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CS Group International is a pioneer and leading science event organizer, which publishes around 40 peer-reviewed journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 1000 editorial board members and 3.5 million followers to its

CS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, New York, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

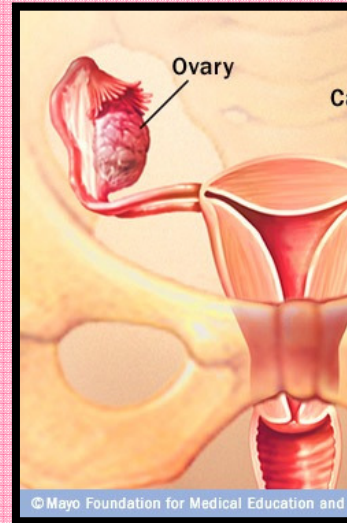
*A proteomic-bioinformatic integrated
approach for studying the effect of a peptide
drug candidate on ovarian Cancer*

*Maria Paola Costi
Department of Life Science
Unimore
Modena*

Ovarian Cancer

Ovarian Cancer (OC) It is the most lethal of the gynecologic cancers

specific symptoms that accompany the early disease → diagnosis in advanced stage → therapeutic options are limited.



FIRST LINE TREATMENT

Surgical cytoreduction + chemotherapy (and/or radiotherapy)

Chemiotherapy Platinum (cisplatin) + Taxane (paclitaxel) combination

High initial response (≈ 70%)

CAUSES OF FAILURE

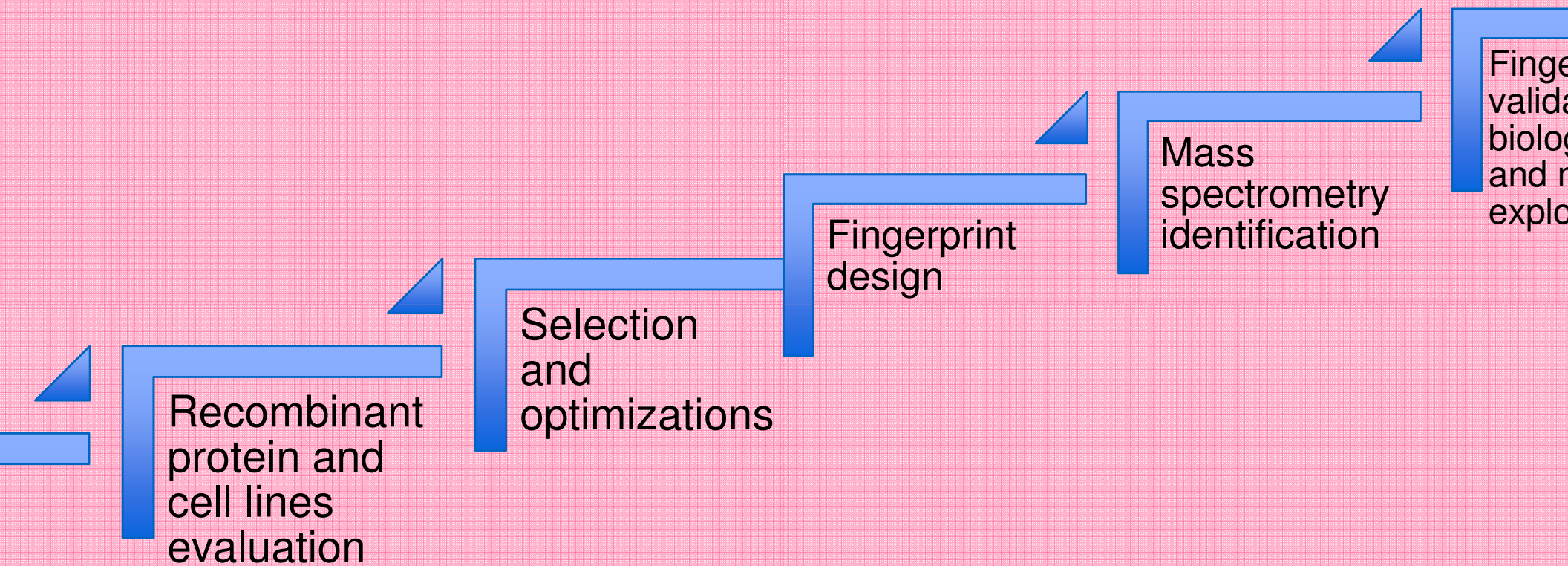
- OC diagnosis in advanced stage (Stages IIB to IV)
- Rapid occurrence of **resistance** to standard systemic therapies

High percentage of relapse after 6 months (> 90%)

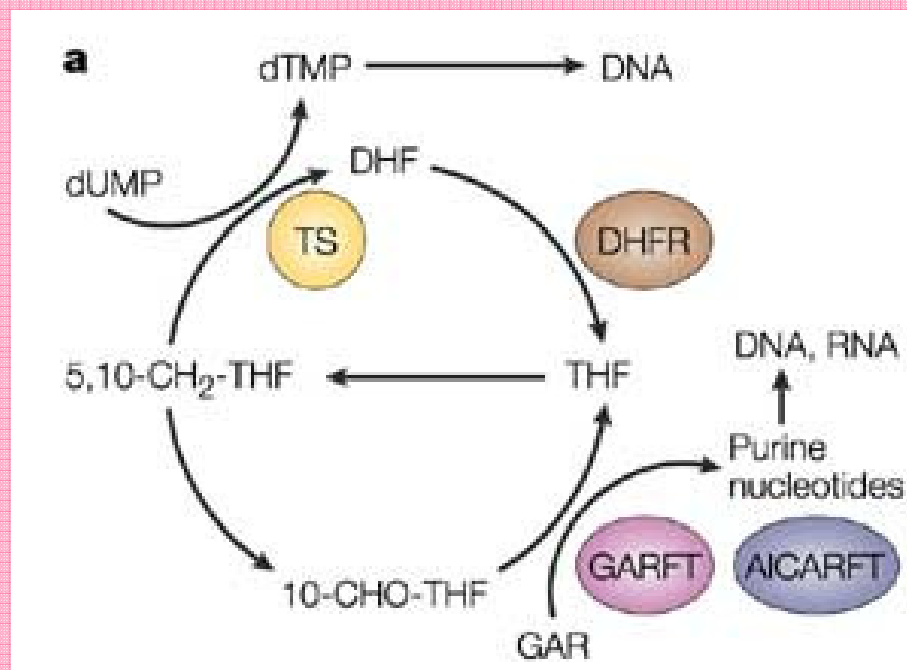
Our aims are

- 1. to develop new drugs against resistant ovarian cancer**
 - 2. to provide a new methodology for fingerprint evaluation of biomolecules changes in cells**
- to translate the concept to clinical sample**

Development of new drugs against resistant ovarian cancer

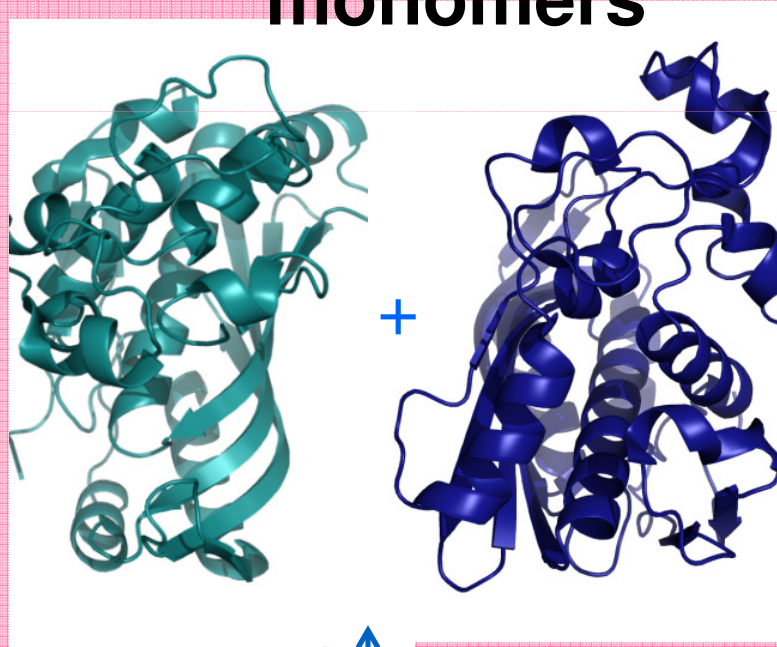


Thymidylate synthase and folate pathway targeting

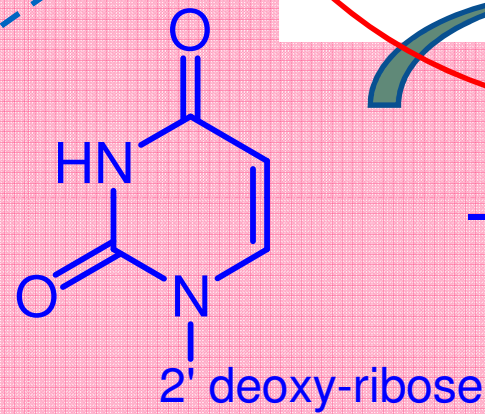
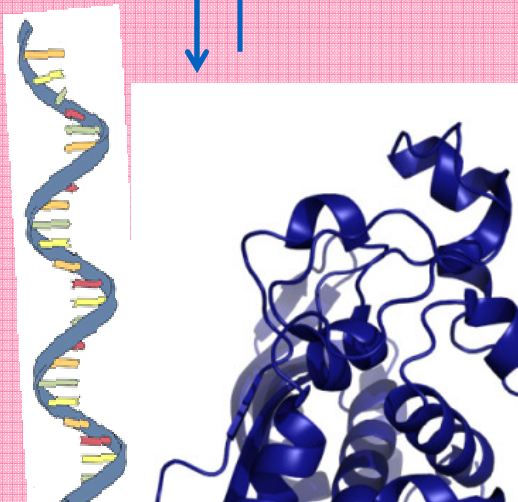
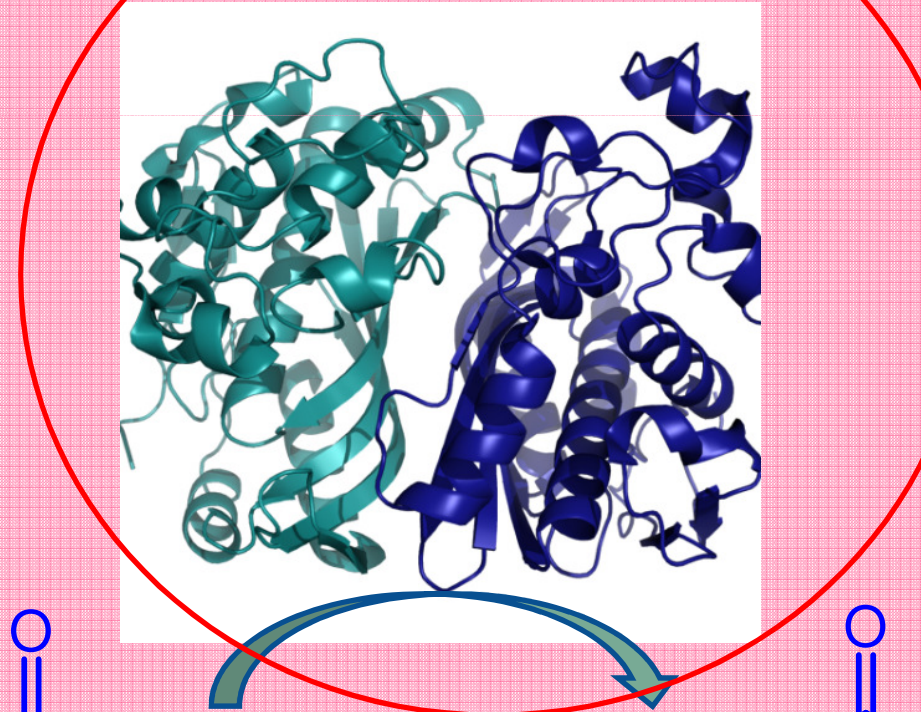


