and especially about individualized therapy, we could suspect that the protective effect of vitamin D on the prostate cancer development is also individual. It may for example result from the polymorphism of the receptor of this vitamin and activity of vitamin D-metabolizing enzymes. *Conclusion:* The concentration of vitamin D in blood of patients with prostate cancer is lower than in the blood of patients with benign prostate hyperplasia.

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HSV1716 (SEPREHVIR): AN ONCOLYTIC HERPES VIRUS FOR CANCER THERAPY

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The HSV-1 mutant HSV1716 has deletions in both copies of the gene encoding the neurovirulence factor ICP34.5. HSV1716 effectively kills tumor cell lines *in vitro* and oncolysis has induced tumor regression and increased survival times in a wide range of solid tumor xenograft models including glioma, hepatocellular carcinoma, melanoma, medulloblastoma, mesothelioma, ovarian carcinoma and teratocarcinoma supporting translation into clinical studies. In completed safety studies, direct intratumoral injection of HSV1716 has been used to treat patients with recurrent glioma, metastatic melanoma and squamous cell carcinoma of the head and neck.

Phase I dose escalation studies of HSV1716 in pediatric/young adult patients with non-central nervous system solid tumors (http://clinicaltrials.gov/ NCT00931931) and in pediatric patients with refractory or recurrent high grade gliomas (NCI Protocol #: PBTC-037) and a phase 1/2a study in malignant pleural mesothelioma (http://clinicaltrials.gov/ NCT01721018) are currently on-going. Regulatory approval has recently been obtained for a phase I/2a study in hepatocellular carcinoma. In total 88 patients have received HSV1716 and the virus is well-tolerated with no spread to surrounding normal tissue or no shedding in patients. The selectivity of HSV1716 for replication only in tumour cells and intimations of efficacy have been demonstrated.

The oncolytic biopotency of HSV1716 can be enhanced *via* the incorporation of exogenous genes that generate novel functionalities or *via* combination with drugs that target specific pathways. For example, expression of the Inhibitor of New Growth 4 protein generates a more efficacious HSV1716 variant with improved replication kinetics and data demonstrated that HSV1716 and mTOR inhibitors frequently combined to enhance cancer cell killing.. Therefore, HSV1716 provides a platform with the potential to generate diverse therapeutic options.

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FOCUSSED TRANSCRANIAL ULTRASOUNDS: APPLICATION TO THE DELIVERY OF GLYCOSYLATED OLEIC ACID/VITAMIN D-BINDING PROTEIN TO BRAIN TUMOURS AND METASTASES

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Glycosylated oleic acid/vitamin D-binding protein, also known as oleic acid/Gc protein-derived macrophage activating factor (OA-GcMAF), has proven effective in the immunotherapy of solid neoplasms and haematological malignancies. The limited permeability of the blood brain barrier (BBB), however, is an obstacle to its widespread use in primary brain tumours, as well as in brain metastases. In order to overcome this limitation, we developed a procedure involving the use of focussed ultrasounds that allow selective permeabilisation of the BBB and targeted delivery of OA-GcMAF. One day before the procedure, OA-GcMAF is injected in the proximity of inguinal nodes; it is administered orally as a fermented milk product and with suppositories or enemas. The following day, OA-GcMAF is administered by nebulisation. Measurement of blood pressure variations and assessment of splenic blood flow after nebulisation are used to determine the individual response (1). Five minutes after nebulisation, transcranial ultrasounds are applied through the temporal acoustic window on the same side where the lesion is located. With proper setting, the cerebral cortex can be visualised, thus indicating that the ultrasound waves reach the gray matter (2). The

ultrasound could then be directed toward the anatomical regions where the lesion is located. Most regions of the brain can be accessed through the temporal acoustic window, with the exception of distal areas of the frontal and occipital lobes. Focussed ultrasounds are known to transiently increase the permeability of the BBB (3) and, therefore, allow passage of OA-GcMAF that is a relatively lipophilic molecule thanks to the presence of oleic acid. The procedure lasts 5-15 min, causes no discomfort or side effects and can be repeated continuously or in cycles. The procedure can be safely performed before, during or after other anti-neoplastic treatments.

