

# Advancing 3D drug development models to the sex and ethnicity specific level

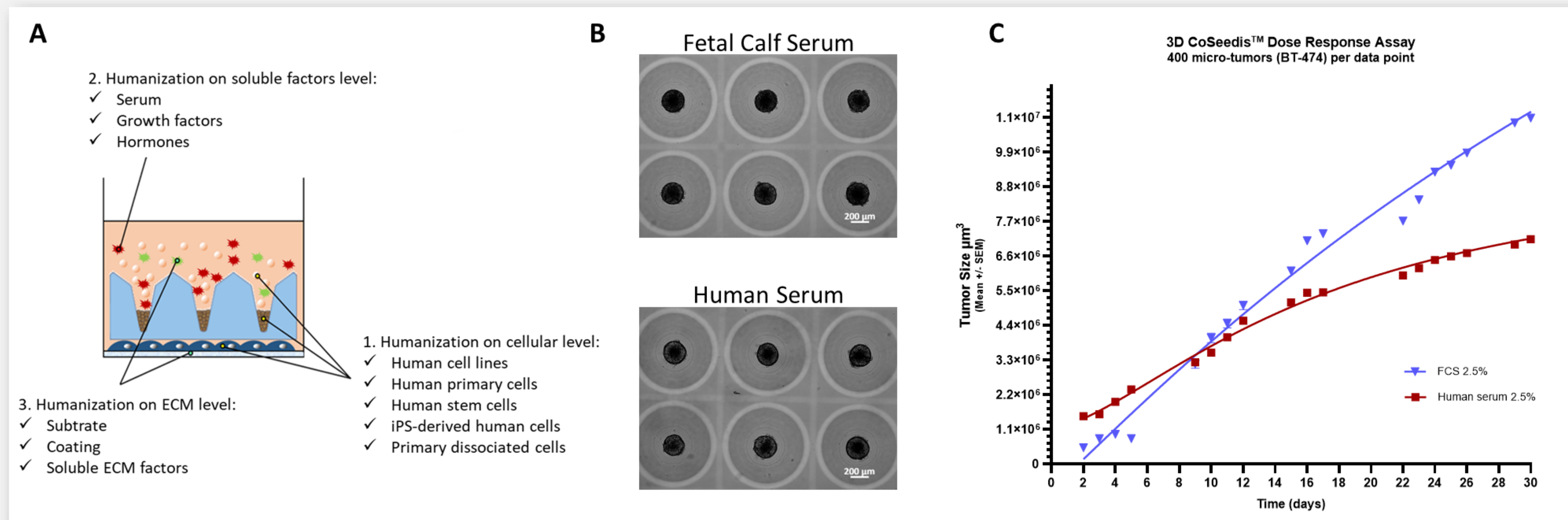
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## Introduction

Conventional cellular or animal disease models have shown that the predictability of patient response to treatment with those models is severely limited<sup>1</sup>. Great efforts have been made to humanize mouse models to better predict certain aspects of human physiology and immunology, but with limited success. abc biopply 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. Thus, they allow us to mimic and maintain physiologically relevant organoids in culture under reproducible and reliable conditions. Furthermore, physiologically accurate studies on human primary tumor cells were able to confirm the predictive power of the 3D CoSeedis humanized multi-organoid disease models. Combined with the unique and statistically powerful predictiveness of the 3D CoSeedis™ chip, we are finally in a position to successfully bridge the translational gap between preclinical predictions and clinical treatments.

Here we present how the innovative 3D CoSeedis *in chip* communication technology™ enables the humanization of 3D multi-organoid models and consequently improves the predictability of patient response. Preliminary data indicates that the model is even capable to make accurate predictions on sex specific drug responses and to address ethnicity specific responses.



