

CURRICULUM VITAE

Alex Sigal, Ph.D.

PROFESSIONAL SUMMARY

I am interested in how immunosuppression caused by unsuppressed HIV infection, aging, and other reasons, affects the immune response to infections at both the level of the individual and the population. Over the past three years, my concentration has been on Covid-19, particularly in people with advanced HIV disease who do not clear SARS-CoV-2 until their HIV viremia is effectively suppressed. My research has shown that in this group, SARS-CoV-2 persists for a long time, evolves many of the same mutations seen in variants like Omicron, but is cleared upon immune reconstitution. I believe this is one example of a broader pattern whereby immune suppression and dysregulation leads to widespread consequences for infectious diseases.

EXPERIENCE

Associate Professor and Principal Investigator/Faculty at the Africa Health Research Institute and University of KwaZulu-Natal (12/2012 – present).

Max Planck Research Group Leader (seconded to Africa Health Research Institute), Max Planck Institute for Infection Biology in Berlin, Germany (12/2012 – 7/2020).

Associate Member at the Centre for the AIDS Programme of Research in South Africa (7/2020 – present).

The initial core support for my laboratory came from a position and associated funding with the Max Planck Society. I was successfully awarded two competitive renewals of the Max Planck Research Group Leader position, the maximum allowed. Funding from the position as well as grants from the NIH, the Bill and Melinda Gates Foundation, Wellcome Trust and others, allowed me to set up and run a research program combining mechanistic science and cohort based human immunology studies at the Africa Health Research Institute (AHRI, formerly K-RITH). I oversaw lab direction and re-directed funding to pivot to Covid-19 work.

MAJOR RECENT ACCOMPLISHMENTS

Covid-19 advances

- First laboratory globally to report on the escape of the Omicron variant from vaccine mediated immunity and isolate live Omicron BA.1.
- First to isolate the live Beta variant and Omicron BA.2.86 subvariant and among the first to report on the Beta and BA.2.86.
- First to report on SARS-CoV-2 evolution of immune escape from neutralizing antibodies in an individual immunosuppressed because of advanced HIV disease, a possible mechanism for how SARS-CoV-2 variants evolved.

HIV and TB advances

- Showed the role of aggregation of *Mycobacterium tuberculosis* bacilli in defeating macrophage defenses.
- Using novel methodology, showed that the HIV reservoir in the brain (as detected in the CSF) in the face of ART may be in T cells.

Other contributions

- Advisor to the South African Government as part of the Technical Working Group on Vaccines.
- Led a consortium of 36 investigators in KwaZulu-Natal, South Africa (the COMMIT-KZN Team) to drive forward Covid-19 research in the province.
- Increased research visibility on international media by multiple interviews.

EDUCATION AND TRAINING

Postdoctoral Fellow, Laboratory of David Baltimore, Biology Division, The California Institute of Technology, Los Angeles, CA (1/2007 – 12/2012).

Postdoctoral Fellow, Laboratory of Uri Alon, Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel (9/2006 – 1/2007).

Ph.D. in Systems Biology, Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel. Advisor: Uri Alon. Completed 9/2006.

M.Sc. in Cancer Biology, Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel. Advisor: Varda Rotter. Completed 6/2000.

B.Sc. in Zoology, University of Toronto, Toronto, Canada. Completed 6/1996.

MENTORING ACTIVITIES

- Primary supervisor for and successful graduation of 7 PhD students and 1 MSc student.
- Two of the PhD students were lead authors on Nature papers.

EDITORIAL AND OTHER EXPERIENCE

- Wellcome Trust Discovery Award Panel member (2023 – present).
- Reviewing Editor, eLife (2021 – present).
- Member, U.S.-SA Collaborative Biomedical Research Program study section ZRG1 AARR-A52 (2019) and Special Emphasis Panel/Scientific Review Group 2020/05 HCAC (2020).
- Organized the First Max Planck Workshop on HIV Reservoirs and Evolution in St. Lucia, South Africa (2019).
- Organized the First South African Workshop on SARS-CoV-2 Variants and Evolution in St. Lucia, South Africa (2022).
- Ad hoc reviewer for NEJM, Science, Nature Communications, Elife, mBio, amfAR Krim Fellowships, MBE, JID, PNAS, Wellcome Trust Henry Dale Fellowships, JAC, German Israeli Foundation grants, Nature Medicine, PLoS Comp Biol., JTM, and others.

AWARDS and HONORS

- John F. Kennedy Prize of the Weizmann Institute of Science (2006).
- European Molecular Biology Organization Fellowship (2006).
- Human Frontier Science Program Fellowship (2007).
- Human Frontier Science Program Career Development Award (2013).

