Johns Hopkins Engineering

Immunoengineering

Immunoengineering—Pathogens

Protein Engineering Design

JOHNS HOPKINS
WHITING SCHOOL
of ENGINEERING

Outline: How to Develop New Therapies

- General Design Considerations
- Engineered Cells
- Engineered Microbes & Viruses
- **Engineered Proteins – Cytokines & Antibodies**
- **Engineered Genetic Material**

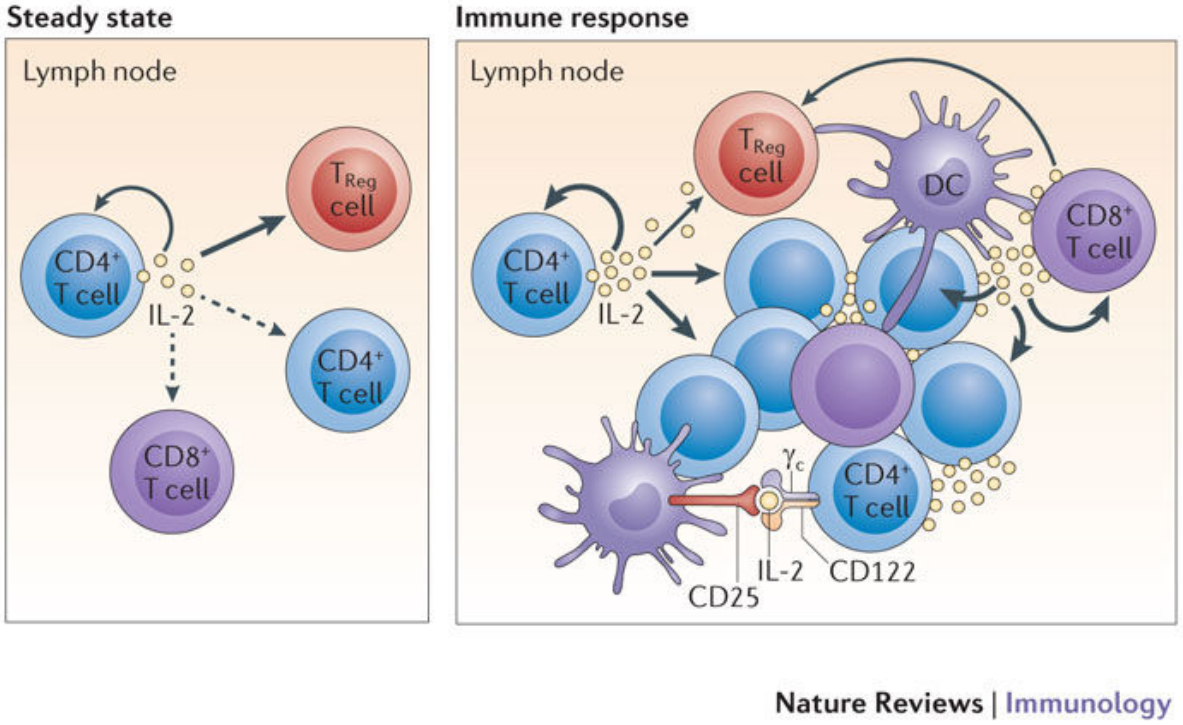
Introduction – Protein Engineering

Why further engineer proteins? – Example Cytokines

Challenges to using endogenous cytokines

- May signal to multiple receptors and cells
- Low production yields and stability
- Rapid clearance from bloodstream (<5 minutes)

