How does QSP modeling support R&D decisions? Case examples of modeling impact in central nervous system and inflammatory diseases.

November 6th, 2019

Christina Friedrich

Acknowledgments

Psoriasis Case

ROSA™ SANOFI

- Vincent Hurez
- Michael Weis
- Rebecca Baillie
- Mike Reed

- M. Rehberg
- K. Beuke
- A. Dietrich
- B. Göbel
- N. Biesemann
- C. Asbrand
- A. Subramaniam
- W. Seiz
- M. Herrmann
- T. Klabunde
- F. Nestle

Opioid Case

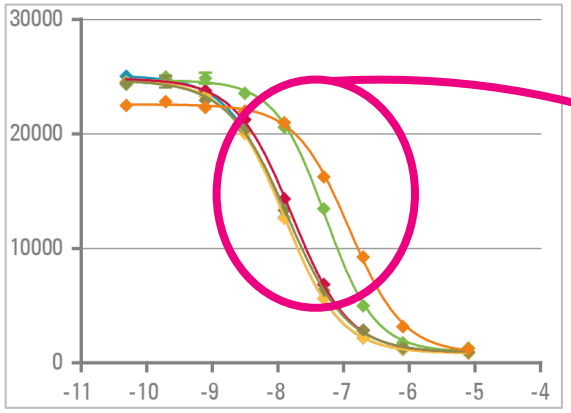
ROSA™ ADAMIS Pharmaceuticals Corporation

- Meghan Pryor
- Rebecca Baillie
- Katherine Kudrycki
- Mike Reed

- Ronald B. Moss
- Dennis J. Carlo

QSP helps reduce risk by improving understanding of how drug mechanism of action influences clinical outcomes.

Preclinical Data



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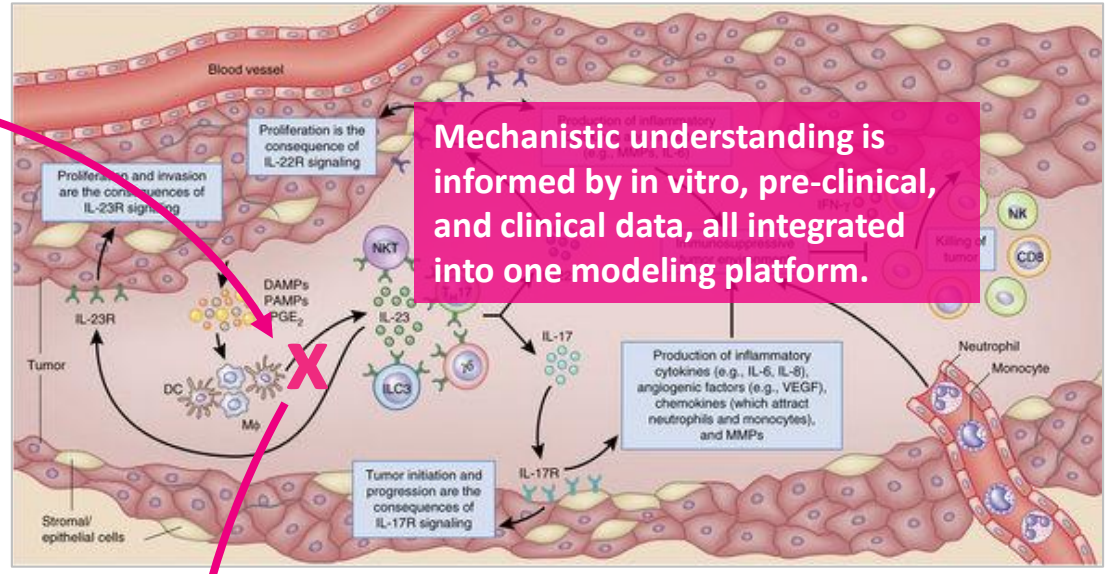
Mechanistic Understanding



Mechanistic understanding is informed by in vitro, pre-clinical, and clinical data, all integrated into one modeling platform.

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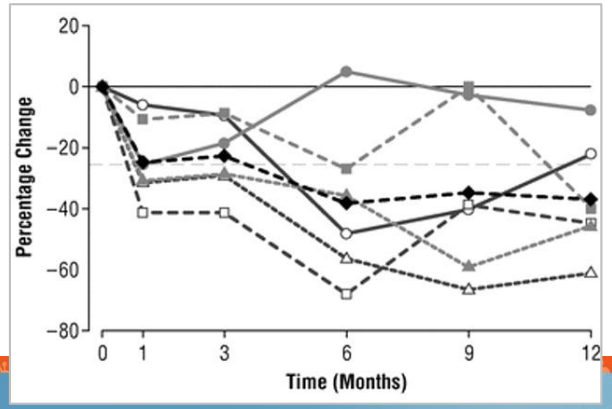
Clinical Outcome



Case Example 1:
Evaluation of Novel Psoriasis Therapies and Identification Of Mechanistic Drivers Of Response

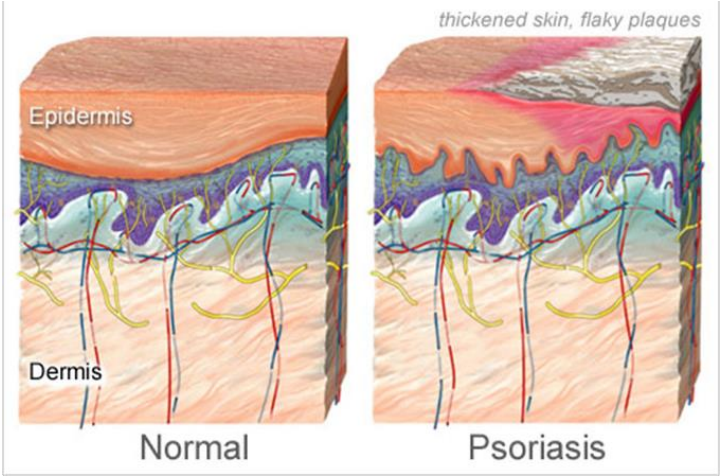
Sanofi-Aventis Deutschland GmbH

Rosa & Co. LLC

Sanofi was interested in evaluating a novel oral drug and an anti-cytokine antibody in psoriasis.

