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Short Communication

# The Trivialization of Subviral Agents

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I don't think that many burghers of Delft in the Netherlands realized in1675 that one of their own would bring about a peaceful revolution that would forever change the way we look at the universe and particularly at its living inhabitants. For eons, we must have assumed---probably without much thought---that the biosphere, the realm of living beings, encompassed only beings that we could recognize with our senses. But when Antonie van Leeuwenhoek, a tradesman and scientist, looked with his self-built and improved microscope---an instrument invented only recently---at a drop of standing water, he must have been incredibly surprised, if not shocked, by what he saw: evidently self-propelled, living organisms swimming across the field of vision.

He had forever changed the emporium of life, adding to the visible living entities---the familiar plants, and animals---smaller, "subvisual" entities, never before dreamed to exist; he thereby founded the science of microbiology.

It was not until 1892 when the second major extension of the biosphere towards smaller organisms occurred. This time, it was a Russian scientist, Dmitri Iosifowitch Ivanovsky, who was assigned to look into a disease occurring in tobacco plants and who discovered that the disease was caused by a minuscule agent capable of permeating porcelain Chamberland filters, something which bacteria could never do. Thus, by discovering the first virus, the tobacco mosaic virus, he had initiated the emporium of "*submicroscopic*" entities and founded the science of virology.

The third, and probably last, major extension of the biosphere to still smaller entities was ushered-in in 1971 by the discovery of the *viroid* [1], the prototype of all "*subviral*" agents. This conclusion became strengthened whenever additional molecular properties of viroids came to light and when the discovery became recognized by the International Committee for Virus Taxonomy (ICTV) with the creation of a new order of *subviral agents* [2], which, in its latest release, encompasses 2 families, 8 genera, and 32 species [3].

As cogently expressed by Flores et al. [4], "viruses (and viroids) share the most characteristic property of living beings: In an appropriate environment, they are able to generate copies of themselves, in other words, they are endowed with autonomous replication (and evolution). It is in this framework where viroids represent the frontier of life (246 to 401nt) [nt = nucleotides], an aspect that should attract the attention of anybody interested in biology."

This attention occurred immediately in plant virology and considerably later in general plant science but, probably because of an excessive anthropocentric bias among investigators of animal (and particularly human) diseases, recognition of the new order was slow, despite the fact that, historically, many important biological discoveries have been made with plant, not with animal systems. Suffice it here to recall the molecular characterization of viruses, which was first achieved with tobacco mosaic virus isolated from infected tobacco leaves.

The term viroid was virtually absent in the animal (and medical) literature at times, when plant virologists and plant biochemists had already made great strides in elucidating many of the unique and intriguing molecular properties of viroids and their modes of replication---in research which resulted, among other achievements, in the first determination of the complete nucleotide sequence of a eukaryotic RNA [5].

Eventually, however, it was not their lifelike properties that

induced some investigators to take notice of viroids, but their particular size and lack of coding capacity, which, in their minds, immediately tagged them as members of a since discovered, huge, and rapidly growing, clan of cellular RNAs, the long, noncoding RNAs (lncRNAs). Never mind that viroids are lifelike, autonomously replicating, exogenous RNAs, whereas lncRNAs are lifeless endogenous transcripts of cellular DNA. Never mind either that the nucleotide sequences of subviral agents and lncRNAs do not display significant homologies.

It goes without saying that if subviral agents, despite their fundamentally different natures, are conflated with lncRNAs, they become trivialized, not only by being submerged in a sea of thousands of lifeless lncRNAs, but also by having to call them "lncRNAs plus life" or "infectious lncRNAs." Such comparisons are equivalent to defining humans as "mannequins with life"" or joining tennis balls with similarly sized oranges as one taxonomic unit, despite their fundamentally distinct natures.

Initially, the conflation of viroids with lncRNAs did not proceed smoothly. Cech and Steitz [6], for example, while eschewing internationally endorsed terminology, apparently listed viroids in a comprehensive table of non-coding RNAs, but ambiguously and incorrectly camouflaged them as "*autonomously transcribed* RNA that does not encode a protein..." (Presumably the authors meant "*autonomously replicating RNAs; if not*, what then is the identity of the "autonomously transcribed RNA"?) [Note to authors: if they know (as is implied) the identity of the DNA from which viroids are transcribed, they might wish to share this exciting information with the scientific community].

Katsaru et al. [7], in a paper entitled: "Infectious long non-coding RNAs," similarly evade the use of internationally designated terminology, except in the text, where one learns that they have written a review on viroids and other subviral agents. Again, the superficial ordering by size only and lack of coding ability distorts the true significance of viroids as the smallest autonomously replicating RNAs known.

Shimura and Masuta [8] at least mention internationally endorsed terminology, but still return to the largely meaningless conflating of viroids with lncRNAs. Their paper. however, is a useful review of the exciting work that deals with the viroid hosts' metabolic functions, as impacted by the viroid infection.

In a comprehensive review of plant lncRNAs, Gago-Zachert [9] alone fully recognized the difference between plant exogenous and endogenous RNAs, by stating that "[a]lthough viroids can be considered lncRNAs, based on their inability to code for proteins and on their genome size, they differ from the endogenous 'canonical' lncRNAs in several aspects, in contraposition to the endogenous lncRNAs, viroids are capable of autonomous replication, have an exogenous origin and several of them are able to induce diseases in their host plants." The author then properly divides her paper into two sections, endogenous RNAs and exogenous RNAs, that is, subviral agents.

Clearly, we are faced with a potentially serious problem of nomenclature, which can easily lead to confusion or worse. Fortunately, a solution immediately comes to mind: I propose that the term "lncRNA" be restricted to solely name endogenous lncRNAs, that is, DNA transcripts and that "lncRNA" not be used for naming exogenous RNAs (viroids or other subviral agents). For the latter, only the internationally endorsed (ICTV) nomenclature should be used.

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