MERCK PCD RUTGERS OUTREACH EVENT

SEPTEMBER 7TH, 2022

Agenda

10:30-10:45 am- Introduction to Merck and PCD

10:45-12:00 am- Overview of the different PCD functional areas

- ADME& DT- *Kerry Fillgrove, Sr. Prin. Scientist*
- Quantitative Pharmacology and Pharmacometrics (QP2)- *Xiaowei Zang, Assoc. Prin. Scientist*
- Bioanalytical (BA)- *Nicole Revaitis, Sr. Scientist*
- Nonclinical Drug Safety (NDS)- *Brian Vega, Assoc. Prin. Scientist*

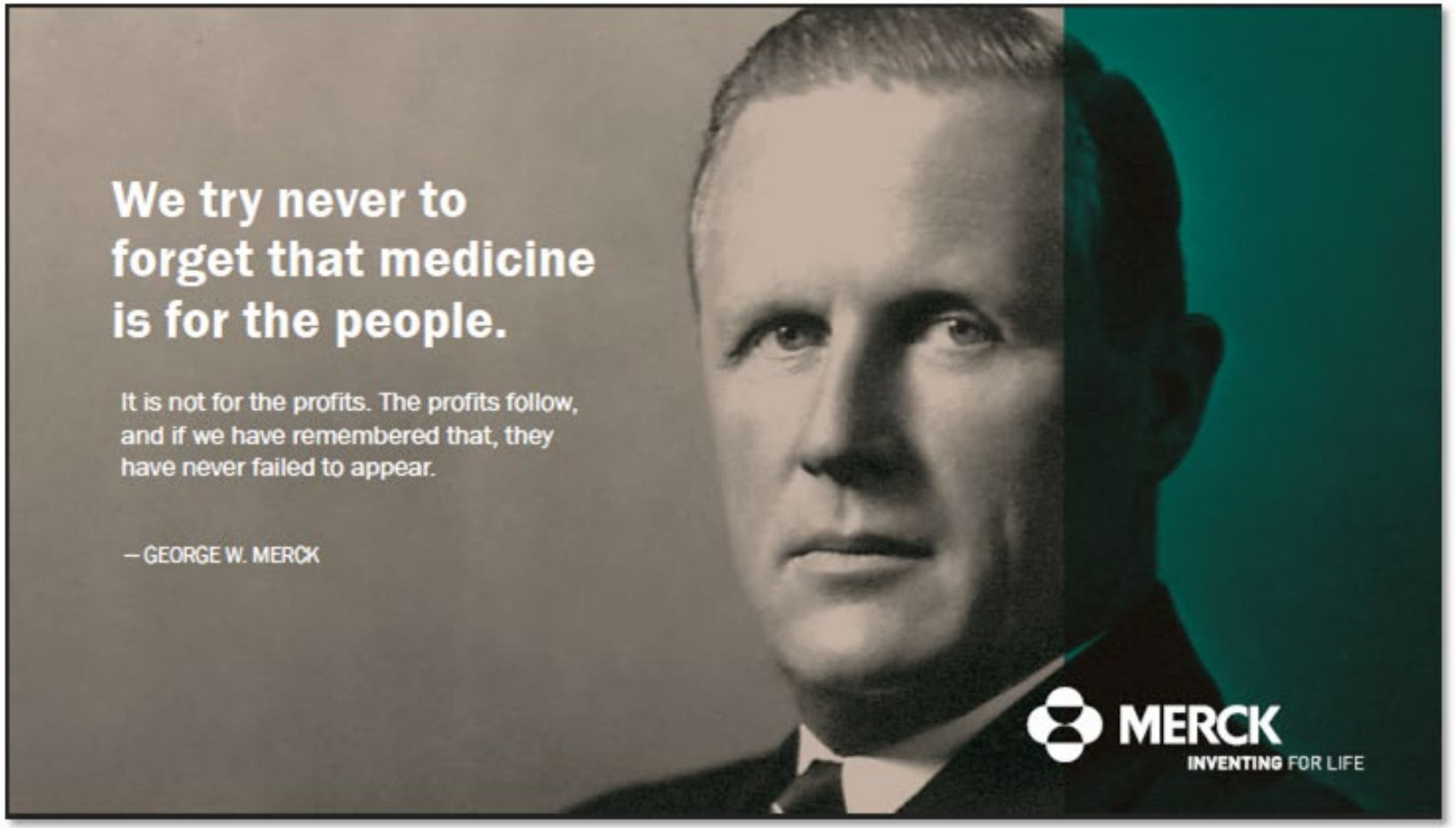
12:00-12:45 pm- Lunch and Round Table Discussion

12:45-1:00 pm - Break

1:00-2:00 pm- Mock interview and Resume review

Merck: Our Mission

Translate breakthrough biomedical research into meaningful new therapies and vaccines that improve and extend the lives of people worldwide



INVENT

IMPACT

INSPIRE

WHO WE ARE

We are a global healthcare company with a 125-year history of working to make a difference

MRK

HEADQUARTERS

Kenilworth, NJ, and operate in 140+ countries

71k

EMPLOYEES

approximately 71,000 worldwide

14.5k

RESEARCH AND DEVELOPMENT

approximately 14,500 colleagues worldwide

293M

ACCESS TO HEALTH

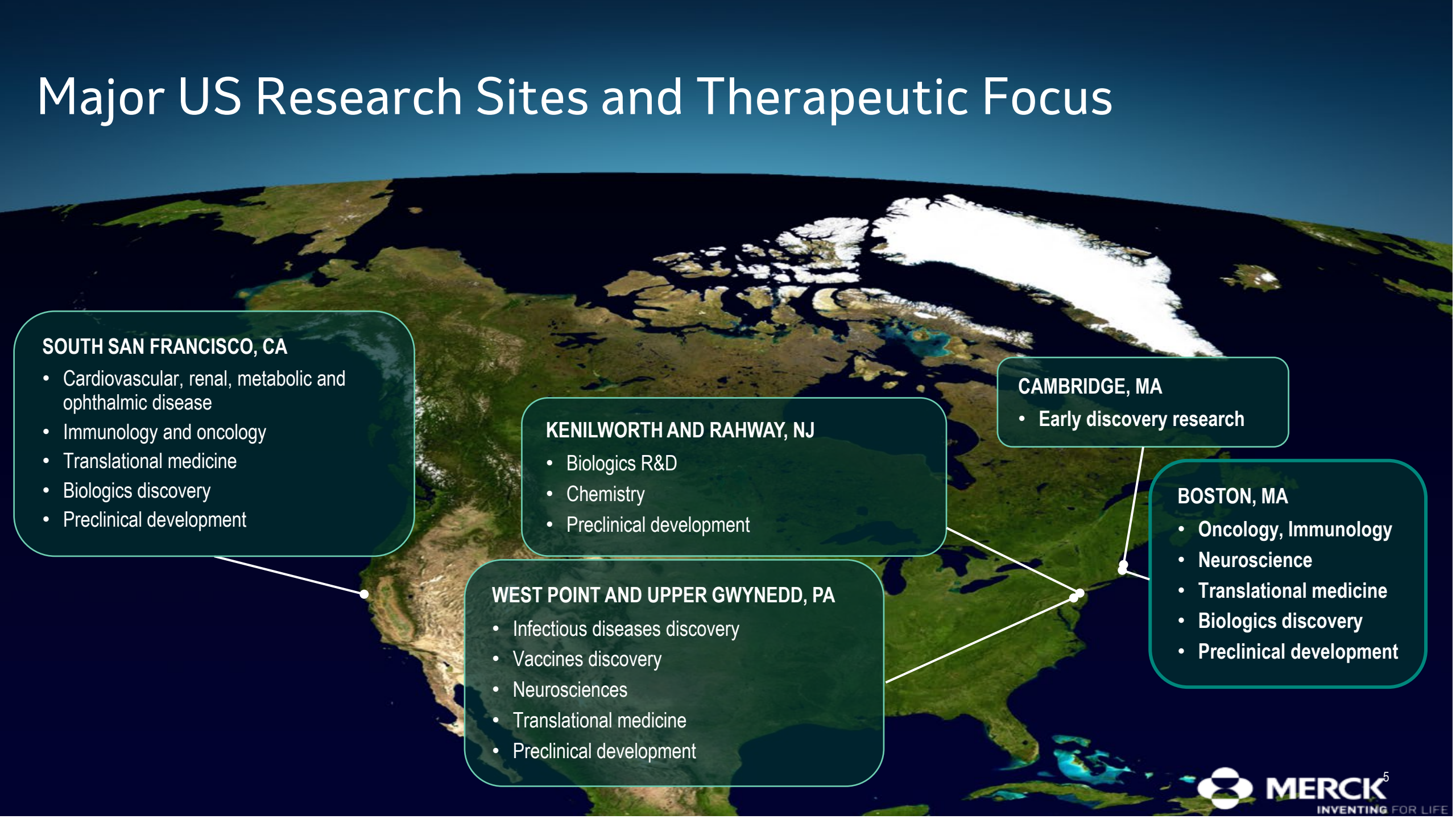
approximately 293M people reached through our major programs and partnerships

2021 R&D Expenses
$12.2 billion

BUSINESSES
Pharmaceuticals, vaccines, and animal health

2021 REVENUE
$48.7 billion

Major US Research Sites and Therapeutic Focus



SOUTH SAN FRANCISCO, CA

- Cardiovascular, renal, metabolic and ophthalmic disease
- Immunology and oncology
- Translational medicine
- Biologics discovery
- Preclinical development

KENILWORTH AND RAHWAY, NJ

- Biologics R&D
- Chemistry
- Preclinical development

CAMBRIDGE, MA

- Early discovery research

BOSTON, MA

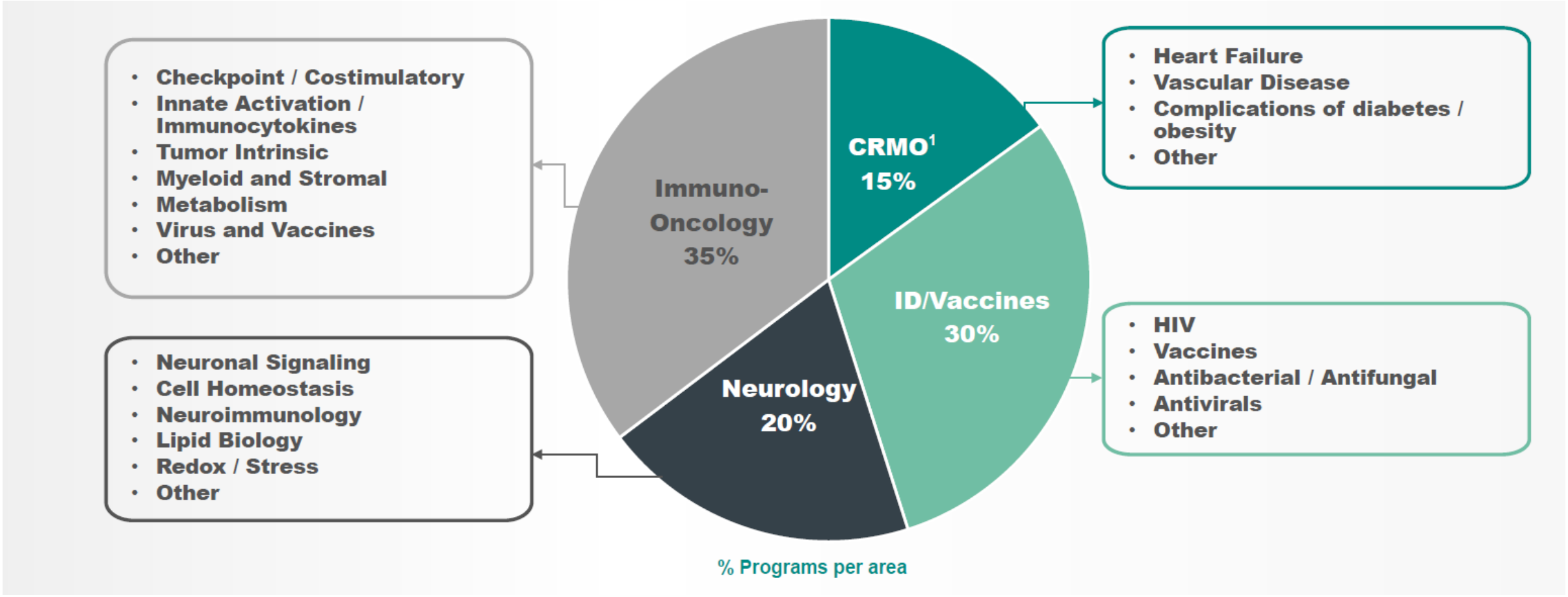
- Oncology, Immunology
- Neuroscience
- Translational medicine
- Biologics discovery
- Preclinical development

WEST POINT AND UPPER GWYNEDD, PA

- Infectious diseases discovery
- Vaccines discovery
- Neurosciences
- Translational medicine
- Preclinical development

