XII Encuentro de Cooperación Farma-Biotech

Santiago de Compostela, 26 de septiembre de 2014

Recombinant human Cystatin-C for the treatment of invasive triple negative breast cancer

ONCOMATRIX

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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2. The Product

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- Current status of development: proof of concept and trials already performed
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- IPR protection
- Pitfalls & Risks to be considered

The Company

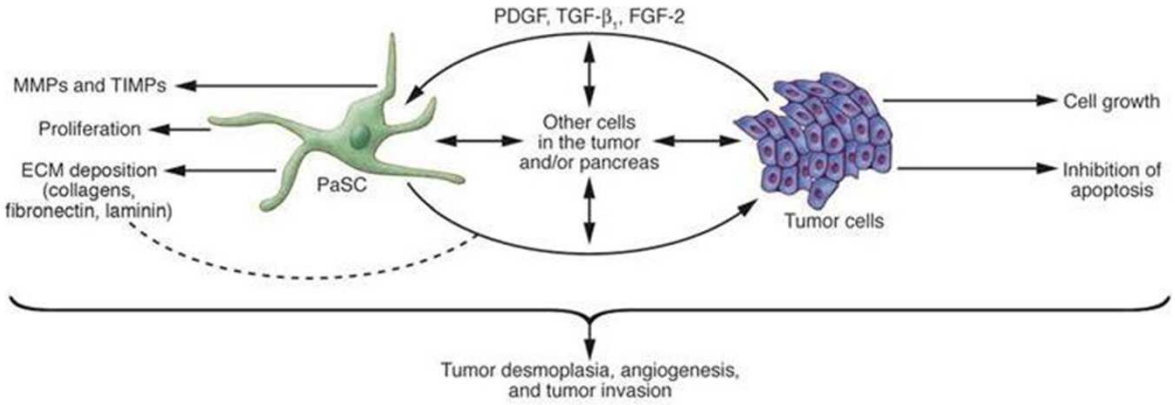
Oncomatryx Biopharma

Mission		Innovation
Development of stroma-targeted biologicals to treat invasive tumors	▶	Novel therapeutic approach
Biological Drugs: Human-derived proteins, Immunotoxins and Antibody-Drug Conjugates	▶	Targeting the connection between tumor cells and tumor microenvironment Novel therapies against the tumor-associated stroma that facilitates tumor invasiveness and drug resistance
Diagnostic and Companion Diagnostic devices	▶	International network of scientific collaborations.

Innovative therapeutic approach

- **Peritumoral stroma:** One of the main promoters of tumor invasiveness, as well as resistance against current anti-cancer therapies.

- **Oncomatryx therapeutic approach** is based on the development of new biological drugs that target proteins located in the peritumoral stroma (fibroblasts, endothelial cells and extracellular matrix): A novel and innovative route for cancer treatment, directed not against tumor cells, but the cells that promote their invasiveness and drug resistance.



The Assets

Intellectual Property	• FTO • Issued patents: EP1611252B1; US8124331; US7282477; US7749958; US8058396; AU-B-2004281152; ES2297953; ES2303390; ES2398328 • Pending patent applications: PCT/ES2012/070616; P201231281; P201330179; EP04795359.1; EP04740556.8; GB1402006.9; GB1402009.3
Facilities	• Laboratories and offices. 550 m^2 • Parque Tecnologico de Bizkaia. 801-b. Derio (Bilbao), Bizkaia, Spain
Funding Resources	• Funds raised: €4M: Founders (€3M), Private Investors (€0,6M) and Seed Fund (Seed Capital Bizkaia: €0,3M capital + €0,15M participating loan) • Government subsidized funds and soft loans: €1,4M. Bank loans: €1,7M
Collaborations	• Universities, Research Centers and Hospitals in USA, Germany, Italy and Spain • Biotech companies, CROs and CMOs in USA, Germany, England and France

