Summaries

The oncolytic measles virus (MeV) vaccine strain provides a flexible vector platform which allows for targeted, tumor-restricted immunomodulation. We have developed MeV vectors to support different phases of the cancer immunity cycle. This enables therapy directly tailored to the specific immune micromilieu of individual tumors.
We have validated MeV vectors for T cell activation in preclinical models. MeV encoding bispecific T cell engagers (BiTEs) recruit cytotoxic T cells to the tumor site. Tumor antigen-specific T cell activation is achieved with MeV oncolytic vaccines. MeV encoding IL-12 directs T cell responses towards a Th1 phenotype. Combining MeV with immune checkpoint inhibition increases the ratio of effector to regulatory T cells. Furthermore, our preclinical data support the notion that MeV-mediated oncolysis can break resistance to checkpoint antibodies.
A clinical Phase Ib/II trial combining MeV with an anti-PD1 antibody in patients with metastatic pancreatic adenocarcinoma is currently in preparation. Aside from safety and anti-tumor efficacy, a main focus of the trial is the accompanying translational research program. Sequential biopsies for analysis of tumor-infiltrating immune cells, cytokine and chemokine profiling, transcriptome and immunoreceptor sequencing are performed to identify biomarkers predictive of response.

Dr. Christine Engeland (National Center for Tumor Diseases, NCT)

****

Oncolytic viruses (OV) are attracting growing interest as cancer therapeutics. This is due to their safety and to their multi-faceted mode of action: these viruses are able to target tumor cells both directly by causing the death of infected cells and indirectly by activating antitumor immune responses. We have unique expertise in protoparvoviruses (PV) which belong to the group of oncolytic viruses presently evaluated at both preclinical and clinical levels. Besides above-mentioned anticancer properties, PVs distinguish themselves by their natural (i.e. non-engineered) oncoselectivity, and their small size (nanoparticles) allowing them to reach and disseminate in tumor's protected by physiological barriers (e.g. brain blood barrier). H-1 PV has been recently tested in a monocentric phase I/IIa trial in patients with recurrent glioblastoma multiforme (GBM), the most common and aggressive form of brain tumour in humans. To date 18 patients have been treated with escalating doses of H-1PV administered both locally and systemically, and results show that virus treatment is well tolerated and is associated with first evidence of efficacy (blood brain barrier crossing, intratumoral virus replication and spreading, signs of induced tumor necrosis and recruitment of immune cells). However, as in the case of other oncolytic viruses, there is a need for improving the anticancer efficacy of PVs in humans. To this end, we are using different complementary strategies to develop second generation PVs and PV-based treatments. We were so far very successful in developing and validating three innovative anticancer principles: (1) chimeric viruses that combine the advantages and circumvent the limitations of two distinct oncolytic viruses, namely adenovirus and PV (Ad-PV chimera); (2) oncolytic, replication-competent PVs armed with silencing cassettes that reinforce the cell-killing capacity of the virus and/or the permissiveness of tumor cells for PV infection (H-1PV silencer); (3) combinations of PVs with other anticancer agents such as epigenetic (HDAC inhibitors) or pro-apoptotic (BH3

mimetics) modulators. Moreover, on a more basic level, we devoted special efforts in the last four years, in the characterization of PV life cycle and we have identified several cellular factors that may be important for virus entry, transduction and cytotoxicity.

Our research program builds upon these promising results with the objective to **develop innovative, more effective, PV-based anticancer therapies.** We will not only improve existing vectors, but more specifically, design new constructs and validate novel combination therapies. The investigation of the PV life-cycle will also be pursued, as we anticipate that a better understanding of PV-host cell interactions will provide key clues to both optimization and patient personalization of PV-based therapies. This cutting edge research is expected to **generate new IP** protecting the novel technologies, products and protocols developed.

After having provided pre-clinical proofs-of-concept for enhanced anticancer efficacy, it is our ambition to ultimately translate major breakthroughs into novel treatment options that improve and save the lives of cancer patients. Therefore an important outcome of our research program will be the **launch of (a) new phase I/IIa clinical trial(s)** in the next 5-years to test safety and (first signs of) efficacy of most promising candidates in patients afflicted with glioma or pancreatic carcinoma.

Prof. Dr. Jean Rommelaere
Tumor Virology/F010
Head of the Division

Dr Antonio Marchini
Tumor Virology/F010

German Cancer Research Center (DKFZ)
Foundation under Public Law
Im Neuenheimer Feld 242
D-69120 Heidelberg
Germany