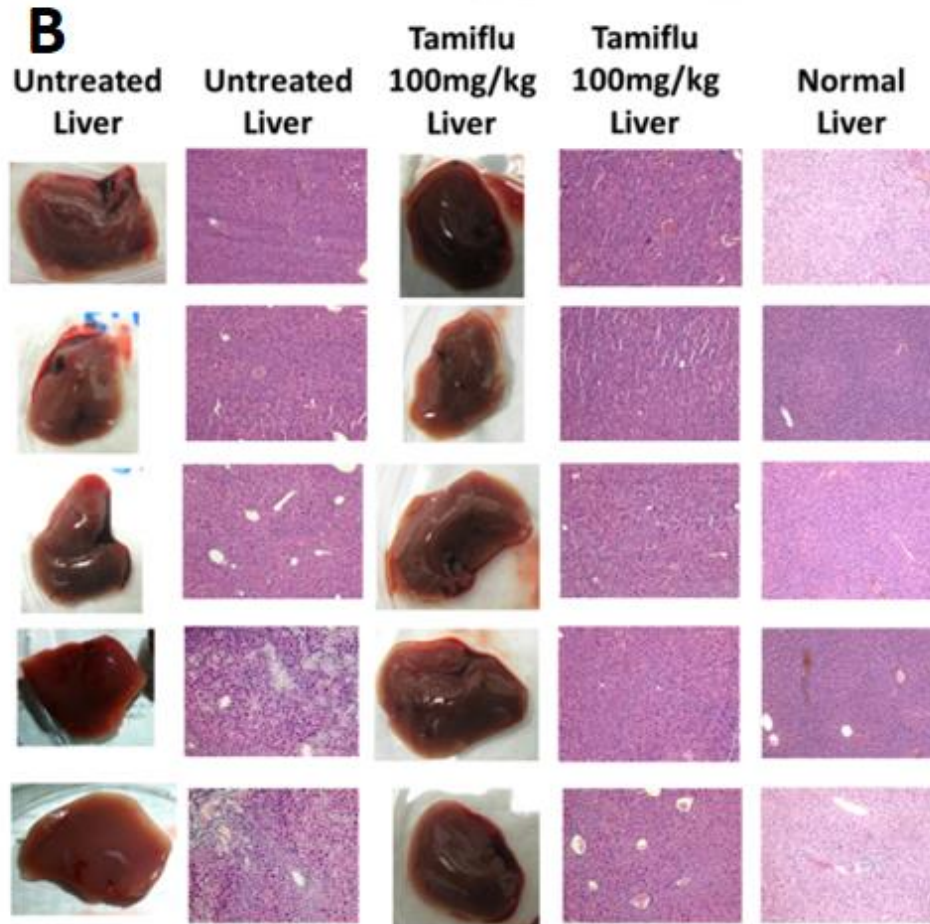
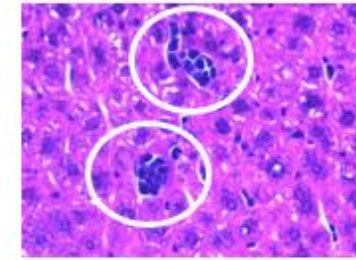
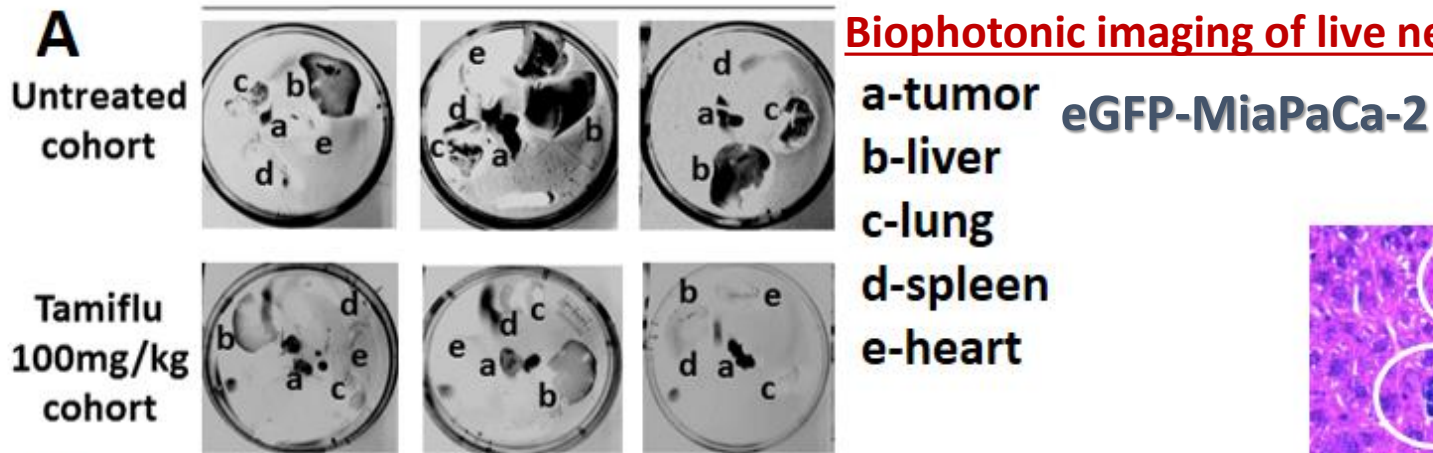
Highlights

- Individual necropsied tumors were taken from untreated and 100 mg/kg OP treated cohorts.
- Freshly frozen tumors were thawed on ice, and lysed in lysis buffer containing proteinase and phosphatase inhibitors.
- Tamiflu treatment at 100 mg/kg (i.p.) attenuated **pEGFR**, **pSTAT1** and **pNFκB** activity in heterotopic xenografts of MiaPaCa-2-eGFP tumors growing in RAGxCy double mutant mice.

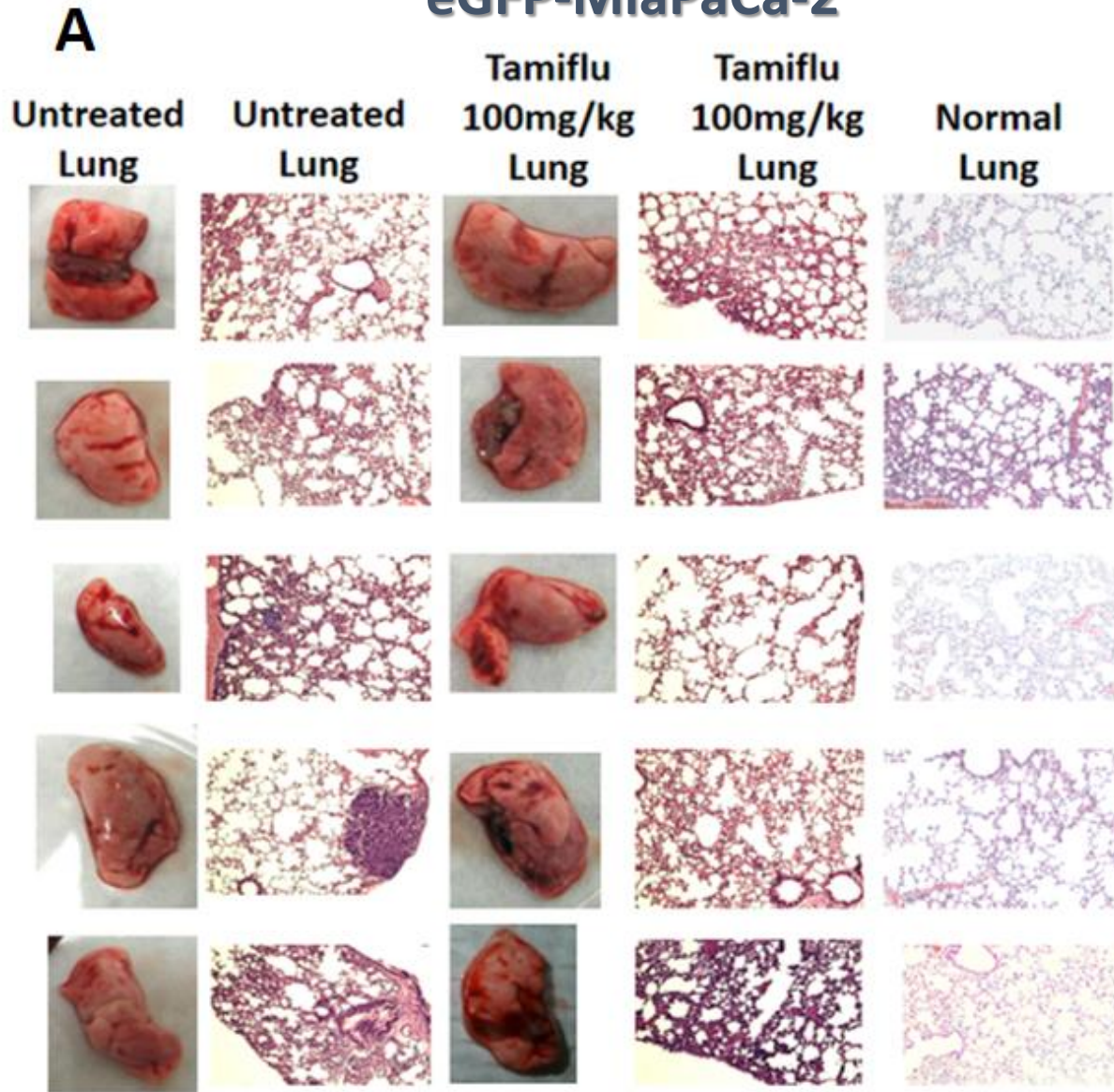


Oseltamivir phosphate targets xenografts of MiaPaCa-2 tumors growing in RAGxCy double mutant mice.

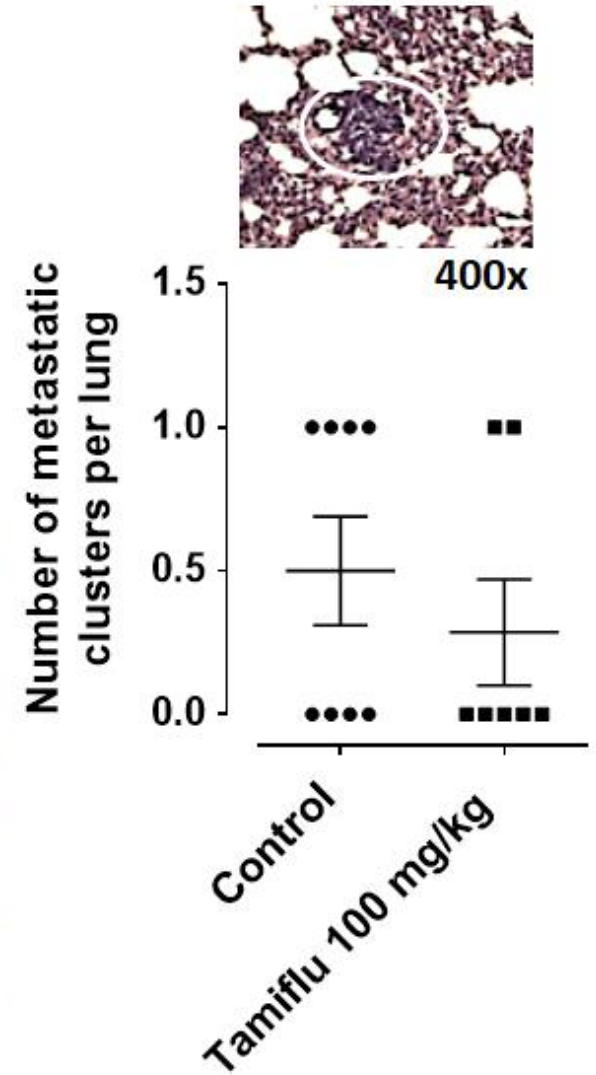
Biophotonic imaging of live necropsy tissues



