P119 Allogeneic Tumor Cell-Based Vaccine to treat Colorectal Cancer : Development and Preclinical Validation

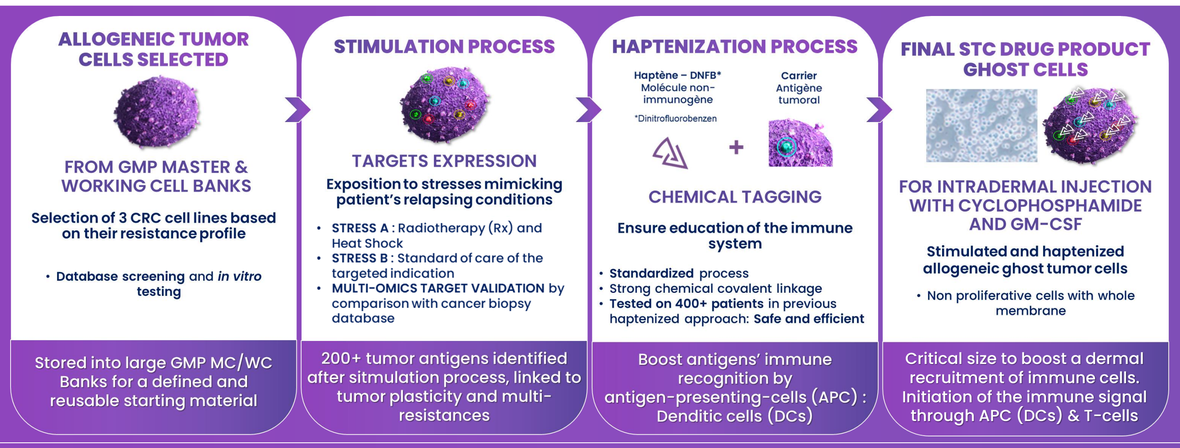
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BACKGROUND

- Colorectal cancer (CRC) is the **second cause of cancer mortality worldwide**.
- Unmet medical need in immunotherapy is high for MSS patients and still present for MSI-H/dMMR patients. Tumor plasticity and treatment resistance are the main drivers of patient's relapse.
- Brenus Pharma has developed a patented platform generating innovative **therapeutic cancer vaccine based on Stimulated Tumor Cells** (STC): STC-1010, lead candidate targeting CRC, educating the immunes system to target and eliminate patient's tumor cells harboring mechanism of relapse.
- This technology has already shown **efficacy in immunocompetent mice models.**

Fig 1. STC (Stimulated Tumor Cells) Technology

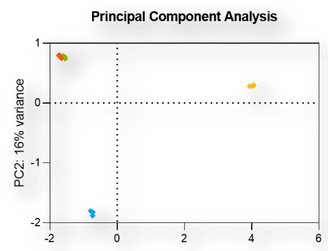


= 6 Drug Substances (DS)

VACCINE CHARACTERIZATION

TRANSCRIPTOMIC

- RCB Raw Cell Bank (not exposed to stimulation)
- MCB Master Cell Bank (RCB + serum depletion)
- DSA Drug Substance with physical stimulation
- DSB Drug Substance with chemical stimulation



PROTEOMIC

Cancer-Related Proteins expressed only in DS after exposition to stimulation and not expressed in RCB	61
Cancer-Related Proteins overexpressed after stimulation A or/and B : DS/RCB>2	35

Batch to batch signature

Batch ID	CRP
STC1010 RD1	211
STC1010 RD2	
STC1010 RD3	

- The transcriptomic and proteomic analysis demonstrate that **each of the physical and chemical stresses, modified protein expression** which **confirms the rationale for using 3 cell lines with 2 stresses to cover the heterogeneity of the CRC.**
- **211 Cancer-Related Proteins (CRP)** from the Atlas proteins' database **were identified in the STC-1010 final product** including CRC-specific linked proteins, tumor plasticity and tumor-associated antigens.

