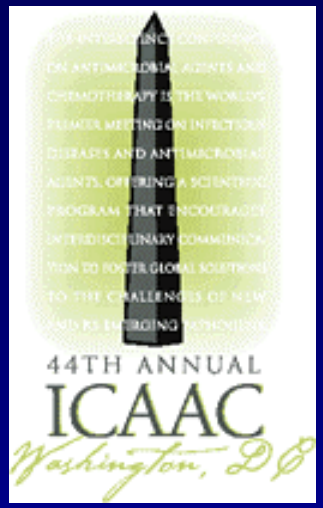

Ciprofloxacin-resistant J774 mouse macrophages show a reduction in the accumulation of quinolones through increased activity of an MRP-like transporter

M. Heremans, J.M. Michot, M.P. Mingeot-Leclercq, P.M. Tulkens, F. Van Bambeke

Unité de Pharmacologie cellulaire et moléculaire
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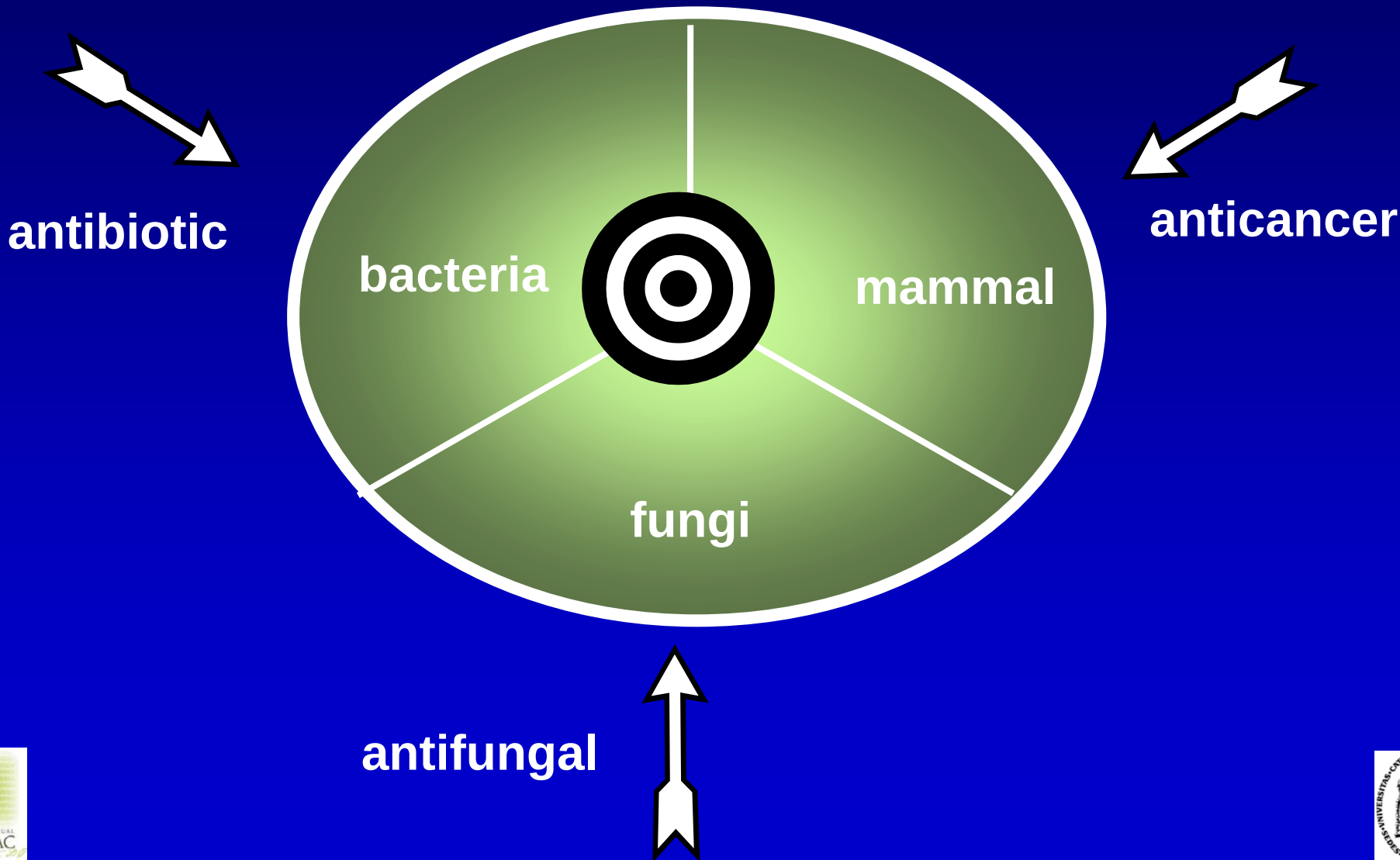
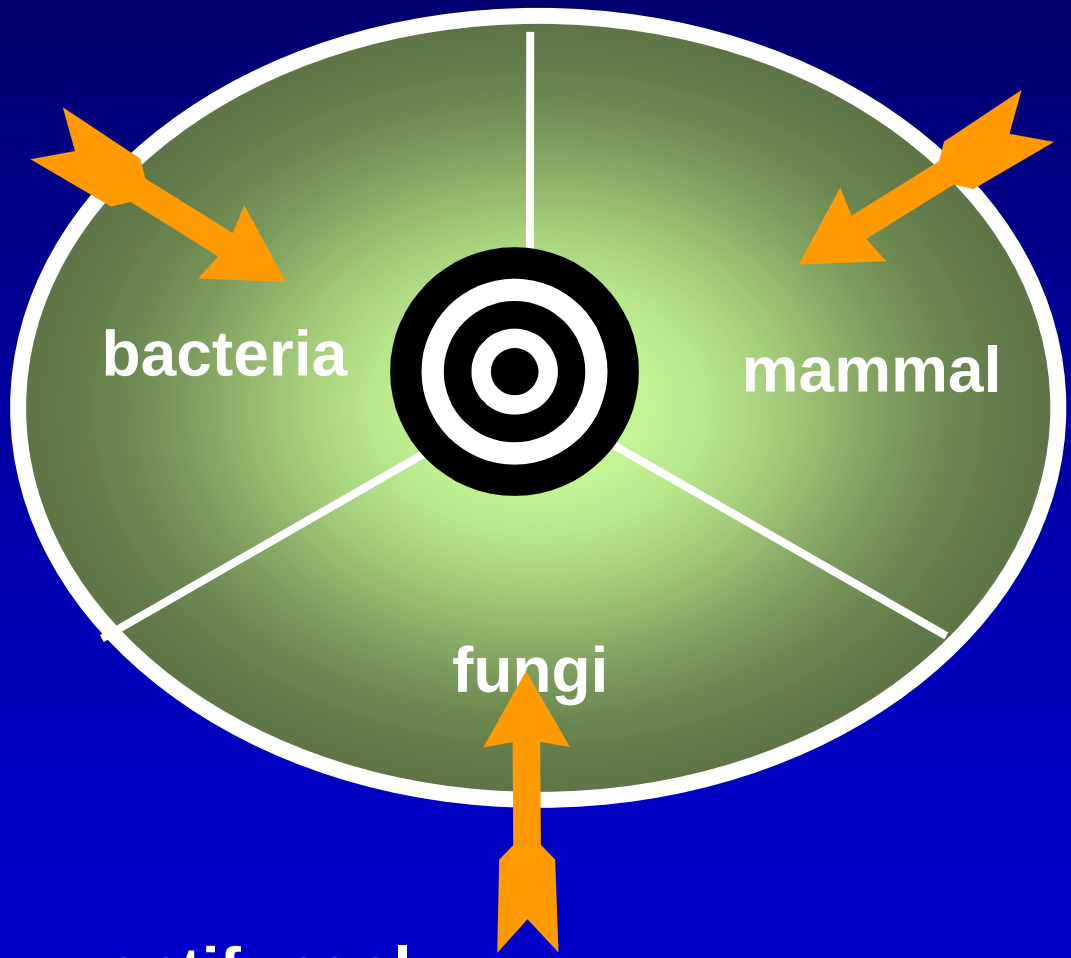
Brussels, Belgium

