

Steele and Dawkins 2016 – Somatic Ig Hypermutation Diversifies HIV

For *viXra.org* : Theoretical Article - 26th December 2016

<http://viXra.org/abs/1612.0346>

viXra number is 1612.0346

New Theory of HIV Diversification

Why it may never be possible to make a protective vaccine

Edward J. Steele and Roger L. Dawkins

CY O'Connor ERADE Village Foundation 24 Genomics Rise, Piara Waters, Canning Vale, Perth, WA 6112 AUSTRALIA

Correspondence : Edward J Steele PhD *Email*: ejsteele@cyo.edu.au

Running Head: *Somatic Ig Hypermutation Diversifies HIV*

Key words : HIV Immune Evasion, Vaccines, Somatic Hypermutation Ig Genes, AID C-to-U Deaminase, ADAR A-to-I Deaminase, DNA Polymerase- η , Reverse Transcription

Abstract

Several observations suggest that the mutation rate of the Human Immune Deficiency Virus (HIV), the causative agent of Acquired Immune Deficiency Syndrome (AIDS), is much higher than generally believed. This evidence is briefly reviewed. A new speculative theory for HIV diversification (in development since 2013) is thus proposed whereby the virus co-opts the host's somatic hypermutation (SHM) machinery normally targeted to rearranged immunoglobulin (Ig) variable genes (VDJs) within antigen-activated Germinal Centre B lymphocytes. The pessimistic conclusion - that a conventional vaccine is impossible - is a message not really welcomed in this modern age addicted to only positive scientific results. We argue this should be taken as a spur to approach viral prophylaxis and therapy from entirely new directions. Viruses, particularly HIV and its antecedents, have had billions of years of both cosmic and terrestrial evolution to figure out, by trial and error, how to multiply and infect the next host cell. The implications of our novel and plausible HIV immune evasion strategy is discussed both for the host-parasite relationship and current vaccine research. Because the straight forward and simple idea in this paper has been in preparation for three years it has been found necessary to add a Post Script to this viXra.org submission.

Introduction

It is now 35 years since HIV/AIDS burst unexpectedly on the scene. The pandemic has unleashed a vast research effort and huge strides have been made in understanding the medical biology of pathogenic retroviruses (Boyd 1997; Ryan 2004) and their effects on the immune system (Brumme et al, 2010) and the evolution of the wider genome (Dawkins et al, 1999; McLure et al, 2013; Wickramasinghe 2012; Steele 2014, 2015; Wickramasinghe and Steele 2016). Indeed the literature is vast – almost every relevant topic has been investigated in depth and this literature can be accessed by a simple Google search with a precise question. Since the mid 1990s HAART (highly affective antiretroviral therapy) allows long term survival and much of the urgency has thus subsided in other areas of protective immunotherapy (Palella et al 1998). Nevertheless it is still an unpalatable fact that all efforts to create a truly protective *immunological* neutralizing vaccine have come to naught. The consensus belief is that the high HIV mutation rate – much like the high mutation rates in other RNA viruses such as influenza, and positive-strand RNA flaviviruses (Sanjuan and Domingo-Calap 2016) – mitigates against success. The belief in eventual success however prevails - eventually a new trick or angle will be found allowing the production of a traditional protective viral vaccine, much like the immunological success with the less variable polio virus, small pox virus and, more recently, Ian Frazer's herpes papilloma virus (HPV) where a protective vaccine can be produced against cervical cancer.

So, in the current era of HAART treatment, the urgency really has eased to produce a genuinely protective vaccine. Nevertheless much highly expensive research, funded by literally hundreds of millions of scarce tax-payer dollars, is still devoted to HIV vaccine research each year. The tacit suspicion is *we are digging the same fruitless hole even deeper*. Indeed, we suspect that the field, and Mankind generally, *knows this* and would welcome truly radicle new ideas to

both tackle HIV and better understand the explosive emergence of new virulent viral epidemics (e.g. see such analyses in Wickramasinghe 2012; Wickramasinghe and Steele 2016). It is in this spirit (and see Post Script) we submit a radically different yet speculative molecular model to explain HIV's highly effective immune evasion strategy, and thus the difficulty this poses for all contemporary vaccine development. If our explanation has scientific value it should stimulate efforts to take our novel proposal seriously, or even disprove our proposal by observation and experiment. Our suggestive mechanism is not overly pessimistic as each HIV survivor would have a degree of immunity if exposed to another new retroviral pathogenic variant.

Multifaceted Immune Evasion Strategies

The striking facts about HIV are its multifaceted immune evasion strategies. Many pathogenic viruses share these but HIV seems to have a patent on the process of keeping one step ahead of the immune system. For antibody-mediated immunity the somatic hypermutation (SHM) process of Ig diversification is clearly not fast enough – it seems always a step behind the latest viral mutant. Why is this so?

The current mainstream theory is that HIV infects CD4⁺ T cells, integrates its provirus in some of them and multiplies thus destroying CD4⁺ cells and causing ineffective adaptive immunity and then rapidly mutates to further evade the residual ongoing immune response (involving potentially neutralising antibodies produced by B lymphocytes and CD8⁺ cytotoxic T lymphocytes, CTLs).

The high mutation rate is attributed to the "error prone" reverse transcription (RT) step, advanced by Howard Temin and colleagues estimated at 10^{-4} to 3.4×10^{-5} mutations per bp per replication cycle (Dougherty and Temin 1988; Mansky and Temin 1995). For a viral RNA genome of 10 Kb this is about one point mutation per proviral cycle. However all the evidence points to a much higher mutation rate during infection.

Known early mutagenic events after infection include error-prone reverse transcription itself; anti-viral activity of APOBEC3G deaminase (Harris et al 2004; Chiu and Greene 2005; Russell et al 2009; Kim et al 2010; Refsland and Harris 2013) targeting single stranded (ss)DNA (C-to-U in first cDNA strand when ssDNA exposed by the digestive action of RNase H); and ADAR deaminase-mediated A-to-I RNA editing, which if affected before the RT step on double stranded (ds)RNA portions of the viral genome (Doria et al 2009) will result in A-to-G mutations in the proviral DNA. Further, it is well known that in any *in vivo* population of newly minted HIV particles most (> 99.9%) are empty or replication defective virions. Fewer than 1 in 1,000 to 1 in 10,000 peripheral blood mononuclear cells in infected individuals have integrated proviral DNA (Harper et al 1986). The frequency of cells carrying transcriptionally active provirus is an order of magnitude or two lower, 10^{-4} to 10^{-5} (Brown 1990). The sensible conclusion, given these facts, is that the *in vivo* mutation rate is much higher than generally believed.

So the highly effective antiretroviral therapy involving three or more different drug targets on the HIV life cycle has been a triumph of clinical medicine (Palella et al 1998). The strategy really has allowed long term survival of HIV-positive patients and their ability to lead productive lives. But this success came at a scientific price - it masked some clear facts that were just emerging in a number of areas, or are emerging now, but are not highlighted as they do not seem relevant under the current explanatory paradigm. Many of these facts are half forgotten but will be revived here in the context of a new model of HIV diversification.

One main early event in HIV infection (as with many other viruses) is sustained polyclonal B cell activation (Lane et al 1983; Schnittman et al 1986). However definitive studies also show that HIV-1 can infect B cells, particularly activated B cells (Gras et al 1993) as well as macrophages and other white cells, not just CD4⁺ T cells. Indeed HIV-1 can infect and produce provirus and then progeny

virus in activated B cells in an efficient antibody and complement-dependent manner *in vitro* (Gras et al 1993).

The HIV virus has, as mentioned, multiple immune evasion strategies including envelope protein molecular mimicry, the capturing and re-expression of portions of host genes (Ig, TCR, MHC), effects on host MHC Class I and Class II gene expression, amongst others. Veljkovic (2005) has reviewed much of this evidence. However there is one set of captured host sequences, now embedded within the *Env* gene sequence which present a puzzle pregnant with implications. viz. Ig RSS. These are immunoglobulin Recombination Signal Sequences which are targeted by the host's Recombination Activating Genes (RAG 1/2) involved in the V,D,J recombination steps in Ig and T cell receptor (TCR) somatic gene assembly in the ontogeny of development of mature B and T lineage cells. In the case of the Ig DNA V->DJ rearrangement, this is an absolute pre-requisite for the next steps viz. a). targeting of activation-induced cytidine deaminase (AID) to VDJ sequences converting cytosines to uracils (C-to-U); b). these C-to-U lesions then mature to Abasic sites and single stranded DNA nicks thus initiating the processes of targeted somatic hypermutation and class switch recombination (Di Noia and Neuberger 2007; Teng and Papvisilliou 2007). The mechanism of Ig SHM is an RNA/RT-based mechanism (the "Reverse Transcriptase Model" of SHM) which produces strand-biased mutations at A:T and G:C base pairs (Steele 2009; Lindley and Steele 2013). All the SHM molecular data gathered since 1980 supports directly or indirectly this RNA/RT-based mechanism (Steele 2016). This involves error-prone cDNA synthesis via an RNA-dependent DNA polymerase (DNA Polymerase- η) copying the Ig pre-mRNA template and integrating the now error-filled cDNA copy back into the normal chromosomal site. That is, AID induced dC-to-dU lesions and long-tract error-prone cDNA synthesis of the transcribed strand by the SHM specific DNA Polymerase- η acting as a reverse transcriptase (Franklin et al 2004).

Why should HIV carry such sequences for DNA binding proteins in its envelope

protein amino acid sequence? Indeed it is worth quoting Veljkovic in full on these and other curious embedded *Env* sequences:

“The nucleotide sequence GCTGGTGG, encoding the amino acids QLV of this motif, represents the *Chi* signal promoting generalized recombination in prokaryotes Downstream from the putative *Chi* sequence, a heptamer sequence, CAGTCTG, has been identified... Five of the seven bases in this nucleotide sequence match the consensus recombination signal CACTGTG already found to be involved in V-(D)-J recombination of the Ig gene ... It is of note that a similar sequence exists at the same position in the gp120 gene of nearly all HIV-1 isolates.. ” (Veljkovic 2005).

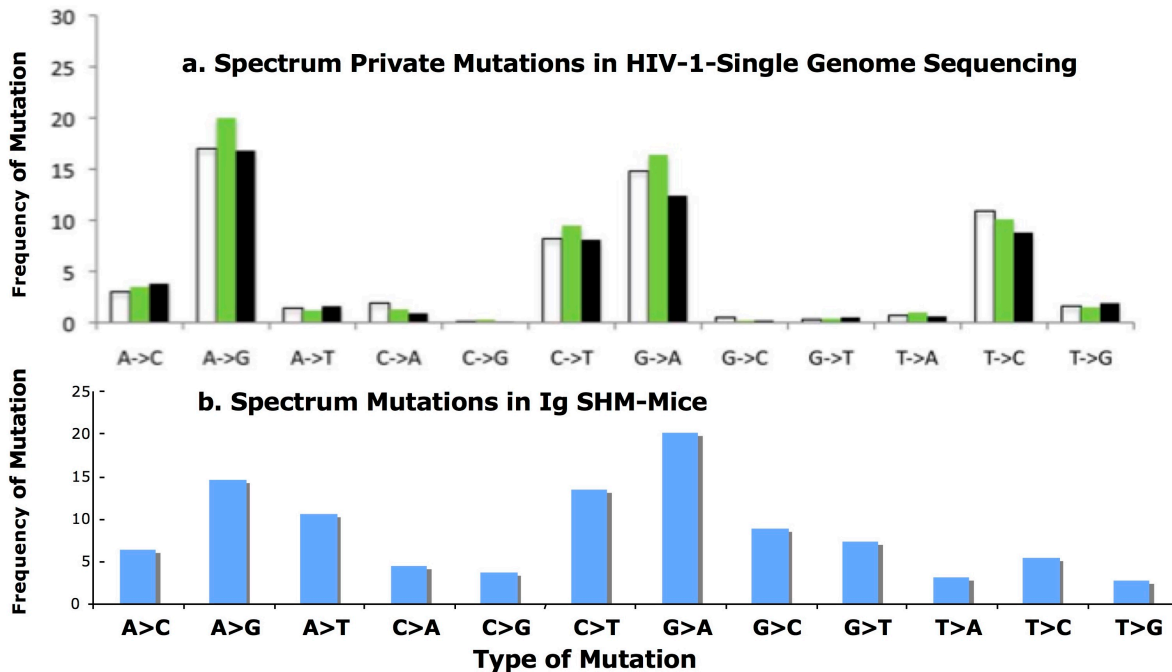


Figure 1 Comparison of the HIV Mutation Spectrum with the Strand Biased Ig SHM Spectrum. *Figure 1a* From control data in Figure 5 in Mullins et al 2011. Specificity of private mutational change over time. Open bars are from day 0, shaded bars are from day 56, and black bars are from day 125 post infection. the Y-axis shows the total number of private mutations in a group of 10 subjects. *Figure 1 b* Adapted from Table 1 Steele 2009 PCR hybrid artefact minimised data.

