

De-risking drug development – a novel *in chip* technology to implement cyclic feedback interfaces between drug discovery and drug development

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Background

Current drug discovery/development is a linear and sequential process whereby each succeeding step in the development of a potential new compound starts only when the previous phase has successfully been passed. More effective drug development models suggest a cyclic feed back/forward loop to increase efficacy of the process and consequently reduce costs substantially ("Quick win, fast fail", see Paul et al., Nature Reviews Drug Discovery 2010).

Results

Up till now this promising theoretical construct was not implemented in drug development successfully due to the lack of a reliable and accurate test system to validate newly discovered leads. abc biopply has developed a novel approach to test new compounds fast, reliably and with very high accuracy. The presented results show an increase in predictiveness of efficacy at later stages and consequently a substantial reduction in failure rates. The abc biopply *in chip* technology fulfills the FDA guidelines for microphysiological systems and takes drug development to the next level. It eliminates animal testing to a large extent, reduces costs and increases speed in the validation cycling of new compounds.

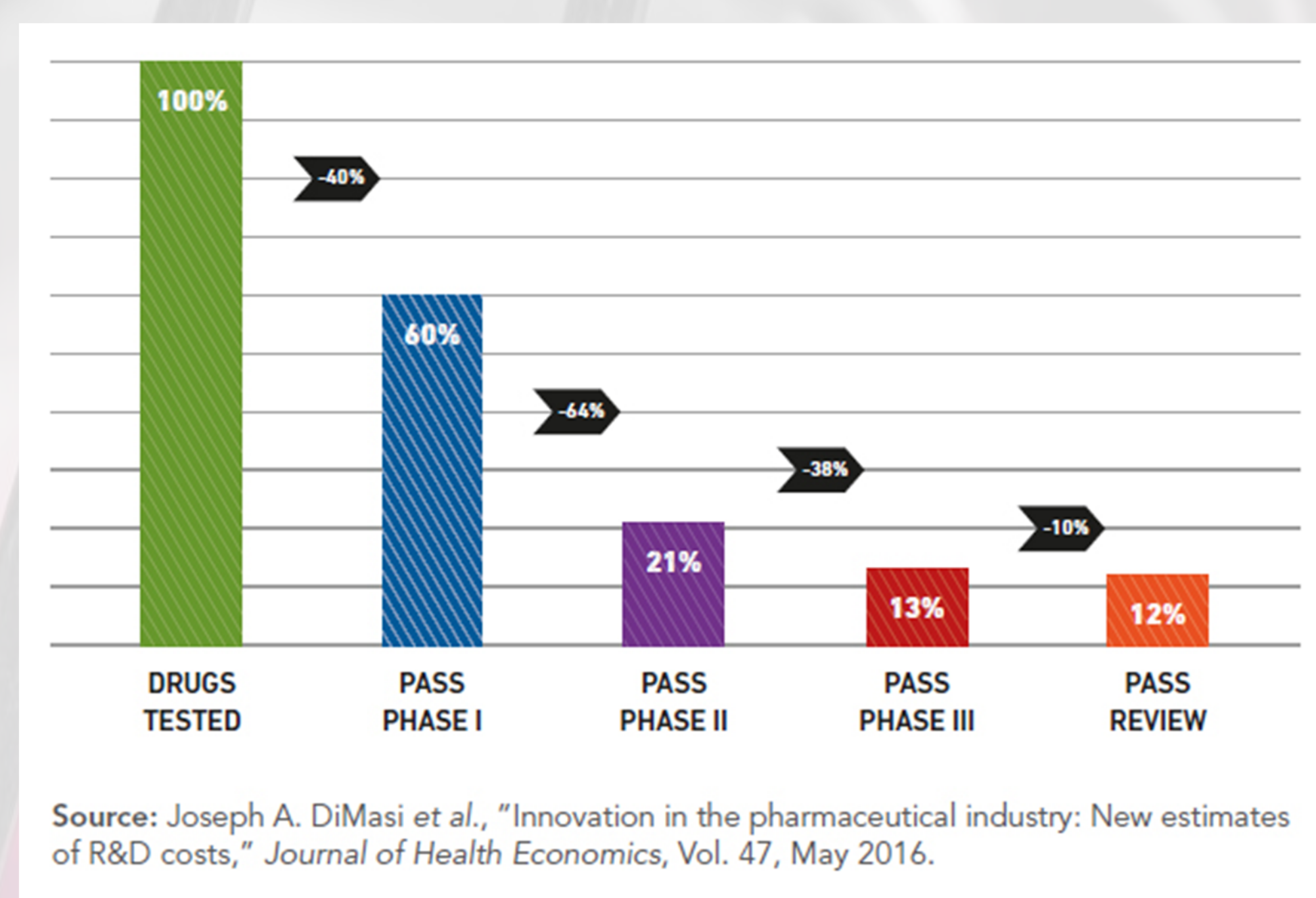


Figure 1: The process for commercializing preclinically confirmed drugs currently has a success rate of only about 12%.

