AMIDD 2024 Lecture 4: Proteins as drug targets

Ill. Niklas Elmehed © Nobel Prize Outreach

John J. Hopfield

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Geoffrey E. Hinton

The Nobel Prize in Physics 2024: "for foundational discoveries and inventions that enable machine learning with artificial neural networks"

Ill. Niklas Elmehed © Nobel Prize Outreach

David Baker

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Demis Hassabis

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John M. Jumper

The Nobel Prize in Chemistry 2024 was divided, one half awarded to David Baker "for computational protein design", the other half jointly to Demis Hassabis and John M. Jumper "for protein structure prediction"

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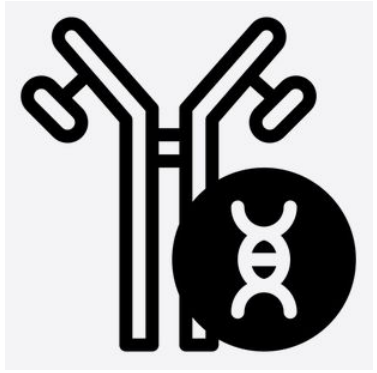
Topics of lecture 4

- The central dogma for drug discovery
- ODE-based mechanistic models
- Key considerations for a drug to work

Five key questions in drug discovery

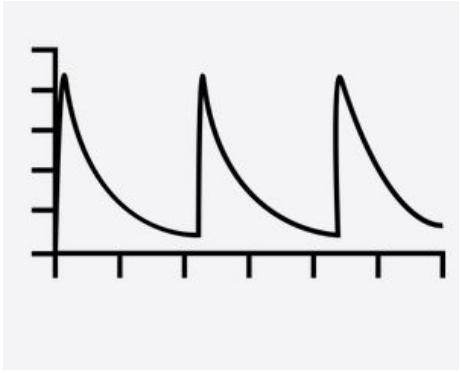
Medical Need

What is the unmet medical need to be addressed?



Target & modality

What is the target? What is the modality?

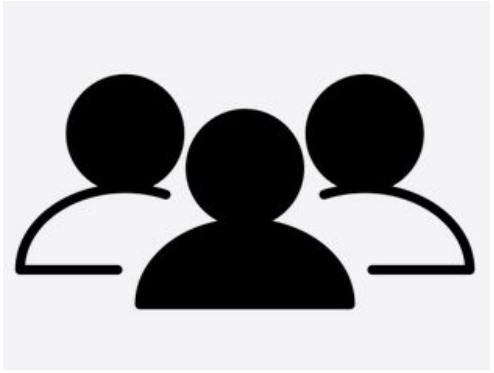


PK/PD

How much drug reach which body part? What does body do to the drug (PK)? What does the drug do to the body (PD)?

