Transcriptional factor Snail and MMP-9 signaling axis controls tumor neovascularization, growth and metastasis in mouse model of human ovarian carcinoma

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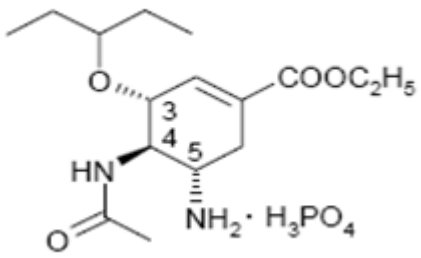
Depts of [1]Biomedical and Molecular Sciences, and [2]Chemical Engineering, Queen's University, Kingston, ON K7L 3N6, Canada.

***speaker**

Cancer therapeutics in the clinical setting

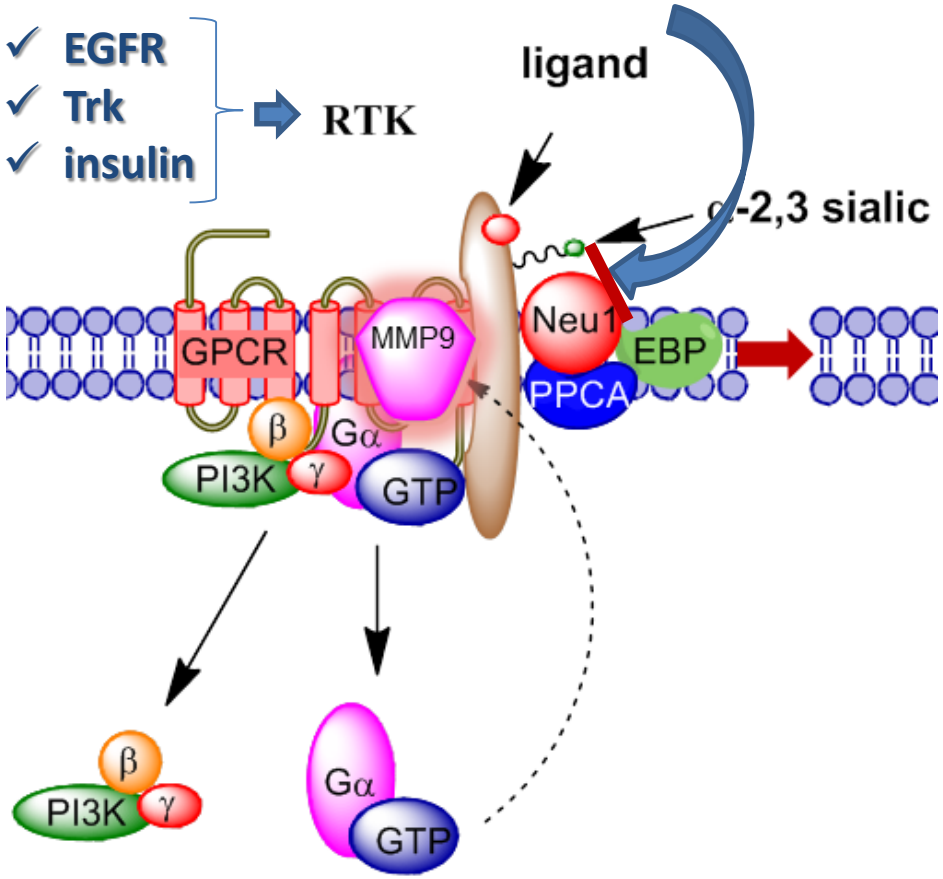
- Need for alternate therapeutics
- Target multiple cancer pathways
- Circumvent the genetic mutations

OP: Oseltamivir phosphate



Published:

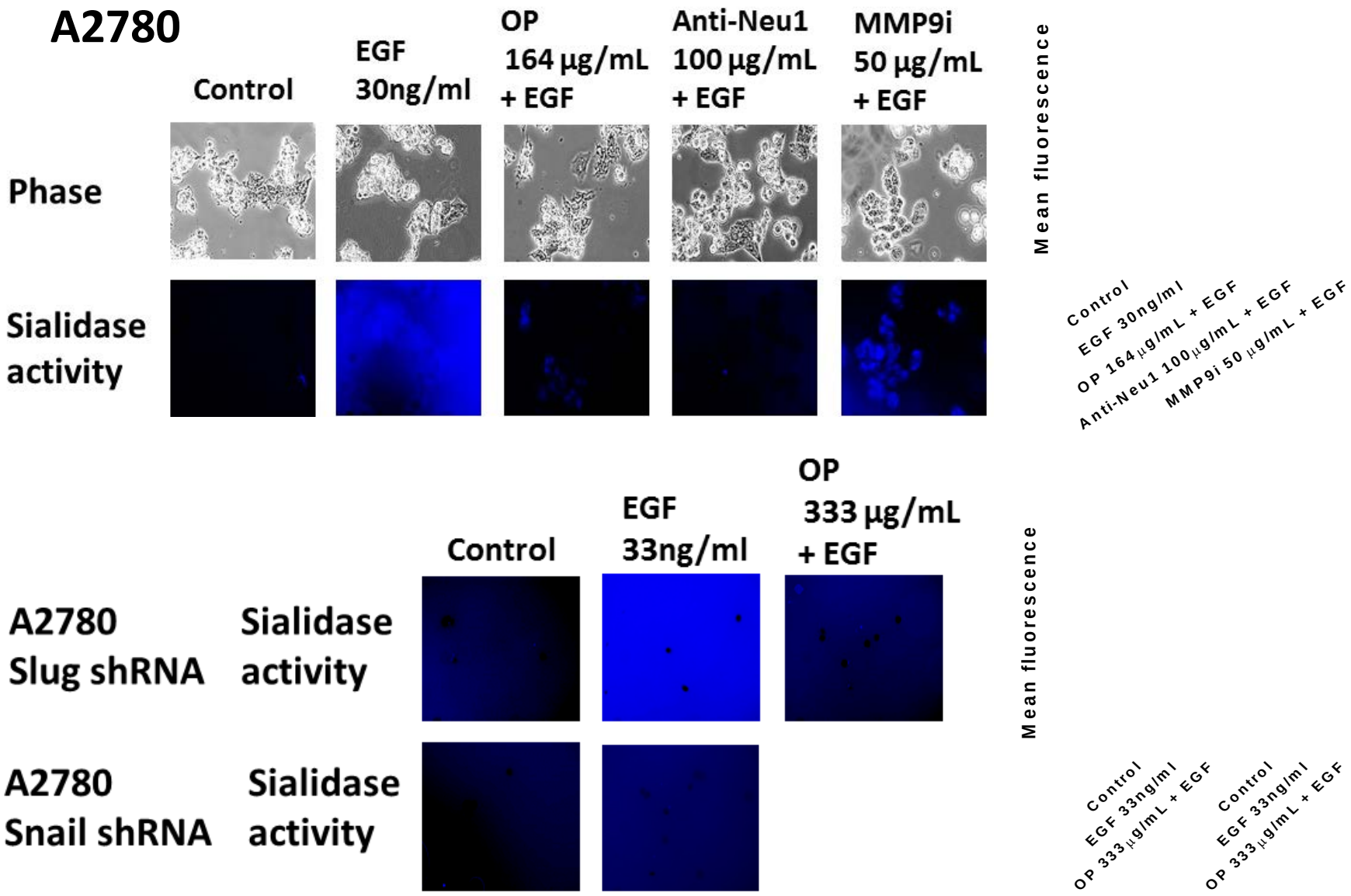
- ✓ TLR-4, -7 & -9
- ✓ EGFR
- ✓ Trk
- ✓ insulin



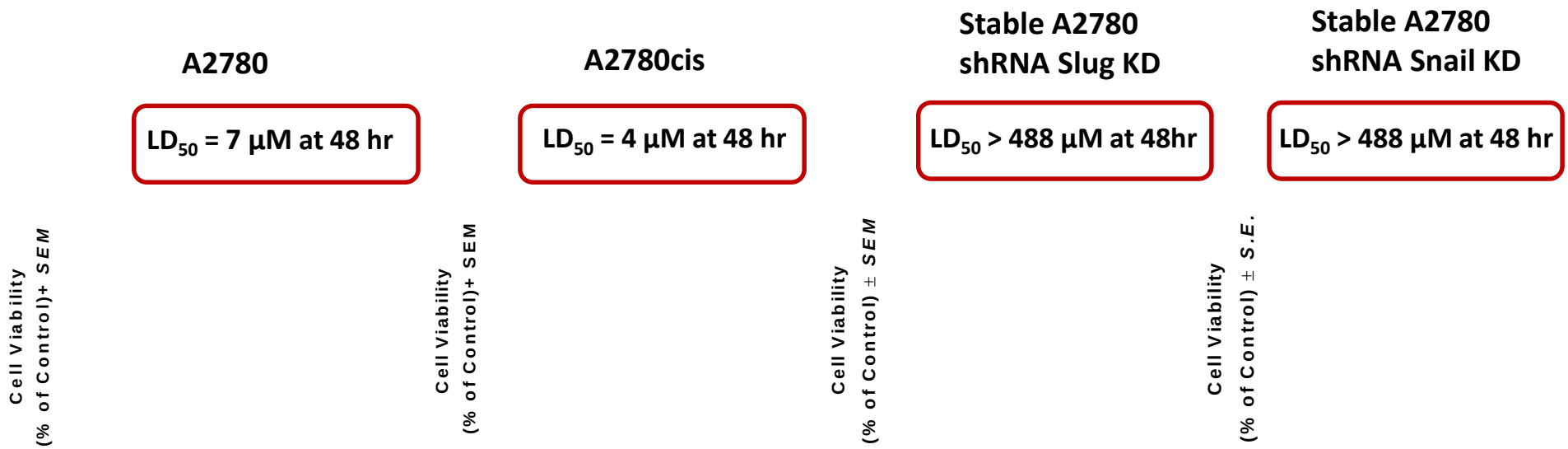
- ➢ **Identified a new anti-cancer therapeutic approach:**

