Early Clinical Drug Development

WP7a Use case 2

AstraZeneca & Ontotext

OUTLINE

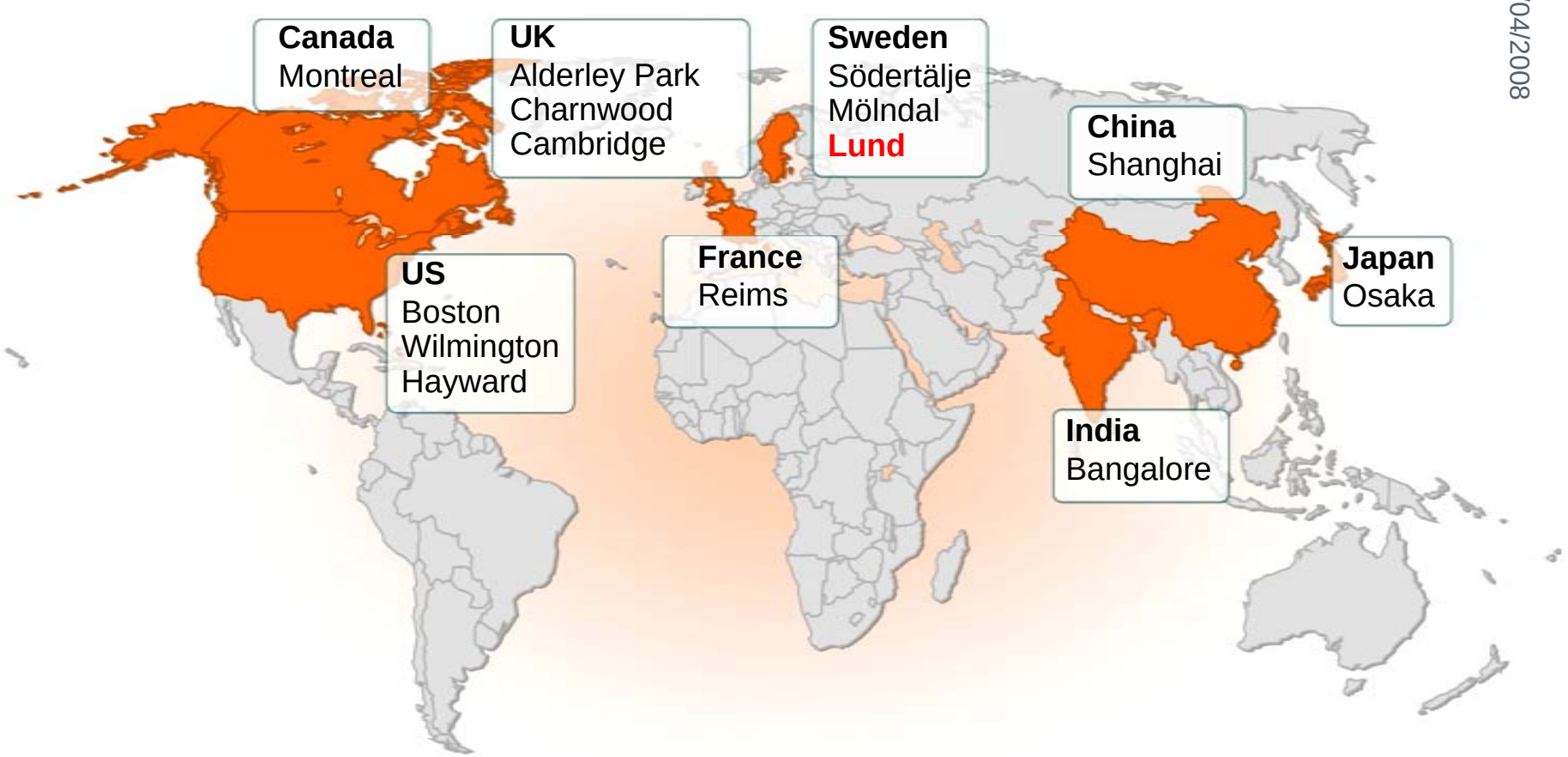
- Introduction
- Drug development
- Use case challenge and objectives

Innovation or Stagnation, What's the Diagnosis?