METHODS

Fig 2. *Ex-vivo* model : Derived Mixed Lymphocyte Reaction

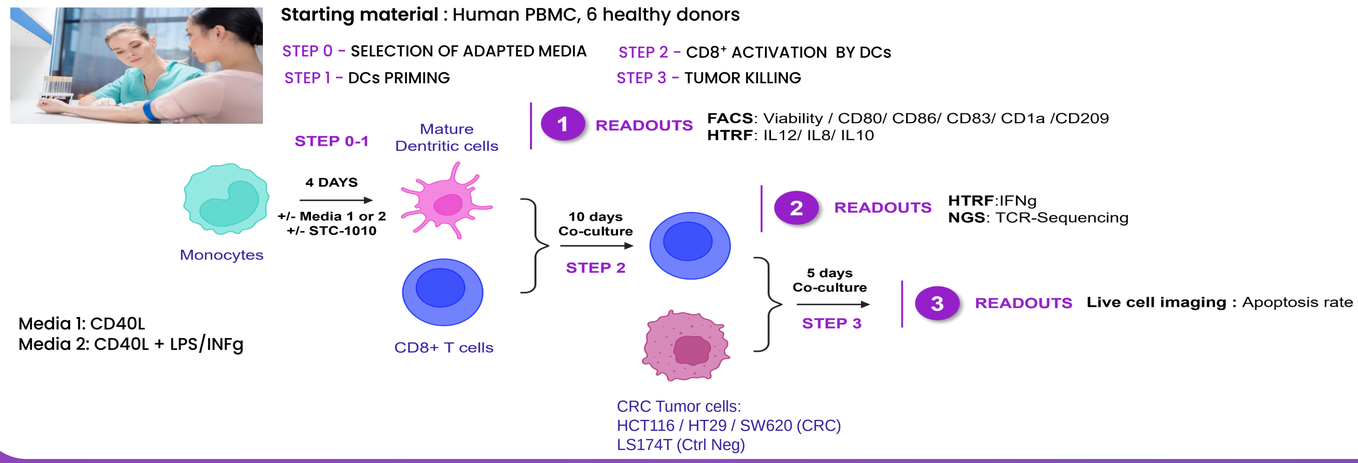
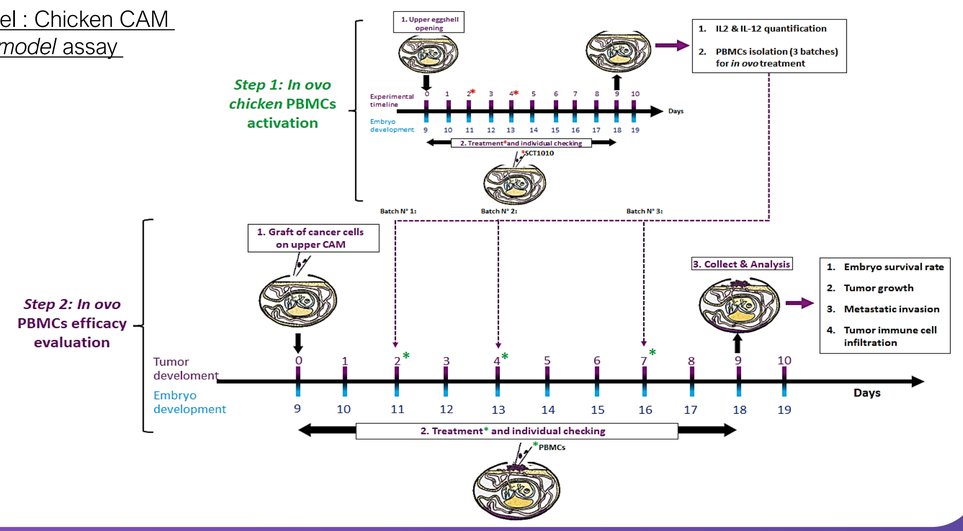


