# **MS-based Interactomics:** Computational resources and tools for studying the physical interactome

**ASMS Bioinformatics MS Interest Group**

Wednesday Evening Workshop

Isabell Bludau & Bill Noble

# What is ‘interactomics’ and why do we discuss it?

- Many MS-omics studies focus on **cataloging and quantifying individual molecules** of a particular type
  - e.g. quantitative protein or metabolite matrix

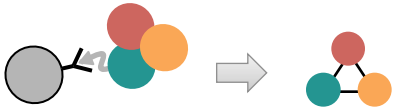
- Most biological **molecules don’t operate in isolation** but they interact with each other
  - protein complexes
  - activity regulation via metabolite/drug binding

- **‘Interactome’** = **comprehensive** set of **molecular interactions** in biological system
  - here we focus only on **physical** (not functional) interactions

# Current MS-based techniques for large-scale interactomics

Protein-protein interaction (PPI) networks:

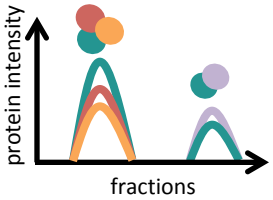
- **Affinity-purification MS (AP-MS)**
- Proximity-dependent labeling: APEX, BioID



➪ Interaction network

Protein-protein complexes:

- **Protein co-fractionation MS (CoFrac-MS)**




➪ Protein complexes

Structural information on PPIs:

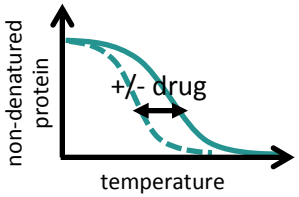
- Cross-linking MS

➪ Structure: interacting protein residues

# Current MS-based techniques for large-scale interactomics

Protein-metabolite/drug interactions:

- **Thermal proteome profiling (TPP)** / Cellular Thermal Shift Assay (CETSA)
- Limited proteolysis-coupled MS (LipMS)




➪ Protein-ligand interactions

Protein-RNA interactions:

- Protein-RNA crosslinking

➪ Protein-RNA interactions at residue resolution

# Available resources and databases

**Databases based on:**

- High-throughput methods
- Low-throughput assays
- Computational predictions

**Goals:**

- Expand current knowledge
- Use knowledge from existing databases
- Look at interactome changes and dynamics

**Databases:**

Protein-protein interactions (PPIs)

- STRING (https://string-db.org/)
- BioPlex (http://bioplex.hms.harvard.edu/)
- PrePPI (https://honiglab.c2b2.columbia.edu/PrePPI/)

Protein complexes

- CORUM (https://mips.helmholtz-muenchen.de/corum/)
- Complex Portal (https://www.ebi.ac.uk/complexportal/home)

Protein-metabolite/drug interactions

- STITCH (http://stitch.embl.de/)

General interactions:

- IntAct (https://www.ebi.ac.uk/intact/)

# Computational challenges and what we would like to discuss today

- **Protein-protein interaction networks: affinity-purification MS (AP-MS)**
  - Many reciprocal pull-downs to map the full PPI network of a cell
  - 100s - 1000s of MS measurements > prevent error accumulation
  - Confidently distinguish true from false interactions

*Eduard Huttlin*

- **Protein-protein complexes: Co-fractionation MS (CoFrac-MS)**
  - Comprehensive interactome map from a single experiment (< 100 MS measurements)
  - Distinguish true interactions from random co-elutions

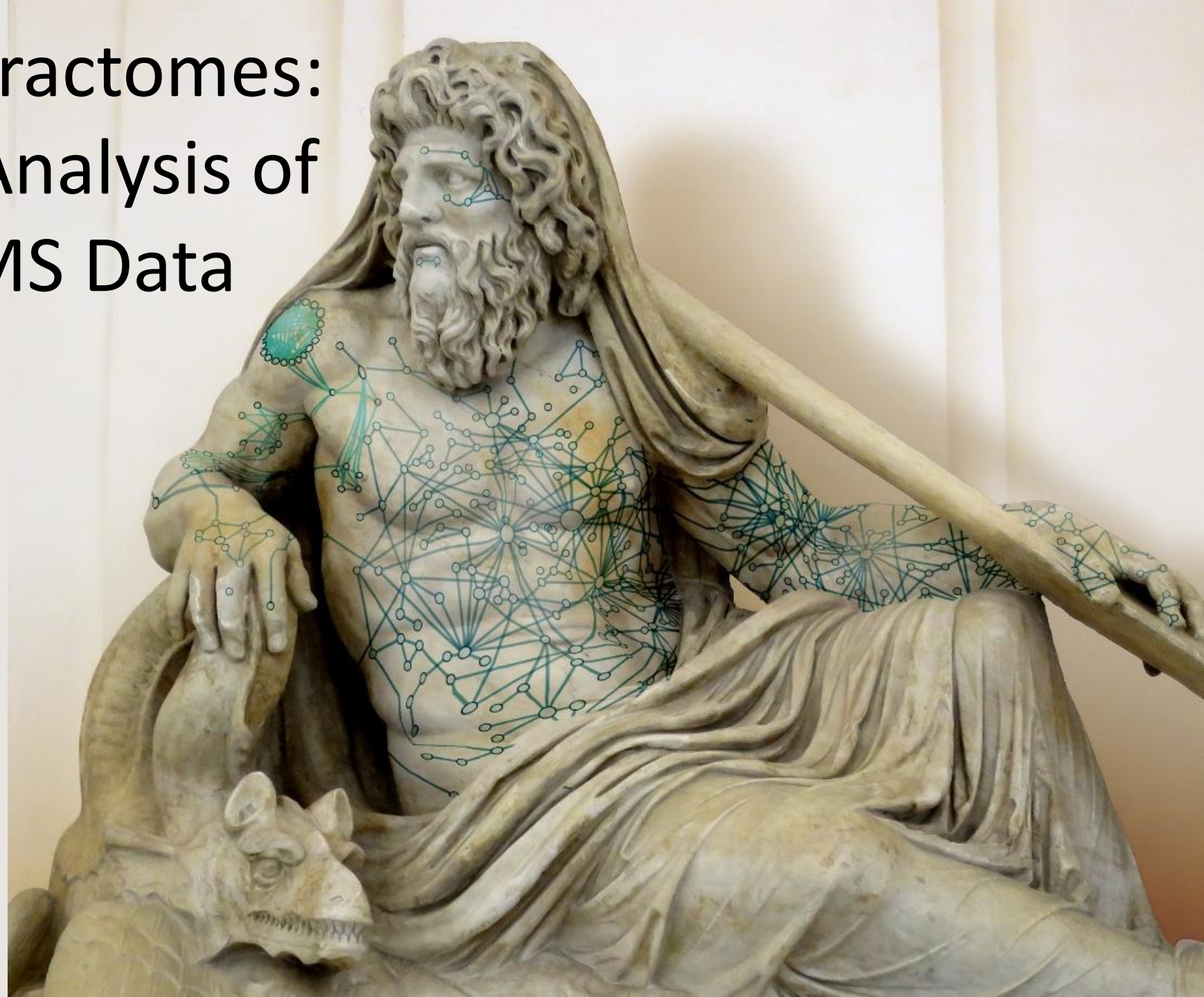
*Isabell Bludau*

- **Protein-drug interactions: thermal proteome profiling (TTP)**
  - Many metabolites are tested against thousands of proteins
  - How to estimate significance?

*Dominic Helm*

Edward Huttlin
Harvard Medical School

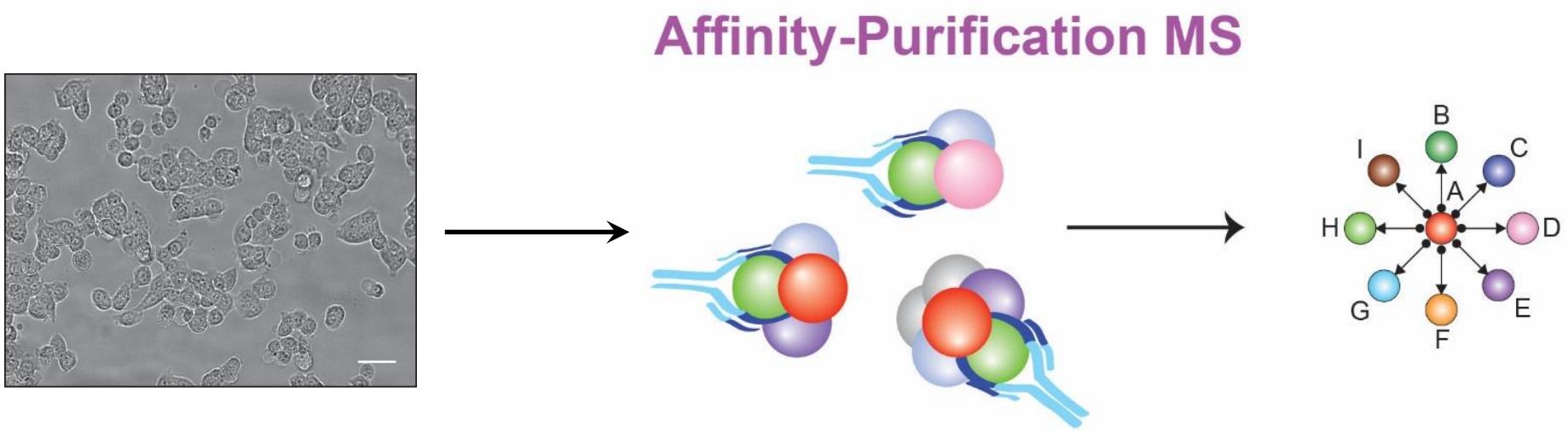
# From IP's to Interactomes: Computational Analysis of Large-scale AP-MS Data

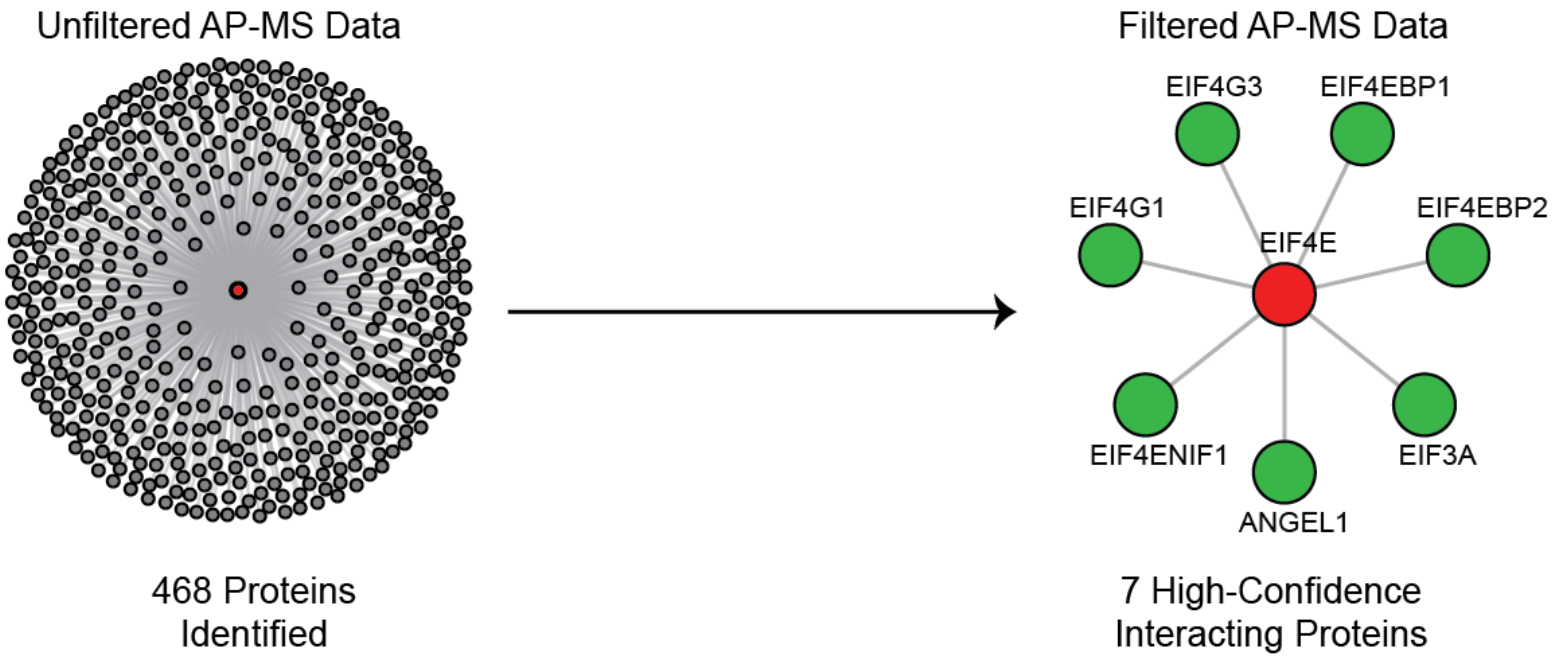


Ed Huttlin

Harvard Medical School
Department of Cell Biology
Boston, Massachusetts

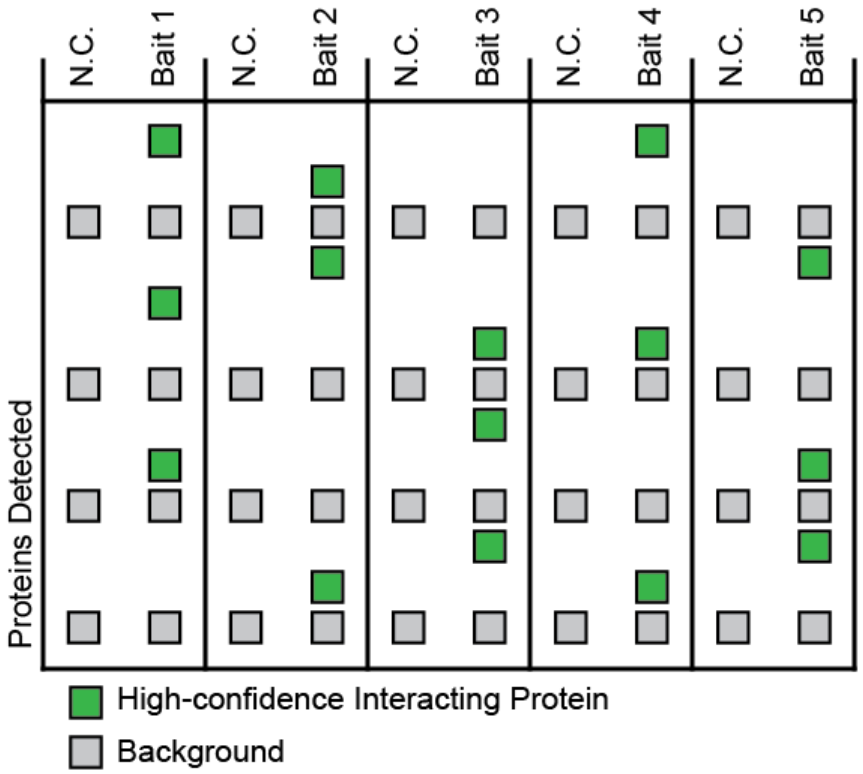
# The Achilles Heel of AP-MS: Which Interactions are Real?



# Computational Strategies for Identifying Interacting Proteins

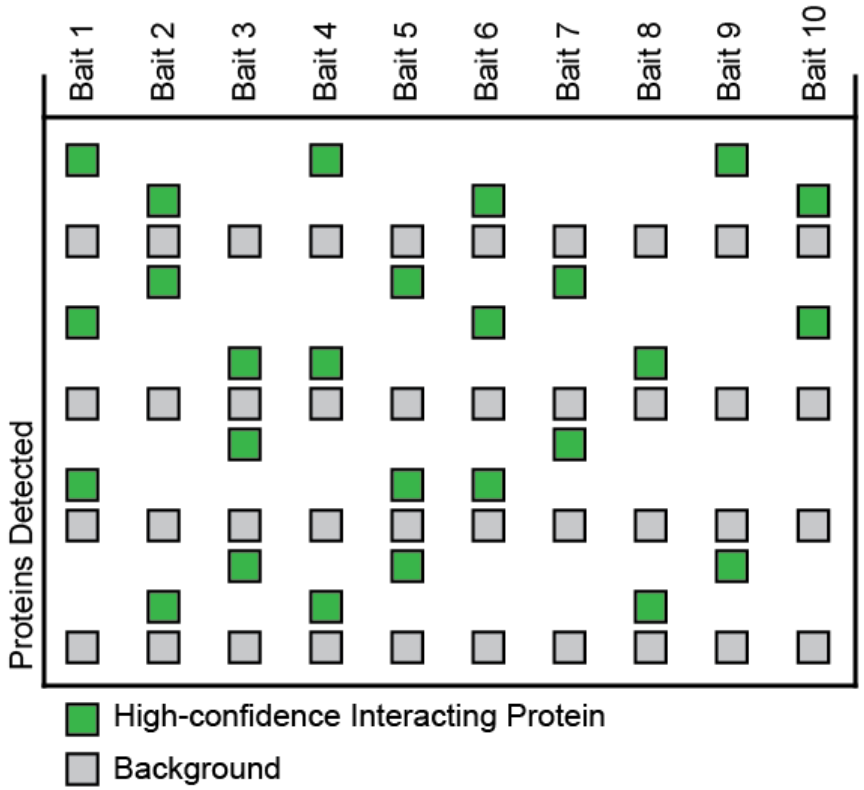
## COMPARISON WITH NEGATIVE CONTROLS




*Negative control IP's are used to Define background. Proteins present At higher abundance than background Are assumed to be interactors.*

***Examples:*** *QUBIC, SAINT, many others*

## COMPARISON ACROSS UNRELATED IP's




*Background is assumed to be constant across IP's. Interacting proteins are found by seeking proteins Whose abundance is increased above their Average across many IP's of unrelated baits.*

***Examples:*** *CompPASS, SAINT, MiST, HGScore, Socio-affinity Index*

# CompPASS Scoring Algorithm

## Stats Table

| | Bait 1 | Bait 2 | Bait 3 | Bait 4 | Bait *k* |
|---|---|---|---|---|---|
| **Interactor 1** | $X_{1,1}$ | $X_{2,1}$ | $X_{3,1}$ | $X_{4,1}$ | $X_{k,1}$ |
| **Interactor 2** | $X_{1,2}$ | $X_{2,2}$ | $X_{3,2}$ | $X_{4,2}$ | $X_{k,2}$ |
| **Interactor 3** | $X_{1,3}$ | $X_{2,3}$ | $X_{3,3}$ | $X_{4,3}$ | $X_{k,3}$ |
| **Interactor 4** | $X_{1,4}$ | $X_{2,4}$ | $X_{3,4}$ | $X_{4,4}$ | $X_{k,4}$ |
| **Interactor *m*** | $X_{1,m}$ | $X_{2,m}$ | $X_{3,m}$ | $X_{4,m}$ | $X_{k,m}$ |

$X_{i,j}$ = Spectral counts for interactor *j* with bait *i*

Is the protein more abundant than usual in this IP?

