PharmaTrain
MASTERING MEDICINES DEVELOPMENT

CEMDC Cooperative European Medicines Development Course

Home Assignment

Actos/Pioglitazone –Bladder Cancer

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Pioglitazone

- Pioglitazone was first approved in 1999 in the United States and in 2000 in the European Union as Actos.
- Pioglitazone is also authorised in the EU as the fixed-dose combination products Competact and Glubrava (pioglitazone + metformin) and Tandemact (pioglitazone + glimepiride).
- Pioglitazone is a member of the thiazolidinedione (TZD) class of antidiabetic agents.

Carcinogenic Potential of Pioglitazone

NON GENOTOXIC

RAT TOXICOLOGY:

Repeated Dose Studies:

-Increased urothelial hyerplasia in males and in females (at 63mg/Kg)

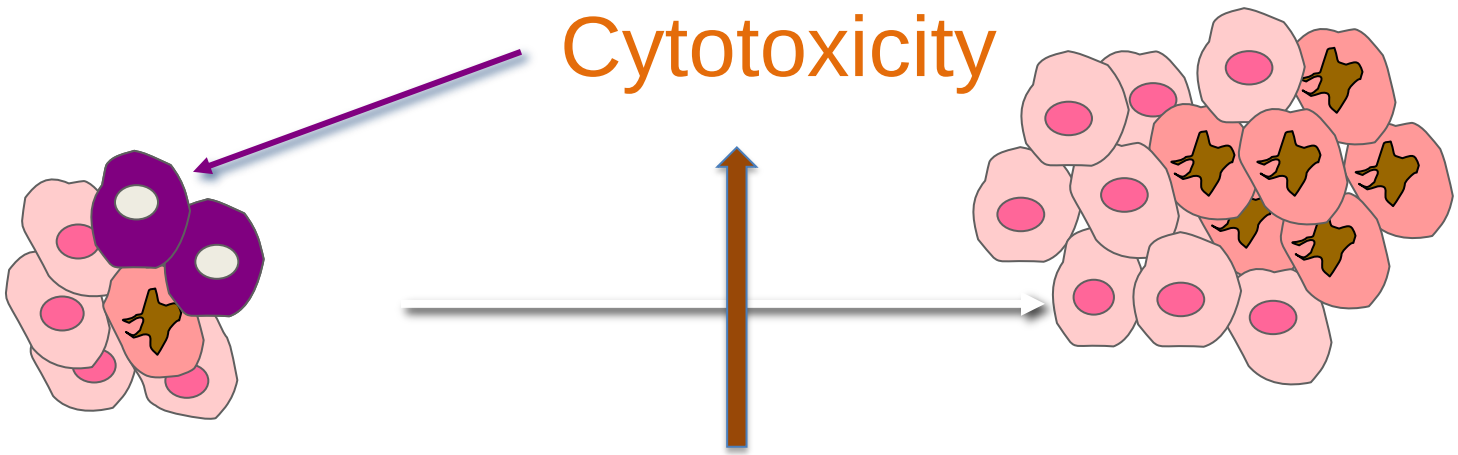
2Y Carcinogenicity:

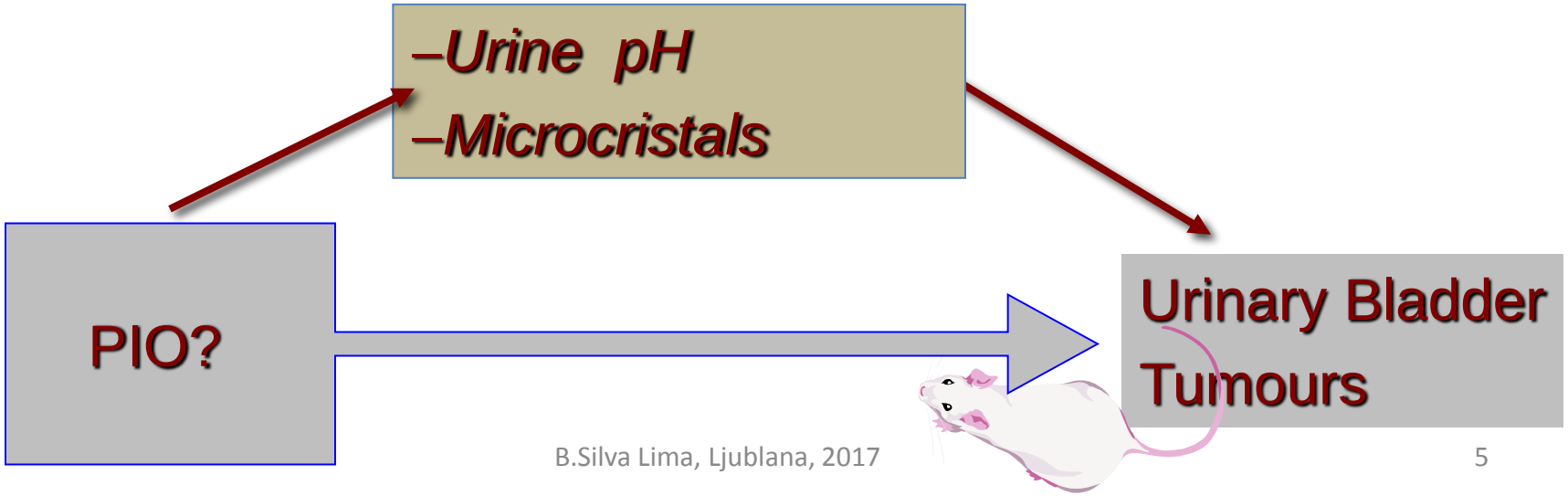
-urothelial transitional cell adenoma/carcinoma in males only (from 4mg/Kg).

ACTOS-Pioglitazone
2Y Rat Carcinogenicity Study

Dosage (mg/kg/day)	Vehicle	Placebo	1	4	8	16	63
Number of animals	60	60	60	60	60	60	60
Hyperplasia							
Simple	1	3	0	2	7	10	7
Papillary	3	0	1	2	1	1	1
Nodular	0	0	0	0	1	0	0
Tumour							
Benign	0	0	0	0	3 [1)]	2	2
Malignant	0	0	0	2	4	5 [2), 3)]	4
Proliferative lesion	4	3	1	6	16	18	14
(%)	6.7%	5.0%	1.7%	10.0%	26.7%	30.0%	23.3%

