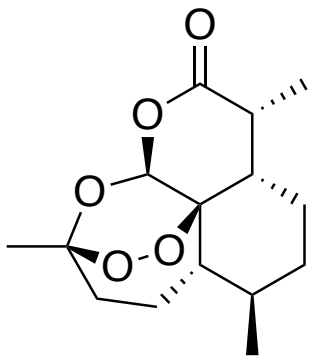
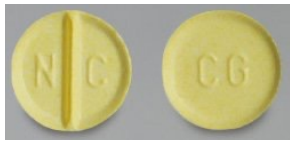
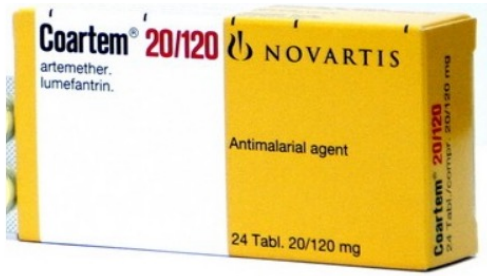
20.109 Module 2

Lecture #3: **Choosing an intervention modality**

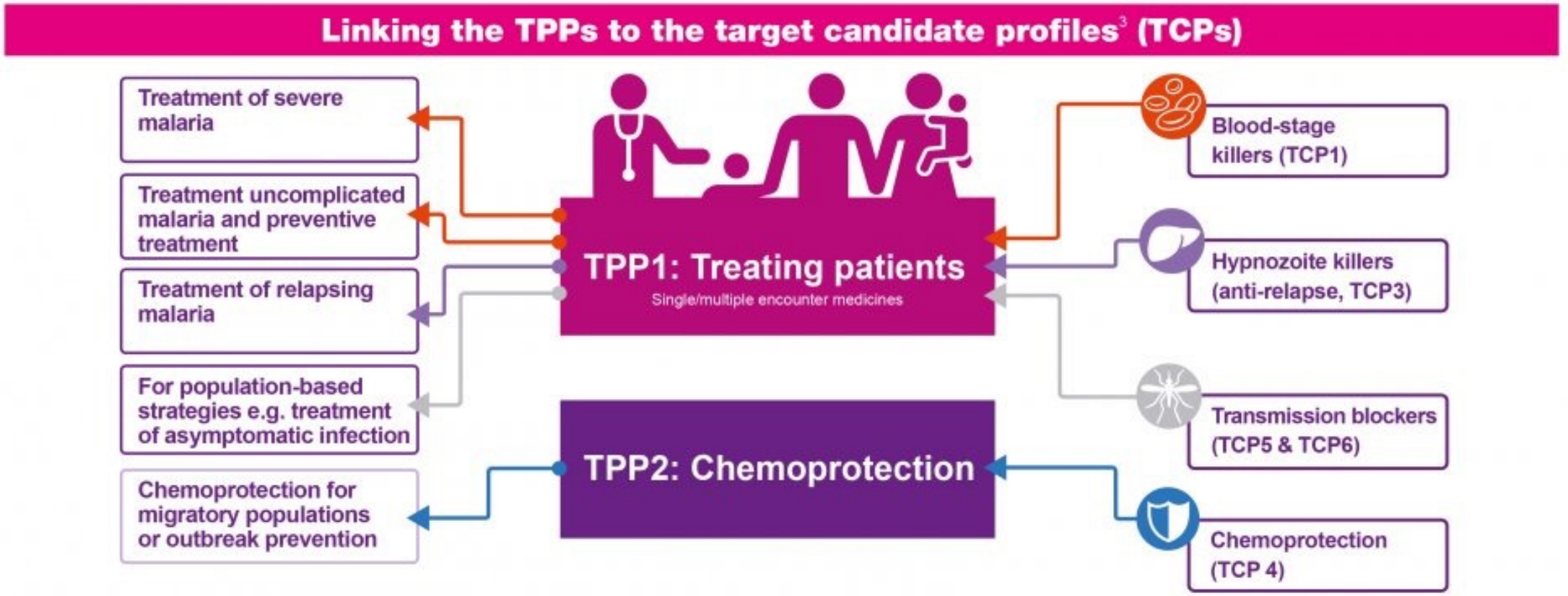
Instructor: Prof. Jacquin C. Niles
Department of Biological Engineering
Email: jcniles@mit.edu
20 October 2022







MMV Target Product & Candidate Profiles



Target Candidate Profile (TCP)

- Describes molecules that act on a biological process

Target Product Profile (TPP)

- Outlines the desired 'profile' or characteristics of a product aimed at a particular disease or diseases
- Outlines intended use, target populations and other desired attributes of products

MMV
Medicines for Malaria Venture

Learning Objectives

A. Understand the available modalities for engaging selected targets

B. Discuss factors guiding selection of an intervention strategy – multifactorial
   A. Target properties
   B. Bioavailability (route of administration – oral, IV, etc.)
   C. Cost