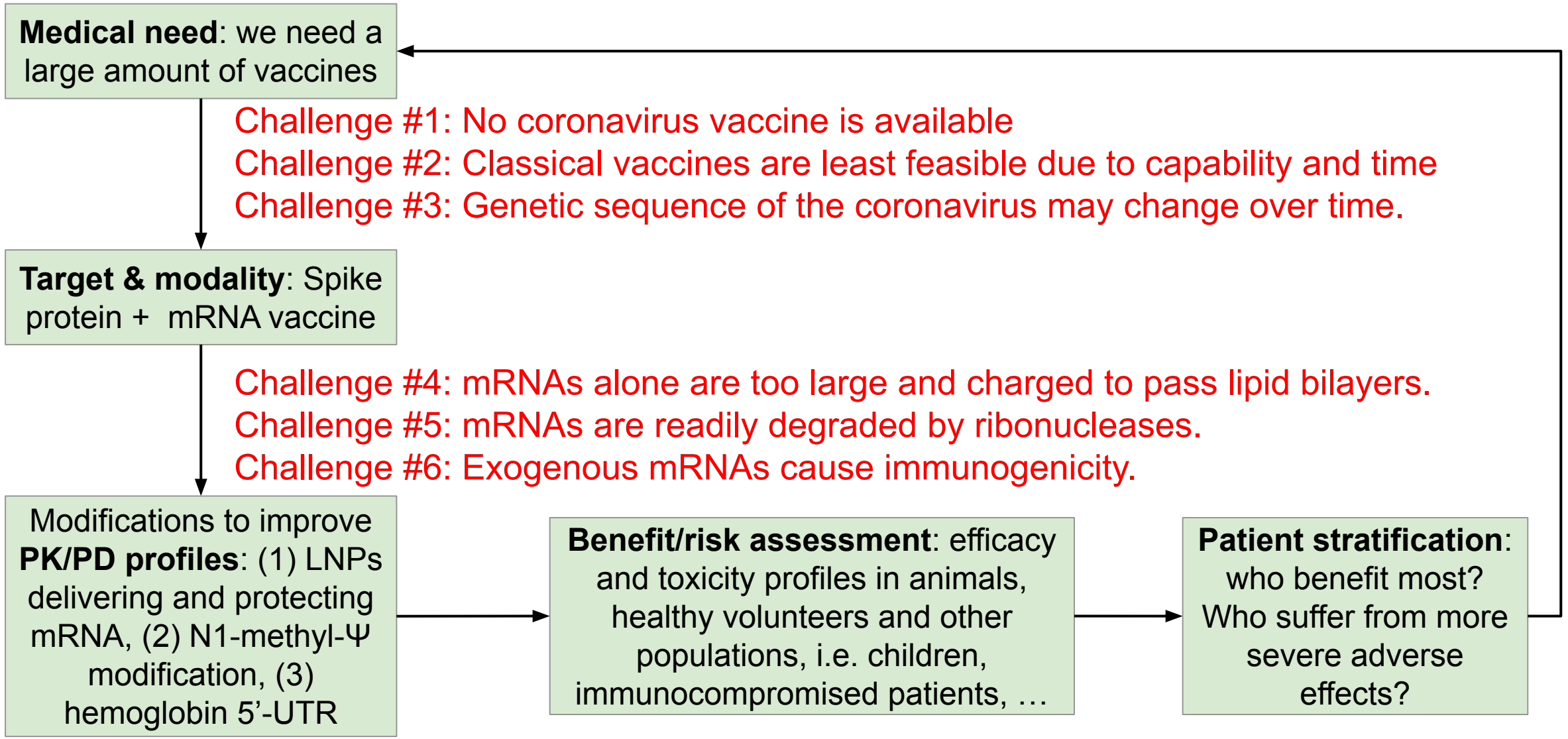
Benefit/risk

What is the toxicity of the drug? Is it justifiable given the benefits?



