



COST ACTION CA 17140
NANO2CLINIC
CANCER NANOMEDICINE - FROM THE
BENCH TO THE BEDSIDE

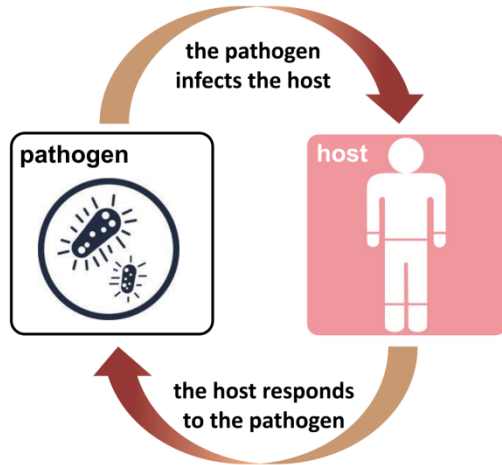
Department of Anaesthesiology and Intensive Care Medicine
Research Group Molecular Mechanism of Life-Threatening Infection

Theranostic nanotherapy of acute life-threatening conditions

Jun.-Prof. Dr. Adrian T. Press
adrian.press@med.uni-jena.de

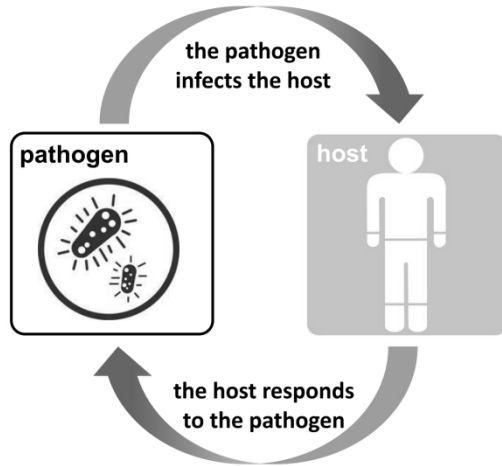
17.06.2022 | Magdeburg, COST 17140

Sepsis – a life-threatening organ dysfunction

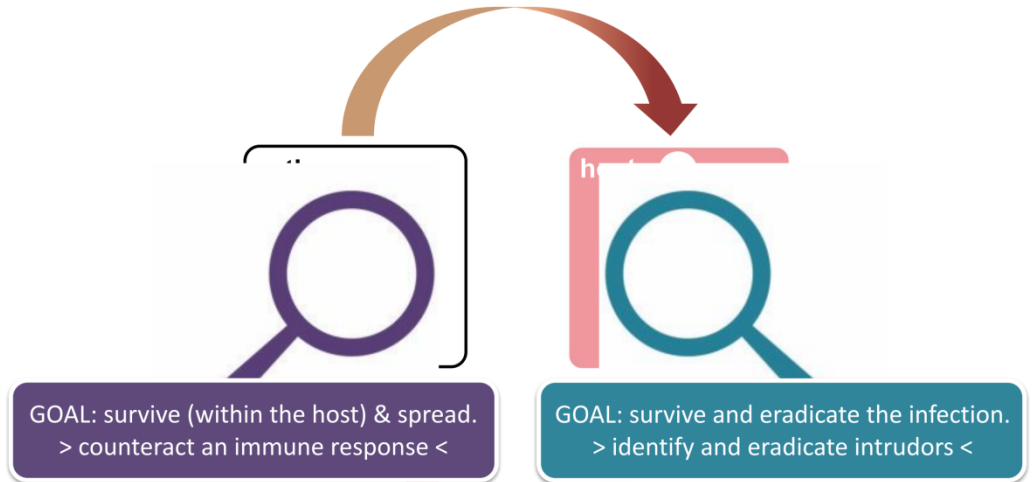


Both, the pathogen and the host carry out various stress responses when they encounter each other

Sepsis – a life-threatening organ dysfunction



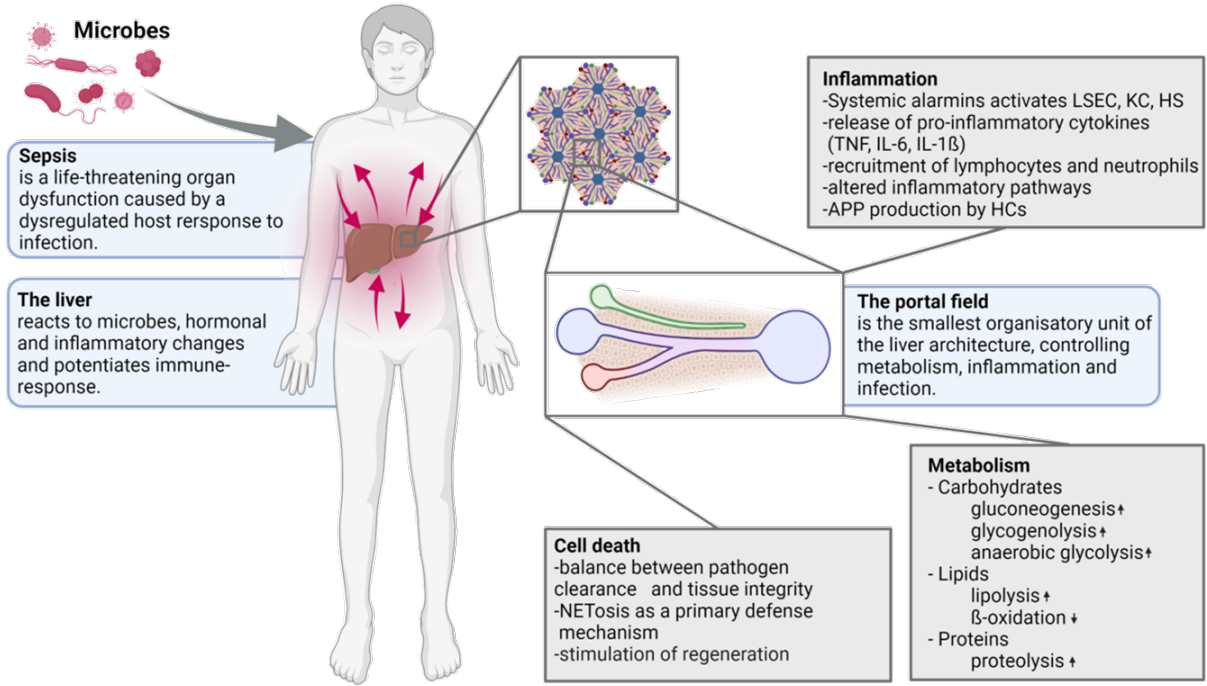
Both, the pathogen and the host carry out various stress responses when they encounter each other



Each pathogen has adaptive and unique strategies to evade the immune response.

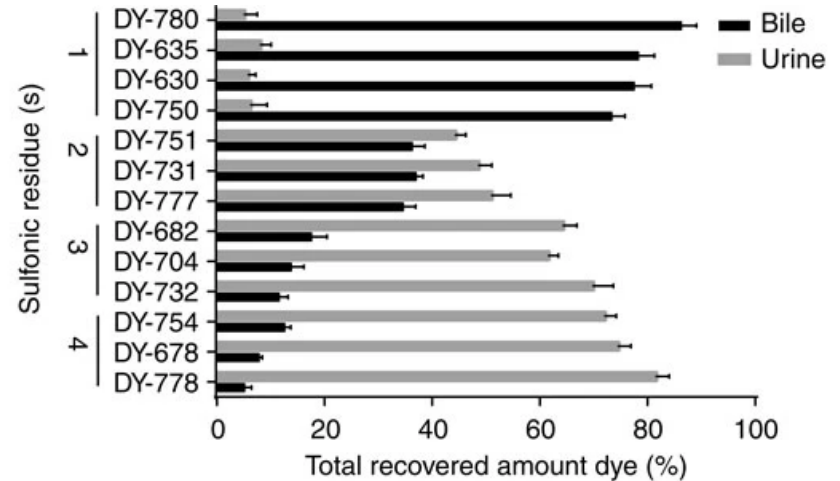
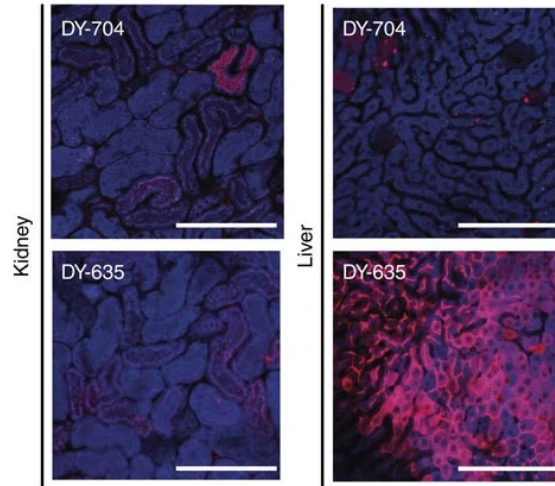
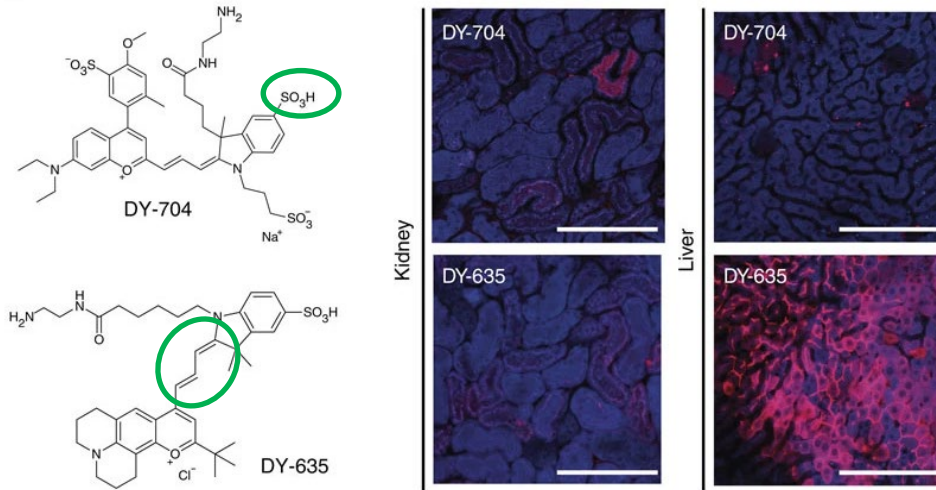
The immune system and other tissues orchestrate and carry out a response tailored to fight the infection.

