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# **Biomarkers in CNS drug development**

Frank Fliegert / 26 April 2007



## ■ Outline

- Definition of terms
- Public-private initiatives in EU and US
- Key challenges for biomarkers
- Conclusions

## ■ Definition of terms

### Biomarker

- *A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. (Biomarkers Definitions Working Group, 2001)*
- *A quantitative measure that is on the causal path between drug administration and effect. (Danhof, 2005)*



## ■ Definition of terms

### Surrogate endpoint

- *An endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome). (ICH guideline topic E8, 1997)*
- *A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. Surrogate endpoints are a subset of biomarkers. (Biomarkers Definitions Working Group, 2001)*

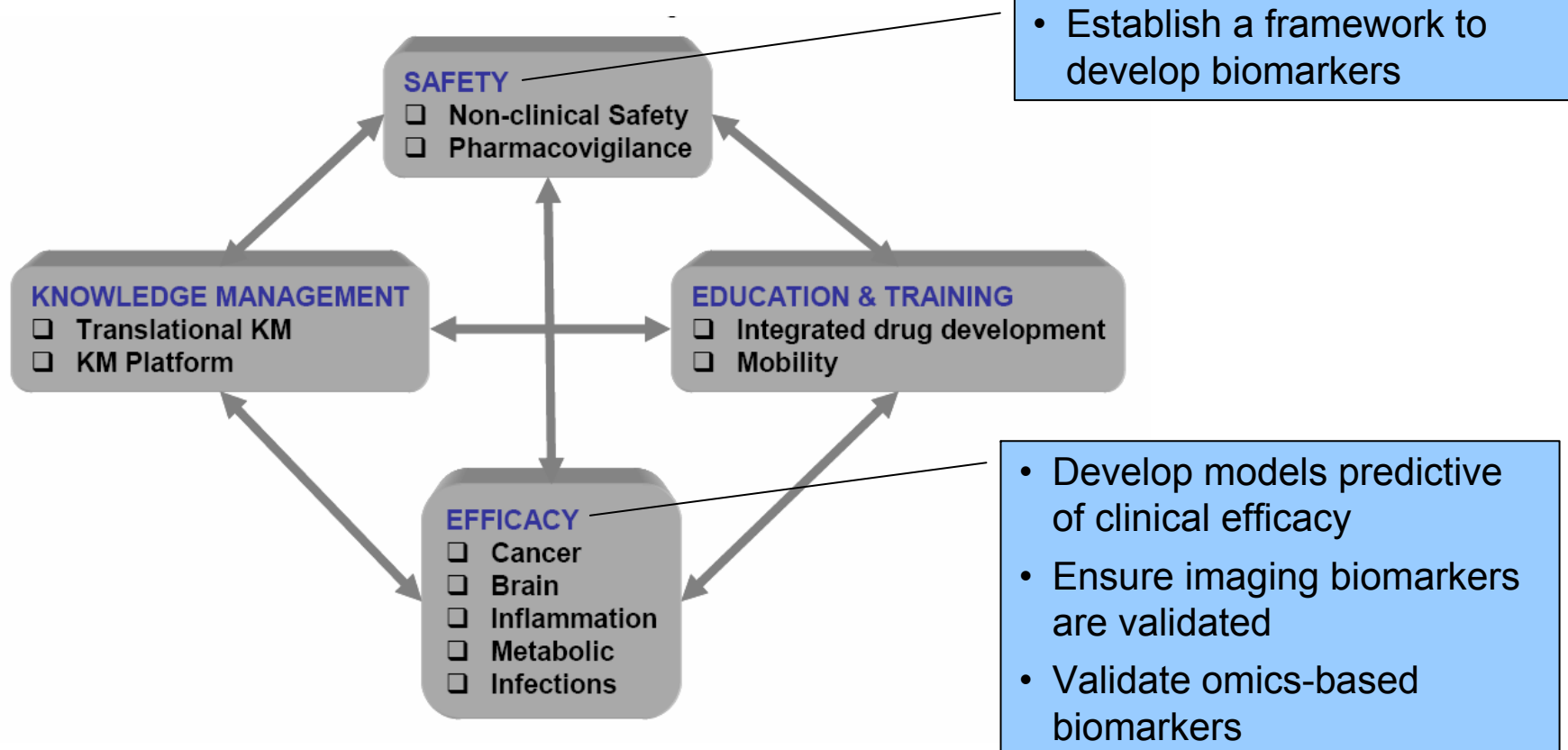
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## ■ Public-private initiatives in EU and US