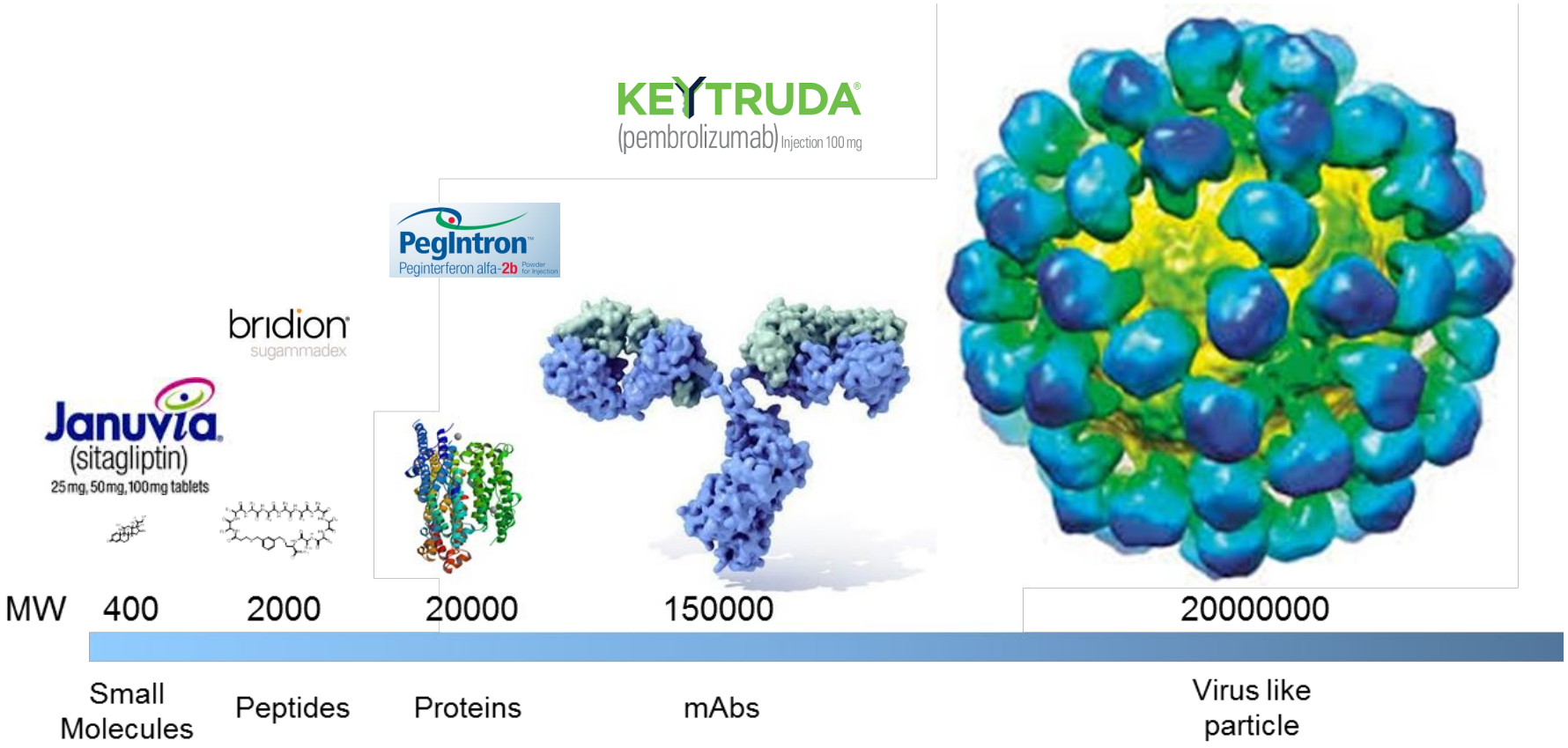
MERCK
INVENTING FOR LIFE

OVER 150 DISCOVERY AND EARLY DEVELOPMENT PROGRAMS



A wide range of human diseases are being studied

DISCOVERY SCIENCE AT MERCK



Working on the best therapeutic approach for the disease

GLOBAL DIVERSITY & INCLUSION **MAKING A DIFFERENCE**

"We are deeply committed to fostering an inclusive environment that embraces different perspectives and values the contributions of each individual. Having a globally and locally diverse workforce makes us a more innovative and agile company — and one better attuned to the needs of our customers, health care providers and patients who ultimately use our products."

— Kenneth C. Frazier
Chairman & CEO

MERCK
INVENTING FOR LIFE

EMPLOYEE BUSINESS RESOURCE GROUP JOURNEY

1970s

1970: Merck's first Employee network, Black Employee Network (BEN) is launched.

1980s

1995: Merck Women's Network EBRG is launched

1990s

1995-1997: Merck Hispanos EBRG is launched.

1998: Merck Asia Pacific EBRG is launched (and again in 2007 with Schering Plough).

2000s

1999: Merck Rainbow Alliance EBRG is launched.

2009: Veterans and Merck Allies for Disabilities EBRG is formed.

2010s

2010: Merck Interfaith Organization EBRG is launched.

2012: Merck Native American and Global Indigenous EBRG launched.

2015: Merck Millennial EBRG formed.

2020s & beyond

MERCK
INVENTING FOR LIFE

PCD Overview

Kerry Fillgrove

Kerry Fillgrove

Background

B.S., Chemistry
Gannon University

Ph.D., Biochemistry
Case Western Reserve University
Enzymology – Protein chemistry

Post-Doc., Biochemistry and Molecular Toxicology
Vanderbilt University
Mechanisms of Antibiotic Resistance

Current Role

Joined Merck in 2004

Senior Principal Scientist
ADME&DT-Discovery Bioanalytics
(formerly DMPK→PPDM→ADM&DT)

- Serve as ADME PI on neuroscience and infectious disease discovery and development programs
- ADME Automation Team lead
- ADME Lead for Islatravir portfolio (HIV)

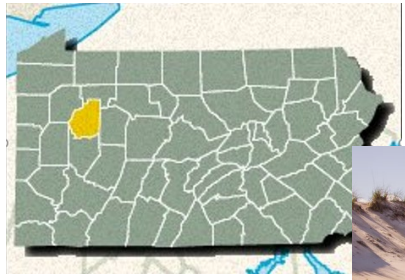
Personal + Interests

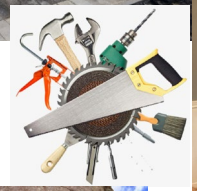
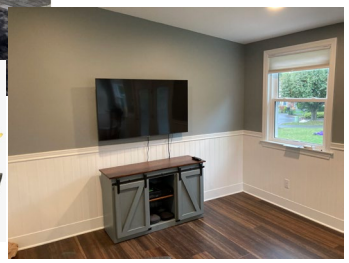
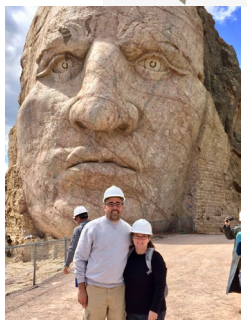
Native of Western PA

Live in Lansdale, PA
with wife and 2 sons

Interests:

- Outdoor activities (landscaping, gardening)
- Home DIY projects
- Traveling
- Volunteering



What we do…

Biologist (Biochem., Cell, Mol. etc.)

Chemist (Med., Org., Anal. etc.)

Mathematician/Statistician

Engineer (Elec. Chem. Biomed.)

Pharmaceutical Scientist

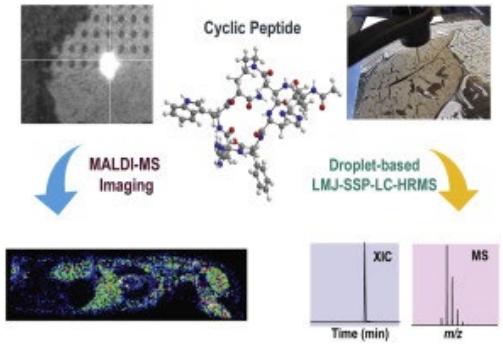
Computer Scientist

and more..

to improve

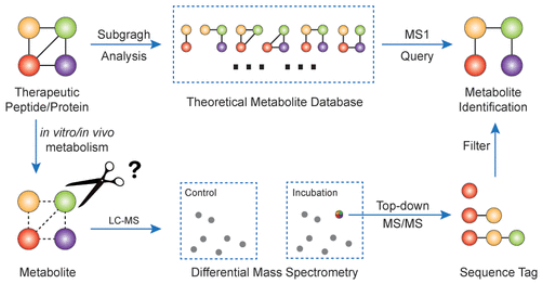
human life

Imaging and Biodistribution



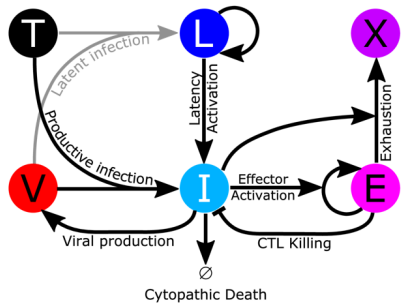
Chen, B. et al. 2020 Anal Chim Acta.

Biotransformation



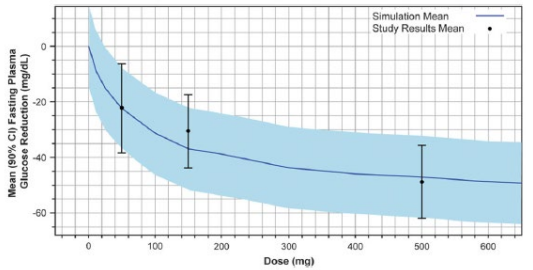
Yu, X. et al. 2020 Anal Chem.

Mathematical Modeling



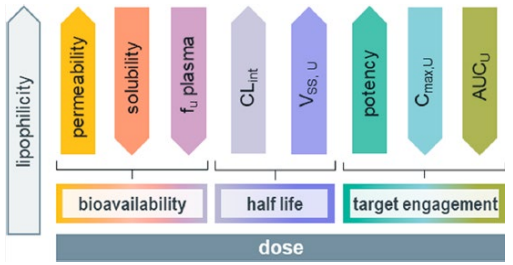
Conway, et al. 2015. *PNAS.*
Cao, et al. 2018. *PLoS Pathog*

Smart Trial and Dose Prediction



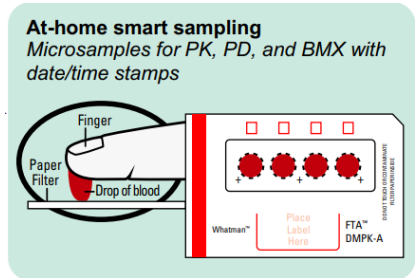
Krug, AW. et al. ,. 2017, Clin Transl. Sci.

Drug Optimization



Miller RR. et al. J Med Chem. 2020

Bioanalysis and Smart Trial



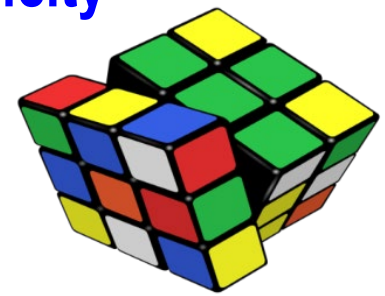
Beckman … et al. …, 2019, Clin Pharmacol Ther

MERCK
INVENTING FOR LIFE

Drug Discovery Challenge: Design With The Patient In Mind

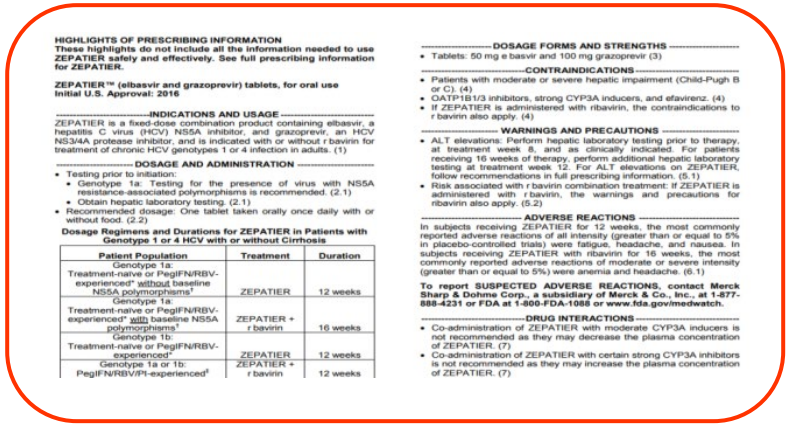
DISCOVERY → PCC-FIH → FIH-POC/ PH2B → PH3-FILE → FILE APPROVAL → APPROVAL POST-LAUNCH

A multiparametric problem!!

Lipophilicity
Clearance
Potency

Absorption
Affinity
Distribution
Avidity
Stability
Promiscuity
(Safety)
Immunogenicity

~5-10 yrs

Safe and Effective!



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPATIER safely and effectively. See full prescribing information for ZEPATIER.

ZEPATIER™ (elbasvir and grazoprevir) tablets, for oral use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
ZEPATIER is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. (1)

DOSAGE AND ADMINISTRATION
- Testing prior to initiation:
  - Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. (2.1)
  - Obtain hepatic laboratory testing. (2.1)
- Recommended dosage: One tablet taken orally once daily with or without food. (2.2)

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naive or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naive or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + r bavirin	16 weeks
Genotype 1b: Treatment-naive or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER + r bavirin	12 weeks

DOSAGE FORMS AND STRENGTHS
- Tablets: 50 mg e basvir and 100 mg grazoprevir (3)

CONTRAINDICATIONS
- Patients with moderate or severe hepatic impairment (Child-Pugh B or C). (4)
- OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. (4)
- If ZEPATIER is administered with ribavirin, the contraindications to r bavirin also apply. (4)

WARNINGS AND PRECAUTIONS
- ALT elevations: Perform hepatic laboratory testing prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, perform additional hepatic laboratory testing at treatment week 12. For ALT elevations on ZEPATIER, follow recommendations in full prescribing information. (5.1)
- Risk associated with r bavirin combination treatment: If ZEPATIER is administered with r bavirin, the warnings and precautions for ribavirin also apply. (5.2)

ADVERSE REACTIONS
In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving ZEPATIER with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended as they may decrease the plasma concentration of ZEPATIER. (7)
- Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended as they may increase the plasma concentration of ZEPATIER. (7)

10,000s of molecules → PCC (1 molecule) → Medicine

MERCK
INVENTING FOR LIFE

Preclinical development designs, conducts and interprets studies that form the scientific basis of the decision to transition programs into and through clinical evaluation

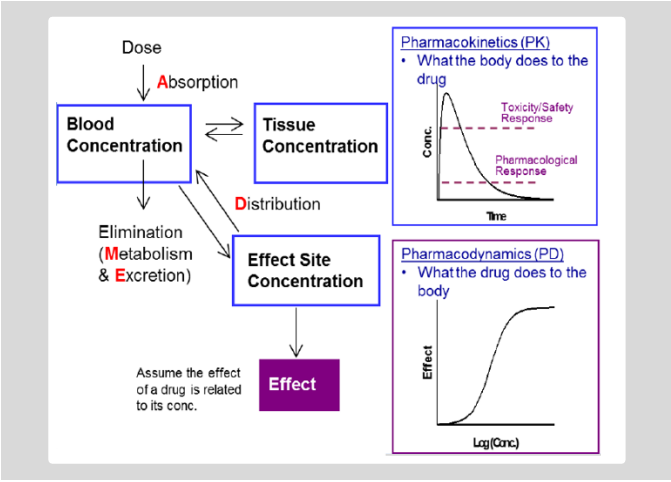
- Establish the safety profile for evaluation in the target patient population.
- Determine the safe and efficacious dose based on the understanding of the pharmacology and pharmacokinetics of the potential new drug
- Provide high quality bioanalytical data that enable decisions on progressing therapeutics and vaccines across the pipeline
- Elucidate the intersection of target biology and drug disposition and define the ADME characteristics needed for clinical success for any modality
- Identify clinical dose, justify dose for special populations or drug interactions and define therapeutic window through quantitative knowledge integrations

Preclinical Development (PCD) – bridging drug discovery and development

ADME & Discovery Toxicology (ADME&DT)

Mission: To influence molecular design to optimize drug disposition and biological properties that are integral to efficacy and safety through research and characterization that translate into differentiated labels.