Strategizing a therapeutic approach

A. Defining the therapeutic intervention

A. What is intended goal/ outcome of the intervention? [Target Product Profile]

B. Precisely defining the therapeutic target(s)

A. What is the biological process(es) to be manipulated? [Target Candidate Profile]

B. Choosing an appropriate operational scale

A. Molecular v. cellular v. tissue/organ v. whole (model) organism level

C. Validating the therapeutic potential of selected target(s)

A. What evidence do you need to establish suitability of a therapeutic target?

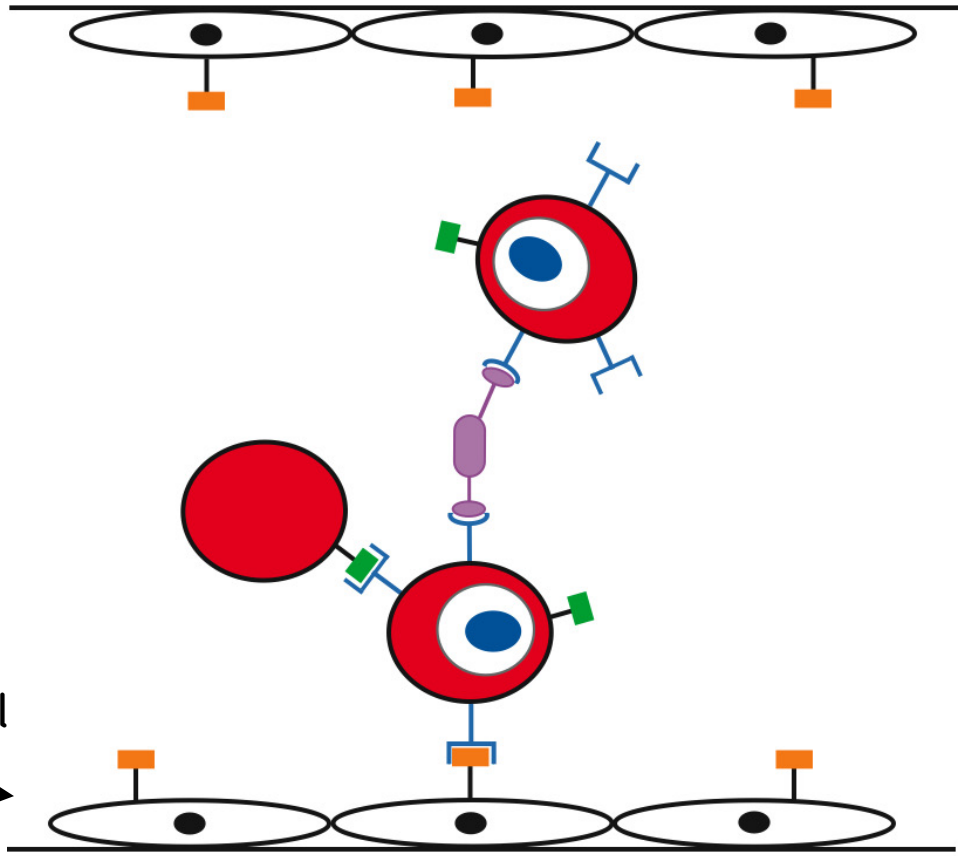
Strategizing a therapeutic approach

A. Defining the therapeutic intervention
   A. What is intended goal/ outcome of the intervention? [Target Product Profile]

B. Precisely defining the therapeutic target(s)
   A. What is the biological process(es) to be manipulated? [Target Candidate Profile]
   B. Choosing an appropriate operational scale
      A. Molecular v. cellular v. tissue/organ v. whole (model) organism level

C. Validating the therapeutic potential of selected target(s):
   A. What evidence do you need to establish suitability of a therapeutic target?

Understanding the molecular and cellular basis for observable clinical outcomes = pathogenesis

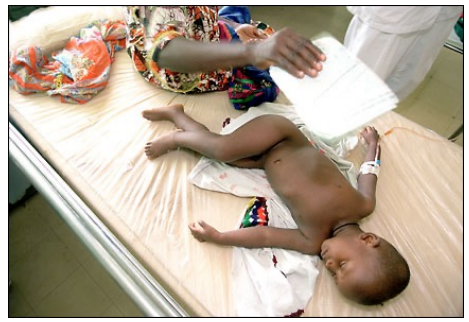


Endothelial cell receptors
CD36
ICAM-1
VCAM
E-selectin

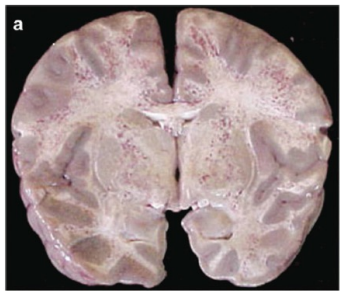
Parasitized RBC ligands
PfEMP-1 family
Modified Band 3

Normal RBC ligands
Complement Receptor 1 (CR1)

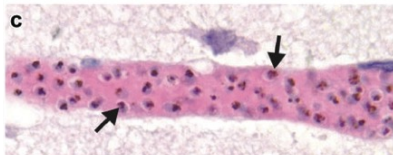
Platelet Ligands
CD36



Cerebral malaria
(fatal complication)



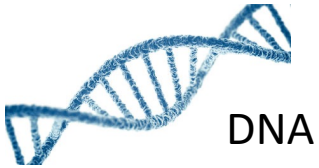
Microhemmorhages



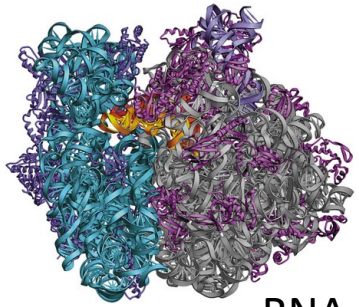
Vascular occlusion

Microbe-host Interactions
- Disease outcomes

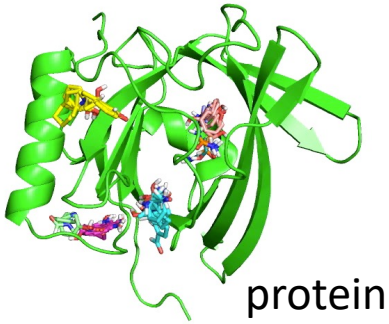
… thinking across scales to visualize processes and molecules to target for therapeutic applications



