20.109 Module 2

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

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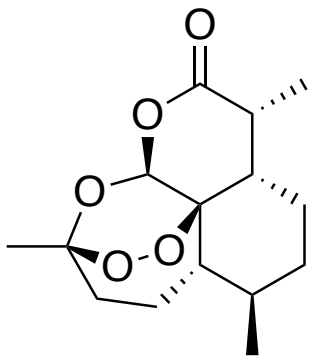
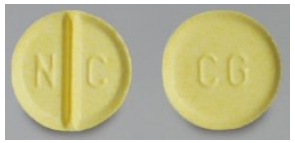
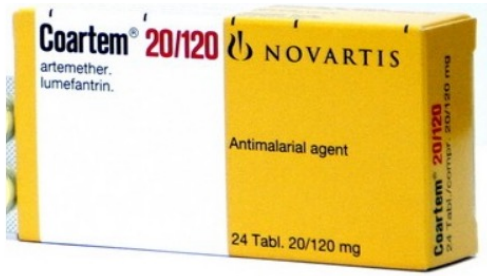




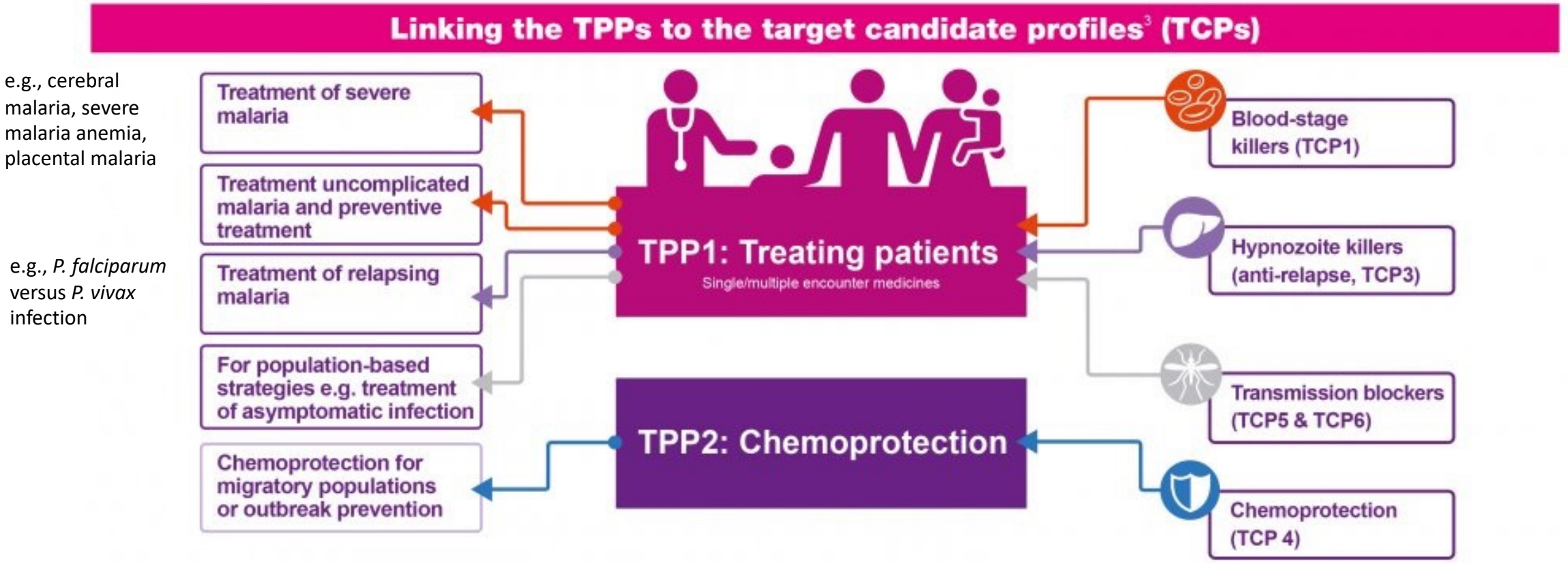


Learning Objectives

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

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

Strategizing a therapeutic approach

A. Defining the therapeutic intervention

A. What is intended goal/ outcome of the intervention? [TPP]

B. Precisely defining the therapeutic target(s)

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

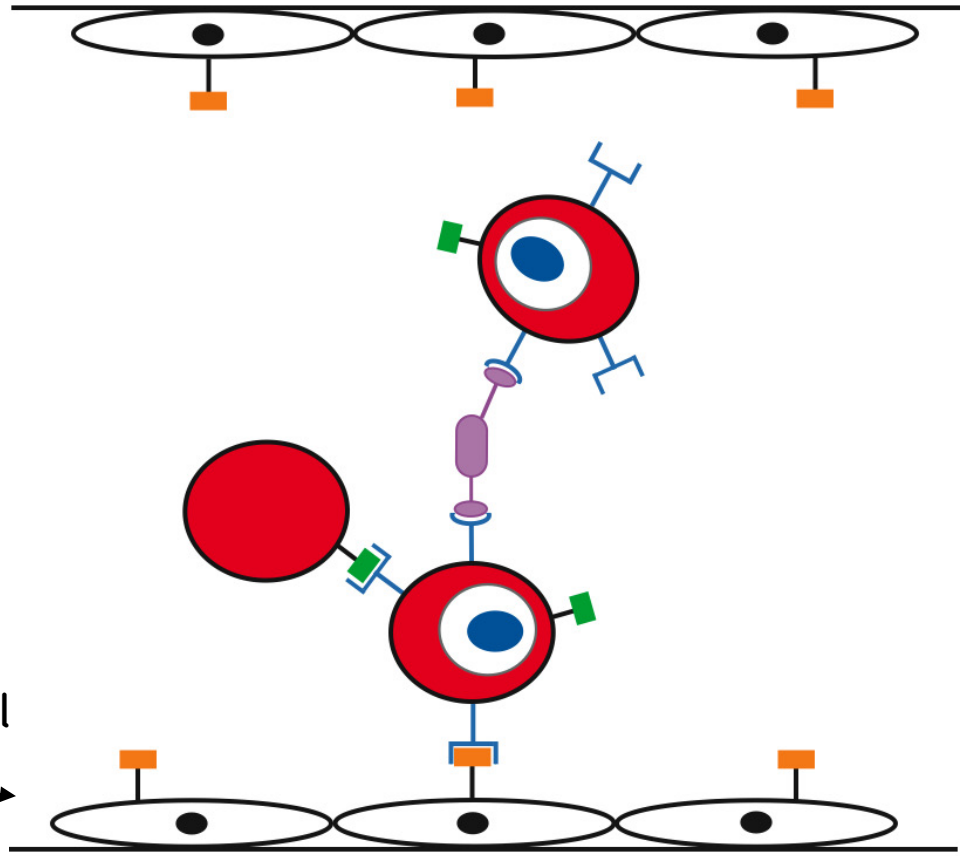
B. Choosing an appropriate operational scale

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

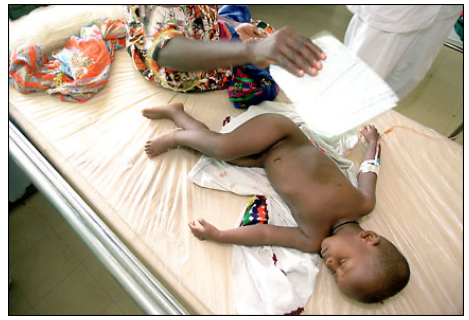


