'The airbag problem' in risk assessment: how background mechanistic frameworks influence the evaluation of new evidence

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STRUCTURE OF THE TALK

1. <u>Introduction</u>. Fallback strategies in risk assessment: how new evidence contributes to mechanistic knowledge.

2. The <u>problem</u> with fallback strategies in risk assessment: better late than never?

3. <u>Analysis</u>. 'The airbag analogy': how mechanistic knowledge contributes to the evaluation of new evidence
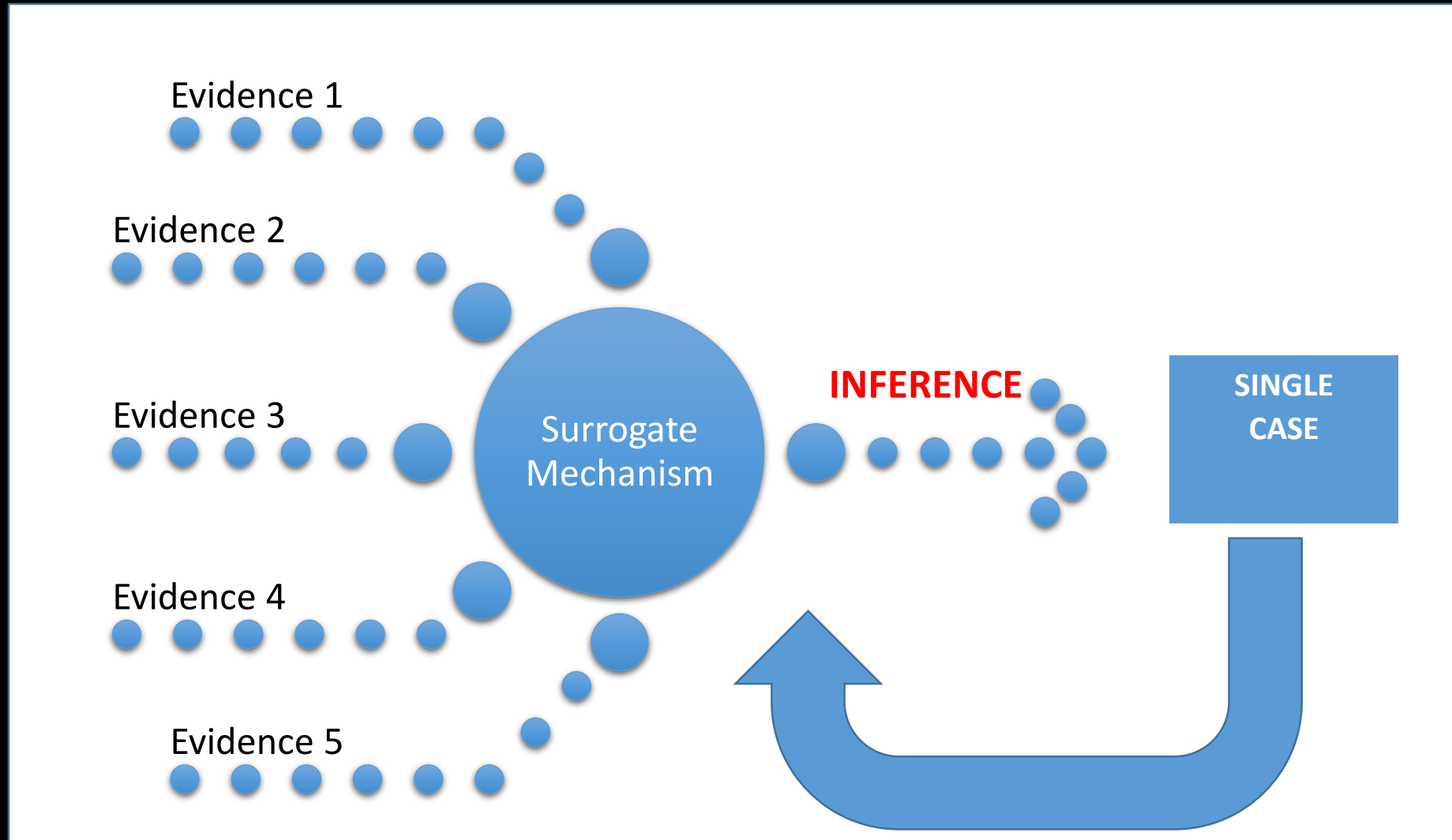
4. Conclusions (so far)

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'Fabricated risk'

'… new risk environments for which history provides us with very little previous experience. We do not really know what the risks are; let alone how to calculate them accurately on terms of probability tables'
(Anthony Giddens,
'Risk and Responsibility', 1999).