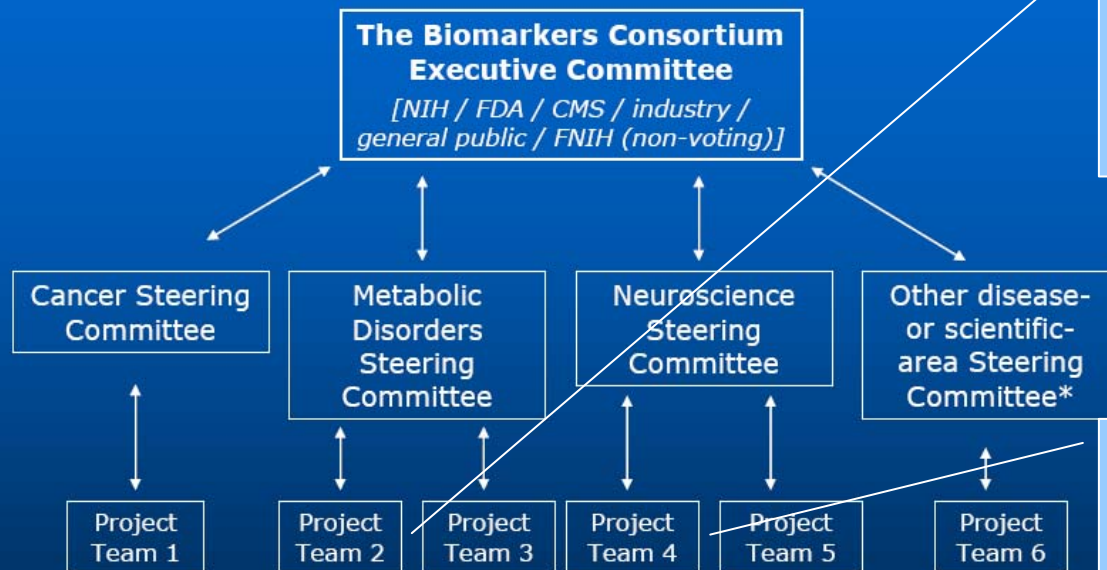
### ➤ Innovative Medicines Initiative (IMI, 2006)



## ■ Public-private initiatives in EU and US

### ➤ Biomarker consortium (FNIH, 2006)

#### The Biomarkers Consortium Governance



- Diabetes and pre-diabetes biomarker
- Utility of adiponectin as a biomarker

- Genomic biomarkers for treatment response
- Development of PET radiopharmaceutical

\* Steering Committees that may be established include those for cardiovascular and pulmonary disease and inflammatory, immunity, and infectious disease

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## ■ Key challenges for biomarkers

- Compound is given to the wrong subjects

Which subject will respond to the drug?



- Compound is given at the wrong dose or regimen
- The favorable effects of the compound are not detected
- The compound has a significant effect in models, but not in patients

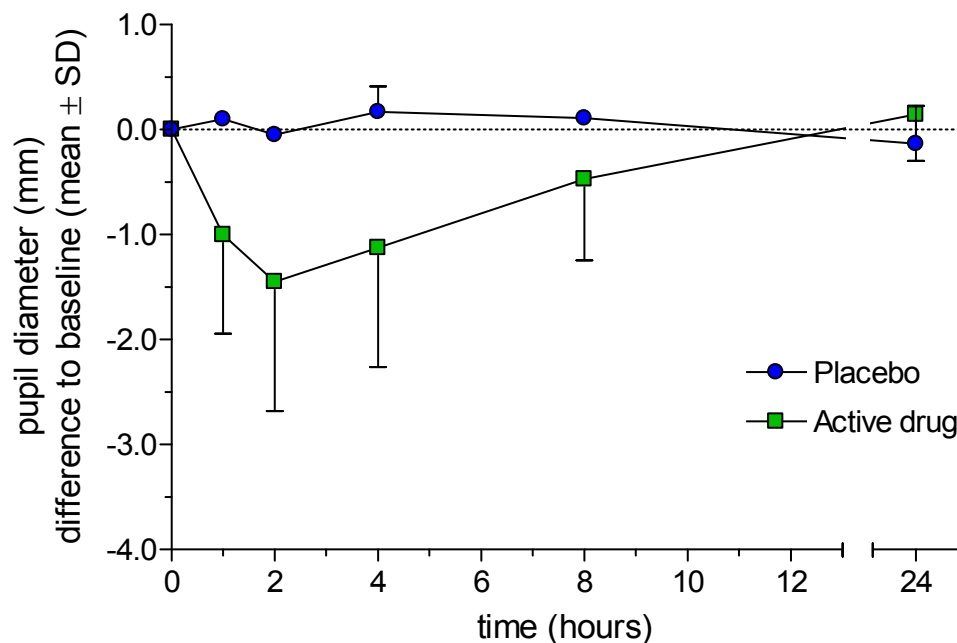
## Which subject will respond to the drug?