Endothelial cell receptors
CD36
ICAM-1
VCAM
E-selectin

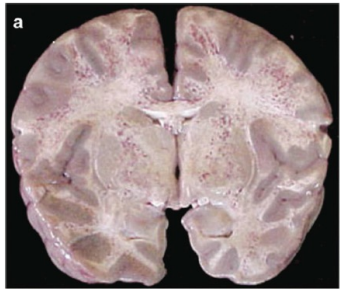
Parasitized RBC ligands
PfEMP-1 family
Modified Band 3

Normal RBC ligands
Complement Receptor 1 (CR1)

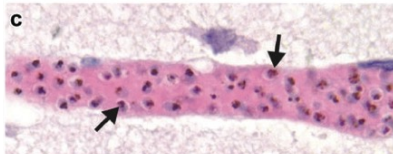
Platelet Ligands
CD36



Cerebral malaria



Microhemmorhages



Vascular occlusion

Microbe-host Interactions
- Disease outcomes

Strategizing a therapeutic approach

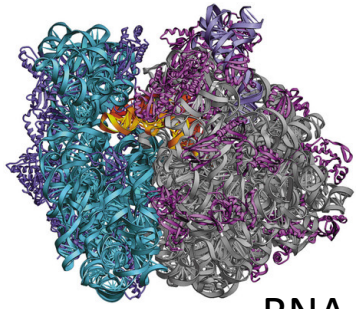
A. Defining the therapeutic intervention
    A. What is intended goal/ outcome of the intervention? [TPP]

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

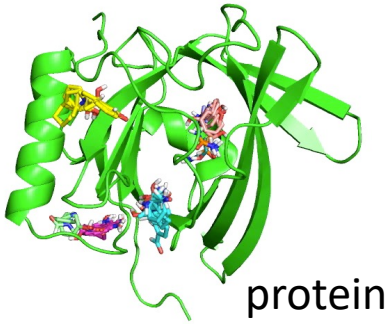
C. Validating the therapeutic potential of selected target(s):
    A. What evidence do you need to establish suitability of a therapeutic target?

… but what *exactly* will you target to accomplish these outcomes?

