Model-Informed Drug Development

2021 Virtual Conference

Revisiting MUT_RISK in ADMET Predictor®

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Mutagenicity

• A mutagen is a physical or chemical agent that changes the genetic material, usually DNA, thus increasing the frequency of mutations



OECD Guidelines TG471

- A substance must be tested in a minimum of five strains with and/or without a mammalian liver homogenate preparation (S9) :
 - <u>TA98</u>;
 - <u>TA100</u>;
 - <u>TA1535</u>
 - any one of <u>TA1537</u>, <u>TA97</u> or <u>TA97a</u>
 - any one of <u>TA102</u>, <u>WP2 uvrA</u>, or <u>WP2 uvrA</u>
 <u>pKM101</u>





Mutagenesis Models in ADMET Predictor

Individual Strain Models

- Eleven Mutagenesis models present in AP-X
 - Five strains (with and without S9 fractions)
 - One model based on NIHS dataset
- Output is

Positive vs Negative





- A qualitative estimate of overall mutagenicity by combining individual positive predictions
- Range: 0.0 3.0
- ~89% of the cmpds from WDI subset have MUT_RISK less than 1





Why MUT_RISK?

In a regulatory context, a compound "fails" the Ames test if a positive result is obtained for any strain

Structure	Identifier	MUT_Risk	MUT 97+1537	MUT m97+1537	<u>MUT 98</u>	MUT m98	MUT 100	<u>MUT m100</u>	MUT 102+wp2	MUT m102+wp2	<u>MUT 1535</u>	<u>MUT m1535</u>	MUT NIHS	
	RIFAMYCIN		Positive	Positive	Negati	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	
ఇం ^{మరు,}	PRAZOSIN		Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	
~`~```````	ALBENDAZOLE			Negative	Negative	Negati	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative
of C.	ONDANSETRON			Negative	Negative	Negati	Positive	Negative	Positive	Negative	Negative	Negative	Negative	Negative
<u>کې</u> د.	NIFEDIPINE		Negative	Negative	Negati	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Positive	
	CISAPRIDE		Negative	Negative	Negati	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Positive	
	Folic-Acid		Negative	Negative	Negati	Negative	Negative	Negative	Positive	Negative	Negative	Negative	Negative	
	WARFARIN		Negative	Negative	Negati	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Negative	
	SUCROSE		Negative	Negative	Negati	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	

MUT_Risk score <= 1 helps to "save" compounds from being labeled toxic

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How Do We Calculate MUT_RISK?

								1			- X-
S_97	0.6	MUT_97+1537	=	Positive							
m_97	0.6	MUT_m97+1537	1	= Positiv	re	AND	MUT_	97+1	537	=	Negative
S_98	0.3	MUT_98 =	Posi	tive							
m_98	0.3	MUT_m98 =	Posi	tive AND) MUT	98	=	Nega	tive	è	
s100	0.3	$MUT_{100} =$	Posi	tive	_	_					
m100	0.3	MUT m100	=	Positive	AND	MUT	100	=	Nega	ative	j
S102	0.6	MUT 102+wp2	=	Positive		_	_				
m102	0.6	MUT_m102+wp2	2	= Positiv	re	AND	MUT	102+	wp2	=	Negative
S535	0.6	MUT 1535	=	Positive				-			
m535	0.6	MUT_m1535	=	Positive	AND	MUT	1535	5	=	Nega	tive
NIHS	0.6	MUT_NIHS	=	Positive		-	_				

- Each individual "Mutagenic" prediction contributes <u>0.6</u> "vote" to the score
- The models and their errors are not mutually independent
- Results of TA98 and TA100 tests overlap mechanistically and hence vote of 0.3









- 7th International Workshop on Genotoxicity Testing
- November 8-10 2017
- National Cancer Centre, Japan



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Are all bacterial strains required by OECD mutagenicity test guideline TG471 needed?



Special Issue on IWGT

Meeting Report, (Published

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Do We Need to Update Test Guidelines?

