


A large, colorful molecular structure composed of various spheres (blue, green, red, yellow, orange, pink, white) connected by thin white rods, set against a light blue background with a faint silhouette of a human head. The spheres have a glossy, 3D appearance.

FROM
MOLECULE TO
PATIENT

ASCPT 2019
ANNUAL MEETING



**Recent Applications of Quantitative Systems
Pharmacology in IQ Consortium:
From Data to Decision**

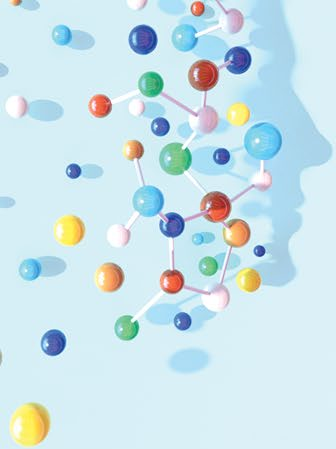
Mindy Magee, Pharm.D.

Clinical Pharmacology Modeling & Simulation

GlaxoSmithKline

On behalf of QSP Working Group in IQ Consortium

March 13th, 2019



IQ QSP Working Group in Clinical Pharmacology Leadership Group (CPLG) Representation across the Industry

FROM
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- **Co-chairs:**

- ❖ CJ Musante, Pfizer
- ❖ Jerry Galluppi, Sunovion
- ❖ Mindy Magee, GSK

- **Members:**

- ❖ Alexander Ratushny, Celgene
- ❖ Brian Topp, Merck
- ❖ Craig Thalhauser, BMS
- ❖ Christina Friedrich, ROSA
- ❖ Gabriel Helmlinger, AstraZeneca
- ❖ Jason Chan, Lilly
- ❖ Loveleena Bansal, GSK
- ❖ Mark Peterson, Pfizer
- ❖ Mohamad Shebley, AbbVie
- ❖ Piet van der Graaf, Certara
- ❖ Saroja Ramanujan, Genentech
- ❖ Sergey Ermakov, Amgen
- ❖ Wayne Chu, Genentech

Diverse membership includes:

- ❖ QSP & PK/PD modelers
- ❖ CRO representation
- ❖ Clin Pharm/PMX
- ❖ Clinical leads
- ❖ Biologists

abbvie

AMGEN

AstraZeneca

Pfizer

gsk

Genentech
A Member of the Roche Group

MERCK

ROSA
Drug Development Advisors

CERTARA

IQ
INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Bristol-Myers Squibb
Company

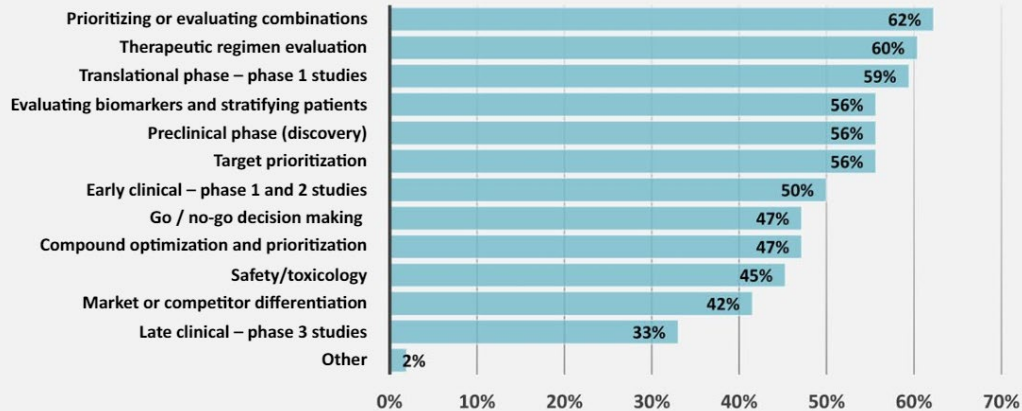
Celgene

Lilly

Insights from ISoP & IQ Surveys

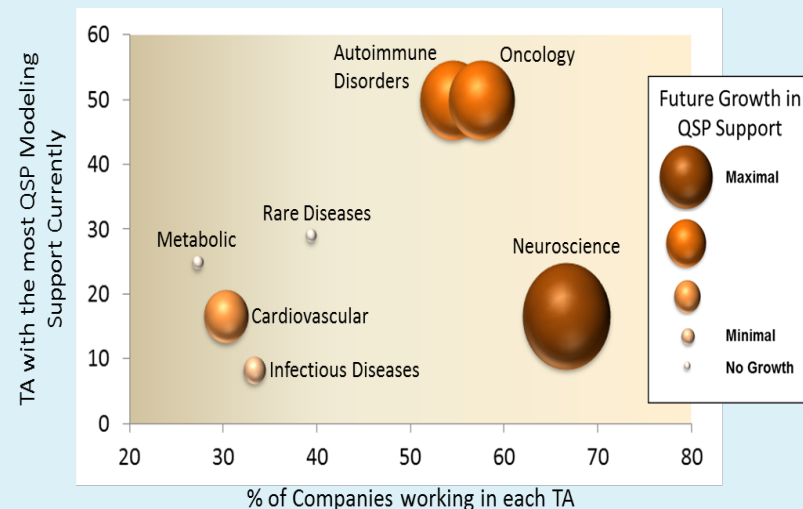
QSP Impact Across All Stages of Drug Discovery and Development

