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Review Article

Commentaries on the Nature of Virus Species and Viral Vaccines and on Anglicized and New Latinized Species Names Used in Viral Taxonomy

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Abstract

Although one often talks of immunogenic viruses as being capable of generating protective antibodies against viral infections, it is actually the immune system of vaccinees that triggers in the host a series of reactions with B cell and T cell receptors that eventually leads to immune protection.

The chemical nature of antigenicity is often confounded with the biological nature of immunogenity and instead of designing a vaccine immunogen capable of generating protective Abs, investigators are sometimes only improving the binding reactivity (i.e. antigenicity) of a single viral epitope.

It is now well-established that the X-ray crystallographic structures of bound epitopes-paratopes visualized in an antigen-Ab complex are usually very different from the structures in the free binding sites before they had been altered by the mutual adaptation and induced fit that always occurs when the two partners interact. This means that the structure of the epitope that is required for inducing neutralizing antibodies by vaccination must be that of the free unbound epitope site, although investigators often opt for using an engineered bound epitope structure for vaccination purposes.

Keywords: *ICTV proposals, Immune systems but not viruses elicit protective antibodies, Definition of virus species, Anglicized non-latinized virus names, Latinized binomial names*

The Nature of Virus Species

Viruses are chemical objects which parasitize the genomes of animals, plants and microbial organisms that they have infected, and it is these living infected host cells that reproduce the viruses since viruses themselves are not alive [1-47]. Viruses are classified by using the hierarchical conceptual taxa known as species, genera, families and orders created by taxonomists which are used in all biological classifications [4,17,23,33]. The members of the lowest virus species class are also members of the classes above it and the relation between a lower taxon and higher ones is called class inclusion. Class inclusion avoids the need to repeat the properties used for defining higher taxa in the definition of the lower taxa that are included in them. Because of class inclusion, higher taxa such as genera and families always have more members than species which means that they require fewer properties (for instance the type of genome replication) to meet the qualification for membership. The logical principle which requires that it is necessary to increase the number of qualifications for defining a species actually invalidates the widespread belief among virologists that it is possible to define a species by the presence of a single short nucleotide in the viral genome [1,11,28], Since a virus species always has fewer members than genera and families, it is actually imperative to use several different properties for demarcating a new species [36]. Since the concept of a polythetic species cannot be described, it can only be defined by listing the number of the species-defining properties of its members which are not all necessarily present is every member of a polythetic species. Only monothetic species are defined by a few properties that are both necessary and sufficient for membership in the class, whereas the members of a polythetic class do not have a common property present in all its members. The term polythetic refers to a particular distribution of properties in the class and the members of the class do not themselves possess polythetic properties [3,15]. Gibbs and Gibbs et al. 2006 argued that the term polythetic should be removed from the species definition because they viewed a virus species as a monothetic class whose members necessarily share a common property inherited from its ancestors and they removed the term polythetic from the definition of a virus species [11]. The species concept has remained controversial in biology [22] and in 1989 the following definition of virus species was proposed: "A virus species is a polythetic class of viruses that constitute a replication lineage and occupy a particular ecological niche [31]. This definition was approved by the International Committee on Taxonomy of Viruses (ICTV) [26].

The ICTV is a committee created in 1966 by the Virology Division of the International Union of Microbiologial Societies which is responsible for the development of a viral taxonomy and nomenclature and it has so far published ten Reports describing thousands of viral taxa [2,7,8,10,16,20,21,24,32,42]. The first Reports advocated a Latinized viral nomenclature for virus species which was abolished after a few years and was replaced by Anglicized species names.

It is important to differentiate between properties useful for defining a virus species and properties used for identifying individual viruses. Species taxa are defined intentionally by what is called the intention of the class which refers to the properties that provide the qualification for membership in the species. The so-called extension of the species class refers to the set of all the concrete members of the class. Since the intention of a class determines its extension, the extension of a class can only be determined if it is possible to distinguish members from non-members, which means that the intention must precede the extension [18]. A species taxon must therefore be established by taxonomists before it become possible to ascertain if a sufficient number of species-defining properties are present in an individual virus to make it a member of the species. Since monothetic species classes are defined by one of very few properties that are both necessary and sufficient for membership in the class, the claim of Gibbs and Gibbs (2006) that it is possible to rely on the presence of a single nucleotide motif for demarcating a new monothetic species is not realistic because it would be necessary to know beforehand that this motif is present in all the members of the species and absent in other species; this means that the extension would need to precede the intension which is of course impossible [11].