Another curious fact which is now becoming evident is the spectrum of base

substitutions within HIV genomes. Mullins and co-workers have provided a good example of point mutation spectra from single genome HIV sequencing (Mullins et al 2011). Note the similarities in these HIV-1 mutation spectra and the somatic mutation pattern observed in murine rearranged Ig VDJ genes following somatic hypermutation *in vivo* (Figure 1). However this comparison while suggestive is also quite misleading if corrected for base composition (which is always applied to the Ig mutation data (Steele 2009) but not the HIV data). Thus the base composition of any single HIV-1 genome is in fact *very similar* to the base substitution spectrum shown in Figures 1a suggesting that the basic strand biased pattern of mutations of A exceeding mutations of T (A>>T) and mutations of G exceed mutations of C (G>>C) has been laid down and embedded in human retroviral genome structures over presumably billions of viral life-cycles over potentially millions if not billions of years (Wickramasinghe 2012; Wickramasinghe and Steele 2016). These are the fundamental strand biases noted in the AID-initiated Ig SHM process (Steele 2009) and human cancer genomes (Steele and Lindley 2010; Lindley and Steele 2013; Steele 2016) which are best understood as being generated via based-modified Ig pre-mRNA template intermediates and error-prone cellular reverse transcription. To this point, as far as we are aware, it is not clear how wide spread these patterns are in other biological systems for DNA diversification; although it is emerging as a fundamental somatic mutation pattern in higher vertebrates.

Why should *Env* have embedded V-D-J RSS?

Let us focus more precisely on why HIV-1 should need to have embedded a captured nucleotide sequence such as the RSS involved in immunoglobulin V-D-J recombination. The RSS DNA sequence in this sense is *never expressed* as protein. It is the target site for binding by the RAG1/2 recombinase enzymes that carry out Ig re-arrangement i.e. V-D-J recombination. Somatic Hypermutation of Ig genes targets (*only*) rearranged V-D-J sequences. However embedded heptamers in the 3' region of V_H regions are known to be involved in V_H

replacement at $V_H D_H J_H$ sites (Chen et al 1995). Thus it is conceivable that the embedded heptamer is involved in recruiting the somatic hypermutation machinery and now targeting the RNA/RT-based Ig hypermutation mechanism just discussed to the integrated 10 kb provirus DNA sequence. Given that in cancer genomes the RNA/RT-based AID and ADAR deamination signatures are targeted (in a codon-context fashion) to numerous non-Ig genic sites across the cancer genome, this is a not unreasonable assumption (Lindley 2013; Lindley et 2016). Maybe the reason HIV-1 has done this is to target the Ig SHM machinery to the viral envelope *Env* gene in particular to produce protein variants that keep a step ahead of specific antibodies - which are also employing the same mutation mechanism in the same hypermutating B lymphocyte!

HIV diversification – A new theory required

The observations outlined above suggest that a new theory to explain HIV diversification is required. Given that the host already has an efficient somatic hypermutation process targeted to immunoglobulin variable genes (Ig SHM) it seems only logical to explore the possibility that HIV may have found a way to co-opt Ig SHM to enhance its ability to evade the immune response. Indeed, Balin et al (2008) have also suggested this and investigated this possibility in part by showing that the HIV envelope coding sequence when transfected into a B cell line *in vitro* mutates in a manner consistent with the direct action of AID deamination of DNA creating C-to-U mutagenic lesions. By itself this is not convincing as we know that any DNA sequence parked in the VDJ locus of a hypermutating B cell (or any where else in the B cell genome as a V(D)J transgene) will be an AID target and hypermutate (Yelamos et al 1995). However full blown Ig SHM *in vivo* is *much more* than just AID deaminase action (producing the strand biased base substitution pattern in Figure 1b). The data suggest involvement of error-prone DNA polymerase- η (Zeng et al 2001), which is the only known error-prone DNA polymerase involved in physiological SHM *in vivo* (Delbos et al 2007), and DNA polymerase- η happens also to be an efficient

reverse transcriptase *in vitro* (Franklin et al 2004). The signatures of other putative base modifications of RNA (adenosine-to-inosine RNA editing, Steele et al 2006) are also implicated in the generation of the complex set of strand-biased base substitution signatures observed at AID-mediated lesions (Steele 2009; Steele 2016).

We suggest the following model:

- HIV-1 infects many different lymphoid and related white cells - but particularly *activated B cells* in the early phase of infection.
- A fraction of infected activated B cells carry a productive provirus.

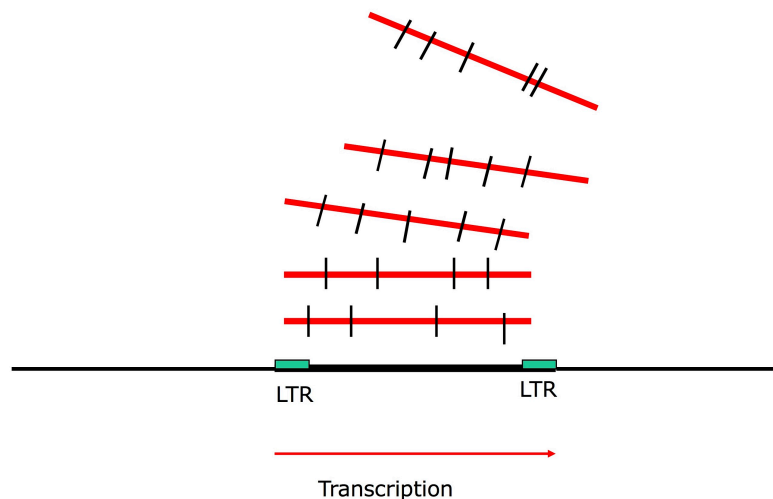


Figure 2 Ig SHM targeted hypermutation at HIV provirus loci. A single provirus bounded by 5' and 3' long terminal repeats (LTR) will produce numerous variant HIV RNA sequences driven by the endogenous Ig SHM process - many of these will integrate back into the proviral site by target site reverse transcription (TSRT, Luan et al 1993; Steele et al 1997; and see, particularly for the mechanistic RT copying and site-specific integration steps, Steele 2009,2016; Lindley and Steele 2013)

- During somatic hypermutation of the HIV-infected B cell in an antigen-activated Germinal Centre (or at other possible non-Germinal Centre sites, Di Niro et al 2015) the SHM machinery involving AID deaminase, Uracil DNA glycosylase, ADAR1 A-to-I RNA editors, RT-Pol- η , subverted mismatch repair MSH-2/MSH-6 (MMR) etc. (Steele 2009; Steele 2016) are recruited and now target the

integrated transcriptionally active HIV-1 provirus (as well as the endogenous Ig V(D)J site).

- The mutant B cell surviving the Germinal Centre reaction will produce a single mutant antibody but also *numerous mutated LTR bounded HIV-1 variants*. The spin-off of mutated HIV-1 RNA genomes is shown schematically in Figure 2.

The implications of this model for HIV vaccine research are two fold:

1. The HIV-1 mutant population will *always* be a step ahead of the somatic antibody variants produced during affinity maturation.
2. It will *never* be possible to produce an effective conventional immunological vaccine for HIV without controlling SHM in B cells.

In this scheme HIV has come up with the ultimate immune evasion strategy. It also has developed a means of diversification, as required or on demand. In this way the virus prepares itself to remain ahead of the host whilst it is also diversifying. Further, the survivors are being exposed to many new retroviral variants. If the explanation is to have any value for vaccine research it may stimulate scientific efforts to take such a possible HIV strategy into account or disprove our proposal.

Postscript : Retroviruses, Evolution and HIV Immunity **26th December 2016**

The formal argument and critical analyses herein was essentially in place by early 2014. However, it is not surprising, on reflection, that our HIV proposal is at the cross roads of many controversial currents in modern biomedical science and social policy. The multiple controversies that have roiled the globe for 35 years can be encapsulated in a series of questions : Who first discovered the HIV/AIDS virus? Where did the virus come from? Is it just another harmless endogenous-

like retrovirus with the host's misdirected inflammatory immune response the main cause of the collateral damage and immune system collapse? Why has the field of Immunology, and thus Immune Prophylaxis, been blindsided by HAART medicines? Will such an explosive, unexpected and virulent retroviral epidemic happen again targeting the human immune system in a sexually transmissible mode (catching the CDC and Pirbright Institutes flat-footed once again)? Why has a vaccine not been developed?

It is to be expected, on further reflection, that after the expenditure of billions of tax-payer dollars, the rise of numerous powerful biomedical centres, and thus prestigious powerful biomedical careers, the last thing the HIV field wants to hear about is a plausible reason why they have been caught flat-footed and why they have failed to develop an effective protective vaccine. The huge social cost of unemployment within the biomedical-bigpharma-industrial complex is just too painful to confront (we would imagine).

However, the back story to this paper is of broad scientific and social interest – for public health and science policies in particular. It is clear that modern science needs to be both reorganized and returned to its tried and true scientific roots. viz. the search for enduring scientific truths by tried and true objective methods, centred on individuals or small groups of collegial yet competing creative scientists. Such an approach is expected to be far less expensive and more cost effective. It might seem old world in its goals, yet quite frankly, modern science is shredding its credibility at a shockingly high paced rate- and as Alexander Unzicker has presciently forecast (Unzicker and Jones 2013) the day of reckoning is nigh and the "bubble" is about to burst.

It was therefore decided to give the paper a decent burial in an online scientific archive yet with a clarifying Post Script putting the problem in its proper perspective. Indeed there have been significant developments since 2013 which can now also be addressed.

Sir Karl Popper and Modern Science

Both Physicists and Biologists are ultimately in the business of providing rational and plausible explanations for the causes of natural physical and living phenomena (for living systems, from a Physics perspective, also see two important books by Mai-Wan Ho (2008) and Chandra Wickramasinghe (2015a).

The guiding philosophical principle, articulated most clearly and comprehensively (in response to David Hume's problem of induction) has been Sir Karl Popper's *Falsification Criterion*. It was advocated to not only decide factual matters in Science but also for the healthy running of a free and open civilized Society (viz. piece-meal social engineering in response to problems as they arise by trial and error elimination).

He first outlined his theory over 80 years ago in his *Logic of Scientific Discovery*, then in a series of great works including his powerful World War II effort written in New Zealand, *The Open Society and its Enemies*. He lived until 1994 (92 yr) and thus witnessed the crushing defeat of both Hitler's Nazi Germany, Mussolini's Fascist Italy, Hirohito's Imperial Japan and then the Reagan/Thatcher-driven collapse of the Soviet Union. We need more Karl Poppers in the world today because dangers and threats like these to civilized open societies still confront us as manifest in radical Islamic Fascism.

Sadly, there has been a distinct drift away in modern times from the scientific necessity to advance testable theories with clear plans for their refutation. If the process is successful it should confirm that the specific part of a theory tested may be true. But if the theory is refuted by severe tests it implies that the causes of the phenomenon under investigation requires a new testable theory – a clear case of *Unended Quest* as Karl Popper articulated in his famous 1976 autobiography. Thus " ..the method of science is the method of bold conjectures

and severe and ingenious attempts to refute them”.

This should be a cold hard law of modern scientific practice. Because if Paul Feyerabend's *Anything Goes* relativism *Against Method* is codified as the acceptable norm of behaviour, it leads to knaves, thieves, mafia types and scoundrels who can game the system gaining wrongful scientific recognition, a phenomenon now blossoming and quite destructive to the credibility of modern Science and the Nobel committee. The scandalous 2011 Nobels in Physiology or Medicine to Bruce Beutler and Jules Hoffman induces incredulity; and, quite frankly, is the final nail in the coffin for the once proud and great Nobel Prizes unless matters are urgently taken to change things fast (Garwood 2011, 2012). Once the indefinable and potentially fragile issue of “credibility” is torn asunder - with both the public and tax-payer, and the scientific community - it is unlikely to be recovered any time soon, if ever. The shattering of the hard won trust in the Nobel tradition must be taken seriously by the committee – such that when the Nobel website invites suggestions it takes submitted suggestions seriously and starts to change the rules for awarding Nobel Prizes. A simple public announcement would do the trick as a 2017 New Year's resolution.

The failure of modern Physics over the last 40 or so years, to adhere to Popper's very sensible advice, is most eloquently illustrated by an important book published in 2013 by the theoretical Physicist, Alexander Unzicker (with Sheilla Jones) entitled *Bankrupting Physics: How Today's Top Scientists are Gambling Away Their Credibility*. Unzicker has gone several important steps further than the previous, and also devastating, critique of “String Theory” by Lee Smolin in his *The Trouble with Physics* (2006); and also Peter Woit in his *Not Even Wrong*. (2006).