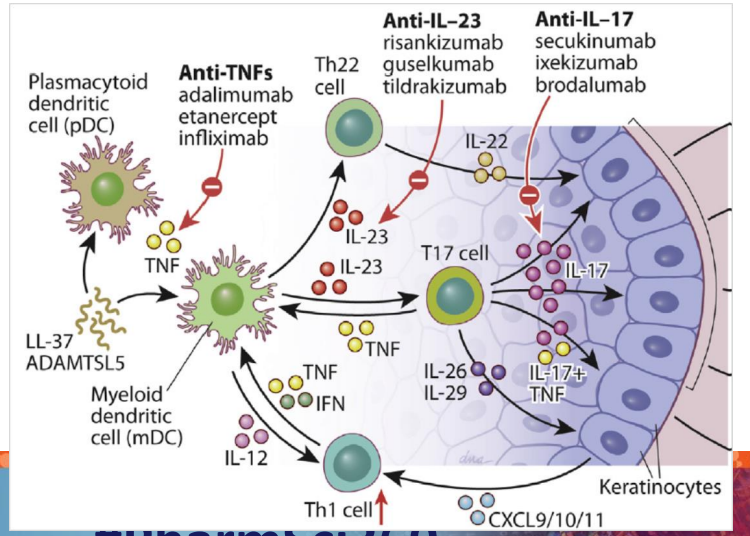
- Compound evaluation:
  - Assess the potential of novel drugs currently in late pre-clinical
  - Gain a deeper understanding of the key biological pathways impacting clinical response
- Competitive differentiation:
  - Compare the efficacy of the novel drugs to standard of care therapies, i.e., methotrexate (MTX) and biologics (anti-TNFα, anti-IL-23, anti-IL-17)
- Patient subtype identification:
  - Identify mechanistic drivers and the impact of patient variability on treatment response

Increase in skin thickness and scaly plaques in psoriasis



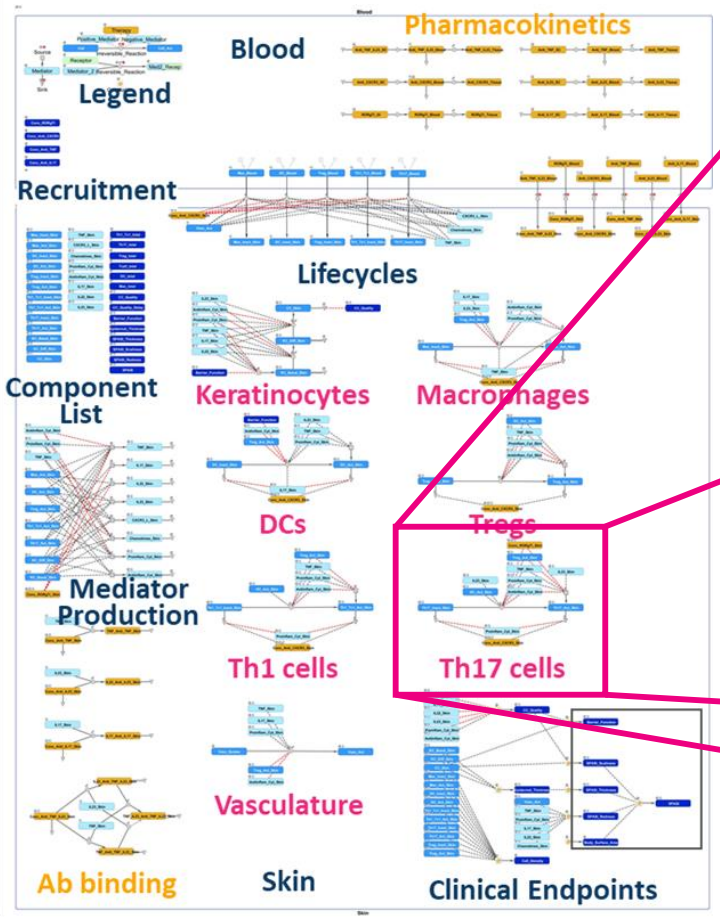
http://www.webmd.com/skin-problems-and-treatments/psoriasis/psoriasis-types