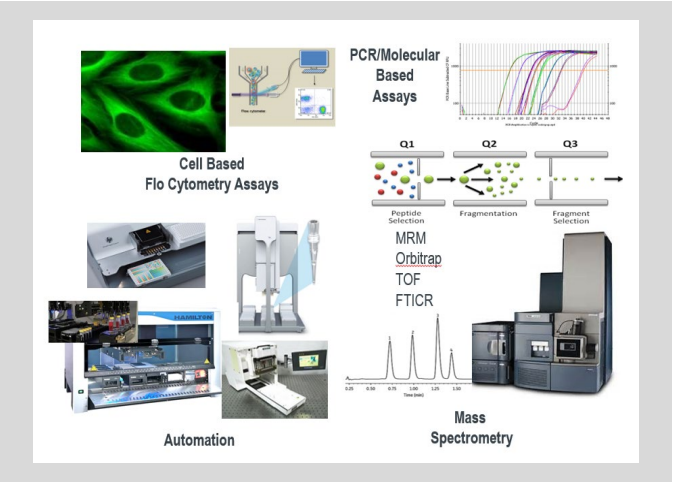
- ❑ Absorption, Distribution, Metabolism and Excretion (ADME) and Drug Metabolism Pharmacology
- ❑ Biotransformation and Distribution (BT&D)
- ❑ Transporter and In Vitro Technologies (T&IVT)
- ❑ Biochemical Toxicology (TK) and in vivo PK
- ❑ Discovery BA
- ❑ Genetic Toxicology (GT)
- ❑ In Vitro Toxicology
- ❑ In Vitro Safety Pharmacology



Regulated Bioanalytics (BA)

Mission: To impact pipeline decisions across all therapeutics and vaccines by understanding the questions our data seek to address and developing appropriately targeted bioanalytical methods and providing high quality bioanalytical data that enable decisions on progressing therapeutics and vaccines across the pipeline

- ❑ PK & ADA
- ❑ Immunogenicity and Molecular
- ❑ Lab Systems and Sample Management



MERCK

Preclinical Development (PCD) – bridging drug discovery and development

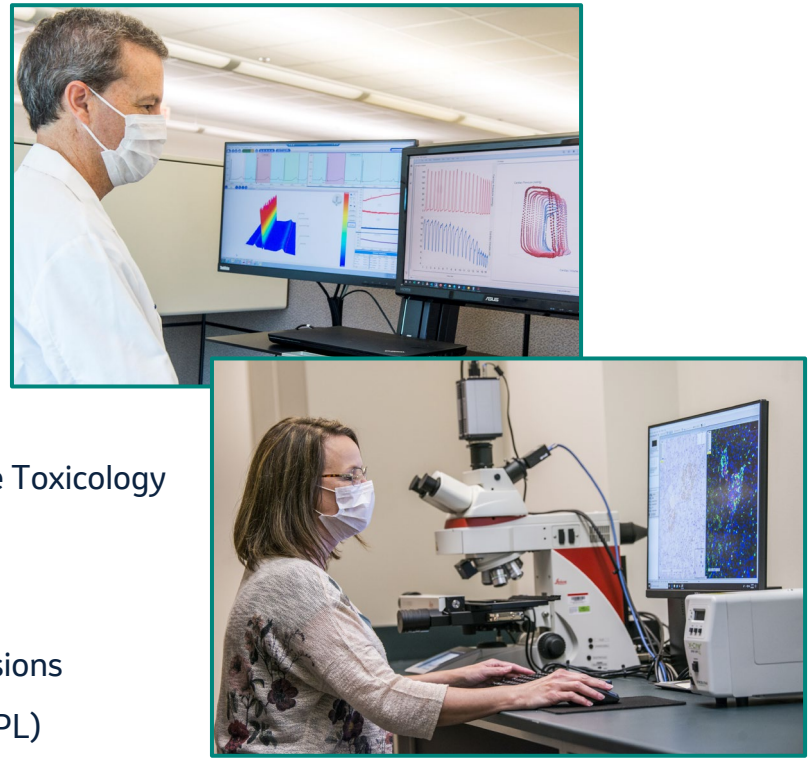
Nonclinical Drug Safety (NDS)

Mission: To empower ground-breaking discovery research that influences the development of safe therapeutics, develops insightful safety assessments for clinical trial safety & flexibility, and delivers the most appropriate commercial label

❑ Pathology
- Anatomical Pathology
- Clinical Pathology
- Investigative Pathology

❑ Toxicological Sciences
- Toxicology Operations
- Central Pharmacy
- Developmental & Reproductive Toxicology

❑ Program Discovery & Development
- Program Planning and Submissions
- Discovery Program Leaders (DPL)
- Therapeutic Area Leaders (TAL)
- Compound Leaders (CL)



❑ In Vivo Safety & Exploratory Pharmacology
- GLP Safety Pharmacology
- Investigative In Vivo Safety Pharmacology

❑ Investigative Toxicology
- Immunotoxicology
- Systems Toxicology
- Analytical & Biochemical Toxicology

❑ Occupational Toxicology

❑ Operations
- Project Planning & Sourcing
- Digital Operations & Innovation
- Information Management

MERCK

Preclinical Development (PCD) – bridging drug discovery and development

Preclinical Development Outsourcing

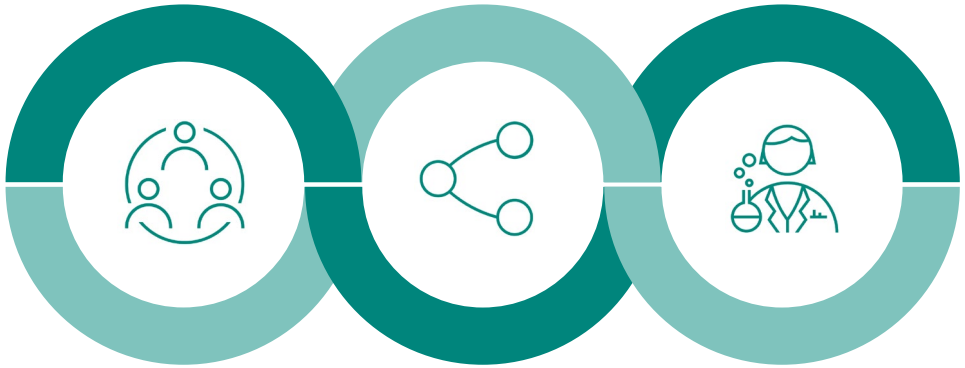
Mission: To advance MRL's therapeutic and vaccine portfolio by proactively developing and leading a network of external partners to generate high quality, timely and cost effective PCD data

- ❑ Preclinical, NDS, QP2 Sourcing
- ❑ Regulated Vaccines BA Sourcing
- ❑ Regulated PK/ADA Sourcing
- ❑ Sourcing Operations

Preclinical Development Strategic Operations

Mission: To generate, advance, and implement best practices that strengthen the broad PCD organization through innovative approaches, drive efficiencies in internal and external collaborative engagements, and create opportunities to ensure training compliance and professional development of PCD staff and leaders.

- ❑ Facilities and Project Management
- ❑ Regulatory Submissions and Document Management
- ❑ PCD Archives
- ❑ Training Strategy and Compliance



MERCK

Preclinical Development (PCD) – bridging drug discovery and development

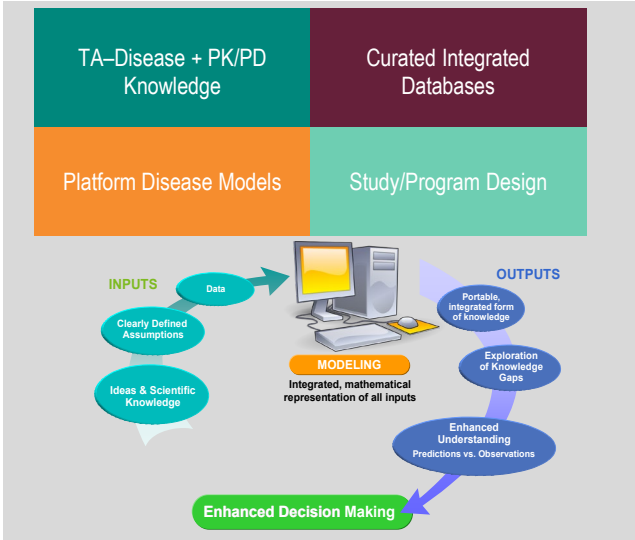
Laboratory Animal Resources (LAR)

Mission: To provide collaborative research support and technical expertise to research programs while promoting the health, well-being and responsible use of animals through optimal husbandry and veterinary care.

- ❑ LAR Boston
- ❑ LAR South San Francisco
- ❑ LAR West Point

Quantitative Pharmacology and Pharmacometrics (QP2)

Mission: To deliver value through optimizing dosage, identifying opportunities to halt development of undifferentiated assets, and streamlining the development of promising compounds and biologics utilizing model-informed drug discovery/development and pharmacokinetics/pharmacodynamics.



External Collaborations

Mission: To deliver thorough and timely stage-appropriate PCD endorsed reviews for external business development opportunities across all TAs and assuring optimal transitions towards integration for agreement(s) with full cross-functional PCD engagement and in partnership with BD&L.

MERCK

Summary

Identifying the *Right Target, Right Drug, Right Dose, Right Patient*

- PCD plays a pivotal role enabling the pipeline from early discovery through post-marketing
- Large lab footprint for experiment execution
  - In vitro assays
  - In vivo studies
  - Bioanalytical data generation
- We focus on understanding how the biological system impacts the molecule (ADME) and how the molecule impacts the biological system (Tox)
- We develop models based on our data to enable decisions across the portfolio (target selection, molecular design and compound selection, clinical study design)
- Collectively, our studies enable the translation of discovery data into clinically safe and effective doses for patients
- For more detailed information regarding our department and each sub-functional group please visit the PCD Website
- If you have any questions, feel free to reach out!
  - James Schiller – BA – PCD Career Center Steward
  - Hillary Regan – PCD Strategic Operations

MERCK

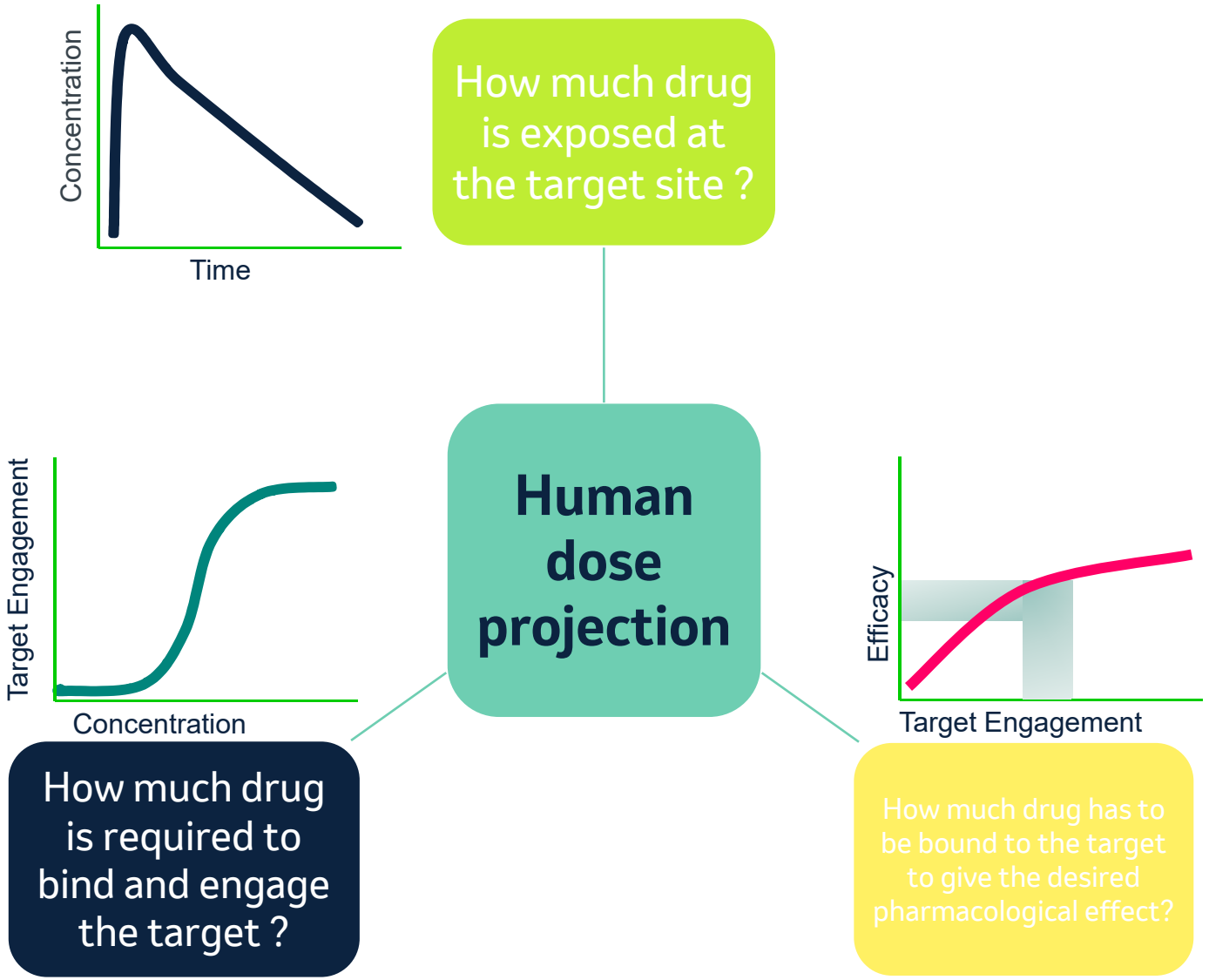
ADME Introduction

Kerry Fillgrove

OUTLINE

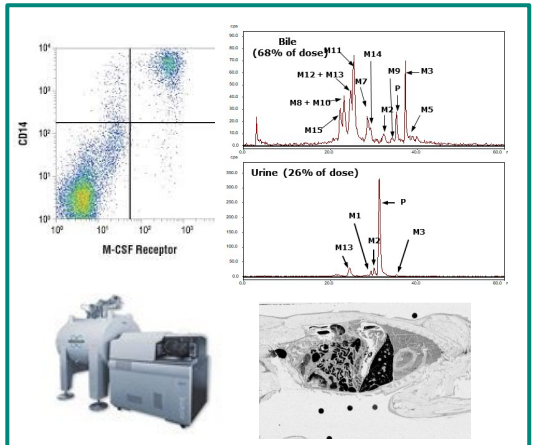
- Introduction to ADME: Role of ADME in drug discovery and development
- Core functional areas that support ADME