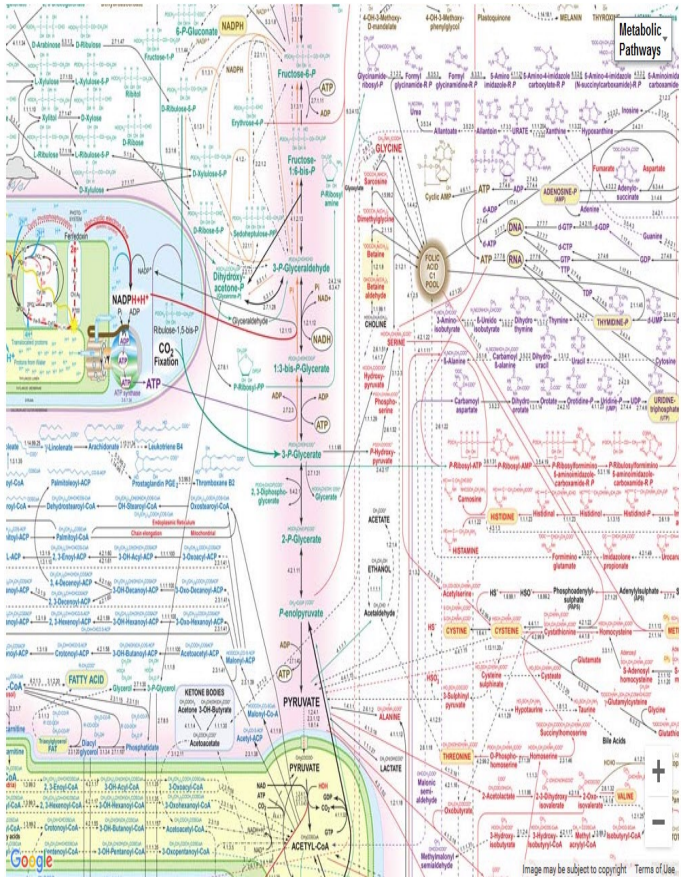
DNA

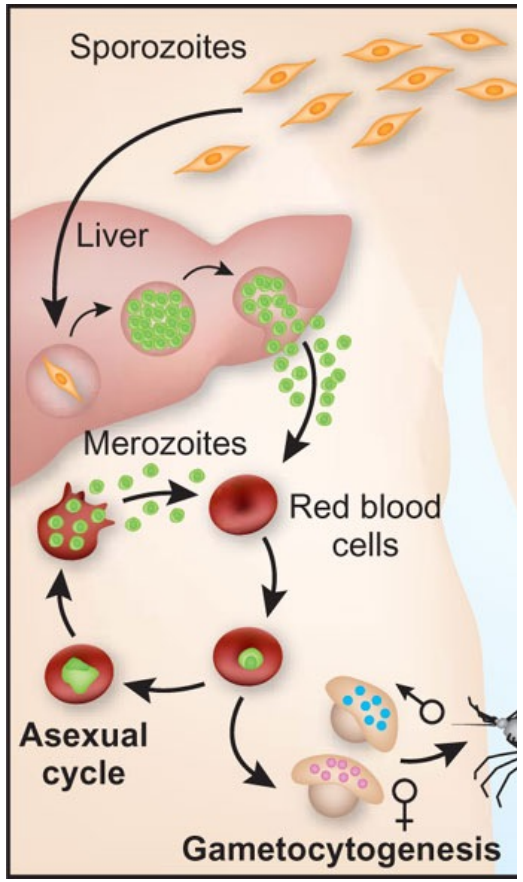


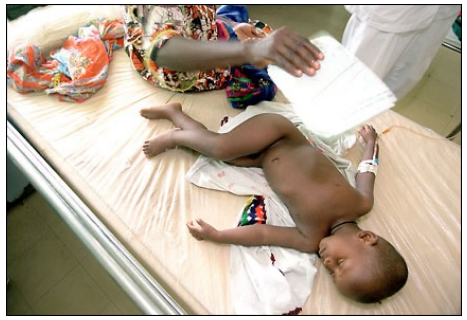
RNA



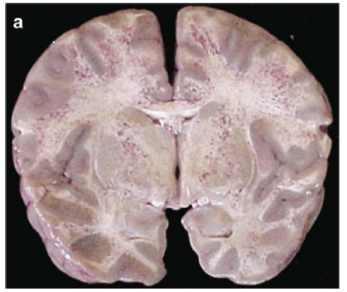
protein



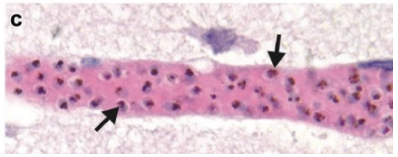




Cerebral malaria



Microhemorrhages



Vascular occlusion

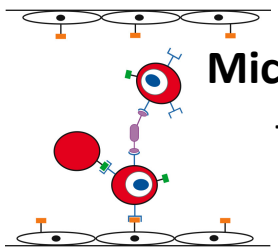
Molecules

- DNA, RNA
- Proteins (e.g., enzymes)
- Carbohydrates

Biochemical/ Metabolic pathways

Cellular behavior

- Replication
