InVEST44™ is a Cost-Effective In Vitro Safety Panel That Identifies Off-Target Effects in Early-Stage Drug Discovery

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Introduction

Drug development costs exceed $172m and increase to over half a billion dollars when clinical trial failures are taken into account[1]. It can take up to 20 years to successfully bring a drug to market, so it is critical to identify any safety liabilities early in the drug discovery process to ensure valuable time and money are not invested unnecessarily in time-consuming and expensive preclinical animal and clinical trials.

Despite the importance of identifying safety liabilities early in drug discovery, over the past 2 decades, the proportion of venture capital investments in early stage (including in vitro safety panels) has decreased from **50%** (2006) to **16%** (2023) while increasing for later stage (including clinical trials) from **20%** to **54%**[2,3]. This indicates an understandable trend towards expensive, **high-risk** but potentially lucrative, clinical trials.

The goal of this study is to demonstrate that early-stage in vitro safety panels are still critical steps in the drug development process both fiscally and scientifically as these identify off-target effects of drug candidates before advancing to expensive and time-consuming animal and human testing.

Methods

- 20 drug candidates from failed oncology clinical trials (2001-2025)[6]
  - Reason for termination: **severe adverse effects**
- Compounds screened at 10 µM against 44 safety liability targets in InVEST44™ and 70 kinases in Diversify™
- Table 1 lists the targets for **InVEST44™ in green**.

Target families include:
- G-protein coupled receptors (GPCRs)
- Ion channels
- Transporters
- Nuclear receptors
- Kinases
- Other enzymes

Assay types include:
- Competitive radioligand binding
- Fluorescence polarization
- Manual patch electrophysiology
- FLIPR calcium mobilization
- Cell reporter
- Enzymatic activity
- ADP-Glo

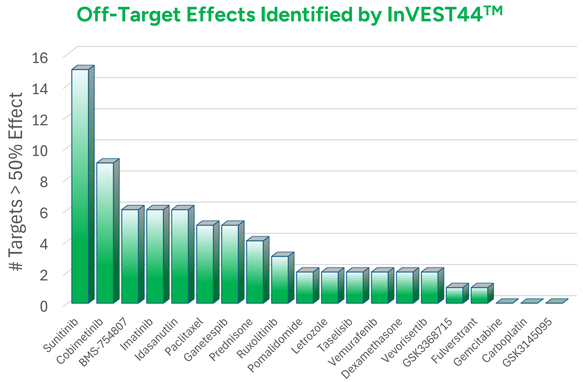
InVEST™ In Vitro Safety Suite

At Reaction Biology we offer a suite of in vitro safety panels – **InVEST18™, InVEST44™, InVEST59™ and InVEST77™** - providing an opportunity to identify potential toxicities of lead compounds in a cost-effective manner and at an early stage in drug development.

The targets selected for **InVEST18™, InVEST44™, InVEST59™** and **InVEST77™** are based on surveys across 4 major pharmaceutical companies[4] and 18 companies overseen by IQ DruSafe[5]. These targets are crucial in both core systems (CNS, CV, respiratory) and secondary organs (GI, renal).

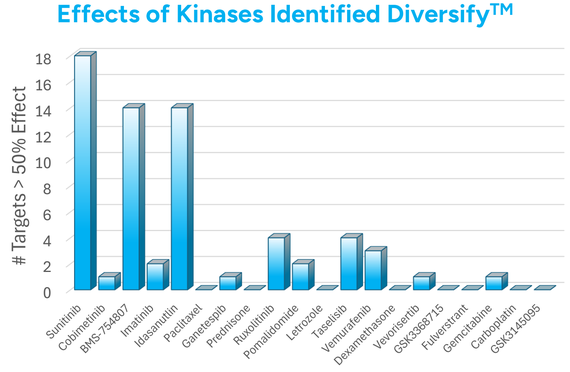
Results

Failed clinical trial candidates exhibit off-target safety liabilities in InVEST44™ panel



17 of the 20 drugs elicited >50% effect on at least 1 target in the InVEST44™ panel, including 8 with 4+ target interactions. One drug candidate interacted significantly with 15 safety targets.