- **Investment & progress in basic biomedical science has for surpassed investment and progress in the medical product development process**
- **The development process – the critical path to patients – becoming a serious bottleneck to delivery of new products**
- **We are using the evaluation tools and infrastructure of the last century to develop this century's advances**

From FDA presentation on Critical Path for Science Board by Janet Woodcock, 2004-04-26

AstraZeneca has 12000 people working in 16 R&D centres in eight countries



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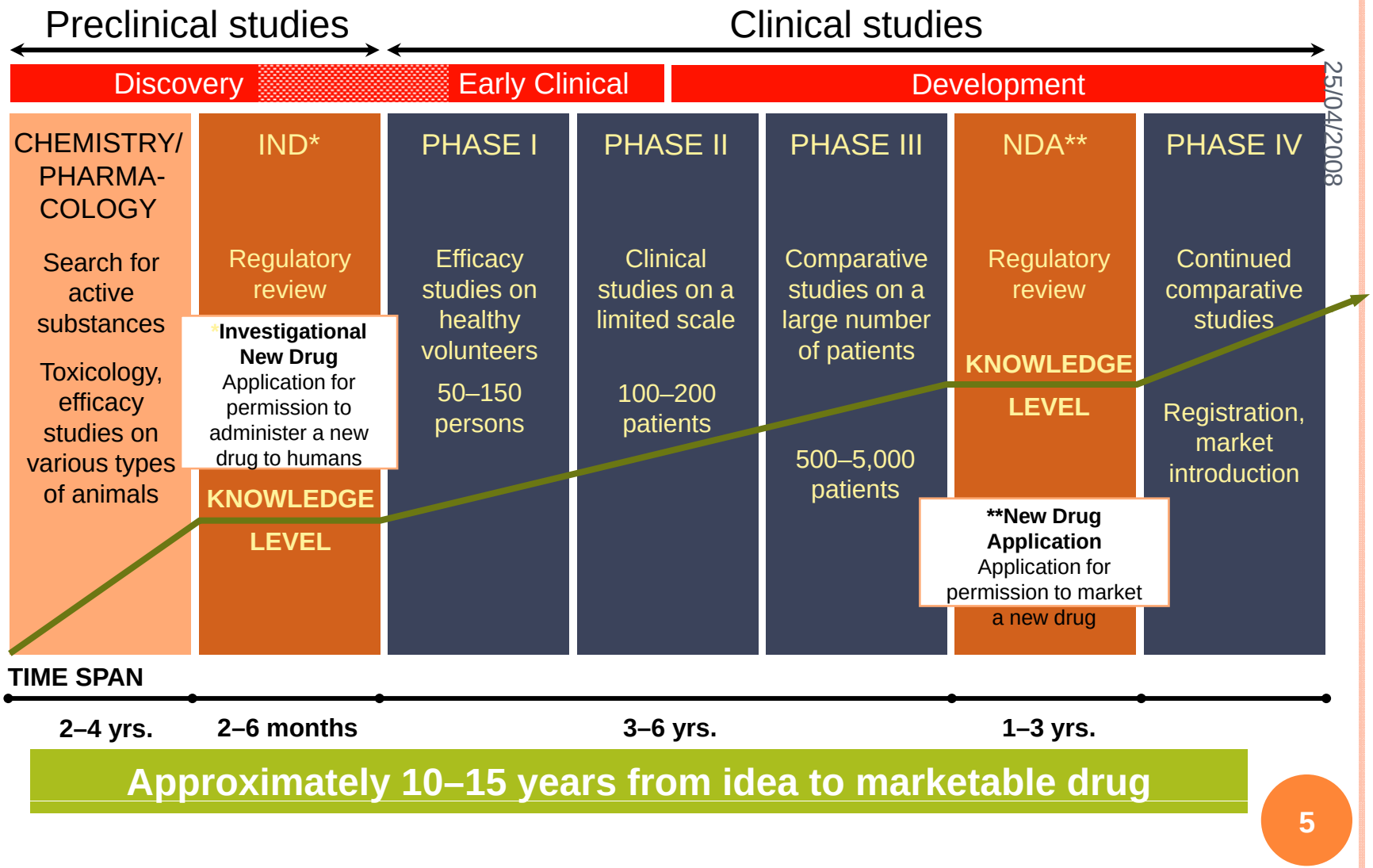
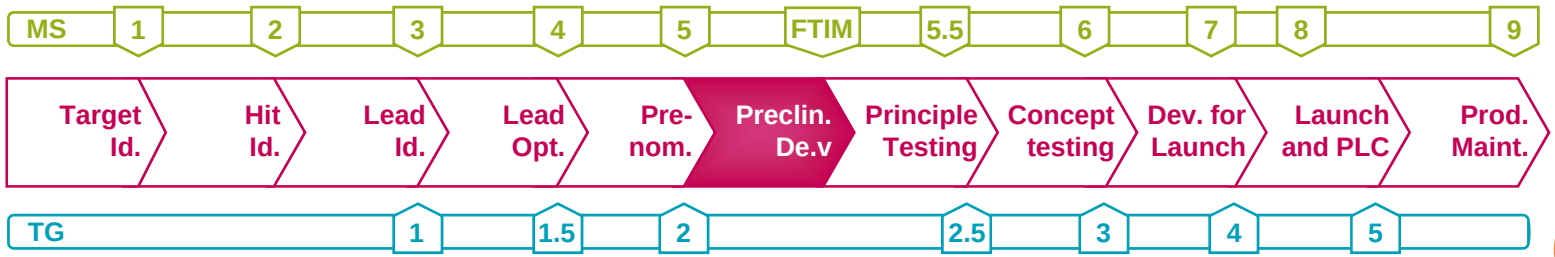
THE R&D PROCESS



