Proposal of the “Parallel and One step” drug design method and simulation study

The new trend of drug design by A-ADME-T-P total prediction

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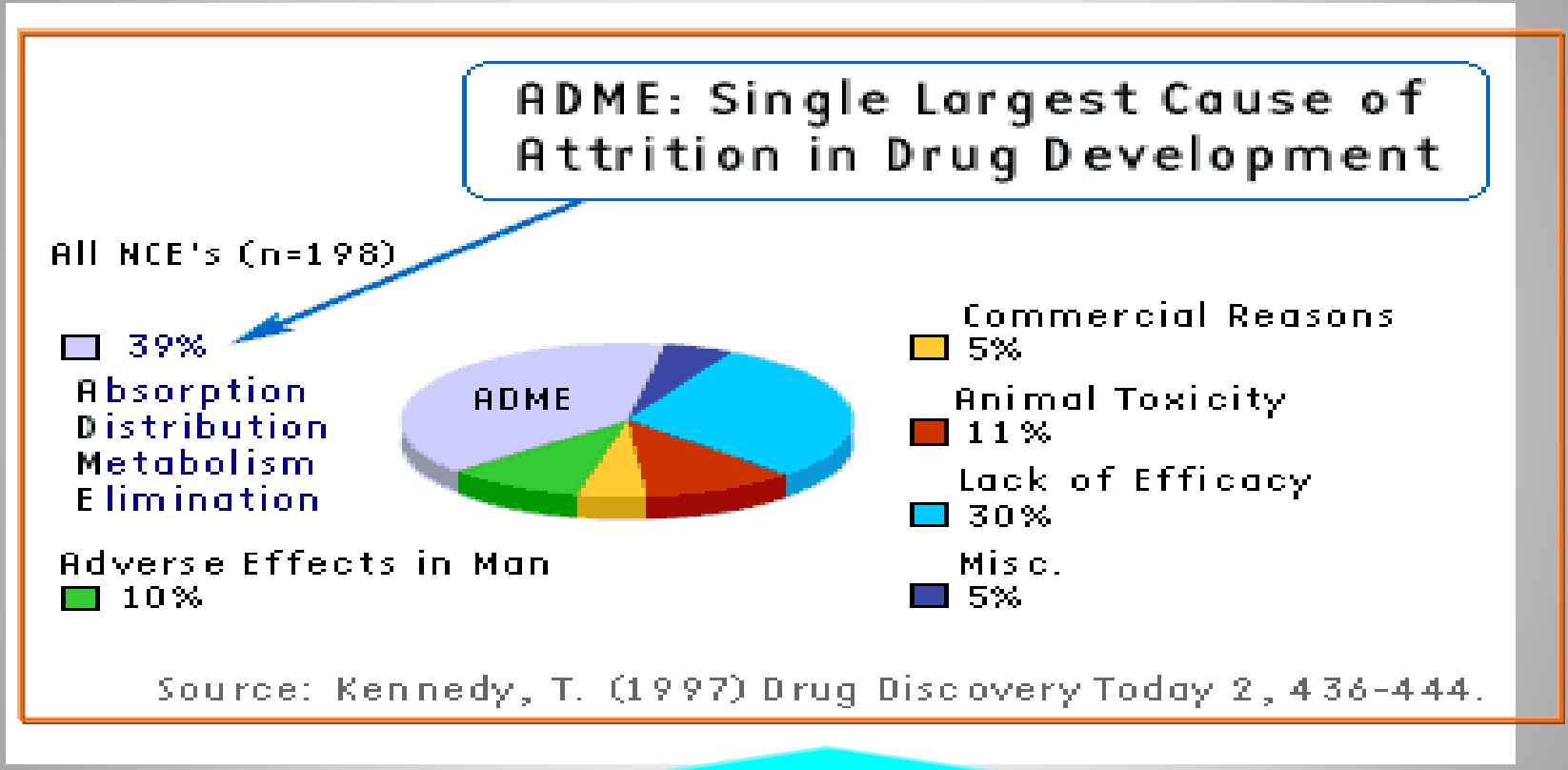
Reasons of Drug Development Failure