QSP impact in MID3

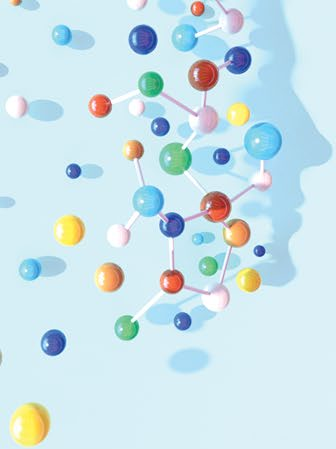


Ermakov *et al.* A Survey of Software Tool Utilization and Capabilities for Quantitative Systems Pharmacology: What We Have and What We Need. *CPT Pharmacometrics Syst Pharmacol* 8, 62-76 (2019).

Current and Future Impact of QSP Across Therapeutic Areas

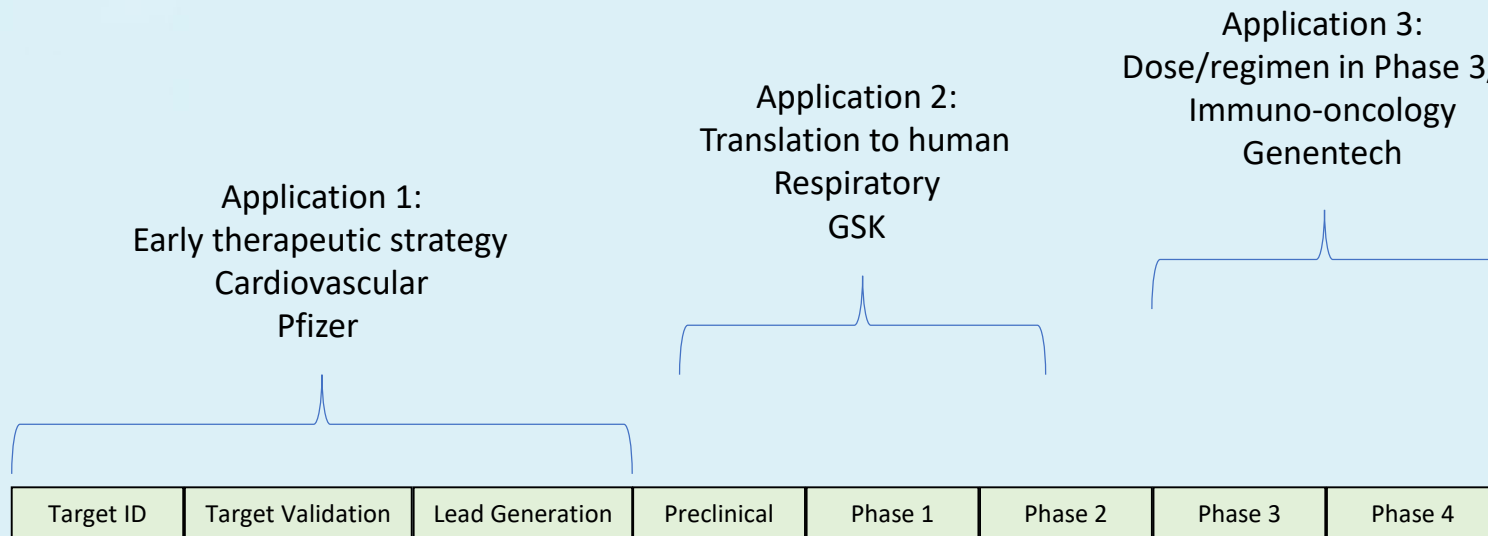


Nijsen, M. J. M. A. *et al.* Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape. *CPT Pharmacometrics Syst Pharmacol* 7, 135-146 (2018).



