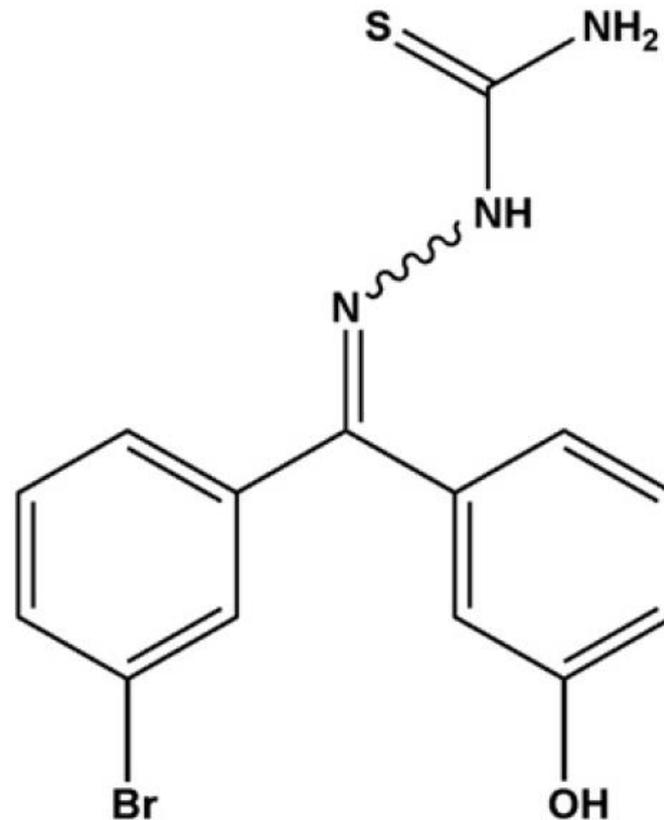


Inhibiting the actions of cathepsin L affects both tumour initiation and metastasis formation.



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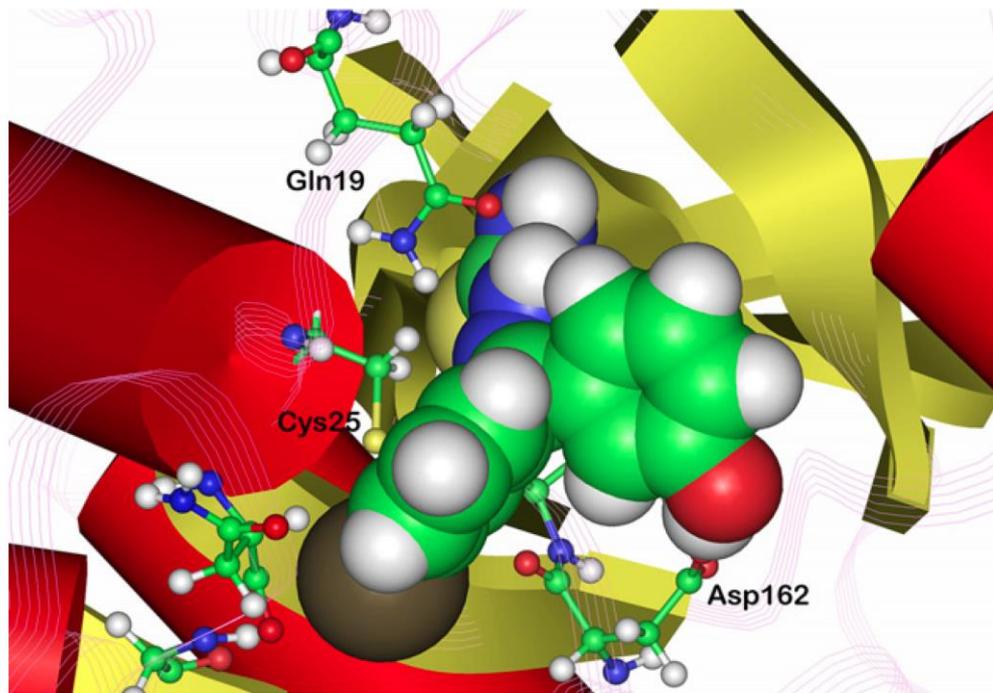
Background

