Applications and Advance in Using Modeling and Simulation (M&S) to Support Drug Product Life Cycle Management

Model Informed Drug Development for Drug Development: the Application & Regulation Considerations of Modeling and Simulation during Clinical Drug Development

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

The presenter is offering his perspective based upon his experiences during regulatory decision-making

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Short Review of M&S in Drug Development

M&S for Drug R&D in the Past

- Compartmental model for pharmacokinetics (PK)
- Model for pharmacodynamics (PD) effect compartment/Direct or indirect response models
- Population PK
- Dose adjustment for specific populations

R&D – Research & Development

M&S for Drug R&D Today

- Exposure-response and PK-PD models
- PK models
  - PBPK
  - Population PK
- Quantitative systems pharmacology
- Quantitative structure activity relationship; Quantitative structure-property relationship
- Drug delivery models

PK: Pharmacokinetics; PD: Pharmacodynamics; PBPK: physiologically based PK model;

M&S for Drug R&D in the Future

- Interdisciplinary science
  - Fluid dynamics
  - Integration with genomics
- Go deeper, go mechanistic
  - Systems biology/pharmacology
- Go empirical, go big data
  - Machine learning and artificial intelligence
  - Big data/real world

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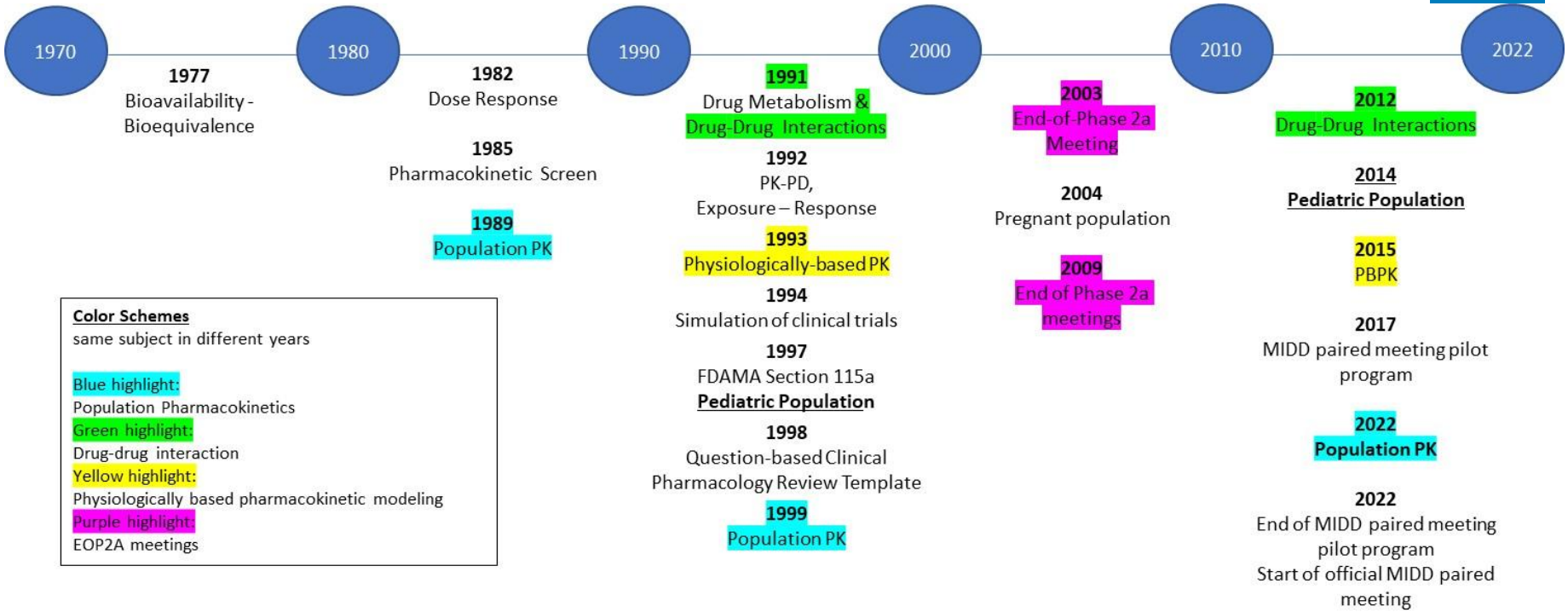
Are M&S a Game Changer for Drug Development?

Key Numbers and Facts for Drug R&D

- One billion[1] and 10-15[2] years to develop an new molecular entity (NME)
- Complex generic and 505(b)(2) products are still facing scientific challenges to develop

