AARHUS UNIVERSITY
DEPARTMENT OF BIOMEDICINE

Adaptive Immunology

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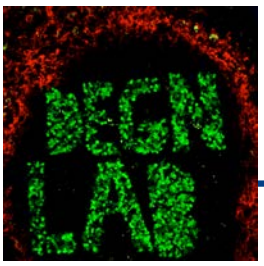
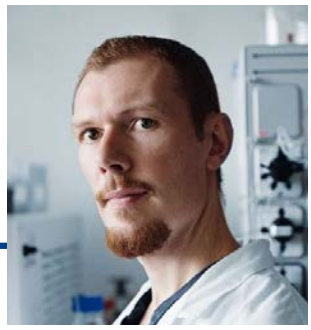
Laboratory for Lymphocyte Biology
Lab members: 2 postdocs, 1 medical student, 2 lab techs





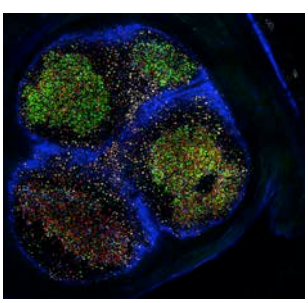
Background

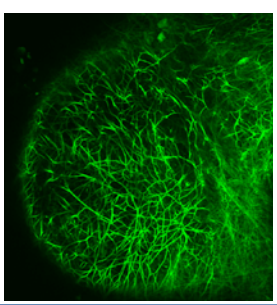
In response to foreign molecules (antigens), B lymphocytes produce antibodies, soluble molecules that are able to bind these antigens with high affinity and to direct their neutralization and clearance. This process takes place in specialized microanatomical structures in secondary lymphoid tissue, called germinal centers. Such immunological responses are assisted by a specialized subset of T lymphocytes, T helper cells, a subgroup of which localize to germinal centers and are termed T follicular helper cells (Tfh). Germinal centers are also central to autoimmune responses, whereby the body attacks its own tissues. In recent years, it has become clear that another subset of T cells, so-called T follicular regulatory cells (Tfr) are involved in regulating germinal center responses, and preventing emergence of specificities towards self. Our group studies germinal centers mainly from the perspective of autoimmunity, comparing and contrasting with responses to foreign antigens.

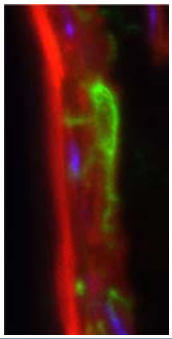
Projects and techniques

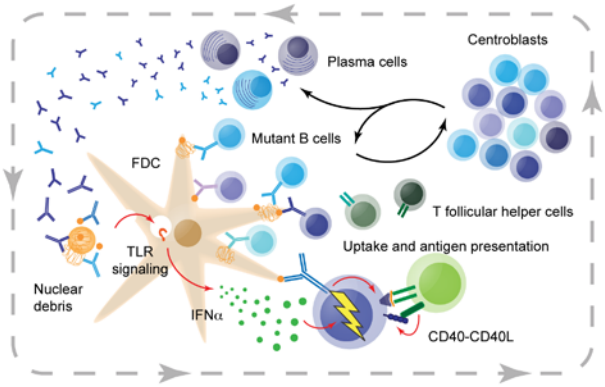
We are approaching central questions in germinal center biology using a breadth of techniques ranging from sequencing of antibody and T cell receptor repertoires, cloning, recombinant expression, protein engineering, over in vitro cell-based assays, nanoscience-based dissection of molecular interactions, to flow cytometry, cell sorting and confocal microscopy, as well as advanced in vivo mouse models and intravital two-photon microscopy, the latter including longitudinal imaging of lymphoid tissues using a novel imaging window chamber implantate.

Projects will depend on the student's background and own wishes. Examples of projects: 1) Develop a ddPCR protocol for advanced genotyping of Ig knock-in mice; 2) Basic characterization of germinal centers in the BXSB/Yaa autoimmune model, using flow cytometry and confocal microscopy; 3) Set up a DropSeq protocol for high-throughput analyses of B cell receptor repertoires; 4) Analyze CD4-Cre/ERT2 Confetti reporter mice using two-photon microscopy.









Model of the autoreactive germinal center and the main mechanisms fueling the 'furnace of autoreactivity'. Follicular dendritic cells (FDCs) take up nucleolar debris, which in turn triggers endosomal TLR signaling, leading to interferon alpha production. Interferon alpha acts on protoautoreactive B cells, which upon antigen engagement take up nuclear components and present derived peptides to T follicular helper cells. T follicular helper cells stimulate the B cells through CD40L-CD40 interactions, among others, to enter or return to the dark zone of the germinal center. Resulting B cell centroblasts divide and hypermutate, then return to the light zone to probe FDCs for antigen, and the process is repeated. Autoantibodies produced by plasma cells derived from B cells in the germinal center facilitate immune complex loading, completing the vicious cycle of autoreactivity. Red arrows indicate the main driving signals and suggest possible points of intervention.

