Cytomics in Pharmaceutical Research

Peter Van Osta

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EWGCCA
Mol, Belgium
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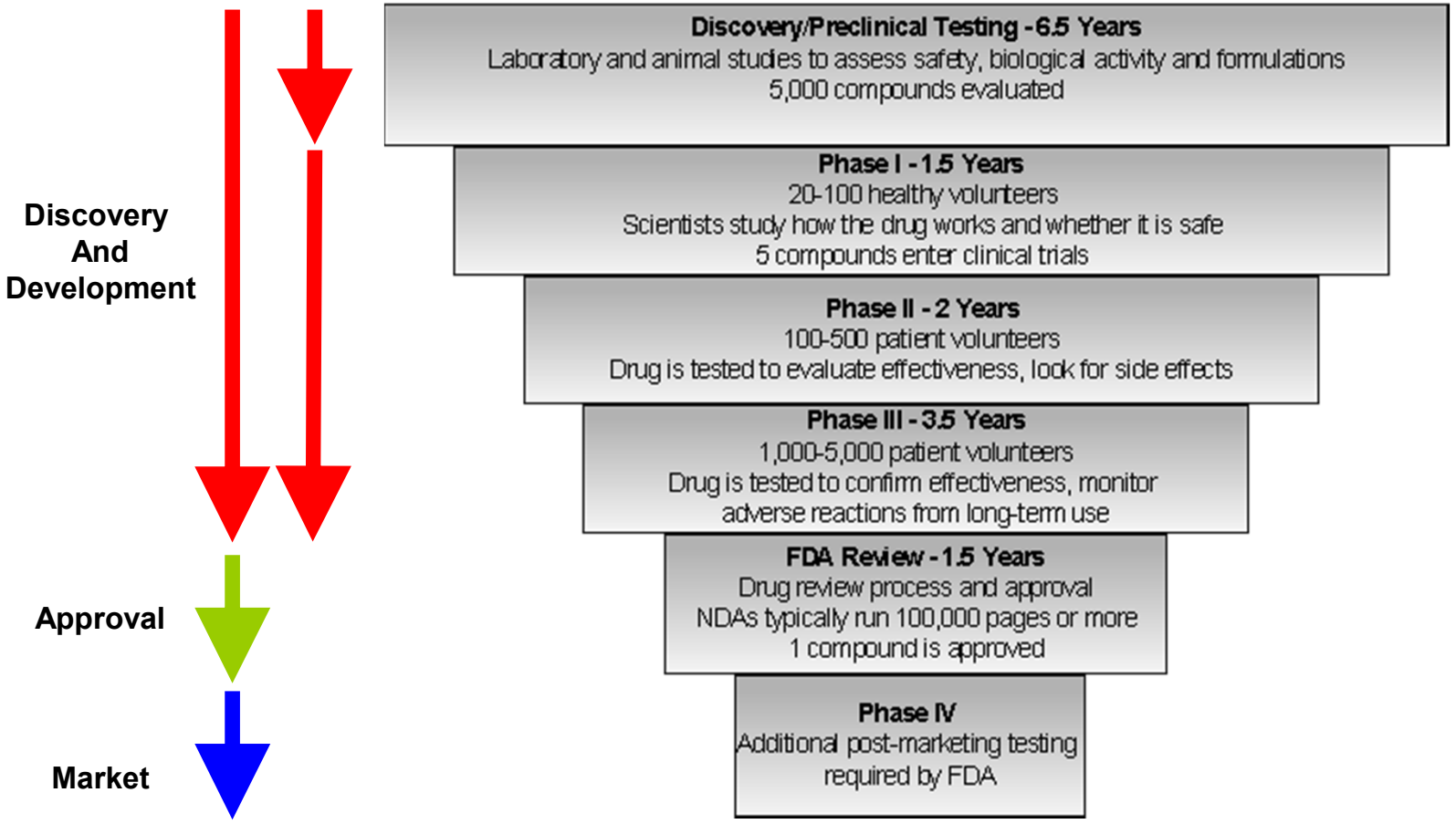
Cytome - Cytomics

- **Cytomes** can be defined as cellular systems and subsystems and functional components of the body.

- **Cytomics** is the study of the heterogeneity of *cytomes* or more precisely the study of molecular single cell phenotypes resulting from genotype and exposure in combination with exhaustive bioinformatics knowledge extraction.

- The word Cytomics was first used in 2001 by:
  Davies E, Stankovic B, Azama K, Shibata K, Abe S.
  "Novel components of the plant cytoskeleton: A beginning to plant "**cytomics**"
  Plant Science, Invited Review, Plant Science (160)2 (2001) pp. 185-196.

Drug Discovery and Development



About 15 years and $500 million to bring one drug to the market

43 % of total time spent in pre-clinical research vs. 46 % of time spent in clinical research

0.1 % of molecules enter phase I and 0.02 % of the original molecules finally reach the market