Recent Applications of QSP in IQ

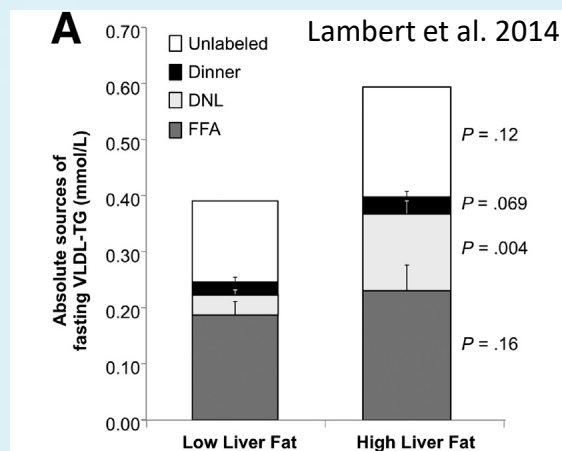
Data to Decision



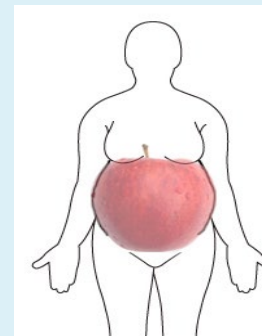
Application 1: Therapeutic Strategy

Data

Plasma FAs are a Large Contributor to Liver Lipids



Hepatic Fat Stores are Small Compared to Adipose



BMI \approx 35, 100kg
 39% body fat, 39kg



Liver Fat %	Liver Fat ~weight
5%	0.070kg
20%	0.300kg

Decision to be informed

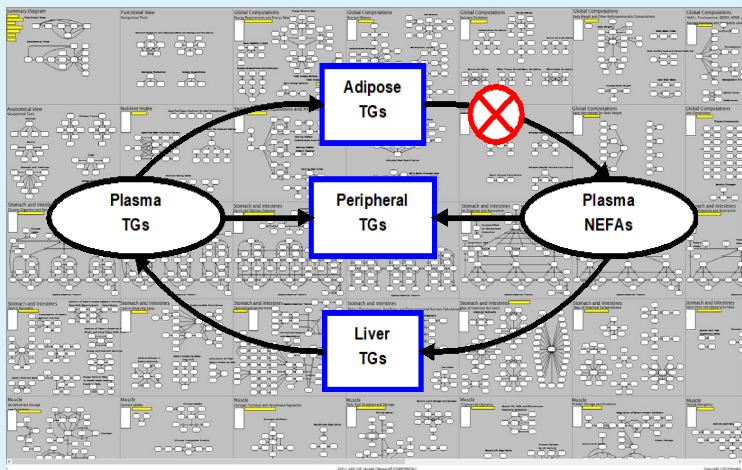
- Is inhibition of lipolysis in adipose tissue predicted to be an effective treatment for Nonalcoholic Fatty Liver Disease (NAFLD)?

Target ID	Target Validation	Lead Generation	Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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Modeling Approach

MOLECULE TO PATIENT

Systems Model of Lipolytic Flux: Metabolism PhysioLab



Data Sources

- Human PK: Dobbins et al. 2013 and 2015
- Human PPB: Pfizer determined
- IC50: Pfizer determined (cAMP)
- Acute PD (Dobbins et al. 2013):
 - NEFAs
 - Glucose
 - Insulin
 - Glycerol

Modeling & Simulation Workflow

Calibrate PK to Phase 1 and Non-Clinical Data

Fit IC50 Using Systems Model

Simulate Acute Dosing Protocol

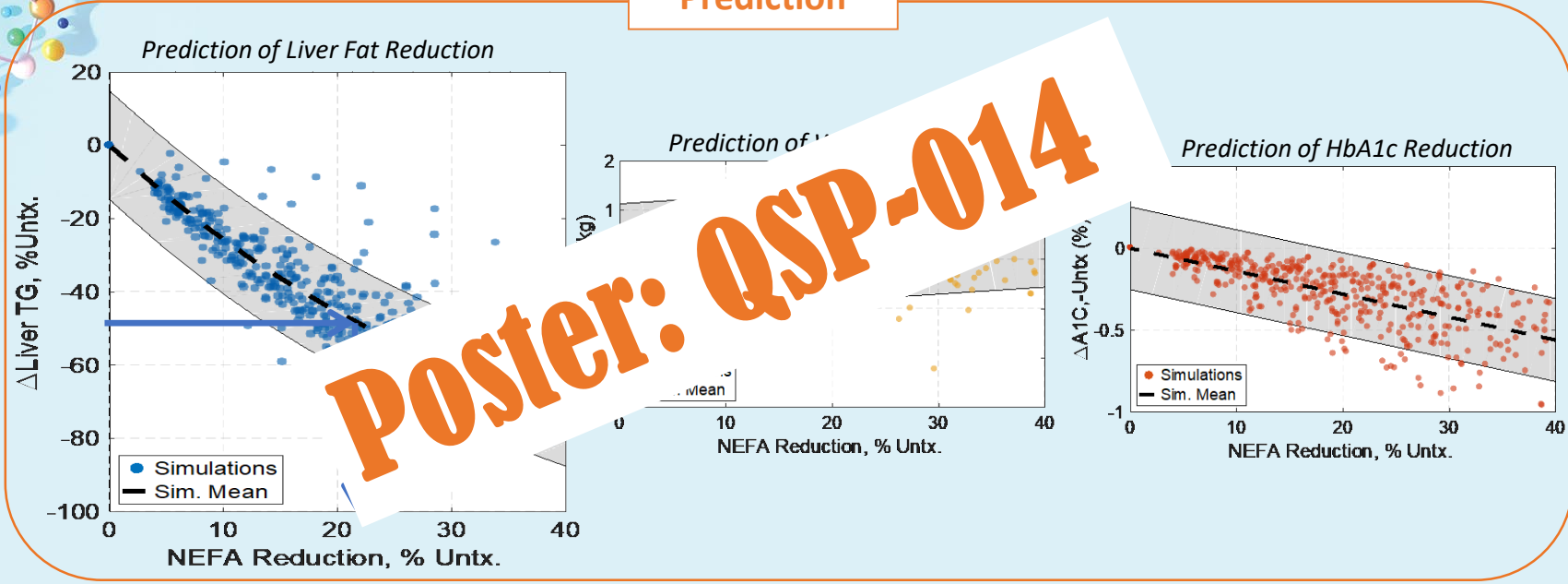
Validate Model Response Against Acute PD Markers

Simulate Chronic Therapy

Target ID	Target Validation	Lead Generation	Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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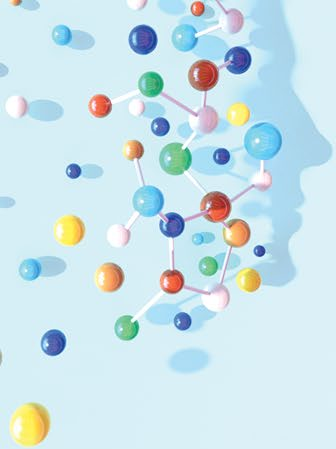
Clinical Prediction & Program Decision