Fig 3. *In-ovo* model : Chicken CAM (*Chorioallantoic) model* assay



RESULTS

EX VIVO MODEL – STEP 1 : DC PRIMING & MATURATION AFTER STC-1010

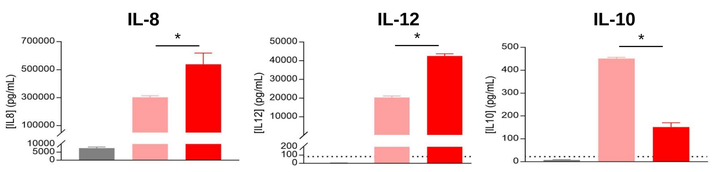


Fig 4. Effect of STC-1010 on cytokine released by DC (Media 2: reproduces better the in vivo immunocompetency)

EX VIVO MODEL – STEP 3 : TUMOR KILLING BY CD8+ T ACTIVATED WITH STC1010

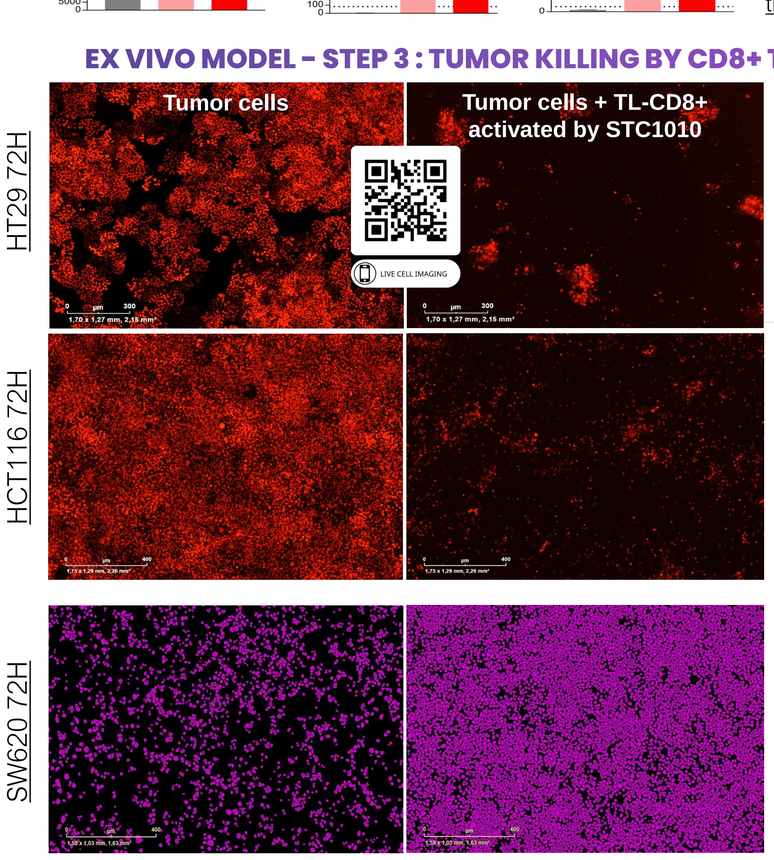


Fig 5. Real-time cell monitoring of NucRed (Red) labelled human CRC HCT116, HT29 and SW620 (Purple = cell apoptotis) tumor cells killing mediated by DC-primed CD8+