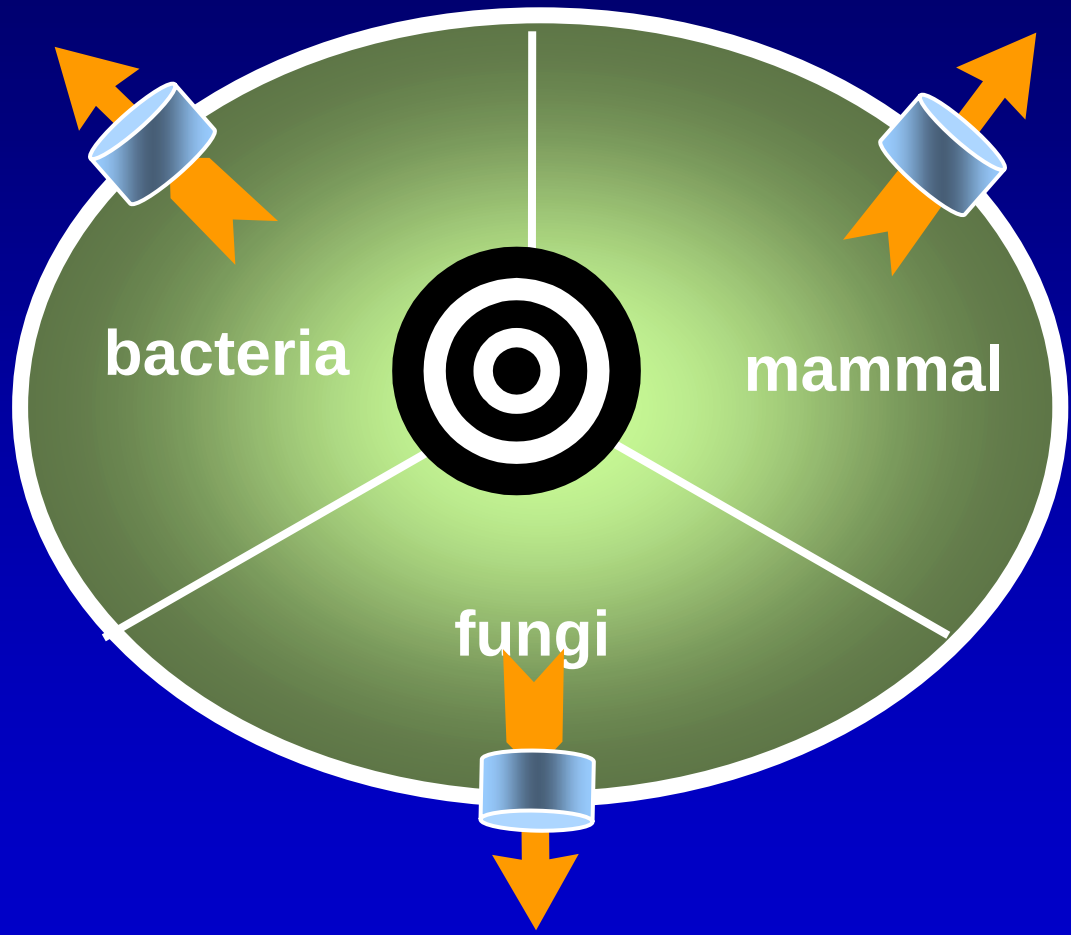
chemotherapeutic agents often need to reach an intracellular target…



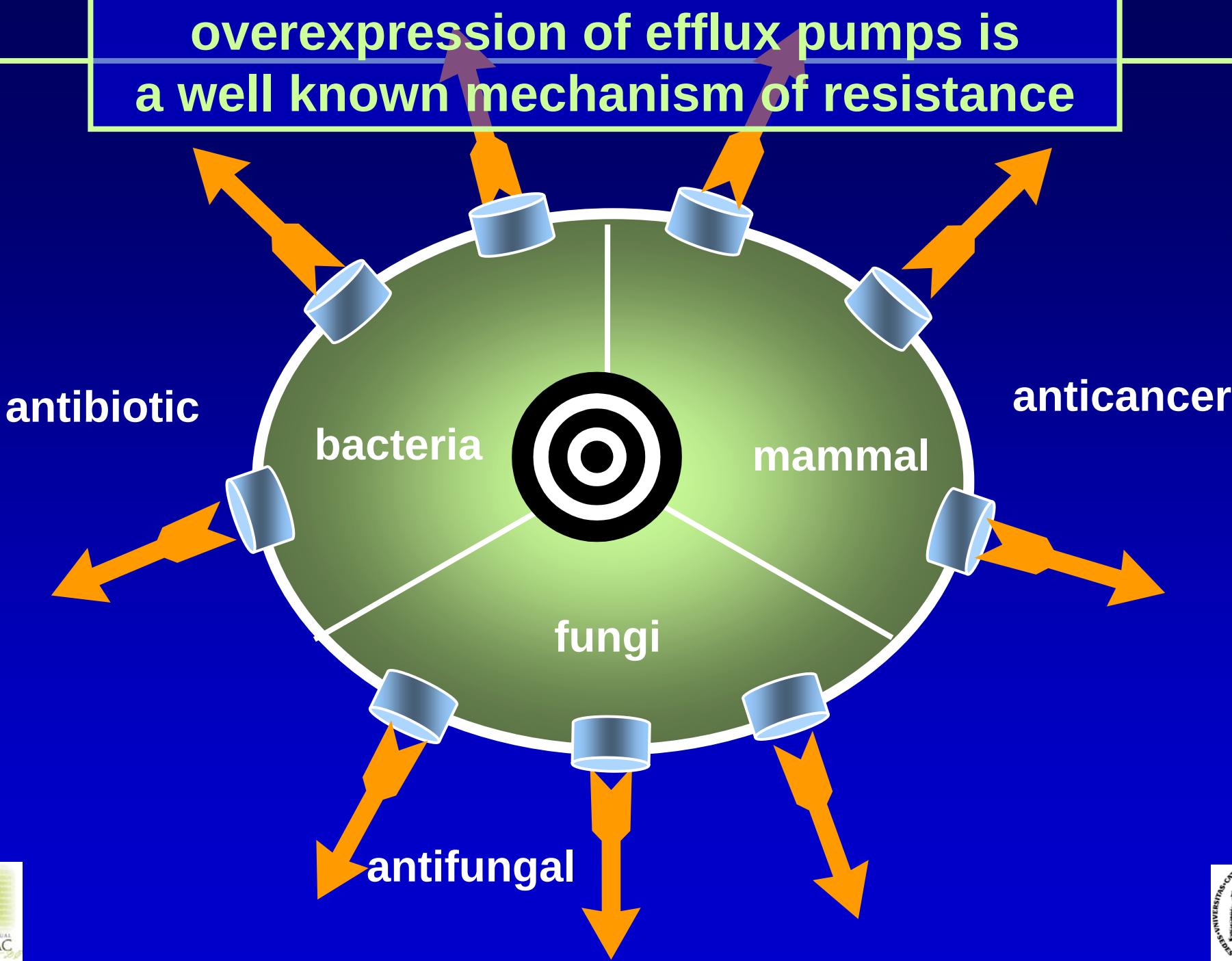
accordingly, they have been made amphipathic to diffuse through membranes…



