

Opening new horizons in humanizing preclinical multi-organoid disease models with the 3D CoSeedis *in chip* communication technology™

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Introduction

Conventional cellular or animal disease models have shown that the predictability of patient response to treatment is severely limited^{1,2}. Great efforts have been made to humanize mouse models to better predict certain aspects of human physiology and immunology³. The abc biopply team has now made a significant breakthrough in humanizing upstream 3D cell models through the revolutionary and proprietary 3D CoSeedis multi-organoid *in chip* communication technology™.

Providing optimized physiological growth conditions and unique ways of intercellular communication, our models are freed from non-human components wherever possible. They allow us to mimic and maintain specific organs and tissues in culture for long periods of time. Thus, we successfully bridge the translational gap with unparalleled physiological responses and unique statistical predictive power. Here, we present how the innovative 3D CoSeedis *in chip* communication technology™ specifically enables the humanization of 3D multi-organoid models and consequently improves the predictiveness of patient's response.

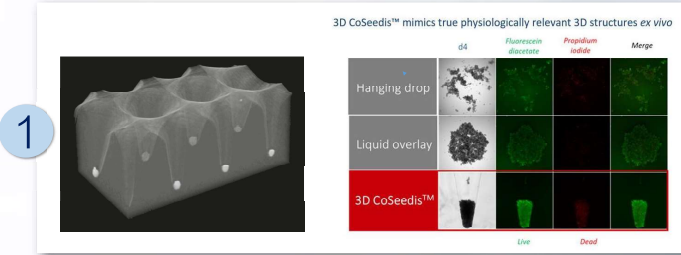


Figure 1: The 3D CoSeedis *in chip* communication technology™ is responsible for two outstanding features that revolutionize the way we can model complex diseases *ex vivo*: intra and inter-tissue communication empowers the setup and in-depth analysis of complex disease models (left panel, eg. cytokine storms etc.); microenvironment formation and the analysis of micro-tissues that were so far hard to grow *ex vivo* (right panel).

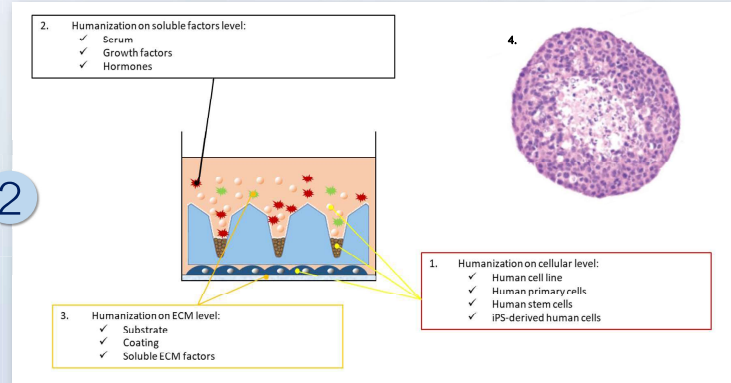


Figure 2: Humanization takes place on multiple levels in 3D CoSeedis humanized multi-organoid models™. Most significantly, the models are unparalleled flexible with respect to the source of cell types and populations. Most simple humanization levels are achieved by the integration of human cells lines already. Highest physiological significance is achieved by freeing the model completely from non-human components:

- the embodiment of human primary patient derived cell populations that mimic entire organs (1).
- the consequent use of human sera or fully defined humanized growth media (2).
- The subsequent mimic of human micro-environment by using e.g. humanized ECM components for feeder cell coating or soluble factors for test cell support (3).

By combining all of these factors, we demonstrated in this work that the 3D CoSeedis humanized model system reliably produces microtumors with necrotic cores that can be stably maintained in culture for up to 75 days (4).

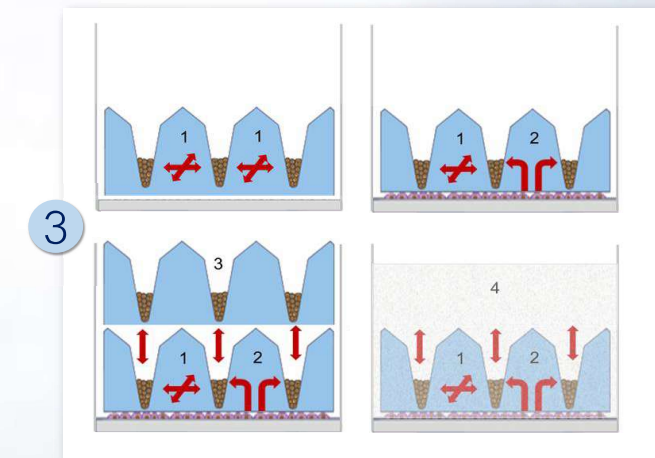


Figure 3: The 3D CoSeedis *in chip* communication technology™ is at the core of humanizing disease models. It is the possibility of 3D micro-tissues to exchange growth factors, hormones, and other communication signals that ensures the micro tissues formed in 3D CoSeedis humanized multi-organoids models™ physiologically resemble the tissue of origin in a donor, both healthy or diseased. However, the technology take humanization to an entirely different level: it allows the simulation of highly complex co-culture systems that reflect and mimic the *in vivo* interaction of various tissues and organs and consequently allow us to mimic complex diseases phenotypes with an unprecedented precision. The system allows the study of cell-to-cell communication (1) and interaction (2), either in contact or distance co-cultures. Likewise, it effectively empowers organ-to-organ communication systems (3) and therefore enables researchers to address complex biological interactions such as cytokine storm and others (4).