- Appropriate selection to reduce/control heterogeneity
  - Genetic polymorphisms with respect to ADME and targets
  - Identification of susceptibility factors (response may depend on sex, age, personality trait, etc.)
  - Valid disease models rather than patients with multiple disorders

## Which subject will respond to the drug?

### ■ Response-modifying polymorphisms of CYP2D6

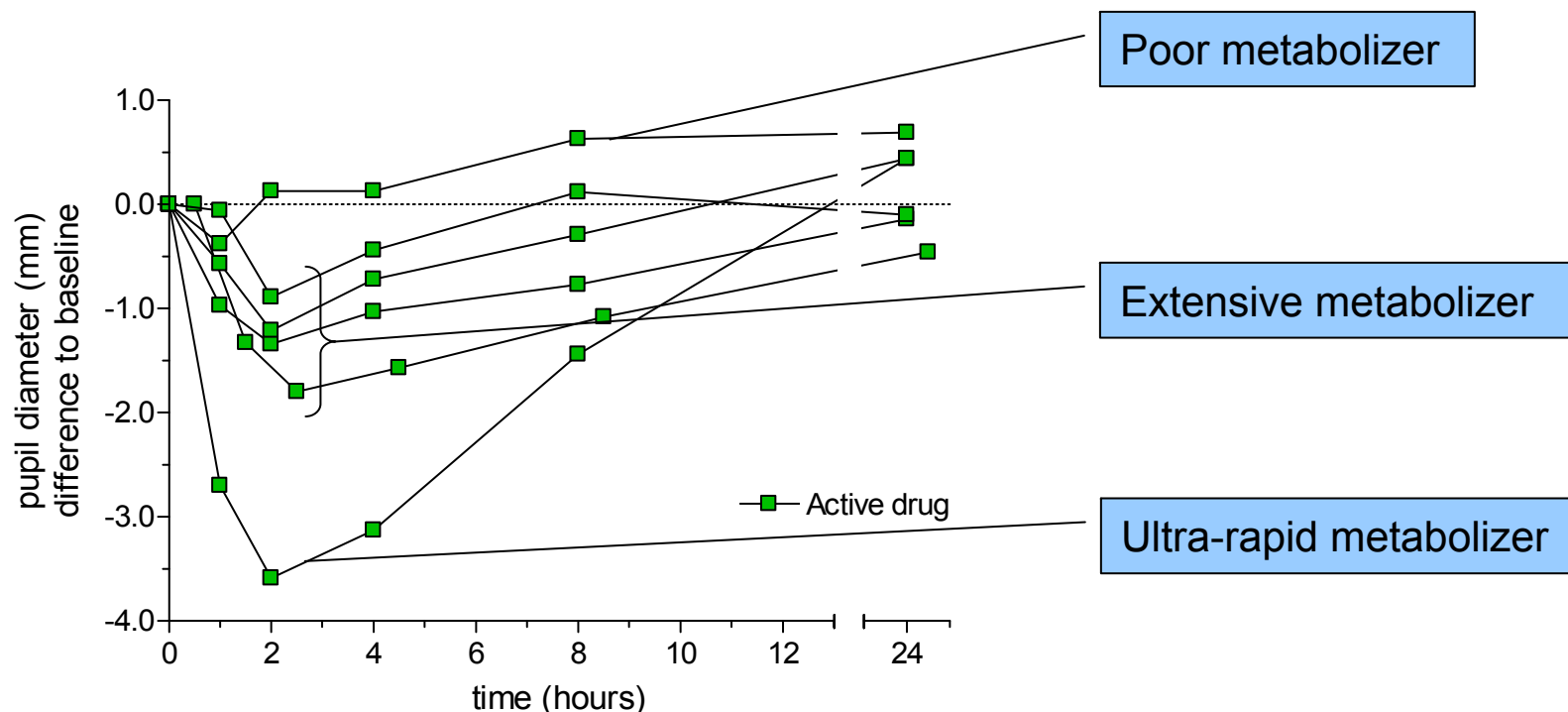
- Pupillary response to an opioid analgesic with an active metabolite



Which subject will respond to the drug?