DNA



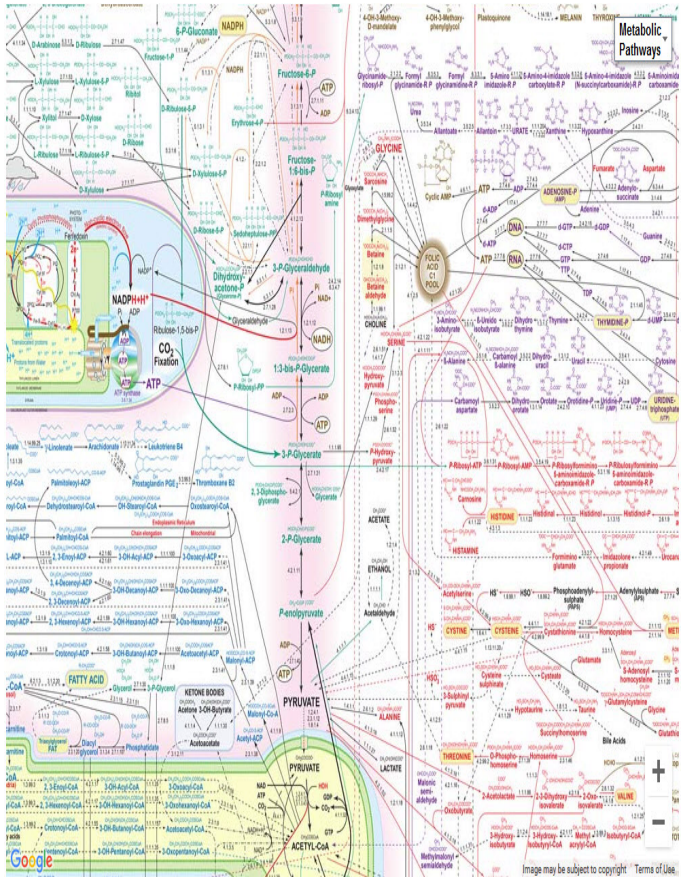
RNA



protein

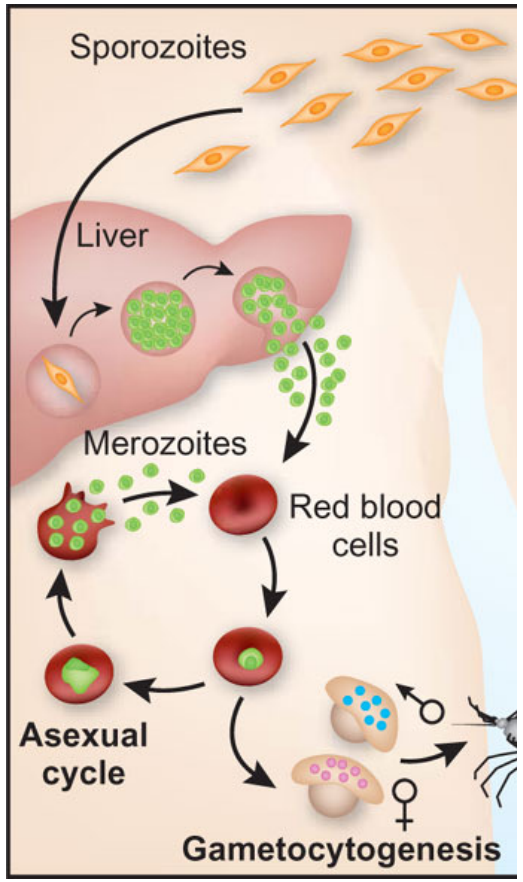
Molecular

- DNA, RNA, protein
- Carbohydrates



Biochemical/ Metabolic pathways

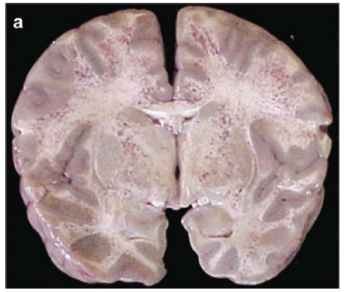
- Enzymes
- Structural proteins



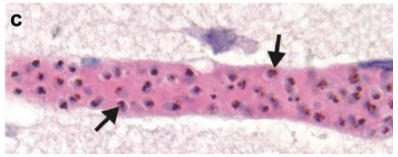
Cellular behavior

- Replication
- RBC invasion/ egress
- Differentiation