Early Clinical Drug Development (1)
PRECLINICAL DEVELOPMENT

Key Activities:

- Toxicology
- Formulation work
- Safety pharmacology
- Drug Metabolism and PharmacoKinetics (DMPK)
- Regulatory
- Planning



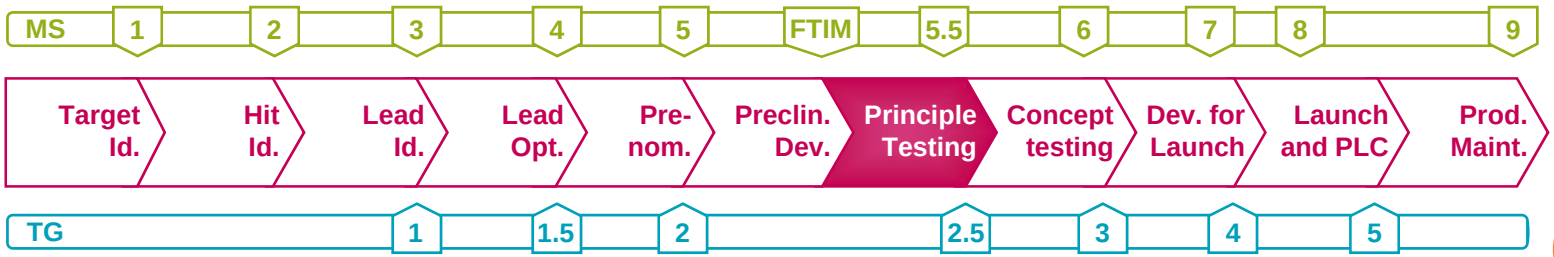
Early Clinical Drug Development (2)
PRINCIPLE TESTING

Key Activities:
- Submission
- Single Ascending Dose study
- Multi Ascending Dose study
- Proof of Principle studies
- Manufacture route identification
- Dev. formulation for concept testing & onwards
- Dev. Patient Risk Management Plans

Principle Testing

Achieved Objectives:
- Safety
- Effectiveness
- Business Plan
- Dose

1-3 years



Challenges and opportunities in Early Clinical Drug Development

Understand the drug in context of;

- the disease
  - How to measure
  - The chemistry/pharmacology
  - What causes the disease
  - How does the disease evolve
- the patient
  - What different phenotypes exists
  - Are there different Genetic profiles

This is Translational Medicine

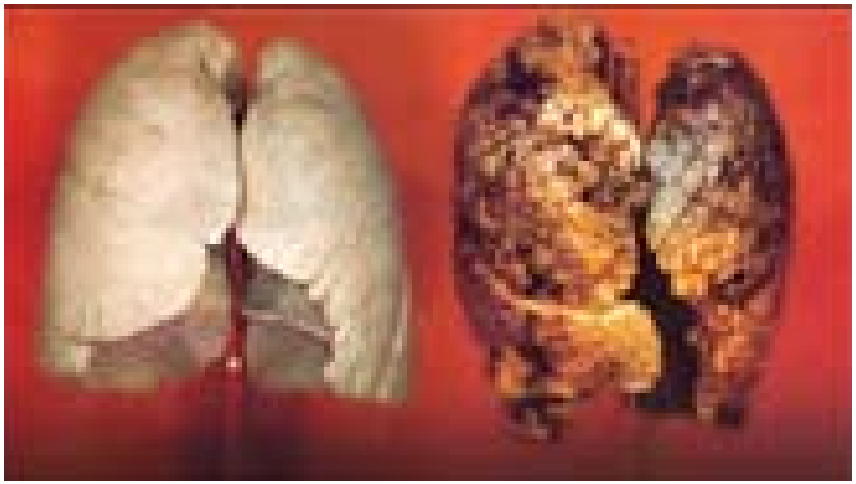
The "translation" of basic research into real therapies for real patients