Indeed, Alexander Unzicker completely exposes an overt and dangerous delusional tendency in modern Theoretical Physics (the “explanation arm” of Physics charged with providing “rational explanations of natural Physical

phenomena” for public consumption). As Unzicker explains, modern Physics has gone completely feral and disconnected itself from testable and observational physical reality (instance Max Tegmark’s very interesting and readable, yet largely untestable, *Our Mathematical Universe*, 2014 – but Max should not be promoted as “Rock God” of Cosmology – what an outrageous marketing campaign). Modern theoretical physicists are advancing theories which no longer are able to be tested by observation and experiment, not even in principle.

Modern science is in deep trouble as the problem identified by Unzicker is not confined to Physics, but also manifest in Biology, particularly its supposed “quantitative” disciplines in the Biomedical Sciences (Molecular and Cellular Biology, Virology, Immunology, Genomics) and Evolutionary Sciences (which would include environmental studies which would take in “Climate Change” phenomena and Ecology).

Cosmic Biology- Fred Hoyle, Chandra Wickramasinghe and Tom Gold

Early 20th Century Physics (till about mid-Century) had a fluid and evolving (revolutionary) series of stages through the work of Planck, Einstein, Rutherford, Bohr, Schrödinger, and Feynman, which was successful through its sheer necessity to completely extend and qualify the limits of Newtonian Physics. A necessary addition now to this Pantheon would be the great Astrophysicists Sir Fred Hoyle, N. Chandra Wickramasinghe and Thomas Gold. The scientific achievements of these three men, separately and together, fully illuminates the great and grand Popperian traditions of Science. Their discoveries and clear explanatory theories have ensured their place in the Pantheon.

Thus the 20th Century achievements in Physics were characterized by the advancing of testable theories – which a cynic would devalue by stating blandly “Yes but it all ended in disaster, culminating in Hiroshima and Nagasaki.”

Be that as it may, that does not negate the necessity to demand in science that all propositions, theories and explanations, *must be Popperian*. The potential for refutation of a theory is what separates science from delusion and superstition.

Indeed Modern Biology has been trapped for over 100 years in a dead theory. It is dogmatic closed loop system of Neo-Darwinism and Population Genetics Statistical Theory (based on simple Mendelian ideas). This trap has only been scientifically fruitful up to a limited extent but its ability to explain and predict is in steep decline – and as we have shown here (and below) the very paradigm it represents hampers our efforts to understand HIV emergence, diversification (virulence) and thus its control. Surely these intangibles illuminated by HIV should herald a thorough root-and-branch overhaul of the main guiding scientific theories as they are almost certainly deeply flawed.

Great strides have been made over the past 50-60 years in understanding the full extent of an all pervasive “Cosmic Biology” driving the origins and evolution of life on Earth (Wickramasinghe 2012; and also see the great synthesizing and contemporary work of N. Chandra Wickramasinghe . *The Search for Our Cosmic Ancestry* 2015a). Further, there is now a far better understanding of clear non-Darwinian evolutionary mechanisms, shaping both the immune and central nervous systems in particular (e.g. Retroviral and RNA/RT-based Lamarckian Inheritance as well as retroviral/retro-element-driven genomic block structure, see Steele 1979; Steele et al 1998; Steele and Lloyd 2015; Steele 2015; Dawkins 2015; Erwin et al 2016). A clear causal chain of new viruses arriving from space driving evolution on Earth can thus be discerned and rationally understood (Wickramasinghe and Steele 2016). Indeed LINE retro-element transposition (and Alu co-mobility) is a *normal* part of genomic rearrangement during specific neuron commitment, much like the V->DJ rearrangement in specific lymphocyte commitment in the Immune System (Erwin et al 2016).

Retroviral/RT Driven Evolution (Terrestrial and Cosmic)

The authors and their colleagues, have worked separately and together on retrovirus-driven issues, including error-prone reverse transcription (RT) processes, in the evolution of higher vertebrate immune systems (and related genomic structure-function issues) since the 1970s (Steele 1979; Steele et al 1998; Steele et al 2011; Williamson et al 2011; Steele and Lloyd 2015; Dawkins et al 1982; Dawkins et al 1983; Dawkins et al 1999; Steele 2015; Dawkins 2015; Lloyd et al 2015). With respect to HIV and “retroviral evolution” in general, viz the genomic duplicative processes generating the polymorphic block (Ancestral) haplotype structure of the human genome, the key concepts can be traced to what is now known as the “*Retroviral-Induction Model*” (Dawkins et al 1999; Steele 2014; Steele 2015 p.95). Thus when a retrovirus infects a human cell all measure of mutagenic processes are unleashed, including: AID/APOBEC-deaminase induced C-to-U events leading to C-to-T mutations, Abasic sites, and ssDNA nicks, as well as ADAR-deaminase induced A-to-I RNA editing events. Both of these DNA and RNA deaminations are now identified as codon-context Targeted Somatic Mutations (TSM) in the human cancer exome. As well as these we have LINE/Alu-retro-element mutagenic mobility (Harris et al 2004; Refsland and Harris 2013; Chiu and Greene 2005; Muotri et al 2008; Doria et al 2009; Jones et al 2013; Lindley 2013; Lindley and Steele 2013; Lindley et al 2016). So as discussed already LINE/Alu retro-mobility now appears as a normal part of specific synaptic neuronal Brain development (Erwin et al 2016). Thus retroviruses and other viruses liberated in Cometary debris trails both add new DNA sequences to terrestrial genomes but also drive further mutagenic change within somatic and germline genomes.

ASI/ICB

For almost 45 years EJ Steele has been a member of the *Australian Society for Immunology (ASI)* and has published often in the Society’s journal *Immunology &*

Cell Biology (ICB, now a Nature Publishing Group (NPG) journal but previously The Australian Journal Experimental Biology and Medical Science, which was edited and run by Professors Derrick Rowley and Ieva Kotlaski of The Department of Microbiology at the University Adelaide where EJS completed his PhD under Derrick Rowley on Secretory IgA Antibodies in Intestinal Immunity to Cholera , 1971-1976). The office for the "Australian" journal, as it was affectionately and colloquially known, was then re-located to The John Curtin School of Medical Research, *JCSMR*, during much of the 1990s and 2000s (under Professor Christopher Parish) but has now re-located to the Walter and Eliza Hall Institute for Medical Research (*WEHI*) in Melbourne (Professors Philip D Hodgkin, Gabrielle Belz and other senior Australian Immunologists in the *ASI* run the journal). With respect to the *JCSMR*, EJS was both a *JCSMR* Post Doc (1976-1977; 1981-1985) and a *JCSMR* Visiting Fellow (to Professors Gordon L Ada and Robert V Blanden 1985-2003). Thus EJS has always considered the *ASI*, *ICB* and the *JCSMR* his *alma maters* or his primary "home" in Australian Immunology and Biomedical Science.

The core mechanistic thesis in the present paper, which was developed through much of 2013 into 2014, was submitted to the *ICB* Editorial Office at *WEHI* on 27th April 2014. As indicated EJ Steele had previously published a number of speculative (yet testable) theoretical papers like this (and other more wet-lab experimental papers) in *ICB*. The expectation on submission was collegial "give and take", or a modified MS exchange to and fro, in the traditional way of science and scientific research.

Acknowledgement of receipt of the paper by a journal assistant was swift. Thus on 29th April 2014 :

From: <icb.office@wehi.edu.au>

Reply-To: <icb.office@wehi.edu.au>

Date: Tuesday, 29 April 2014 7:36 am

To: <ejsteele@cyo.edu.au>

Subject: ICB-14-TA-0123V1 Receipt of New Paper by Immunology and Cell Biology

Dear Dr. Steele

On 28th Apr 2014, I received your manuscript entitled "New Theory of HIV Diversification: Why it

may never be possible to make a protective vaccine" by Edward Steele and Roger Dawkins.

Your manuscript has been assigned the Paper #: ICB-14-TA-0123V1.

You may check on the status of this manuscript by selecting the "Check Manuscript Status" link under the following URL:

<http://mts-icb.nature.com/cgi-bin/main.plex?el=A2Bq1BKb3A7Fnq7F1A9RRYtvIWJ3ycqLP4Bp42AZ>

However a little while later, on the same day, when the email system was checked there was a message from an *ICB* Editor in Leuven, Belgium (!! ??). The following email was received:

From: <icb.office@wehi.edu.au>

Reply-To: <icb.office@wehi.edu.au>

Date: Tuesday, 29 April 2014 7:39 am To: <ejsteele@cyo.edu.au>

Subject: Decision on Manuscript ICB-14-TA-0123V1

Dear Dr Steele

Thank you for the submission of your research manuscript to our editorial office.

The Editorial Board has examined your manuscript and has, unfortunately, deemed it unsuitable for publication in *Immunology and Cell Biology*. An alternative journal may be more appropriate.

Thus, I regret to advise that we are unable to consider your manuscript for publication in *ICB*.

I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

Yours sincerely

So effectively we were informed almost instantly that the paper was unsuitable as soon as it arrived at *ICB*. Immediate contact was made by EJS with the journal in Melbourne to inquire why the rejection was so swift (as that had never happened before). The contact was Professor Phillip D Hodgkin, Professor of Immunology at *WEHI*. He was an old colleague of EJS (a scientific generation younger than EJS) from The John Curtin School of Medical Research (*JCSMR*) and Hodgkin was now both a senior officer (or officer emeritus) in the *ASI* and very familiar with the practices of the society's *ICB* journal – he is now one of Australia's most senior immunologists. The following email was sent:

From: Ted Steele <e.j.steele@bigpond.com>

Date: Tuesday, 29 April 2014 at 1:54 PM

To: <Hodgkin@wehi.edu.au>

Subject: Current editorial policy at *ICB*?

Dear Phil:

How are you? It has been sometime since we have been in touch. But I am curious to know what the current *Immunol Cell Biol* publication policy is, particularly with respect to *ASI* members and those who have published in the Australian journal over many years.

I have written, I thought, a considered (well within my expertise) Theoretical article “ to challenge and provoke discussion in the international scientific community” and just submitted it Sunday night to ICB. Today within 3 mins apart I receive an email with assignment of a MS number. Then 3 minutes later I received notification it had been rejected! (see below)

Not only do I think this is strange but unjustified – is a new form of censorship now transposed to science?

I attach the paper and associated submission details – I named you, FN Papvassiliou, GW Both, AJ Hapel, and PJ Gearhart as senior scientists suitable as reviewers.

I have tried to contact Simone Farrer but to no avail thus far.

I am sorry to bring this matter up with you like this but if this is general ICB editorial policy sooner or later it will destroy the journal.

I will try and ring you about this.

Ted

--

Edward J Steele PhD
CYO Honorary Research Fellow
CY O'Connor ERADE Village Foundation

Phil Hodgkin then replied:

From: Phil Hodgkin <hodgkin@wehi.EDU.AU>
Date: Wednesday, 30 April 2014 at 1:54 PM
To: Ted Steele <e.j.steele@bigpond.com>
Subject: Re: Current editorial policy at ICB?

Hi Ted,

Thanks for your message. I agree something is amiss - I'm investigating and will get back to you. I don't think there is any policy change.

All the best,

Phil

The next day the Editor-in-Chief of *ICB* at WEHI Professor Gabriel Belz made contact:

On 1/05/2014, 8:45 AM, "Gabrielle Belz" <belz@wehi.EDU.AU> wrote:

Dear Ted,

I have been looking into the decision that was made on your manuscript recently. I did not handle this manuscript but am looking into it and believe the editor was not completely aware of our Theoretical Article category and how these are normally handled (since I do usually do these but was away).

I expect we will reinstate the submission and be able to send the work for review in the next few

days. I do however, as a courtesy, need to discuss this with the deputy editor who did handle the work in my absence.

I also appreciate that the emails you received suggested that any decisions that were made were done within 3 mins - this is not actually the case, at least as recorded on the Nature site, so it is unfortunate that the acknowledgement and decision emails arrived to you with this type of message.

In any case, I hope that I will be able to convey positive news in the next day or so and thank you for your patience.

Best regards,
Gabrielle

Gabrielle Belz BV Biol, BVSc, PhD, DVSc
Division of Molecular Immunology,
Walter and Eliza Hall Institute of Medical Research,

Within 24 hours we had a stock rejection response which EJS considered quite shocking.

On 2/05/2014, 6:12 AM, "Gabrielle Belz" <belz@wehi.EDU.AU> wrote:

Dear Ted,

The manuscript has been considered at some length. The work is on an interesting topic but one that is perhaps more suited to a specialist clinical journal as it is a little outside the scope of ICB. The manuscript poses some big questions, but the arguments are unfortunately not well supported in the manuscript by the large base of data in the research area. Thus, we do not feel that the topic is dealt with in sufficient depth to draw the conclusions of the work.