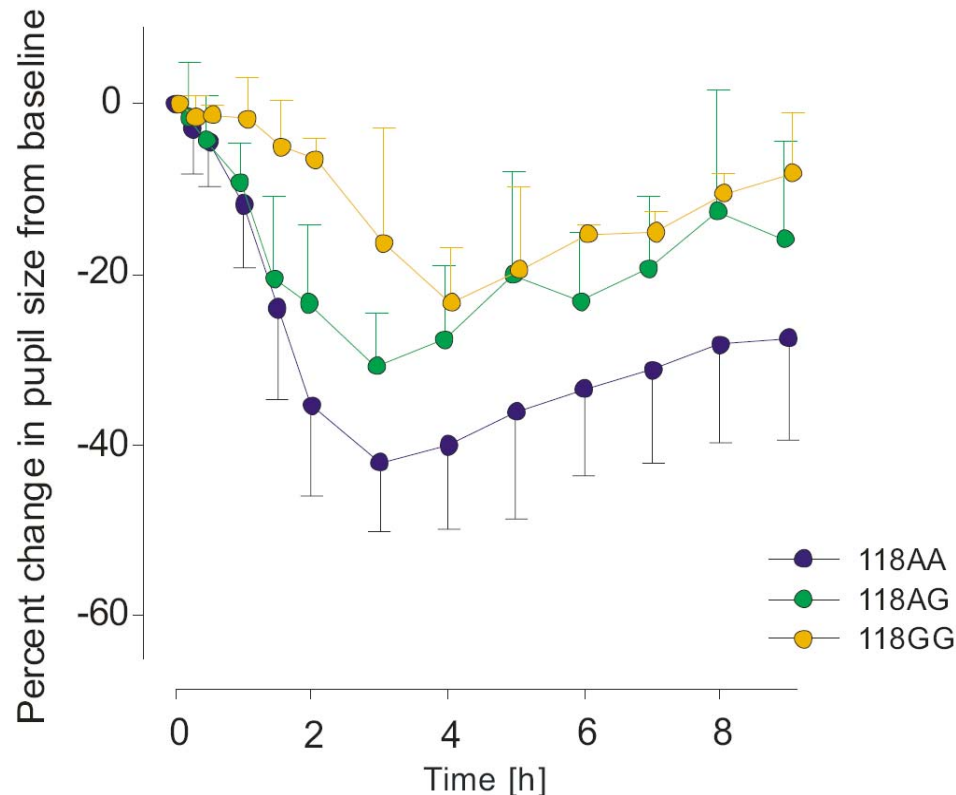
## ■ Response-modifying polymorphisms of CYP2D6

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## Which subject will respond to the drug?

- Response-modifying polymorphisms of the  $\mu$ -receptor
  - SNP 118A>G reduces pupillary response (Lötsch, 2006)



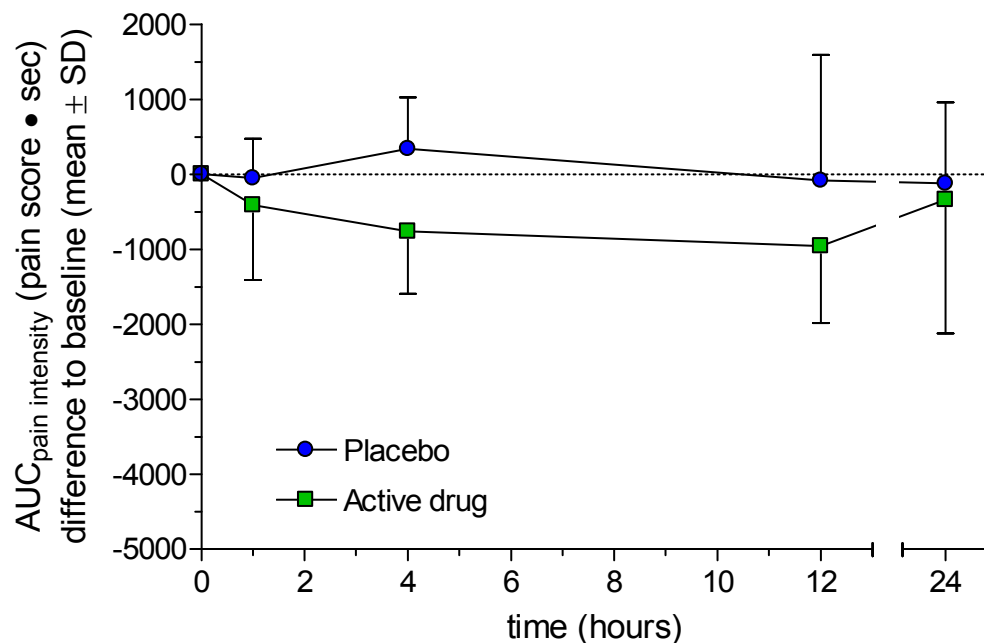
## Which subject will respond to the drug?

