Science Dynamics Masterclass

Vaccine, eee...

The greatest Czech poet, Karel Kryl, once said that our principles end where they clash with our intentions. By generalizing this rule, our principles end where they clash with the intentions of someone or something stronger than us ...

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Salvation, Ltd.

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Abstract: Article focused on the systems context of mRNA vaccines. The reader will get acquainted with two types of vaccines and the mechanism of their action. At the end of the article, some questions are asked, to which there is no answer yet, or to which some interviewers have not been answered sufficiently or acceptably. The author presents a causal loop diagram of the process and assigns students development of a dynamic model. Last but not least, the student is taught the ability to read between the lines.

In recent weeks, many responses, ideas and questions have arrived in reaction to the cheeky forehead and the farmyard proverb from SDR nr. 10. We are very grateful for all of them. But a series of sharp petitions and requests followed, demanding a systems evaluation of the **main topic of the present**. I did not respond to any until an urgent question arrived from the family of my **Eternal Beloved**: "Should we have our grandma vaccinated?!," which led me into a desperate situation. If I answer **yes** and the grandmother develops serious post-vaccination side effects, I will be at fault. If I answer **no** and my grandma becomes seriously ill *in relation to* uglyvirus (whatever that means...), I will become a **murderer**! That is why, as many times before, I have chosen, hopefully for the last time, the third path. For before there is another situation where I would have to choose between bad and evil, perhaps a **merciful Reaper with a scythe** will come and get me. All the following considerations and conclusions are **hypothetical** and **do not** point to any legal or ilegal person, living or dead, and any resemblance to any existing micro- or macro-organisms, products or (creatures) is purely coincidental.

So let's have a virus that threatens the **world peace** and **World health**, I'll call it FauCo7, so there's the need for a **vaccine** to protect (and maybe even serve) against such a virus.

Let's speculate some more, that it will be a **relatively unstable** encapsulated ss + RNA virus. Why don't we set aside the primary reasons for instability and focus on the type of vaccine. We do not succeed with the flu type, there is no point in blocking neuraminidase, since there is none. It must be kinda RNA polymerase based, but relatively flexible... But wait a minute. Let's try to resurrect a 30-year-old design with the **mRNA**! Even if the originally promising idea of "training" vaccines was over the years abandoned by many companies. Why? In drugs, there are usually one to four reasons. Either someone else has it **patented** (and we **do care** about it), or its production is **too expensive**, or the product is **too toxic**, or it **doesn't work much**. Which of these four reasons decided to stop research / production of mRNA vaccines is not difficult to determine, if you are interested, the Internet is filled up with the data. But suppose not everyone abandons the idea and two variants of anti-apocalyptic vaccines appear on the market. It is not important who is behind them, let's look together at the theoretical mechanism of action. Why theoretical? Because it's scientifically honest. No one is able to oversee **all the consequences** of changing conditions in a **complex biological system**, so we focus on what is presented to us to believe and / or accept.
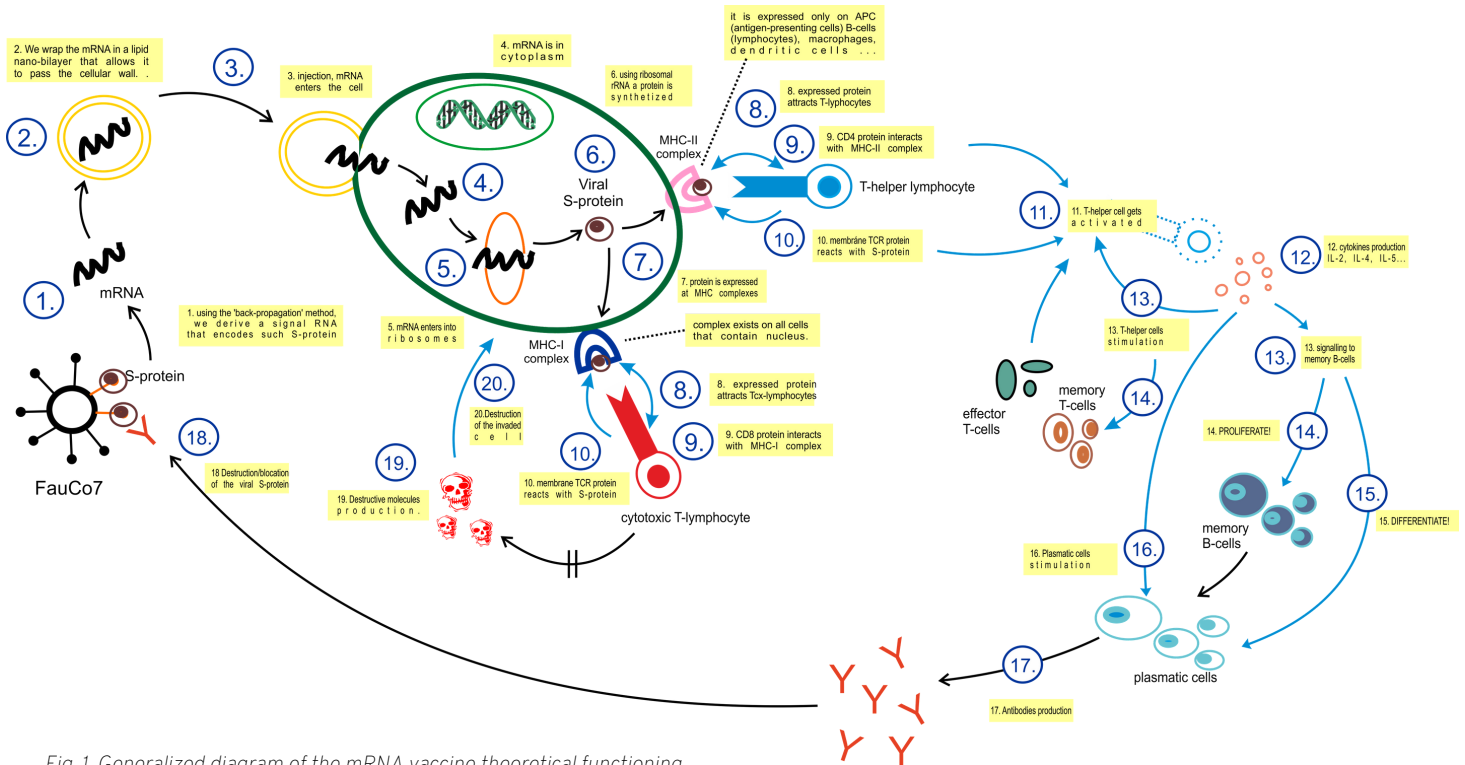
Fig. 1 Generalized diagram of the mRNA vaccine theoretical functioning

