Advancing the toxicology toolbox using predictive, human in-vitro 3D models

Predictive Toxicology Roadmap Hearing

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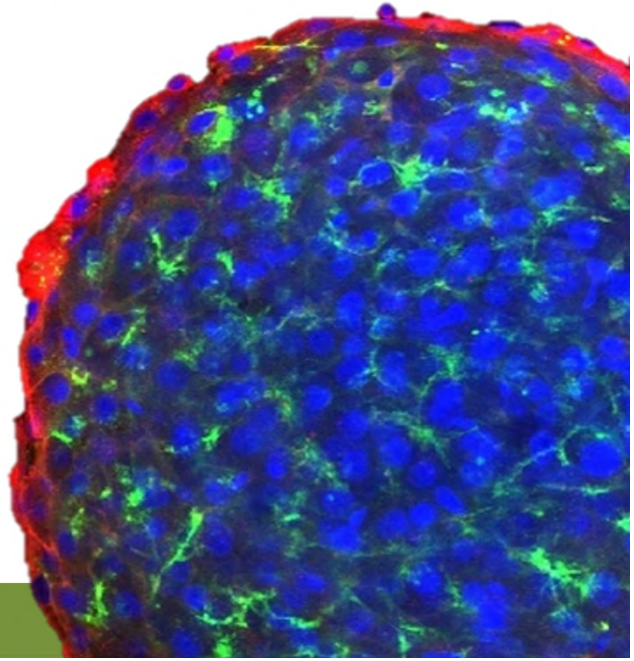
September 12, 2018