Role of PCD ADME in drug discovery and development



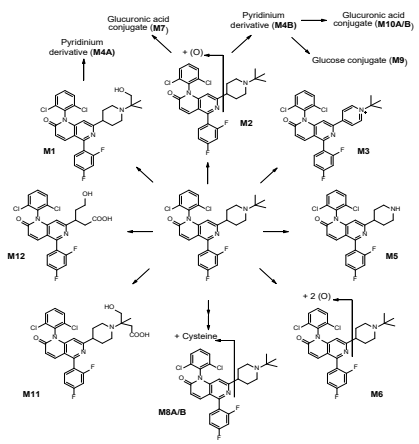
- One of the key role of ADME is to project dose in human for potential drug candidates.
- For this purpose, detailed knowledge and thorough characterization of the pharmacokinetic and pharmacodynamic properties of the drug candidate is required
- ADME provides information to contextualize safety margins and to inform pharmaceutical sciences strategy

PCD ADME has 4 core areas to achieve Merck's goals of bringing new medicines to patients



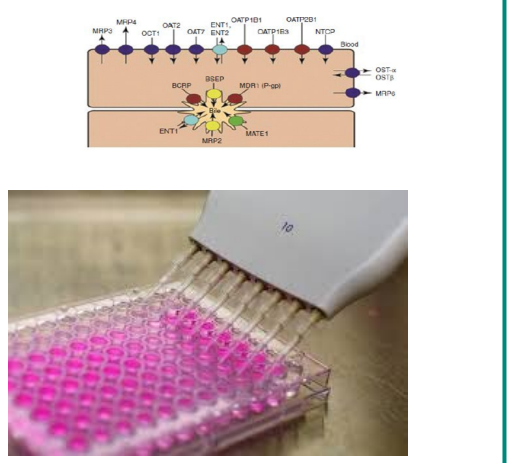
Bioanalytical Science

- ✓ Quantification of drug in biological matrices of preclinical species – Enables assessment of PK properties
- ✓ Quantification of biomarker in biological matrices of preclinical species– Enables assessment of PD properties.



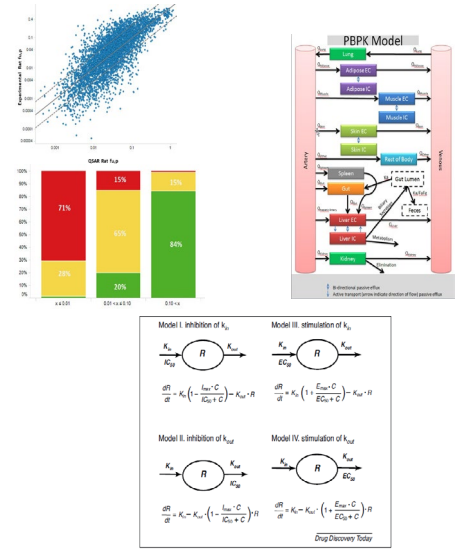
Biotransformation

- ✓ Provides metabolite identification studies to support optimization or advancement of drug candidates.
- ✓ Studies inform on potential toxic pathways, DDI and elimination routes of drug candidates



In vitro ADME

- ✓ Investigates permeability, metabolic clearance, transporter efflux/uptake, in vitro binding to enable in vitro-in vivo extrapolation of PK
- ✓ Victim and perpetrator DDI liability risk assessment



Predictive & Translational Sciences

Finally, data from preclinical species and in vitro sources is modeled with the end goal of predicting outcome in humans

INVENTING FOR LIFE

MERCK

QP2 Introduction

Xiaowei Zang

Xiaowei Zang

My Background

B.S., Biology

Shandong University

Northern Arizona University

M.S., Genetics

West Virginia University

Ph.D., Pharmaceutics **2013-2018**

Rutgers University

PI: Leonid Kagan

- PBPK Modeling
- PK-PD Modeling
- Controlled Release Formulation

Current Role

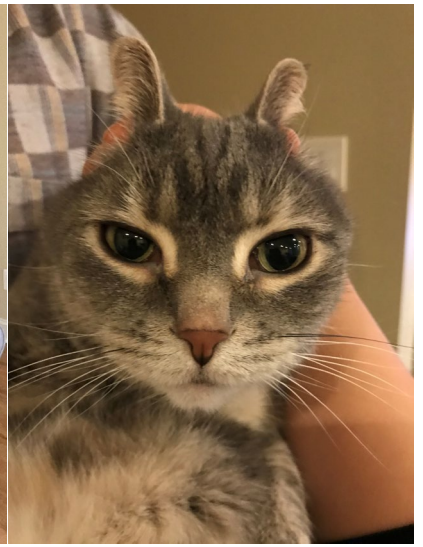
Merck ***2018 to present***

- Quantitative Pharmacology & Pharmacometrics (QP^2)
- Based in West Point
- Infectious Disease & Vaccine
- HIV, RSV, Antibacterial

MERCK

Personal + Interests

- **From Beijing, China**
- **Live in Lansdale, PA**
  - with my husband, son, and a cat
- **Hobbies:**
  - Travel, Outdoor activities (hiking, cycling, running)
  - Cooking (trying out different recipes)

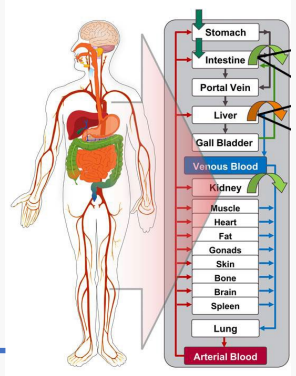


MERCK

Would you like to use quantitative tools to bring benefit to patients?

Pharmacy/
Pharmaceutical Sciences

Data Science



Physiology

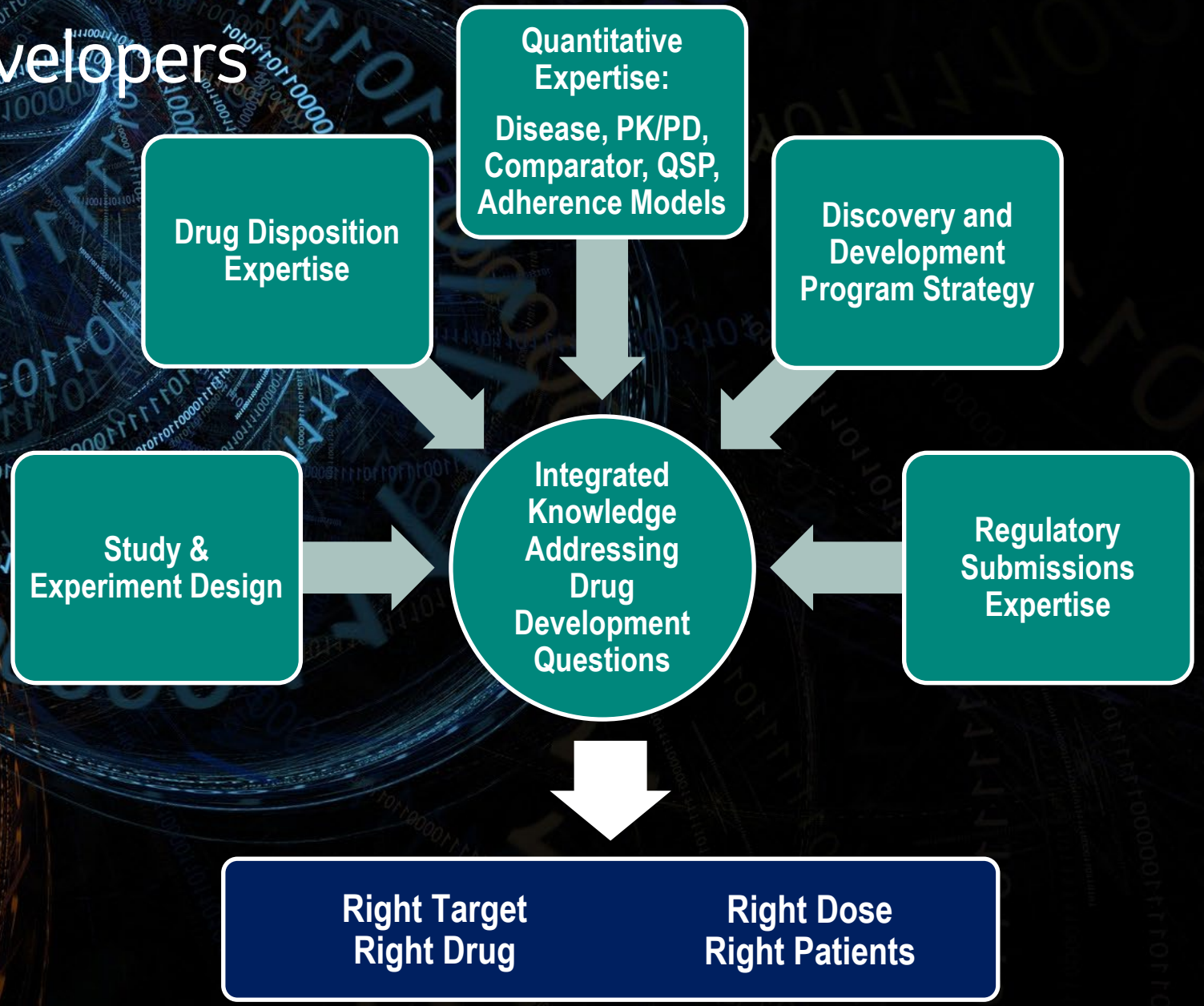
Mathematics/Statistics

$$\frac{dx}{dt} = f(x_t, u_t, t, \theta)$$

$$\frac{dC}{dt} = \frac{V_{max}\,Q}{(K_m + Q)V} - \frac{CL}{V}C$$

Engineering

Quantitative Drug Developers

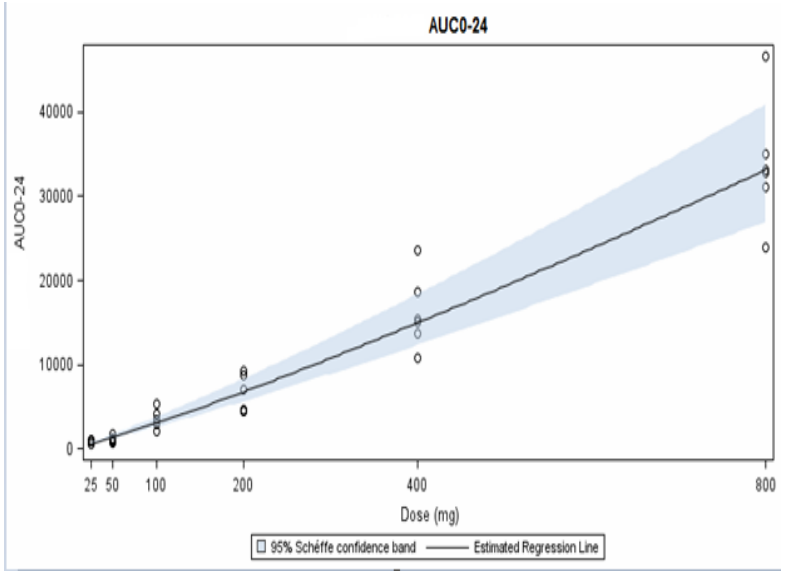


Vignette 1: Leveraging Quantitative Approaches to Advance Novel Therapies Across All Stages of Drug Development

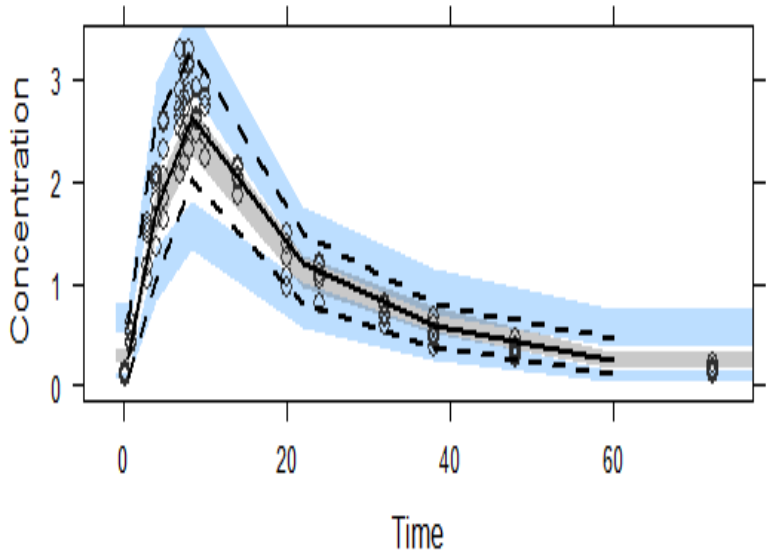
Preclinical Phase I → Phase IIa → Phase IIb → Phase III Approval → Launch Phase IV/V LCM