1. Brown, et al. Nature Reviews of Drug Discovery, 2021
2. Wouters, et al. JAMA, 2020

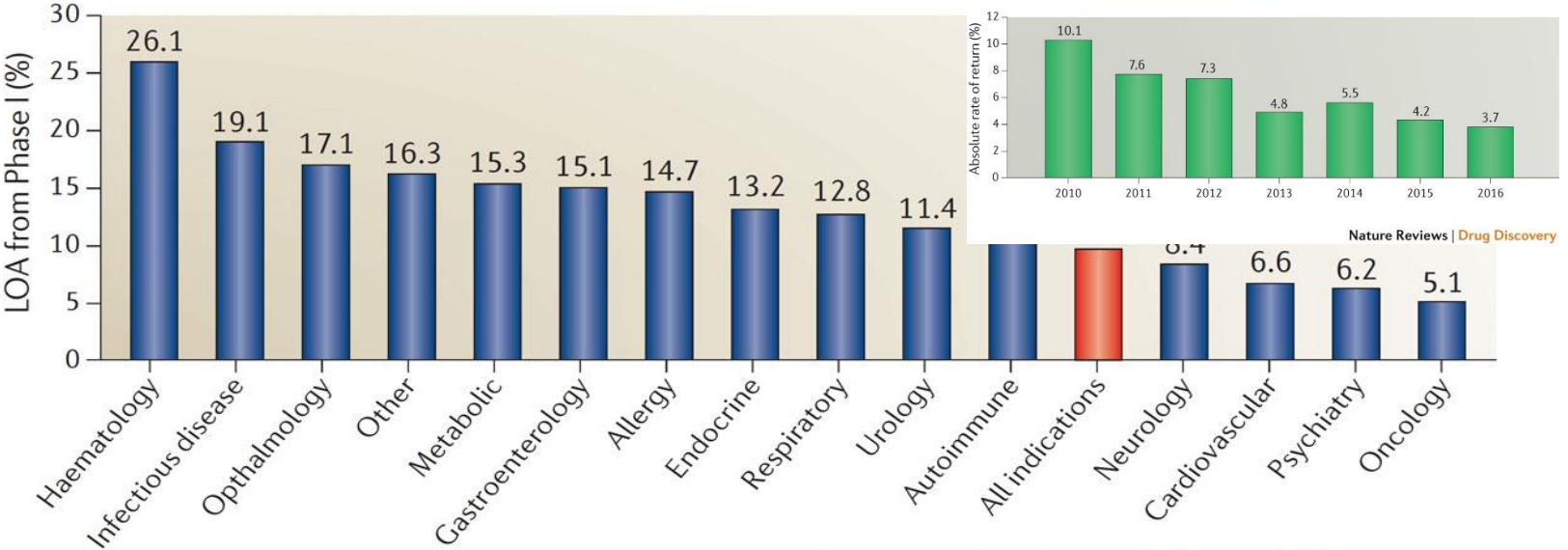
Major Timelines on QCP Related Regulations



Is the timeline correlated with efficiency of drug development?

QCP: Quantitative Clinical Pharmacology

Only 10% of Clinical Drug Development Succeeds From Phase I, II, III, to Approval



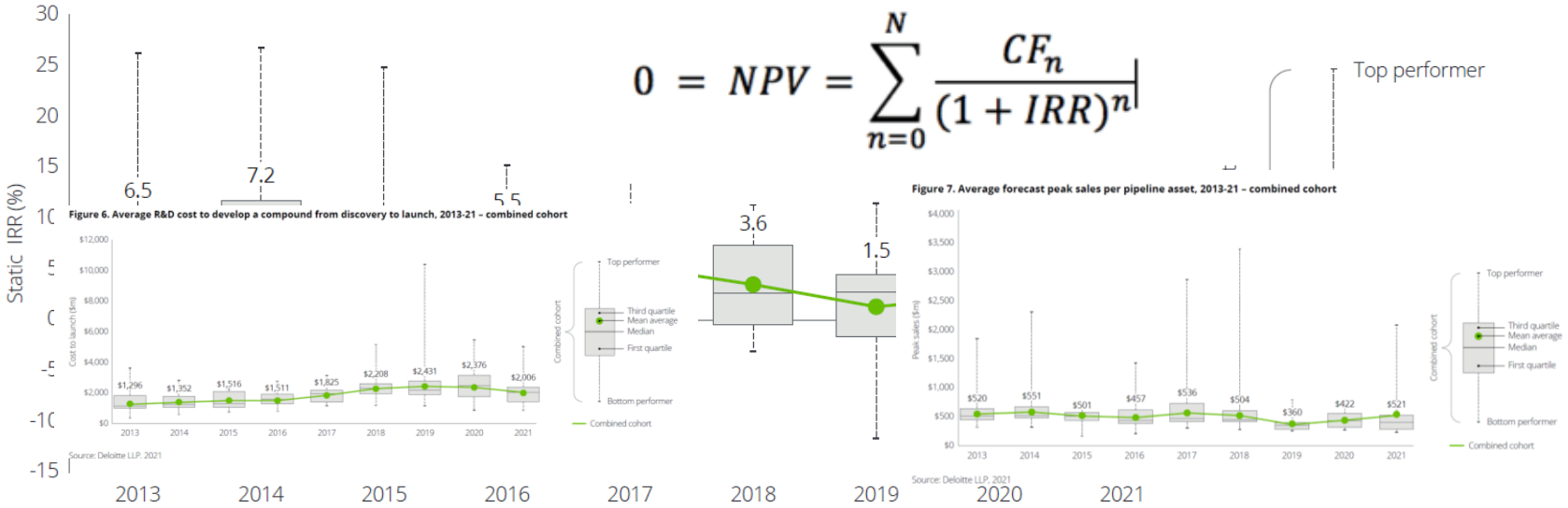
Success of Phase I: 63%
Success of Phase II: 31%
Success of Phase III: 58%
Overall Success: 9.6% (63% x 31% x 58%)