- Cathepsin L (CTSL) is a proteolytic enzyme belonging to the group of lysosomal cysteine proteases
- Expression and activation of CTSL is elevated in cancer cells
- Secretion of CTSL from tumour cells enhances migration and aids in tumour invasion and angiogenesis formation

Aim

To investigate the effects of KGP94 (a CTSL-inhibitor) on primary and metastatic tumours

KGP94 - Cathepsin L inhibitor

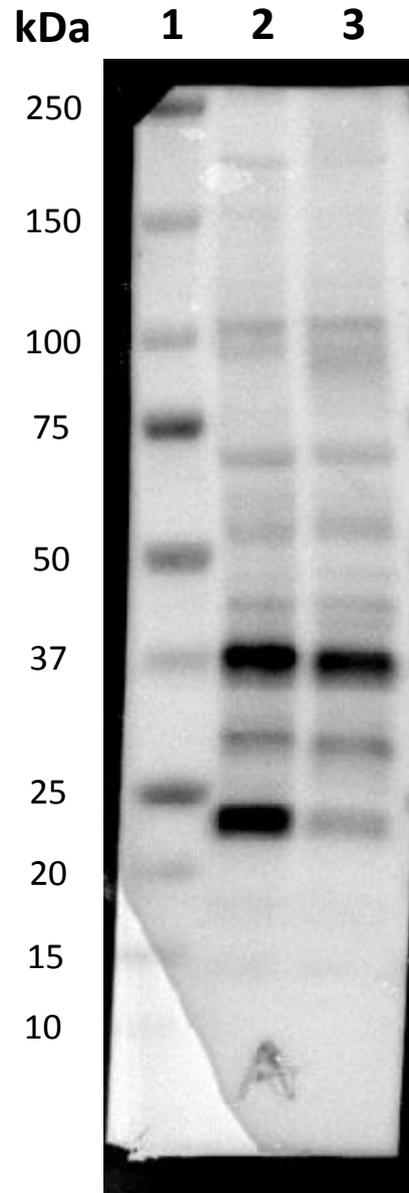


- Acts reversibly at the active site of cathepsin L.
- Inhibits cathepsin L's collagenase activity.
- Inhibits invasion and migration of MDA-MB-231 cells.

Binding of KGP94.

From Chavarria et al. *European Journal of Medicinal Chemistry* 58 (2012) 568-572.

Cathepsin L in the C3H mammary carcinoma



Lane 1: Protein marker

Lane 2: Foot with tumour

Lane 3: Foot without tumour

← Procathepsin L

← Mature cathepsin L

Tumour growth experiments

- *Tumour initiation*
 - KGP94 was intraperitoneally injected daily from the day of tumour implantation and for five days.
 - Growth delay as a function of KGP94 dose. Dose varied from 1-20 mg/kg. C3H and SCCVII murine models.
- *Established tumours*
 - KGP94 was intraperitoneally injected daily for five days when tumour reached a volume of 200mm³
 - Growth delay as a function of KGP94 dose. Dose varied from 1-20 mg/kg. C3H murine model.

C3H is a mammary carcinoma, and SCCVII is a squamous cell carcinoma
Both are subcutaneously implanted on the right rear foot of the animals

Tumour growth experiments

The tumours were measured on a daily basis.