eGFP-MiaPaCa-2



B



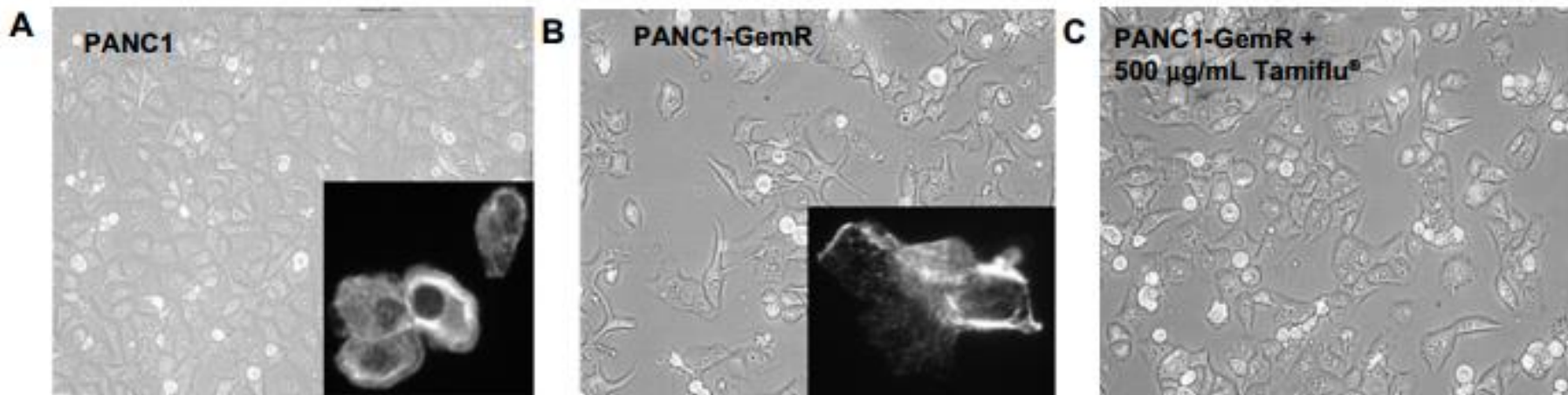
Therapeutic targeting of Neu1 sialidase with oseltamivir phosphate (Tamiflu®) disables cancer cell survival in human pancreatic cancer with acquired chemoresistance

Leah K O'Shea¹
Samar Abdulkhalek¹
Stephanie Allison²
Ronald J Neufeld²
Myron R Szewczuk¹

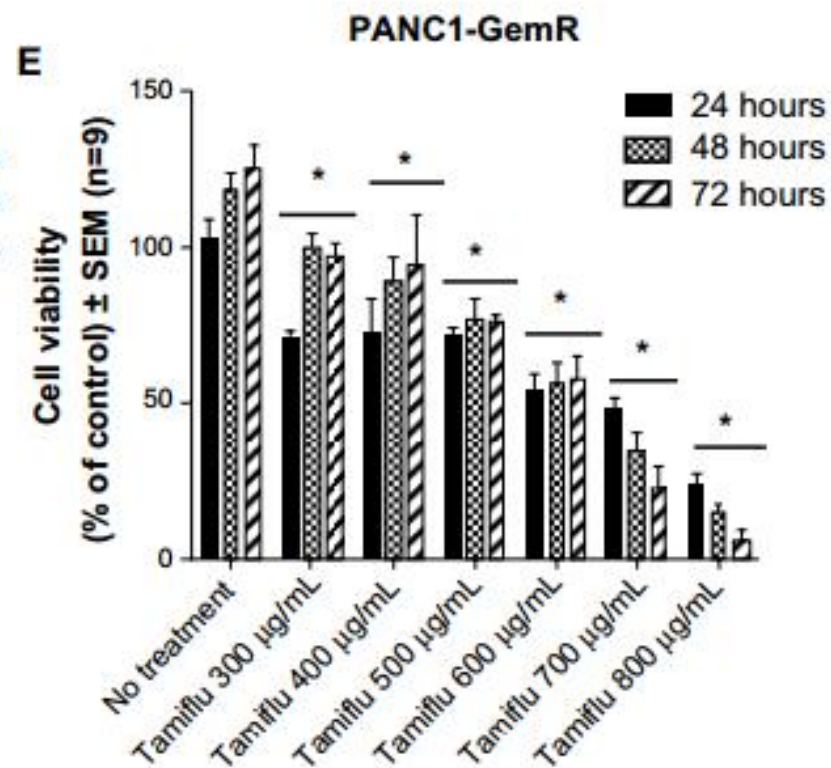
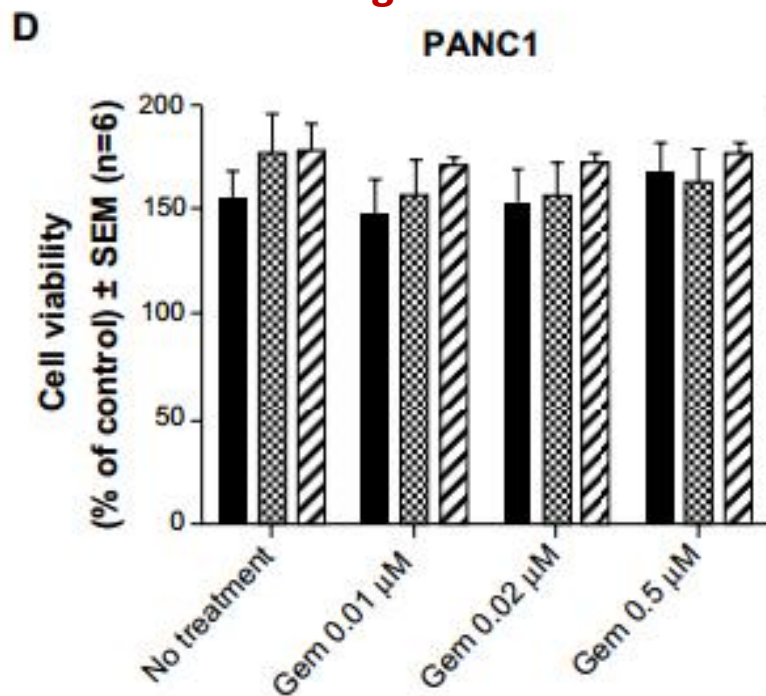
¹Department of Biomedical and Molecular Sciences, ²Department of Chemical Engineering, Queen's University, Kingston, ON, Canada

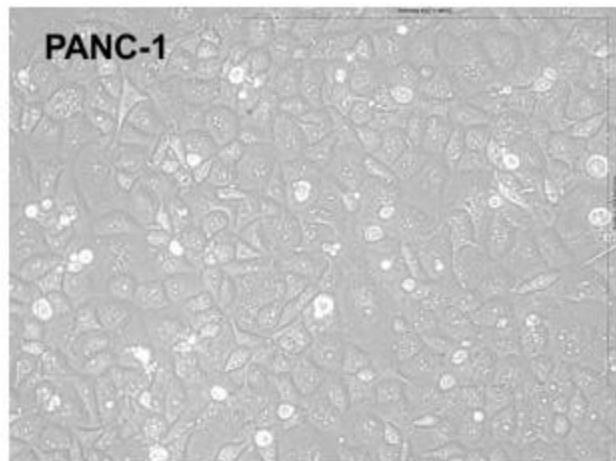
Clinical problem...

➤ Resistance to drug therapy, along with high rates of metastasis, contributes to the low survival rate in patients diagnosed with pancreatic cancer.

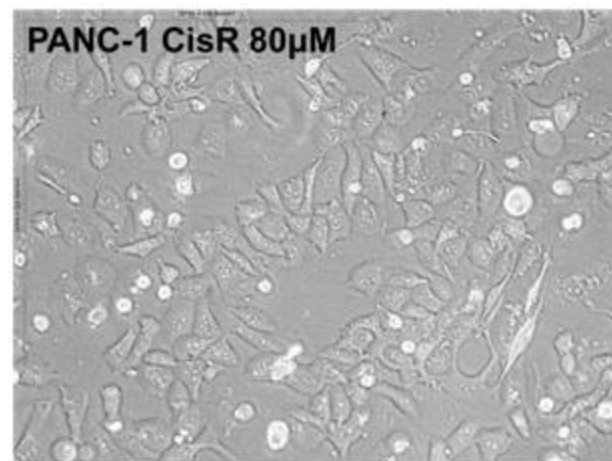
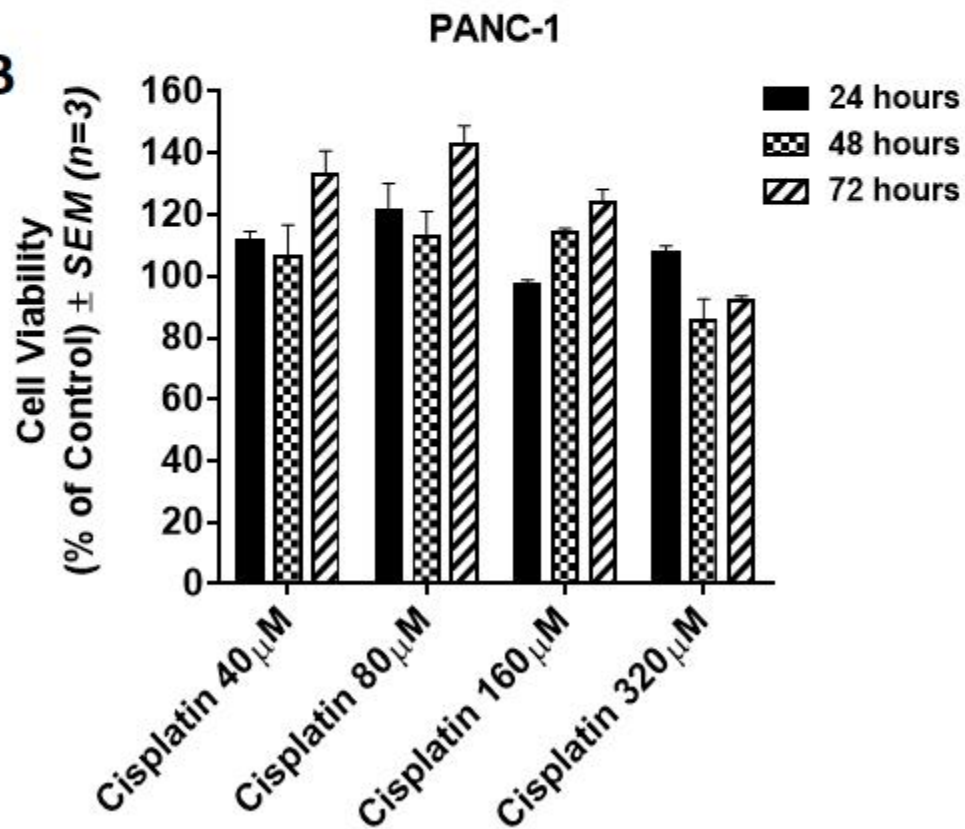
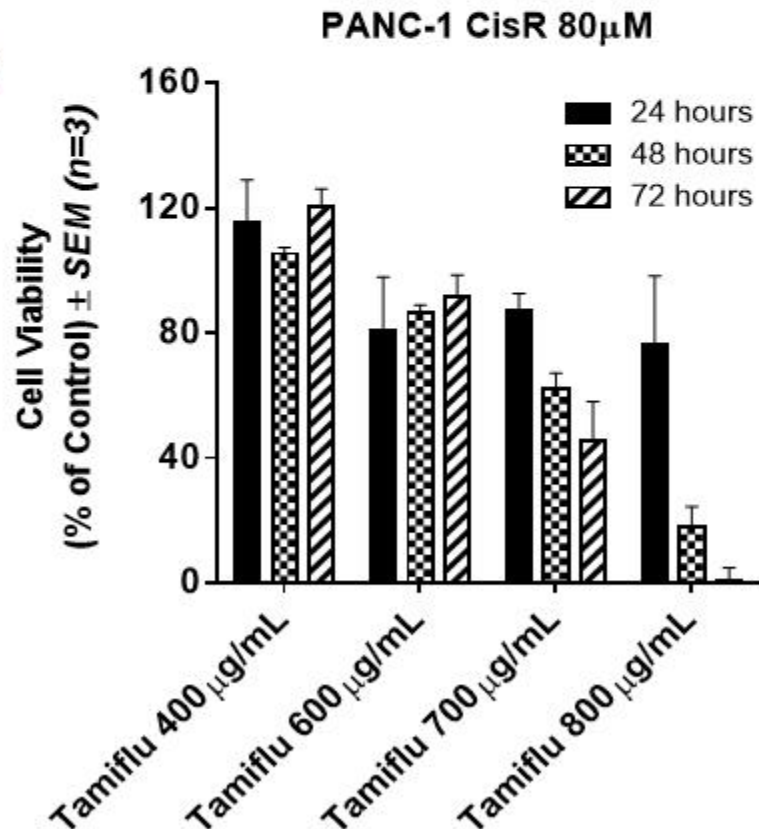