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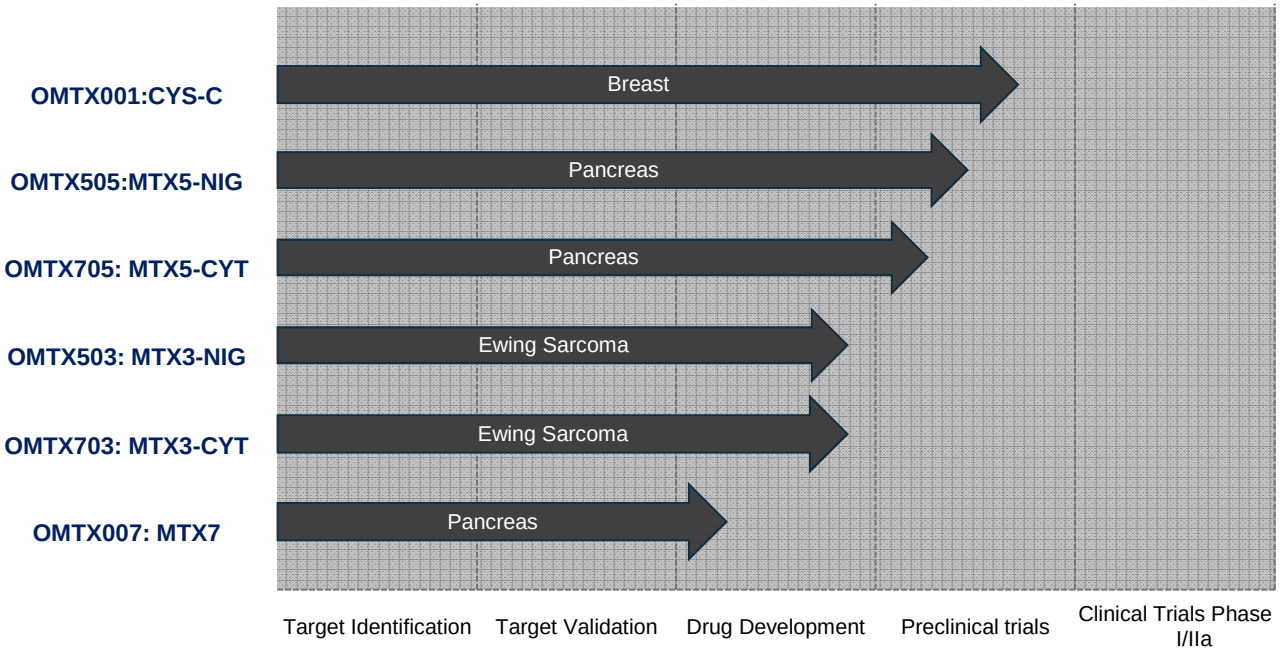
Oncomatryx Pipeline