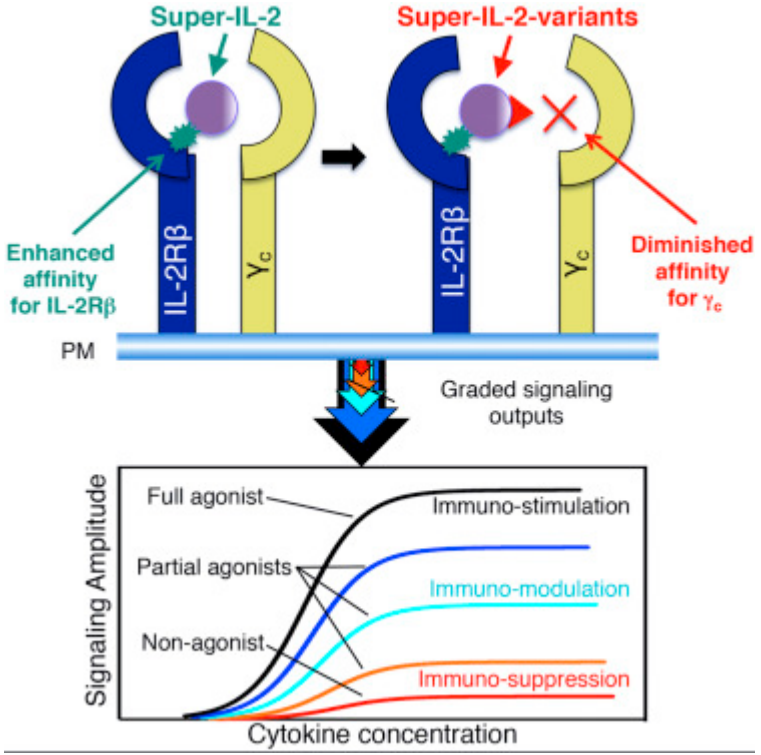
The Importance of IL-2



Boyman, Onur, and Jonathan Sprent. "The role of interleukin-2 during homeostasis and activation of the immune system." *Nature Reviews Immunology* 12.3 (2012): 180.