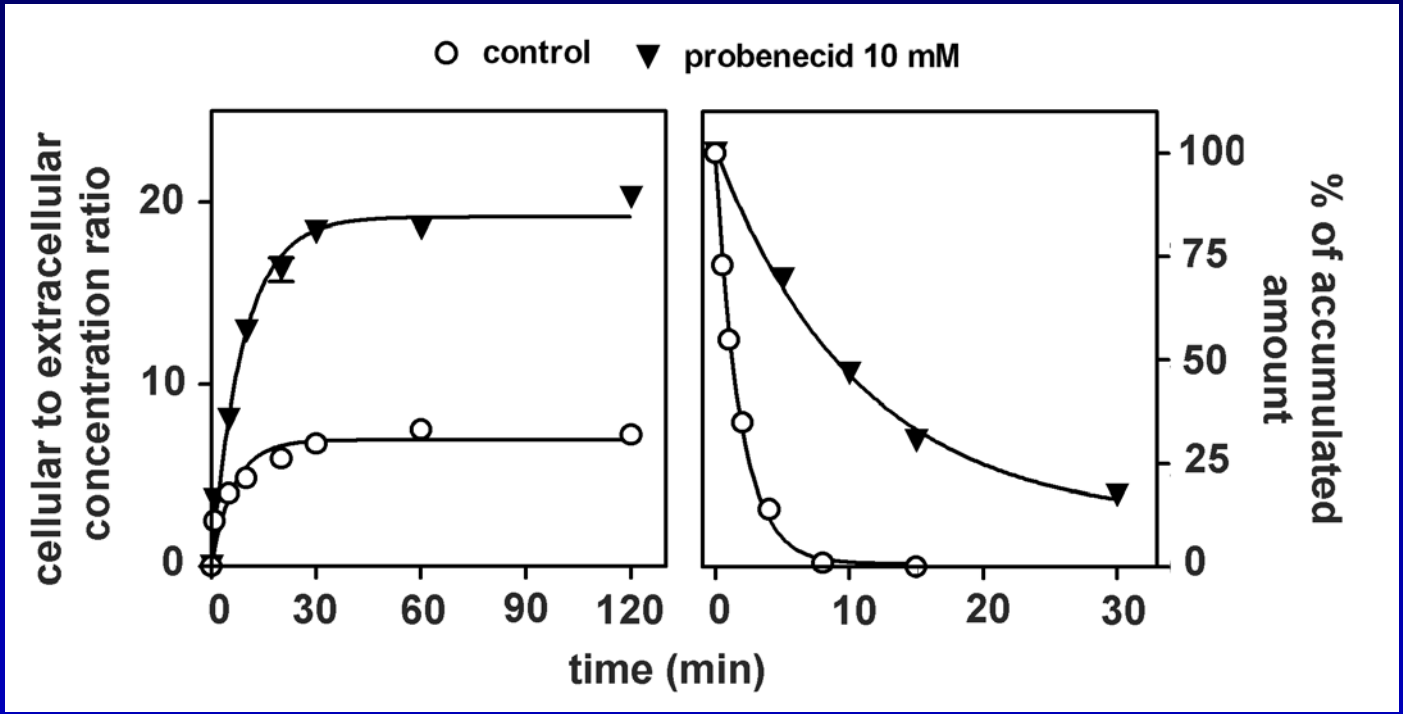
… but efflux pumps extrude amphipathic molecules and, hence, reduce their concentration in contact with the target…