It would be possible to send the manuscript for review. I could not provide any guarantee that the comments would be more positive though.

I appreciate this is perhaps not the feedback you would have liked.

Regards,
Gabrielle

Then a response from Professor Phil D Hodgkin:

On 2/05/2014, 12:21 PM, "Phil Hodgkin" <hodgkin@wehi.EDU.AU> wrote:

Dear Ted,

Sorry that the paper was not reviewed but, of course, Gabrielle and Adrian have to make a lot of decisions and stand by them, and I can't really intervene more than I have. For the record I haven't seen your paper and can't comment on the decision itself, although of course I understand your disappointment.

I presume you copied to me as I also have a fondness for theory and would like to see such papers supported in ICB, which is true. I will do my best to engender more sympathy in future amongst the executive editors. However, it is regrettably true that the term 'theory' does not have the impact or resonance amongst the up and coming generations it did for us.

Do theoretical papers have to be shocking and clash with accepted wisdom to have any value? While I agree your position has an element of truth, it is an extreme view. An idea can be right or wrong and either could be shocking, with the former a lot more valuable than the latter. Also a valuable theoretical paper might simply point out deficiencies in current thinking without offering an alternative (ie. pointing out the need to find an alternative). A well reasoned paper in that vein may not be shocking at all while being very valuable.

All the best,

Phil

This story of rejection, so familiar to many scientists no doubt, is recounted in detail for a reason. I believe it reveals deep changes that are underway in the normal Popperian practice of modern science. It also reveals potentially other destructive under-currents now overt and manifest in "academic science" and the small mindedness and petty behavior of the current generation of many institutional scientists either running, or enveloped within, "big science" and "big institute" environments. There seems to be in play the inbuilt mental censor "to not rock the boat" – straight out of Soviet Russia and other 20th and 21st Century Communist Totalitarian societies.

Dare it also be said there are other destructive human emotions are at play here, which would take too long to recount the full cause-and-effect chain in detail, such as: virulent destructive envy (Gillman 1998; Schoeck 1966), over weening pride and conceit, and an arrogance associated with the absolute control of new scientific information, and, dare it be said, a *genuine fear* based on a colleague's desire to not break ranks and thus keep "Running with the Herd" where it is far safer scientifically and academically for one's career (Gold 1989).

But the rejection by *ICB* necessitated the above EJS response in 2014 because the decision from his "*alma mater*" journal was totally uncharacteristic. The editor was contacted again and then Professor Phil Hodgkin was contacted (not shown).

On 2/05/2014, 8:18 AM, "Ted Steele" <e.j.steele@bigpond.com> wrote:

Dear Gabrielle:

Thank you for taking the time to review the decision.

However, as I indicated to Phil Hodgkin theoretical papers are a different category entirely – they are a different scientific beast. To be of any value they must be shocking and clash with accepted wisdom – that is their role. A theoretical paper supported by current mainstream data in the field has no value at all as a theory paper.

A specialist clinical journal would be outside the scope of this paper - as clinicians have no track record at all in developing viable immunological theory (if MacFarlane Burnet can be considered a clinician he was a clear exception - they don't mint them like that anymore in the current era, in my view).

The paper was not written lightly. I have indeed spent a lot of time reviewing all the relevant data in the HIV field over the past 30 years pertinent to the issues raised in the paper. The new model is in fact not inconsistent with all current data. The biggest thing I found in reviewing the field is that few if anyone was or is looking critically and directly at B cells – except that French group of Gras et al in the early 1990s. So the additional data discussed in the theory remains to be discovered.

Thanks again

Ted

--

Edward J Steele PhD

CYO Honorary Research Fellow
CY O'Connor ERADE Village Foundation

None of the correspondences were of any avail, the Editor-in-Chief of *ICB* still rejected it – on the flimsiest of grounds. Plausible theoretical papers clearly are a *different category* entirely now – to be of any value they must conform to existing norms and paradigms, they must address and support popular positions, they certainly cannot be potentially shocking and clash with accepted wisdom. Their new role at *ASI/ICB*, despite the positive promos at the ICB website (check it out), is they *must consolidate the existing dogma*.

A theoretical article supported completely by immediate and extant data in a given field has no real value at all as a theory paper, which hopes to predict (and be tested by) new phenomena. Theory must go beyond its immediate data domain and make surprising or interesting predictions in the Popperian spirit. This was at one time always understood in Physics but it has not been part of the

development of modern in Biology (the caveat now is this approach would be: "at least it was understood in modern Physics").

The entire HIV field was carefully reviewed by the authors over a number of years – the paper was not written flippantly or lightly. The new model is in fact not inconsistent with current data, however it goes much further than the current data. The important aspect in reviewing the HIV field was that few investigators, *if any*, were looking critically at B cells – except the French group Gras et al in the early 1990s (Gras et al 1993).

Group Think and *Running with the Herd* are powerful forces in modern scientific research (Gold 1989).

EJ Steele's faith in Physics has also been shaken over the past few years. The seminal work discussed above, of Fred Hoyle and N. Chandra Wickramasinge (H-W) on Cosmic Biology and Panspermia is shockingly avoided or *under cited* by mainstream Physics particularly scientists at NASA and other space agencies (extensive references can be found in Wickramasinghe 2012; Wickramasinghe and Steele 2016). Why is this?

From the biological perspective all the assembled H-W data since the 1970s (or earlier) in books and papers is coherent, specific, multifactorial and Popperian in all relevant details viz. all the Cosmic Biology predictions (which have been confirmed) were all potentially falsifiable *in advance* of the testing (see Wickramasinghe 2015a and the compendium of H-W papers in Wickramasinghe 2015b). It is clear to EJ Steele, who has read many of the H-W books and critically evaluated the key primary published data, that the Solar System (via its ubiquitous Comets acting as "cosmic incubators") and the wider Universe is teeming with living systems (e.g. microorganisms, viruses etc) implying proliferating cellular reservoirs (to allow viral replication) on a Cosmic scale. The spherical Oort Cloud, the source of long period Comets, around our solar system

is the dead give away here. Possibly the majority of these billions of comets *did not* originate from our Solar System accretion plane – they have most likely arisen by capture of Comets by our Sun's gravity from other passing Solar Systems (see Hal Levison 2010 -

https://science.nasa.gov/science-news/science-at-nasa/2010/23nov_aliencomets). The Oort Cloud then is the interface exchange connecting Life in our Solar System with Life in other parts of our Galaxy and the wider Universe.

The dramatic revelations of Tom Gold on the existence of terrestrial life to about 10 Km inside the Earth's crust confirms a clear fact : if microbial life can thrive at such great depths (Gold 1992,1999) it can also thrive on Solar System bodies (Planets, Moons, Comets, etc) and thus throughout the Universe. The Hoyle-Wickramasinghe best guess is that cellular Life emerged at least by 12-13 Billion years ago, in the early stages of the present observable Universe.

That Fred Hoyle did not share the Nobel with Willy Fowler in 1984 for his theoretical work, with the Hoyle predictions confirmed by Fowler on nucleosynthesis in the Sun, was truly shocking. This fact shock EJS to his core as well as his faith in Physics – which to EJS has been his anchoring guide and *exemplar* of the objectivity of the scientific enterprise. And it added to his already deep skepticism about the Nobel nomination process (above and below).

That skepticism has been engendered by watching the awarding of recent Nobel Prizes up close in modern Immunology. Some are beyond dispute – Sir McFarlane Burnet's contribution to modern immunology via the Clonal Selection Theory is a monumental achievement, as is Sir Peter Medawar's experiments on neonatal tolerance in Transplant Rejection studies of the ontogeny of The Self-NonSelf Discrimination. Susumu Tonegawa fully deserved his 1987 Nobel for discovering the V->DJ rearrangement process, as well as molecular (DNA) evidence confirming previous amino acid sequencing data that somatic hypermutation was

a fact during immune responses. The latter $V\lambda$ myeloma protein sequence data was provided by the group of Melvin Cohn and Martin Weigert in a famous *Nature* paper in 1970, four years before Tonegawa's observations at the DNA level. So Tonegawa should have shared the prize with Melvin Cohn and Martin Weigert.

However, it must now be said publically and very clearly (and unequivocally) - Professor Robert V Blanden should have shared the 1996 Nobel on MHC-Viral Restriction with Rolf Zinkernagel (his PhD student) and Peter Doherty (a Post Doc at the time in the laboratory next door to Blanden's in the Department of Microbiology at the *JCSMR*).

Unzicker and Jones' *Bankrupting Physics* should be required reading in undergraduate science degrees. The analyses and dissections in the book are also a *must read* for all contemporary scientists. The corrupting influence of big science, big data, and nationalistic big government tax-payer funding, big corporations is laid out clearly. The associated clear shift in the upper echelons of Physics (the fundamental arenas of Theoretical Physics) is striking. It is a clear move away from Popper's *Falsification Criterion* on a massive scale. Paul Feyerabend's advocacy of base and uncivilized human behavior has triumphed. This is all clearly outlined by Unzicker and Jones. The shift really is, to call a spade-a-spade, to delusion and fantasy. All budding young Physicists have been warned by the Unzicker diagnosis. (The upside is that Unzicker reveals so many potentially rich fields in modern Physics ripe for exploration by young enthusiastic creative scientists).

There is a parallel in Biomedical Science in this Whole Genome Sequencing era. Indeed critical analyses of data, deep and nuanced historical analyses and reflection of the data and concepts in a given field, insights into novel molecular mechanisms etc. have been sidelined by big data, big groups, big institutes, research by large committees and multi-institute teams, with papers of > 20 co-authors not uncommon (much like sub-atomic particle Physics!) . The

opportunities for knaves, sharp operators, game players, dare we say “criminal scientists” to pervert Science are all pervasive (Garwood 2011,2012). This is now coupled to a blind adherence to the outdated, and very limited, Neo-Darwinian-Population Genetics Paradigm in Biology (Wickramasinghe and Steele 2016).

As a consequence Biomedical Science is riddled with fundamental contradictions in data analyses and interpretations in both genetics, genome structure and evolution (Steele 2014; Steele 2015; Wickramasinghe and Steele 2016).

Fraudulent and highly dubious publications are now rampant, published in the high impact journals.

EJS has a rule to not look at *Nature* and *Science* until an excitable colleague emails him and urges him to pay attention to it and sends him the PDF.

However so few in *Nature* and *Science* are worthy of serious consideration any more. The last really important papers in *Nature* on, for example, Ig SHM appeared 2001-2003, led by Patricia J Gearhart’s ground breaking paper on DNA Polymerase- η as the A:T mutator in 2001 (Zeng et al 2001), the key work of Igor B Rogozin and Thomas A Kunkel defining WA hotspots for DNA Polymerase- η action ($W = A$ or T ; Rogozin et al 2001); and then the revolutionary papers on AID-mediated DNA deamination by the Cambridge group of Michael S Neuberger, Reuben S Harris, Svend Petersen-Mahrt, and Javier Di Noia (reviewed in Harris et al 2003; Di Noia and Neuberger 2007; Teng and Papavisiliou 2007; see also Steele 2009, 2016). The follow up work reporting AID-deaminase action on ssDNA substrates at Transcription Bubbles should also be noted from the laboratories of Myron F Goodman (Pham et al 2003) and Frederick W Alt (Chaudhuri et al 2003, 2004). However the really big multi-author and multi-centre combines (> 20 coauthors) publishing in *Nature*, *Science* and *Cell*, on somatic mutation investigations make seriously big mistakes, particularly in cancer research (e.g. Wellcome Trust Sanger Institute papers, and see critiques in Lindley and Steele 2013; Steele 2016).

The Nobel Prize

This tragic conclusion now applies to the Nobel Prize which has now become a totally bankrupt annual farce. The clear rule with the Nobel should be this: a discovery should be coupled to, and absolutely related to, the *character* and intelligence of the scientist who *made* the discovery.

But why “Character”? The question is “Surely you can have a really great scientific discovery in Science without looking at the scientist’s “Character”?”

Not so, and there is complete agreement here with Alexander Unzicker who has been devastating, and quite unrelenting, on this very crucial point (read the book and also check out the interview at <https://www.youtube.com/watch?v=OtHWw0bwm4w>). We must look at the real record of those in the Pantheon i.e. whom all serious objective observers agree “should be in the Pantheon”.

There have always been great scientific discoveries, but the “Character” of the person making the discovery has been the key in all cases – the uniqueness of the discovery relates to the individual analytical mind that “*first made the connection*”. This is the key. Why? In such an answer we run the risk of spelling it out in kindergarten terms and thus alienating the reader. However, genuine dedicated scientists know exactly what is meant here.