Applicant's proposed Mechanism
The Cristal Theory of PIO-induced tumorigenesis



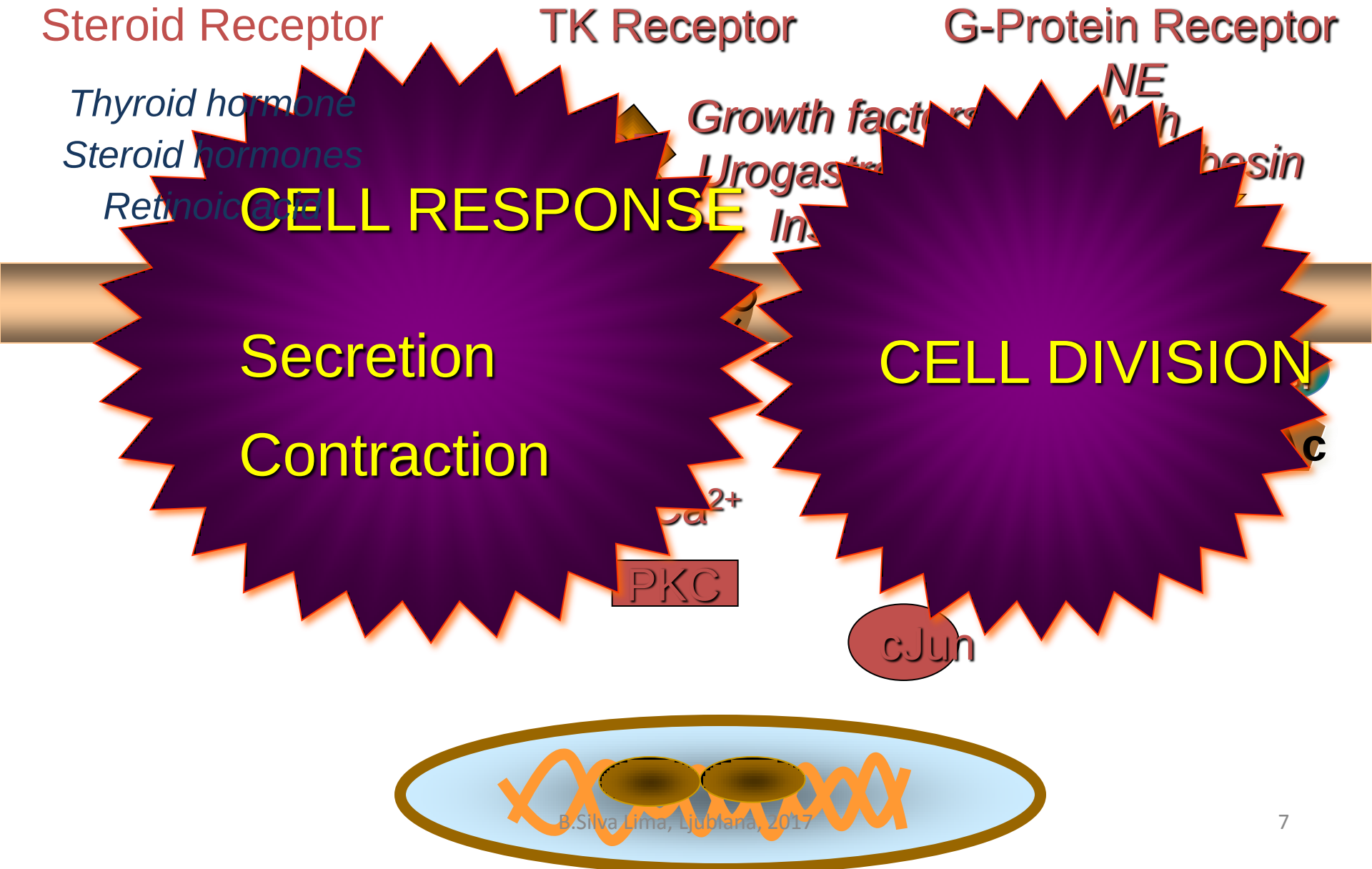


CHMP Position

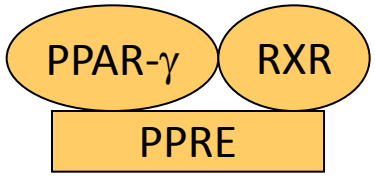
- 1st mechanistic study:
  - Only 60% correlation between urinary cristals and tumors was observed.
  - Although cristals may be involved, a PPAR-gama-mediated promoting effect cannot be excluded.
  - -Human relevance to be further addressed.
  - (PPARgama presence in the bladder not known yet)

Mechanisms of Non-genotoxic Carcinogenesis

Receptor-mediated tumorigenesis



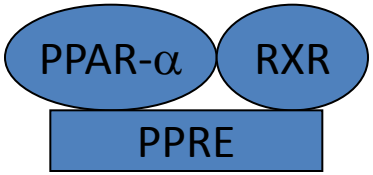
PPAR – Mediated Effects



Cellular:
↓cytokines, resistin, FFA, NF-kB;
↓ TNF-α; ↑GLUT4,

Skeletal muscle: ↑glucose uptake;
Glicogen synthesis;

Insulin sensitivity
Glucose homeostasis
Vascular integrity

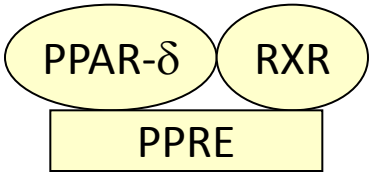


Liver:
↑FA oxidation; ApoA-1; LPL; ↓ApoC-III

Vessel wall:
↓cytokines, NF-kB;
↑ACBA1, APO-E

Heart:
↓LPL, FA oxydation

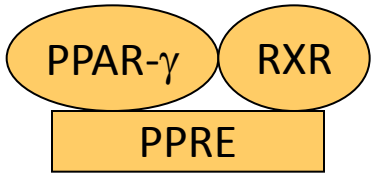
Blood:
↓ FFA oxidation; TG; VLDL
↑HDL



Skeletal muscle / liver / adipocyte:
↑FA oxidation; UCP;
↓TG; HDL

Lipid Homeostasis
Glucose homeostasis
Vascular integrity

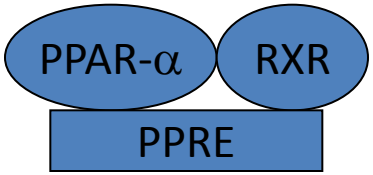
PPAR – Mediated Effects

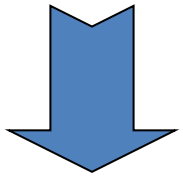


- Cell proliferation promoting Effects
- Apoptosis Modulatory Effects

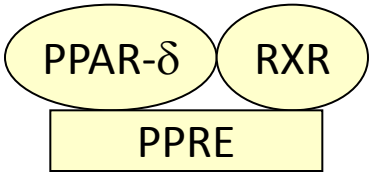
Influencing:

adypocyte differentiation (multiple receptors involved; Through stem cells??)





