High-throughput 3D spheroid co-culturing platform for screening of organ-organ interactions

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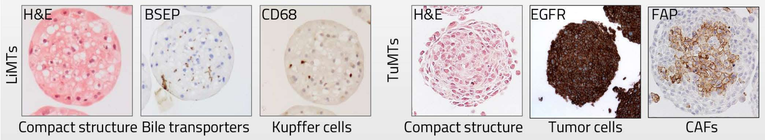
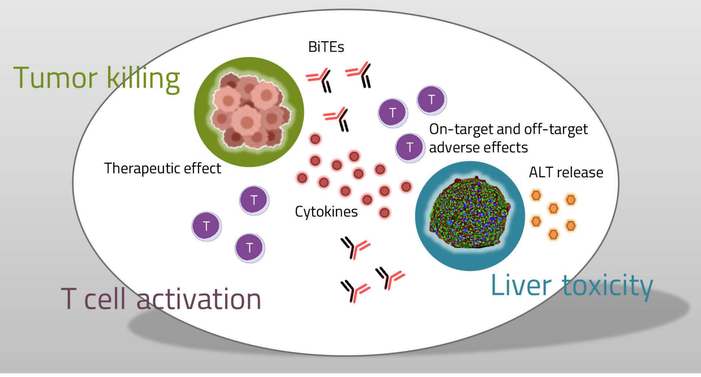
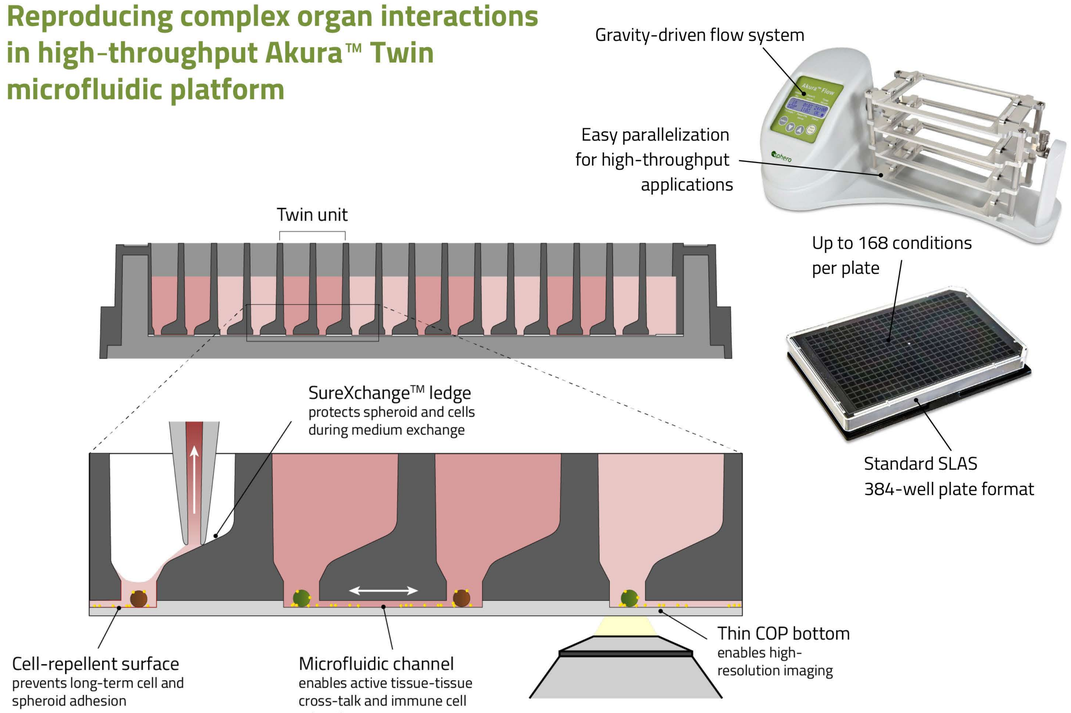
Experimental design

- Accurate 3D InSight ™ liver microtissue model with primary human hepatocyte, Kupffer cells and endothelial cells co-culture
- 3D InSight ™ Tumor-CAF co-culture model to recapitulate TME
- Non-autologous immune cells and clinical candidate HER2xCD3 BiTE (runimotamab, RG6194)



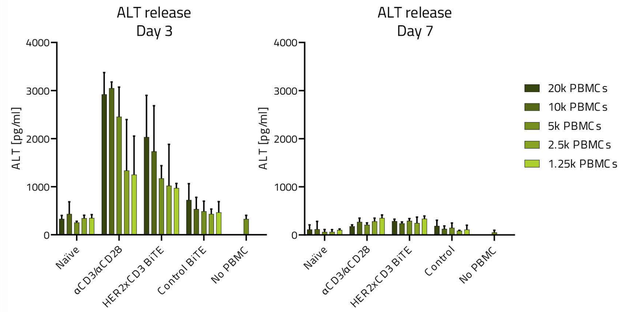


Reproducing complex organ interactions in high-throughput Akura™ Twin microfluidic platform