## Z-Score

$$Z = \frac{X_{i,j} - \bar{X}}{S}$$

$\bar{X}$ = Average spectral counts for protein across baits
$X_{i,j}$ = Spectral counts for interactor j with bait i
S = Standard Deviation spectral counts across baits

## $WD^N$-Score

$$WD^N = \sqrt{\left(\frac{N}{n}\ \frac{S}{\bar{X}}\right)^p X_{i,j}}$$

N = Number of runs
n = Number of runs in which the protein is found
p = Number of replicates observed (1 or 2)

How frequently is this protein detected? Is It detected reproducibly?

**Mat Sowa**

**CompPASS:** Sowa et al. (2009) *Cell,* 138:389-403.

**Wade Harper**

# An R Implementation of CompPASS

CompPASS

Comparative Proteomic Analysis Software Suite

**Experiments**

Browse... SampleData_Set1.tsv

Upload complete

**External Stats**

Browse... No file selected

**Normalization Factor**

0.98

## Input Instructions

Download Sample Input

The input file must be a tab-delimited text file no larger than 5Mb with the following five columns:

1. Experiment ID
2. Replicate
3. Bait
4. Prey
5. Spectral Count

Download

Show 25 entries

Search: EIF4E

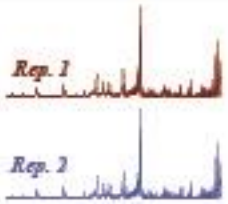
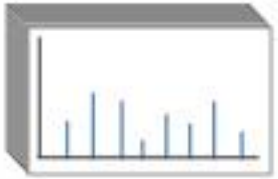
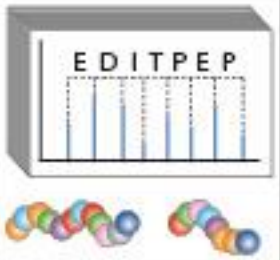
| Experiment.ID | Bait | Prey | AvePSM | Z | WD | Entropy |
|---|---|---|---|---|---|---|
| 14613 | EIF4E | EIF4G3 | 95.0 | 6.92955050 | 7.83625947 | 0.9992880 |
| 14613 | EIF4E | ANGEL1 | 10.5 | 6.92964646 | 5.23832034 | 0.8756634 |
| 14613 | EIF4E | EIF4ENIF1 | 30.0 | 6.92579623 | 4.28384182 | 0.9805264 |
| 14613 | EIF4E | EIF4EBP2 | 21.0 | 6.89832377 | 3.39071344 | 0.9859094 |
| 14613 | EIF4E | EIF4G1 | 134.0 | 6.92246807 | 2.18340357 | 0.9910094 |
| 14613 | EIF4E | CBR3 | 1.0 | 6.92964646 | 1.61658075 | 1.0000000 |
| 14613 | EIF4E | MAPRE3 | 1.0 | 6.92964646 | 1.61658075 | 1.0000000 |
| 14613 | EIF4E | EIF4E | 56.0 | 151.52528743 | 1.57844143 | 0.9888990 |
| 14613 | EIF4E | PABPC4 | 3.5 | 0.69158986 | 1.35581151 | 0.9886994 |
| 14613 | EIF4E | EIF4EBP1 | 30.5 | 6.92011991 | 1.33350970 | 0.9450667 |
| 14613 | EIF4E | EIF3A | 3.5 | 5.61111102 | 1.07350240 | 0.8960382 |
| 14613 | EIF4E | EIF3F | 1.5 | 6.26471601 | 0.43204938 | 0.9544340 |
| 14613 | EIF4E | EIF3B | 5.0 | 6.13449264 | 0.40000000 | 1.0000000 |
| 14612 | SFN | EIF4EBP1 | 1.0 | 0.07426017 | 0.24146059 | 1.0000000 |

**David Nusinow**

https://github.com/dnusinow/cRomppass

http://bioplex.hms.harvard.edu/comppass/

# From IP's to Interactomes: Meeting the Challenges of Scale

| |  |   |  |   |  |
|---|---|---|---|---|---|
| Parameter: | AP-MS Baits | LC-MS Runs | MS² Spectra | Peptide-Spectral Matches | Protein Identifications |
| Median Statistics Per Run: | 1 | 2 | 14,090 | 3,923 | 805 |
| 293T: | 10,128 | 20,256 | 285,407,040 | 79,464,288 | 16,306,080 |
| HCT116: | 5,522 | 11,044 | 155,609,960 | 43,325,612 | 8,890,420 |
| Total: | 15,650 | 31,300 | 441,017,000 | 122,789,900 | 25,196,500 |

## CHALLENGES OF SCALE

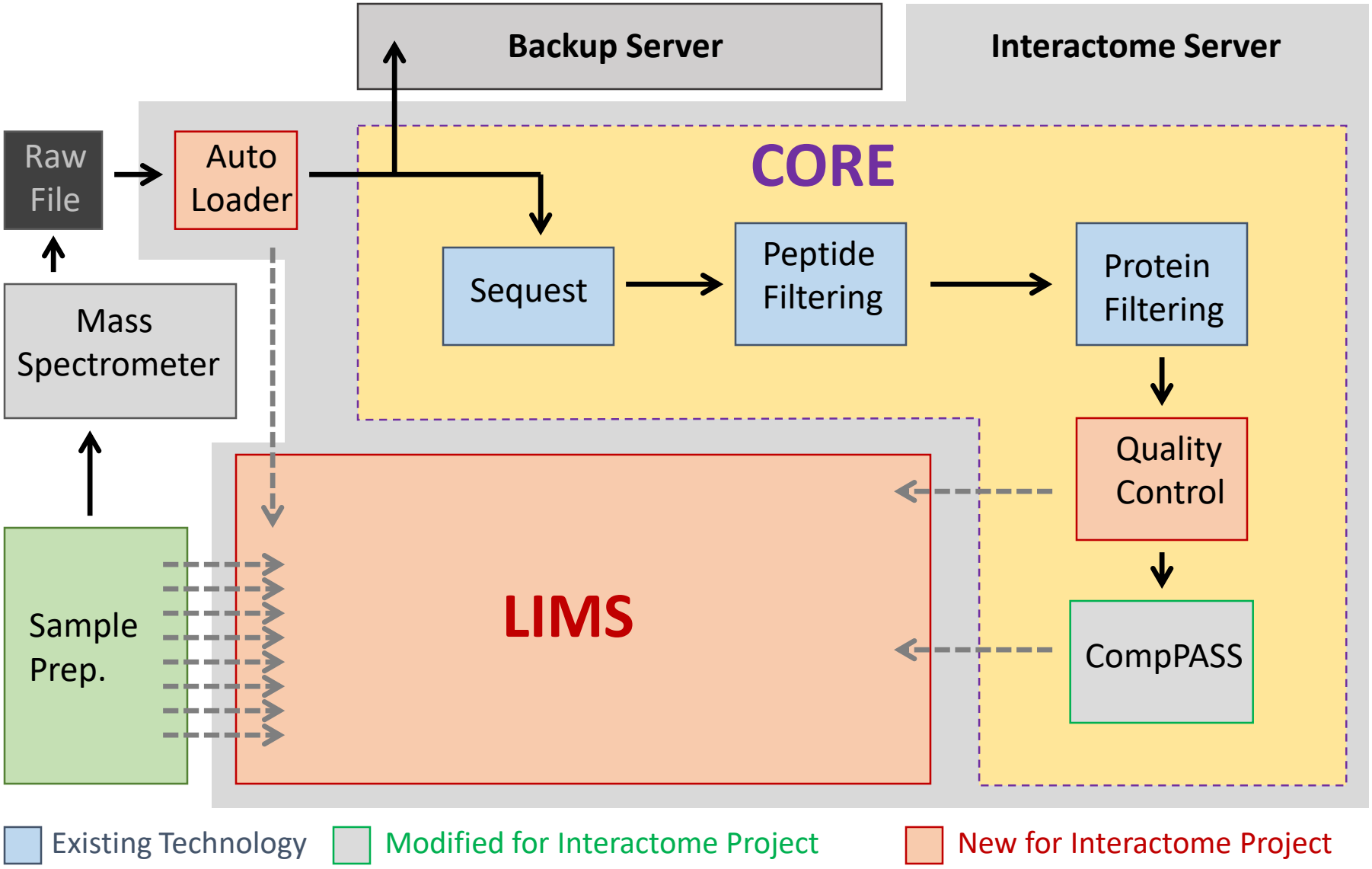
**1.**
How to do all those searches?

**2.**
How to ensure quality across thousands of runs?

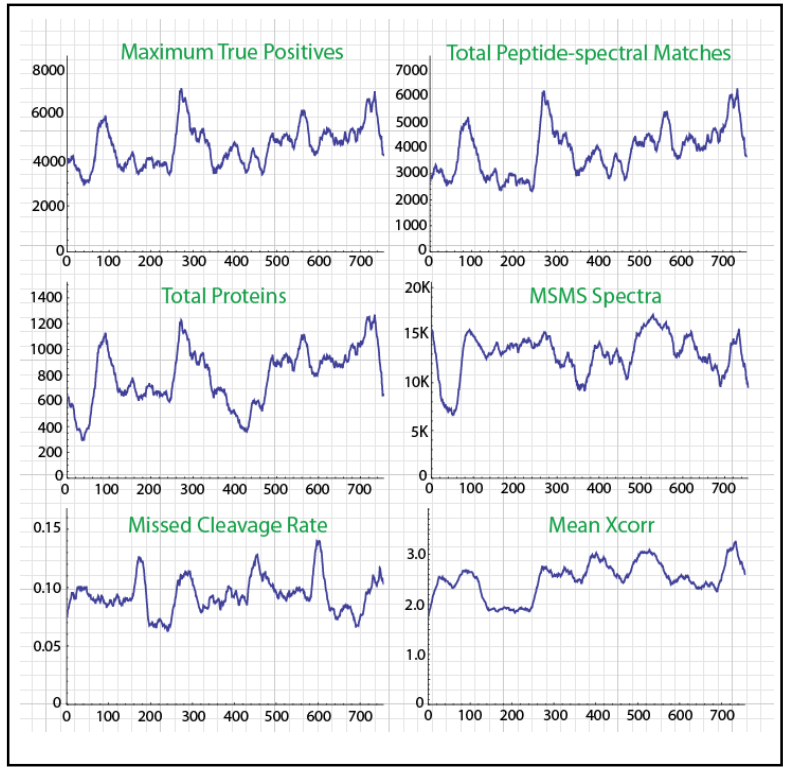
**3.**
How to minimize errors due to false positive ID's?

**4.**
How to rapidly and accurately identify interactors?

# Data processing overview

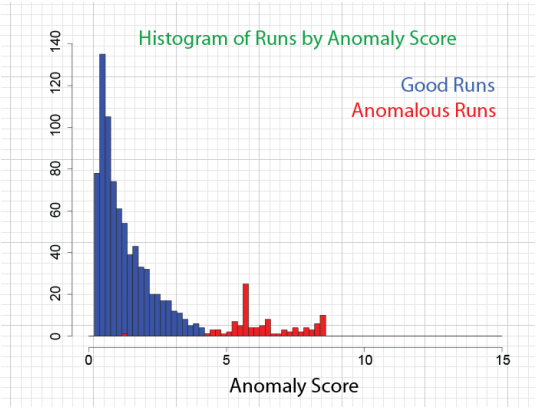


# Automated and Adaptive Run QC





TRAINING DATA




PREDICTIVE MODEL

Cycle repeats
For every run.


CLASSIFICATION

NEW RUN


PREDICTION

# Automatic Notification of Problematic Runs

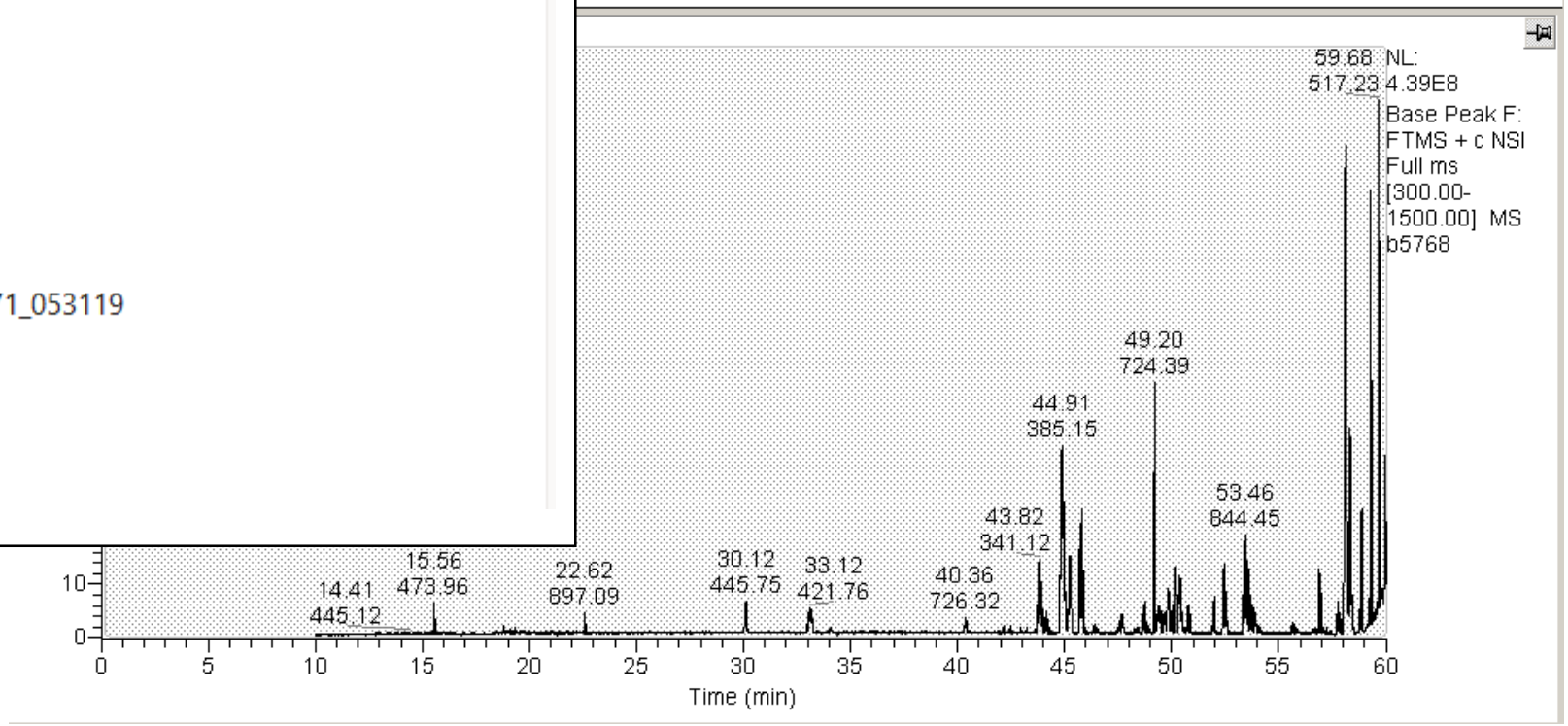
## Problems with search 71455

S

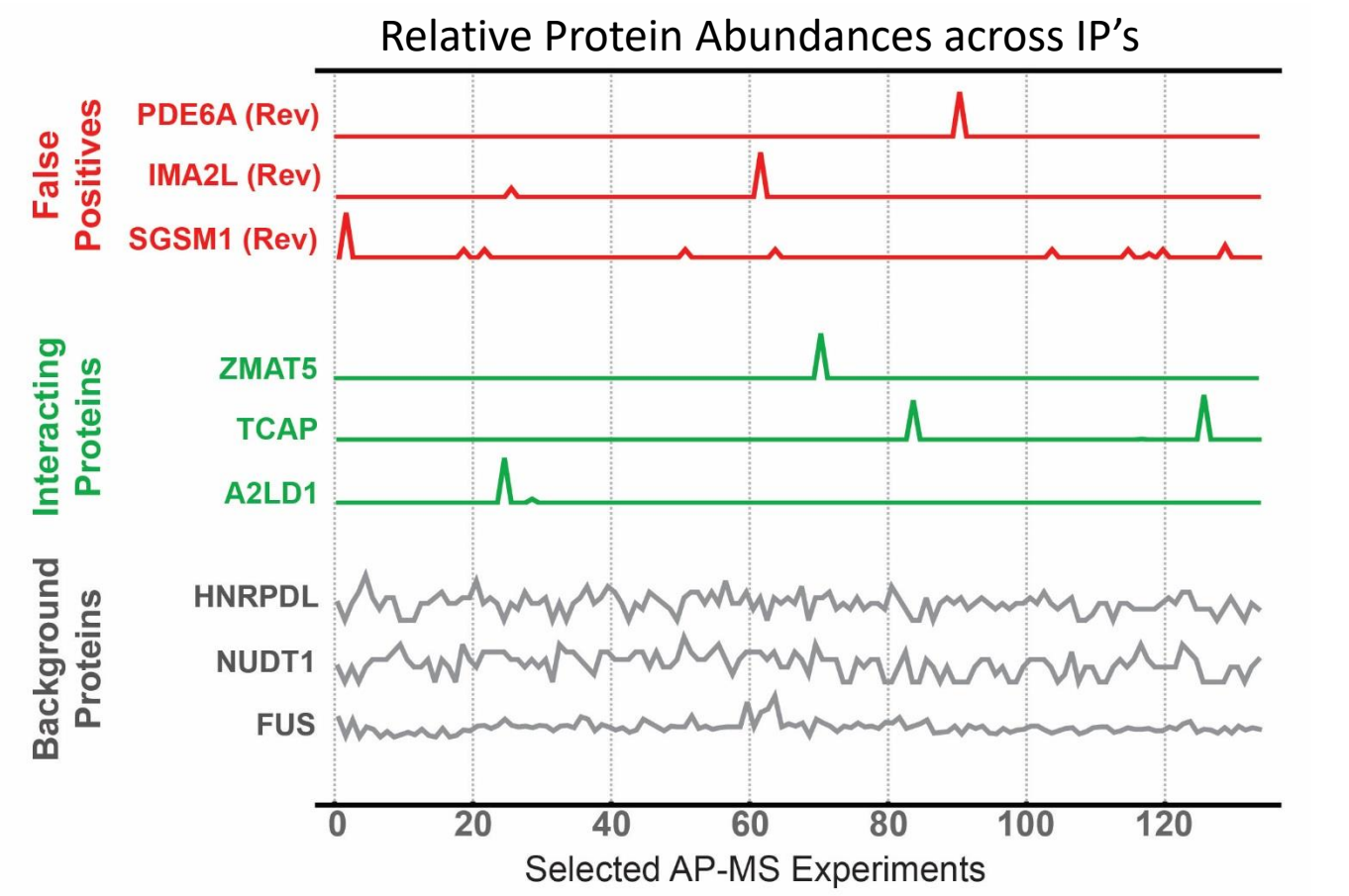
SewerRat@harperfs.med.harvard.edu
Mon 6/3/2019 1:44 AM
Huttlin, Edward Leo; Paulo, Joao A; joe_cannon@hms.harvard.edu +2 others