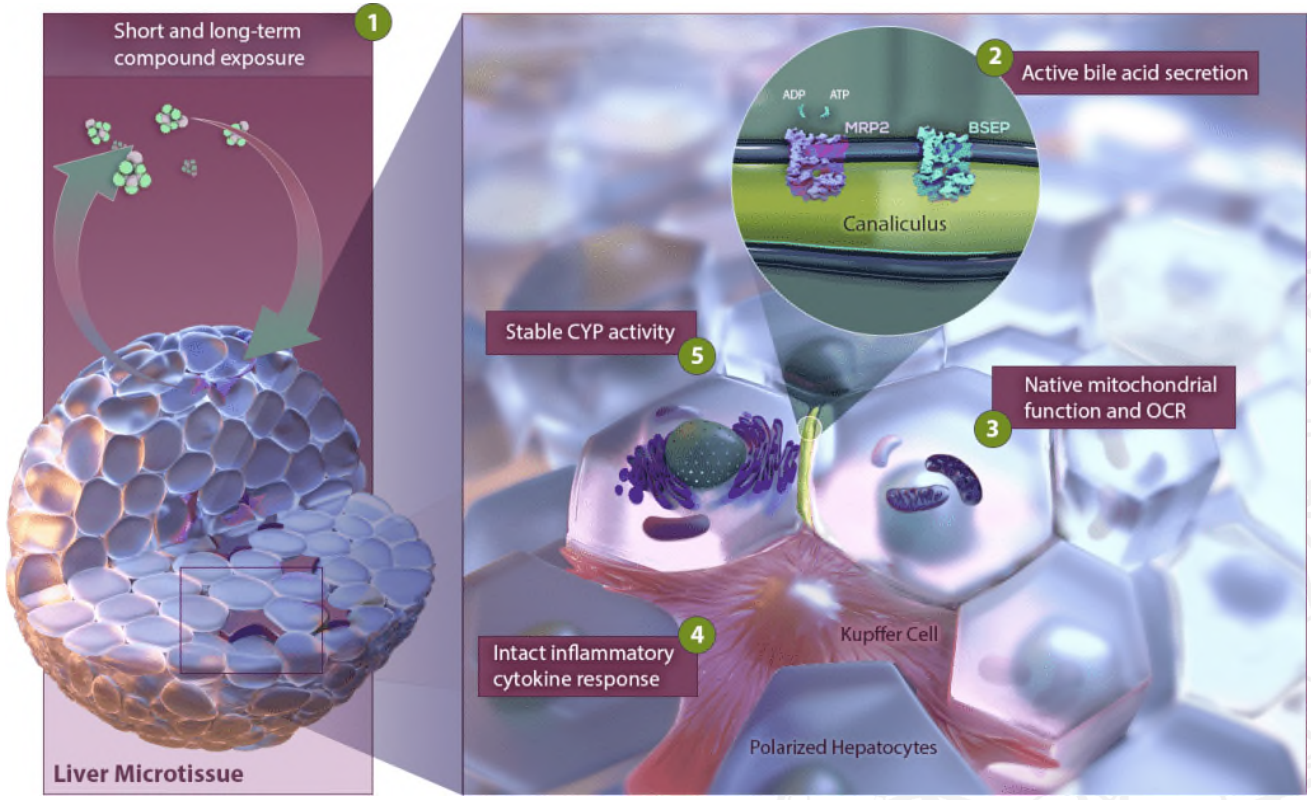
In-vitro liver models: State of the art

- Wide variety of technologies
  - Scaffold-free and gel-based 3D liver microtissues
  - Co-cultures (multiple donors, non-parenchymal cells)
  - Primary cells, IPS cells
  - Scalable up to 384-well format

- Substantial achievements
  - 2x improvement of sensitivity for liver-toxic compounds
  - No compromise on specificity
  - Long-term, multiple dose treatments
  - Toxic effect on diseased liver microtissues (inflammation, steatosis)

Industry-grade, robust and validated liver toxicology models are readily available

InSphero's 3D InSight™ Liver Microtissues



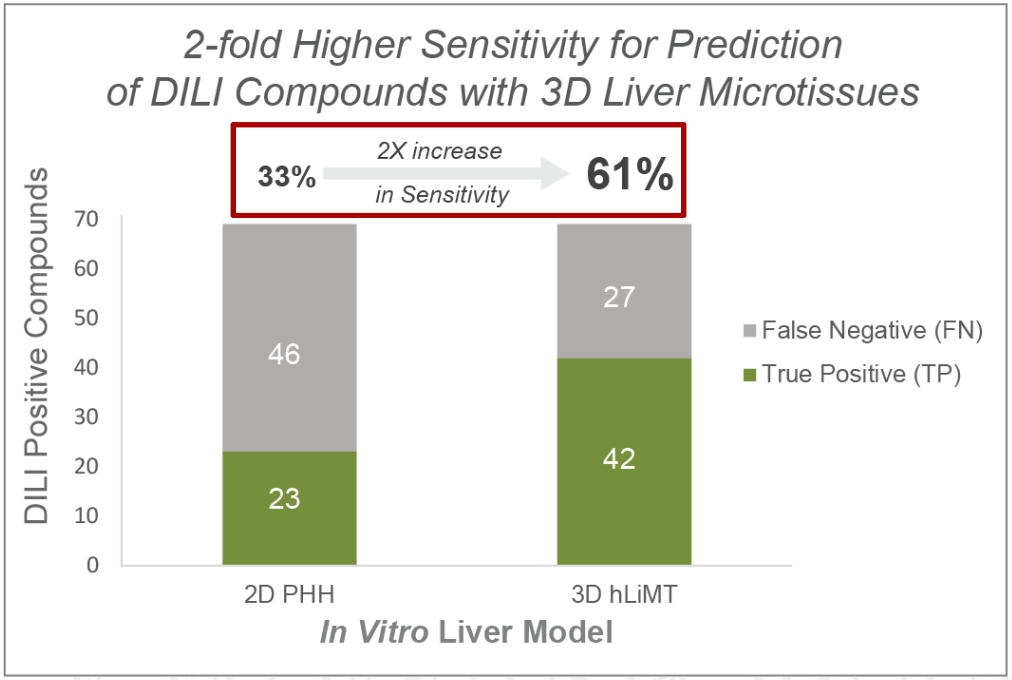
Substantial validation:

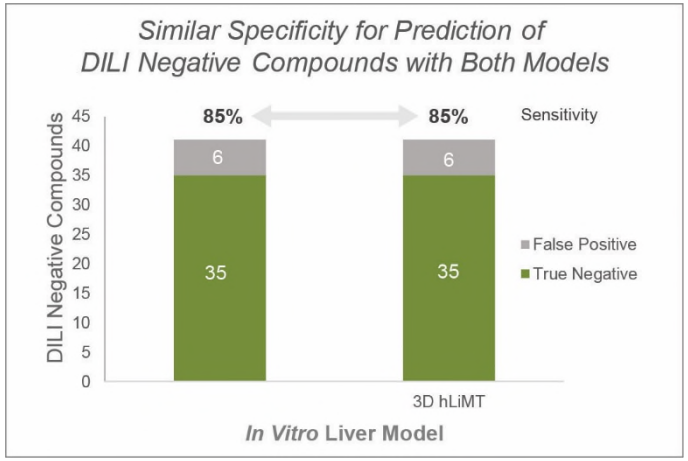
- **DILI prediction**
  Proctor et al (2017) Arch Toxicol
- **Mechanistic toxicology**
  Paech et al (2017) Arch Toxicol
- **Nanotoxicology**
  Kermanizadeh et al (2014) PFT

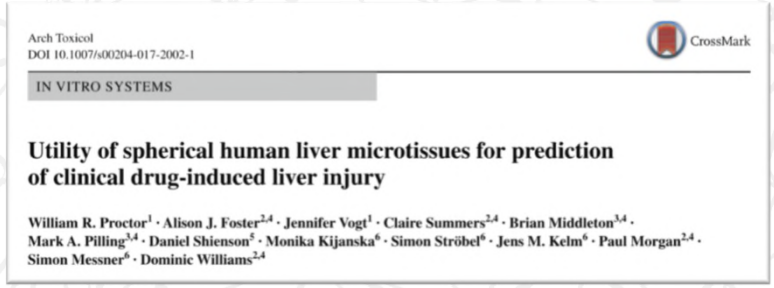
Other models:
Ascendance (Hepregen)
CN Bio
Organovo
Hurel

Success study: Genentech and AstraZeneca

- **3D InSight™ Liver Tissues were 2-fold more sensitive** in identifying known hepatotoxicants in comparison to 2D
- **Specificity for prediction of non-DILI drugs remained very high** (>85%), even after 14 days of compound exposure