And why should the Nobel be awarded every year? “...Because it has to be awarded each year”. What if there is nothing worthy that has been discovered? “We award it any way – it is in the Will”.

And this is the problem. The Nobel has become a “bureaucratic exercise” – it must be awarded each year. Think about that for a minute – the inevitable result

is the dumbing down of the prize. This is coupled to the fact that previous winners have a say in the nomination! Because many undeserving non-entities have now received the Nobel Prize this means the awarding of future prizes will be dumbed down further by the nomination process. Clearly it is time for the Nobel committee, dare it be said, to use Donald J Trump's very apt conclusion to "Drain the Swamp."

So, since about 1980 the provenance of many Nobel awards is suspect. There are clearly well deserved ones as well. But it is the rising incidence of 2nd order awards that is destroying the credibility of the Nobel as an institution. This is a tragic development for young scientists who grew up in the 20th Century.

Surely only the truly great scientists should be allowed entry to the Pantheon? There is clearly only one solution. The Nobel Committee must now make a decision to award the Prizes *occasionally* – and on real Pantheon entry merit criteria. Many Nobels over the past 30 years or so need careful expert scrutiny, many do not make the grade. What a tragedy for Mankind!

The "Occasional Nobel Award" will restore the credibility of the Nobel Prize, otherwise the Prize and its prestige will go extinct. The Nobel must be for highly original work and discoveries at the very highest level of human achievement, and that involves a human factor – "Character". Because it is clear to the authors that only men and women of real character make *enduring* discoveries.

So this leads to a key issue "Why have the extensive and voluminous data and logical analyses published by Hoyle and Wickramasinghe not been *completely* accepted by the wider Physics and Biology communities? It is really quite outrageous for anyone that has examined and evaluated the data.

So it seems really deep emotional factors are at play here affecting scientific judgement. That is the only conclusion that can be reached. The requirement that

an objective scientist “must confront the data before reaching a conclusion” seems to be abandoned when it comes to the data showing that the Cosmos is teeming with life and organisms (microbial in the main, and viruses) which are falling to Earth from Comet debris trails each day. The cost to monitor this in-fall is a fraction of the cost to build and maintain, for example, the Large Hadron Collider run by CERN near Geneva. Balloon collection surveys of the stratosphere, carefully controlled, are, by comparison, very cheap to run and are already yielding interesting results with many novel microorganisms and viral clusters (Combe et al 2015) identified coming in vertically, and at great cosmic speed, from Space (Wainwright et al 2014; Wainwright et al 2015a, 2015b).

Individual Human Brains – The Real Integrative Super Computer

We should not underestimate the great creative and analytical power of the individual human Brain. It is the individual Brain confronting the data that makes scientific breakthroughs. That has always been the case - and all true scientists know that this claim is a true statement. It far exceeds the power of the “Big Research Committee” or “the Big Institute”, or the individual “Brain” directing such a “Big” enterprise (because, obviously, the enterprise in an authoritarian structure will bend its will to the “Director” who is usually in the game for “Power” *only* – the outcome depends thus on the quality of the “Director’s” Brain – which is a huge risk and waste of tax-payer funds given that “Power” *per se* is being rewarded here, not the creative scientific work of responsible individual scientists.

Thus it must go to “Character”, that really is the bottom line, otherwise science and Nobel awards descend into corruption and chaos (Garwood 2011.2012).

“Big Data” pipelines suffer from the same problem. We must assert that the analytical power of an individual Brain far exceeds the power of the Algorithm, and the Big Data, multi-author publications currently in vogue.

Robyn A Lindley and Targeted Somatic Mutation (TSM)

A contemporary and real-time unfolding example is the discovery of Targeted Somatic Mutation (TSM) mutation signatures in cancer genomes which are clearly in “Codon-Context” in genome-wide exome DNA sequence data (Lindley 2013; Lindley et al 2016). This creative process has been observed up close. The discovery was not made by a “Pipeline” or a by “Committee” or by a “ Multi-Centre” Research conglomerate, nor was it achieved under the protective umbrella of a cosy academic institution. It was made under difficult working conditions, with scarce funds under great physical hardship by an individual analytical “Brain” curating and analyzing the data manually (Lindley RA 2017 *Targeted Somatic Mutation (TSM) Signatures: A Review*. Submitted). Thus to the genuine relief of all true scientists, it is still the “individual scientific Brain” which is the “Super Computer” of the 21st Century.

Peter A Bretscher, HIV Immunity and Overdue Scientific Recognition

We close this extended Post Script by drawing attention to the great scientific contribution (over almost 55 years) of Peter A Bretscher a remarkable Physicist who moved into Cellular Immunology in the early 1960s mentored by Francis Crick. Together with the brilliant Melvin Cohn, Peter published (1970) the *Two Signal Model of the Self- Non Self Discrimination*, which, along with Sir MacFarlane Burnet’s *Clonal Selection Theory of Acquired Immunity*, is now recognized as a bedrock principle of modern Immunology. Peter, quite unabashedly, is in the genius class, as that description is traditionally understood. He is already in the Pantheon.

His work is summarized in extensive lucid detail in his first great book published in Canada earlier this year (Bretscher 2016). To cut to just one of his numerous basic insights and predictions with respect to HIV Immunity: the key in Immune Class Regulation is to induce Cell Mediated Immunity (CMI) against HIV virus

infected cells (whether they be T cells, Macrophages, Dendritic cells, or B cells) by *Low Dose vaccination* strategies. Or, manoeuvres to ensure T lymphocyte subset ratios are flipped (e.g. Th1/Th2 (IgG2/IgG1) >1) ensuring a CMI response, rather than antibodies, against HIV infected cells. In such a situation curative HIV immunity is predicted to be delivered, and the same strategy can be applied to Cancer immunotherapies. Needless to say Peter's book documents the very Popperian struggle (over 55 years) he and his associates endured to publish extensive experimental data to consolidate his theory of Immune Class Regulation. Clinical Immunologists, Oncologists and Vaccine developers are urged to become familiar with Bretscher's discoveries and testable theories.

Why submit to viAra.org?

The viAra.org site was found by reading Unzicker and Jones (p.245) and that is why this new model of HIV immune diversification, and thus immune evasion, has now been archived and published at this website. The viAra.org website gives all the reasons why other scientists felt such a site was necessary in modern times. Our paper will be widely cited in future publications and books, and circulated as a PDF reprint to colleagues.

Acknowledgements

This is publication MS1404 of the C.Y.O'Connor ERADE Village Foundation. We thank Sally Lloyd, Joe Williamson, Sue Lester, Charlie Stewart, John Millman, John Schuster, Barry Rolfe, Harry Rothenfluh, Gerry Both, Georg Weiller, Peter Bretscher, Reg Gorczynski, Bob Blanden, Andrew Franklin, Mai-Wan Ho, Robyn Lindley and Chandra Wickramasinghe for discussion and critical comments; and Sue Lester is also thanked again for help in tracking down key references.

Conflict of Interest

The authors have no commercial conflicts of interest that would compromise the objectivity of this paper.

References

Balin SJ, Ross TM, Cascalho M. HIV genes diversify in B cells. *Curr HIV Res.* 2008; **6**: 10-18

Boyd GW. An evolution-based hypothesis on the origin and mechanisms of autoimmune disease. *Immunol. Cell Biol.* 1997; **75**: 503 - 507.

Bretscher P. *Rediscovering the Immune System as an Integrated Organ.* FriesenPress, Victoria, BC, Canada. 2016.

Brown L. Human immunodeficiency virus-infected individuals contain provirus in small numbers of peripheral mononuclear cells and at low copy numbers. *J. Virol.* 1990; **64**: 864 - 872.

Brumme ZL, Poon AFY, Carlson JM, Walker BD. Identifying HLA-Associated Polymorphisms in HIV-1. pp. 3-8 in HIV Molecular Immunology 2010. Yusim, K, Korber B, Brander, C, Barouch, D, de Boer, R, Haynes, BF, Koup, R, Moore, JP, Walker, BD, Watkins, DI, Eds. Published by Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM. 2010. LA-UR 11-11696.

Chaudhuri J, Tian M, Khuong C, Chua K, Pinaud E, and Alt FW. Transcription-targeted DNA deamination by the AID antibody diversification enzyme. *Nature* 2003; **422** : 726 - 730.

Chaudhuri J, Khuong C, and Alt FW. Replication protein A interacts with AID to promote deamination of somatic hypermutation targets. *Nature* 2004; **430** : 992-998.

Chen C, Nagy Z, Prak EL, Weigert M. Immunoglobulin heavy chain gene replacement: a mechanism of receptor editing. *Immunity* 1995; **3**:747 - 755.

Chiu Y-L, Greene WC. APOBEC3 Cytidine Deaminases: Distinct antiviral actions along the Retroviral Life Cycle *J. Biol. Chem.* 2006; **281** : 8309 - 8312.
Doi:10.1074/jbc.R500021200

Combe M, Garijo R, Geller R, Cuevas JM, and Sanjuan R. Single-Cell Analysis of RNA Virus Infection Identifies Multiple Genetically Diverse Viral Genomes within Single Infectious Units. *Cell Host & Microbe* 2015 **18** : 424 - 432
doi.org/10.1016/j.chom.2015.09.009

Dawkins RL. *Adapting Genetics: Quantal Evolution After Natural Selection – Surviving The Changes To Come.* Dallas, TX: Nearurban Publishing, ISBN 978-0-9864115-1-9 2015.

Dawkins RL, Christiansen FT, and Zilko PJ. Editors : *Immunogenetics in Rheumatology : Musculoskeletal Disease and D-Penicillamine*. Excerpta Medica. Amsterdam-Oxford-Princeton. 1982.

Dawkins RL, Christiansen FT, Kay PH, Garlepp M, McCluskey J, Hollinsworth PN, and Zilko PJ. 1983. Disease Associations with Complotypes, Supratypes and Haplotypes. *Immunol Rev* 1983; **70** : 5-22.

Dawkins RL, Leelayuwat C, Gaudieri, S, Tay G, Hui J, Cattley S, et al. Genomics of the major histocompatibility complex: haplotypes, duplication, retroviruses and disease *Immunol. Rev.* 1999; **167**: 275-304.

Delbos F, Aoufouchi S, Faili A, Weill J-C, Reynaud C-A. 2007 DNA polymerase- η as the sole contributor of A/T modifications during immunoglobulin gene hypermutation in the mouse. *J. Exp. Med.* 2007; **204** : 17-23.

Di Niro R, Lee S-J, Vander Heiden JA, Elsner RA, Trivedi N, Bannock JM, et al. Salmonella infection drives promiscuous B cell activation followed by extrafollicular affinity maturation *Immunity*. 2015 **43** : 120-131.

Di Noia JM, sNeuberger MS. Molecular mechanisms of somatic hypermutation. *Annu. Rev. Biochem.* 2007 **76** : 1 - 22.

Doria M, Neri F, Gallo A, Farace MG, Michienzi A. Editing of HIV-1 RNA by the double-stranded RNA deaminase ADAR1 stimulates viral infection. *Nucleic Acids Res.* 2009; **37**: 5848 - 5858.

Dougherty JP, Temin HM. Determination of the rate of base-pair substitution and insertion mutations in retrovirus replication. *J. Virol.* 1988; **62** : 2817 - 2822.

Erwin JA, Paquola AC, Singer T, Gallina I, Novotny M, Quayle C, Bedrosian TA, Alves FI, Butcher CR, Herdy JR, Sarkar A, Lasken RS, Muotri AR, Gage FH. L1-associated genomic regions are deleted in somatic cells of the healthy human brain. *Nat Neurosci.* 2016; 19:1583 - 1591. doi: 10.1038/nn.4388.

Franklin A, Milburn PJ, Blanden RV, Steele EJ. Human DNA polymerase- η , an A-T mutator in somatic hypermutation of rearranged immunoglobulin genes, is a reverse transcriptase. *Immunol. Cell Biol* 2004; **82** : 219 - 225.

Garwood J. A Nobel Prize not Immune from Error?
(December 12th, 2011) http://www.labtimes.org/editorial/e_270.lasso

Garwood J. Nobel Prize Critiques: Bruce Beutler Lab Times
(February 14th, 2012) http://www.labtimes.org/editorial/e_288.lasso

The above two Garwood news articles on the 2011 Nobel Prize have been stripped from the web as 31 Aug 2019. So I attach science writer's Jeremy Garwood's other post on the matter of the 2011 Nobel to the end of this article - the attempt to purge his *Lab Times* articles can only be coming from the deeply ashamed and guilty Nobel committee- which also tells us how far standards have fallen! All current announced Nobels must be accompanied with the question: **What for?** Before proceeding further- it really is that bad. To access the attached on the net Goggle "Garwood J. A Nobel Prize not Immune from Error?" then go to [PDF][Borrowed Plumes - EPFL](https://documents.epfl.ch) <https://documents.epfl.ch> > ...