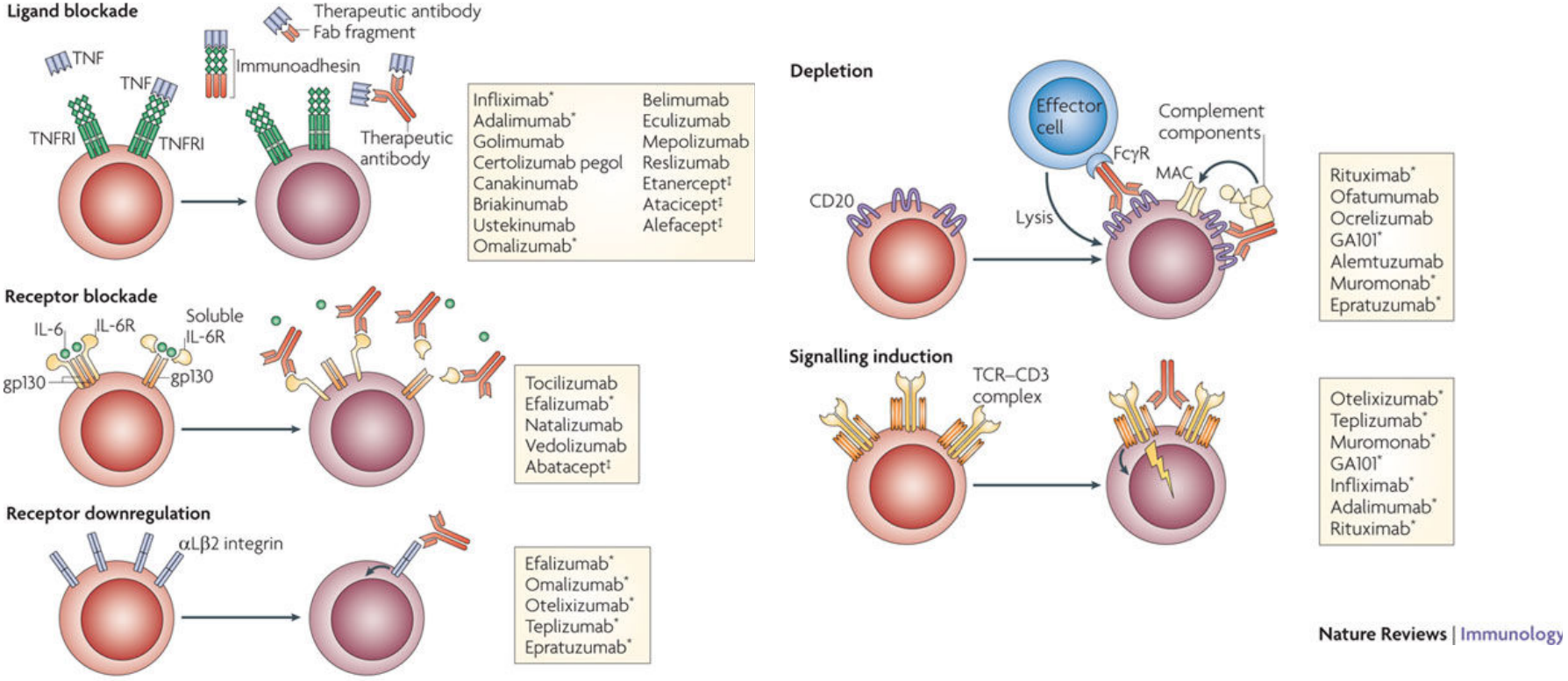
Engineering IL-2 for Blocking

- Off-target effects
- Blocking for GVHD, T cell tumors, autoimmunity
- Similar studies for targeting effector or regulatory cells



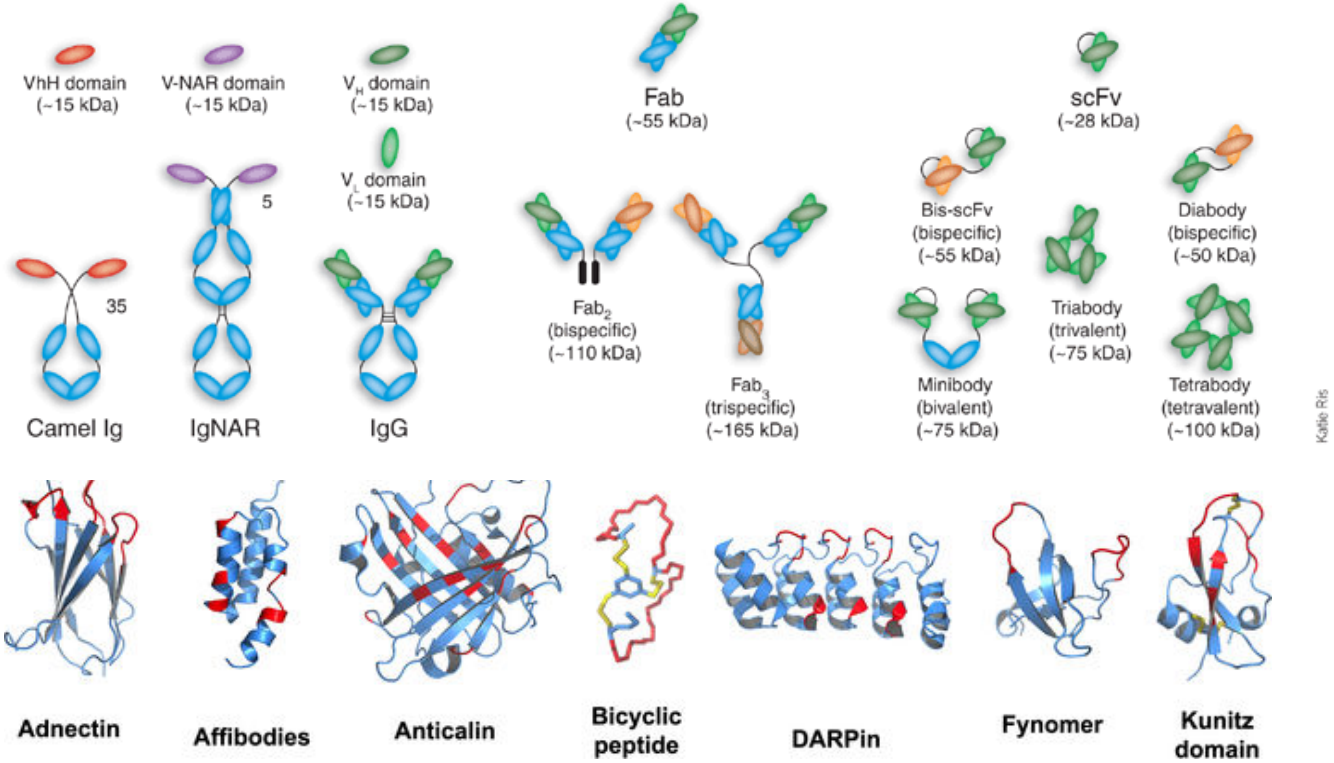
Mitra, Suman, et al. "Interleukin-2 activity can be fine tuned with engineered receptor signaling clamps." *Immunity* 42.5 (2015): 826-838.