- RBC invasion/ egress
- Differentiation

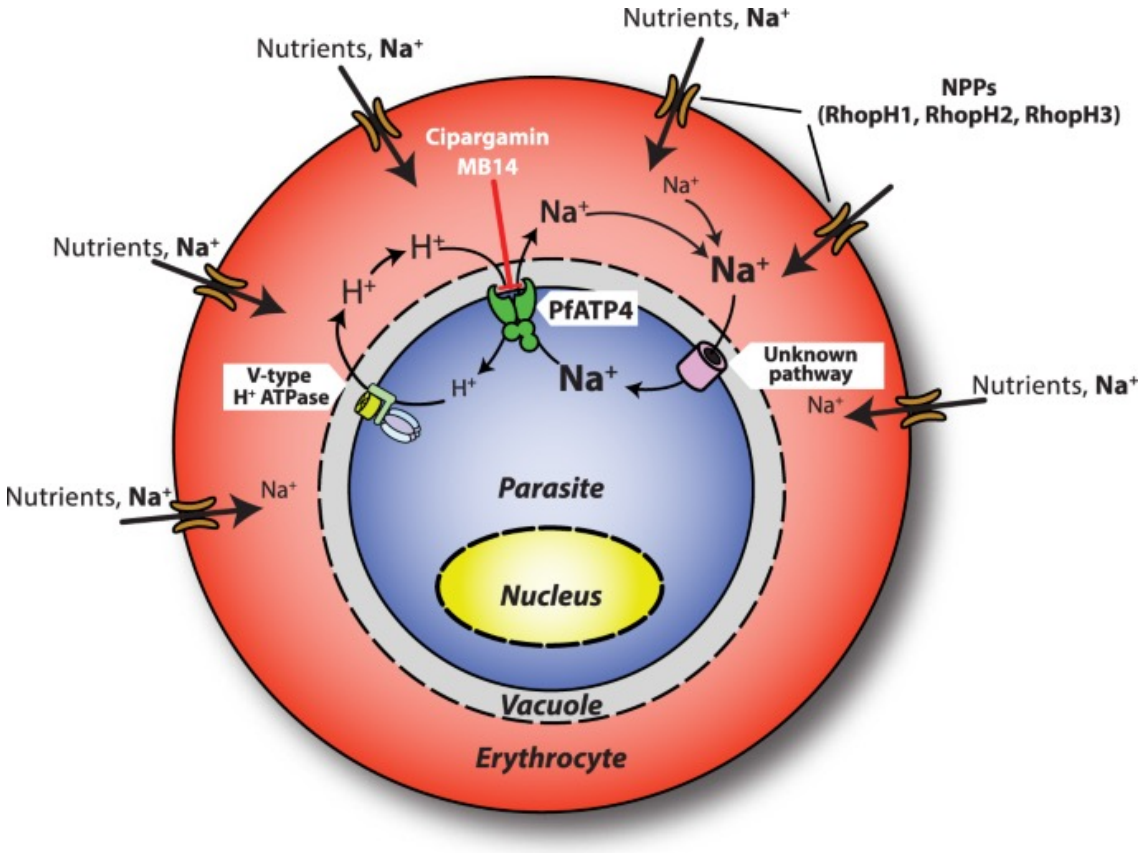


Microbe-host Interactions

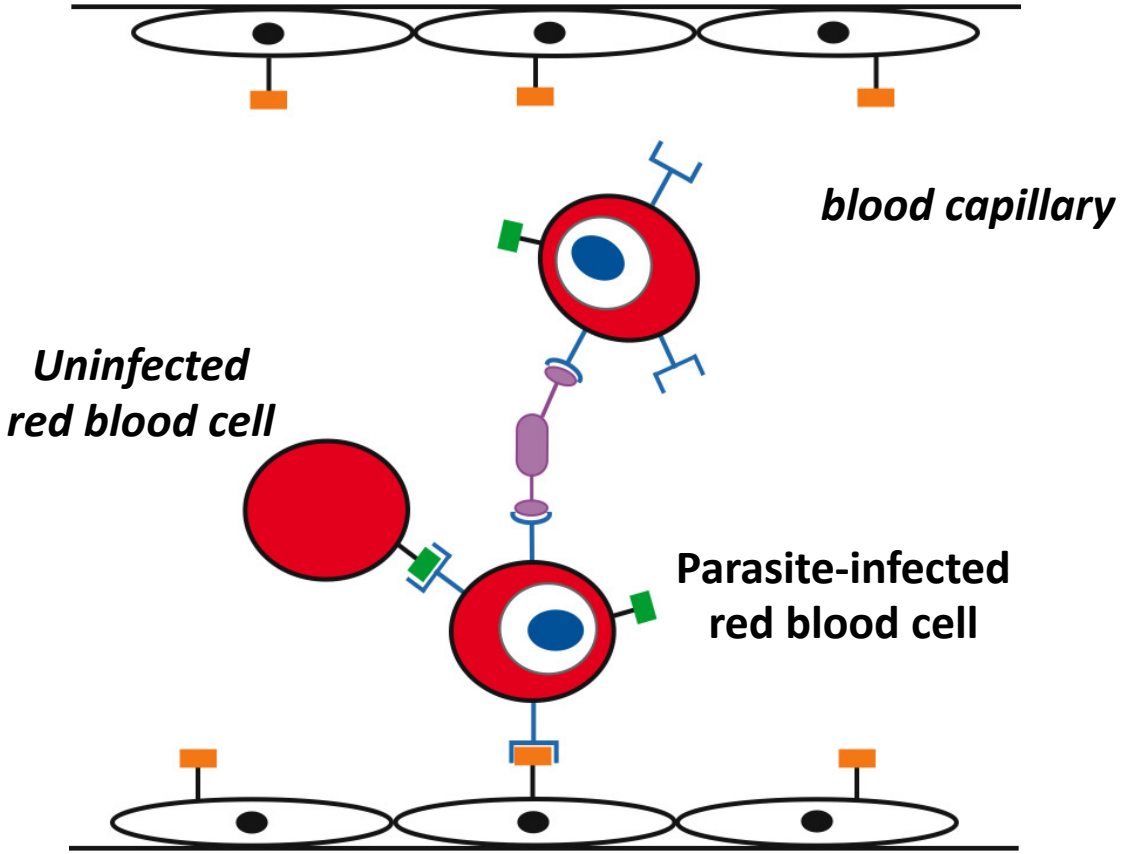
- Disease outcomes

Consider these targets …

***Question**: What are some requirements for effectively disrupting these targets?*



Target 1:
Parasite transporter, protein (PfATP4) regulating Na^+/ H^+ exchange in cells



Target 2:
Parasite ligand protein interacting with host cell receptor protein on cell surface