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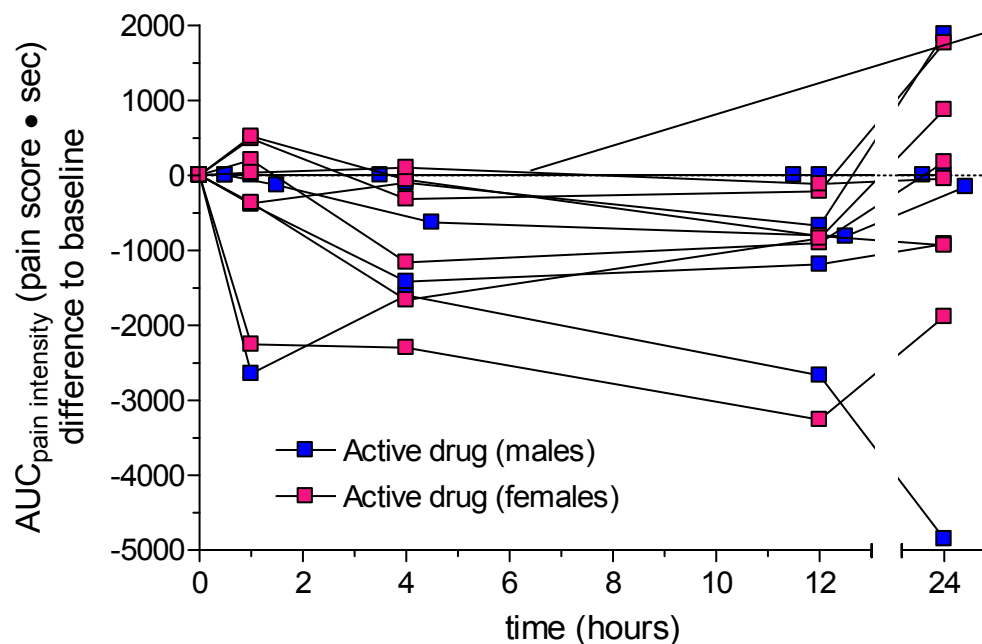
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- Cold pressor test response to an opioid analgesic with an active metabolite (via CYP2D6)



## Which subject will respond to the drug?

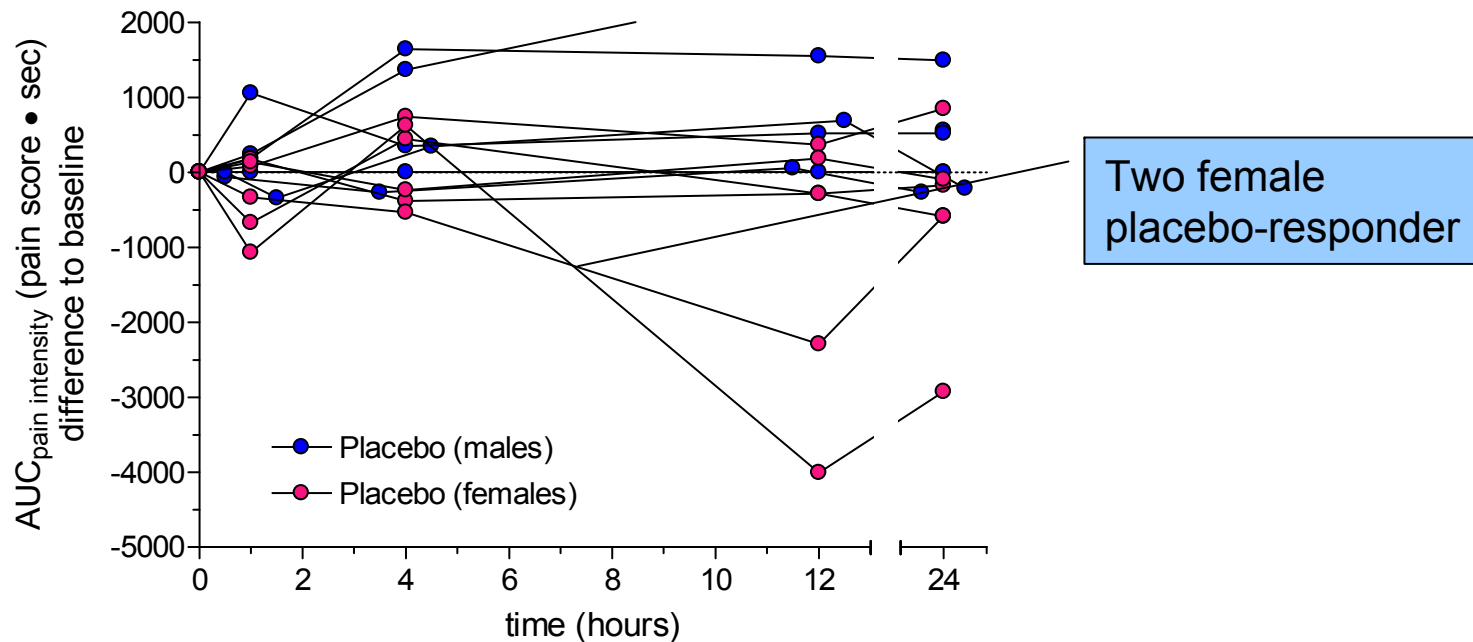
- Cold pressor test response to an opioid analgesic with an active metabolite (via CYP2D6)