Thymidylate synthase pathways

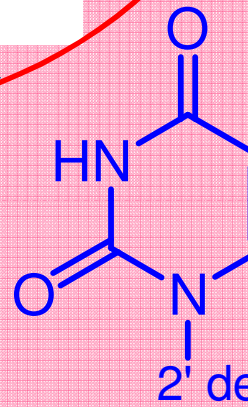
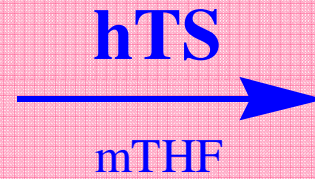
**hTS
monomers**



hTS dimer active/inactive



dUMP

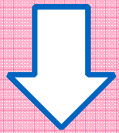


dTMP

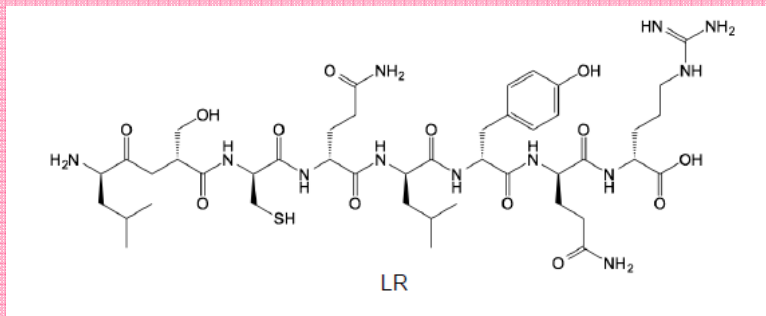
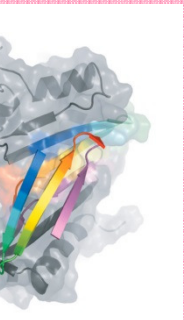


A

New strategies against resistant ovarian cancer (ROC)



Antifolate peptides



Binding at TS dimeric interface

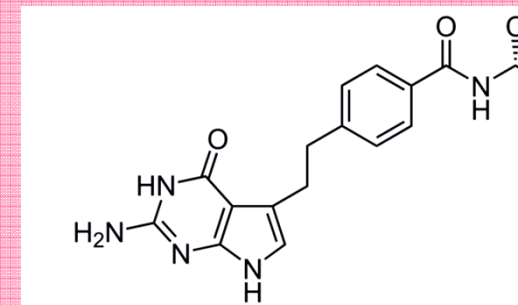
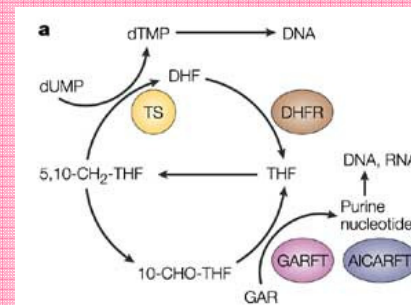
Proteomic evaluation of the effect of peptides on:

cell lines

primary tumor tissues

Male D. et al., PNAS, 2011, Pelà et al, J Med

Pemetrexed (Alimta)



Binding at TS active site
Under clinical evaluation for

- **PMX** (Alimta™) is an antifolate that inhibits GART and ATIC.
- 14 clinical trials Pemetrexed phase II

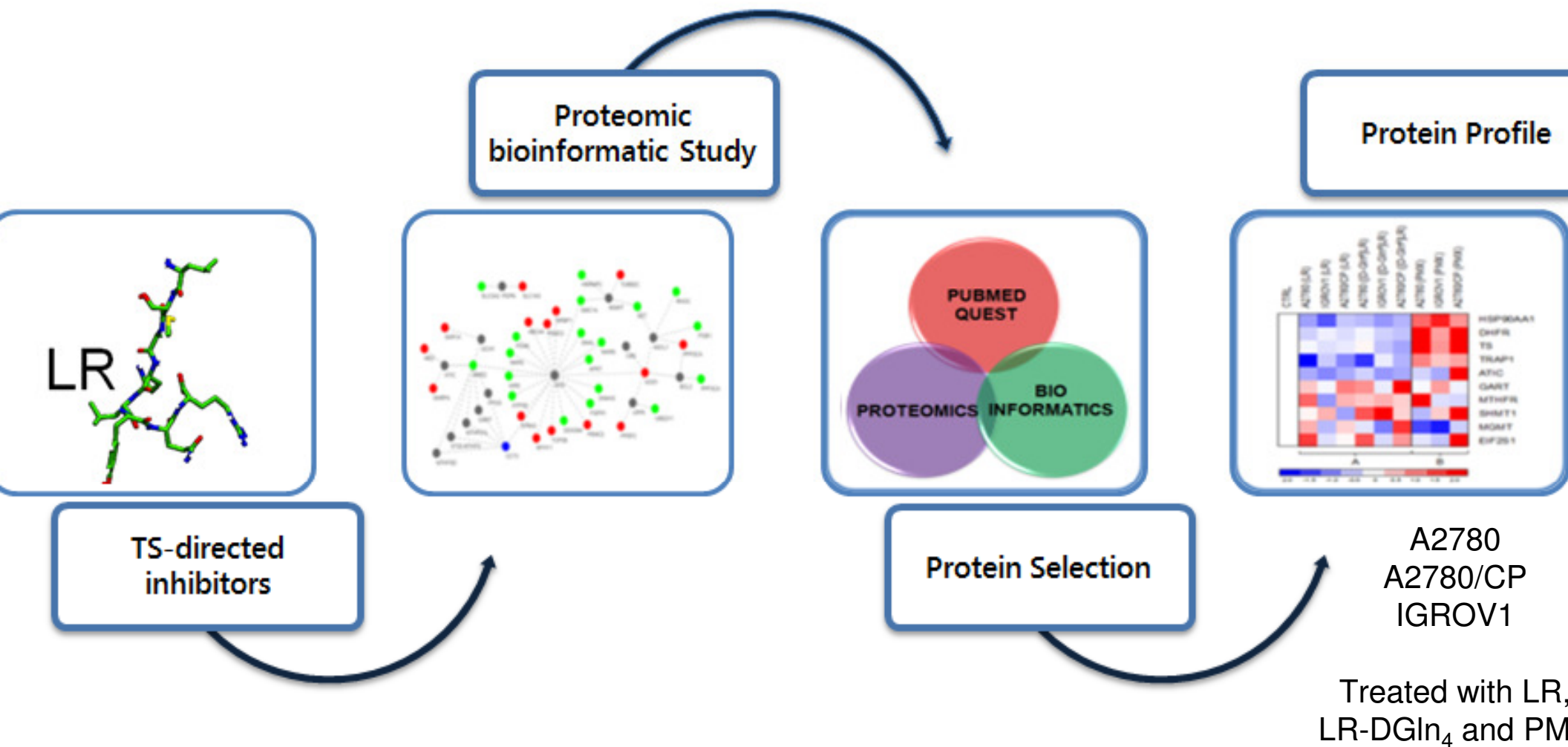
Proteomic evaluation of the effect of PMX on:

Can we approach the whole proteomic/targeted proteomic approach for a wider view of lead/drugs effect?

Targeting the same target,
different mechanism of inhibition
Different cellular protein profile?

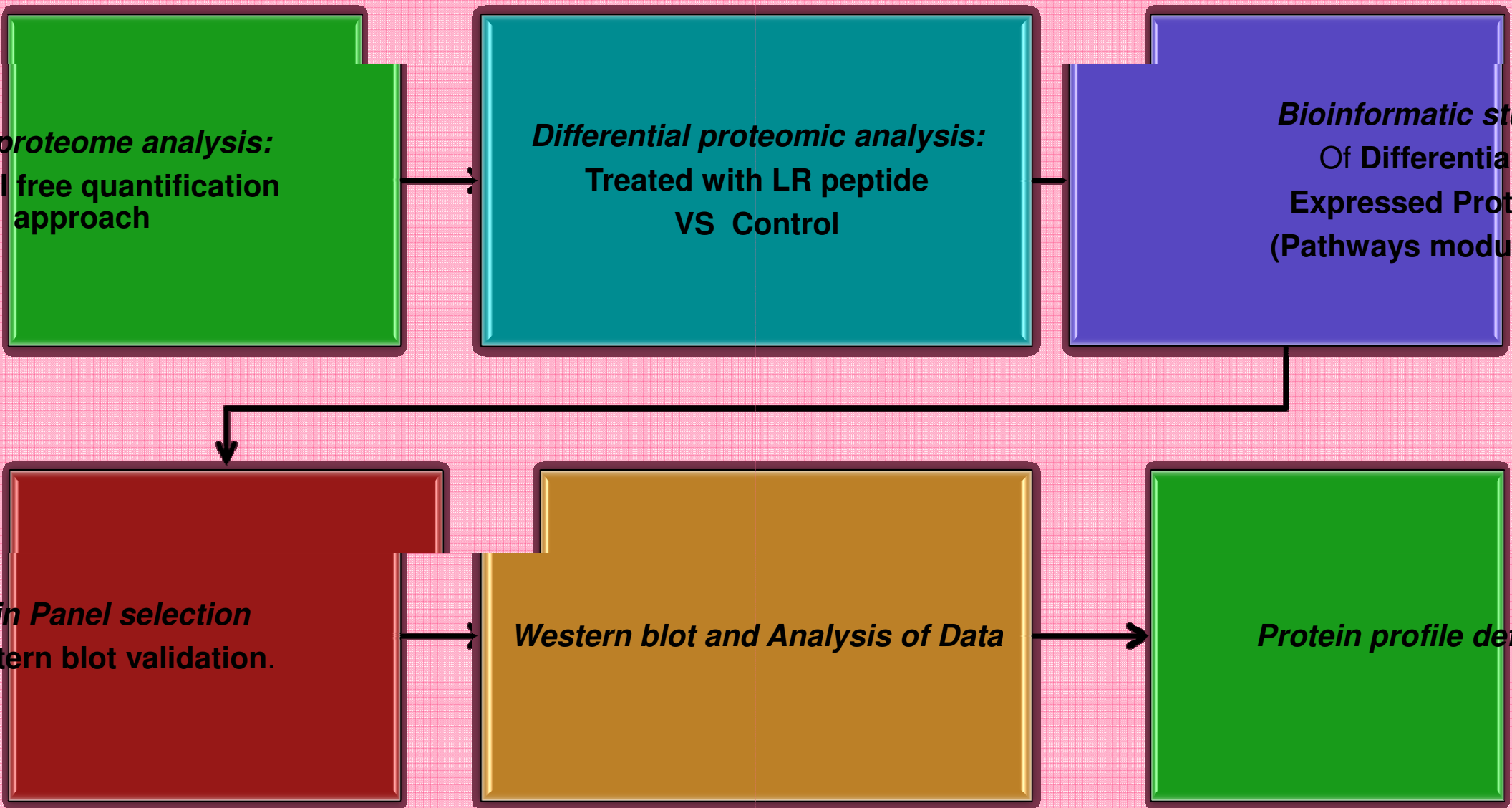
Need for a more integrated non
reductionistic approach