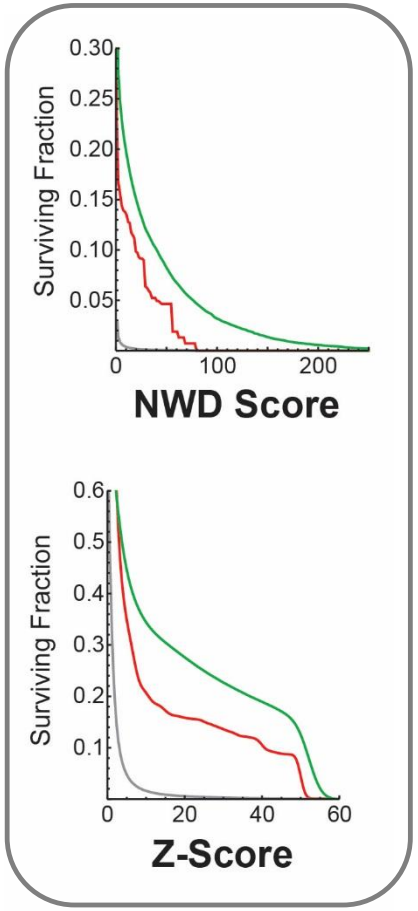
Problems with search 71455: qb01088_HCT-REPEAT03_A03_A_00671_053119.

| Parameter | Value |
|---|---|
| tpMax | 553 |
| totalPSMs | 553 |
| totalProteins | 100 |
| ratioUPepsToTPeps | 0.47377852842942 |
| sensitivity | 0.99999819168501 |
| msmsSpectra | 14565 |
| successRate | 0.037967730861655 |
| aveXcorr | 2.5170851717902365 |
| MCRate | 0.094032379688283 |
| search_name | qb01088_HCT-REPEAT03_A03_A_00671_053119 |
| score | 22.6033451322409 |
| manualTraining | no |
| class | bad |
| notes | |



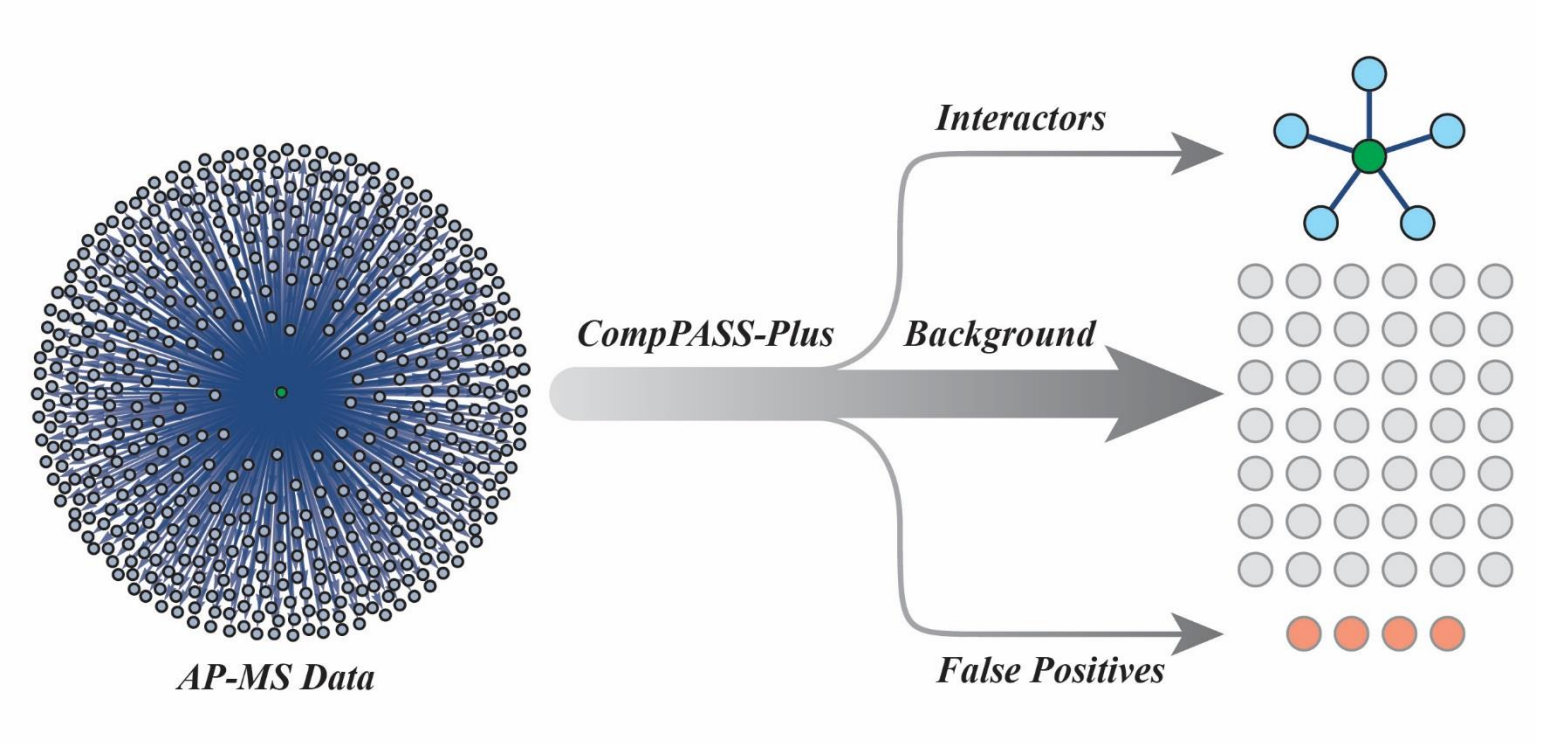
# Distinguishing Interactors from Background and False Positives




Both *bona fide* interactors and false positives appear in AP-MS experiments as "rare" events that score as likely interactions. Unless precautions are taken, enrichment of these false positives can cause surprisingly high false discovery rates among AP-MS datasets.

# Distinguishing Interactors from Background and False Positives




- A key challenge of AP-MS is distinguishing the few **true interacting proteins** (~1-2%) from a much larger number of **background proteins** (~98%), **false positives** (~1%), and other **experimental artifacts**.

- While existing algorithms for AP-MS distinguish enriched interacting proteins from nonspecific background, CompPASS-Plus uniquely accounts for false positive ID's.

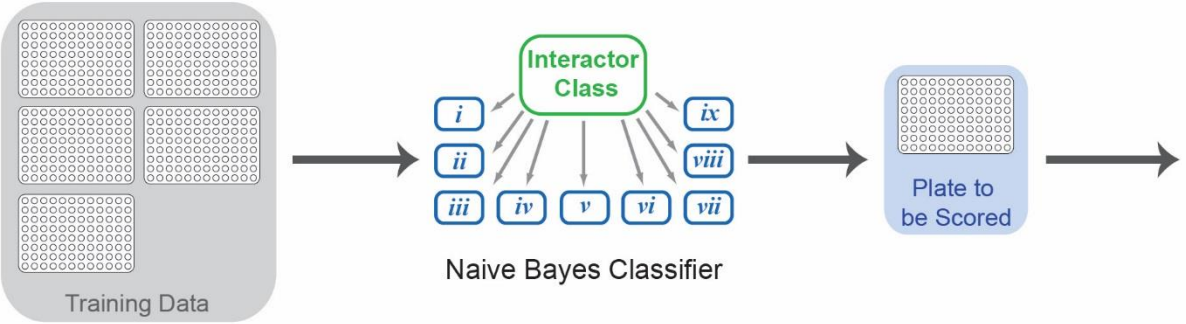
# CompPASS-Plus for Interactor Identification

**Initial Training Data**

| Class | Description | Percent |
|---|---|---|
| Likely Wrong ID | *Modeled by distribution of decoy prey ID's.* | 0.05 |
| Non-Interaction | *Bait-prey pairs not reported in STRING/GeneMania* | 98.6 |
| Likely Interaction | *Bait-prey pairs confirmed by STRING/GeneMania.* | 1.35 |

**Features**

*i.* NWD Score
*ii.* Z-Score
*iii.* Plate Z-Score
*iv.* Entropy
*v.* Unique Peptides (Binned)
*vi.* Ratio
*vii.* Total PSM's
*viii.* Ratio Total PSM's
*ix.* Unique:Total Peptide Ratio

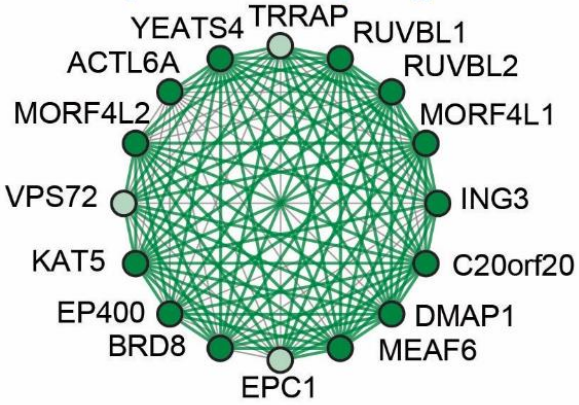



| Bait | Prey | P(Wrong) | P(NoInt) | P(Int) |
|---|---|---|---|---|
| FBXO6 | FBXO6 | 0 | 0 | 1 |
| FBXO6 | UBB | 0 | 0 | 1 |
| FBXO6 | CUL1 | 0 | 0.002 | 0.998 |
| FBXO6 | COPS2 | 0 | 0.121 | 0.879 |
| FBXO6 | HSPA8 | 0 | **0.974** | 0.026 |
| FBXO6 | PSMD2 | 0 | **0.986** | 0.014 |
| FBXO6 | SLC25A6 | 0 | **0.995** | 0.005 |
| FBXO6 | TMEM30A | 0.258 | **0.738** | 0.004 |
| FBXO6 | PLA2G15 | 0.999 | 0 | 0.001 |

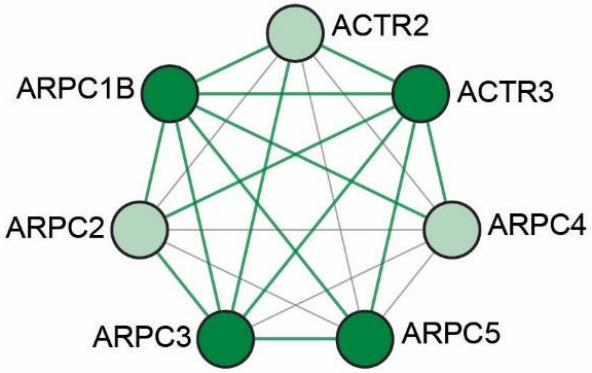
- CompPASS-Plus is a Naive Bayes classifier that extends CompPASS for improved Identification of interacting proteins.
- Features include standard CompPASS scores as well as customized scores.
- Training data is obtained from STRING/GeneMania and from Target/Decoy methods
- Leave-one-out cross-validation is incorporated at the 96-well-plate level for classification.

# CORUM Validation

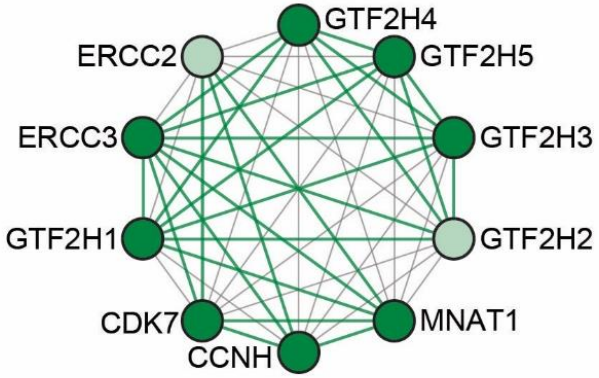
**NuA4/Tip60-HAT Cmplx. ($p = 5.7e^{-240}$)**



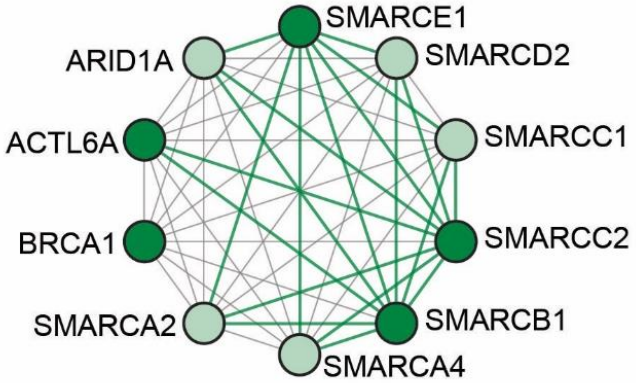

**Arp2/3 Complex ($p = 1.1e^{-35}$)**



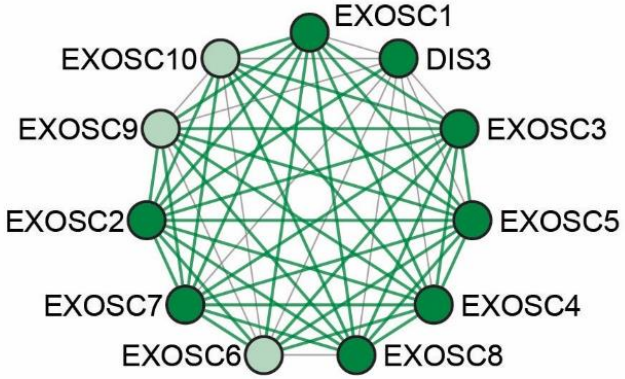

**TFIIH Cmplx. ($p = 3.8e^{-60}$)**



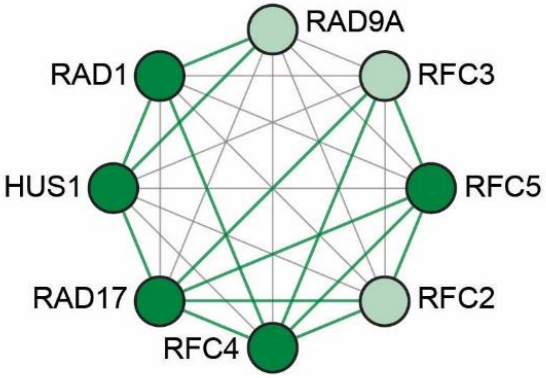

**SWI-SNF Complex ($p = 1.1e^{-45}$)**



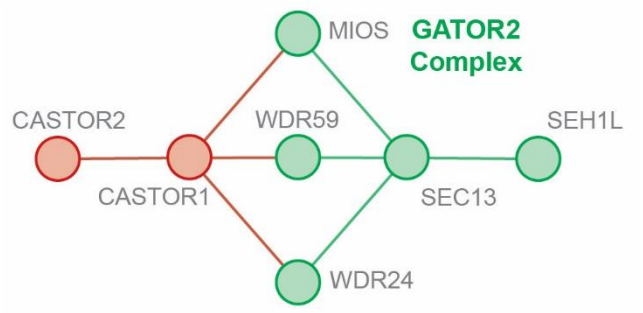

**Exosome ($p = 9.5e^{-110}$)**



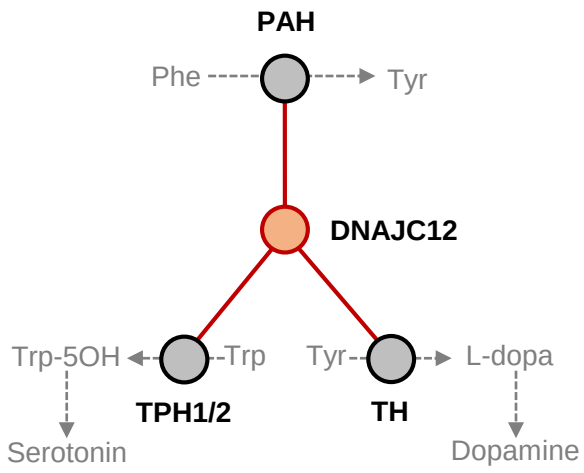

**Checkpoint Rad Complex ($p = 3.5e^{-33}$)**



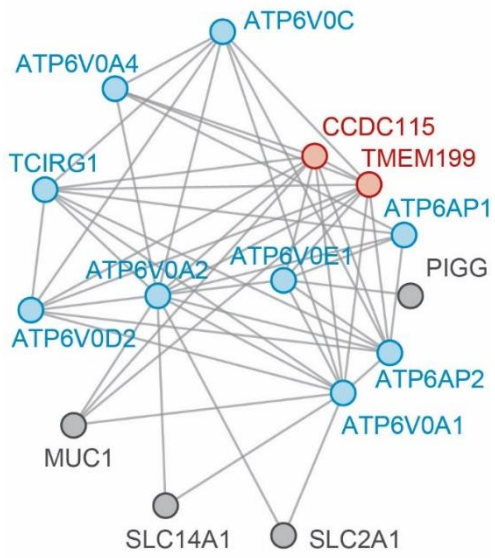
# BioPlex Associates New Proteins with Known Complexes



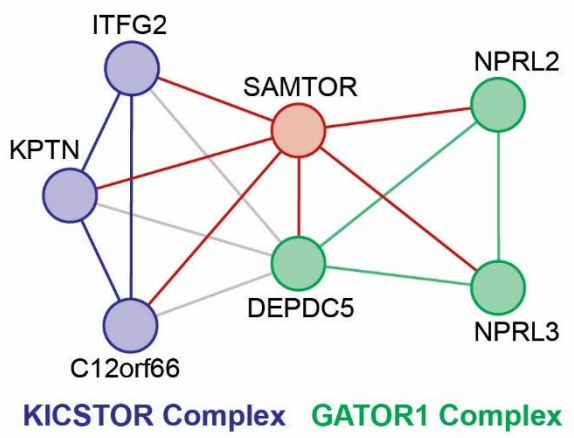

Chantranupong (2016) Cell, 165:153.
Saxton (2016) Nature, 536:229.



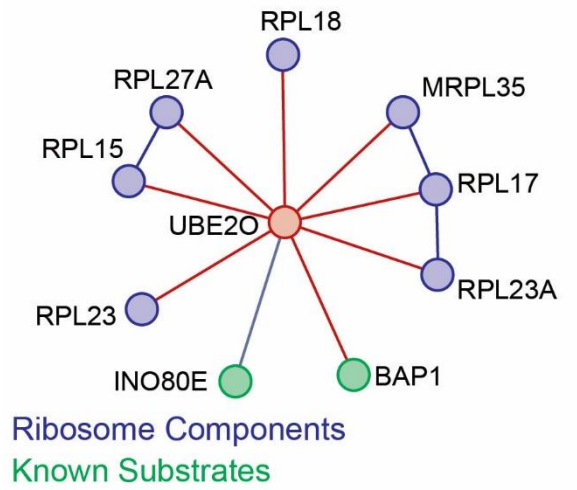

Anikster et al. (2017)
*Am. J. Hum. Genet.* 100, 257.



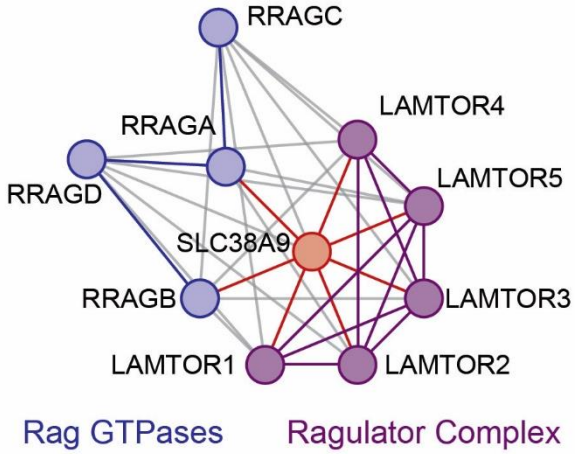

Miles (2017) eLife, 6:e22693.