Mullard, Nature Reviews of Drug Discovery, 2016

Slide Adapted from Dr. Duxin Sun

R&D Returns on Investment

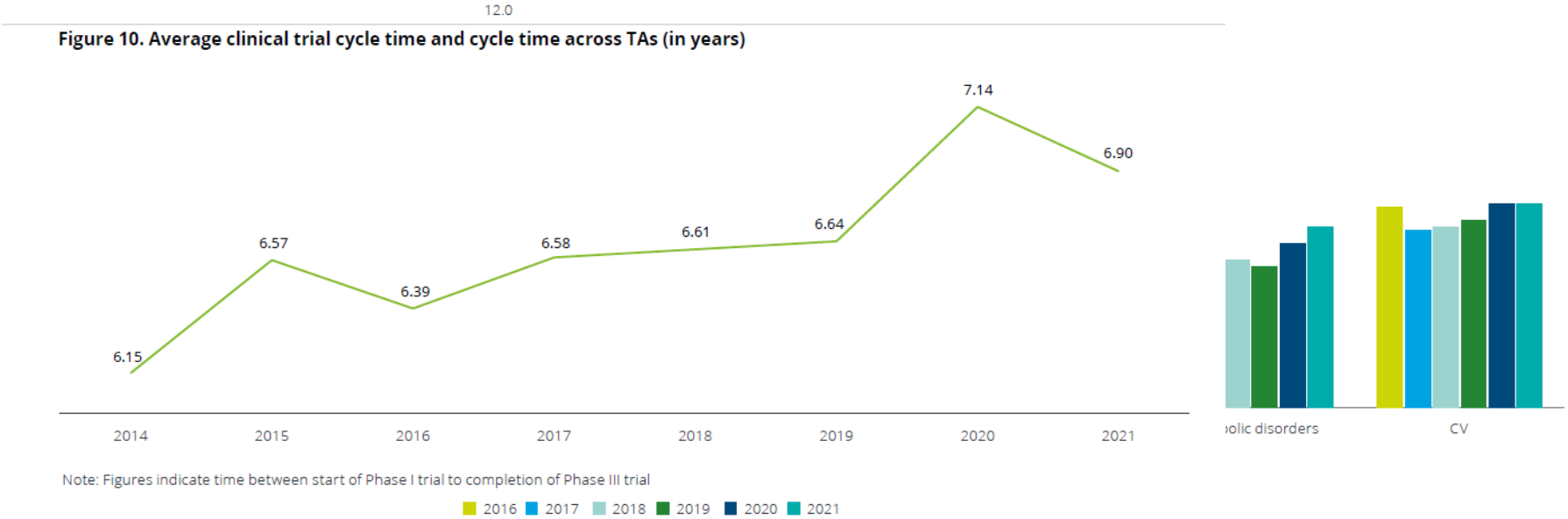
$$0 = NPV = \sum_{n=0}^{N} \frac{CF_n}{(1+IRR)^n}$$



Source: Deloitte LLP, 2021

The internal return on investment (IRR) for drug R&D has not increased in the past years, with a sign of deteriorating before the pandemic

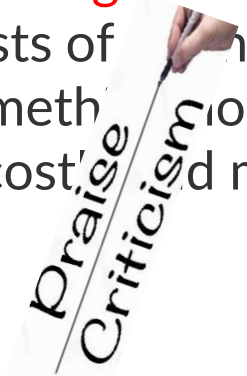
Has the Cycle Time for Clinical Trials Been Shortened?



There is slight increase in cycle time from start to finish from start if Phase I studies to the completion of Phase III studies; decrease in year 2021 is mainly driven by the pandemic

M&S: Now an Indispensable Part of Drug Development

- "The cost of drug development is growing enormously, as well as the costs of new medicines. We need to do something now, to make the entire process less costly and more efficient."



- "Almost 100 percent of all new drug applications for new molecular entities have components of modeling and simulation."

Scott Gottlieb, 2017 Regulatory Affairs Professional Society speech

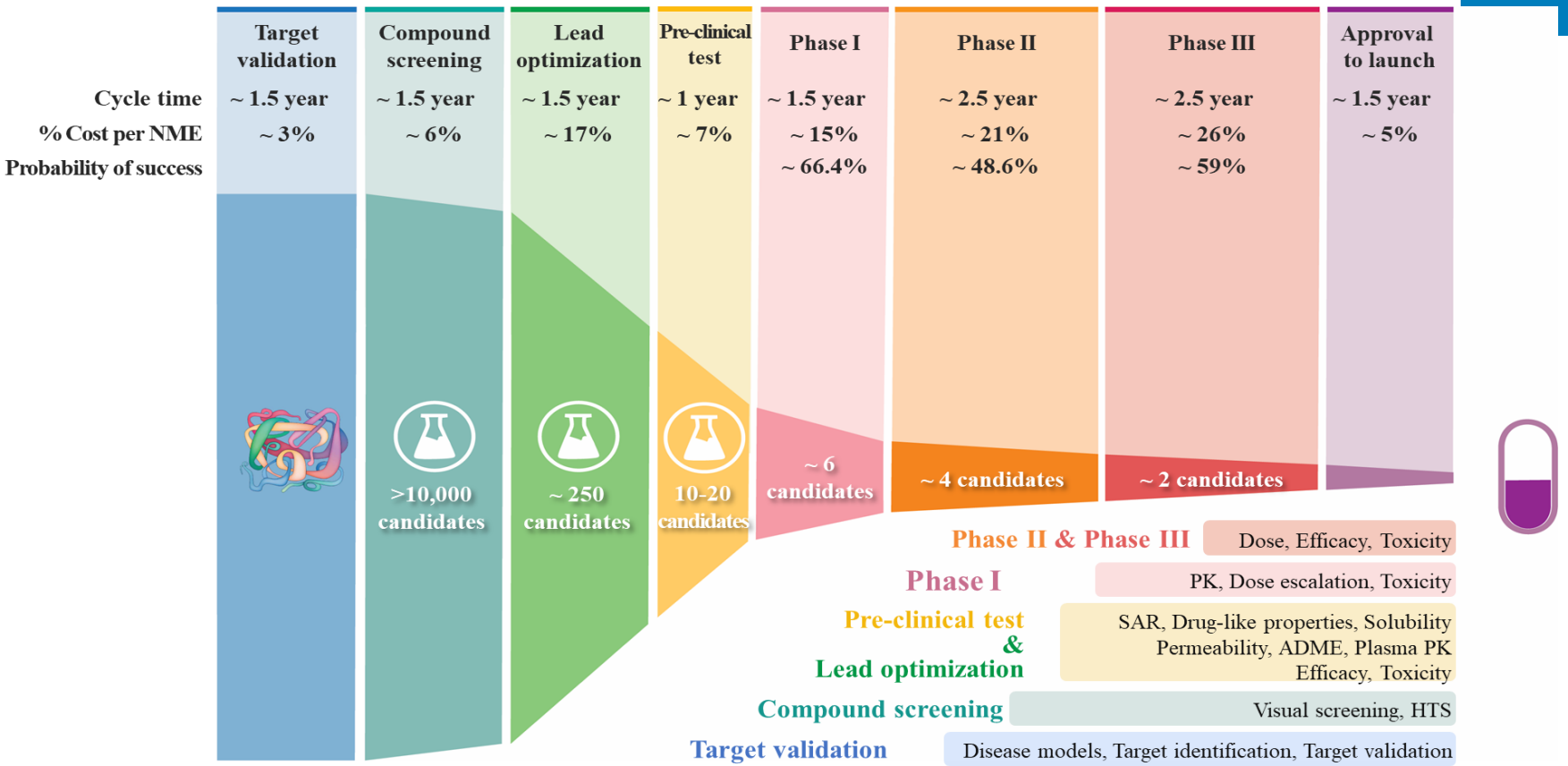
What has M&S contributed so far?