overexpression of efflux pumps is a well known mechanism of resistance



ciprofloxacin is substrate of an MRP-like transporter in macrophages

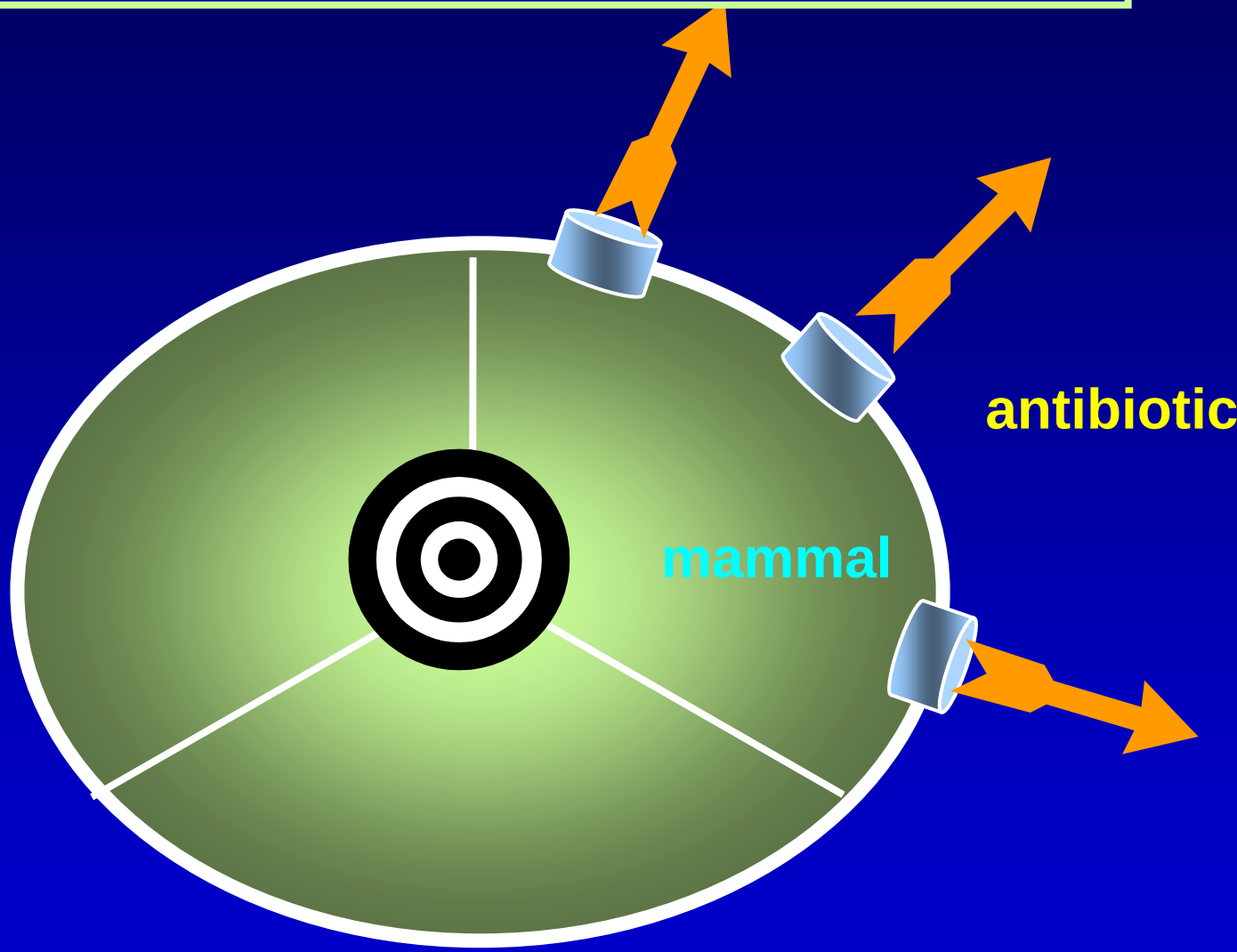


CIP transport is inhibited by

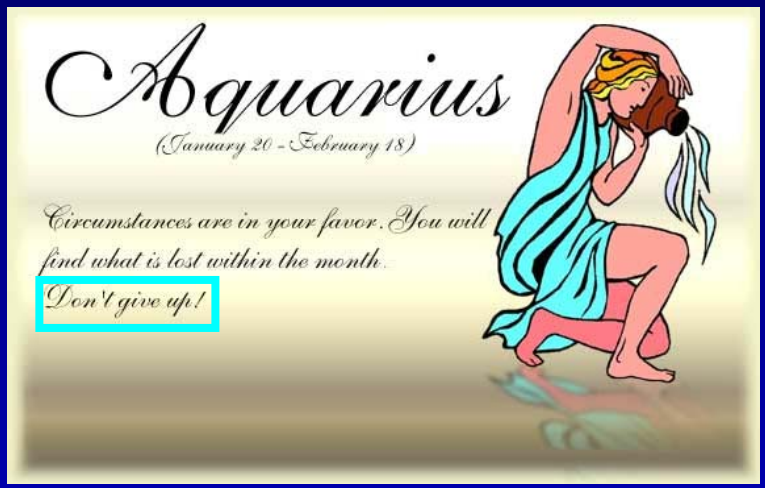
- **ATP-depletion**
- **probenecid (inhibitor of organic anions transporters)**
- **MK 571 (inhibitor of MRP transporters)**

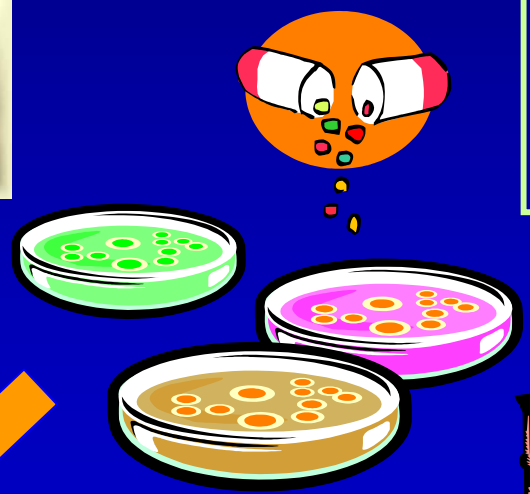
Michot *et al*, AAC 2004; 48:2 673-82.

is ciprofloxacin susceptible to select « resistance » in macrophages ?



CIP-resistant macrophages can be selected by chronical exposure to increasing CIP concentrations





- step-wise increase in CIP concentration
- several passages at each step

time and drug consumming!

multifactorial multidrug resistance

Gottesman *et al*, Methods Enzymol. 1998 ; 292: 248-58

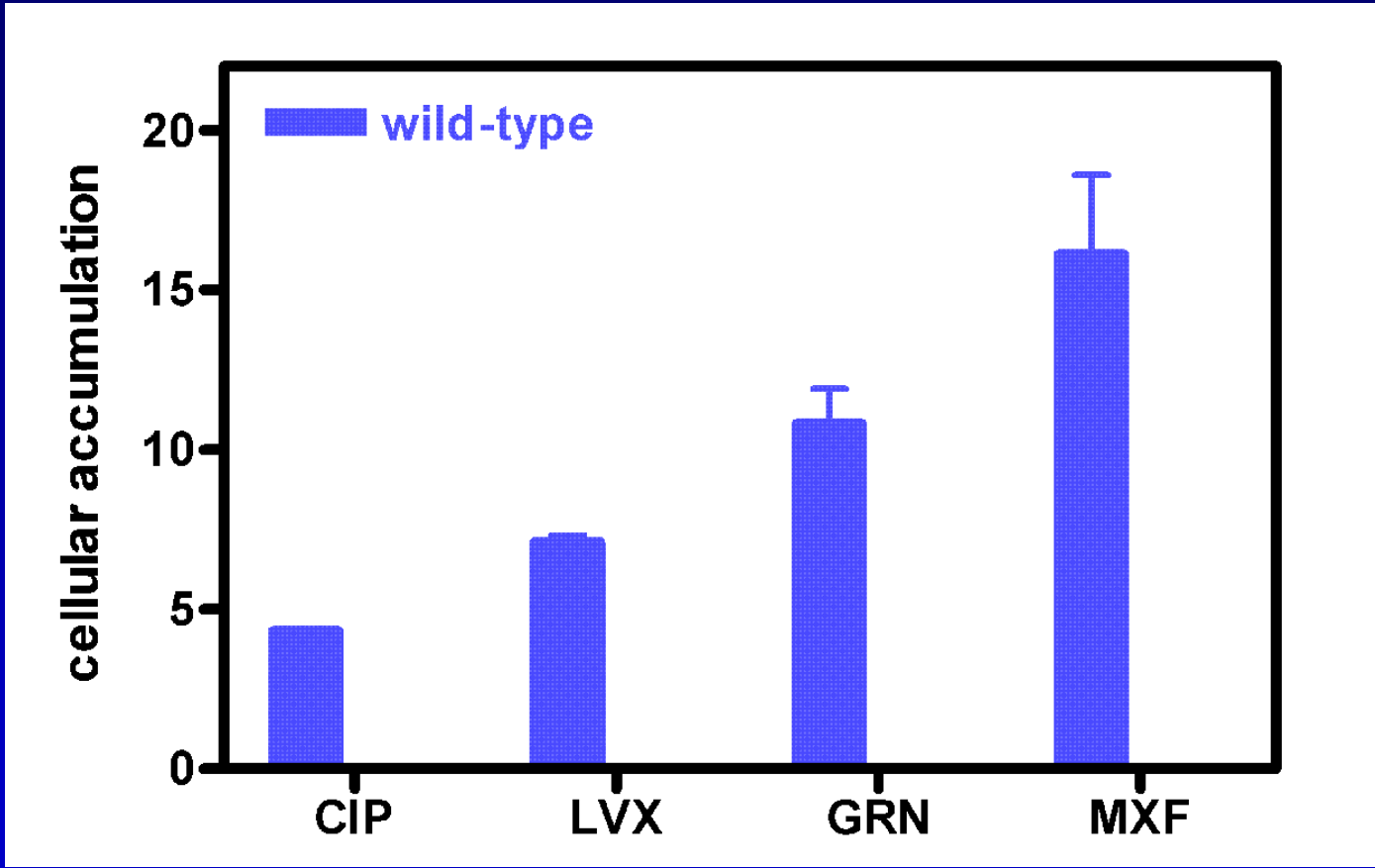
phenotypic characterization of the resistant cells