80% fallout in clinical trials

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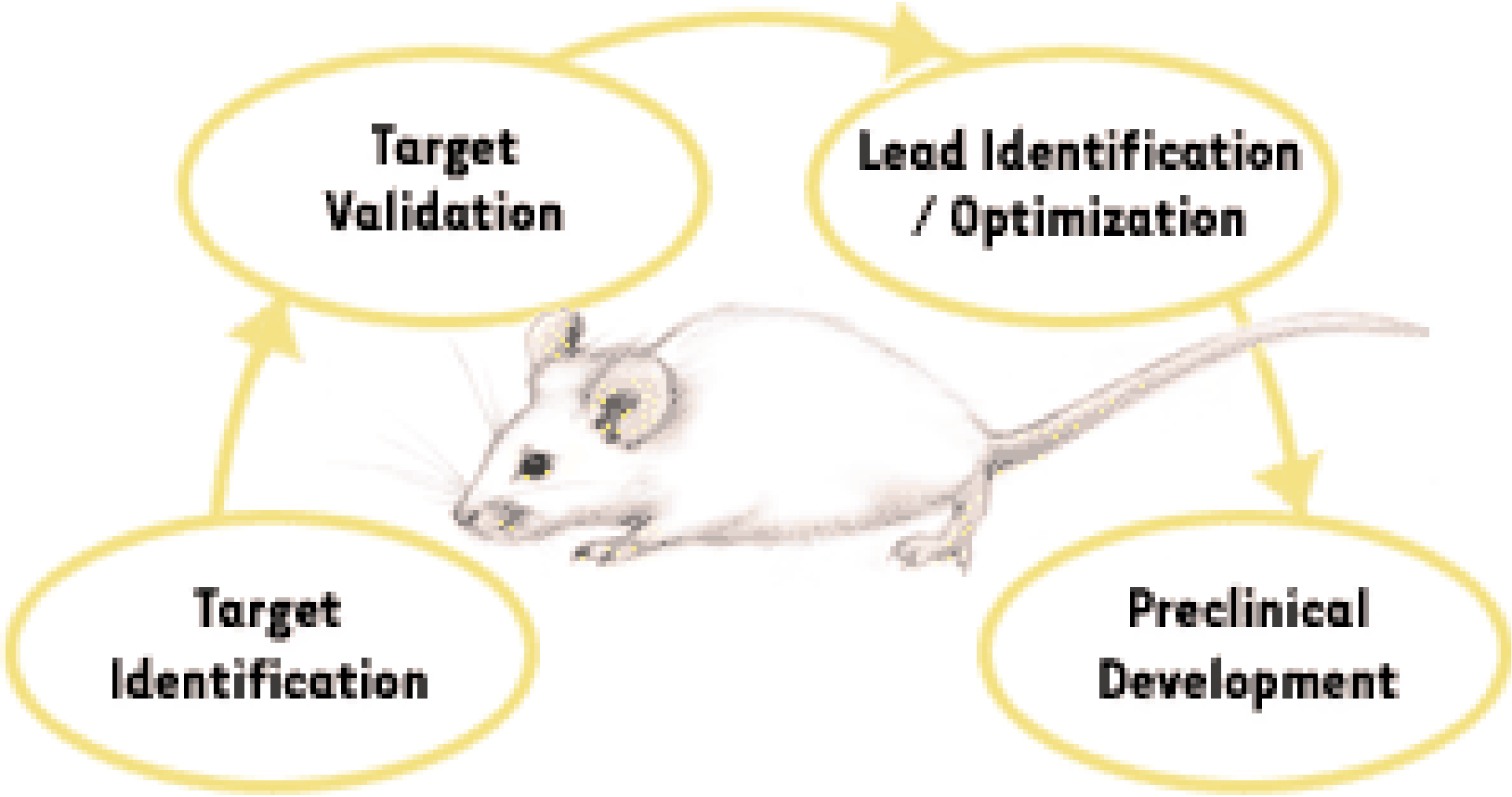
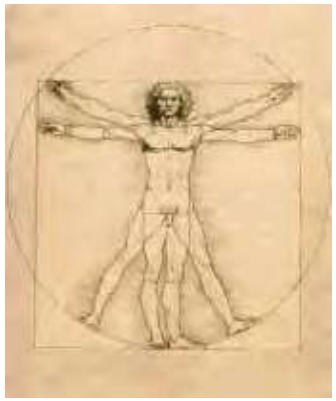
Drug Discovery
Disease Models from Genome to Organism

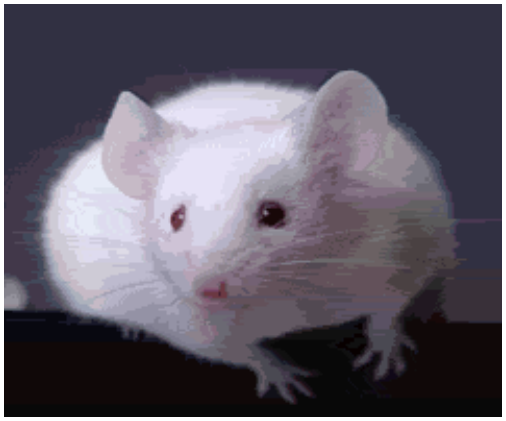


Which biological level of integration do we use in our drug discovery pipeline
as a disease model with sufficient predictive power

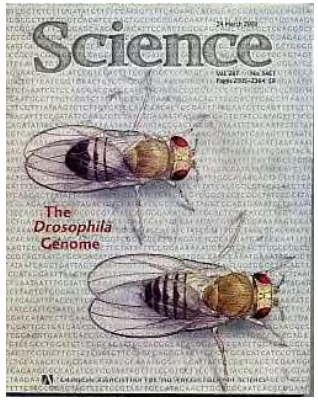
Drug Discovery
From Genome to Organism and Disease



Human ≅ 30,000 genes
3,2000 Mb or 3.2 billion base pairs



Mouse ≅ 30,000 genes
2,500 Mb



Drosophila ≅ 13,601 genes
165 Mb

C. elegans ≅19,000 genes
97 Mb

Complexity and differentiation of organisms is not only explained from the relative complexity of their genomes