- **Product pipeline and development**

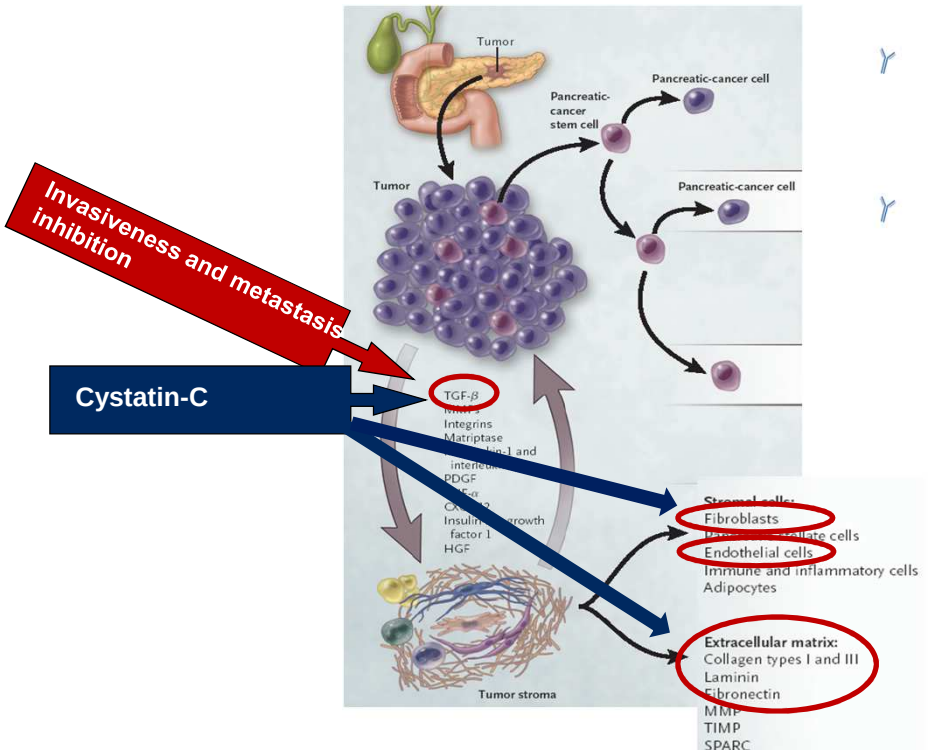
Activities



The Product

Cystatin-C

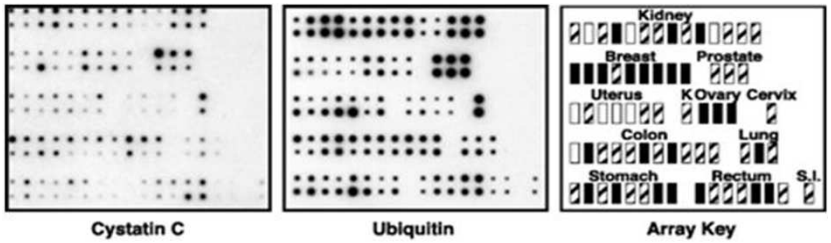
A human protein that inhibits tumor-stroma interactions



- Cystatin-C is a human secreted protein that regulates bone resorption, inflammatory response and neutrophil chemotaxis.
- Cyst-C has an antitumor function with different activities on the tumor microenvironment:
  - Cyst-C is a well-characterized cathepsin-B inhibitor.
  - Cyst-C inhibits TGFβ by binding to TGbβ-RII (Oncomatryx IP). Cyst-C blocks TGFβ signaling in endothelial cells, antagonizing angiogenesis, as well as in breast tumor cells, inhibiting tumor growth and metastasis in vivo.
  - Cyst-C has the potential to increase the anti-tumoral activity of existing anticancer drugs, acting on the tumor-associated stroma.

Cystatin C - Target Indications (I)

- ✓ Cystatin-C expression was altered in 49% of human malignancies analyzed (91% of the alterations were downregulation of Cystatin-C expression).



J.Sokol & W. Schiemann (2004) Mol.Can.Res., 2:1

Cystatin C Expression in Human Tumors:		
Altered	Downregulated	Upregulated
49% (33/68 cases)	91% (30/33 cases)	9% (3/33 cases)

- ✓ Prostate cancer patients with low expression of Cystatin-C and high expression of androgen receptor (AR) have worse overall survival than patients with high expression of Cystatin-C and AR.

B.Wegiel et al. (2009) PlosOne 4(11): e7953

- ✓ There is a significant depressed expression of Cystatin-C in glioblastomas compared with low-grade astrocytomas suggesting that there is a low level of Cystatin-C expression in gliomas of patients with unfavorable clinical outcome.

H.Nakabayashi et al. (2005) Human Pathol. 36:1008-1015

Cystatin C - Target Indications (II)

✓ Cystatin-C for breast tumor therapy

- Approximately 15% of all breast cancers are triple negative (TNBC). TNBC are aggressive tumors, which lack hormone receptors and do not overexpress HER2.
- High rate of TNBC mortality (42.2% vs 28.0% of other breast tumors) and distant recurrence in 5 years.
- Prognosis is poor in advanced disease, median overall survival of 13.3 months.
- TNBC resistant to treatment with standardized therapies used for other breast cancers, as endocrine therapies or mAbs against HER2 receptor.
- Standard cytotoxic chemotherapy remains the preferred treatment for TNBC (single-agent or combination chemotherapy).
- Cystatin-C inhibits tumor growth and metastasis of breast tumor in mice.
  M.Tian & W.Schiemann (2009) Trans. Oncol 2(3):147-183

Cystatin C - Target Indications (III)

✓ Cystatin-C for macular degeneration and diabetic retinopathy therapy

- **Cystatin C can play an important role in the protection of the conjunctiva and regulates inflammation and angiogenesis in the inner surface of the eye.**
  - *"Over-expression of human cystatin C in pterygium versus healthy conjunctiva" Barba-Gallardo et al. BMC Ophthalmology (2013)13:6*