Prediction



Decision

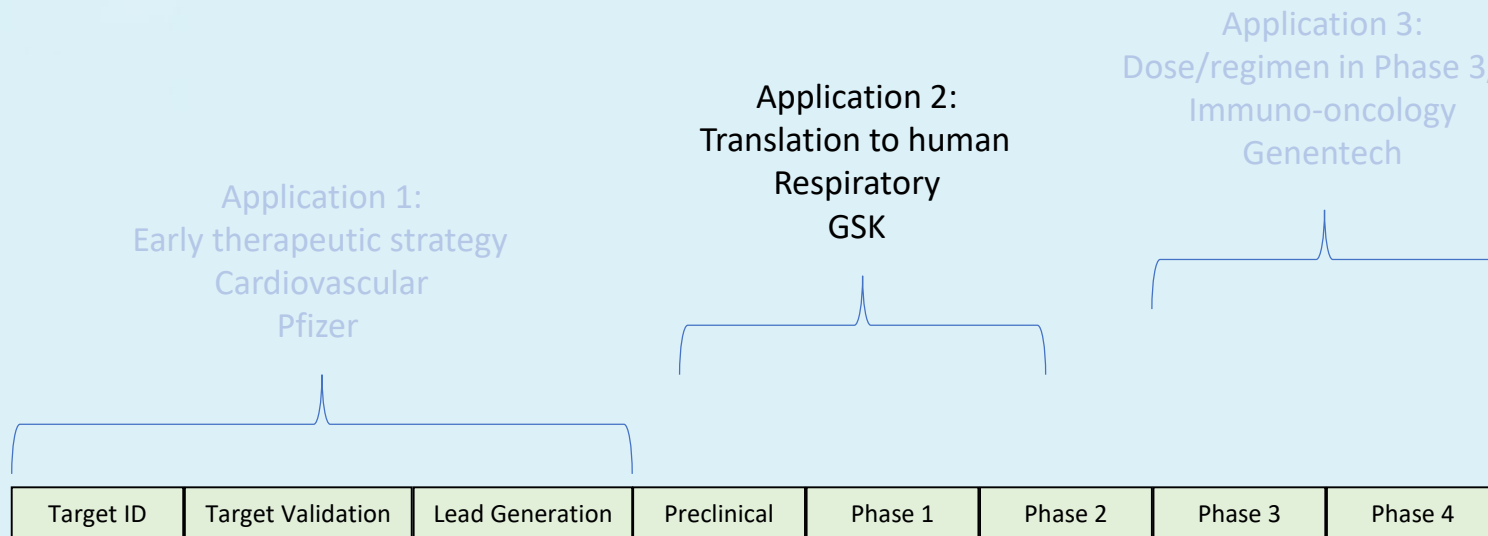
Proceed to interrogate anti-lipolysis targets in adipose tissue for the treatment of NAFLD



Recent Applications of QSP in IQ

FROM
MOLECULE TO
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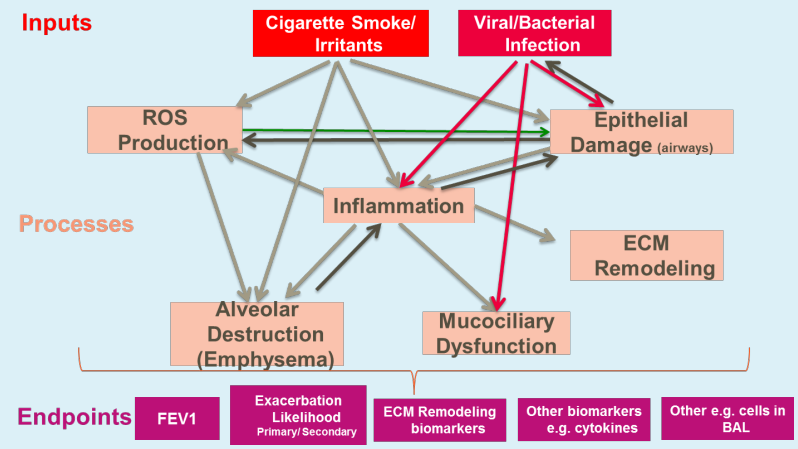
Data to Decision



