

Screening for Biotransformation Products of Pharmaceuticals in Water-Sediment Tests



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“ There are **known knowns**;
there are things we know that we know.

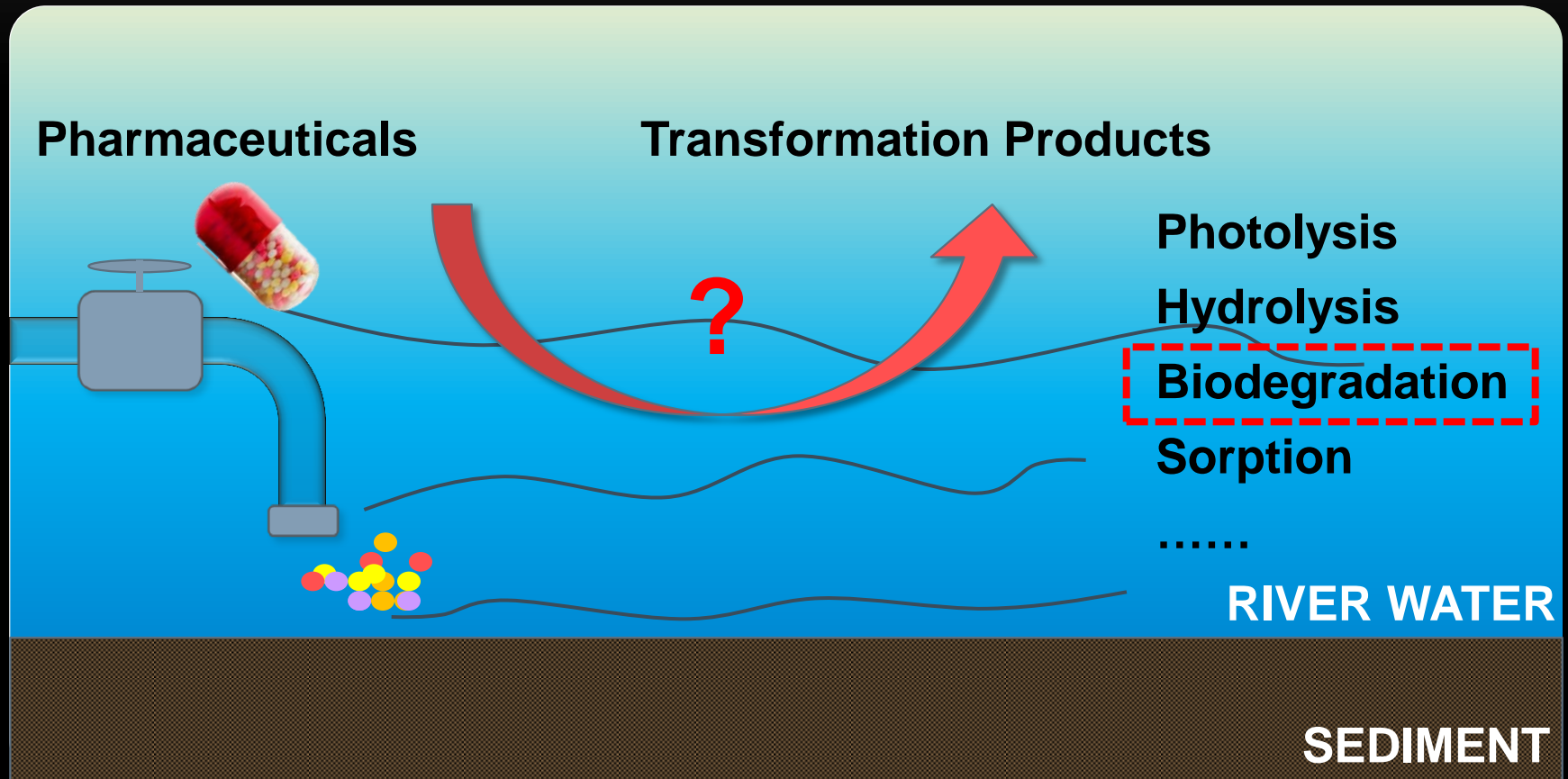
There are **known unknowns**;
that is to say there are things that, we now know we don't know.

But there are also **unknown unknowns**
– there are things we do not know we don't know.

”

