A NOVEL APPROACH TO THE TREATMENT OF VIRAL INFECTIONS

FLAIG RŰDIGER MARCUS & LANGE-FLAIG IRÉN

The problem

Currently, (apart from hygiene measures) there are basically two antiviral approaches:

(I) The preventive approach by immunisation with a dead or weakened ("attenuated") virus or an immunogenic fragment thereof; and

(II) the curative approach employing biochemical-pharmacological inhibition of crucial viral functions with low-molecular-weight agents.

Both approaches are costly in terms of time and money and involve elusive molecular interactions, necessitating a lot of trial and error, which is why these approaches are particularly insufficient for emergent and/or mutation-prone viruses: The evolution of RNA viruses in particular – which include the vast majority of human pathogenic viruses, from covid and influenza through measles and rubella, Lassa and Ebola to rabies and polio – can simply outrun the development of therapeutics. The biochemical-pharmaceutical approach also suffers from the low number of usable molecular targets in the comparatively simple viral architectures, while the immunological approach is encumbered by the practical problems of supplying millions, possibly even billions of people with side-effect-free vaccines within a very short time.

Task at hand and approach to a solution

Our novel curative approach is based on linking a molecular mechanism with a pharmaceutical drug delivery system. This approach opens the perspective of developing effective and tolerable therapeutics for the highly specific treatment of acute (and chronic) viral infections, and most importantly, doing so sufficiently quickly and cheaply to open up a real prospect for combating even emergent and rapidly mutating viruses (including those specifically engineered as biological weapons).

Developed primarily with coronaviruses in mind, our approach should as a matter of principle be adaptable to all RNA viruses, most DNA viruses and possibly also certain non-viral diseases characterised by aberrant gene expression.

Strategy

The basic idea (illustrated in Fig. 2 on p. 4) is **indeed not to block certain essential functions of the virus, but to use them quasi-parasitically in order to trigger antiviral processes in – and only in – virus-infected cells**. In the interest of easier comprehension, this is explained below in more specific terms using the example of an agent against a coronavirus, although it is understood that it is not limited to this. A more general presentation can be found in patent application DE 10 2021 001 841.9; details are available and illustrated at http://www.sanctacaris.net/strategem.pdf (or as a LibreOffice presentation at http://www.sanctacaris.net/strategem.odp).

A word about viral architecture

A coronavirus particle consists of an information-carrying RNA molecule in an envelope structure ("capsid") made of proteins and lipids, which protects the RNA from environmental influences and effect its introduction into the target cells. The genetic information on the RNA is logically (though not physically) divided into several “chapters” and comprises building instructions for proteins, which can be roughly grouped into 3 functional areas:

A) Formation of the capsid for the construction of progeny viruses

B) Suppression of the host’s immune response

C) Replicase, a protein (enzyme) that selectively copies RNA for the construction of progeny viruses, starting each time at the “chapter start marks” of the coronavirus, which are found only on the viral RNA. This specificity has a dual consequence:

(i) The RNA of the host cell – which is of no interest to the virus – is ignored and only the viral RNA itself amplified to build progeny viruses; and

(ii) “working copies” of the individual “chapters” are produced, which makes it easier for the virus to coordinate its functions.

Furthermore, the viral RNA moreover includes a so-called **packaging signal** as “imprimatur”, which marks it for its packaging into the newly formed capsids (the packaging of the RNA naturally present in the host cell is just as little in the interest of the virus as the replication of this host cell RNA is).

NB: Since RNA is as a matter of principle not copied in cellular organisms, but is always formed by reading from a DNA template, all RNA viruses need to possess a replicase with such specificity for the respective viral RNA.

The generality of our approach is based on the fact that viruses basically use a packaging signal, and all RNA viruses use a replicase (and no mutations are possible that might circumvent this).