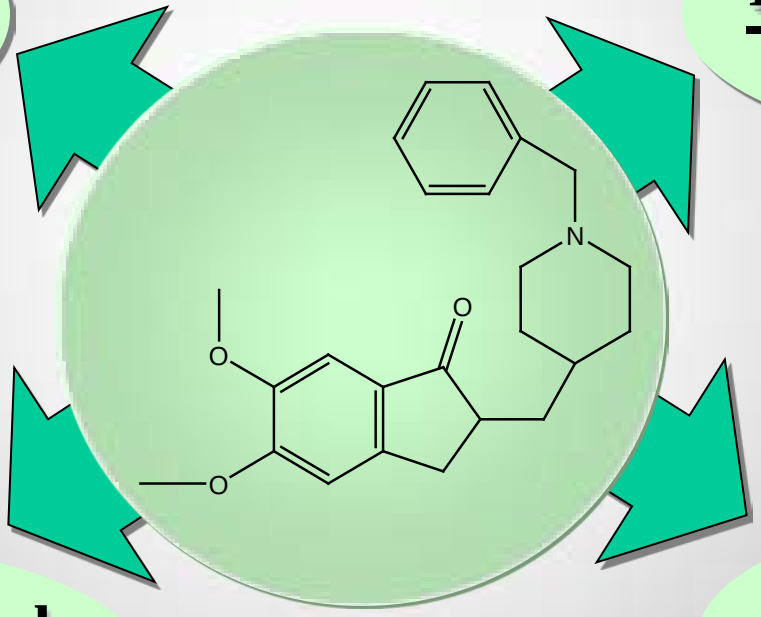
ADME, Toxicity (60%) > Activity (30%)