Failed clinical trial candidates exhibit multiple kinase interaction in kinase Diversify™ panel



12 of the 20 drugs elicited >50% effect on at least 1 target in the Diversify™ panel, including 5 with 4+ target interactions. One drug candidate interacted significantly with 18 kinase targets. The Diversify™ panel comprises 70 kinases selected to represent multiple kinase families.
For a complete list of targets, see https://www.reactionbiology.com/list-kinase-targets-us-facility/?panel=Diversify%20Panel

InVEST™ Targets

Target Family	InVEST18	InVEST44	InVEST59	InVEST77
Kinase			ATM	ATM
			AURKA	AURKA
			AURKB	AURKB
			BRD4	BRD4
			EGFR	EGFR
			FGFR1	FGFR1
			FLT1	FLT1
			GSK3B	GSK3B
			INSR	INSR
			KDR	KDR
			KIT	KIT
	Lck	Lck		Lck
			MAP2K7	MAP2K7
			NTRK1	NTRK1
			PDK1	PDK1
			PIK3CG	PIK3CG
			PTK2	PTK2
			ROCK1	ROCK1
			ROCK2	ROCK2
			SRC	SRC
			STK35	STK35

Target Family	InVEST18	InVEST44	InVEST59	InVEST77
GPCR		ADORA2A	ADORA2A	ADORA2A
	ADRA1A	ADRA1A		ADRA1A
		ADRA2A	ADRA2A	ADRA2A
		ADRB1	ADRB1	ADRB1
	ADRB2	ADRB2		ADRB2
	CNR1	CNR1		CNR1
		CNR2	CNR2	CNR2
		CCK1	CCK1	CCK1
			CCK2	CCK2
	D1	D1		D1
		D2	D2	D2
			D3	D3
		ETA	ETA	ETA
			GPBAR1	GPBAR1
	H1	H1		H1
		H2	H2	H2
		OPRD1	OPRD1	OPRD1
		OPRK1	OPRK1	OPRK1
	OPRM1	OPRM1		OPRM1
		CHRM1	CHRM1	CHRM1
		CHRM2	CHRM2	CHRM2

Target Family	InVEST18	InVEST44	InVEST59	InVEST77
GPCR	CHRM3	CHRM3		CHRM3
		HTR1A	HTR1A	HTR1A
		HTR1B	HTR1B	HTR1B
		HTR2A	HTR2A	HTR2A
	HTR2B	HTR2B		HTR2B
			HTR6	HTR6
			MRGPRX2	MRGPRX2
			TACR3	TACR3
		AVPR1A	AVPR1A	AVPR1A
Ion Channel	CaV1.2	CaV1.2		CaV1.2
	GABR	GABR		GABR
		HTR3	HTR3	HTR3
			KCNQ1	KCNQ1
	KV11.1	KV11.1		KV11.1
			CHRNA1	CHRNA1
		CHRNA4		
		NMDA	NMDA	NMDA
	SCN5A	SCN5A		SCN5A

Target Family	InVEST18	InVEST44	InVEST59	InVEST77
Enzyme	ACHE	ACHE		ACHE
		COX1	COX1	COX1
		COX2	COX2	COX2
			CTSD	CTSD
			MALT1	MALT1
		MAOA	MAOA	MAOA
		MAOB	MAOB	MAOB
	PDE3A	PDE3A		PDE3A
	PDE4D2	PDE4D2		PDE4D2
Transporter	DAT	DAT		DAT
	NET	NET		NET
			GAT1	GAT1
		SERT	SERT	SERT
Nuclear Receptor		AR	AR	AR
			ESR1	ESR1
		GR	GR	GR
			PGR	PGR
			RARA	RARA

Table 1: Safety liability targets **for InVEST18™, InVEST44™, InVEST59™ and InVEST77™**

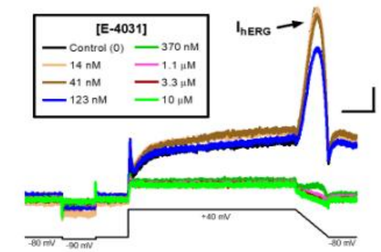
Conclusion

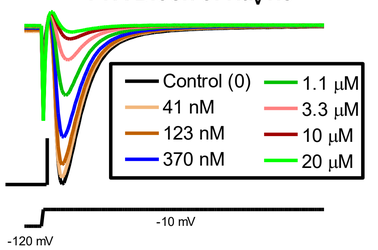
In vitro safety panels, such as **InVEST44™**, are critical in identifying off-target effects of lead compounds prior to time-consuming, expensive animal testing and failed clinical trials.

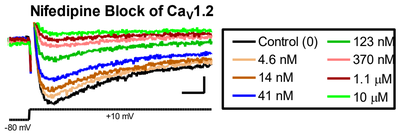
By providing cost-efficient, early-stage identification of off-target effects by lead compounds, in vitro safety panels, such as **InVEST44™**, have become integral components of drug discovery and warrant increased early-stage consideration and investment in the future.

Other In Vitro Safety Offerings

Reaction Biology offers manual and automated patch whole-cell electrophysiology for **cardiac safety, including hERG, NaV1.5 and CaV1.2.** Ask for more details.







Scale bars: hERG: 100pA, 1s; $Na_V1.5$: 5nA, 1ms; $Ca_V1.2$: 100pA, 5ms

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6. clinicaltrials.org

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