Oncogenic properties of Neuropilin-2

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- **Neuropilins (Nrp1 and Nrp2)**: single-pass transmembrane non tyrosine-kinase glycoproteins
- **Ligands**: VEGF, semaphorins, growth factors
- **Ellis, J. Natl Cancer Inst, 2008**: Inhibition of NRP-2 expression in colorectal carcinoma inhibited cancer development (VEGF/PI3K/AKT)

NRP-2: target for anti-tumoral therapy

Neuropilins in tumor biology
Fig. 1 Expression of NRP2 in human cancer cells

Fig. 2 Generation of colon cancer cell lines expressing or not NRP2
Fig. 3
NRP2 promotes tumor proliferation.

Fig. 4 NRP2 ablation using siRNA blocks xenograft progression.
**Fig 5.** NRP2 induces epithelial to mesenchymal transition.

- Prud'homme G. J, Glinka Y, J. Leuk. bio, 2008: NRP1 is a receptor for transforming growth factor B-1, activates its latent form and promotes T regulatory T cell activity

- **TGF-β1 signaling pathway**

**NRP-2 promotes TGF-β1 pathway (1)**
Fig. 6 NRP2 promotes TGF-β1 pathway.

« Innovative immune TArgeting of Cancer » platform
Besançon, France

Production of mouse monoclonal antibody targeting hNRP-2: ITAC-B1

- Immunization of Balb/c mice
- Screening and identification of a secretant hybridoma: ITAC-B1

ITAC-B1: specific anti-NRP2
Targeting hNRP-2: Biological effects

- Co-culture in soft agar: colony formation
  - ITAC-B1 inhibits colony formation

- Cell apoptosis test: Annexin V staining
  - ITAC-B1 induces cell apoptosis in a dose-dependent manner

Neutralizing NRP-2 to induce p53 expression

- Cao et al., Cancer Research, 2008: Neuroptin-1 Uprights Dedifferentiation and Propagation Phenotypes of Renal Cell Carcinoma Cells by Activating Akt and Sonic Hedgehog Axes
  - Intracellular staining
  - Xenografts: IHC
Neutralizing NRP-2 to induce p53 expression

- Western-blot:
  - ITAC-B1, 36h: induction of p53

- Pretreatment with Pifithrin-α attenuates ITAC-B1 induced apoptosis

ITAC-B1 induces in part p53-dependant apoptosis

Preclinical model: Neutralizing NRP-2 to increase the cytotoxicity of classic chemotherapy

- Combination of ITAC-B1 and 5FU

<table>
<thead>
<tr>
<th>Group</th>
<th>Doses (mg/kg)</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>Control</td>
<td>Yearly</td>
<td>x100</td>
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<tr>
<td>5FU</td>
<td>Single x</td>
<td>Days 15-19</td>
</tr>
<tr>
<td>ITAC-B1</td>
<td>Single x</td>
<td>Days 0, 5</td>
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<tr>
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<tr>
<td>5FU+</td>
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<td>Single x</td>
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</tbody>
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ITAC-B1 combined to 5FU treatment significantly reduces tumor progression
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