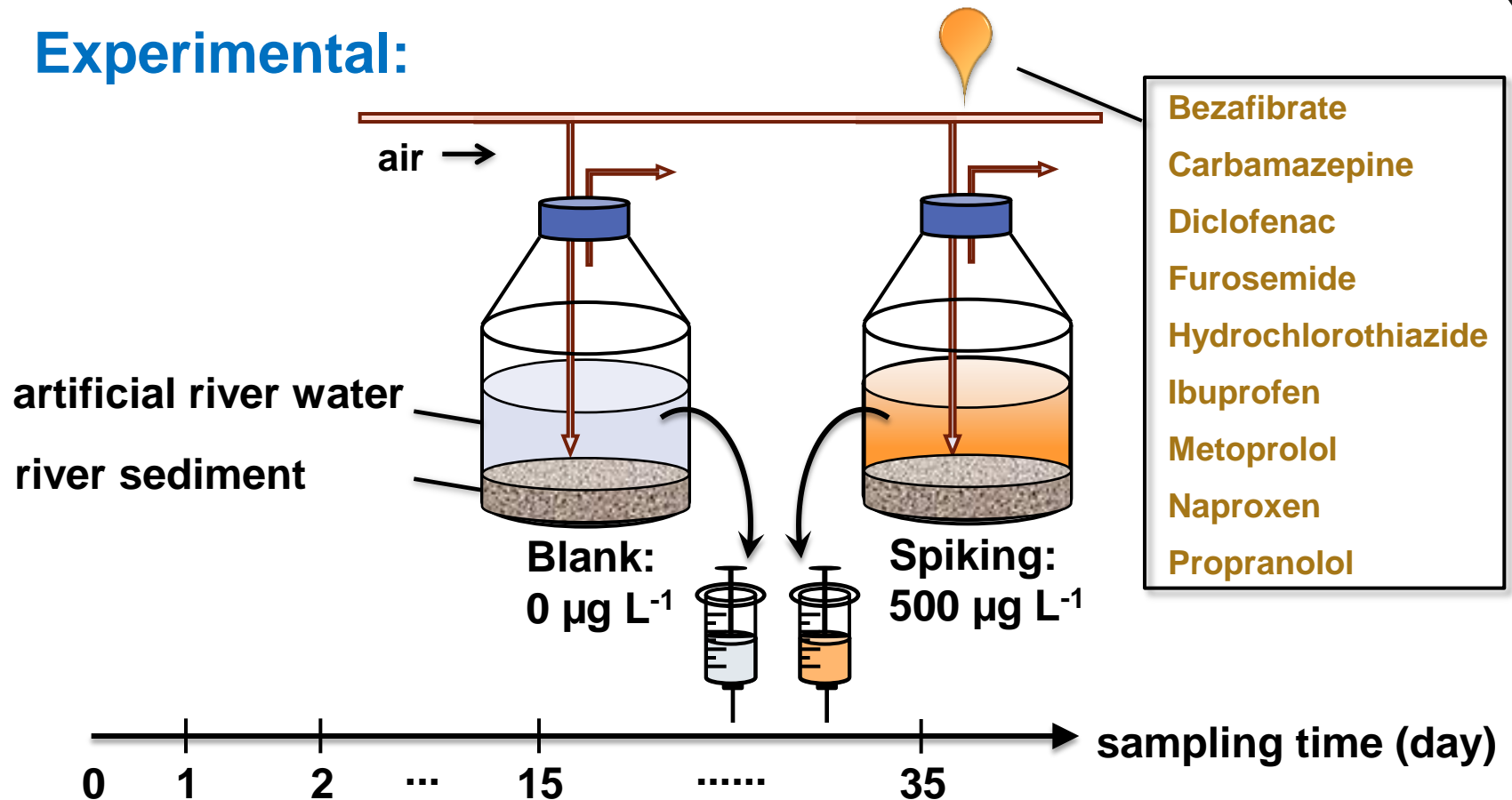
----- Donald Rumsfeld

Transformation Products (TPs)



Water-Sediment Tests

Experimental:



- Bezafibrate
- Carbamazepine
- Diclofenac
- Furosemide
- Hydrochlorothiazide
- Ibuprofen
- Metoprolol
- Naproxen
- Propranolol

UHPLC / ESI-QToF-MS

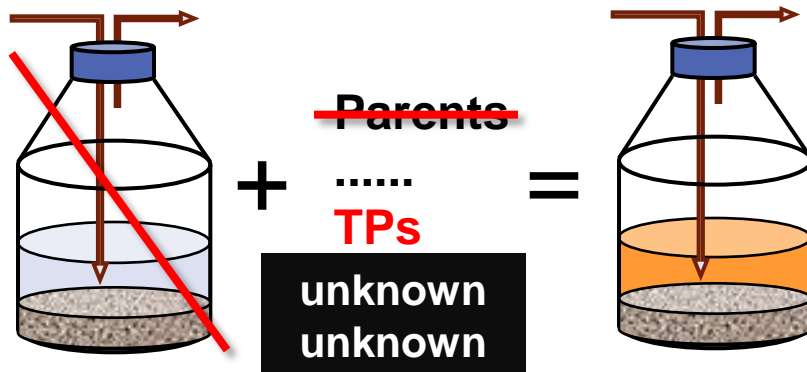
ESI positive/negative
Full spectra, $R \approx 8\ 000$