accumulation of quinolones

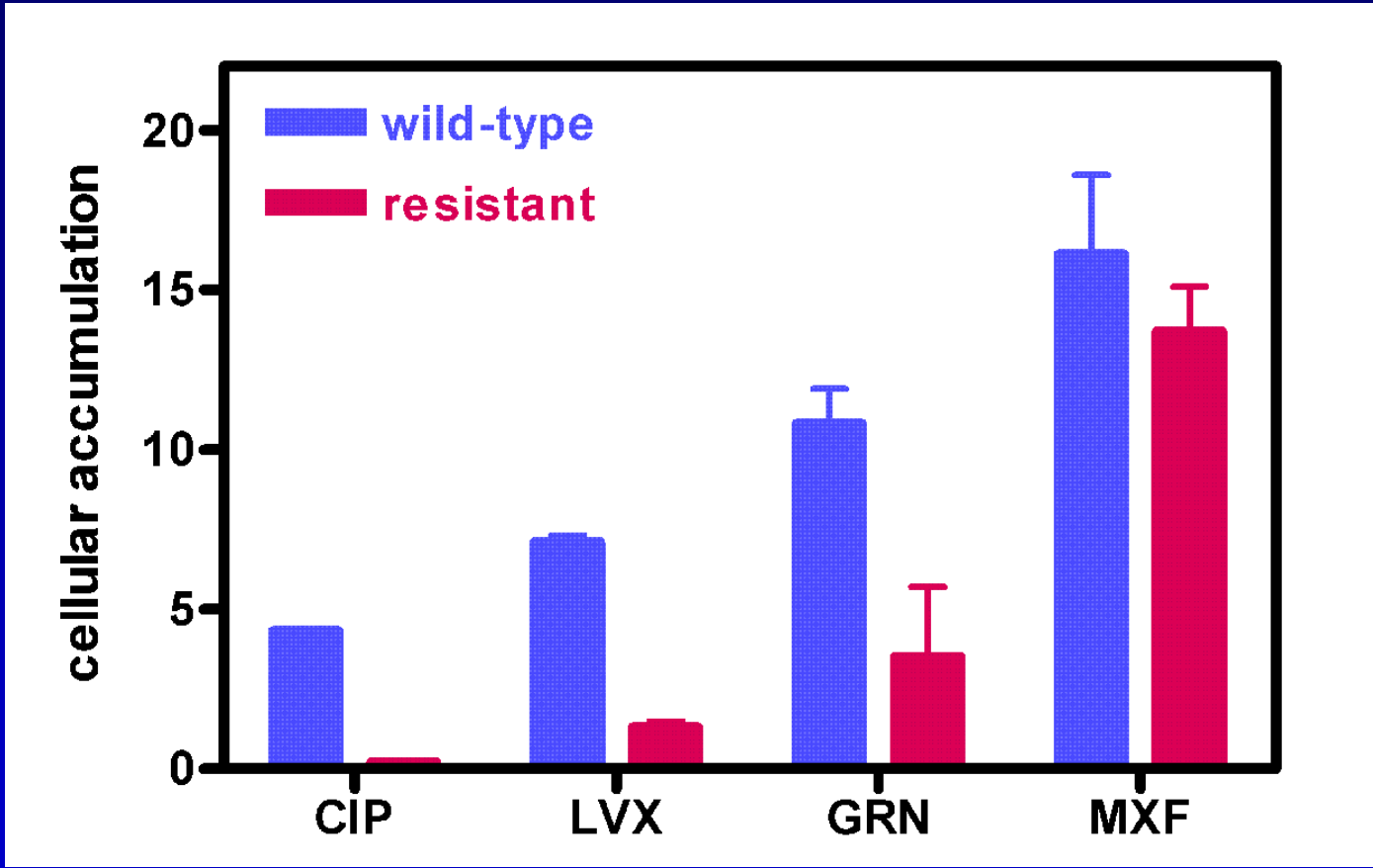
reversibility of the resistant phenotype

effect of efflux pump inhibitors

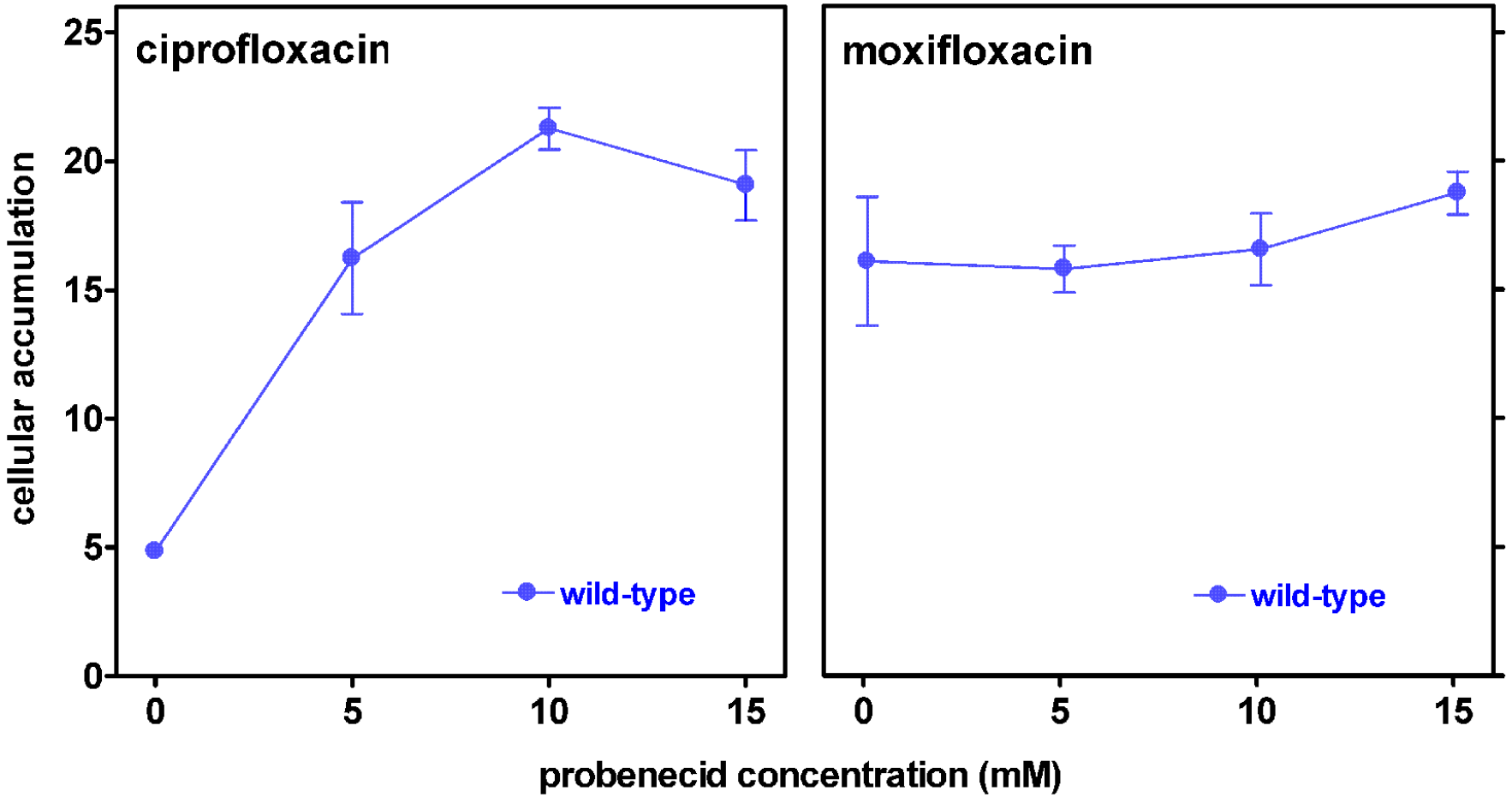
quinolone differ in their accumulation in wild-type macrophages