in the cell lines through *Proteomic-bioinformatic approach*



To define a **Protein Profile**: *proteins expression could be*

Flow chart

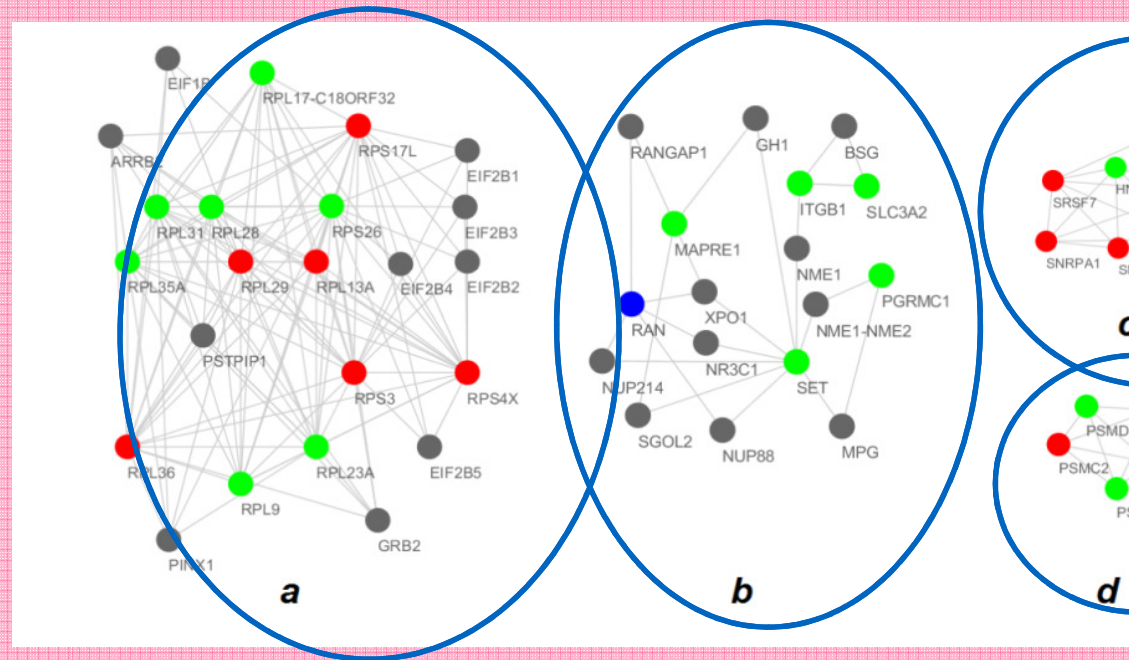
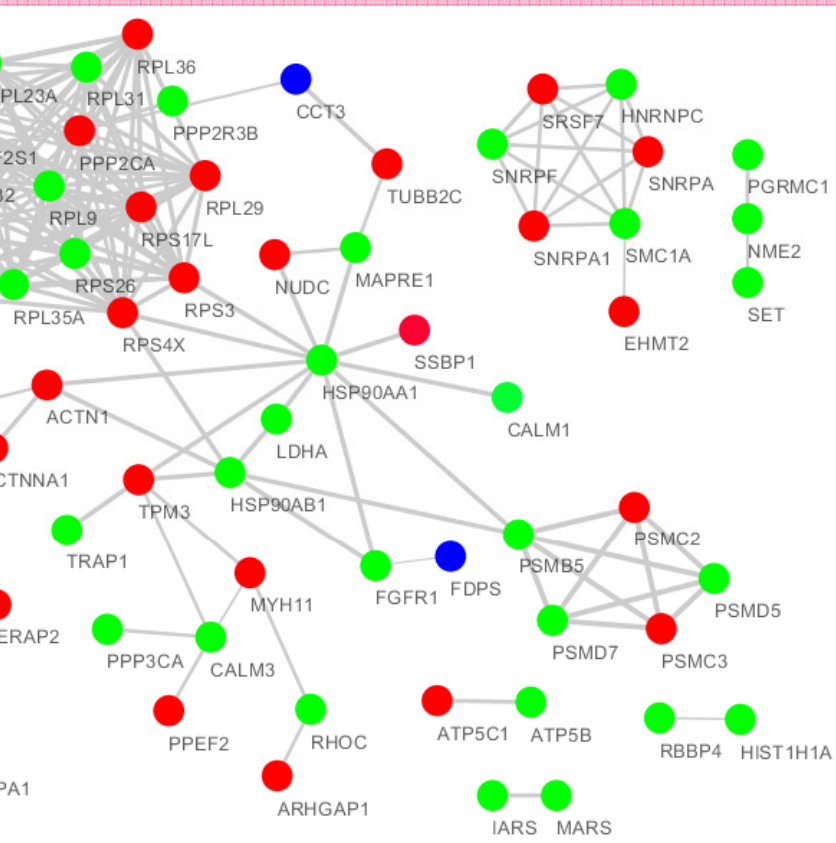


bioinformatic approach

NETWORK ANALYSIS OF DEPS:

160 DEPs resulted connected through:

IntAct and Reactome



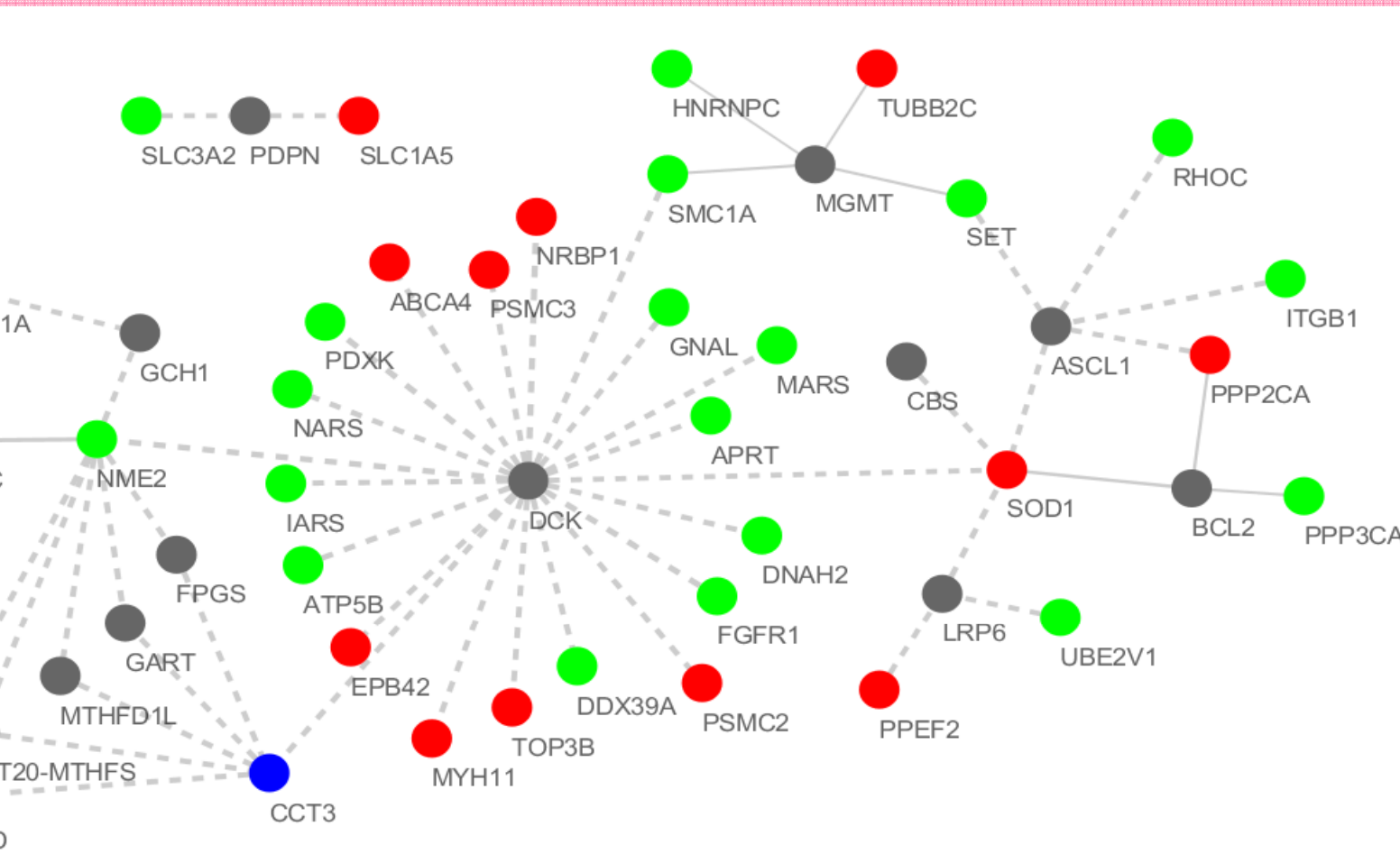
FOUR MAIN CLUSTER ARE MODULATED BY LR:

- Cluster **a** ribosomal proteins.
- Cluster **b** proteins of pyrimidine ribonucleotide metabolic process, proteins RNA-connected and protein transport-connected.
- Cluster **c** ribonucleoproteins.
- Cluster **d** proteasome complex.

