BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Goran Bajic

eRA COMMONS USER NAME (credential, e.g., agency login): gbajic

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Université Claude Bernard – Lyon 1, Lyon, France	B.Sc.	06/2009	Biochemistry
Université Claude Bernard – Lyon 1, Lyon, France	M.Sc	06/2011	Biochemistry
Aarhus University, Aarhus, Denmark	Ph.D.	08/2015	Immunology, Structural Biology
Harvard Medical School and Boston Children's Hospital, Boston, MA	Postdoctoral	08/2019	Immunology, Virology, Structural Biology

A. Personal Statement

\My extensive training in biochemistry, immunology and structural biology permits me to appreciate biological problems at molecular and atomic level – this aspect is essential to tackling complex biological systems such as germinal center reactions and the development of next-generation vaccine immunogens.
My graduate work focused on innate immunity and in particular how complement C3 activation products (C3b, iC3b and C3d) serve as ligands for receptors (Mac-1 and CD21) on phagocytic effector cells to help clear invading pathogens or diseased host cells. I worked in the group of Gregers Andersen where I learned complement biology and X-ray crystallography and in the group of Tim Springer who instilled in me the appreciation for the intricacies of integrin-ligand interactions. My thesis work has laid foundations for structural and molecular understanding of how complement-tagged immune complexes are recognized by phagocytes and how, in turn, these cells shuttle immune complexes to germinal centers for antigen presentation. Hypothesizing about how immune complex shuttling occurs, on a molecular level, in germinal centers led me to pursue my post-doctoral training exploring the processes of antibody affinity maturation in response to influenza infection and vaccination and the notion of original antigenic sin. For the past 5 years I have been contributing to a Program Project Grant, under the mentorship of Stephen Harrison, that characterizes germinal center and antibody repertoire responses to influenza infection and vaccination. I have been leveraging my expertise in protein biochemistry and structural biology to learn more about adaptive immune responses to viruses and the perpetual virus-host arms race. A key question I focused on during my postdoctoral work, and directly pertinent for this proposal, was to understand how to define immunodominance on a biochemical and structural level and how to leverage this information for rational immunogen design. In one example, with guidance from Aaron Schmidt at the HMS Department of Microbiology, I used protein engineering to introduce glycans onto the influenza virus hemagglutinin protein to determine how the resulting antibody responses were altered by characterizing molecular features of the elicited antibodies. I found that glycans changed the initially diverse repertoire into an epitope-focused, genetically restricted response. Structural analyses of antigen-antibody complexes showed an enrichment of one gene family targeting a previously uncharacterized but broadly protective epitope. These results have potential implications for next-generation vaccines aimed at directing B-cell responses to preferred epitopes for other pathogens such as dengue and malaria. I recently started my own group in structural biology at the Department of Microbiology at Icahn School of Medicine at Mount Sinai.

B. Positions and Honors

Positions and Employment

2006-09	**Undergraduate Student**, Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France
2008	**Summer Research Intern**, Biochemistry, bioMérieux, France
2008-11	**Tutor**, Biology/Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France
2009-11	**Master Student**, Structural and Functional Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France
2012-15	**Graduate Student**, Immunology/Structural Biology, group of Gregers Rom Andersen, Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark
2013-14	**Visiting Graduate Student**, Immunology/Structural Biology, group of Timothy A. Springer, Harvard Medical School, Boston, MA
2012-15	**Teaching Assistant**, Molecular Biology/Biochemistry, Aarhus University, Aarhus, Denmark
2015-	**Postdoctoral Research Fellow**, Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA
2017-	**Teaching Fellow**, Immunology, Harvard University Extension School, Cambridge, MA
2017-	**Mentor** at the Howard Hughes Medical Institutes (HHMI) undergraduate EXROP program
2017-	**Invited Lecturer**, Immunology, Harvard Medical School, Boston, MA
2019-20	**Instructor in Pediatrics**, Harvard Medical School & Boston Children's Hospital, Boston, MA
2020	**Assistant Professor**, Icahn School of Medicine at Mount Sinai, New York, NY

Honors

2019	**Finalist** for the Michelson Prizes in Immunology - Human Vaccine Project
2019	**Travel award** from the American Society for Biochemistry and Molecular Biology to attend the annual meeting and present research (Orlando, FL)
2017	**Scholarship** from The National Institute of General Medical Sciences to attend The Cold Spring Harbor course on Antibody Engineering, Phage Display & Immune Repertoire Analysis
2017	**Finalist** for the Life Sciences Research Foundation Post-Doctoral Fellowship
2015	**Best poster award** at the 15th European Meeting on Complement in Human Disease
2014	**EMBO fellowship** to work on leukocyte integrins with Tim Springer at Harvard Medical School
2013	**Article of the month award** from the French Society for Biochemistry and Molecular Biology for *Proc Natl Acad Sci U S A* 2013 110 (41); 16426-31
2013	**Travel award** from the Scandinavian Society of Immunology to present at the International Congress of Immunology (Milano, Italy; 2013)
2012	**Travel award** from the Erice International School of Crystallography