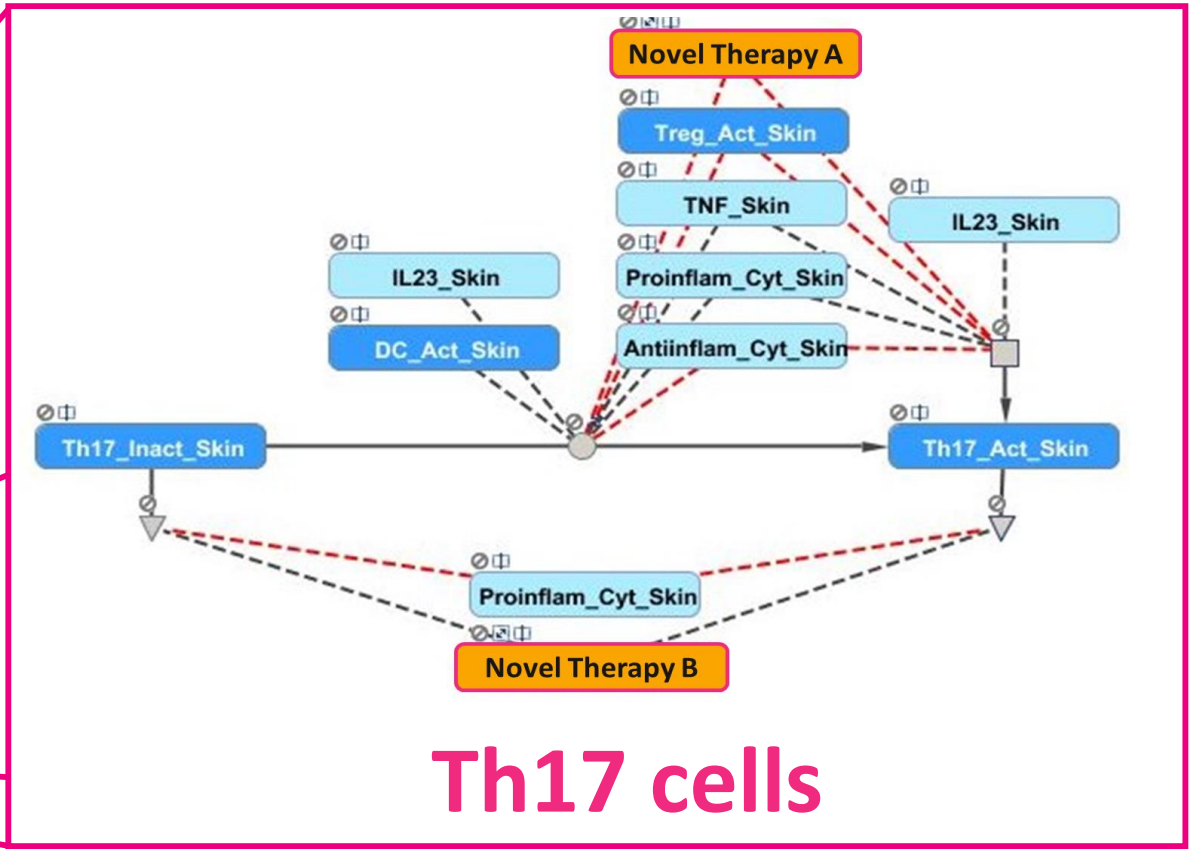
Relevant pathways and treatment effects



Hawkes, et al. 2017 PMID: 28887948

The Psoriasis Platform includes mechanistic pathways targeted by the existing and novel therapies.

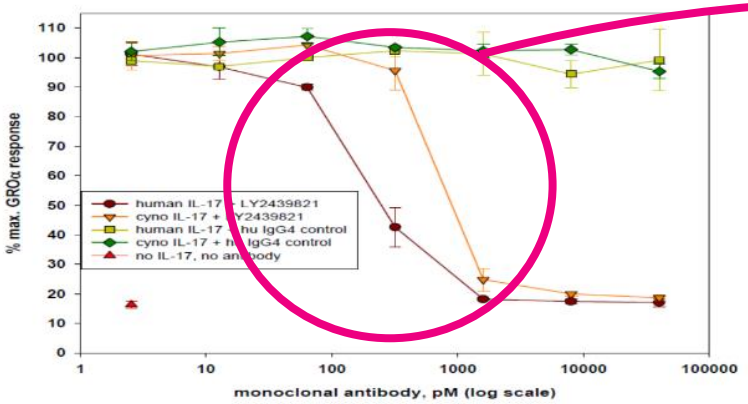




PhysioPD Platform was developed in MATLAB® SimBiology®.

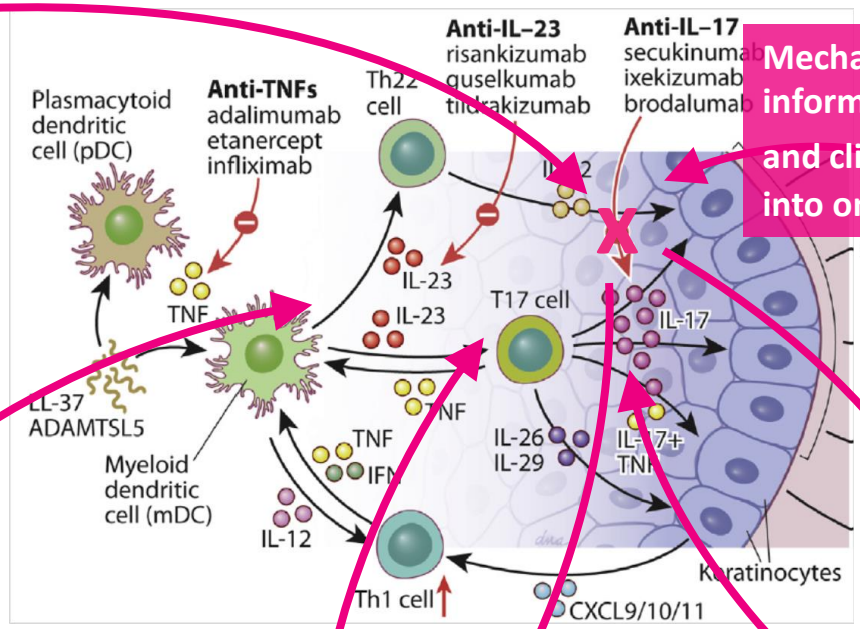
What does it mean to implement existing therapies?

Anti-IL-17 Antibody Inhibits IL-17 Effects



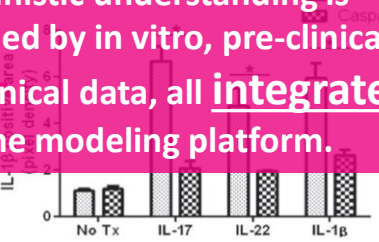
https://www.ema.europa.eu/en/documents/assessment-report/taltz-epar-public-assessment-report_en.pdf

Mechanistic Understanding



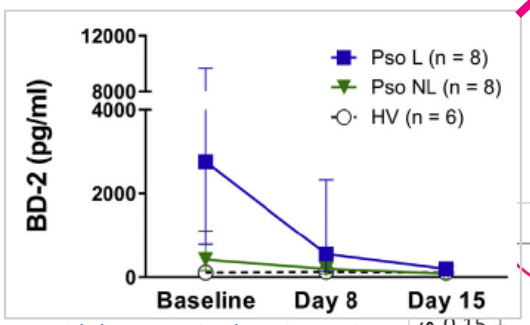
Hawkes, et al. 2017
PMID: 28887948

Preclinical Evidence of IL-17 Effects



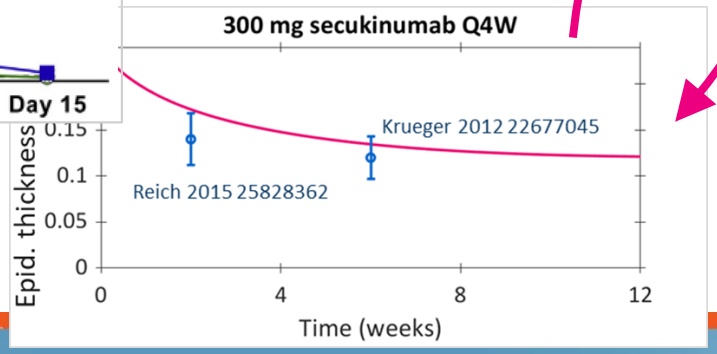
Increase in IL-1β⁺ cells in skin of mice injected with IL-17, IL-22, or IL-1β. Figure from (Cho et al. 2012).