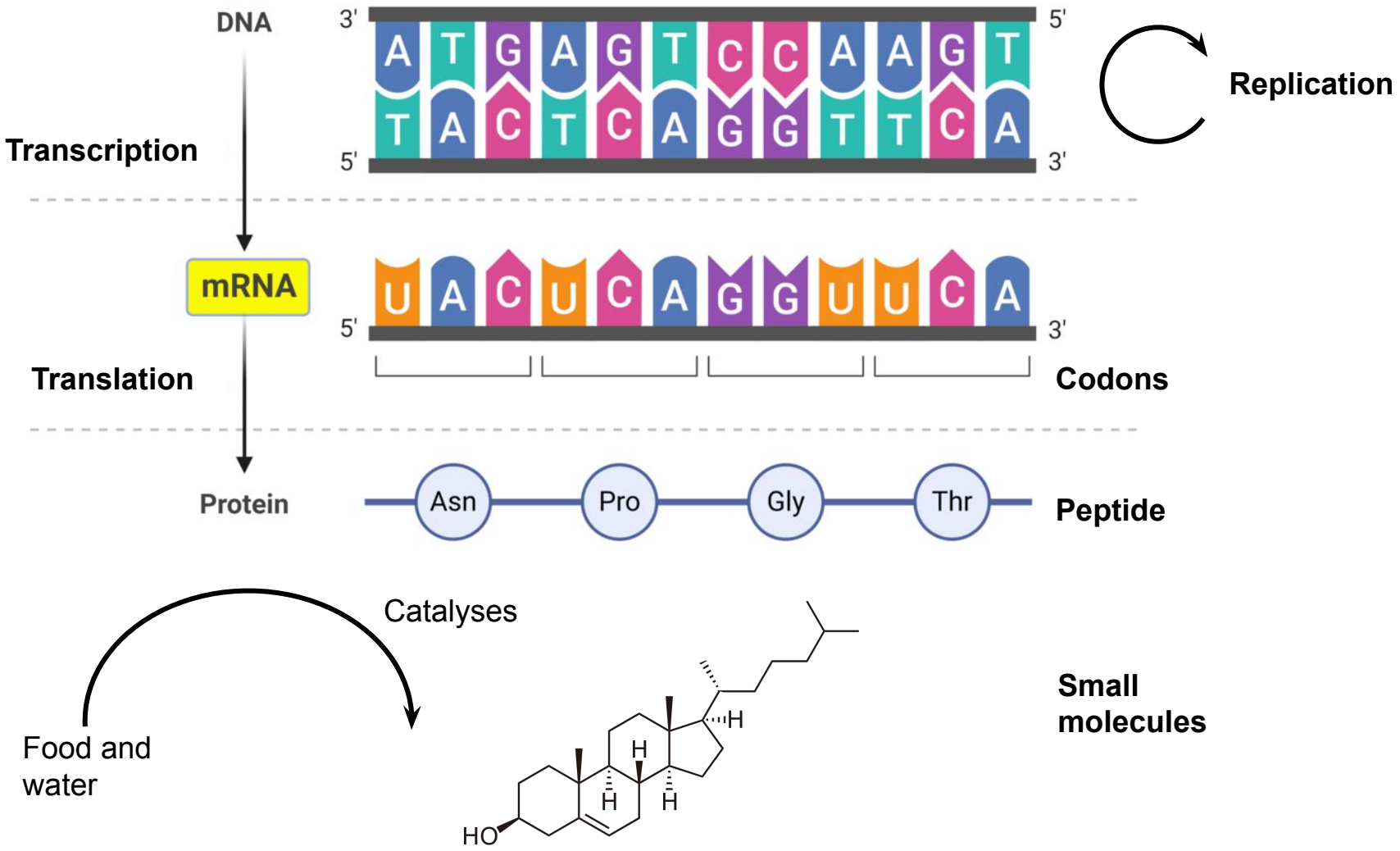
Patient stratification

Who are responsive to the drug? Who are susceptible to adverse events?

