Structure and Antimalarial Activity of Immunomodulator P-MAPA

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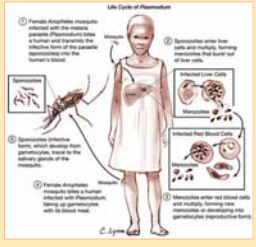
- **Background:** Malaria is one of the world's most common diseases caused by: ***Plasmodium vivax, P. falciparium, P. malariae and P. ovale.***

- **Female *Anopheles* mosquito**
- **500 million of people/year**
- **Children < 5 years-old – Africa**
- **One child dies every 30 seconds**
- **1 to 3 million deads/year**

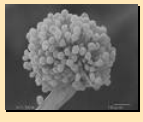


The drug resistance has reduced the effectiveness of several commonly used antimalarials, such as chloroquine.

P-MAPA

- **Obtained from *Aspergillus oryzae***

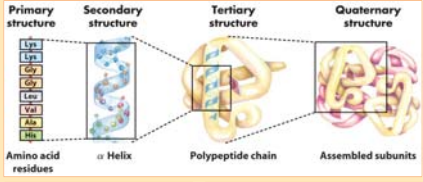
o **Micro crystals**

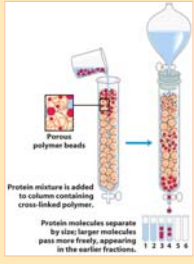


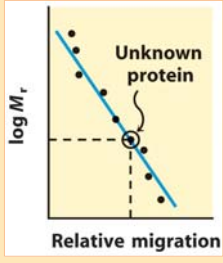
o **Strong Activity**
  - o **Antitumoral**
  - o **Antimalarial**
  - o **Immunomodulation**
    - o **IL-2, IL-12, IL-7**
    - o **IFN**
    - o **GM-CSF and TNF**

Farmabrasilis

- **Proteic agregate (MW = 316 kDa)**
- **White powder - fine crystals**
- **P-MAPA's composition:**
  - **PO_4^{3-}**
  - **Mg^{2+}**
  - **Lipid component: linoleic acid**
- **Protein - 0.5 % (MW~16 kDa)**
  35.2 % - Arg





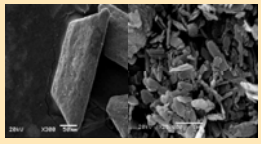


- o **Mass spectrometry (MALDI-Tof/MS)**
- o **Circular dichroism (CD)**
- o **Fluorescence**
- o **NMR**

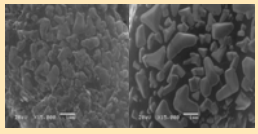
Goals:

To determine P-MAPA´s (micro-, nano-crystals, and protein) activity(ies) on *Plasmodium falciparum*, and in experimental infection models. Elucidate P-MAPA´s structure and mechanisms of action (SAR).

Results: P-MAPA crystals have been tested and the strong bioactivity against malaria was observed *in vivo*. The two nanonization method's conditions with aim to achieve as uniform as possible nanocrystals are being optimized.

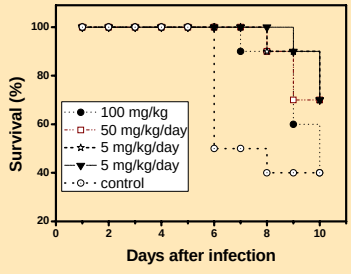


High pressure homogenization of P-MAPA in surfactant: crystals (x 300) and micro and nano-crystals (x25000).



Nano-crystals with sizes of 200-1000 nm (polymorph) obtained by a re-precipitation method.

The P-MAPA activity against malaria was evaluated in groups of 7-10 C57BL/6 female mice, 5-8 week-old and pathogen-free. Upon infection with lethal cells of *Plasmodium chabaudi* AJ, P-MAPA was administrated in one, unique, dose of 100 mg/kg one day after infection, and in diary doses of 50 and 5 mg/kg/day - 1 h upon infection. P-MAPA inhibited the parasitemia up to 100 % with only one dose of 100 mg/kg during six days of the infection, while the control survival was only 50 %. With administration of 5 mg/kg per day, 90 % of animals survived during nine days, meanwhile 60 % of the control animals died.



- o **Structure Activity Relationship**
- o **Mechanisms of action**
- o **Protein – active?**
- o **Nanonization?**
- o **New drug? 2010***