Gu et al. (2017) Science, 358:813.

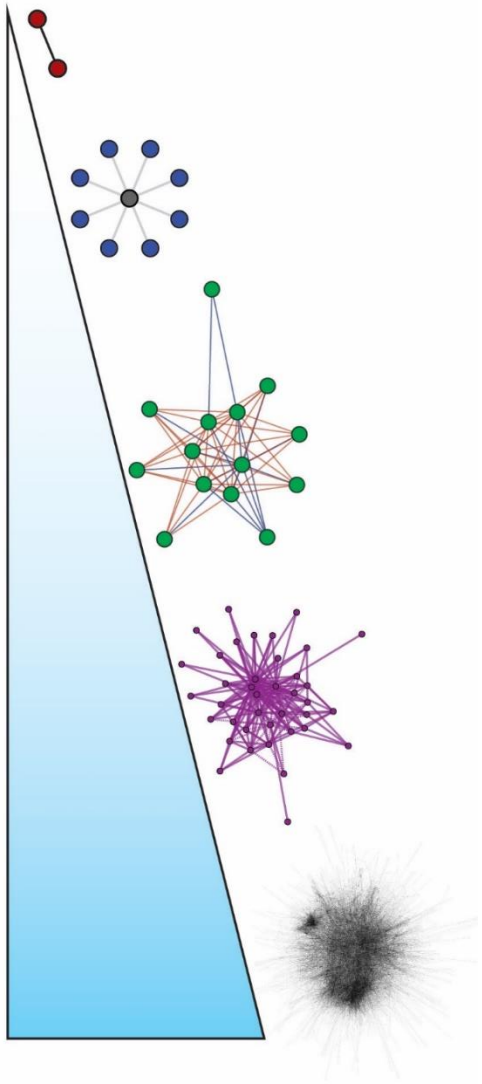



Nguyen (2017) Science, 357:eaan0218.



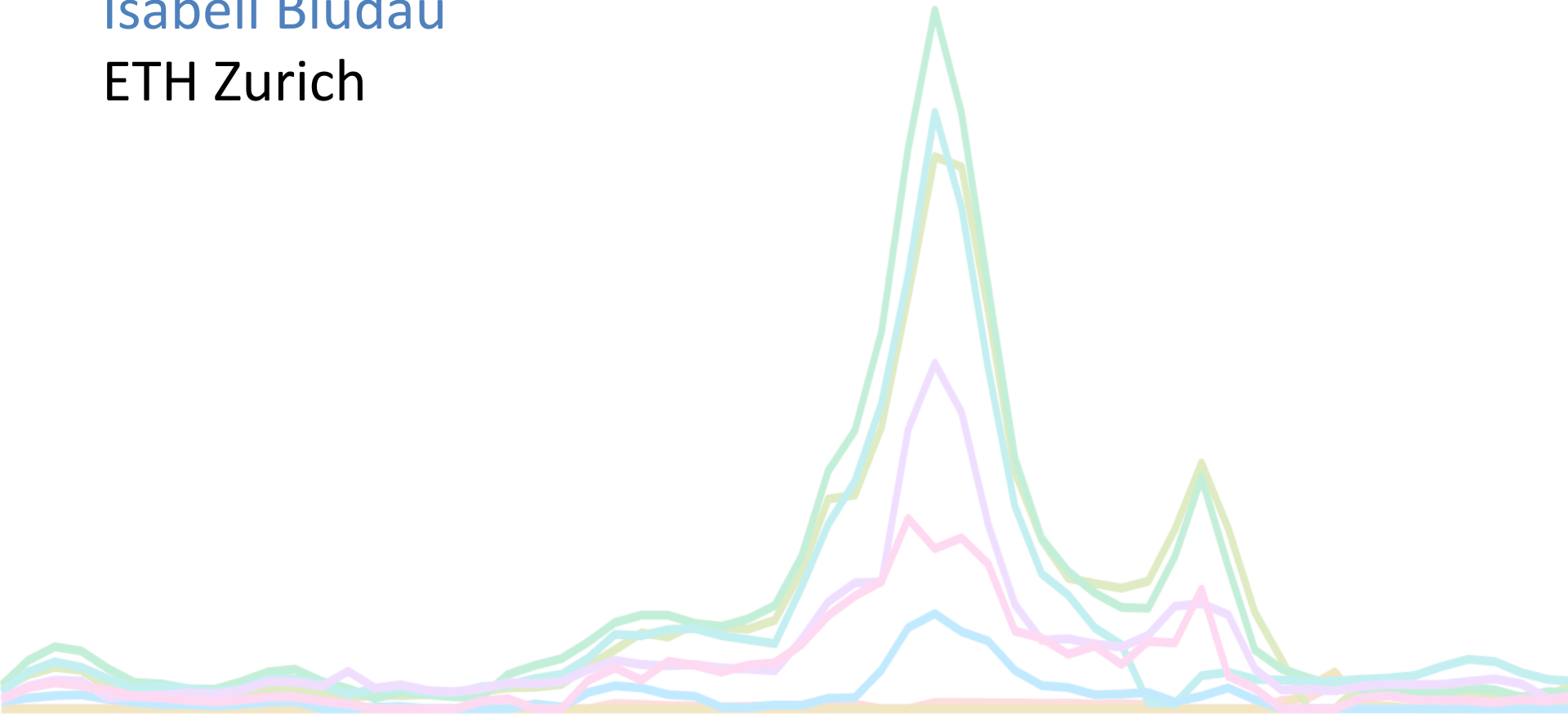

Rebsamen (2015) Nature, 519:477.

# Summary



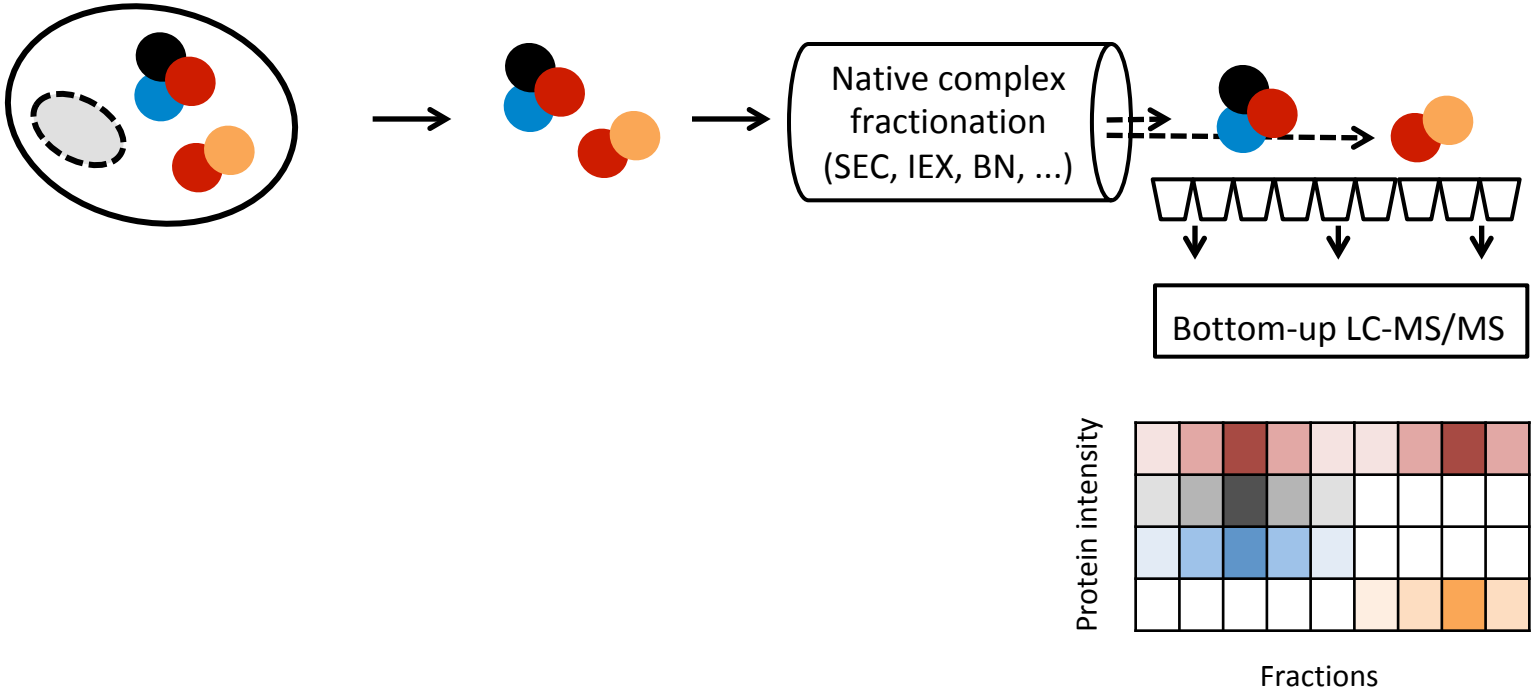
- Separating true interacting protein partners from background is a serious challenge for AP-MS
- A variety of algorithms have been developed to address this that accommodate a variety of experimental designs
- Performing AP-MS at truly large scale leads to additional challenges that must be addressed.
- Our CompPASS-Plus algorithm has enabled us to efficiently identify interacting proteins and produce reliable maps of the human interactome in multiple cell types.

Isabell Bludau
ETH Zurich



Underlying technology for data acquisition:

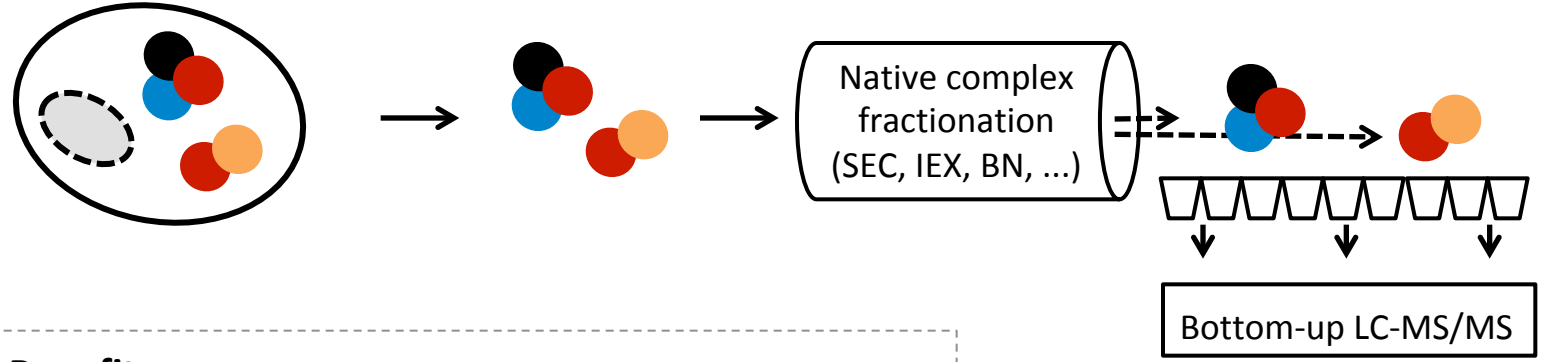
# Protein co-fractionation mass spectrometry




Andersen et al. (2003), Dunkley et al. (2004), Foster et al. (2006), Scott et al. (2015), Wan et al. (2015)

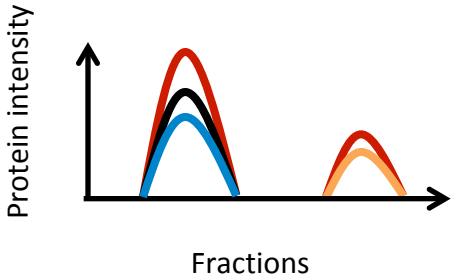
Underlying technology for data acquisition:

# Protein co-fractionation mass spectrometry




**Benefits:**

+ Independent of genetic engineering or antibody availability
+ Parallel detection of protein complexes on a proteome-wide scale

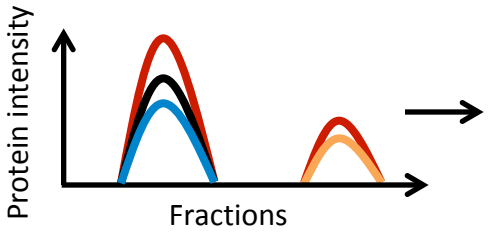



Andersen et al. (2003), Dunkley et al. (2004), Foster et al. (2006), Scott et al. (2015), Wan et al. (2015)

Established data analysis strategy:

# Protein correlation profiling

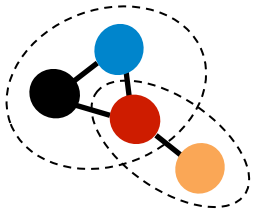
**Protein correlation profiling**



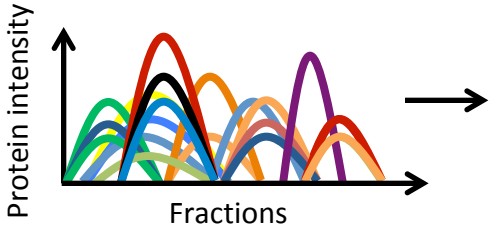

**Pairwise scoring**

| | | | |
|---|---|---|---|
| 1 | **0.9** | **0.8** | **0.9** |
| **0.9** | 1 | **0.9** | 0.1 |
| **0.8** | **0.9** | 1 | 0.2 |
| **0.9** | 0.1 | 0.2 | 1 |

**Clustering**



**PrInCE** (Stacey et al. 2017)




**Data properties:**

- Profiles for thousands of proteins (~5000)
- Limited peak capacity (~20-30)

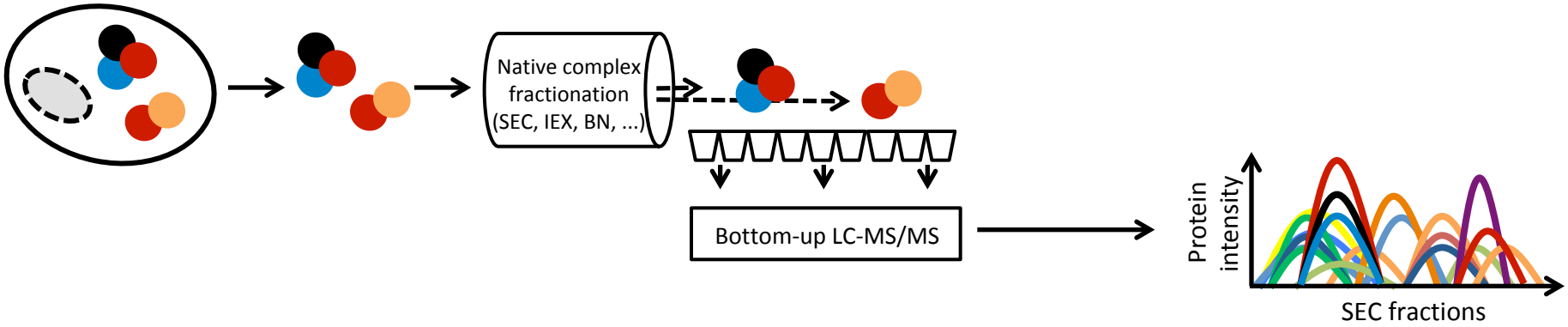
**Consequences:**

- Random co-elution of proteins
- Limited selectivity and sensitivity

Scott et al. (2015), Wan et al. (2015), Stacey et al. (2017)

Targeted anaysis strategy:

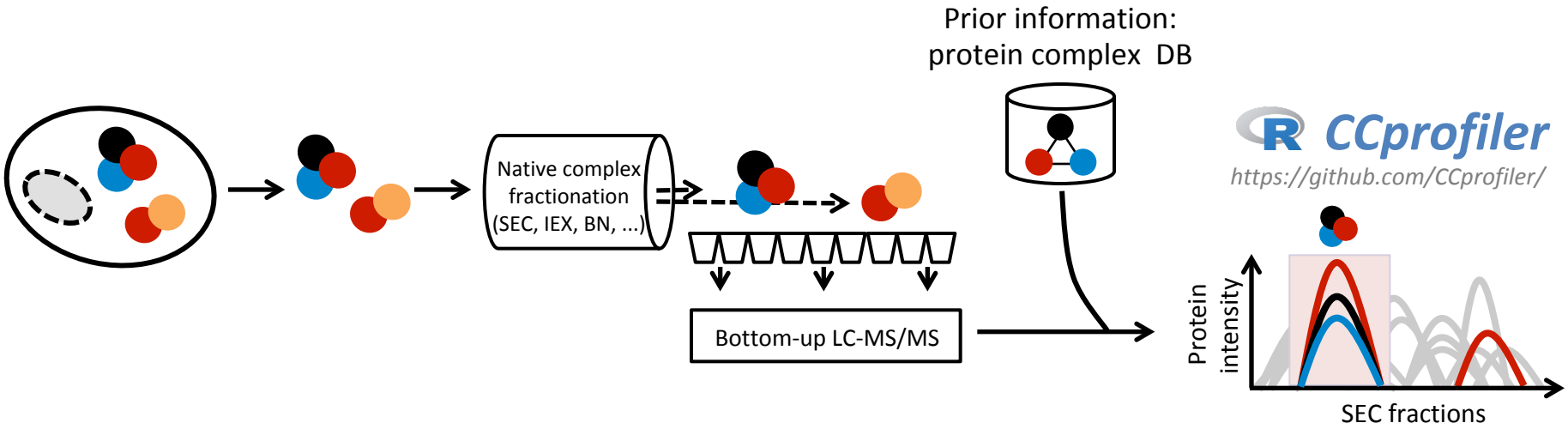
# Complex-centric proteome profiling




Heusel & Bludau et al. (2019)

Targeted anaysis strategy:

# Complex-centric proteome profiling




- ✓ Automated software for targeted complex-centric analysis
- ✓ Parallel and sensitive protein complex detection
- ✓ Complex-level FDR estimation

Heusel & Bludau et al. (2019)

Complex-centric proteome profiling:

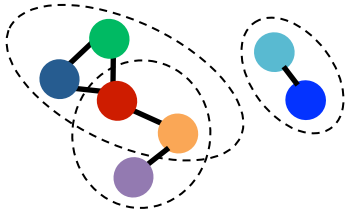
# Decoy based FDR estimation

CCprofiler
https://github.com/CCprofiler/

## Targets

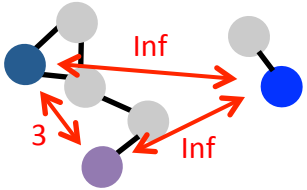
a) Defined hypotheses (e.g. CORUM)

b) Interaction network
(e.g. AP-MS, BioPlex, StringDB)
Select 1st degree neighbors of each protein as one target hypothesis



## Decoys

- Generate matching decoy for each target (same complex size distribution)
- Require minimum network distance between decoy proteins to avoid overlap with targets