Oseltamivir phosphate (OP) monotherapy or in combination with chemotherapeutics against human ovarian cancer regulates ***tumour neovascularization, growth and invasiveness.***

Neu1 sialidase activity is associated with epidermal growth factor (EGF) stimulation of A2780 ovarian carcinoma cells

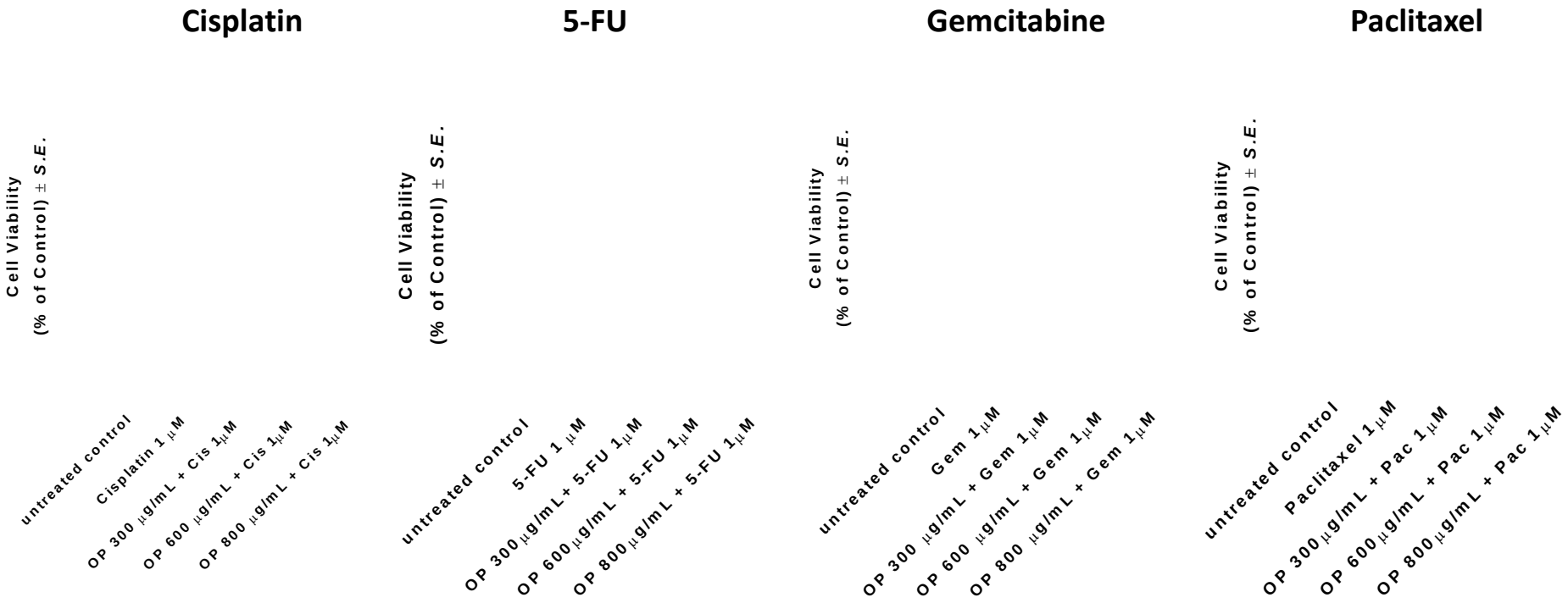


Oseltamivir phosphate (OP) decreases the cell viability of A2780, A2780cis, A2780-shRNA Slug and A2780-shRNA Snail cells



- OP LD_{50} of 7µM for A2780
- OP LD_{50} of 4µM for cisplatin-resistant A2780cis
- OP LD_{50} of 488µM for A2780 shRNA Slug and Snail KD

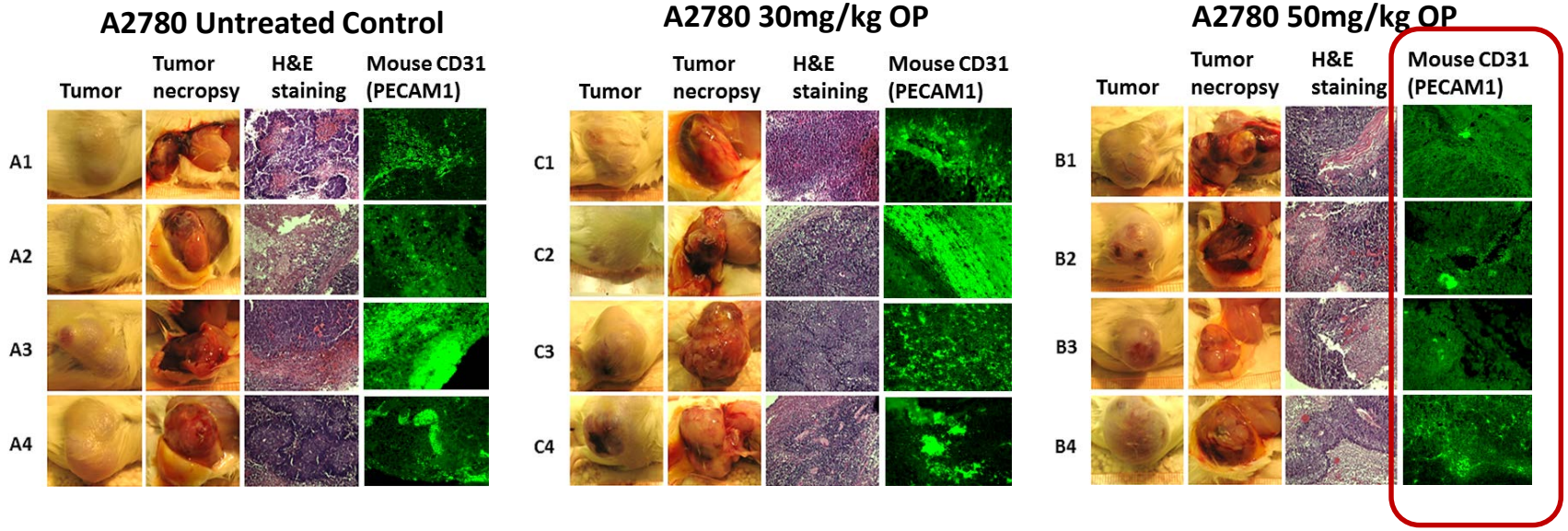
Cell viability of A2780 cells treated with different dosages of OP in combination with 1μM of cisplatin, 5-FU, gemcitabine and paclitaxel



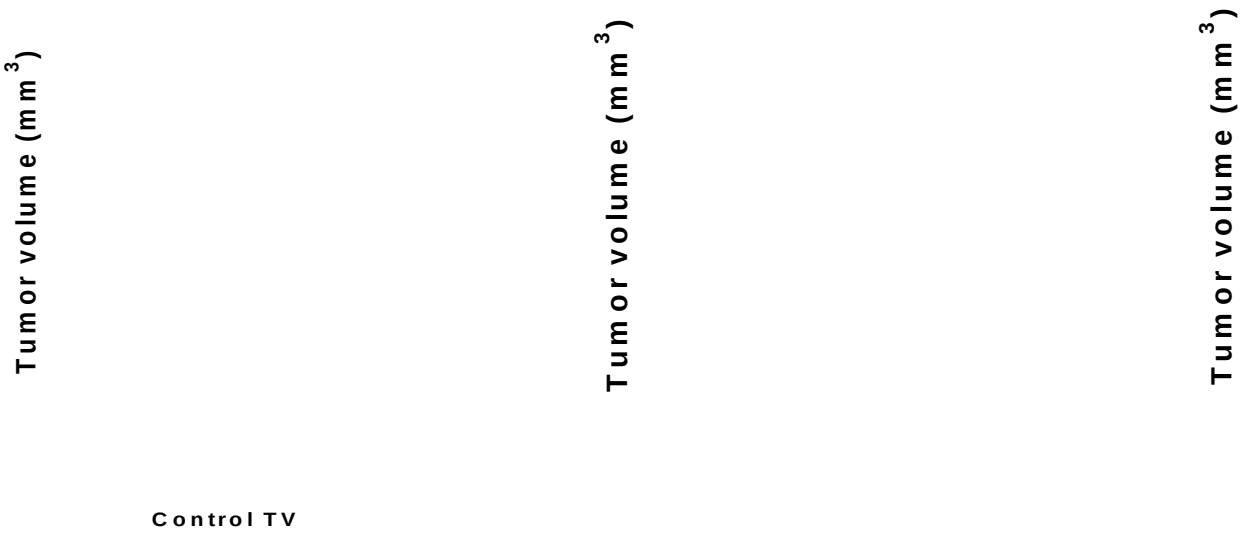
- **Beneficial effect using combination therapy of OP and standard clinical chemotherapeutics on amplifying chemo-drug sensitivity.**
- **Hypersensitivity reactions to oxaliplatin, gemcitabine are noted complications in cancer patients.**

A2780 human ovarian cancer cell line implanted cutaneously in RAGxCγ double mutant mice

