# Pre-clinical evaluation of $^{188}$Re(V)-oxo complexes as potential agents for melanoma therapy


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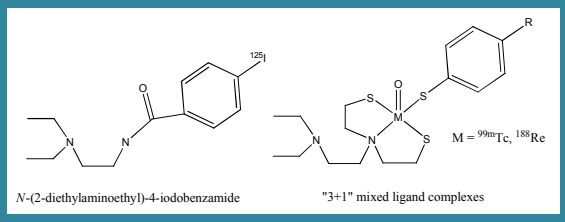
## Introduction

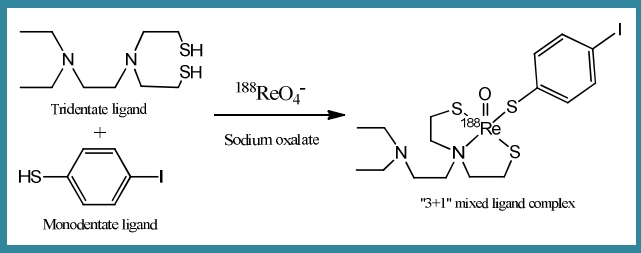
Melanoma is a disease with high increase over the years. As there are no effective treatments for patients in advanced stages, it is essential to develop new therapeutic options.

Our research group has developed oxotechnetium and oxorhenium "3+1" mixed ligand complexes of high affinity for melanoma tumor cells. Those complexes were designed by an "integrated" concept that takes the chemical similarity between them and the *N*-(2-diethylaminoethyl)-4-iodobenzamide, of high affinity for melanoma .




## Synthesis of the $^{188}$Re-oxo complex

The $^{188}$Re-OXO complex was prepared by simultaneous coordination of the tridentate ligand *N*-(2-mercaptoethyl)-*N*`,*N*`-diethylethylendiamine with the monodentate coligand *p*-iodo-tiophenol, using sodium oxalate to expand the coordination sphere.




The complex was obtained with radiochemical purity higher than 90% and resulted stable in labelling milieu for more than 4 hours.

## *In vivo* biodistribution studies and Dosimetric evaluation

In vivo biodistribution studies were performed in normal C57 mice (n=3) (8-10 weeks) after intravascular injection of the complex and in mice bearing melanoma induced by subcutaneous inoculation of B16-F1 cells. The complex was injected in the peritumoral area (74-370 kBq). Main results are shown in the table.

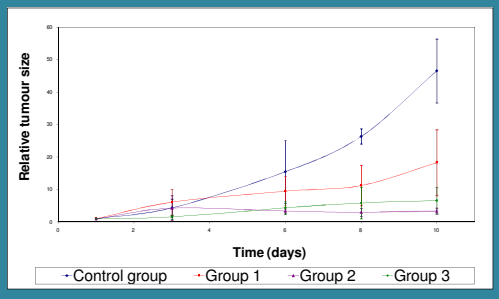
| Organ | % Injected dose | | | |
|---|---|---|---|---|
| | 2 h | 1 2 h | 24 h | 48 h |
| Blood | 11.4 ± 6.5 | 5.9 ± 1.7 | 4.5 ± 1.8 | 3.1 ± 0.6 |
| Liver | 4.1 ± 0.9 | 1.9 ± 0.7 | 1.5 ± 0.6 | 0.7 ± 0.2 |
| Muscle | 8.7 ± 1.2 | 5.1 ± 2.5 | 1.6 ± 0.3 | 1.6 ± 0.3 |
| Bladder + Urine | 11.6 ± 2.8 | 28.6 ± 8.1 | 33.5 ± 0.1 | 38.9 ± 0.1 |
| **Organ** | **% Injected dose per gram** | | | |
| | 2 h | 12 h | 24 h | 48 h |
| Tumour (T) | 24.0 ± 2.3 | 16.7 ± 6.0 | 22.6 ± 4.8 | 3.3 ± 0.9 |
| Muscle (M) | 0.9 ± 0.1 | 0.6 ± 0.3 | 0.17 ± 0.03 | 0.19 ± 0.03 |
| Blood (B) | 7.0 ± 3.9 | 4.0 ± 1.4 | 2.9 ± 1.2 | 2.2 ± 0.5 |
| T/M | 28 | 30 | 133 | 17 |
| T/B | 3.4 | 4.2 | 7.8 | 1.5 |

Dosimetric evaluation was performed using MIRD concept calculation code SAAM II and S values for 188Re in mice model kindly provided by Dr. M. Stabin. Dose tumour was 1.56 Gy/MBq. Effective doses in organs of main interest are shown in the following table.

| Organ | Effective dose (mSv/MBq) |
|---|---|
| Large bowel | $6.14 \times 10^{-3}$ |
| Red Marrow | $5.20 \times 10^{-3}$ |
| Kidney | $2.12 \times 10^{-3}$ |
| Urinary bladder | $2.90 \times 10^{-2}$ |

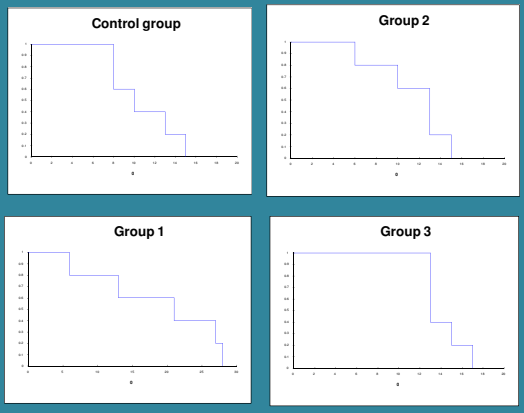
## Terapeutic efficacy

Studies of the effect of treatment on tumour growth showed significantly lower average sizes in all treated groups compared with the control.




**Control group: No injection**
**Group 1: single dose of 11.1 MBq**
**Group 2: single dose of 22.2 MBq**
**Group 3: 2 doses of 11.1 MBq in a week**

Effects on animal survival were evaluated by Kaplan-Meier curves, resulting in a greater chance of survival for those who received a single dose of 11.1 MBq.




## Conclusions

These early studies show promising results which indicate a positive impact of the treatment on murine melanoma in all cases evaluated. Further therapeutic studies will be performed in order to corroborate these initial findings.


## Acknowledgements

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