Screening Procedure

Automated Peak Detection

MZmine noise removal

enviMass blank subtraction
target elimination
isotopic peaks grouping



Structure Confirmation

Meaningful Time-Trend

Structure Assignment

Screening Procedure

Automated Peak Detection



Meaningful Time-Trend

MZmine

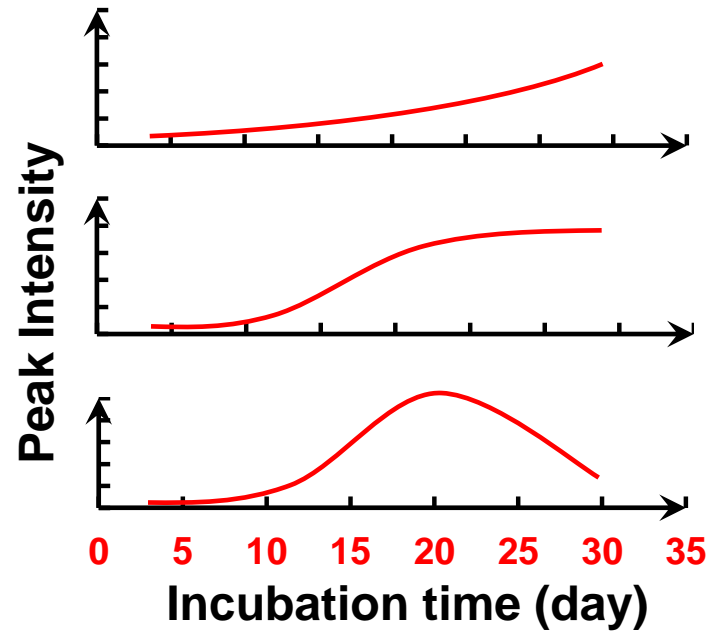
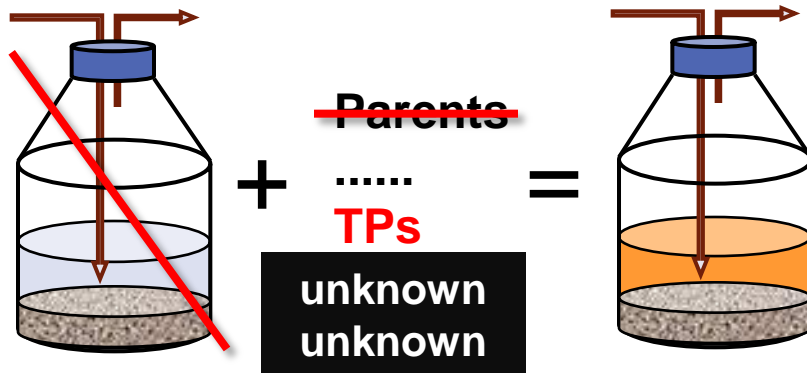
noise removal