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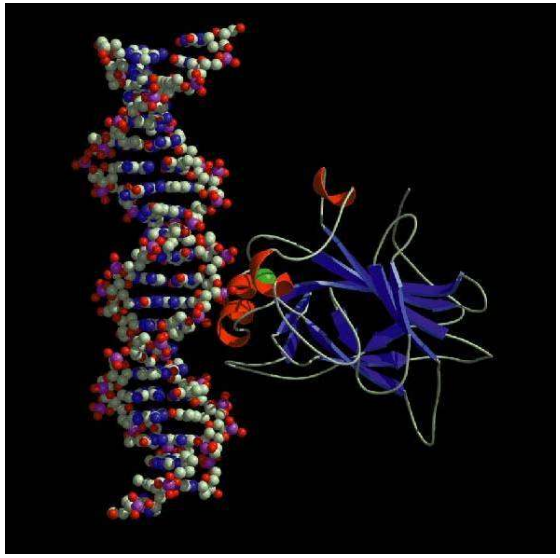
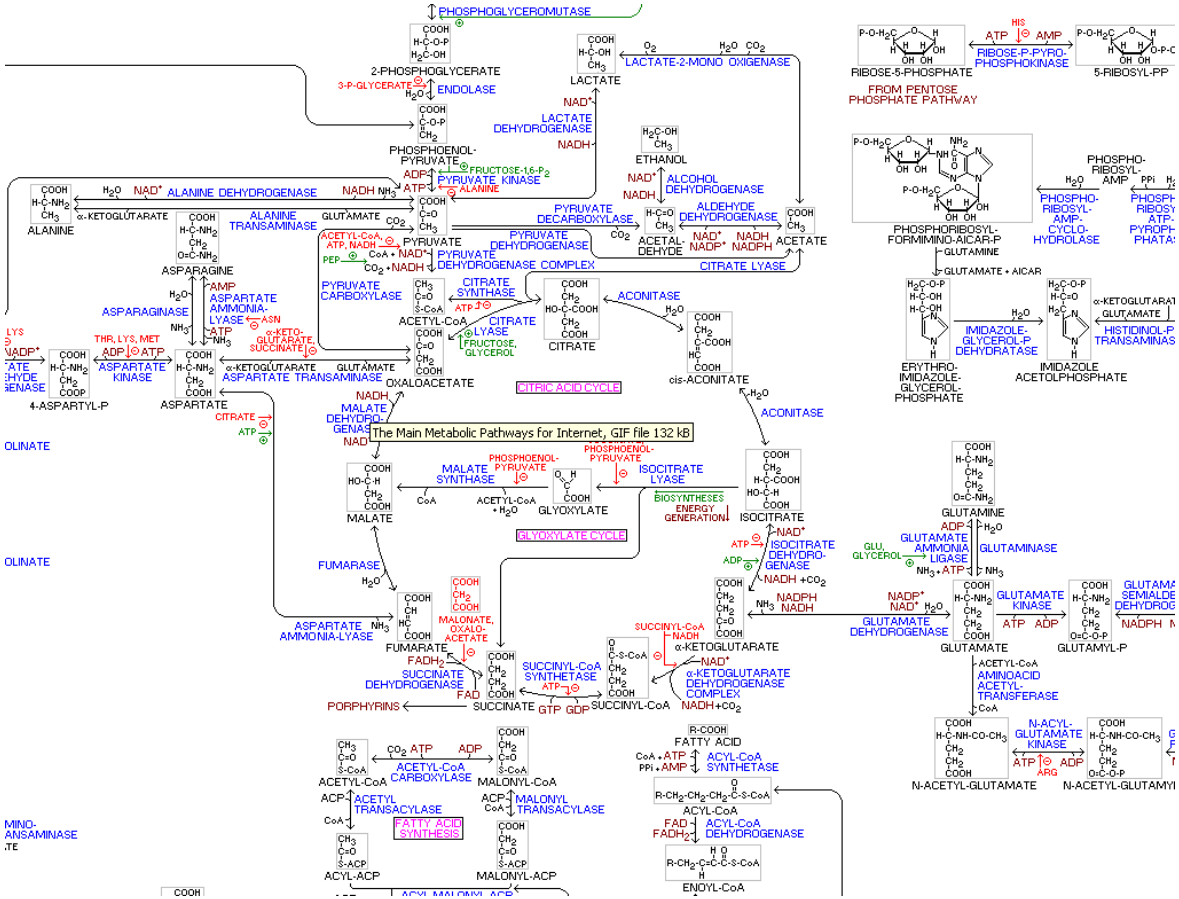
Drug Discovery
From Genes to Proteins to Pathways





From gene to 3D protein structure

From protein to a network of metabolic pathways

The complexity of interacting metabolic pathways is not only predicted from the gene or protein structure