Two male non-responder  
(no change of pain intensity)

Which subject will respond to the drug?

- Cold pressor test response to an opioid analgesic with an active metabolite (via CYP2D6)



## Which subject will respond to the drug?

- Inadequate response to the CPT
  - Insensitivity and placebo sensitivity (Grach, 2004)
- Susceptibility factors confounding the CPT
  - Personality trait (Pud, 2004, 2006)
  - Gender differences (Jones, 2003 and Mitchell, 2004)

## Which subject will respond to the drug?

- Susceptibility factors confounding the CPT
  - Personality trait (Pud, 2004, 2006)

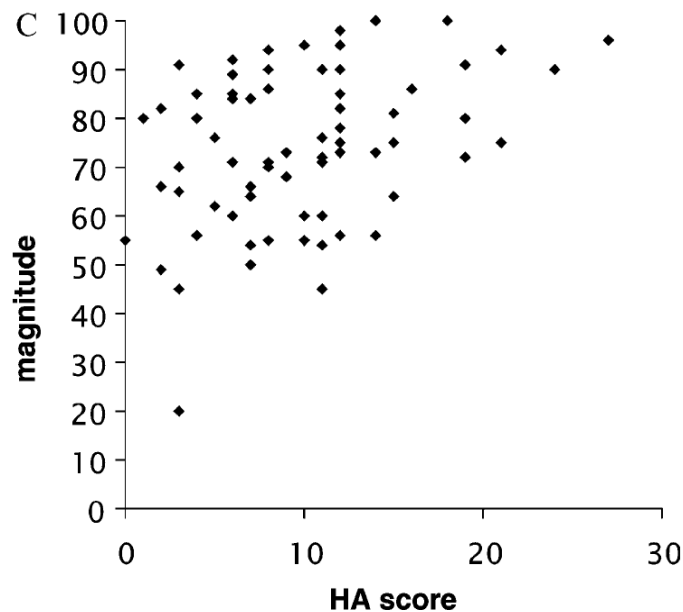


Table 2

Linear regression analysis determine predictors of analgesic response

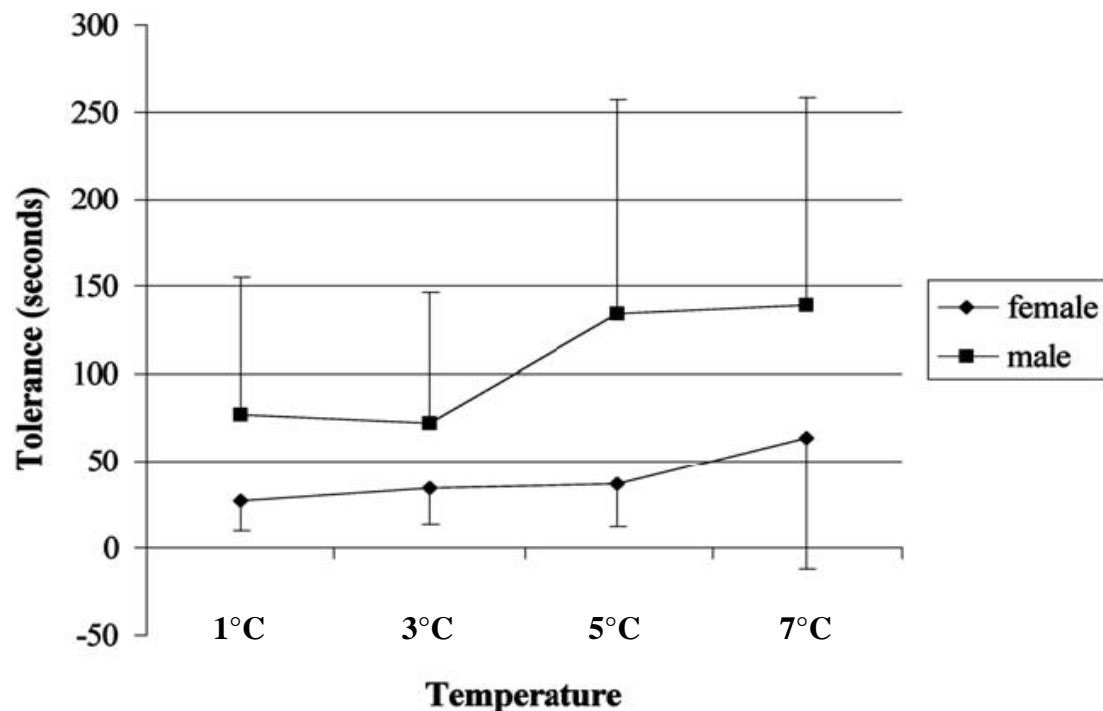
Factor	$\Delta$ Threshold		$\Delta$ Tolerance		$\Delta$ VAS	
	Coefficient	<i>p</i>	Coefficient	<i>p</i>	Coefficient	<i>p</i>
NS	0.09	0.77	-0.29	0.86	0.07	0.94
HA	<b>0.45</b>	<b>0.04</b>	-0.18	0.87	<b>1.44</b>	<b>0.03</b>
RD	0.66	0.15	0.92	0.70	0.61	0.67
Baseline	0.28	0.43	-0.07	0.67	0.24	0.35