DISEASE IN FOCUS FOR THE USE CASE IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- A new definition of COPD has recently been adopted by **GOLD**:

  a disease state characterized by airflow limitation that is not fully reversible.
  The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.

  (GOLD: Global Initiative for Chronic Obstructive Lung Disease)

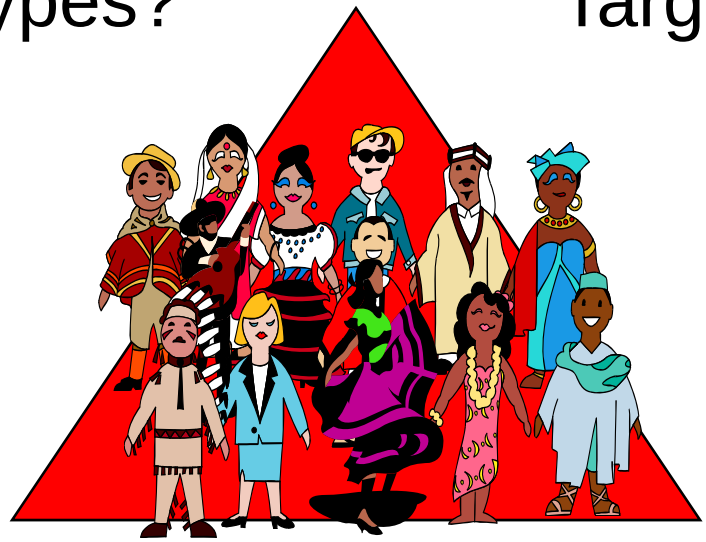


NEED TO KNOW MORE ABOUT...

Pathophysiology?

Phenotypes?

Targets?



Costs?

Biomarkers?

