TARGETED EXTERNAL OR INTERNAL RADIOTHERAPY IN COMBINATION WITH IMMUNOTHERAPIES AND COMPANION IMAGING DIAGNOSTICS

#4082

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Onco design BIOTECHNOLOGY — *Vector of innovation.*

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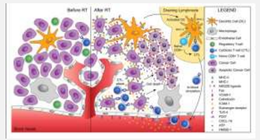
1 CONTEXT & OBJECTIVES

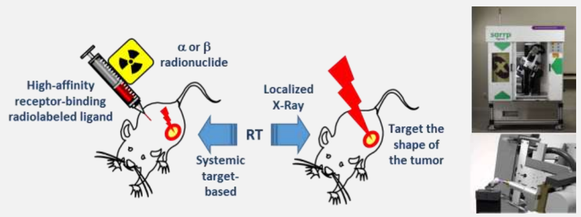
✓ Combination of immunotherapies and either targeted external or internal radiotherapies (RT) may enhance the therapeutic efficacy through the induction of "hot" tumors

- Increase of DNA damage in targeted tumor cells
- Induction of tumor immune infiltrate (cold immune status => hot immune status)
- Mitigation of both radioresistance and immune-checkpoint break



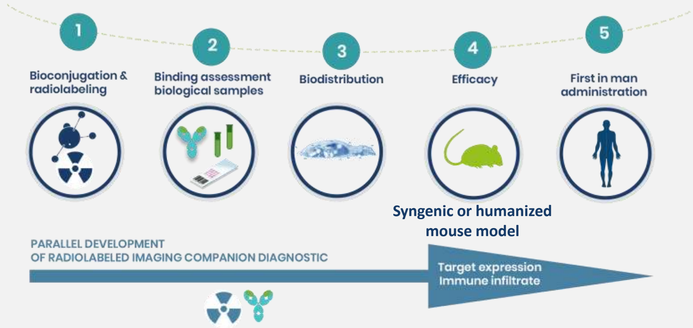
Demaria and Formenti, 2012, Front. Oncol.

✓ Targeted internal RT vs external 3D image guided RT



✓ Preclinical evaluation process to combine radiotherapies with immunotherapies requires:

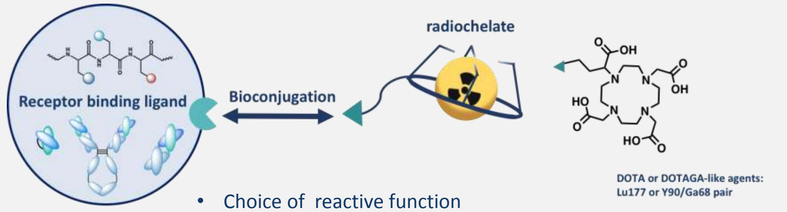
- Bioconjugation and radiochemistry (i.e. Lutetium-177 or Yttrium-90) or X-ray radiotherapy equipment
- Monitoring of RT target, immune checkpoint target and immune cell infiltrate
- Studies of imaging biomarker (i.e. Gallium-68 radiotracer), PK/PD and activity with single or fractionated treatment doses



2 RESULTS

✓ Bioconjugation and radiolabeling strategies suited for theranostic pairs of radionuclides

- Use of specific chelator for trapping radiometals
- Radiolabeling process optimization (specific activity, injected dose, radiochemical purity and stability)

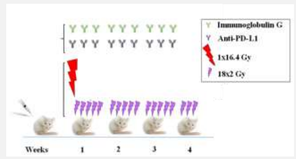


DOTA or DOTAGA-like agents: Lu177 or Y90/Ga68 pair

Other specific chelator/radiometal combinations : DFO for Zr89, NODAGA for Cu64

- Choice of reactive function
- Optimization of conjugation conditions
- Random or site-specific labeling

✓ Optimization of external radiotherapy schedule to improve the efficacy and synergistic effect of the association radiotherapy/ immunotherapy such as anti-PDL1

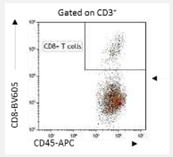


Methods: CT26 colon cancer cells were engrafted on Balb/c mice. Immuno-monitoring was performed 7 and 14 days after treatment using flow cytometry method.

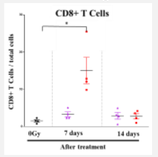
Objective: Evaluation of RT fractionation schedule effect on:

- Microenvironment (immune cells infiltrating tumor)
- Immunotherapy target expression
- Tumor growth

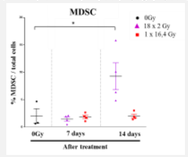
Immuno-monitoring by flow cytometry at day 7 and 14 (illustration of CD45+/CD8+ T cells)



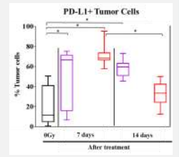
Immune effective CD8+ T cells infiltrating tumor

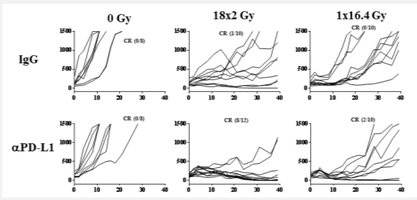


Immune suppressive MDSC cells infiltrating tumor (CD45+, CD11b+, F4/80-, Ly6g+/Ly6c+)



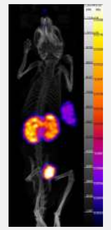
PD-L1+ expressing tumor cells



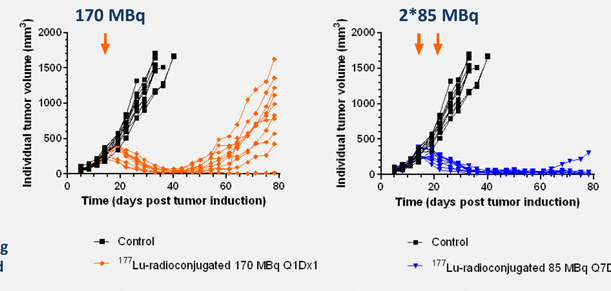


Results: RT induced differential immune response according to fractionation schedules delivering the same radiobiological dose.
RT delivered in one fraction induced an important but transient CD8+ lymphocyte infiltration and PD-L1 expression.
Both RT schemes improved the antitumor activity of anti-PDL1, the fractionation 18x2Gy induced the best efficacy with 8/12 complete responses. Further immuno-monitoring is required to understand this pattern.

✓ Monitoring of tumor uptake and tumor volume activity of ^{177}Lu-radioconjugated



Tumor uptake monitoring of ^{177}Lu-radioconjugated (SPECT)



Activity of targeted internal RT in preclinical tumor model after 1 or 2 treatments

3 CONCLUSION

✓ Evaluation of immunotherapies and RT combination requires expertise and exquisite processes in multiple fields:

Bioconjugation/Radiochemistry/Radiotherapy
Immunotherapy/Preclinical pharmacology/Nuclear imaging

✓ The design of radioconjugated (therapy and/or imaging) involves the appropriate combination:

Ligand pharmacokinetics/Radionuclide half-life
Bifunctional chelating agent/Bioconjugation strategy

✓ The RT induces an anti-tumor immune response and immuno-therapy target over expression

RT fractionation schedule has to be optimized to improve efficacy of RT/immunotherapy association

✓ High potential to combine targeted internal and/or external RT with immune checkpoint inhibitors

Perspective to improve efficacy with optimized RT cumulated dose and reduce toxicity of each therapy

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