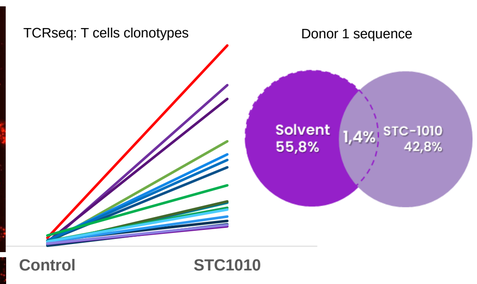


Fig 7. Impact of STC-1010 on CD8+ specific clonotype selectivity vs solvent

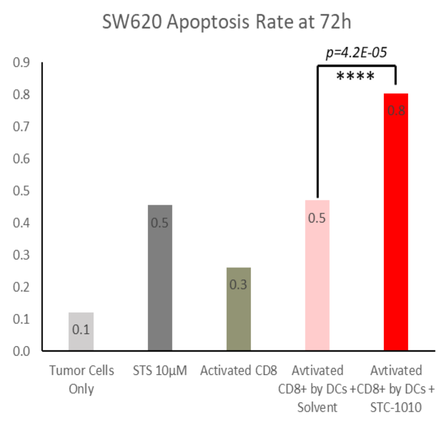


Fig 6. Impact of STC-1010 on apoptosis state of SW620 Tumor cells vs solvent at 72h

IN OVO MODEL : IMMUNE SYSTEM ACTIVATION & METASTATIC REDUCTION AFTER STC-1010

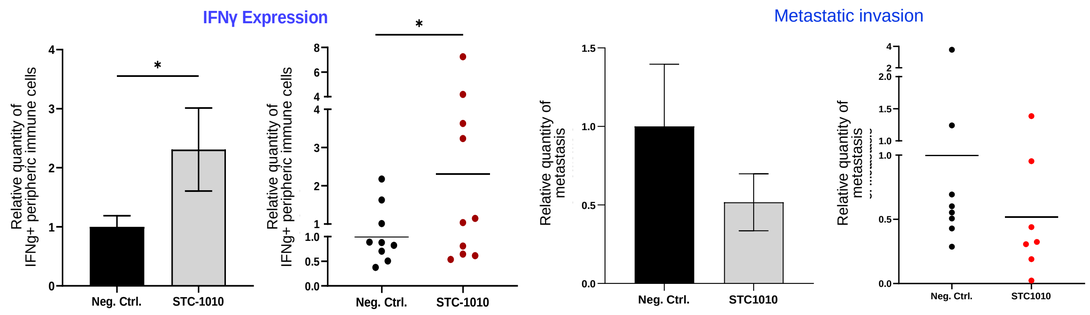


Fig 8. Effect of STC-1010 on [IFNg] expression in tumor vs control

Fig 9. Impact of STC-1010 on relative quantity of metastasis vs control

Ex vivo results:

- **STC-1010 human vaccine induces an immune stimulatory response** on human monocyte-derived dendritic cells (moDCs) with the increase of IL-8 and IL-12 and the decrease of IL-10 during moDCs maturation with no viability issue. *(Fig.4)*
- **Anti-tumor effect of CD8+T activated by STC-1010 against 3 different human CRC cell lines** was observed with massive apoptosis (+62% SW620) and large reduction of tumor cells viability. (90% HCT-116 – 80 % HT29) *(Fig.5,6)*
- **TCRseq shows an increase of selectivity of specific CD8+ cells after the stimulation by STC-1010** vs solvant. Increase of medium and large populations of CD8+ cells. *(Fig.7)*

In ovo data confirm the ex-vivo results with an STC-1010 vaccine efficacy by:

- A significant expression of IFN-gamma in tumor (+130,83%, p=0.0185); 3) *(Fig.8)*
- A tendency of metastasis regression (-49%) *(Fig.9)*

With no embryonic toxicity/mortality (daily evaluation of embryonic viability) induced by STC-1010.

CONCLUSION

- **Brenus STC-1010** therapeutic vaccine combining 3 stimulated cell lines (LoVo, HCT116 and HT-29) stressed and haptenized, **allows to form an immunogenic complex covering the CRC heterogeneity.**
- These **ex-vivo** and **in-ovo assay** confirms the **specificity of the immune response** induced by Brenus Pharma STC therapeutic vaccine and **validates the strong anti-tumor efficacy against human CRC cell lines, without inducing toxicity.**
- Our results showed that **STC-1010 is an efficient strategy** to **educate the immune system against various targets linked to tumor plasticity** and **promote CRC cell death.**

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