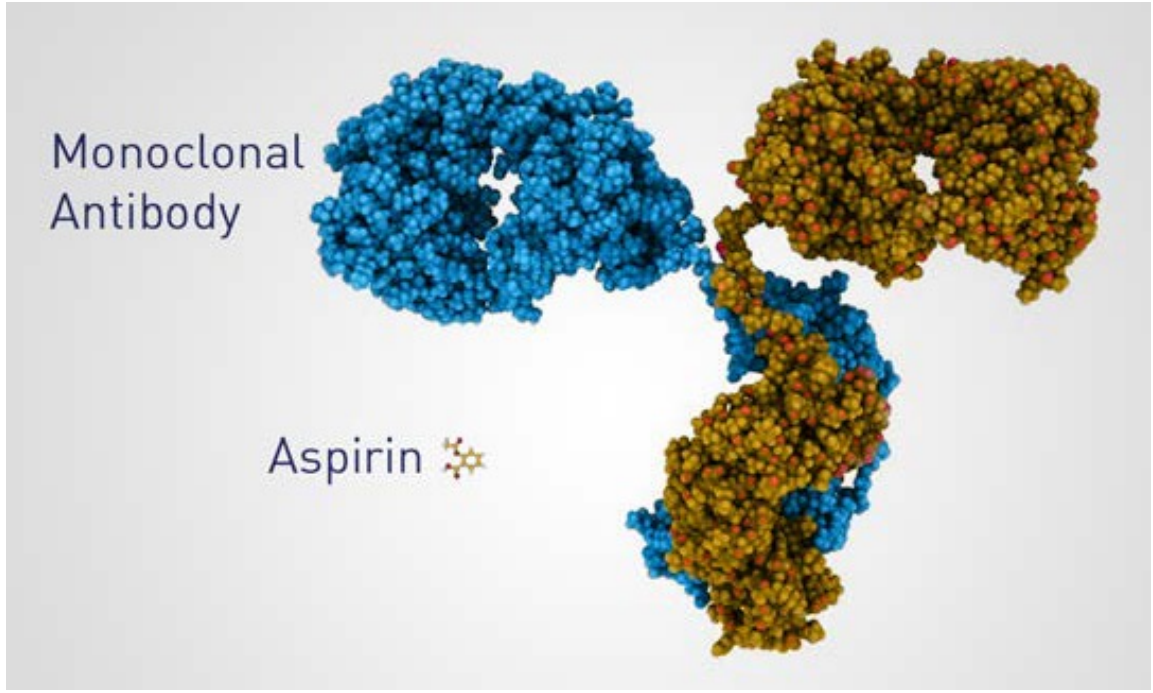
Strategies available for disrupting target function

***Question**: What are some molecular mechanisms by which you can disrupt the function of a selected target?*

- Small molecules (Mw ≤ 500 Da)

- Peptides (500 Da < Mw < 5,000 Da)
- Nucleic acids (Mw ~ kDa)
  - Aptamers;
  - Antisense oligonucleotides
  - siRNAs

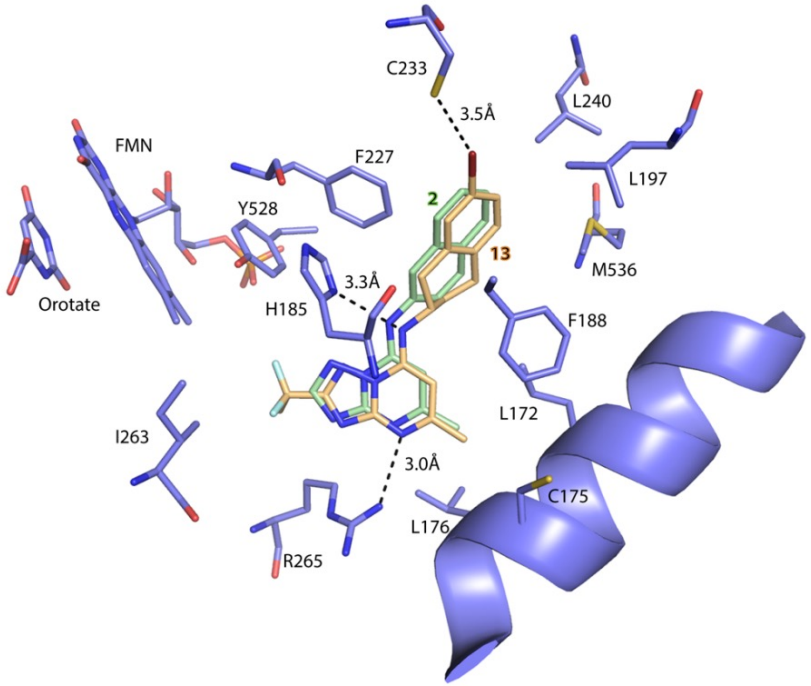
- Biologics* (Mw ~ kDa)
  - Proteins (antibodies, enzymes …)



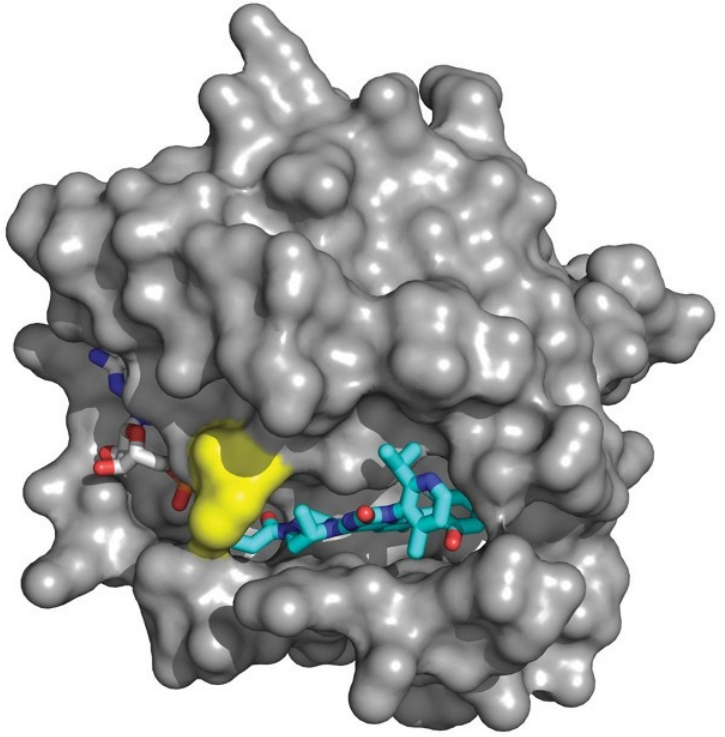
– Biological products are a diverse category of products and are generally large, complex molecules.
– Usually produced through biotechnology in a living system or cells (microorganisms, plants or animals)