Cerebral malaria



Microhemmorhages



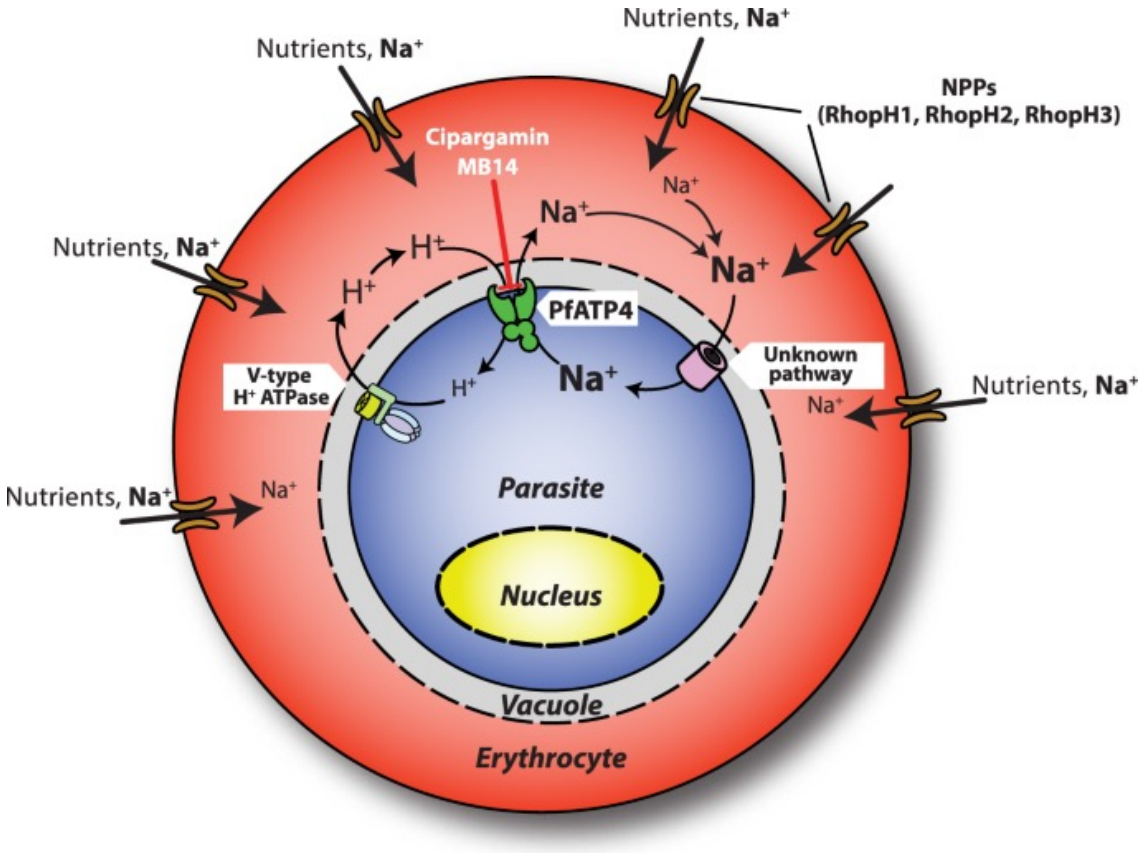
Vascular occlusion

Microbe-host Interactions

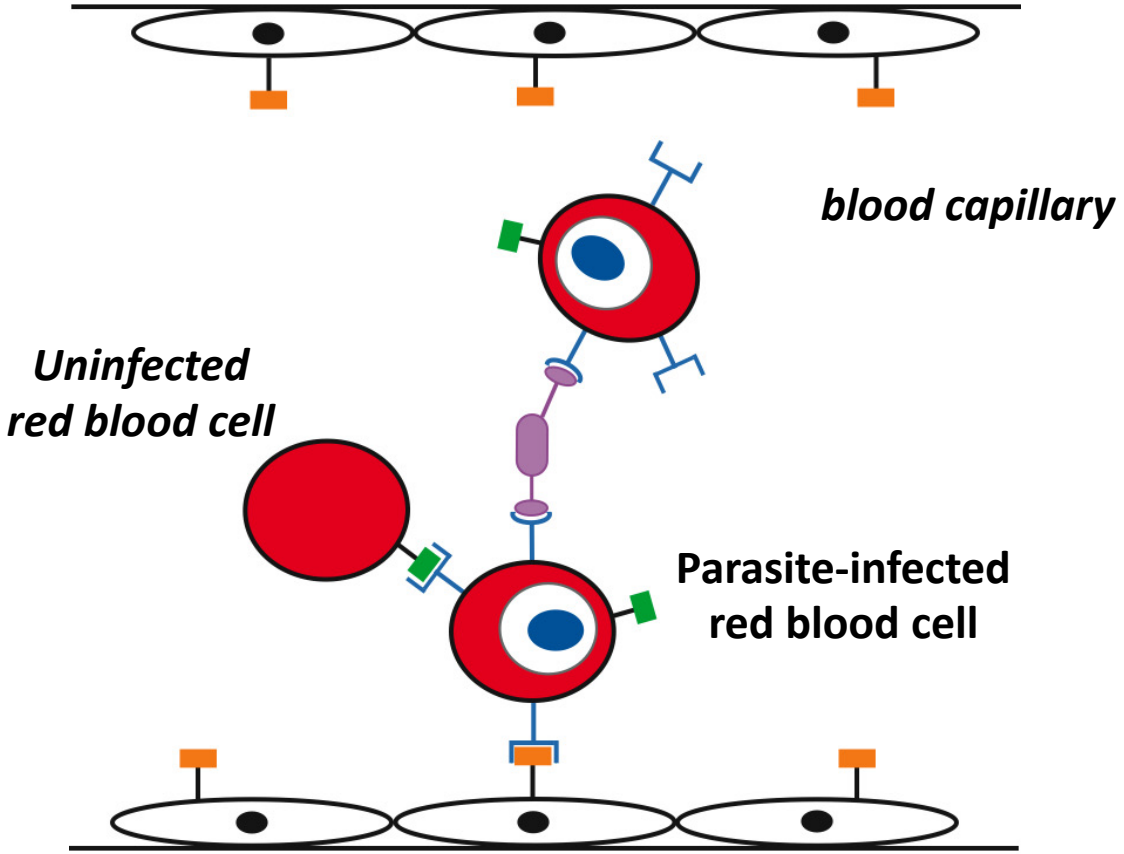
- Disease outcomes

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

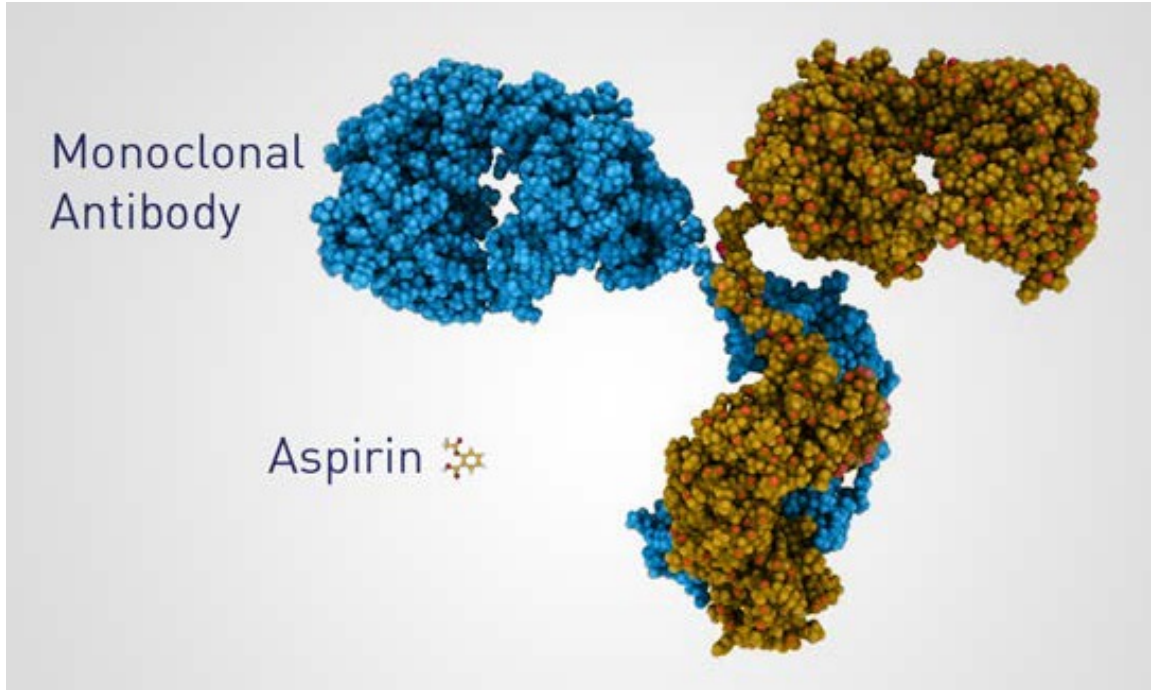
Strategies available for disrupting target function