Characterize PK, PK/PD relationships, Disease Process

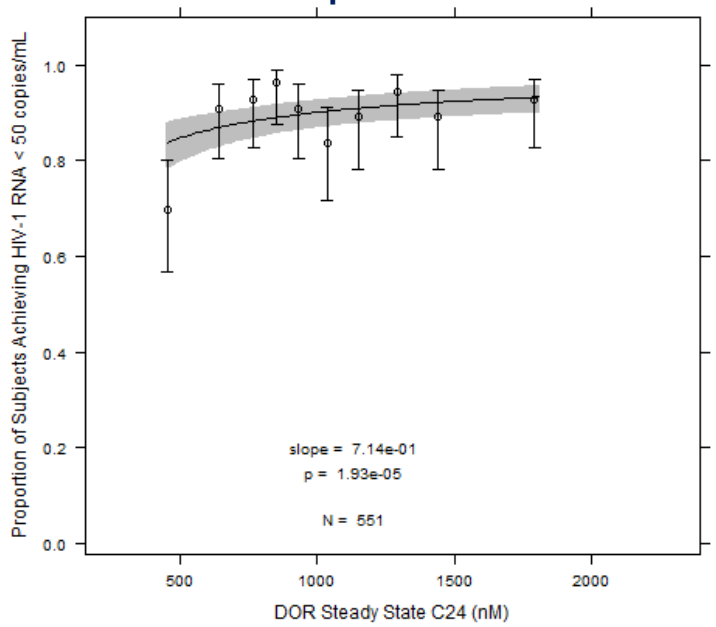
Dose and Exposure Relationship



Drug Concentration over Time Curve



Dose/Exposure- Response (PK/PD to define Therapeutic Window

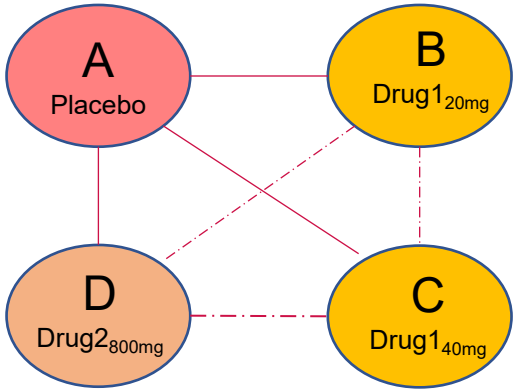


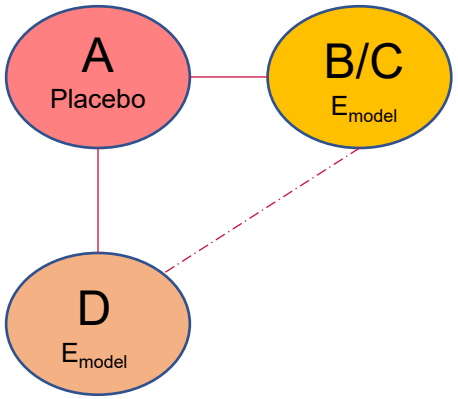
To inform label recommendations for Marketed Product

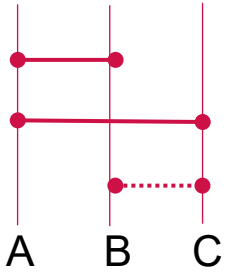
Vignette 2: Model-Based Meta-Analysis (MBMA)

Network meta-analysis

$$\Delta Y_{ij} = A_i + f(E_j, x_i) + \epsilon_{ij} \qquad \Delta Y_{ijt} = A_{it} + \frac{f(E_{max,class}, x_i).Dose_{ijt}}{Dose_{ijt} + f(ED_{50,drug}, x_i)} + \epsilon_{ijt}$$







ΔAB

ΔAC

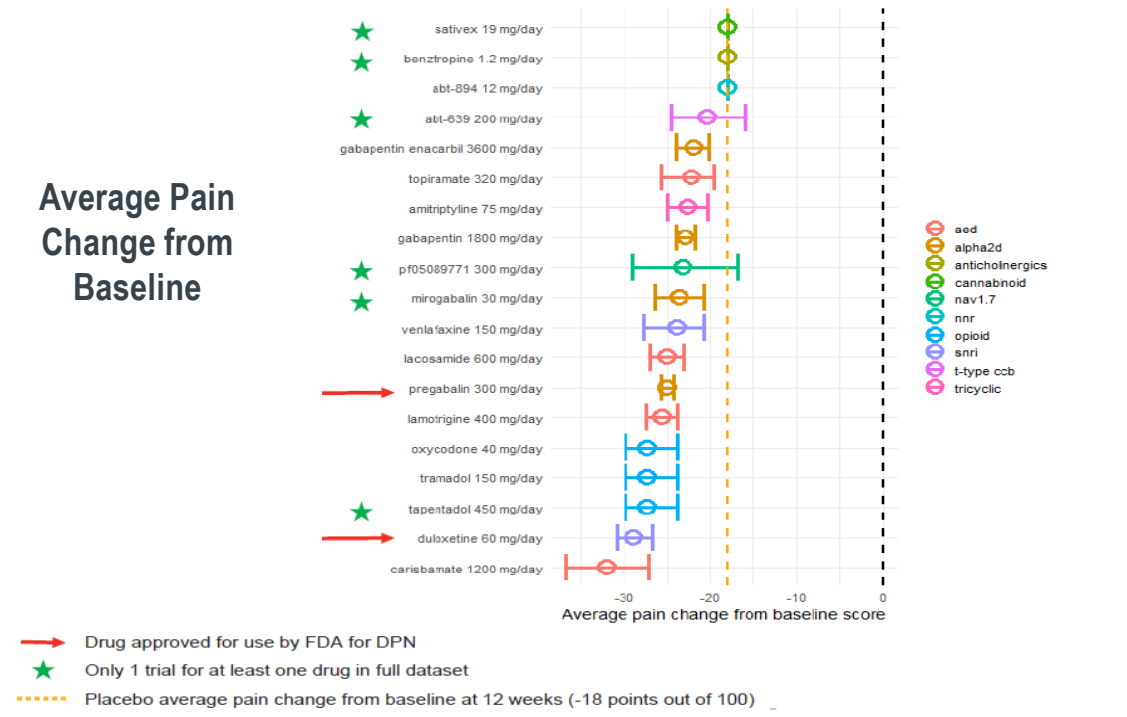
ΔBC = ΔAC - ΔAB

An extension of NMA, taking into consideration of dose responses, longitudinal effect and pharmacology.

MBMA to Support Development of Medicines for Treatment of DPN, PHN and Fibromyalgia

Database: publicly available, summary-level clinical trial data from 74 trials, 26,000 patients, 21 drugs across 9 classes

$$Effect_{ijt} = Eo_{it} + Emax_{class} \cdot \frac{Dose_{ijt}}{ED_{50,\,drug} + Dose_{ijt}} \cdot \frac{time_{ijt}^{\gamma}}{ED_{50,drug}^{\gamma} + time_{ijt}^{\gamma}} + \varepsilon_{ijt}$$



MBMA predicted relative treatment effect at 12 weeks relative to placebo in diabetic peripheral neuropathy in Standard of care for benchmarking of internal compound

Interested? Want to learn more?

computational biology
mathematical modeling
strategic thinking
communications
experimental design
data science
informed drug development
machine learning
exposure
pk
clinical trial development
collaboration
pd
response modeling
pharmacology
programming
pharmacometrics

Please contact us! Reach out to xiaowei.zang@merck.com

MERCK

BA Introduction

Nicole Revaitis

Nicole Revaitis

Background

B.S., Biology
Stockton University

M.S., Biology
Rutgers University
PI: Nir Yakoby

Ph.D., Computational and Integrated Biology
Rutgers University
PI:Nir Yakoby

Areas of Study:

- EGFR signaling and its ligand, Gurken
- Tissue patterning and morphogenesis during *Drosophila* oogenesis

WuXi Advanced Therapies: 2019-2021

- Based in Philadelphia
- Molecular Biology Group
- GMP testing (routine, assay qualification, and validation) for Residual Host Cell DNA, Mycoplasma, and Viral PCR platforms

Current Role

Joined Merck in 2021

Senior Scientist
PCD Regulated BA
Molecular Biologist supporting BD Studies and PCR platforms

Outside Work

Live in Franklinville, NJ

with my husband, 2 children (Ella:13, Michael:4), and pets

Interests:

- Outdoor activities (Gardening, Running, Beach)
- Crafting, Dining Out, Traveling
- Spectator for kids (Field hockey, Cheer, Soccer) and husband (Drag racing)

MERCK

Global Bioanalytics:
Role and Impact in Drug Discovery and Development

MERCK RESEARCH LABORATORIES
GLOBAL PPDM BIOANALYSIS

FOR SCIENTISTS DEDICATED TO PROTECTING HEALTH

"We try never to forget that medicine is for the people. It is not for the profits."
—George W. Merck

PPDM = Pharmacokinetics, Pharmacodynamics & Drug Metabolism

MERCK
INVENTING FOR LIFE

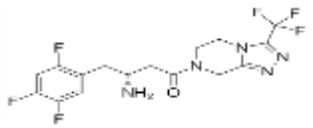
Bioanalytics: Definition and Role in Drug Discovery and Development

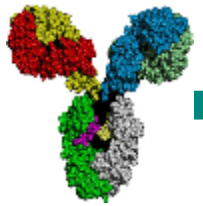
Bioanalytics (BA): Quantitative measurement of drug and/or drug effect/response markers in samples from preclinical and clinical studies

Goal/Impact: Create knowledge of drug and/or PD marker exposure at given time points in relevant sample types (e.g. serum, blood, saliva, urine, other) to enable establishment of pharmacokinetics and pharmacodynamics relationship for a given drug in a specific study environment (preclinical animal efficacy model, PK/PD study, clinical studies)

Global organization with site-based groups

- Discovery BA in SSF, Bos, WP
- Development BA in NJ and PA

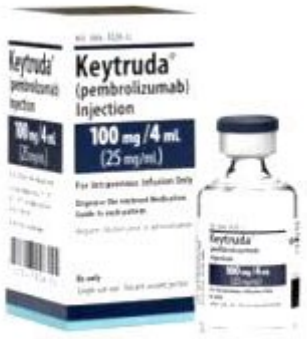




Discovery BA

Analyte	Dose	Regimen	mIFN-g [pg/mL]	mIL-1b [pg/mL]	mIL-5 [pg/mL]	mIL-6 [pg/mL]
mIgG	30 mg/Kg	Q7DX3	< MRC	1.7	2.3	38.0
mIgG	30 mg/Kg	Q7DX3	< MRC	2.8	3.3	107.6
mIgG	30 mg/Kg	Q7DX3	0.4	4.0	1.7	98.6
mIgG	30 mg/Kg	Q7DX3	0.8	5.5	2.8	33.5
mIgG	30 mg/Kg	Q7DX3	0.6	5.3	3.3	95.2
mIgG	30 mg/Kg	Q7DX3	0.7	2.4	2.1	100.4
mIgG	30 mg/Kg	Q7DX3	0.7	5.4	3.3	57.7
mIgG	30 mg/Kg	Q7DX3	0.5	2.4	2.5	65.6
mIgG	30 mg/Kg	Q7DX3	0.4	5.3	3.1	43.0
mIgG	30 mg/Kg	Q7DX3	0.6	11.0	2.6	81.1
mu0X400	5 mg/Kg	Q5DX5	1.7	5.2	4.5	36.1
mu0X400	5 mg/Kg	Q5DX5	2.9	6.2	10.6	22.1
mu0X400	5 mg/Kg	Q5DX5	0.6	2.5	2.6	103.0
mu0X400	5 mg/Kg	Q5DX5	0.8	8.4	2.7	23.8
mu0X400	5 mg/Kg	Q5DX5	1.2	10.9	5.5	34.8
mu0X400	5 mg/Kg	Q5DX5	1.6	6.0	9.3	18.6
mu0X400	5 mg/Kg	Q5DX5	0.7	4.2	3.9	69.7
mu0X400	5 mg/Kg	Q5DX5	1.2	6.2	8.9	17.3
mu0X400	5 mg/Kg	Q5DX5	1.0	4.4	19.9	39.5
mu0X400	5 mg/Kg	Q5DX5	1.5	4.2	96.0	14.9
E06	0.3 mg/kg	Q7DX3	0.4	6.7	2.6	25.7
E06	0.3 mg/kg	Q7DX3	0.4	4.7	3.4	92.1
E06	0.3 mg/kg	Q7DX3	0.7	3.9	2.3	33.1
E06	0.3 mg/kg	Q7DX3	0.4	2.2	2.5	82.3
E06	0.3 mg/kg	Q7DX3	0.5	3.9	3.0	42.3
E06	0.3 mg/kg	Q7DX3	1.5	2.6	2.2	64.0
E06	0.3 mg/kg	Q7DX3	0.4	6.9	2.2	45.0
E06	0.3 mg/kg	Q7DX3	0.4	11.2	2.1	39.8
E06	0.3 mg/kg	Q7DX3	0.8	10.5	4.2	50.8
E06	0.3 mg/kg	Q7DX3	1.1	4.4	3.2	46.6

Development BA
(preclinical, clinical)

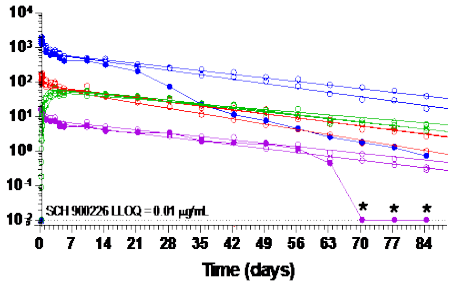


Quantitative Bioanalytical Assays In Support of Therapeutics

DISCOVERY → GLP → CLINICAL

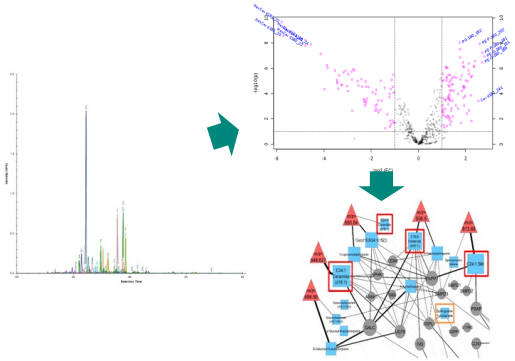
Pharmacokinetics

LC/MS LBA



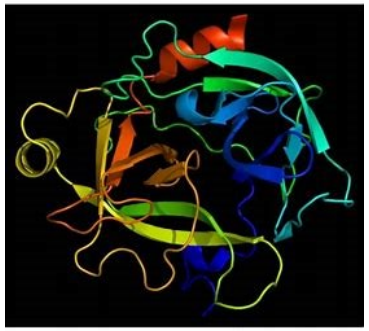
Pharmacodynamics/Target Engagement

LC/MS LBA



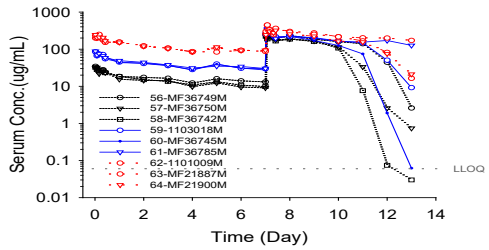
Target/Protein Quant.