＊WEBサイトより借用　http://www.camitro.com/

Drug properties and compound structure

ADME properties

Pharmacological activity



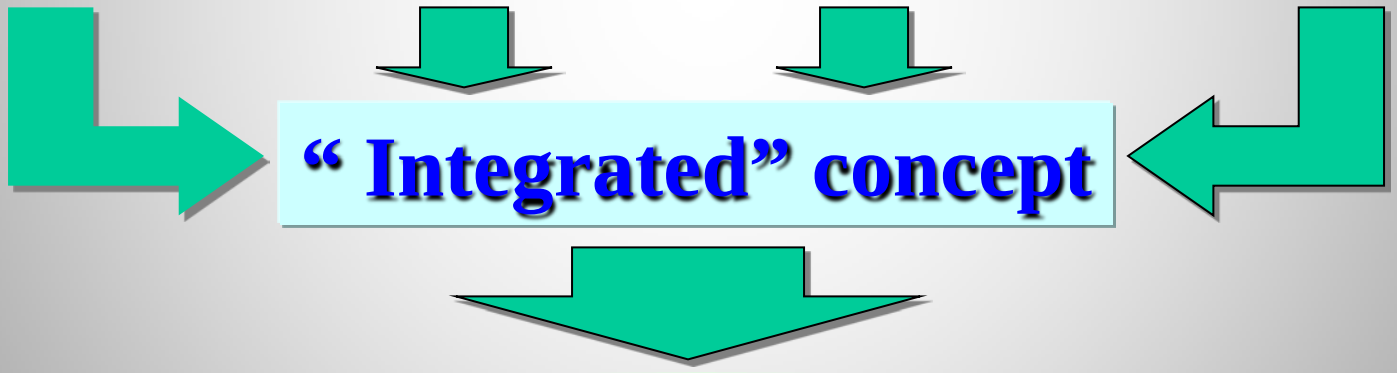
Physico chemical properties

Toxicity

“Integrated” concept for drug development

Activity + ADME + Toxicity + Property

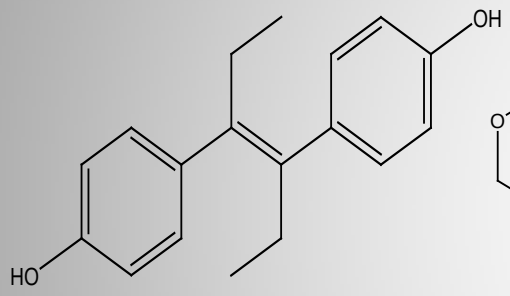
All drug properties shall be considered at the same time



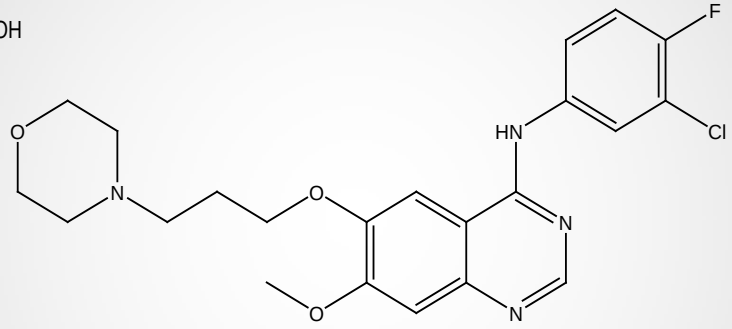
“ Integrated” in silico screening & drug design