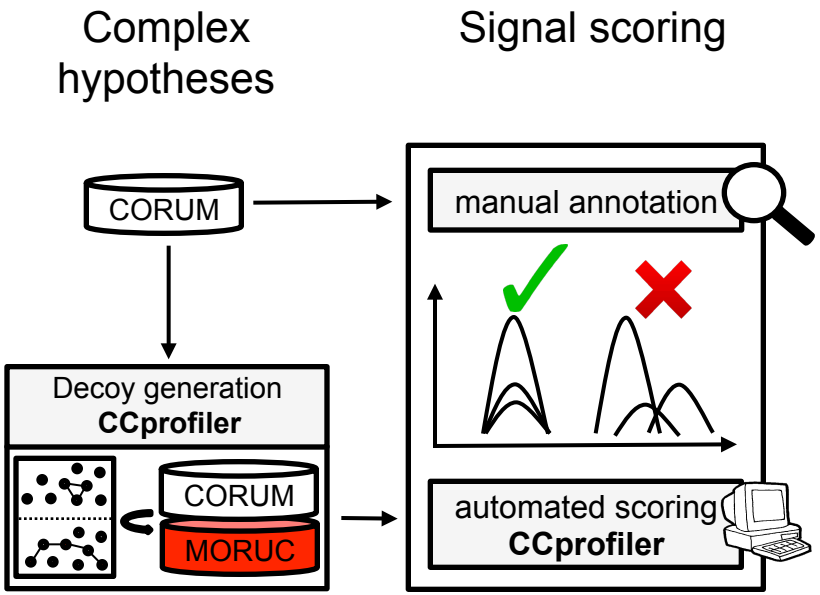


Complex-centric proteome profiling:

# Benchmark

CCprofiler

https://github.com/CCprofiler/



Complex-centric proteome profiling:

# Benchmark

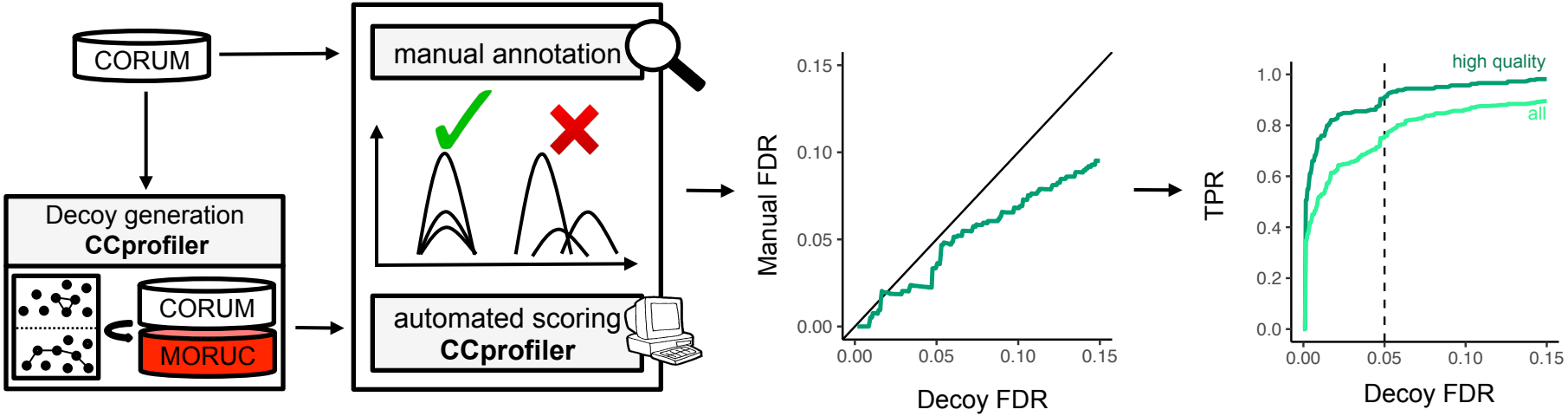
CCprofiler

https://github.com/CCprofiler/

## Complex hypotheses

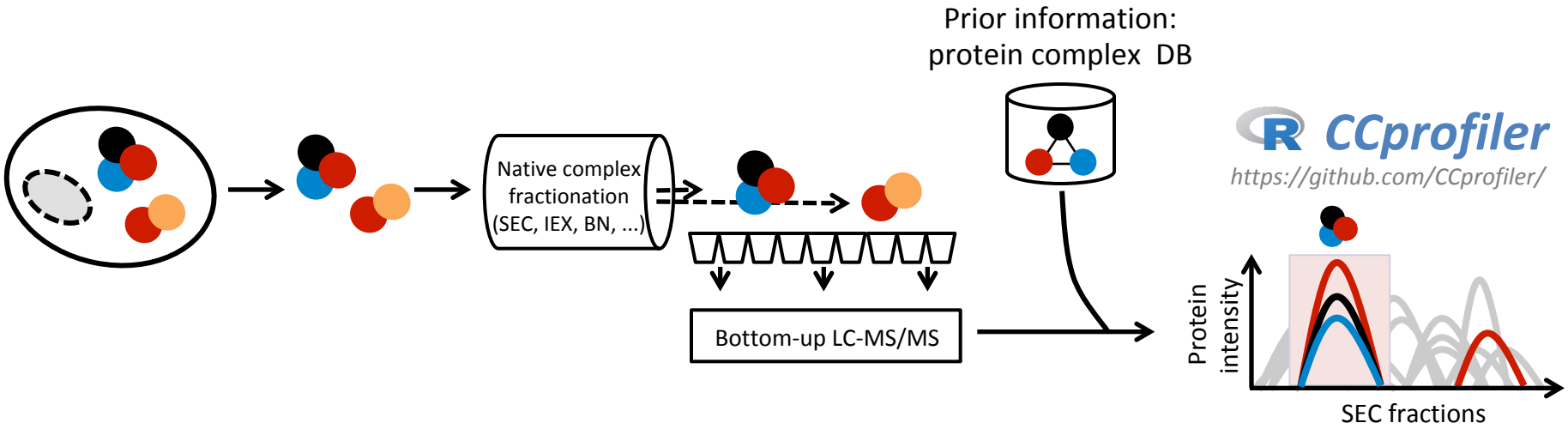
## Signal scoring

## Manual benchmark



Targeted anaysis strategy:

# Complex-centric proteome profiling

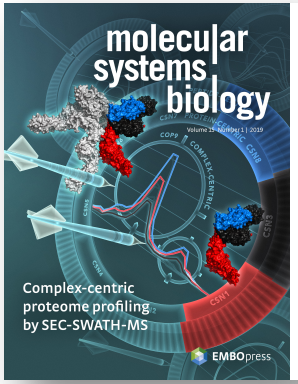



- ✓ Automated software for targeted complex-centric analysis
- ✓ Parallel and sensitive protein complex detection
- ✓ Complex-level FDR estimation

Heusel & Bludau et al. (2019)

Targeted anaysis strategy:

# Complex-centric proteome profiling




Published online: January 14, 2019

Article

TRANSPARENT PROCESS OPEN ACCESS

molecular systems biology

## Complex-centric proteome profiling by SEC-SWATH-MS

Moritz Heusel[1,2,†], Isabell Bludau[1,3,†], George Rosenberger[1], Robin Hafen[1,4], Max Frank[1], Amir Banaei-Esfahani[1,3], Audrey van Drogen[1], Ben C Collins[1], Matthias Gstaiger[1,**] & Ruedi Aebersold[1,5,*]

[†] These authors contributed equally to this work.

- ✓ Automated software for targeted complex-centric analysis
- ✓ Parallel and sensitive protein complex detection
- ✓ Complex-level FDR estimation

Heusel & Bludau et al. (2019)

# Complex-centric proteome profiling by SEC-SWATH-MS

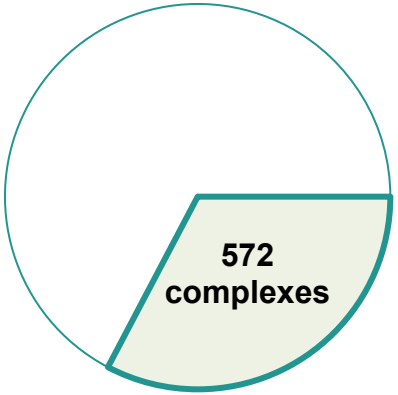
✓ **Detect and quantify hundreds of protein complexes**

HEK293 soluble proteome

- SEC fractionation: 1 mg, Yarra-SEC-4000, 81 fractions
- SWATH-MS: Triple-TOF 5600, 64 vw, 120 min gradient

➤ Consistent quantification of 4916 proteins

Detection of 572 out of 1753 CORUM complexes (5% FDR)



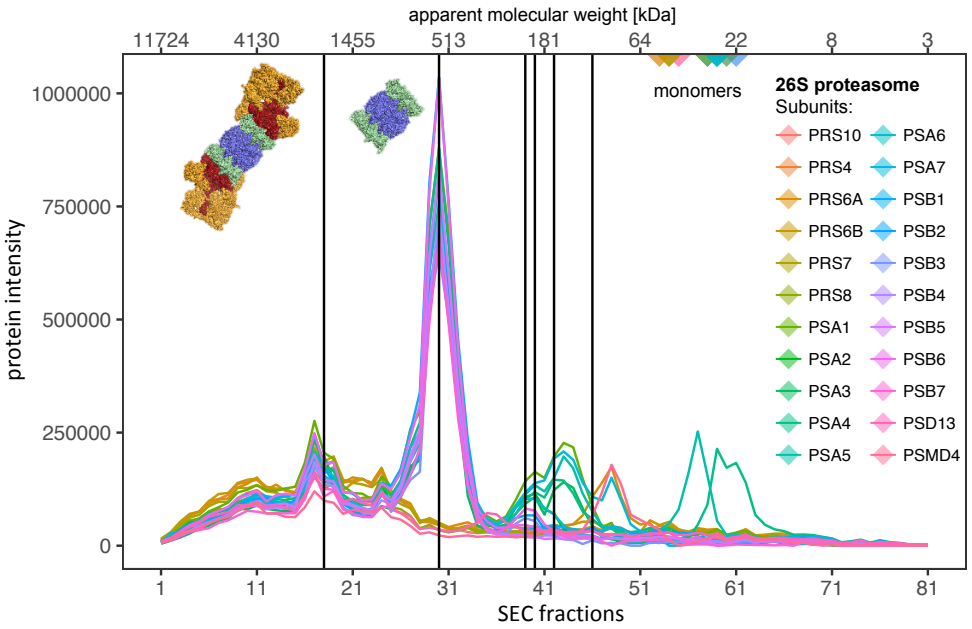

Heusel & Bludau et al. (2019)

# Complex-centric proteome profiling by SEC-SWATH-MS

- ✓ Detect and quantify hundreds of protein complexes
- ✓ **Investigate sub-complexes and assembly intermediates**

HEK293 soluble proteome

**Proteasome assembly**




Heusel & Bludau et al. (2019)

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- ✓ Detect and quantify hundreds of protein complexes
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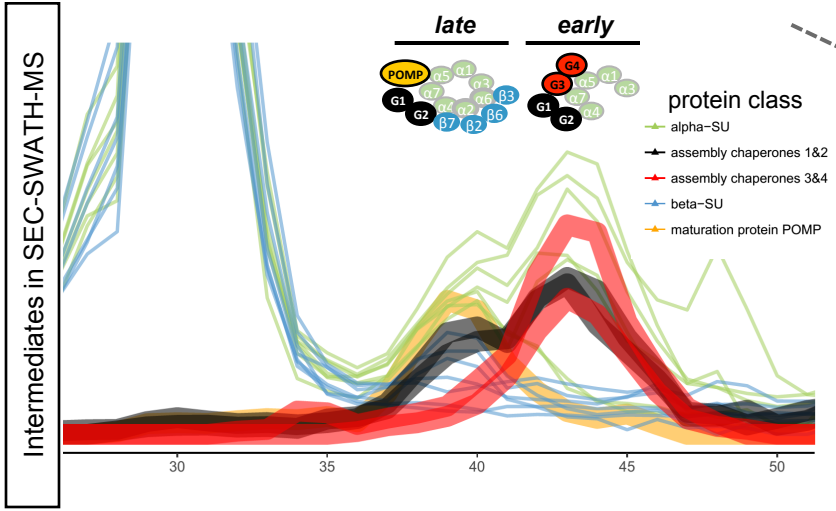
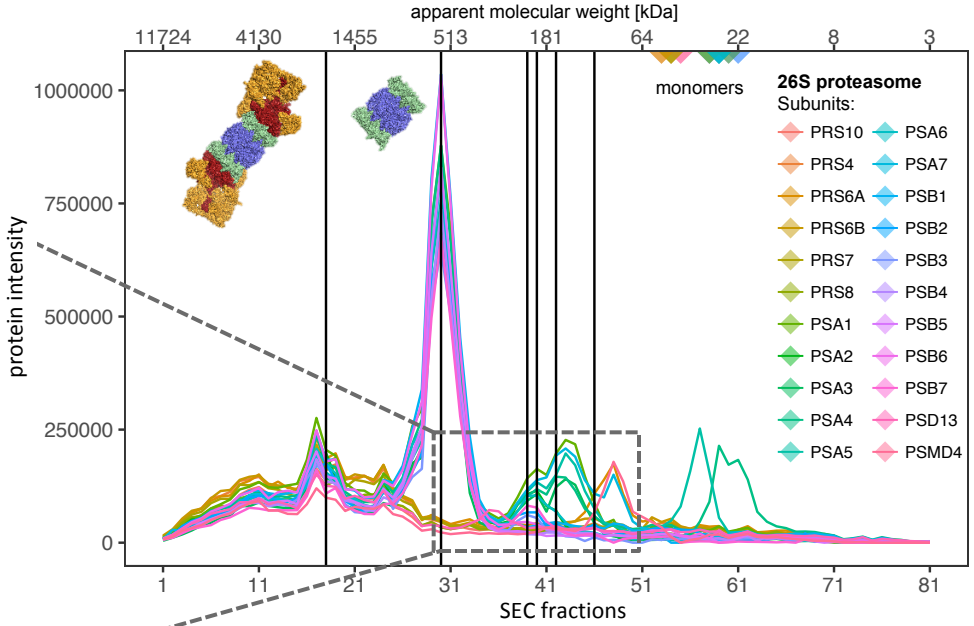
HEK293 soluble proteome

**Proteasome assembly**

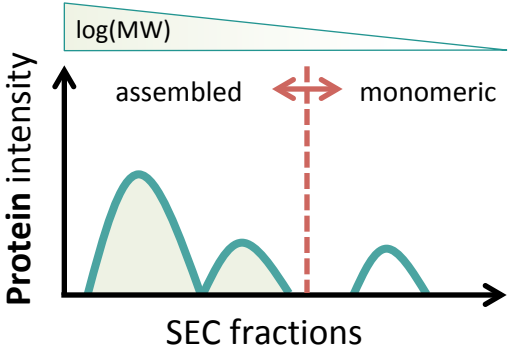


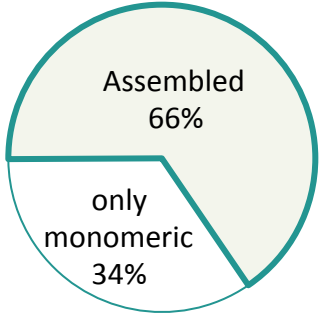

Heusel & Bludau et al. (2019)

# Complex-centric proteome profiling by SEC-SWATH-MS

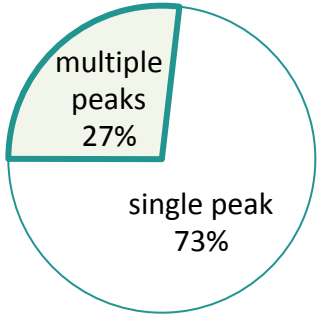
- ✓ Detect and quantify hundreds of protein complexes
- ✓ Investigate sub-complexes and assembly intermediates
- ✓ **Evaluate global proteome assembly characteristics**




HEK293 soluble proteome




➤ The majority of the proteins appear in at least one assembled state



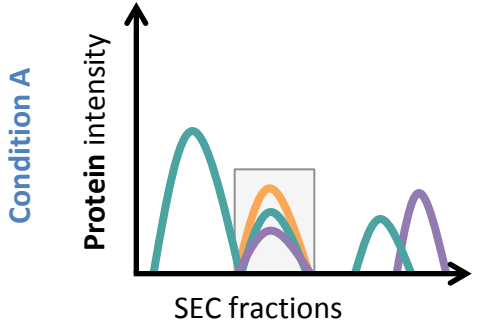

5503 elution peaks for 4065 proteins

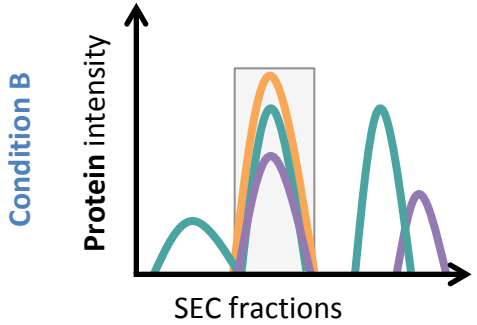
➤ Many proteins are observed in multiple distinct assembly states

Heusel & Bludau et al. (2019)

Current developments:

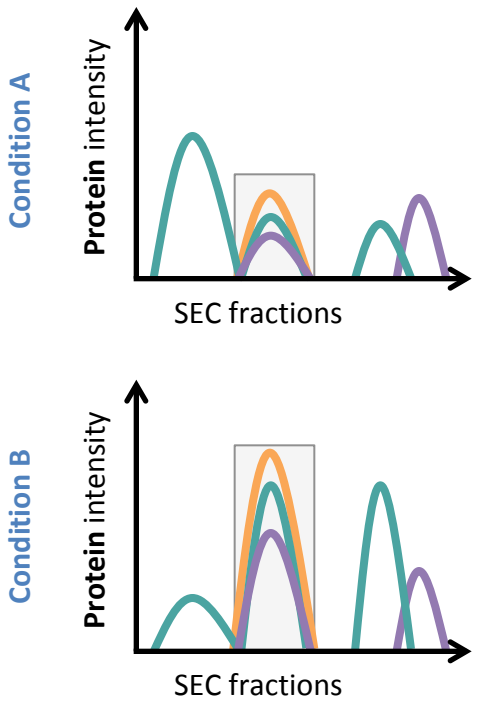
# Quantitative comparison of protein complexes across conditions



Current developments:

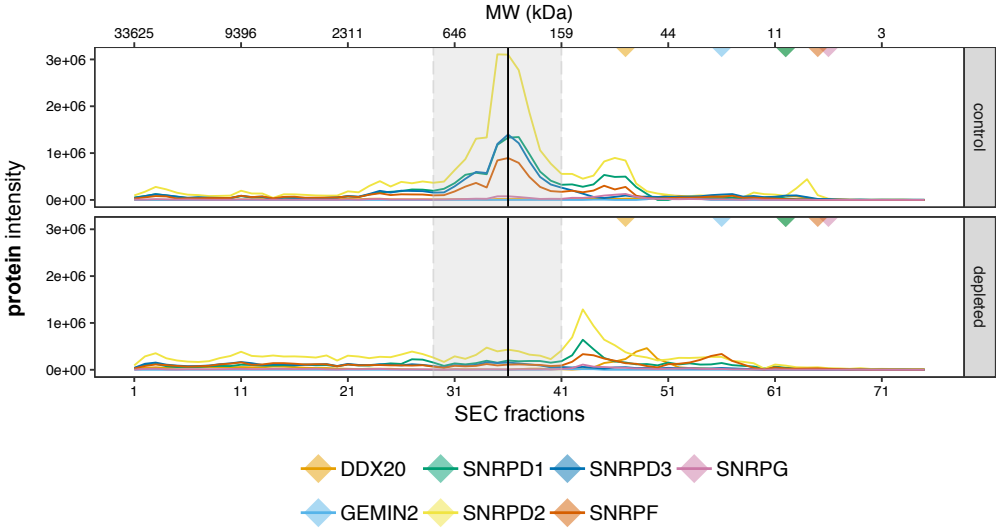
# Quantitative comparison of protein complexes across conditions




**Splicing efficient and PRPF8 depleted human cells**

- 110 out of 553 complexes are differentially abundant (FDR < 0.05)
- Spliceosome biogenesis is down-regulated

*SMN complex*



Current developments:

# Data-driven detection of assembly specific proteoforms

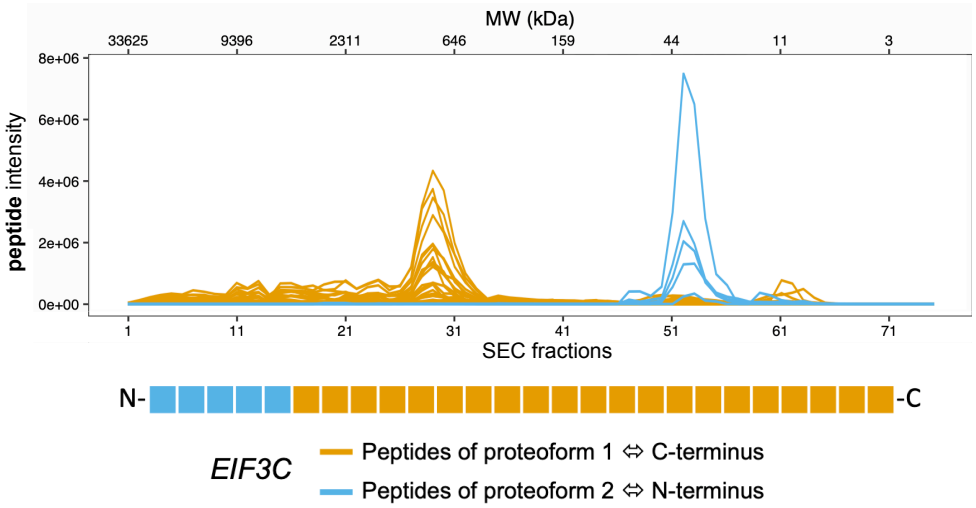
'**Proteoforms**' = protein variants that originate from the **same gene**,
but that have a **unique amino acid sequence and post-translational modifications**

- ➪ Make use of peptide-level information available in SEC-SWATH-MS
- ➪ Distinguish assembly specific proteoforms based on unique peptides

✓ Parallel detection of 1,378 assembly specific proteoforms

**Poster *ThP626***

*Eukaryotic translation initiation factor 3 subunit C (EIF3C)*



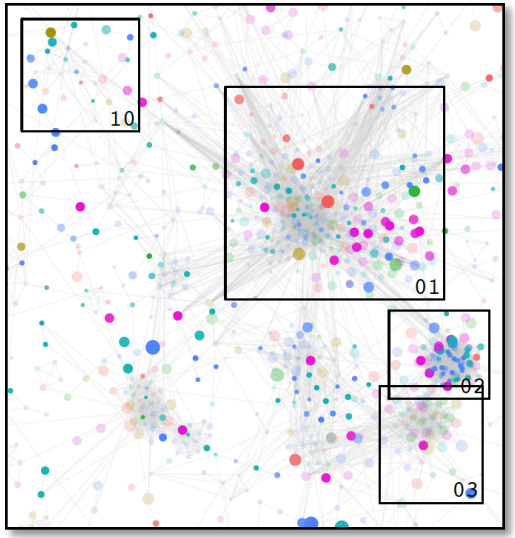
Current developments:

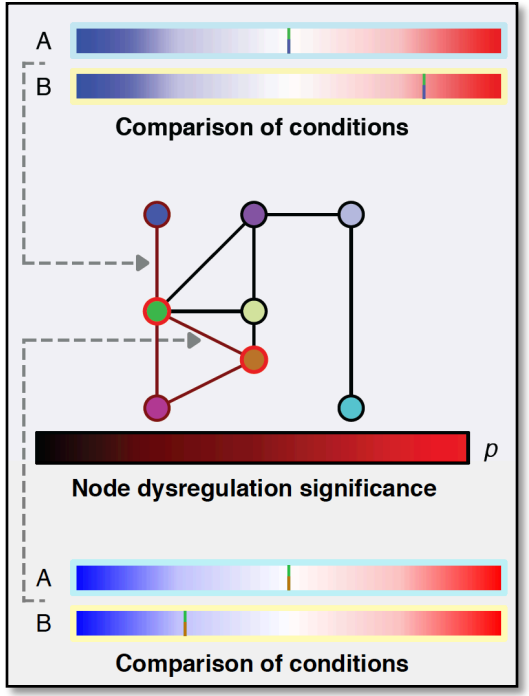
# Network-centric analysis

## SEC analysis toolkit (SECAT)

➪ Determine perturbed nodes in the PPI interaction network

Rosenberger et al. *(in preparation)*

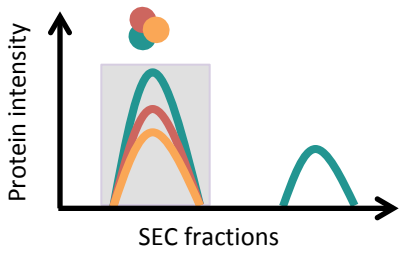


Take home message:

# Complex-centric analysis of CoFrac-MS data

- ✓ Consistent detection and quantification of 100s protein complexes on a proteome-wide scale
- ✓ Controlled complex-level FDR
- ✓ Sub-complex resolution




CCprofiler
https://github.com/CCprofiler/

**Requirements:**

- Quantitative peptide or protein matrix (DIA or DDA)
- Annotation table that matches MS runs to the sampled fractions
- Prior protein connectivity information (e.g. CORUM, BioPlex, StringDB)

- ✓ Coming next: quantitative complex comparison, proteoform detection, network-centric analysis

# Thank you for your attention!

**Aebersold lab**

- Ruedi Aebersold
- Ben Collins
- **Moritz Heusel**
- **Max Frank**
- George Rosenberger
- Claudia Martinelli
- Peng Xue
- Robin Hafen
- Amir Banaei-Esfahani
- Audrey van Drogen
- Yansheng Liu
- Matthias Gstaiger

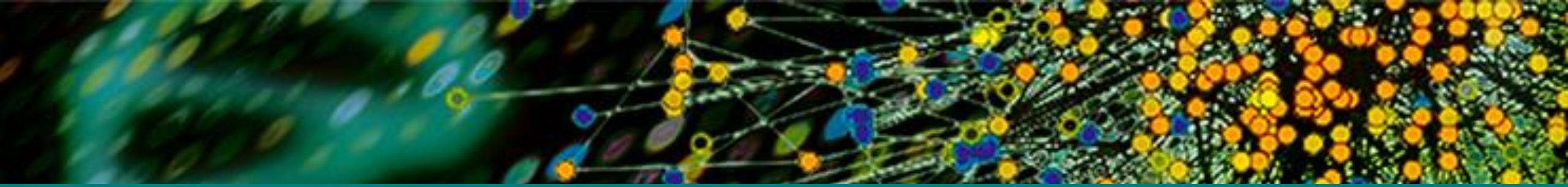
**External collaborators**

- Hannes Röst
- Yuija Cai
- Vihandha Wickramasinghe
- Ashok Venkitaraman

ETH Zürich

life science zurich graduate school

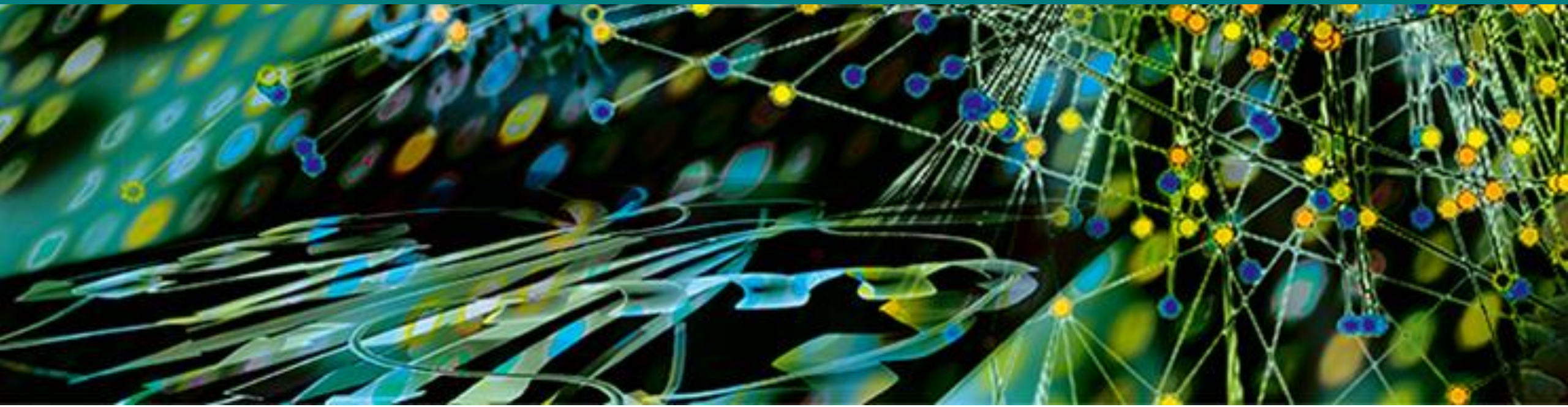
Dominic Helm
EMBL Heidelberg



# Thermal proteome profiling for interactomics

ASMS 2019 – MS-Based interactomics

dominic helm





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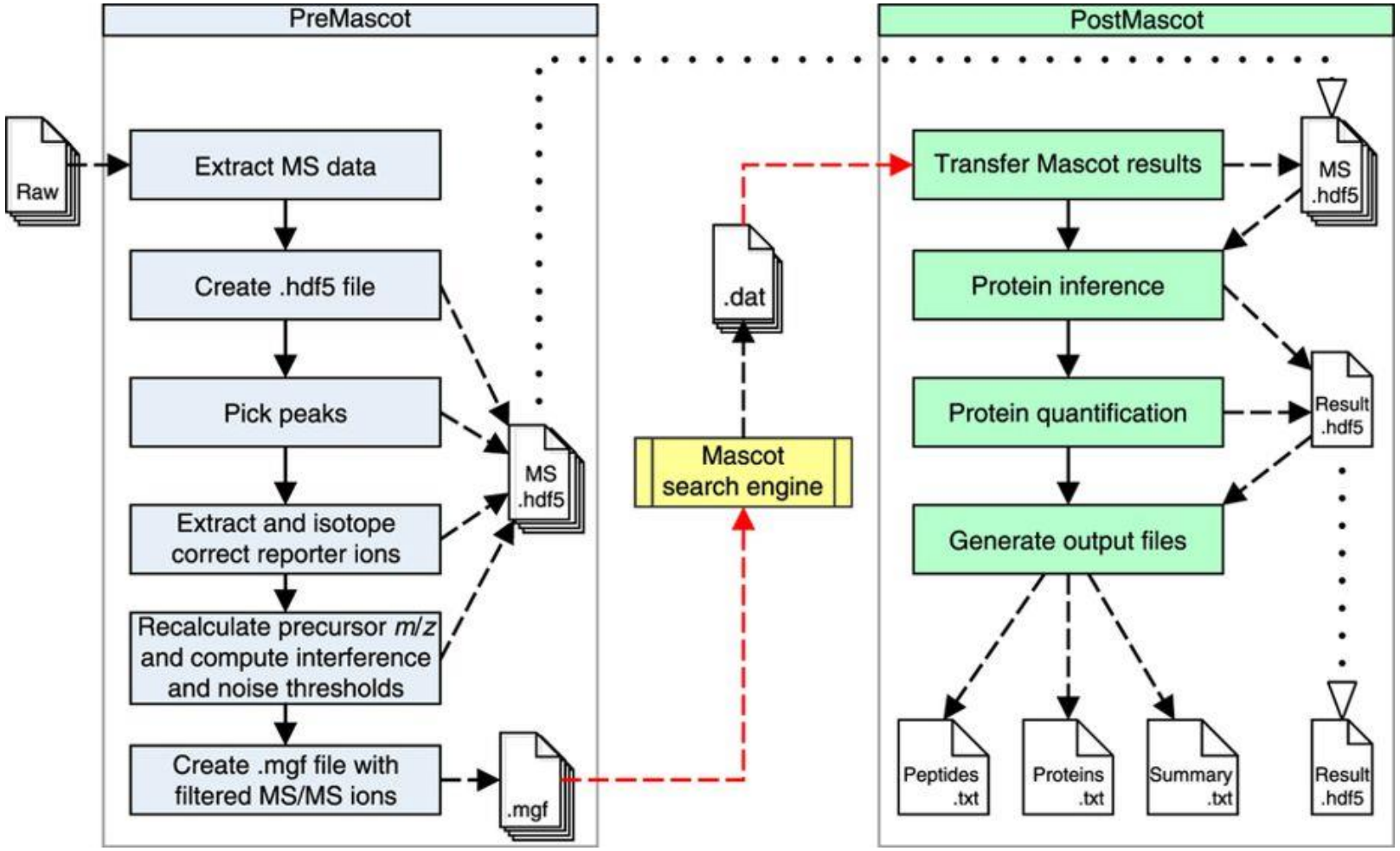
Friedrich Reinhard
Holger Franken
Celia Berkers (Utrecht University)

Proteomics Core Facility
Flow Cytometry Core Facility
Advanced Light Microscopy Core Facility
Mechanical Workshops

**Sindhuja Sridharan, Nils Kurzawa, Isabelle Becher, Frank Stein, Dominic Helm, Tomi Määttä, Andre Mateus, Per Haberkant, Mandy Rettel, Jianguo Zhu, Henrik Hammaren, Clement Potel, Malay Sha, Vallo Varik, Kerri Malone, Cecilia Perez-Borrajero, Matteo Perino**

**Former members: Johannes Hevler, Maike Schramm**

# Prelude: Isobarquant




Franken et al., 2015, Nature Protocols

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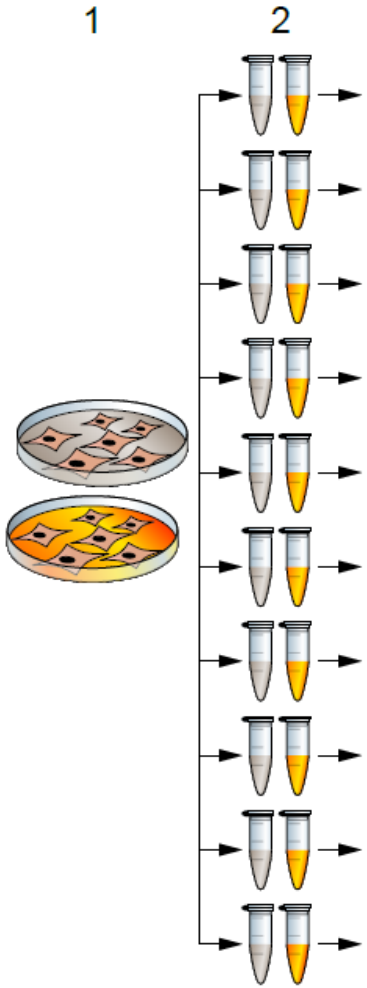
# Protein/drug interactions in living cells proteome-wide




Savitski MM et al Science 2014

EMBL

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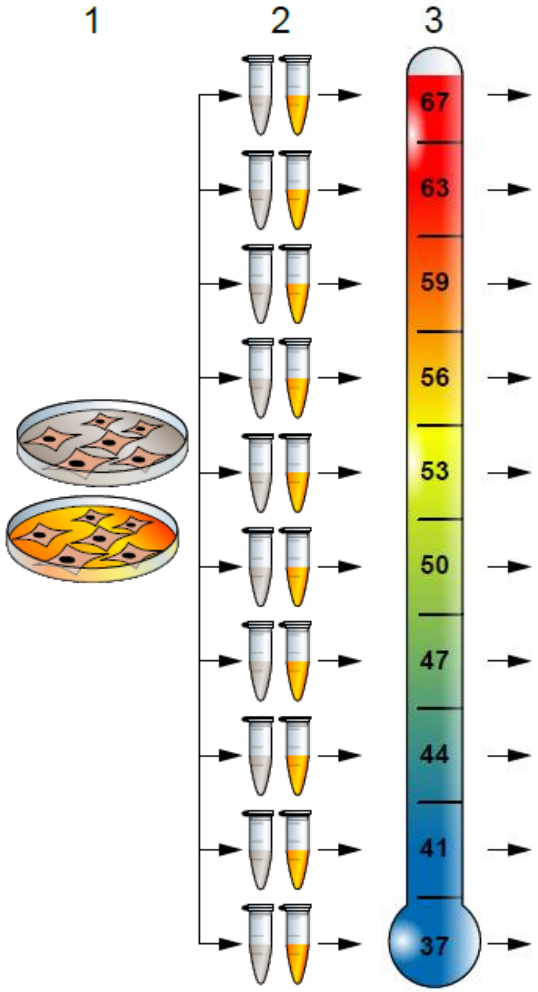


Savitski MM et al Science 2014

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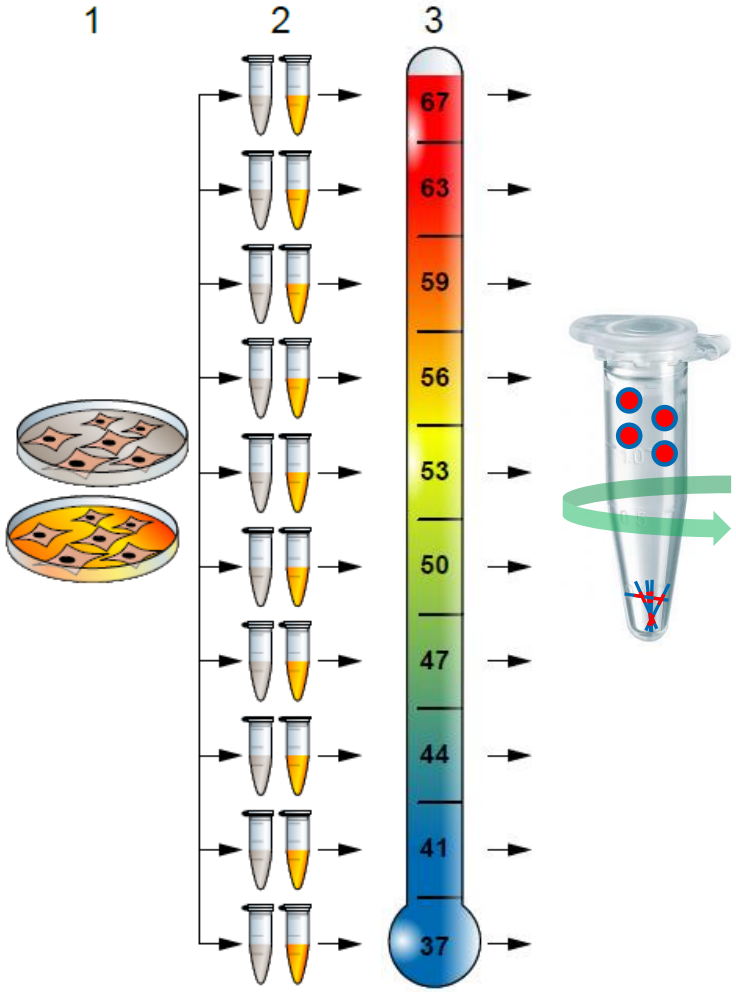