Bionominalism in taxonomy views species as individual and historical entities [15] that form cohesive wholes and accepts that a species lineage is a concrete object although it is a case of logical reification (i.e. viewing an abstract concept as if it were an object). The relational concepts of ancestry and lineage are actually not real objects and they cannot act upon each other unless they exist at the same time [18] Species also cannot descent from each other in a literal sense since only concrete organisms and viruses can do this. A species must therefore first be established and defined by taxonomists before it becomes possible to allocate a virus to a species by using so-called diagnostic properties. Such specific tools can be obtained by developing polyclonal or monoclonal antibodies against viruses that are members of the species although such antibodies are not species-defining properties that could have been used for demarcating the species taxon initially.

The term species in virology is used to refer 1) to the many individual species classes created by virologists that have viruses as their members and 2) to the lowest "category" in a virus classification which is the class of all the species that virologists have demarcated. The 1989 polythetic species definition actually refers to the species category which is of little help to virologists when they attempt to allocate viruses to a new species taxon.

The members of a polythetic virus species always share several relational phenotypic properties that arise by virtue of relations between the virus and its hosts and vectors which become actualized only during the transmission and infectious processes. These species-defining properties are easily altered by a few mutations which could modify the host range, the pathogenicity and cell and tissue tropism, and taxonomists often have to create species by drawing boundaries across a continuum of phenotypic and genetic variability.

Anglicized Non-Latinized Virus Species Names and Latinized Linnaean Binomial Names

Anglicized non-Latinized binomial names (NLBNs) for species were initially introduced by Fenner [8] by replacing the terminal word virus that occurs in all English virus names with the name of the genus to which the virus belongs and will also ends in virus. Measles virus for instance became a member of the italicized species *Measles morbillivirus* and thousands of such names became very popular since genus names and English names of viruses are well known to all virologists. This is due to the fact that the major reference books in virology as well as the numerous ICTV Reports published during the last 45 years were written in English which is the predominant communication language used by scientists. In 2016, the ICTV initiated a so-called thought exercise in which they converted currently existing 175 NLBNs into an inverse Latinized Linnaean binomial format (LLBNs) that consists of the genus name followed by a Latinized epithet [25]. Adelaide River virus for instance became the NLBN Adelaide River Ephemerovirus while the LLBN was Ephemerovirus fiumeadelaidense. NLBNs are easily recognized by virologists and quarantine officials whereas the epithets may be less obvious. The ICTV nevertheless approved the introduction of LLBNs [42] and the ICTV Study Groups were given the task of converting thousands of NLBNs into the new LLBN format which is expected to be completed in 2013. No explanation was presented for removing thousands of popular Anglicized NLBNs for non-living virus species and for following the Linnaean format used for

living organisms. Virus species were redefined as groups of living physical isolates in line with the definition of all the biological species of organisms as being abstract conceptual classes [42].

Adrian Gibbs has for years been a regular critic of ICTV proposals and decisions [11-13] and in a recent review [14] he analyzed two proposals that the ICTV had presented as a consensus statement [29] and a consultation [27]. With the rapid development of high-throughput sequencing methods for viral genomes, large numbers of virus-like gene sequences called metagenomes had been obtained from a variety of living materials.