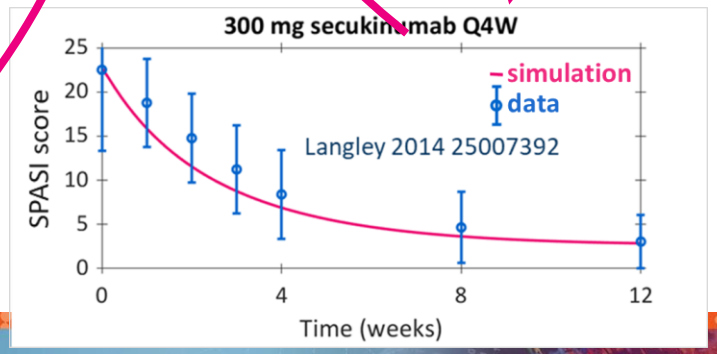
Mechanistic understanding is informed by in vitro, pre-clinical, and clinical data, all integrated into one modeling platform.



Rapid decrease in dermis BD-2 (KC activation) after anti-IL-17 treatment. (Kolbinger et al. 2017).

Clinical Outcomes and Biomarkers





Additional virtual patients explore the impact of variability.

- Simulations **reproduced clinical trial outcomes and biomarkers** such as histology data (immune cell infiltration) and SPASI score and subscores (redness, epidermal thickness) in moderate to severe psoriasis patients

- **Sensitivity analyses** identified **IL-17 pathways** and **keratinocyte proliferation** as critical pathways for the predicted efficacy of the novel therapies

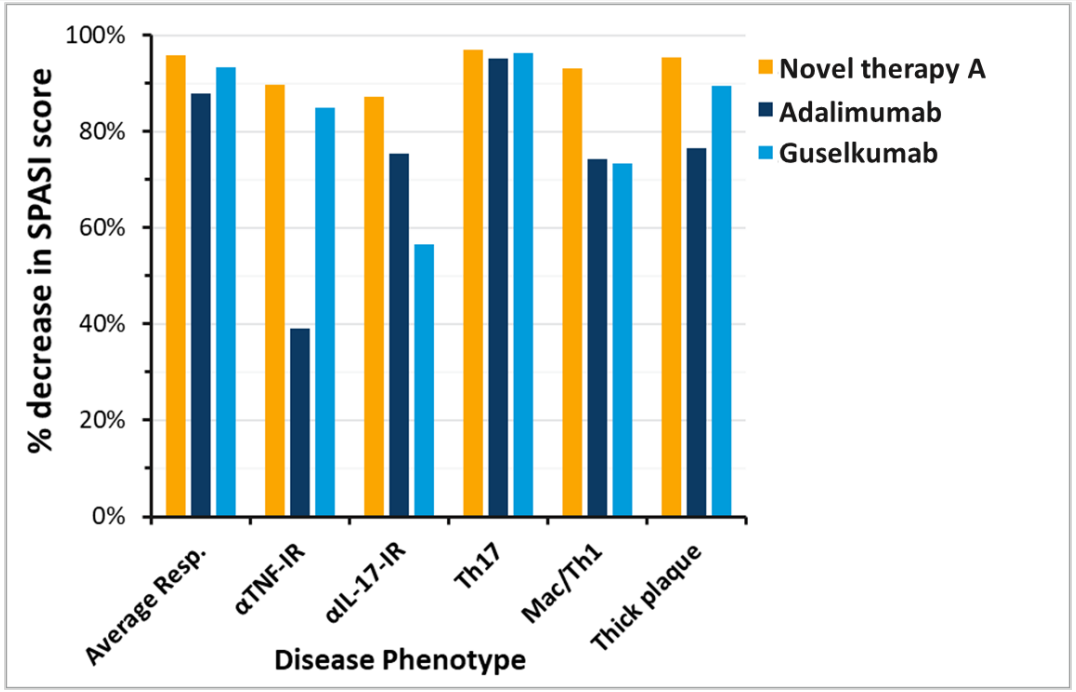
- Additional **virtual patients** (VPs) covered:
  - A range of disease phenotypes and responses to other therapies
  - A range of parameter values for sensitive parameters

VP phenotype	Mechanisms
Average responder	▪ Average response to standard therapies
Anti-TNF-IR*	▪ Reduced baseline TNFα levels / effects
Anti-IL-17-IR	▪ Reduced baseline IL-17 levels / effects
Th17 phenotype	▪ Increased in Th17 cells ▪ Reduced Th1/Mac/Tregs
Mac/Th1 phenotype	▪ Increased Mac/Th1 cells ▪ Reduced Th17 effects
Thick plaque†	▪ Increased cellular infiltration, more severe

*IR = inadequate responder; †: Kim 2015, PLoS One 10, e0132454, PMID 26176783

The novel anti-cytokine therapy is predicted to be more efficacious than competitor biologics in all VPs.

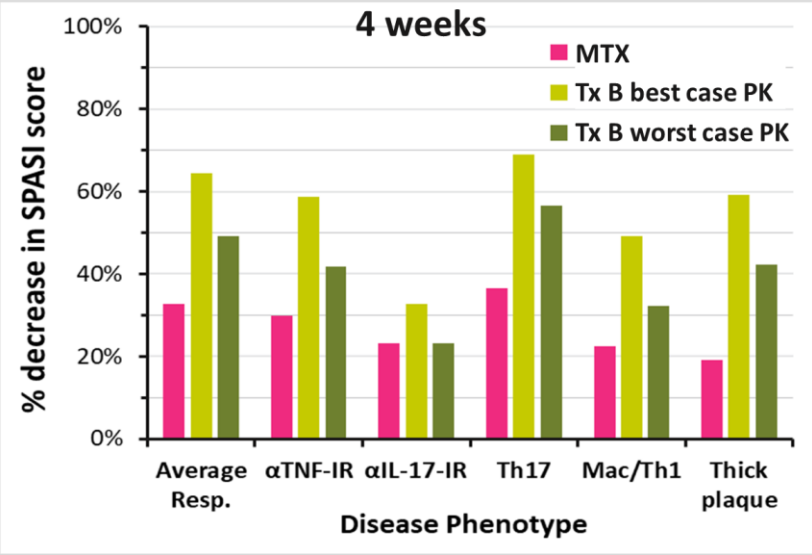
Decrease in SPASI score at 16 weeks with adalimumab, guselkumab or therapy A



