COMPLEMENT-TARGETED THERAPEUTICS

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Agenda

- Complement therapeutics: historical challenges
- Targets for therapy in the complement pathways
- Inhibitors of complement pathways
- Future of complement-targetd therapeutics

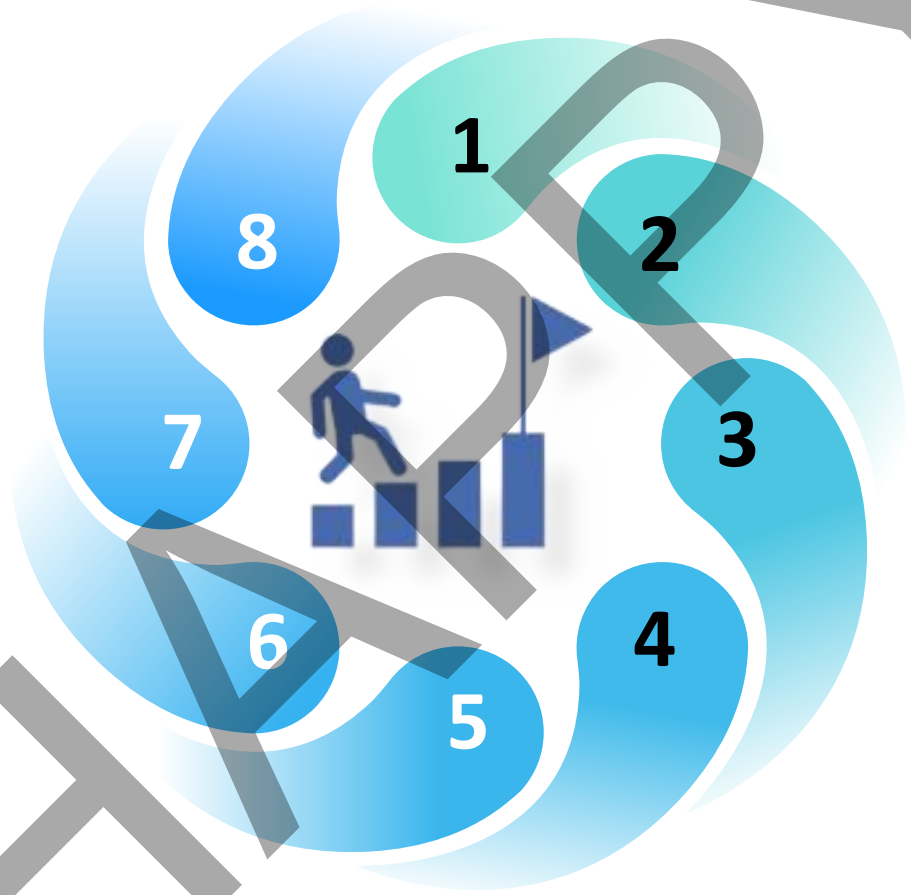
Challenges in development of complement-targeted therapeutics

Others 8
Regulatory and ethical issues

Cost of development 7
Biologics are expensive

Long-term safety 6
Unforeseen consequences, and the potential for adverse effects

Immunogenicity 5
Therapeutic agents may provoke an immune response (forming Ab)



1 **Complexity of CS**
Targeting specific components without disrupting 'overall balance of the system

2 **Disease-specific variability**
Designing effective therapies across a range of diseases while minimizing off-target effects

3 **Delivery challenges**
Delivery of complement-targeted therapies to specific tissues or cells

4 **Off-target effects**
Ensuring specificity while avoiding interference with normal immune function

Semin Immunopathol (2018) 40:125–140

Historical Perspectives

CVF (cobra venom factor)

Binds factor B, depletes C for days
Toxic - antigenic

Heparin & other polyionic agents

Binds C1, iterefers with MAC
Weak – non-specific effect

C1 inhibitors (HAE)

Protease inhibitors (purified plasma proteins & recombinant human C1-INH)

Therapeutic mAb

Recombinant soluble C regulators

Receptor antagonists

……

Which targets are the best to inhibit?

01 **What is the pathophysiological mechanism of the disease?**

Some diseases (PNH) are completely C-dependent while others partly dependent

02 **Differences between chronic (life-long) and acute (life-threatening) diseases**