'Fallback strategies' to build surrogate mechanisms (Baetu 2016)

Mechanistic insights from failure: 'fallback strategies' in oil toxicity
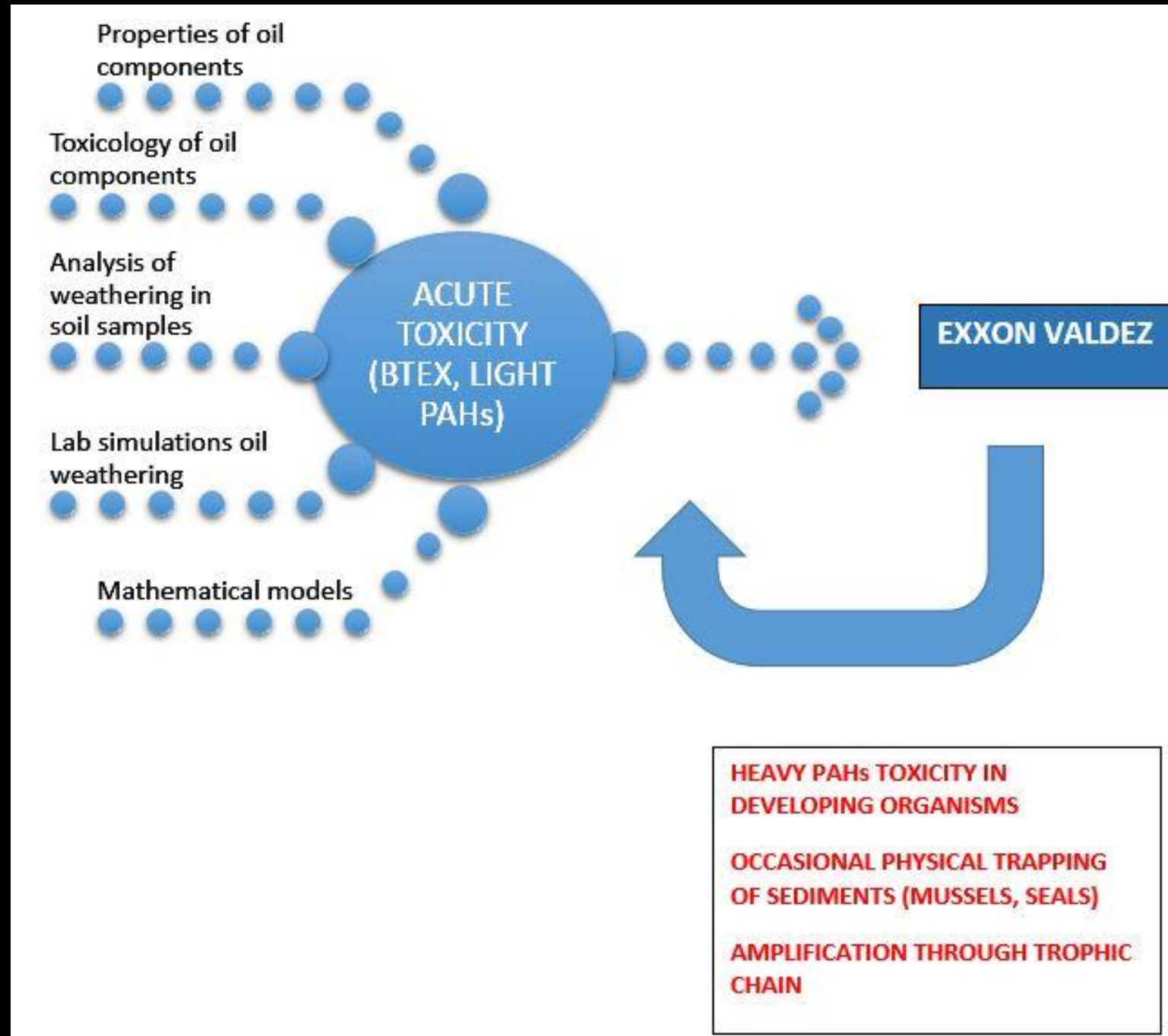
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TIME
The Big Spill
Special Report: The Times Square Bomber
Faisal Shahzad's double life + Why Pakistan is terror's new source
What the disaster in the Gulf means for the future of energy
BY BRYAN WALSH

Oil-spill plan still a work in progress
By GEORGE FROST and DAVID POSTMAN
Daily News reporters

Alyeska Pipeline Service Co.'s dra to protect Prince William Sound fr spills is missing many important chapters, but state environmental officials say it's a
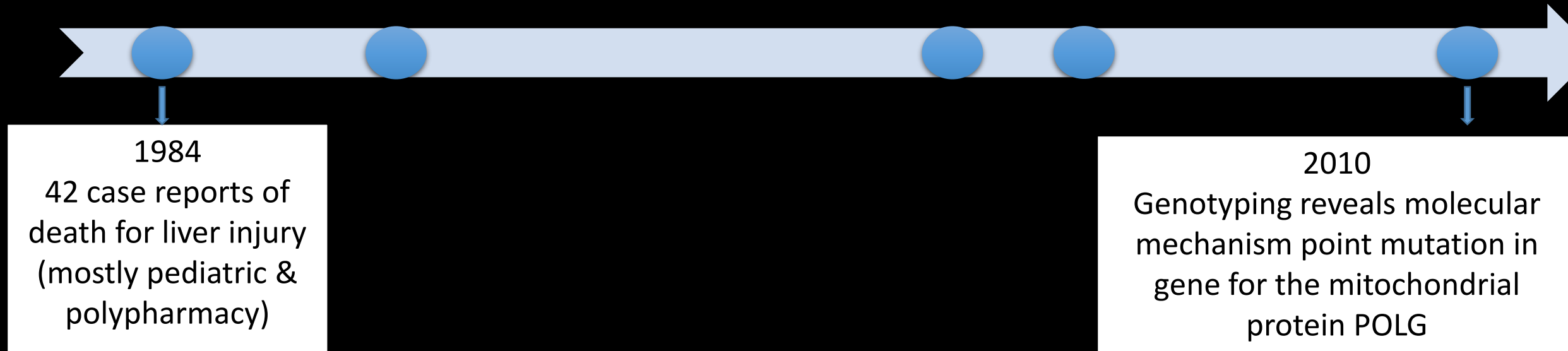
THE EXXON VALDEZ OIL SPILL WAS 25 YEARS AGO
The fisheries for herring, king crab, and dungeness crab have NEVER recovered. -- Source New York Times