C. Contributions to Science

a) Complement is the body's first defense against pathogens, tagging them for elimination. It recognizes molecular patterns and undergoes a complex series of proteolytic activation steps, similar to those of the blood coagulation cascade. Complement C3, a central molecule in this system, is activated by proteolytic cleavage yielding 2 major fragments, C3a and C3b, which have different functions in inflammation and host defense. C3a is a chemoattractant that functions by binding its cognate GPCR, C3aR. C3b becomes covalently coupled to activating surfaces through a thioester domain (TED) and operates as a ligand for complement receptors (CR1, 2, 3, etc.) in phagocytosis. C3a activity is regulated by a peptidase that removes the last Arg residue, yielding an inactive C3a desArg. I compared the activities of recombinant C3a and reference material purified from human plasma and showed the loss of function of the desArg form. I also determined the structures of C3a and C3a desArg to see whether structural rearrangements could be the basis for their marked functional differences. This, however, turned out not to be the case and I proposed alternative mechanisms involving differential receptor engagement. The second part of my thesis focused on the interaction of an integrin-type receptor, CR3 (also known as CD11b/CD18 or Mac-1), with C3 proteolytic fragments. I identified the minimum C3 domain sufficient for CR3 binding and performed extensive SPR

sensorgram analyses using unconventional algorithms to separate multicomponent interactions. I determined the structure of CR3 ligand-binding domain (I domain) in complex with C3 TED. The structure shed light onto integrin recognition of complement. In particular, it suggested a second contact point (supported by biochemical assays) between the full integrin receptor and a larger C3 fragment (iC3b) that contains TED. To visualize the interaction in atomic detail, we sought to determine the structure of the full receptor ectodomain in complex with the C3 fragments. To learn how to recombinantly express and purify the full receptor, I visited the laboratory of Prof. Tim Springer (Harvard Medical School), who has a long-standing interest and expertise in integrins. I spent almost a year in the Springer group designing different constructs, testing their expression in mammalian cells, establishing stable cell-lines and purifying large quantities of the integrin for structural studies

1. **Bajic G**., Yatime L., Klos A. and Andersen G.R. Human C3a and C3a desArg anaphylatoxins have conserved structures, in contrast to C5a and C5a desArg. ***Protein Science***, 2013 22(2): 204-212.
2. **Bajic G**., Yatime L., Sim R.B., Vorup-Jensen T. and Andersen G.R. Structural insight on the recognition of surface-bound opsonins by the integrin I domain of complement receptor 3. ***Proc Natl Acad Sci U S A*** 2013 110(41) ; 16426-31
3. **Bajic G**., Degn S.E., Thiel S. and Andersen G.R. Complement activation, regulation and molecular basis for complement-related diseases. 2015 ***EMBO J***. 34**:** 2735–57
4. Yatime L., **Bajic G**., Schatz-Jakobsen J.A. and Andersen G.R. Complement regulators and inhibitors in health and disease: A structural perspective. 2016 ***Nanomedicine***, CRS Advances in Delivery Science and Technology Book Series.
5. Jensen R.M.*, **Bajic G.***, Zhang X.*, Laustsen A.K., Koldso H., Kirkeby Skeby K., Schiott B., Andersen G.R., and Vorup-Jensen T. Structural basis for simvastatin competitive antagonism of complement receptor 3. 2016 ***J. Biol. Chem*** 291(33):16963-76
   * co-first author

c) Understanding the interplay of a rapidly evolving virus and the host humoral immune system can lead to better vaccines. As the virus evolves to escape host immune pressure, so too does the host response evolve, resulting in a so-called host-pathogen arms race. The adaptive immune system responds to the pathogen by producing antibodies with high affinity and specificity. This response can be recalled with reexposure to the same (or similar) antigen in a process called memory recall response. Due to re-exposure or routine vaccination, the initial, naïve immune response can bias later responses to antigenically drifted viral variants (a phenomenon, once called "original antigenic sin" in studies of influenza immunity). Herd immunity drives antigenic drift of seasonal influenza viruses. Even when they reduce or eliminate neutralization, the accumulating mutations in the major glycoprotein, hemagglutinin (HA), do not completely prevent binding to previously elicited antibodies, and thus exposure to drifted virus still allows recall of memory B cells. Subsequent affinity maturation by selection of somatic mutations updates that memory, generating new pressure on HA and starting a new cycle in an evolutionary arms race. I have identified and characterized an antibody clonal lineage from a donor infected in his childhood by a seasonal H1 influenza strain and showed, biochemically and structurally, that the initial infection shaped his immunological memory and that the subsequent immunization with a shifted pandemic H1 strain brought out, until then subdominant, immune response to a conserved epitope on HA and offered protection.