The liver in sepsis

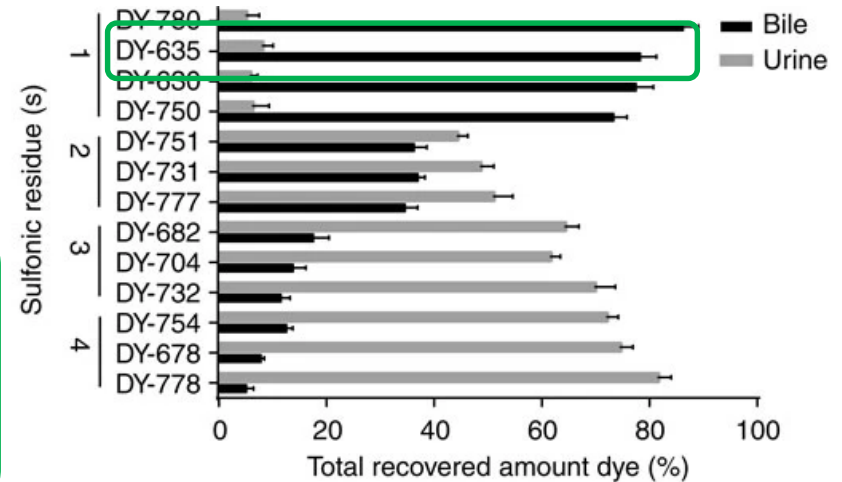
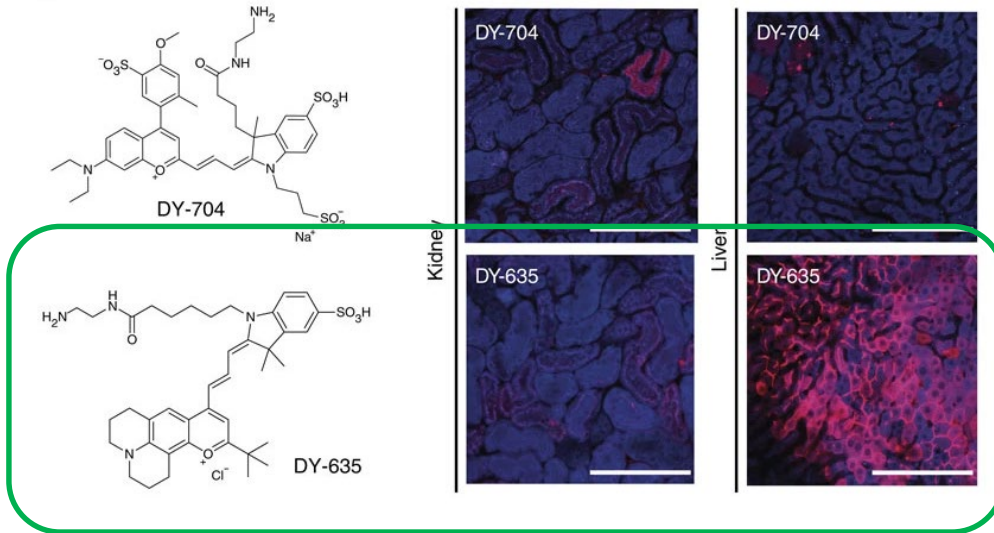


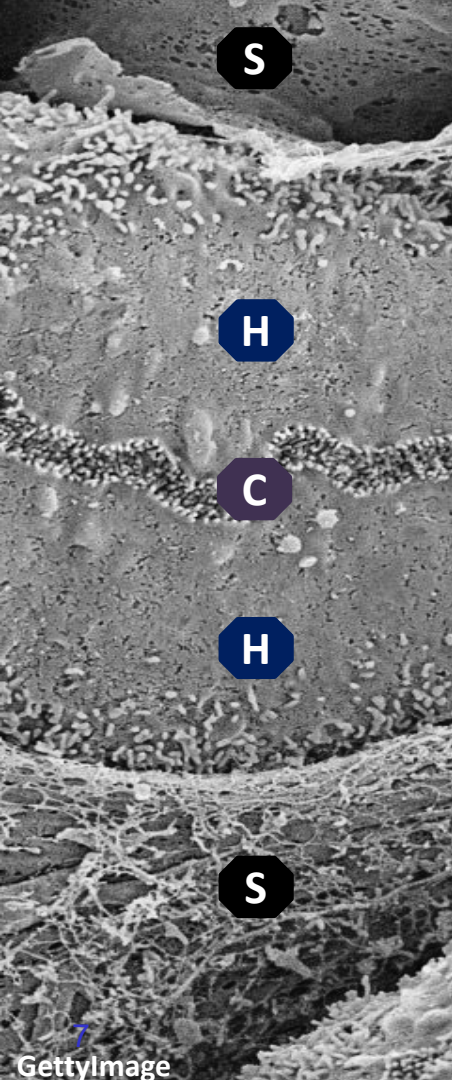
- **40% of patients with sepsis** suffer liver failure
- **50% mortality risk in sepsis** with liver failure
- **27 to 48% of long-term mortality** is associated with cholestasis.

Polymethine dyes with tissue specific clearance

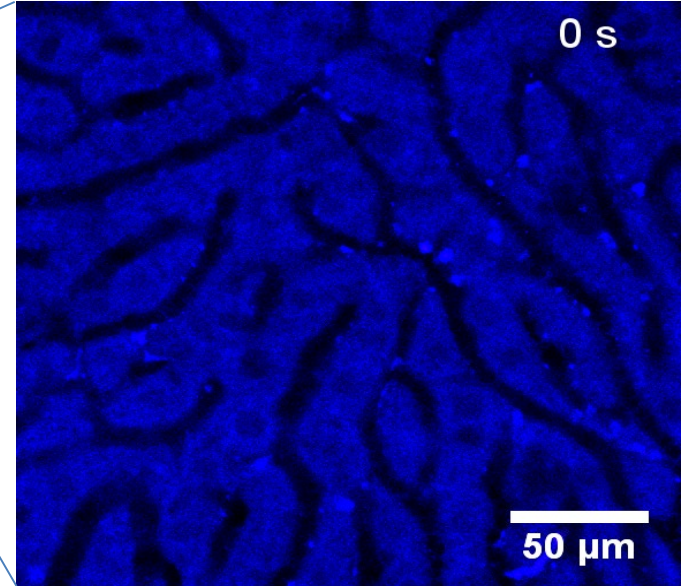
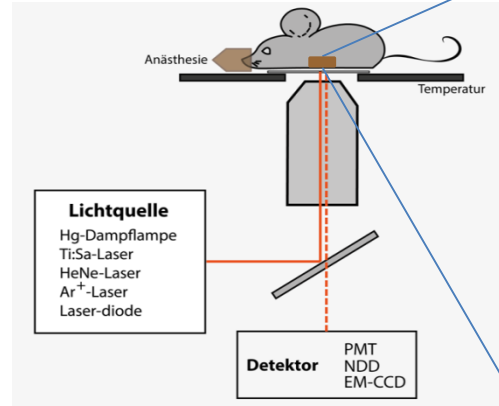


Polymethine dyes with tissue specific clearance





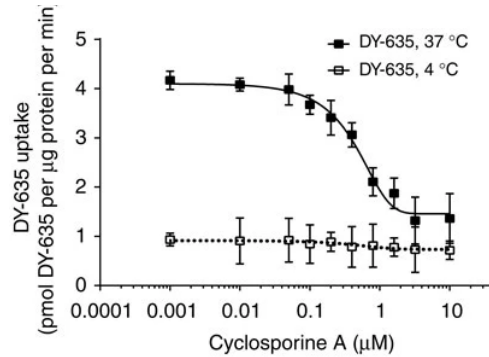
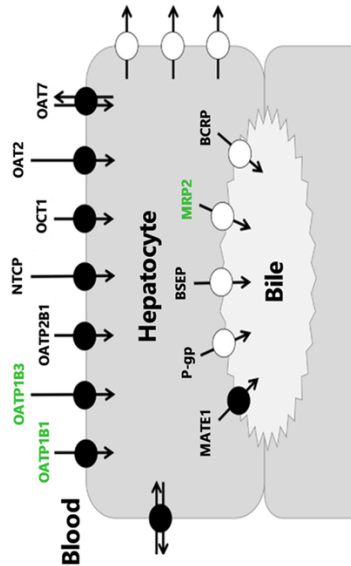
Liver function: Live



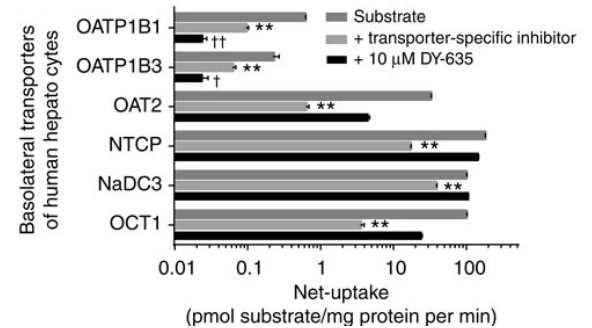
Mice injected with an **DY-635** (an **ICG analogue**) which is cleared by **hepatocytes** exclusively. The liver is viewed by intravital microscopy.

