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# Animal extrapolation in preclinical studies: An analysis of the tragic case of TGN1412

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ABSTRACT

According to the received view, the *transportation view*, animal extrapolation consists in inductive prediction of the outcome of a mechanism in a target, based on an analogical mechanism in a model. Through an analysis of the failure of preclinical studies of TGN1412, an innovative drug, to predict the tragic consequences of its first-in-man trial in 2006, the received view is challenged by a proposed view of animal extrapolation, the *chimera view*. According to this view, animal extrapolation is based on a hypothesis about how human organisms work, supported by the amalgamation of results drawn from various experimental organisms, and only predicting the 'predictive grid', that is, a global framework of the effects to be expected.



## 1. Introduction

On March 13th, 2006, a new drug called TGN1412, designed for balancing the immune system in rheumatoid arthritis and B Cell Lymphocytic Leukemia, came to a first-in-man (FIM) trial in London with the disastrous outcome of a so-called cytokine storm (CRS: Cytokine Release Syndrome). Previous preclinical studies (PCS), i.e. a set of *in vitro*, *ex vivo*, and *in vivo* experiments, had come to a sound prediction that a CRS was very unlikely to happen. To assess how sound such failed predictions were before the accident, it is necessary to establish what kind of reasoning they consisted in.

Extrapolation from experimental organisms[1] is usually seen by philosophers as an inference of the sort:

(1) TGN1412 balances the immune system in those experimental organisms that have been observed;
(2) the underlying mechanisms of action of TGN1412 in animals are hypothesized to be similar in humans based on evidence xyz about underlying physiology, genetic conservation, etc.;
(3) hence it is likely that TGN1412 also will balance the immune system in humans.

Traditionally, philosophers see such an inference as being *1)* inductive, *2)* analogical, *3)* predictive and *4)* based on mechanistic reasoning. Indeed, it consists in predicting that an outcome will also arise in human organisms because it has already been observed in some experimental organisms that are mechanistically analogical. Of course, this consensus leaves room for controversy. How far should the analogy go, how conclusive is it? Let us call this the *transportation* view of animal extrapolation, because it consists in transporting a mechanistic pathway from a model system to a target system.

Based on a careful study of TGN1412, this paper challenges the transportation view, and proposes an alternative. Several recent papers have drawn attention to the importance of "regimes of piece-meal modelling" and "incomplete animal models" (Huber & Keuck, 2013), "the mosaic nature of big picture accounts" (Baetu, 2016), and the "epistemic scaffold" of partial analogies

*Abbreviations:* Ab, Antibody; ADCC, Antibody-Dependent Cell-Mediated Cytotoxicity; ADME, Absorption, Distribution, Metabolism, Excretion; CDC, Complement-Dependent Cytotoxicity; CT, Clinical Trial; CT1, Phase I clinical trial; CRS, Cytokine Release Syndrome; Fc, Fragment Crystallizable region; FIM, First-in-man; LOAEL, Low Observable Adverse Effect Level; LOEL, Low Observable Effect Level; MAb, Monoclonal Antibody; MABEL, Minimal Anticipated Biological Effect Level; NOAEL, No Observable Adverse Effect Level; NOEL, No Observable Effect Level; PCS, Preclinical Studies; $T_{reg}$ Cells, regulatory T Cells; TCR, T Cell Receptor.

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[1] The kind of animal extrapolation referred to in this paper does not rely on *model organisms*, in a narrow, strict sense (*Drosophila*, *C. Elegans*, etc.), but on *experimental organisms* more generally, following the useful distinction by Ankeny and Leonelli (2011).

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strengthening or weakening each other so that riskier arguments can be made (Nelson, 2013). The present article draws the consequences for the logic of preclinical extrapolation, and labels them the 'chimera view'. The chimera view holds that the hypothetic causal pathway is not always investigated in one existing experimental organism, where it would be fully realized. This pathway is often stipulated first, and verified piecemeal in many different experimental organisms, in the way Baetu suggests a "big picture" results from "cross-model extrapolation" (Baetu, 2014, 2016). Consequently, it does not consist in the prediction of *events*, but rather of the various *dimensions* of the expected outcome, i.e. the relevant variables describing it. Whereas it is not very efficient at the former, it is generally efficient at the latter.

Section 2 is a short presentation of the received view. Section 3 presents the case of TGN1412 in some detail and shows why the transportation view does not account for it. Section 4 describes the chimera view. As a conclusion, section 5 summarizes the chimera view and addresses the question of whether it should replace or correct the transportation view.

## 2. The transportation view of extrapolation from preclinical studies

The first subsection summarizes how such extrapolation is often presented in the philosophical literature. The second subsection explains why, according to this view, PCS are intended to conceive a final experiment that summarizes every piece of information gathered during the preclinical stage, for the final extrapolation to be made.