A



B



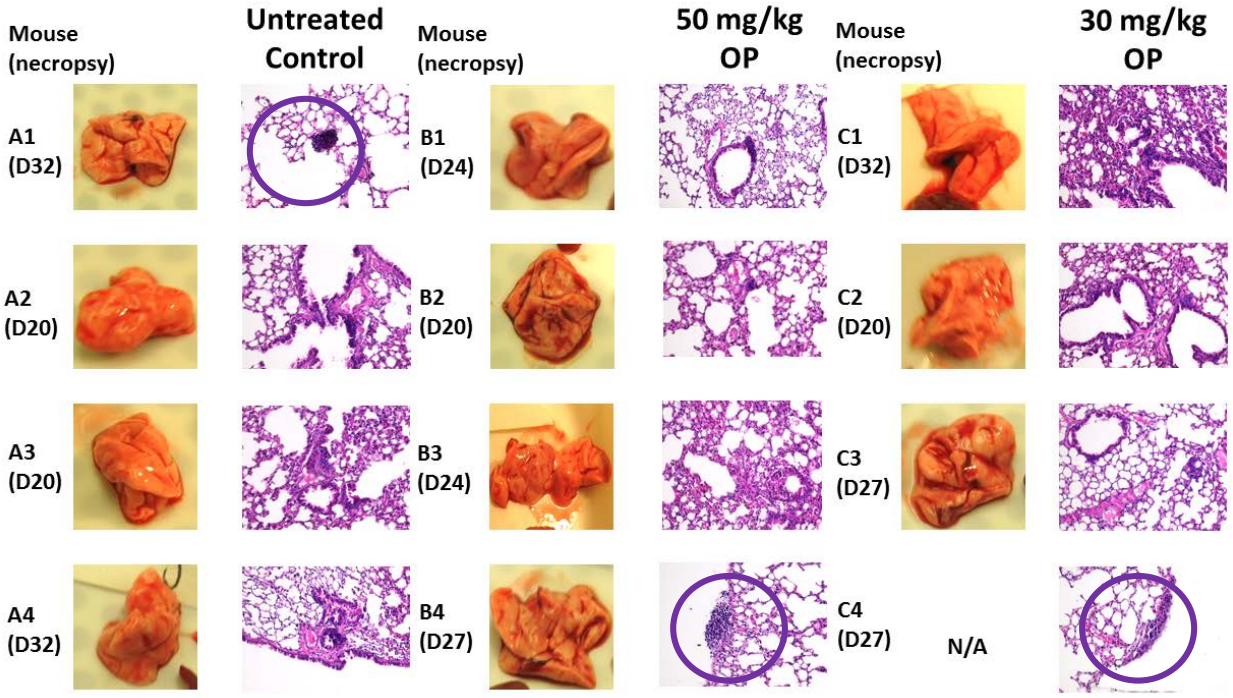
H&E staining of microtome 5µm sections of paraffin-embedded necropsy lungs taken from A2780 tumor-bearing RAGxCy double mutant mice

Lungs

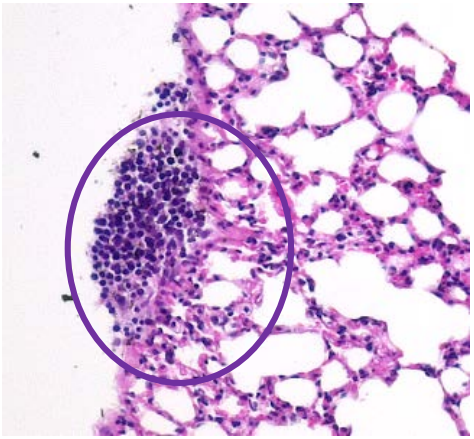
Untreated

OP 50mg/kg

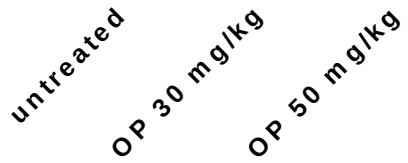
OP 30mg/kg



B

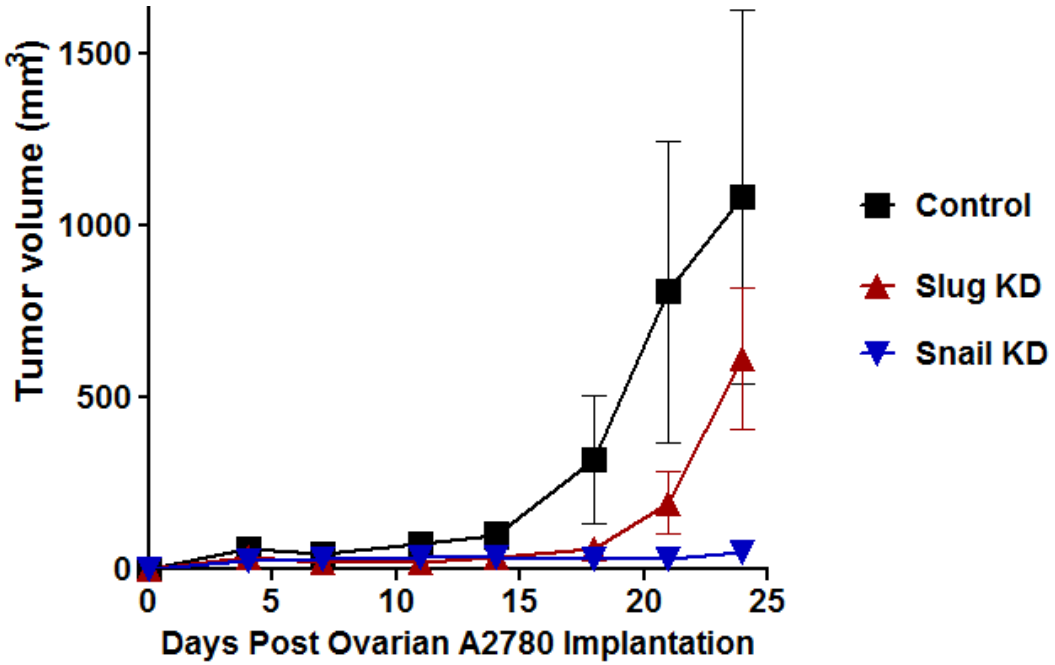






OVARIAN CANCER

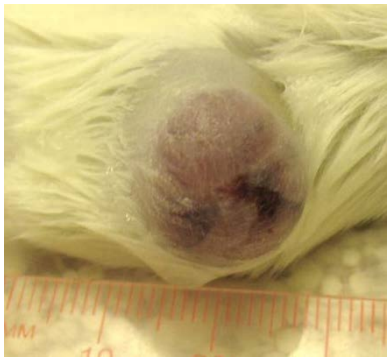
A2780 human ovarian cancer cell line in RAGxCy double mutant mice

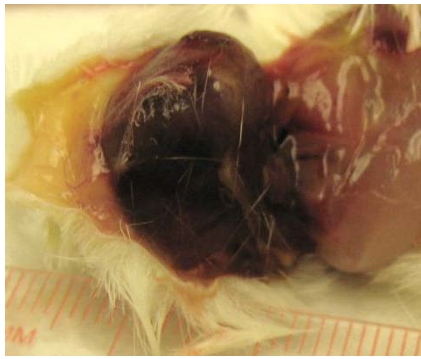


SLUG: represses E-cadherin expression and induces epithelial to mesenchymal transitions

SNAIL: repressor of E-cadherin gene expression in epithelial tumour cells

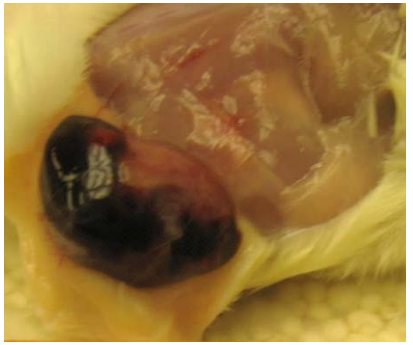
Ovarian A2780



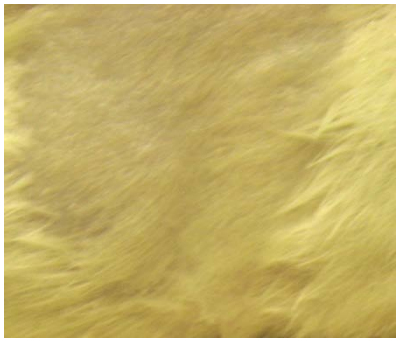


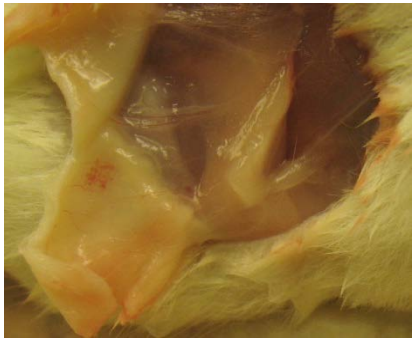
Ovarian A2780 SLUG KD





Ovarian A2780 SNAIL KD





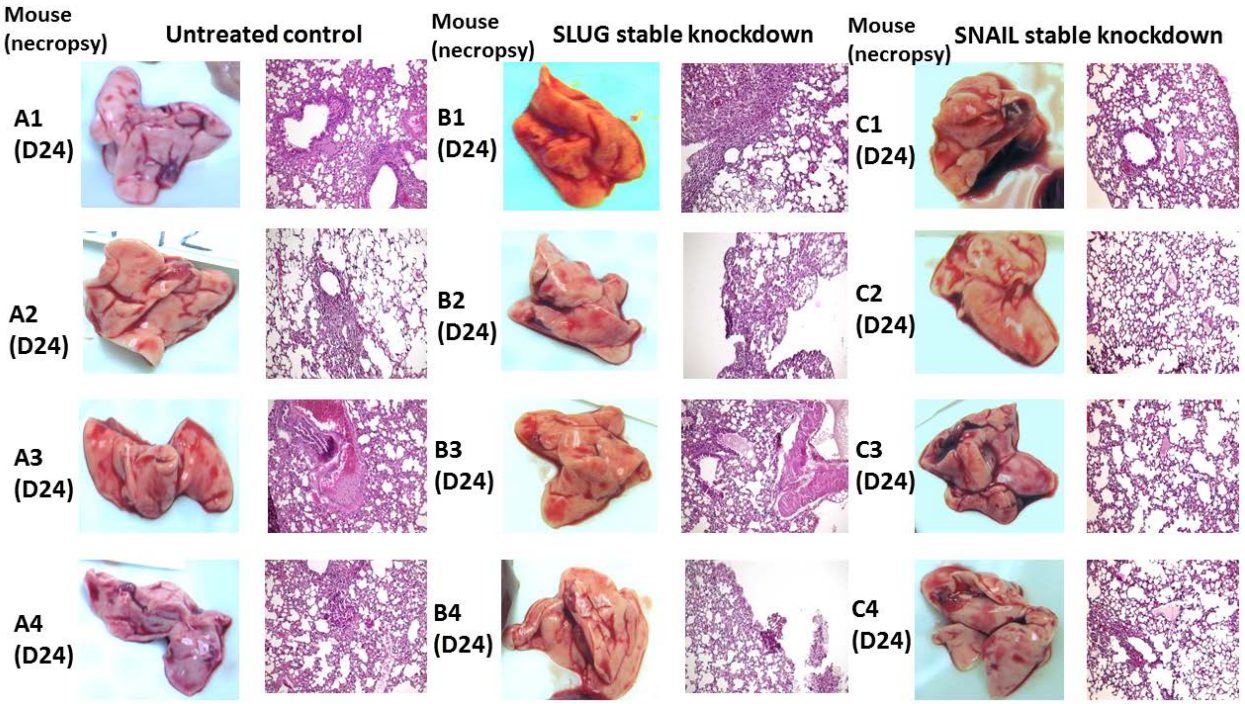
H&E staining of microtome 5µm sections of paraffin-embedded necropsy lungs taken from tumor-bearing RAGxCy double mutant mice