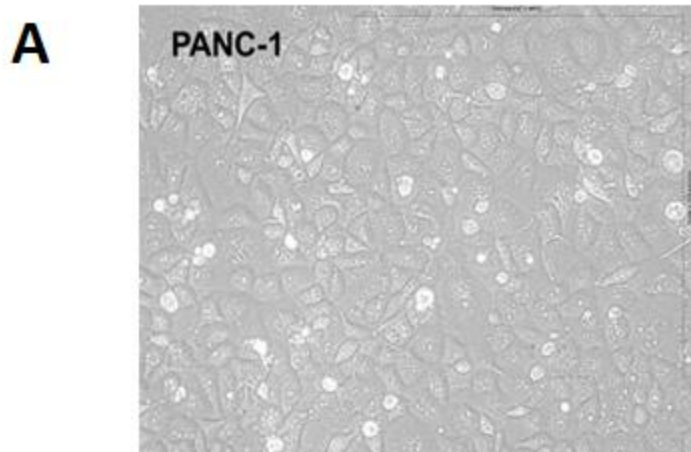
Established chemo-resistant PANC1 against 0.01µM gemcitabine for over 1 yr



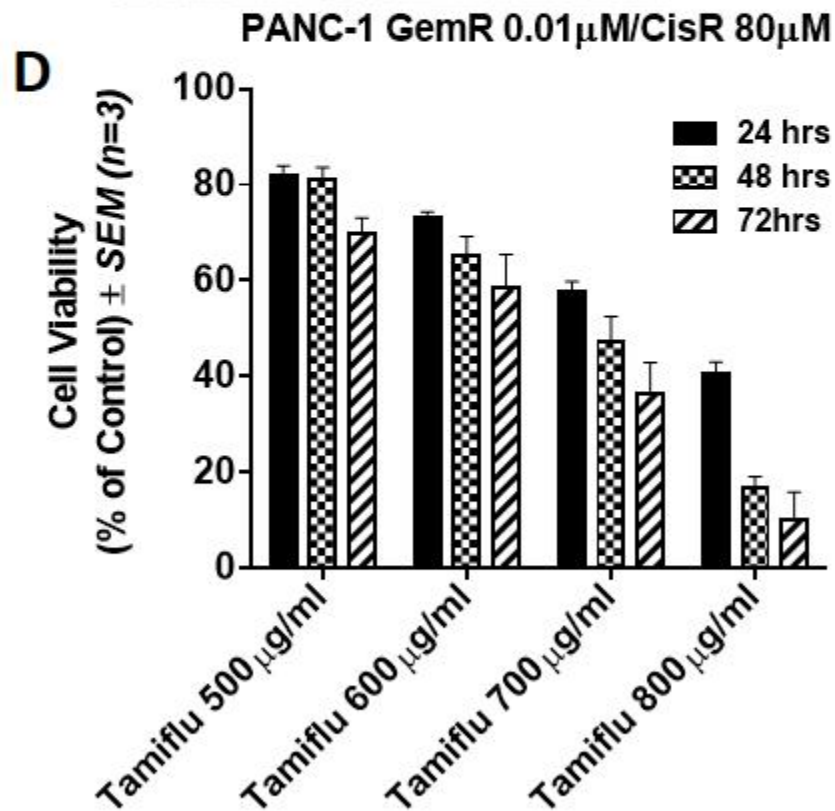
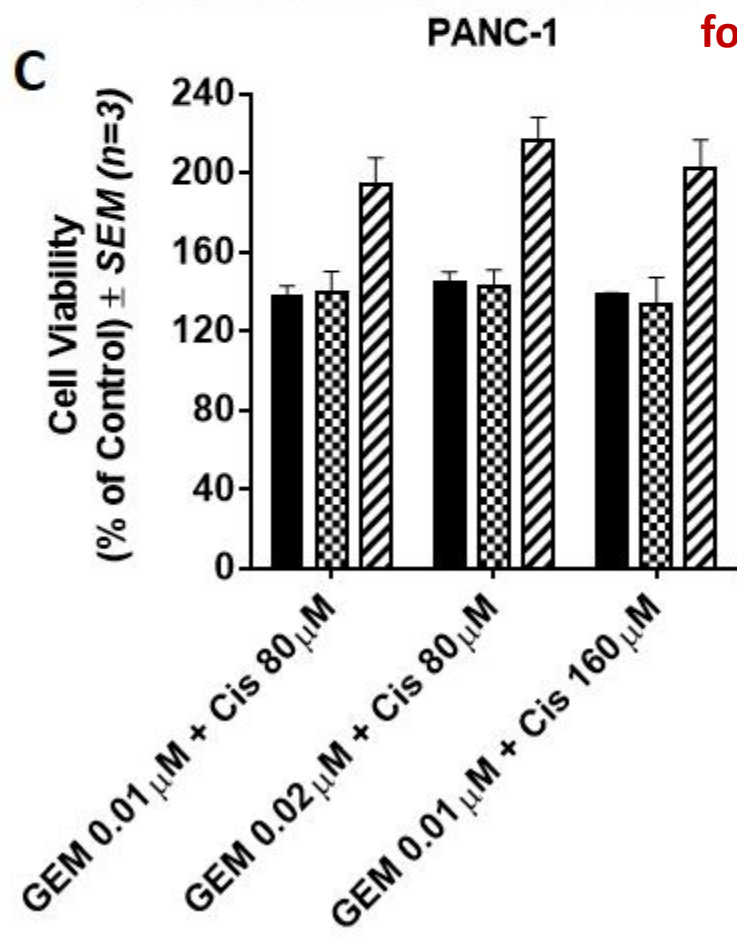
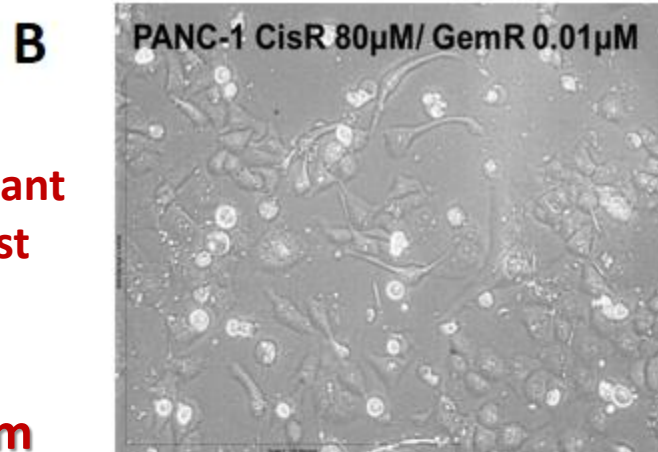
A

Established
chemo-resistant
PANC1 against
80 μ M
Cisplatin
for over 1 yr

C**B****D**



Established
chemo-resistant
PANC1 against
80 μ M
Cisplatin +
0.01 μ M Gem
for over 1 yr

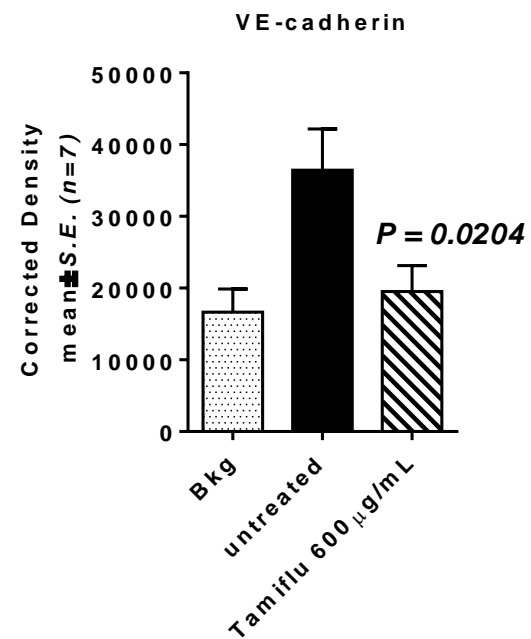
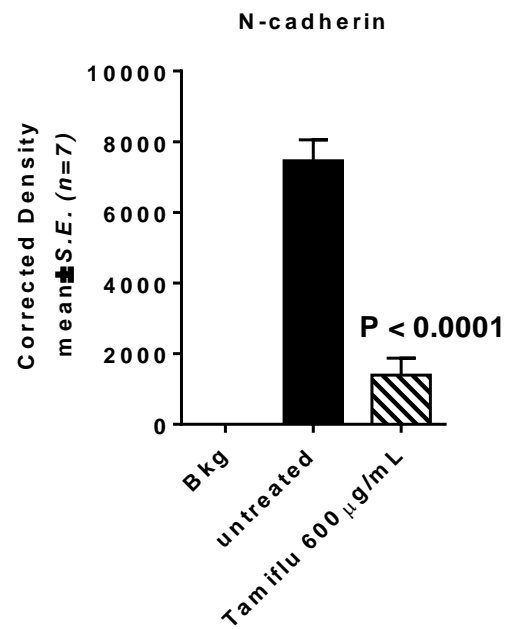
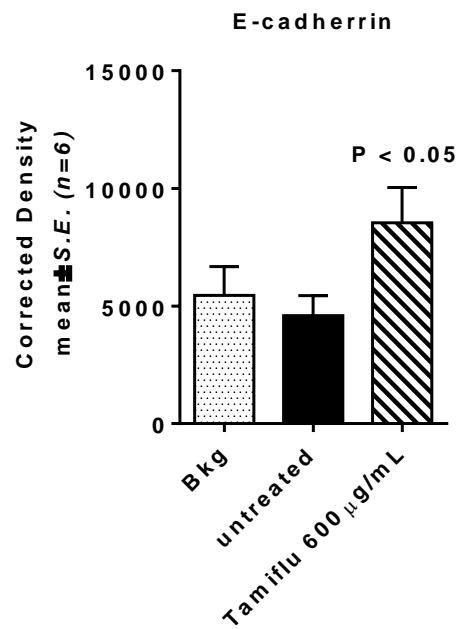
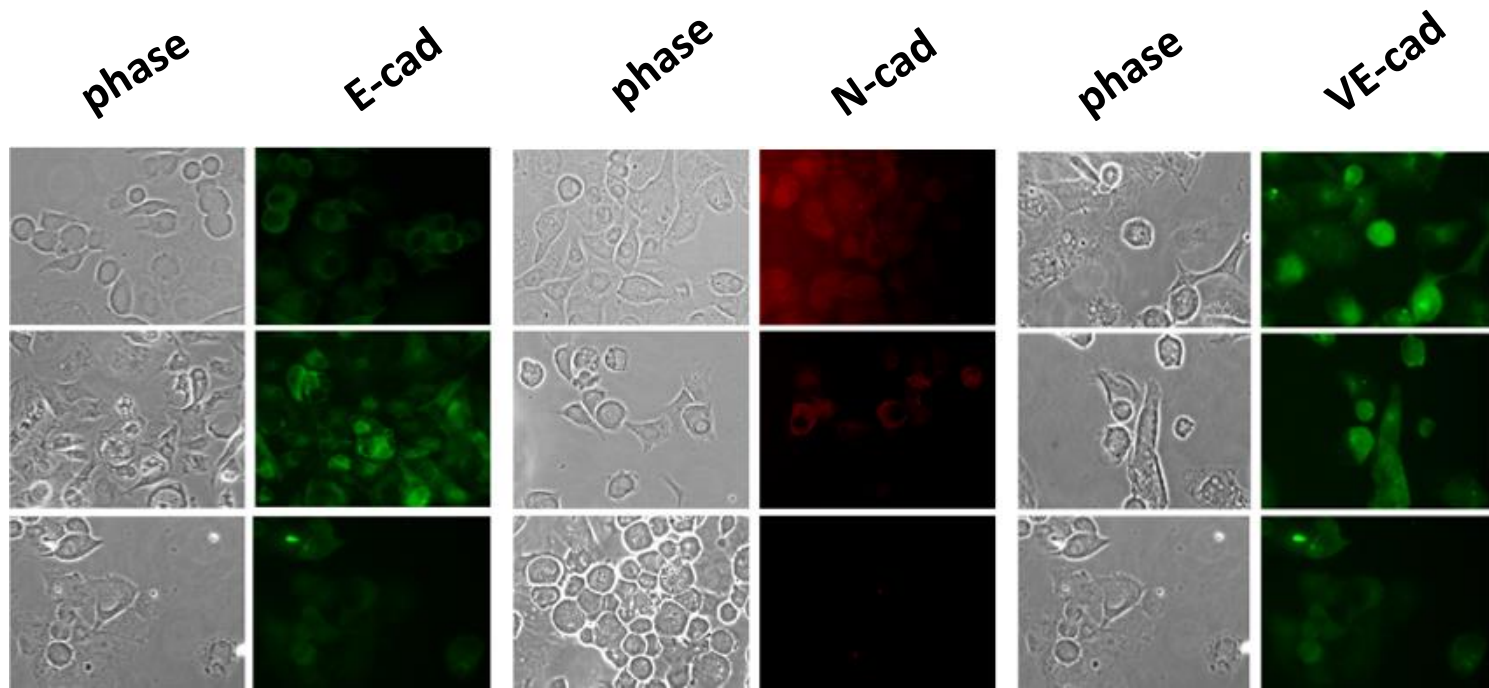