Drugs which possesses Side-Effect

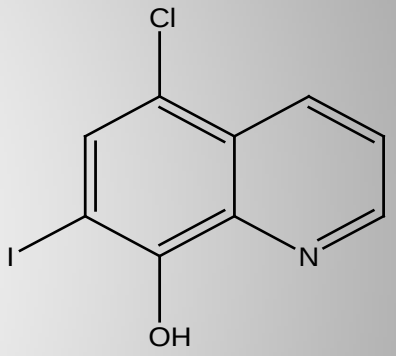
DESPLEX



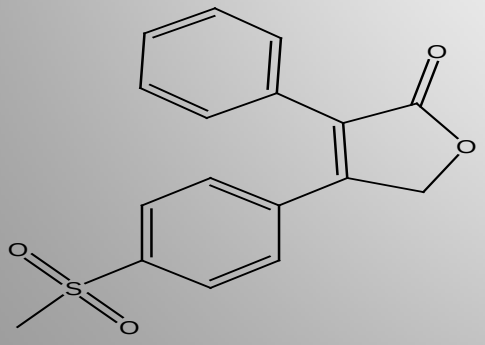
IRESSA



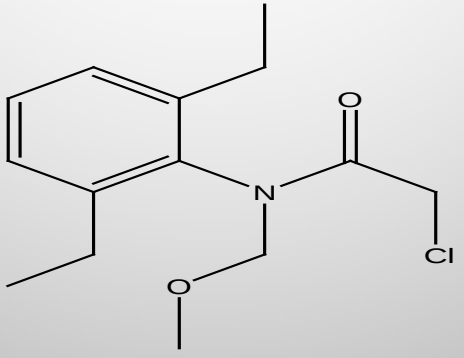
CLIOQUINOL



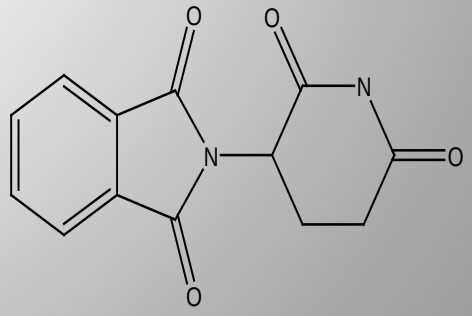