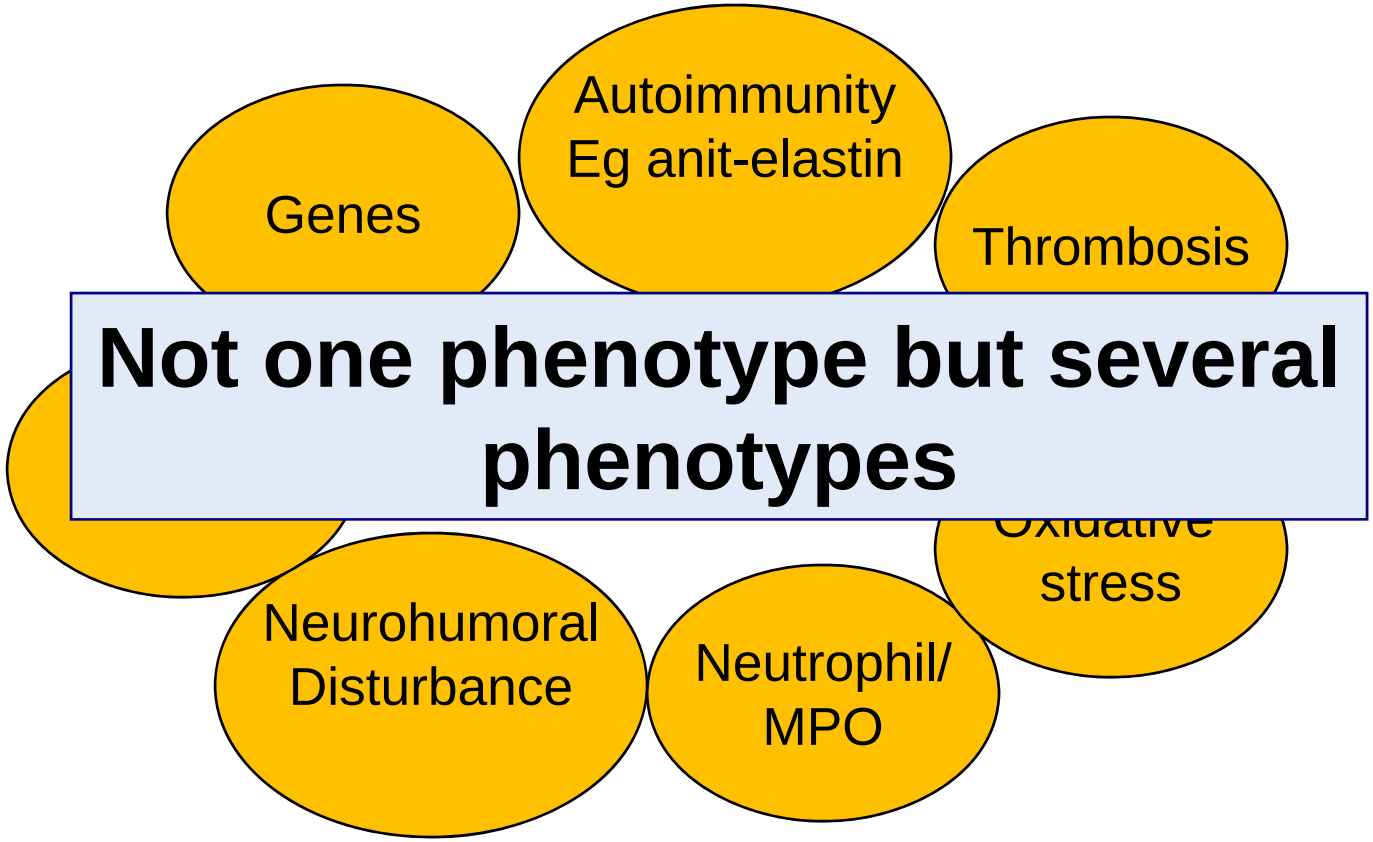
QoL?

Outcomes?

WHAT WE KNOW?

- Cigarette smoking is the cause of many diseases, e.g. Lung Cancer, COPD and Ischaemic Heart disease (IHD)
- Patients with COPD have a greater risk of IHD and Lung Cancer, the greater the degree of loss of FEV1, the greater the risk (especially in women)
- A measure that reflects acute phase response, the CRP, when raised predicts risk of IHD and Lung cancer and is in COPD patients with respiratory failure a predictor of survival as important as BMI and hypoxia
- Treatments that lower CRP in COPD patients reduce the risk of dying from IHD and may reduce the risk of dying from Lung Cancer (Statin reduces the risk for Lung Cancer

OTHER POTENTIAL CONTRIBUTORS



WHAT WE WANT TO KNOW?

- Which phenotypes exist among susceptible smokers, ~ are there characteristics we can define?
- Is there a non-susceptible phenotype to smoking diseases ~ are there characteristics we can define?
- Do the diseases have different times of onset in smokers?
- Which phenotype among these is driving the costs
  - What is the pathophysiology
  - What is the population size of this phenotype
- Protein-to-Pathway-to-Disease-Drug-to-Patient connection

The use case challenge and objective

- We need to integrate (not complete) data from different sources and domains;
  - Proteomics and Genetics data (Biology)
  - Pre-clinical data (Animal models)
  - Clinical data (Study data and documents)
  - Health Care data (Patient Records, register data)
  - Publications
- To improve our knowledge about;
  - The disease COPD
  - Patients with COPD