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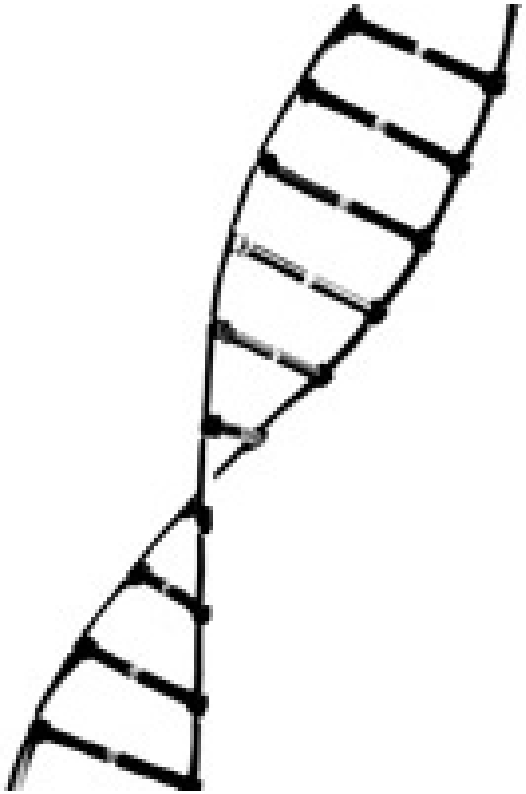
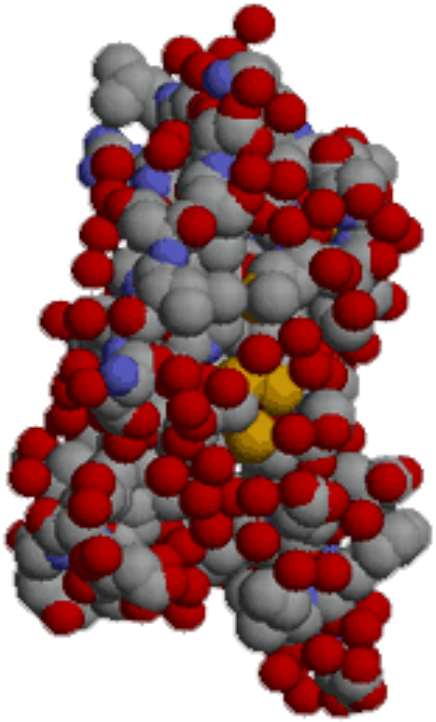
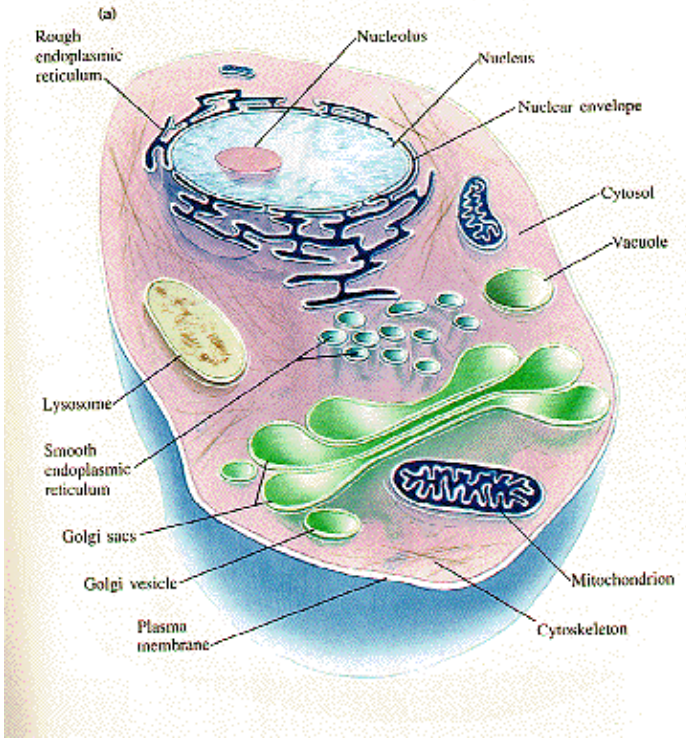
Drug Discovery by Cytomics
Speed vs. Information Content







DNA sequencing
DNA expression

Protein structure
Protein expression

Cellular phenotype
Cellular function

Increasing the complexity of the biological level of integration, leads to a decrease in speed but an increase in information content

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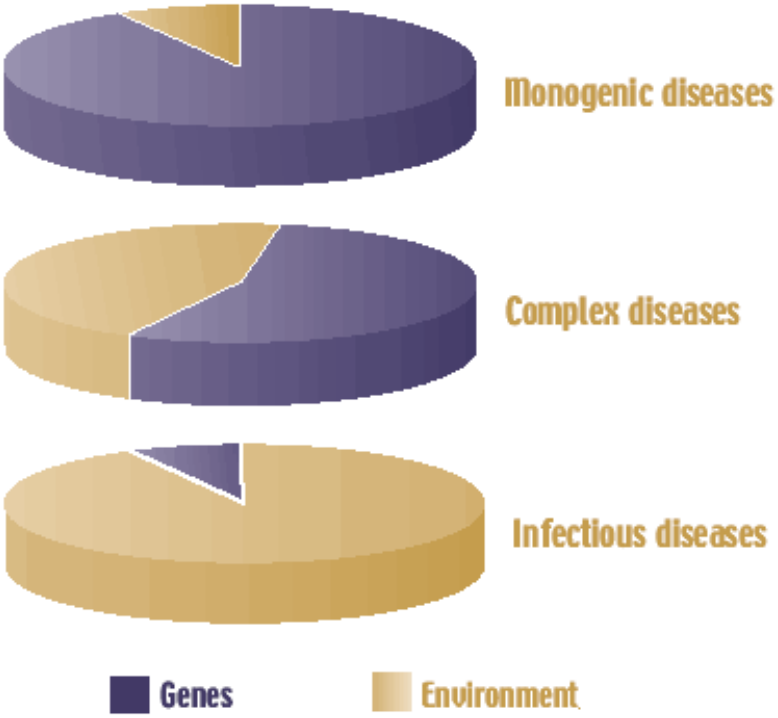
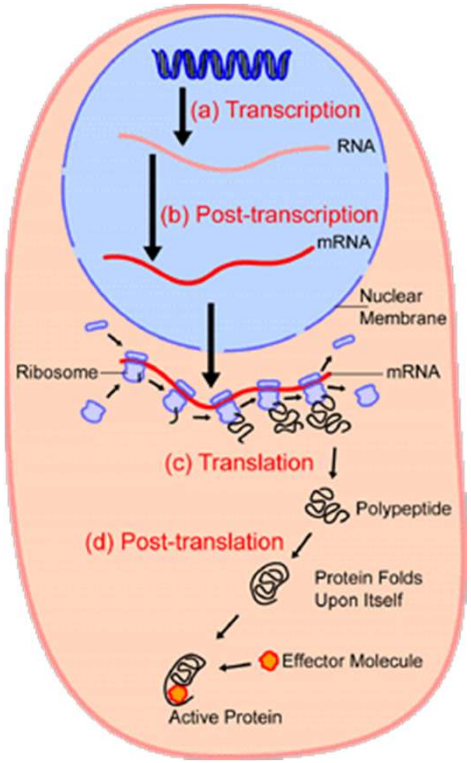
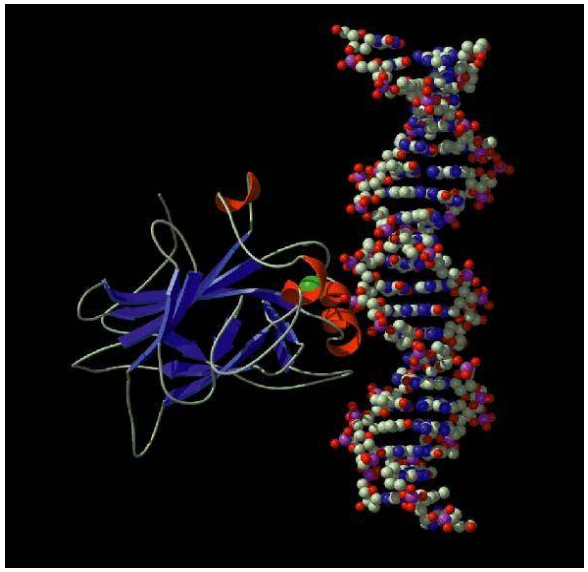
Drug Discovery by Cytomics
Diseases - A Web of Interactions