In the second part, I will ask a few questions, and you, the students and other readers, will find the answers, right? The general diagram of the **theoretical** operation of the vaccine is shown in Figure 1. If you have healthy eyes, you may want to decipher a small text on a yellow background with detailed descriptions of the individual steps. For the rest of us, we will look at the diagram in smaller sections. Don't expect it to be a highly professional debate. The purpose of our efforts is to help general public to decide, and ordinary generals do not have an (extensive biological) education. Let's start with the virus we want to get rid of. Such a virus is dangerous mainly due to the S-protein, which penetrates into the cells of the infected organism and causes mischief. The purpose of the vaccine is to disable the virus, i.e. to destroy/block/humiliate its S-protein by all means necessary, of course. However, a relatively complicated path leads to this goal. The numbers in parentheses refer to the process sequence numbers in the diagram.

If there are identical sequence numbers for different events in the diagram, this means that the processes take place **simultaneously**. First, it is necessary to capture the virus, read its S-protein, and re-produce the mRNA that synthesized it - (1) in Figure 2.
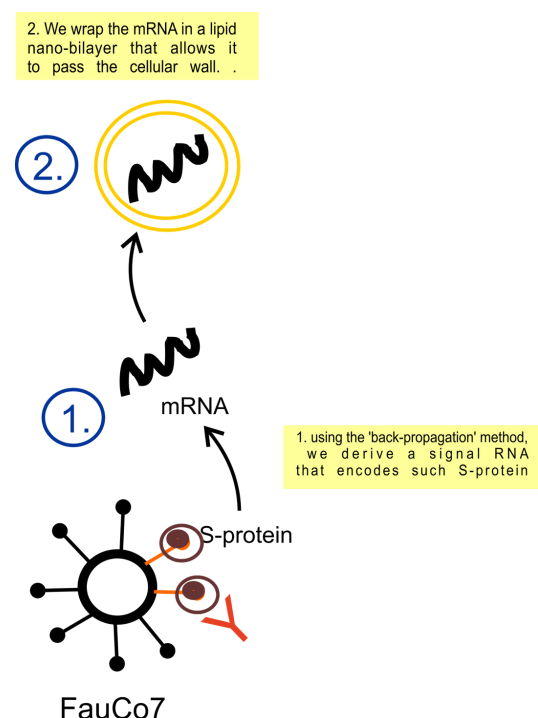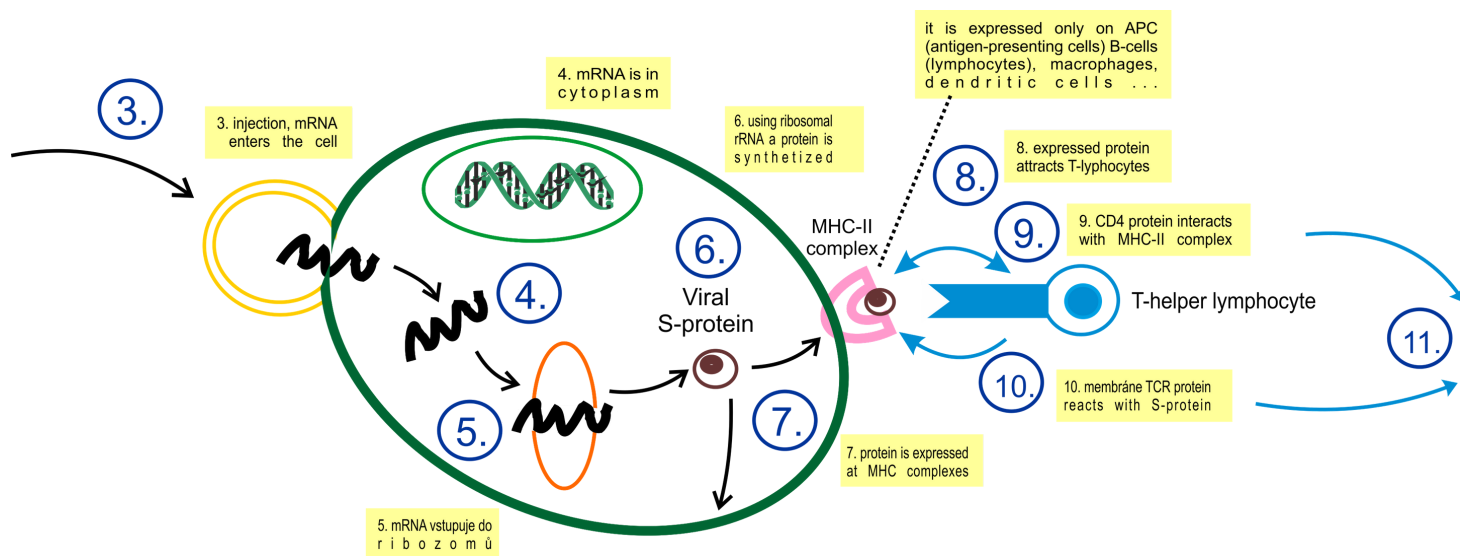
Fig. 2 Detail of the vaccine creation beginning