Antibody Therapeutic Mechanisms



Chan, Andrew C., and Paul J. Carter. "Therapeutic antibodies for autoimmunity and inflammation." *Nature Reviews Immunology* 10.5 (2010): 301.

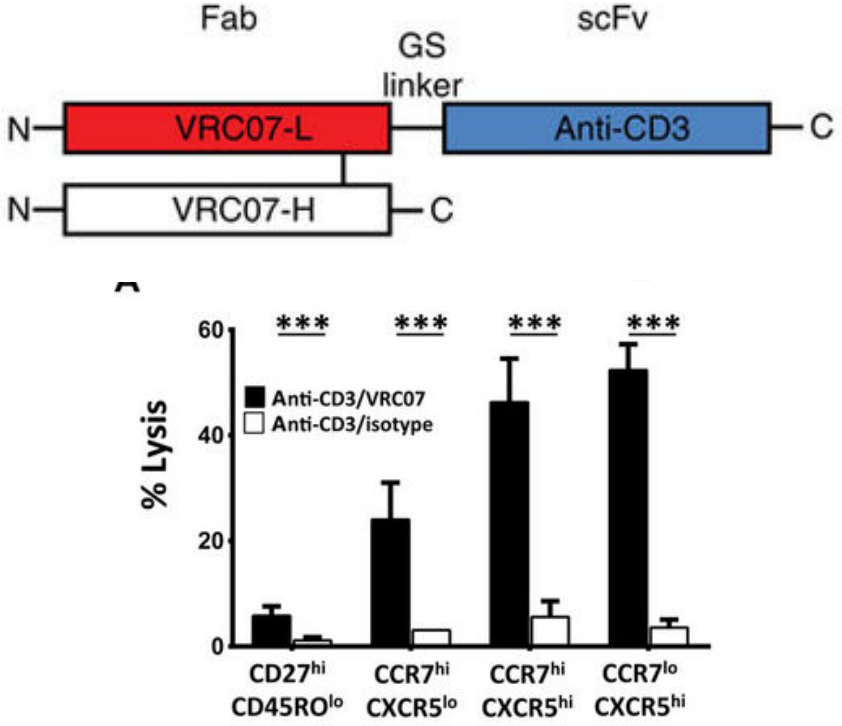
Antibody Engineering – Unique Recognition



Holliger, Philipp, and Peter J. Hudson. "Engineered antibody fragments and the rise of single domains." *Nature biotechnology* 23.9 (2005): 1126.
Owens, Brian. "Faster, deeper, smaller—the rise of antibody-like scaffolds." (2017): 602.