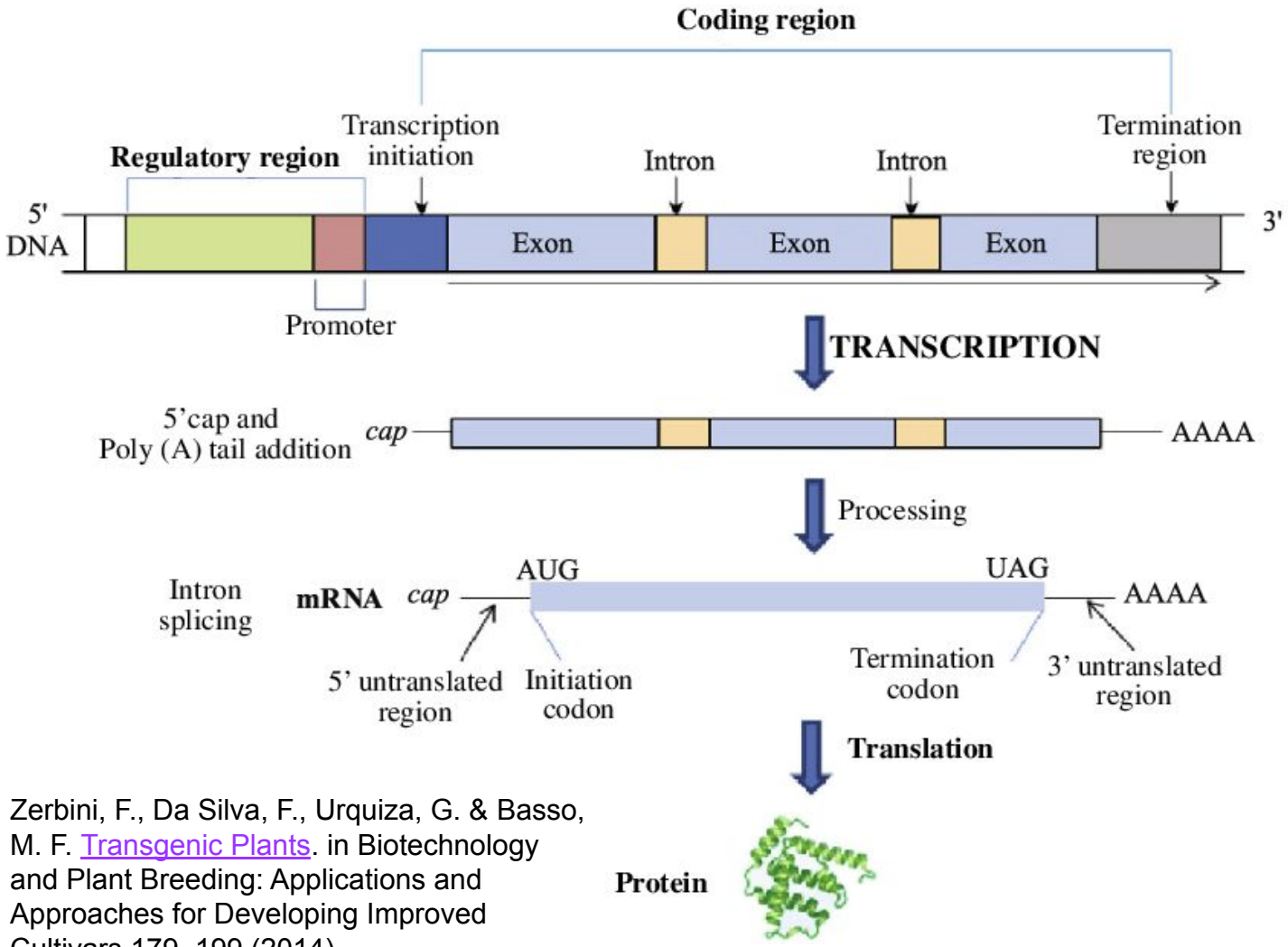


LNP: lipid nanoparticles

The central dogma



Coding sequence of the spike protein alone is not enough: mRNA transcription depends on 5’-UTR and 3’-UTR, too