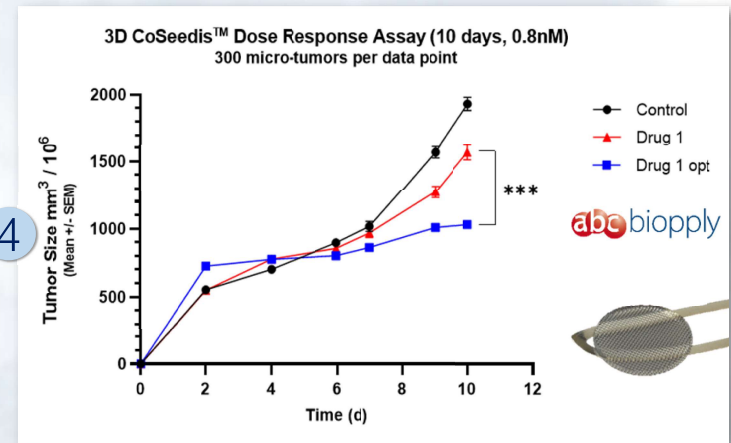


Figure 4: In this study 3D CoSeedis humanized multi-organoid models™ lead ultimately to much more reliable disease modeling. The IC₅₀ determinations we measured were much more physiologic and lead to reliable dosage predictions for later downstream *in vivo* or *in patient* trials. Data presented show a typical dose response assay set-up. Results with comparable predictive value as the mouse model are achieved in 7-8 days (mouse model 45-50 days, data not shown).

| Criteria | Existing Commercialized ADC | | | |
|--|--|--|--|---|
| | 2D cell culture results (n=36) | Conventional 3D cell culture results (n=341) | Small and large animal results (n=1-6) | 3D <i>in chip</i> Assay Results (n=3,500) |
| Serum Stability | 76% (NHS 37°C) | nd | nd | tbtd |
| Target Binding Specificity | positive | positive | nd | positive |
| Cytotoxic IC ₅₀ (nM) | 0.907/24.8 ^a (0.98 own 2D data) | 0.04-17.26 ^a | nd | 6.8 |
| Tumor Growth Inhibition (50% after x days at dose) | 4 days at 10/16/42 mg/kg | 20 days at >50 ^a / <80 ^a mg/kg | 20 days at 10 mg/kg | 8 days at 1 mg/kg |
| Tumor Relapse Inhibition | No model available | No model available | No model available | Relapse inhibition negative at 3-5 mg/kg |
| Resulting Anti-Tumor Dosage recommendation (mg/kg) | Not conclusive | 15 / 32 ^a | >31 ^a / >51 ^a | >5 |
| Off-Target Toxicity Liver / Kidney (mg/kg) | | | >3 | >10 / >20 |
| Systemic Toxicity | | | | nd |
| Effective nontoxic dosing range recommendation (mg/kg) | | | | >5 / <10 |
| Definitive Clinical Dosage | | | | 3x3 mg/kg (9 mg/kg) |

Figure 5: The summary of results in the context of comparison with non-humanized conventional preclinical models shows that 3D CoSeedis humanized multi-organoid models™ in combination with the 3D CoSeedis *in chip* communication technology™ is able to provide more accurate predictions on drug efficacy, dosage and drug safety than current state-of-the-art technology. As a consequence, dosing range predictions are not only more reliable but consistent with drug safety data (compare second last column with last column on the right). Furthermore, 3D CoSeedis humanized multi-organoid models™ allow to substantially reduce the number of test animals, they speed up the time to result and are highly sensitive to identify new compounds.

Conclusion

With the 3D CoSeedis humanized multi-organoid models™ and *in chip* communication technology™ we have finally some effective tools at hand to investigate physiologically relevant disease models *ex vivo* and thereby lift the entire preclinical drug development process to a new level. Due to the unique and intrinsic characteristics of the technology, we can now humanize disease models to an unprecedented degree. Likewise, intercellular and inter-organ communication are the basis to create micro-tissues that resemble donor physiology and consequently allow to more accurately predict dosage windows and potential toxicity.

In addition, the technology presented here can effectively help to eliminated the need for animal tests to a large extend, accelerates the time to result substantially and increases sensitivity in drug function detection. 3D CoSeedis humanized multi-organoid models™ and *in chip* communication technology™ therefore safe on resources and increase overall drug development efficacy.

Sources:
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 3) Chagnin J, Buelmer H, Seeshorn M O, et al. Humanized mouse models for immuno-oncology research. Nat Rev Clin Oncol. 2021; 19:2-206 (2023).
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