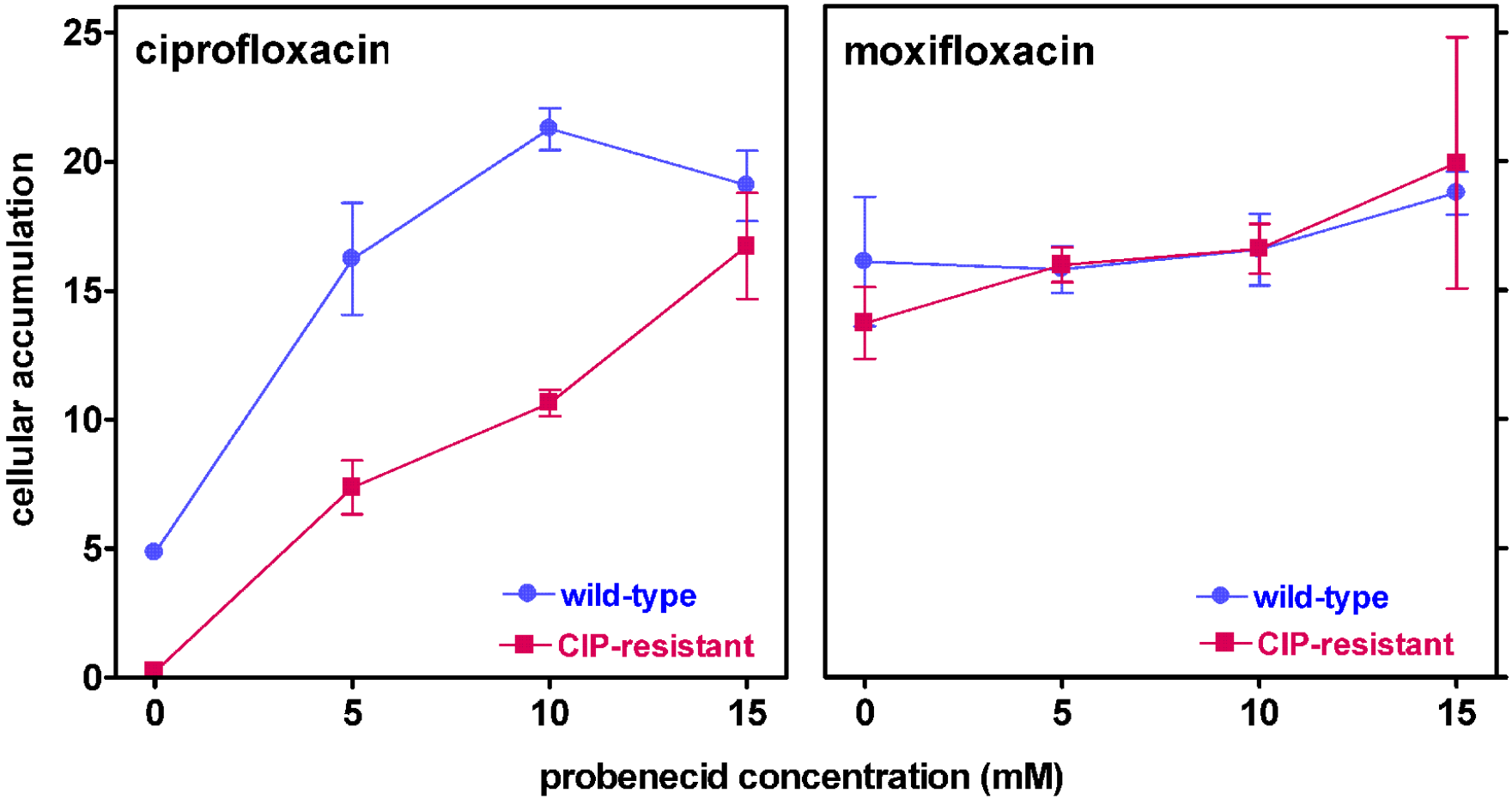
quinolone accumulation is reduced to variable extent in CIP-resistant macrophages



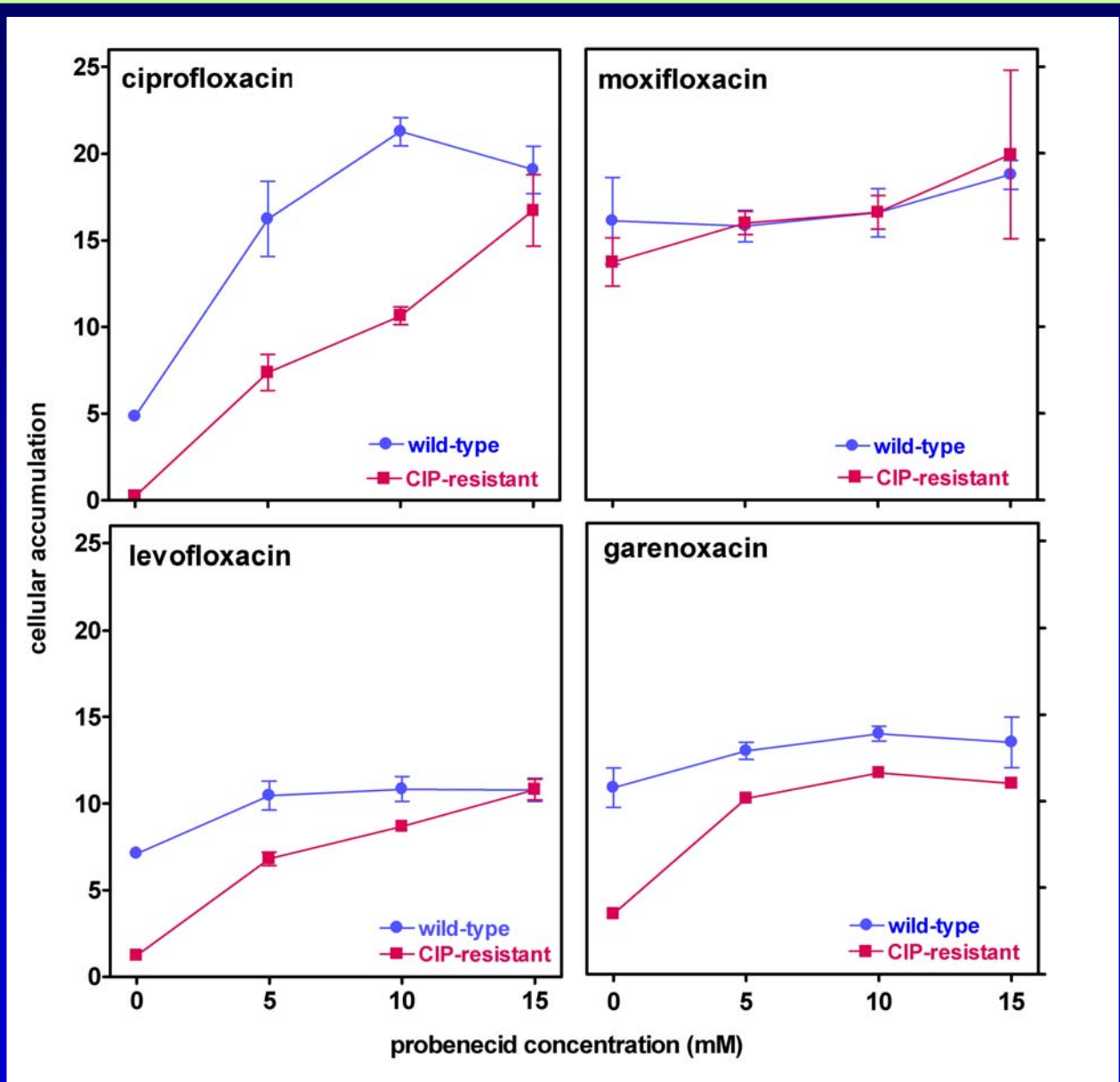
probenecid increases CIP but not MXF accumulation in wild-type cells