Reference: Clonal Evolution of Autoreactive Germinal Centers. Degn SE, van der Poel CE, Firl DJ, Ayoglu B, Al Qureshah FA, Bajic G, Mesin L, Reynaud CA, Weill JC, Utz PJ, Victora GD, Carroll MC. Cell. 2017 Aug 24;170(5):913-926.e19. doi: 10.1016/j.cell.2017.07.026.

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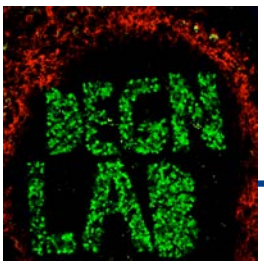
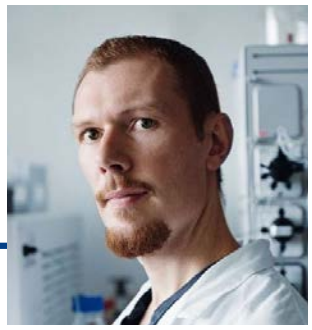




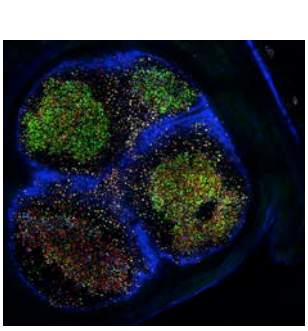
Baggrund

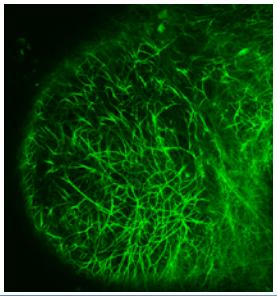
Som svar på fremmede molekyler (antigener) producerer B lymfocytter antistoffer, soluble molekyler der kan binde antigener med høj affinitet, neutralisere disse, og føre til deres fjernelse. Dannelsen af antistoffer foregår i specialiserede mikroanatomiske strukturer i sekundære lymfoide væv, såkaldte kimcentre. B cellernes antistofsvar assisteres af specialiserede T lymfocytter, T hjælper celler, hvoraf et subset lokaliserer til kimcentre og betegnes T follikulære hjælper celler (Tfh). Kimcentre er også centrale i autoimmune sygdomme, hvor immunsystemet angriber kroppens egne væv. I de senere år er det blevet klart, at endnu et subset af T celler, såkaldte T follikulære regulatoriske celler (Tfr), er involveret i reguleringen af kimcenter responser, og forhindrer fremkomsten af autoreaktive B celler. Vi studerer kimcentre, hovedsageligt i forbindelse med autoimmunitet.

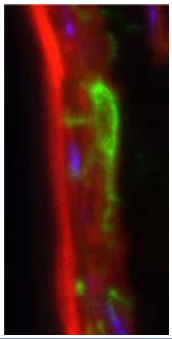
Projekter og metoder

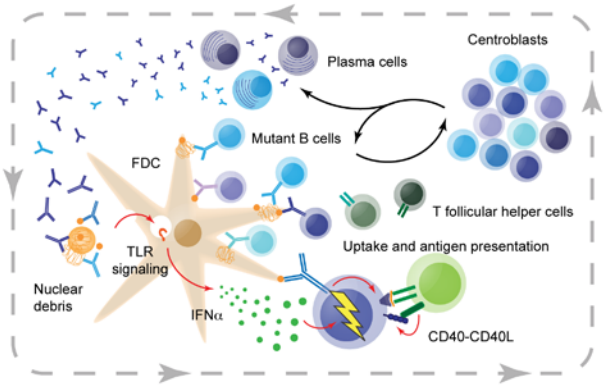
Vi angriber centrale spørgsmål indenfor kimcenter biologi med en bred vifte af teknikker, der spænder fra sekventering af antistof og T celle receptor repertoiret, kloning, rekombinant ekspression, over cellebaserede assays in vitro, nanoteknologi-baseret dissektion af molekylære interaktioner, til flow cytometri, cellesortering og konfokalmikroskopi, såvel som avancerede in vivo musemodeller og intravital to-foton mikroskopi, hvor sidstnævnte blandt andet omfatter longitudinal imaging af lymfevæv gennem et nyudviklet lymfeknudevindue implantat.

Projekter afhænger af den studerendes baggrund og egne ønsker. Eksempler på projekter: 1) Udvikling af en ddPCR protokol til avanceret genotyping af Ig knock-in mus; 2) Basal karakterisering af kimcentre I BXSB/Yaa autoimmune mus vha. flow cytometri og konfokalmikroskopi; 3) Opsætning af en DropSeq protokol til high-throughput analyse af B celle receptor repertoirer; 4) Analyse af CD4-Cre/ERT2 Confetti reporter mus vha. to-fotonmikroskopi.









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