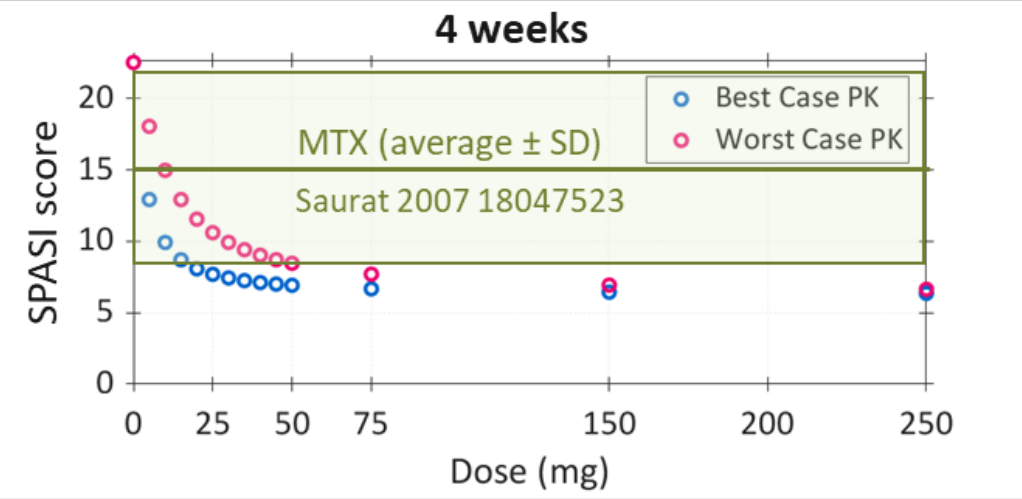
- The VP cohort covered a range of response to standard anti-TNFα (40 mg Q2W adalimumab) and anti-IL-23 (100 mg Q8W guselkumab) therapies
- Novel anti-cytokine therapy A on a Q8W dosing schedule demonstrate strong efficacy in all psoriasis disease phenotypes tested, even in anti-TNFα or anti-IL-17 inadequate responders

A short 4-week trial should be sufficient to demonstrate that the novel oral drug is more efficacious than MTX.

Simulated decrease in SPASI at 4 weeks with 20 mg QD oral therapy B (Tx B) in comparison to MTX in all VPs



SPASI score at 4 weeks in average responder VP treated with novel oral therapy (0-250mg QD) compared to MTX clinical data



- Two different sets of pharmacokinetic (PK) parameters and a range of doses were tested for the novel oral therapy B
- The novel oral drug at 20-50 mg QD was predicted to be more efficacious than MTX at 4 weeks, suggesting that a 12-week trial is not necessary

Conclusions and Impact

- The novel **drugs share some mechanisms** (direct and indirect) with existing therapies
- Novel and existing therapies are both included in the QSP model
- The QSP model's ability to **mechanistically reproduce** outcomes and biomarker responses to the existing therapies increases confidence in the model's predictions for the novel drugs
- Virtual patient exploration ensured that predicted efficacy was robust to patient variability

- R&D Impact:
  - Increased confidence in therapeutic potential of novel drugs at the pre-clinical stage
  - Reduction in clinical trial duration required to demonstrate efficacy
  - Recommendations for relevant PD biomarkers for future clinical trials

Case Example 2: Efficacy of Higher-Dose Naloxone to Reverse Opioid Overdoses

Adamis Pharmaceuticals Co

Rosa & Co. LLC

Adamis needed to demonstrate efficacy of higher-dose naloxone to regulators without a clinical trial.

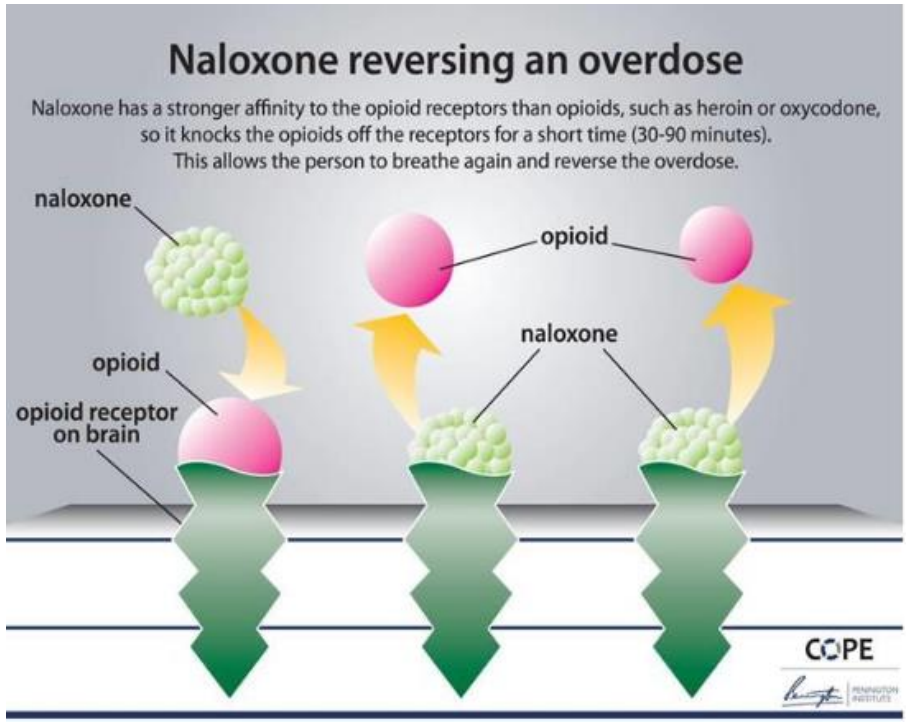
- Naloxone is an opioid receptor antagonist used to treat opioid overdose, often in a non-clinical setting
- Naloxone may be administered by laypersons, e.g., caregivers or family members
- Recent increases in overdose deaths are attributed to increased use of synthetic opioids (e.g., fentanyl) with faster onset and higher potency than heroin
- At the approved dose of 2 mg (intramuscular) multiple doses are often required to reverse overdose
- Adamis is looking for approval of an injection device with higher naloxone content

- **Due to the individuals administering the drug and its use in opioid overdose, clinical trials are logistically and ethically problematic**
- **FDA recommended modeling of displacement of opioids with naloxone to support the application**

The Opioid PhysioPD Research Platform was used to investigate efficacy of higher-dose naloxone.

