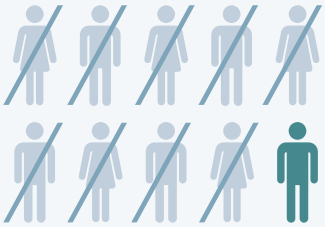
TTX-MC138

Targeting microRNA-10b

TransCode's lead therapeutic candidate, TTX-MC138, is focused on treating patients with metastatic cancer, an area traditionally overlooked because, from a therapeutic perspective, non-metastatic and metastatic tumor cells are often viewed as being the same. However, metastatic tumors are fundamentally different from primary tumors. As a result, existing cancer treatments only incrementally improve patient outcomes for later stages of the disease and, consequently, Stage III/IV cancer has an overall poor prognosis.

- Small, non-coding strands of RNA (microRNAs) have been identified as a significant player in the pathology of cancer
- Our research observed that microRNA-10b acts as a master regulator of the viability of metastatic tumor cells
- miR-10b is shown to be largely dispensable for normal development but critical to tumorigenesis
- Treatment with TTX-MC138 in pre-clinical studies led to durable regression/elimination of established metastases in murine models of metastatic breast and pancreatic cancers as well as in felines with spontaneous end-stage metastatic breast cancer.
- miR-10b has been shown to have broad applicability across multiple cancer types
- Delivery strategy expected to overcome previous delivery challenges to targets outside of the liver and kidneys

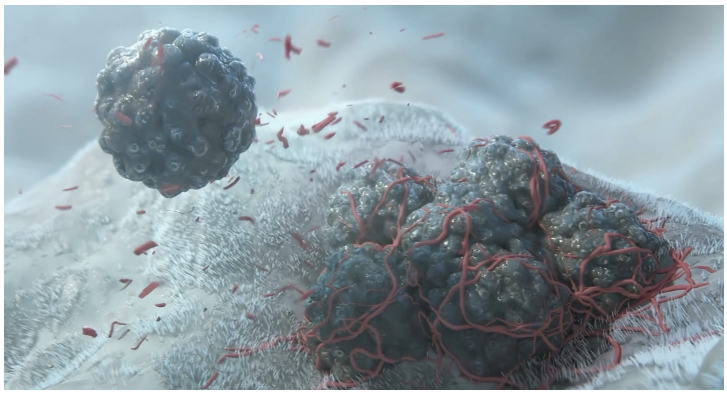
*" ... over **90%** of cancer patients who succumb to adenocarcinoma are victims of **metastatic disease.**"*



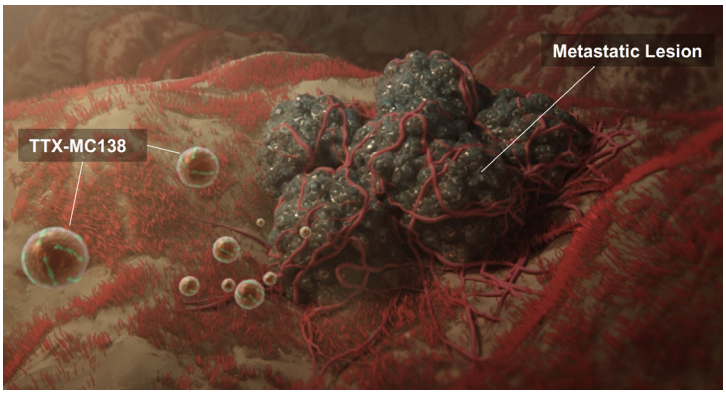
Underlying Mechanism

The underlying mechanism of metastasis relies on two key events demonstrated in pre-clinical studies:

- First, a population of cells in the primary tumor over-express microRNA-10b and acquire the ability to migrate and invade surrounding tissues to form new metastases in the body
- Second, after these cells have upregulated the expression of microRNA-10b, they become molecularly "dependent" on this high level of expression for their survival



When upregulated miRNA-10b allows for tumor cells to detach from the primary tumor, migrate through the blood stream and proliferate elsewhere in the body



TransCode's TTX platform has the potential to treat a variety of tumor indications through effective delivery and targeting

TTX-MC138 Pre-Clinical Results

Within pre-clinical studies, TTX-MC138 resulted in the complete regression of established metastases with no recurrence and no toxicity

- Targets the mechanism that has been shown to regulate metastatic tumor cell survival
- Non-invasive imaging can inform of drug bioavailability & delivery success
- Broad utility across multiple metastatic cancers
- Eliminated pre-existing local metastases in 100% of the animals treated, and distant metastases in 65%

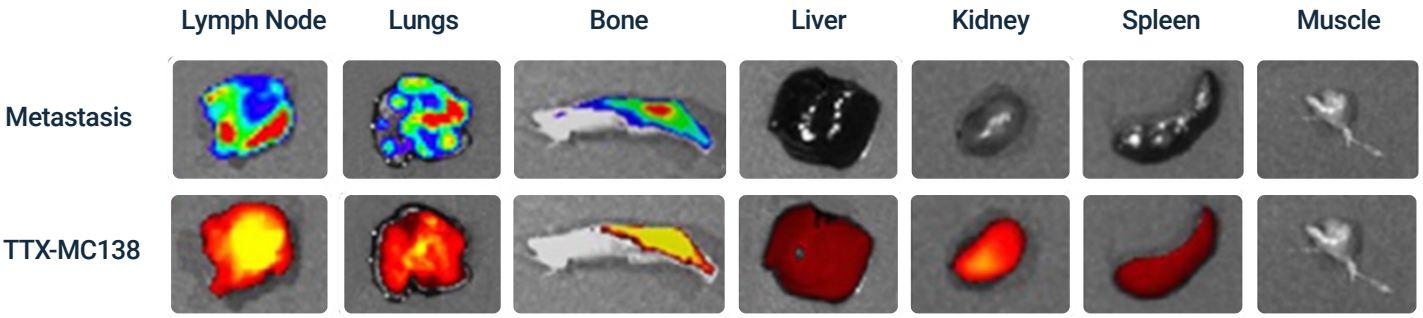
100%

TTX-MC138 eliminated pre-existing ***local*** metastases (cancer spread to lung and lymph node area) in **100% of the animals treated**