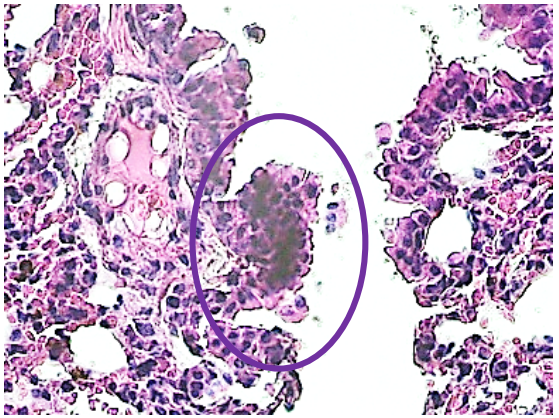
Necropsy Lungs

Untreated

Slug shRNA

Snail shRNA





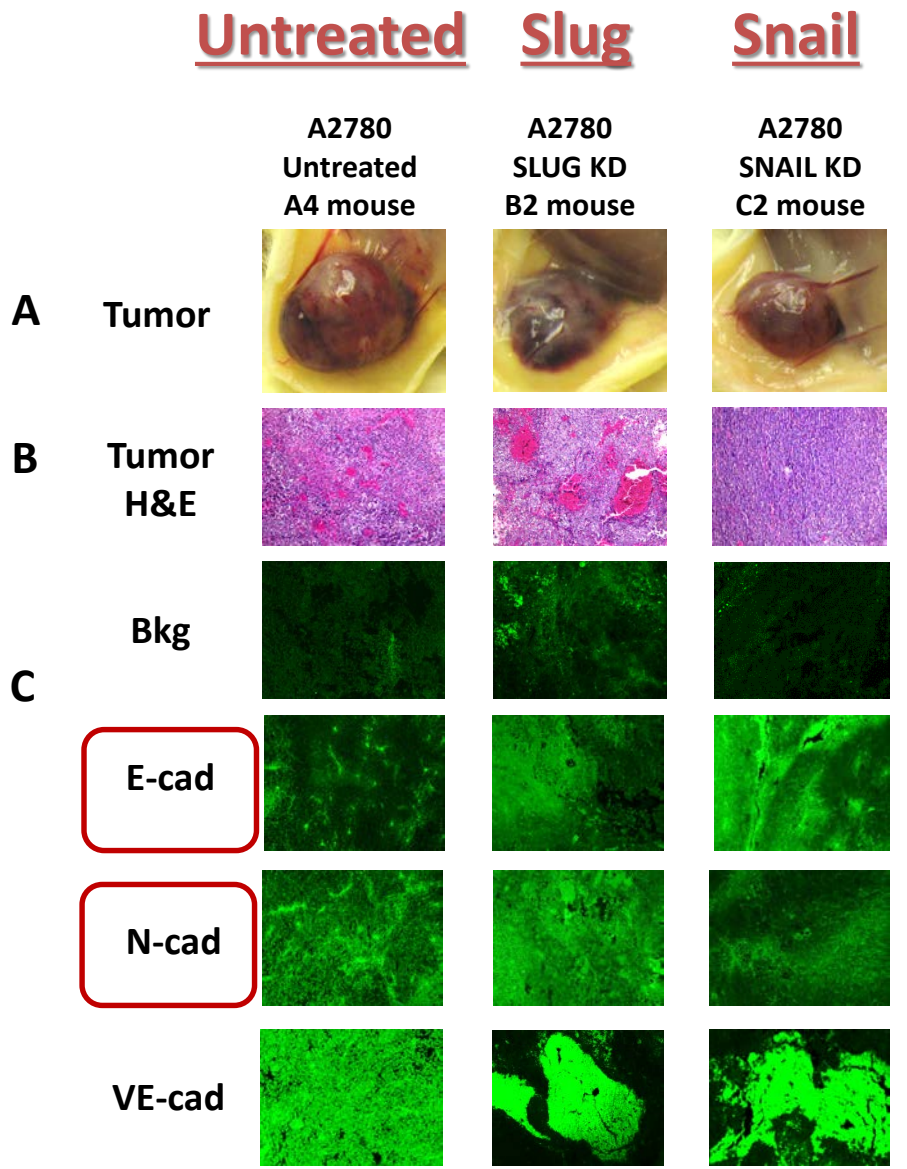
Number metastatic clusters per lung

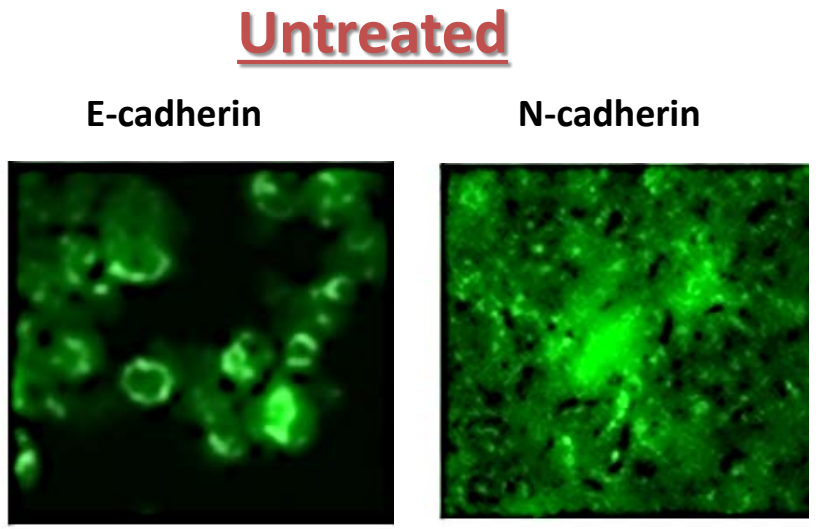
A2780

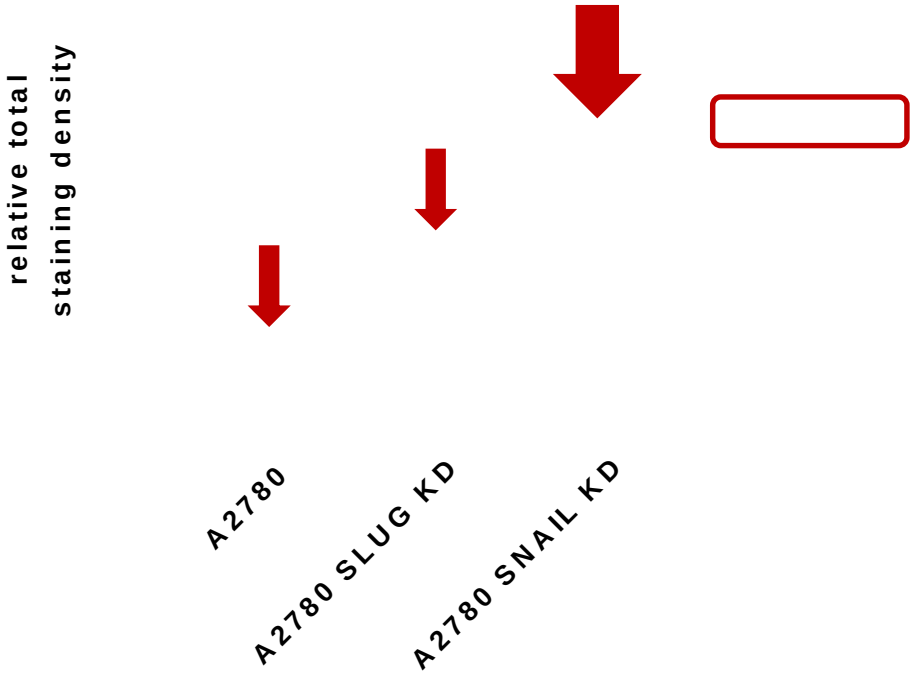
A2780 Slug KD

A2780 SNAIL KD

Necropsy tumors

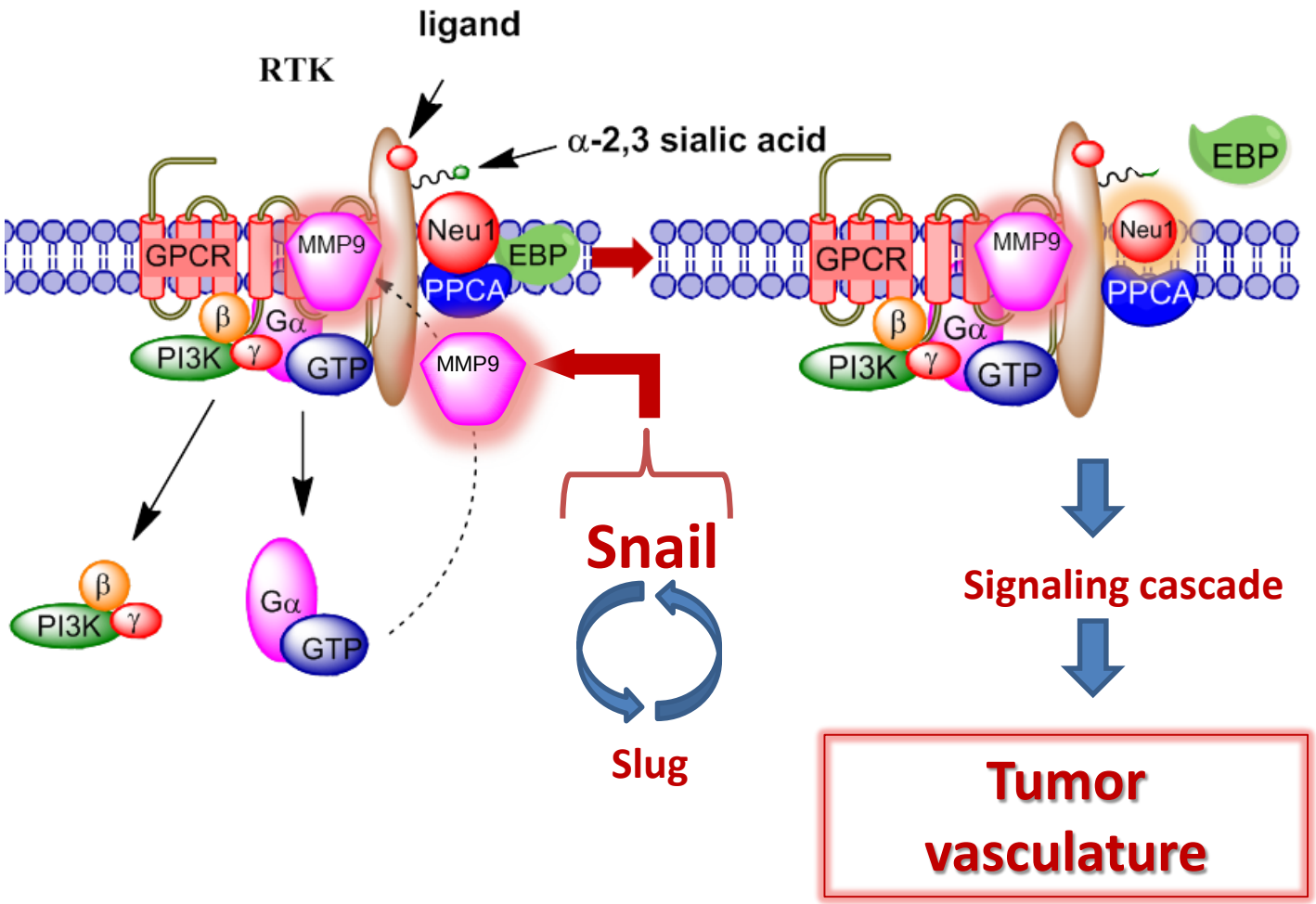






Snail-MMP-9 signaling axis potentiates Neu1 sialidase and MMP-9 cross-talk in regulating RTK receptors, tumor neovascularization, growth and invasiveness

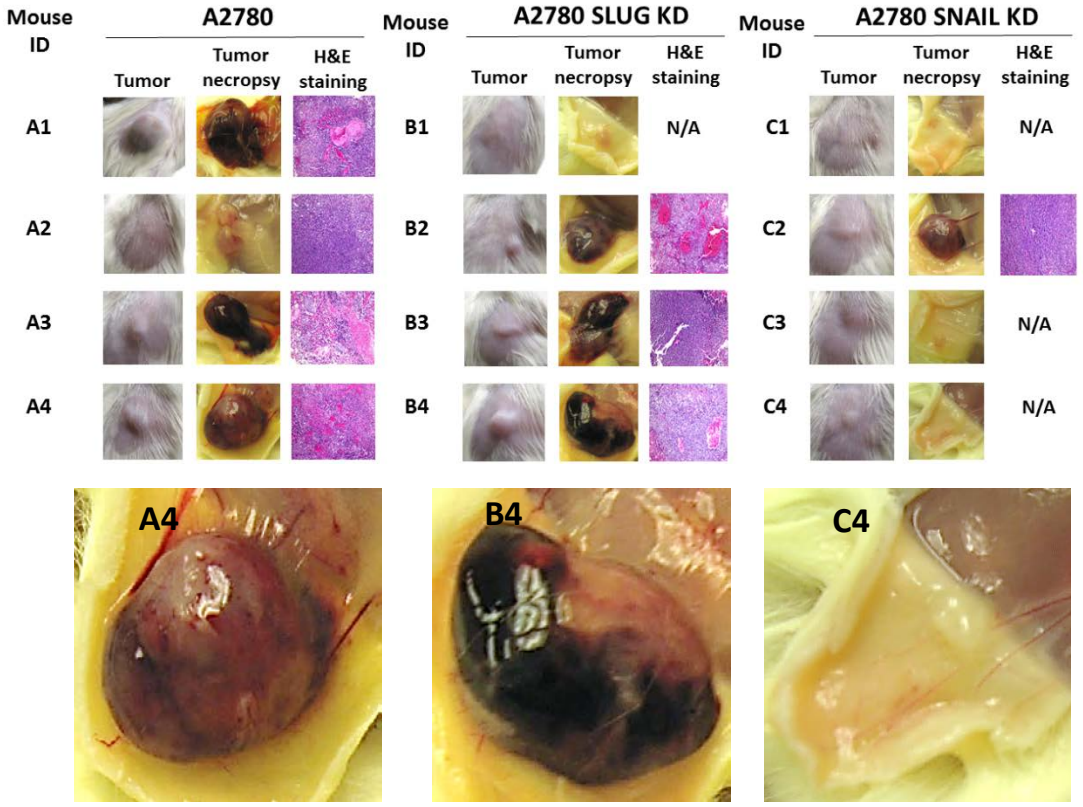
Abdulkhalek et al 2014 Clinical and Translational Medicine 3:28 (open access)



A

Tumor volume (mm^3)