Where Has M&S Mainly Contributed?

- Centered at dosing regimen optimization
  - First time in human dose
  - Trial simulation to support dose selection
  - Dose adjustment for patients with organ dysfunction
  - Pediatric dose
  - Precision medicine based on intrinsic/extrinsic factors including pharmacogenomics
  - Clinical study design
- Main regulatory impact
  - Labeling (mostly about PK)

Drug Development Failure Modes and Opportunities for M&S

Drug Development Process and Successful Strategies



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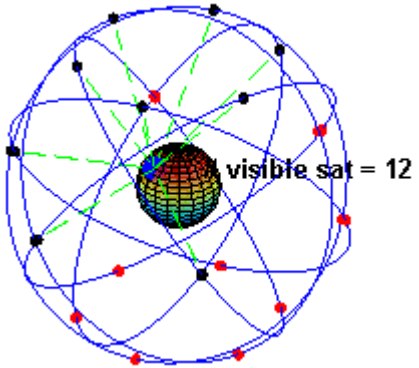
Slide Adapted from Dr. Duxin Sun

What Are the Drug Development Failure Modes?



- Ineffective target
  - Lack of efficacy
  - On target safety
- Failed drug delivery
  - State of art formulation
  - Common challenge for oligonucleotide treatment
- Inefficient design of drug molecule
  - Lack of efficacy
  - Off target safety
- Wrong dose/dosing regimen

Scope of Business for Modeling

- Models for dosing regimen optimization for the best benefit/risk profile
- Models for drug delivery
  - Target site delivery
  - Bioequivalence (BE)
- Models for drug discovery

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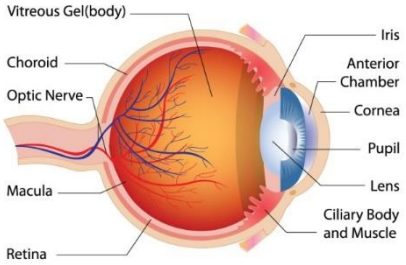
Drug Delivery

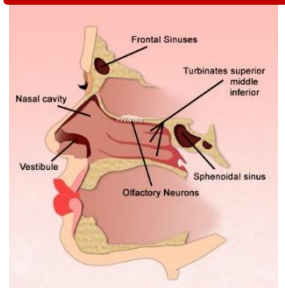
Drug Delivery Models

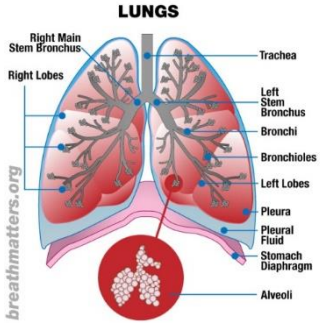
- Oral absorption
- Oral inhalation
- Intranasal drug delivery
- Ophthalmic
- Topical dermatological
- Female reproductive tract/rectal/otic
- Oligonucleotide delivery (e.g., mRNA)

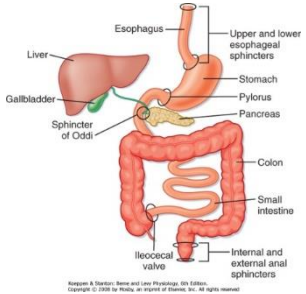
Physiologically Based Models for Drug Delivery

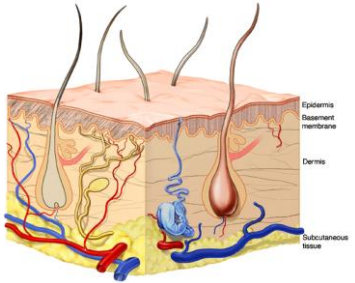
Drug Substance Formulations In Vitro Testing → **Physiological System** → **In Vivo Performance**