- S** sinusoid
- H** hepatocyte
- C** canaliculus

DY-635 is a substrate for organic anion transporter in the liver

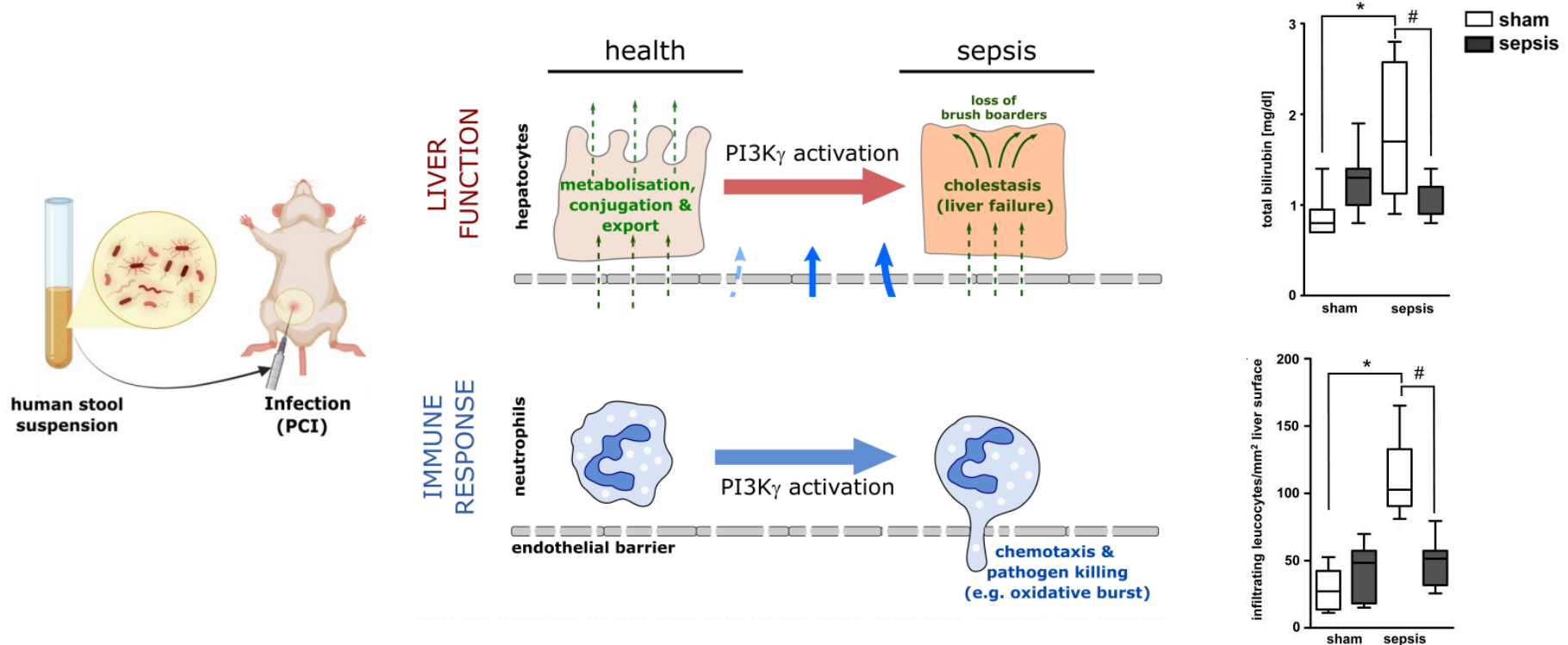


DY-635 uptake is sensitive to cyclosporin A in primary human hepatocytes

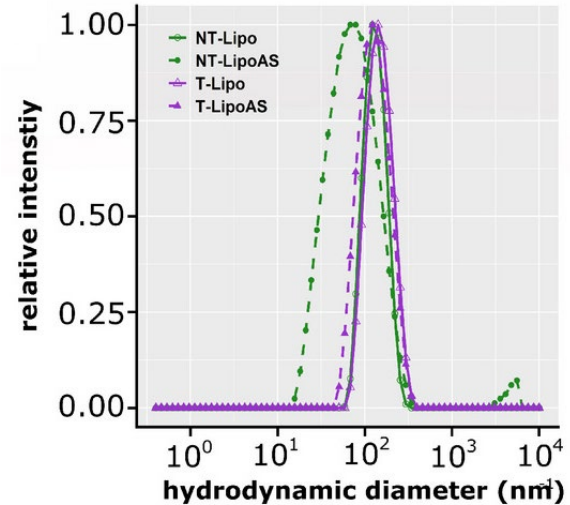
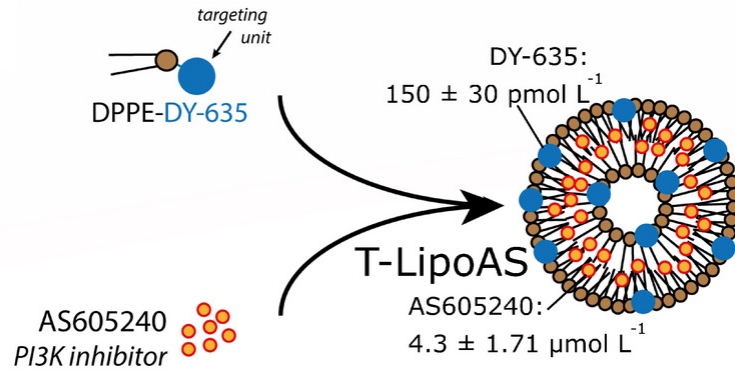


DY-635 is a strong competitive inhibitor of human OATPs

PI3K γ in sepsis

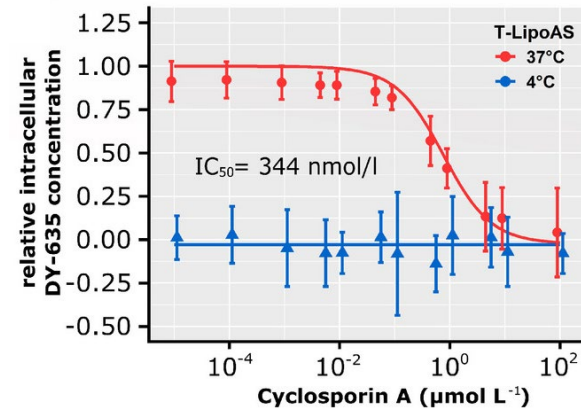
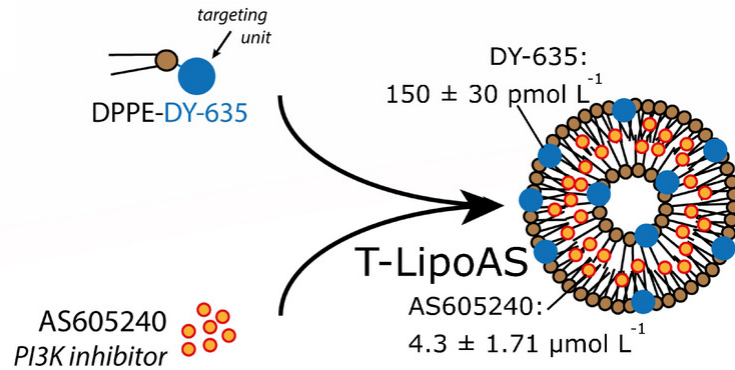