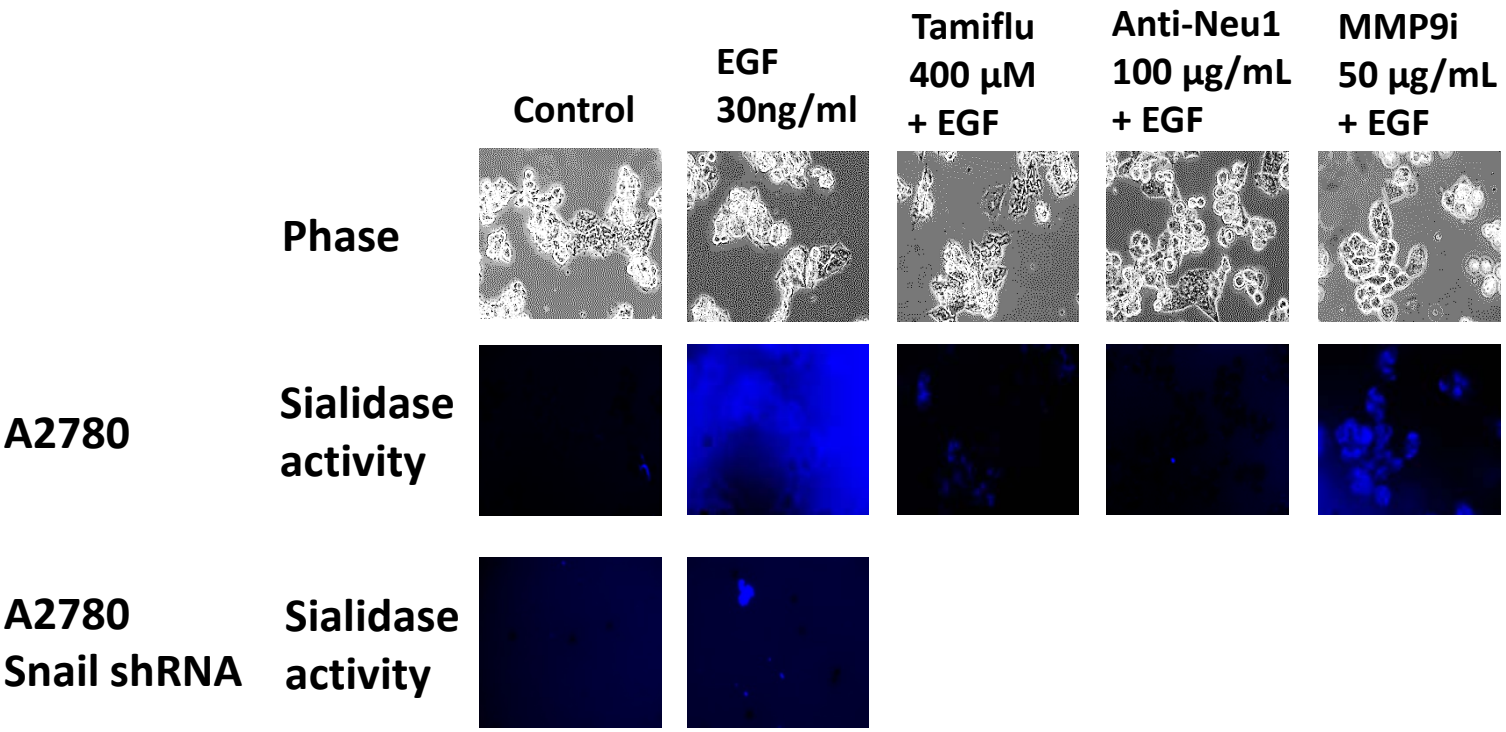
B



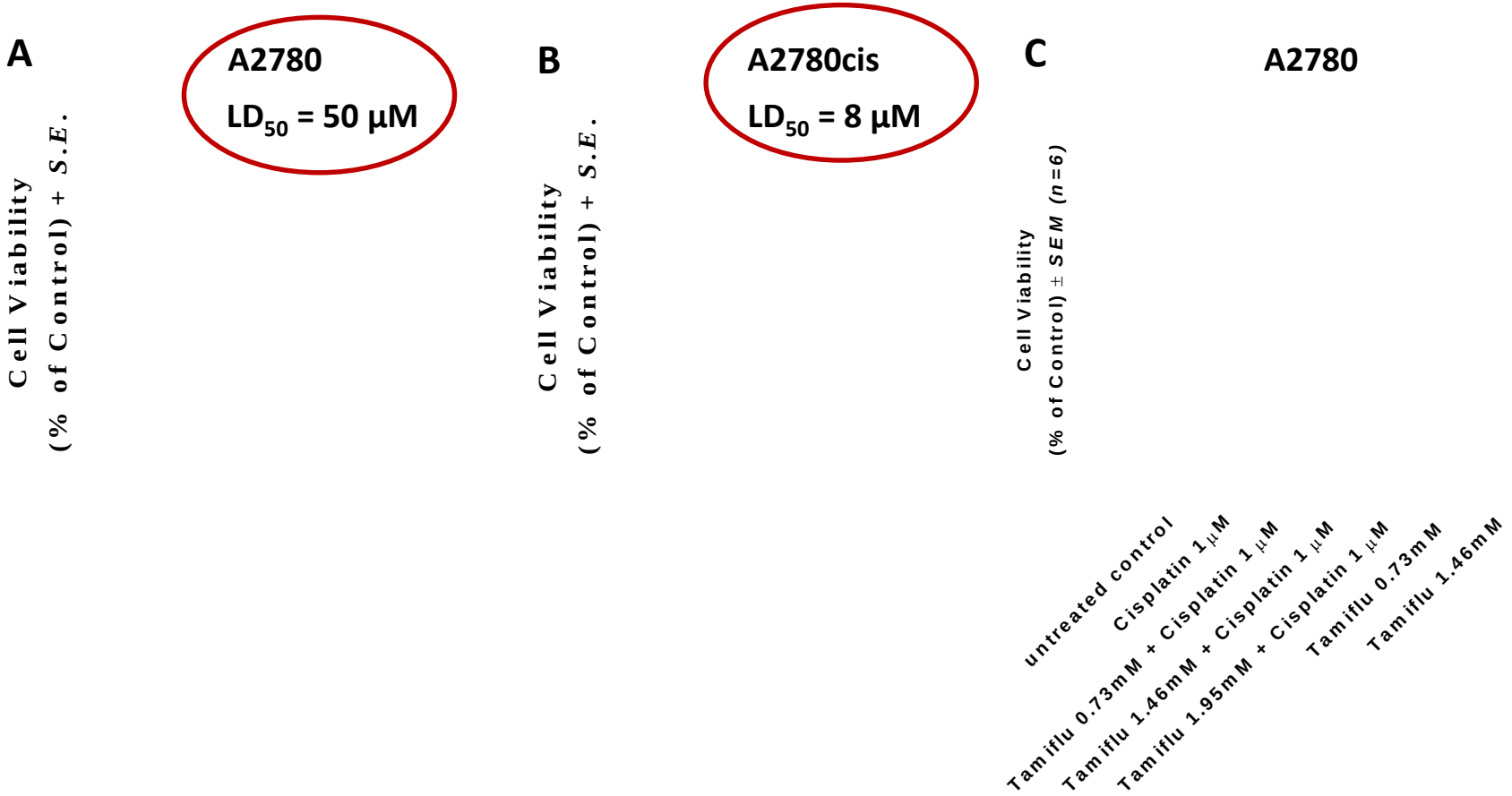
Confidential unpublished data

OVARIAN CANCER

A2780 human ovarian cancer cell line was established from tumour tissue from an untreated patient



Confidential unpublished data



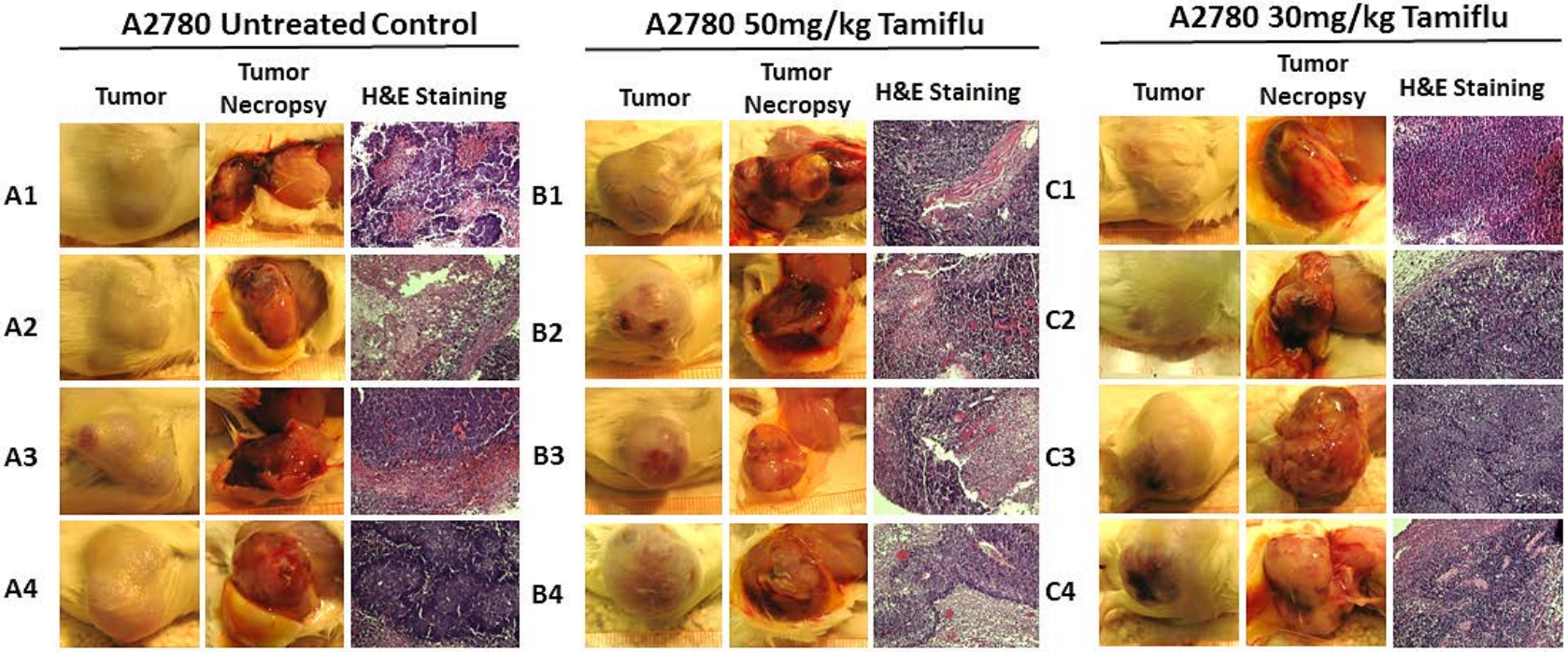
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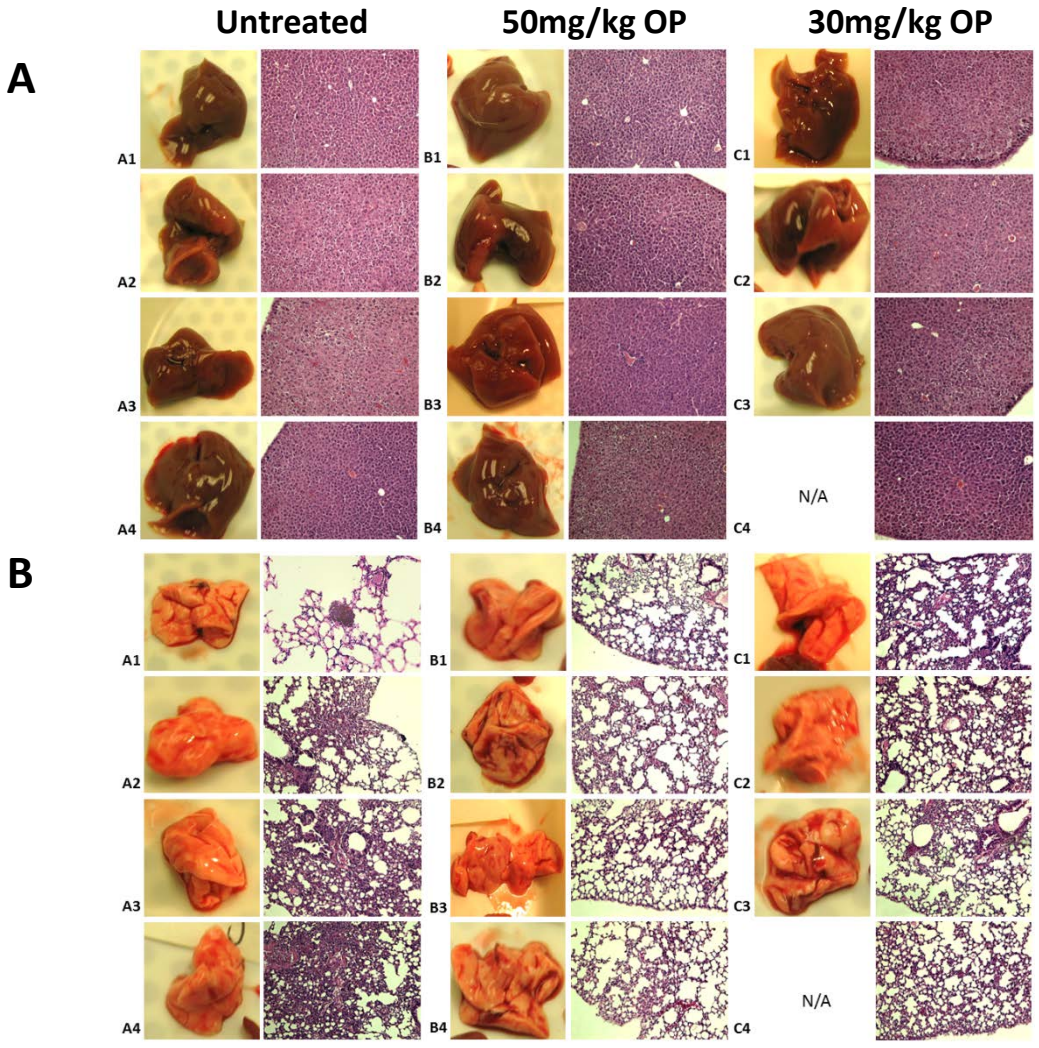
A

