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How Drug Safety Strategies are Crafted

Virtual Human Global Summit

Georg Rast | Oct 24 th 2025 | Barcelona

Life forward

Goals

Always start with the end!

1. Protect volunteers and patients
2. Select the right molecules as early as possible
3. „Safety by Design“

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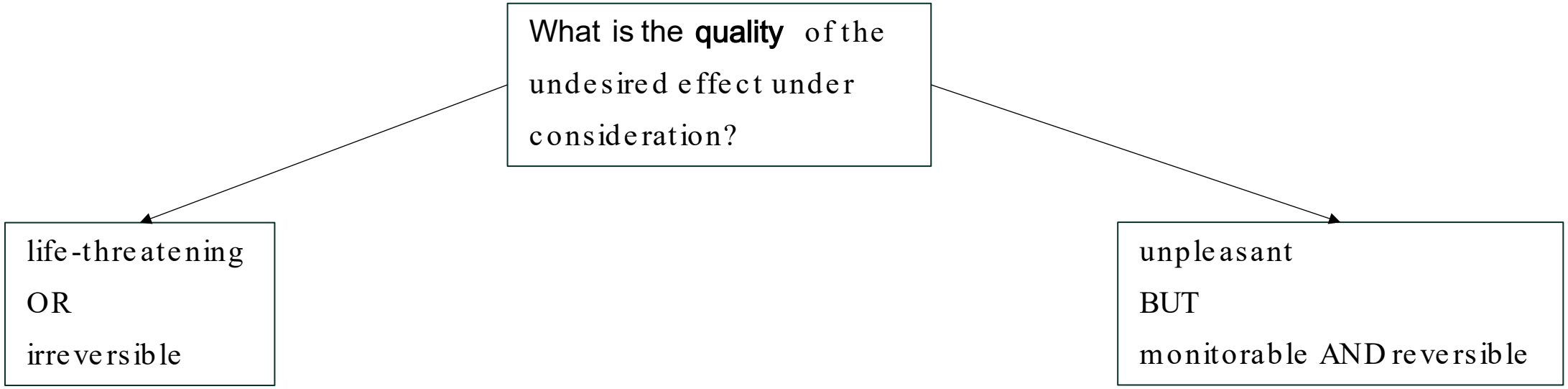
Protect volunteers and patients



➢ Required test performance

Highly sensitive:

We want to avoid this effect at any rate

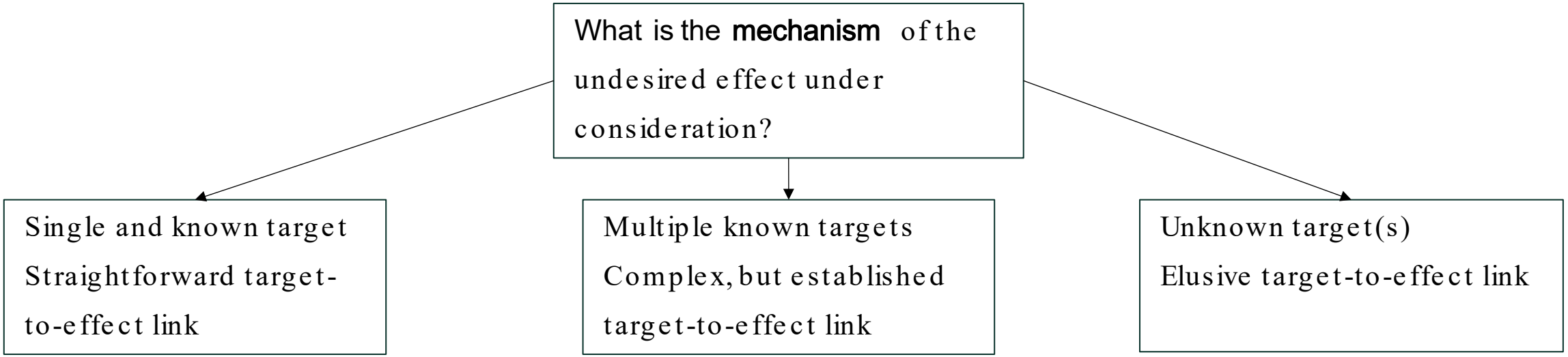
e.g. DILI

Highly specific :

We do not want to lose compounds due to false positive results

e.g. QT prolongation

Select the right molecules as early as possible



➢ <u>Feasibility of frontloading</u>

- Target-specific assay
- Translation by concentration-effect model
- Easy, high throughput
- Only exceptional cases, if at all