Properties favoring small molecule therapeutics

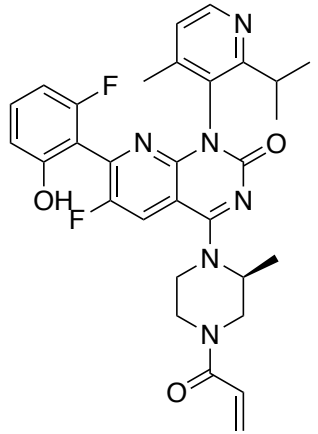
- Can make intimate molecular contact with relevant target protein surface features



Flavin and substrate binding sites in the *Plasmodium* DHODH protein



AMG510 bound to KRAS



AMG510 (2D)

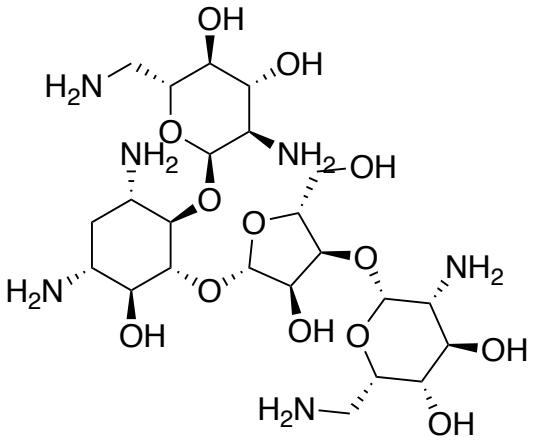
References:
DOI: 10.1038/s41586-019-1694-1
DOI: 10.1021/acs.jmedchem.6b00275

Properties favoring small molecule therapeutics

- Can make intimate molecular contact with relevant target protein surface features

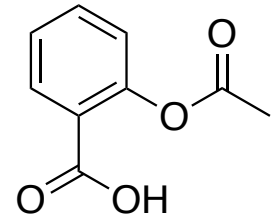
- Cell membrane permeable
  - Intracellular
  - Extracellular targets

- Orally bioavailable



Log P: -9.55
MR: 139.78 [cm3/mol]
tPSA: 353.11
CLogP: -6.46605

Log P: 1.18
MR: 43.29 [cm3/mol]
tPSA: 63.6
CLogP: 0.804



Lipinsky's 'Rule of 5': Predicting oral bioavailability likelihood

1. Molecular weight is less than ~500 Da

2. The calculated log P value is less than five
- Measure of lipophilicity (propensity to partition into cell membranes, fatty tissues)

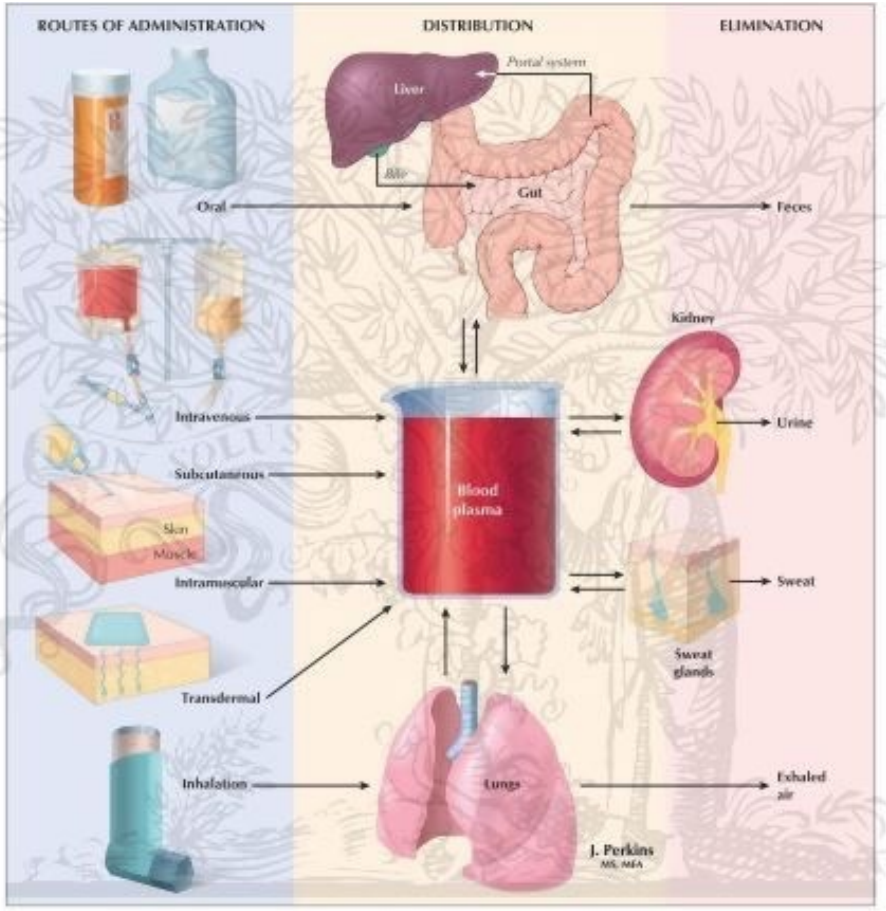
3. There are less than five hydrogen bond donors (–NH–, –OH)

4. The number of hydrogen bond acceptors (–N6-point double bond, –O–) is less than ten

Properties favoring small molecule therapeutics

- Can make intimate molecular contact with relevant target protein surface features
- Cell membrane permeable
  - Intracellular
  - Extracellular targets
- Oral bioavailability
- Stability
  - Gastrointestinal tract (e.g. pH, enzymes, …)
  - Metabolic transformation (liver, gut microbiome)
  - Excretion