Environment

Cell
Cytome

From Gene to Protein
Genome - Proteome

Instead of concentrating on molecular targets within the relatively infinite network of highly redundant molecular pathways of cells, one can primarily focus on the end result, represented by molecular phenotypes of cells as a consequence of both genotype and environment.

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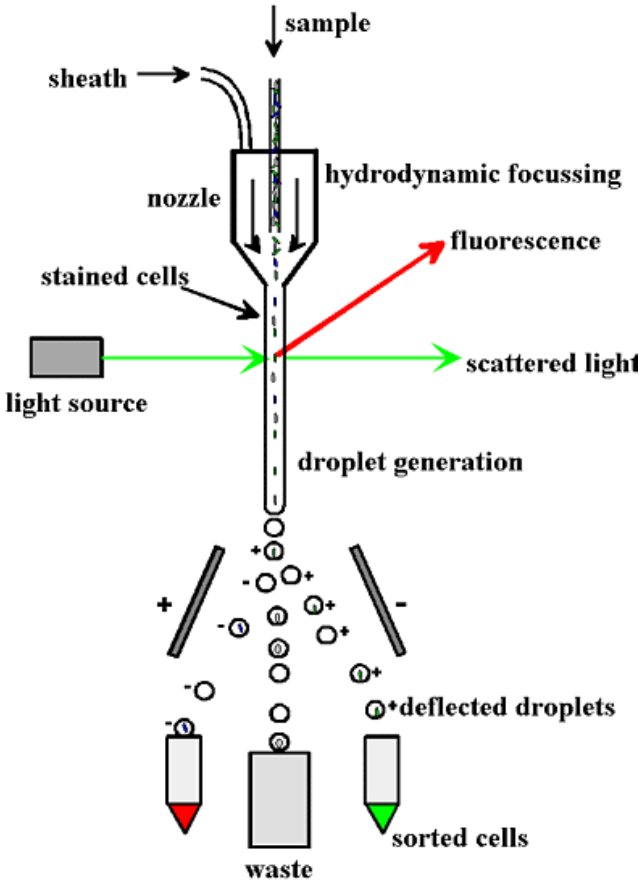
Drug Discovery by Cytomics Technology

- High Content Screening:
  - High speed combined with multi-parametric analysis

- Advanced microscopy techniques:
  - LM, EM, Confocal and laser scanning microscopy, spectral imaging, FRET, SEM, TEM, digital microscopy, …
- Flow Cytometry
  - Fast imaging in flow, …
- Biomolecular analysis techniques:
  - Single-cell polymerase chain reaction (PCR), labeling of biomolecules by quantum dots, …
- Bioinformatics:
  - Data exploration, statistics and data management, …

