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NEW CHANCES FOR A RENAISSANCE OF THE HSCT- SUPPORTED HIGH-DOSE CHEMOTHERAPY BY THE ACTIVELY PREVENTED TOLERANCE-REINDUCTION AGAINST INEVITABLE RESIDUAL TUMOR CELLS IN THE CRITICAL EARLY PHASE OF THE TREATMENT-RELATED IMMUNO-INCOMPETENCE.

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One of the main reasons for the rather disillusive long- term results of the high-dose chemotherapy appears to be the reinduction of the tumor-specific tolerance in the critical early phase of patient's treatment-related generalized immunoincompetence.
We therefore propose to bridge this high-risk interphase by adding immunocompetent cells either of host or of donor origin (or a 1:1 mixture of both) immediately after the high-dose chemotherapy; in the case of donor immunocytes, these must be pretreated in vitro by a multistep procedure, conferring on these cells a preprogrammed lifespan, resistence against early hypoergy or anergy and the potency to exert a GvHD-free GvM effect (MIS-BM/SC effectors). Due to the highly beneficial effect of such premanipulated allogeneic effector cells, we recommend to integrate this novel principle routinely even into the conventional autologous BMT and PBSCT or PBPCT. Our improved technology, based on the DNA-premanipulated MIS/MIT-effectors, allows a selective potentiation of the tumoricidal GvM(GvT) effect without the adverse GvHD side-effect. This opens new ways both (a) in the improvement of the conventional rescue therapy by autologous stem cells and (b) in the introduction of allogeneic transplants in patients with solid tumors, treated by high-dose chemotherapy. To prevent the risk of reinduction of contaminating tumor cells along with the autologous stem cell graft, we recommend the same cell death-preprogramming procedure like in the case of donor-derived cells or the use of a 1 : 1 mixture of lifespan-predetermined allogeneic and autologous mature T cells or PBMCs.

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TUMOR THERAPY : A GRADUAL REPLACEMENT OF MYELOABLATIVE PREPARATIVE REGIMENS BY NON-ABLATIVE ONES REFLECTS THE RECENT TREND TOWARDS AN INDIRECT, IMMUNOREGULATORY INTERVENTION INSTEAD OF THE DIRECT ATTACK ON THE TUMOR CELLS.
SOME IMPORTANT CLINICAL IMPLICATIONS OF OUR EXTENSIVE ANIMAL EXPERIMENTS

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The recent trend to replace myeloablative preconditioning by the non-ablative one is associated with a shift from the direct attack on tumor targets toward the indirect, immunoregulatory intervention. This shift results in the reactivation of patient's own immune response which profits of both, the preservation of patient's immunocompetent cells and their modulation (deblocking) by donor's allospecific T cells. The latter effect is based on the GvM reaction, i.e. the tumoricidal effect of patient's tumor-specific CTLs whose activity is restored after the in vivo inactivation of patient's tumor-protecting Ts (and Th2) by donor alloreactive T cells. Our detailed animal experiments have led to the conclusion that it is of crucial importance that this in vivo elimination of preexisting tumor-specific Ts (and Th2) cells is radical, i.e occurring on the humoral plus cellular level, the former by pan T- or T-subset specific Mabs and the latter by our novel MIS/MIT-effectors, recognizing up to 11 (hyper)activation structures on Ts (and Th2) targets, e.g. the MHC class 2 complex.
A further paramount implication of our comprehensive animal experiments, implicating over 120 single protocols, is the separation of T cell subsets, inducing the beneficial GvM effect from those, responsible for the adverse GvHD side-effect which allows for the first time a selective GvM potentiation without a parallelly increased GvHD risk. In this way, all GvM- based adoptive immunotherapies could be freed of their GvHD side- effect.

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Induction of an Effective Immune Response against Tumor-Cell-Spheroids Induced by the Trifunctional Antibody BiUIII (anti-EpCAM X anti-CD3)

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Bispecific antibodies are an innovative strategy in cancer therapy. They recognize tumor antigens with one arm and effector cells with the other redirecting immune cells towards tumors. The trifunctional Ab BiUIII has one arm binding to the Epithelial Cell Adhesion Molecule (EpCAM), the other recognizes CD3 on T cells. Because of an unique Fc-region, this Ab format simultaneously binds and activates Fc-receptor + cells. Thereby, the formation of a tri-cell-complex of tumor cell, T cell and Fc-receptor+ cell was postulated. To clear that point, Cell-cell-interactions were studied using immunocytochemically stained cytospins of single cell suspensions consisting of EpCAM+ tumor cells and effector cells (PBMCs). Moreover, tumor cell spheroids (TCS) were treated with PBMC and BiUIII to investigate whether 3-dimensional structures can also be eliminated. Immunohistochemistry was performed using TCS-cryocuts. Viability of tumor cells was tested by FACS-analysis and in replating experiments. PBMC-activation was monitored by testing supernatants in a TNF-alpha bioassay. For the first time, we could show the formation of a tri-cell-complex by immunostaining and provide evidence for phagocytosis as one BiUIII-mediated effect. Using the TCS model we investigated the immune cell infiltration and observed significant changes in the infiltrate following BiUIII-treatment resulting in an effective elimination of TCS. Since micrometastases are supposed to play an important role in tumor development this new Ab format may be a promising approach especially in minimal residual disease