- Target-specific assays
- Translation by QSP models
- Complex, lower throughput
- E.g. cardiac ion channel panel, QT prolongation

- Phenotypic assay
- Translation by correlation
- Simple to challenging, variable throughput
- E.g. seizures

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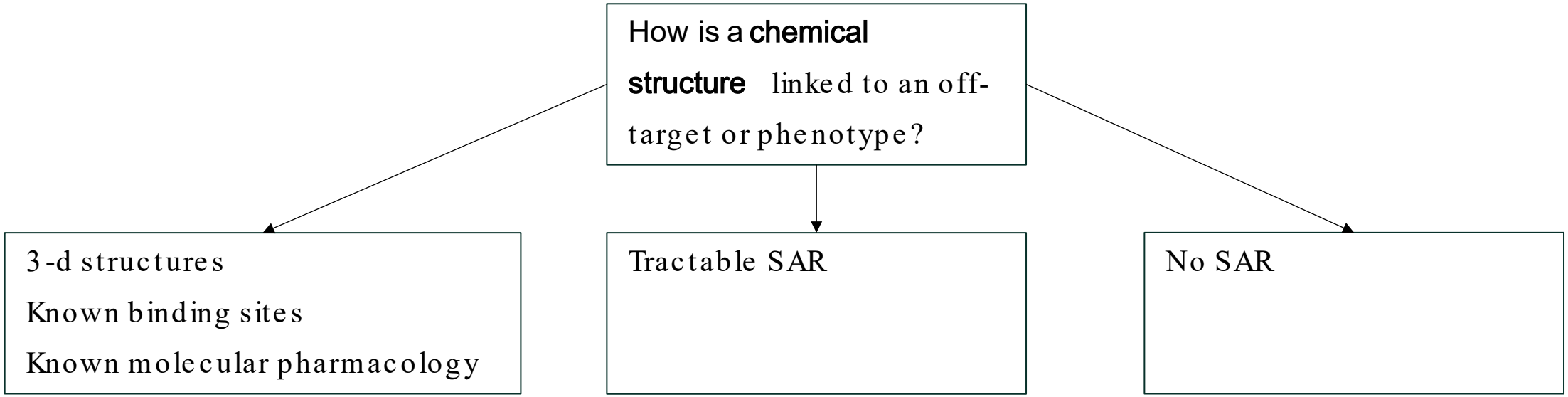
Safety by Design



➢ Options for design

- Based on ligand-target interaction
- Off-targets mostly not „structurally enabled“
- Usually too resource-intensive

- Empirical ligand-based models with some capability of extrapolation
- SAR exploration
- Most panelized off-targets

- Correlation with physicochemistry or other properties
- Worst case: trial & error
- Some cytotoxicities

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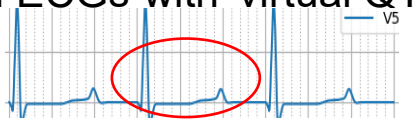
Examples

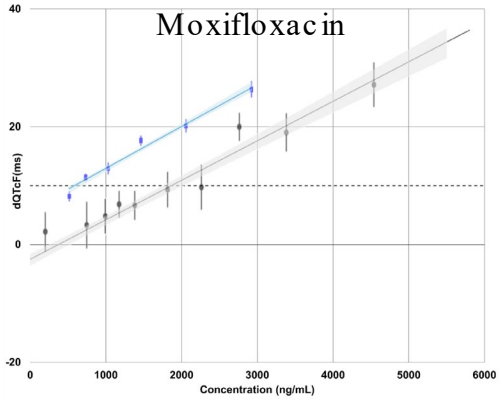
Why are we so paranoid about $CI_{90\%}^{upper}$(ΔΔQTc) < 10 ms?