Duration of C inhibition from days to weeks or months

03 **The cost of complement inhibition**

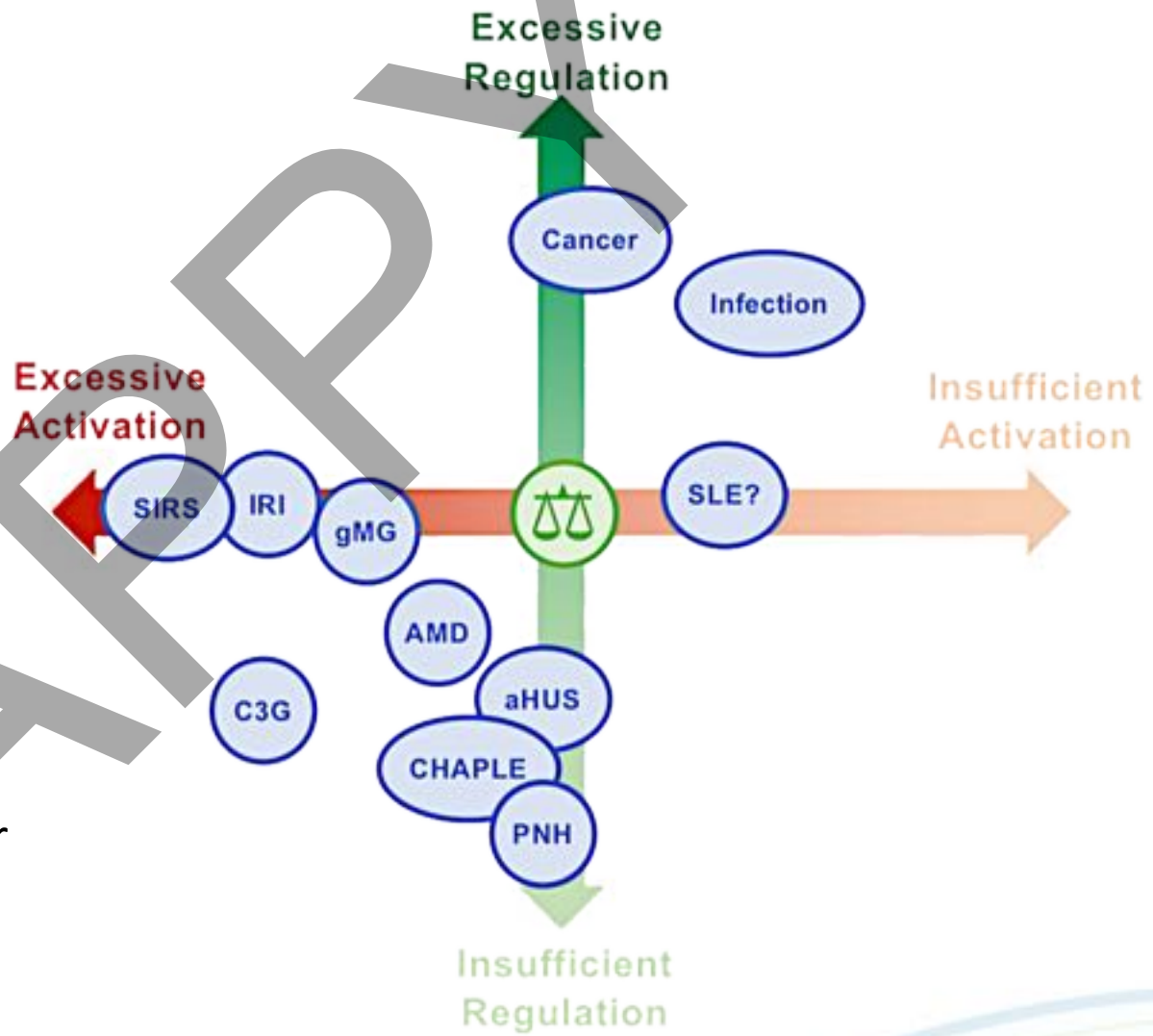
Nat Biotechnol 2007; 25(11): 1265-1275

Which targets are the best to inhibit?

A very sensitive BALANCE in C activation & regulation is required

EXAMPLE

Hyperactivation of the system by massive influx of bacteria (sepsis) may lead to strong bystander attack of host cells that overpower the regulatory capacity >>> SIRS



Seminars in Immunopathology (2021) 43:757–771

Which targets are the best to inhibit?

Classic

C1q/r/s

The main concern of blocking the classical pathway activation is that the Ab-mediated effects of C are lost.

Lectin

MASP-2

The main concern of blocking the lectin pathway activation is substantial part of the recognition of danger function of C is lost.

Alternative

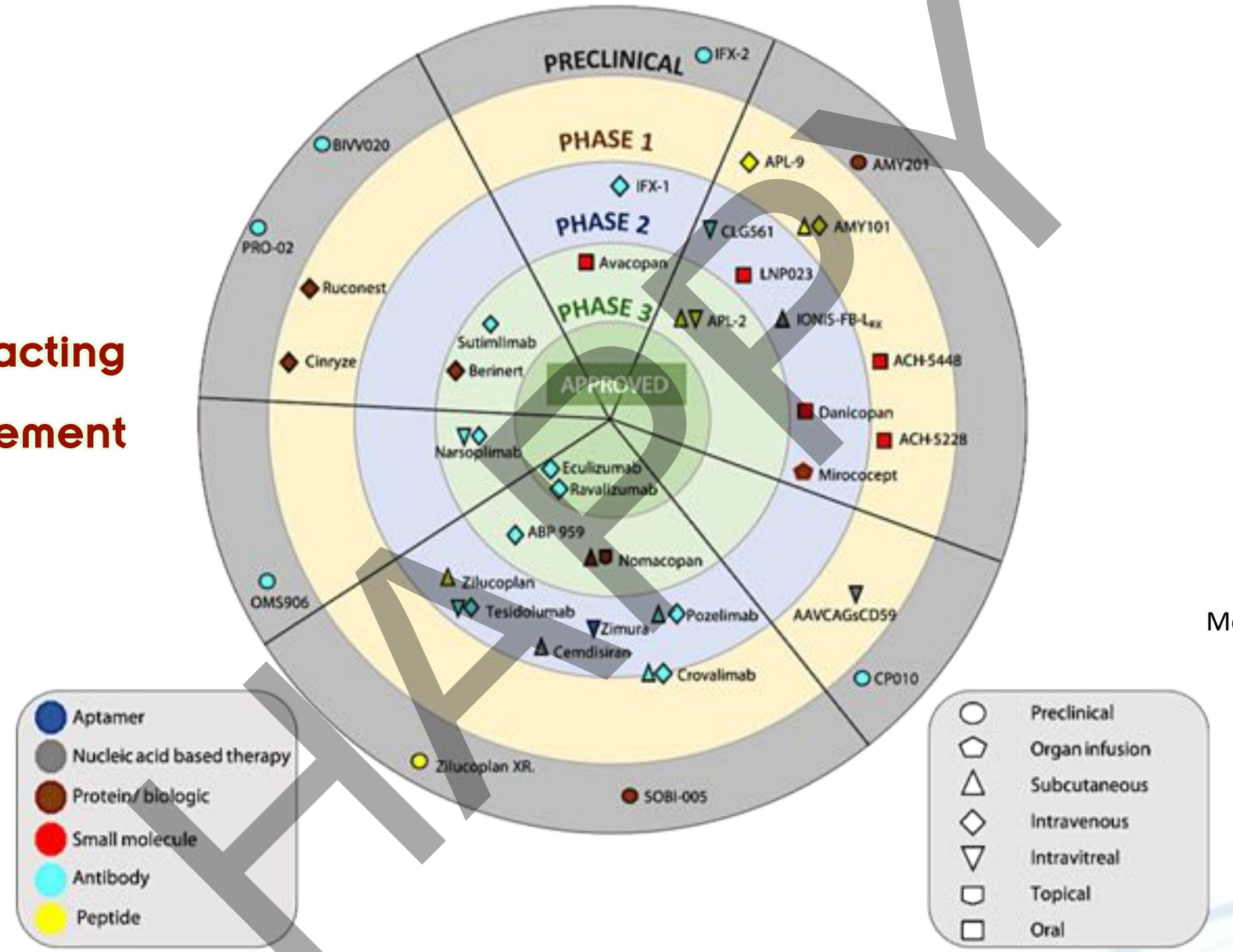
C3/FB/FD

- Blocking C3>>> blocks the whole system from C3 and downstream.