The 2011 **Nobel Prize** for Medicine or Physiology has been dogged by controversy. The only one ... Here, Jeremy **Garwood**, investigates the "case" of Hoffman, whereas ... **not** Im- mune from **Error?** From locust endocrinology to Drosophila **immunity** in absolutely **no** time. from Phornia (blow fly) larvae (Eur **J** Bio- chem ..

Gillman MA. *Envy as a retarding force in science*. Avebury Series in Philosophy. Ashgate Publishing Ltd. ISBN 1-85972 -397 -7, 1996.

Gold T. New Ideas in Science. *J. Sci. Explor.* 1989; **3** (2) : 103 -112.

Gold T. The Deep Hot Biosphere. *Proc. Natl. Acad. Sci. USA* 1992; **89**: 6045 - 6049.

Gold T. *The Deep Hot Biosphere: The Myth of Fossil Fuels*. Copernicus, Springer Verlag, New York, 1999.s

Gras G, Richard Y, Roques P, Olivier R, Dormont D. Complement and virus-specific antibody-dependent infection of normal B lymphocytes by human immunodeficiency virus type 1 *Blood* 1993 **81** : 1808 - 1818.

Harper ME, Marselle, LM, Gallo RC, Wong-Staal. F. Detection of lymphocytes expressing human T-lymphotropic virus type III in lymph nodes and peripheral blood from infected individuals by in situ hybridization. *Proc. Natl. Acad. Sci. USA* 1986; **83** :772 - 776.

Harris RS, Liddament MT. Retroviral restriction by APOBEC proteins. *Nat Rev Immunol* 2004 ; **4**: 868 - 877.

Ho. M-W *The Rainbow and the Worm. The Physics of Organisms*. World Scientific . Singapore. 3rd Edit 2008.

Jones RB, Song H, Xu Y, Garrison KE, Buzdin AA, et al. LINE-1 Retrotransposable element DNA accumulates in HIV-1- infected cells. *J. Virol.* 2013; **87** : 13307 - 13320.

Kim E-Y, Bhattacharya T, Kunstman K, Swantek P, Koning FA. Human APOBEC3G-Mediated Editing Can Promote HIV-1 Sequence Diversification and Accelerate Adaptation to Selective Pressure. *J Virol.* 2010; **84**: 10402 - 10405.

Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N. Engl. J. Med.* 1983; **309** : 453 - 458.

Lindley R. The importance of codon context for understanding the Ig-like somatic hypermutation strand-biased patterns in TP53 mutations in breast cancer *Cancer Genet.* 2013; **206** : 222 - 226

Lindley RA, Humbert P, Larmer C, Akmeemana EH, Pendlebury CRR. Association between Targeted Somatic Mutation (TSM) signatures and HGS-OvCa progression. *Cancer Med.* 2016; **5** : 2629 - 2640

Lindley RA, Steele EJ. Critical analysis of strand-biased somatic mutation signatures in TP53 versus Ig genes, in genome -wide data and the etiology of cancer *ISRN Genomics.* Vol 2013; Article ID 921418, 18 pages.

Lloyd SS, Steele EJ, Dawkins RL. Analysis of Haplotype Sequences. In: *Next Generation Sequencing – Advances, Applications and Challenges.* Edited by Jerzy K. Kulski. INTECH Chapter 12. 2015 <http://dx.doi.org/10.5772/61794>

Luan DD, Korman MH, Jakubczak JL, Eichbush TH. Reverse transcription of R2B mRNA is primed by a nick at the chromosomal target site; A mechanism for non-LTR retrotransposition. *Cell* 1993; **72** : 595 - 605

Mansky LM, Temin HM. 1995 Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase *J. Virol.* 1995; **69**: 5087 - 5094.

McClure CA, Hinchliffe P, Lester S, Williamson JF, Millman JA, Keating et al. Genomic evolution and polymorphism: Segmental duplications and haplotypes at 108 regions on 21 chromosomes. *Genomics* 2013; **102**: 15-26.

Mullins JI, Heath L, Hughes JP, Kicha J, Styrchak S, Wong KG, et al. Mutation of HIV-1 Genomes in a Clinical Population Treated with the Mutagenic Nucleoside KP1461. *PLoS ONE* 2011; **6**: e15135.

Muotri AR, Marchetto MCN, Coufal NG, and Gage FH. The necessary junk: new functions for transposable elements. *Hum. Mol. Genet.* 2007; **16**: Review Issue 2 R159–R167 doi:10.1093/hmg/ddm196

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; **338**: 853–860.

Pham P, Bransteitter R, Petruska J, Goodman MF. Processive AID-catalysed cytosine deamination on single-stranded DNA simulates somatic hypermutation, *Nature* 2003; **424** : 103 - 107.

Refsland EW, sHarris RS. The APOBEC3 Family of Retroelement Restriction Factors. *Curr Top Microbiol Immunol*. 2013 **371**: 1 - 27. doi:10.1007/978-3-642-37765-5_1.

Rogozin IB, Pavlov YI, Bebenek K, Matsuda, Kunkel TA. Somatic mutation hotspots correlate with DNA polymerase eta error spectrum. *Nat. Immunol*. 2001 **2** : 530 - 536.

Russell JP, RA, Pathak VK, Coffin JM. Likely Role of APOBEC3G-Mediated G-to-A Mutations in HIV-1 Evolution and Drug Resistance. *PLoS Pathog* 2009; **5** (4): e1000367.

Ryan FP. Human endogenous retroviruses in health and disease: a symbiotic perspective. *J R Soc Med* 2004; **97** :560 - 565

Sanjuan R, Domingo-Calap P. Mechanisms of viral mutation *Cell. Mol. Life Sci*. 2016 2016; **73** : 4433 - 4448 doi:10.1007/s00018-016-2299-6

Schnittman SM, Lane HC, Higgins SE, Folks T, Fauci AS. Direct polyclonal activation of human B lymphocytes by the acquired immunodeficiency syndrome. *Science* 1986; **233** :1084 -1086.

Schoeck H. *Envy : A theory of social behaviour*. Liberty Fund. Indianapolis. ISBN 0-86597-064-5, 1966.

Smolin L. *The Trouble with Physics* Houghton Mifflin, Boston, 2006.

Steele EJ. *Somatic Selection and Adaptive Evolution : On the Inheritance of Acquired Characters*. 1st edit. Williams-Wallace, Toronto, 1979; 2nd Edit. University of Chicago Press, Chicago, 1981.

Steele EJ. Mechanism of somatic hypermutation: Critical analysis of strand biased mutation signatures at A:T and G:C base pairs. *Molec. Immunol* 2009 ; **46** : 305-320.

Steele EJ. Reflections on Ancestral Haplotypes: Medical Genomics, Evolution and Human Individuality. *Persp. Biol. Med*. 2014; **57** : 179 - 197.

Steele EJ. *Ancestral Haplotypes: Our Genomes Have Been Shaped in the Deep Past*, Nearurban Dallas,Tx, ISBN 978-0-9864115-0-2, 2015.

Steele EJ. Somatic hypermutation in immunity and cancer: Critical analysis of strand-biased and codon-context mutation signatures *DNA Repair* 2016 **45**: 1-24.

Steele EJ, Williamson JF, Lester S, Stewart BJ, Millman JA, Carnegie P, Lindley RA, Pain G, Dawkins RL. Genesis of ancestral haplotypes: RNA modifications and RT-mediated polymorphism. *Hum.Immunol.* 2011; **72** : 283-293

Steele EJ and Lindley RA. Somatic mutation patterns in non-lymphoid cancers resemble the strand biased somatic hypermutation spectra of antibody genes. *DNA Repair.* 2010 ; **9** : 600 - 603.

Steele EJ, Lindley RA, Blanden RV. *Lamarck's Signature : How retrogenes are changing Darwin's natural selection paradigm* Allen & Unwin, Frontiers of Science: Series Editor Paul Davies , Sydney, Australia, 1998. In the USA published by Addison-Wesley-Longman. 1998

Steele EJ, Lindley RA, Wen J, Weiler GF. Computational analyses show A-to-G mutations correlate with nascent mRNA hairpins at somatic hypermutation hotspots. *DNA Repair* 2006 ; **5** : 1346 - 1363.

Steele EJ, and Lloyd SS. Soma-to-germline feedback is implied by the extreme polymorphism at IGHV relative to MHC.s *BioEssays.* 2015 **37** : 557 – 569.

Tegmark M. *Our Mathematical Universe*, Penguin Books, Random House, London , 2014.

Teng G, Papavasiliou FN. Immunoglobulin somatic hypermutation. *Annu. Rev. Genet.* 2007 **41** : 107 - 120.

Steele EJ, Rothenfluh HS, Blanden RV. Mechanism of antigen-driven somatic hypermutation of rearranged immunoglobulin V(D)J genes in the mouse. *Immunol. Cell Biol.* 1997; **75** : 82-95.

Unzicker A, Jones S. *Bankrupting Physics: How Today's Top Scientists are Gambling Away their Credibility*, Palgrave MacMillan New York, 2013.

Veljkovic, N. Molecular mimicry of HIV gp120: Possible implications on prevention and therapy of AIDS. *Arch Oncol* 2005; **13** : 126-130.

Wainwright M, Rose CE, Baker AJ, Wickramasinghe NC, Omairi T . Biological Entities Isolated from Two Stratosphere Launches-Continued Evidence for a Space Origin *J. Astrobiol Outreach* 2015a ; **3** :2

<http://dx.doi.org/10.4172/2332-2519.1000129>

Wainwright M, Wickramasinghe NC, Harris M, Omairi T
Masses Staining Positive for DNA-Isolated from the Stratosphere at a
Height of 41 km. *J. Astrobiol Outreach* 2015b ; **3** :2
<http://dx.doi.org/10.4172/2332-2519.1000130>

Wainwright M, Wickramasinghe NC, Rose CE, Baker AJ,
Recovery of Cometary Microorganisms from the Stratosphere. *J. Astrobiol
Outreach* 2014 ; **2** :1
<http://dx.doi.org/10.4172/2332-2519.1000110>

Wickramasinghe NC. DNA sequencing and predictions of the cosmic theory of life.
Astrophys. Space. Sci 2012; **343** : 1-5.

Wickramasinghe, Chandra. *The Search for our Cosmic Ancestry*. World Scientific,
Singapore. 2015a

Wickramasinghe , Chandra. *Vindication of Cosmic Biology. Tribute to Sir Fred
Hoyle (1915-2001)*. Edit. Chandra Wickramasinghe, World Scientific, Singapore,
2015b

Wickramasinghe NC, and Steele EJ. Dangers of adhering to an obsolete
paradigm: Could Zika virus lead to a reversal of human evolution? *J. Astrobiology
& Outreach* 2016 4:1
<http://dx.doi.org/10.4172/2332-2519.1000147>

Williamson JF, Steele EJ, Lester S, Kalai O, Millman JA, Wolrige L, Bayard D,
McLure C, Dawkins RL. Genomic evolution in domestic cattle:ancestral haplotypes
and healthy beef. *Genomics* 2011 ; **97**: 304 - 312.

Woit P. *Not Even Wrong*. Vintage, New York. 2006.

Yélamos J, Klix N, Goyenechea B, Lozano F, Chui YL, González Fernández A,
Pannell R, Neuberger MS, and Milstein C. Targeting of non-Ig sequences in place
of the V segment by somatic hypermutation. *Nature*. 1995 **376** :225 - 229.

Zeng X, Winter DB, Kasmer C, Kraemer KH, Lehmann AR, Gearhart PJ. DNA
polymerase eta is an A-T mutator in somatic hypermutation of immunoglobulin
variable genes. *Nat. Immunol*. 2001 ; **2**: 537 - 41.

Borrowed Plumes

Photo: Fotolia/ Yehia LOUKKAL

The 2011 Nobel Prize for Medicine or Physiology has been dogged by controversy. The only one of the three recipients not to be accused of unethical behaviour, Ralph Steinman, had the misfortune of dying before he could hear of his award for dendritic cells. Meanwhile, Jules Hoffmann and Bruce Beutler have since been accused of unfairly promoting their own contributions to these discoveries. Here, Jeremy Garwood, investigates the “case” of Hoffman, whereas Beutler is at the centre of an accompanying article at *Lab Times* online (www.labtimes.org).

Bruno Lemaitre, now professor at Lausanne’s EPFL, says Jules Hoffmann took unjust credit for his discoveries concerning genetic regulation of innate immunity in *Drosophila*.