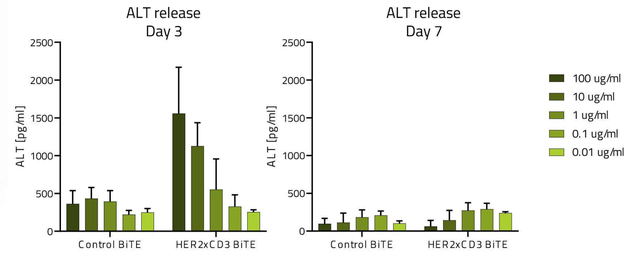


Liver Toxicity

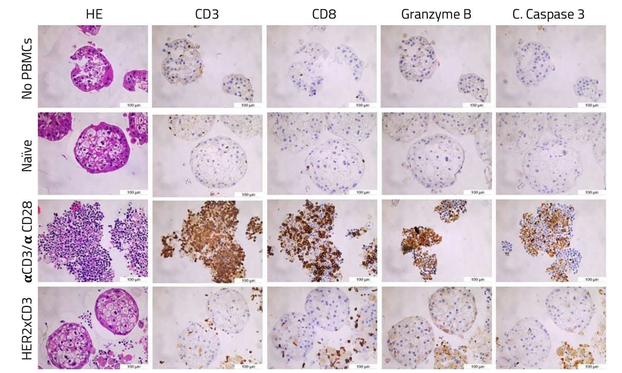
Administration of αCD3/αCD28 or HER2xCD3 BiTE (1 µg/ml) in presence of increasing number of PBMCs resulted in a cell number-dependent acute ALT release at day 3 timepoint, but not at later time point (day 7).



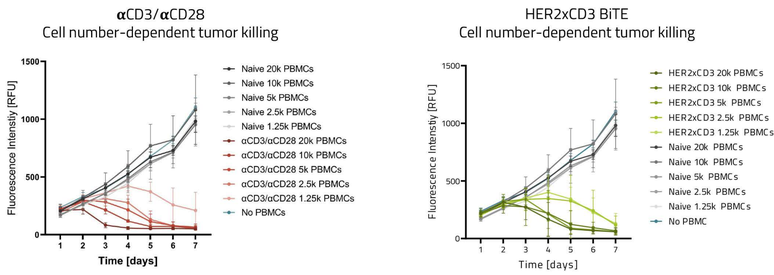
Treatment with increasing concentration of HER2xCD3 BiTE in presence of PBMCs (5k cells, E:T ration 1:5) resulted in a dose-dependent acute liver toxicity measured as ALT release at day 3 timepoint, but not at day 7.

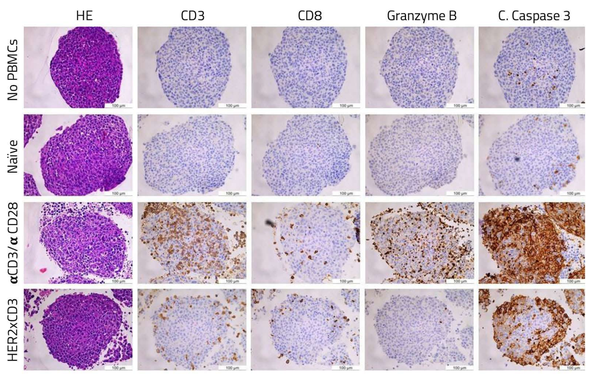


Treatment with αCD3/αCD28 but not HER2xCD3 BiTE (1 µg/ml) in presence of PBMCs (5k cells, E:T ration 1:5) resulted in significant infiltration of CD3+, CD8+ and Granzyme B+ cells into the liver spheroid at the day 7. Immune cells induced liver cell death visualized by staining for the cleaved caspase 3. Lack of immune cell infiltration into HER2xCD3 BiTE group suggest Cytokine Release Syndrome (CRS) related liver damage.



Tumor killing



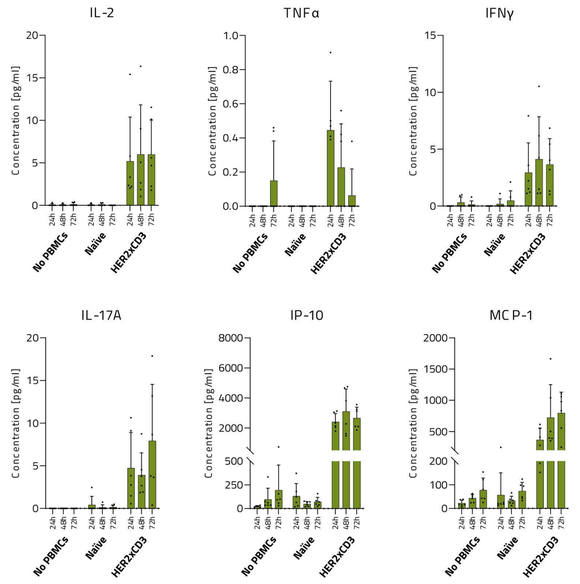


▲ Administration of increasing number of PBMCs resulted in a cell number-dependent tumor regression for αCD3/αCD28 and HER2xCD3 (1 µg/ml) treated groups, while no toxic effect was observed with Naïve PBMCs. Treatment with increasing concentration of HER2xCD3 BiTe in presence of PBMCs (5k cells, E:T ration 1:5) resulted in a dose-dependent tumor killing .

◀ Treatment with αCD3/αCD28 or HER2xCD3 BiTe (1 µg/ml) in presence of PBMCs (5k cells, E:T ration 1:5) resulted in significant infiltration of CD3+, CD8+ and Granzyme B+ cells into the tumor spheroid at the day 7. Immune cells induced tumor cell death visualized by staining for the cleaved caspase 3. In the No or Naïve PBMCs groups we did not observe immune infiltrates or induced cell death.

T cell activation

Treatment with HER2xCD3 BiTE (10 µg/ml) in presence of PBMCs (5k cells, E:T ration 1:5) resulted in secretion of cytotoxic T-cell cytokines.



Conclusions

Combined evaluation of efficacy and safety of BiTEs in Akura™ Twin platform improves definition of therapeutic window with limited liver adverse effects.