'The immense research effort after the Exxon Valdez Oil Spill has contributed considerably to our knowledge on the potential impact of large oil spills. However, because of lack of pre-spill baseline data and lack of understanding of ecosystem dynamics it was very difficult to measure the size of the impact reliably.'
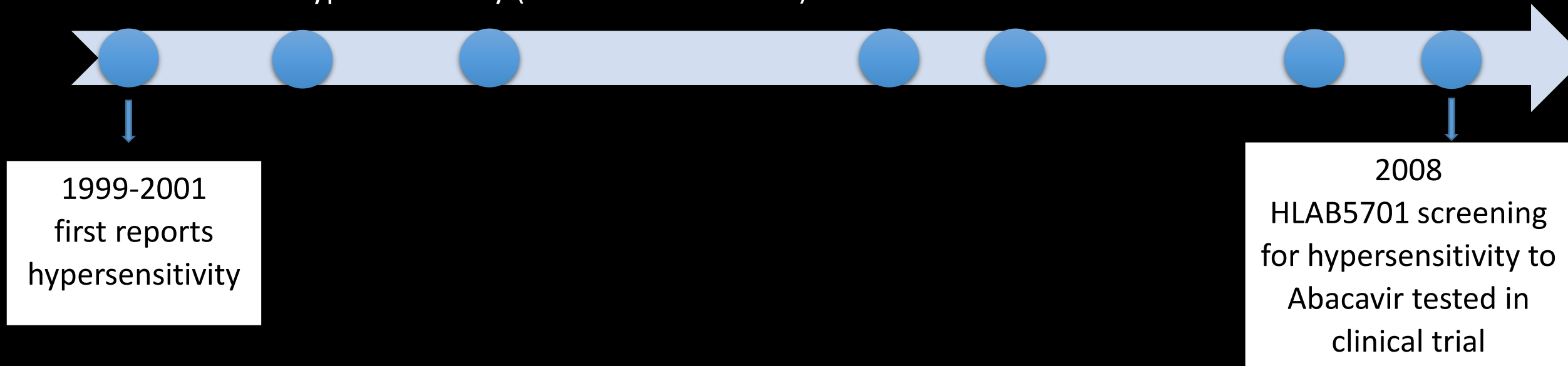*(Paine et al, 1996)*
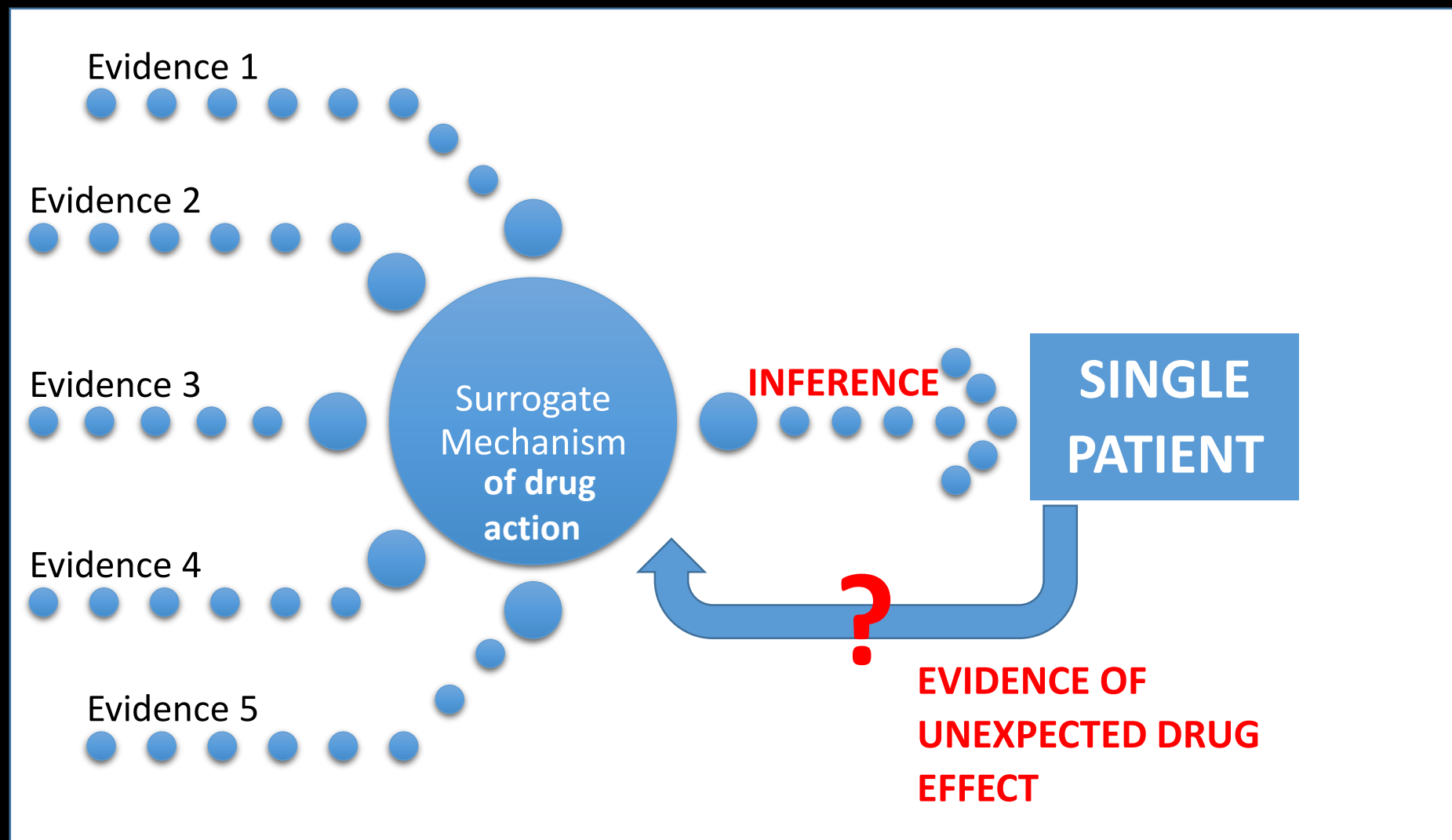
There is variability in the way different evidence of unexpected drug effects are pursued by drug agencies. Why?