Arch Toxicol
DOI 10.1007/s00204-017-2002-1

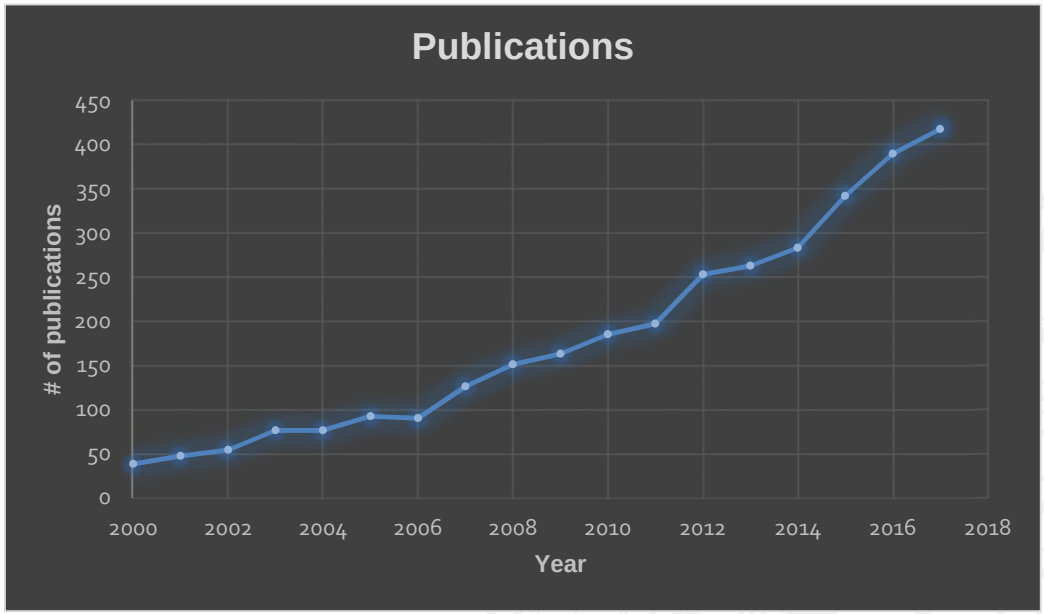
IN VITRO SYSTEMS

Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury

William R. Proctor[1] · Alison J. Foster[2,4] · Jennifer Vogt[1] · Claire Summers[2,4] · Brian Middleton[3,4] · Mark A. Pilling[3,4] · Daniel Shienson[5] · Monika Kijanska[6] · Simon Ströbel[6] · Jens M. Kelm[6] · Paul Morgan[2,4] · Simon Messner[6] · Dominic Williams[2,4]

In-vitro liver models: Adoption

- Rapid increase of PubMed publication on 3D liver models



- But: Adoption in the pharmaceutical/biotech environment is <u>still low</u>
  - An estimated 20% of the top 50 pharmaceutical companies used 3D liver models for toxicology testing routinely

Obstacles: Characterization/validation

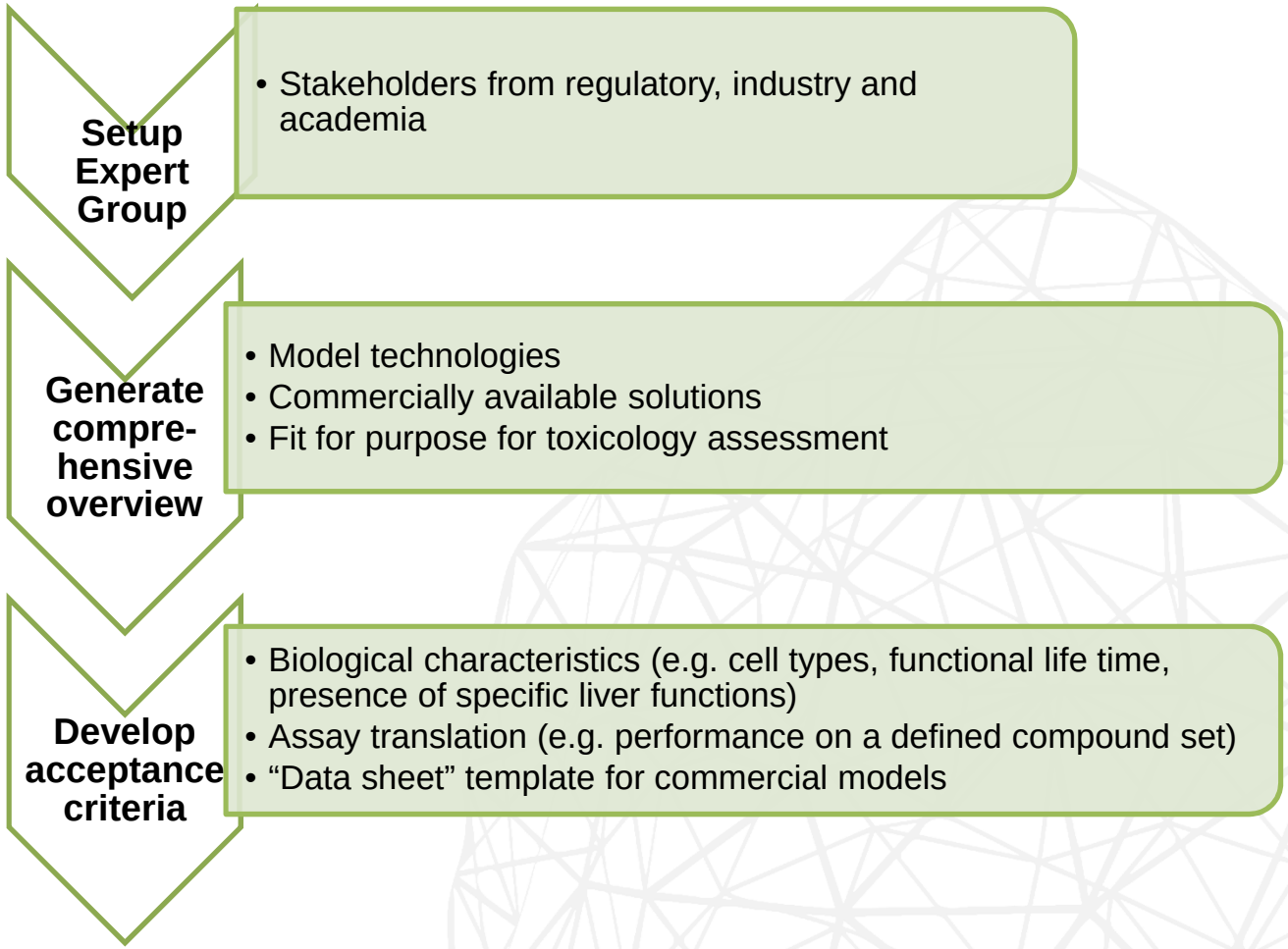
- Characterization not comparable between models
- No agreed validation guidelines
  - Compound sets
  - End points
  - Exposure times
  - Clinical reference frame
- Acceptance and rejection criteria for truly predictive models remain undefined