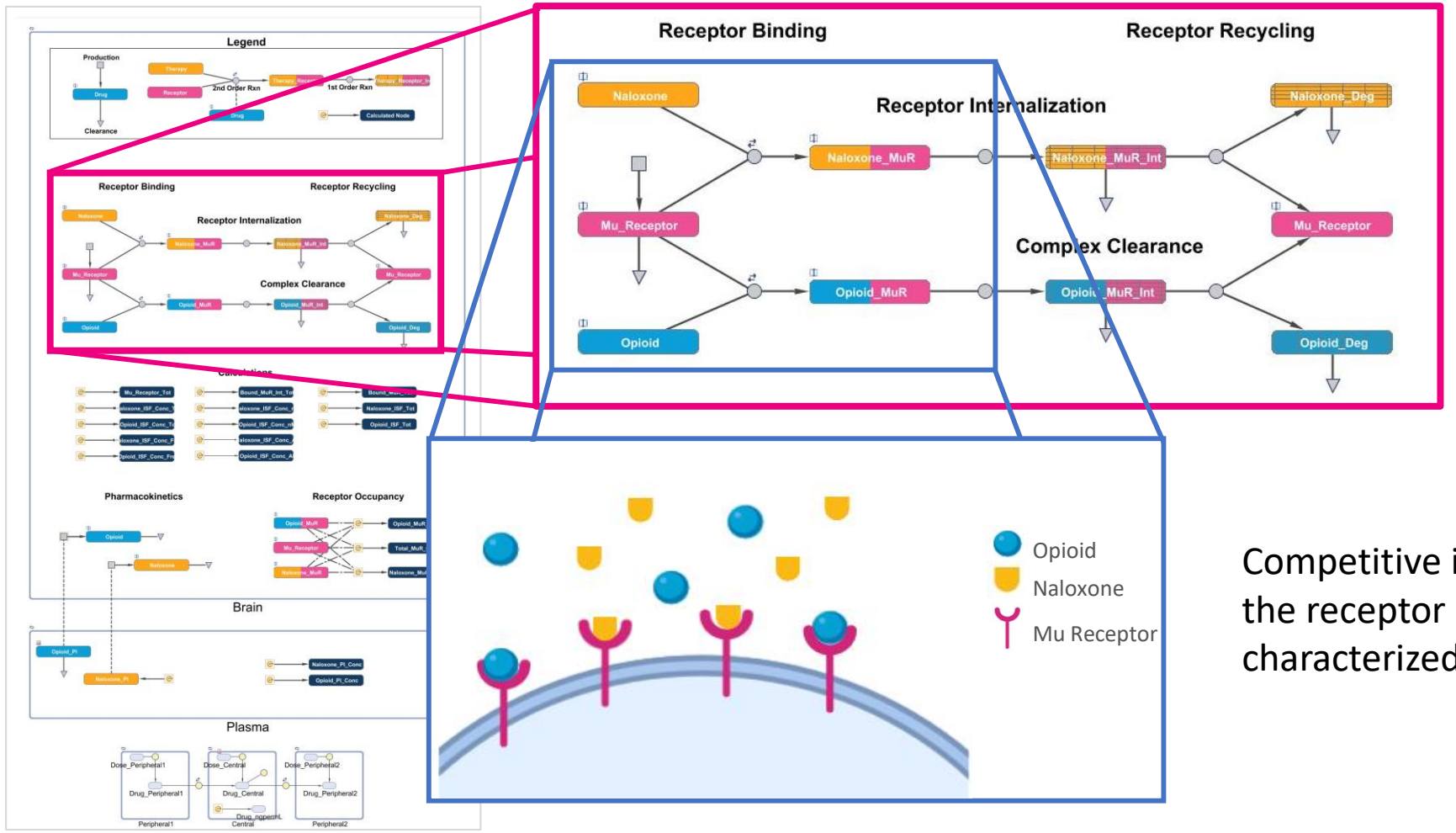
Research Approach:

- Develop the Opioid PhysioPD Research Platform representing relevant **opioid, naloxone, and mu opioid receptor dynamics**
- Evaluate different doses of naloxone in combination with a range of opioid (fentanyl) concentrations
- Assess the added benefit of higher doses of naloxone in displacing fentanyl from the receptor



https://www.gov.mb.ca/health/publichealth/docs/training_manual_overdose.pdf

The Opioid PhysioPD Platform represents opioid – naloxone competition for the mu opioid receptor.

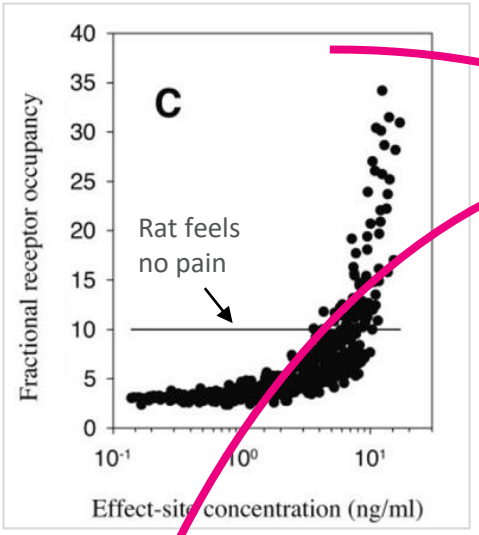


PhysioPD Platform was developed in MATLAB® SimBiology®.