PUBLICATIONS

- 1 Lustig, G., Ganga, Y., Rodel, H. E., Tegally, H., Khairallah, A., Jackson, L., Cele, S., Khan, K., Jule, Z., Reedoy, K., Karim, F., Bernstein, M., Ndung'u, T., Moosa, M.-Y. S., Archary, D., de Oliveira, T., Lessells, R., Neher, R. A., Abdool Karim, S. S. & **Sigal, A.** SARS-CoV-2 infection in immunosuppression evolves sub-lineages which independently accumulate neutralization escape mutations. *Virus Evolution* (2023). 10.1093/ve/vead075
- 2 Allué-Guardia, A., Torrelles, J. B. & **Sigal, A.** Tuberculosis and COVID-19 in the elderly: factors driving a higher burden of disease. *Front Immunol* 14, 1250198 (2023). PMC10569613. 10.3389/fimmu.2023.1250198
- 3 Khan, K., Lustig, G., Römer, C., Reedoy, K., Jule, Z., Karim, F., Ganga, Y., Bernstein, M., Baig, Z., Jackson, L., Mahlangu, B., Mnguni, A., Nzimande, A., Stock, N., Kekana, D., Ntozini, B., van Deventer, C., Marshall, T., Manickchand, N., Gosnell, B. I., Lessells, R. J., Karim, Q. A., Abdool Karim, S. S., Moosa, M. S., de Oliveira, T., von Gottberg, A., Wolter, N., Neher, R. A. & **Sigal, A.** Evolution and neutralization escape of the SARS-CoV-2 BA.2.86 subvariant. *Nat Commun* 14, 8078 (2023). PMC10700484. 10.1038/s41467-023-43703-3
- 4 Kaufmann, S. H. E., **Sigal, A.**, Sawitzki, B. & Sher, A. Editorial: The Covid-19 and TB syndemic: differences and similarities. *Front Immunol* 14, 1340231 (2023). PMC10716789. 10.3389/fimmu.2023.1340231
- 5 Krause, R. G. E., Moyo-Gwete, T., Richardson, S. I., Makhado, Z., Manamela, N. P., Hermanus, T., Mkhize, N. N., Keeton, R., Benede, N., Mennen, M., Skelem, S., Karim, F., Khan, K., Riou, C., Ntusi, N. A. B., Goga, A., Gray, G., Hanekom, W., Garrett, N., Bekker, L. G., Groll, A., **Sigal, A.**, Moore, P. L., Burgers, W. A. & Leslie, A. Infection pre-Ad26.COV2.S-vaccination primes greater class switching and reduced CXCR5 expression by SARS-CoV-2-specific memory B cells. *NPJ Vaccines* 8, 119 (2023). PMC10423246. 10.1038/s41541-023-00724-9
- 6 Tan, C. W., Zhu, F., Chia, W. N., Young, B. E., Yeoh, A. Y. Y., Althaus, T., Yung, C. F., Yap, W. C., Lim, B. L., Chen, M. I. C., Zhang, J., Mah, Y. Y., Voiglio, E., **Sigal, A.**, Huo, J., Xu, S., Tan, Y. J., Lam, K.-P., Lye, D. & Wang, L.-F. Distinctive serotypes of SARS-related coronaviruses defined by convalescent sera from unvaccinated individuals. *hLife* (2023). <https://doi.org/10.1016/j.hlif.2023.07.002>
- 7 **Sigal, A.** Boosting in the age of Omicron. *Elife* 12 (2023). PMC10110234. 10.7554/eLife.87358
- 8 Naicker, N., Rodel, H., Perumal, R., Ganga, Y., Bernstein, M., Benede, N., Abdool Karim, S., Padayatchi, N., **Sigal, A.** & Naidoo, K. Metformin Increases Cell Viability and

Regulates Pro-Inflammatory Response to Mtb. *Infect Drug Resist* 16, 3629-3638 (2023).
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- 18 Greaney, A. J., Eguia, R. T., Starr, T. N., Khan, K., Franko, N., Logue, J. K., Lord, S. M., Speake, C., Chu, H. Y., **Sigal, A.** & Bloom, J. D. The SARS-CoV-2 Delta variant induces an antibody response largely focused on class 1 and 2 antibody epitopes. *PLoS Pathog* 18, e1010592 (2022). PMC9275729. 10.1371/journal.ppat.1010592
- 19 Keeton, R., Tincho, M. B., Ngomti, A., Baguma, R., Benede, N., Suzuki, A., Khan, K., Cele, S., Bernstein, M., Karim, F., Madzorera, S. V., Moyo-Gwete, T., Mennen, M., Skelem, S., Adriaanse, M., Mutithu, D., Aremu, O., Stek, C., du Bruyn, E., Van Der Mescht, M. A., de Beer, Z., de Villiers, T. R., Bodenstien, A., van den Berg, G., Mendes, A., Strydom, A., Venter, M., Giandhari, J., Naidoo, Y., Pillay, S., Tegally, H., Grifoni, A., Weiskopf, D., Sette, A., Wilkinson, R. J., de Oliveira, T., Bekker, L. G., Gray, G., Ueckermann, V., Rossouw, T., Boswell, M. T., Bhiman, J. N., Moore, P. L., **Sigal, A.**, Ntusi, N. A. B., Burgers, W. A. & Riou, C. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* 603, 488-492 (2022). PMC8930768. 10.1038/s41586-022-04460-3