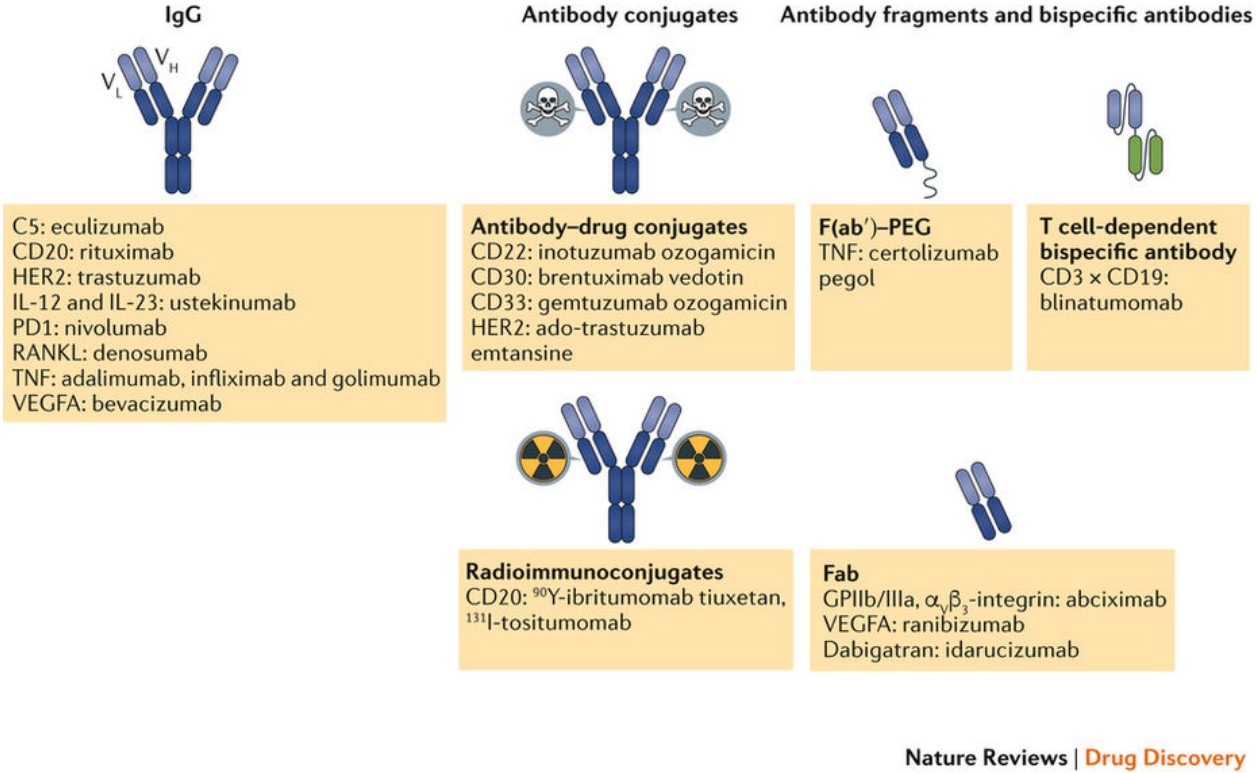
Example - Engineering Bi-specific Antibodies for HIV

- Target infected CD4+ T cells
- Activate CD4+ T cells that are latently infected
- Direct CD8+ T cells to kill infected cells



Petrovas, Constantinos, et al. "Follicular CD8 T cells accumulate in HIV infection and can kill infected cells in vitro via bispecific antibodies." *Science translational medicine*9.373 (2017): eaag2285.
Pegu, Amarendra, et al. "Activation and lysis of human CD4 cells latently infected with HIV-1." *Nature communications* 6 (2015): 8447.