- Their blockade reduced opsonization and probably risk of increased infection

Pharmacol Rev. 2021;73(2):792-827

> 38 molecules acting targeting complement pathways



Mol Immunol 2019; 114: 341-352

Complement-targeted therapeutic reagents

Monoclonal antibodies and their derivatives

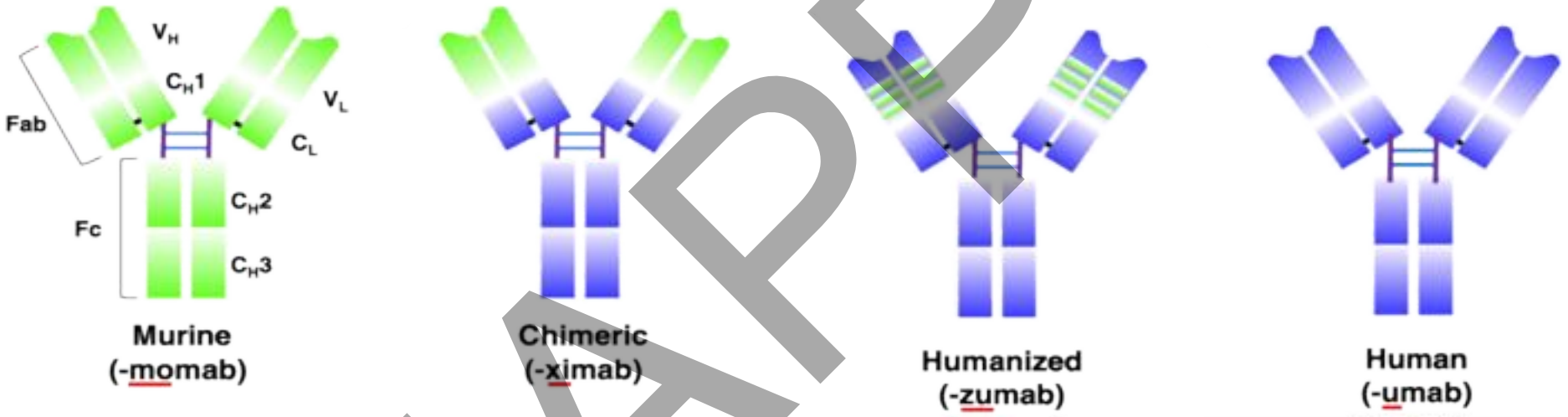
Small molecular peptides and peptidomimetics

Recombinant proteins and conjugates

Others (e.g. Aptamers)

1. Monoclonal antibodies (mAbs)

mAbs are produced by B cells and specifically target antigens.



Examples: ecluzimab and ravulizumab (anti-C5)

J Biomed Sci. 2020;27(1):1

2. Small molecular peptides & peptidomimetics

Peptidomimetics: chemical structures that mimic the effect of peptides but

1. Higher metabolic stability
2. Good bioavailability
3. Enhanced receptor affinity and selectivity

- Advantages over mAbs: less cost and more importantly, the potential access to tissue, including the CNS

Example: Avacopan (C5aR1 antagonist)

Pharmacol Rev. 2021;73(2):792-827

3. Recombinant proteins

The genes encoding the C regulators are all located in the RCA gene cluster on ch. 1 and they are structurally related

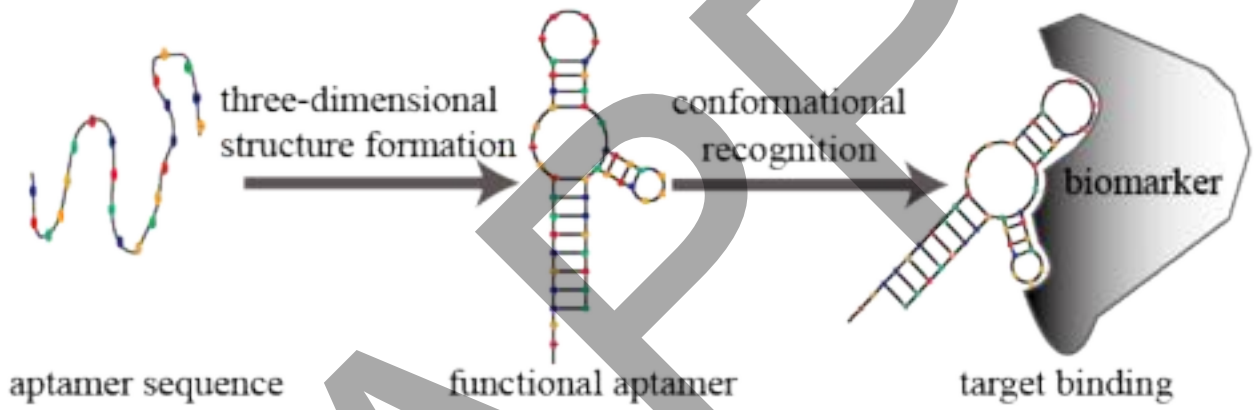
- **A breakthrough**: sCR1 (soluble form of complement receptor 1) produced recombinantly and used in IRI

Another approach: is to take only a small part that is the active domain in the protein and conjugate this to a specific targeting molecule, which leads to binding to the actual site that needs to be treated

Pharmacol Rev. 2021;73(2):792-827

4. Aptamers [nucleic acids antibodies]

A short, chemically synthesized, ssDNA or, more frequently, RNA molecules that can bind specifically to a target and neutralize the function of a protein