Obstacles: Uncertain assay parameters

- Advanced models require agreement on more assay parameters than classical tools
  - Cell types
  - Tissue size
  - Medium conditions
  - Exposure time
  - Number of medium exchanges and re-dosings
  - Read outs and end points
  - Controls
  - Reference compounds

Predictive Toxicology Roadmap Suggestions I

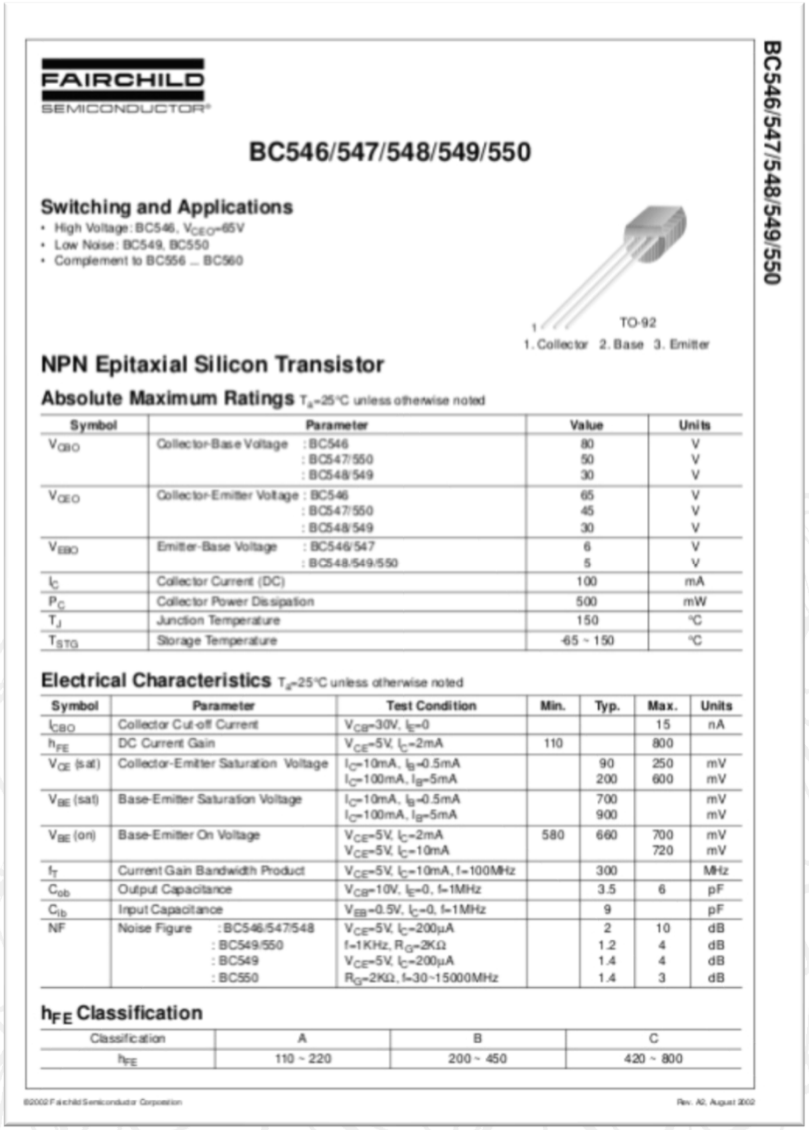
- Developing model- and vendor-independent acceptance criteria