Dye-mediated targeting of PI3K γ inhibitors



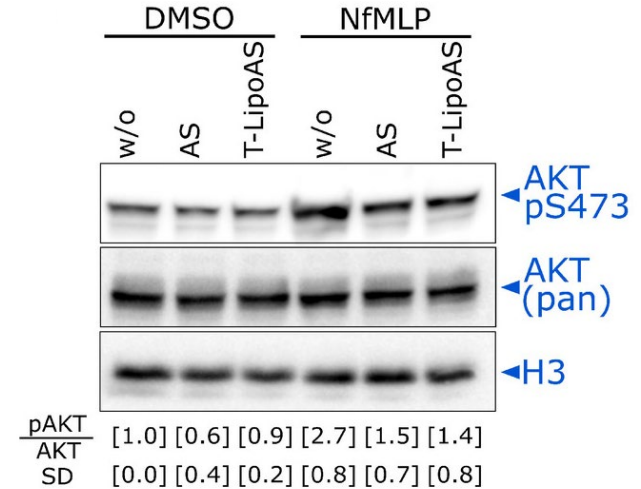
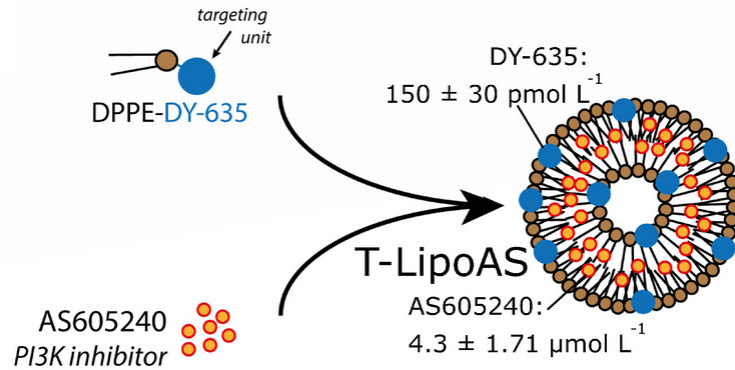
AS605240 is a potent PI3K γ inhibitor with strong immunosuppressive properties

Dye-mediated targeting of PI3K γ inhibitors



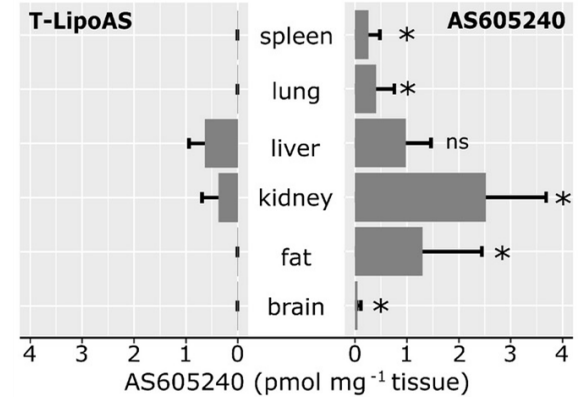
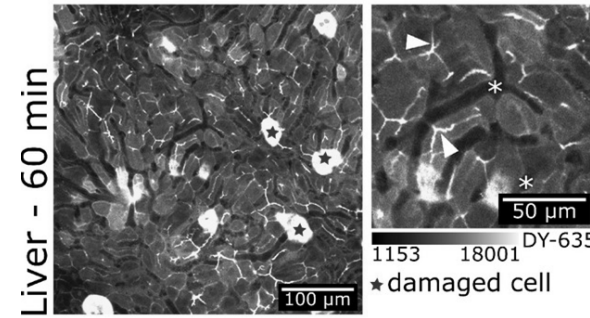
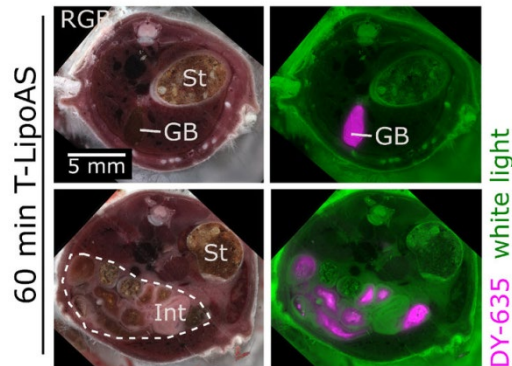
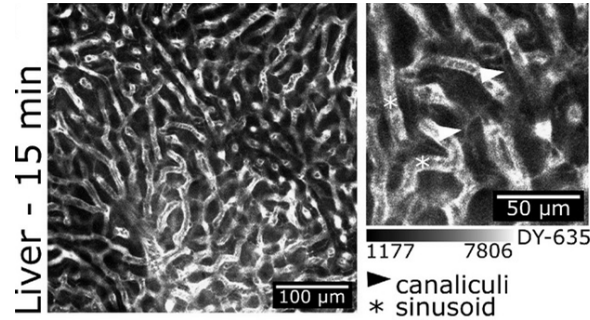
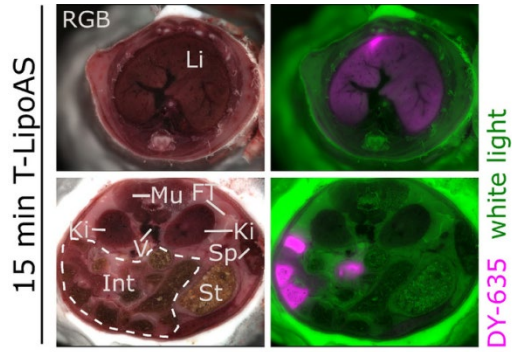
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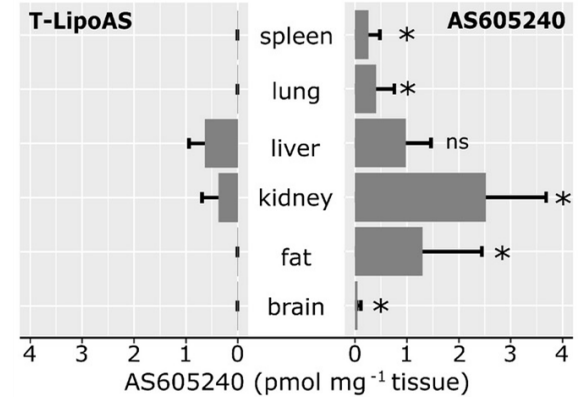
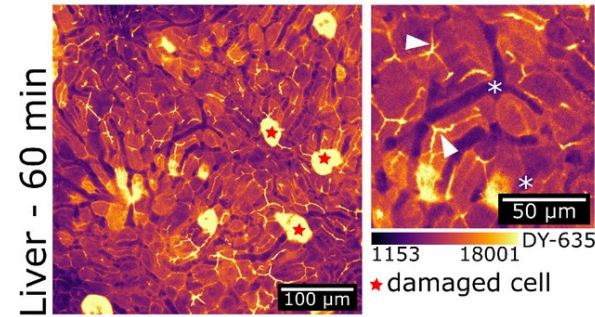
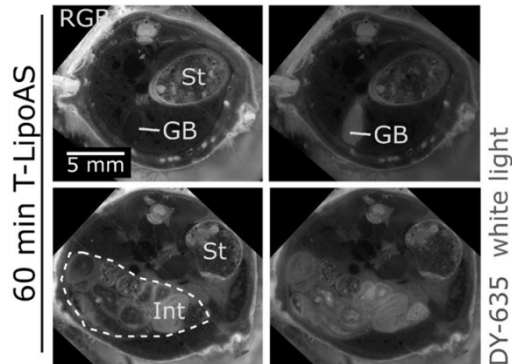
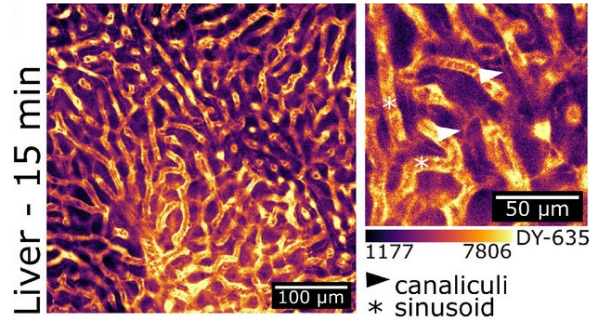
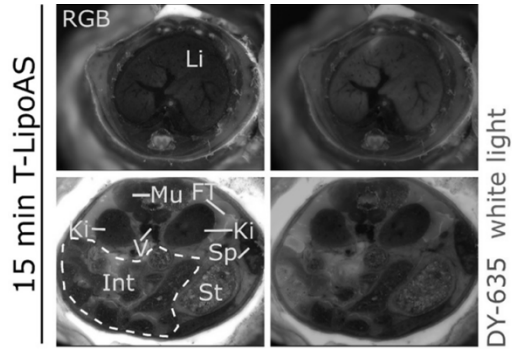
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Dye-mediated targeting of PI3K γ inhibitors



LC-MS detection of AS605240
1 h after 0.1 mg/kg T-LipoAS, 1 mg/kg AS i.v.