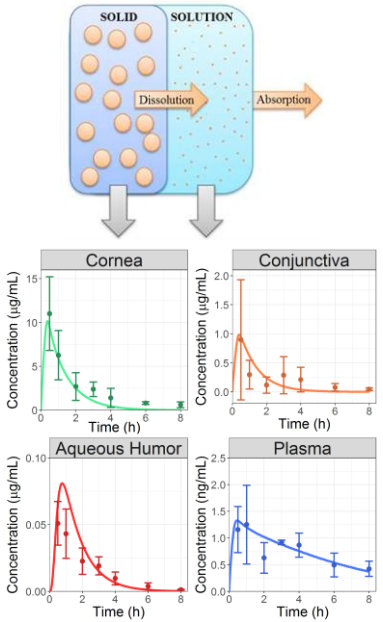
Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

Case Example 1

Recognize Critical Quality Attribute (CQA) for Ophthalmic Suspensions

Case study - Dexamethasone

- After instillation, several routes of dexamethasone transport:
  - Dissolved dexamethasone diffusing from tear film through cornea or conjunctiva
  - Solid particles and dissolved dexamethasone cleared from eye surface through nasolacrimal drainage -> systemic circulation
- OCAT Model Development – internally conducted rabbit study with PK sampling from multiple ocular tissues and plasma
- Model Verification with multiple datasets showing:
  - Particle size impact on ocular absorption
  - Viscosity impact on ocular absorption
  - Non-linear dose-exposure relationship

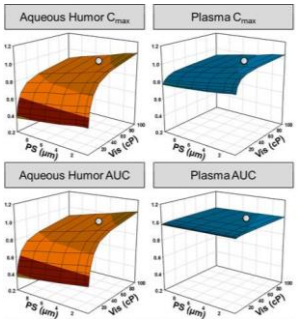


Chockalingam, Ashok, et al. "Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model." Journal of pharmacological and toxicological methods 96 (2019): 9-14.
LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." The AAPS Journal 21.4 (2019): 65

Case Example 1 Summary

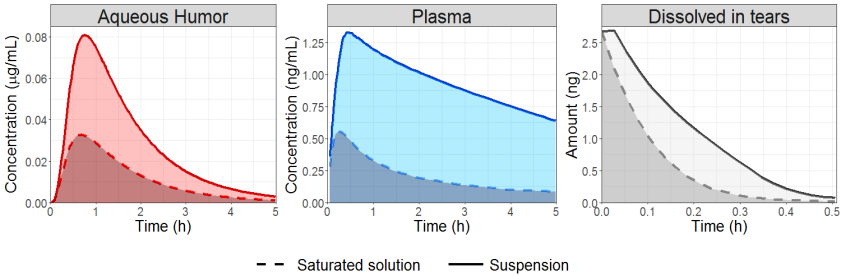
Recognize Critical Quality Attribute (CQA) for Ophthalmic Emulsions

Case study – Dexamethasone (cont'd)



Parameter sensitivity analysis in rabbit on PS and viscosity

- Viscosity is a critical attribute affecting BE
- Plasma/systemic PK is not reflective of local concentrations



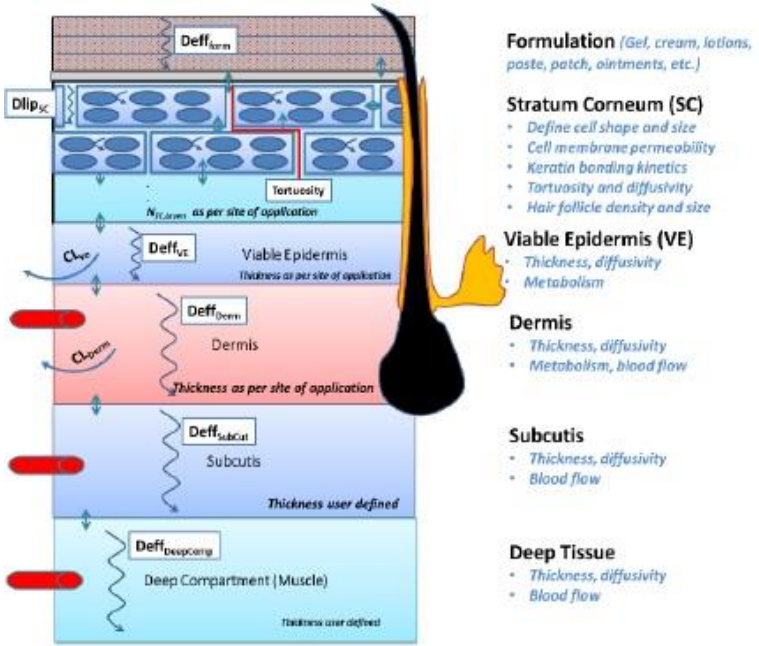
Saturated solution vs. suspension simulations

- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks

LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." The AAPS Journal 21.4 (2019): 65
Le Merdy, Maxime, et al. "Physiologically based pharmacokinetic model to support ophthalmic suspension product development." The AAPS journal 22.2 (2020): 1-10.

