BIOGRAPHICAL SKETCH

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NAME: Sanjay Arvind Desai

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

POSITION TITLE: Senior Investigator

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
Duke University, Durham, NC	B.S.E.	5/1985	Biomedical engineering
Washington University, St. Louis, MO	M.D., Ph.D.	1992	Cell biology and biophysics
Duke University, Durham, NC		1995	Internal Medicine residency
Duke University, Durham, NC		1998	Infectious Diseases fellowship
NIAID/NIH, Bethesda, MD		2001	Parasitology research fellowship

A. Personal Statement

My laboratory studies transmembrane transport of ions, nutrients, and other solutes in malaria parasites. We use a multidisciplinary approach to examine the cell, molecular and structural biology of *Plasmodium falciparum*, the most virulent agent of human malaria. We pioneered patch-clamp studies of infected human erythrocytes and have discovered unique parasite ion channels required for solute trafficking between host plasma and parasite compartments. We developed, miniaturized, and used new biochemical assays for solute transport. We combine these methods with cutting-edge parasite DNA transfection, *in vitro* selection, genetics and epigenetics, high-throughput chemical screens and drug discovery, and cryo-EM structure determination with the goals of understanding unique pathogen adaptations and translating these findings into new antimalarial therapies.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1992-1995 Internal Medicine Residency, Duke University, Durham, NC
1995-1998 Clinical Investigator Pathway, Infectious Diseases Fellow, Duke University, Durham, NC
1998-2001 Research Fellow, NIAID, NIH, Bethesda, MD
2001-2007 Tenure-track Investigator, NIAID, NIH, Bethesda, MD
2008-present Senior Investigator, NIAID, NIH, Bethesda, MD

Other Experience and Professional Memberships

1990-present Member, American Society of Tropical Medicine and Hygiene
1994-present Member, Red Cell Club, Biophysical Society
2007-present Member, American Society for Clinical Investigation
2015-present Member, American Society for Microbiology

Honors and Awards

1985-1992 Scholarship for M.D.-Ph.D. program (Medical Scientist Training Program)
1986 A.F. Dames Award in Cell Biology and Physiology
1990 Young Investigator Award, American Society of Tropical Medicine and Hygiene, New Orleans, LA

1992	Alexander Berg Award in Molecular Microbiology
1998	Young Investigator Award, ICAAC, American Society of Microbiology, San Diego, CA
2006	The 2006 NIH Distinguished Mentor Award
2007	Election to American Society for Clinical Investigation
2011	The 2011 NIAID Merit Award "For outstanding discoveries on the channel and drug target by which malaria parasites take up essential nutrients through the red blood cell membrane"
2013	Federal Laboratory Consortium Technology Transfer Award for Therapeutics in Malaria

C. Contributions to Science

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/sanjay.desai.2/bibliography/public/

1. **Identified mechanism and molecular basis of increased host cell permeability after infection with *Plasmodium* spp.** > 70 years of research had established increased uptake of ions and organic solutes by infected erythrocytes, but the responsible mechanisms were unknown. My laboratory pioneered patch-clamp of infected cells and identified the mechanism as a shared, broad selectivity ion channel, now known as the plasmodial surface anion channel (PSAC). Our key contributions to this project include:

- First described PSAC activity with cell-attached and whole-cell patch-clamp of infected human erythrocytes.
- Defined PSAC's essential role in parasite nutrient acquisition and validated this channel as a conserved antimalarial target. Demonstrated that a long-standing alternate role in host cell cation remodeling is not essential for intracellular parasite growth.
- Discovered a new antimalarial drug resistance mechanism based on reduced drug uptake via PSAC.
- Identified the molecular basis of PSAC activity with linkage analysis, DNA transfection, and genome-wide studies of PSAC mutants generated by *in vitro* selection. This ternary RhopH complex is unique to *Plasmodium* spp. and is encoded by the *clag* multigene family and single-copy *rhoph2* and *rhoph3* genes. The CLAG proteins are the only malaria parasite antigens exposed on the surface of all vertebrate host erythrocytes.
- Described epigenetic switching between these proteins and overlapping roles of CLAG family members in PSAC selectivity to nutrients and toxins.
- Solved a high-resolution cryo-EM structure of the RhopH complex to gain insights into protein trafficking and insertion at the host membrane.
- Developed and miniaturized a transmittance assay for PSAC. We executed high-throughput chemical screens with this method, have identified potent and specific PSAC inhibitors, and are pursuing antimalarial drug development with academic and pharmaceutical partners.