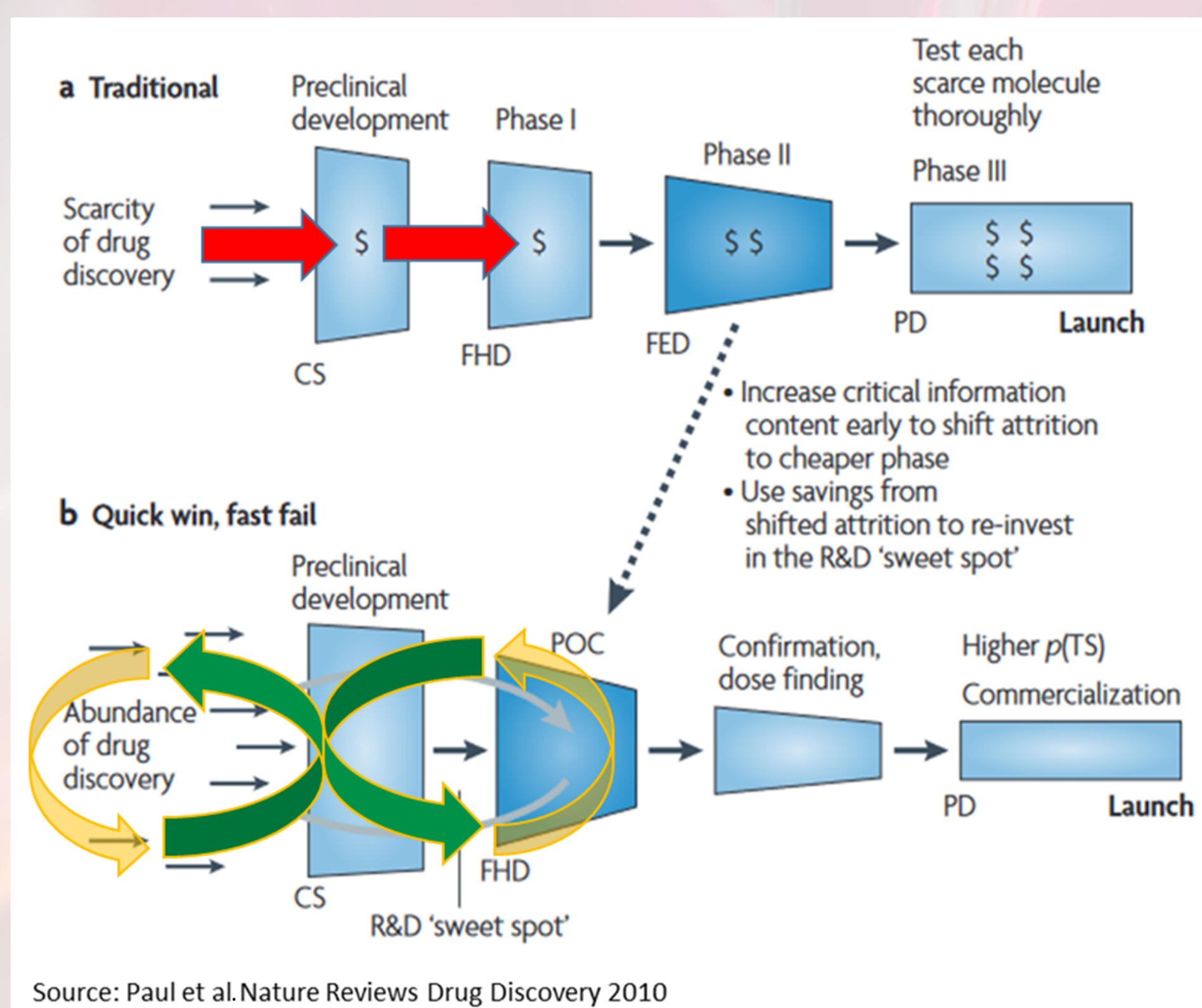


Figure 2:

→ **Traditional:** Linear interface between drug discovery and drug development

- Only a limited number of input components
- Ineffective preselection in 2D cell models
- Full discovery load on pdx models
- Non-cyclic process without feedback output
- PC only time: 1-4 years
- PC only costs: ca. 150 Mio

↻ **abc biopply:** Cyclic feedback interface between drug discovery and drug development