Case Example 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval



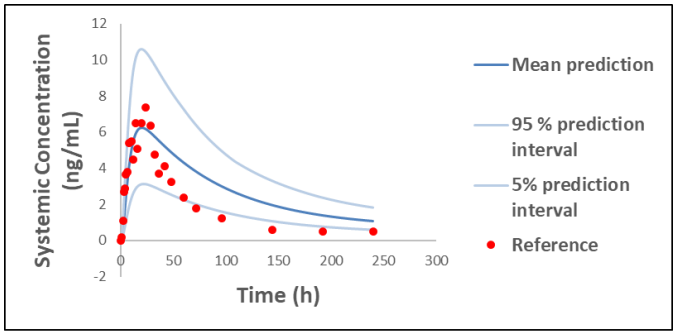
- Diclofenac sodium topical gel, 1%
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model supported alternative to in vivo comparative clinical endpoint BE study
- Model development:
  - API physicochemical properties
  - API ADME properties
  - Formulation attributes for Reference and Test drug products (e.g., viscosity, globule size, pH)

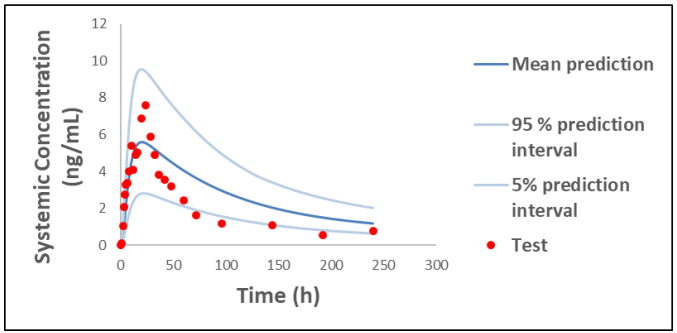
API: active pharmaceutical ingredient; ADME: absorption, distribution, metabolism, and elimination

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case Example 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval





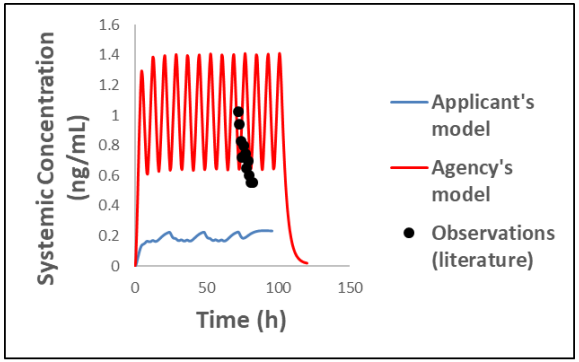
- Platform performance assessment:
  - >10 PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments
  - Satisfactory model performance
- Model performance assessment for diclofenac sodium topical gel, 1%:
  - Literature and application data on doses, product strengths, dosing regiments, routes of administration and local/systemic exposure data
  - Formulation attributes for R and T
  - Good predictions of systemic exposure

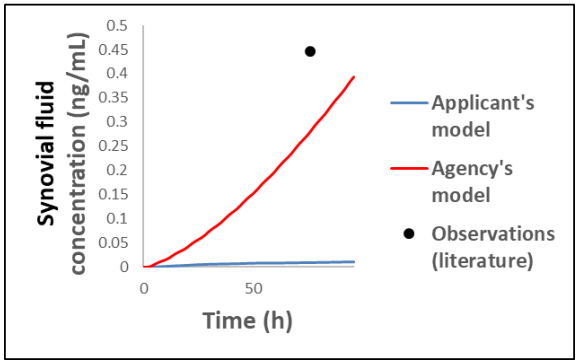
R: Reference, T: Test, TDS: Transdermal Delivery System

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case Example 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval





- Refined model to improve synovial fluid exposure predictions (by the Agency)
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified leveraging observed local drug amounts

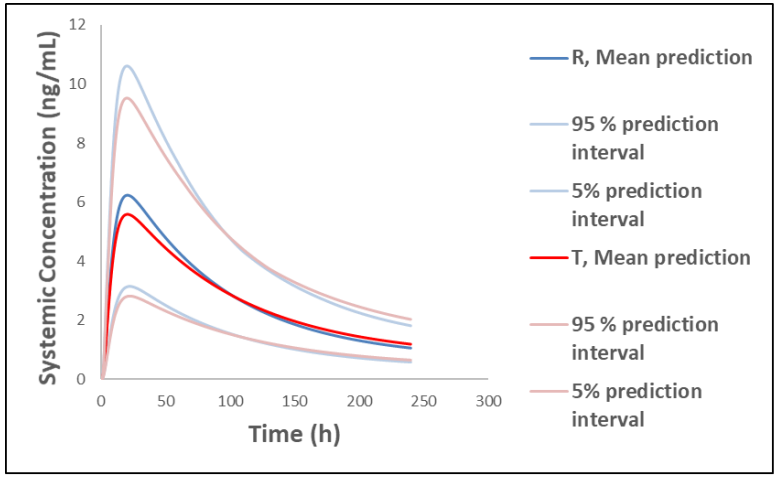
Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

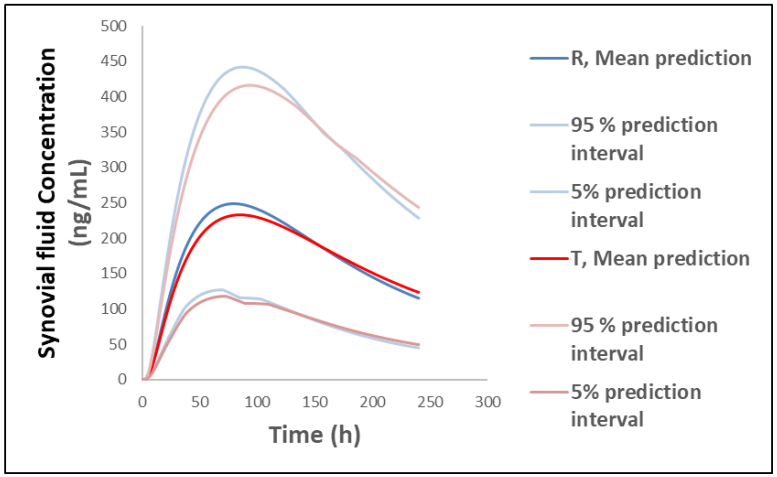
Case Example 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- Conducted virtual BE assessments on predicted systemic and local exposure data