VIOXX



ALACHLOR



ISOMIN



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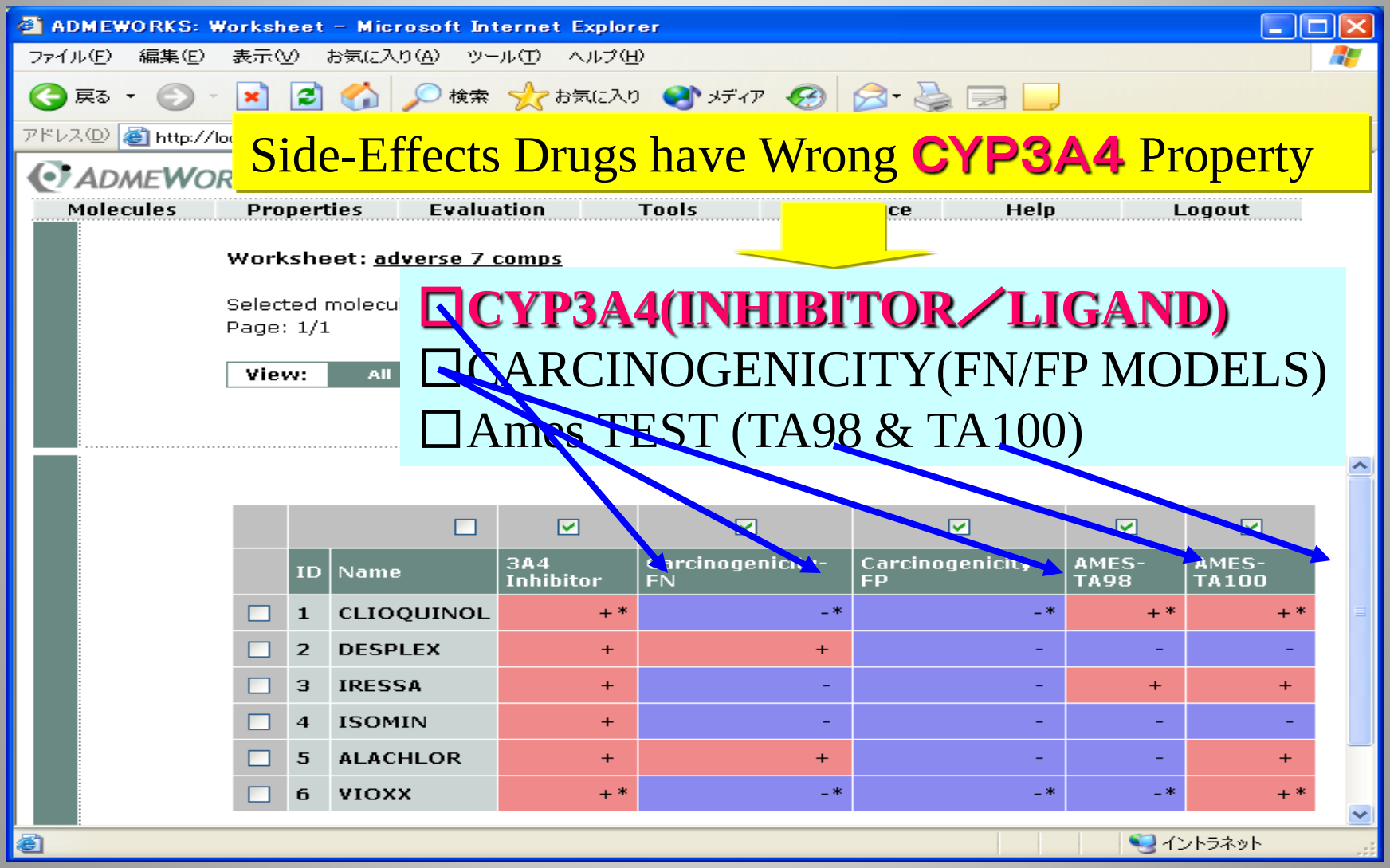
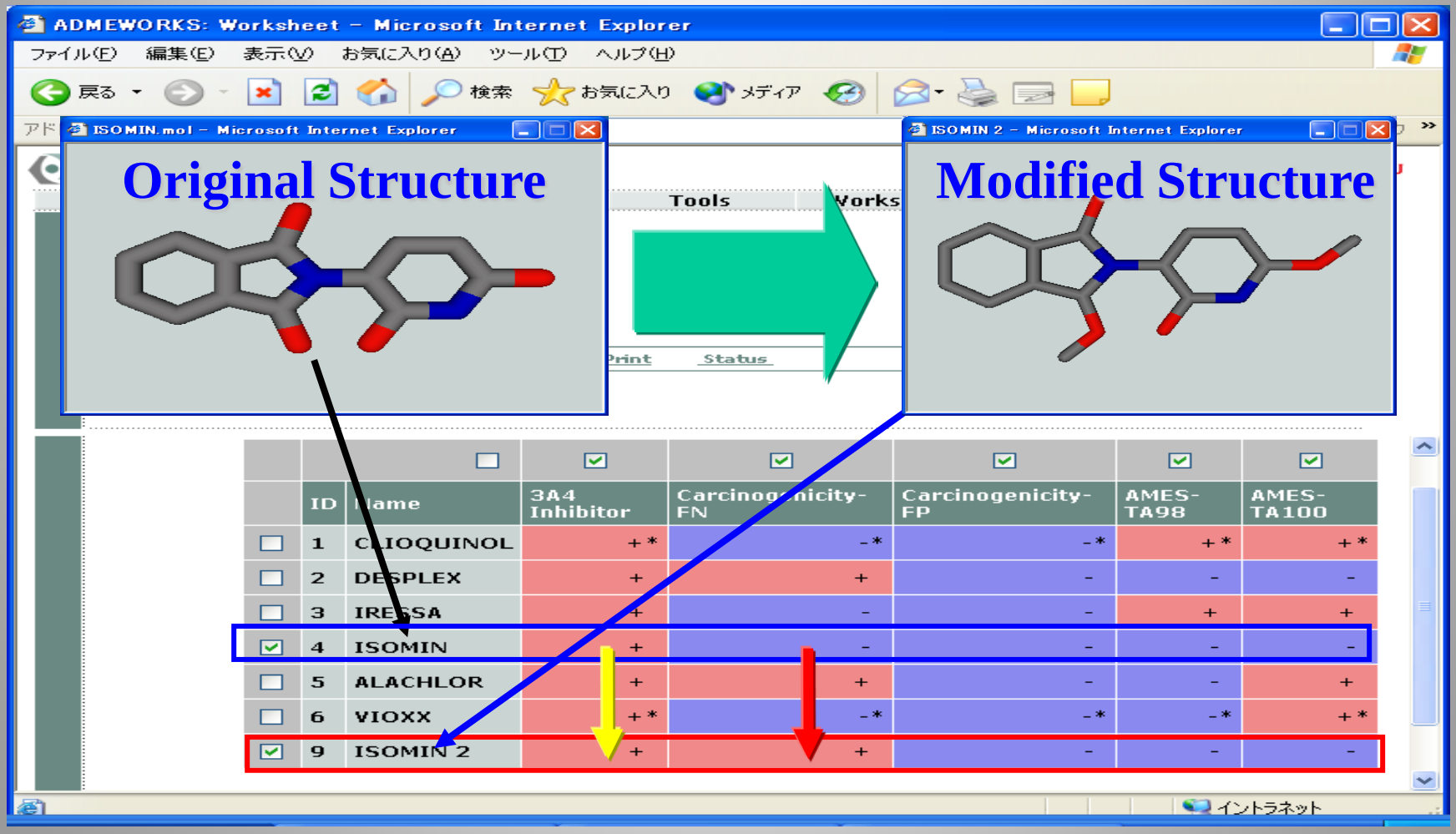
Miracles by the KY-methods