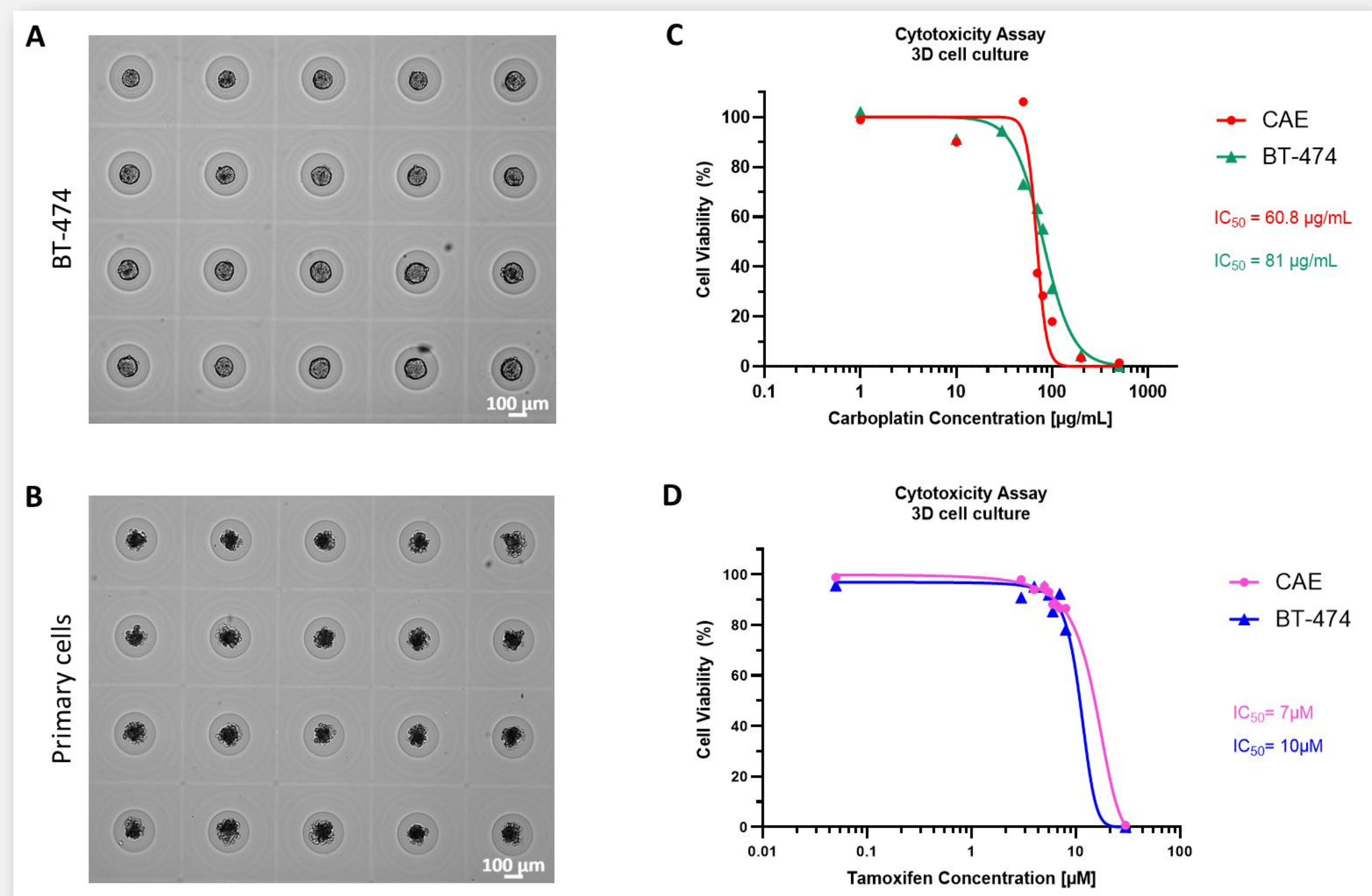
**Figure 1: Humanizing predictive disease models - Serum**

The humanization of the 3D CoSeedis system can be done at different levels (Fig. 1A). In a first step, we replaced the FCS by human serum. No morphological differences were observed in BT-474 micro-tumors (Fig. 1B). However, differences in growth rate were observed (Fig. 1C). The currently used standard *in vitro* tumor models using FCS often have a significantly higher growth rate than the rates observed in patients. This may have an impact on metabolic activity and consequently affect the response to compounds and lead to bias. Consequently, slowing *ex vivo* tumor growth, by using human serum instead of FCS, is a step closer to physiological *in patient* conditions and helps to make more accurate and reliable drug efficacy predictions.

