Host-directed therapy for the treatment of tuberculosis: rewiring the host to recover control

Heemskerk, M.T.

Stellingen
behorend bij het proefschrift getiteld
"Host-Directed Therapy for the Treatment of Tuberculosis"

1. In the battle between the host and *Mycobacterium tuberculosis*, the decisive factor is not the initiation of autophagic flow, but the TFEB-mediated expansion of lysosomal capacity to overcome the pathogen's phagosomal blockade (this thesis).

2. The disparate efficacy of Akt1 inhibition against *Salmonella enterica* versus its limited effect on *Mycobacterium tuberculosis* infection, reveals that host-directed strategies must be tailored to the unique signaling 'fingerprint' of the pathogen (this thesis).

3. Reductionist models can identify chemical scaffolds, but only systemic models are able to prove therapeutic potential (this thesis).

4. Epigenetic reprogramming demonstrates that 'training' the macrophage is a promising potentially more persistent alternative compared to simply 'arming' it to kill the pathogen (this thesis).

5. Targeting the host's evolutionary stability should offer a superior long-term strategy against drug resistance compared to targeting the pathogen's plastic genome.

6. To overcome biological redundancy in complex pathogenesis, a 'magic shotgun' (polypharmacology) is inherently more effective than a 'magic bullet' (single-target strategy).

7. Intracellular pathogens are more alike than they are different; modulating conserved host pathways is key to a truly broad-spectrum HDT-antimicrobial.

8. Host-directed therapy should not be positioned as a replacement for antibiotics, but primarily as a tool to shorten treatment duration and possibly in combatting drug resistant TB.

9. Scientific understanding, although preferred, is not a strict prerequisite for a compound's therapeutic application; an effective drug with an elusive mechanism is infinitely more valuable to a perfectly characterized failure.

10. In complex systems, order is often a prerequisite for freedom, a principle nowhere more evidently illustrated than in the choreographed chaos of morning bicycle traffic in Leiden.