***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

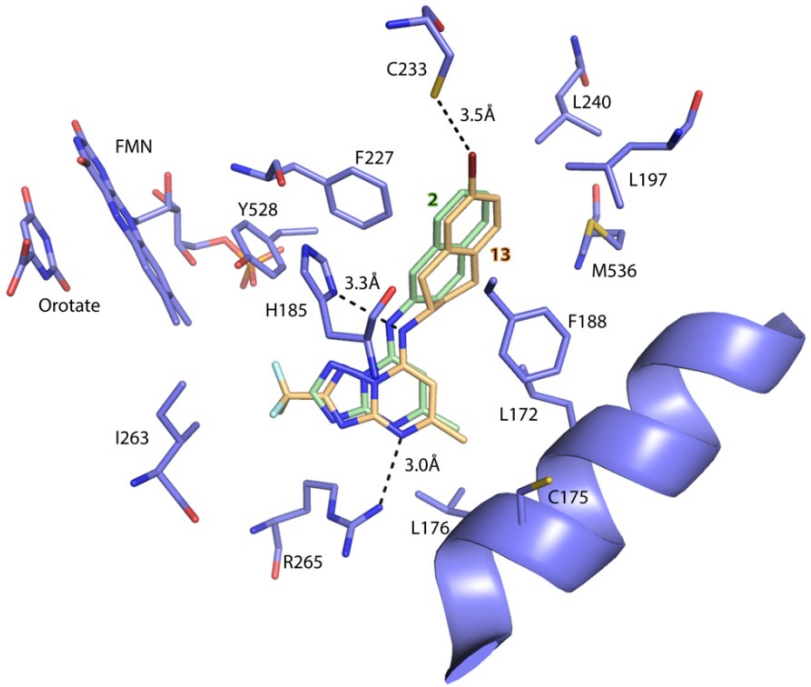
- Biologics* (Mw ~ kDa)
  - Proteins (antibodies, enzymes …)



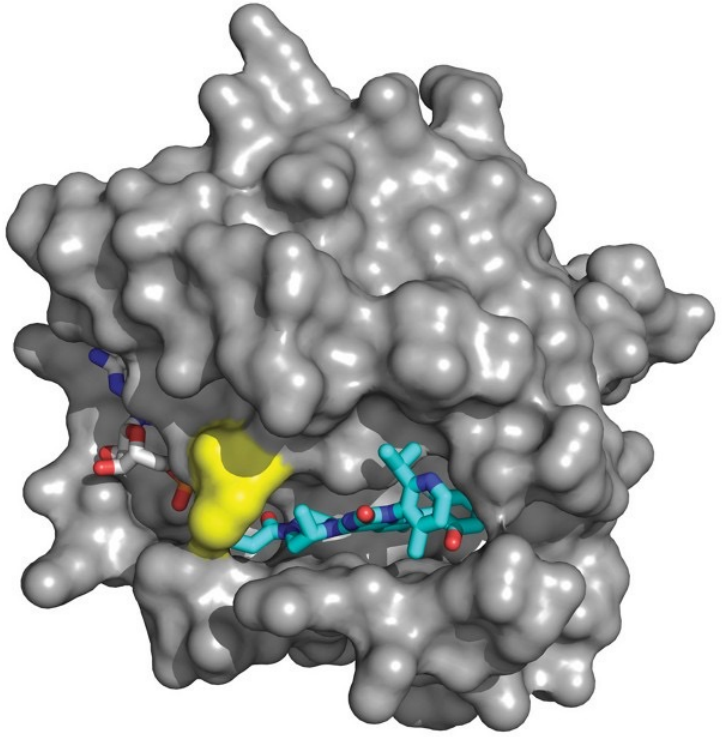
– Biological products are a diverse category of products and are generally large, complex molecules.
– Usually produced through biotechnology in a living system or cells (microorganisms, plants or animals)