Application 2: Translation to Human

Data

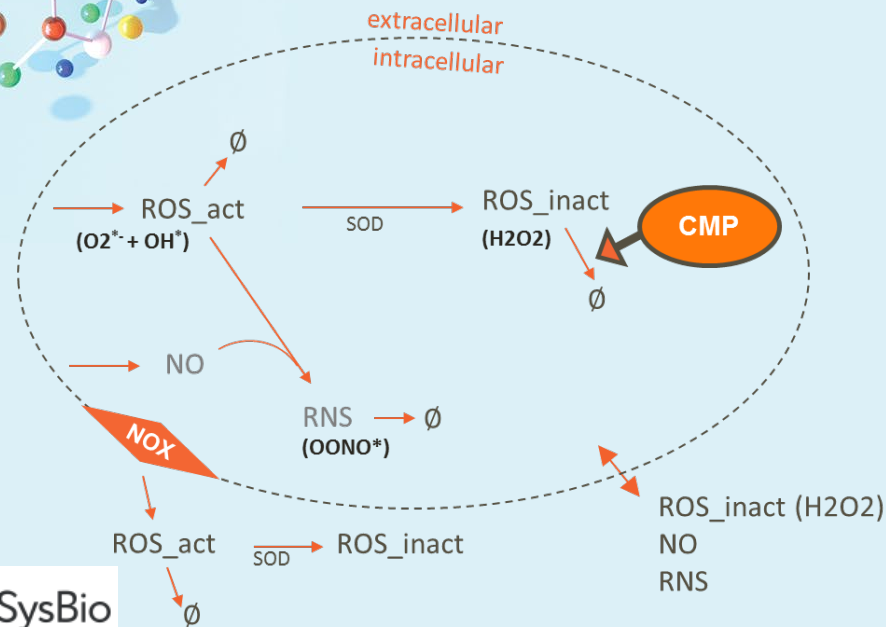
- Chronic Obstructive Pulmonary Disease (COPD) is caused by long term (several years) exposure to irritants, primarily by cigarette smoke.
- Complex disease, with coupled processes involving altered immune and tissue cell populations, leading to inflammation, mucus production and tissue destruction.



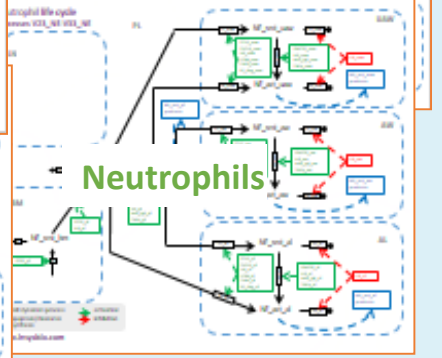
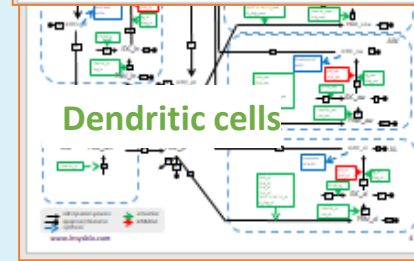
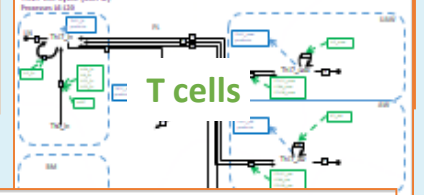
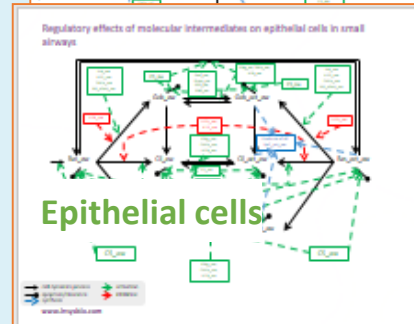
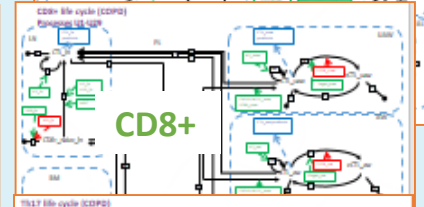
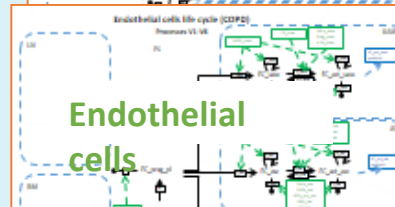
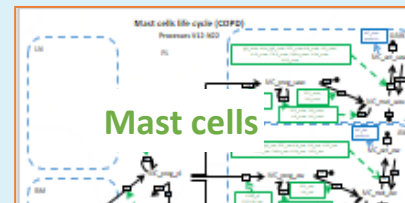
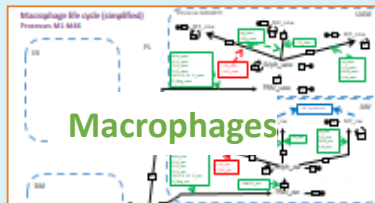
Decision to be informed

- How long does it take for biomarker changes resulting from target modulation to be measurable?