Tumor response

Established

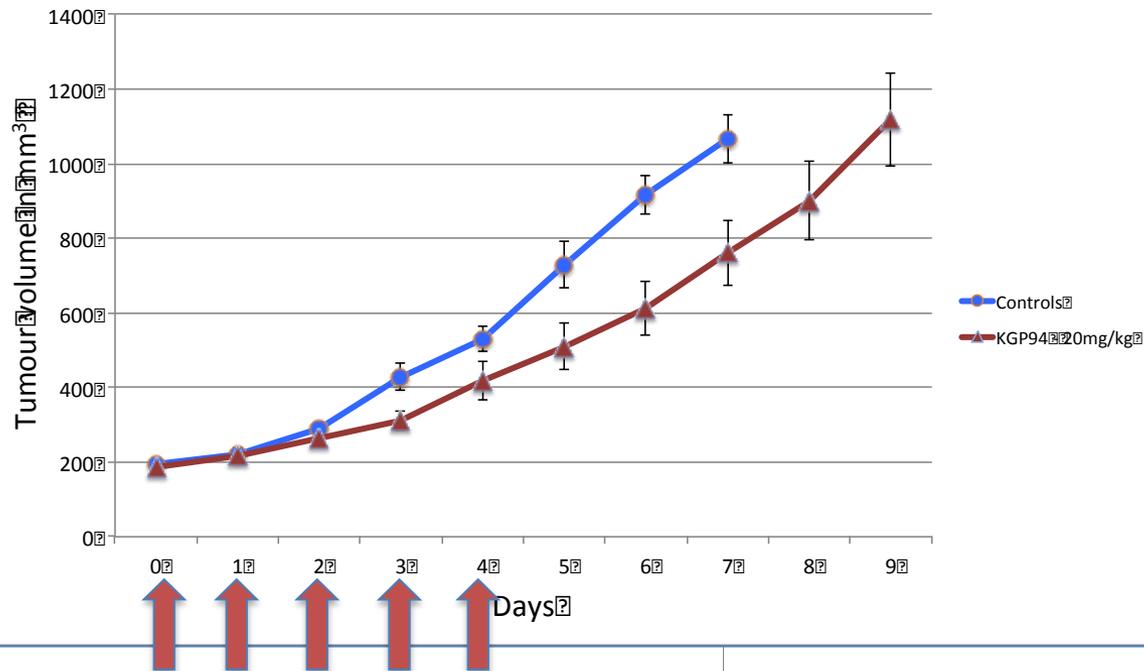
-Time in days to reach 5 times starting volume (TGT₅)

Initiation

-Time in days to reach a tumour volume of 500 mm³ (TGT₅₀₀)