Roadmap parts D and E, plus C

“Data sheet” for liver models

- Objective:
  Provide comparative performance data in a standardized, easy-to-use document
- Comparable to electronic components



FAIRCHILD SEMICONDUCTOR®

BC546/547/548/549/550

BC546/547/548/549/550

Switching and Applications

- High Voltage: BC546, V_{CEO}=65V
- Low Noise: BC549, BC550
- Complement to BC556 ... BC560

TO-92

1. Collector 2. Base 3. Emitter

NPN Epitaxial Silicon Transistor

Absolute Maximum Ratings T_a=25°C unless otherwise noted

Symbol	Parameter		Value	Units
V_{CBO}	Collector-Base Voltage	: BC546	80	V
		: BC547/550	50	V
		: BC548/549	30	V
V_{CEO}	Collector-Emitter Voltage	: BC546	65	V
		: BC547/550	45	V
		: BC548/549	30	V
V_{EBO}	Emitter-Base Voltage	: BC546/547	6	V
		: BC548/549/550	5	V
I_C	Collector Current (DC)		100	mA
P_C	Collector Power Dissipation		500	mW
T_J	Junction Temperature		150	°C
T_{STG}	Storage Temperature		-65 ~ 150	°C

Electrical Characteristics T_a=25°C unless otherwise noted

Symbol	Parameter		Test Condition	Min.	Typ.	Max.	Units
I_{CBO}	Collector Cut-off Current		V_{CB}=30V, I_E=0			15	nA
h_{FE}	DC Current Gain		V_{CE}=5V, I_C=2mA	110		800	
V_{CE} (sat)	Collector-Emitter Saturation Voltage		I_C=10mA, I_B=0.5mA		90	250	mV
			I_C=100mA, I_B=5mA		200	600	mV
V_{BE} (sat)	Base-Emitter Saturation Voltage		I_C=10mA, I_B=0.5mA		700		mV
			I_C=100mA, I_B=5mA		900		mV
V_{BE} (on)	Base-Emitter On Voltage		V_{CE}=5V, I_C=2mA	580	660	700	mV
			V_{CE}=5V, I_C=10mA			720	mV
f_T	Current Gain Bandwidth Product		V_{CE}=5V, I_C=10mA, f=100MHz		300		MHz
C_{ob}	Output Capacitance		V_{CB}=10V, I_E=0, f=1MHz		3.5	6	pF
C_{ib}	Input Capacitance		V_{EB}=0.5V, I_C=0, f=1MHz		9		pF
NF	Noise Figure	: BC546/547/548	V_{CE}=5V, I_C=200μA		2	10	dB
		: BC549/550	f=1KHz, R_G=2KΩ		1.2	4	dB
		: BC549	V_{CE}=5V, I_C=200μA		1.4	4	dB
		: BC550	R_G=2KΩ, f=30~15000MHz		1.4	3	dB