Valproic acid and liver injury (total incidence around 5%)

1984
42 case reports of death for liver injury (mostly pediatric & polypharmacy)

2010
Genotyping reveals molecular mechanism point mutation in gene for the mitochondrial protein POLG

Abacavir and hypersensitivity (total incidence < 5%)

1999-2001
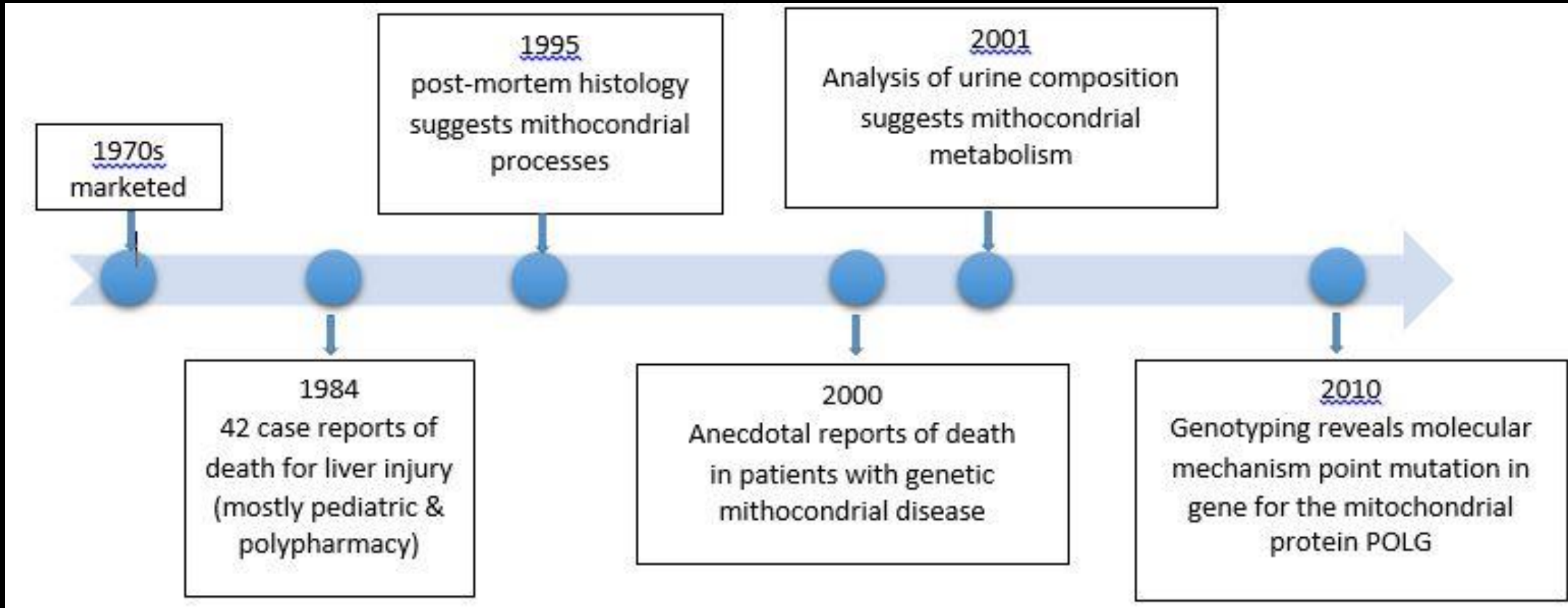first reports hypersensitivity

2008
HLAB5701 screening for hypersensitivity to Abacavir tested in clinical trial
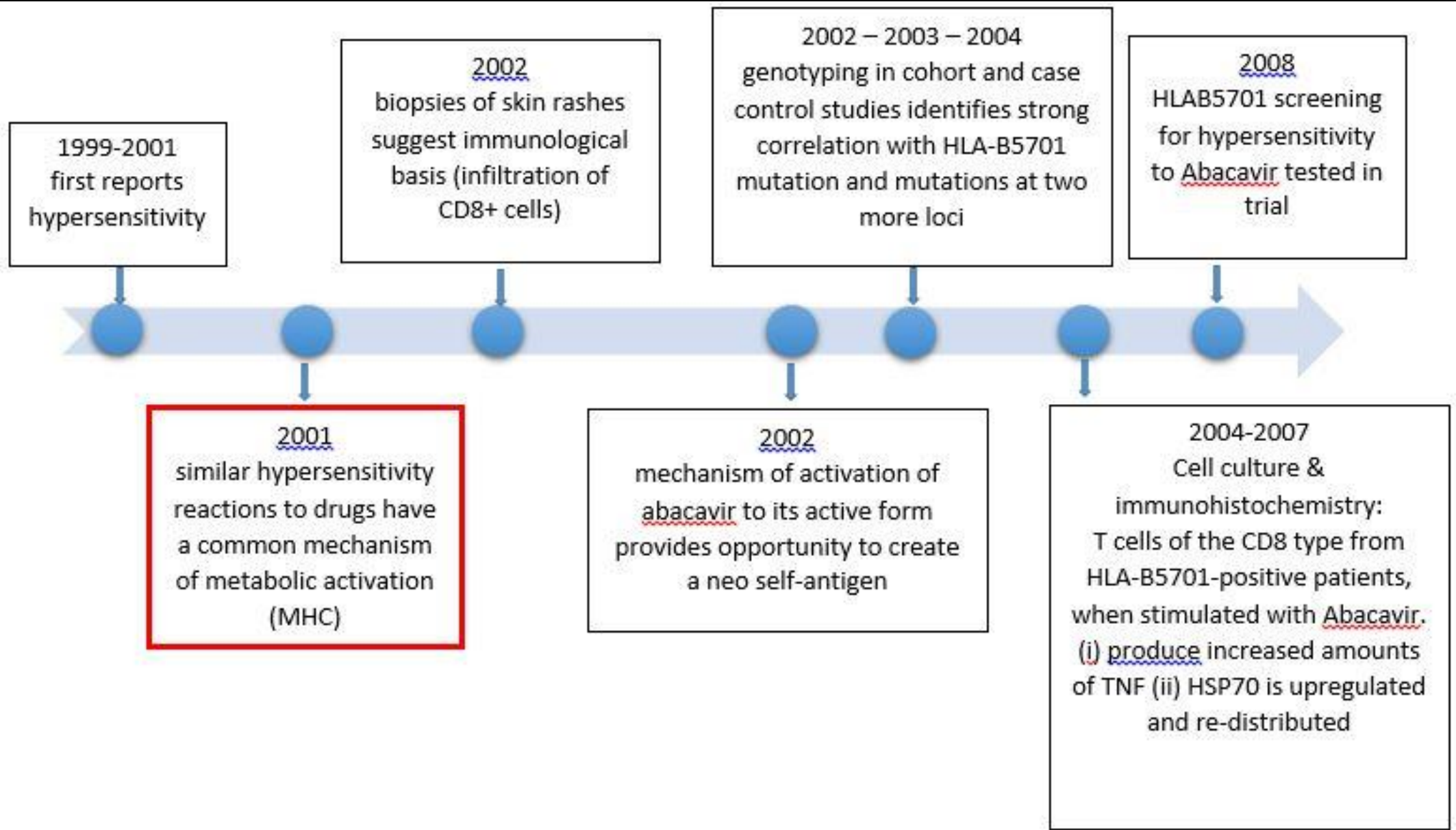
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Analysis, part 1: does the type of evidence used affect the efficiency of the whole harm-detection process?