PANC1

untreated

Tamiflu
24 hrs

no 1⁰ Ab



PANC1
GemR 0.01 μ M

phase

E-cad

phase

N-cad

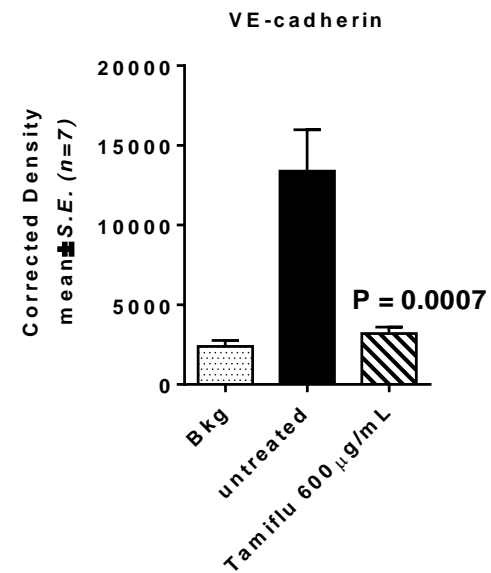
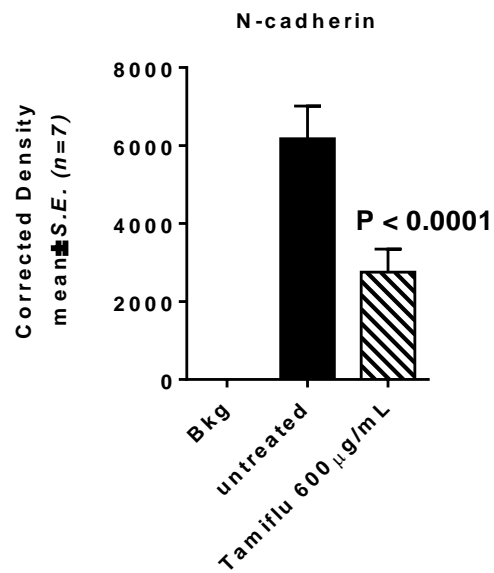
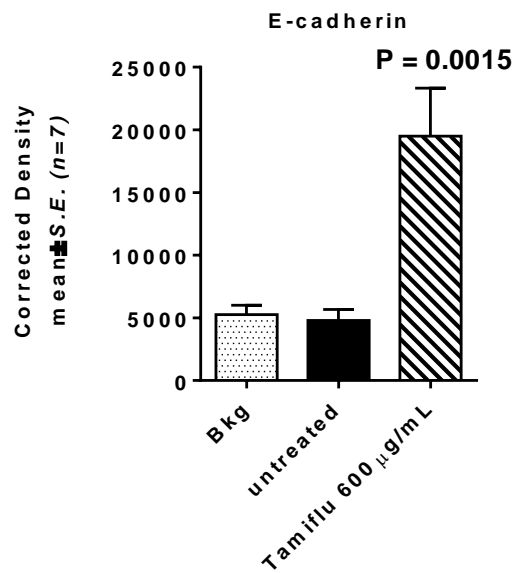
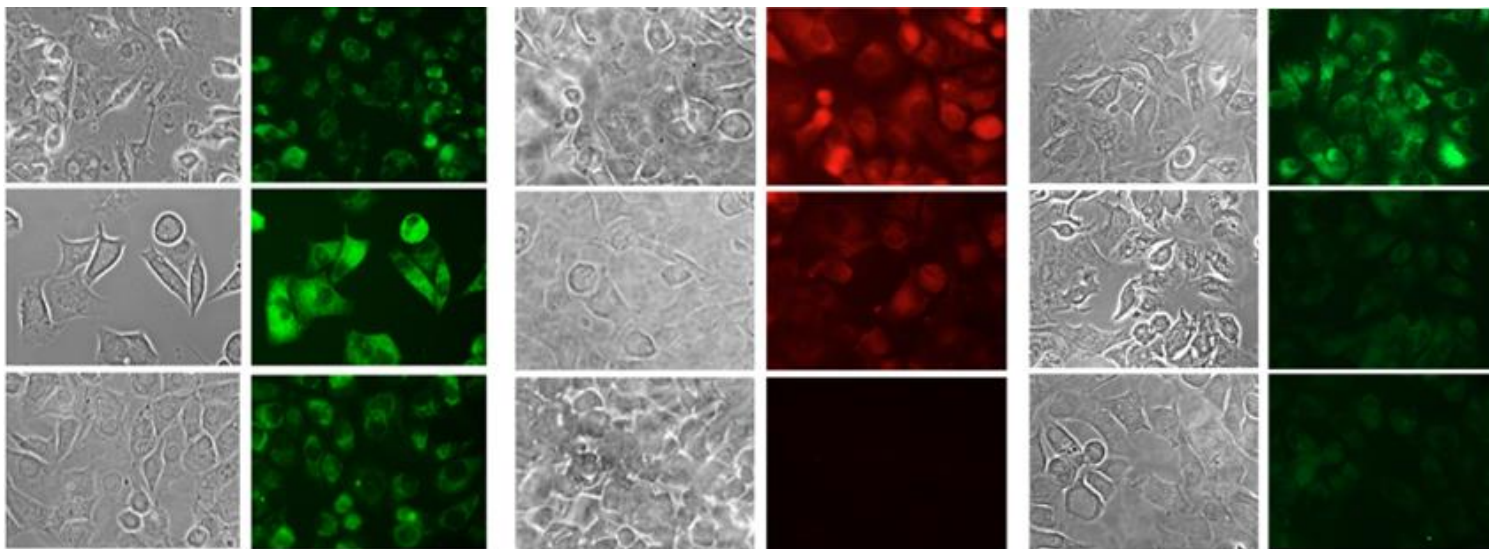
phase