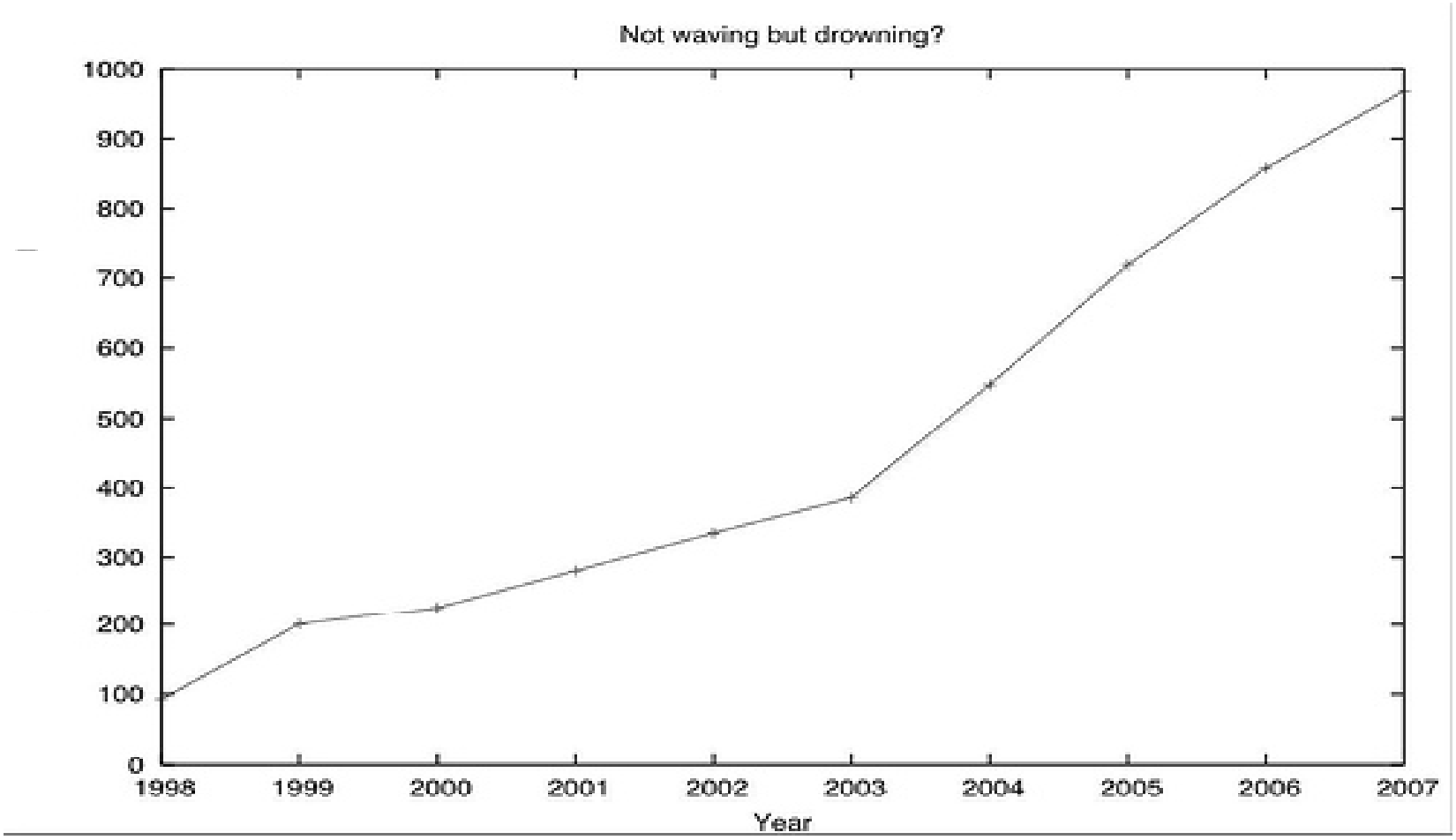
To provide scientists with computational support to conceptualize the breath and depth of relationships between data

PHARMACEUTICAL INDUSTRY IS FACING A TREMENDOUS CHALLENGE

" … scientists are unable to conceptualize the breath and depth of relationships between relevant databases without computational support."

Muggleton Nature, 440, 409, 23 March 2006

PLEASE TAKE YOUR TIME TO GUESS



How to do knowledge discovery if…

- The data is supported by different organizations
- The information is highly distributed and redundant
- There are tons of flat file formats with special semantics
- The knowledge is locked in vast data silos