Properties favoring small molecule therapeutics

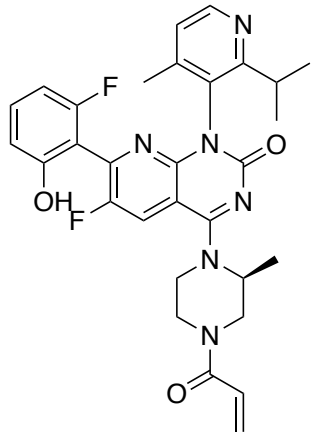
- Can make intimate molecular contact with relevant target protein surface features



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



AMG510 bound to KRAS



AMG510 (2D)

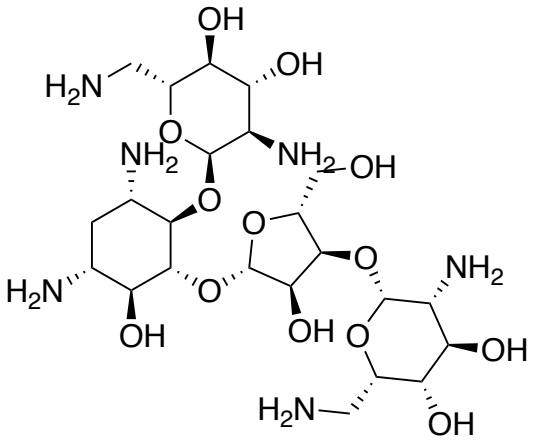
References:
DOI: 10.1038/s41586-019-1694-1
DOI: 10.1021/acs.jmedchem.6b00275

Properties favoring small molecule therapeutics

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

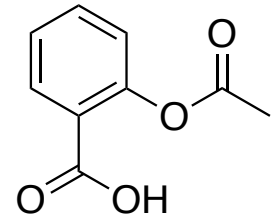
- Cell membrane permeable
  - Intracellular
  - Extracellular targets

- 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)

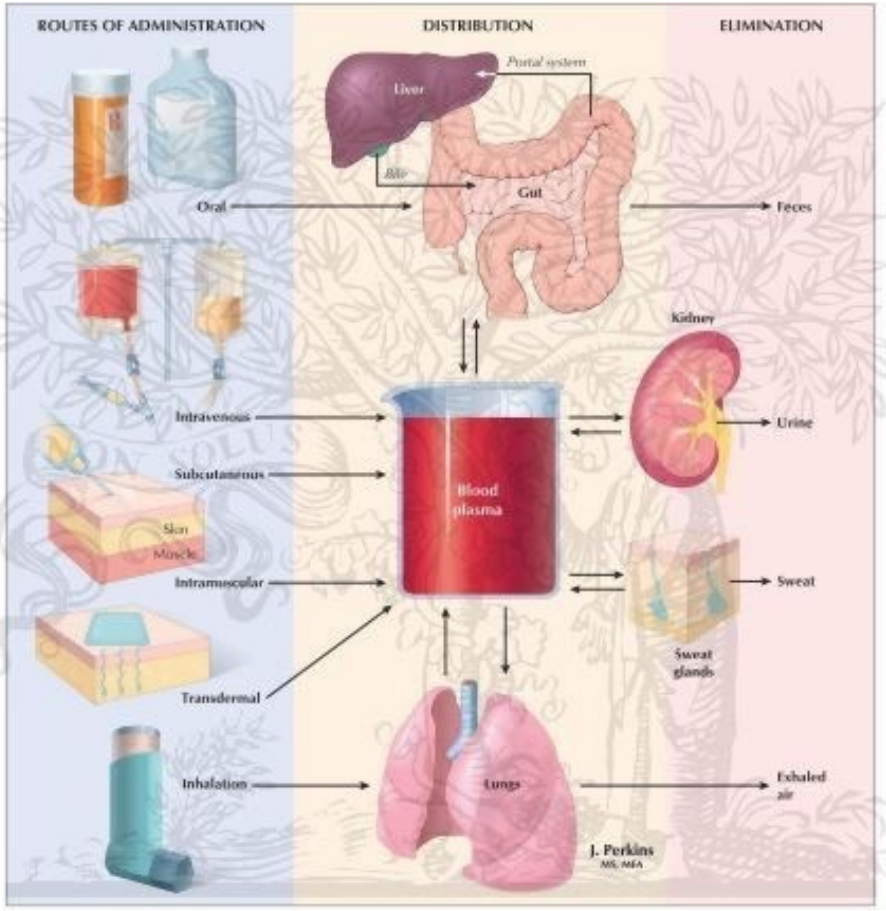
3. There are less than five hydrogen bond donors (–NH–, –OH)