● Up – reg

● Down –

Complete Pathway Members Connected to DCK

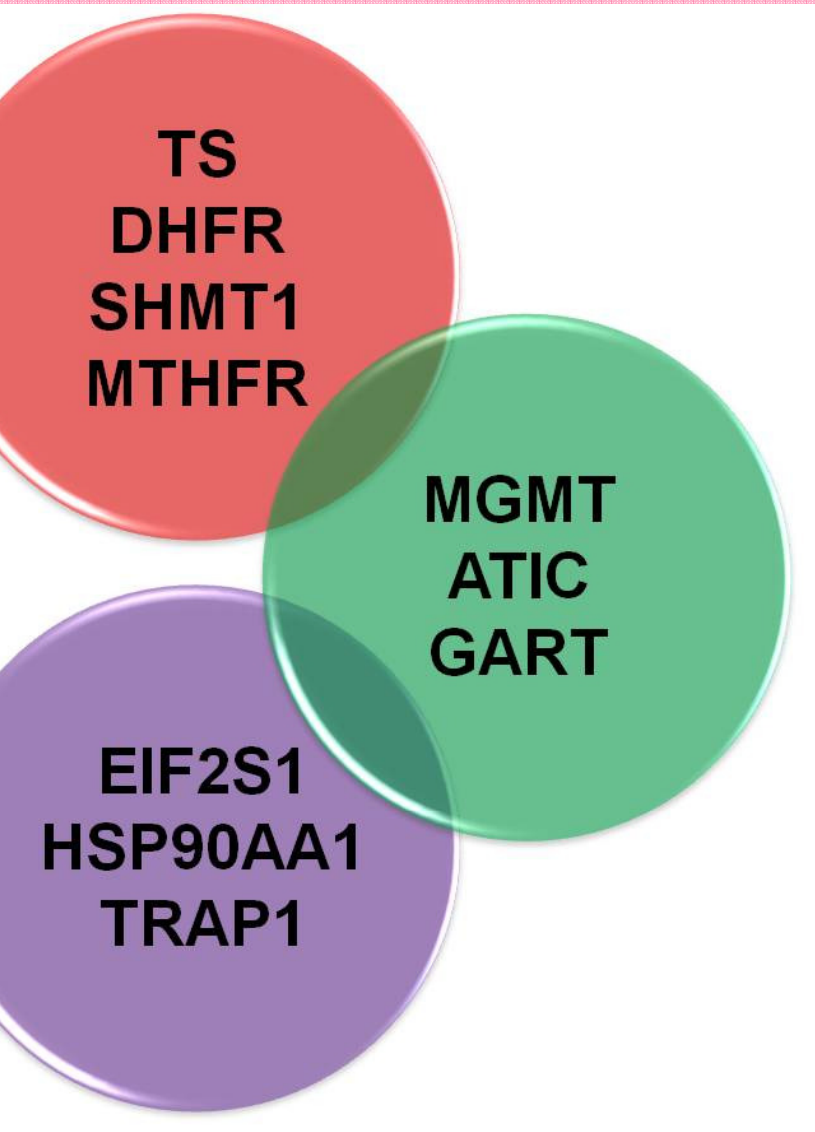


- Up-regulated
- Down-regulated
- Up/Down-regulated
- Folate-related
PMX-related
- Physical protein interactions
- Literature protein interactions

proteins from the original dataset and 14 folate-

Proteins Panel Selection

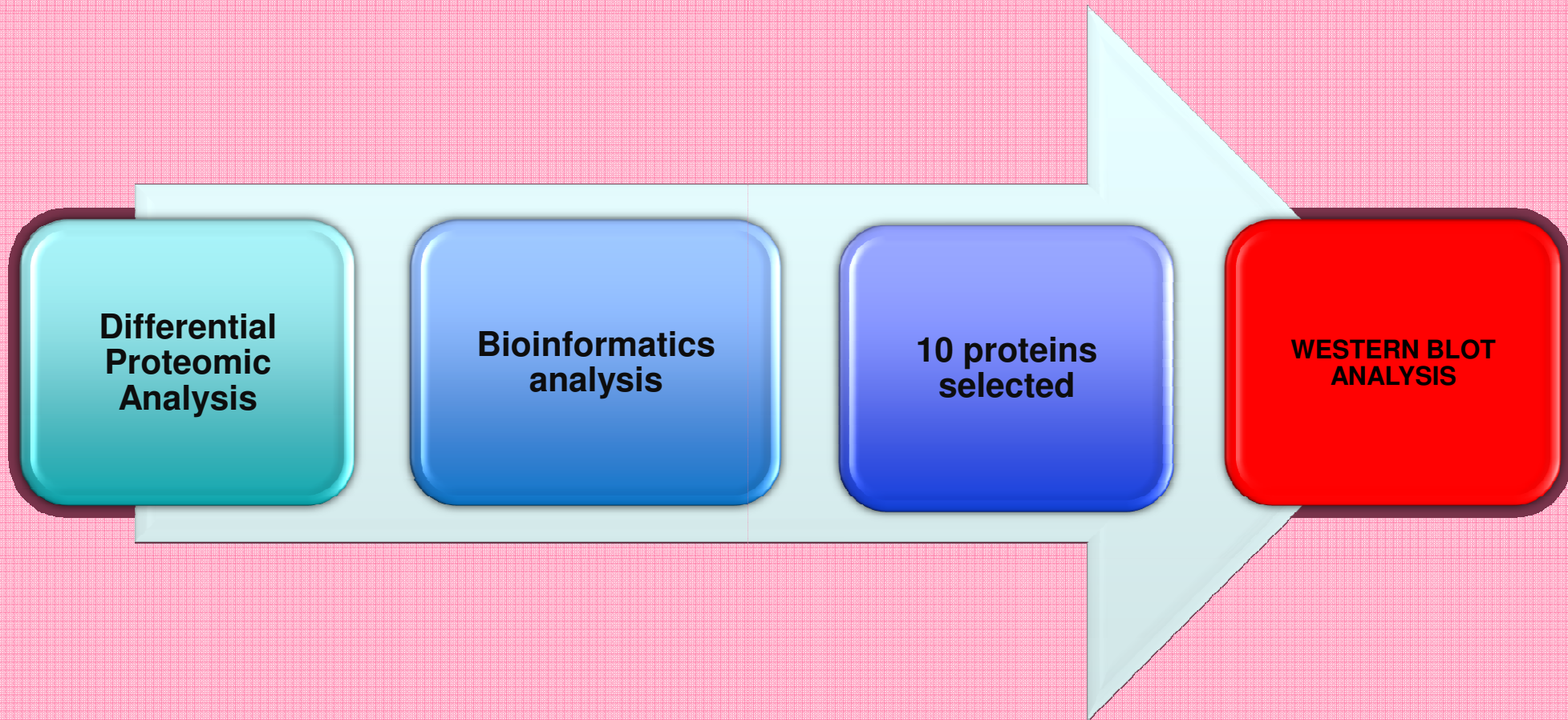
proteins known to be directly involved in the folate cycle



3 folate related protein neighbors
proteins deregulated by LR treatment

differentially expressed proteins

Western Blot targeted approach an panel validation

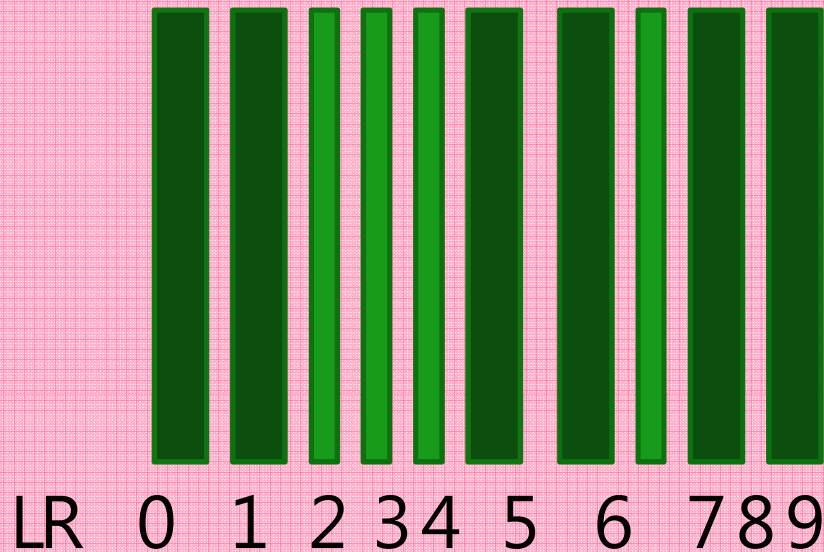


How can we translate the profile in a easy read-out?

