Integrating omics-driven digital avatars with patient-derived experimental models to accelerate precision oncology

Abstract #6879

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Oncology Drug Development Is Limited by Molecular Data Bottlenecks

The use of patient multi-omics —including genomics, transcriptomics, proteomics— is central to oncology drug development. However, translating these data into clinically actionable strategies (i.e. patient stratifications, biomarker discovery, single and combination treatments) remains a major challenge, particularly in preclinical and translational settings.

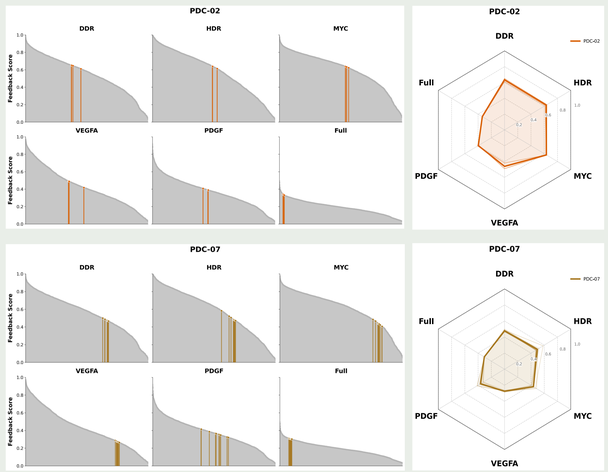
Current approaches are constrained by three fundamental bottlenecks:

1. **Limited and Noisy Data**
- Small patient cohorts in oncology subtypes limit statistical power
- High-dimensional molecular profiles with low sample size (low-N / high-p)
- Batch effects and cross-platform variability reduce data reliability

2. **Fragmented Data Landscape**
- Molecular and clinical data remain siloed across institutions and systems
- Limited interoperability restricts linking molecular features to treatment outcomes
- Restricted access and delayed data release hinder model development

3. **Lack of Mechanistic Interpretability**
- Multi-omics data are difficult to integrate into coherent, system-level models
- Tumour heterogeneity obscures true drivers of response
- AI-driven associations often fail to translate into robust and reproducible stratification

👉 As a result, molecular insights rarely translate into predictive and testable treatment hypotheses.

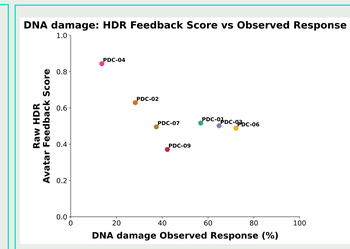


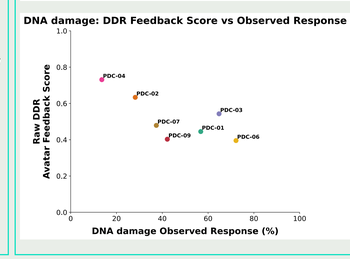
Embedding of PDC Avatars into a Patient Tumour Avatar Space

PDC-derived Digital Avatars were embedded into a ~10K patient tumour avatar collection, spanning **multiple cancer types**, enabling positioning of **patient-derived cell models** within a patient-scale molecular landscape.

PDC avatars were generated from **baseline RNA-seq profiles**, capturing the tumour system represented in the input material.

Distributions represent **mechanistic pathway activity scores** derived from regulatory network interactions (feed-forward and feedback propagation), across treatment-relevant axes (DDR, HDR, MYC, VEGFA, PDGF and global "Full"). These axes correspond to the **drug mechanisms evaluated in PDC experiments**, enabling parallel assessment across multiple treatment classes.





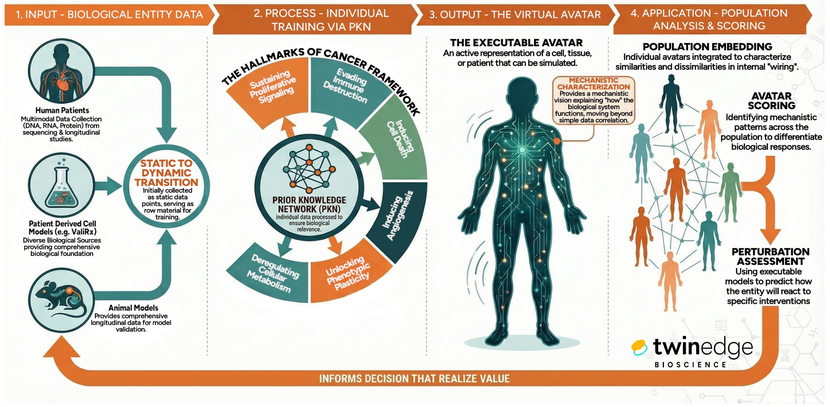
Mechanistic Pathway Scores (Raw) Capture Treatment-Relevant States

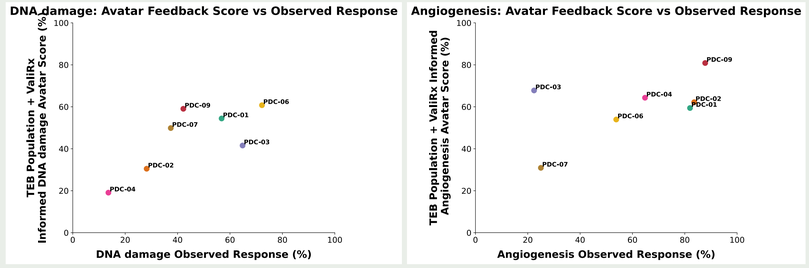
Avatar-derived pathway scores (e.g. DDR/HDR, for DNA damage response capacity) quantify **regulatory network interactions** linked to drug response mechanisms. These scores are derived **without use of treatment response labels, across both PDC models and the broader avatar population**.