Obr. 3 Detail of vaccine behavior in the cell and the S-protein expression

The messenger RNA needs to be delivered into the host cell in some way, for example **enveloped in a lipid nano-bilayer** (2) as in Figure 2. Inject mRNA encapsulated in a lipid nano-bilayer (3). "Fooled" cells open itself to the nano-capsules and the mRNA enters cellular cytoplasm (4). There, *as the manufacturer says*, it will **not** fiddle with the nucleus at all, mRNA just enters the ribosomes, and this *conjunctio honorabilium* will result in the viral S-protein synthesis (6) in Figure 3, which begins to be expressed on MHC-I and MHC-II complexes (7).

In the picture 3 we see only the MHC-II complex, we get to the other one after closing the main feedback loop. The MHC-II complex is present only in APC-antigen presenting cells. Expression of the unwanted antigen attracts **T-helper cells** and everything becomes a bit complicated from now on. The helper T-cell CD4 protein begins to react with the MHC-II complex (9) and the helper T-cell membrane TCR protein reacts with the S-protein (10). The helper T-cell gets activated and cytokines production begins. The list is not exhaustive, but we are talking about interleukins 2,4,5 and others.
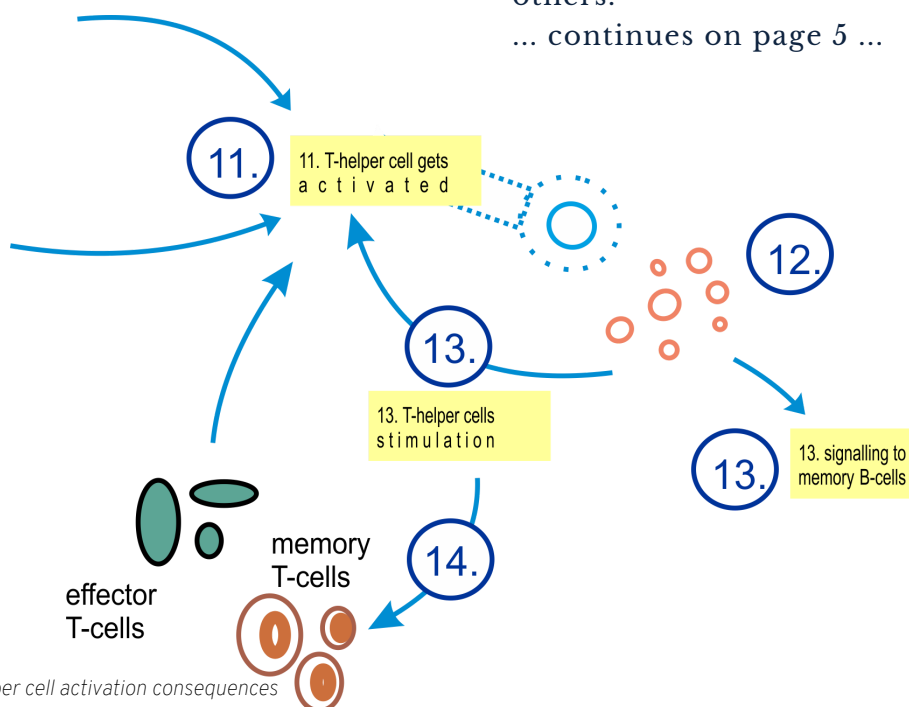
Fig. 4 Detail of the T-helper cell activation consequences

Cytokines (via the feedback) stimulate additional T-helper cells (13) and trigger the production of **memory** and **effector** T cells (14) as in Figure 5. At the same time, the interleukins signal to memory B-cells (13) to **proliferate** (14) and **differentiate** (15). Cytokines also **stimulate production** of the **plasma cells** (16), which start to produce antibodies (17). The antibodies are then able to block the S-protein thereby preventing the

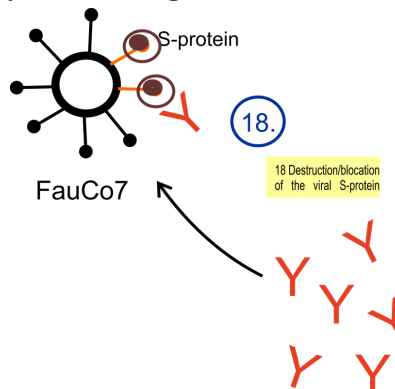virus from engaging in further malicious activity (18) in Figure 6.

S-protein

18.

18 Destruction/blocation of the viral S-protein

FauCo7

Fig. 6 The circle closes, the antibodies fight the virus.

11. 11. T-helper cell gets activated

12. 12. cytokines production IL-2, IL-4, IL-5...

13. 13. T-helper cells stimulation

13. 13. signalling to memory B-cells

effector T-cells

memory T-cells

14.

14. PROLIFERATE!

14.

15.