VE-cad

untreated

Tamiflu
 24 hrs

no 1⁰ Ab



PANC1
CisR 80μM

untreated

Tamiflu
24 hrs

no 1^o Ab

phase

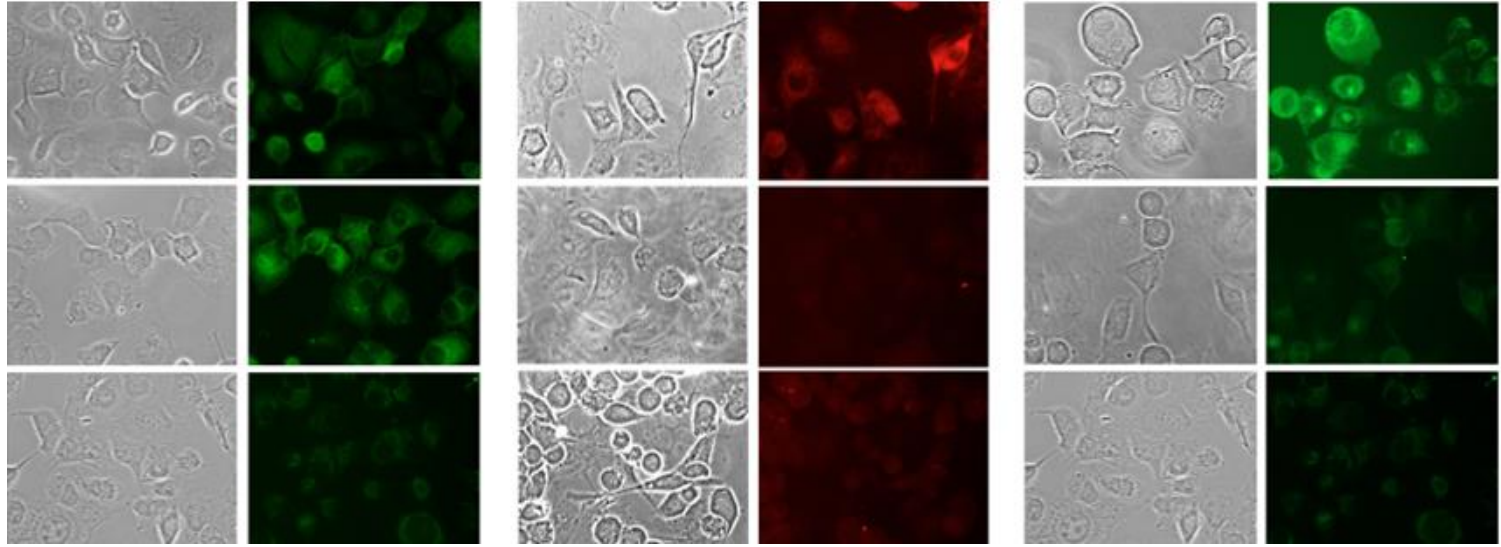
E-cad

phase

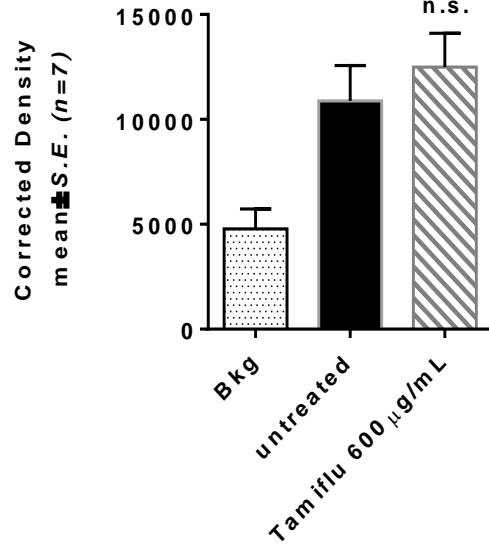
N-cad

phase

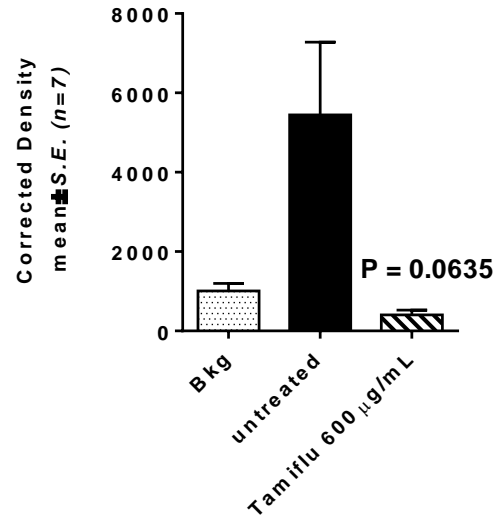
VE-cad



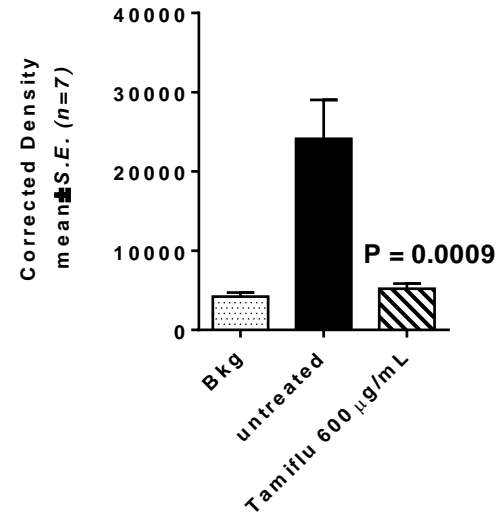
E-cadherin



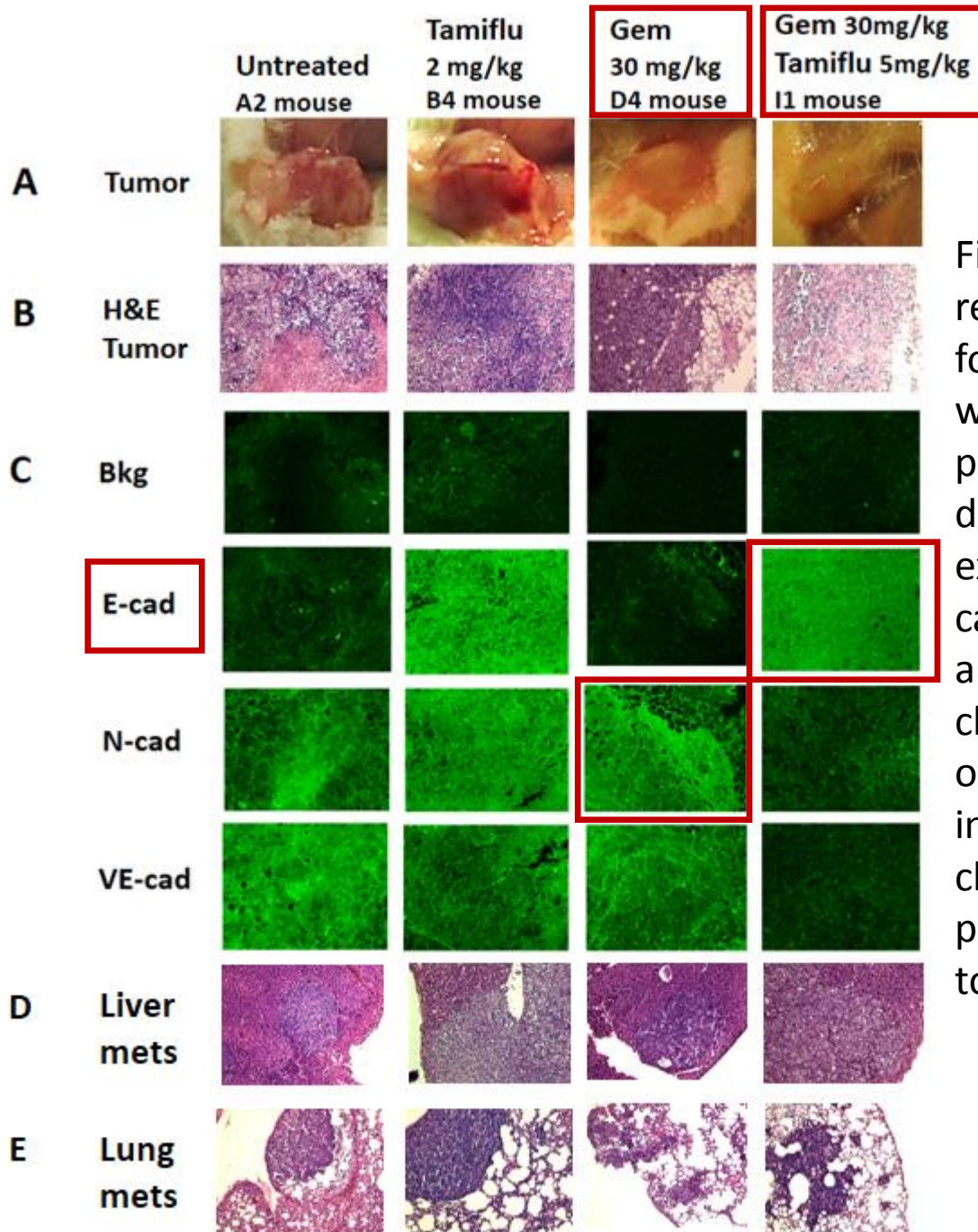
N-cadherin



VE-cadherin



Paraffin-embedded tumor staining: Fluorescence microscopic analyses



Findings indicate a reversal of EMT following treatment with oseltamivir phosphate, as demonstrated by expression of N-cadherin, VE-cadherin, and E-cadherin as characteristic markers of EMT, and an increase in the sensitivity of chemoresistant pancreatic cancer cells to drug therapy.

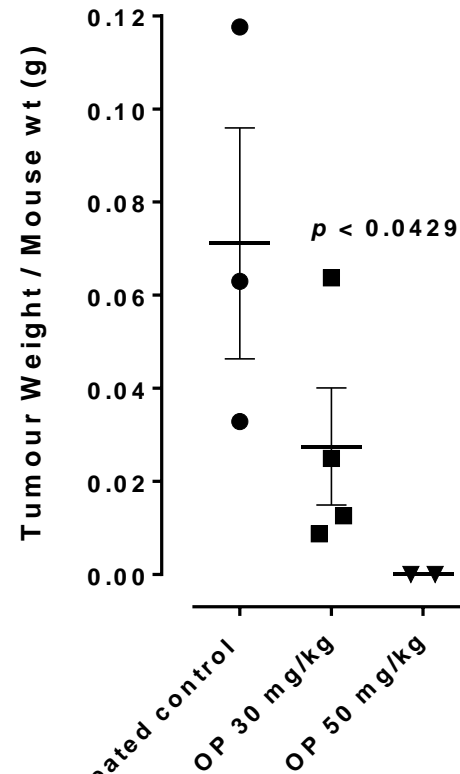
Osetamivir phosphate monotherapy ablates tumor neovascularization, growth, and metastasis in mouse model of human triple-negative breast adenocarcinoma

Fiona Haxho¹
Stephanie Allison²
Farah Alghamdi^{1,3}
Lacey Brodhagen¹
Victoria EL Kuta¹
Samar Abdulkhalek^{1,4}
Ronald J Neufeld²
Myron R Szewczuk¹

¹Department of Biomedical and Molecular Sciences, ²Department of Chemical Engineering, Queen's University, Kingston, ON, Canada; ³The King Fahd Armed Forces Hospital, Serology, Jeddah, Saudi Arabia; ⁴Department of Molecular Genetics, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Highlights

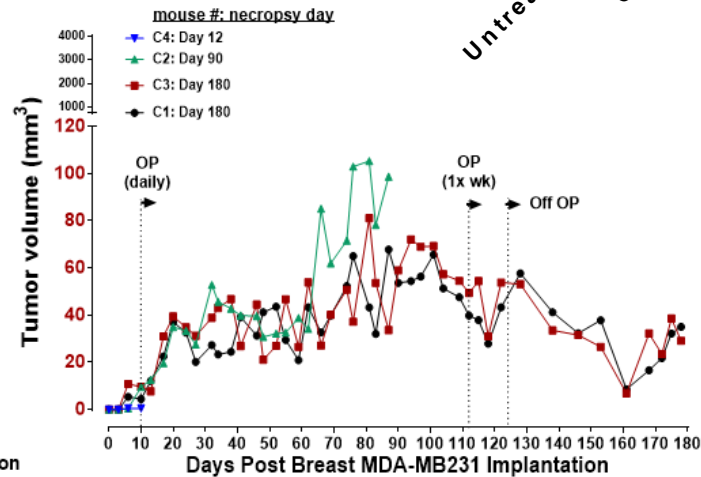
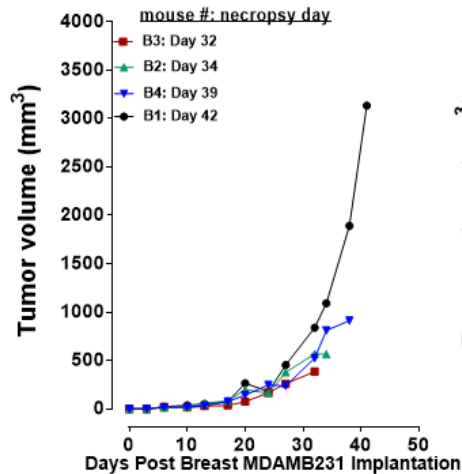
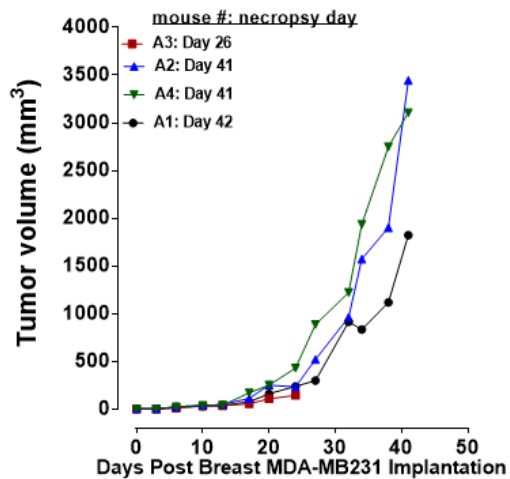
- Triple-negative breast cancers (TNBCs) lack the estrogen, progesterone, and epidermal growth factor (EGF) receptor-2 (HER2/neu) receptors.
- Patients with TNBC have typical high grading, more frequent relapses, and exhibit poorer outcomes or prognosis compared with the other subtypes of breast cancers.
- Currently, there are no targeted therapies that are effective for TNBC.