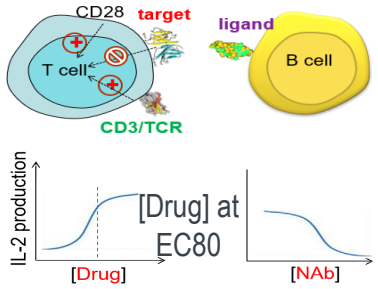
LC/MS LBA



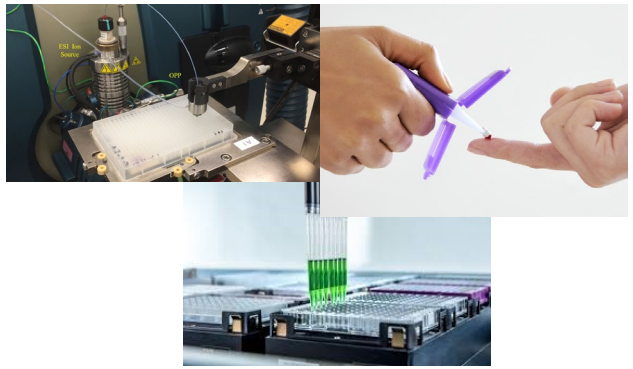
Immunogenicity

Capillary Electrophoresis LBA Cell-Based





New Technologies & Automation



High fidelity quantitative data are a foundation for model informed discovery and development (MIDD) work and decisions

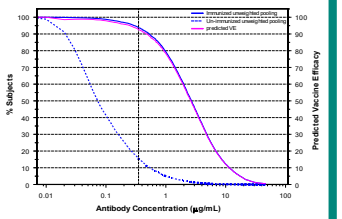
Quantitative Bioanalytical Assays In Support of Vaccines and Oncolytic Virus

DISCOVERY → GLP → CLINICAL

Immunogenicity – Total Antibodies

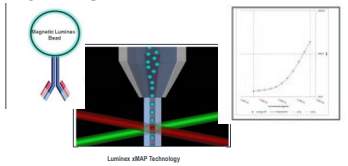
LBA

Correlate of Protection for pediatric PCV (WHO ELISA)

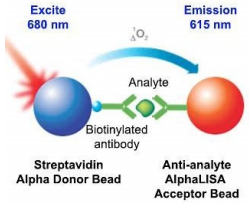


Data from Dr. Kohberger, WHO 2003

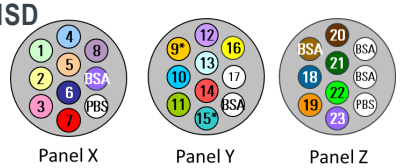
Luminex

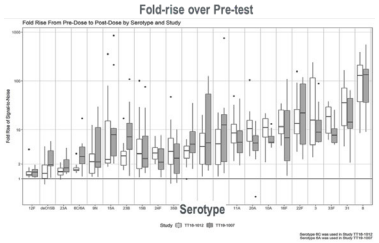


AlphaLISA



MSD

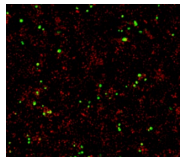




Immunogenicity – Functional Antibodies

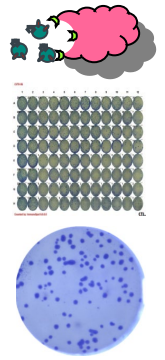
Cell-Based

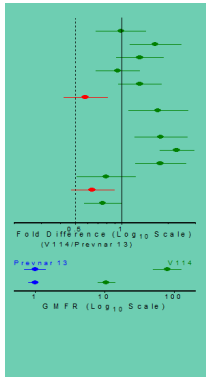
VRNT



Valency of DENV Seropositivity

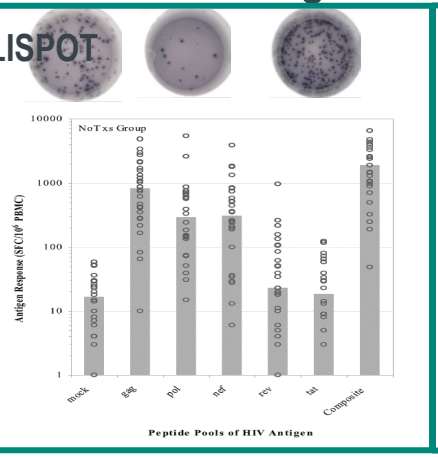
Bacteria + sera (containing **neutralizing antibodies**) + C'



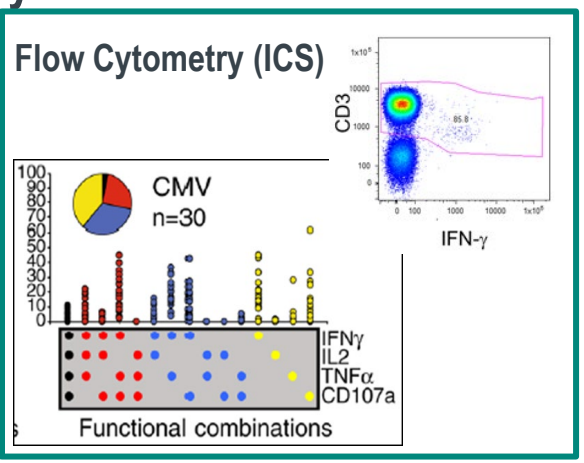


Immunogenicity – Functional T-cell

ELISPOT

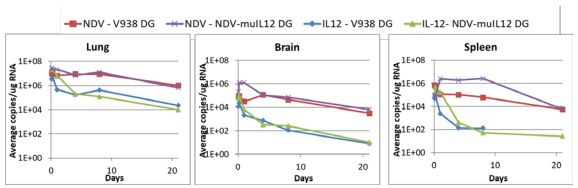


Flow Cytometry (ICS)



Molecular - qPCR

Blood
Brain
Lung
Heart
Kidney
Liver
Gonads
Lymph nodes
Injection Site



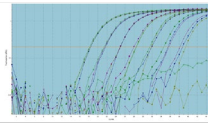


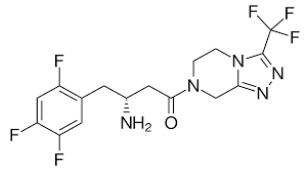
Table 6: Analysis of Efficacy of GARDASIL in the PPE* Population for Vaccine HPV Types

Disease Endpoints	GARDASIL N	GARDASIL Number of cases	AAHS Control N	AAHS Control Number of cases	% Efficacy (95% CI)
16- through 26-Year-Old Girls and Women†					
HPV 16- or 18-related CIN 2/3 or AIS	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)

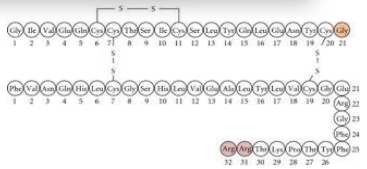
Immunogenicity and molecular data demonstrating a durable response/protection are often a basis for vaccines licensure

Bioanalysis: The Foundation of Drug Discovery and Development

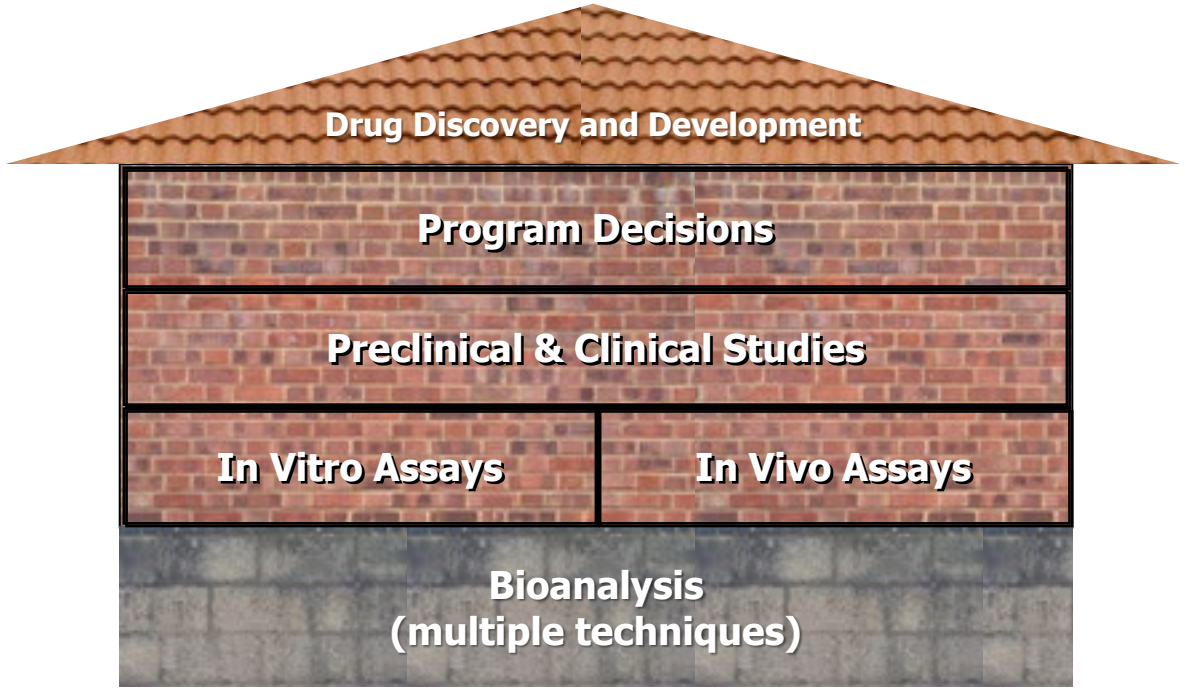
Small Molecules



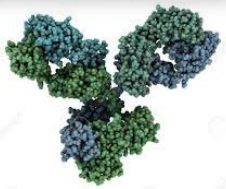
Peptides



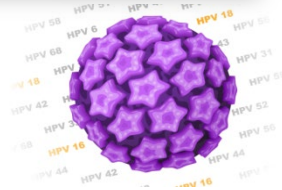
Oligonucleotides



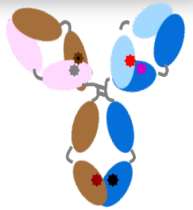
mAbs



Vaccines



Emerging Modalities
(example: Bispecific mAbs)

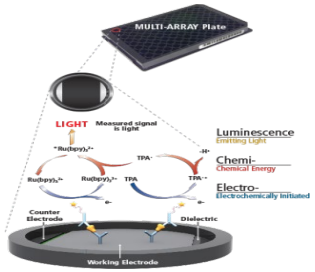


- Bioanalysis, or quantitative analysis, is used in all programs at Merck
- Liquid Chromatography Mass Spectrometry, Ligand Binding Assays, PCR, Cell-based assays, etc.