h_{FE} Classification

Classification	A	B	C
h_{FE}	110 ~ 220	200 ~ 450	420 ~ 800

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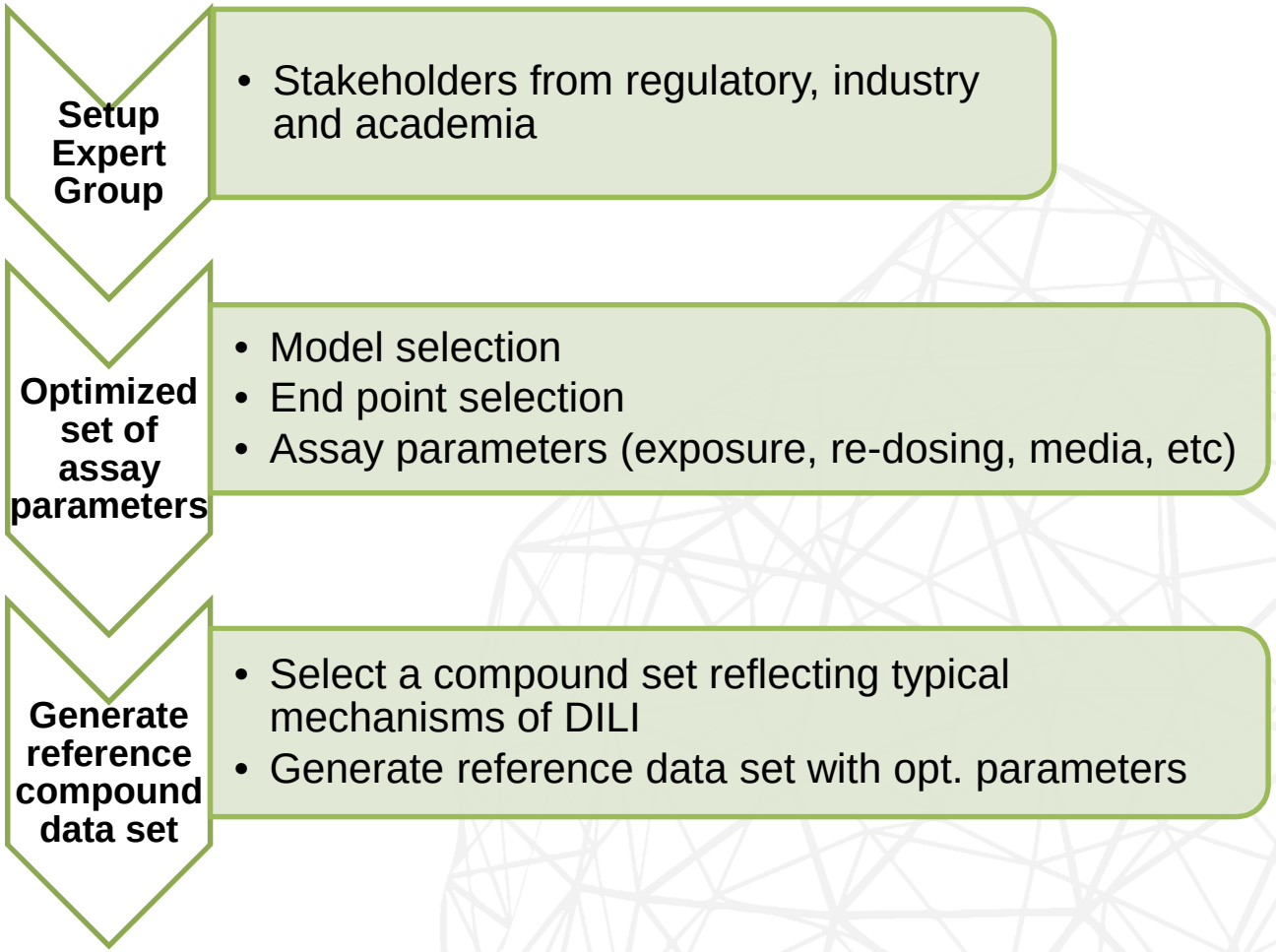
Rev. A2, August 2002

Predictive Toxicology Roadmap Suggestions II

- Developing model-specific assay guidance



Roadmap parts D and E, plus C

Thank You