Target-cell turnover abolishes the in-vitro hook effect in bispecific drug PK/PD models

Model-informed dose selection: assay artefact vs. real in-vivo hook risk

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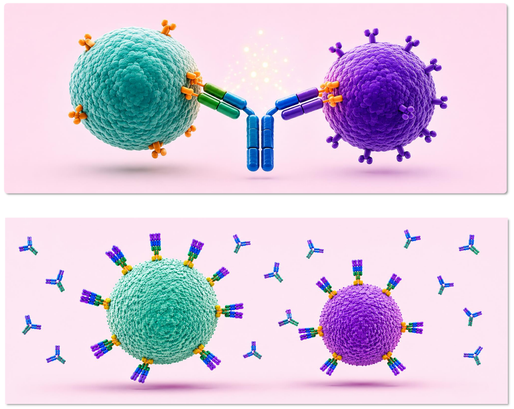
Thesis The hook is not only a molecule property. **It is an emergent property of a closed assay system.** Once target cells and receptors turn over, binding partners are replenished and the high-dose loss of productive bridging largely disappears.

So what? A static in-vitro bell shape should not set the dose. **Turnover-aware PK/PD modelling** turns it into a confident, defensible dose decision.

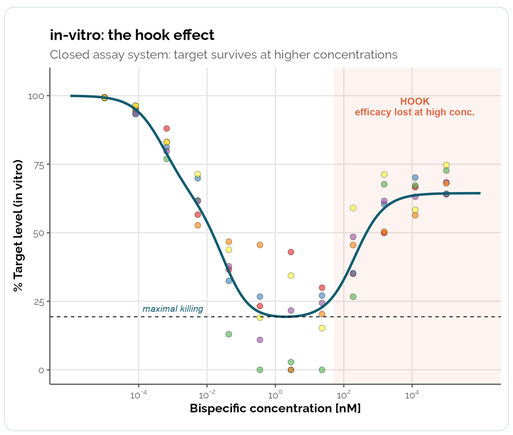
1 Why a hook can occur

Effector-engaging bispecifics work by bridging target cells and effectors into a productive ternary complex. At drug excess, both arms can saturate separately, producing non-bridging binary complexes instead of the productive bridge.



2 The static in-vitro warning

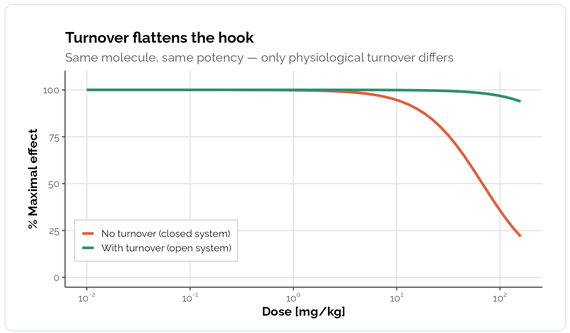
Closed assays preserve drug excess and do not replenish target cells. The model reproduces the bell-shaped response seen in reductionist assay architectures.



In vitro: high concentrations enter a hook zone where efficacy falls.

3 Open the system: turnover flattens the hook

Adding target turnover, receptor re-expression, internalisation and systemic PK changes the high-dose regime. Binding partners are continually restored, so productive complexes are sustained rather than permanently displaced.



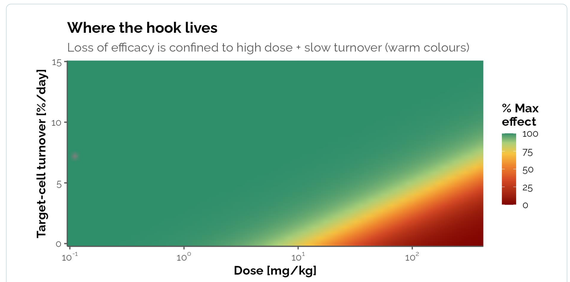
Same molecule, same potency: closed system hooks; turnover system stays near maximal effect.

4 The decisive parameter: turnover rate

Fast turnover abolishes the hook. Slow-turnover or quiescent targets remain closer to the static-assay limit and should still be treated as genuine high-dose risk cases.

In-vivo hook is ultimately a function of turnover rate.

5 Where the hook still lives



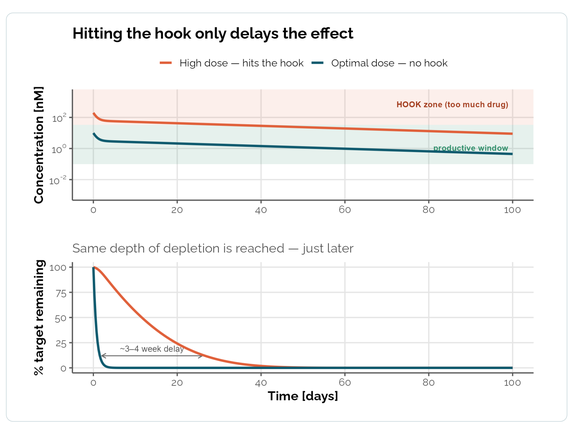
Loss of efficacy is confined to the high-dose, low-turnover corner.

Target-specific caution

If target cells turn over slowly, the hook can persist in vivo. **Modelling tells you which case you're in — per target — instead of assuming format-level safety.**

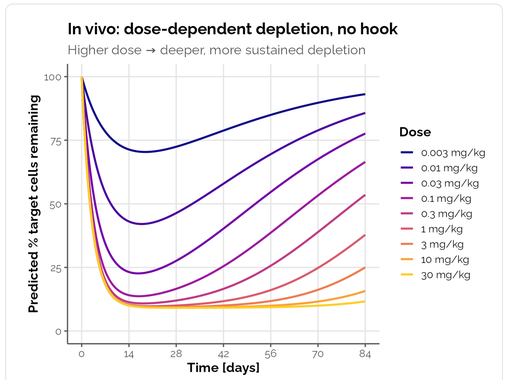
6 If you overshoot, PK washout self-corrects

A transient high-dose hook is not necessarily a treatment failure. As concentrations clear back through the productive window, the same depth of depletion can be reached, just delayed.



High dose begins in the hook zone, then returns through the productive window as drug clears.

7 In vivo: dose-dependent depletion, no hook



Higher dose → deeper and more sustained depletion, without loss of effect at high exposure.

8 Lessons for dose selection

- Static systems can overstate hook risk. In vitro hook behaviour is strongest in closed or artificial assay architectures.
- Turnover changes the regime. Target turnover and receptor re-expression substantially attenuate high-dose loss of efficacy.
- Dose range remains favourable. Simulations predicted minimal clinically relevant hook or TMDD risk in in-vivo contexts.
- Do not ignore slow targets. Low-turnover systems should still be stress-tested mechanistically.

Take-home

Do not let an in-vitro hook dictate the dose alone. Mechanistic, **turnover-aware PK/PD modelling** distinguishes assay artefact from real in-vivo risk.