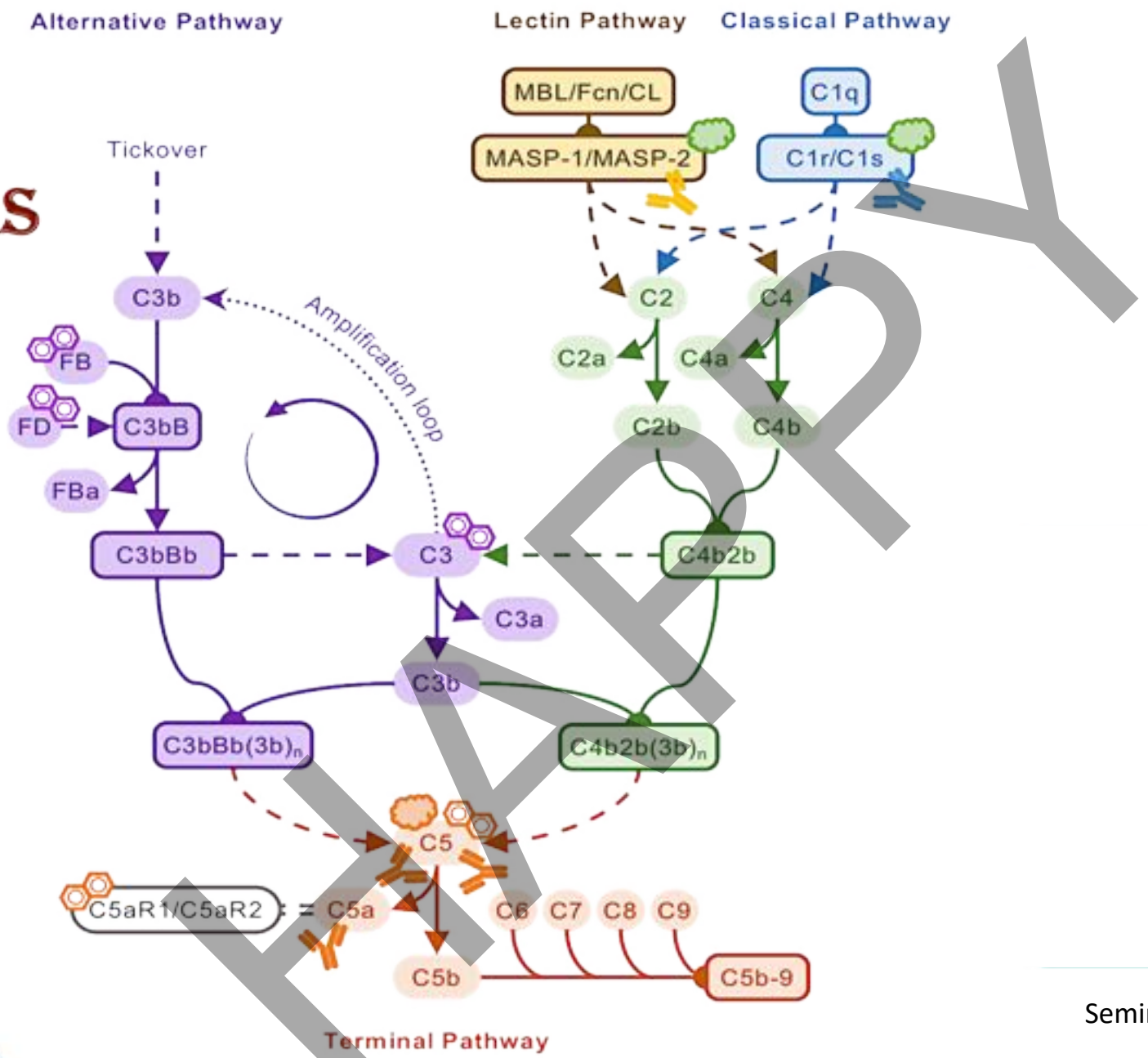


The beauty of an aptamer lies in its versatility to bind to a plethora of molecules, i.e. the small molecules, ions, toxins, peptides, protein, viruses, bacteria and even the whole cells.

Example: Zimura (C5 inhibitor)

Pharmacol Rev. 2021;73(2):792-827

INHIBITORS



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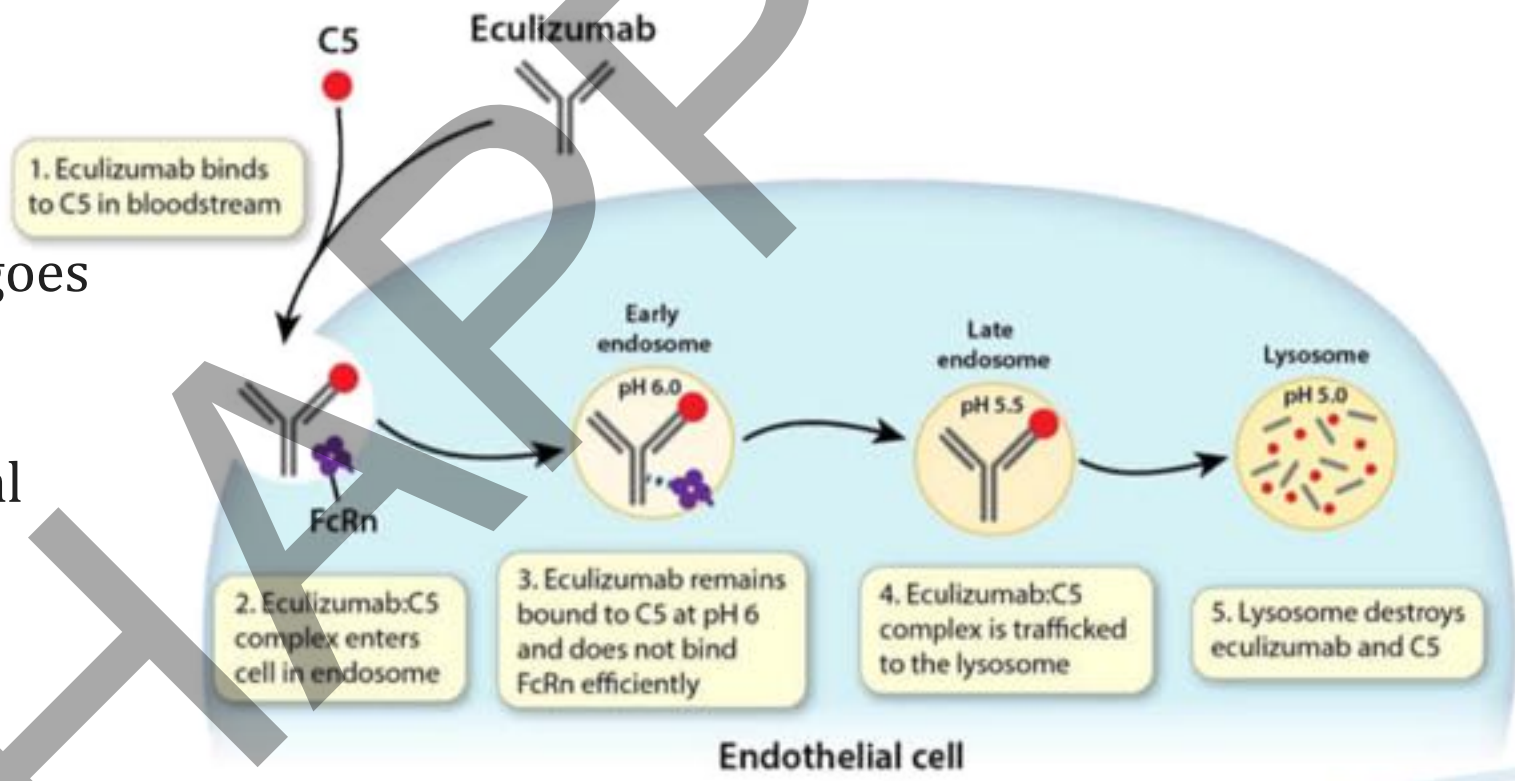
Soliris (Eculizumab)

Humanized mAb approved in 2007 by FDA, is the world's first approved C5 inhibitor, administered weekly or every 2 weeks

Like other IgG Ab, undergoes continual nonspecific pinocytosis by endothelial cells and trafficking to acidified endosomes