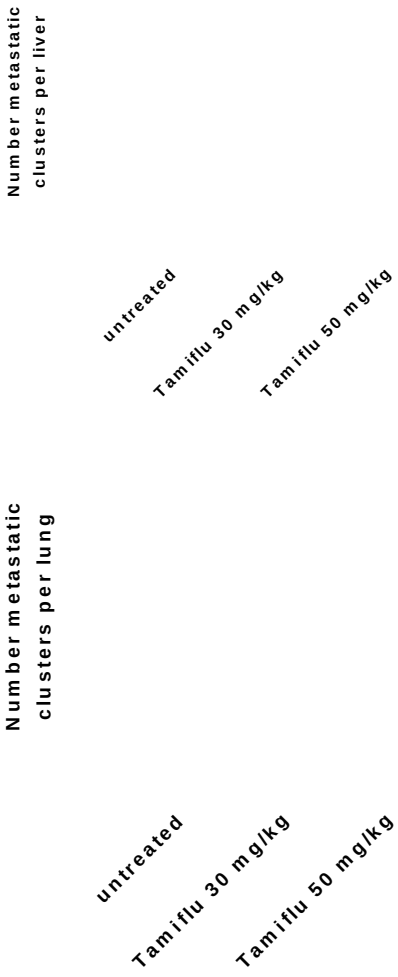
Tumor volume (mm^3)