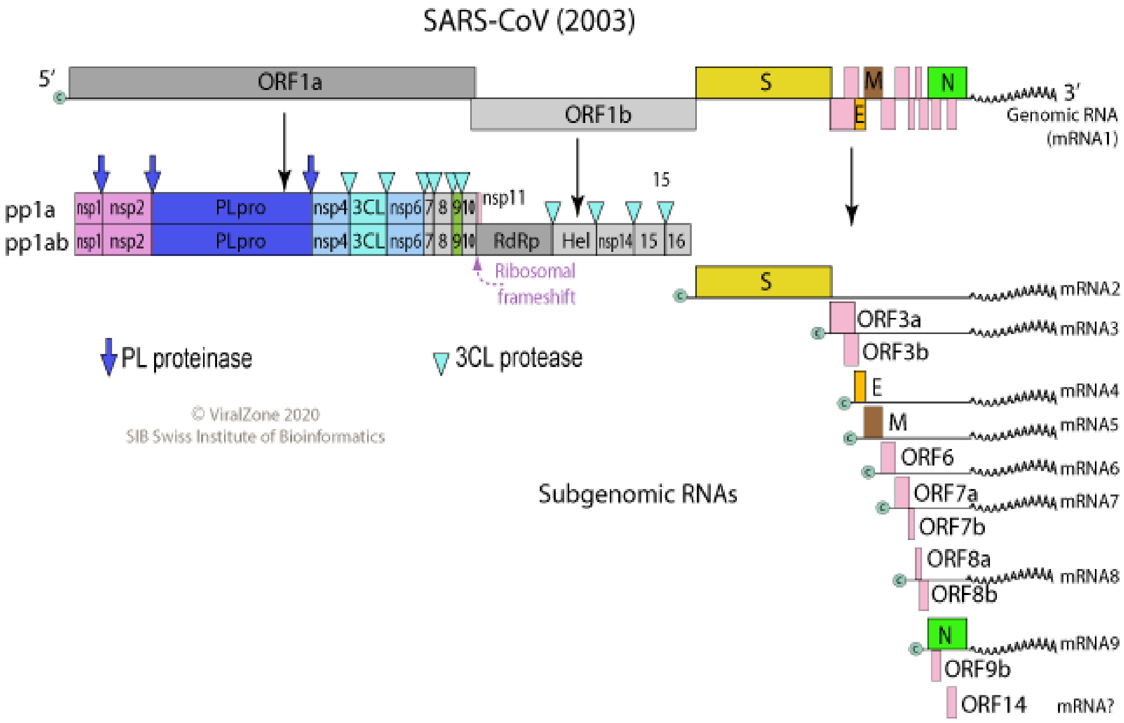

Fig. 1: Genomic structure of a coronavirus (Source: https://viralzone.expasy.org/30?outline=all_by_species) showing the “working copies”, technically referred to as “subgenomic RNAs”; the positions of the individual “chapter start marks” are marked with small © symbols. It is understood here that the © dots on the complete viral RNA (at the very top) are located at the same points and are shown only at the beginning of the respective RNA.

Mode of action

Our approach is that by means of a suitable pharmaceutical formulation, e.g. an inhalable liposome suspension, a synthetic **therapeutic RNA** is introduced into the patient's tissues, wherein the sequence of said therapeutic RNA basically comprises 3 elements:

№ 1) the "chapter start marks" of the coronavirus (one of the "©" points in Fig. 1);

№ 2) the packaging signal of the coronavirus;

№ 3) a functional area that interferes with the above-mentioned (→ p. 2) "functionality B" of the virus, i.e. in its turn disrupts the viral functions that serve to suppress the immune defence, e.g. by antisense/siRNA, reading frames for signalling molecules, proteases, ribonucleases, intracellular single-chain antibodies, etc. *(In coronaviruses, the main activity of replication takes place in so-called virus factories, compartments separated from the rest of the cell, so that e.g. activation of the interferon system is avoided; these factories are built up by the proteins Nsp3, Nsp4 and Nsp6, which are therefore attractive as potential targets.*
There are numerous alternative possibilities.)

In healthy cells, the therapeutic RNA does not trigger any activity, but is simply degraded after a while.

In virus-infected cells, by contrast, the "chapter start mark" on our synthetic RNA is detected by the viral replicase, i.e. the therapeutic RNA is amplified (thereby already hampering the virus by competing for the replicase); the anti-interference function (element № 3) on the therapeutic RNA becomes active and **ensures that the immune system is able to home in on the virus**.

Last but not least, the amplified therapeutic RNA also competes with the viral copies for packaging, "hijacks" newly formed capsids and ideally spreads the protection over the infected tissue.

Healing and immunity result.

The following is – of course – a largely minimalist sketch:

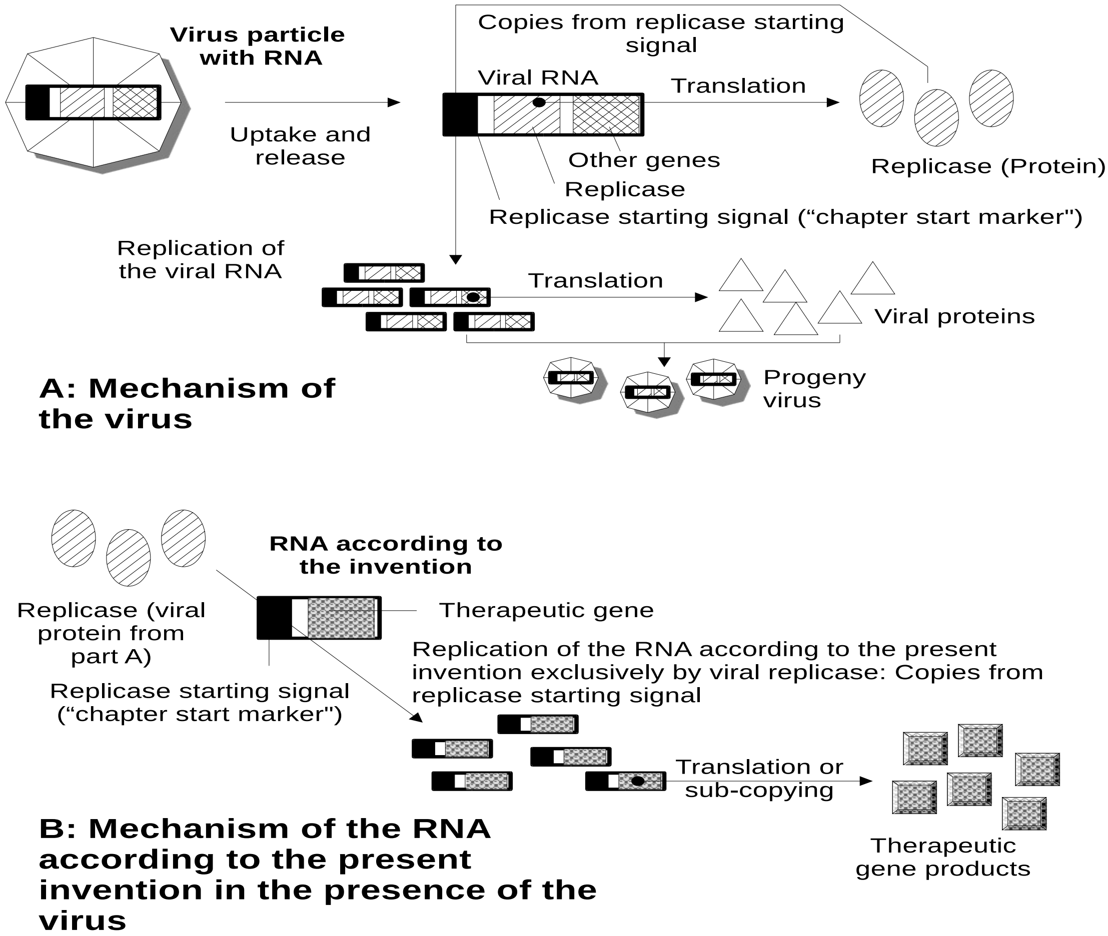

Fig. 2: Mechanism. *(NB: The genome of the virus is shown in a highly simplified form; a real genome of a similar kind can be found in the togaviruses, to which e.g. the rubella virus belongs.)*

Concerning the above illustration:

In the course of infection, the virus particle with the RNA it contains is taken up into the host cell and releases the viral RNA there, of which only 3 functional units are shown here for the sake of simplicity:

1) the replicase starting signal ("chapter start mark")

2) the replicase

3) the other genes (for building new capsids and disrupting the immune defence).

Replicase is formed by reading of the viral RNA (= translation); then it begins to replicate the viral RNA at the replicase starting signals (”chapter start marks”).

By translation of the other genes, among other things the viral proteins are formed, which assemble into new capsids into which the copied RNAs are packaged.

Our therapeutic RNA also begins with a replicase starting signal, but this is followed by a therapeutic gene.

In the presence of the viral replicase, the therapeutic RNA is also replicated by it**, parasitises the virus, so to speak,** and can unfold its antiviral effect:

1) Activation of the immune system

2) Inhibition / destruction of viral components and functions (e.g. specific degradation by proteases and ribonucleases, interferon, intracellular antibodies, ...)

3) Competition for replicase and packaging

etc.

CONCLUSION

With our therapeutic approach, we hijack the replication mechanism of viruses and turn it against them in order to suppress infections and enable immune defence, followed by development of immunity.

The medical significance of such a system for the treatment of viral infections would match that of antibiotics for the treatment of bacterial infections, albeit with the difference that no problems due to the development of resistance are possible, since the system can be adapted to each new virus mutant without further ado. It is suitable for humans, animals and also plants.

Steps towards realisation

The basic feasibility of the individual components – including a test kit built on them that is also suitable for mass testing – can be demonstrated very quickly and cheaply, most quickly and cheaply on bacteriophages (Biosafety 1). In parallel, a coronavirus model system can already be set up (Biosafety 3).
See separate document for details.