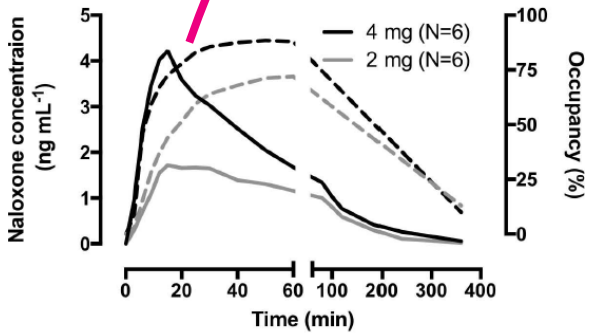
Competitive interaction at the receptor is well characterized in literature

Mechanistic data were combined with clinical data to infer effective brain concentrations and extrapolate results to higher naloxone doses.

Mechanistic Evidence

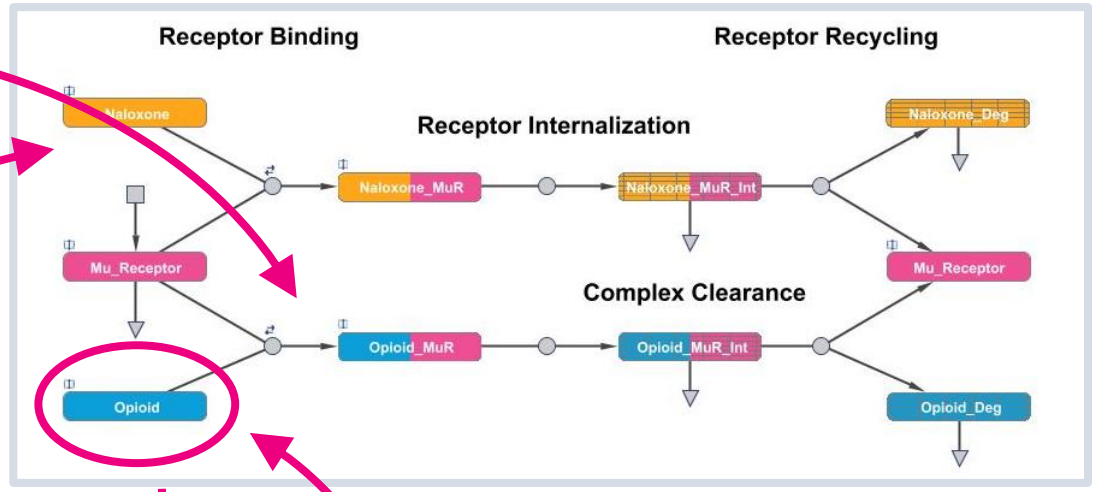


Yassen 2005 PMID: 15701707

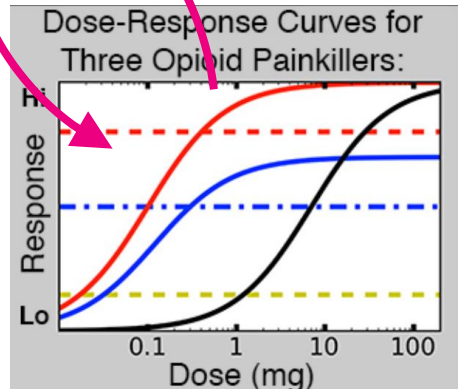


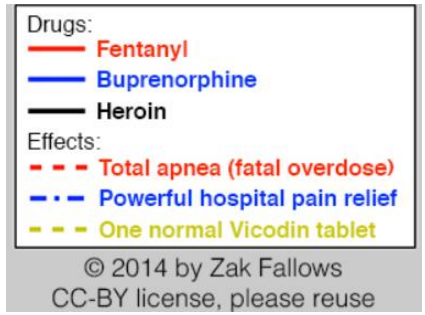
Johansson 2019 PMID: 30867551

Mechanistic Understanding



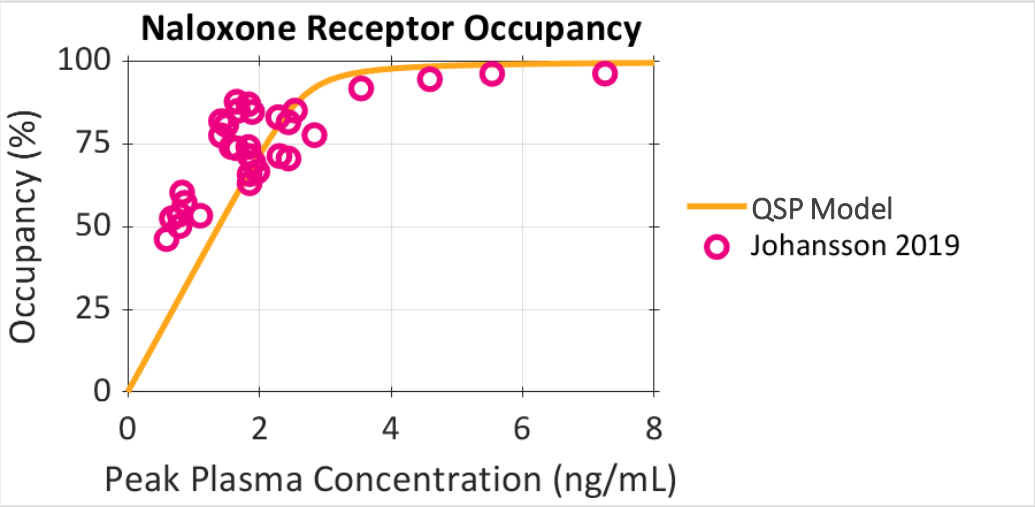
Clinical Outcome

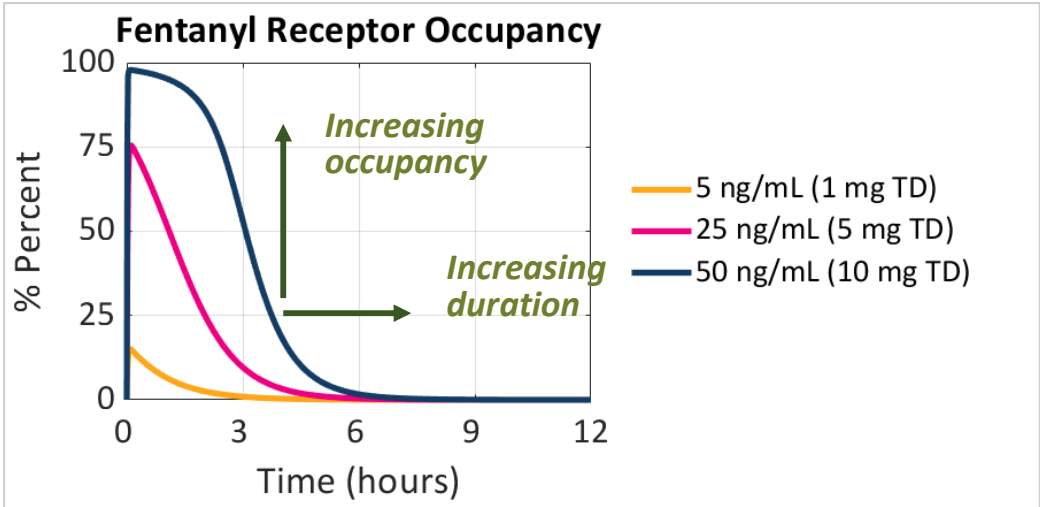




https://www.chcf.org/wp-content/uploads/2017/12/PDF-CINwebinar03242017ManagingPainMAT.pdf

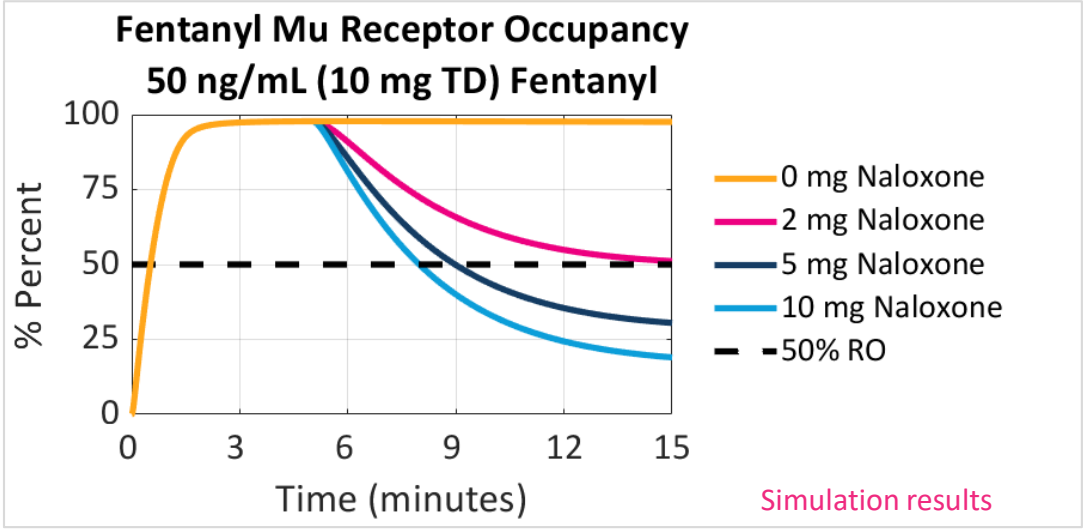
Brain opioid receptor occupancy for each drug is consistent with data.





- Naloxone receptor occupancy increases as naloxone dose increases, consistent with data from Johansson 2019 PMID: 30867551 (left)
- Fentanyl receptor occupancy dose response and duration are consistent with reported therapeutic ranges and outcomes
  - Dahan 2005 PMID: 15833777, Foster 2008 PMID: 18728103, Bovill 1980 PMID: 7426257, Takahashi 2004 PMID: 14991468

Higher-dose naloxone can reverse fentanyl mu receptor occupancy faster and to a greater degree than 2 mg.



In these simulations, fentanyl is given at time 0, naloxone is added at 5 minutes

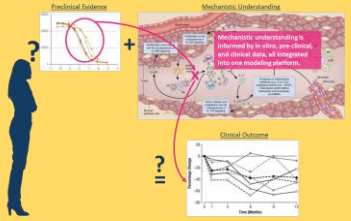
- The model's predictions for fentanyl-naloxone interactions are consistent with clinical evidence
- Increasing doses of naloxone achieve greater, faster reductions in fentanyl mu receptor occupancy