enviMass

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isotopic peaks grouping



Structure Confirmation

Structure Assignment

Screening Procedure

Automated Peak Detection

MZmine

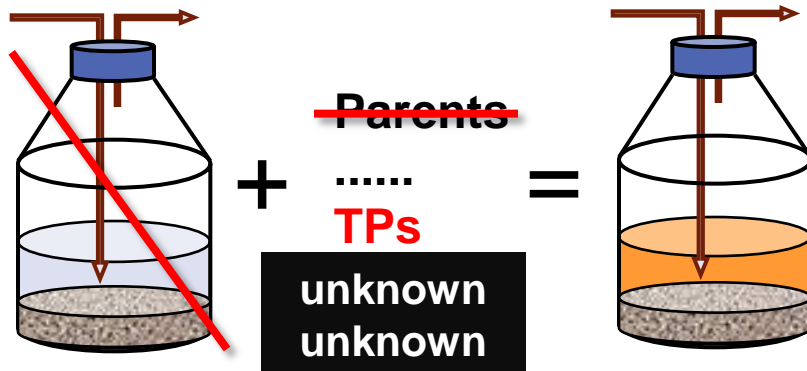
noise removal

enviMass

blank subtraction

target elimination

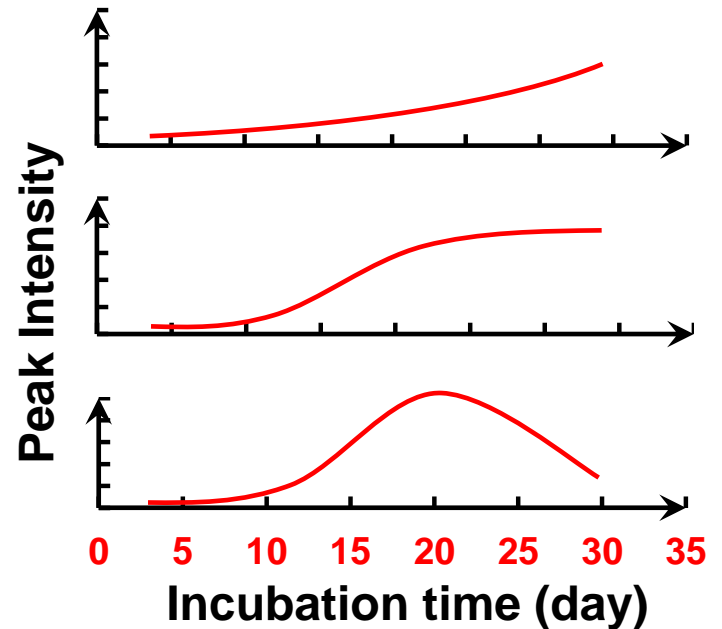
isotopic peaks grouping



Structure Confirmation



Meaningful Time-Trend



Structure Assignment

UM-PPS + Literature

Screening Procedure

Automated Peak Detection

MZmine

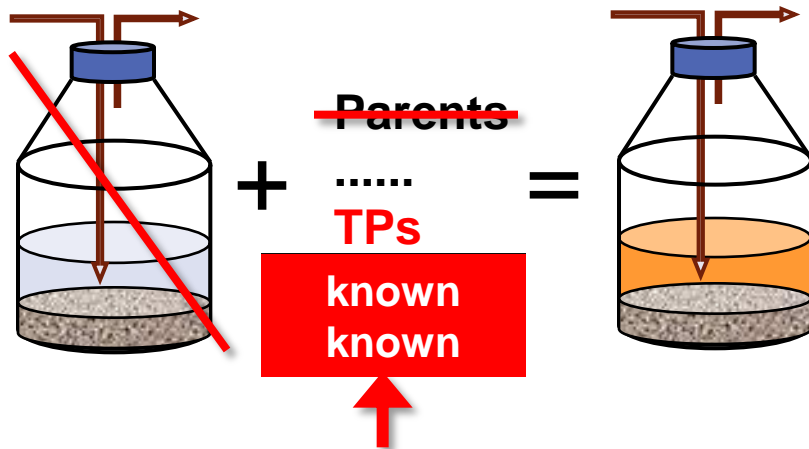
noise removal

enviMass

blank subtraction

target elimination

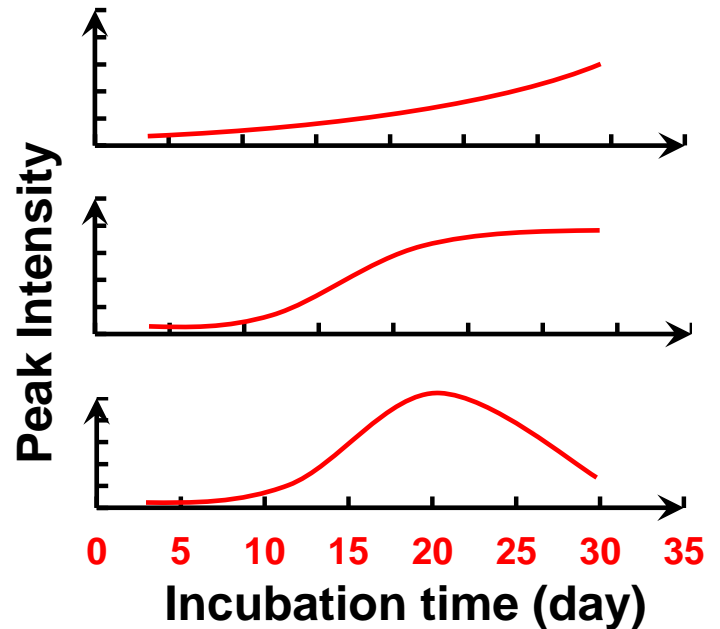
isotopic peaks grouping



Structure Confirmation

Authentic standard available?