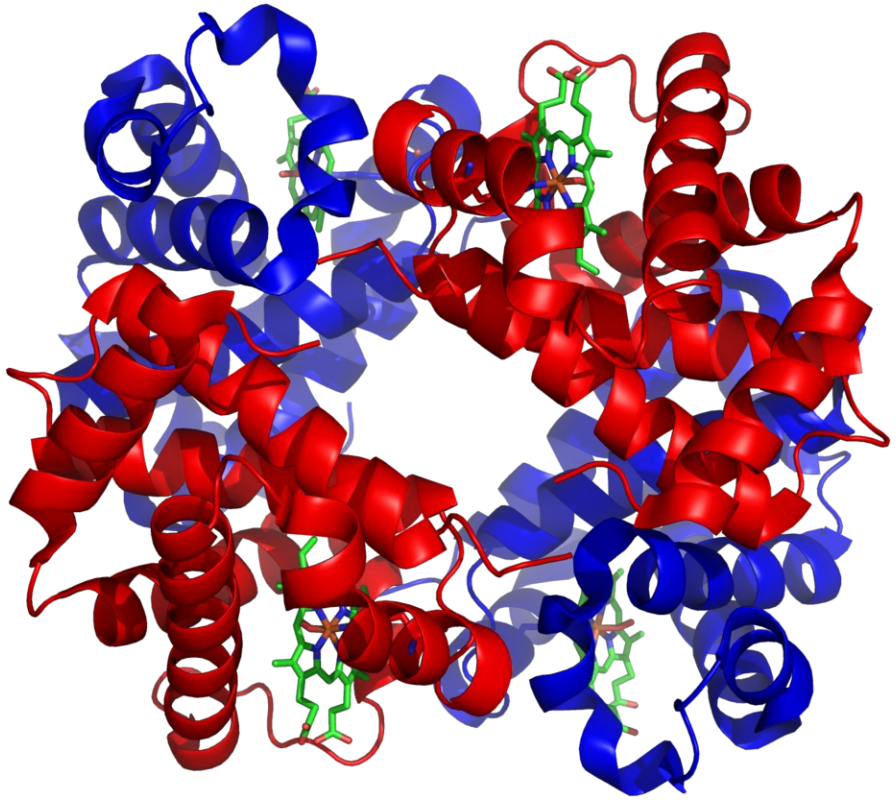


Zerbini, F., Da Silva, F., Urquiza, G. & Basso, M. F. Transgenic Plants. in Biotechnology and Plant Breeding: Applications and Approaches for Developing Improved Cultivars 179–199 (2014).

The process of gene expression in eukaryotes:

1. RNA polymerase, an enzyme, binds to the promoter region of the gene. It reads the DNA from the 5′ untranslated region (UTR) to the 3′ UTR to synthesize pre-mRNA.
2. Pre-mRNA receives a modified nucleotide (7-methylguanosine triphosphate) at the 5′ end as a cap, and a repeated adenine sequence (poly-A tail) at the 3′ end.
3. Pre-mRNA is spliced to remove introns. Mature mRNA contains the 5’ cap, 5’-untranslated region (5’-UTR), coding sequence, 3’-untranslated region (3’-UTR), and a poly-A tail.
4. Mature mRNA is transported from the nucleus to the cytoplasm for translation.

5’-UTR of human hemoglobin is a good choice to make sure that the vaccine sequence is stable and highly translated



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1    -MVLSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHFD------LSHGS   53  P69905   HBA_HUMAN
1    MVHLTPEEKSAVTALWGKVNV--DEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGN   58  P68871   HBB_HUMAN
1    MVHLTPEEKTAVNALWGKVNV--DAVGGEALGRLLVVYPWTQRFFESFGDLSSPDAVMGN   58  P02042   HBD_HUMAN
      : *:* :*: *.* **** .     *.*** *::: :* *: :*  *          *.

54   AQVKGHGKKVADALTNAVAHVDDMPNALSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAH  113  P69905   HBA_HUMAN
59   PKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHH  118  P68871   HBB_HUMAN
59   PKVKAHGKKVLGAFSDGLAHLDNLKGTFSQLSELHCDKLHVDPENFRLLGNVLVCVLARN  118  P02042   HBD_HUMAN
      :**.*****  *::::.:**:*::  ::: **:**..**:*** **:**.. *: .** .