65%

TTX-MC138 eliminated ***distant*** metastases (cancer spread to all areas of the body) in **65% of the animals treated**

Successful delivery of TTX-MC138 to metastatic sites has been demonstrated in pre-clinical studies (as shown in the images below):

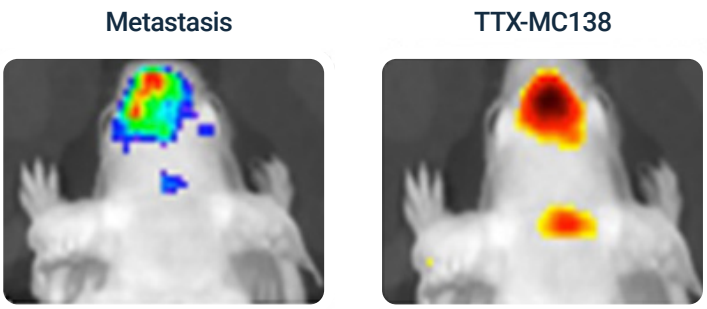


Images above: TTX-MC138 accumulation in metastatic lesions (TTX-MC138 accumulates in distant organs & the foci of accumulation are co-localized with the metastatic lesions).

Top row: Under heading of Metastasis on the upper left - Imaging of metastatic burden (bioluminescence imaging) in excised organs (Lymph node, Lungs, Bone).

Bottom row: Under heading of TTX-MC138 on the lower left - Fluorescence intensity in metastatic lesions in the same excised organs was associated with high uptake of TTX-MC138. Additional organs (liver, kidney and spleen) demonstrated expected high uptake of TTX-MC138 based on the natural pathway of metabolism and excretion of the nanoparticles.

TTX-MC138 accumulation in metastatic lesions in brain



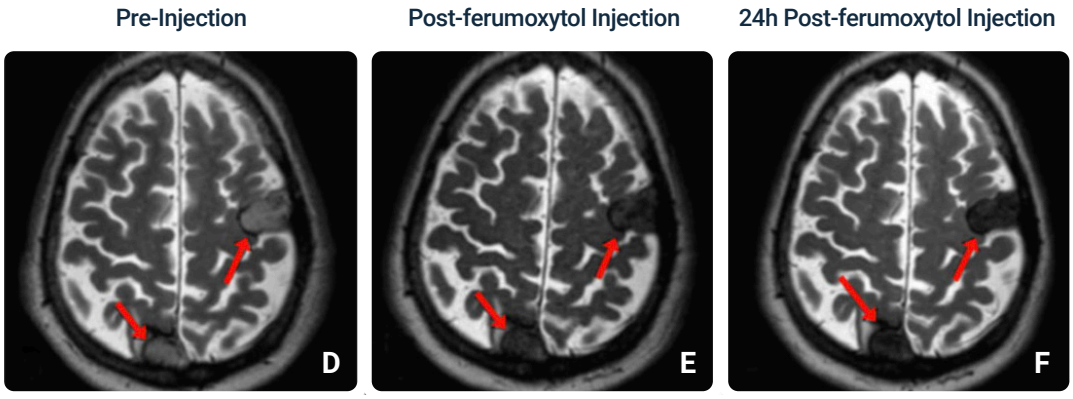
Left image:
(Under heading of **Metastasis**) - Imaging of metastatic tumor lesions (bioluminescence imaging) in brain

Right Image:
(Under heading of **TTX-MC138**) - Presence of TTX-MC138 shown via fluorescence in the same metastatic lesions in the brain

Clinical Evidence

Proof of Delivery to Metastatic Sites with Ferumoxytol (nanoparticles similar to the ones used in TTX-MC138)

The **red** arrows in the images below demonstrate that patients with metastatic lesions in the brain **(images D, E, F)** had an accumulation of nanoparticles in the lesions immediately after injection **(image E)** of ferumoxytol (iron-oxide nanoparticle formulation similar to the nanoparticles in TTX-MC138) and continued to accumulate 24 hours later shown by the darkening of the lesions **(image F)**.



TTX-MC138 Mechanism of Action

- After infusion, TTX-MC138 is avidly taken up by metastatic tumor cells due to hemodynamic and metabolic targeting with our nanoparticle delivery system. Once inside metastatic tumor cells, the therapeutic Oligo and microRNA-10b target readily bind together
- This binding leads to inhibition/inactivation of microRNA-10b which leads to the death of metastatic tumor cells and overall regression of the disease

Importantly, TTX-MC138 is also hormone receptor independent and its mechanism of action could allow treatment of metastatic breast cancer regardless of hormone receptor type (ER+/-, PR+/-, HER2+/-, or combinations thereof). This approach could be especially beneficial for patients with triple negative breast cancer (TNBC) for whom treatment options are limited.

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The FDA has not evaluated or approved TTX-MC138 and it is currently not available for patient use.