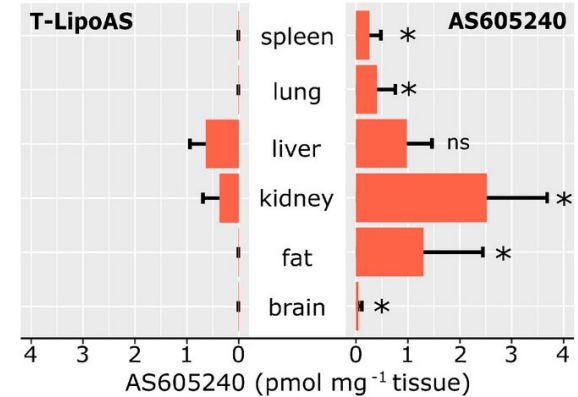
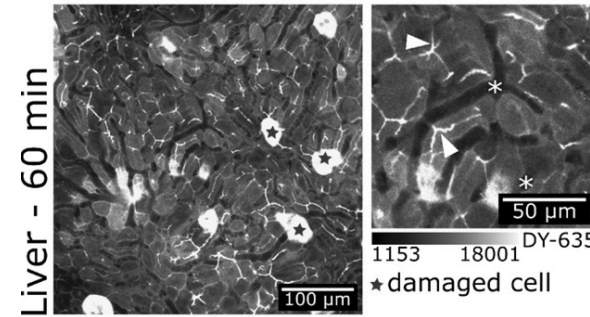
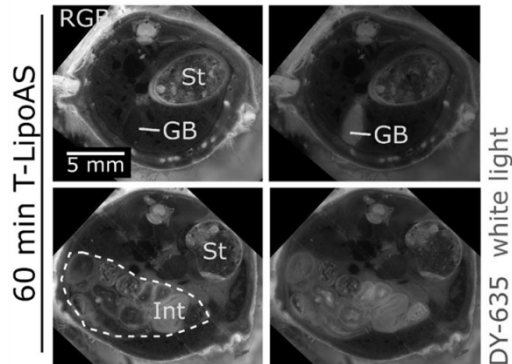
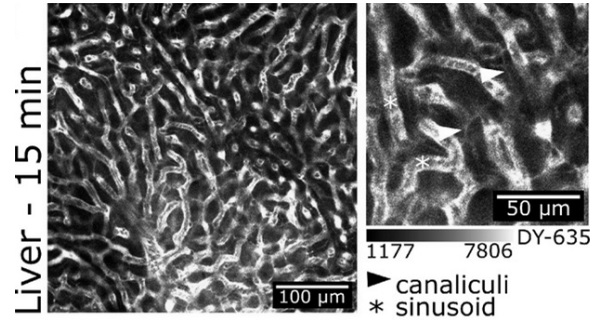
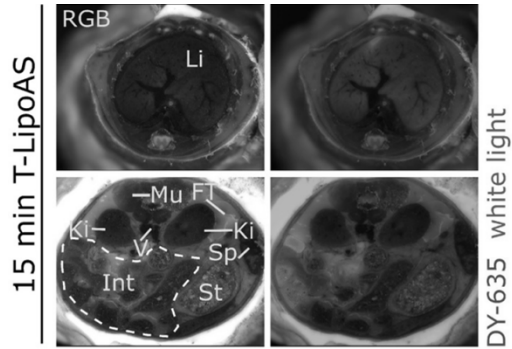
Dye-mediated targeting of PI3K γ inhibitors



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Shkodra Pharmaceutics 2020
Press et al. EMBO Mol Med. 2021
Foo et al. Biomed. Optics Express 2022

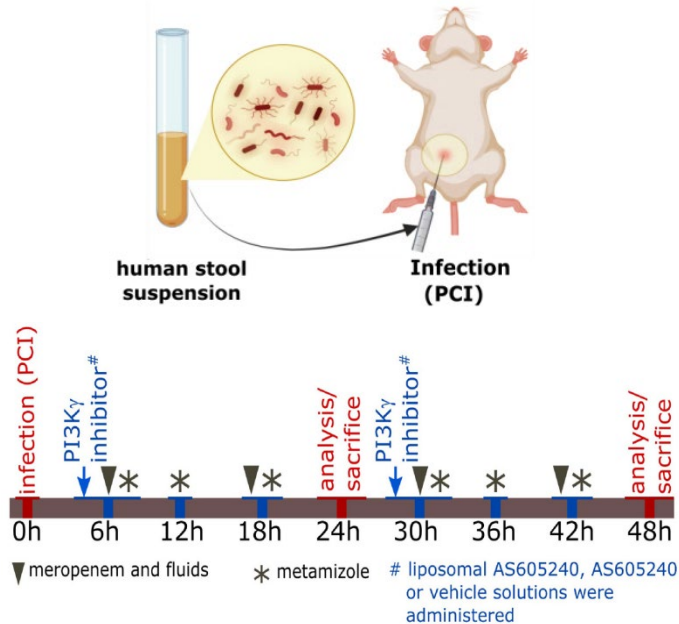
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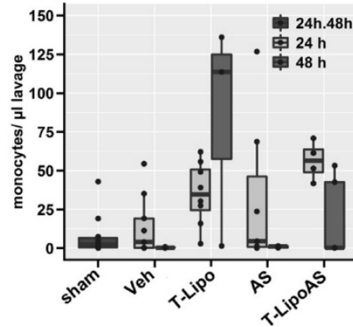
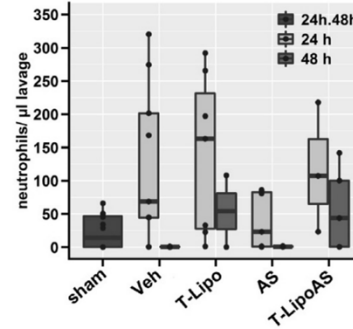
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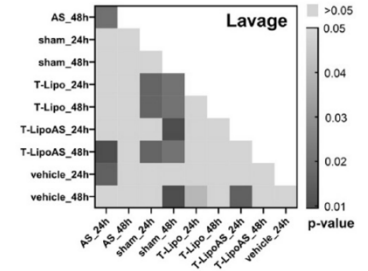
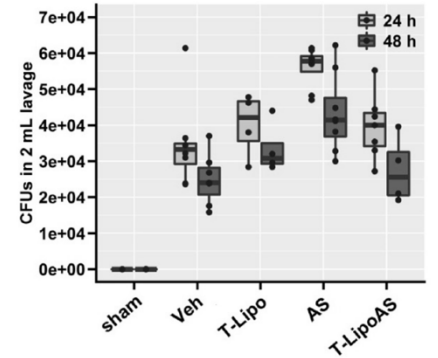
Targeting AS605240 prevents immunosuppressive effects in septic mice



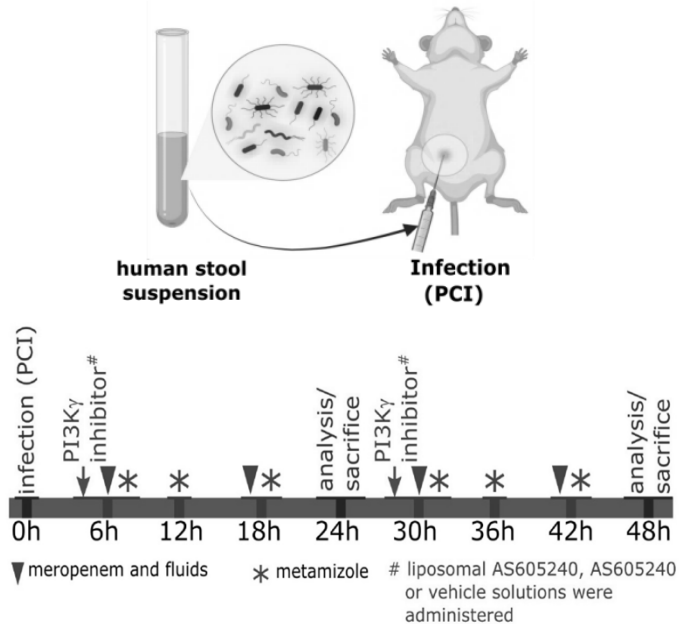
immune cell infiltration



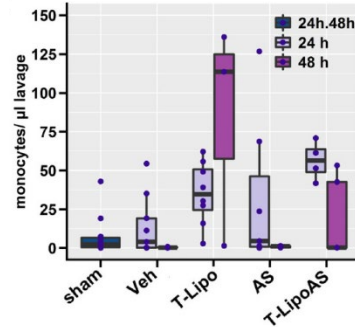
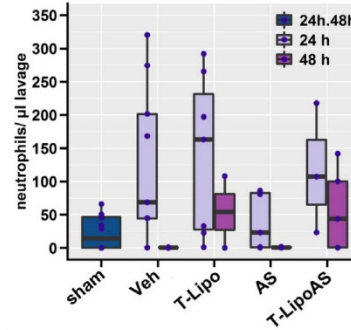
pathogen load