Savitski MM et al Science 2014

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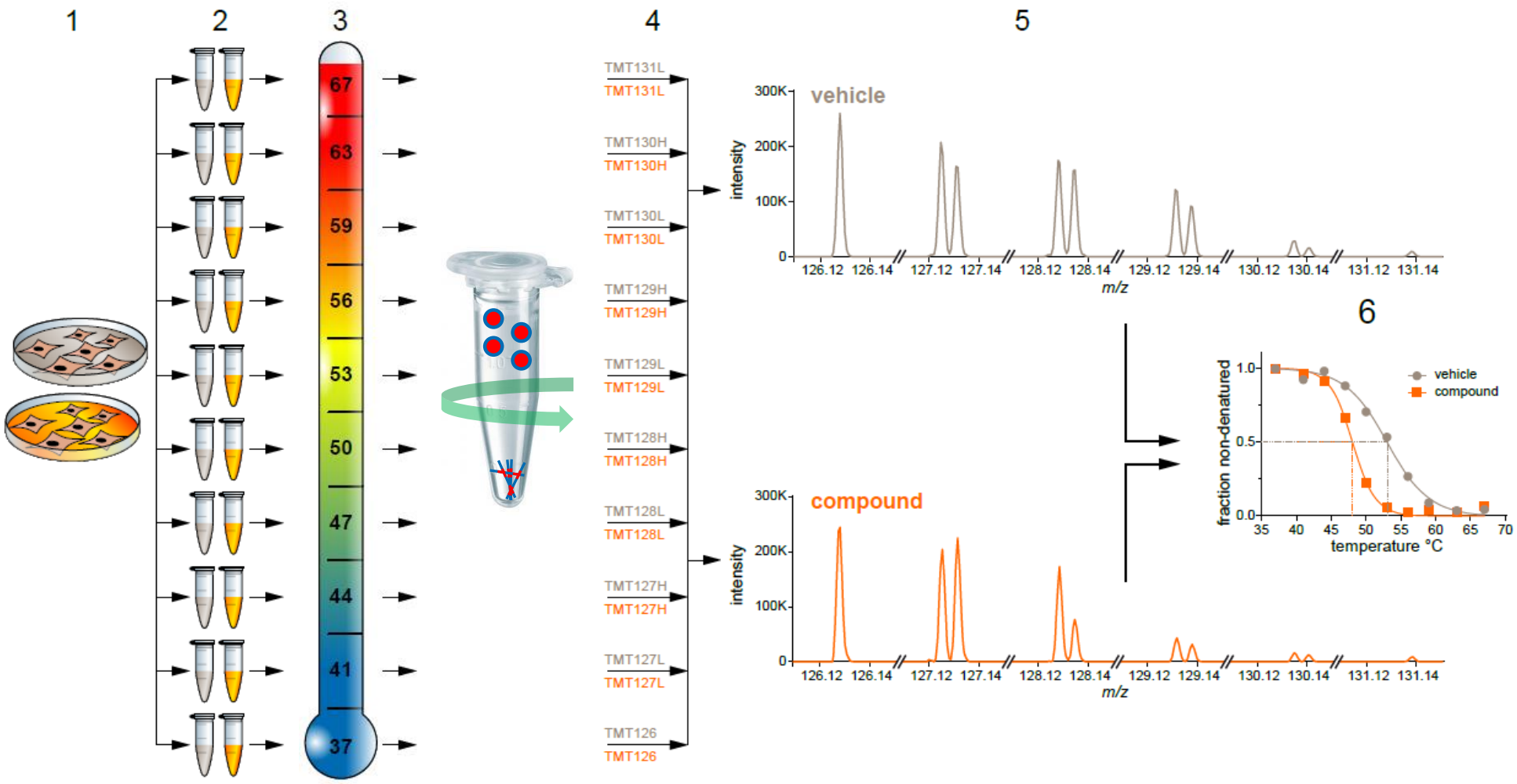
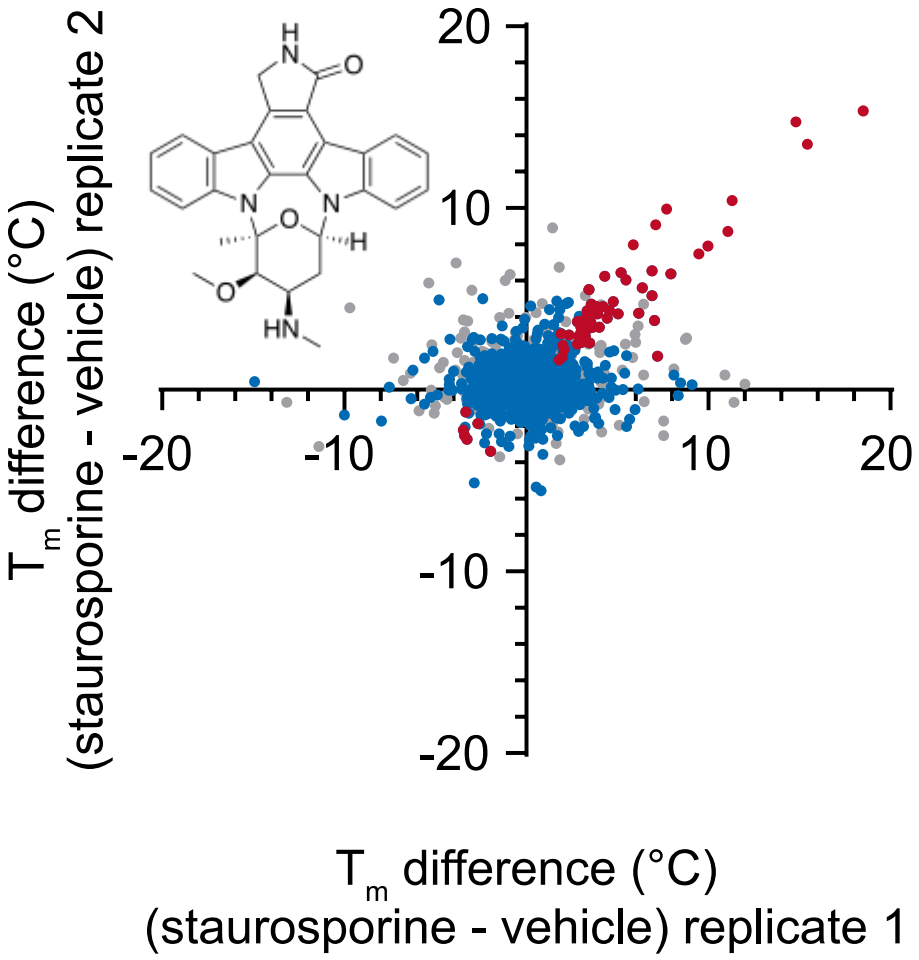
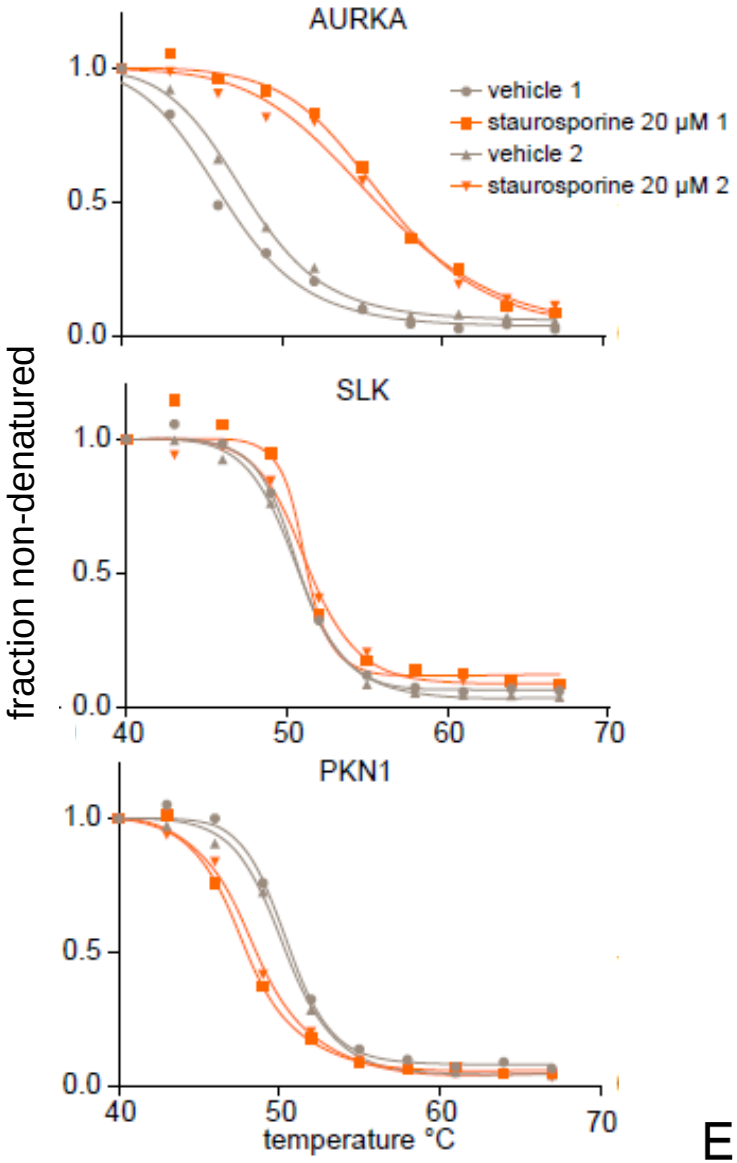



Savitski MM et al Science 2014

EMBL

# Protein-Drug interaction: Staurosporine targets




Savitski MM et al Science 2014

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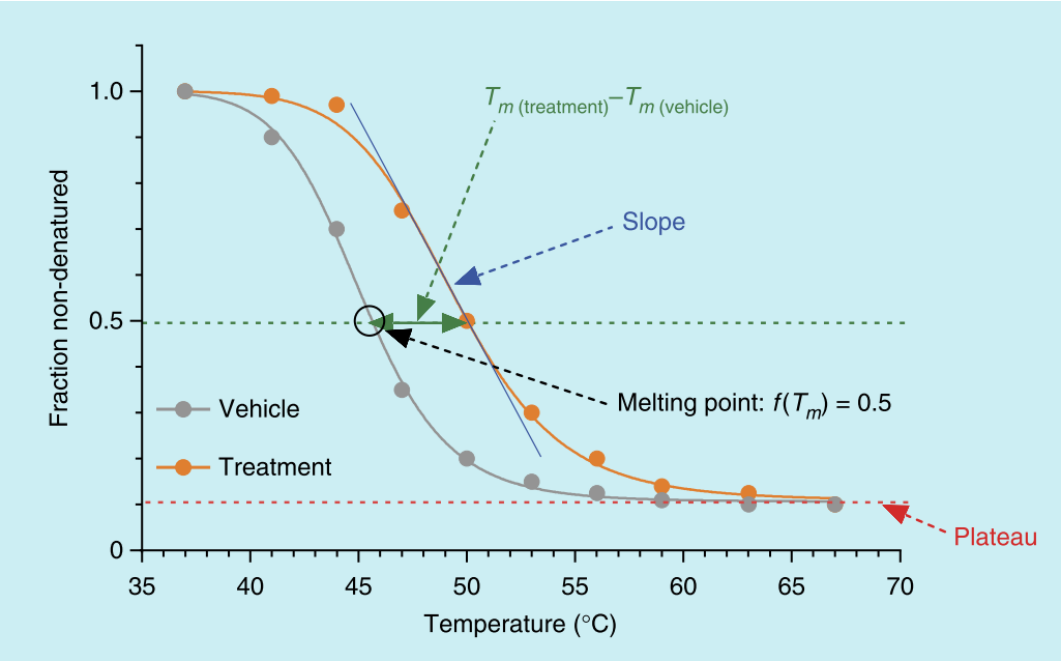
# Melting curve fits

- Fit parametric sigmoidal curves for each condition
- Estimate melting points
- Compare melting points between the treatment conditions using a z-Test




Franken et al., 2015, Nature Protocols

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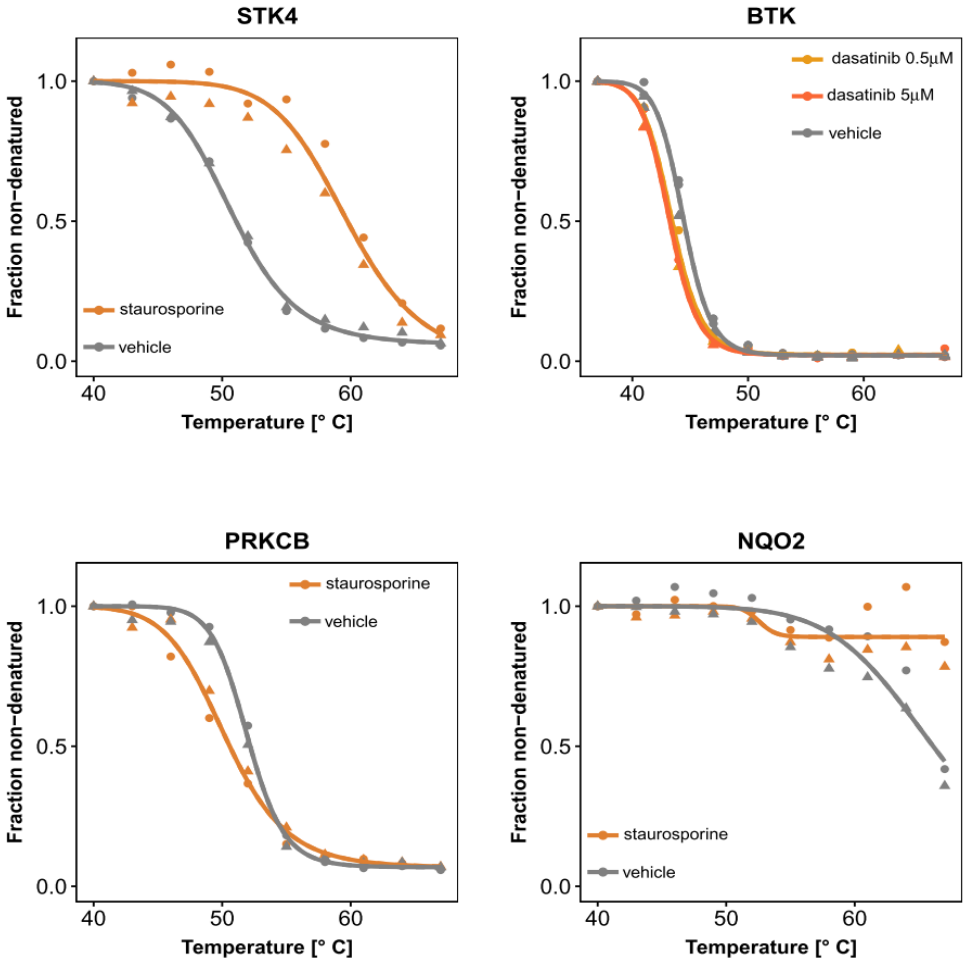
# Problems with the melting point (Tm) comparison

Several reasons can lead to Tm shift being insufficient to detect ligand effect:

- Small but reproducible shifts (BTK)
- Shifts in non-centered curve areas (PRKCB)
- Melting points outside the temperature range (NQO2)




Childs*, Bach*, Franken* et al. (2018) bioRxiv

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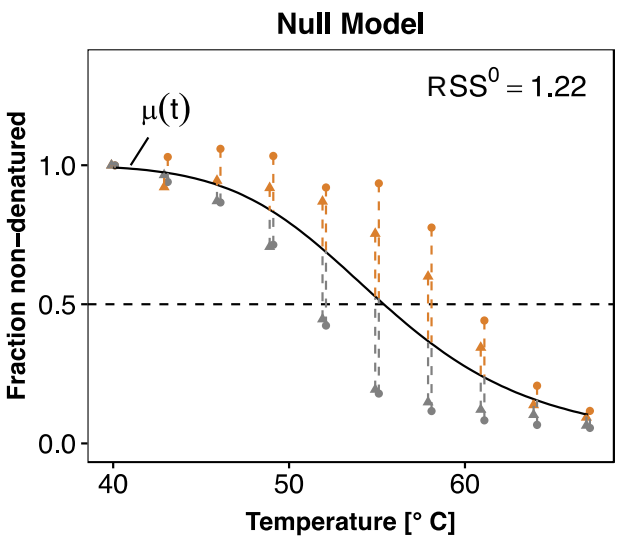
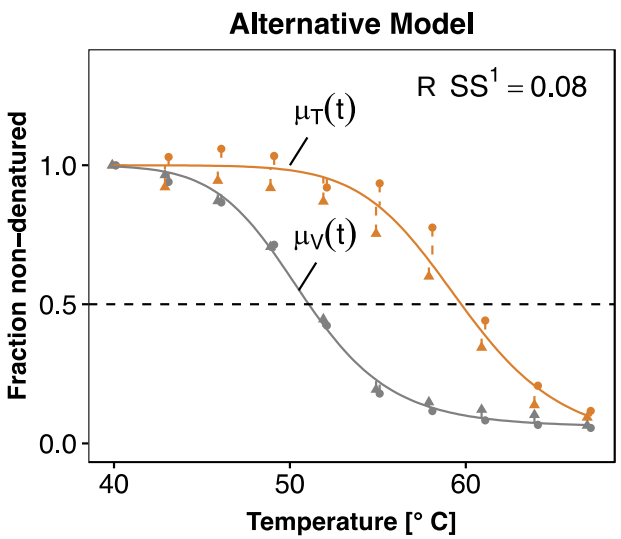
# Our solution: Functional melting curve analysis