Peptide L-barcode

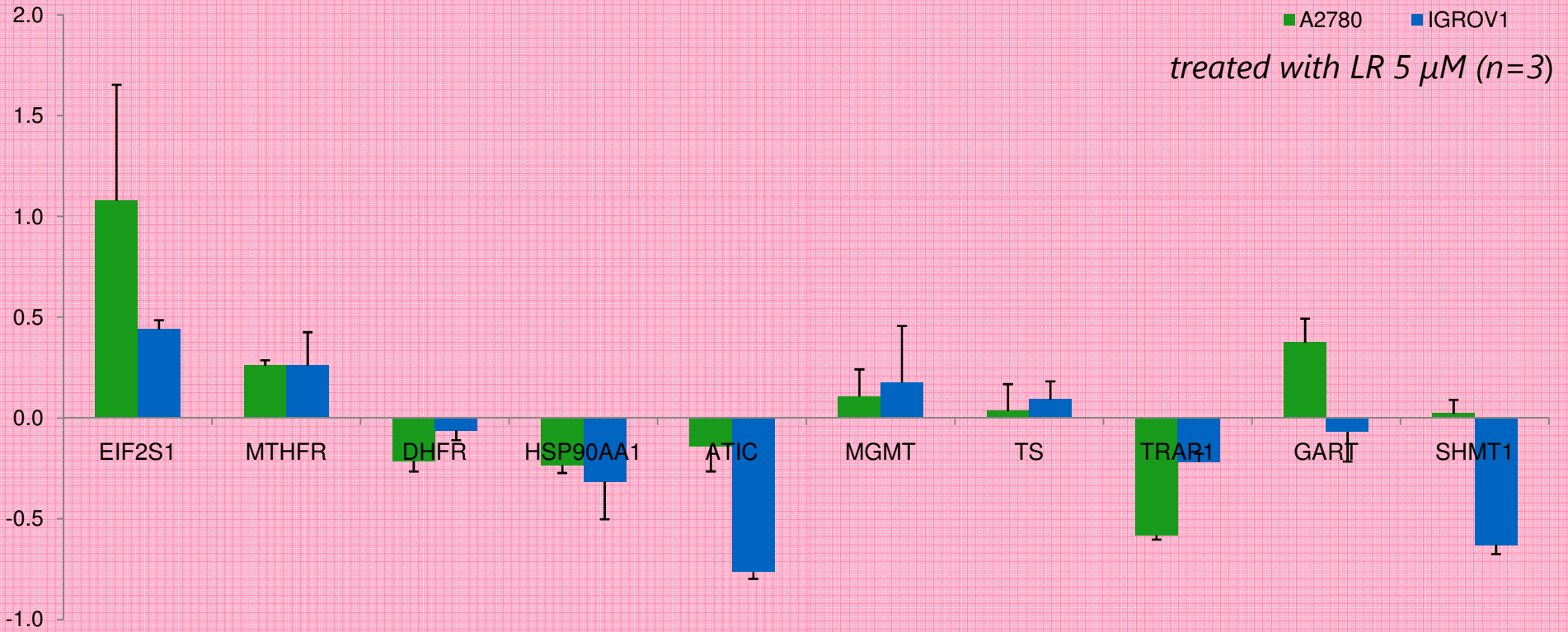


***A2780* peptide barcode**

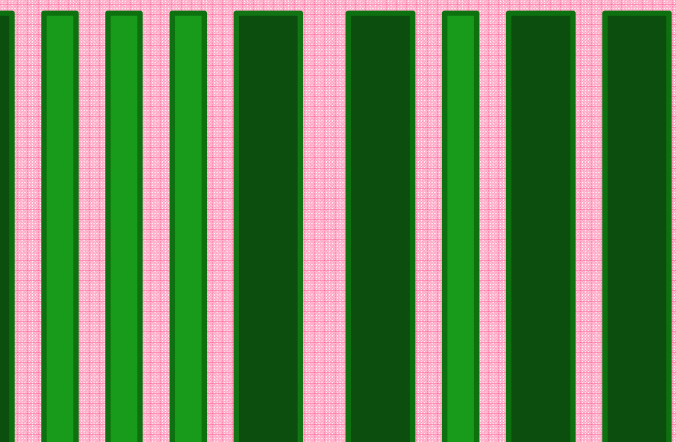


PROTEIN CODE: 0=GART, 1=TRAP1, 2=DHFR, 3=HSP90AA1

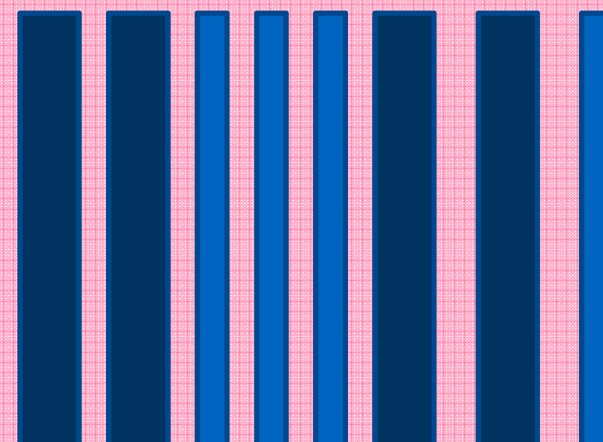
Comparison of A2780 vs IGROV1



A2780

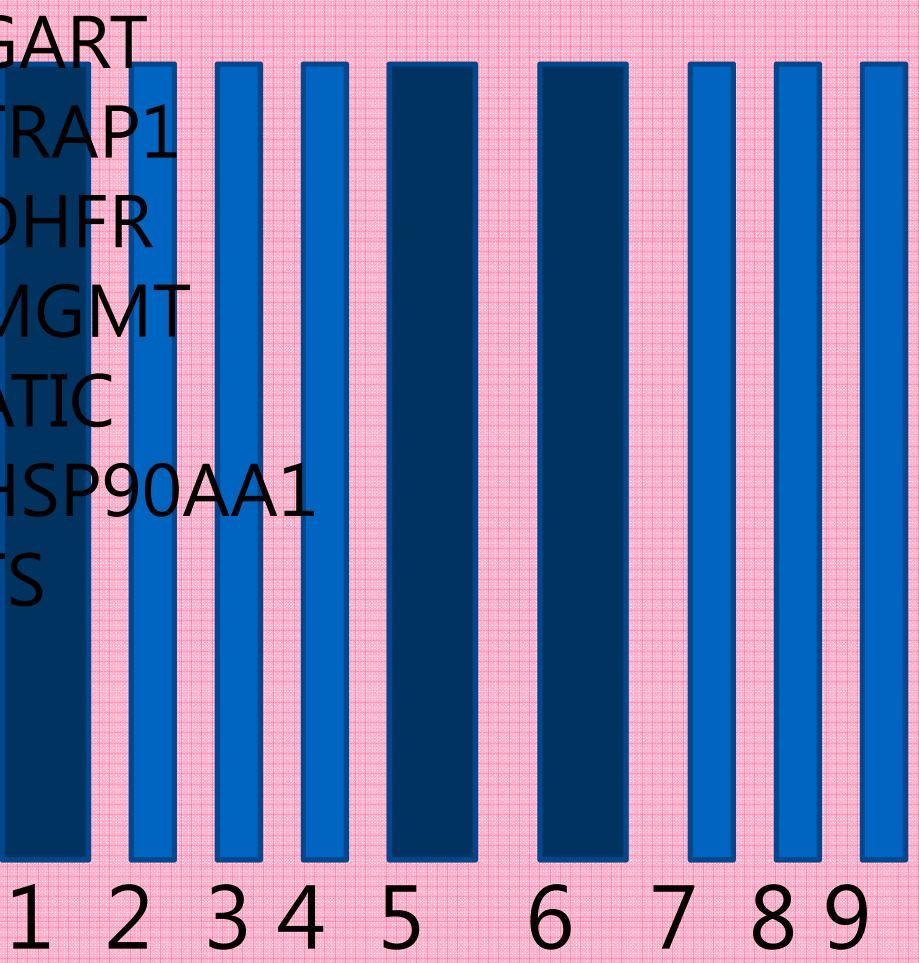


IGROV1

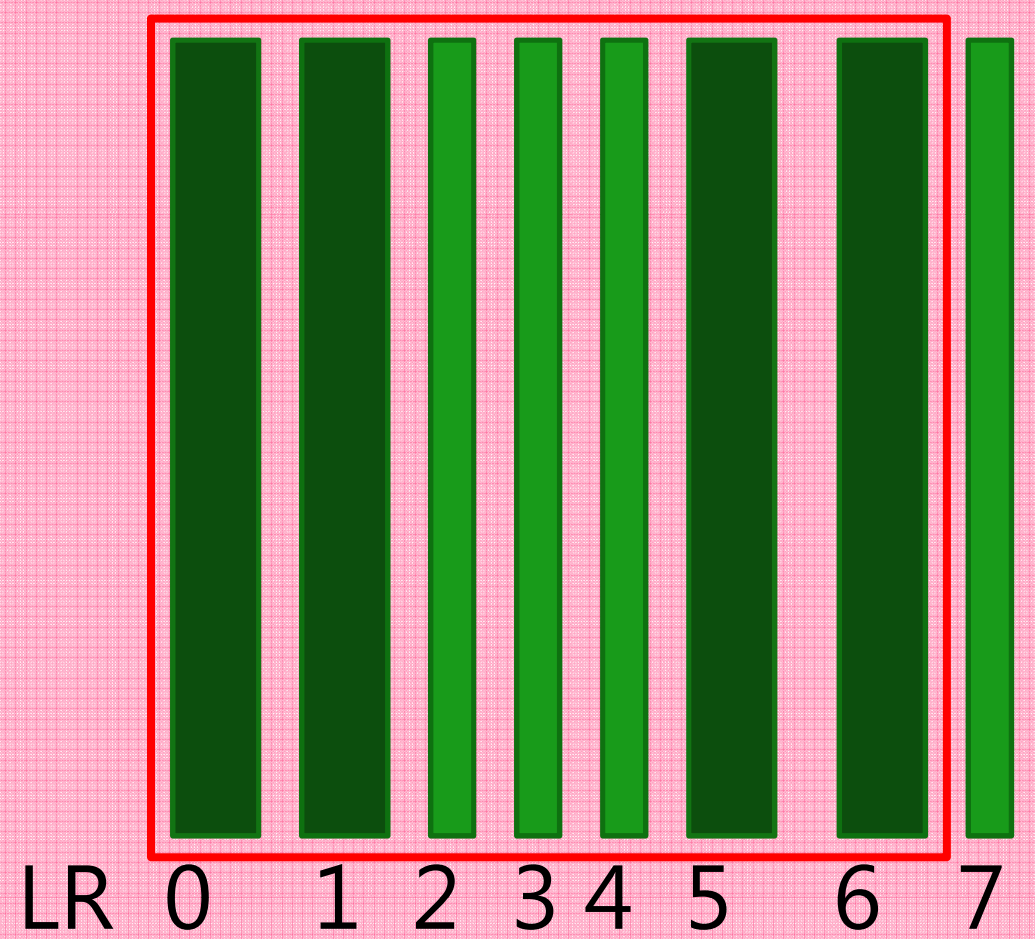


LR effect in sensitive OC cell lines

IGROV1 peptide barcode



IGROV2/802780 peptide barcode

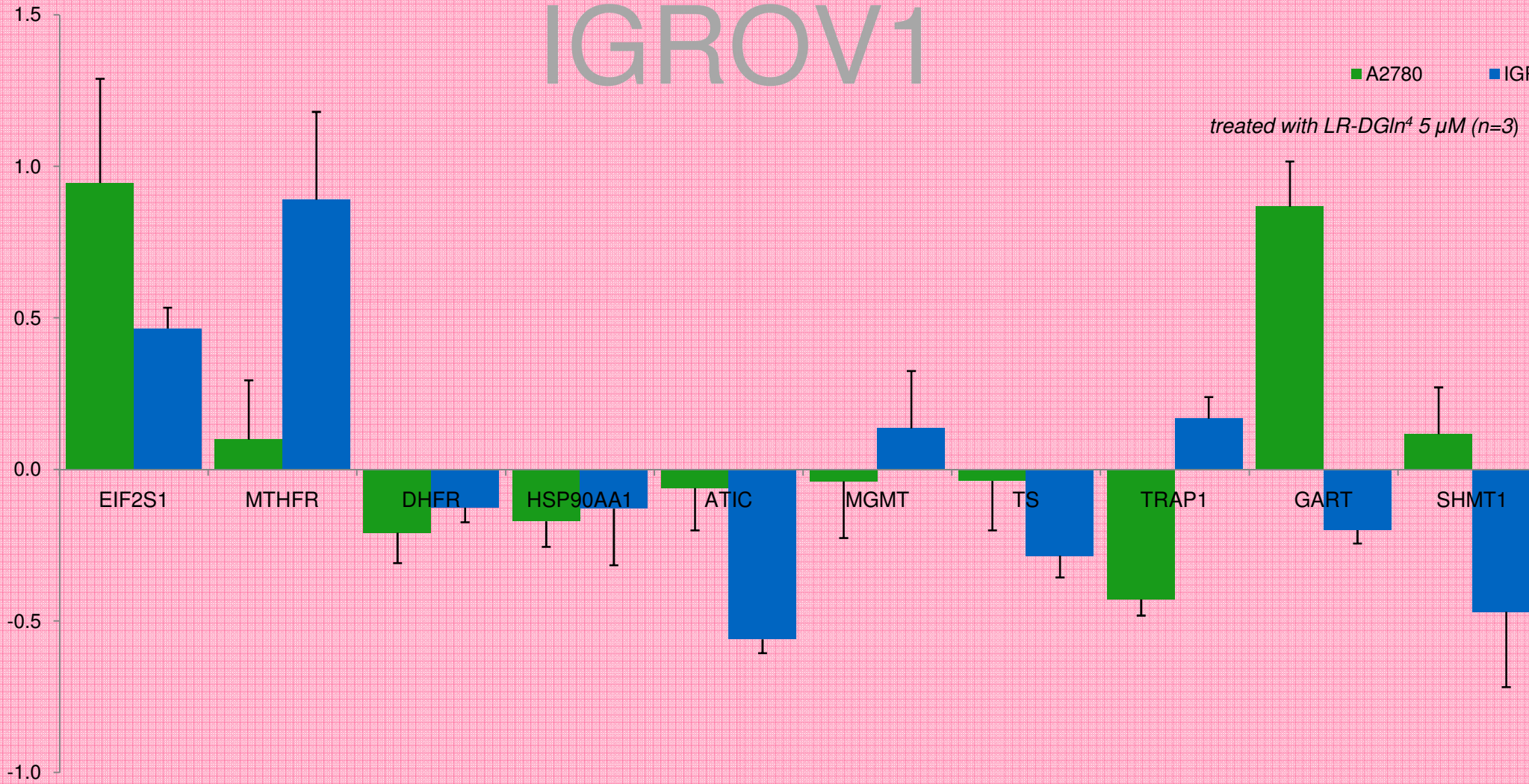


R 0 1 2 3 4 5 6 X X X