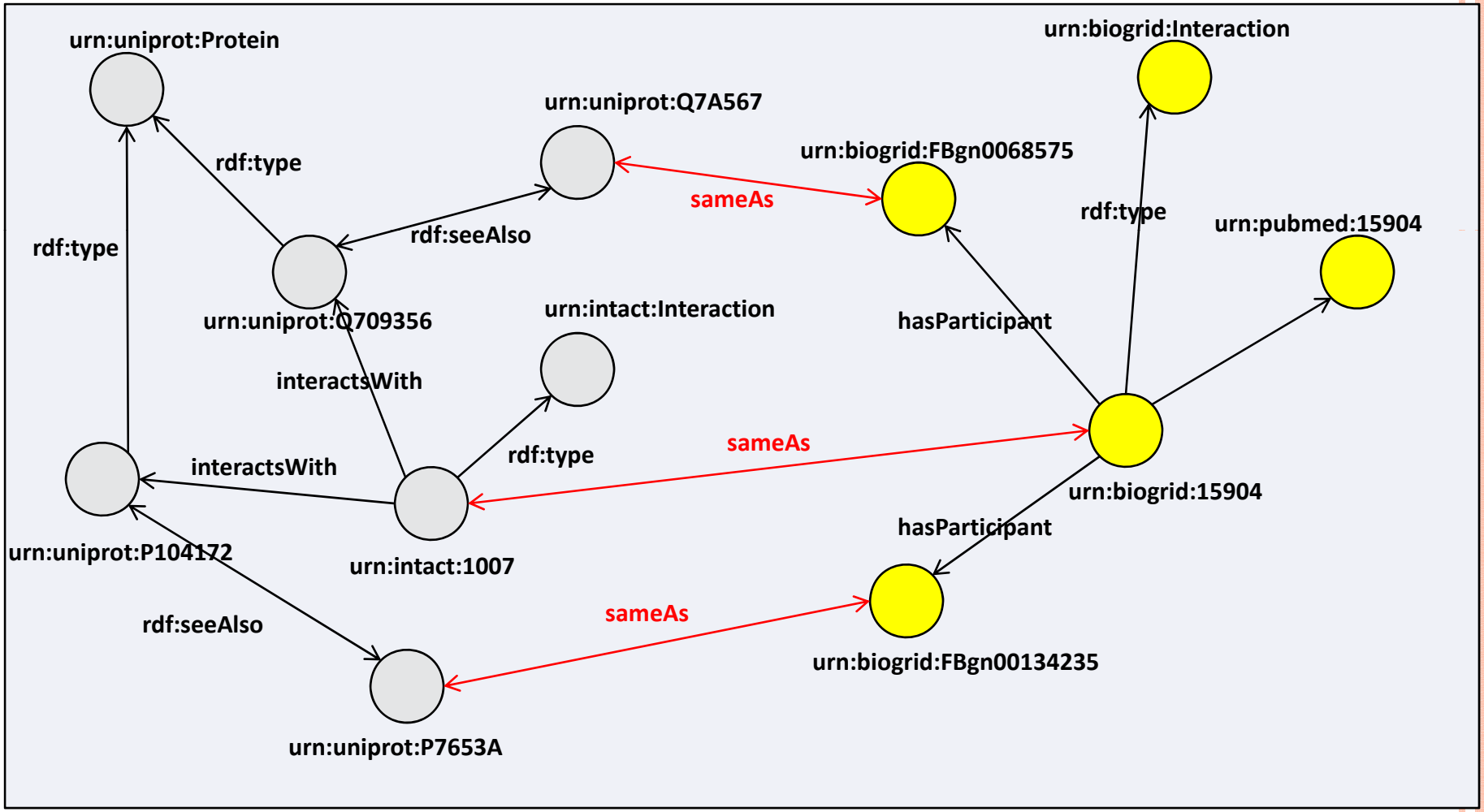
WHY THE SEMANTIC DATA INTEGRATION MAKES THE DIFFERENCES?

- To interlink datasets
- To describe different objects to appear in different formats as truly equivalent and create non-redundant datasets based on flexible rules
- To maintain complex relationships between objects in a standardized declarative formalism

WHY THE SEMANTIC DATA INTEGRATION MAKES THE DIFFERENCES?

- To handle inconsistencies problems related to incomplete data or different versions
- To unlock the R&D data stored in distributed silos
- To provide better abstraction of data model than data schema or Object-Relational Mapping (ORM) solutions
- To unlock the data stored in silos and overcome container-reference dichotomy – data once stored and connected is hard to rearrange and connect in new ways

SEMANTIC DATA INTEGRATION BENEFITS



CONCLUSION

- LarKC need to easily integrate data from different sources and domains
- LarKC should provide scientists with computational support to conceptualize the breath and depth of relationships between data

CONCLUSION 2

- Use LarKC to better understand the disease
  - Identify causes the disease
  - Learn how does the disease evolve
  - Protein-to-pathway-to-disease-drug-to-patient connections
- Use LarKC to better understand the patient
  - Identify different phenotypes
  - Learn the different Genetic profiles