Fit two competing models per protein
Compute F-statistic:

$$F = \frac{\mathrm{RSS0} - \mathrm{RSS1}}{\mathrm{RSS1}}$$




RSS: residual sum of squares

Karsten Bach

Dorothee Childs

Holger Franken

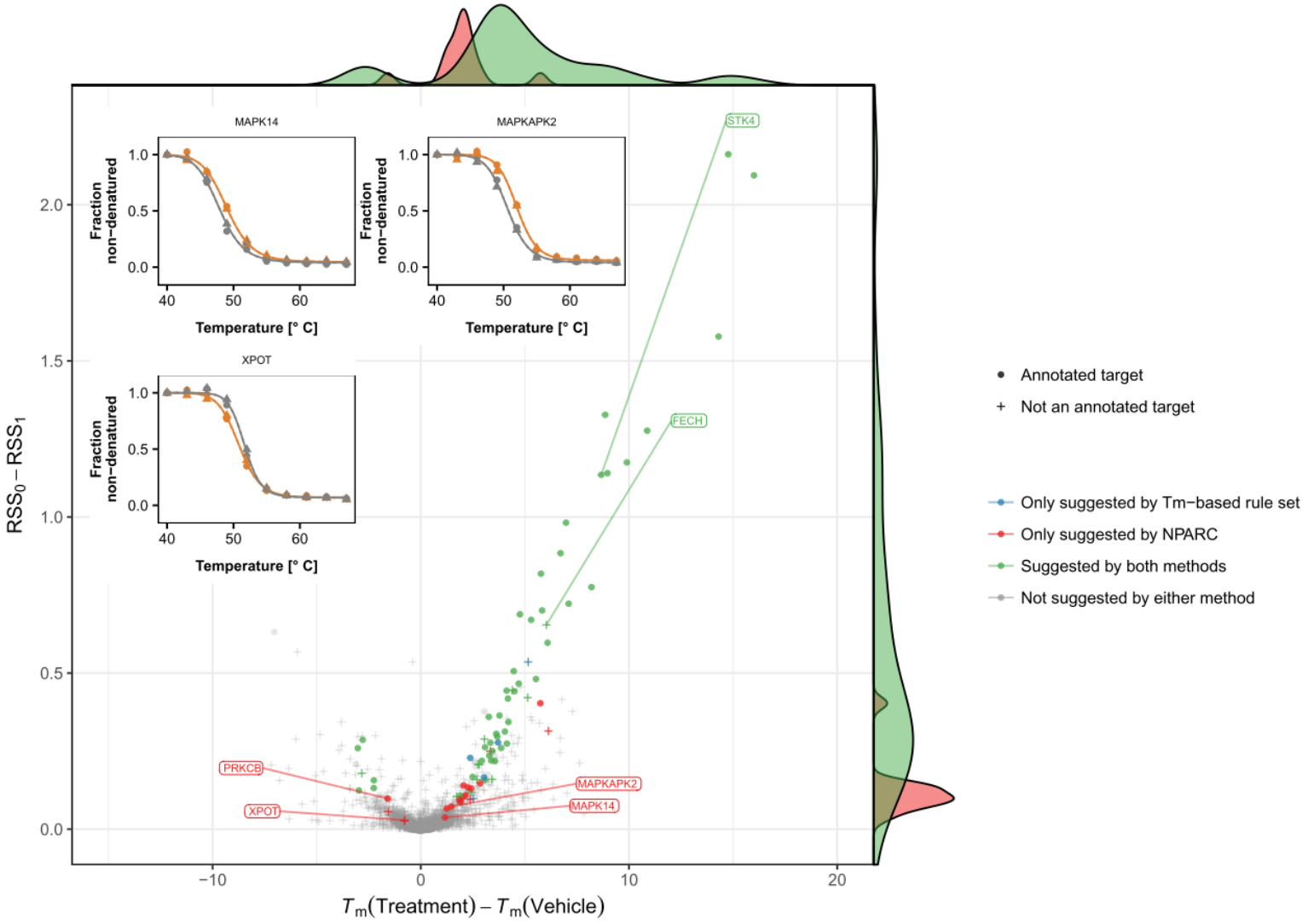
Childs*, Bach*, Franken* et al. (2018) bioRxiv

EMBL

# Functional melting curve analysis

New method captures old targets

+ cases with more subtle effects




Childs*, Bach*, Franken* et al. (2018) bioRxiv

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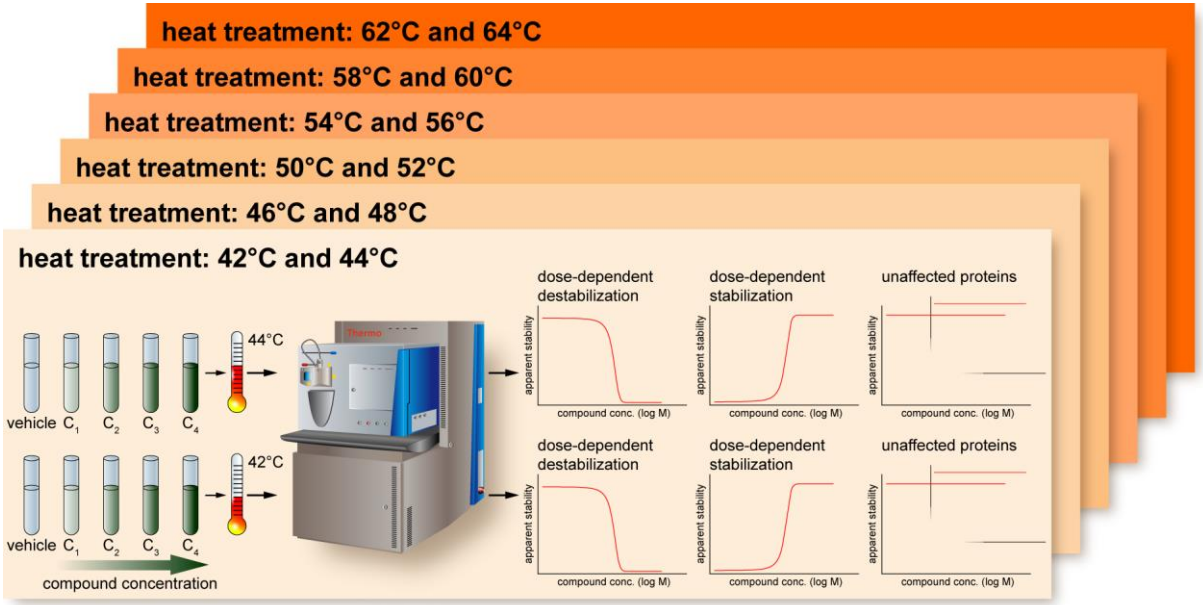
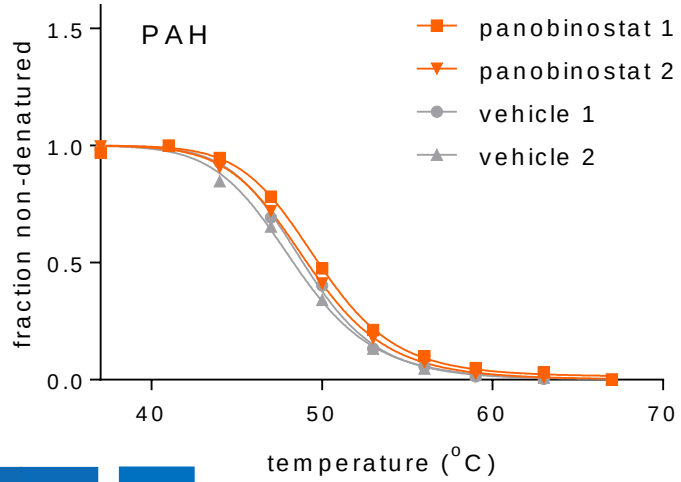
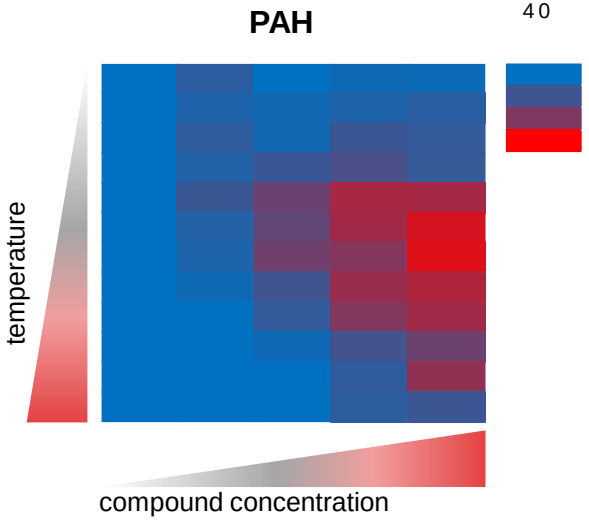
# More sensitive experimental design: 2D-TPP

Compound concentration-dependent profiling over a range of temperatures

Instead of statistics: More experiments – more data – more targets



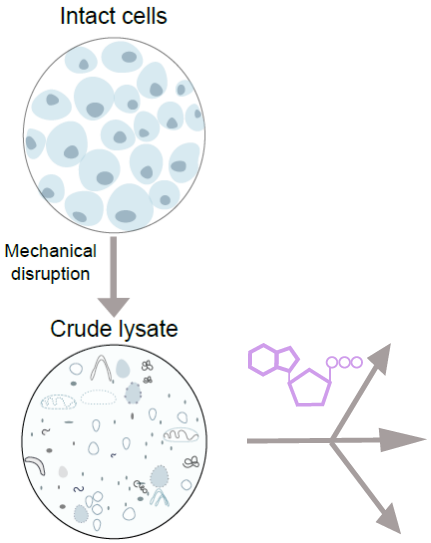



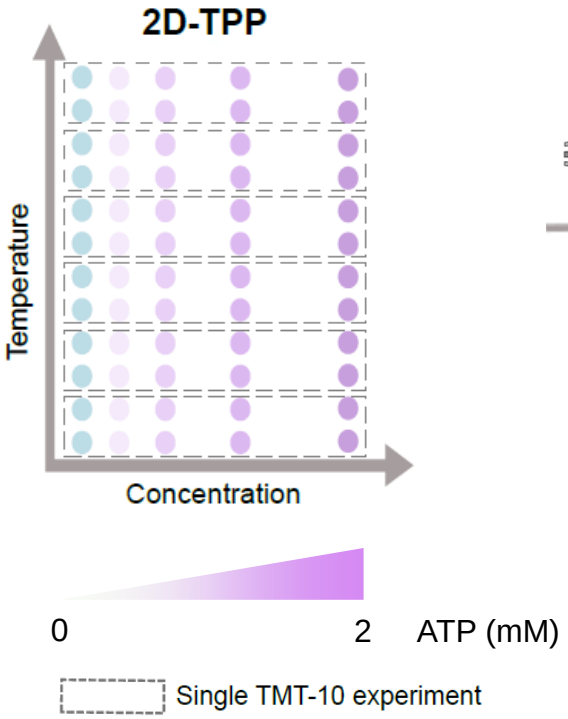

Becher I, … , Bantscheff M*, Savitski MM* Nature Chemical Biology 2016

# Protein-Metabolite interaction: Adenosine triphosphate (ATP)

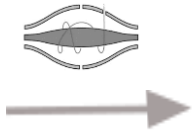
**Model system**




**Metabolite and heat treatment**

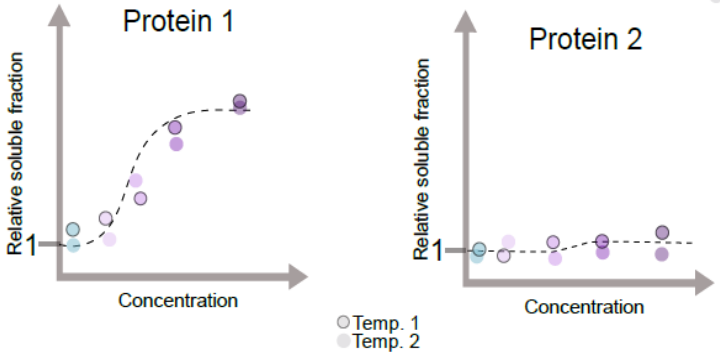



**MS-analysis**



**Data analysis**

**FDR controlled dose-response assessment**




$pEC_{50}$ – measure of affinity

Sridharan S#, Kurzawa N#, Werner T, Guenthner I, Helm D, Huber W, Bantscheff M*, Savitski MM* **Nature Communications** 2019

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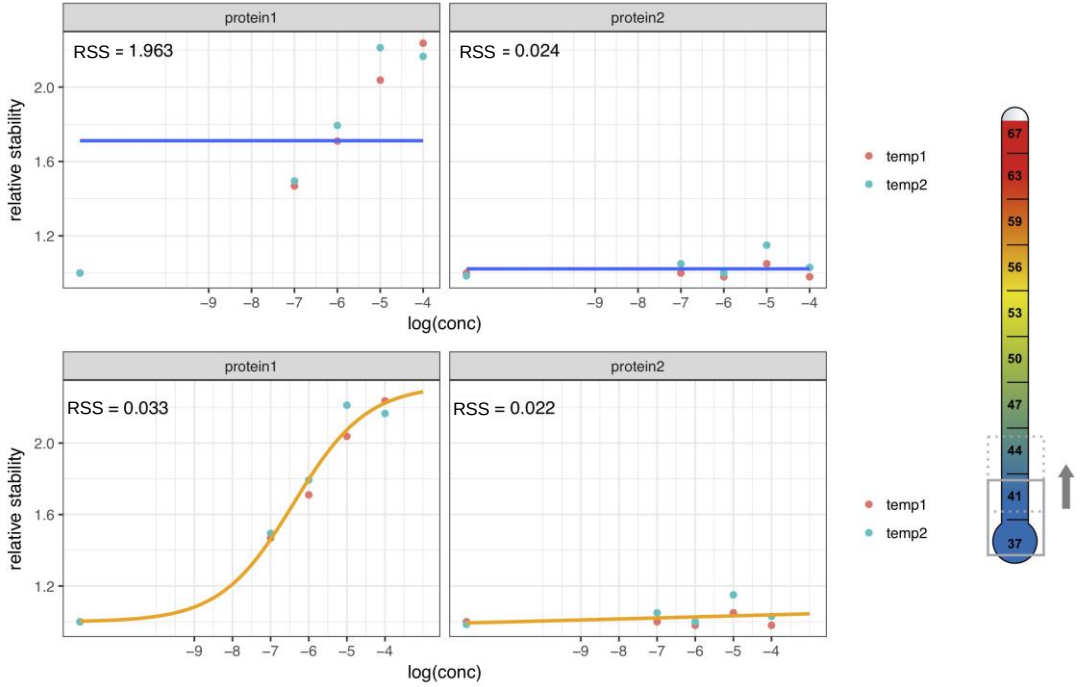
# Functional 2D-TPP data analysis using sliding temperature windows

- Fit models to adjacent temperatures
- **H0 Model**: intercept model (blue)
- **H1 Model**: dose-response curve (orange)
- Compare goodness of fit
- Summarize per protein score $F^{comb}$
- Estimate the FDR for given scores by repeating the procedure with permuted data and ranking results jointly




RSS: residual sum of squares

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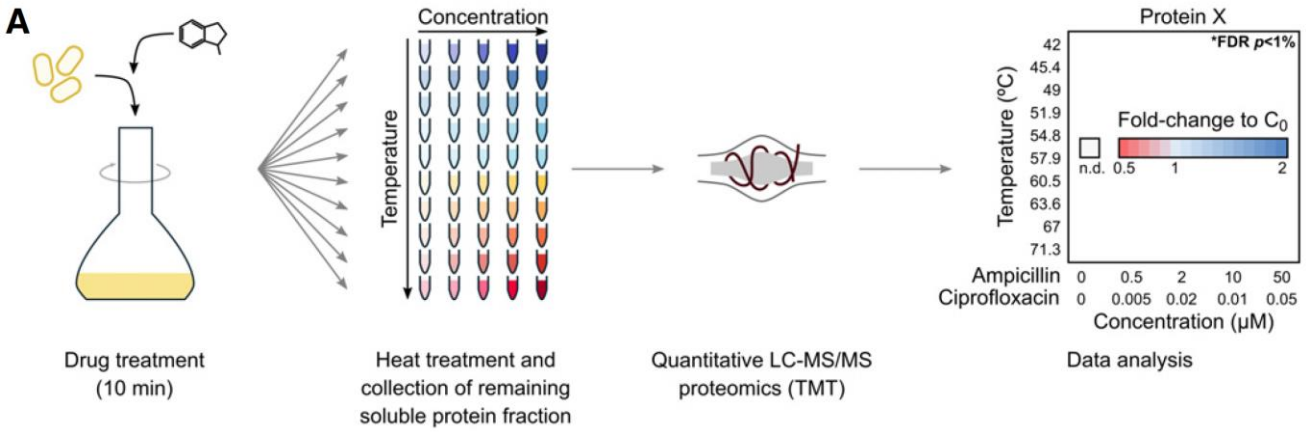
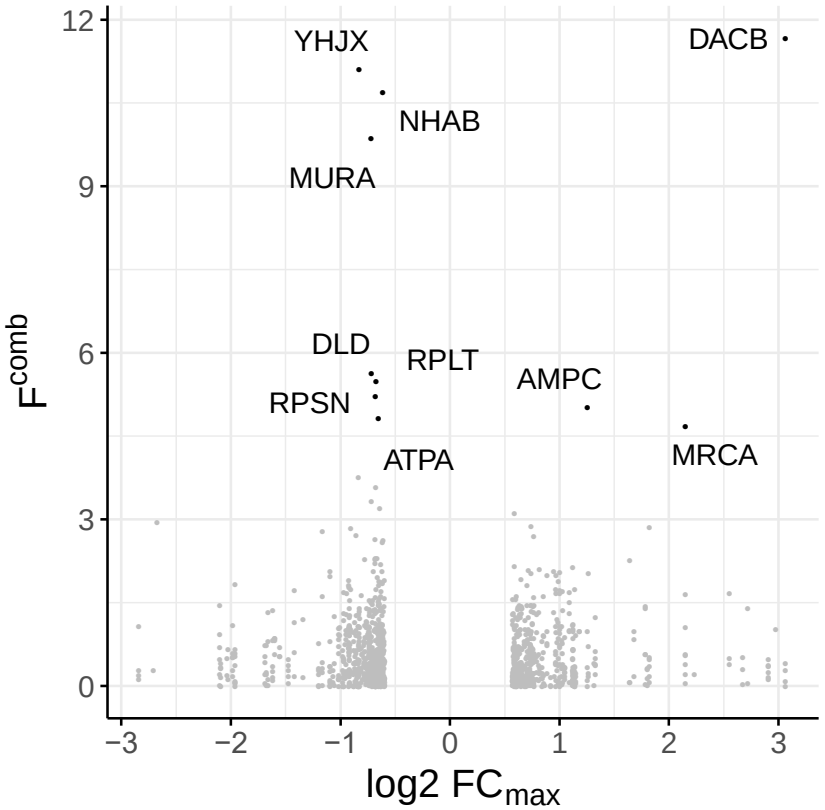
# Validation of the approach on drug datasets with known targets

- Ampicillin treated *E. coli* lysate
- beta-lactam antibotic, inhibting bacterial cell-wall synthesis
- Known targets: MrcA, FtsI, DacB & PbpG
- Other binders: AmpC




André Mateus




Mateus et al. Mol. Sys Biol. 2018

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# Thermal proteome profiling

- Unbiased
- Proteome wide
- Versatile


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# Thank you for your attention!