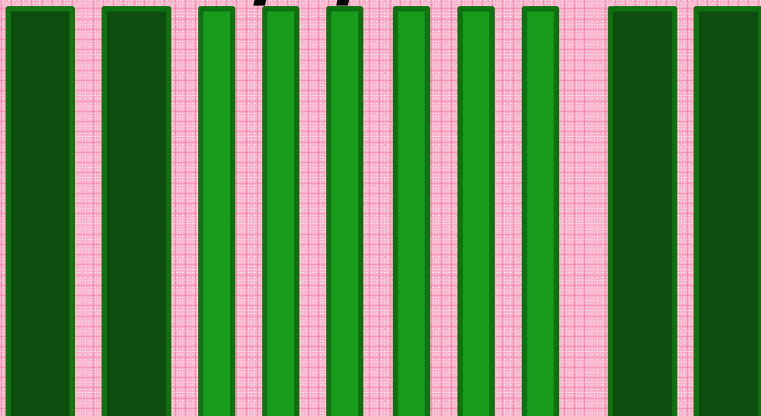
CONSERVED
code

VARI

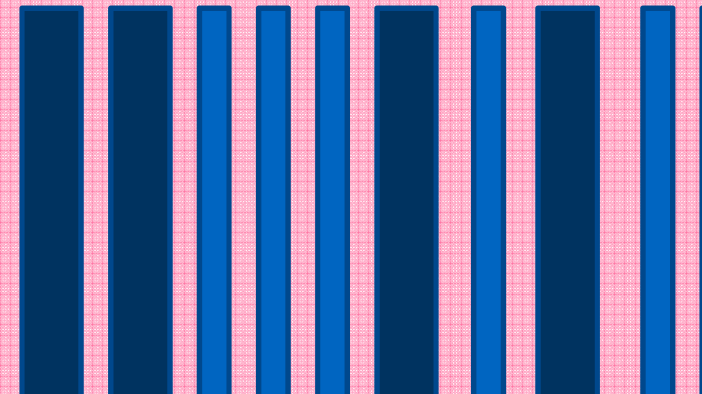
IGROV1



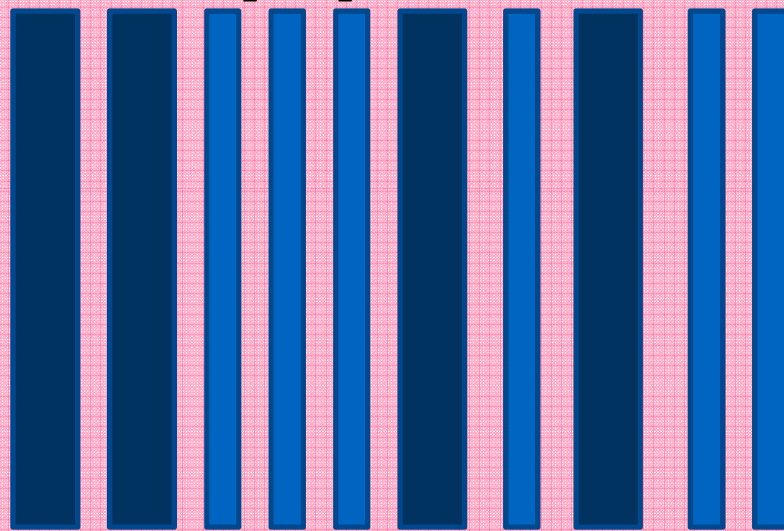
A2780 peptide barcode



IGROV1 peptide barcode

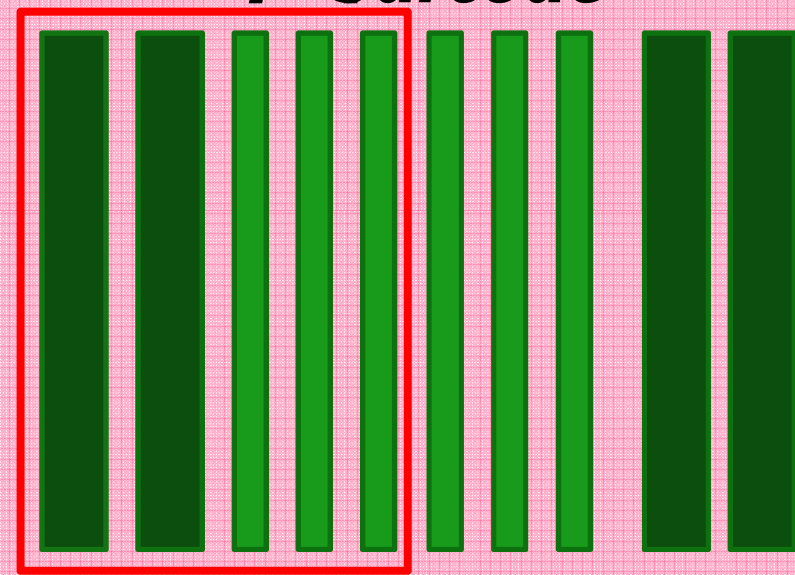


IGROV1 peptide barcode



Gln⁴ 0 1 2 3 4 5 6 7 8 9

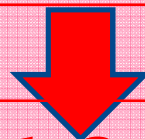
IGROV1/A2780 peptide barcode



DGln⁴ 0 1 2 3 4 5 6 7 8 9

SIMILAR CONSERVED CODES

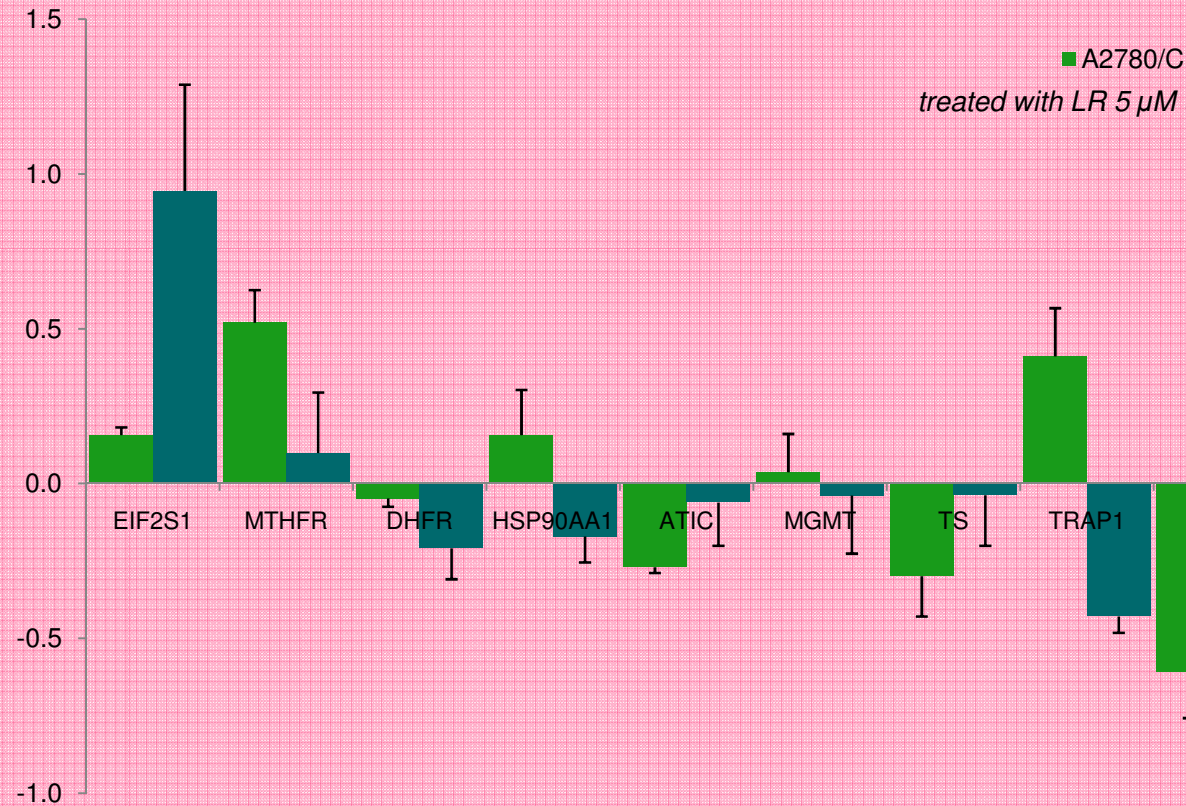
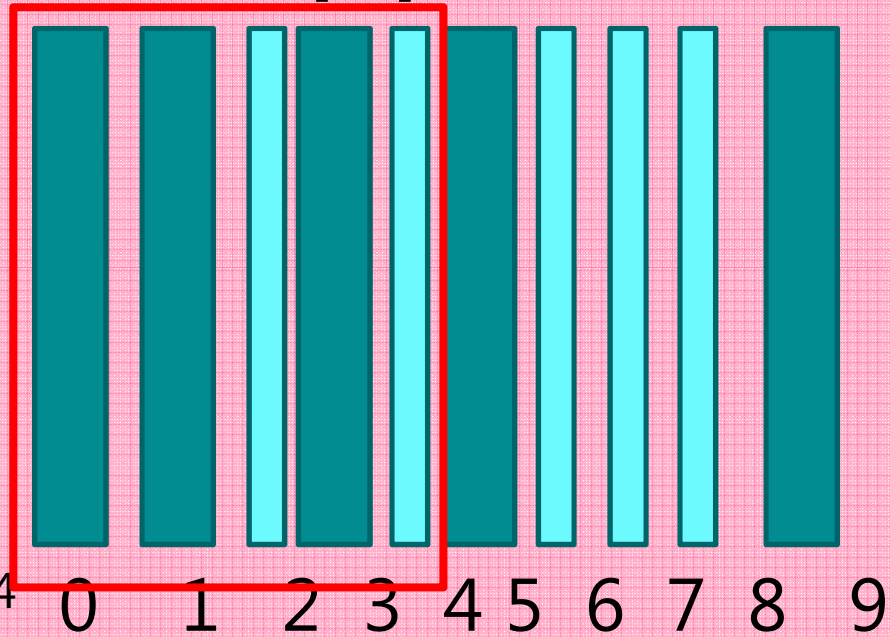
LR 0 1 2 3 4 5 6 X X X