Modeling Approach

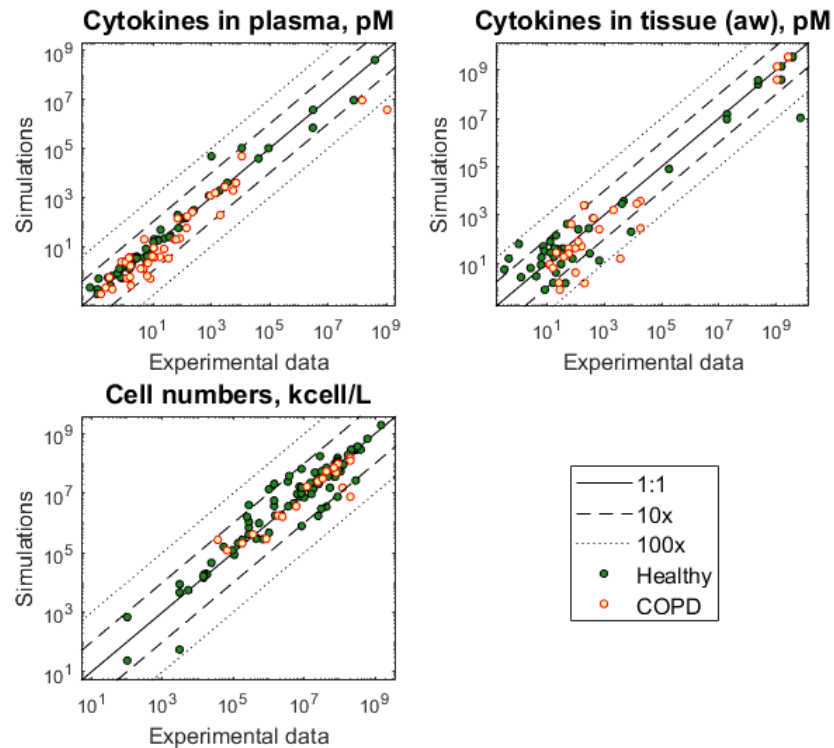


* Simplified scheme



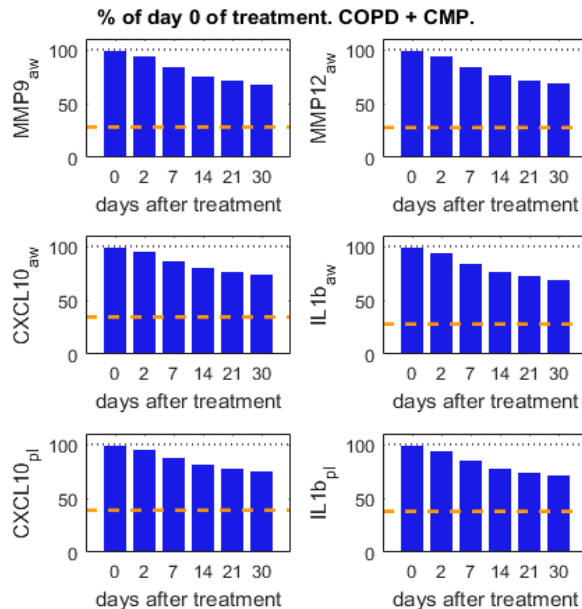
Target ID	Target Validation	Lead Generation	Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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Literature-based Clinical Calibration



Clinical Prediction & Program Decision

Prediction



← COPD, no treatment

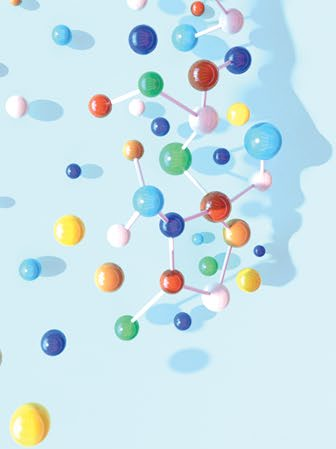
← Healthy non smoker

Predicted intensity of response relative to predicted response after a full year of treatment (preliminary results)

	Airway	Plasma
Day 14	60%	70%
Day 30	80%	90%

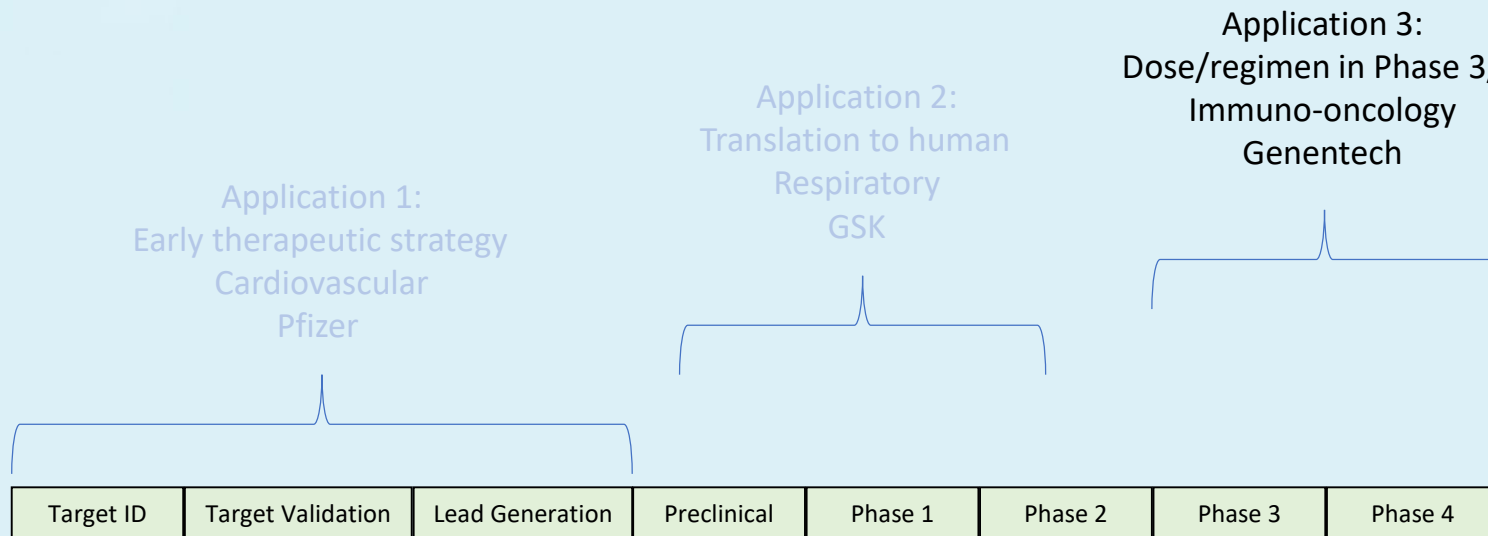
Decision

A shorter dosing duration would provide similar results



Recent Applications of QSP in IQ

Data to Decision



Target ID	Target Validation	Lead Generation	Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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Application 3: Dose Selection in Phase 3/4