Drug Discovery with Cytomics
High Content Screening



Flow Cytometry

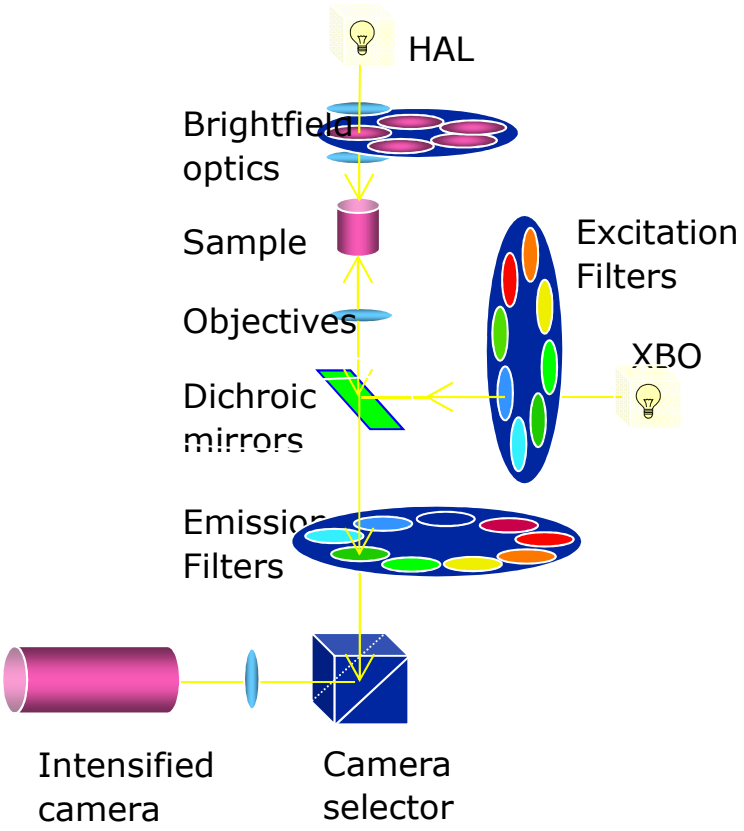


Image Based Cytometry

Complementary technology

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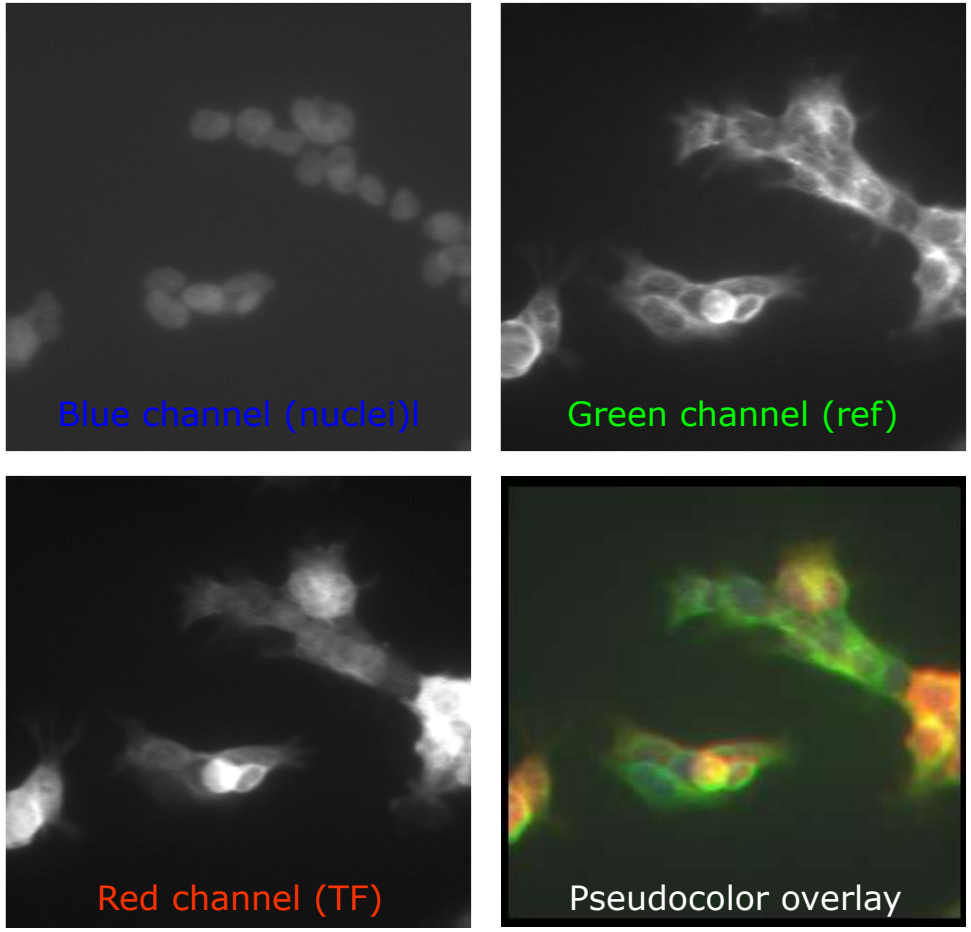
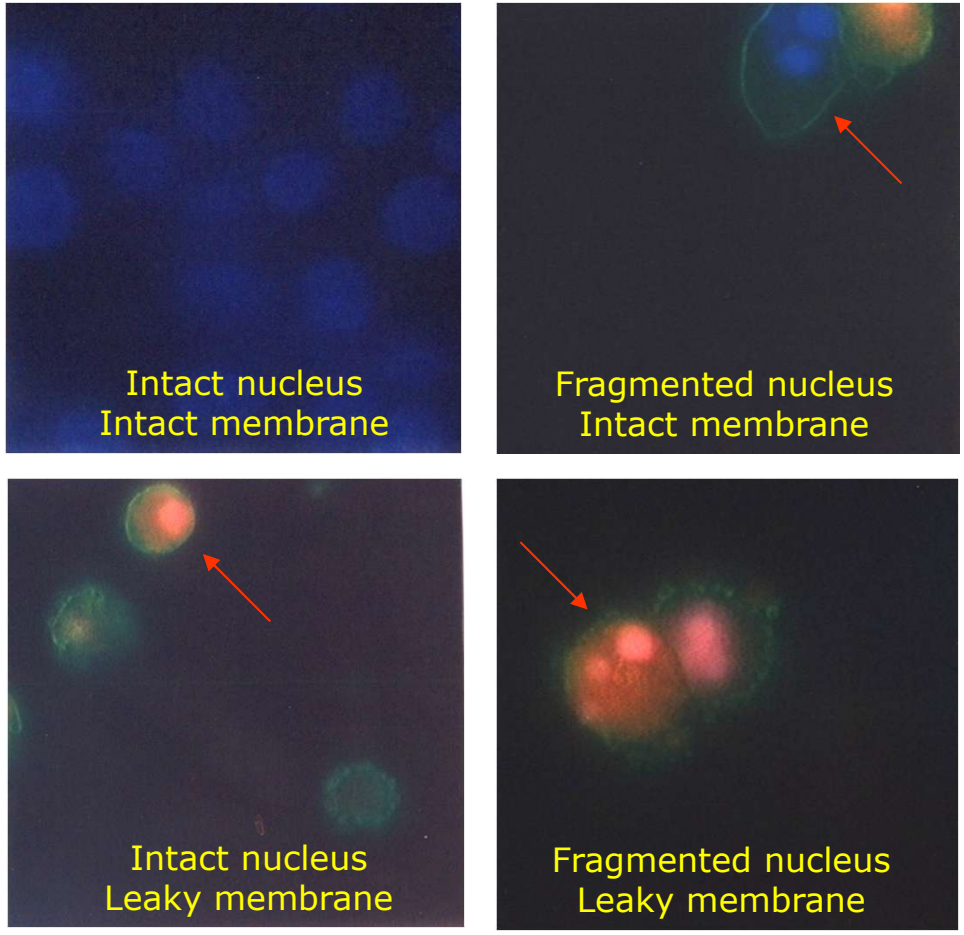
High Content Screening
Multidimensional Objects