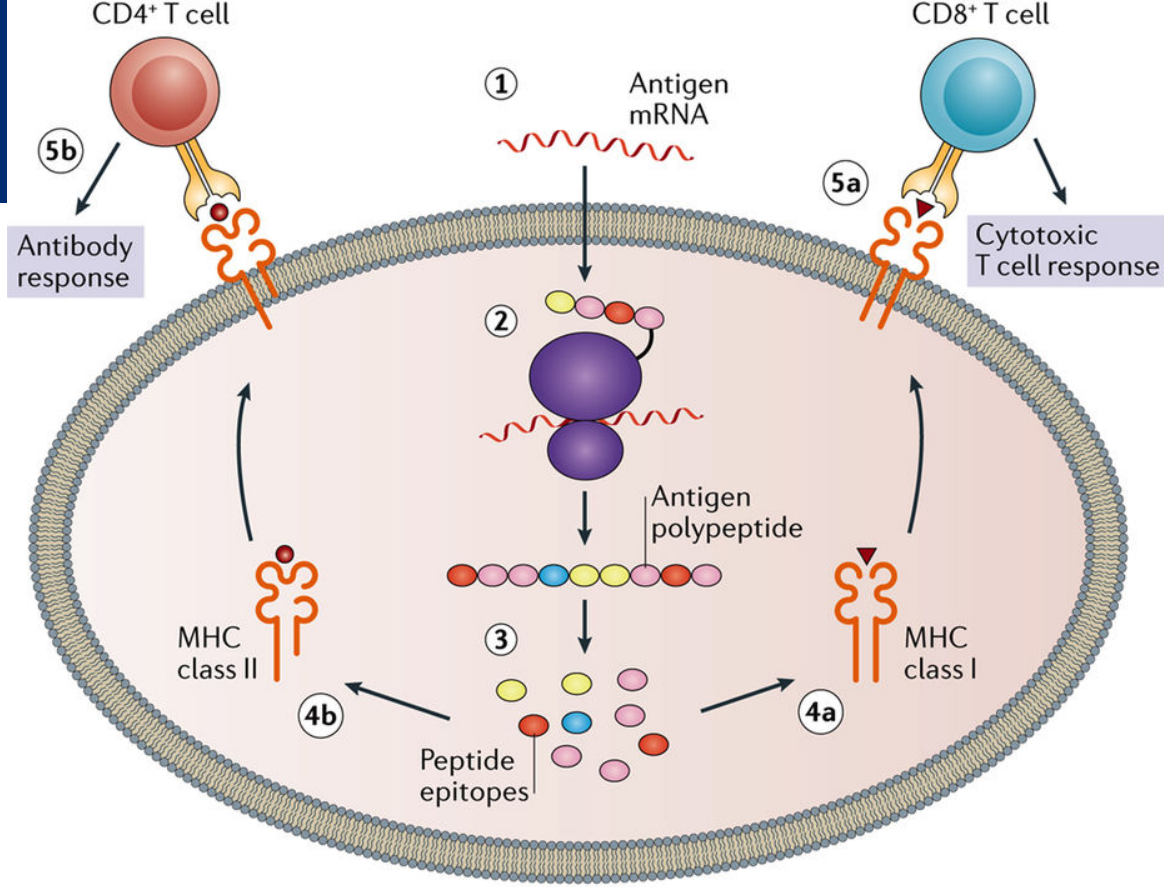
Antibody Drug Engineering



Carter, Paul J., and Greg A. Lazar. "Next generation antibody drugs: pursuit of the'high-hanging fruit'." *Nature Reviews Drug Discovery* (2017).

Nucleic Acid Engineering

- Transfection for other therapies
  - Cellular
  - Protein
- Source of vaccines



Hajj, Khalid A., and Kathryn A. Whitehead. "Tools for translation: non-viral materials for therapeutic mRNA delivery." *Nature Reviews Materials* 2.10 (2017): 17056.

Example - mRNA Flu Vaccines

Challenges of flu vaccines

- Manufacturing scale up
- Quality standards
- Variable antigens
- Potency in all age groups
- Allergies

Petsch, Benjamin, et al. "Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection." *Nature biotechnology* 30.12 (2012): 1210.