This table is based on ANOVA-model linear regressions, with NS, HA, RD and the initial level of each pain measure as predictor variables in separate regressions for each sensory measure. Only HA proved significantly related to  $\Delta$ threshold and  $\Delta$ VAS (bold).

Which subject will respond to the drug?

## ■ Susceptibility factors confounding the CPT

- Gender differences (Jones, 2003 and Mitchell, 2004)



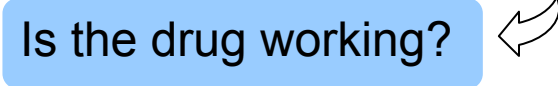
## ■ Key challenges for biomarkers

- Compound is given to the wrong subjects
- Compound is given at the wrong dose or regimen
  - Reaches the drug its site of action?
- The favorable effects of the compound are not detected
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## Reaches the drug its site of action?

- Positron Emission Tomography (PET)
  - Imaging studies may indicate if (1) the drug reaches its target, (2) there is a linear relationship between dose and target occupancy, (3) occupancy reflects drug levels in plasma, and (4) how long the drug remains at its target.
- Sampling of cerebrospinal fluid

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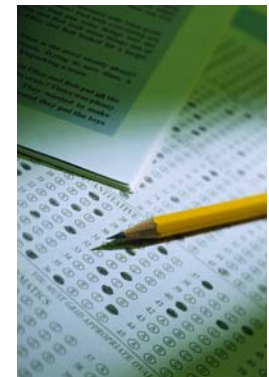
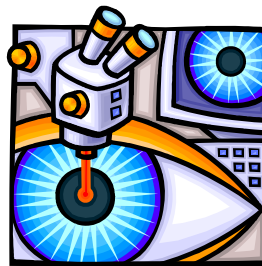
## Is the drug working?

### ■ Drug-receptor interaction

- Relief of pain

### ■ Parallel pathways

- Performance (reaction time, attention)
- Subjective effects (drug liking, mood changes)
- Hormone response (depression of sexual hormones)
- Physiological response (constipation, miosis)



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Which models are predictors of clinical efficacy?



Which models are predictors of clinical efficacy?