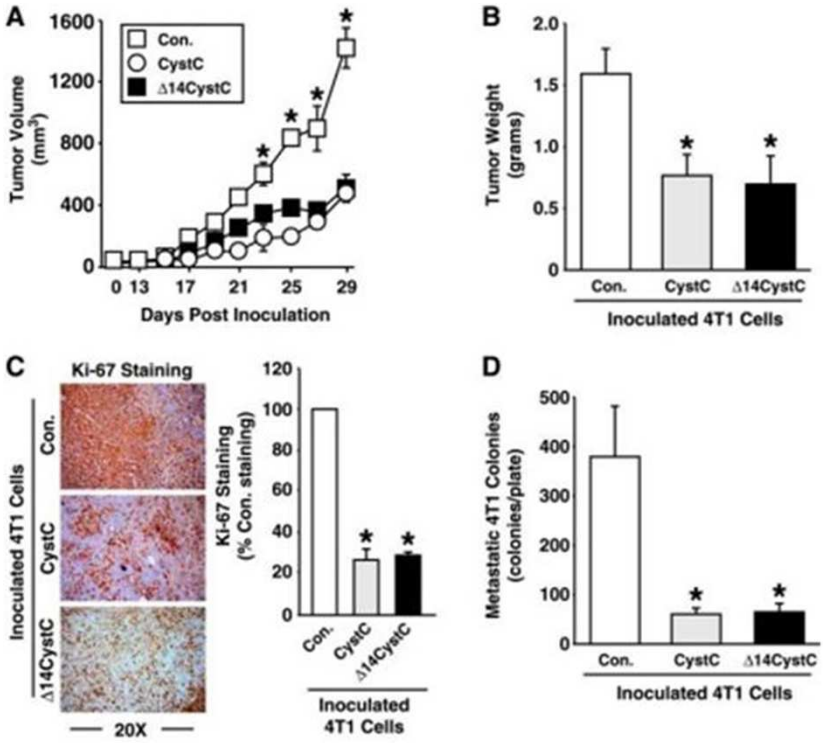
- **Cystatin C is abundantly secreted by the retinal pigment epithelium (RPE). Expression is reduced with age and correlates with macular degeneration.**
  - *"Implications for mechanism of age-related macular degeneration» Paraoan et al. Vision Research 50 (2010) 737–742*
  - *"Age-related changes of cystatin C expression and polarized secretion by retinal pigment epithelium: potential age-related macular degeneration links" Kay et al. nvest Ophthalmol Vis Sci (2014)55(2):926-34.*

- **Low expression of Cystatin C in eye fluids can be correlated with choroidal melanoma.**
  - *"Cystatin C and lactoferrin concentrations in biological fluids as possible prognostic factors in eye tumor development" Dikovskaya et al. Int J Circumpolar Health (2013) 72: 21087.*

- **We foresee that Cystatin C could be used locally as anti-angiogenic drug to treat eye cancer and inflammatory pathologies.**

Cystatin C Current status of development

CystC inhibits tumor growth and metastasis in vivo in 4T1 induced tumor mice



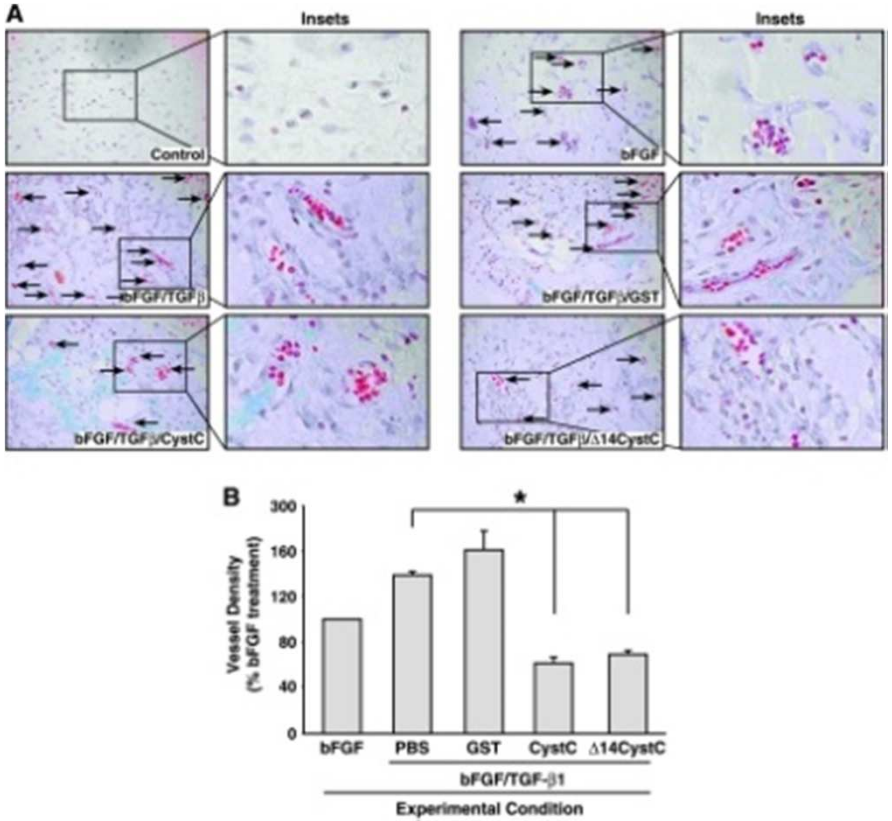
M.Tian & W.Schiemann (2009) Trans. Oncol 2(3):147-183