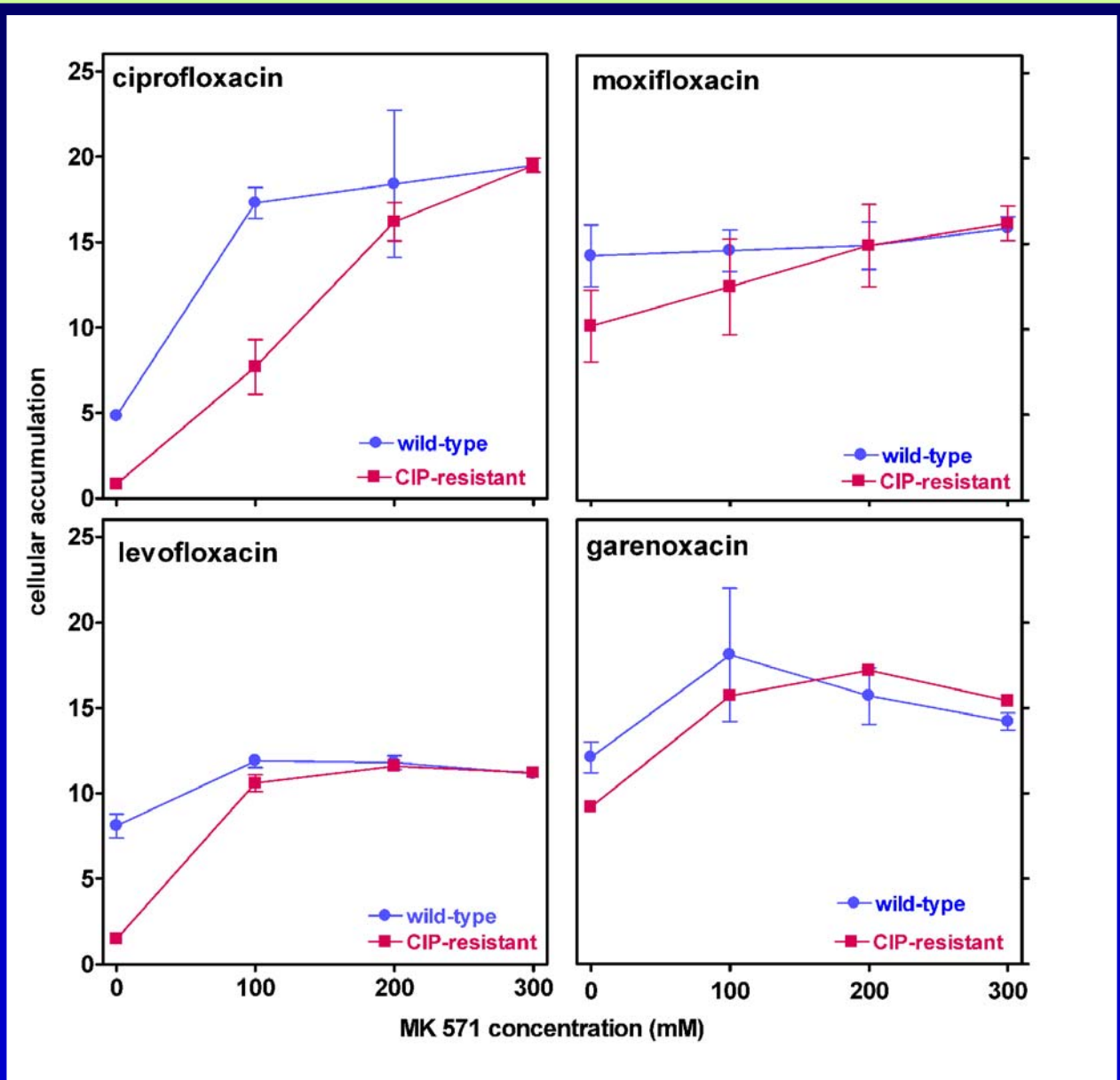
higher probenecid concentrations are needed to restaure CIP accumulation in CIP-resistant cells



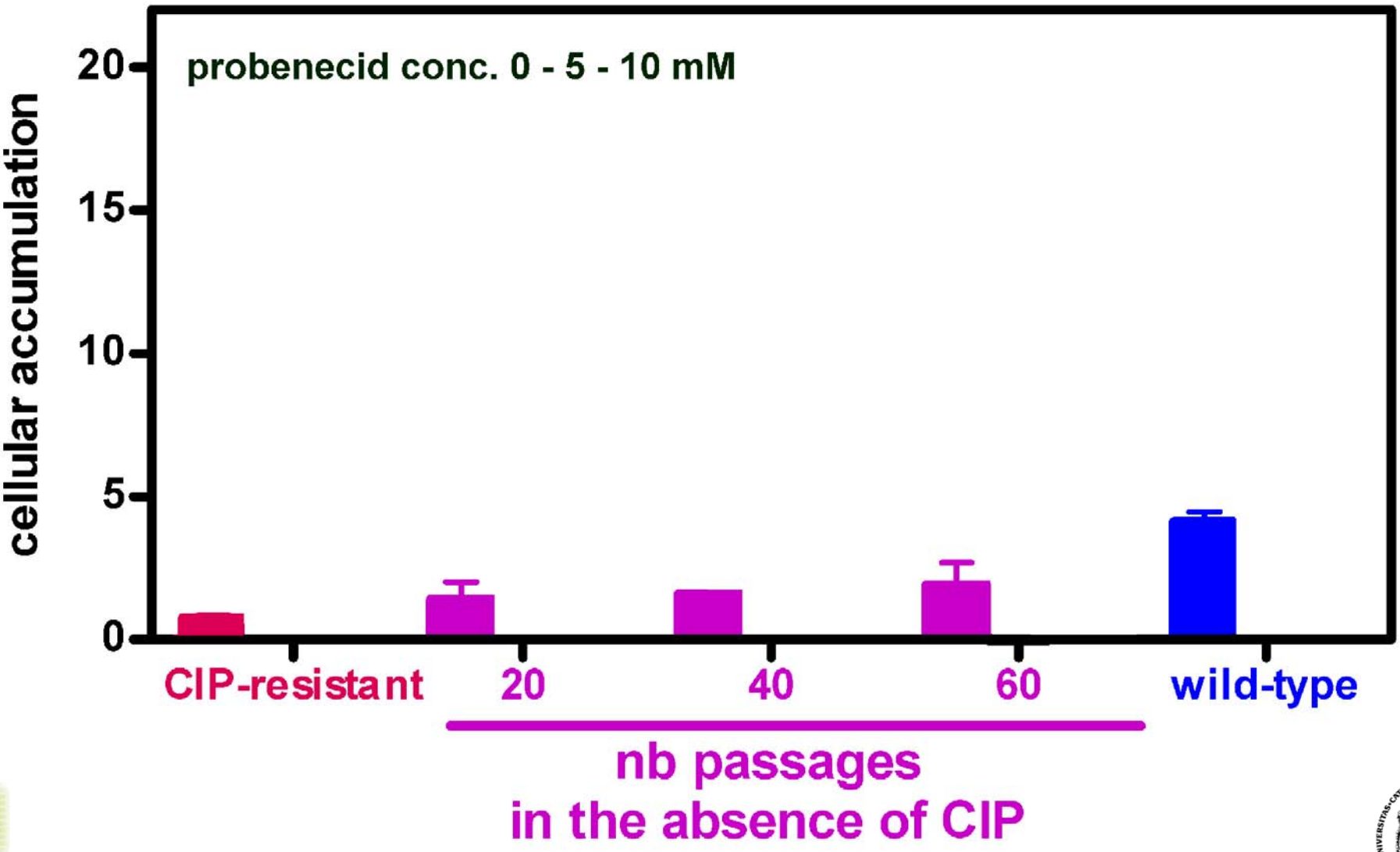
influence of probenecid on quinolone accumulation in wild-type and CIP-resistant cells