✓ **R and T drug products were found bioequivalent**





R: Reference, T: Test

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

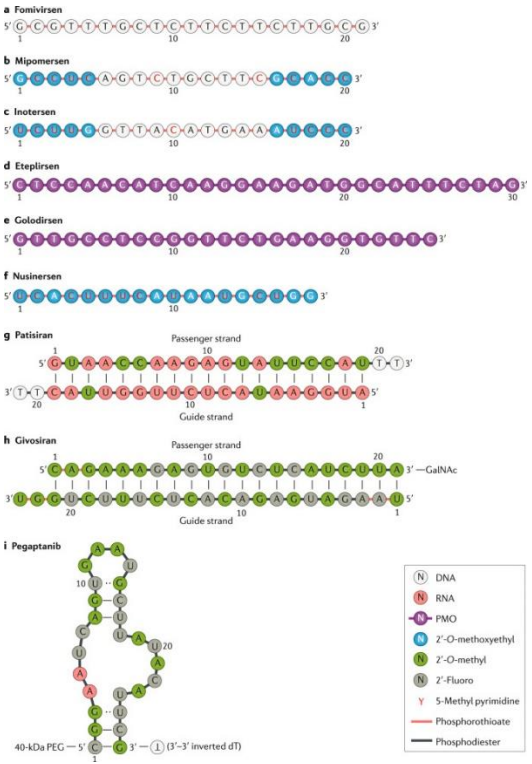
Case Example 2 Summary

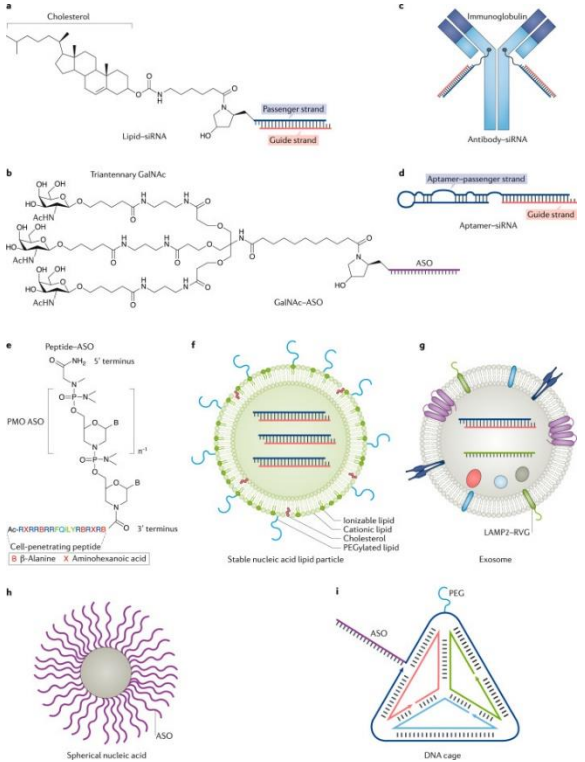
Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- PBPK models can be used to inform product development decisions and support alternative BE approaches for generic locally-acting drug products.
- Applicants are encouraged to follow best practices when developing PBPK models for generic locally-acting drug products as these are communicated by the Agency in guidances and other public forums.
- Applicants are encouraged to engage with the Agency early in their product development program by making use of the pre-ANDA meeting request program (GDUFA II) – case example of the approved ANDA for a complex topical drug product.

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

FDA Approved Oligonucleotide and Delivery Systems





Nat Rev Drug Discov. 2020 Oct;19(10):673-694

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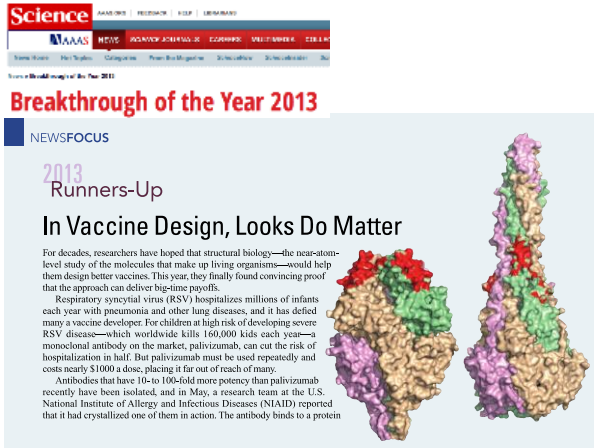
Drug/Antigen Design

Scope of Business for Modeling

- Models for dosing regimen optimization for the best benefit/risk profile
- Models for drug delivery
  - Target site delivery
  - Bioequivalence (BE)
- Models for drug discovery

Technology: Structure-Based Vaccine Design


Science

AAAS

NEWS

Breakthrough of the Year 2013

NEWSFOCUS

2013 Runners-Up

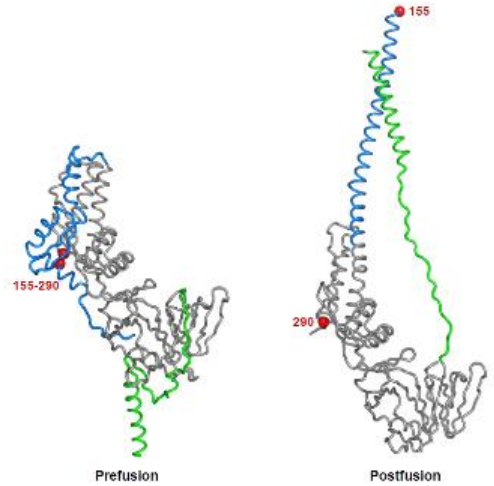
In Vaccine Design, Looks Do Matter

For decades, researchers have hoped that structural biology—the near-atom-level study of the molecules that make up living organisms—would help them design better vaccines. This year, they finally found convincing proof that the approach can deliver big-time payoffs.