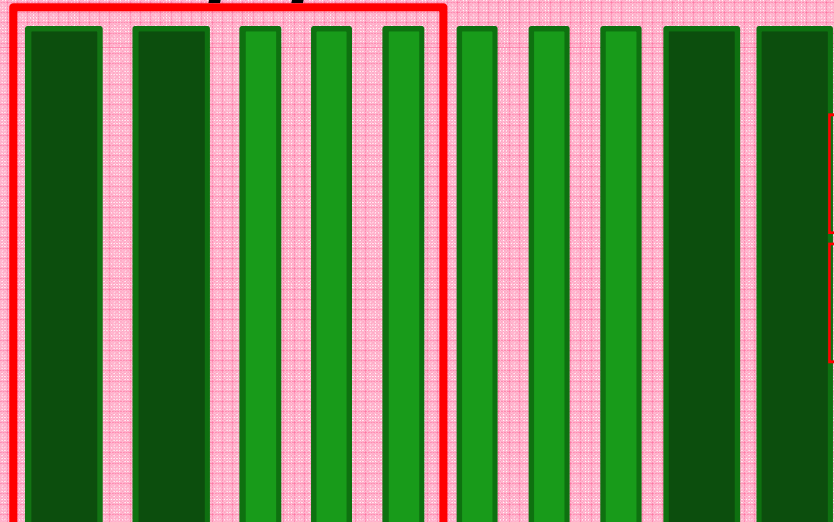
LR/LRDGln⁴ 0 1 2 3 4 X X X X X

SUGGESTING

2780/CP peptide barcode

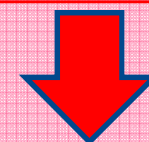


A2780 peptide barcode

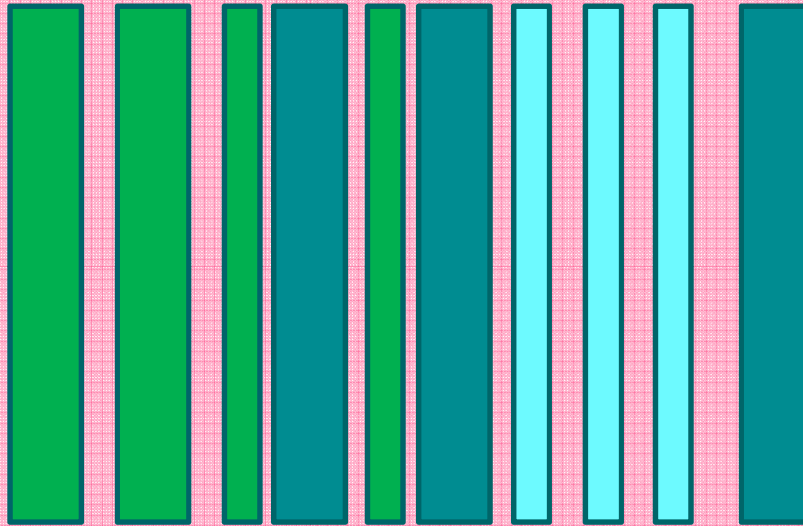


SIMILAR CONSERVED COD

A2780/CP	LR-DGln ⁴	0	1	2	X	4	5	X
A2780	LR-DGln ⁴	0	1	2	3	4	X	X



1. Optimal barcode



LR/LR-DGln⁴ 0 1 2 3 X 5 X X X X X

0 = GART

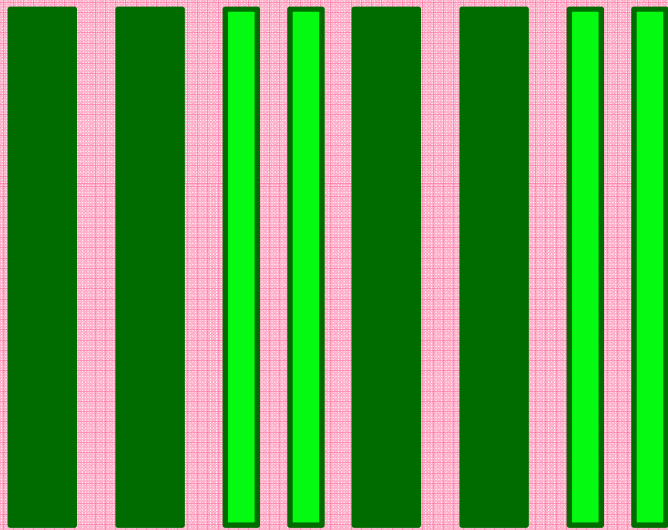
1 = TRAP1

2 = DHFR

5 = HSP90AA1

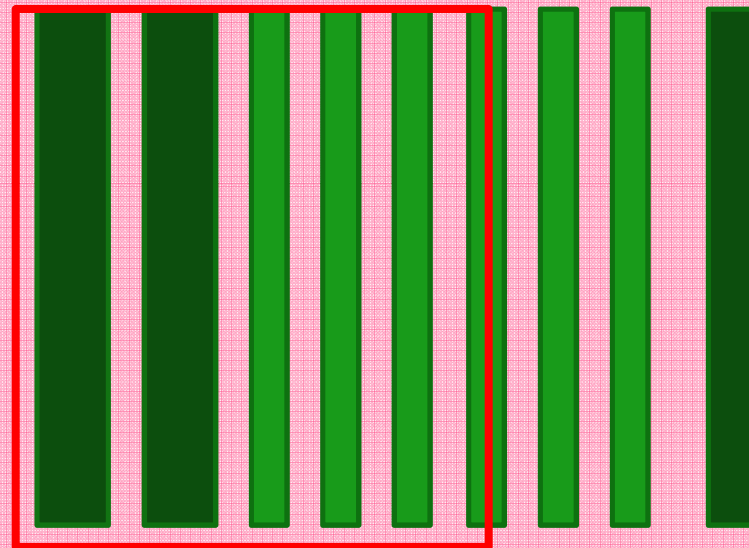
X = ...