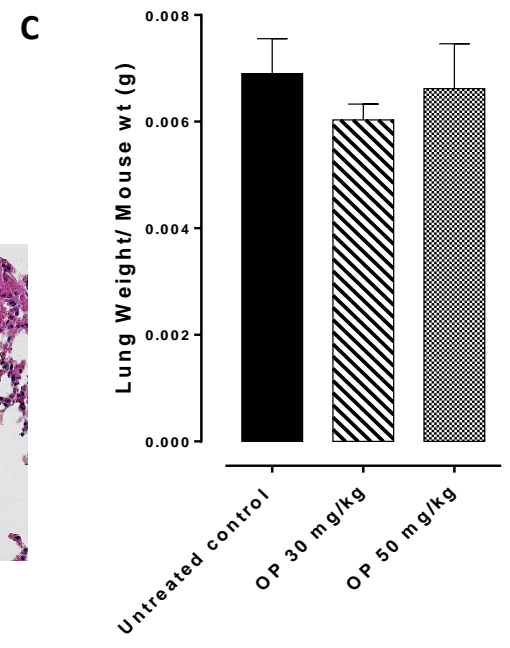
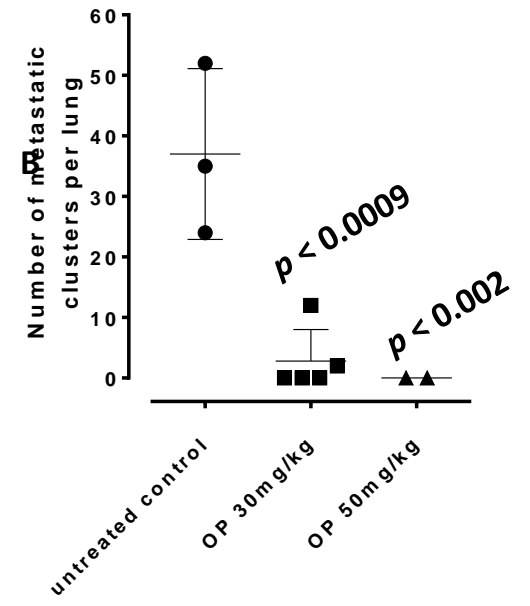
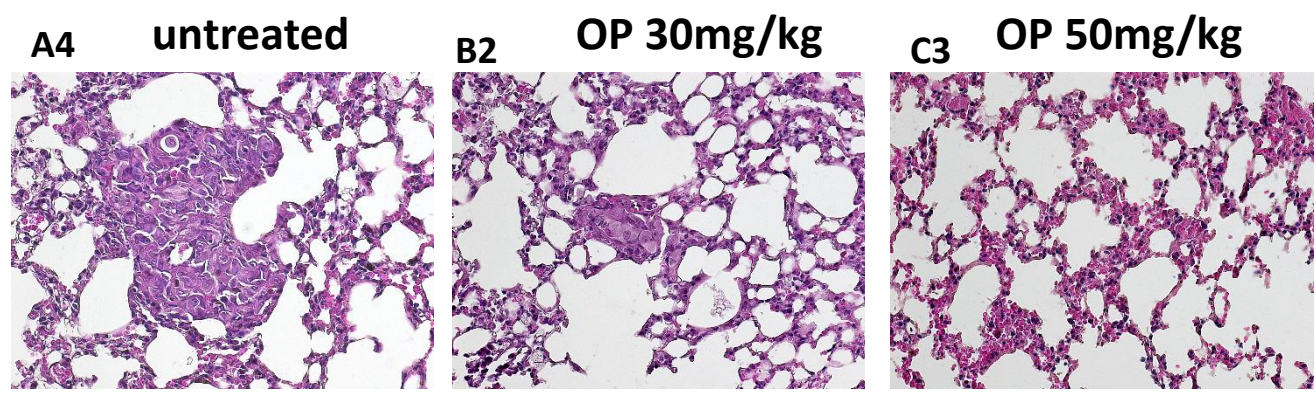
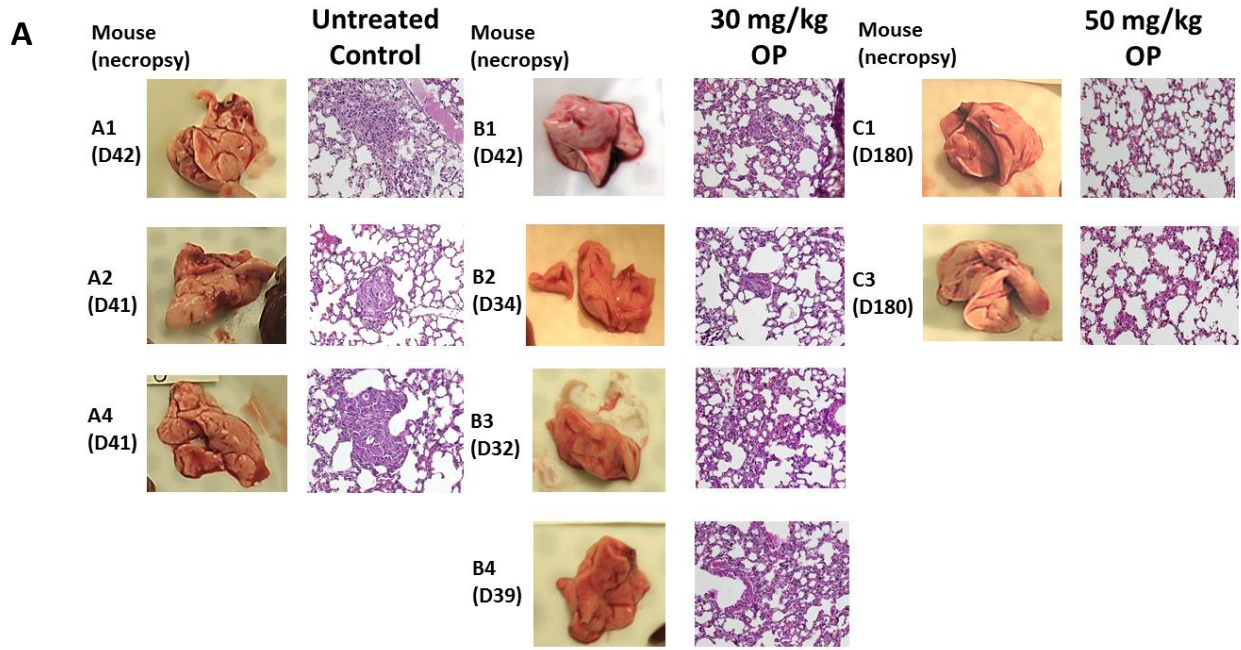


untreated

OP 30mg/kg

OP 50mg/kg





RESEARCH

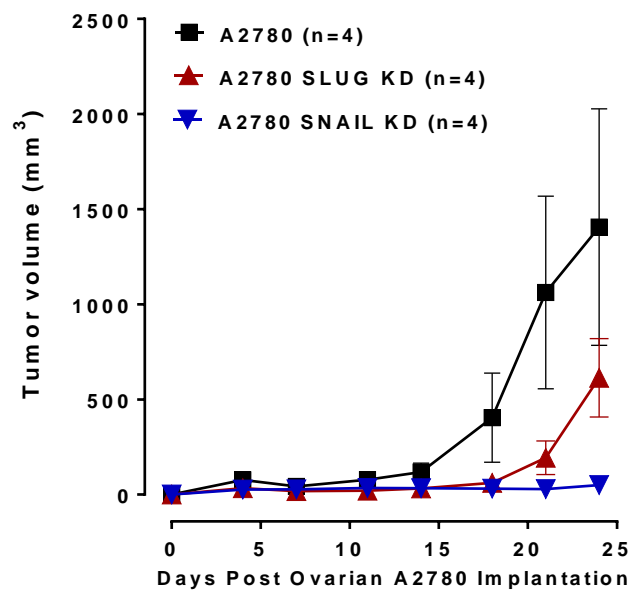
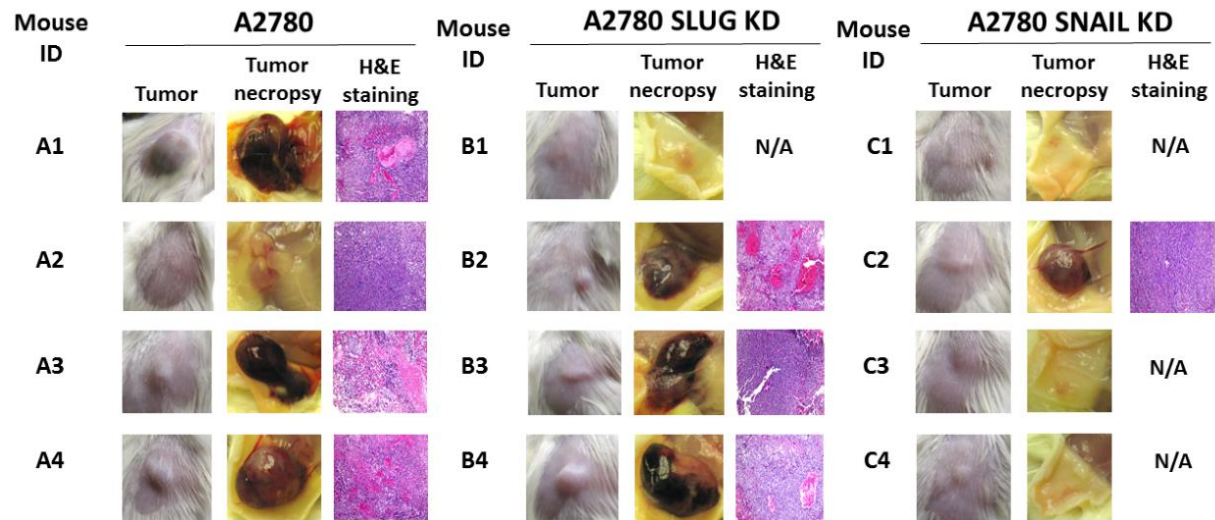
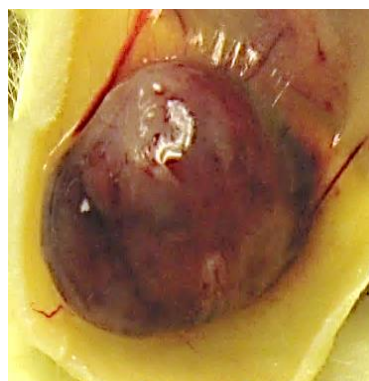
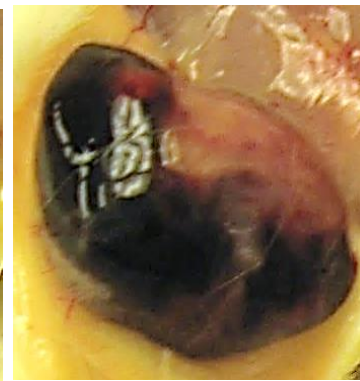
Open Access

Transcriptional factor snail controls tumor neovascularization, growth and metastasis in mouse model of human ovarian carcinoma

Samar Abdulkhalek^{1,3}, Olivia D Geen¹, Lacey Brodhagen¹, Fiona Haxho¹, Farah Alghamdi^{1,4}, Stephanie Allison², Duncan J Simmons¹, Leah K O'Shea^{1,5}, Ronald J Neufeld² and Myron R Szewczuk^{1*}

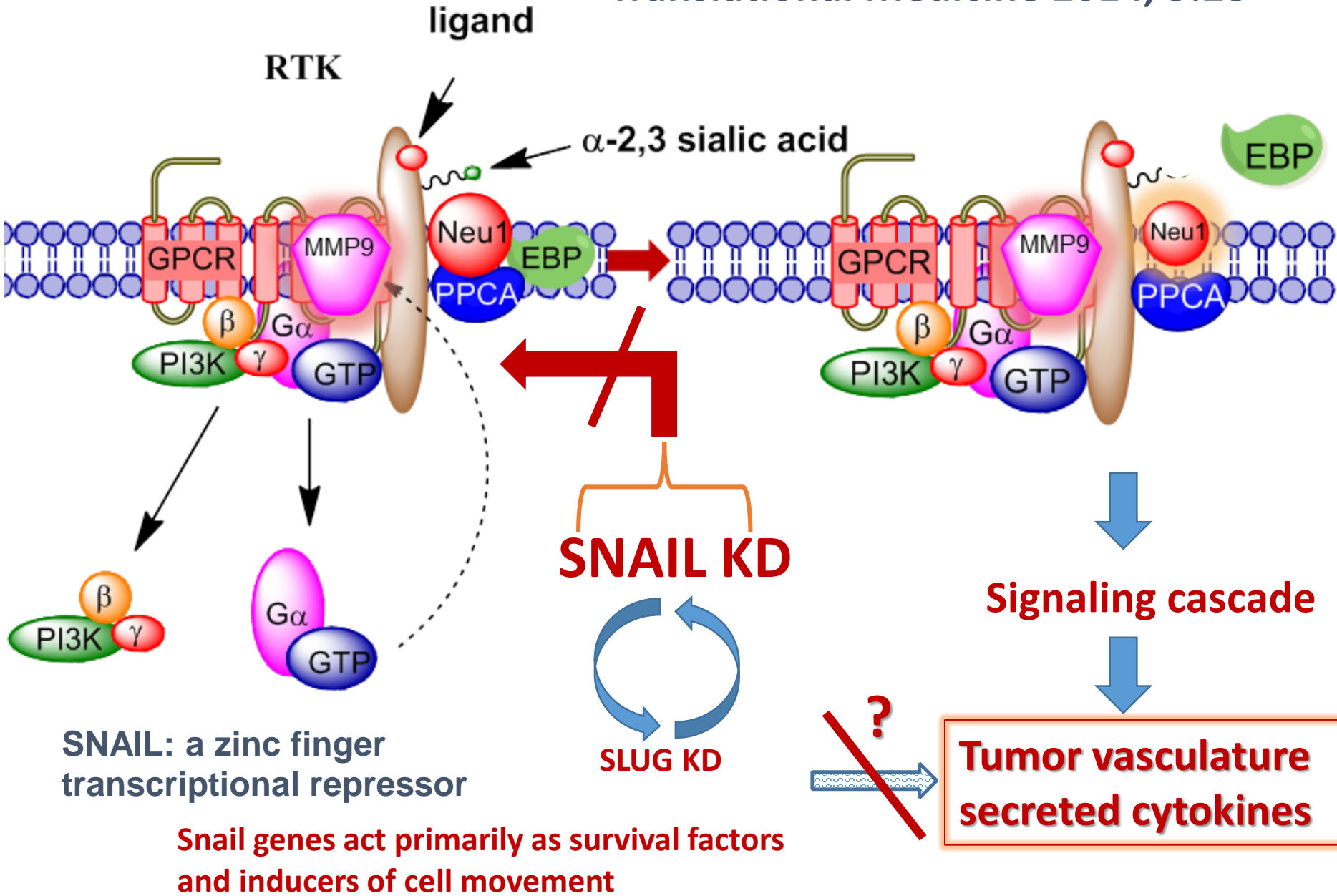
Highlights

- **Snail, a transcriptional factor and repressor of E-cadherin is well known for its role in cellular invasion.**
- **It can regulate epithelial to mesenchymal transition (EMT) during embryonic development and in epithelial cells.**
- **Snail also mediates tumor progression and metastases.**
- **Silencing of Snail and its associate member Slug in human A2780 ovarian epithelial carcinoma cell line was investigated to identify its role in tumor neovascularization.**