Data

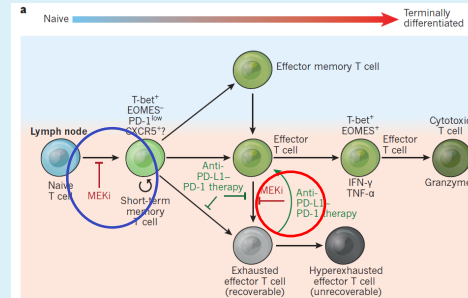
- Preclinical/clinical data suggest MAPK inhibition can increase tumor T cells and possibly anti-PD(L)1 efficacy.
- Phase III trials underway for atezolizumab (anti-PDL1) + cobimetinib (MEKi) in various indications.
- Preclinical study (Ebert et al 2016) suggests opposing effects of MEKi on lymph node vs. tumor T cells
 - **Favorable:** increased tumor T cell accumulation and activity (reduced exhaustion)
 - **Unfavorable:** reduced de novo priming of T cells, which can be overcome by short break from MEKi

Immunity Article

Ebert et al 2016

MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade

Peter J.R. Ebert,¹ Jeanne Cheung,¹ Yagui Yang,¹ Erin McNamara,¹ Rebecca Hong,¹ Marina Moskalenko,¹ Stephen E. Gould,¹ Heather Maecker,^{1,2} Bryan A. Irving,^{1,3} Jeong M. Kim,¹ Marcia Belvin,¹ and Ira Mellman^{1,*}
¹Genentech, 1 DNA Way, South San Francisco, CA 94080, USA
²Present address: Gilead, Foster City, CA 94040, USA
³Present address: Cytomics Therapeutics, South San Francisco, CA 94080, USA
 *Correspondence: mellman.ira@gene.com
<http://dx.doi.org/10.1016/j.immuni.2016.01.024>



Chen & Mellman 2017

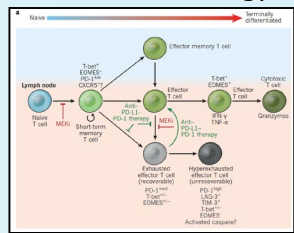
Decision to be informed

- Ongoing trials are using approved cobimetinib regimen of QD for 21-Day on a per 28-Day cycle
- Will shorter treatment with MEKi in each cycle (e.g., 7 vs 21-Day) improve efficacy in combo trials by enabling replenishment of newly primed cells that can infiltrate tumor?

Target ID	Target Validation	Lead Generation	Preclinical	Phase 1	Phase 2	Phase 3	Phase 4
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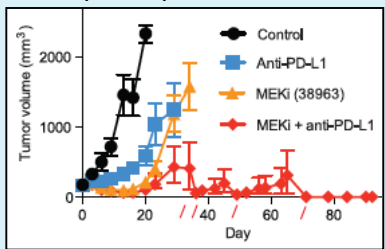
Modeling Approach

1. Model biology



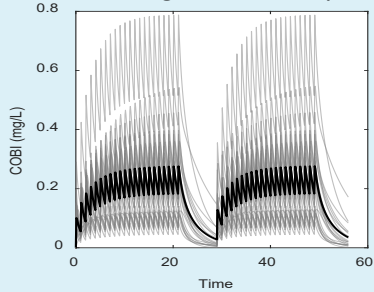
Chen & Mellman 2017

2. Capture preclinical data

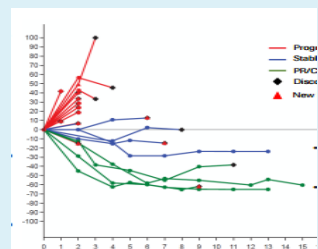


Ebert et al 2016

3. Include human PK & biological variability



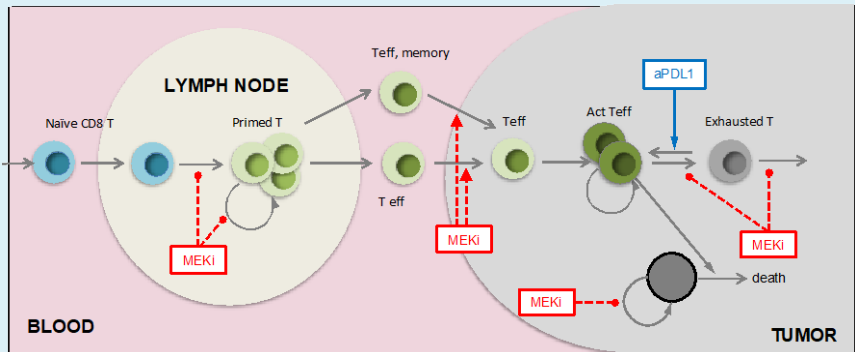
4. Capture limited clinical data



ASCO 2016

QSP MODEL

MEKi and anti-PDL1 effect on LN CD8+ T cell priming, tumor infiltration, anti-tumor cytotoxicity, exhaustion, and death.