Respiratory syncytial virus (RSV) hospitalizes millions of infants each year with pneumonia and other lung diseases, and it has defied many a vaccine developer. For children at high risk of developing severe RSV disease—which worldwide kills 160,000 kids each year—a monoclonal antibody on the market, palivizumab, can cut the risk of hospitalization in half. But palivizumab must be used repeatedly and costs nearly $1000 a dose, placing it far out of reach of many.

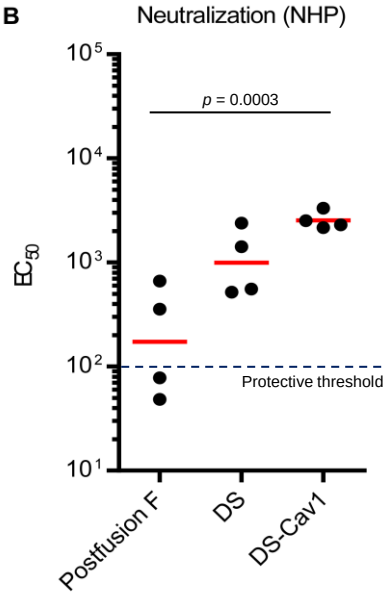
Antibodies that have 10- to 100-fold more potency than palivizumab recently have been isolated, and in May, a research team at the U.S. National Institute of Allergy and Infectious Diseases (NIAID) reported that it had crystallized one of them in action. The antibody binds to a protein

The design has been applied to other paramyxoviruses, such as HMPV, HPIVs, BRSV



How to lock up antigen in the profusion configuration?

10x higher neutralization titers in NHP



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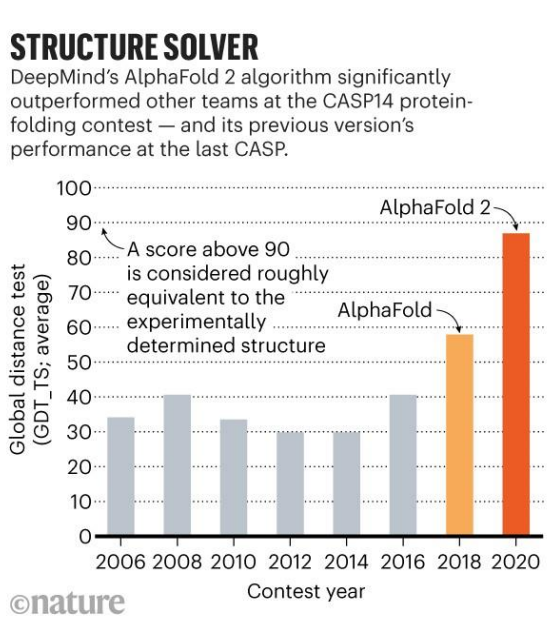
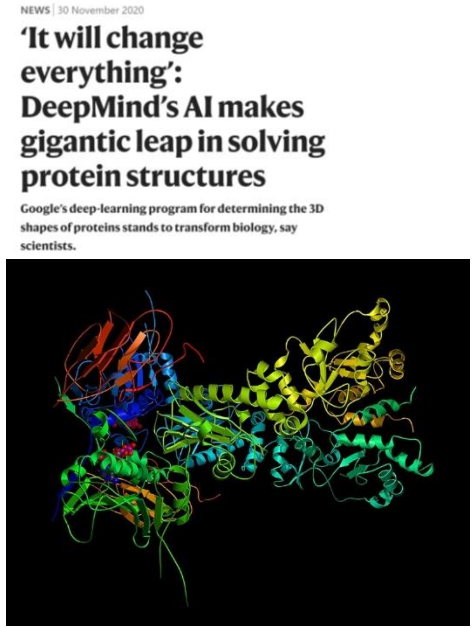
Adapted from Dr. Baoshan Zhang

AlphaFold on Protein Folding





The deep learning-based modeling to predict protein folding can revolutionize the way of finding the right amino acid mutations that can stabilize the profusion configuration of antigens

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Summary

Changing Landscape of Drug R&D Calls for Novel Models, Methods and Entrepreneurship in the Regulatory Setting

- Innovative medical products/technologies
  - Revolutionary biologics (e.g., ADC + Bispecific antibodies)
  - Emerging nucleotide-based therapies
    - mRNA, siRNA, anti-sense RNA, gene editing, cell-based therapies & in vivo expressed biologics in CBER
- Novel drug delivery systems (e.g., LNP for mRNA)
- Advances in AI/ML and QSP
- Advances in human genome data (big data) for response
- Use of real-world data
- Precision medicine

Broadening Value Proposition of Modeling

- From life cycle perspective
- Drug delivery models
- Drug design models
- Call for next generation modelers with forward looking
  - Post Lewis Sheiner era
  - Go mechanistic go big data!

Acknowledgement

- Case Contributors
  - –Eleftheria Tsakalozou, PhD
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- ORS/OGD
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  - – Lei Zhang, PhD