15. DIFFERENTIATE!

memory B-cells

16. 16. Plasmatic cells stimulation

plasmatic cells

17. 17. Antibodies production
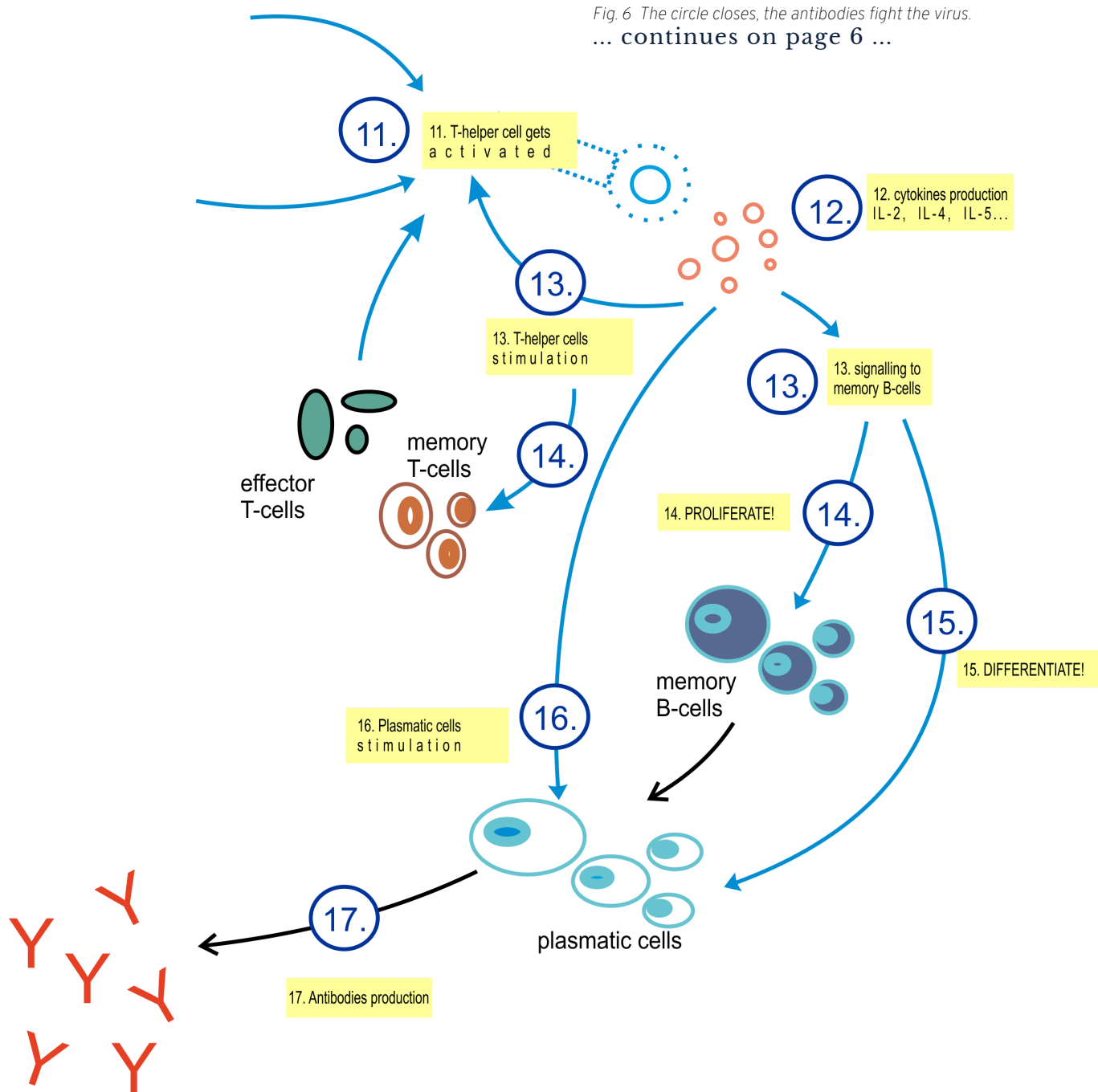
Fig. 5 Detail of the consequences of the T-helper cells stimulation

4. mRNA is in cytoplasm

6. using ribosomal rRNA a protein is synthetized

MHC-II complex

6.

Viral S-protein

4.

5.

7.

7. protein is expressed at MHC complexes

5. mRNA enters into ribosomes

complex exists on all cells that contain nucleus.

MHC-I complex

20.

8.

8. expressed protein attracts Tcx-lymphocytes

20.Destruction of the invaded cell

9.

9. CD8 protein interacts with MHC-I complex

19.

10.