Valproic acid and liver injury (total incidence around 5%)
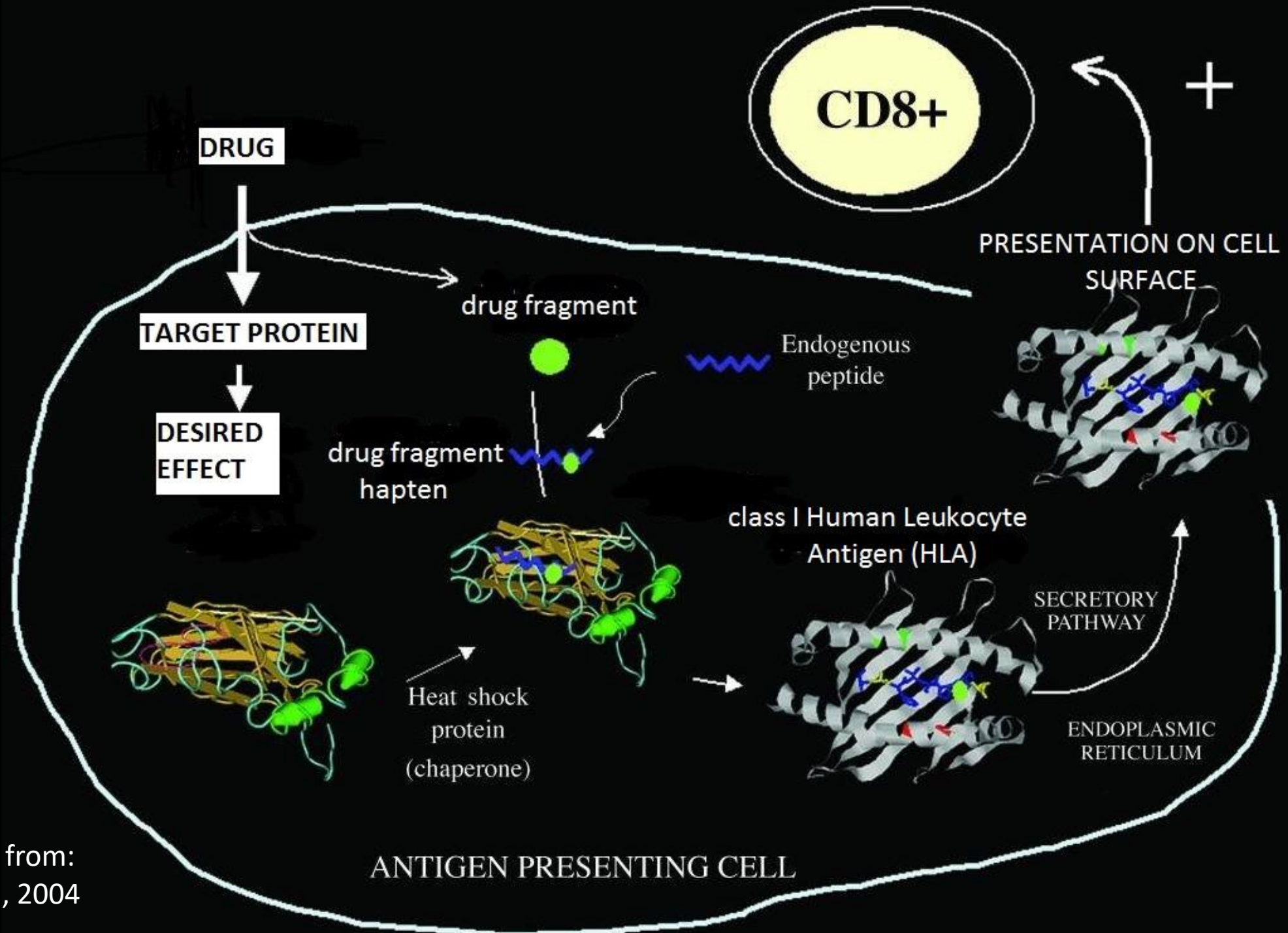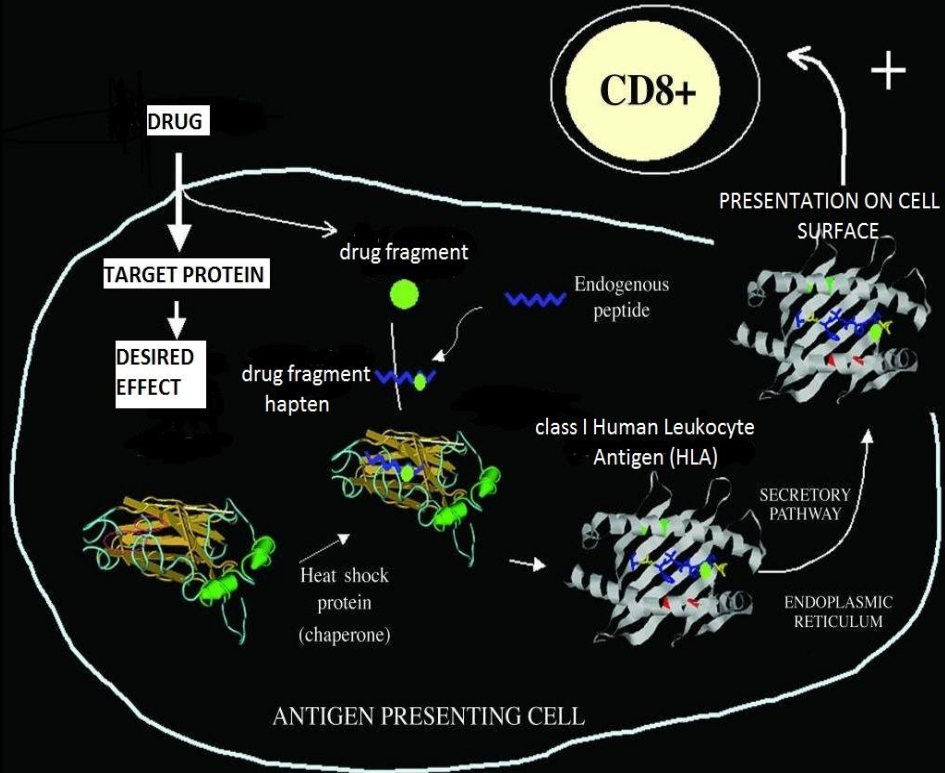
Abacavir and hypersensitivity (total incidence < 5%)