CystC inhibits 4T1 tumor growth and pulmonary metastasis. (A and B) Control (Con.), CystC-, or Δ14CystC-expressing 4T1 cells were injected orthotopically into the mammary fat pads of Balb/C mice. Ten days after injection, tumor volumes were measured every second day until they were killed on day 30. Data are mean (±SE) tumor volumes (A) or wet weights (B) observed in three independent experiments. (C) Tumor sections were stained with antibodies against Ki-67. Accompanying data are the mean (±SE) proliferating tumor cells (brown) relative to those present in sections of control 4T1 tumors. (D) Lung single-cell suspensions were cultured onto 10-cm plates supplemented with 6-thioguanine (60 µM). After 14 days, the surviving metastatic colonies were fixed, stained with crystal violet, and counted. Data are mean (±SE) surviving colonies per plate observed in three independent experiments.

*P < .05, Student's t test.

Cystatin C Current status of development

CystC shows anti-angiogenic activity in vivo in Matrigel plug implantation studies in mice

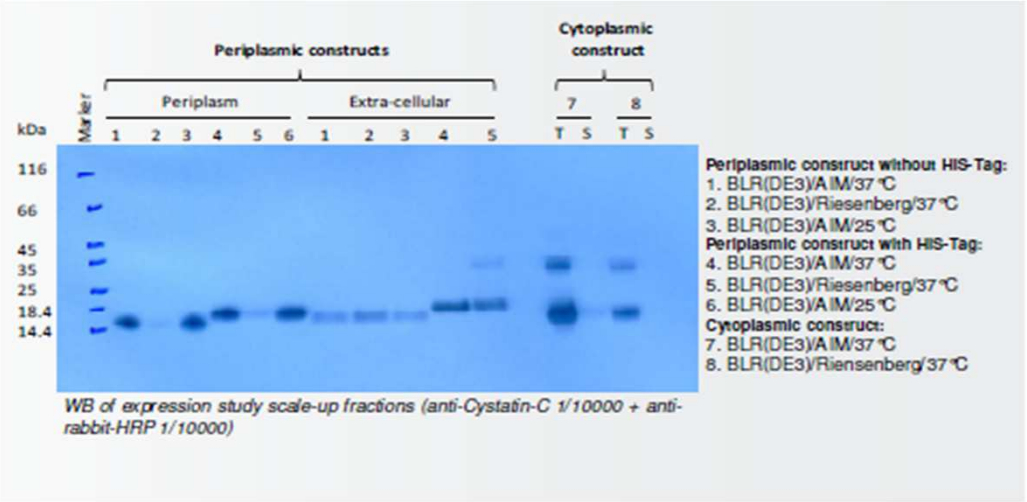


M.Tian & W.Schiemann (2009) Trans. Oncol 2(3):147-183

CystC inhibits TGF-β-stimulated angiogenesis and vessel development in genetically normal mice. C57BL/6 female mice were injected subcutaneously with Matrigel supplemented with diluent (i.e., PBS), bFGF (300 ng/ml), or bFGF (300 ng/ml) in combination with TGF-β1 (5 ng/ml) in the presence of recombinant (20 µg/ml) of GST, GST-CystC, or GST-Δ14CystC as indicated. Mice were killed on day 10, and the resulting plugs were harvested, fixed, sectioned, and stained with Masson's trichrome to visualize infiltrating blood vessels [denoted by arrow heads (A)], which were subsequently quantified by counting 10 independent fields per slide under a light microscope (B). Data are the mean (±SE) vessel densities relative to bFGF treatment observed in three independent experiments. *P < .05, Student's t test.