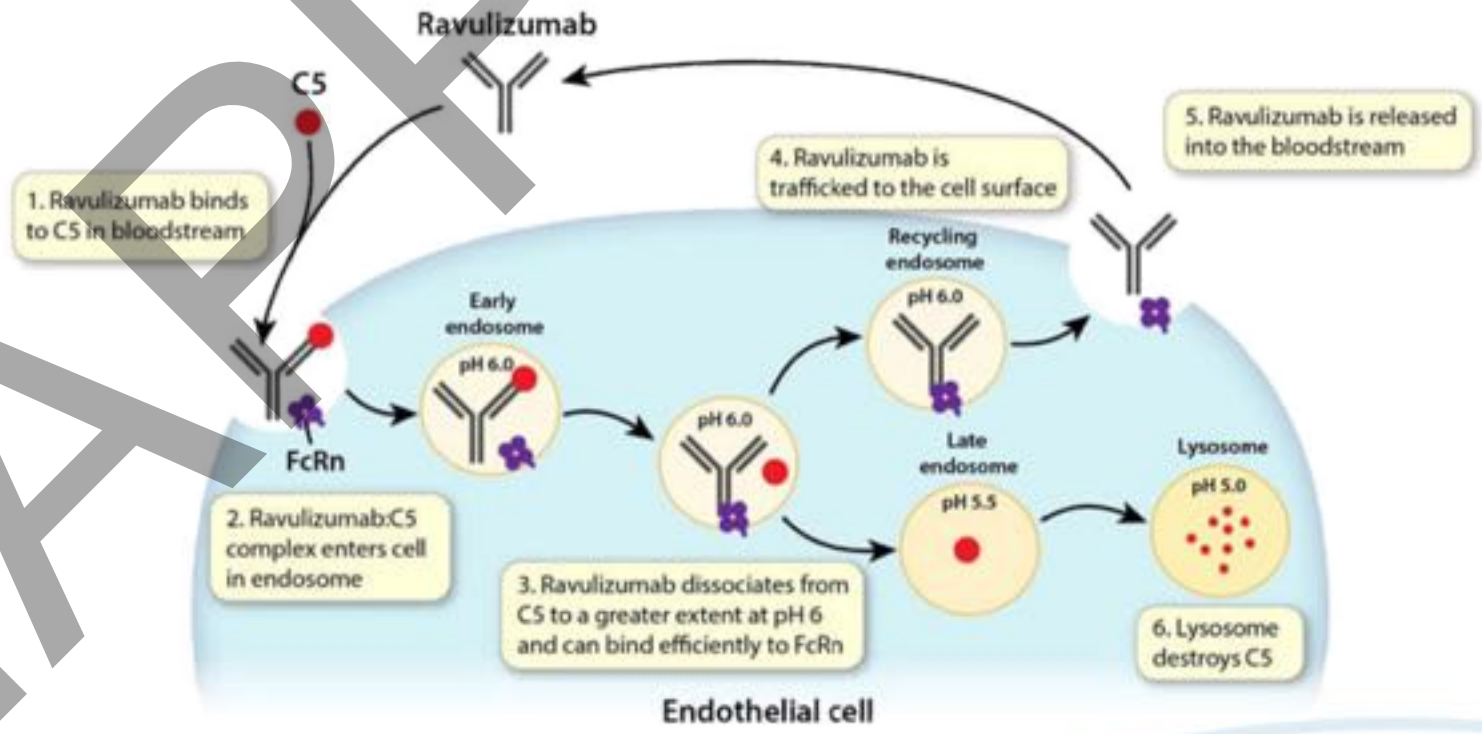


https://onlinelibrary.wiley.com/doi/full/10.1111/jcpt.13642

Ultomiris (Ravulizumab)

Humanized mAb approved in 2018 by FDA, is the first and only long-acting C5 inhibitor administered every 8 weeks

Ravulizumab was engineered by substituting 4 AA in eculizumab, which alter the molecule's binding affinity for C5 and FcRn at the endosomal pH



https://onlinelibrary.wiley.com/doi/full/10.1111/jcpt.13642

According to Alexion's historical financial reports

Sales of Soliris have climbed each year since it was approved in 2007, reaching $4.064 billion in 2020.

Sales of Ultomiris exceeded $1 billion in its second year on the market

THE MOST RECENT

Pozelimab (Veopoz)

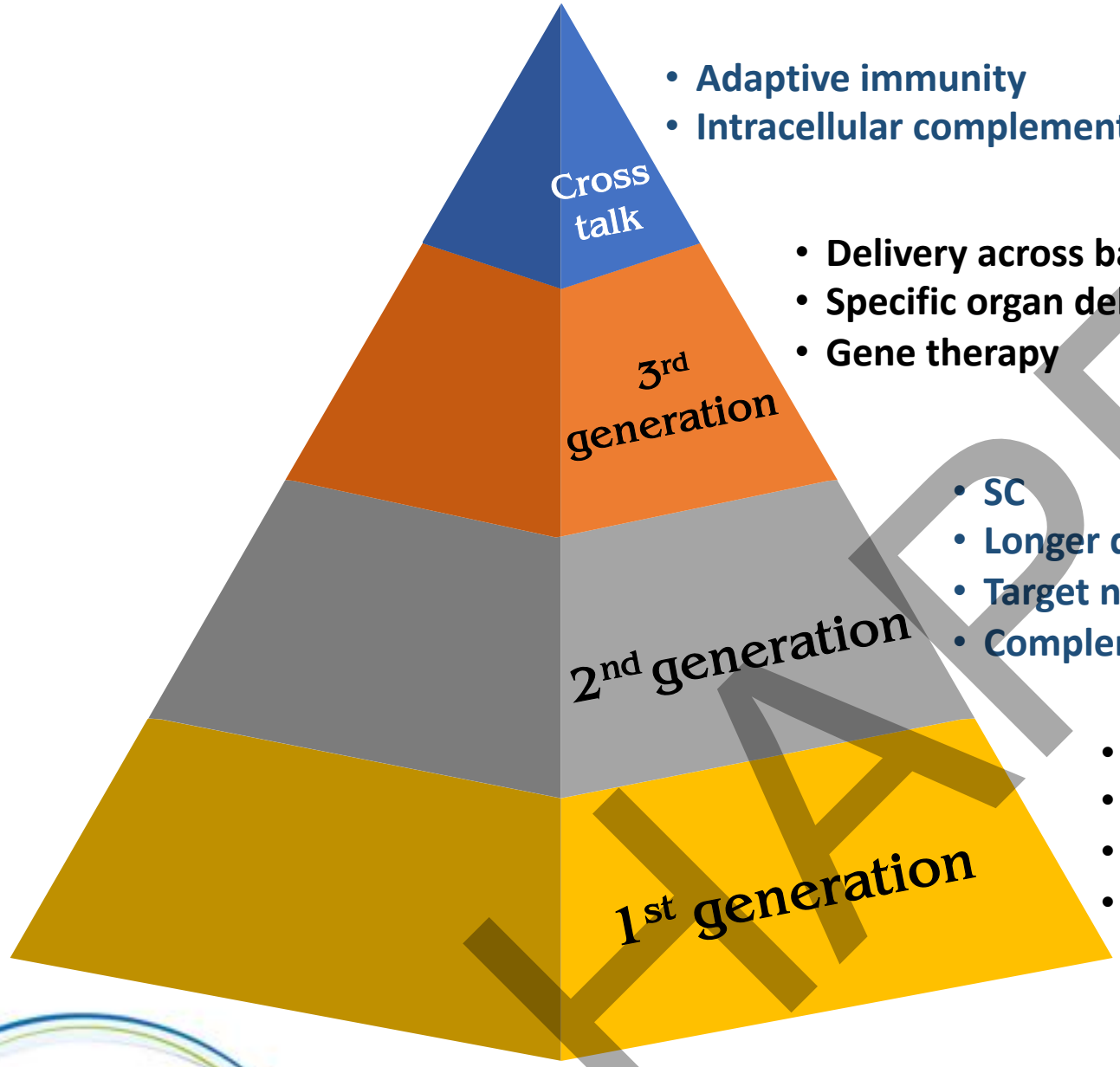
Fully human mAb against C5

For CHAPLE disease

Zilucoplan (Zilbrysq)

Peptide inhibitor of C5

For adult myasthenia gravis (with AchR Ab)



- Adaptive immunity
- Intracellular complement?