Of the mutagens detected by the full TG471 strain panel, TA100 93 % were mutagenic in either TA98 and/or TA100

TA100 is derived from TA1535; detects more mutagens than TA1535. TA100 alone would suffice TA97, TA102, and WP2*uvrA* <u>could be removed</u> from OECD TG471 with little, if any, loss of sensitivity





Proposed MUT_RISK Changes

- Contribution of individual "Mutagenic" prediction needs to be updated
 - TA97 and TA102 could be given lower weights
 - TA100, TA98 and TA1535 deserve higher weights
- Interactions amongst TA98, TA100 and TA1535 results should be considered
 - All positive to get higher score
 - Either one positive to get relatively lower score
- Independent external test set compiled by Hansen et al.
 - NO manual intervention involved



Proposed MUT_RISK

1	S 97	0.35	MUT 97+153	7 =	Positiv	е						
2	m 97	0.20	MUT m97+15	37	= Pos	itiv€	Э	AND	NOT	MUT	97+3	1537 =
3	S 98	1.06	MUT 98 =	Posi	itive	AND	(MUT	100	=	Nega	ative
4	m 98	0.70	MUT_m98 =	Pos	itive	AND	MUT	98	=	Nega	ative	e A
5	S100	1.01	$MUT_{100} =$	Pos	itive	AND	(MUT	98	=	Nega	ative
6	m100	0.86	MUT_m100	=	Positiv	е	AND	MUT	100	=	Nega	ative
7	S102	0.11	MUT_102+wp	2 =	Positiv	е						
8	m102	0.13	MUT_m102+w	rp2	= Pos	itive	Э	AND	MUT	_102-	+wp2	= 1
9	S535	0.70	MUT_1535	=	Positiv	е	AND	(MUT	_100	=	Negat
0	m535	0.40	MUT_m1535	=	Positiv	е	AND	MUT_	_1535	5	=	Negat
1	NIHS	0.37	MUT_NIHS	=	Positiv	е						
2	S_cl	1.17	$MUT_{100} =$	Posi	itive	AND	MUT_	98	=	Pos	itiv	e A
3	<u>m_c1</u>	1.21	MUT_m98 =	Posi	itive	AND	MUT_	_m10()	=	Pos	itive
4	S_c2	0.92	MUT_98 =	Posi	itive	AND	MUT_	1535	5	=	Pos	itive
5	<u>m_c2</u>	0.75	MUT_m98 =	Posi	itive	AND	MUT_	m153	35	=	Pos	itive
6	S_c3	1.23	$MUT_{100} =$	Posi	itive	AND	MUT_	153	5	=	Pos	itive
7	m_c3	0.97	MUT_m100	=	Positiv	е	AND	MUT	_m153	35	=	Posit
8	S_c4	1.21	$MUT_{100} =$	Posi	itive	AND	MUT_	98	=	Pos	itiv	e <i>I</i>
9	m c4	1.17	MUT m1535	=	Positiv	е	AND	MUT	m98	=	Pos	itive



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Performance on Hansen Dataset

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MUT_RISK_10 Prediction

MUT_RISK_11 Prediction

Sensitivity = 0.804; Specificity = .0670 MCC = 0.480: Youden = 0.486: False Rate = 0.257



Model-Ir

Sensitivity = 0.813; Specificity = 0.740 MCC = 0.556; Youden = 0.558; False Rate = 0.220



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Comparison of Two MUT_RISK Models

203 Positive cmpds were labeled "<u>safe</u>" by MUT_RISK_10. MUT_RISK_11 could identify them correctly



293 Negative cmpds were flagged "<u>mutagenic</u>" by MUT_RISK_10. MUT_RISK_11 could save them correctly



Performance on WDI Subset

Hand-curated Subset (2269 cmpds) of World Drug Index used for analysis





89% cmpds are labeled safe with new MUT_RISK_11 in contrast to only 85% by older MUT_RISK_10



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Conclusion

- Consolidation of results from various strains in a single RISK factor provides better prediction of mutagenicity of small molecules than individual models
- Latest IWGT meeting report suggested relative importance of various strains in Mutagenicity
- Newly proposed MUT_RISK is found to perform better in identifying toxic compounds than existing MUT_RISK





Questions & Answers

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