10. membrane TCR protein reacts with S-protein

19. Destructive molecules production.
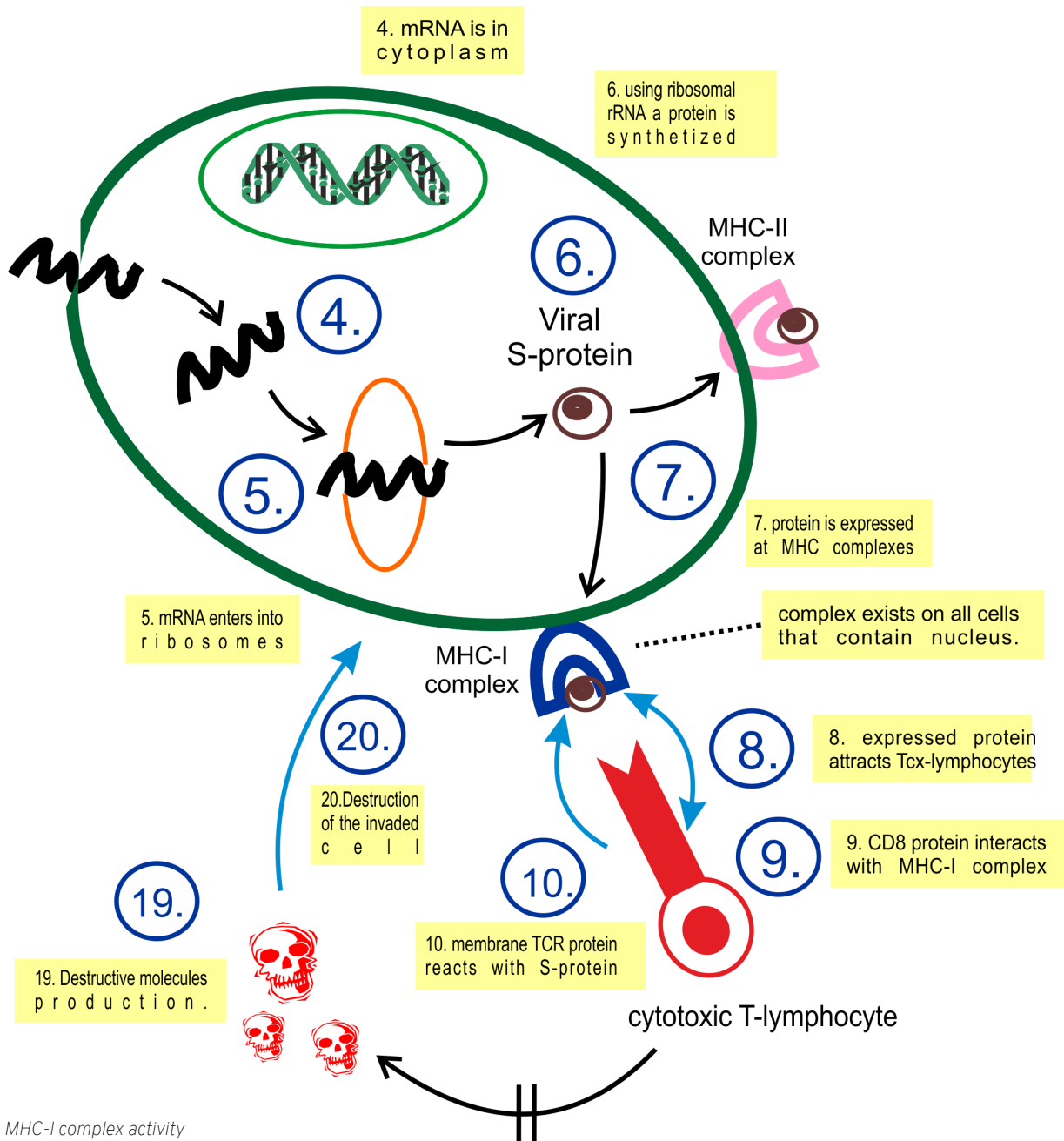
cytotoxic T-lymphocyte

Fig. 7 MHC-I complex activity

The activity of the MHC-I complex, which is found on all cells that contain a **nucleus**, remains to be described. The expressed S-protein on the MHC-I complex attracts cytotoxic T-lymphocytes (8) in Figure 7. The CD8 protein interacts with the MHC-I complex (9) and the membrane TCR protein of the cytotoxic T-lymphocyte interacts with the expressed S-protein, which activates the lymphocyte resulting in delayed production of destructive molecules (19) and subsequent destruction of the invaded cell (20).