Bioanalytical Platforms (examples)

Ligand Binding Assays

Meso Scale Discovery



Luminex

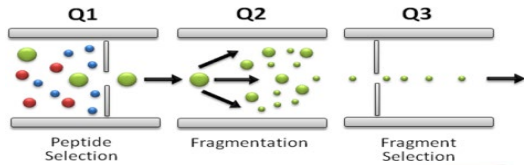
Gyro

CE

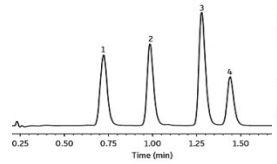
Automation

Deacon Automation System

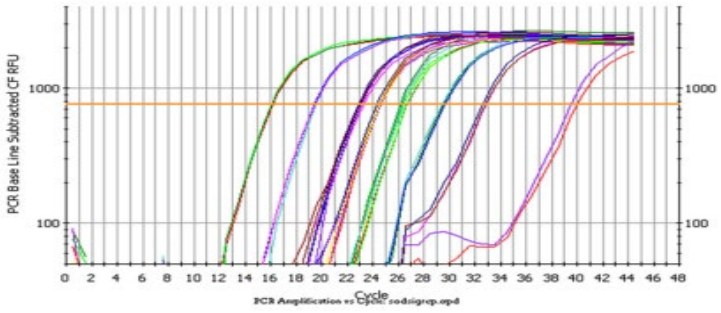
LC-Mass Spectrometry



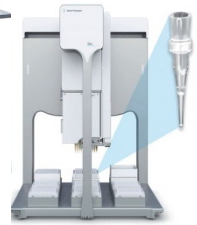
MRM
Orbitrap
TOF
FTICR



PCR/Molecular Based Assays



Hamilton

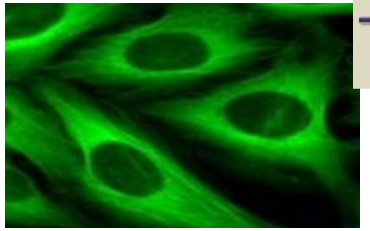


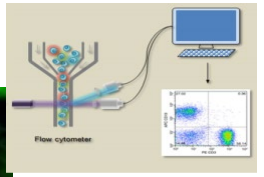
Assay Map

IDOT

Cell Based Assays

Cytation/ EnSight Reader/Imager





LSRFortessa X-20

Academic, Regulatory, and Industry Engagement

Academic collaboration

Merck - Purdue Center for Measurement Sciences

Contributing to New Regulatory Guidance

ICH M10 Comments on guidances

Cross Industry Collaborations

IQ working groups

Organizing External Meetings

APA
ASMS
AAPS
Land O'Lakes

Leadership in the External BA Community

ASMS
AAPS
WRIB

Training the Regulators

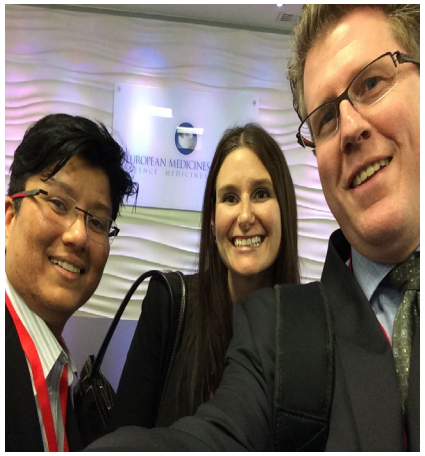
Presenting at FDA programs

Hosting tours for new FDA staff

White Paper Publications

Micro-sampling
Peptide Analysis

AAPS Meeting on **Global harmonization of regulated BA guidelines**



Staff at EMA Discussing Use of DBS

Team at NIFDC
Strengthening our relationship with regulatory authorities in China on vaccine clinical assays

aaps American Association of Pharmaceutical Scientists

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Training and Skillset for a BA Scientist

- A quantitative mindset with training in Analytical Chemistry, Biology, Biochemistry, Cell Biology, Immunology, Molecular Biology, Engineering, etc.
- A passion for new technology and data science
- A team player with strong oral and written communication skills as evidenced by scientific publications and presentations at scientific meetings.
- Successfully be able to provide input into the design of experiments to optimize methods, evaluate new techniques, validate, and trouble-shoot assays and test pre-clinical and/or clinical samples as needed
- Be able to work collaboratively in a fast-paced environment
- Communicate results effectively in presentations to stakeholders in partner organizations or at external scientific meetings, to author technical reports, and to participate on cross-functional teams

Our ability to excel depends on the integrity, knowledge, imagination, skill, diversity and teamwork of our Scientists

MERCK

NDS Introduction

Brian Vega

Brian Vega

Background

University of Notre Dame
B.S. in Biology

Rutgers University
Ph.D. in Biomedical Sciences
Infection, Immunity, & Inflammation

- PI: Scott Kachlany
- Studied mechanisms of leukotoxin-mediated cell death

RUTGERS School of Dental Medicine

RSDM, Postdoctoral fellow
Leukotoxin as a therapeutic agent for treatment of Crohn's disease and Ulcerative Colitis

Actinobac Biomed, Inc.
Nonclinical Consultant
Pharmacology and toxicology support for IND filing

Actinobac Biomed. Inc.

Current role at Merck

Joined Merck in 2020 at West Point

Investigative Toxicology

- Immunotoxicology Group
- NDS lead for pseudoanaphylaxis de-risking strategy
- Mechanistic investigations lead
- Develop animal models for immunotoxicology assessments
- Provide SME input on drug hapten immune activation and T-cell activation
- Program development support
  - Discovery Program Leader
  - Compound Leader

Interests/Other

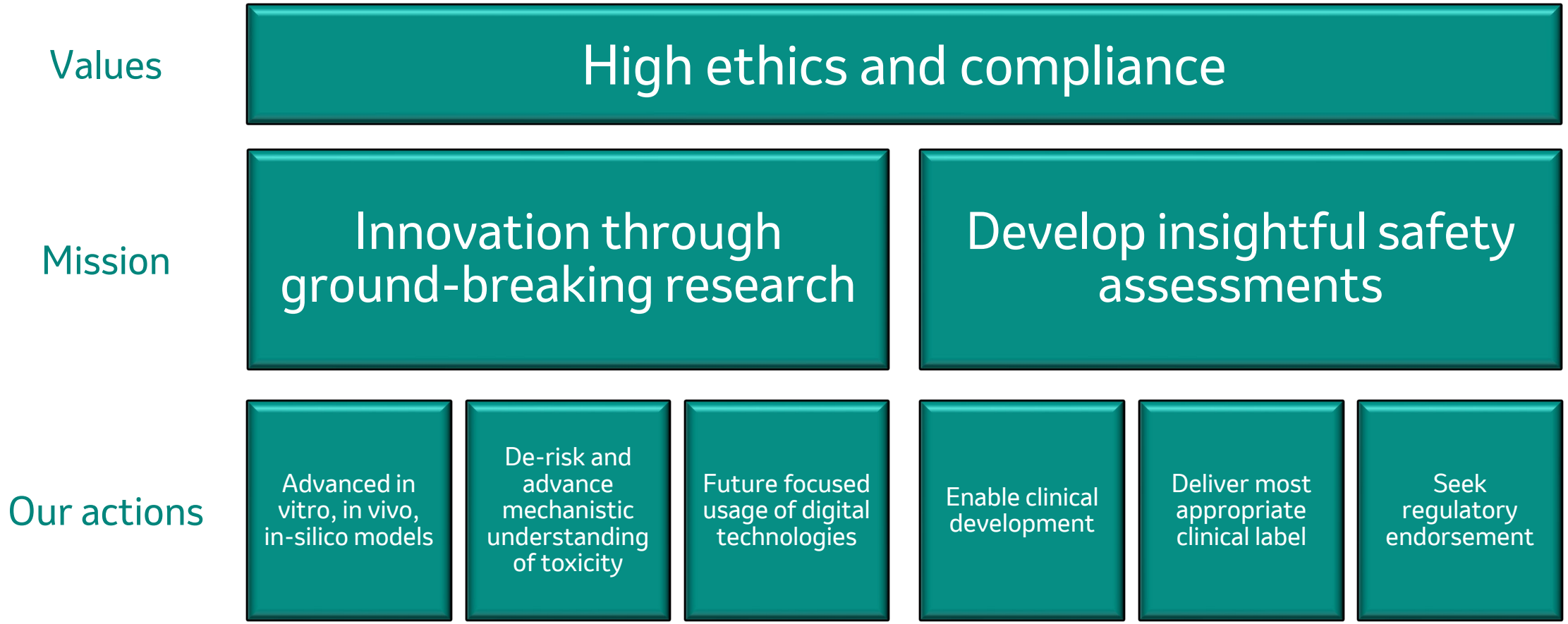
Live in Conshohocken, PA

- Grew up in North Jersey

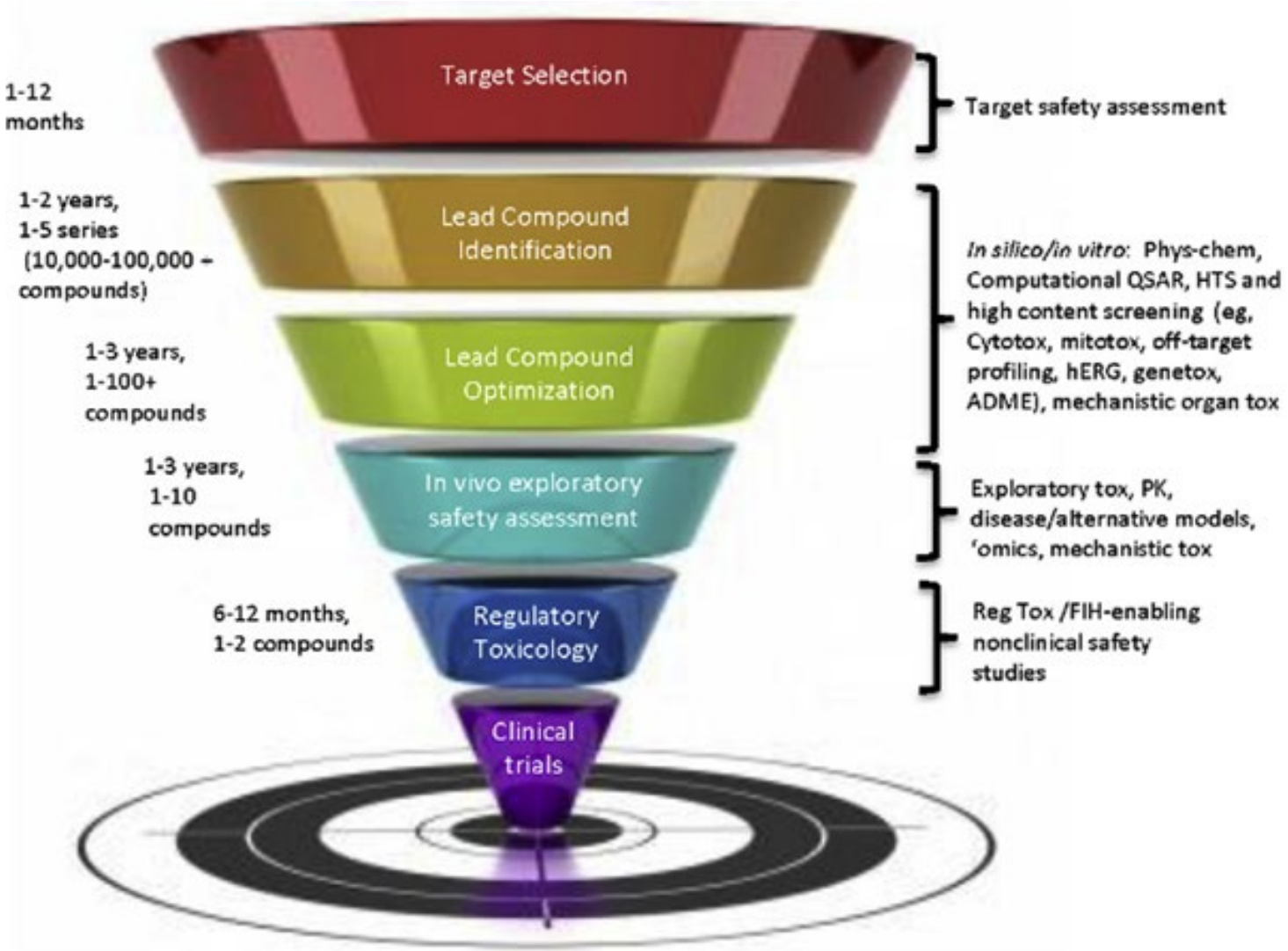
Hobbies:
- Running
- Travel
- Cooking
- Beach
- Avid College Football fan

MERCK

NDS Mission: Discovery and Development of Safe Therapeutics



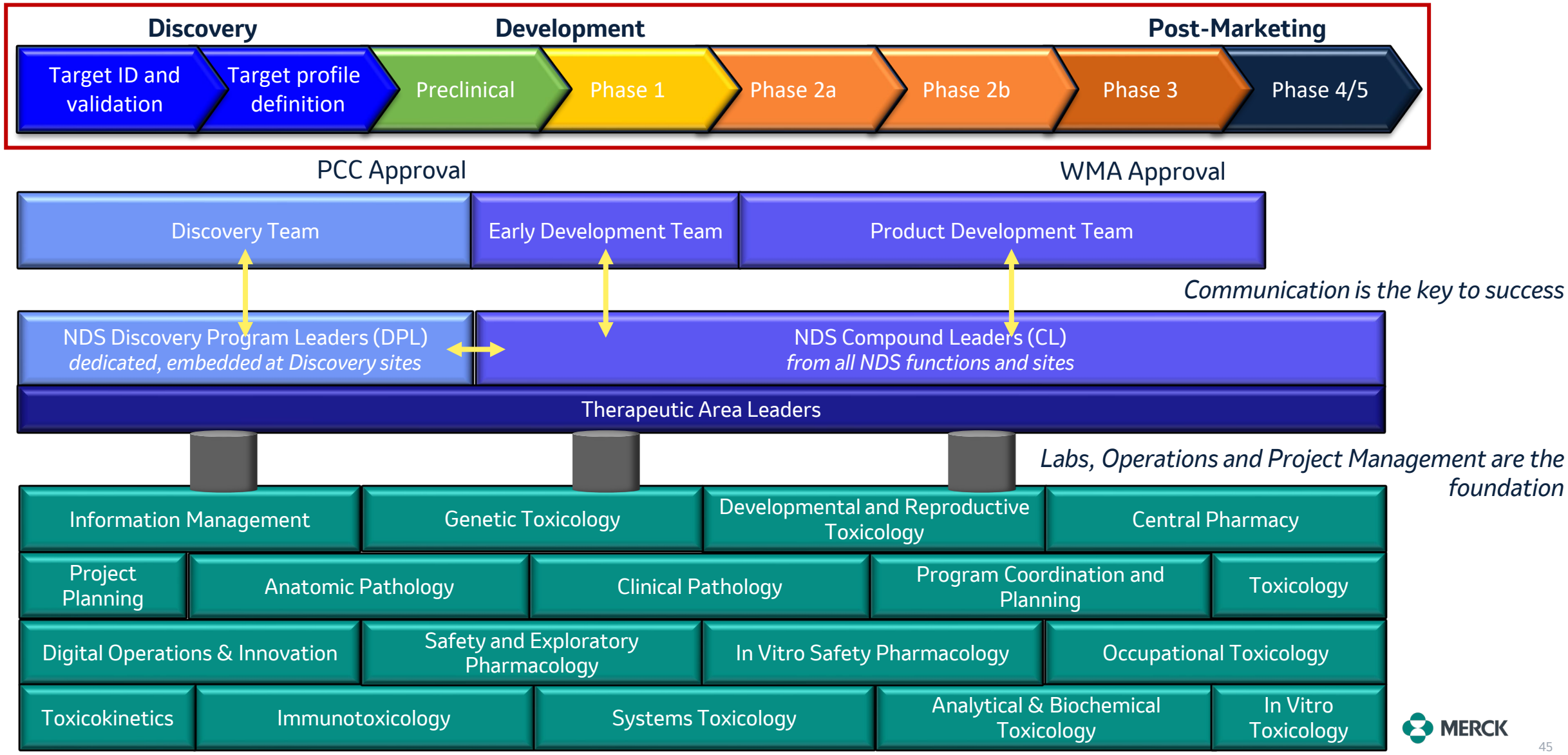
High Attrition Rate of Molecules Before Start of Clinical Trials*