6. Raymond D.D.*, **Bajic G.*,** Ferdman J., Suphaphiphat P., Settembre E.C., Moody M.A., Schmidt A.G., Harrison S.C. Conserved epitope on influenza-virus hemagglutinin head defined by a vaccine-induced antibody**.** 2017 ***Proc Natl Acad Sci U S A***. doi: 10.1073/pnas.1715471115.
   * co-first author

I helped demonstrate that the antibody responses elicited (or recalled and affinity matured) by vaccination with material that was derived from chicken eggs were dependent on an amino acid mutation on HA due to the growth in eggs (virus adapted to bind the avian sialic acid receptor). Recombinant antibodies as well as polyclonal sera from the donors shower dependence/preference for the mutated HA and failed to recognize the circulating viral strain. The study indicated that vaccines produced in eggs may be suboptimal in eliciting broadly-neutralizing antibodies and may offer diminished protection to the original, circulating viral strain.

7. Raymond D., Stewart S., Lee J., Ferdman J., **Bajic G**., et al. and Harrison S.C. Influenza immunization elicits hemagglutinin receptor-site antibodies specific for an egg-adapted vaccine strain. 2016 ***Nature Medicine*** 22(12):1465-1469

d) Viral glycoproteins are under constant immune surveillance by human adaptive immune responses and rapidly evolve to evade host pressure. Antigenic variation including glycan introduction or removal is among the mechanisms of escape from host immunity. Understanding how glycosylation affects immunodominance on complex antigens may help describe underlying B-cell biology. We systematically engineered glycans onto the influenza virus HA to determine how the resulting B-cell responses of normal mice were altered by characterizing molecular features of the elicited humoral immunity. We found that glycan addition changed the initially diverse repertoire into an epitope-focused, more genetically restricted response. Structural analyses showed that one of three enriched gene families targeted a previously subdominant and hitherto uncharacterized epitope at the head interface. Mouse challenge studies showed Fc-dependent protection. Thus, glycan engineering in context of influenza HA, can redirect host adaptive immune responses by exposing subdominant epitopes. These results have potential implications for next-generation viral vaccines aimed at directing B-cell responses to preferred epitope(s).

8. **Bajic, G**., Maron, M. J., Adachi, Y., Onodera, T., McCarthy, K. R., McGee, C. E., Sempowski, G. D., Takahashi, Y., Kelsoe, G., Kuraoka, M., and Schmidt, A. G. Influenza Antigen Engineering Focuses Immune Responses to a Subdominant but Broadly Protective Viral Epitope. 2019 ***Cell Host Microbe*** 25, 827-835
9. Watanabe, A., McCarthy, K. R., Kuraoka, M., Schmidt, A. G., Adachi, Y., Onodera, T., Tonouchi, K., Caradonna, T. M., **Bajic, G**., Song, S., McGee, C. E., Sempowski, G. D., Feng, F., Urick, P., Kepler, T. B., Takahashi, Y., Harrison, S. C., and Kelsoe, G. Antibodies to a Conserved Influenza Head Interface Epitope Protect by an IgG Subtype-Dependent Mechanism. 2019 ***Cell*** 177, 1124-1135

e) Germinal centers (GCs) are the primary sites of clonal B cell expansion and affinity maturation, producing high-affinity antibodies. This response is a central driver of pathogenesis in autoimmune diseases, such as lupus (SLE). Whether autoreactive B cell clones seed germinal centers and drive clonal expansion was unclear. I helped characterize GC responses in a novel mouse model generated by the Carroll group at Harvard Medical School. We showed that a single autoreactive B cell clone is sufficient to drive the expansion of other autoreactive B cells in spontaneous GCs. The antibodies that were generated from such GCs showed affinity maturation and changes in breadth towards self-antigens, a phenomenon known in autoimmunity as epitope spreading.

10. Degn S.E., van der Poel C.E., Firl D.J., Ayoglu B., Al Qureshah F.A., **Bajic G.**, Mesin L., Reynaud C.A., Weill J.C., Utz P.J., Victora G.D., Carroll M.C. Clonal evolution of autoreactive germinal centers. 2017 ***Cell***. 170(5):913-926

Viral infections lead to antibody-mediated responses, including, in rare cases, broadly neutralizing antibodies (bnAbs) that protect against many viral variants. Because bnAbs are often low in frequency and because viral infections are often associated with the onset of autoimmune disease, we hypothesized that some bnAbs may be autoreactive and thus eliminated through the mechanisms of self-tolerance. The two conserved epitopes on the influenza hemagglutinin (HA) and thus targets of bnAbs - the "stem" and the receptor-binding site (RBS) on the "head" - are the focus of the current "universal" influenza vaccine development efforts. In our recent study we compared autoreactivity profiles of a set of stem- and head-directed bnAbs. Most of the stem bnAbs we examined bound autoantigens supporting the idea of bnAb elimination by tolerance mechanisms.

11. **Bajic, G**., van der Poel C.E., Kuraoka M., Schmidt A.G., Carroll M.C., Kelsoe G. and Harrison S.C. Autoreactivity profiles of influenza hemagglutinin broadly neutralizing antibodies. 2019 **Sci Rep.** 9(1):3492. doi: 10.1038/s41598-019-40175-8

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/10ITkxufBWO5p/bibliography/52924624/public/?sort=date&direction=descending