Selected publications:

a. S.A. Desai, S. Bezrukov, and J. Zimmerberg. A voltage-dependent channel involved in nutrient uptake by malaria parasite-infected red blood cells. **Nature** (2000) 406:1001-1005. PMID:10984055
b. A. Alkhalil, J.V. Cohn, M.A. Wagner, J.S. Cabrera, T. Rajapandi, and S.A. Desai. *Plasmodium falciparum* likely encodes the principal anion channel on infected human erythrocytes. **Blood** (2004) 104:4279-86. PMID: 15319279
c. D.A. Hill, A.D. Pillai, F. Nawaz, K. Hayton, L. Doan, G. Lisk, and S.A. Desai. A blasticidin S-resistant Plasmodium falciparum mutant with a defective plasmodial surface anion channel. **Proc. Natl. Acad. Sci. USA** (2007) 104:1063-1068. PMID: 17213308
d. A.D. Pillai, M. Pain, T. Solomon, A.A.B. Bokhari, and S.A. Desai. A cell-based high-throughput screen validates the plasmodial surface anion channel as an antimalarial target. **Mol. Pharmacol.** (2010) 77:724-733. PMID: 20101003
e. W. Nguitragool, A.A. Bokhari, A.D. Pillai, K. Rayavara, P. Sharma, B. Turpin, L. Aravind, S.A. Desai. Malaria parasite *clag3* genes determine channel-mediated nutrient uptake by infected red blood cells. **Cell** (2011) 145:665-677. PMID: 21620134
f. A.D. Pillai, W. Nguitragool, B. Lyko, K. Dolinta, M.M. Butler, S.T. Nguyen, N.P. Peet, T.L. Bowlin, and S.A. Desai. Solute restriction reveals an essential role for *clag3*-associated channels in malaria parasite nutrient acquisition. **Mol. Pharmacol.** (2012) 82:1104-14. PMID: 22949525

g. A.D. Pillai, R. Addo, P. Sharma, W. Nguitragool, P. Srinivasan, and S.A. Desai. Malaria parasites tolerate a broad range of ionic environments and do not require host cation remodelling. **Mol. Microbiol.** (2013) 88:20-34. PMID: 23347042
h. P. Sharma, K. Wollenberg, M. Sellers, K. Zainabadi, K. Galinsky, E. Moss, W. Nguitragool, D. Neafsey, and S.A. Desai. An epigenetic antimalarial resistance mechanism involving parasite genes linked to nutrient uptake. **J. Biol. Chem.** (2013) 288:19429-40. PMID: 23720749.
i. D. Ito, M.A. Schureck, and S.A. Desai. An essential dual-function complex mediates erythrocyte invasion and channel-mediated nutrient uptake in malaria parasites. **eLife** (2017) e23485. PMID: 28221136
j. A. Gupta, A.A.B. Bokhari, A.D. Pillai, A.K. Crater, J. Gezelle, G. Saggu, A.S. Nasamu, S.M. Ganesan, J.C. Niles, S.A. Desai. Complex nutrient channel phenotypes despite Mendelian inheritance in a *Plasmodium falciparum* genetic cross. **PLoS Pathog.** (2020) 16(2):e1008363. PMID: 32069335
k. M.A. Schureck, J.E. Darling, A.M., J. Shao, G. Daggupati, P. Srinivasan, P.D.B. Olinares, M.P. Rout, B.T. Chait, K. Wollenberg, S. Subramaniam, S.A. Desai. Malaria parasites use a soluble RhopH complex for erythrocyte invasion and an integral form for nutrient uptake. **eLife** (2021), 10:e65282. PMID: 33393463
l. M.M. Butler, S.L. Waidyarachchi, J. Shao, S.T. Nguyen, X. Ding, S.C. Cardinale, L.R. Morin, S.M. Kwasny, M. Ito, J. Gezelle, M.B. Jiménez-Díaz, I. Angulo-Barturen, R.T. Jacobs, J.N. Burrows, Z.D. Aron, T.L. Bowlin and S.A. Desai. Optimized pyridazinone nutrient channel inhibitors are potent and specific antimalarial leads. **Mol Pharmacol.** (2022) 102:172-182. PMID: 35798366