Expression / Translocation



Apoptosis



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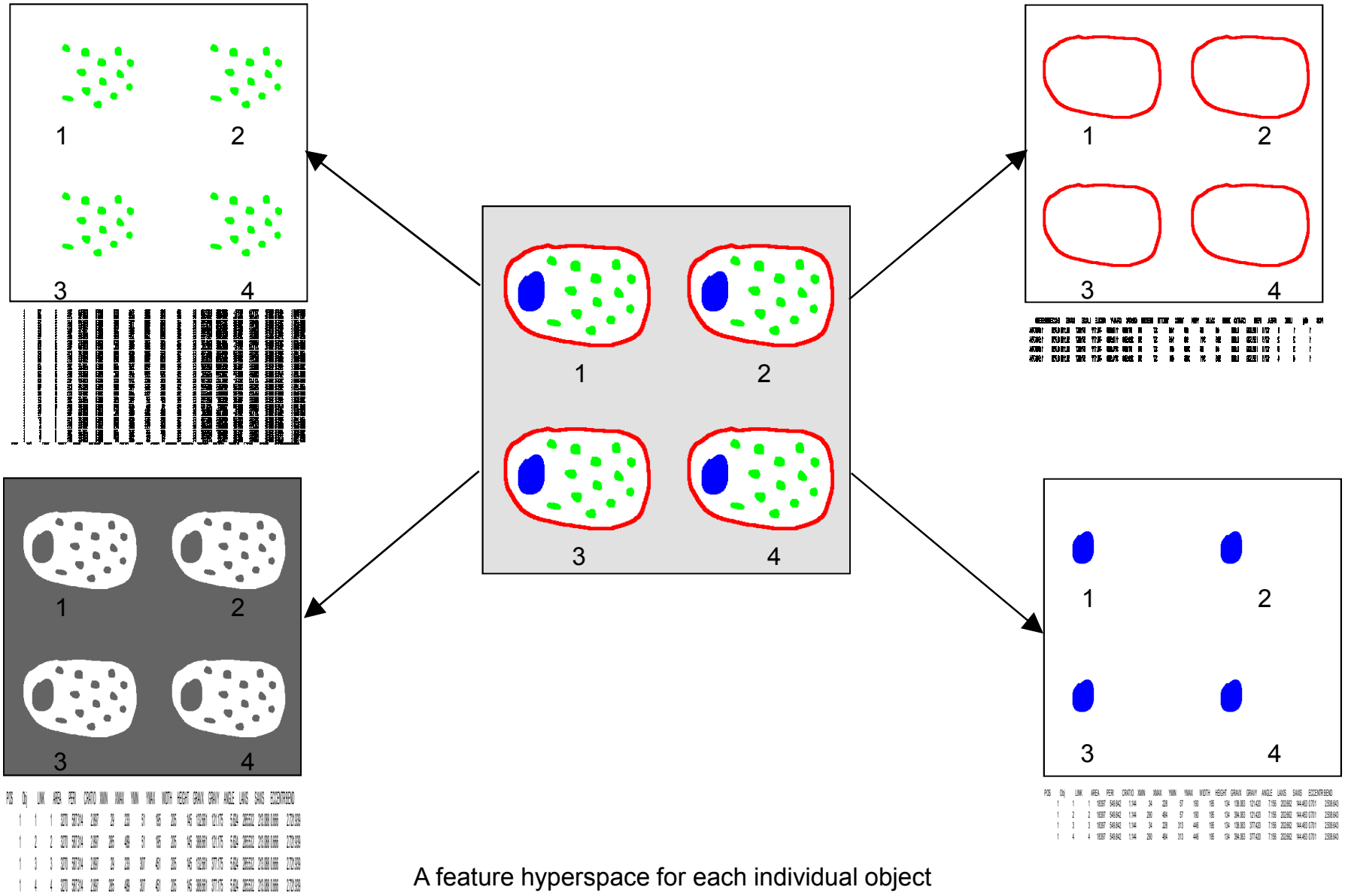
Courtesy of Anne-Marie Michon