Across PDC models, raw scores were **consistent with mean inhibition of cell viability following treatment with DNA-damaging agents**, capturing variation in underlying pathway states associated with sensitivity.

Even without treatment-specific training, avatars capture **intrinsic pathway configurations**, reflecting mechanisms rather than fitted associations.

The Virtual Avatar Workflow: From Biological Data to Mechanistic Insight





Population-Contextualised Scoring for Cross-System Mechanistic Alignment

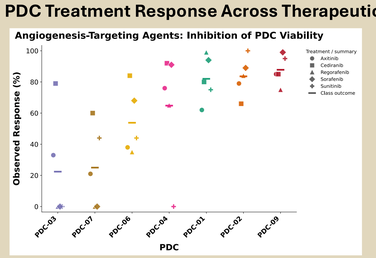
Raw scores were further contextualized using the combined **patient avatar population** (~10K tumors) and PDC models, generating **treatment label–informed scores** that place preclinical samples within a shared pathway activity reference across tumors.

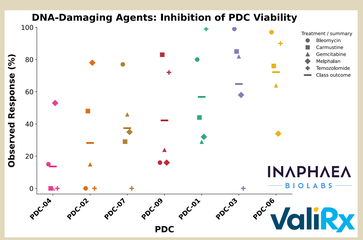
These scores show consistent alignment with **measured viability responses** across both DNA damage and angiogenesis axes. Population-contextualized scoring links **preclinical models and patient tumours** through shared (fully or partially) feedback pathway states, enabling:

- simultaneous interrogation of **multiple drug-relevant mechanisms**
- comparison of treatment responses across systems within a unified framework

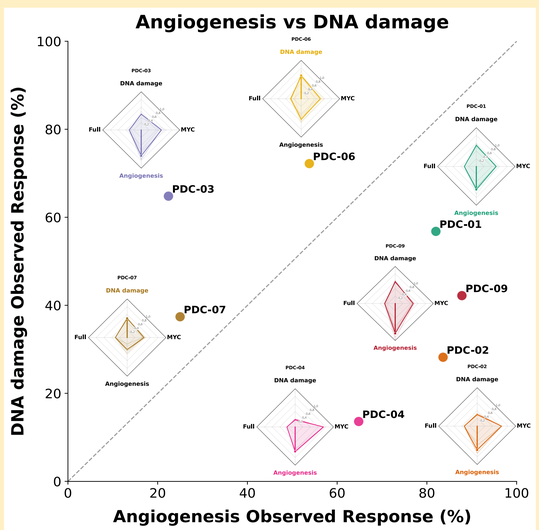
👉 This supports **in silico exploration of MoA and combination strategies**, guiding follow-up experimental testing.

PDC Treatment Response Across Therapeutic Classes





• Ovarian cancer patient-derived cells (PDCs) are ex vivo tumour models used to assess drug response, quantified here as **cell viability inhibition after 72 hours** using a high-content imaging live/dead assay.
• PDCs exhibited **heterogeneous responses** to DNA-damaging and angiogenesis-targeting therapies, with variability across and within treatments.
• Angiogenesis inhibitors showed a relatively consistent class effect, with several models (e.g. PDC-01, -02, -09) displaying high sensitivity, while others showed limited response. In contrast, DNA-damaging agents produced greater heterogeneity, defining distinct sensitive and resistant subgroups.
• These responses reveal **non-overlapping sensitivity profiles** between treatment classes, highlighting distinct biological vulnerabilities across PDC models, with reciprocal sensitivity patterns observed between angiogenesis inhibition and DNA damage.



Integrated Multi-Pathway View of Treatment Response

- PDC models are positioned in a **joint DNA damage–angiogenesis space**, enabling simultaneous assessment of multiple therapeutic mechanisms
- Avatar-derived scores reflect **regulatory network wiring** (feed-forward and feedback interactions), capturing **mechanistically grounded pathway states**
- Distinct PDC responses are associated with **coherent multi-axis pathway profiles**, rather than single-marker effects

Mechanistic Integration & Exploration

- Digital Avatars enable **integration of multi-omics into unified feedback pathway states**
- Support **simultaneous interrogation of multiple drug-relevant mechanisms** within the same model
- Allow in silico exploration of MoA and pathway cross-talk, enabling mechanistically **guided follow-up experimental testing**

Translational Potential for Drug Development

- Link **preclinical models (PDCs)** to **patient tumour populations (~10K avatars)** through shared pathway states
- Provide a framework to **contextualise experimental responses within patient-relevant biology**
- Enable **cross-system comparison of treatment strategies** and prioritisation of therapeutic hypotheses / intervention

👉 Digital Avatars enable **mechanistically interpretable**, **population-aware** mapping of treatment responses within **patient-relevant biological contexts**.

Conclusions

- Digital Avatars use a **mechanistic, network-based framework** to capture intrinsic tumour biology through regulatory pathway interactions
- Embedding PDC models within a large patient-derived reference enables **interpretation of experimental responses in the context of comparable tumour states across a broader population**
- The consistency between experimental responses and avatar-derived pathway states highlights the potential to **interrogate multiple drug-relevant mechanisms beyond single markers**
- This framework enables a **closed loop between wet lab and in silico modelling**, supporting hypothesis generation and **mechanistically guided follow-up experimentation**
- For drug development, Digital Avatars offer strong **translational potential** by enabling selection of more representative models, exploration of mechanism of action, and prioritisation of therapeutic strategies in a patient-relevant context

👉 **Together, this approach extends preclinical models into a system that supports translational decision-making across discovery and development.**