Fly credits and miscredits

In 1992, Lemaitre came to Hoffmann’s CNRS laboratory in Strasbourg. He had just obtained his PhD in Paris. He was the only geneticist in the lab. His project was to study the genes regulating the expression of antimicrobial peptides. By the time he left Strasbourg, in 1998, to set up his own lab group, he had published three key papers describing the discovery of a new mutation, *imd* (immune deficiency), that regulated the immune response of flies to bacterial infection and had established that the gene, *Toll*, regulated the response to fungal infection. It is for the second of these three papers, Lemaitre *et al.* (*Cell*, 86(6):973-83) that Jules Hoffmann was awarded the Nobel Prize in 2011.

Lemaitre told *Le Monde* (10/12/11), “I’m disappointed that the jury chose a personality who was very far from the reali-

ties of experimental research, someone who knew how to gain personal benefit from discoveries made by other researchers. He does not correspond to my model scientist, who is closer to the lab bench and shows more respect for other people’s work. The Toll story was the fruit of a complex adventure involving numerous laboratories. Scientific marketing and networking has certainly played a predominant role in attributing the credit.”

Lemaitre has created a website (www.behinddiscoveries.com) where he presents extensive documentary evidence to support his claim. He had been wanting to protest for a long time but it was the award of the Nobel that finally precipitated his response, “I know some of you may think this is a little too late but this has not been easy for me.”

I have already discussed the key points of Lemaitre’s case elsewhere, in my LT online article “A Nobel Prize not Immune from Error?” (www.labtimes.org/editorial/e_270.html). In this current article, I will present the results of my own investigation into the research career and practices of Jules Hoffmann. At the end,

you can judge for yourselves whether you think he merited the Prize.

The main accusation

“Subsequent to the publication of my Toll research (and my departure from the lab) Jules Hoffmann never gave me enough credit for it. I was informed of this by colleagues who heard his talks and confirmed this through my own personal investigations. Immunologists ought to understand just how far Jules Hoffmann was from the realities of experimental work. This is in total contrast to the enormous respect that I have for other members of the Strasbourg research institute who produced high quality research,” Lemaitre wrote to *Science* magazine (*Science*, ‘Nobel Prize for Immunologists Provokes Yet Another Debate’ 16/12/11).

“In France,” Lemaitre says, “it is hardly a secret that Jules Hoffmann has been mostly involved in networking and communication rather than a dedicated experimenter. He was far away from the bench work before, during, and after my work on Toll. To put it simply, he has been the wonderful

spokesperson for a fantastic lab but in reality, in the background, the good science and creative work was performed by other researchers. Moreover, his powerful place in the field makes him an unavoidable part of the domain. But is this really sufficient to win a Nobel Prize?”

The main point is that Jules Hoffmann claimed overall credit, not just for Lemaitre's discoveries but also for key results from other talented young researchers in the lab. He did this by promoting himself when presenting the results in conference meetings, seminars and written reviews. Lemaitre provides examples of this on his website. His main tactic was never to name individual researchers in association with their discoveries but instead to refer to an impersonal “group” effort. Published results are always the work of “this laboratory” – “we have”, “we did”, “our” research. The only name to retain is that of the lab director, presenting **his** version of the story.

Lemaitre explains how “in seminars, Jules Hoffmann never mentions my contribution as the key step. The story is described

as an «épopée» (“epic”) that started a long time ago and my contribution, i.e. the one that has made him famous and got him the Nobel Prize, is never really acknowledged. I am usually cited in a general acknowledgment with the photos of all the other lab members at the end of the talk.”

Uninvited

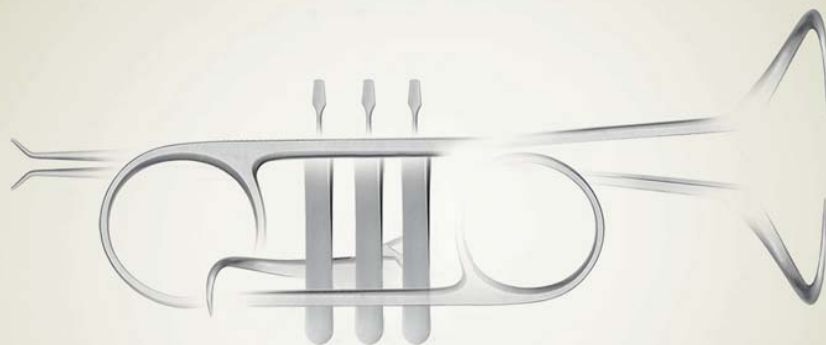
In addition, Hoffmann seems to have made sure that Bruno Lemaitre was not present to contradict him at meetings. In 1998, Lemaitre set up his own research group near Paris continuing to do highly respected research on immunity, yet, “During the ten years that followed the 1996 *Cell* paper, I was rarely invited to present at ‘immunology’ meetings, especially at key meetings on innate immunity that were frequent at that time. I was certainly never invited to any meeting organised by Jules Hoffmann.” It was not until 2006, ten years after ‘the’ *Cell* paper, that Lemaitre was finally invited to Toll meetings where, at last, he could meet some of the main vertebrate immunologists.

To date, Jules Hoffmann has not replied to Lemaitre's accusations. He did not answer queries from the *Times Higher Education* when they wrote about the matter (‘Hoffmann's Nobel input ‘distant’ from bench work’ 15/12/11, ‘Did Hoffmann take Nobel for the team?’ 22/12/11), nor has he replied to *Lab Times*' request.

Science magazine managed to get a few words when they phoned him. He told *Science* that Lemaitre had informed him of the website but that he has not visited it because colleagues warned him he might find it “distressing” (‘Nobel Prize for Immunologists Provokes Yet Another Debate’ 16/12/11).

I decided to investigate further. I found abundant evidence to support Lemaitre's description of Hoffmann as the lab's administrative director, rather than an active researcher. Other biologists have confirmed this view, including Pat Simpson (now Professor of Comparative Embryology in Cambridge), who had a fly research group from 1983-2002 at the nearby IGBMC in Strasbourg. She said Hoffmann was “more of

Instruments that are music to your **hands**.



FINE SURGICAL
INSTRUMENTS
FOR RESEARCH™

SHIPPING GLOBALLY
SINCE 1974

Request a catalog
at finescience.de or call
+49 (0) 62 21 – 90 50 50.

F · S · T®
FINE SCIENCE TOOLS

an administrator and communicator than a bench scientist. While he deserves credit for administering the unit, he should have highlighted Bruno's role in the research, as well as others, more forcefully." (*Times Higher Education* 15/12/11).

The strangest thing I found, however, was that Jules Hoffmann claims to have been actively involved in immunity research from the very start of his research career in 1963. I've read his PhD thesis and looked at his publication record – neither of them supports these 'recollections'.

"A long story"?

Jules Hoffmann gave a telephone interview to Nobel Media two days after the official announcement that he had won the Prize (05/10/11, www.nobelprize.org).

Interviewer: "What started you studying immunity in flies anyway?"

Hoffmann: "It's a long story – we started looking at antimicrobial defences in insects, initially in grasshoppers, in the 1960s. And the reason we did that was that I did my

avoid microbes in the environment; there were no aseptic conditions. My thesis supervisor suggested that I take up the question of what helps the insects fight infections. And so that's what, then, I did. And initially it was experimental biology with X-ray treatments and so on. And from there, we got into the biochemistry of the effector molecules and then we discovered the antimicrobial peptides and so on."

The 1960s bench scientist

Jules Hoffmann was born in 1941. He completed his undergraduate studies in Luxembourg in 1963, then moved to the University of Strasbourg, France. In 1964, having become a salaried CNRS scientist, he began his thesis (research jobs were a lot easier to get in those days!). Under the supervision of Pierre Joly, head of the Laboratory of General Biology (LGB), he obtained his PhD ('Docteur ès sciences naturelles') on 22nd September, 1969 (age 28).

Hoffmann's doctoral thesis was on blood cells in the locust ('Etude des cellules

study of locust blood cells using the optical microscope. He describes four different cell types.

The second part describes how he bled locusts – he removed up to 80% of their blood – in order to stimulate production of new blood cells that he then quantified under the microscope. In the third section, he looked for the blood cell-producing organs before and after he bled various locusts and crickets (*Gryllus bimaculatus*).

Finally, he looks at the endocrine control of blood cell production. However, this is still at a time when no one knew, which parts of the insect were actually producing the hormones, so Hoffmann's study involved insect surgery. He removed organs (the corpora allata, pars intercerebralis and corpora cardiaca) and looked to see if their absence had any effect on the insect's capacity to generate more blood. After his blood cell quantification, he concluded that the corpora allata had the most direct effect.

Early works

Hoffmann lists 14 articles he published from his doctoral work. These are all written in French and are mostly two to three page notes in French journals. However, only two of them can really be considered full research articles: *Z Zellforsch Mikrosk Anat*, 1970;106:451-72 and *Gen Comp Endocrinol*, 1970;15:198-219. In the latter, Hoffmann notes that cardiectomy (removal of the heart) only slows down the differentiation of two types of blood cell but that this is 'almost entirely blocked' when the locusts are not fed.

Nowhere in his PhD thesis is there any mention of infection, bacteria, or anything remotely resembling immunity. When the function of blood cells is mentioned it is with respect to insect development. For example, during insect moulting, blood cells phagocytose larval cells to make way for adult structures.

Why then does Hoffmann claim to have had links to immunity in the 1960s?

For example in 1993, as administrative director for the CNRS research lab, URA 1490 (previously the LGB), he edited its bi-annual activity report for the CNRS. Such official reports explain what research has been done during the previous two years, with a description of plans for future research. The 1993 report begins with a one page essay on the 'History of the Laboratory of General Biology'.

In the second paragraph, he says Professor Joly had noted that insects did not get



From locust endocrinology to *Drosophila* immunity in absolutely no time...

PhD in the laboratory, which was working on grasshoppers and grasshoppers were, at that time, still a very big plague in countries, which were administered by the British and the French. And, so, our laboratory was doing endocrine studies, that is to say transplanting endocrine tissues or organs from one insect to the next, when they noted that it was never infection coming up – never *opportunistic* infection coming up – without any special care being taken to

sanguines chez *Locusta migratoria*'). It is in two volumes with 102 pages of text (including bibliography) in the first and 51 photographs of locust blood cells in the second. In the introduction, he explains he is studying the postembryonic development of blood cells in order to understand more about how insect hormones regulate the physiology of the blood system (endocrinology).

His experimental work is divided into four parts. The first is a morphological

bacterial infections. “Curious to know the explanation for this antibacterial resistance, he gave Jules Hoffmann as subject for his thesis the study of blood cells and their role in immune defence.” He then writes that with the help of Aimé Porte, a cytophysiologist, he discovered a reticulo-hematopoietic organ in the locust. “Selective irradiation of this tissue with X-rays had two dramatic consequences: the insects lost their capacity to resist bacterial infections and the moulting cycles were blocked in irradiated larvae.” The same essay appears in the 1997 CNRS report (the lab was now UPR 9022).

A 1974 paper from Porte’s lab did look at the development of the prothoracic gland

after irradiation (but at the time the prothoracic gland had just been identified as the organ producing the moulting hormone, ecdysone – *Science*, 183(4124):529-30; *PNAS*, 71(3):793-6). Hoffmann is the third of four authors. No mention of infection. In another 1974 paper (*Gen Comp Endocrin*, 22(4):489-98), it is simply noted that irradiation-sensitive cells appear to be necessary for hormone transport and/or mode of action.

Grasshopper infections

In September 2011, when Hoffmann was awarded the Shaw Prize (‘Asia’s Nobel’), he wrote the ‘Autobiography of Ju-

les A. Hoffmann’ (www.shawprize.org – 28/09/11). In it, we learn that “Professor Joly offered me a position with the French National Research Agency (CNRS) and I started studying the antimicrobial defenses in grasshoppers. During the studies which led to my PhD defence in 1969, I focused on the origin of blood cells in grasshoppers and discovered a well-developed blood-forming tissue (hematopoietic tissue) in the vicinity of the heart vessel. Selective X-ray treatment of this tissue resulted in a massive septicemia.”

He then says that he went to Karlson’s lab in 1973 “while our group in Strasbourg started analysing the biological and biochemical contexts of infections in grasshoppers.”

In the CNRS magazine for December, there is a three-page article based on an interview with Jules Hoffmann (p. 6-8): “Who would believe that when the young student in natural science at Strasbourg university decided to do his thesis on the mechanisms of antimicrobial defence in locusts, he was going to revolutionise the understanding of innate immunity?” It seems “this choice of thesis was not due to chance.” Indeed! Later he says, “Looking back, I sometimes regret that during all these years I neglected studies on the mechanisms of antimicrobial defence in favour of endocrinology.” Similar quotes have appeared elsewhere in the press.