*Source: *Current nonclinical testing paradigms in support of safe clinical trials: An IQ Consortium DruSafe perspective,* Lynne D. Butler et. al, Regulatory Toxicology and Pharmacology 87 (2017) S1 S15

Select molecules with the highest probability of success through early "predictive" screening

Our Integrated and Coordinated Organization Provides High Quality Risk Assessment



NDS Enabling Drug Development

Help to Select Best Drugs, Cheaper, Faster

- Maximize safety attributes of successful Preclinical Candidates (PCCs)

Help to Keep the Right Drugs Alive

- Implement effectual development strategies and effectively communicate risk assessments

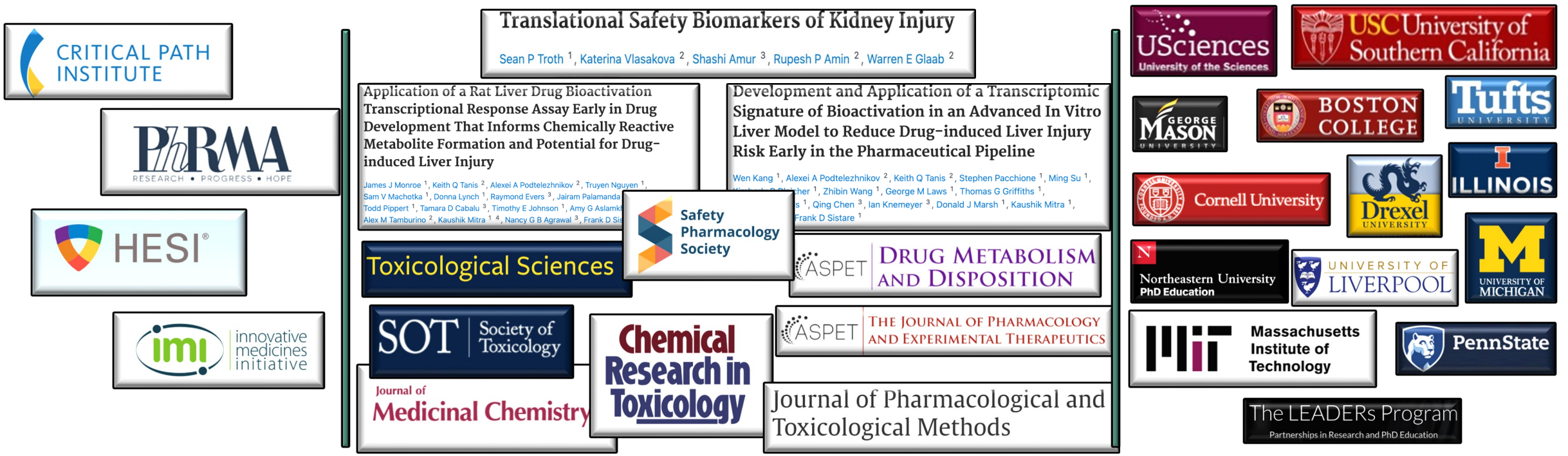
Learn From Failures

- Application of learning from tox-related drug failure

Help Shape the External Environment

- Drive regulatory change through external scientific and regulatory engagement

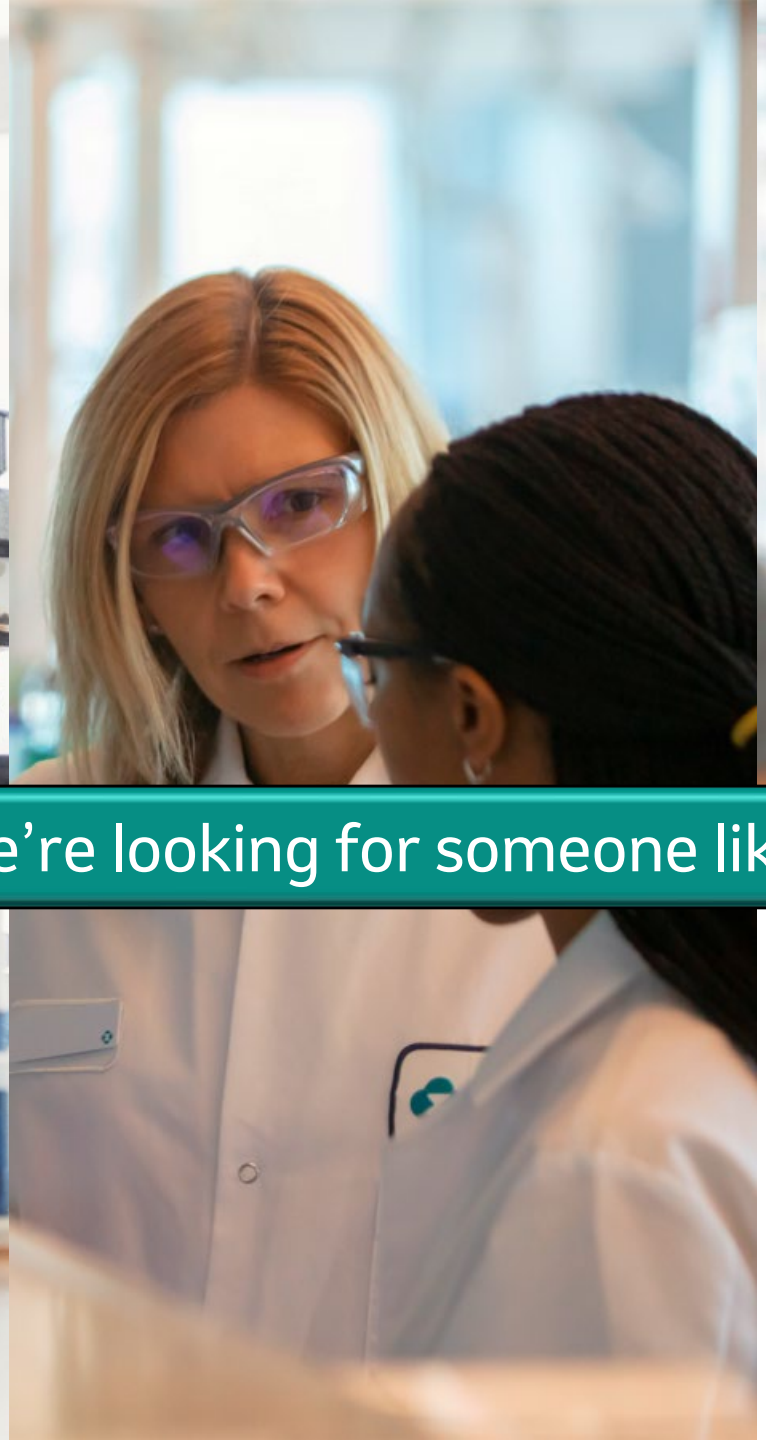
NDS Encouraging Growth through Scientific Contributions



External Consortia & Partnerships

Publications & Awards

Academic Collaborations & Internships


We're looking for someone like you

B.S., B.A., M.S., M.B.A, Ph.D., D.V.M.

Biology
Animal Science
Immunology
Toxicology
Zoology
Pharmacology
Business
Molecular Biology
Biochemistry
Veterinary Pathology
Analytical Chemistry
Data Science
Project Management
Bioinformatics

MERCK

Career Opportunities at Merck

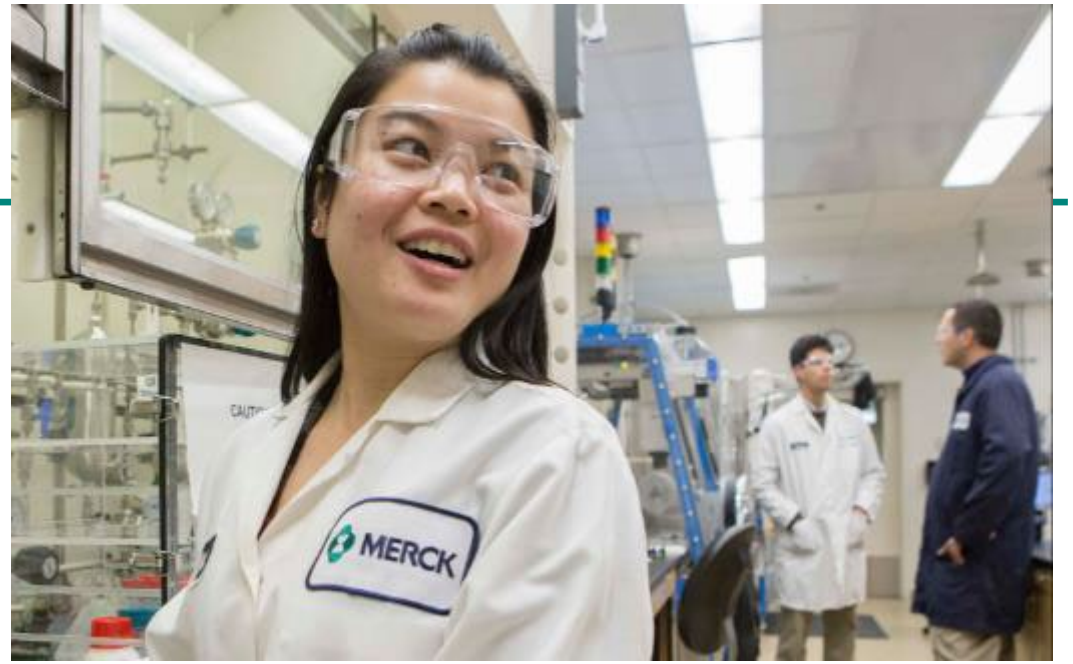
Kerry Fillgrove

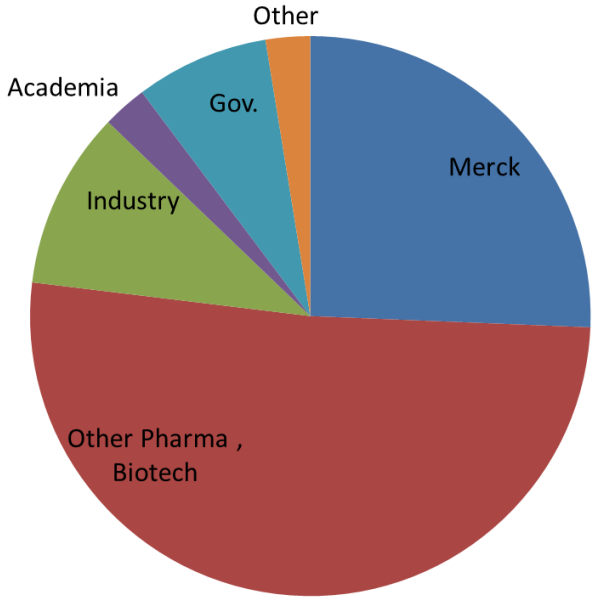
MRL Intern/Co-op Program

- Intern/co-op positions in 4 states (CA, MA, NJ, PA)
- Program is open to undergraduate and graduate students
- Internship: 10 - 12 week assignments between June and August
- Co-Op: 4 - 6 month assignments throughout year
- Intern job posting available late fall with offers extended before April
  - For more info visit: https://www.merck.com/careers/student-opportunities.html
  - Final interview conducted by phone
  - Merck covers travel expenses between school & Merck. Intern/co-op responsible for housing

The MRL Postdoctoral Program

- Program launched in 2012
  - Around 60 postdocs at any time, across all Merck sites
  - 30-36 new postdocs added each year - up to three years duration for each postdoc
- Original research projects in Merck Labs
  - Related to Merck's discovery and development work, but pre-competitive/non-proprietary projects
  - Objective is high profile publications and presentations by the postdoc
- Provides immersion for the postdoc in collaborative industrial research teams
  - an academic focus in a commercial environment
- Positions posted January-March





Postdoc destinations - over 140 alumni have graduated from the MRL postdoc program

MERCK

Finding and Applying for MRL Positions

- Finding open positions:
  - Merck website: https://jobs.merck.com/us/en
  - LinkedIn: https://www.linkedin.com/company/merck/careers
  - Twitter: @MerckIMInspired
- Resumes and applications are only processed and screened through our online Workday portal
- You will receive a confirmation email when your application is submitted

Contact Information for Merck Participants

Kerry Fillgrove, Ph.D.	Absorption, Distribution, Metabolism, and Excretion (ADME)	kerry_fillgrove@merck.com
Nicole Revaitis, Ph.D.	Bio-analytics (BA)	nicole.revaitis@merck.com
Brian Vega, Ph.D.	Nonclinical Drug Safety (NDS)	brian.vega@merck.com
Xiaowei Zang, Ph.D.	Quantitative Pharmacology & Pharmacometrics (QP^2)	xiaowei.zang@merck.com

Breakout Sessions

Three major topics but please feel free to discuss any topics you would like

- General Question about Merck – All
- Applying for Jobs at Merck, Resumes, Networking & beyond - All
- What is our role in ADME and How do we interact with our partner functions at Merck? - Kerry
- What is our role in NDS and How do we interact with our partner functions at Merck? - Brian
- What is our role in BA and How do we interact with our partner functions at Merck? - Nicole
- What is our role in QP2 and How do we interact with our partner functions at Merck? - Xiaowei
- Interview tips from hiring manager – Kerry
- Employee Business Resource Groups (EBRG) – Xiaowei
- Internship/Post-doc – Brian/Xiaowei

THANK YOU FOR YOUR PARTICIPATION!