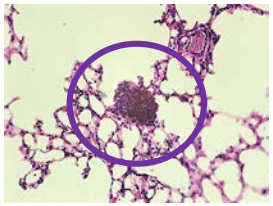
Confidential unpublished data

B

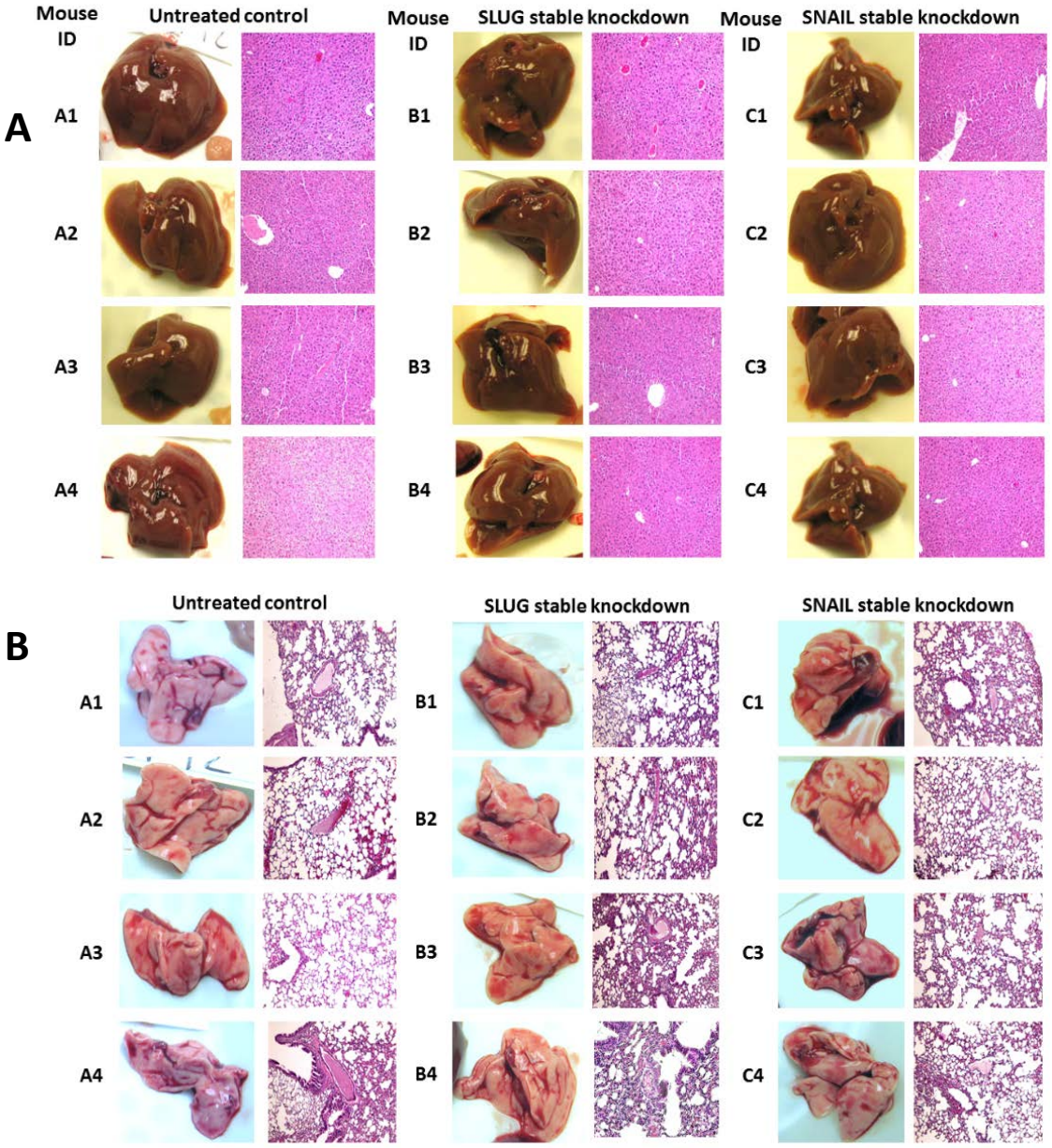


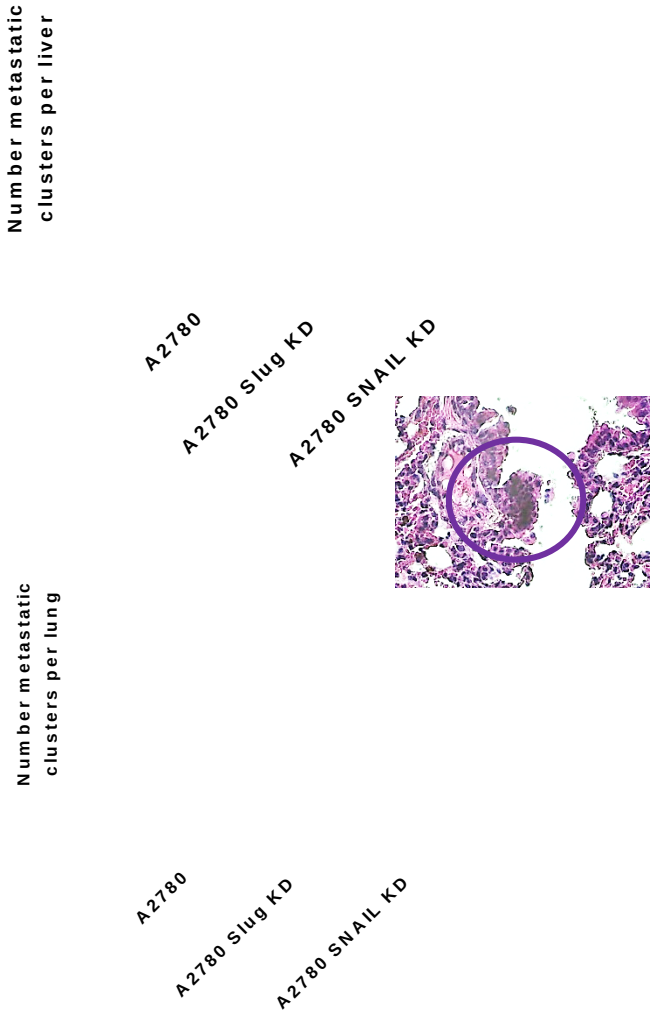




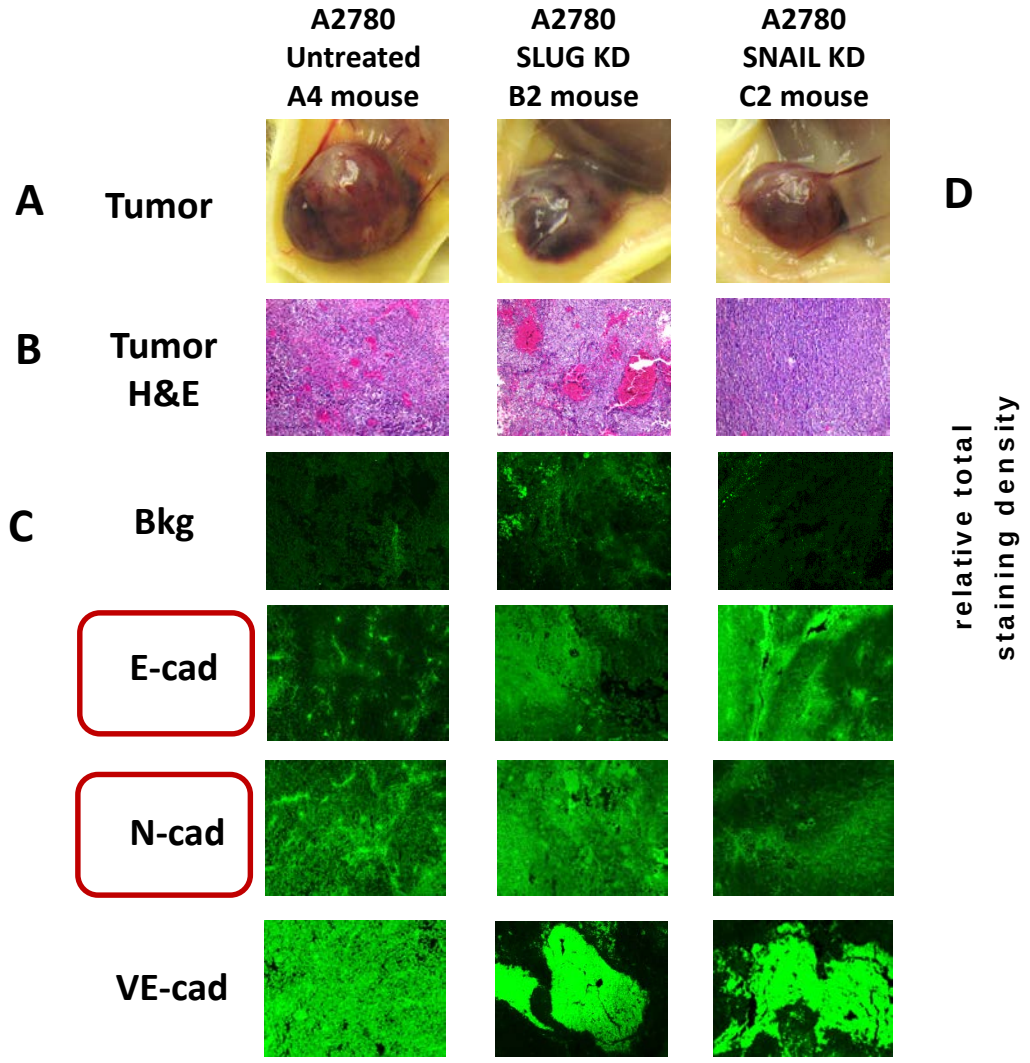


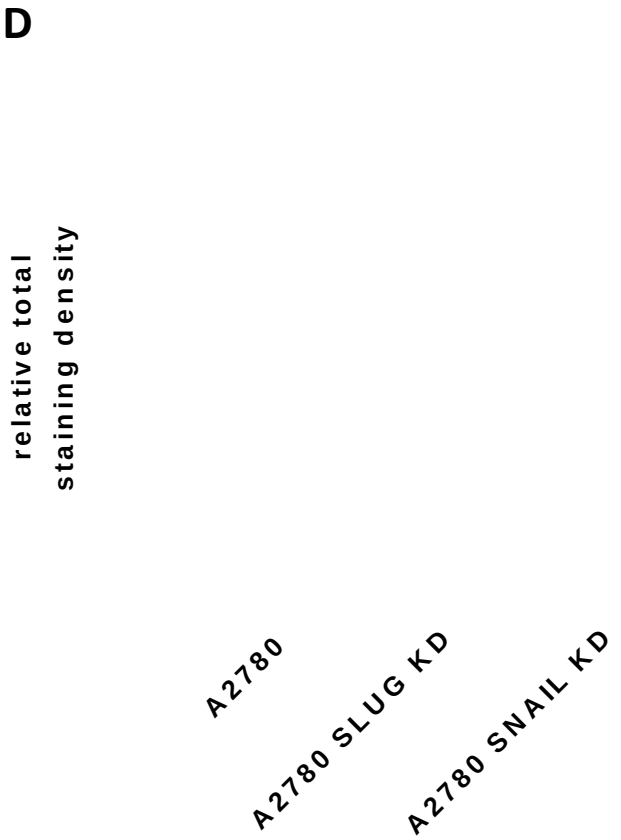
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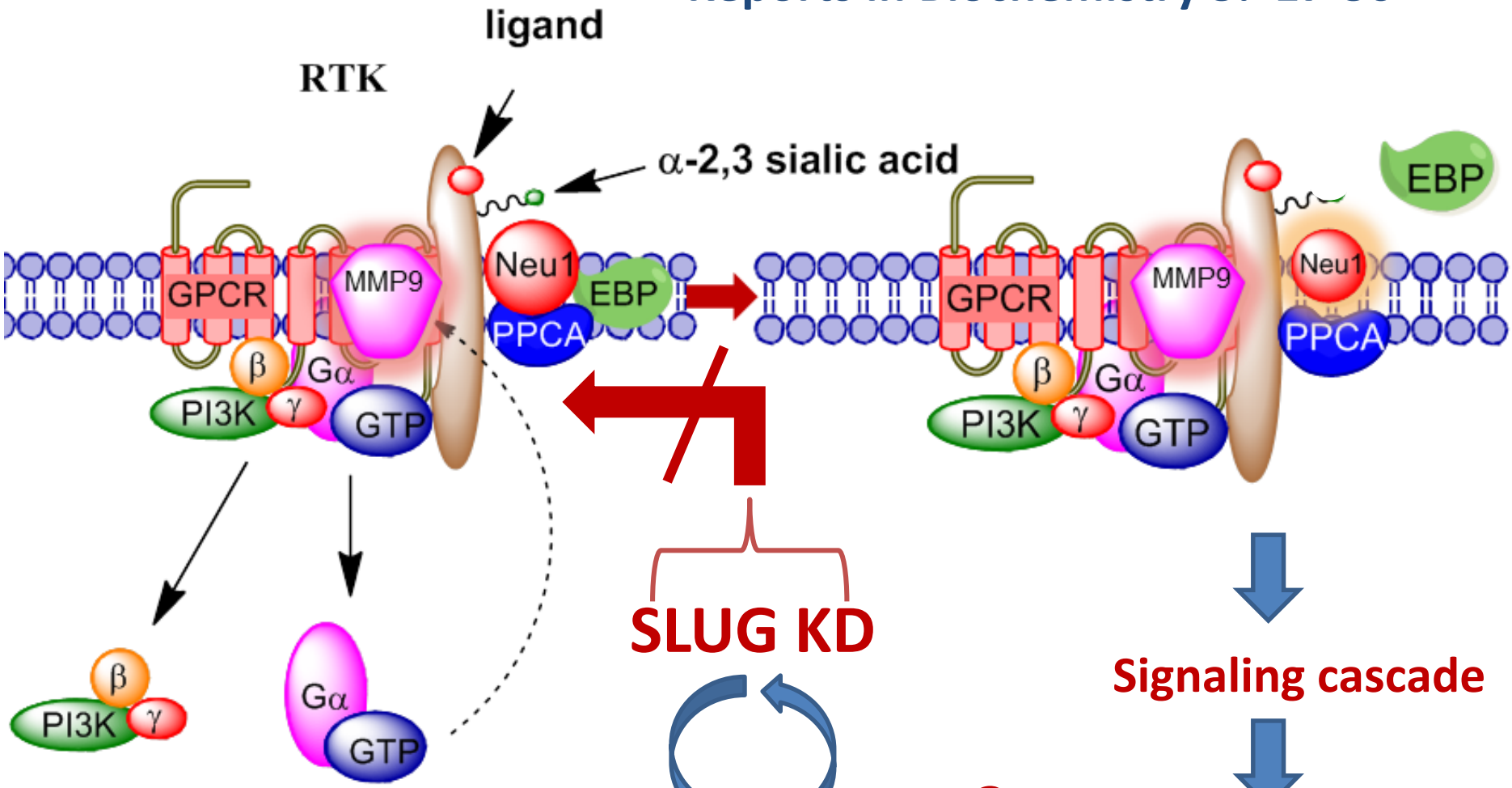
Confidential unpublished data


A2780
Untreated
A4 mouse
A2780
SLUG KD
B2 mouse
A2780
SNAIL KD
C2 mouse
A
Tumor
B
Tumor
H&E
C
Bkg
E-cad
N-cad
VE-cad


D
relative total
staining density
A2780
A2780 SLUG KD
A2780 SNAIL KD

Novelty

Abdulkhalek *et al* *2013* Research and Reports in Biochemistry 3: 17-30



SLUG KD

Signaling cascade

SNAIL: a zinc finger transcriptional repressor

SNAIL KD

?

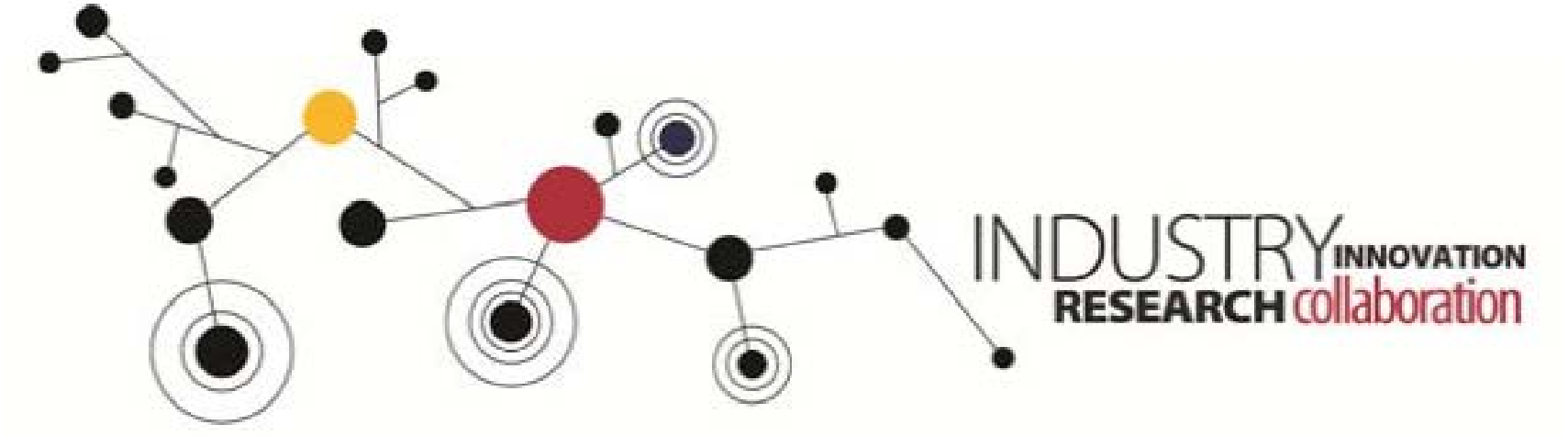
Tumor vasculature secreted cytokines

Snail genes act primarily as survival factors and inducers of cell movement

Conclusions

- **Tamiflu provides an unexpected therapeutic benefit in cancer, by**
  - **interfering with growth factor receptor-induced survival signals and**
  - **disabling cancer cell survival in acquire chemo-resistance.**

- **Tamiflu alone or in combination with chemotherapeutics against pancreatic and breast impedes the *growth* and *metastatic spread*, *tumor neovascularization* and *chemo-resistance* in heterotopic xenograft of tumors growing in RAGxCγ double mutant mice.**



Priority #1: **"Clinical trials"**

Priority #2: **To study the broad range efficacy of Tamiflu therapy in combination with standard chemotherapeutics.**

Priority #3: **To test this novel therapy on surgically obtained patient primary tumors in culture**