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

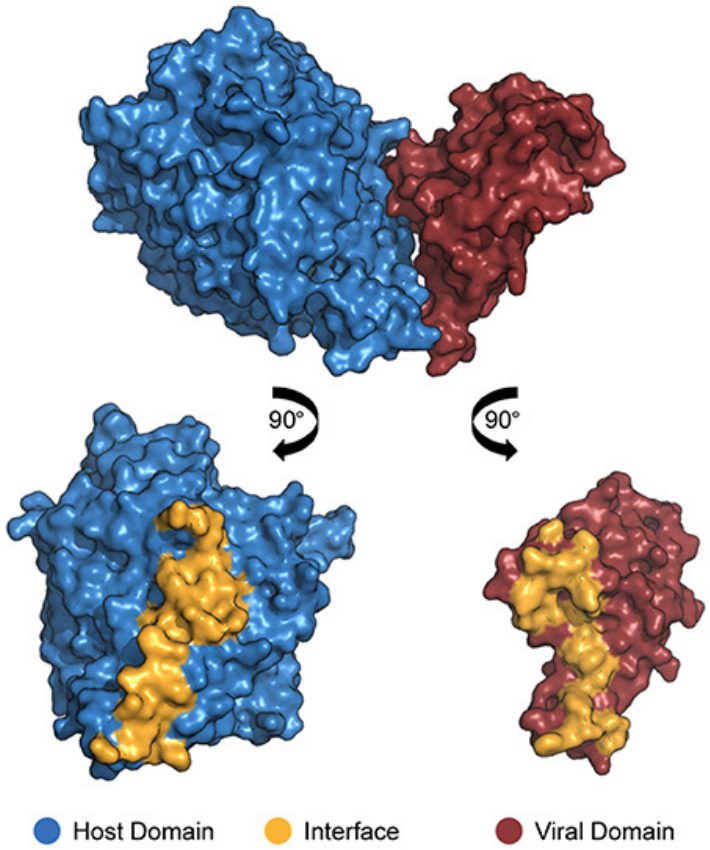


Properties favoring small molecule therapeutics

- 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.)

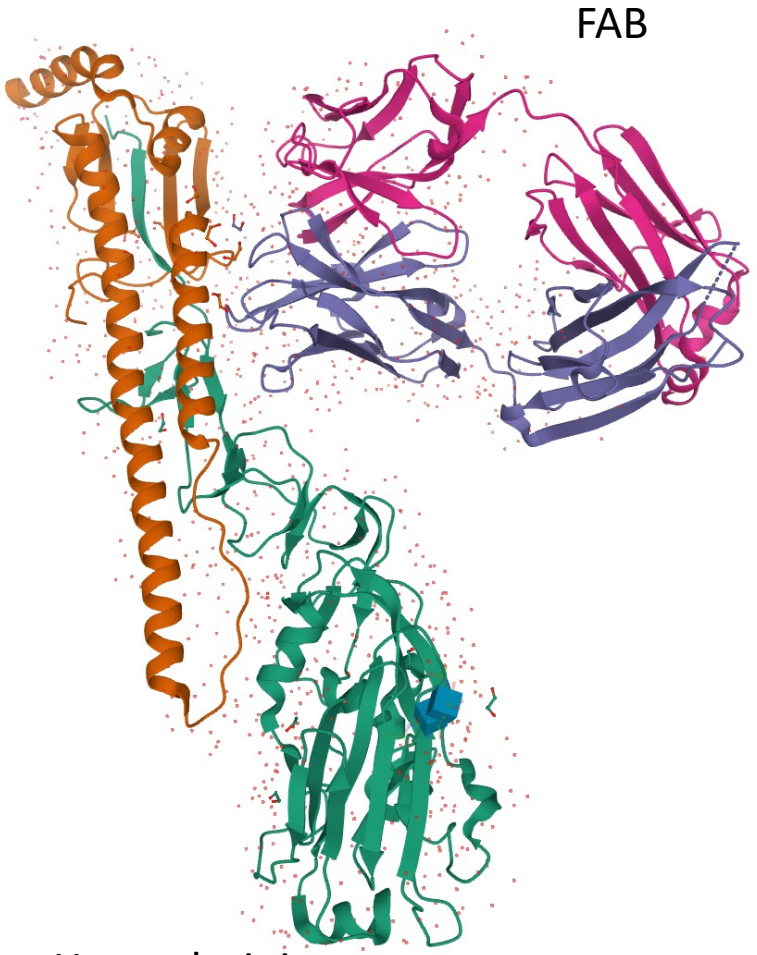
Comparing properties of (protein) biologics to small molecules