Cystatin C Current status of development -Manufacturing

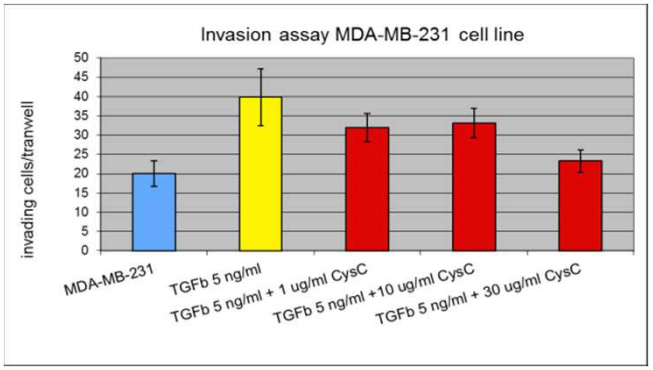
- The CST3 gene is conserved in different species, the human protein has 75% of homology with mouse protein.
- To directly assess its anti-tumour activity, recCystatin-C was expressed in *E. coli* as a soluble form, with codon optimization for bacterial expression.
- The recombinant protein could be expressed in mammalian cells *(myeloma cell line-R&D Systems)* or purified from bacterial insoluble/cytoplasmic fraction. Cystatin-C has been already expressed in *E.coli* as insoluble form for high level expression. *Codon Preference Optimization Increases Prokaryotic Cystatin C Expression. Wang Q. et al. J Biomed Biotechnol. 2012:732017 (2012)*
- The recombinant protein was produced with >90% purity and <10 EU/mL endotoxin level to test its activity in vitro and in vivo studies.

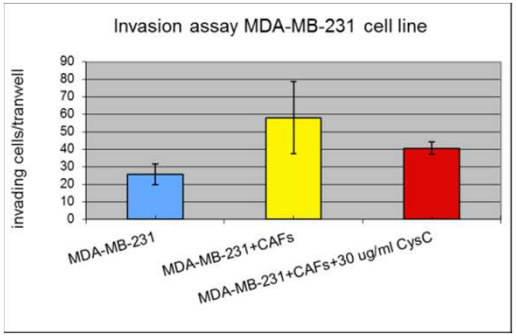


WB of expression study scale-up fractions (anti-Cystatin-C 1/10000 + anti-rabbit-HRP 1/10000)

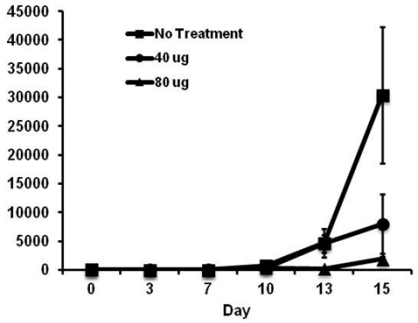
Cystatin C Current status of development

- Recombinant Cystatin-C inhibits TGFβ or activated fibroblast -induced cell invasion of human triple negative breast cancer cell line MDA-MB-231 in Matrigel tests