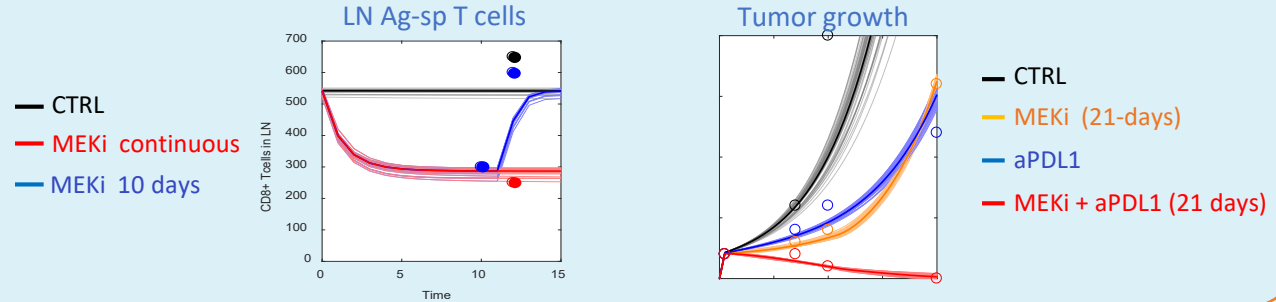
Preclinical and Clinical Simulations & predictions

Preclinical Calibration and Prediction

Calibration

- Model captures LN Ag-specific T cells, tumor T cells, and tumor growth for mono & combo treatment

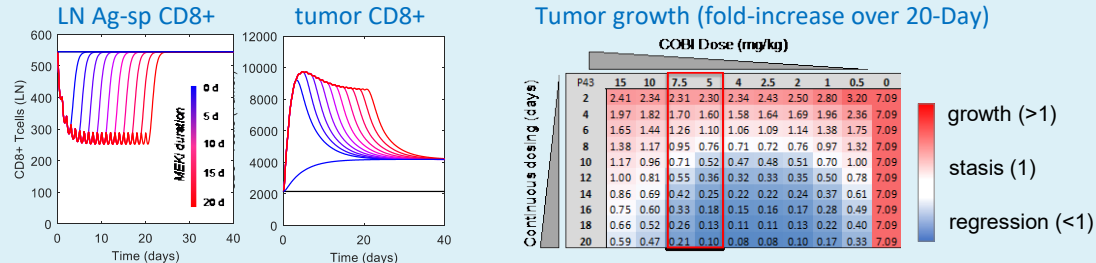
Effect of Tx on CT26-bearing mice (example results)

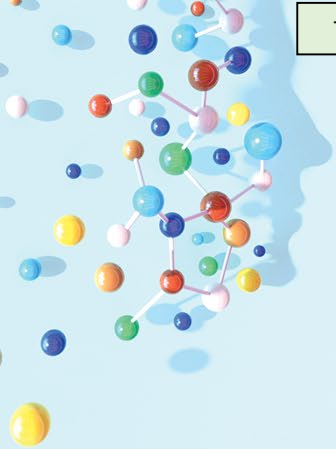


Preclinical Prediction & Validation

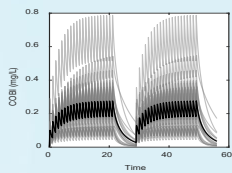
Simulations predict no advantage for shorter dosing of MEKi in MEKi + aPDL1 combo

- Despite reduction in LN priming, longer dosing favors greater (AUC) Ag-specific tumor T cells and tumor regression
- Validation:** experiments in CT26 and other models subsequently showed similar or worse outcome with shorter dosing

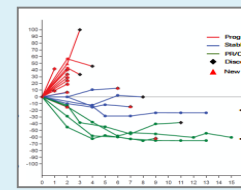
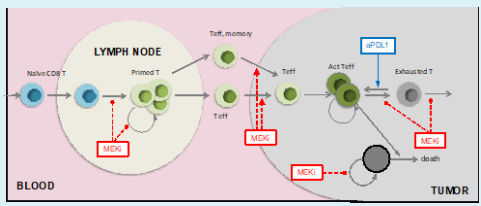




Clinical Prediction & Program Decision



Clinical PK



Clinical PD

Clinical Simulations

- For shorter treatment to be favorable in clinical context, effect of MEKi on tumor T cell activity /exhaustion would need to be much weaker in patients than preclinical data and mechanistic rationale would indicate
- Even if so, differentiating between 7d vs. 21d MEKi treatment would require much larger trial than desired

Decision

- Continuation with approved dose/regimen for cobo in P3 atezo + cobo trials
- No current plans to test reduced duration of MEKi per cycle

Summary

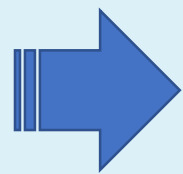
- Quantitative Systems Pharmacology Models have been applied across **all stages** of drug discovery and development
- Quantitative Systems Pharmacology Models have been applied across **various therapeutic areas**
- Quantitative Systems Pharmacology Models integrate **data** to reach model-informed **decisions**

Data to Decision

Data Tsunami



Informed Decision



Acknowledgments

- IQ Consortium
- CJ Musante (Pfizer)
- Theodore R Rieger (Pfizer)
- Saroja Ramanujan (Genentech)
- Cibeles Falkenberg (GSK)
- ASCPT and Pre-conference Organizing Committee

THANK YOU

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