Clinical trials failures due to undetected off-targets

Off-targets were in blind spot of the drug development assays

* Need the clinical trials info
* How many known off-targets
* Key limitations

Solution: EpiTox

Technical validation

Experimental data validation

**Abstract**

**Introduction**:

Drug X failed in clinical trials due to undetected off-target Y

Current tools missed this critical off-target

We developed a comprehensive workflow-kit that catches these missed off-targets

Knew already of it in the patent it has low risk

but in clinic MAGEA12 paper 1

then another group used bioinformatic EPS2L8 as the real reason rather than MAGEA12

this was then patented, and the reference came from; the reference still recognized magea12

entire MAGEA family (kick off slides)

none MAGEA members (patent or published)

**Results:**

**Experimental validation**:

(1)

show catching the known off-targets

Ein Bild, das Kreis, Diagramm, Screenshot enthält.

KI-generierte Inhalte können fehlerhaft sein.

KVADLIHFL: found in melanoma, TVAELVQFV: synthetic & FLWGPRALV is a different sequence (edit distance =9); all are considered true negative since they are not in healthy tissues and one surpasses the edit distance threshold of EpiTox for this target.

(2)

Enrichment analysis:

-rate of validated OT in top ranked predictions vs. random selection, e.g. top 100 contain x% validated OT vs Y% expected by chance -> fisher’s exact test or chi-square test

(3) ranking quality metrics:

- precision-recall curve

- area under the precision-recall curve

- enrichment at top-k: % of known OT in top 50, 100, 200 predictions

Enrichment analysis and ranking score:

N = total number of OT

K = number of known OT (truth set)

n = number of top predictions (bi-features score)

k = number of known OT in n

enrichment = (k/n)/(K/N) >1 great, = 1 same as random, <1 doing worse

Ein Bild, das Text, Reihe, Diagramm, Schrift enthält.

KI-generierte Inhalte können fehlerhaft sein.

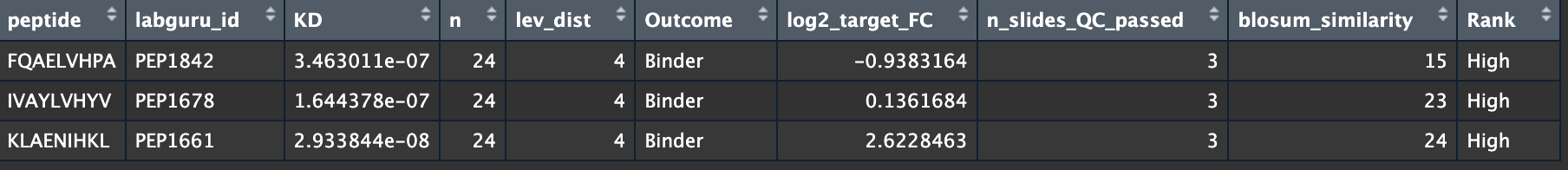
Top 10% (136 predictions): 16/17 (94.1%) known off-targets

Top 20% (272 predictions): 16/17 (94.1%) known off-targets

Top 30% (408 predictions): 16/17 (94.1%) known off-targets

Top 50% (680 predictions): 17/17 (100.0%) known off-targets

Show case: SNPs can lead to discovering highly risked off-target



Ein Bild, das Reihe, Diagramm, parallel, Screenshot enthält.

KI-generierte Inhalte können fehlerhaft sein.

log2(gxp off target +1) - log2(gxp target +1)

mutated off-targets were ranked as high, bind to the antibody and on top highly expressed compared to the target in these normal tissues

the KLA… happens to have a mutation on genomic level that on protein level produces the same peptide sequence. Making the individual carrying the mutation still at risk of side effect

**Compare performance**

Ein Bild, das Kreis, Diagramm, Screenshot, Darstellung enthält.

KI-generierte Inhalte können fehlerhaft sein.Ein Bild, das Diagramm, Text, Screenshot, Reihe enthält.

KI-generierte Inhalte können fehlerhaft sein.Ein Bild, das Text, Screenshot, Diagramm, Reihe enthält.

KI-generierte Inhalte können fehlerhaft sein.

The one peptide that CrossDome identifies has 9 mismatches! So nothing to do with the target!

SCORE measurements

**Materials and methods:**

Technical implementation details

Computational methodology – algorithms, DBs, parameters

Experimental protocols for validation

Statistical analysis methods

**Discussion**:

asfsa