- Delivery across barriers (e.g. BBB)
- Specific organ delivery
- Gene therapy

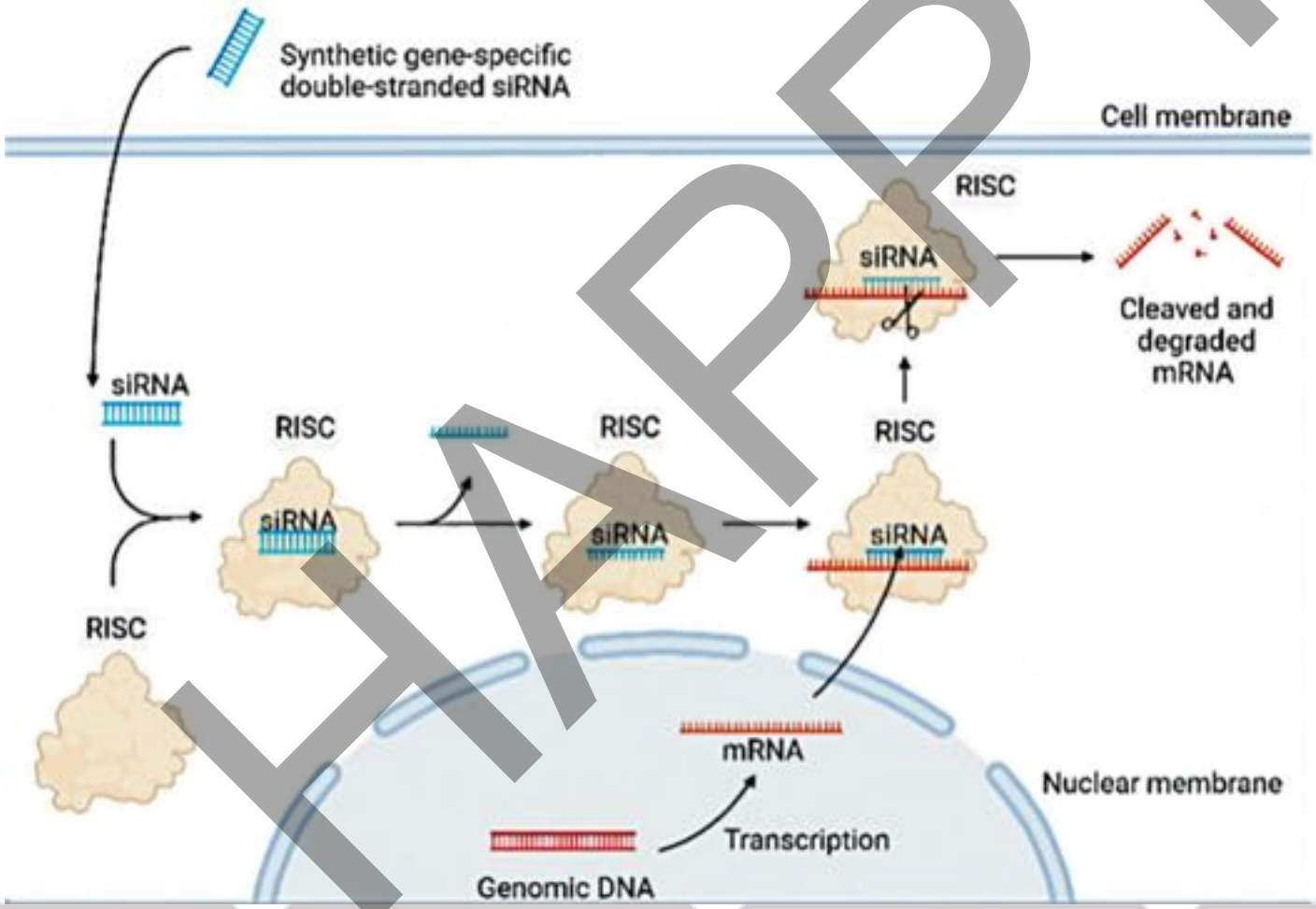
- SC
- Longer duration of action
- Target neoepitopes
- Complement modulation

- IV
- High dose
- Frequent dosing
- Total complement blockade

Mol Immunol 2019; 114: 341-352

Gene targeting as a therapeutic avenue

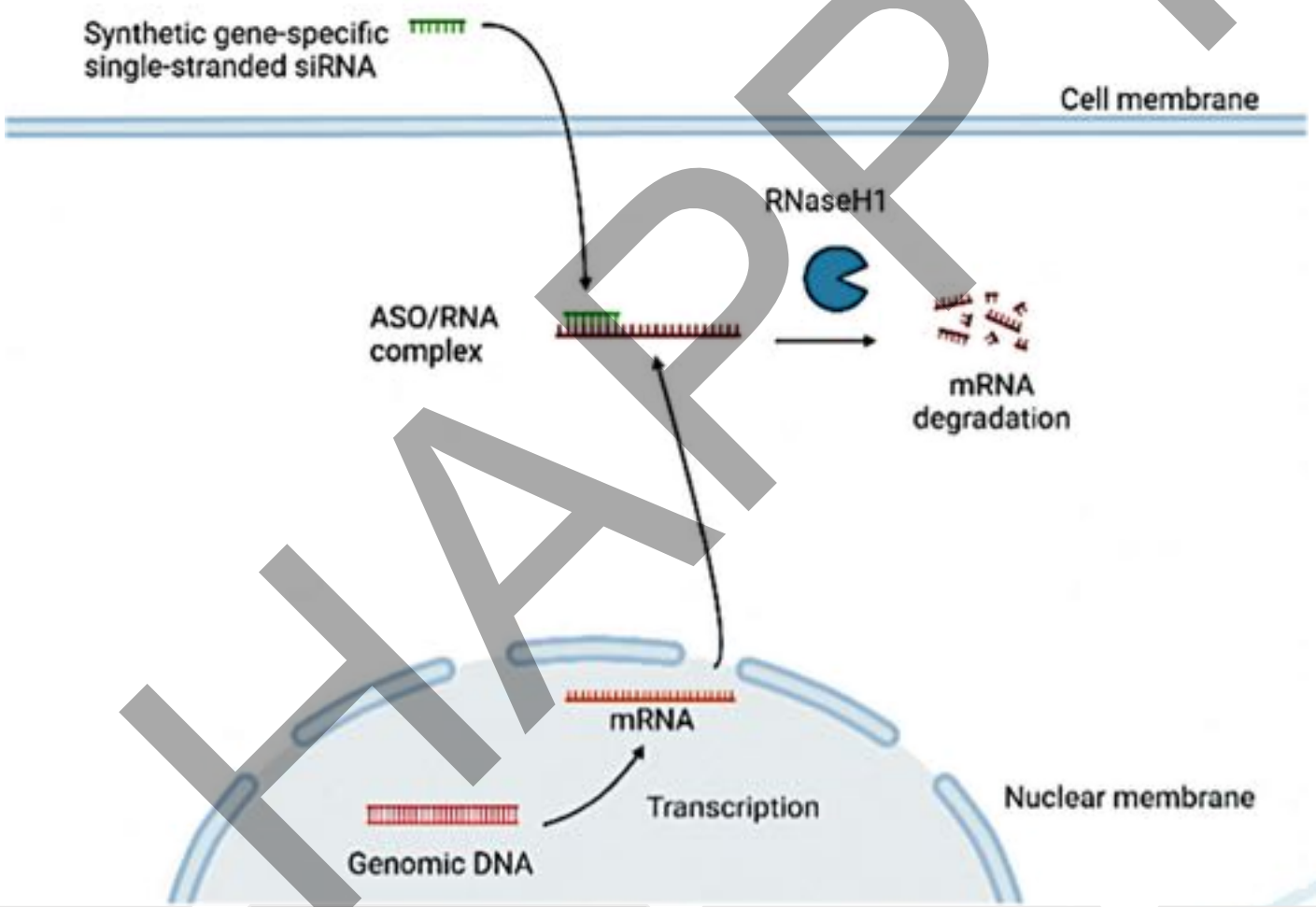
(1) RNA interference (RNAi)



