BIOGRAPHICAL SKETCH

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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	Postdoctoral	08/2019	Immunology, Virology, Structural Biology

A. Personal Statement

I am an Assistant Professor of Microbiology and my research program uses structural biology approaches coupled with biochemistry, immunology, and virology techniques to understand biological problems at molecular and atomic level. This aspect is essential to tackling complex biological systems such as understanding immune imprinting on a molecular structure level and the development of next-generation vaccine immunogens. I bring the necessary research skills required to help achieve the goals outlined. Specifically, I have demonstrated expertise in viral glycoprotein engineering, vaccine immunogen design and protein structure determination by X-ray crystallography and electron cryomicroscopy (cryo-EM). Structural studies of molecules of the immune system have been a common theme throughout my career. By studying how complement C3 activation products (C3b, iC3b and C3d) bind integrin receptors, my graduate thesis has laid foundations for 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 immune imprinting or the so-called original antigenic sin. I leveraged 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 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, 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 like dengue and malaria. More recently, I have been using cryo-EM to characterize antibody responses to SARS-CoV-2 infection and vaccination. This research direction leverages my expertise with influenza and allows me to study the similar immunological problems such as the molecular basis of immune imprinting and B-cell memory usage. Since starting my independent group, I have been able to start collaborations with Ali Ellebedy at Washington University and Florian Krammer and Viviana Simon at Mount Sinai, particularly relevant for this proposal. I continue to collaborate with Aaron Schmidt at Harvard. Achieving

the goals outlined in this proposal will be aided by my demonstrated expertise in structural biology, protein biochemistry and innate and adaptive immune profiling.

Citations:

1. Amanat F, Thapa M, Lei T, Ahmed SMS, Adelsberg DC, Carreno JM, Strohmeier S, Schmitz AJ, Zafar S, Zhou JQ, Rijnink W, Alshammary H, Borcherding N, Reiche AG, Srivastava K, Sordillo EM, van Bakel H; Personalized Virology Initiative, Turner JS, **Bajic G***, Simon V*, Ellebedy AH*, Krammer F*. The plasmablast response to SARS-CoV-2 mRNA vaccination is dominated by non-neutralizing antibodies that target both the NTD and the RBD. *medRxiv.* 2021 Mar 9:2021.03.07.21253098. PMCID: PMC7987037 PMID: 33758878 (***Cell***, in press)
2. Tong P, Gautam A, Windsor I, Travers M, Chen Y, Garcia N, Whiteman NB, McKay LGA, Lelis FJN, Habibi S, Cai Y, Rennick LJ, Duprex WP, McCarthy KR, Lavine CL, Zuo T, Lin J, Zuiani A, Feldman J, MacDonald EA, Hauser BM, Griffths A, Seaman MS, Schmidt AG, Chen B, Neuberg D, **Bajic G**, Harrison SC, Wesemann DR. Memory B cell repertoire for recognition of evolving SARS-CoV-2 spike. bioRxiv 434840 [Preprint]. 2021 Available from: https://doi.org/10.1101/2021.03.10.434840
3. Schmitz AJ, Turner JS, Liu Z, Aziati ID, Chen RE, Joshi A, Bricker TL, Darling TL, Adelsberg DC, Alsoussi WB, Case JB, Lei T, Thapa M, Amanat F, O'Halloran JA, Shi PY, Presti RM, Krammer F, **Bajic G**, Whelan SPJ, Diamond MS, Boon ACM, Ellebedy AH. A public vaccine-induced human antibody protects against SARS-CoV-2 and emerging variants. bioRxiv 436864 [Preprint]. 2021 Available from: https://doi.org/10.1101/2021.03.24.436864

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-	**Assistant Professor**, Icahn School of Medicine at Mount Sinai, New York, NY
2019-2020	**Instructor in Pediatrics**, Harvard Medical School & Boston Children's Hospital, Boston, MA
2017-2019	**Invited Lecturer**, Immunology, Harvard Medical School, Boston, MA
2017-2020	**Mentor** at the Howard Hughes Medical Institute (HHMI) undergraduate EXROP program
2017-2019	**Teaching Fellow**, Immunology, Harvard University Extension School, Cambridge, MA
2015-2019	**Postdoctoral Research Fellow,** Harvard Medical School, Boston, MA
2013-2014	**Visiting Graduate Student** with Timothy A. Springer, Harvard Medical School, Boston, MA
2012-2015	**Graduate Student** with Gregers R. Andersen, Aarhus University, Aarhus, Denmark
2009-2011	**Master Student**, Structural and Functional Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France
2008-2011	**Tutor**, Biology/Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France
2008	**Summer Research Intern**, Biochemistry, bioMérieux,
2006-2009	**Undergraduate Student**, Biochemistry, Université Claude Bernard – Lyon 1, Lyon, France

Honors

2020	**Guest editor** of a special issue for *Frontiers in Immunology*
2019	**Finalist** for the Michelson Prizes in Immunology - Human Vaccines 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.

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. 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

b) 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). I have identified and characterized antibody clonal lineages 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. I also demonstrate that the antibody responses elicited (or recalled and affinity matured) by vaccination with material 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 showed 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.

5. **Bajic G.**#, Harrison SC. Antibodies That Engage the Hemagglutinin Receptor-Binding Site of Influenza B Viruses. 2021 ***ACS Infect Dis***. 7(1):1-5.
   # corresponding

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
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

c) 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., Caradonna T.M., Tian M., Mermelstein A., Fera D., Kelsoe G., Kuraoka M., Schmidt A.G. Structure-Guided Molecular Grafting of a Complex Broadly Neutralizing Viral Epitope. 2020 ***ACS Infect Dis***. 6(5):1182-1191
9. **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
10. 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

d) 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. I also showed that one of the two conserved epitopes on the influenza hemagglutinin (HA) and thus targets of bnAbs - the "stem" - elicited antibodies that also bound autoantigens. This finding supports the idea of bnAb elimination by tolerance mechanisms.

11. 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
12. **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