This process (at least according to the vaccine authors) takes place only **after** the main antibody-producing process has taken place (Figure 6). This theoretically describes the mechanism of action of the mRNA vaccine with lipid encapsulation. The manufacturer can choose **another path**. The alternative is described in Figure 8. This time it involves **complete DNA** of the virus in question. It is inserted into the chimpanzee adenovirus (DNA encapsulated ds icosahedral virus - there are more than 40 human adenoviral serotypes, but why not engage a monkey?).
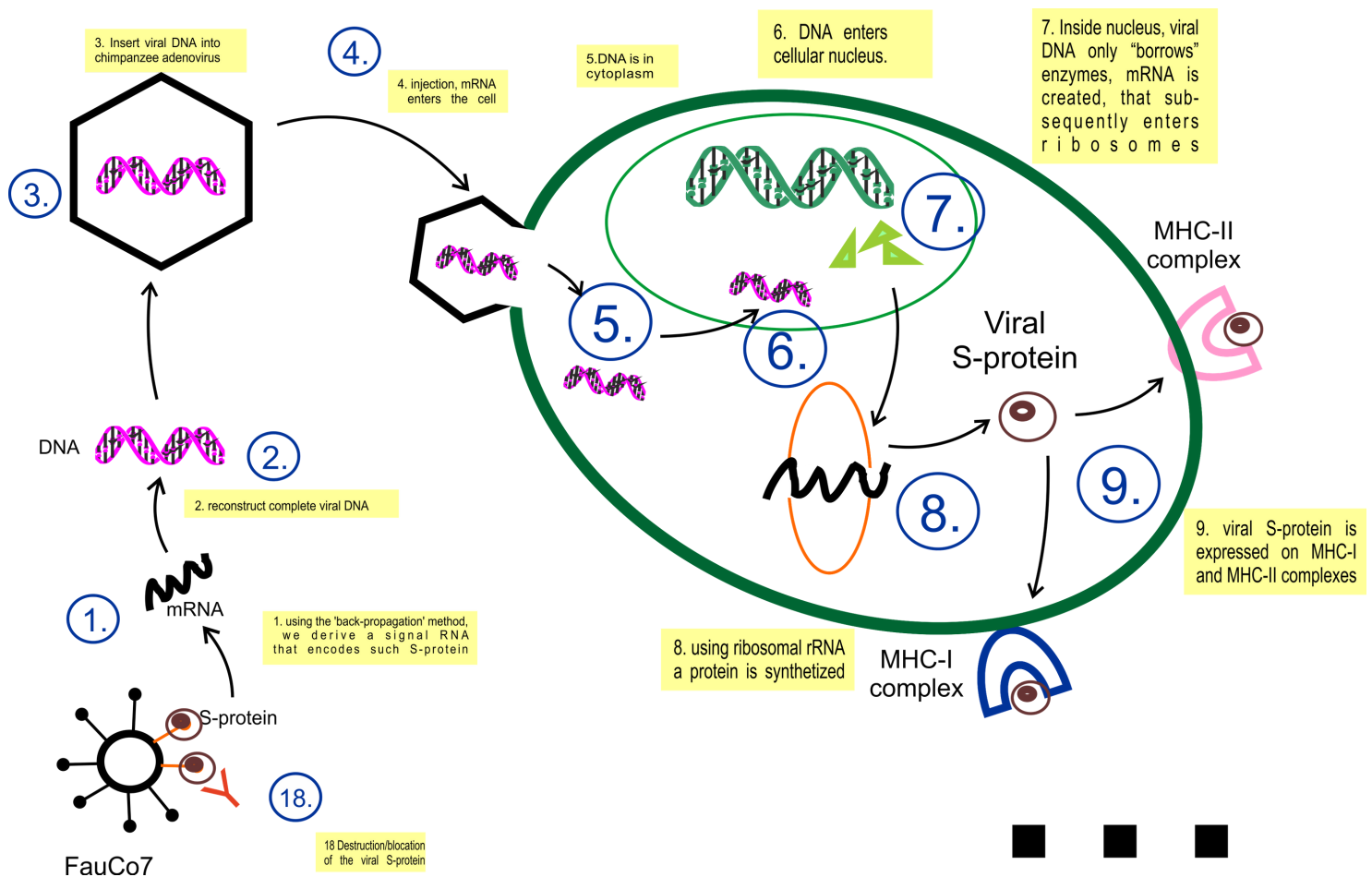
3. Insert viral DNA into chimpanzee adenovirus

4.

4. injection, mRNA enters the cell

5. DNA is in cytoplasm

6. DNA enters cellular nucleus.

7. Inside nucleus, viral DNA only "borrows" enzymes, mRNA is created, that subsequently enters ribosomes

7.

MHC-II complex

3.

Viral S-protein

5.

6.

DNA

2.

2. reconstruct complete viral DNA

9.

9. viral S-protein is expressed on MHC-I and MHC-II complexes

1.

mRNA

1. using the 'back-propagation' method, we derive a signal RNA that encodes such S-protein

8.

8. using ribosomal rRNA a protein is synthetized

MHC-I complex

S-protein

18.

18 Destruction/blocation of the viral S-protein

FauCo7

Fig. 8   Chimpanzee adenovirus vaccine variant

Even in this case, signal RNA (1) is synthesized from the S-protein, complete viral DNA (2) is reconstructed and inserted into the chimpanzee adenovirus (3), which serves as a means of transport to get the viral DNA into the target cell. (4). The DNA first enters the cytoplasm (5) and from there travels into the nucleus (6). In the nucleus, viral DNA, **according to manufacturers**, does not even notice the original DNA, let alone to modify it in any way. It acts like a **disciplined guest** who borrows only some enzymes (7), uses them to make mRNA, and **disappears like a ghost**. The mRNA produced reacts with the ribosomal rRNA (8) and the rest is the same as with the mRNA vaccine described on previous pages.