1999-2001
first reports hypersensitivity

2002
biopsies of skin rashes suggest immunological basis (infiltration of CD8+ cells)

2002 – 2003 – 2004
genotyping in cohort and case control studies identifies strong correlation with HLA-B5701 mutation and mutations at two more loci

2008
HLAB5701 screening for hypersensitivity to Abacavir tested in trial

2001
similar hypersensitivity reactions to drugs have a common mechanism of metabolic activation (MHC)

2002
mechanism of activation of abacavir to its active form provides opportunity to create a neo self-antigen

2004-2007
Cell culture & immunohistochemistry: T cells of the CD8 type from HLA-B5701-positive patients, when stimulated with Abacavir. (i) produce increased amounts of TNF (ii) HSP70 is upregulated and re-distributed

CD8+

DRUG

PRESENTATION ON CELL SURFACE

drug fragment

Endogenous peptide

TARGET PROTEIN

DESIRED EFFECT

drug fragment hapten

class I Human Leukocyte Antigen (HLA)

SECRETORY PATHWAY

Heat shock protein (chaperone)

ENDOPLASMIC RETICULUM

ANTIGEN PRESENTING CELL

Fig adjusted from: Martin et al., 2004

DRUG → TARGET PROTEIN → DESIRED EFFECT

drug fragment

drug fragment hapten

Endogenous peptide

class I Human Leukocyte Antigen (HLA)

Heat shock protein (chaperone)

SECRETORY PATHWAY

ENDOPLASMIC RETICULUM

ANTIGEN PRESENTING CELL

CD8+ +

PRESENTATION ON CELL SURFACE

2002
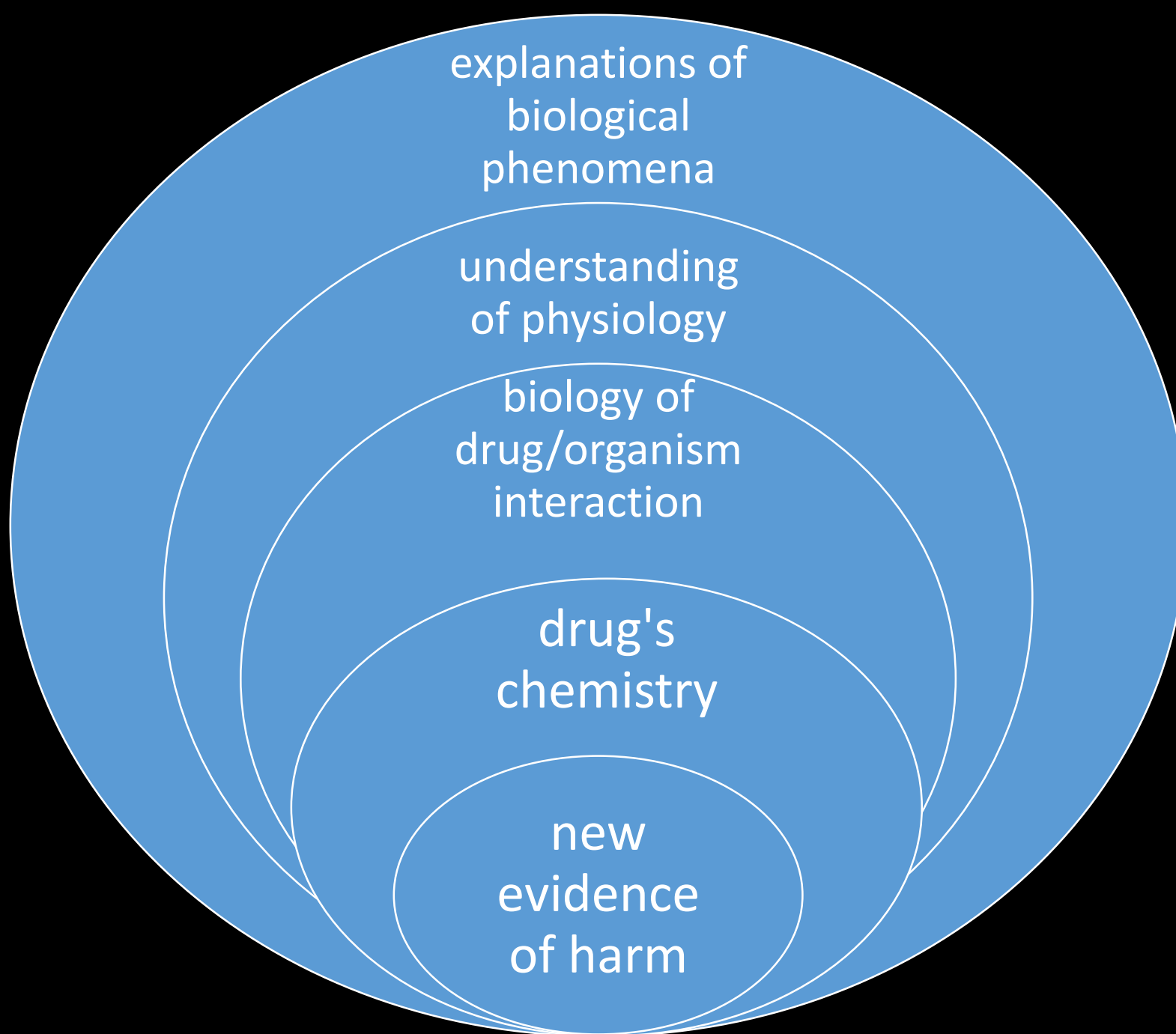biopsies of skin rashes suggest immunological basis (infiltration of CD8+ cells)