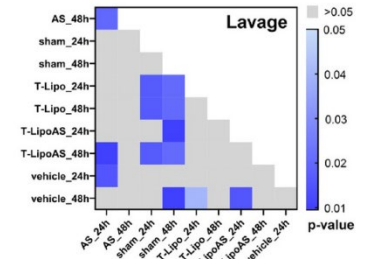
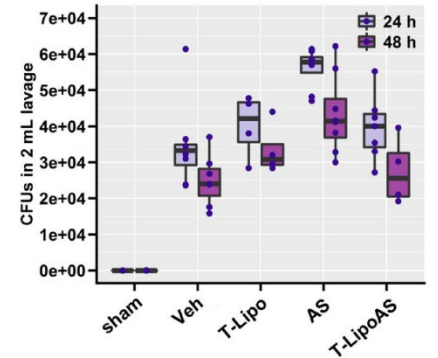
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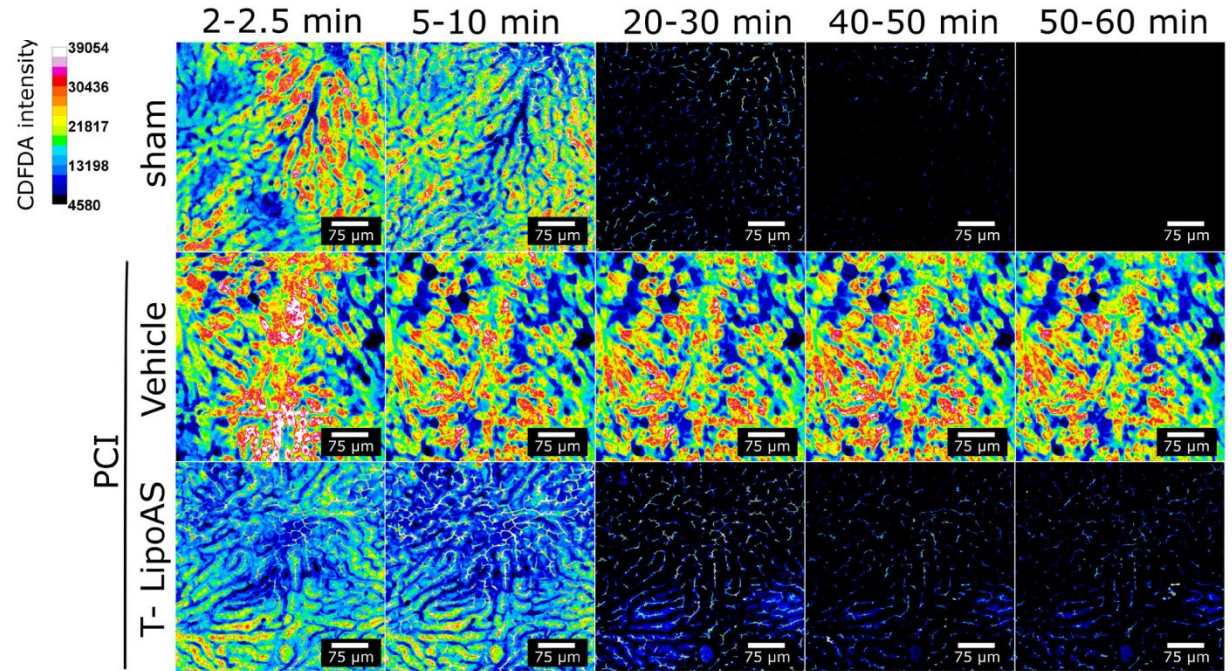
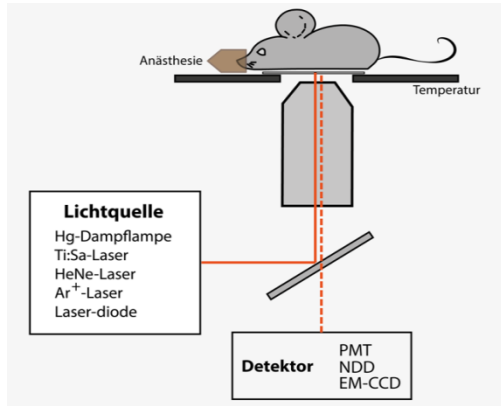
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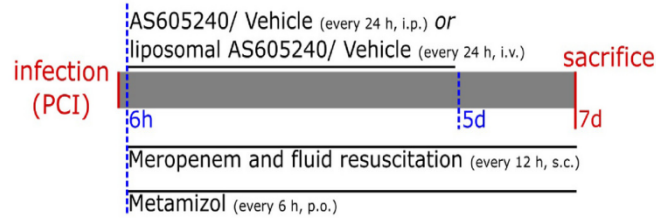
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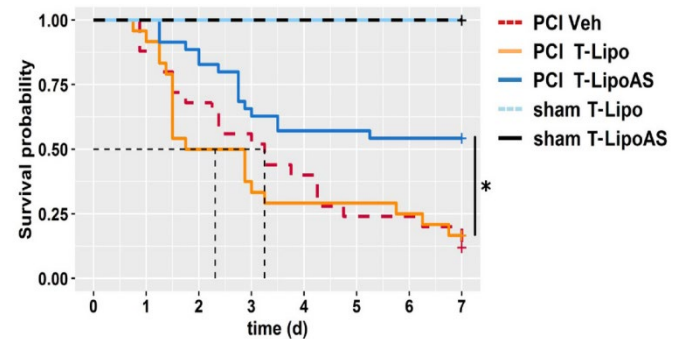
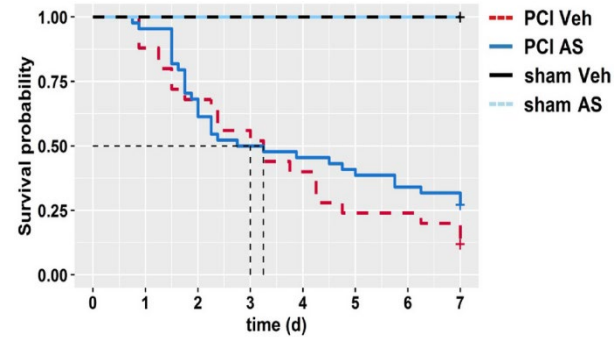
Targeting AS605240 restores liver function in septic mice



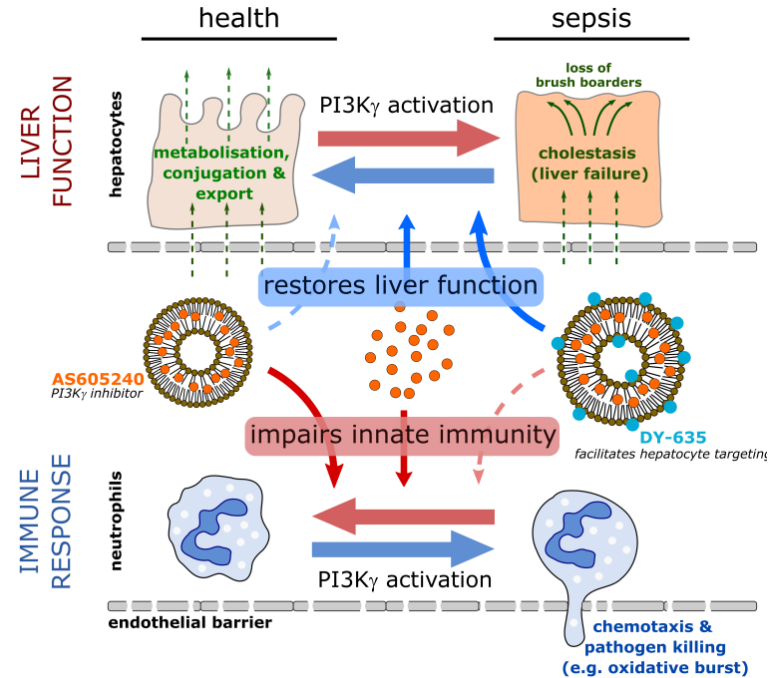
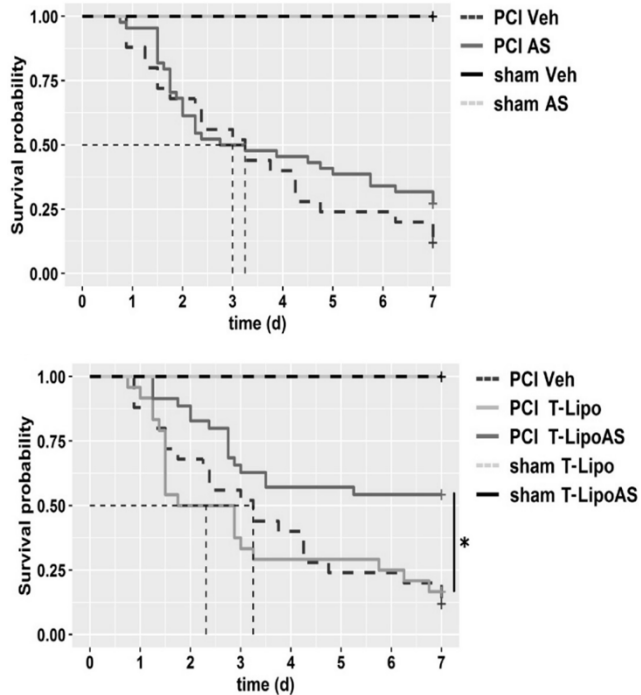
Targeted delivery of PI3K γ inhibitor AS605240 improves survival in a murine sepsis model