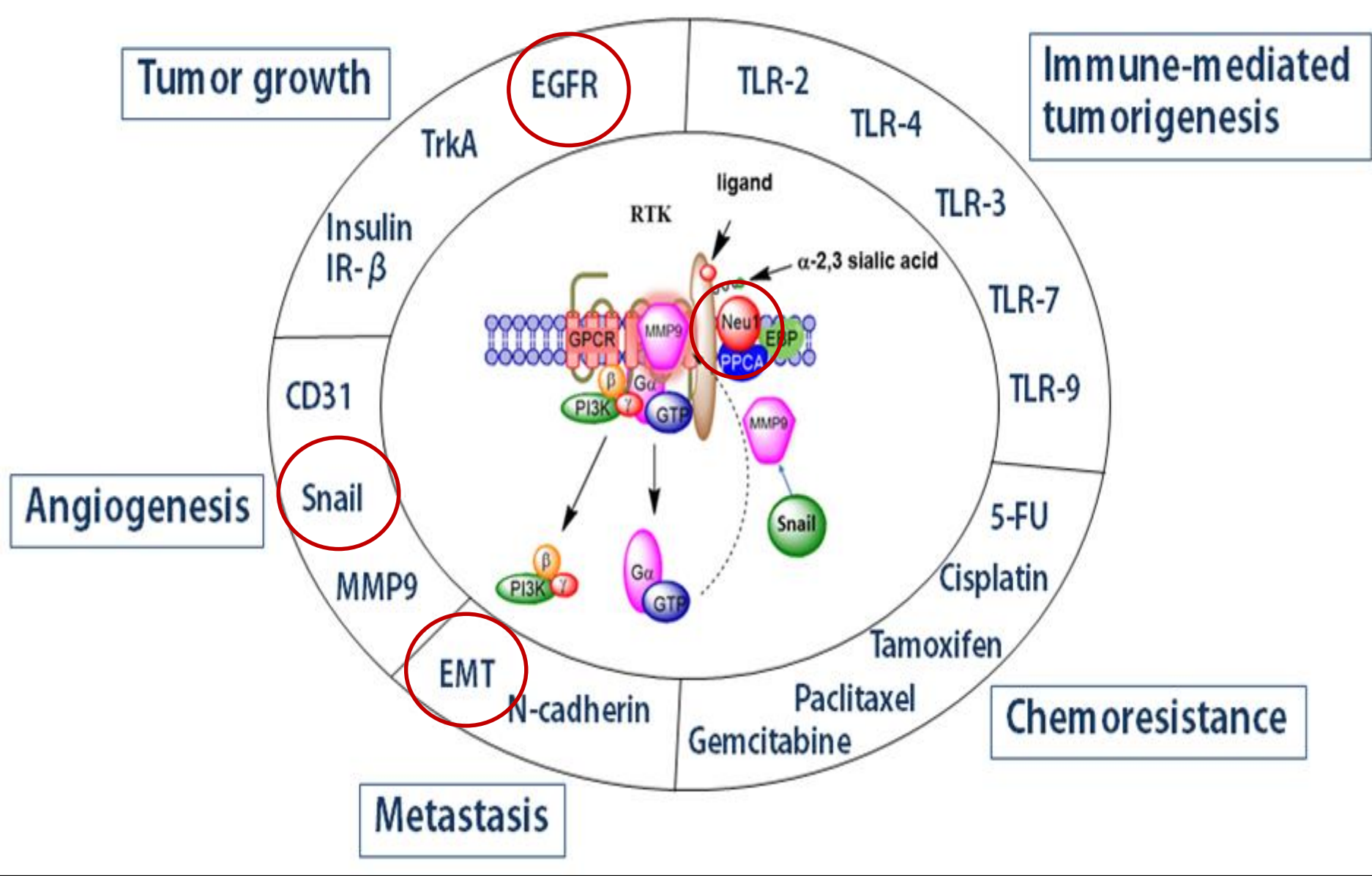
A**B****A4****B4****C4**

Novelty

Abdulkhalek et al. Clinical and Translational Medicine 2014, 3:28

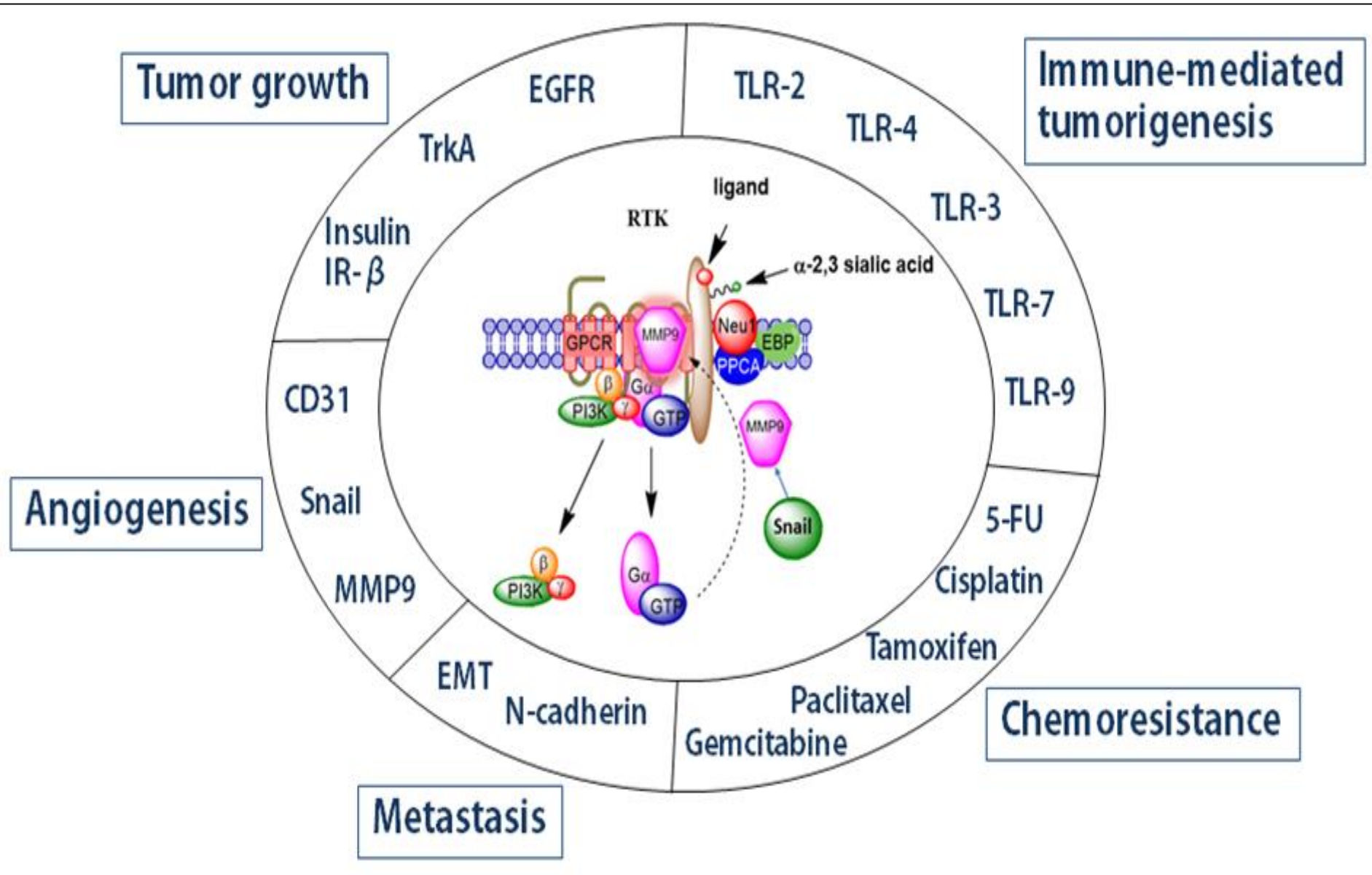


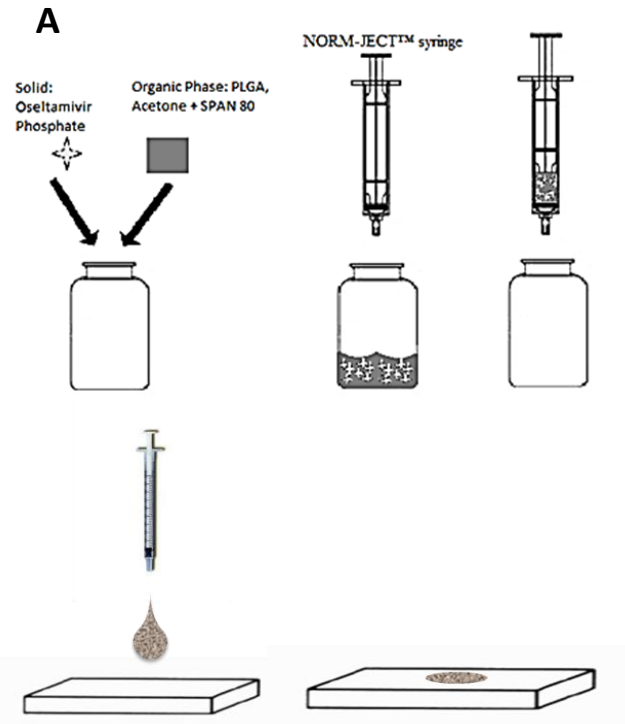
Therapeutic targeting neuraminidase-1 in multi-stage of tumorigenesis



Conclusions

- The role of mammalian neuraminidase-1 (Neu1) is identified as a major target in the multi-stage of tumorigenesis.
- An innovative and promising entirely new targeted therapy for cancer.

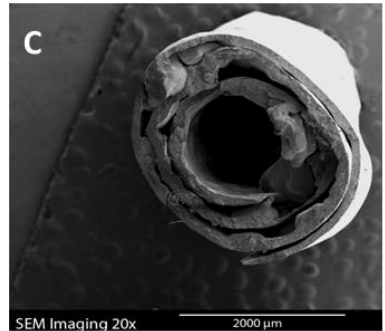
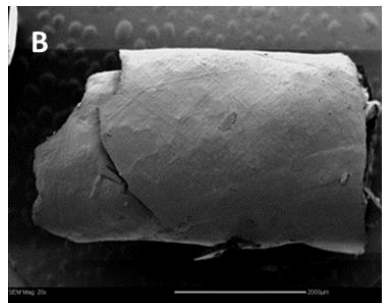
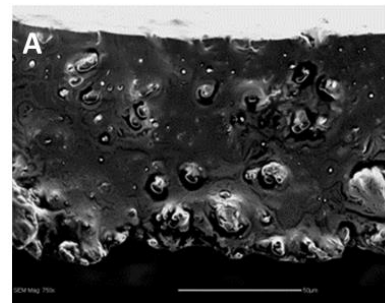
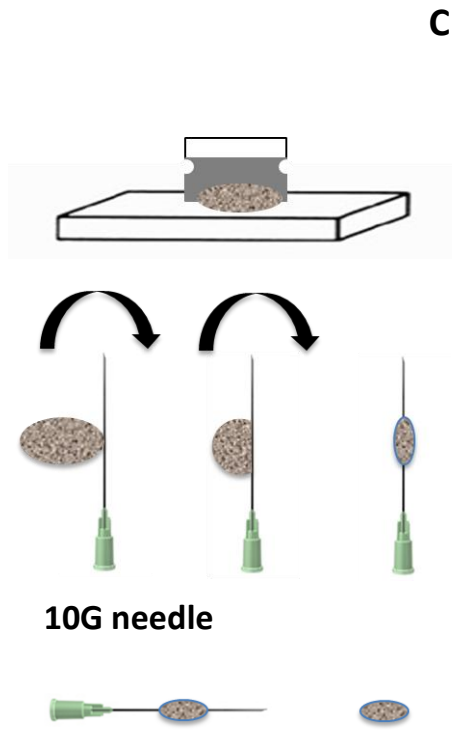