TUMORIGENIC / ANTITUMORIGENIC??



2004 (AFSSAPS Meeting)

- High number of developing compounds

Were discussed (SWP invited)

MOST Molecules were Rodent Tumorigens
(in different species/sexes)

-bladder tumors

-hemangiosarcomas

-fibrosarcomas

SWP ad-hoc Group formed to advise on EU CTs With PPARgama

Ad-Hoc Group Conclusions

- 13 PPAR γ and α/γ agonists have been assessed, (3 in CTs in FR + 2 marketed) carcinogenicity studies were concluded.

- 7 induced tumours in different animal species in both sexes

- Tumour appear delayed (generally after one year of exposition to the molecule).
- Types of malignant tumours more frequent:
  - bladder tumours, hemangiosarcoma, fibrosarcoma,
  - in different organs and several animal species,
  - With unknown mechanism (sex- and / or species-related effect to be excluded)

FURTHER MECHANISTIC INVESTIGATION

Testing the Cristal Theory

Table 1: Overall Study Design:

Test animal	Crl:CD(SD) male rats, 6 weeks old			
Group No.	1	2	3	4
Test article	Placebo		AD-4833 (HCl)	
Dosage level (mg/kg/day)	0	0	16	16
NH4Cl concentration in diet (%)	0	1.5	0	1.5

STUDY OUTCOME

- ***NH4CL reduced crystals:***

  Group 1 and 3 (diet): higher level of microcrystals than Group 2 and 4 (diet with NH4CL) irrespective of PIO.

- ***Histopathology***
  - *hyperplastic changes not correspondent to microcrystals*
  - *hyperplastic changes (simple, nodular and papillary) only significantly occurred with PIO. irrespective of diet or level of microcrystal formation.*
  - *Animals with PIO + NH4Cl had reduced microcrystal formation and lower severity of the histopathological findings*

STUDY OUTCOME

CONCLUSION:

Results indicates that microcrystals are not responsible for the observed hyperplastic changes.

- *The presence of microcrystals may exacerbate the response BUT ARE NOT considered to be the cause of the hyperplastic changes.*
- *The "crystal hypothesis" to explain the carcinogenic bladder cancer findings in the original carcinogenicity study in rats administered Pioglitazone is contradicted.*

Rodent vs Human

- Tumorigenesis in males only
- Emerging late in rodents (>1Y) but early (from 1 Y or less) in humans.
- Low Tumor incidence
- Potential effect taken into consideration in B/R at MA.

Post-Marketing Studies on Bladder Cancer

- **Studies analysed:**
  PROactive/CT meta-analysis, KPNC, French cohort study)
- **CHMP conclusion**:
- Evidence, together with nonclinical indicate a small increased risk of bladder cancer associated with pioglitazone.
- The impact of this increased risk on the overall B/R profile of pioglitazone in the treatment of T2DM was assessed by the CHMP.
- As the absolute risk is small, a key consideration is whether there is a subpopulation of diabetic patients for which pioglitazone remains a useful therapeutic option.
- SAG Consultation needed.

Conclusions After SAG Consultation

- The majority of observed bladder cancers were superficial tumours with a low invasive potential, which are treated endoscopically
- and for which the survival rate at 5 years is high.
- Pioglitazone continues to fulfil a therapeutic role as an antidiabetic agent
- To reduce the risks and to ensure that B/R remains positive, the CHMP considered further restrictions of use to be necessary. Eg contraindications in :
  - patients with current bladder cancer or
  - history with bladder cancer
  - patients with uninvestigated macroscopic haematuria

CHMP Recommendations

- The adequacy of response to treatment with
- pioglitazone should be reviewed after initiation of therapy

- The maintenance of benefit should be regularly confirmed.

- In addition, risk factors for bladder cancer should be assessed.

- Any macroscopic haematuria should be investigated before initiation of pioglitazone therapy

Work Group Task

- Please analyse the Pioglitazone – Actos EPAR
- Please Analyse the CHMP discussions and decisions
- Please Argue in favour or against and justify!