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"Malaria – Advent of biologics: The role of malaria monoclonal antibodies"

Malaria remains a global threat and is increasing.

- ½ billion cases and 616, 000 deaths worldwide in 2022 – 95% and 93% in Africa, respectively.
- Progress plateaued in the years preceding the COVID-19 pandemic, followed by an uptick in malaria cases during the pandemic (COVID-19 contributed to 18 million excess cases and 83,000 deaths).

The malaria lifecycle is complex – vaccine targets include the liver, blood, and mosquito stages.

Liver or "pre-erythrocytic" stage: asymptomatic, but metabolically active.

- Within minutes of a female mosquito bite, 20 to 100 sporozoites (SPZs) translocate from the skin to the liver.
- A lot of immunity occurs within the 5 to 5.5 days before Merozoites enter the bloodstream.
- ***High-stakes vaccine target*** – 100% blockade of SPZs is required to prevent bloodstream infection.
- ***Lead vaccine candidates being rolled out in Africa are based on the circumsporozoite protein (CSP)*** – a surface antigen that completely envelopes SPZs.

Blood-stage: symptoms, morbidity, and mortality occur.

- 45K Merozoites enter the bloodstream and home to erythrocytes, a metabolic sanctuary.
- A portion of Merozoites will morph into gametocytes.

Mosquito-stage: completion of the lifecycle.

- Blood/parasites enter mosquito salivary glands during a blood meal; a male and female gametocyte must be taken up to continue fertilization and sexual stage to complete the cycle.

Background – approved pre-erythrocytic vaccines contain truncated CSP and are protective, but there is room for improvement.

Overview of the RTS,S and R21 vaccine platform.

- CSP comprises three regions: N-terminal region; central-repeat region with B-cell epitopes: and C-terminal region with T-cell epitopes.
- RTS,S/adjuvant AS01 and R21/adjuvant Matrix-M contain HBsAg fused to the CSP C-terminal and central-repeat regions.
  - RTS,S contains additional soluble HBsAg in a 3:1 ratio.
  - R21 contains no soluble HBsAg to target more of the immune response towards CSP.

Clinical studies demonstrate efficacy in children aged 5 to 17 months.

- RTS,S: 36% protection over 4 years.
- R21: 68% and 75% protection over 1 year at sites with year-round and seasonal transmission, respectively.

Novel approaches – potent, high affinity mAbs for malaria prevention.

RTS,S approach: natural malaria and RTS,S-derived mAbs (WRAIR, PATH-MVI, Atreca).

- mAbs 311, 317, and 224 **target CSP contained in the RTS,S vaccine**
  28K heavy/light chain sequences were identified from plasmablasts isolated from protected volunteers after controlled human malaria infection (CHMI), followed by down-selection through mice.
- Bioengineered MAM01 **targets the central-repeat region in RTS,S.**
  Clonal line MS-1797 (renamed MAM01) is derived from bioengineered mutations of mAb 224 (Atreca).
  - PI/2a study underway (Univ of Md).
    Study schema: MAM01 (1.5 to 40 mg/kg IV and SC) administered to volunteers; follow-up period (18-26 weeks); then CHMI and assessment of protection. *Participants will undergo CHMI in March 2024.

Whole organism approach: *P. falciparum* sporozoite (PfSPZ)-derived mAbs (Sanaria).

- mAb CIS43 **maps to a highly conserved and unique CSP junctional region, not in RTS,S or R21.**
  Numerous mAbs were identified from memory B-cells and plasmablasts isolated from protected volunteers post vaccination with radiation-attenuated PfSPZs (confers sterile protection); 73 mAbs were targeted for study and down-selected through mice.
- Bioengineered CIS43LS **has enhanced affinity for the CSP junctional region.**
  Exchanging leucine and serine in the CIS43 Fc binding site alters the electrostatic charge and enhances binding affinity.
  - P1/2a studies demonstrated 100% protection with SC dosing and long-lasting PK (NIH-VRC/Univ of Md).
    *100% protection at CIS43LS doses >1mg/kg (5,10 mg/kg IV and SC; 40mg/kg IV).
    *SC and IV dosing are equally protective.
    *Single-dose CIS43LS (5 and 10mg/kg IV and SC) maintained target immunity (>22.5mcg/mL) up to 6 months.
  - Clinical study demonstrated up to 88% protection in Malian adults (Kayentao et al NEJM 2022).
    *Placebo: 80% to 90% had incident Pf infection over a 6-month period.
    *CIS43LS (10 mg/kg or 40 mg/kg): 75% and 88% protection, respectively, at 6 months.
- Reverse-engineered L9 **targets minor repeats within the CSP junctional region**.
  CSP junctional probes for locations of interest identified high-affinity mAbs derived from memory B-cells isolated from protected volunteers post vaccination with radiation-attenuated PfSPZs (Wong et al and NIH-VRC).
  - Preclinical studies characterize L9 mechanism.
    *Limited hepatocyte traversal of SPZs
    *Limited egress of SPZs through sinusoids due to "dotty death" (L9-induced CPS shedding, leading to complete SPZ breakdown).
  - Clinical study demonstrated up to 100% protection in US adults.
    *L9LS (5mg/kg SC and 20mg/kg IV): 80% and 100% protection, respectively.
  - Pediatric studies are ongoing in Mali and Kenya

Risks and benefits of mAb vaccines for malaria.

Benefits.

- Passive immunity/seems to be inert; Single dose; Ideal for pregnant women, children with severe malarial anemia (prevent second infection), and travelers; another tool against malaria; and successful SC dosing.

Risks.

- Expense (cost will hopefully decrease with mass production); Immune evasion needs to be determined; Anti-drug antibodies are theoretical (none have been detected to date); Short-to-medium term protection (protection wains).

Summary.

- Malaria prevention requires out-of-the-box solutions to tackle the complex lifecycle.
  - Most known Pf mAbs target CSP (CIS43LS, L9, and MAM01) – clinical trials in Africa are the next step.
  - Numerous other studies are ongoing and include blood-stage and mosquito-stage targets.
- Understanding the basis for protection has led to novel and long-lasting mAbs.
  - Bioengineered next-gen mAbs hold promise as we unravel the science behind protection and reverse-engineer new products.
  - There is potential to move beyond short-term prevention and contribute to malaria eradication.