114  LPAEFTPAVHASLDKFLASVSTVLTSKYR  142  P69905   HBA_HUMAN
119  FGKEFTPPVQAAYQKVVAGVANALAHKYH  147  P68871   HBB_HUMAN
119  FGKEFTPQMQAAYQKVVAGVANALAHKYH  147  P02042   HBD_HUMAN
     :  **** ::*: :*.:*.*:..*: **:
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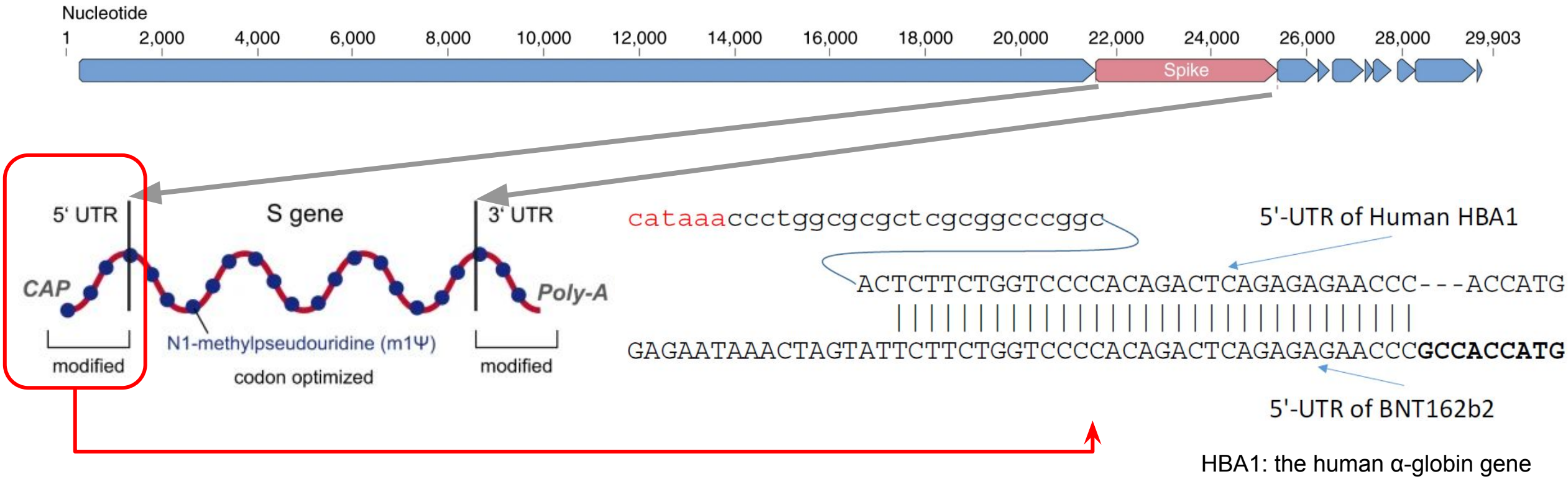
- Hemoglobin (left) is a protein that transports oxygen.
- Hemoglobin consists of three subunits: alpha, beta, and delta. They are encoded by three highly similar genes known as HBA, HBB, and HBD (above).
- Hemoglobin is present in erythrocytes (red blood cells) of almost all vertebrates.
- The protein is essential, therefore the mRNA is relatively stable and highly translated.

LNP, modified RNA, and 5'-UTR of HBA are all essential to make effective *and safe* vaccines against coronavirus



HBA1: the human α-globin gene

References: Heinz, Franz X., and Karin Stiasny. "Distinguishing Features of Current COVID-19 Vaccines: Knowns and Unknowns of Antigen Presentation and Modes of Action." Npj Vaccines 6, no. 1 (August 16, 2021): 1–13. https://doi.org/10.1038/s41541-021-00369-6; Assemblies of putative SARS-CoV2-spike-encoding mRNA sequences for vaccines BNT-162b2 and mRNA-1273 (github.com/NAalytics); Xia, Xuhua. "Detailed Dissection and Critical Evaluation of the Pfizer/BioNTech and Moderna MRNA Vaccines." Vaccines 9, no. 7 (July 3, 2021): 734. https://doi.org/10.3390/vaccines9070734.

A summary of what we have learned so far in the context of coronavirus

1. What is the unmet medical need to be addressed? We need a vaccine to prevent a large population of individuals from being infected by coronavirus, which have severe consequences.
2. What are the target(s) of our drug? Spike protein is conserved: immune reaction is desired.
3. Where should the drug go in patient's body, what does body do to the drug, and what does the drug do to the body? Thanks to LNP, N1-mythel-Ψ, and 5'-UTR of HBA1, the mRNA vaccination can enter cells with minimal side effects. In cells, spike protein RNA is synthesized into proteins, which are digested, presented, and elicit immune response.
4. What is the safety profile of the drug in light of its benefits? Initial study: Polack, F. P. et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine 383, 2603–2615 (2020), and watch this video.
5. Who are responsive to the drug, or susceptible to adverse events? Updated regularly by regulatory agencies, for instance European Medicines Agency

Interested in learning more? Read this report by WHO on potential benefits and limitations of mRNA vaccines.

Most drugs work by binding to and modulating protein targets

Table 1 | **Molecular targets of FDA-approved drugs**

Drug target class	Targets			Drugs		
	Total targets	Small-molecule drug targets	Biologic drug targets	Total drugs	Small molecules	Biologics
Human protein	667	549	146	1,194	999	195
Pathogen protein	189	184	7	220	215	5
Other human biomolecules	28	9	22	98	63	35
Other pathogen biomolecules	9	7	4	79	71	8

The list also includes antimalarial drugs approved elsewhere in the world.

End of lecture on 11.10.2024