780 PTX barcode



2 3 4 5 6 7 8 9

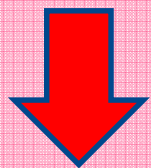
A2780 PTX peptide barcode



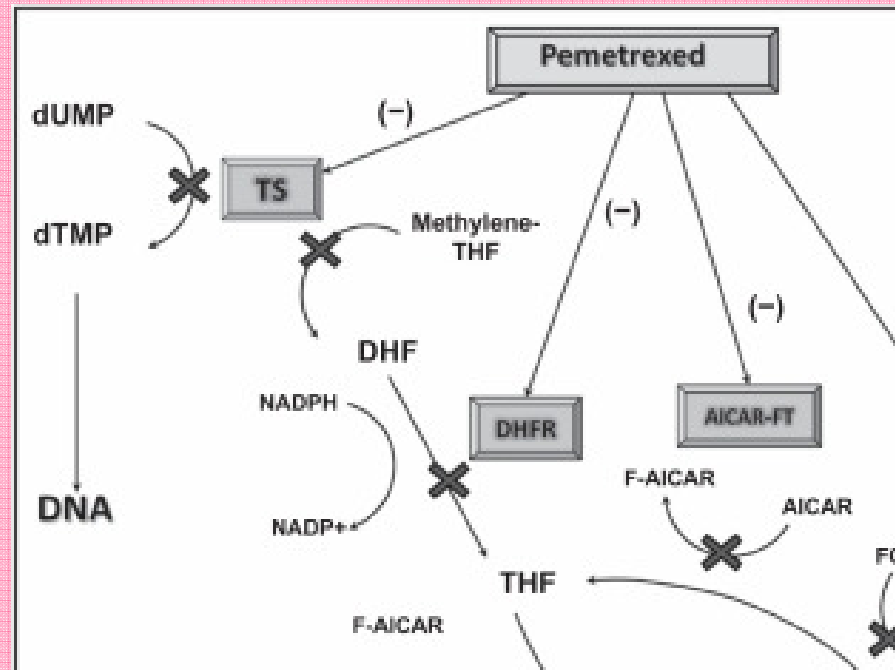
LR-DGIn4 0 1 2 3 4

7

DIFFERENTS BARCODES

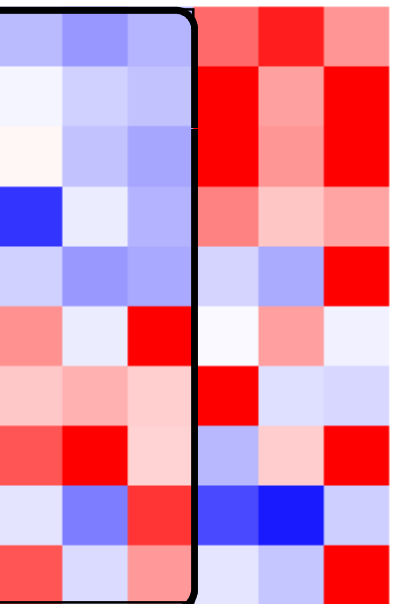


DIFFERENT MECHANISM OF ACTION

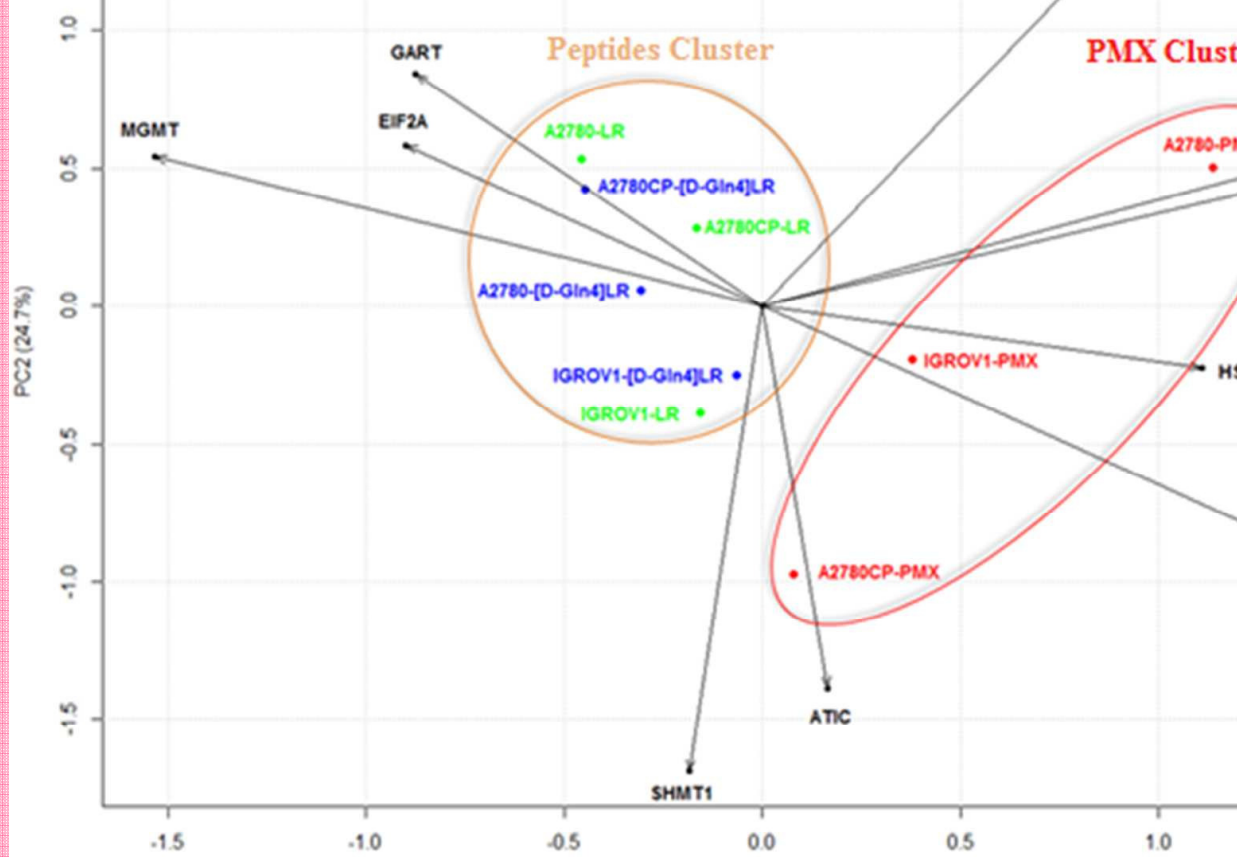


Statistical analysis of the WB results

A2780 (LR-DGln4)
 IGROV1 (LR-DGln4)
 ACP (LR-DGln4)
 A2780 (PMX)
 IGROV1 (PMX)
 ACP (PMX)



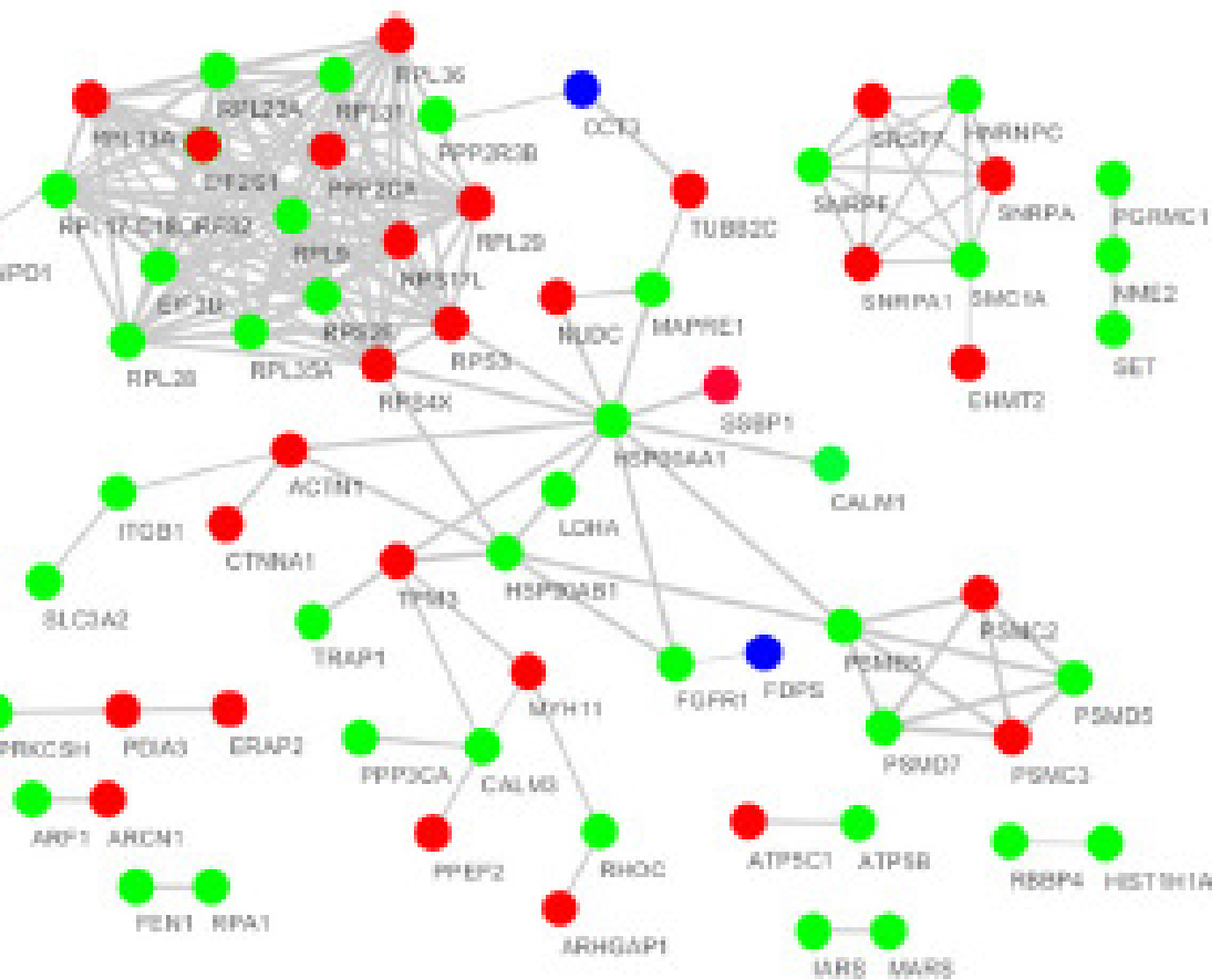
HSP90AA1
 DHFR
 TS
 TRAP1
 ATIC
 GART
 MTHFR
 SHMT1
 MGMT
 EIF2S1



PCA. Different clusters for a different mechanism

Heatmap. Blue down expression, red high expressing

What is the biological meaning of the proteomic signature identified?



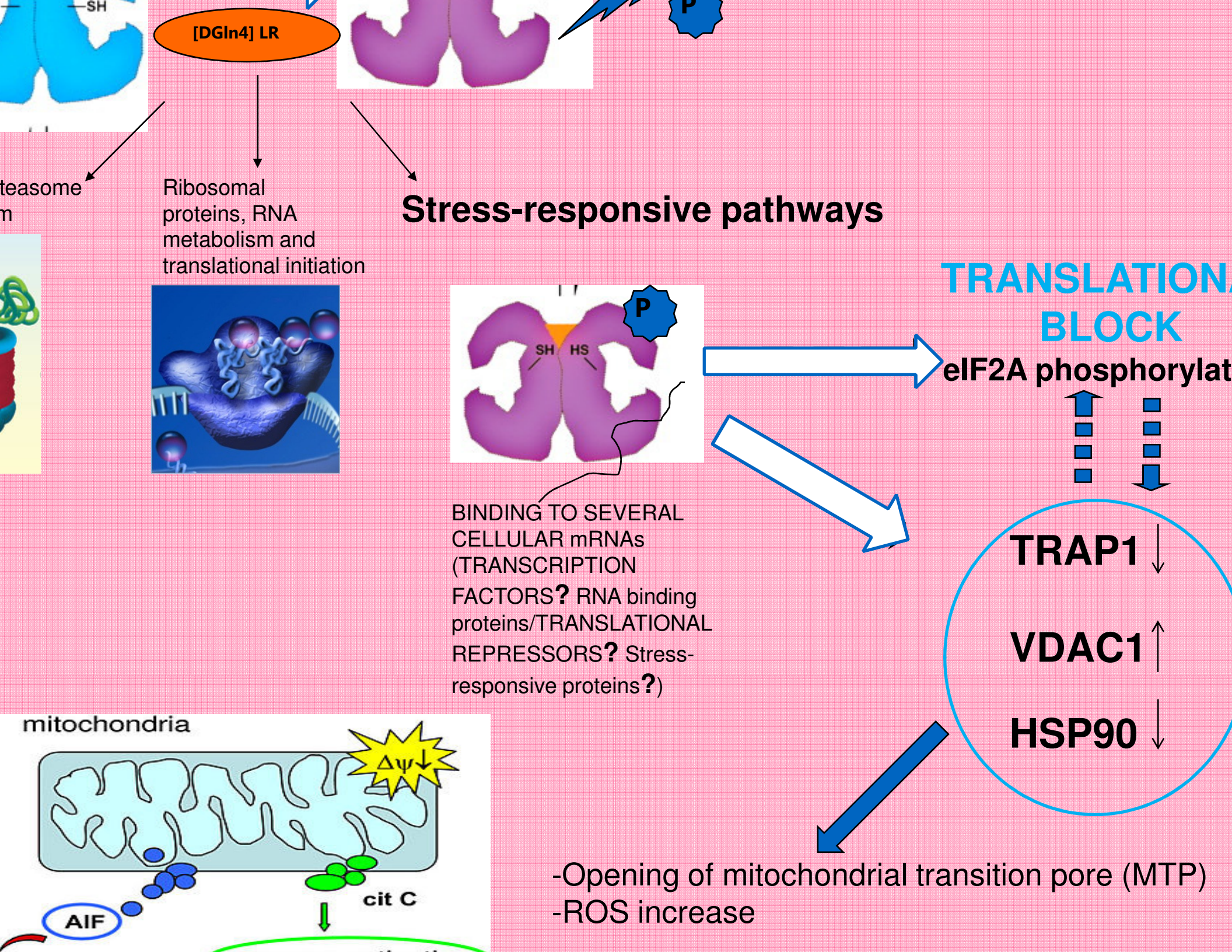
OC A2780 C



CONTROL vs LP
TREATMENT

..a proteomics-
bioinformatics
combined approach
to the identification
of a set of proteins reg
ulated upon treatment wi
th drug-derived peptides.

INTERPRETATION OF THE PROTEOMIC RESULTS INTO BIOLOGICAL/MOLECULAR
PATHWAYS ON OVARIAN CANCER CELLS!



[DGI4] LR

Stress-responsive pathways

TRANSLATION BLOCK

eIF2A phosphorylat

BINDING TO SEVERAL CELLULAR mRNAs (TRANSCRIPTION FACTORS? RNA binding proteins/TRANSLATIONAL REPRESSORS? Stress-responsive proteins?)

mitochondria

$\Delta\Psi \downarrow$

AIF

cit C

-Opening of mitochondrial transition pore (MTP)
-ROS increase

TRAP1 ↓

VDAC1 ↑

HSP90 ↓

Conclusions

The results confirm that our new methodology provides:

) An approach to the discovery of molecular drug targets/off-targets would be part of a pharmacodynamic profile to monitor candidate activity since the very early phases of the drug development process.

Deregulations can be mainly assigned to the following processes or functions:

- regulation of translational initiation,
- termination of RNA Pol-II transcription,
- transport,
- proteasome.

different expression level changes observed consequently to des treatment in comparison with a folate antagonist currently used. Remetrexed, are in agreement with the hypothesized diffe



Targeting Drug Resistance in Ovarian Cancer

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Gaetano Marverti
Paul Perco
Michela Pelà
Remo Guerrini

Glauco Ponterini
Maria Paola Costi

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