The insect endocrinologist

In 1973, four years after he completed his PhD, Hoffmann spent a year in Peter Karlson’s lab in Marburg, Germany (salaried CNRS scientist, age 32). Karlson had discovered the insect hormone, ecdysone, in 1954. It was only in 1974 that the prothoracic gland was finally identified (elsewhere) as the organ secreting it.

This was the only time Hoffmann went to another lab to do research. Subsequently, he directed a research group that investigated insect endocrinology and ecdysone metabolism, publishing over 50 articles during the next 20 years.

Hoffmann’s biography at the French ‘Académie des Sciences’ (founded 1666) makes no mention of any early interest in immunity. Perhaps it was written in 1992, the year Hoffmann became a Member. Instead, it notes that Jules Hoffmann’s main scientific work was on the neuroendocrine control of development and insect reproduction. He looked at the “biosynthesis and metabolism of ecdysone, the steroid hormone controlling insect moulting. His

The ‘PI’ and the ‘IP’ argument

Some commentators, particularly from the US, have argued that even if Hoffmann and Lemaitre shared credit for the Toll discovery, Hoffmann should win as ‘PI’ (Principal Investigator). However, was he really a PI in the US sense? In the US, a PI is under enormous pressure to attract research funds, endlessly writing grant applications for their research projects. Besides funding scientific experiments, this money is used to directly pay the lab’s graduate students, postdoctoral researchers and technicians.

In the French research system, CNRS scientists and university teacher-researchers have stable, salaried jobs. There is an annual block grant given to research labs based on the number of permanent researchers (although reforms since 2007 are changing this – see *LT* 01/08 and 02/08). PhD students receive government grants. Furthermore, Bruno Lemaitre actually financed himself during his first year in Strasbourg from student teaching/research grants he’d received in Paris.

Meanwhile, French research scientists have their own independent research projects, approved by the CNRS and in harmony with the lab unit’s general theme.

This is not quite the same stressful pressure that a PI, at the head of a lab group in the US, or even the UK or Germany, must face. Indeed, the earliest mention of a successful research grant in Hoffmann’s c.v. dates from 1995 – he shared (‘co-coordinator’) an HFSP grant with some big names from immunology: Charles Janeway (Yale), Alan Ezekowitz (Boston), Shunji Natori (Tokyo) and Fotis Kafatos (EMBL).

If instead of a scientific discovery we were talking about a patent dispute, the question of credit would be assessed on the basis of ‘Intellectual Property’ (IP).

In such a case, the legally binding judgement is often based on dated laboratory records of the experimental work. This determines who has made the discovery first and who, therefore, has the legal right to a patent and any subsequent commercial royalties.

Bruno Lemaitre says he still has all his Strasbourg lab books and many associated documents (for example, details of requests for fly mutations): “I still have all of my laboratory notebooks in my office with me – neither of my lab chiefs ever looked carefully at my data.”

Not that there is a patent dispute about Toll. Instead, this is about fair credit and just recognition for good scientific research. However, Hoffmann may have benefited financially from his enhanced reputation. For example, would investors have otherwise been so willing to support ‘Entomed’, the company he founded in 1999? Entomed absorbed over 20 million euros of investors’ money before going bankrupt in 2005.

And then there’s all that prize money for his immunity research. Starting with the Coley in 2003 (\$5,000), these included the Balzan (2007 – half of CHF750,000), Keio (2010 – half of ¥20 million), Shaw (2011, third of \$1million) and Nobel (half of €600,000). Amazing what a good research reputation can do for you! But was it justified?

research led to the discovery of a maternal contribution of ecdysone in the form of phosphoconjugates and to the understanding of their function in the generation of the embryonic cuticle." This matches his publication record through to 1991 (age 50).

The real immunity link – His wife!

In fact, the Hoffmann that worked on insect immunity was Daniele, Jules Hoffmann's wife. Her research career is fairly modest. She started as a lab technician. In between having their two children (in 1970 and 1974), she obtained a position with the CNRS (1973) in the same lab and began doing research. In 1976, she first published a note on the 'Role of phagocytosis and soluble antibacterial factors in experimental immunization of *Locusta migratoria*', in which she says that larvae "can be protected ('vaccinated') against lethal doses of *Bacillus thuringiensis* by previous injections of low doses of this pathogen." (*C R Acad Sci Hebd Seances Acad Sci D*, 282:1021-4). That's to say, she was looking at the possibility of adaptive, not innate, immunity.



Did he rightfully enjoy his "Lobster with pickled winter vegetables and Jerusalem artichoke purée" at the Nobel banquet in December?

Meanwhile, Sweden's Hans Boman, the researcher who really "wondered why in-

sects exposed to pathogenic bacteria don't get ill", published his breakthrough report on "Inducible antibacterial defence in *Drosophila*" (*Nature*, 237:232-5). In 1981, Boman's lab was also the first to report the isolation of antimicrobial peptides from insects and presented the first sequenced peptides, cecropin A and B (*Nature*, 292:246-8).

In 1979, Daniele Hoffmann duly went to Boman to learn techniques. Her next paper, in 1984, describes 'Detection of distant antigenic relationships between insect and bird lysozymes by ELISA' (*J Mol Evol*, 21:14-8).

It was around this time that some younger researchers started working with her. By 1988, they had purified, sequenced and cloned some antimicrobial peptides from *Phormia* (blow fly) larvae (*Eur J Biochem*, 171:17-22; *Eur J Biochem*, 182:423-7). Subsequently, their research group switched to *Drosophila*. Two key researchers at this time were Philippe Bulet, who purified a whole succession of novel antimicrobial peptides from *Drosophila*, and Jean-Marc Reichhart, who used molecular biology to look at their genes. This brings us to

Be informed. Be inspired. Be there.

Frankfurt am Main · 18 – 22 June 2012

ACHEMA 2012

www.achema.com

- +++ 4,000 exhibitors from 50 countries +++
- +++ 180,000 participants from 100 countries +++
- +++ 30,000 executives +++
- +++ 140,000 m² exhibition space +++
- +++ 900 lectures +++



1992 when Bruno Lemaître arrived in the lab to do the first genetic analyses.

Hoffmann has told a story that seems to be at odds with the facts. Yes, he worked on insect blood cells, but his largely microscopic and physiological studies were all directed towards questions of endocrinology. Wouldn't it have been simpler (and more accurate) to have said something along the lines of: I worked on insect endocrinology for 30 years. In the mid-1980s, a small group in the CNRS lab that I directed began to make the first of a significant series of discoveries in insect immunity. In 1991, the rest of the lab agreed to switch from endocrinology research to insect immunity?

Why did he feel the need to tell a modified tale from 1993 on? Was the story for vertebrate immunologists with whom he had begun to establish contacts?

Perhaps it doesn't really matter that he claims an active involvement in immunity research since 1963. But what other details might have been adjusted to present himself in a more favourable light?

The administrator

In 1978, Jules Hoffmann succeeded Pierre Joly as administrative director of the Laboratory of General Biology. This was a 'mixed' lab, combining teacher-researchers from the University of Strasbourg and full-time CNRS researchers. His research group continued to make advances in their studies of ecdysone biochemistry and insect endocrinology. However, it seems unlikely that Jules Hoffmann did much experimental work himself, and for cause! A look at his c.v. reveals that he took on a considerable number of administrative tasks outside the lab.

For example, he was often in Paris, either as a member of the CNRS Life Sciences steering committee (1983-91/1995-2000) or as President of the CNRS national committee controlling Developmental Biology researchers and their activity (1983-91/1995-2000); he was also on the Research council of the Ministry of Higher Education and Research (1994-97). With-

in the University of Strasbourg, he directed the DEA courses in cellular and molecular biology (one-year research diplomas that select future PhD students) from 1990-2002. And there's the international travel – a list of CNRS-approved official conference 'missions' includes: 40 trips to the US (10 months in total), Germany (20 trips, 6 months), the UK (15 times, 2 months), China (12, 2 months), Japan (15, 2 months), Canada (8), Russia (6), etc.

In 1993, his renamed CNRS lab, 'UPR 9022' ('Insect immune response and development') had grown to 30 'statutory' staff



A fateful meeting of two men who are not without their controversies, King Carl XVI Gustaf of Sweden (right) and Jules Hoffmann (left).

(i.e. with permanent jobs) – 9 CNRS researchers, 6 university teacher-researchers, 5 research engineers and 9 technicians.

There were also 4 PhD and 9 DEA students. In the same year, he became director of the CNRS Institute of Cellular and Molecular Biology (IBMC), incorporating two other CNRS labs (UPR 9002 and 9021), all under his overall administration.

Last author credits

Lemaître admits he was naïve about the co-author question, "It did not seem important to me since I was obviously the first author." Some journals now ask authors to briefly explain their contribution to research articles. This was not the case then but Lemaître now details the respective roles of his four co-authors (text S2 on his website).

He states that he "ordered the Toll pathway mutant lines, designed all the experiments, organised the work with other people, analysed all the experiments, and wrote the paper". Meanwhile, the two PhD students, Emmanuelle Nicolas and Lydia Michaut (2nd and 3rd authors), aided with his Northern blots; Jean-Marc Reichhart's name appeared 4th as group leader, and Hoffmann helped write the final version of the manuscript (last author).

By a cruel irony, it was at around this time that the lab's perception of 'last author' status changed. Prior to 1996, Hoffmann appears as last author on many papers where closer inspection suggests he was not the main researcher. For example, Philippe Bulet's PhD student, Pascale Fehlbaum, published two important articles on antimicrobial peptides (*J Biol Chem*, 269(52):33159-63; *PNAS*, 93(3):1221-5). Yet Bulet, 'PI' on peptide purification since 1991, only appears as 2nd author,

while Hoffmann is last. After this date, the 'PIs' appear to have asserted their rights – Lemaître was senior author when his stu-

OPTICAL FILTERS

For fluorescence spectroscopy



AHF ANALYSENTECHNIK

OUR EXPERIENCE ... YOUR PROFIT!

www.ahf.de :: info@ahf.de

dent, Emmanuelle Nicolas, published her two papers. Subsequently, Hoffmann is in before last position.

Why weren't the French researchers more concerned before? Perhaps because the order of authors did not have the same significance it had acquired elsewhere. They already had stable, permanent research positions. Besides, the CNRS did not use 'bibliometry' to judge their activity until later. Sure, they had to publish papers for promotions but the order of authors was not so important. How times have changed!

Re-interpreting history?

When he received the Shaw Prize, Hoffmann wrote, "It goes without saying that the scientific achievements of our laboratory over the many years, as recounted above, are to be credited to a long list of collaborators of high intellectual and human caliber." But he never does quite manage to say who they are!

One week later, Jules Hoffmann learned he had been awarded the Nobel Prize for Bruno Lemaître's 1996 *Cell* paper. Instantly, he tried discussing the participation of Lemaître in the Toll discovery.

It wasn't easy for him.

In his Nobel Media interview, two days later, he recounts "we hired in a *Drosophila* geneticist, Bruno Lemaître and later Dominique Ferrandon, and the team then became both biochemistry, cell biology, molecular biology and molecular genetics" and so on. Finally, at a given moment ... "Well,

the way we came to Toll was through the work of Nüsslein-Volhard ..." (Christiane Nüsslein-Volhard had already won the Nobel Prize in 1995).

Initially, he told the French press, "With notably Bruno Lemaître and Jean-Marc Reichhart, we found a receptor, a molecule, that recognised substances common to many bacteria." (*Le Monde* 4/10/11). By December 2011, he had decided that "with Bruno Lemaître, we succeeded in showing that the receptor Toll..." (*Le Point* 14/12/11).

Meanwhile, JM Reichhart accused Lemaître of "re-interpreting history" (*Science* magazine 16/12/11). But Reichhart agreed that Hoffmann was indeed a skilled communicator, "If he had been less talented at telling the Toll story, the Nobel Prize would not have happened at all! You have to tell the people what you have discovered. Jules is a very good ambassador for the field of innate immunity."

Lessons learned

Reichhart succeeded Hoffmann as head of the CNRS lab in 2006. He appears to have learnt a thing or two. In his research profile (on the IBMC website), he explains how in 1992 he became interested in *Drosophila* embryonic development and the formation of the dorsoventral axis, "In 1996, this led me to the Toll discovery (Lemaître *et al.* *Cell* 1996)..." No mention of Hoffmann there!

JEREMY GARWOOD

ONE FINE DAY IN THE LAB...

BY LEONID SCHNEIDER



ROTH supplies ready-to-use reagents ...



... and
CHEMICALS

for everyday use and
special applications.



All products
can also be found in our
INTERNET-SHOPS!

+ News
+ Special prices

Labware - Life Science - Chemicals

Carl Roth GmbH + Co. KG

Schoemperlenstraße 3-5 - 76185 Karlsruhe
Tel: (+49)721/5606 0 - Fax: (+49)721/5606 149
info@carlroth.com - www.carlroth.com