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To comprehend is essentially to draw conclusions from an already accepted logical system'.
(Einstein 1953,
foreword to Galilei's 'Dialogue concerning the two major world systems').

explanations of biological phenomena

understanding of physiology

biology of drug/organism interaction

drug's chemistry

new evidence of harm

Analysis, part 2: how can the background mechanistic knowledge affect the efficiency of the whole harm-detection process?

The airbag analogy
(from Krstic & Knuesel 2013)

INTACT CAR

CRASHED CAR

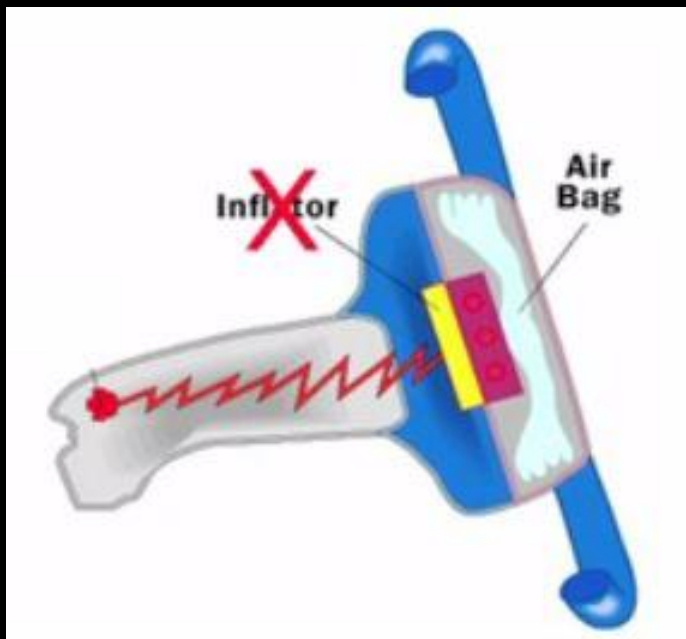# Anecdotes of spontanously exploding airbags

Example 1. Placenta as a perfect barrier: pre-Thalidomide couterevidence

- Gregg, 1941: maternal *Rubella* can damage the fetus
- Since the 19th century: descriptions of alcohol effects in the fetus
- Baker, 1960: 354 references of the effects of drugs on the fetus

Example 2: causal connection between inflammation and cancer

1863, Virchow observes correlation between cancer and inflammation cells (TAM). Causal hypothesis

1907, Hardley observes correlation between TAM and a regression of cancer. Protective hypothesis

CONTRADICTORY EVIDENCE: correlation between degree of infiltration of TAM and prognosis, Histopathology, level of activation of TAM, cytokine production

However, a prominent inflammatory reaction = more favorable prognosis

1990s: molecular characterization of TAM reveals that thay express oncogenic proteins

2001: 'Inflammation and cancer: back to Virchow?' (Balkwill & Mantovani). TMA contribute to cancer growth

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4. Conclusions (so far)

- a background mechanistic understanding/explanation is necessary for the interpretation of evidence and construction of a new understanding/explanation

- a background mechanistic understanding can facilitate of hinder the interpretation of new evidence

- harm detection in risk assessment of technologies has an urgency element, and therefore the background mechanistic understanding should be object of constant scrutiny

-    the first steps toward scrutiny would be

(i) acknowledging that mechanistic thinking is an important part of harm detection,

(ii) making explicit the background mechanistic assumptions, and

(iii) keeping a degree of skepticism toward such assumptions