To: Alain Bussard <106304.2427@compuserve.com>
Cc: me
Fcc: INBOXY
Subject: How to falsify "clonal selection"
Reply-to: lederberg@mail.rockefeller.edu

AUG - 4 2003

Dear Alain

It was so good to hear from you! (Your reprint from the Bull. Acad. Med. Belg.)

You raise an interesting challenge, I go back to the formal statement: from my 1989 Science paper.

P/80. tenets

Table 1. Nine propositions. (Clonal Selection)

A1. The stereospecific segment of each antibody globulin is determined by a unique sequence of amino acids.

A2. The cell making a given antibody has a correspondingly unique sequence of nucleotides in a segment of its chromosomal DNA: its "gene for globulin synthesis."

A3. The genic diversity of the precursors of antibody-forming cells arises from a high rate of spontaneous mutation during their lifelong proliferation.

A4. This hypermutability consists of the random assembly of the DNA of globulin gene during certain stages of cellular proliferation.

A5. Each cell, as it begins to mature, spontaneously produces small amounts of the antibody corresponding to its own genotype.

A6. The immature antibody-forming cell is hypersensitive to an antigen-antibody combination: it will be suppressed if it encounters the homologous antigen at this time.

A7. The mature antibody-forming cell is reactive to an antigen-antibody combination: it will be stimulated if it first encounters the homologous antigen at this time. The stimulation comprises the acceleration of protein synthesis and the cytological maturation which mark a "plasma cell".

A8. Mature cells proliferate extensively under antigenic stimulation but

are genetically stable and therefore generate large clones genotypically preadapted to produce the homologous antibody.

A9. These clones tend to persist after the disappearance of the antigen retaining their capacity to react promptly to its later reintroduction.

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Some of these have been modified or made more specific in subsequent history; so obviously they were falsifiable.

A1-2-3 are the core.

So CS would be falsified e.g. by

contra A1
finding: 2 antibodies with identical a.a. sequence.
This perhaps has already been done (Foote-Milstein); so we have to alter the tenet to accomodate that exception: differential folding is possible.
Do we have any evidence that the immunogen plays any role in differential folding?

or contra A2
finding some determinant other than DNA sequence that specifies the a.a. sequence.

Well we now know about alternative splicing, RNA-editing, posttranslational modifications. So they have to be taken into account.
Again
Do we have any evidence that the immunogen plays any role in that processing? The nearest analogue is in prion replication.

Finding clones with manifold specifities would also complicate the CS theory, Yes, there are exceptions, but they hardly falsify CS in the sense of supporting another comprehensive alternative theory.

To assert the non-falsifiability of a theory is akin to denying that it is a scientific proposition. I would not go so far!

I send you some matters of interest,

Fondest best wishes,
Joshua