KGP94 Established tumours (C3H) Growth curves

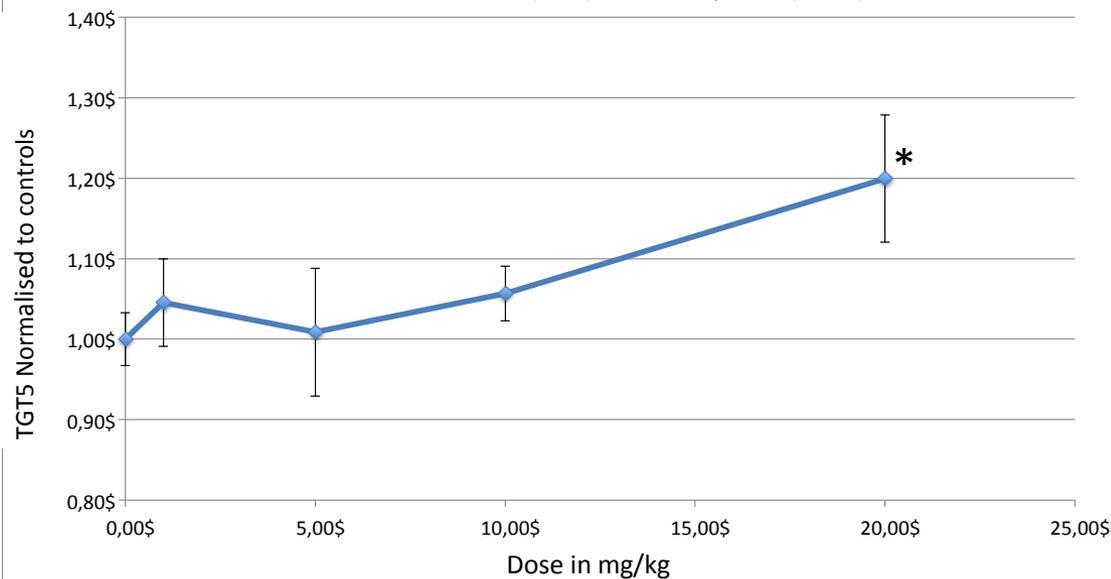


TGT5

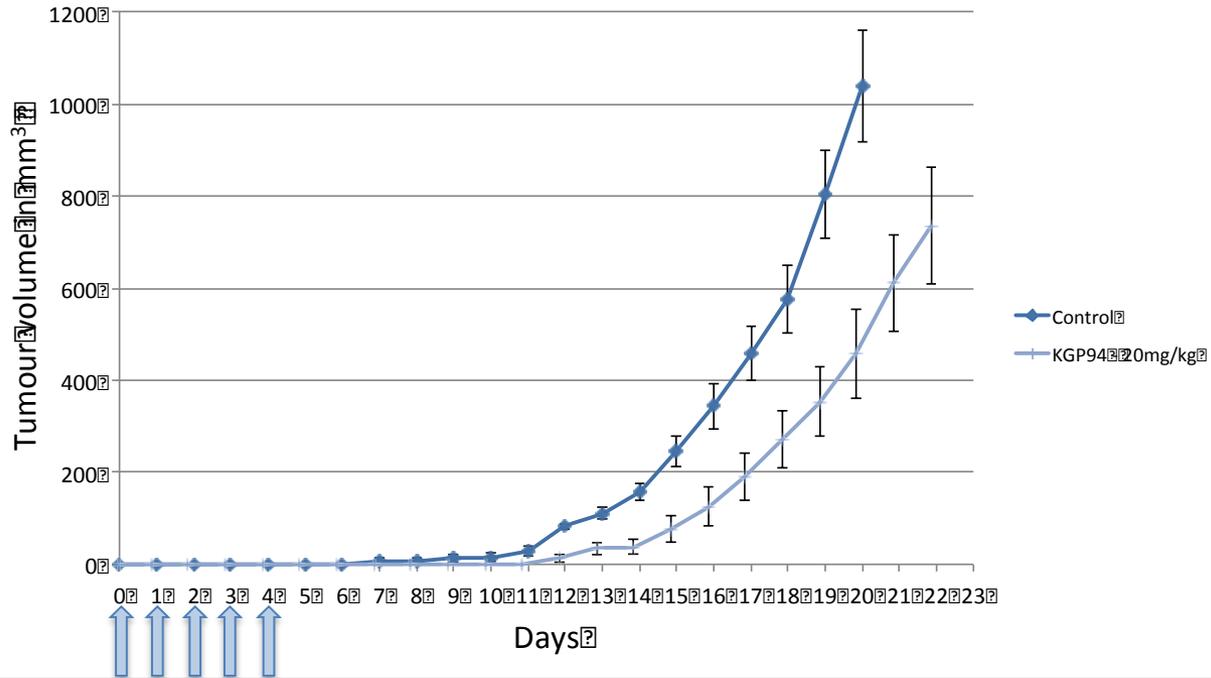
- Controls 6.5 days
- KGP94 (20 mg/kg) 8.5 days

Dose at 20 mg/kg was significant.

KGP94 Established tumours (C3H) - Dose response (TGT5)