The ICTV Executive Committee reacted to this avalanche of sequences by organizing a workshop attended by viral taxonomists who produced a so-called consensus statement that accepted that these virus-like metagenomes corresponded to viral genomes that should be incorporated in the existing ICTV taxonomy, in spite of the absence of any known biological properties of what were nevertheless referred to as sequence-viruses [47]. Since the hosts and vectors linked to most of these sequences had not been identified these sequence-viruses were indeed only sequences. Gibbs [14] reminded virologists that the ICTV taxonomy should be a taxonomy of viruses but not of virions nor of gene sequences. Gibbs endorsed the view that viruses are subcellular organisms with a two-part so-called life cycle, namely virions and virus-infected host cells which is a terminology proposed earlier by Forterre [9], in spite of the fact the majority of virologists still consider viruses to be non-living genetic parasites [17] devoid of any metabolic activity [36]. Many virologists remain convinced that species and other taxonomic classes in virology and biology are

not abstract constructs of the human mind and they do not accept that conceptual taxonomic classes can have tangible, material objects and organism as their members. In 2013 the ICTV has ratified the following species definition: A species is a monophyletic group of viruses whose properties can be distinguished from those of other species by multiple criteria [1]. This definition which is applicable to any taxonomic class is incompatible with the logic of classes based on class inclusion used in all biological classifications and this has given rise to numerous debates [16,36].

The Immune System of Vaccinees rather than Immunogenic HIV Viruses are Able to Elicit Anti-viral Protective Antibodies against AIDS

Although one often talks of immunogenic viruses as being capable of generating protective antibodies against viral infections, Although it is actually nearly always the immune system of vaccinees that triggers in the host a series of reactions with B cell and T cell receptors which eventually leads to immune protection [30], many vaccinologists have for many years elucidated the structure of the antigenic epitopes in virions because they assumed that these epitopes when used as immunogens would be able to induce protective antibodies against viral infection. They used an approach [5] called structure-based reverse vaccinology (SBRV) to determine the structure of complexes between viral epitopes and neutralizing Monoclonal Antibodies (nMAbs) obtained from patients infected for instance with HIV, in an attempt to design HIV immunogens by reverse molecular engineeing that would elicit neutralizing antibodies (nAbs) [39]. This approach was called reverse vaccinology because investigators assumed that if an antigenic epitope did bind strongly to an nMA, it would also be able to induce similar nAbs when used as a vaccine [34]. They also assumed that when an epitope binds to a free antibody molecule, the recognition process is exactly the same as when that epitope (which is now called an immunogen) binds to a cognate B cell epitope receptor embedded in a lipid membrane.

An additional problem with the SBRV approach was that it ignored the fact that all Abs are always polyspecific or even heterospecific [35] and that antigenic and immunogenic regions in a protein antigen are often located in different parts of the molecule [39].

Many constituents of immune systems are known to control the types of Abs that are produced, such as the host Ab gene repertoire, as well as other regulatory mechanisms, although investigators may only pay attention to individual recognition processes between single epitope and paratope pairs. When it was found that HIV Env epitopes recognized by affinity-matured Abs obtained from HIV-infected individuals did not bind the germline predecessors of these Abs [30,44] it became obvious that potential vaccine immunogens would only be discovered if one took into account the extensive Ab affinity maturation that is required for obtaining Abs that neutralize HIV. A huge research effort was then initiated to analyze the innumerable maturation pathways that can lead to protective Abs [19].

The chemical nature of antigenicity is often confounded with the biological nature of immunogenity and instead of designing vaccine immunogens capable of generating protective Abs, investigators may only attempt to improve the binding reactivity (i.e. antigenicity) of a single viral epitope.

Epitopes in antigens and paratopes in immunoglobulins are rather flexible and dynamic binding sites and their plasticity has been compared to flexible keys and adjustable locks [6]. It is now well-established that the X-ray crystallographic structures of bound epitopes and paratopes visualized in an antigen-Ab that are mostly very different from the structures in the free binding sites before they have been altered by the mutual adaptation and induced fit that always occurs when the two partners interact [43]. The epitope structure observed in the epitope-paratope complex is therefore a poor experimental model for trying to elicit again the type of Ab that was used in the crystallograhic binding experiment. It is in fact even difficult to comprehend why adepts of SBRV continued for many years to try to develop HIV vaccines using that approach, since the crystallographic structure of the bound model epitope clearly showed that it was unlikely to be able to elicit the type of protective Abs that is aimed for [35-37,40].

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