Example - mRNA Flu Vaccines

Addresses challenges of flu vaccines

- Manufacturing scale up
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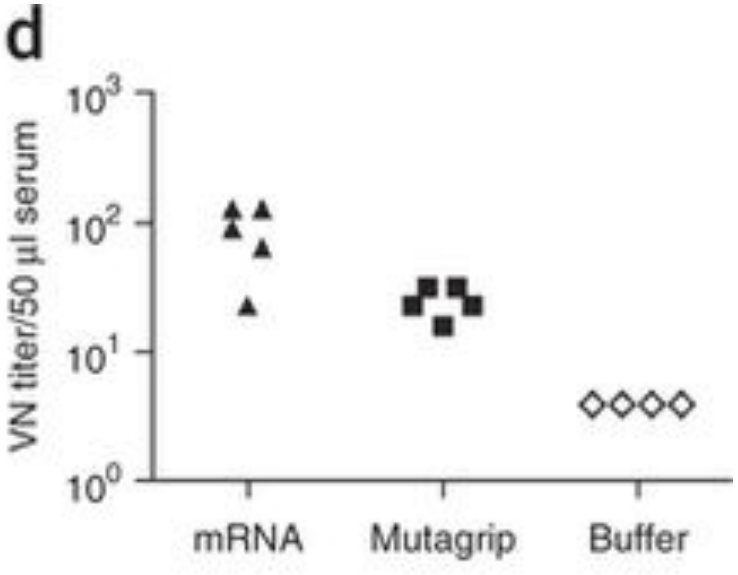


Petsch, Benjamin, et al. "Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection." *Nature biotechnology* 30.12 (2012): 1210.

Challenges and Opportunities for Biologics

Advantages

- Biocompatible
- Bioinspired
- Specificity
- FDA
- Potency

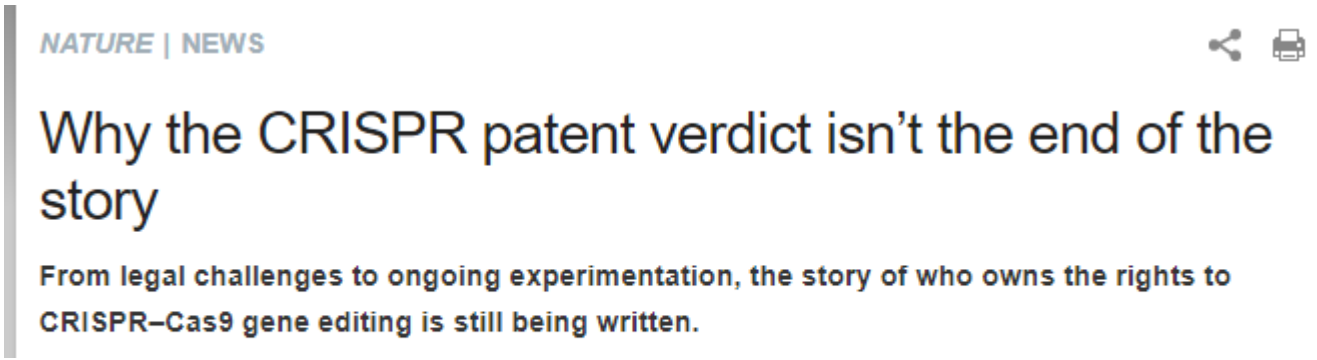
Disadvantages

- Manufacturing/Cost
- Shelf-life/storage
- Administration
- Control
- Patents

Issues with Patents for Biologics

- Example: Rise of monoclonal antibodies approved by the FDA for therapy
  - What counts as a unique antibody:
  - Unique sequence? Unique sequence of Fab portion? Unique isotype or species? Unique format such as Fab?

- Example # 2



NATURE | NEWS

Why the CRISPR patent verdict isn't the end of the story

From legal challenges to ongoing experimentation, the story of who owns the rights to CRISPR–Cas9 gene editing is still being written.