Meaningful Time-Trend

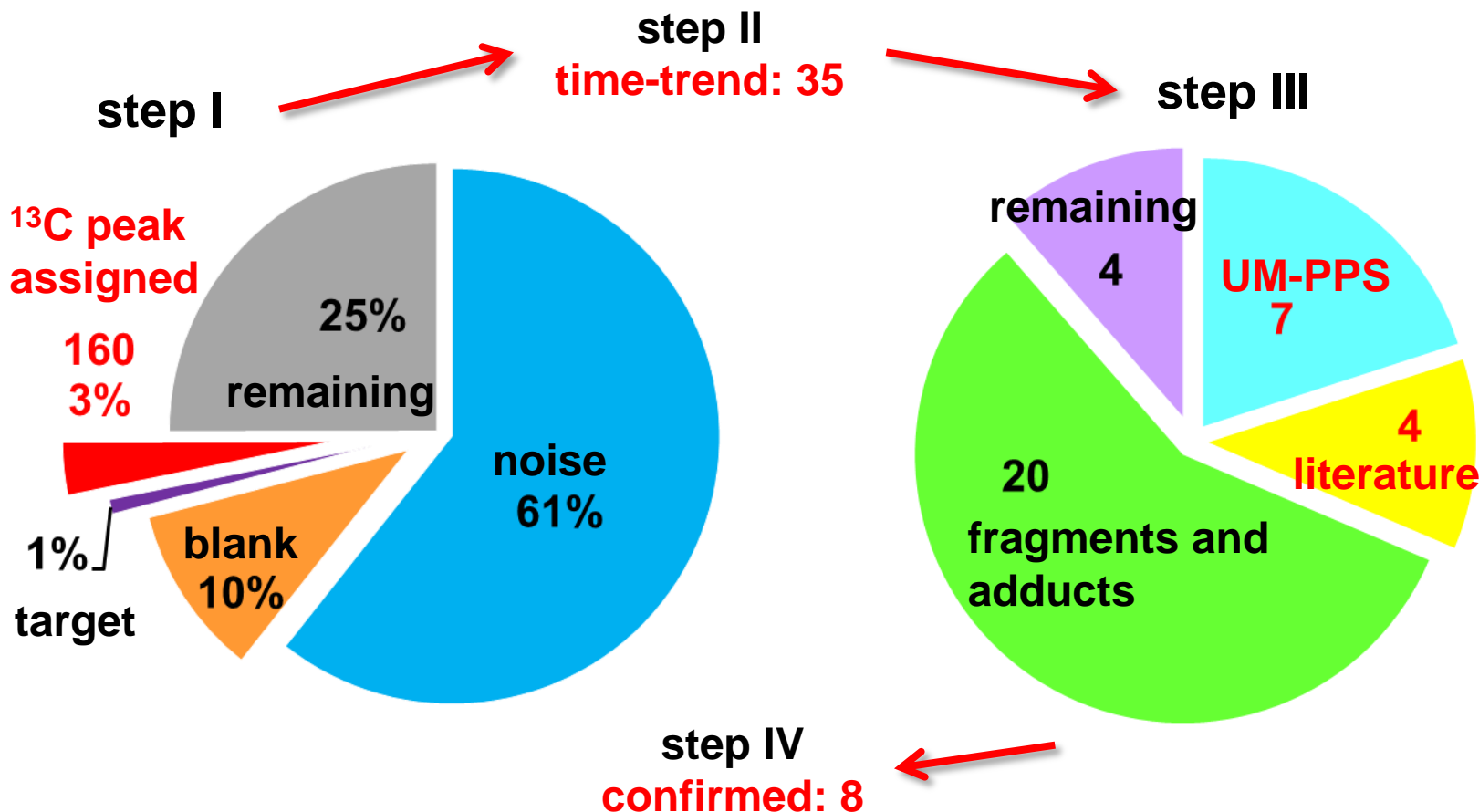


Structure Assignment

UM-PPS + Literature

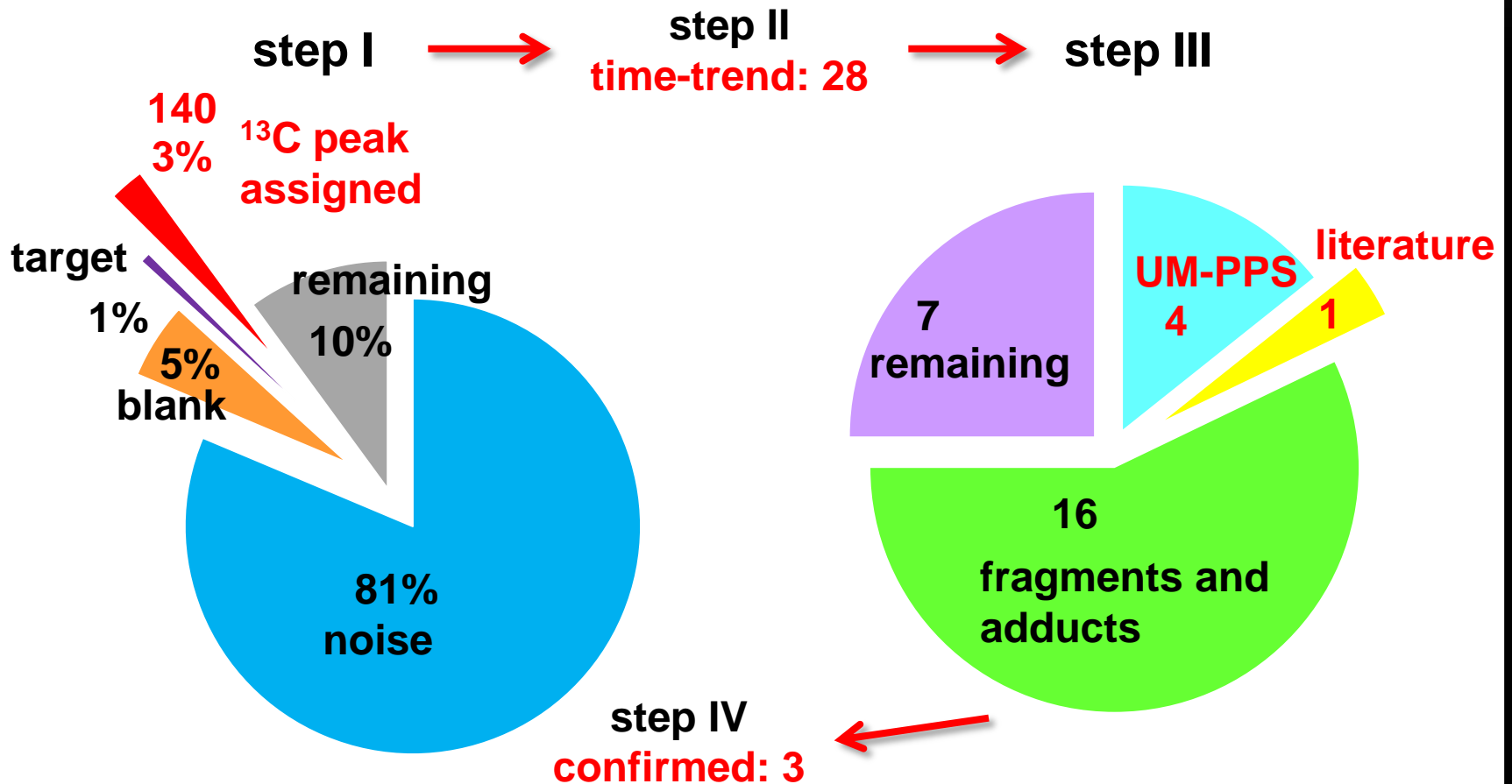
Procedural Performance

in ESI negative mode: ≈ 5057 peaks per sample

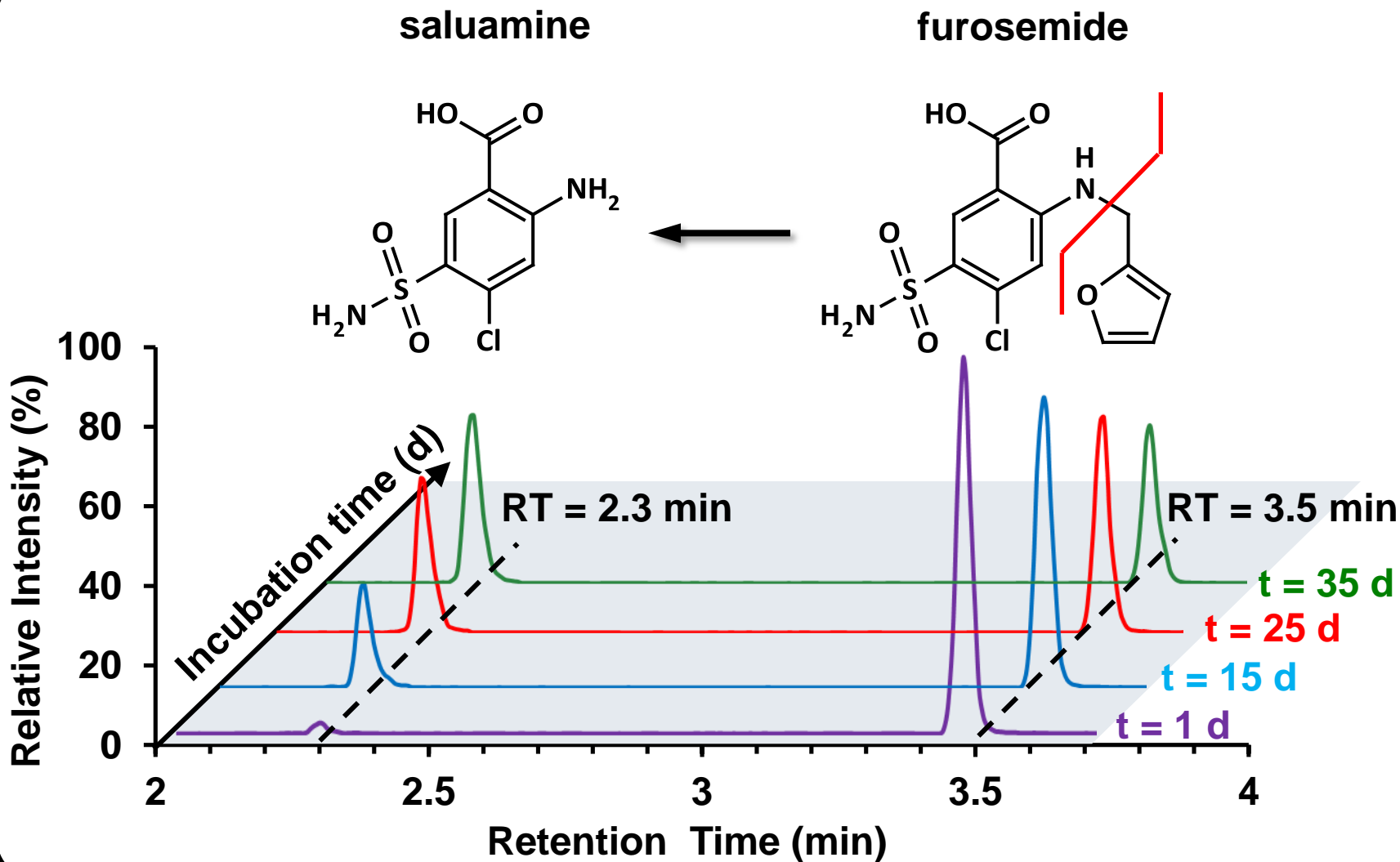