A viral protein (9) is created, expressed on MHC-I and MHC-II complexes ... and the story happily ends with the production of antibodies that block the viral S-protein. So what's the problem? Apart from the government inability to create a **meaningful vaccination strategy** as revealed and addressed by our **VaccineSIM** simulator, perhaps there's no problem at all. Nevertheless, we will return to certain parts of the diagram and comment on the places that potentially raise questions. The first, A (Figure 9), and this is nothing new, is the dosing problem. How much to make it effective, but as less harmful as possible? This should normally be determined during the first or second phase of clinical trials (in case these were not skipped...). A standard dose for a standard person? But
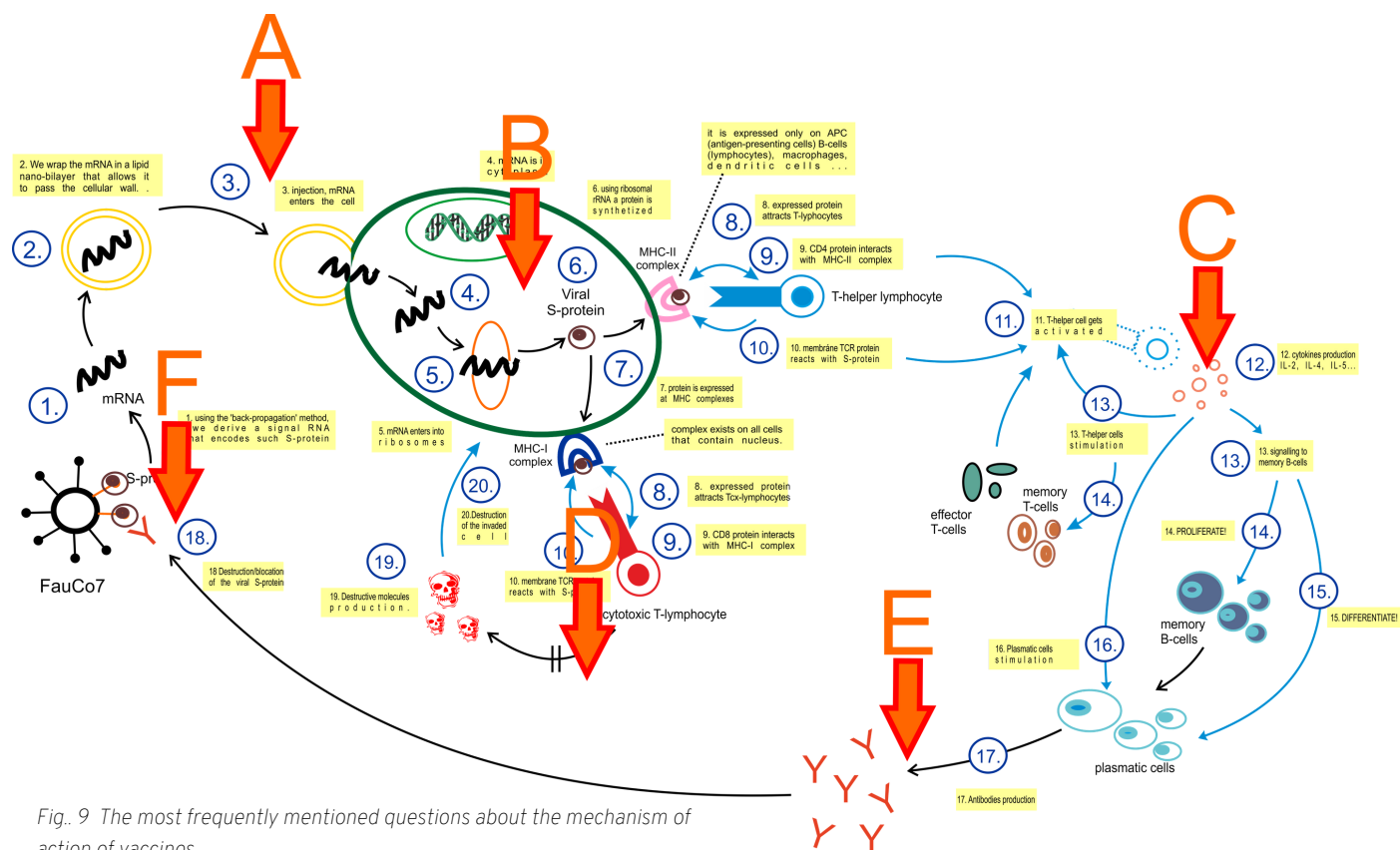
Fig.. 9 The most frequently mentioned questions about the mechanism of action of vaccines

what about non-standard ones? Why am I talking about this? Imagine there is a country in the world where the vaccine arrived and they did not have syringes for accurate dosing .... That you don't believe? Believe my friends, believe! Faith moves mountains! May their faith bring them a competent leaders one day... The second question mark, B, has left many people curious. Does the vaccine modify the original DNA? The **manufacturer says no**. If that's true, that's good news. The third question is in the production of cytokines, C. Is there always (or at least in the vast majority of cases) a negative feedback at work that prevents the **cytokine storm**? Published data from pre- and clinical trials should satisfactorily answer this question as well, if these steps were not, for sake of "emergency", **skipped**. Whether they really give the answer is a question. Delays in the production of destructive molecules, D. Is the delay **sufficient** for the main process to take place, including the production of memory

cells? The dead cell tells no tales (and will not start the production process ...).