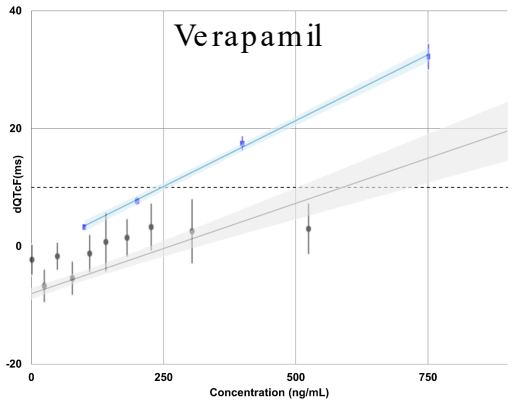
- $CI_{90\%}^{upper}$(ΔΔQTc) < 10 ms in clinical studies is a regulatory risk biomarker, although per se no risk for healthy volunteers.
- Therefore, high specificity in predicting QT is critical. CiPA has dedicated huge resources to it.
- Virtual humans, i.e. virtual hearts placed in virtual thoraxes allow the recording of virtual ECGs with virtual QT intervals to predict the biomarker of interest, based on in vitro ion channel inhibition data only.

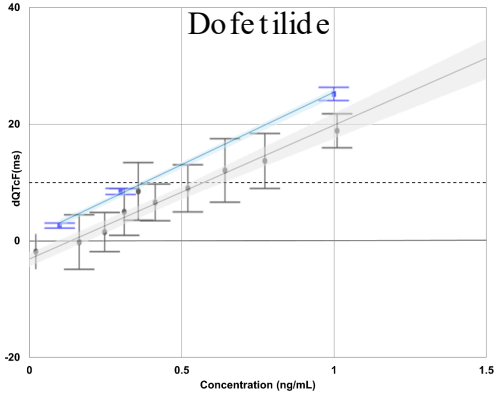


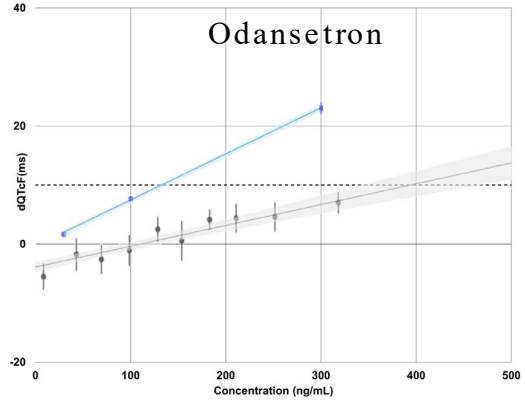
- Confidence Intervals can be estimated when variability of a clinical population including placebo can be modelled.

➢ **Virtual clinical study**









Aguado-Sierra et al. (2024) doi.org/10.1016/j.vascn.2024.107498

Examples

Why is QSP modelling of QT prolongation a blueprint for safety strategies ?

- The long-QT-story is an example for a complex mechanism that can be modeled from structures to targets to cellular effects to organ effects to symptoms in clinical populations with a single translational biomarker as readout :

Compound to target	Target to cell	Cell to individual organ	Individual organ to population
Ion channel panel data	*Cardiomyocyte data*	*Langendorff prep. data*	*Clinical ECG study*
Ligand-based models	Pore block or Markow model	Organ level simulation (e.g. vHeart)	Virtual population (e.g. virtual clinical study using vHeart population)
	Cellular QSP model (e.g. O'Hara-Rudy)		

- Next steps: special populations (diseased); simulataneous action of multiple compounds (i.e. comeds, metabolites), more mechanistic description of molecular pharmacology (Markov models of ion channle inhibition).
- Use blueprint for not yet fully accessible undesired effects, like cardiac contractility alterations, cerebral seizures.

Examples

How can we feed molecule designers with ligand-target interactions ?

Designers' dreams

- Structure-based predictions for virtual compounds (synthesis planning): large historical data sets covering broad chemical space required.
- 14-day Design-Make-Test-Analyze cycle: quick and high-volume assays.

The reality

- Pharmacophore models exist for some ion channels.
- Sufficient structural information for docking studies is often missing.
- Except for hERG, legacy data foundation is often too thin to build ligand-based models.
- Cost-effective, high-throughput assays are often not not available for off-targets.

➢ **To make virtual humans a valuable tool for drug safety in the drug discovery value chain multiple steps from virtual drug to virtual human need to be enabled.**

Summary, Conclusions , and Outlook

- Virtual human data come in various flavors , at several levels of complexity and integration , employing diverse methodologies .
- All methodologies implement specific levels of biological understanding and require accurate input data for their set-up and productive performance .
- Methodologies need to be diligently chosen to meet the specific expectations regarding their output .
- The main opportunities for innovation are:
  - Improvement of quantitative biological understanding in the drug safety arena.
  - Improvement of input data quality , scope , and testing methods .
  - Reaching a higher level of integration (model complexity).

Thank you!

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Disclaimer