### 2.1. The received view on the nature of extrapolation from PCS

It can probably never be said that the effect of a new drug on humans is completely unknown. But it is safe to assume that the effect of a new drug on humans is unknown to a certain extent and must be tested on experimental organisms first. The observation will then be extrapolated to humans. A causal pathway investigated and established in an experimental organism is transferred on to a target organism: this is the transportation view of animal extrapolation. Four main consequences follow: extrapolation from experimental organisms is an inductive, analogical and predictive kind of inference, whose object is a mechanism.

1) *Extrapolation is inductive.* Extrapolation from experimental organisms is an inference of the sort:

I on experimental organism $O_1$ does E → I ontarget organism $O_2$ does E.

It is inductive because it develops into

$$\text{I on } O_1 \text{ does E} \rightarrow \text{I on all } O_x \text{ does E} \quad (1)$$

$$\text{I on all } O_x \text{ does E} \rightarrow \text{I on } O_2 \text{ does E} \quad (2)$$

in which (1) is inductive. It holds if and only if $O_1$ and $O_2$ belong to the same set of organisms $O_x$ sharing one property, namely, the same causal chain of events from I to E. This population need not be the whole animal kingdom: in drug development, it probably rarely is. What matters to medical research is that both human organism ($O_2$) and experimental organism ($O_1$) present the defining features that supposedly make possible that I does E. It possibly includes other species which the investigator does not need to know of. This must be assumed, yet this is precisely what is unknown. To avoid this "extrapolator's circle" (Steel, 2008), a weaker claim about all $O_x$ is resorted to, namely, that they are *known to sufficiently resemble* one another for one further unknown fact to be inferred from $O_1$ to $O_2$.

From then on, authors differ about what should supplement "simple induction", as Steel calls it, for the resemblance to be sufficient. To Weber (2005), it is phylogenetic reasoning, to Steel (2008), a mechanistic approach he calls "comparative process tracing". Importantly, experimental organisms in biomedical research can be actively manipulated in order to improve analogies and remove disanalogies (Maugeri & Blasimme, 2011). They are therefore not *only* based on homology and evolutionary reasoning (Schaffner, 1998, 2000, 2016). The common assumption underlying these debates is that extrapolation is inductive, albeit, a sophisticated, and possibly very weak, form of inductive inference.

2) *Extrapolation is analogical.* The so-called 'sufficient resemblance' in formula 1 is often developed into a form of analogy of causal relations. This part of extrapolation from experimental organisms can be framed as follows ($I_1$, $M_1$, $E_1$ being respectively intervention, linking mechanism and effect in *model*, and $I_2$, $M_2$, $E_2$, in *target*; '≅' stands for 'is analogical to'):

$$I_1 \rightarrow M_1 \rightarrow E_1 \quad (3)$$

$$I_2 \cong I_1 \quad (4)$$

$$E_2 \cong E_1 \quad (5)$$

$$M_2 \cong M_1 \quad (6)$$

$$I_2 \rightarrow M_2 \rightarrow E_2 \quad (7)$$

In most cases, (4) and (5) may be assumed to hold. The *onus probandi* generally falls upon (6), that is, the analogy of mechanisms. As Steel showed, extrapolation from mechanisms observed in models to mechanisms present in targets is based on comparatively tracing mechanisms step by step (Steel, 2008). This consists in filling in a schematic causal pathway of what happens in humans, by comparing a known part of this pathway to a similar known mechanism in an experimental organism, then observing what the next step is in the model, and concluding what it is in the target human population. Hesse (1970), LaFollette and Shanks (1995), Steel (2008), agree to admit that $M_1$ and $M_2$ are known to bear both analogies and disanalogies, and also that possibly important parts of them remain unknown. They all express the problem in the form of an inference from the $n$ parts of $M_1$ and $M_2$ known to be analogical, to $part_{n+1}$ known in $M_1$ but unknown in $M_2$. At this point, LaFollette and Shanks (1995, p. 147) state that there must be no causally relevant known disanalogy between model and target, whereas Steel (2008, p. 8) states that there can be. Degeling and Johnson propose a taxonomy of acceptable forms of similitude (Degeling & Johnson, 2013). The common assumption underlying the transportation view is that animal extrapolation relies on analogy. Note that analogy should not be considered another form of extrapolation, the first one being 'induction'. In fact, extrapolation in the transportation view is both inductive and analogical, that is, an induction from a sample of tested organisms to a larger population of organisms that include humans, the population being defined by analogous mechanisms.

3) *Extrapolation is mechanistic.* There is an important difference between the two following sorts of inference:

$$I_1 \text{ on } O_1 \text{ does } E_1 \rightarrow I_2 \text{ on } O_2 \text{ does } E_2 \quad (8)$$

$$M_1 \text{ in } O_1 \text{ links } I_1 \text{ to } E_1 \rightarrow M2 \text{ in } O_2 \text{ links } I_2 \text{ to } E_2 \quad (9)$$

Indeed, similar interventions I may have one similar effect E on