Point E, **how long** will the system **remember** the viral S-protein and trigger a **sufficient immune response**? Since SDR is a journal focused on dynamic systems, look at Figure 10. It shows the CLD [1] of the vaccine's functioning. Mark the feedback loops in the diagram, find out, whether the upper part reminds you of one of the **archetypes** [2] and finally decide under what conditions the acquired **post-vaccination immunity** will take place, marked in the graph in Figure 11 in **blue** (S1), when immunity is **established and persists** after vaccination, **orange** (S2), when immunity develops, lasts briefly and disappears, or **red** (S3), when the response does not even reach the immunity threshold. Point F. Even if the system remembers the S-protein against which the vaccine was made, will it work for subsequent mutations of the virus?
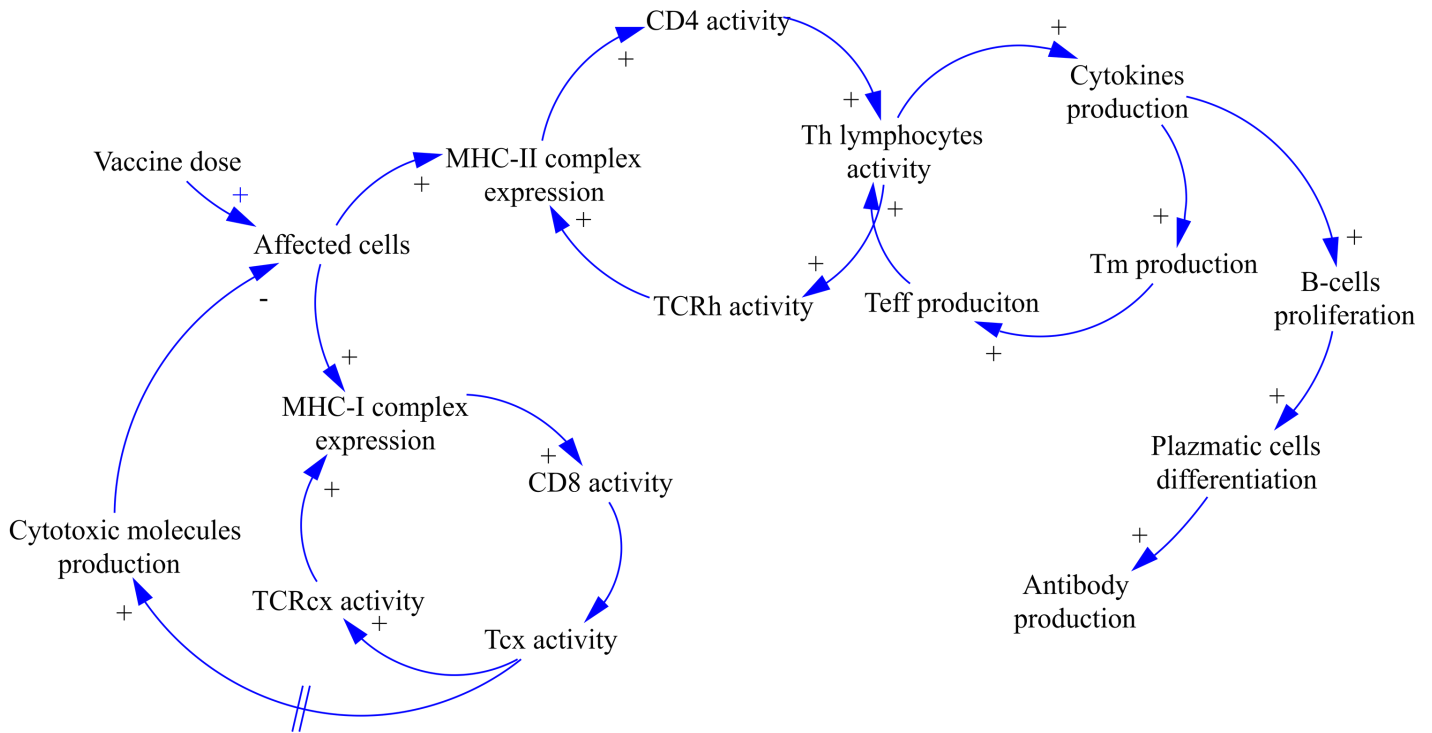
Fig. 10 CLD of the mRNA vaccine mechanism

Verify your mental simulation with a model simulation and communicate the simulation results to the nearest **scandalmonger**. No one else will know what you are talking about anyway. But why bother. After all, the **salvation** in refrigerated boxes has already arrived, or will arrive in no time!

Reference
1. Susta, M., The Systems Thinking Guide. 2.ed. 2016, Praha: Proverbs. 136.
2. Susta, M., Public Health - a Systems Perspective. 2021, GB: CSP pending. 250
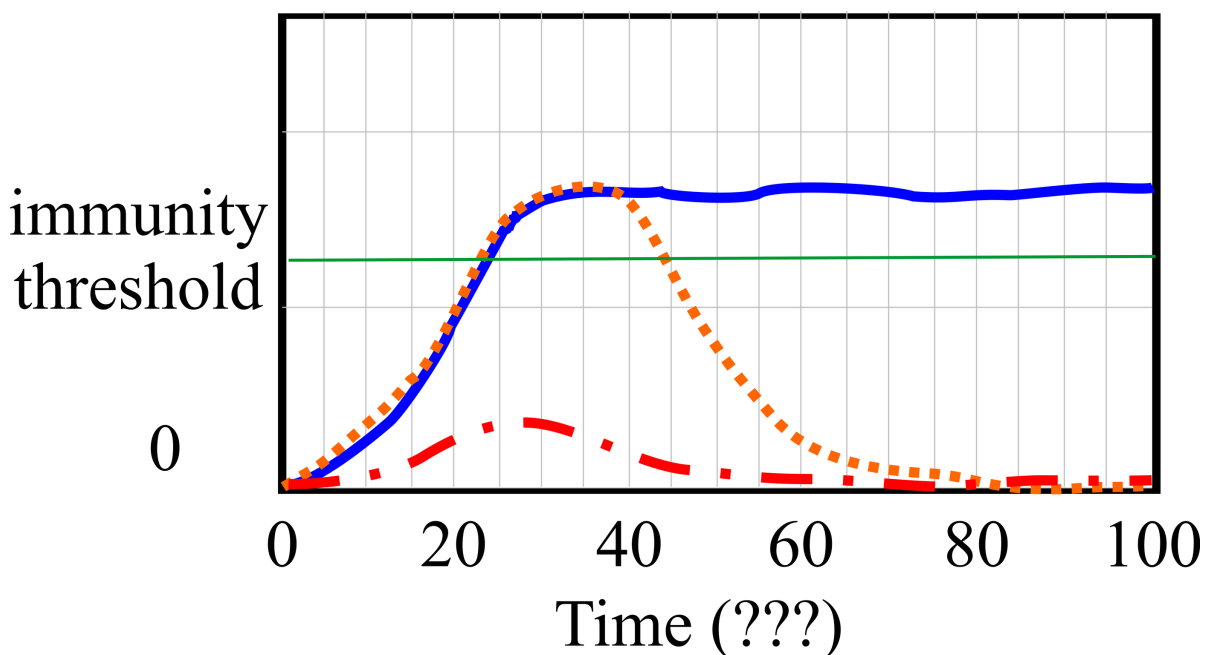
Fig. 11 Possible FauCo7 post-vaccination immunity patterns

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