Spatial, spectral and temporal dimensions lead to 5D

High Content Screening
From Object to Feature Hyperspace



A feature hyperspace for each individual object

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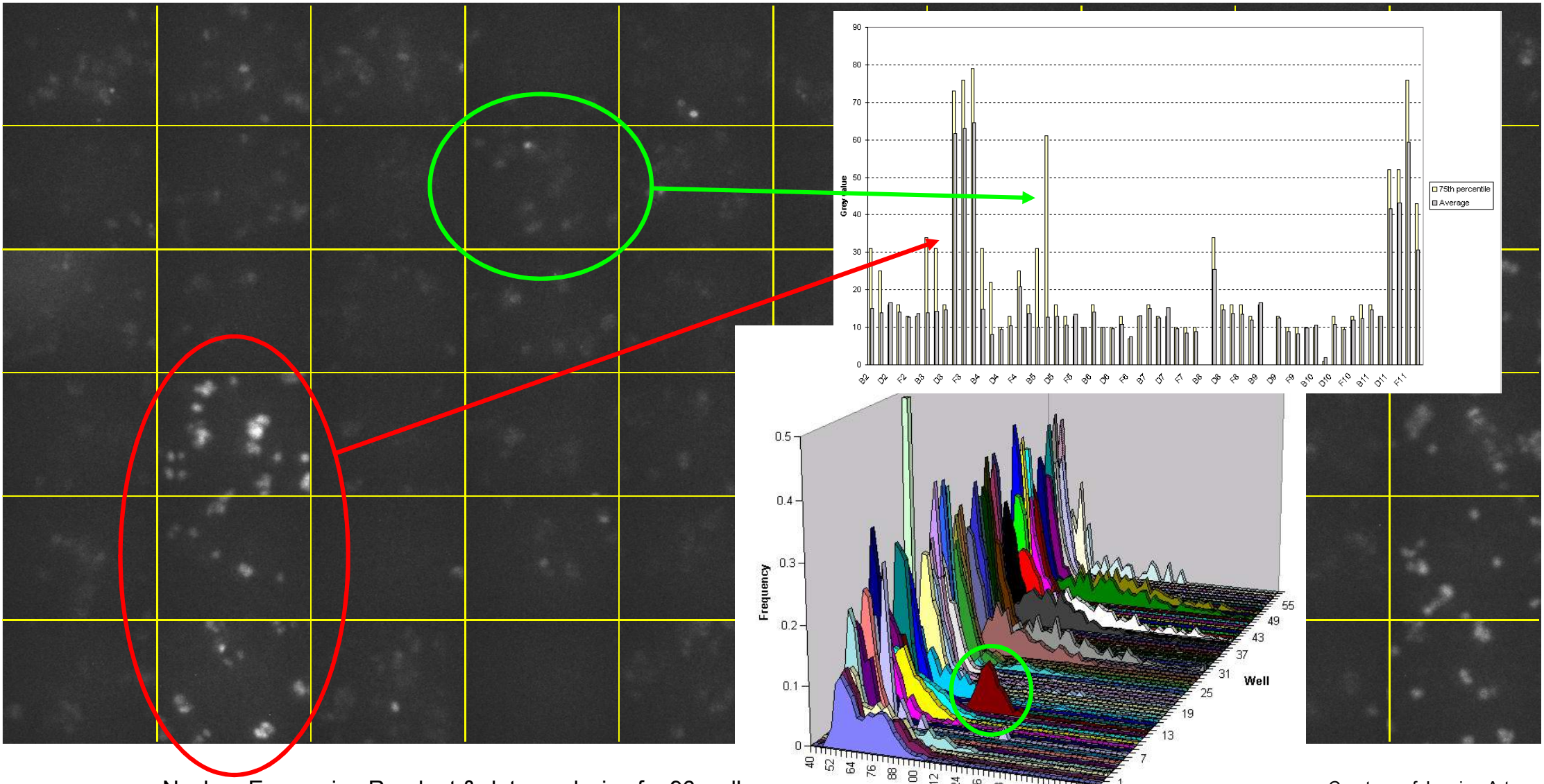
High Content Screening
Differential Screening - High Density Data



Nuclear Expression Readout & data analysis of a 96 well array
Cell cycle effect 40x, 0.7 N.A. – intensified camera

Courtesy of Jannine Arts

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Cytomics in Pharmaceutical Research Standardization and Quality Control

- Standardization of experimental procedures
  - Instrument Set-Up and Calibration
  - Experimental protocols (reagents,…)
  - Data Exchange (XML, …)
  - Data Analysis
  - Data presentation and visualization
- Quality Control
  - Standards
    - Cell types and cell lines
    - Calibration of size and density
  - QA procedures
- Organizations
  - EWGCCA
  - ATCC, ECCC

Cytomics in Pharmaceutical Research Conclusion

- Cytomics improves the predictive power of drug discovery
- Cytomics allows for multi-parametric data analysis
- Further standardization and quality control is necessary

Achnowledgements

- Johan Geysen
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- Leen Geuens
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References

- A Human Cytome Project ?

  P. Van Osta

  http://news-reader.org/article.php?group=**bionet.cellbiol**&post_nr=14902 (1 Dec. 2003)

- Cytomics - New Technologies Towards a Human Cytome Project

  G Valet, A Tárnok

  Cytometry 59A:167-171 (2004)

- The Challenge of a Human Cytome Project

  G.Valet, R.F. Murphy, J.P. Robinson, A.Tárnok, A.Kriete

  Imaging and Microscopy CD, Volume 2, Purdue Univ. (2004)

- Cytomics in predictive medicine

  G Valet, A Tárnok

  Cytometry 53B: 1-3 (2003)

A Human Cytome Project ?

Monday 01 December 2003 at 10:57:46
bionet.cellbiol newsgroup

Hi,

I was wondering if there is already something going on to set up a sort of "Human Cytome Project" ?
In my opinion the hardware and most of the software seems to be available to set up such a project ?
For the cellular level, light-microscopy based reader technology would be very interesting to use ?

Studying and mapping the genome, transcriptome and proteome at the organizational level of the cell for various cell types and organ models could provide us with a lot of information of what actually goes on in organisms in the spatio-spectro-temporal space ?

I have been thinking (working) about a concept which could provide the basic framework for exploring and managing this cellular level of biological organization research on a large scale, but I would like to know if there is already some thought/work going on in the direction of setting up an initiative such as a "Human Cytome Project" ?

This is just an idea, so I am really interested to hear if there is something in it, or even if it is not worth while what I just wrote.

Best regards,

Peter Van Osta.