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- 21 Lustig, G., Cele, S., Karim, F., Derache, A., Ngoepe, A., Khan, K., Gosnell, B. I., Moosa, M. S., Ntshuba, N., Marais, S., Jeena, P. M., Govender, K., Adamson, J., Klooverpris, H., Gupta, R. K., Harrichandparsad, R., Patel, V. B. & **Sigal, A.** T cell derived HIV-1 is present in the CSF in the face of suppressive antiretroviral therapy. *PLoS Pathog* 17, e1009871 (2021). PMC8509856 10.1371/journal.ppat.1009871
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- 23 Frenkel-Morgenstern, M., Cohen, A. A., Geva-Zatorsky, N., Eden, E., Prilusky, J., Issaeva, I., **Sigal, A.**, Cohen-Saidon, C., Liron, Y., Cohen, L., Danon, T., Perzov, N. & Alon, U. Dynamic Proteomics: a database for dynamics and localizations of endogenous fluorescently-tagged proteins in living human cells. *Nucleic Acids Res* 38, D508-512 (2010). 2808965. 10.1093/nar/gkp808
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- 25 Boulle, M., Muller, T. G., Dahling, S., Ganga, Y., Jackson, L., Mahamed, D., Oom, L., Lustig, G., Neher, R. A. & **Sigal, A.** HIV Cell-to-Cell Spread Results in Earlier Onset of Viral Gene Expression by Multiple Infections per Cell. *PLoS Pathog* 12, e1005964 (2016). 10.1371/journal.ppat.1005964
- 26 Farkash-Amar, S., Zimmer, A., Eden, E., Cohen, A., Geva-Zatorsky, N., Cohen, L., Milo, R., **Sigal, A.**, Danon, T. & Alon, U. Noise genetics: inferring protein function by correlating phenotype with protein levels and localization in individual human cells. *PLoS Genet* 10, e1004176 (2014). PMC3945223. 10.1371/journal.pgen.1004176

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- 28 Puliafito, A., Hufnagel, L., Neveu, P., Streichan, S., **Sigal, A.**, Fygenson, D. K. & Shraiman, B. I. Collective and single cell behavior in epithelial contact inhibition. *Proc Natl Acad Sci U S A* 109, 739-744 (2012). PMC3271933. 10.1073/pnas.1007809109
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U.S. SER. No. 62/573,049. MYCOBACTERIUM TUBERCULOSIS HOST-PATHOGEN INTERACTION.

U.S. SER. NO. 62/573,025. MARKERS OF ACTIVE HIV RESERVOIR.

RESEARCH SUPPORT (LAST 5 YEARS)

2022-2025	Wellcome Trust	Adaptive responses to SARS-CoV-2 variants in the context of hybrid immunity and immune impairment	\$3,890,304	Principal Investigator
2020-2025	BMGF	COVID-19 Mechanisms and Multi-omics in KwaZulu-Natal	\$4,027,703	Principal Investigator
2022-2023	NIH	Evolution of innate immunity and antibody neutralization escape mutations in prolonged SARS-CoV-2 infection in people with advanced HIV (part of United World Antiviral Research Network (UWARN) collaboration)	\$216,156	Co-Investigator
2022-2023	BMGF	BaSiS Trial Phase 2 clinical study extension	\$471,512	Co-Investigator
2022-2023	South African Medical Research Council	Phase II randomised open label trial of full and half dose J&J Ad26.COVID.S and Pfizer BNT162b2 booster vaccinations after receiving the J&J Ad26.COVID.S prime vaccine through the SISONKE phase IIIB implementation study (BaSiS Trial)	ZAR 1,496,796 (\$91,921)	Co-Investigator
2022-2025	South African Medical Research Council	Immunogenicity studies for mRNA vaccine candidate development	ZAR 4,659,787 (\$286,166)	Co-Investigator
2021-2023	South African Medical Research Council	Neutralization escape from antibodies elicited by vaccines	ZAR 2,525,313 (\$155,084)	Principal Investigator
2012-2020	Max Planck Society	Group Leader Award:	€1,924,192	Principal Investigator

		The purpose of this award is to set up a Systems Infection Biology Group at K-RITH/AHRI investigating persistent infection of TB and HIV in the face of the immune response and therapy.		
2018-2023	NIH-NIAID	Identification of the HIV Reservoir in Lymph Nodes Using Single Cell RNA-Seq	\$721,310	Principal Investigator
2014-2021	HHMI	IgG penetration into the TB granuloma	\$72,000	Principal Investigator
2018-2021	amfAR	HIV persistence in lymph nodes in the face of ART in TB-infected individuals.	\$50,000	Principal Investigator
2020-2021	AHRI	COVID-19 Infection Dynamics in PLWH vs HIV- Individuals	ZAR 998,832 (\$61,605)	Principal Investigator
2014-2019	BMGF	Quantitative assessment of the tipping point in Mycobacterium tuberculosis transmission and infection	\$2,214,804	Principal Investigator
2015-2019	EU commission	Role of TB antibodies (part of TBVAC2020 consortium)	€167,227	Principal Investigator
2017-2019	HHMI	Identification and Targeting HIV in the CNS Reservoir	\$60,000	Principal Investigator