- 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

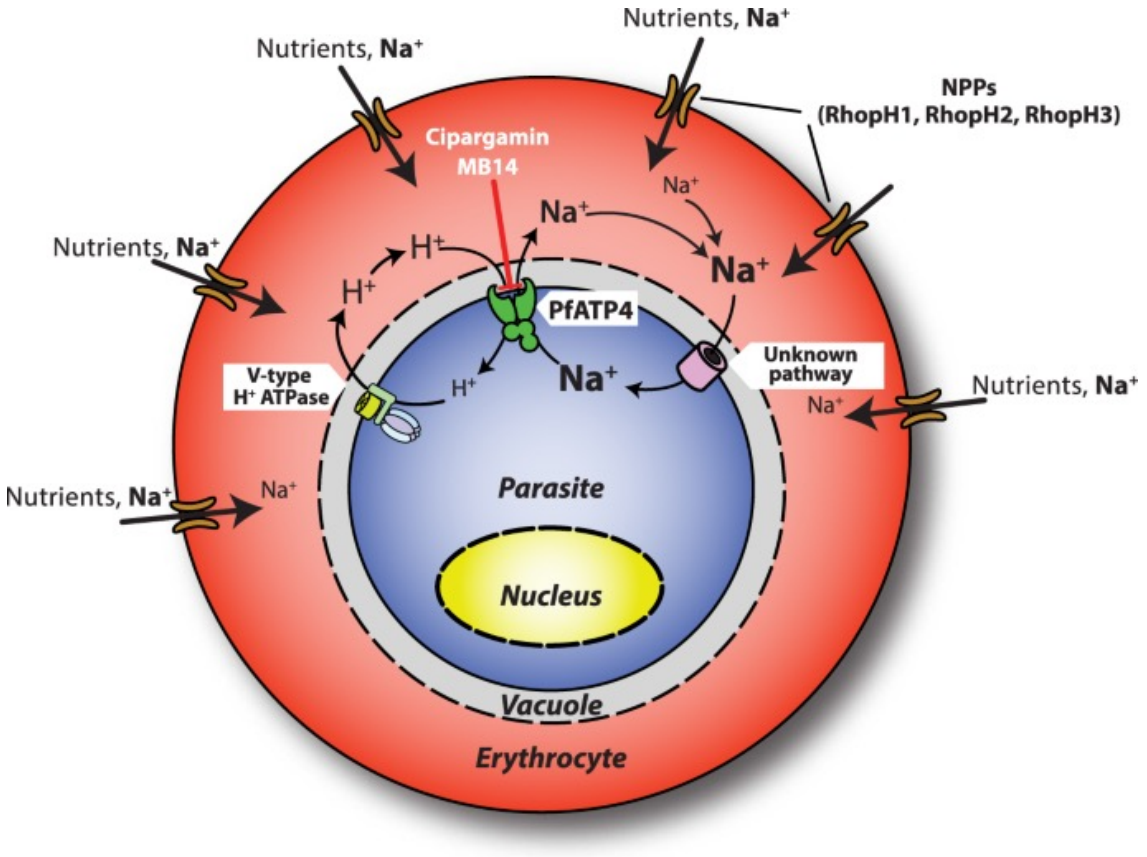
- Oral bioavailability:

- 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?*



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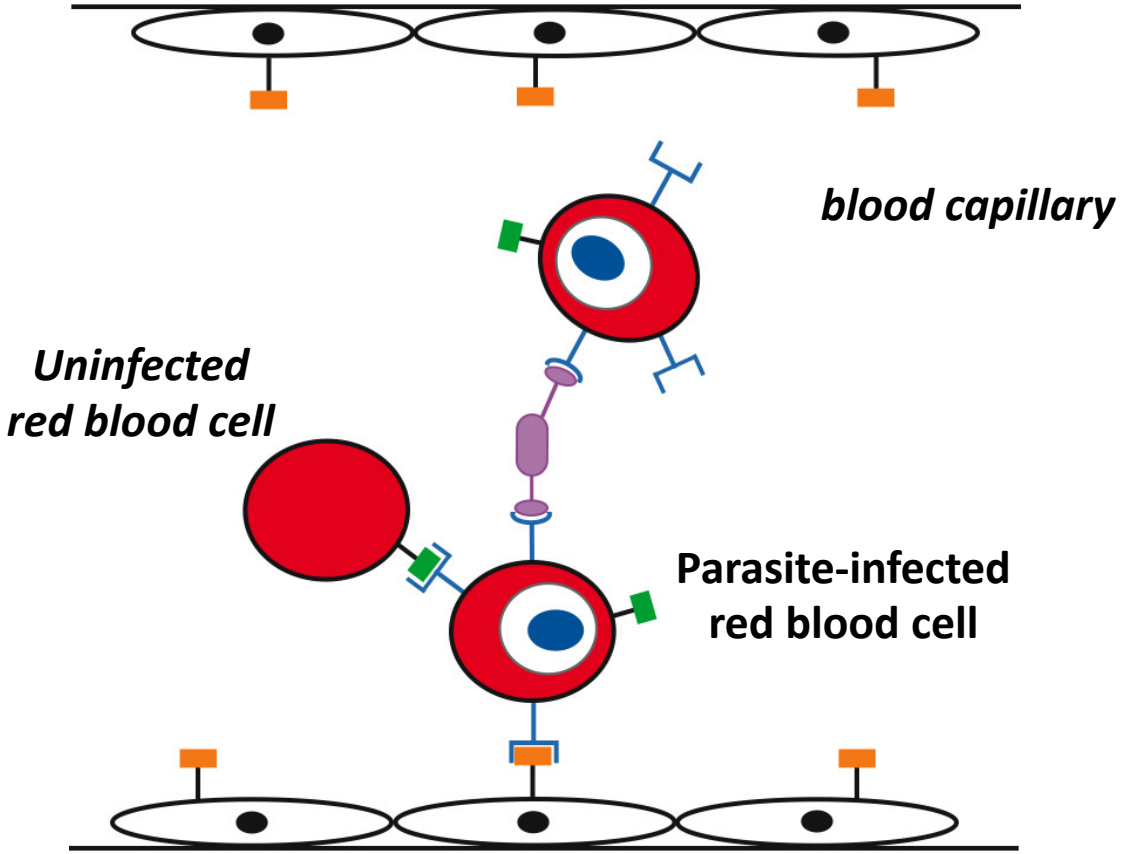

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