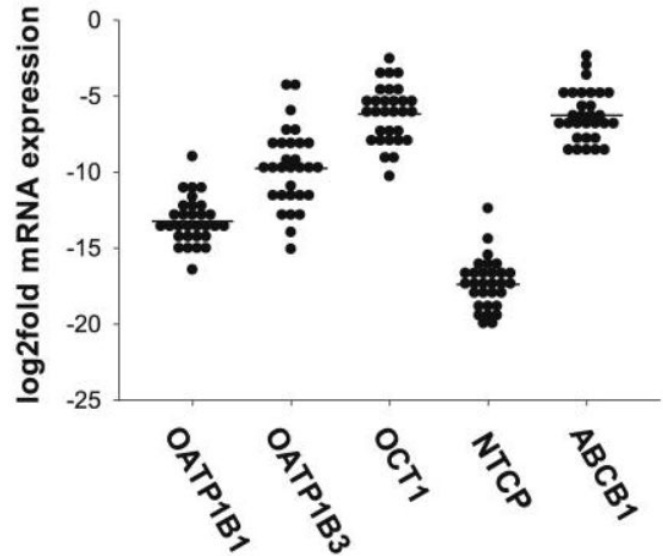
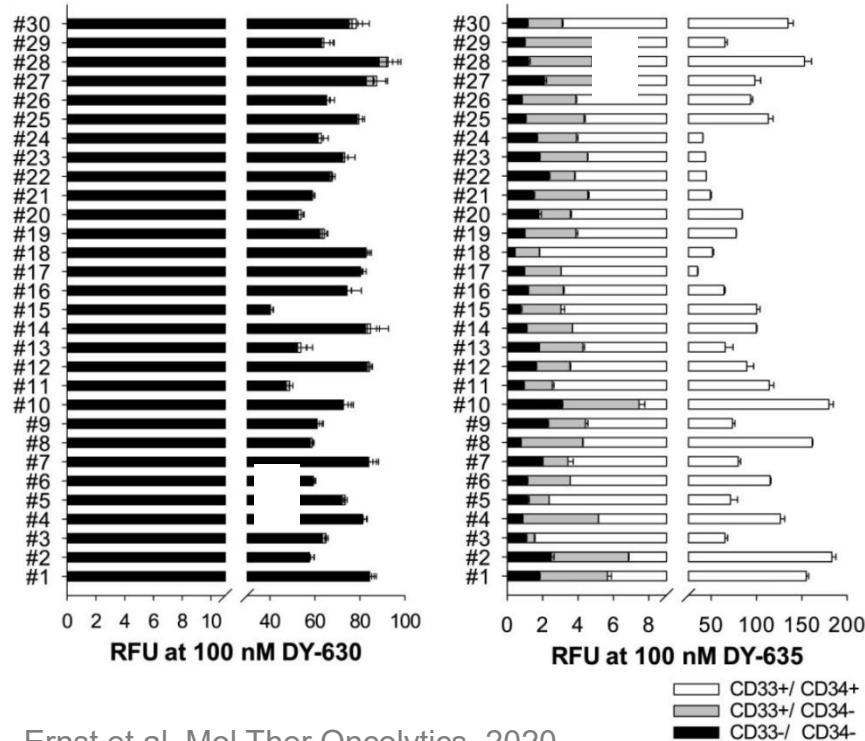
Only targeted PI3K γ delivery improved survival significantly



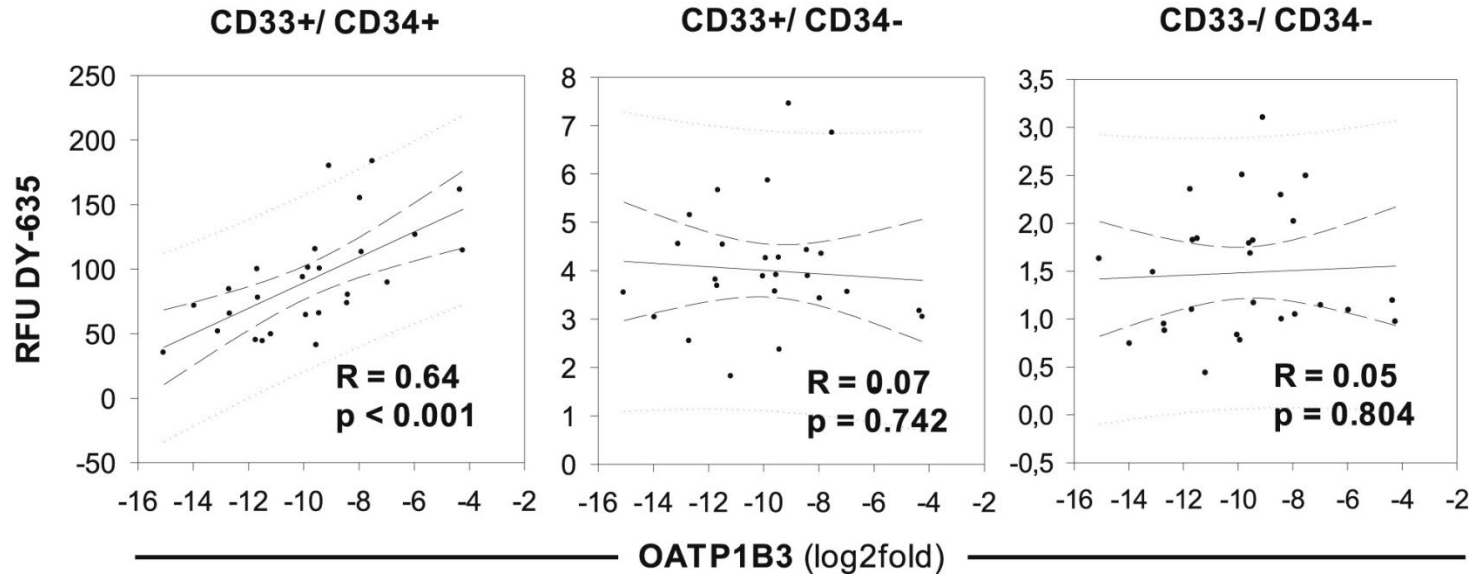
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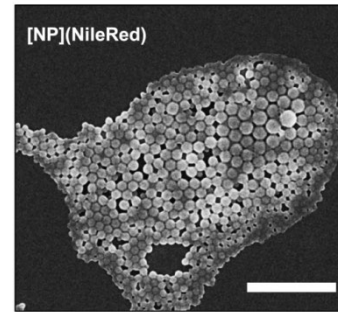
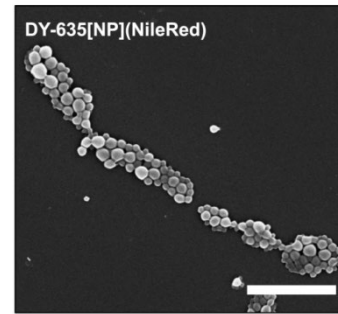
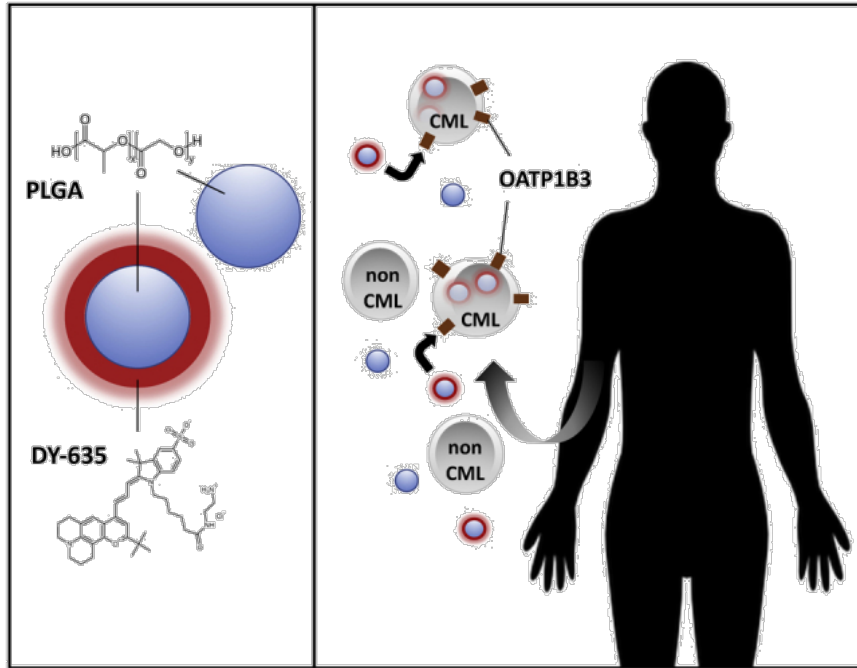
OATP-dependent uptake of DY-635 in CML stem cells



