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approach

Genetically modified vaccinia virus (vvDD-CDSR) that replicates and kills
cells that have an elevated nucleotide pool (cycling cells) better than those that do not (resting cells)

deletion of the Thymidine Kinase gene (important for viral replication
in resting cells (such as neuron, T-cells etc)
and Vaccinia growth factor gene that induces proliferation of neighboring cells

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Target

superficial ,easily accessible, non connected with important vascular sites
solid tumors
ie: breast , melanoma, squamous cell carcinoma (methastatic**)**

primary end point:
maximally –tolerated dose given IT
safety of IT administration

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- Supporting data *in vitro*: severely reduced viral replication in human embryonic fibroblast and NIH3T3 cells

- Supporting data *in vivo: selective replication and cytolytic effect of the vvDD-GFP in MC38 transplanted tumors and other tumor types in mice*

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Additional features of the vector

addition of Cytosine Deaminase(CD) prodrug-activating enzyme
5-fluorocytosine (5FC)
to further increase the cytolytic effect of the vector

(biological effect of this system will not be evaluated)

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Additional features of the vector

addition of Somatostatin Receptor (SR)
for non invasive imaging)

How often , criteria of selection etc

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important issue

how much the pre-existing vaccinia immunity will influence the primary end points?

maximally –tolerated dose and safety may well depend on pre-existing immunity which in turn
may vary among
the enrolled subjects

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Issues

As data on neutralizing antibody levels will be available before enrollment should their level became a parameter to model the phase I trial?

A sufficient number of Vaccinia- naïve tumor bearing individuals may be necessary to evaluate the true safety of vvDD in humans

Is the tumor cytolytic activity of vvDD maintained in nude mice treated with VIG?

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Issues

Tumor reduction

Is the tumor cytolytic activity of vvDD maintained in nude mice treated with VIG?

other issues

*Criteria of inclusion : four weeks after last treatment .Could a criteria that reflect the immunological status of the individual be used?

* There are no detailed guidelines for treatment in case of undesired level of vaccinia replication (source of VIG ,quantity etc,)

*Treated individuals should be informed to avoid household contact not only with infant but also with young children.

*How HIV infection is excluded is not spelled out ? Serology, RT/PCR in plasma RNA? Both?