Prediction Results on Side-Effect Drugs



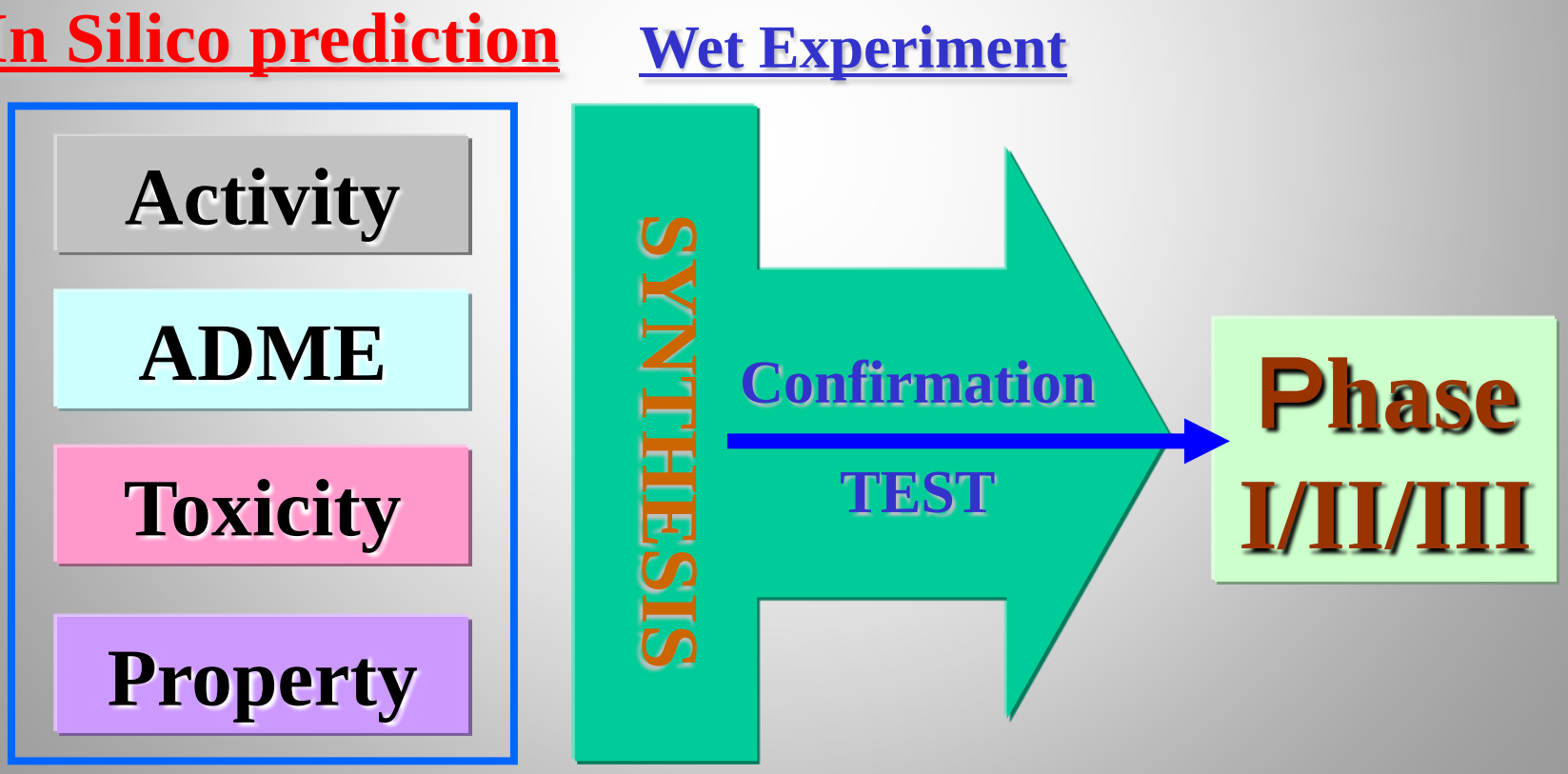
ID	Name	3A4 Inhibitor	Carcinogenicity-FN	Carcinogenicity-FP	AMES-TA98	AMES-TA100
1	CLIOQUINOL	+*	-*	-*	+*	+*
2	DESPLEX	+	+	-	-	-
3	IRESSA	+	-	-	+	+
4	ISOMIN	+	-	-	-	-
5	ALACHLOR	+	+	-	-	+
6	VIOXX	+*	-*	-*	-*	+*