Immunol Rev. 2023;313(1):402-419

Gene targeting as a therapeutic avenue

(2) Antisense oligonucleotides (ASO)



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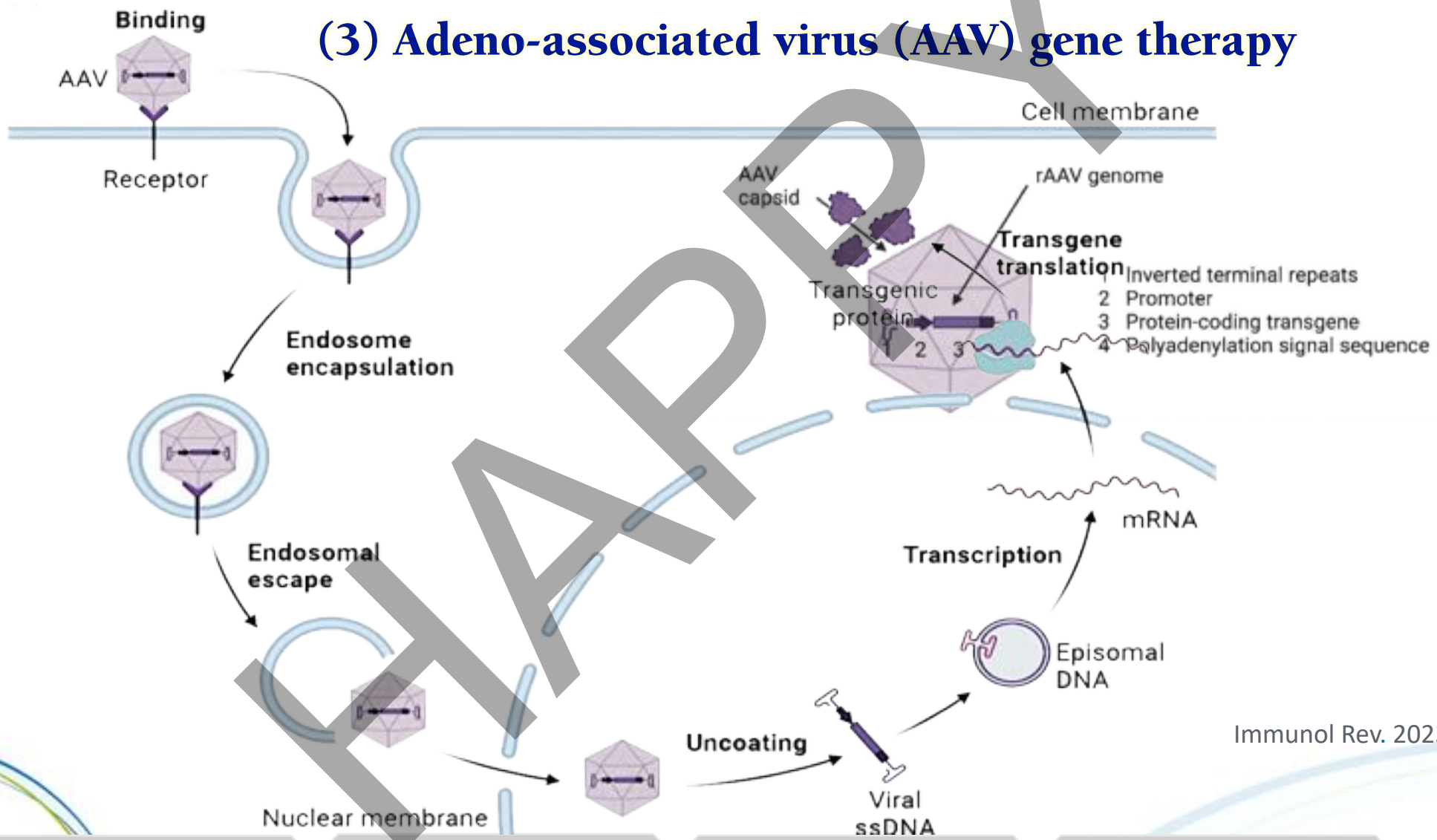
Gene targeting as a therapeutic avenue