- Technology 1: Fast creation of high number of input variants
- Technology 2: Fast and effective preselection in physiological 3D *in chip* model (FDA certified microphysiological system)
- Confirmatory character of pdx models
- High level of standardization leads to improved predictiveness at higher feedback cycles
- PC only time: 3-6 months
- PC only cost: 1.5 Mio

Criteria	Validation of predictiveness values of new <i>in chip</i> preclinical models			
	Existing Commercialized ADC			
	2D cell culture results (n=3-6)	conventional 3D cell culture results (n=5x1)	small and large animal results (n=1-6)	3D <i>in chip</i> assay results (n=3x500)
Serum Stability	76% (NHS 37°C)	nd	nd	tbd
Target Binding Specificity	positive	positive	nd	positive
Cytotoxic IC ₅₀ (nM)	0.907 ¹ /24.8 ² (0.98 own 2D data)	0.04 - 17.26 ³	nd	6.8
Tumor Growth Inhibition (50% after x days at dose)	4 days at 10/16/42 mg/kg	20 days at >30 ¹ / <60 ¹ mg/kg	20 days at 10 mg/kg	8 days at 1 mg/kg
Tumor Relapse Inhibition	no model available	no model available	no model available	Relapse Inhibition negative at 3-5 mg/kg
Resulting Anti-Tumor Dosage recommendation (mg/kg)	not conclusive	15 / 32 ¹	>3 ¹ / >5 ⁴ / >10 ²	>5
Off-Target Toxicity Liver / Kidney (mg/kg)			>3 / nd	>10 / >20
Systemic Toxicity				nd
Effective nontoxic dosing range recommendation (mg/kg)				>5 / <10
Definitive Clinical Dosage			3x3 mg/kg (9 mg/kg)	3x3 mg/kg (9 mg/kg)

Figure 3: green = predictiveness high, yellow = non conclusive

1 Tumor Extrinsic Factors Mediate Primary T-DM1 Resistance in HER2-Positive Breast Cancer Cells, Yukinori Endo and Wen Jin Wu, Cancers 2021, 13, 2331

2 Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor, Yusuke Ogitani et al., Cancer Sci 107 (2016) 1039–1046

3 Activity of trastuzumab emtansine (T-DM1) in 3D cell culture, Jean Zheng Boyer et al., Breast Cancer Research and Treatment (2021) 188:65–75

4 Clinical pharmacology strategies in supporting drug development and approval of antibody–drug conjugates in oncology, Stephanie N. Liu, Chunze Li, Cancer Chemotherapy and Pharmacology (2021) 87:743–765

Criteria	New generation anti-HER2 ADC preclinical study results (<i>in chip</i> study model)					
	New anti-HER2 ADC vs Reference ADCs					
	ENHERTU® Reference Results	Kadcyla® Reference Results	Kadcyla® <i>in chip</i> Results	New ADC <i>in chip</i> Results	New ADC vs ENHERTU®	New ADC vs Kadcyla®
Serum Stability	2 years at 8°C	76% (NHS 37°C)	nd	tbd	nd	nd
Target Binding Specificity	positive	positive	positive	positive	comparable	comparable
Cytotoxic IC ₅₀ (nM)	4	6.71	6.8	0.81	superior	superior
Tumor Growth Inhibition (50% after x days at dose y)	20 days at 3 mg/kg	20 days at 10 mg/kg	8 days at 1 mg/kg	5 days at 1 mg/kg	superior	superior
Tumor Relapse Inhibition	no model available	no model available	Relapse Inhibition negative at 3-5 mg/kg	Relapse Inhibition positive at 1 mg/kg	nd	superior
Resulting Anti-Tumor Dosage recommendation (mg/kg)	3 / <10	>3 / >10	>5	>1	superior	superior
Off-Target Toxicity Liver / Kidney (mg/kg)	>10 / >20	>3 / nd	>10 / >20	>3 / >10	comparable	superior
Systemic Toxicity (Rat LD mg/kg)	197	nd	nd	on demand	nd	nd
Effective nontoxic dosing range recommendation (mg/kg)	3 to 10	non conclusive	5 to 10	1 to 3	superior	superior
Definitive Clinical Dosage	Breast 5.4 mg/kg Lung 10 mg/kg	3x3 mg/kg (9 mg/kg)	3x3 mg/kg (9 mg/kg)	nd		

Figure 4: Results Pilot Study

Conclusion

The novel *in-chip* technology of abc biopply shows superior predictiveness of preclinical study results against conventional 2D and 3D models. The new technology is fast, reliable and cost effective and will help to reduce animal testing substantially. Enabling the drug development process to become cyclic will effectively help pharma companies to de-risk their drug development process.