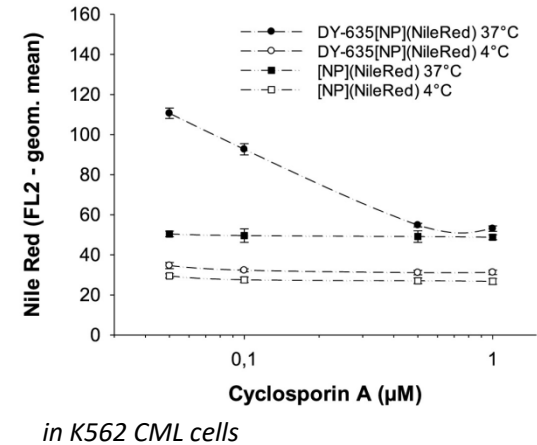
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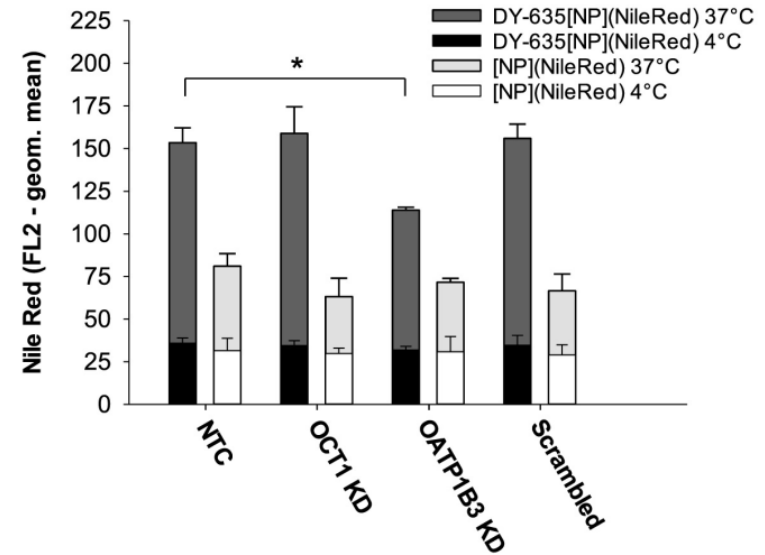
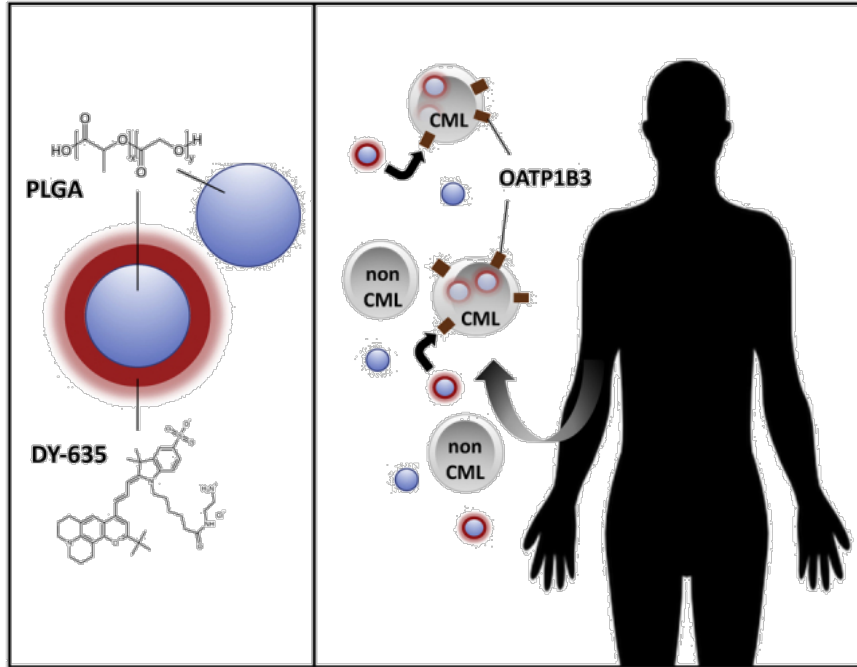
DY-635 as theranostic agent for CML therapy?



Scale 2 μ m

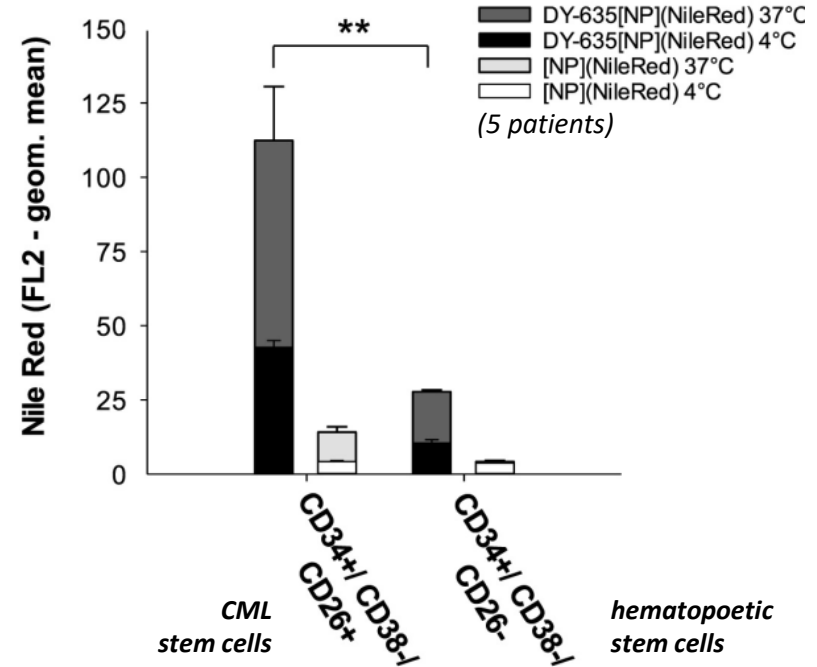
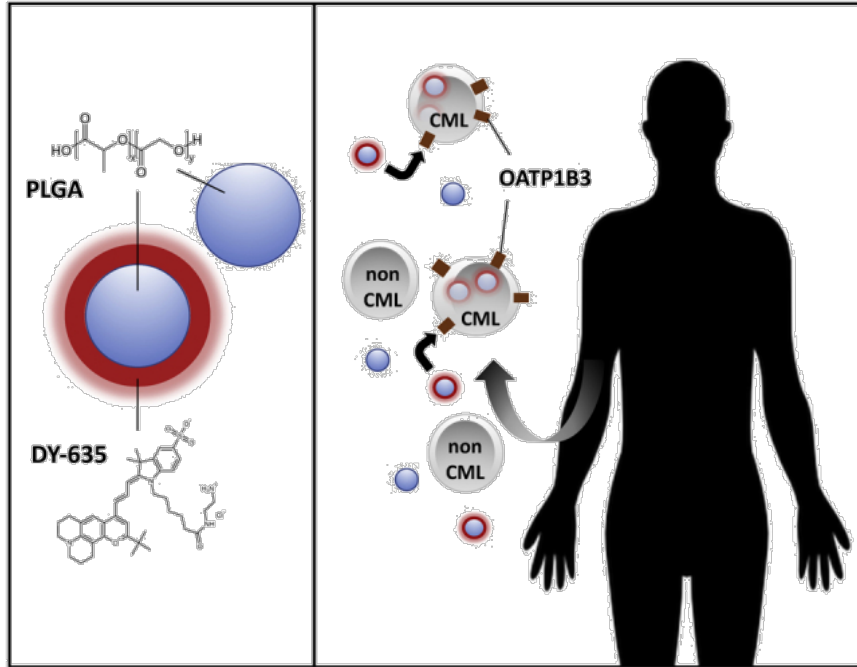


DY-635 as theranostic agent for CML therapy?



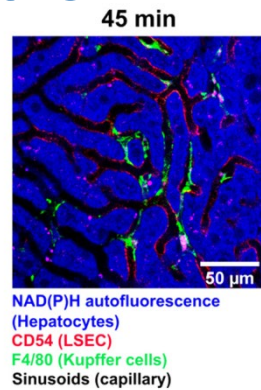
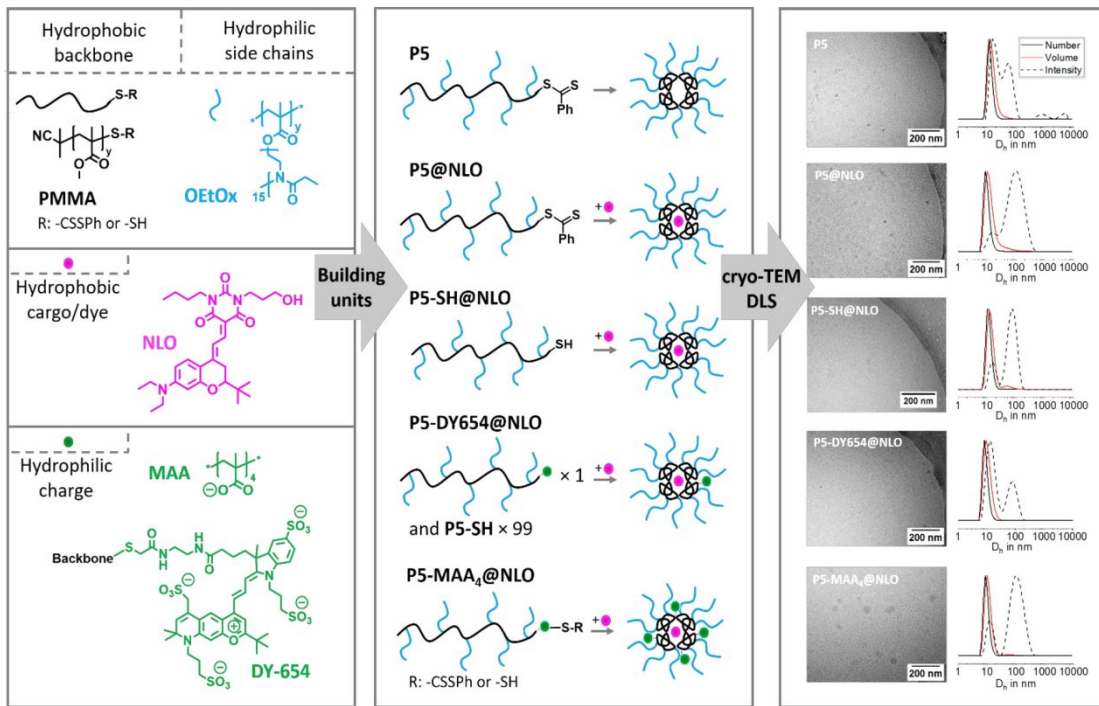
in K562 CML cells

DY-635 as theranostic agent for CML therapy?



Where are we heading?

– Surface architecture in nanocarriers



Uptake in Kupffer cells (45 min)