2. **Defined and characterized increased Ca^{++} permeability of *P. falciparum*-infected human erythrocytes.** Ca^{++} is required for intracellular parasite development and exhibits increased uptake after infection. We are actively pursuing the responsible mechanism and its molecular basis. Our key contributions to this project include:

- Defined passive Ca^{++} uptake mechanisms in human erythrocytes.
- Quantified and characterized increases after infection with *Plasmodium* spp. to exclude simple upregulation of endogenous transporters and inhibition of the host Ca^{++} ATPase extrusion pump.
- Developed and optimized a fluorescence-based assay for the parasite-induced Ca^{++} permeability.
- Executed the first high-throughput chemical screen for inhibitors of Ca^{++} transport in malaria parasites.
- Obtained the first experimental evidence for parasite genetic elements in increased Ca^{++} permeability.

Selected publications:

a. S.A. Desai, P.H. Schlesinger, and D.J. Krogstad. Physiologic rate of carrier-mediated Ca^{2+} entry matches active extrusion in human erythrocytes. **J. Gen. Physiol.** 98: 349-364 (1991). PMID: 1658194.
b. S.A. Desai, E.W. McCleskey, P.H. Schlesinger, and D.J. Krogstad. A novel pathway for Ca^{++} entry into *Plasmodium falciparum*-infected blood cells. **Am. J. Trop. Med. & Hyg.** 54: 464-470 (1996). PMID: 8644899.
c. E.M. Zipprer, M. Neggers, A. Kushwaha, K. Rayavara, and S.A. Desai. A kinetic fluorescence assay reveals unusual features of Ca^{++} uptake in *Plasmodium falciparum*-infected erythrocytes. **Malaria J.**, 13:184 (2014). PMID:24885754.
d. A.K. Kushwaha, L.Apolis, D. Ito, and S.A. Desai. Increased Ca^{++} uptake by erythrocytes infected with malaria parasites: evidence for exported proteins and novel inhibitors **Cell. Microbiol.** (2018) 20(9):e12853. PMID: 29726084
e. L. Apolis, J. Olivas, P. Srinivasan, A.K. Kushwaha, S.A. Desai. Multiple genetic loci define Ca^{++} utilization by bloodstream malaria parasites. **BMC Genomics** (2019) 20(1):47. PMID: 30651090
f. J.N. Sims, E. Yun, J. Chu, M.A. Siddiqui MA and S.A. Desai. A robust fluorescence-based assay for human erythrocyte Ca^{++} efflux suitable for high-throughput inhibitor screens. **Eur Biophys J**. (2023) 52:101-110. PMID: 36512028

3. **Discovered and characterized intracellular ion channels in malaria parasites.** We developed and have used organelle-attached patch-clamp methods to identify and characterize intracellular ion channels in bloodstream malaria parasites. Our key contributions to this project include:

- Identified a large-conductance, high-abundance ion channel on the parasitophorous vacuolar membrane (PVM), providing the first insights into transport at this interface between the intracellular parasite and its host cell. We determined that this non-selective channel functions as a molecular sieve for nutrient uptake. Subsequent studies identified similar channels in other intracellular parasites.
- Reconstituted the PVM channel into planar lipid bilayers to determine that large organic polymers have high permeability and to define the channel's pore size.
- Designed and implemented a novel ligand-gated channel to examine ion regulation at the parasite plasma membrane (PPM).
- Performed the first direct measurements of ion transport at the digestive vacuole (DV), the metabolic hub of intracellular malaria parasites and site of action of many approved antimalarial drugs.