- In an overdose scenario, the minutes saved by not having to dose naloxone multiple times could mean the difference between life and death

QSP research showed that available evidence strongly supports the idea that higher naloxone doses would prevent more overdose deaths.

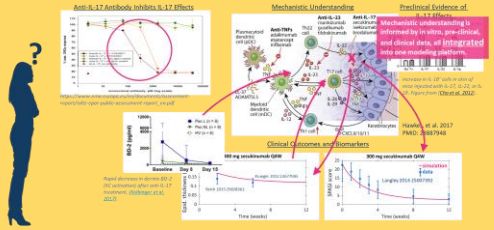
- QSP modeling incorporated mechanistic data including dynamics of fentanyl and naloxone appearance and half-life in brain, mu receptor dynamics, and receptor occupancy
- Fentanyl concentration at the receptor was inferred from clinical dose response for fentanyl
- The model recapitulated individual dose responses and predicted fentanyl – naloxone interactions that are very consistent with experiences in the field
- Compared to the approved 2 mg dose, higher doses of naloxone displace fentanyl from the mu receptor faster and to a degree more likely to prevent overdose death
- Adamis is using simulation results to support higher-dose intramuscular injection product application

➢ **QSP modeling allowed Adamis to prepare their argument efficiently**

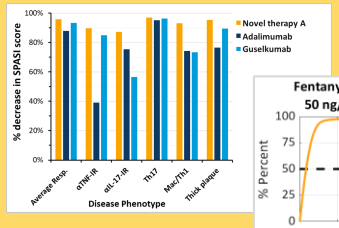
KEY TAKE-AWAYS

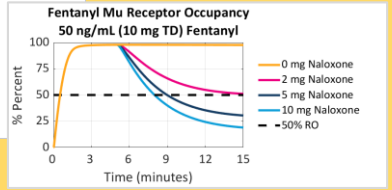


QSP models integrate mechanistic and clinical data to support investigation of new targets, compounds, or protocols.



Clinical data are **reproduced mechanistically**, increasing confidence in **informed extrapolation** to new scenarios.





Modeling transparency and stakeholder involvement are crucial for QSP impact.

Questions

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