Nanoparticle-based strategies in Oncology

Prof. Jean-Pierre BENOIT

Innovating treatments in Oncology

Standard chemotherapy

Targeted therapies:
- Monoclonal antibodies
- Tyrosine kinase inhibitors

Gene therapy: CAR-T cells
Glioblastoma

- The most common primary brain tumor in adults
- After treatment, median survival <15 months
- Infiltrating tumor

Surgery
Tumor removal
Stupp's protocol
Evolution of the tumor after treatment

Relapse
Recurrence in the 2 cm of the resection cavity (90%)

Temozolomide

Design and development of intracerebral microparticulate implants

From bench...
Radiosensitization of malignant glioma
5-FU Microspheres

…to bedside
5-FU release %
50-60µm
Phase I/II and IIb clinical trials

Phase IIb clinical trial

- 77 patients, 2 arms with or without MS
- No observed toxicity
- No recurrence at the vicinity of the tumor
- Significant prolongation of the median survival
- But need to extend the phase IIb to 200 patients or more to continue the development!

5-FU PLGA Microspheres

PLGA = Poly(lactide-co-glycolide)

Menei, et al, Cancer, 1999; Cancer, 2004; Neurosurgery, 2005, 56(2), 242

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Nanomedicine: Nanotechnologies applied to Medicine

1 nm = 10^{-9} m = one billionth meter!

1 nm/1 m = Hazelnut/Earth

⇒ New properties

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RES Targeting Nanocarriers
(first generation)

RES avoiding Nanocarriers
(second generation)

Third generation of nanocarriers: decorated nanocarriers with ligands

![Diagram of nanocarriers decorated with various ligands]

EPR-positive tumors
Stealth nanosystems will work nicely


EPR-negative tumors

- New nanomedicines, new strategies and new routes of administration to induce new antitumoral activity profile
  - Chemotherapy
  - Radiotherapy
Lipid Nanocapsules (LNC)

- Biomimetic System: to mimic the structure of a lipoprotein
- Ø < 100nm, monodisperse and stable
- Only FDA-approved excipients


Cancer immunology and immunotherapy. Realizing the promise

According to the National Cancer Institute definition, immunotherapy is any 'treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases'
Two main MDSC populations have been characterized: monocytic M-MDSCs and polymorphonuclear PMN-MDSCs.

- Non specific immunosuppression
- Production of cytokines and soluble factors that support tumor angiogenesis

MDSCs

Tumor

Peripheral lymphoid organs

Bone marrow

VEGF
GM-CSF

IL-6
Others...

IFNy
IL-1β, 14, 13
Others...

\[M-MDSCs\]

\[PMN-MDSCs\]

Induce: antigen-specific T cell tolerance

\[TAM\]

\[Tumor cell killing\]

\[T cells, NK cells\]

\[Spleen\]

\[Tumor\]

\[Xenografted (EG7)\]

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LNC uptake by immune cells in EG7-bearing mice

\[Spleen\]

\[Tumor\]

\[Xenografted (EG7)\]

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GemC12-loaded lipid nanocapsules (GemC12-LNC)

- Synthesis of Gemcitabine derivative: 4-(N)-lauroyl gemcitabine (Gem C12)

Reduction of M-MDSC by GemC12-LNC

SC injection of GemC12-LNC (11 mg/kg) enhanced M-MDSC reduction as compared with IV injection

In vivo Antitumor activity: the effect of a combined therapy

Phase I: Preconditioning
- Revert immunosuppression
- Myeloid Derived Suppressor Cell
- GemC12-loaded LNC, SC route

Phase II: Expansion of tumor-specific T cell populations
- Stimulate immune response
- Tumor
- Fragmentation of tumor mass
- Adoptive T cell Transfer (ACT)
- Expansion of tumor-specific T cell populations


Antitumor activity of Gem-C12 LNC combined with ACT: EG7-OVA tumor

Schedule
- Preconditioning + ACT
- Dose 11 mg/kg Gemcitabine
- GemC12-LNC or any treatment
- OVA-Specific T cells
- Day 0 EG7-OVA
- Day 8
- Day 9

Preconditioning with low dose of GemC12-LNC, SC infused, enhances Adoptive T Cell Transfer (ACT) efficacy

EPR-positive tumors
Stealth nanosystems will work nicely

EPR-negative tumors

• New nanomedicines, new strategies and new routes of administration to induce new antitumoral activity profile
  – Chemotherapy
  – Radiotherapy

\( ^{188}\text{Re-LNC for in situ radiotherapy} \)
Local administration

\( 9L \text{ glioma cell injection} \)

Model Induction
Tumoral growth follow-up

\( \text{MRI} \)
SURVIVAL CURVES

\( 8 \text{ grays} \)
**Conclusion: contribution of nanomedicines to Oncology**

- **EPR-positive tumors:** +++ if stealth nanosystems
- **EPR-negative tumors:**
  - Design of nanocarriers having new properties (i.e. interaction with specific immune subsets,...)
  - Exploring other routes of administration to reveal new biodistribution profiles
  - Setting new paradigms: nano-immunotherapy, *in situ* radiotherapy,...
Marie-Claire Venier, Guillaume Bastiat, Elodie Moysan, Marion Pitorre, Claire Vanpouille

In collaboration with Prof V. Bronte (Univ.Verona), Dr G. Lollo (Univ. Lyon)

Radioactive LNC for in situ radiotherapy

**Rhenium-188**
- $^{188}$W/$^{188}$Re generator
- High $\beta^-$ energy (2.12 MeV)
- Low $\gamma$ emission (155 keV)
- Short half-life (17h)

Conductivity

- o/w
- w/o

Temperature

$^{188}$Re-SSS + thermal shock

Phase inversion zone

Collaboration: Pr. N Noiret, Pr. E Garin (Rennes)


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