Absorption, Distribution, Metabolism, Excretion (ADME) Concept

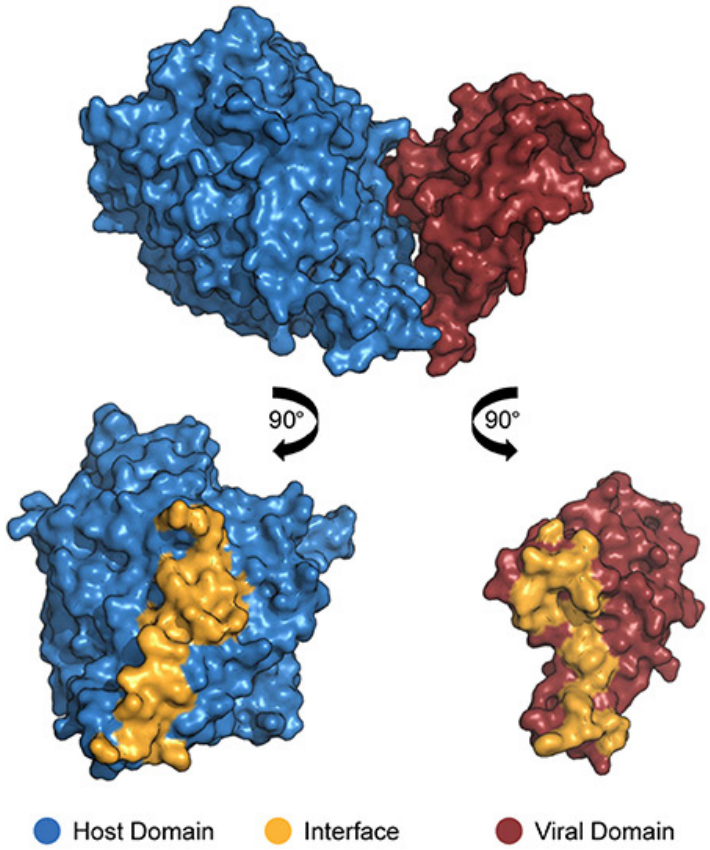


Properties favoring small molecule therapeutics

- Can make intimate molecular contact with relevant target protein surface features
- Cell membrane permeable
  - Intracellular targets
  - Extracellular targets
- Oral bioavailability
- Stability
  - Gastrointestinal tract (e.g. pH, enzymes, …)
  - Metabolic transformation (liver, gut microbiome)
  - Excretion
- Cost
  - Cheaper to manufacture on large scale
  - Cheaper to distribute (little need for refrigeration, etc.)

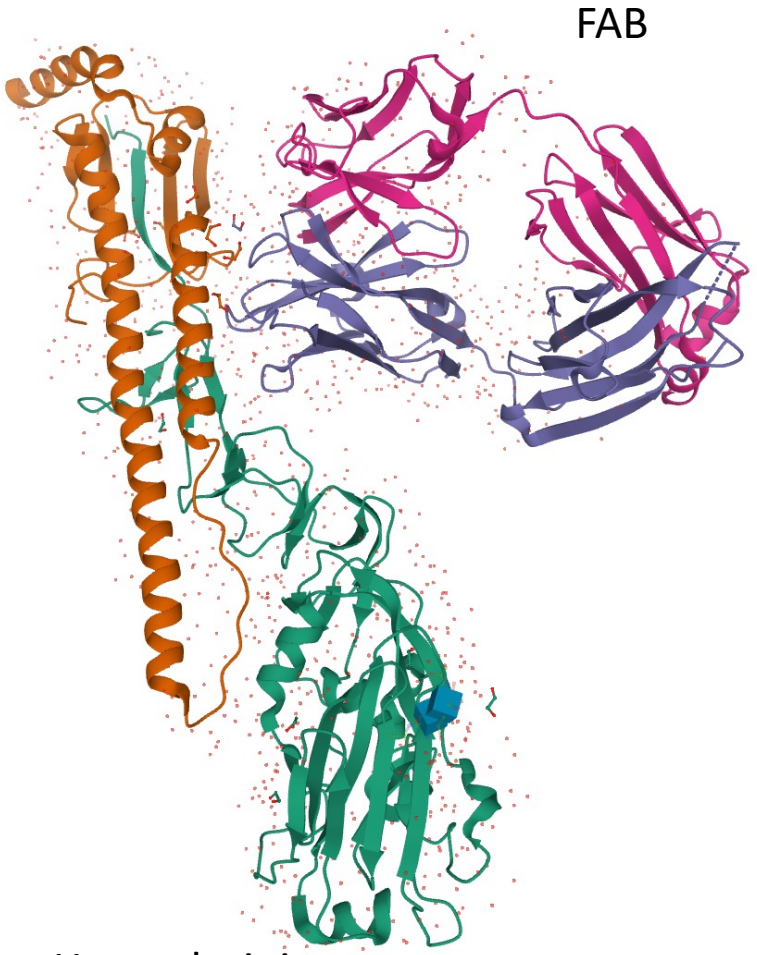
Comparing properties of (protein) biologics to small molecules

- Can make intimate molecular contact with relevant target protein surface features



Host-virus protein-protein interaction

Broadly neutralizing anti-hemagglutinin antibody



PDB: 4FQI

Comparing properties of (protein) biologics to small molecules

- **Can make intimate molecular contact with relevant target protein surface features**