Procedural Performance

in ESI positive mode: ≈ 5678 peaks per sample



Known Knowns

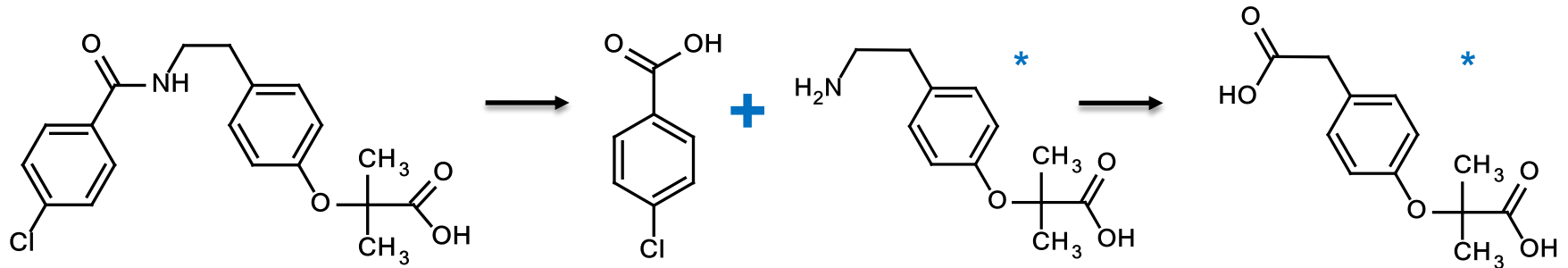


Known Knowns

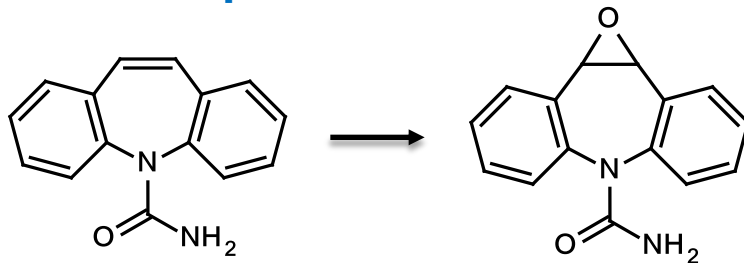
Parent Compound	Transformation Products
bezafibrate	4-chlorobenzoic acid
carbamazepine	carbamazepine-10,11-epoxide
diclofenac	4'-hydroxydiclofenac
furosemide	saluamine
hydrochlorothiazide	chlorothiazide; 4-amino-6-chloro-1,3-benzenedisulfonamide
ibuprofen	2-hydroxyibuprofen; carboxyibuprofen
metoprolol	metoprolol acid; α -hydroxymetoprolol
naproxen	--
propranolol	1-naphthol