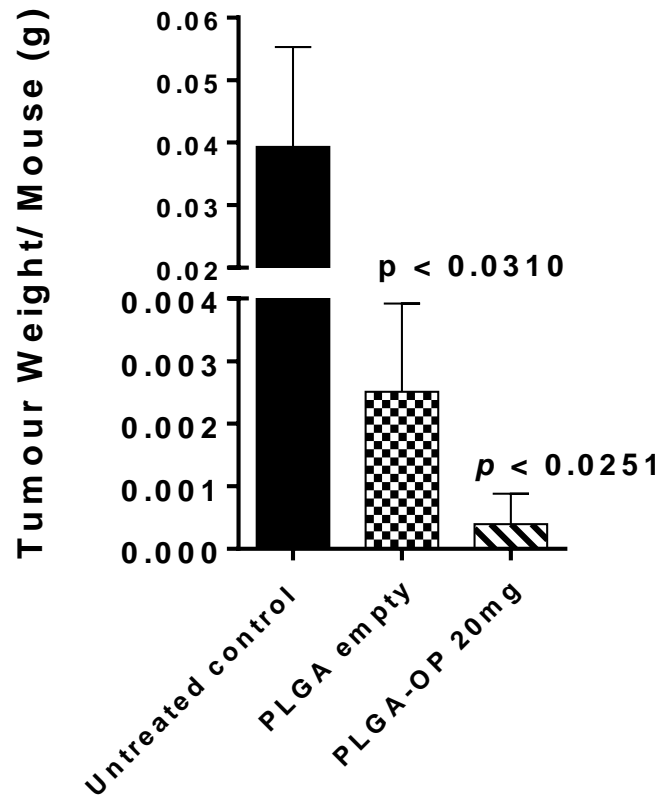
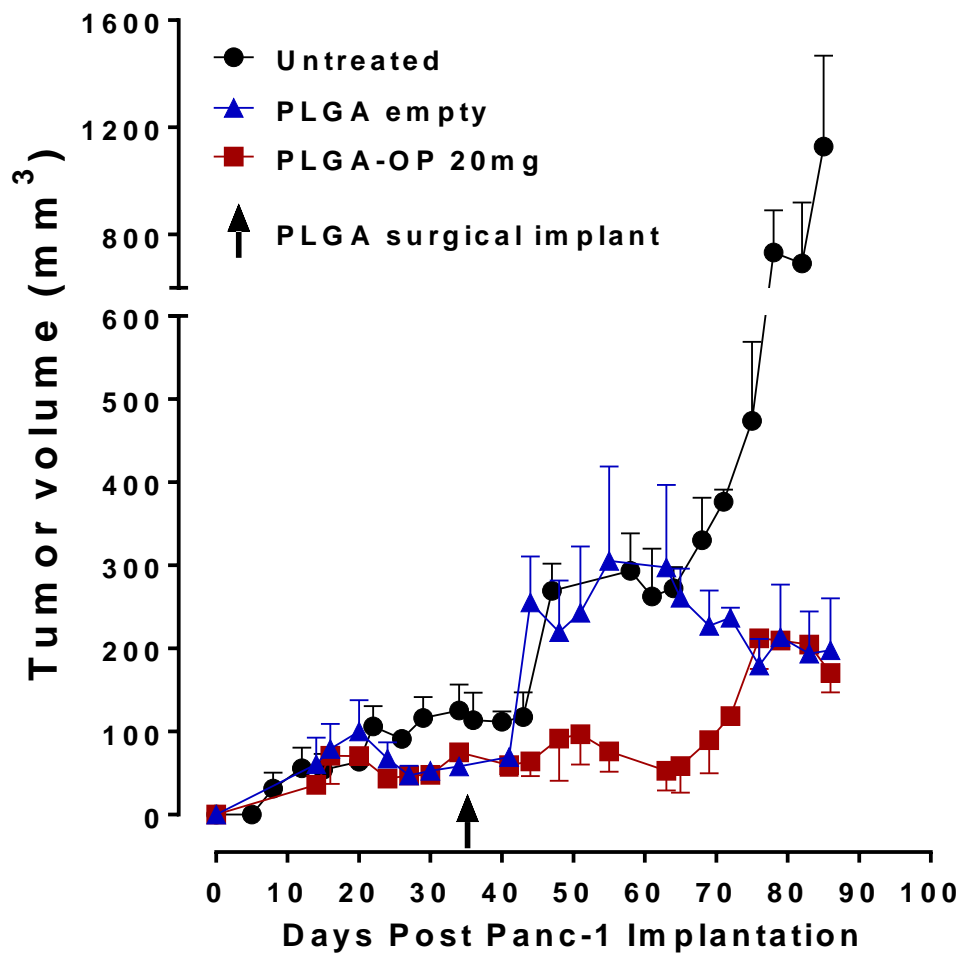


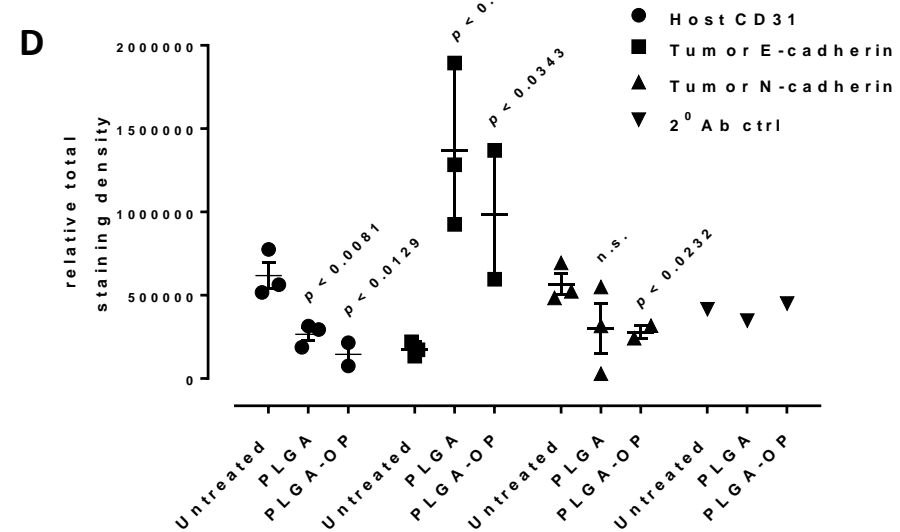
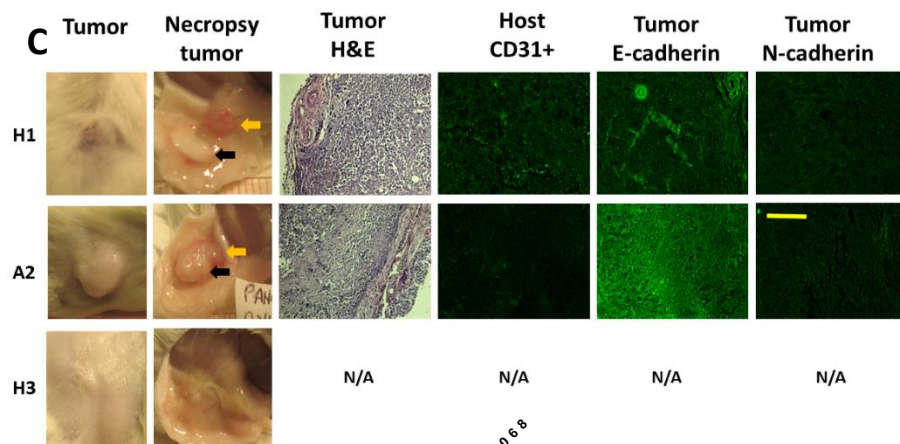
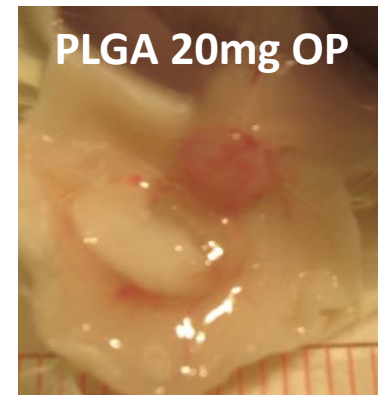
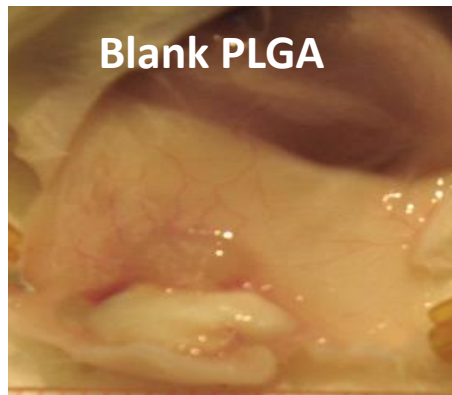
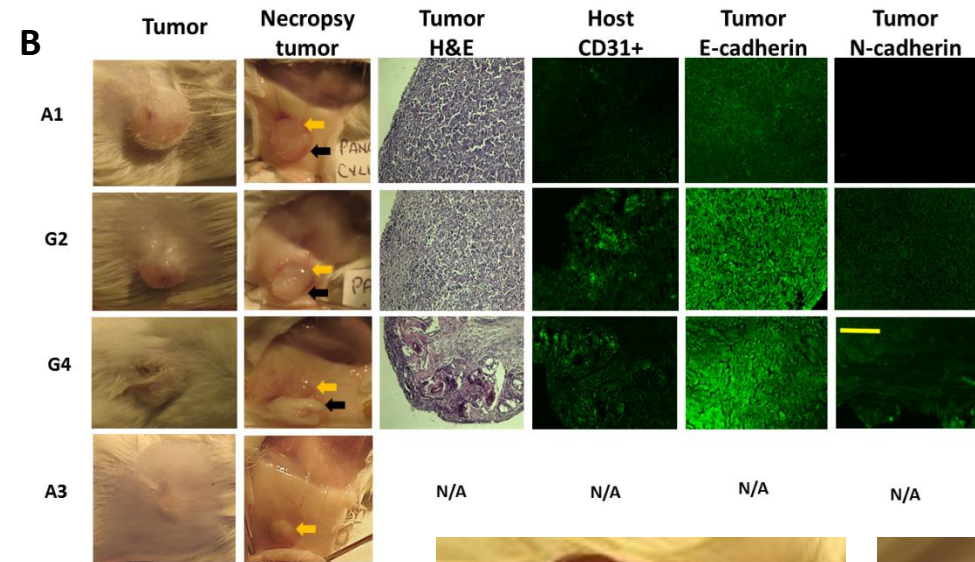
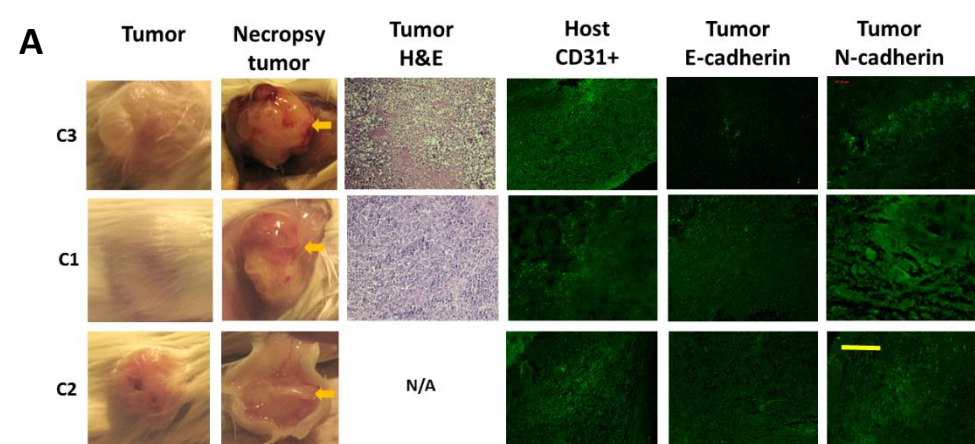
PLGA-empty



PLGA-OP 20mg







Blank PLGA

PLGA 20mg OP