- Cell membrane permeability:
  - Intracellular
  - Extracellular

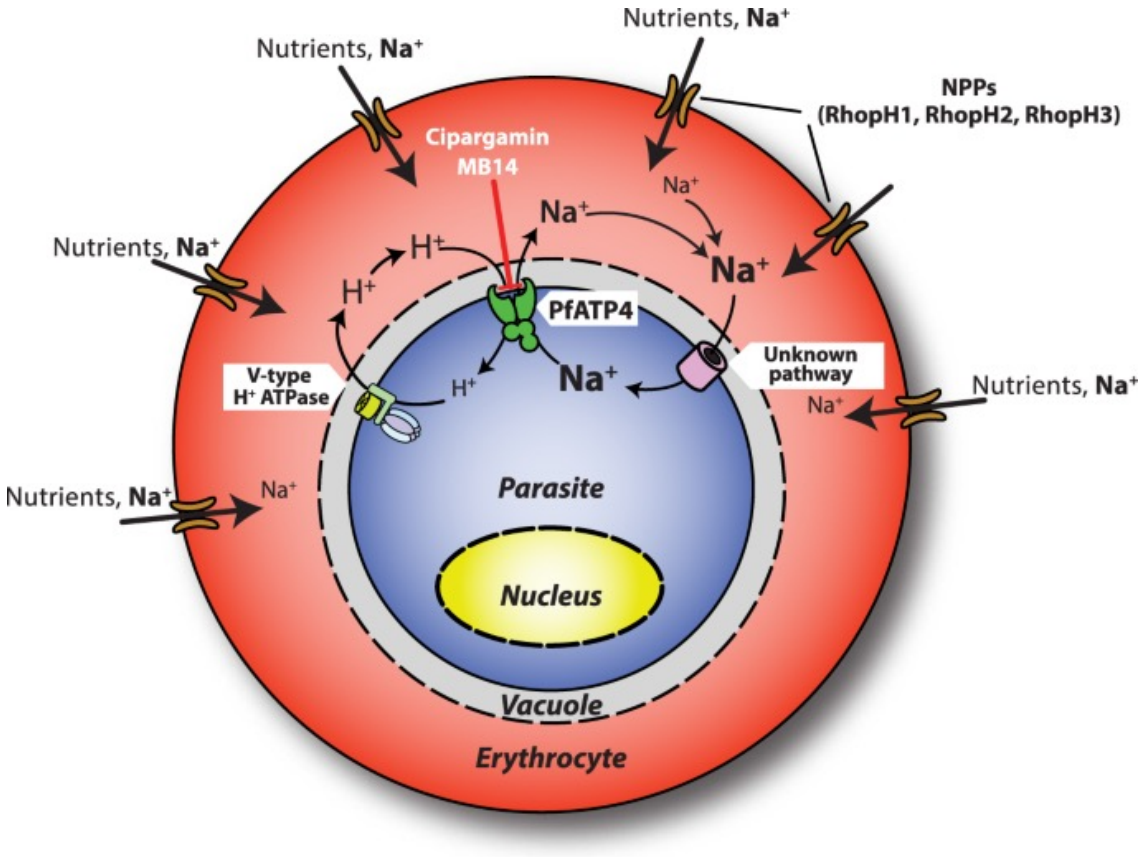
- Oral bioavailability:

- Stability
  - Gastrointestinal tract (e.g. pH, enzymes, …)
  - Metabolic transformation (liver, gut microbiome)
  - Excretion

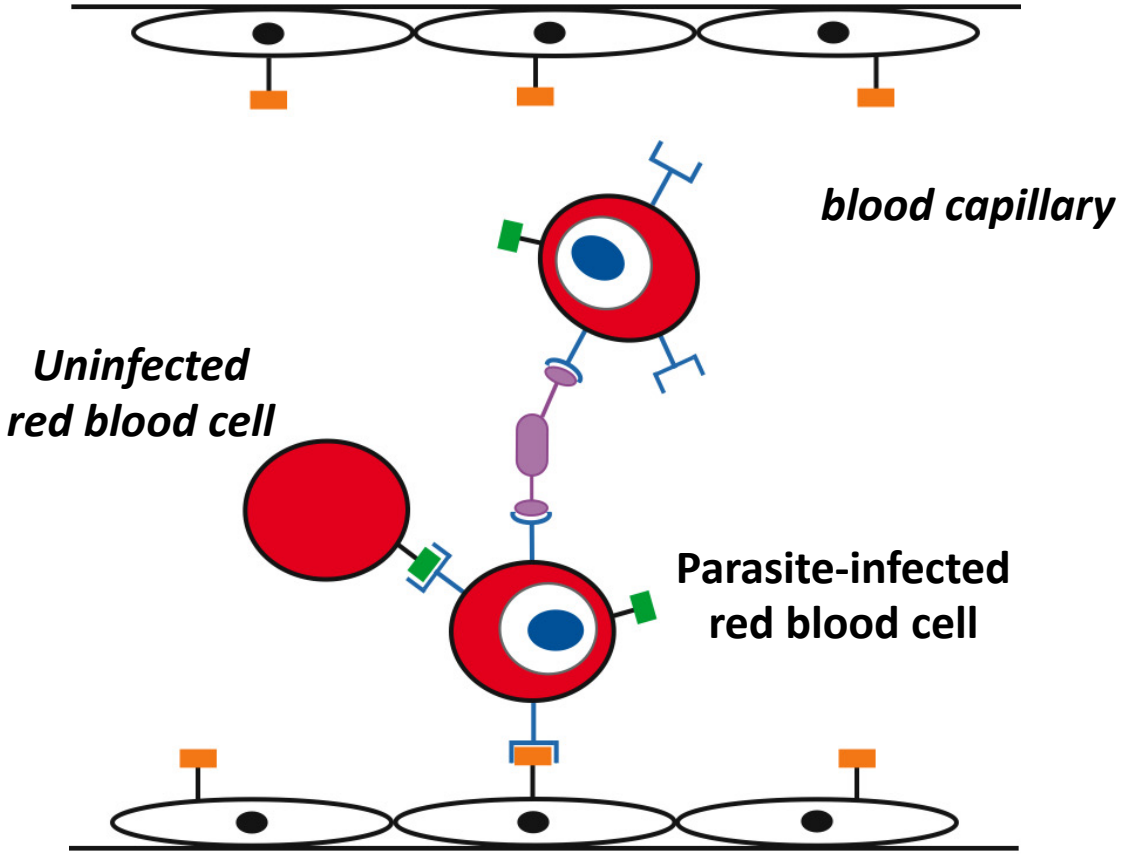
- Cost
  - Manufacture on large scale

OK … describe your therapeutic strategy

***Question**: What are some constraints in effectively disrupting the functions of these targets?*



Target 1:
Parasite transporter, protein (PfATP4) regulating Na^+/ H^+ exchange in cells



Target 2:
Parasite ligand protein interacting with host cell receptor protein on cell surface