- Comparison of various pain models in healthy volunteers

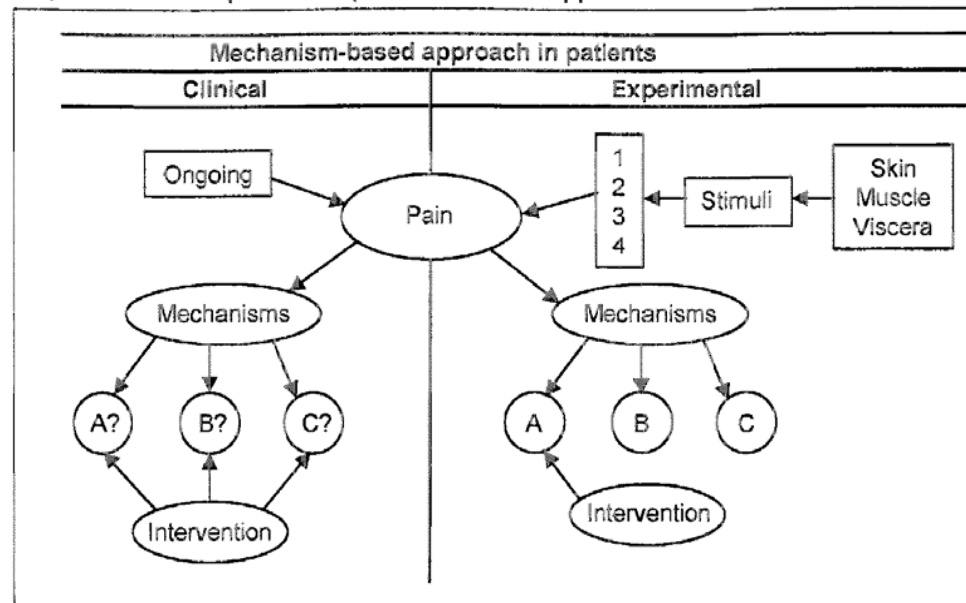
	Koltzenburg 2006	Angst 2004	Gustorff 2003	Naef 2003	Enggaard 2001	Luginbühl 2001
cold	+	NT	-	+	+	+
heat	+	+	+	-	NT	-
electrical	-	+	+	+	+	+
pressure	NT	NT	NT	+	+	+

## Which models are predictors of clinical efficacy?

### ■ Multimodal approach

#### ➤ Arendt-Nielsen, 2007

Figure 3. The multi-modal, multi-tissue experimental pain assessment approach.



Using experimental methods (1, 2, 3, 4), the evoked pain activates different mechanisms (A, B and/or C) and the effect of a given intervention on the given mechanisms (eg, on A) can be assessed quantitatively. It is also possible to investigate which mechanism is affected in a patient with pain by systematic activation of different pathways and mechanisms. Using clinical methods only, it is not possible to know which mechanism (A, B and/or C) is involved, and hence which mechanism to modulate using a given drug.

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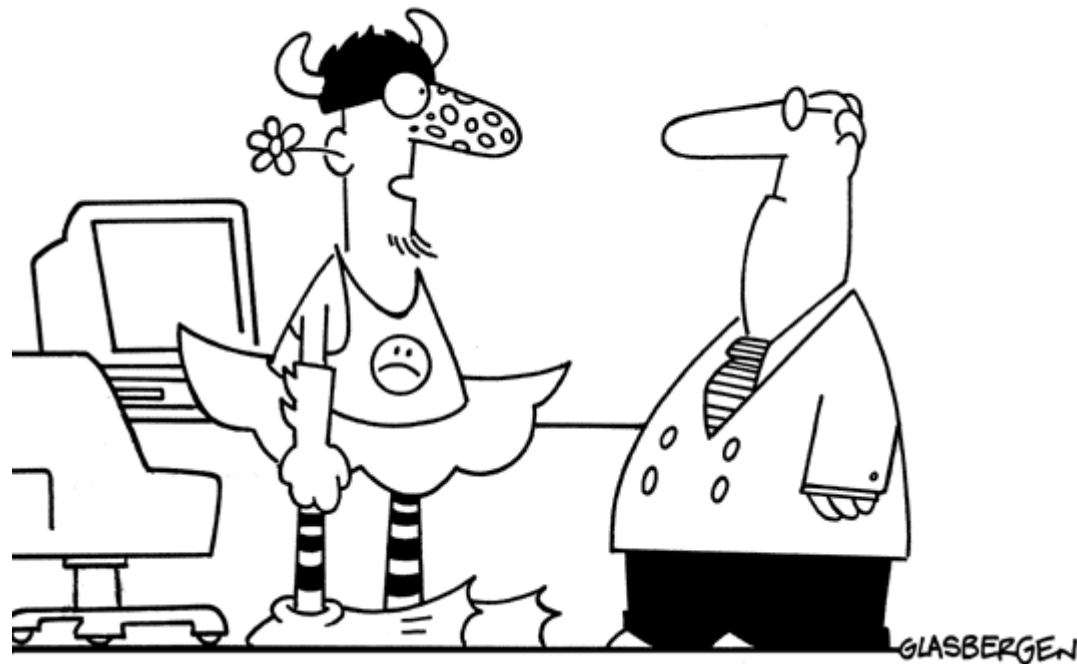


## ■ Conclusions

- Recently launched public-private research initiatives will foster the development and validation of relevant biomarkers.
- In CNS drug development, this will help to minimize the risk of drug candidate failure and accelerate confirmation of clinical safety and efficacy.
- Biomarkers in clinical trials require a well-controlled environment to obtain comparable and reliable results.



Thank you for your attention!



**“Of course, my view on biomarkers  
may not exactly be the same as yours.”**