(3) Adeno-associated virus (AAV) gene therapy



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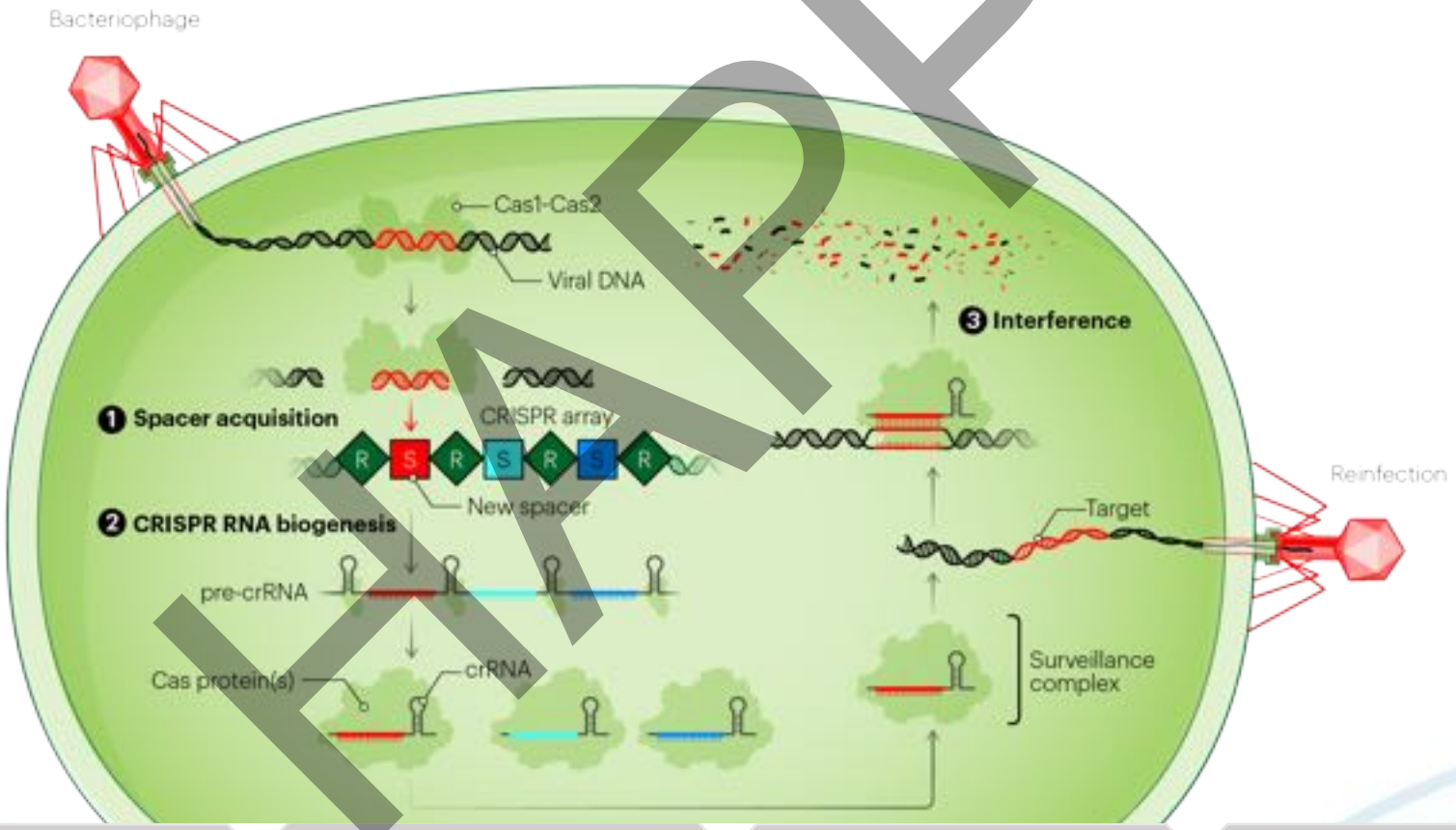
Gene targeting as a therapeutic avenue

(4) CRISPR/Cas

A naturally occurring defense mechanism employed by bacteria to defend against bacteriophages

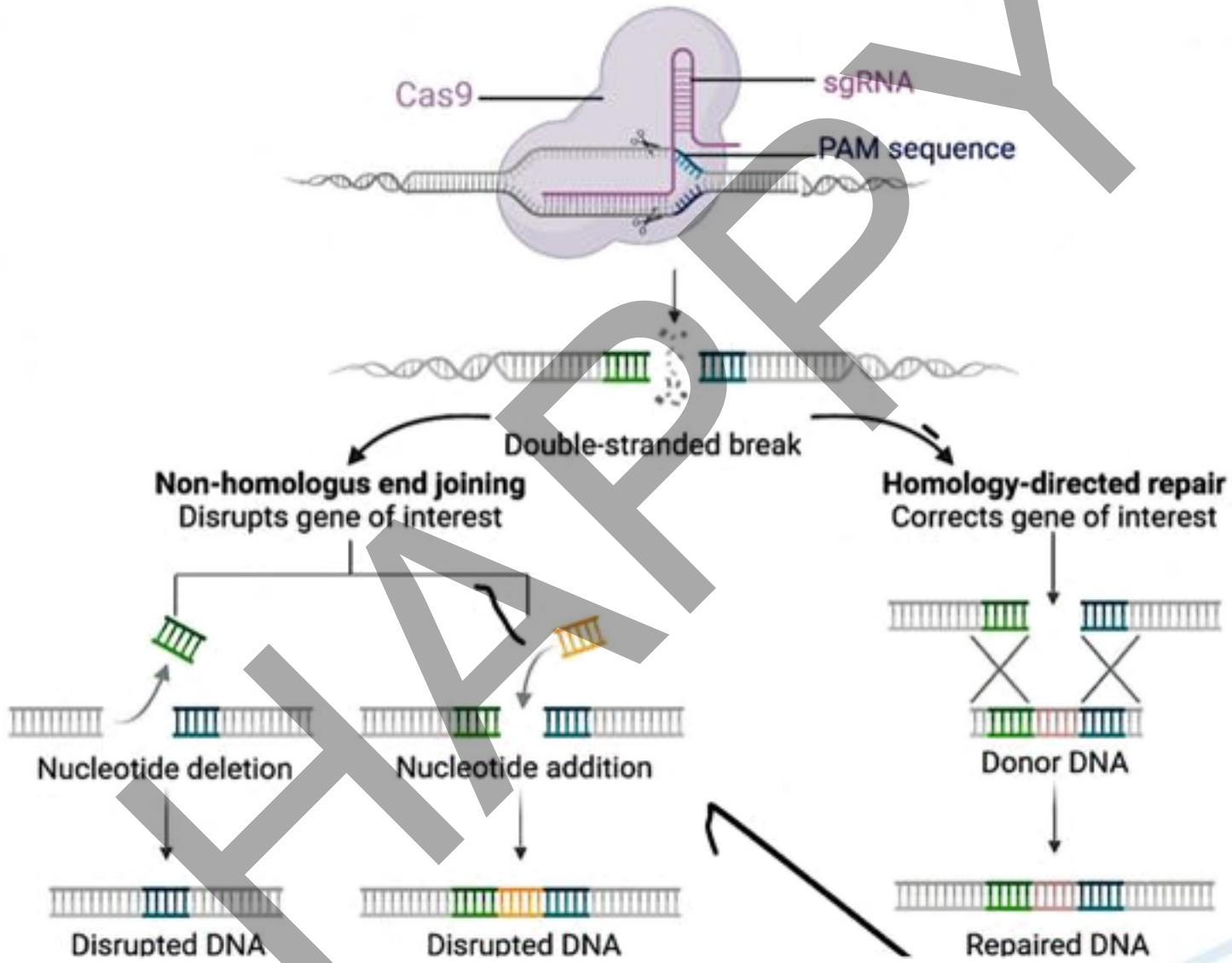


CRISPR/Cas9

MAYO CLINIC

Gene targeting as a therapeutic avenue

(4) CRISPR/Cas



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CONCLUSION

- C-target therapy is a real challenge because of the complexity of the system and disease-specific variability.
- Currently available C-target therapies fall in the following categories: mAb, small molecule peptides, recombinant proteins and aptamers.
- The future is directed towards genetic therapy as a new avenue for therapy