influence of MK571 on quinolone accumulation in wild-type and CIP-resistant cells



the CIP-resistant phenotype is not easily reversible



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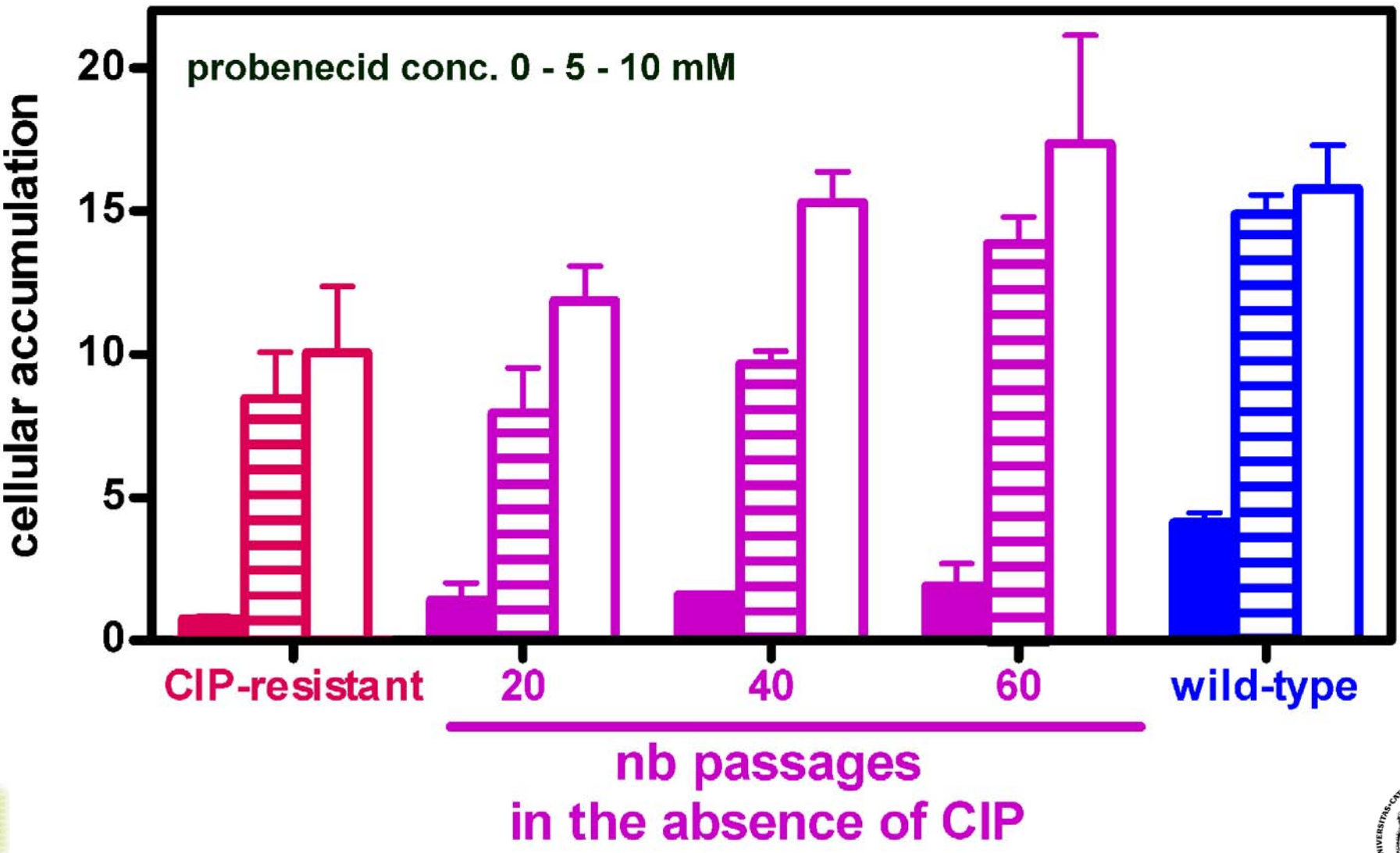
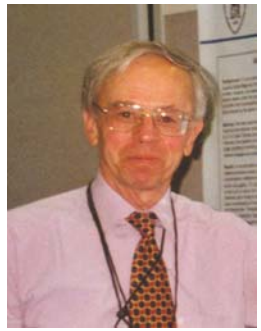


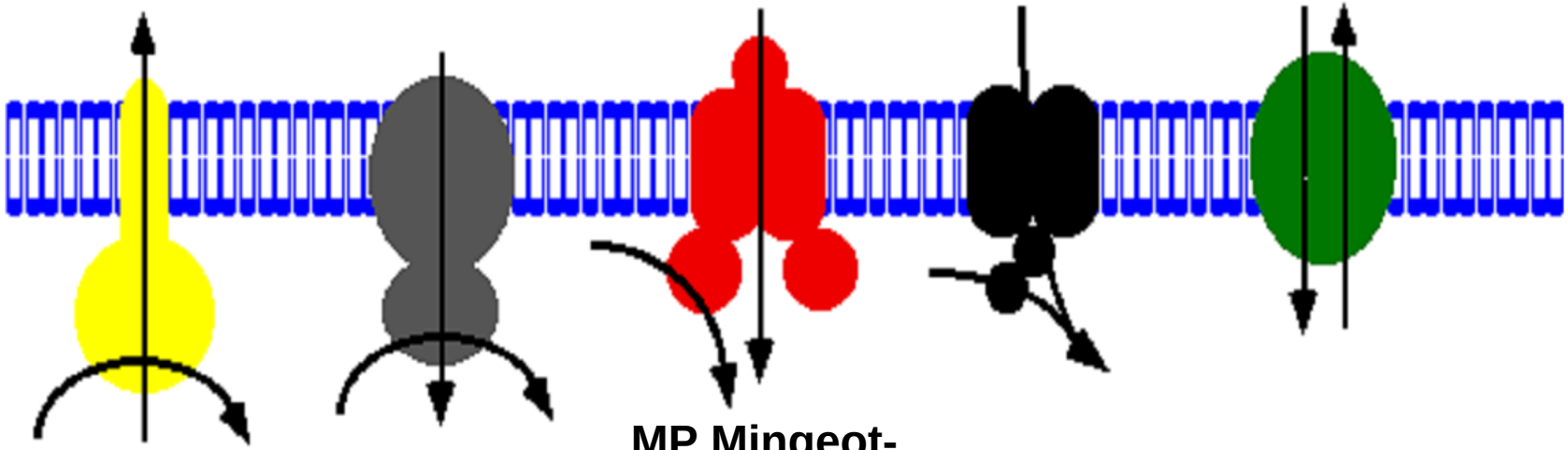
conclusions

- eucaryotic cells can become resistant to antibiotics !
  - macrophage resistance to CIP is mediated by an increase in expression / activity of an MRP – like transporter
  - active efflux affects to variable levels the cellular accumulation of quinolones
- pharmacological consequences still under investigation ….

thanks to …



M Heremans JM Michot MP Mingeot-Leclercq PM Tulkens F Van Bambeke