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GLYCOSYLATED OLEIC ACID/VITAMIN D-BINDING PROTEIN SUPPRESSES HER2 ONCOGENE EXPRESSION IN HUMAN BREAST CANCER

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A woman was diagnosed with mammary adenocarcinoma in the right breast in 1985 at the age of 37, followed by quadrantectomy, lymphadenectomy and irradiation. In 1999, an adenocarcinoma was diagnosed in the left breast, followed by ample resection and anti-oestrogen receptor treatment for 6 years. In April 2014, an infiltrating adenocarcinoma was diagnosed in the right breast that had been operated in 1985. Pre-operative biopsy showed weak positivity for progesterone receptor (PgR, <1%) and high positivity for the oncogene HER2 (>10%, score 2+). With the goal of boosting her immune system during the 3 weeks preceding surgery, glycosylated oleic acid/vitamin D-binding protein (OA-GcMAF) was administered by subcutaneous injections, nebulisation and with a fermented milk product rich in OA-GcMAF. No drug was administered in the 3 weeks preceding surgery, nor had the patient received any treatment for the previous 8 years. Following right mastectomy, analysis of the surgical specimen showed no positivity for HER2 expression (negative, score 0) and significant increase in positivity of PgR, from <1% to 20%. These results indicate that OA-GcMAF treatment suppressed oncogene expression and induced differentiation of cancer cells. *Introduction:* The healthy properties of oleic acid (OA) in breast cancer have been known for centuries (1) and recent evidences suggest that these properties are amplified by association of OA with proteins such as α-lactalbumin and lactoferrins. These proteins form OA-protein complexes that exhibit highly selective anti-tumour activity *in vitro* and *in vivo* (2). We recently demonstrated that also a serum protein with the capability to bind OA shows anticancer effects; this is the glycosylated vitamin D-binding protein also known as Gc-protein-derived macrophage activating factor or GcMAF (3). This protein binds both OA and vitamin D and exerts its immune-stimulating and anticancer effects through cross-talk with the vitamin D receptor (4). Here we report a clinical observation suggesting that OA-GcMAF, that is GcMAF-complexed with OA, suppresses the expression of a major oncogene involved in human breast cancer that is the human epidermal growth factor receptor 2 (HER2). *Patients and Methods:* A woman was diagnosed with mammary adenocarcinoma in the right breast in 1985 at the age of 37, followed by quadrantectomy, lymphadenectomy and irradiation. In 1999, an adenocarcinoma was diagnosed in the left breast, followed by ample resection and anti-oestrogen receptor treatment for 6 years. In April 2014, an infiltrating adenocarcinoma was diagnosed in the right breast that had been operated in 1985. With the goal of boosting her immune system during the 3 weeks elapsing between biopsy and programmed surgery, OA-GcMAF (Goleic®, Immuno Biotech Ltd.) was administered by subcutaneous injections (880 ng) and nebulisation (880 ng) as indicated in (3). The patient followed a nutritional regime based on a low carbohydrate, high protein diet (5). To this end, the patient was provided with food containing only 2% carbohydrates (Le Gamberi Foods, Forlì, Italy), and with essential aminoacids (Master Aminoacid Pattern®, dr. reinwald healthcare gmbh, Schwarzenbruck, Germany) (6). The patient was also provided with a fermented milk product containing colostrum and microorganisms known to produce OA-GcMAF from the Gc-protein present in milk (Bravo Probiotic®, Les Alpes, Wellington, NZ). No drug was administered or was programmed in the 3 weeks preceding surgery, nor had the patient received any treatment for the previous 8 years. The analyses on HER2 and other gene expression on the biopsy and surgical specimens were performed by the laboratory of the University Hospital of Careggi of the Italian Public Health Service, in Firenze, Italy. Analyses were performed according to the European standards of quality (UNI EN ISO 9001:2008) and were examined and countersigned by four different professionals. The original documents are conserved in the archives of the Department of Biomedicine of the Careggi