**Figure 2: Humanizing predictive disease models – Primary human tumor cells**

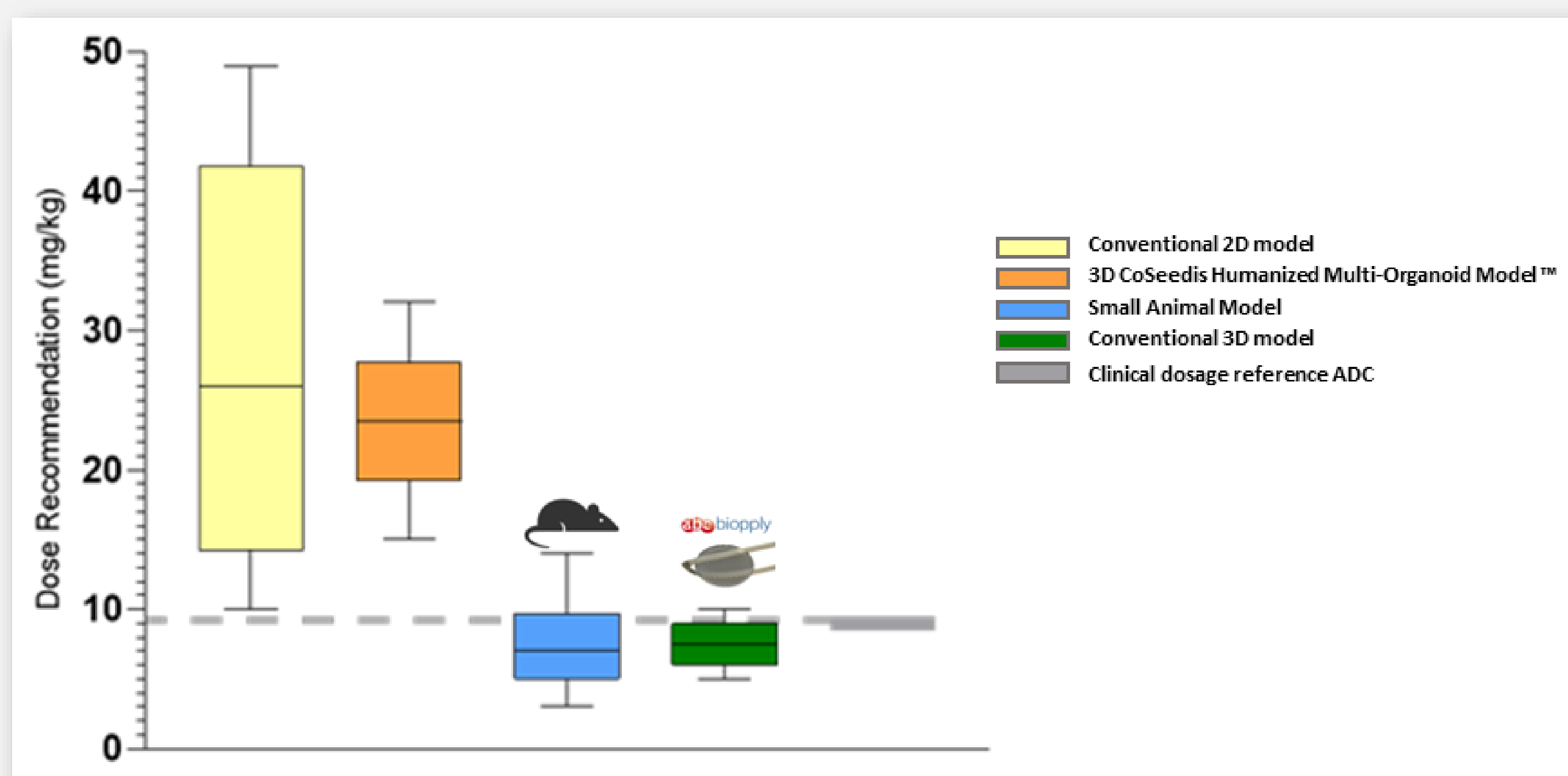
Although morphologically different from the micro-tumors formed by BT-474 (Fig. 2A), primary breast cancer-associated epithelial cells aggregate nicely into micro-tumors in the 3D CoSeedis chip (Fig. 2B).

The graphs show the comparison of Carboplatin (Fig. 2C) and Tamoxifen (Fig. 2D) IC<sub>50</sub> values obtained from BT-474, and primary breast cancer-associated epithelial cells. For both cell types, and for both drugs, the IC<sub>50</sub> values obtained are very similar, indicating that the humanization of the system, even when using cell lines, is indeed very physiological and leads to highly accurate predictions of dosage and drug efficacy.



**Figure 3: Increased predictive power due to the 3D CoSeedis humanized multi-organoid model™**

This figure summarizes the impact of extensive humanizing steps (as described in Figure 1 and 2) on dosage predictions. Comparing the clinical relevance of different preclinical models, conventional 2D models, as well as standard 3D models are not capable to predict the dosage of reference ADCs used in clinics with accuracy. In contrast, lab animals and the humanized 3D CoSeedis model very accurately determine the dose recommendation range that is currently used in clinics. In fact, the 3D CoSeedis humanized *in chip* multi-organoid model™ has shown the highest accuracy of all the test models in this test series and can do so in absence of all non-human components.



## Conclusion

- Humanization leads to better efficacy, dosage, and toxicity predictions.
  - Better predictions reduce failure rates at later clinical stages;
  - Better predictions reduce the number of animals required for *in vivo* tests.

## Outlook

- Develop a sex-specific preclinical model to distinguish sex-specific drug responses and toxicity effects.
- Develop a model to distinguish drug responses based on ethnic background.