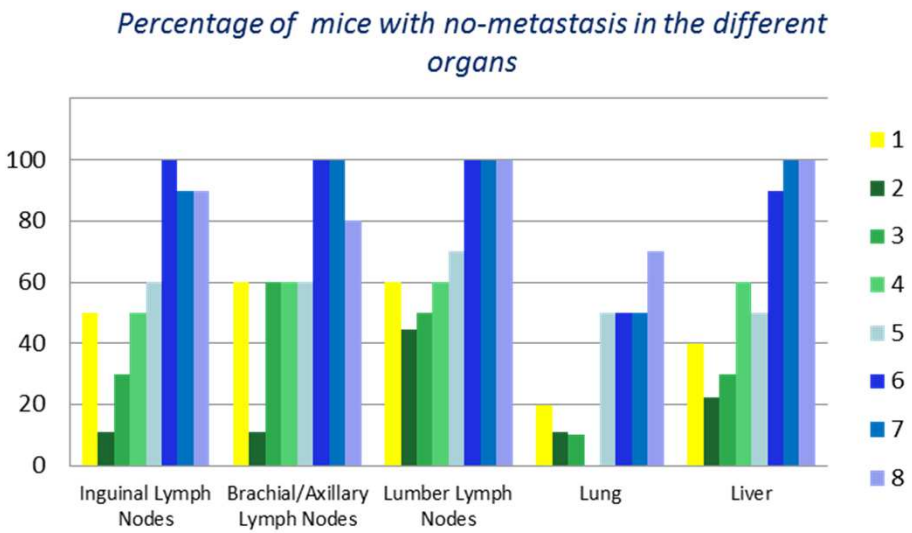


- Recombinant Cystatin-C inhibits lung metastasis in mice grafted with murine 4T1 breast cancer cells in a metastatic model (tail vein injection)



Cystatin-C Current status of development

- Recombinant Cystatin-C inhibits metastasis when combined with taxotere in mice grafted with human triple negative breast cancer cell line MDA-MB-231, but it does not inhibit tumor growth (breast orthotopic xenograft model)



Group 1: Cystatin-C Vehicle i.p. daily + Taxotere vehicle i.v. biw
Group 2: 14mg/kg Cystatin-C i.p. daily + Taxotere vehicle i.v. biw
Group 3: 2.8mg/kg Cystatin-C i.p. daily + Taxotere vehicle i.v. biw
Group 4: 0.56mg/kg Cystatin-C i.p. daily + Taxotere vehicle i.v. biw
Group 5: Cystatin-C Vehicle i.p. daily + 2.5mg/kg taxotere treatment i.v. biw
Group 6: 14mg/kg Cystatin-C i.p. daily +2. 5mg/kg taxotere treatment i.v. biw
Group 7: 2.8mg/kg Cystatin-C i.p. daily + 2.5mg/kg taxotere treatment i.v. biw
Group 8: 0.56mg/kg Cystatin-C i.p. daily + 2.5mg/kg taxotere treatment i.v. biw

Cystatin C – Differential features facing the market

- The recombinant protein produced by Oncomatryx with a pleiotropic activity, similar to the natural protein, is a first-in-class therapeutic product for the treatment of metastasis in aggressive breast tumors.

  - Cystatin-C is down-regulated in different aggressive and metastatic tumors
  - Cystatin-C has a natural inhibitory function of tumor growth and invasiveness (inhibitor of cathepsin-B and TGFβ functions)
  - Recombinant Cystatin-C has the potential to increase the antitumoral activity of existing anticancer drugs, acting on the tumor-associated stroma
  - Recombinant Cystatin-C shows anti-angiogenic activity on endothelial cells, and inhibits epithelial-mesenchymal transition (EMT) of breast tumor cells
  - The recombinant Cystatin-C, as the natural Cystatin-C, is expected to have a good safety profile

Cystatin C – Competitors

✓ Recombinant Cystatin-C is a first-in-class therapeutic product for the treatment of metastasis in aggressive breast tumors, no competitors have been identified up to now.

TGF-β Inhibitors -

- The most promising molecules in clinical trials against TGFβ for the treatment of aggressive tumors are LY2157299 receptor kinase inhibitor and the neutralizing TR1 antibody. LY2157299 is in Phase I-II for different tumor indications (glioblastoma, hepatocellular carcinoma and pancreatic cancer). TR1 antibody is an inhibitor of TGFβ receptor II which is in Phase I for the treatment of solid tumors.

TNBC treatment -

- There is a lack of approved standardized TNBC specific therapy. Doxorubicins, Taxanes, Capecitabine or Gemcitabine, as a single agents or in combination are the common approach for first-line therapy.

Cystatin C – IP protection

- *US Patent # 7,282,477 (Issued) (2007)* ***"Cystatin-C as an antagonist of TGF-β and methods related thereto"***
- *US Patent # 7,749,958*
- *US Patent # 8,058,396*
- *Australian Patent # AU-B-2004281152*

- *Patents pending:*
  - *European # EP04795359.1*

Risks to be considered

- Few risks to be considered in the development of recombinant Cystatin-C. The main risks are those related to the development of a biotechnological product.

- Manufacturing costs would be considerably reduced, due to the possibility to produce Cystatin-C in bacteria

- Similar to the natural protein, we expect that recombinant Cystatin-C will have a good overall safety profile.

Oncomatryx looks for licensing agreements of Cystatin-C biological drugs to treat Triple Negative Breast Cancer and ocular fibrotic disorders

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