AARHUS UNIVERSITY

Press release

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Basic information

Name: Line Khalidan Vibholm Email: line.vibholm@clin.au.dk Phone: 27146486

Department of: Clinical Medicine

Main supervisor: Lars Østergaard

Title of dissertation: TLR9 agonist therapy as part of an HIV-1 curative strategy

Date for defence: 15/11/2019 at (time of day): 15.30 Place: Auditorium B, G206-142, Palle Juul-Jensens Boulevard, AUH (Indgang G6)

Press release (Danish)

TLR9 Agonist Behandling som del af en Kurativ Behandlingsstrategi af HIV-1 Infektion

Kronisk HIV-1 infektion er karakteriseret ved persisterende CD4+ T celler, der bærer et stabilt integreret HIV-1 provirus. Dette latente reservoir kan undertrykkes i årtier med antiretroviral behandling (cART), men hvis behandlingen afbrydes vil virus vende tilbage efter 2-3 uger. Da cART er livslang, har bivirkninger og ikke er frit tilgængelig for alle HIV-smittede, er udviklingen af en kur mod HIV-1 infektion en vigtig prioritet. En hypotetisk metode til at helbrede HIV-1 infektion er "shock og dræb", hvor medicinsk behandling aktiverer virus i de latent inficerede celler. Dette medfører at HIV-antigener udtrykkes på overfladen af de inficerede celler, hvilket muliggør genkendelse og immunmedieret destruktion af disse celler. Denne hypotese er testet i kliniske forsøg, men resultaterne har antydet, at immuneffektor-funktionerne, som skulle eliminere de latent inficerede celler, er utilstrækkelige til at kunne reducere det latente reservoir. I de to første studier forsøgtes dosering af en TLR9 agonist, MGN1703, til kronisk HIV-1+ individer med det formål at styrke det innate og adaptive anti-HIV-1 respons. Resultaterne viste, at vigtige komponenter af immunforsvaret blev aktiveret, uden dog at reducere mængden af latent HIV-1. Perspektiverne er kombinations-studier, hvor TLR9 agonist behandling administreres sammen med anden immunmodulerende behandling, for eksempel bredt neutraliserende antistoffer. Et andet vigtigt emne i forskningen i HIV-1 er en mere dybdegående forståelse af den grundlæggende biologi og dynamik i det latente HIV-1 reservoir. Herunder betydningen af latent HIV-1 i lymfoide væv og hvilken rolle disse vira spiller når cART afbrydes og plasmavirus hastigt vender tilbage (kaldet ”virus rebound”). I det tredje studie undersøgtes de virologiske mekanismer bag virus rebound ved afbrydelse af cART, herunder betydningen af latent HIV i lymfeknuder vs. blod.

Ph.d.-projektet er udført ved Aarhus Universitet, Health. Projektet er gennemført af Line K Vibholm.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 15/11/2019 kl. 15.30 i auditorium B, G206-142, Palle Juul-Jensens Boulevard, AUH, Aarhus. Titlen på projektet er ”TLR9 agonist therapy as part of an HIV-1 curative strategy”. Yderligere oplysninger: Ph.d.-studerende Line Khalidan Vibholm, e-mail: line.vibholm@clin.au.dk, tlf. 27146486.

Bedømmelsesudvalg:

Christian Kanstrup Holm, Lektor, Institut for Biomedicin, Aarhus Universitet- chairman of the committee and moderator of the defence:

Arthur Krieg, MD, Professor, University of Massachusetts, RNA Therapeutics Institute.

Devi Sengupta, MD, PhD, Senior Director Clinical Research, Gilead Sciences, Inc.

Press release (English)
TLR9 agonist therapy as part of an HIV-1 curative strategy

Chronic HIV-1 infection is characterized by the persistence of CD4+ T cells, carrying stably integrated HIV-1 provirus. Antiretroviral therapy (cART) can suppress this latent reservoir for decades, but plasma viremia rapidly reemerges 2–3 weeks after therapy interruption. As cART is life-long, has side effects and is not freely accessible to all infected individuals, a cure for HIV-1 is an unmet medical need worldwide. One approach to cure HIV-1 is the "shock and kill", where a pharmacological intervention induces viral transcription in latently infected cells, leading to antigen expression and subsequent recognition for immune-mediated elimination of these cells. However, clinical trials testing this hypothesis have suggested that immune effector functions are insufficient to reduce the size of the latent HIV-1 reservoir. In our first two studies, a TLR9 agonist, MGN1703, was administered to chronically HIV-1+ individuals. The aims of the studies were to enhance the innate and adaptive anti-HIV-1 response. The results showed that important parts of the immune defense were activated. However, the size of the latent reservoir was not reduced. The perspectives are combination trials with a TLR9 agonist is co-administered with other immune modulatory agents, like broadly neutralizing antibodies. Another important aspect of HIV-1 cure research is a more profound understanding of the fundamental biology and dynamics that maintains the latent reservoir. Among others, the contribution of latent HIV-1 in lymphoid tissue and the role of these viruses when cART is interrupted and plasma virus returns (viral rebound). In the third study, the distribution of latent virus in blood vs. lymph nodes and the virological mechanisms behind virus rebound upon interruption of cART were investigated.

Ph.d.-project was carried out at Aarhus University, Health. The project was carried out by Line K. Vibholm.

The defence is public and takes place on 15/11/2019 at 3.30 PM, in auditorium B, G206-142, Palle Juul-Jensens Boulevard, AUH, Aarhus. For more information, please contact PhD student Line Khalidan Vibholm, e-mail: line.vibholm@clin.au.dk, phone:27146486.

Assessment committee:
Christian Kanstrup Holm, Associate Professor, Institut for Biomedicin, Aarhus Universitet- chairman of the committee and moderator of the defence

Arthur Krieg, MD, Professor, University of Massachusetts, RNA Therapeutics Institute.

Devi Sengupta, MD, PhD, Senior Director Clinical Research, Gilead Sciences, Inc.

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