KGP94 Tumour Initiation (C3H) Growth curves

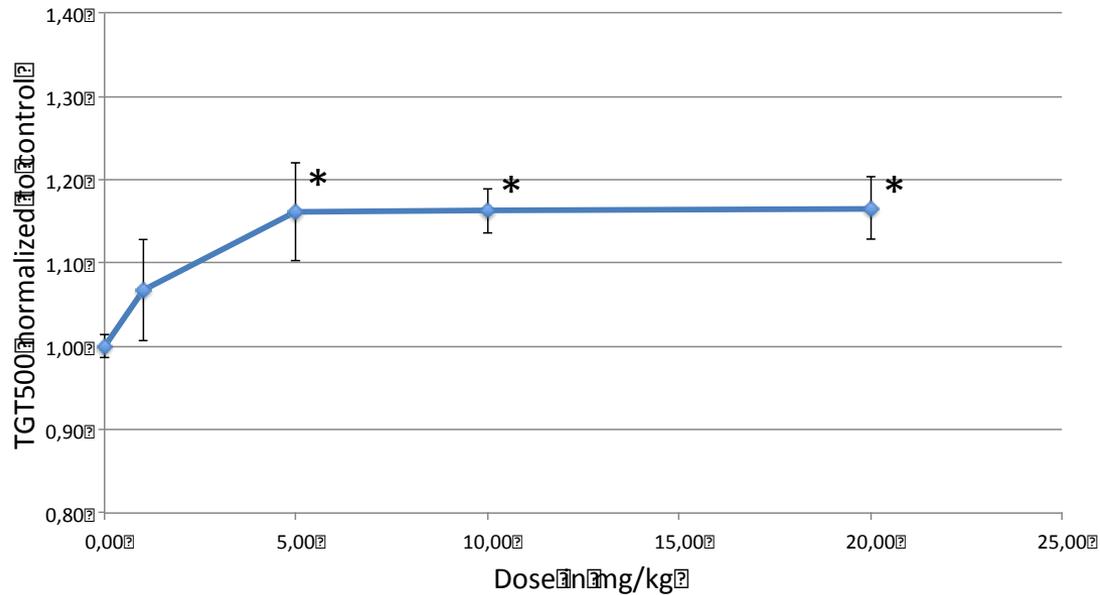


TGT₅₀₀

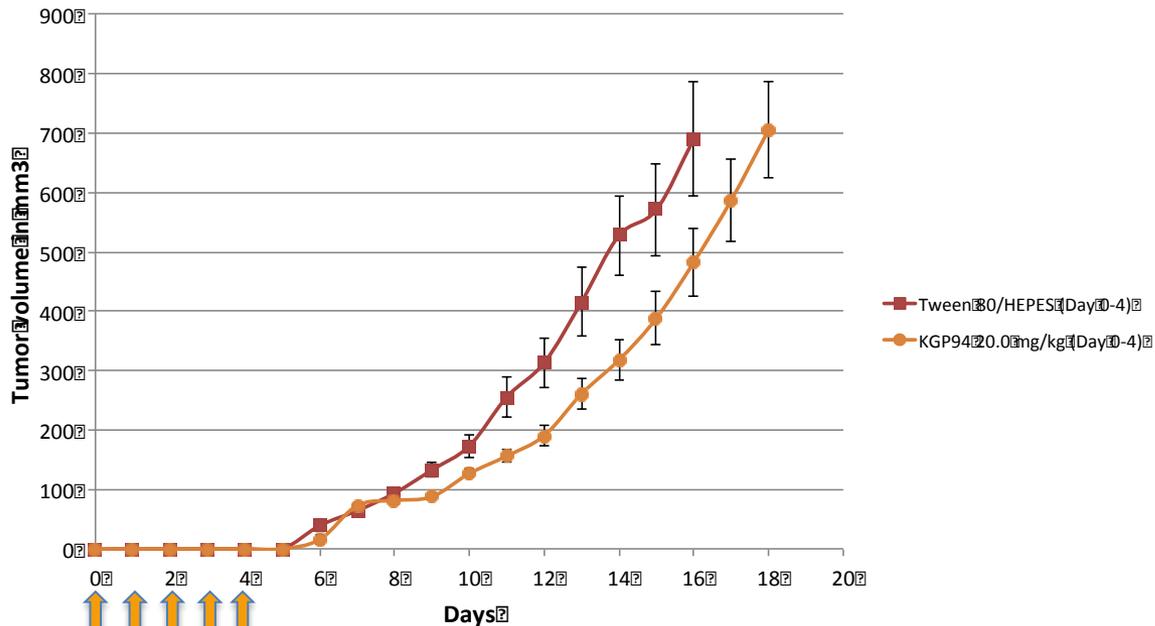
- Control 18.5 days
- KGP94 (20 mg/kg) 21 days

KGP94 doses at 5 mg/kg or higher were significant

KGP94 Tumour Initiation (C3H) Dose response (TGT500)