Structure Modification Introduce Mutagenicity in spite of the "CYP3A4" Property have no changed



Flow of the “Parallel & One Step” D.D.

“Parallel & One Step” D.D.



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Comparative Simulation Test of "Parallel D.D." and "Step by Step D.D." Approach

■ "Parallel D.D."

1. In Silico Screening of ADME-T Property.
2. Prediction Ratio will be Changed from 70%, 80%, 90% and 100%.

■ "Step by Step D.D."

1. Screening by Wet Experiment of ADME-T Property.
2. Success Rate of Experiment will be Fixed to 50%.

Used Monitoring Parameter of Comparative Simulation Test of D.D.

■ **Efficiency Ratio by Parallel D.D.**

$$\text{Efficiency Ratio} = \frac{\text{‘Parallel’ Drug Design}}{\text{‘Step by Step ’ Drug Design}}$$

Condition 1 : Number of test : Total 8

ADME related test = 5 Items

Toxicity related test = 3 Items

Condition 2 : Prediction Ratio 100%, 90%, 80%, 70%

‘Step by Step’ Method was Fixed on 50%

Condition 3 : Number of Redesign Process

The case1; 1 trial (Pass through by 1 trial)

The case2; 3 trial (Pass through by 3 trials)

Case1 : Only One Time Screening to reach PhaseI

Parallel Approach:

		Efficiency Ratio
1. Prediction Ratio 100% ADME-T In Silico Screening ＝1.0000	$\frac{1.0000}{0.0039}$	= 256 times
2. Prediction Ratio 90% ADME-T In Silico Screening ＝0.4308	$\frac{0.4308}{0.0039}$	= 111 times
3. Prediction Ratio 80% ADME-T In Silico Screening ＝0.1678	$\frac{0.1678}{0.0039}$	= 43 times
4. Prediction Ratio 70% ADME-T In Silico Screening ＝0.0576	$\frac{0.0576}{0.0039}$	= 15 times

Case2 : Three Times Feedback Screening to reach PhaseI

Parallel Approach:

		Efficiency Ratio
1. Prediction Ratio 100% ADME-T In Silico Screening ＝1.0000	$\frac{1.0000}{59\ E\text{-}9}$	= 16858005 times
2. Prediction Ratio 90% ADME-T In Silico Screening ＝0.4308	$\frac{0.4308}{59\ E\text{-}9}$	= 1347824 times
3. Prediction Ratio 80% ADME-T In Silico Screening ＝0.1678	$\frac{0.1678}{59\ E\text{-}9}$	= 79649 times
4. Prediction Ratio 70% ADME-T In Silico Screening ＝0.0576	$\frac{0.0576}{59\ E\text{-}9}$	= 3221 times

Results of Simulation Test of "Parallel & One Step" Drug Design

■ Screening Test (8 Items)

	"Parallel D.D." Efficiency Ratio of Pre-clinical Stage		"Step by Step D.D."
Case 1	15 Times	～ 256 Times	1
Case 2	3,221 Times	～ 16,858,005 Times	1

Case 1:

Drug Development is cleared only one time in silico screening and ADME-T wet screening process.

Case 2:

Drug Development is cleared by three time in silico screening and ADME-T wet screening processes.

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