Proposed Transformation Pathway

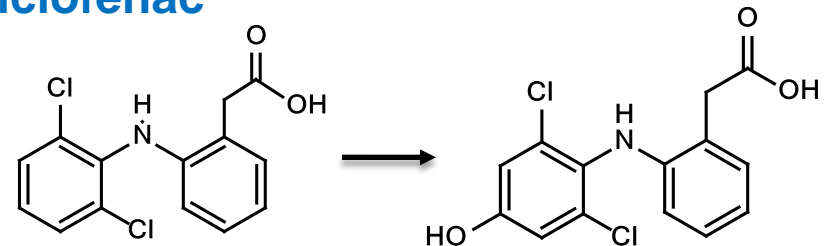
Bezafibrate



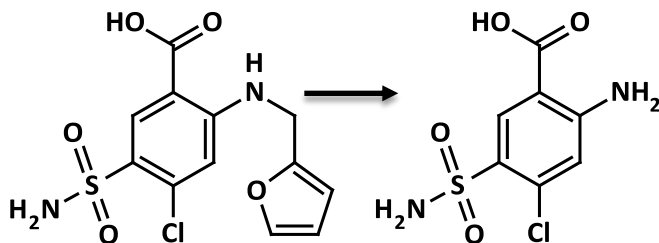
Carbamazepine



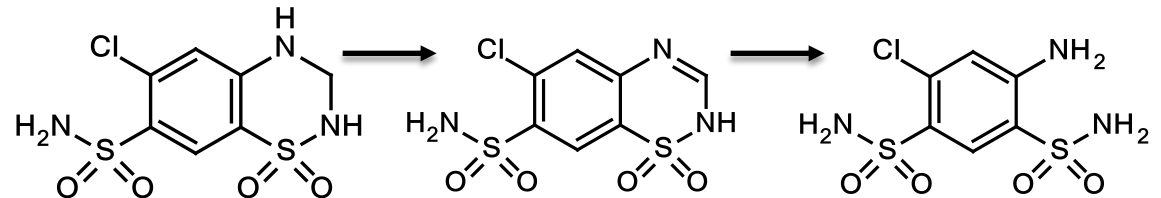
Diclofenac



Furosemide

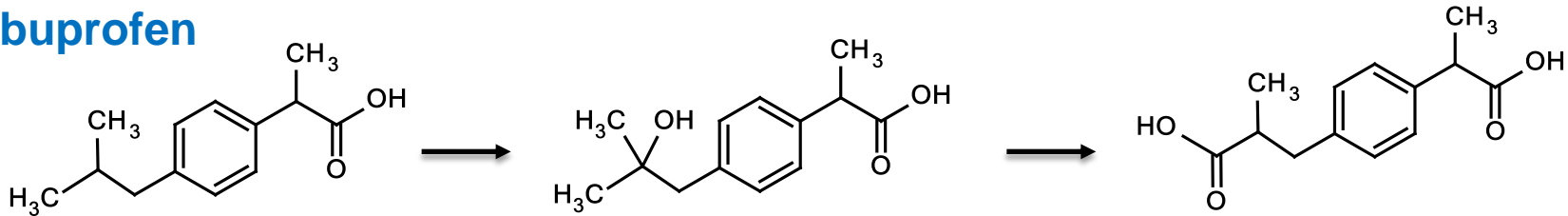


Hydrochlorothiazide

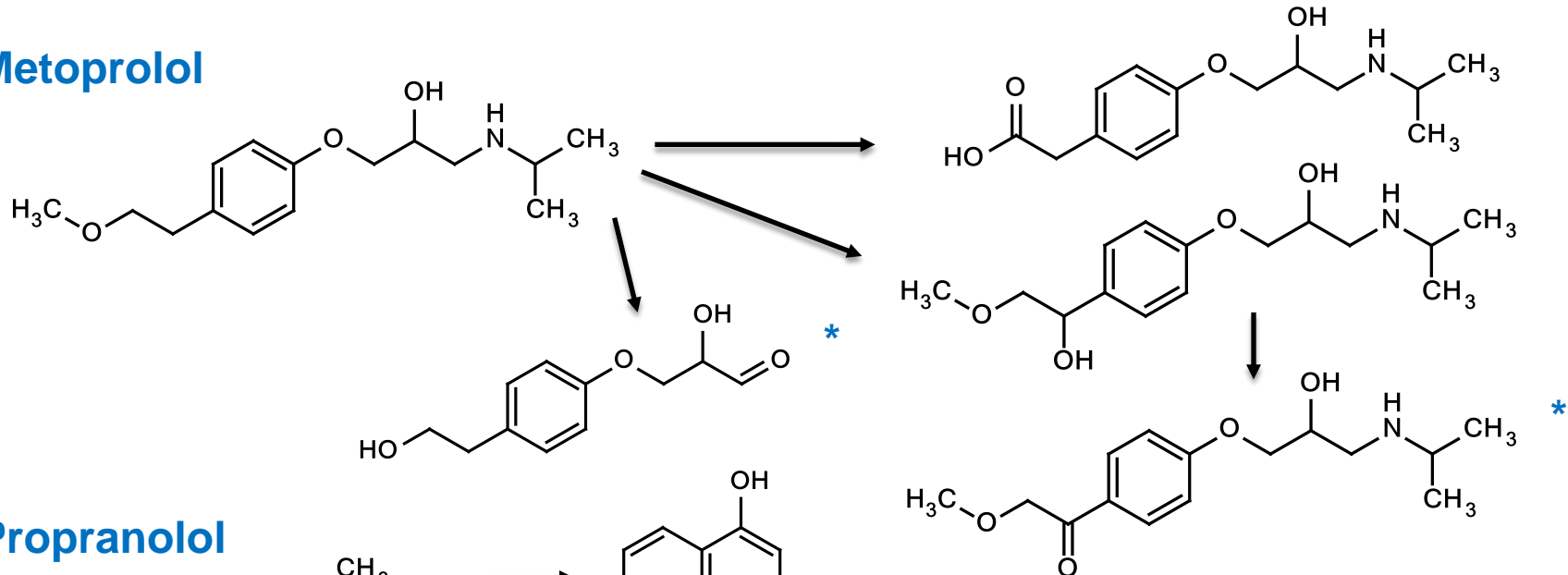


Proposed Transformation Pathway

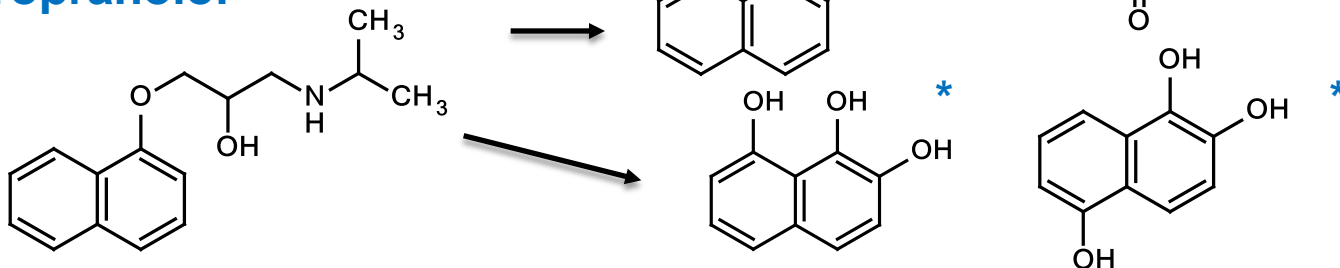
Ibuprofen



Metoprolol



Propranolol



Conclusions

- **The integrated water-sediment test and screening procedure is suitable for identifying TPs.**
 - Time-trend provides helpful information for filtering TPs.
 - UM-PPS prediction allows reasonable assignments, but should be complemented with literature.
- **Be cautious to conclude all are biotransformation products.**
 - e.g. Hydrochlorothiazide TPs are from abiotic transformation process.
- **The number of TPs is on average 2 per parent.**

Acknowledgement

Hereby I would like to thank:

- ❖ **Michael Maier for the incubation experiments;**
- ❖ **German Research Foundation (DFG) and German Academic Exchange Service (DAAD) for supporting the collaborators;**
- ❖ **Damian Helbling for kindly helping on the UM-PPS relative-off prediction lists.**

THANK YOU!