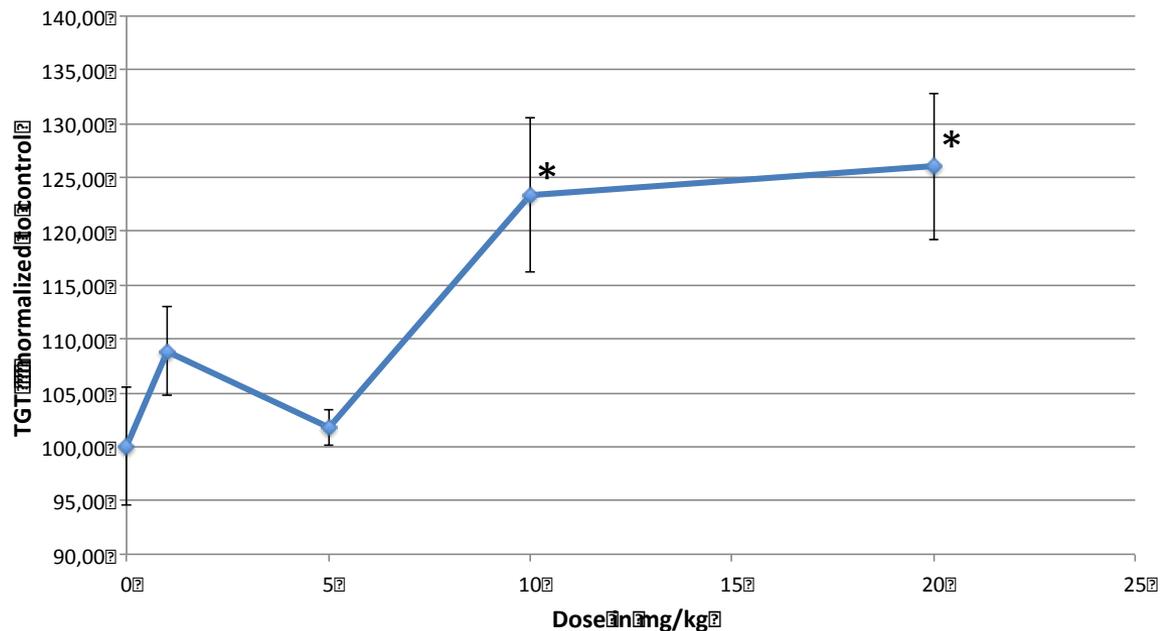
KGP94 Tumour Initiation (SCCVII) Growth Curves



TGT₅₀₀ Controls 13.5 days
 TGT₅₀₀ KGP94 17 days

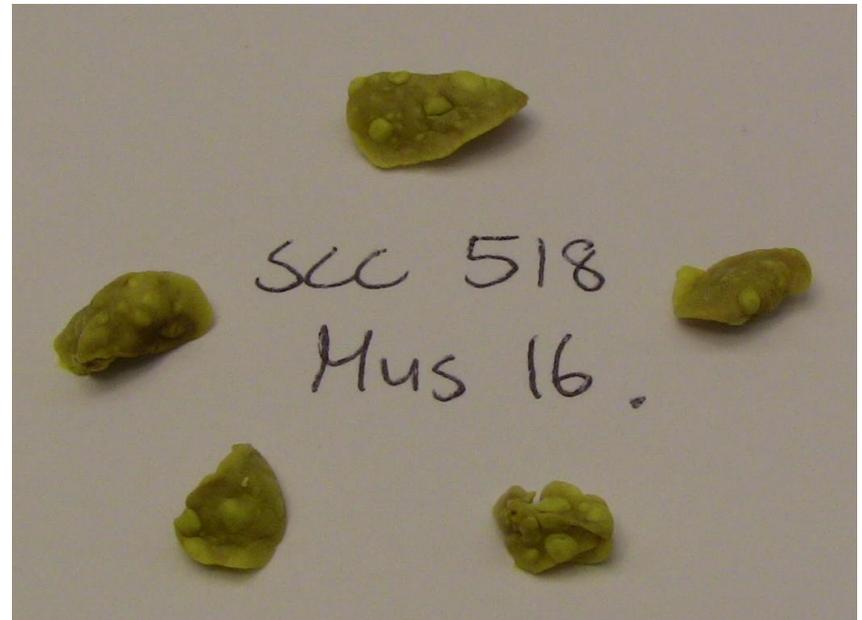
KGP94 doses of 10 and 20 mg/kg significantly increased TGT₅₀₀

KGP94 Effect on Tumour Initiation (SCCVII) TGT₅₀₀ as a function of dose



Metastasis experiment

- Metastasis study
 - SCCVII-tumour inoculated on foot
 - 5 days after inoculation mice were treated with KGP94 10 mg/kg or drug solvent for 10 days.
 - 15 days after inoculation, mice were euthanized
 - Lungs excised, stained in Bouins solution
 - Number of lung metastasis counted



Treatment	No. of mice with metastasis	Average number of metastasis
Control	5/10	16 +/- 15
KGP94 (10 mg/kg)	3/10	5 +/- 4

Summary

- KGP94 significantly delayed tumour growth of the murine C3H and SCCVII carcinomas, when treatment was initiated on the day of tumour inoculation
- Results from the metastasis study showed decreased metastasis formation in KGP94 treated animals
- This suggests that KGP94 treatment can affect both tumour initiation and metastasis formation

Pharmacokinetics of KGP94

Single and multiple injections