Selected publications:

a. S.A. Desai, D.J. Krogstad, and E.W. McCleskey. A nutrient permeable channel on the intraerythrocytic malaria parasite. **Nature** (1993) 362:643-646 PMID: 7681937
b. S.A. Desai and R.L. Rosenberg. Pore size of the malaria parasite's nutrient channel. **Proc. Natl. Acad. Sci. USA** (1997) 94:2045-2049. PMID: 9050902
c. M. Sylla, A. Gupta, J. Shao and S.A. Desai. Conditional permeabilization of the *P. falciparum* plasma membrane in infected cells links cation influx to reduced membrane integrity. **PLoS One** (2023) *in press.*

4. Developed and promoted state-of-the-art DNA transfection technologies in *P. falciparum*.
Because insights into parasite cell and molecular biology depend critically on facile manipulation of the parasite genome, we have contributed significantly to improved DNA transfection of malaria parasites. Our key contributions to this project include:

- Developed and used a silent *attB*-intron to allow facile, site-specific introduction of indels and mutations in essential parasite genes.
- Tabulated CRISPR efficiency scores and developed novel algorithms for editing members of multigene families.
- Developed a robust high-throughput method for limiting-dilution cloning of parasite transfection pools.
- Executed small molecule screens to identify novel agonists of plasmid uptake that may improve transfection efficiency.

Selected publications:

a. B. Lyko, E.A. Hammershaimb, W. Nguitragool, T.E. Wellems, and S.A. Desai. A high-throughput method to detect *Plasmodium falciparum* clones in limiting dilution microplates. **Malaria J.** (2012) 11:124. PMID: 22531353.
b. A. Gupta, P. Balabaskaran-Nina, W. Nguitragool, G.S. Saggu, M.A. Schureck, and S.A. Desai. CLAG3 self-associates in malaria parasites and quantitatively determines nutrient uptake channels at the host membrane. **mBio** (2018) 9(3): e02293-17. PMID: 29739907
c. P. Balabaskaran-Nina and S.A. Desai. Diverse target gene modifications in *Plasmodium falciparum* using Bxb1 integrase and an intronic *attB*. **Parasit. Vectors**. (2018) 11(1):548. PMID: 30333047
d. J.M. Ribeiro, M. Garriga, N. Potchen, A.K. Crater, A. Gupta, D. Ito, and S.A. Desai. Guide RNA selection for CRISPR-Cas9 transfections in *Plasmodium falciparum*. **Int. J. Parasitol.** (2018) 48(11):825-832. PMID: 29906414
e. J. Shao, G. Arora, J. Manzella-Lapeira, J.A. Brzostowski and S.A. Desai. Kinetic tracking of *Plasmodium falciparum* antigens on infected erythrocytes with a novel reporter of protein insertion and surface exposure. **mBio** (2022) 13(3):e0040422. PMID: 35420481

5. Patents and applications for therapeutics and diagnostics

S.A. Desai and A.D. Pillai, inventors. Inhibitors of the Plasmodial Surface Anion Channel as Antimalarials. PCT patent PCT/US09/50637. 2009 Jul 15.

S.A. Desai, inventor. Plasmodial surface anion channel inhibitors for the treatment of malaria. HHS reference E-145-2011-0-US-01. 2011 Apr 12.

T. Sawetzki, D. Marr, C. Eggleton, and S.A. Desai, inventors. Dynamic Viscoelasticity as a Rapid Single-Cell Biomarker. PCT application in process. 2013.

S.L. Waidyarachchi, S.T. Nguyen, X. Ding, S. Adhikari, J.D. Williams, N.P. Peet, Z.D. Aron, S.A. Desai, and M.M. Butler, inventors. Compounds and Methods for Treating Malaria. U.S. Patent Application No. 63/140,308. 2021 Jan 22.

S.L. Waidyarachchi, S.L. Nguyen, X. Ding, S. Adhikari, J.D. Williams, N.P. Peet, Z.D. Aron, S.A. Desai and M.M. Butler, inventors. Compounds and Methods for treating Malaria. PCT patent PCT/US2022/013223. 2022 Jan 21.

D. Additional Information: Research Support

Ongoing Research Support

Division of Intramural Research Desai (PI) 2/01/2001 - ongoing
The Plasmodial Surface Anion Channel and Malaria Parasite Nutrient Acquisition.
Molecular and cellular biology research on intraerythrocytic malaria parasites.
Role: PI

PHS SBIR-Advanced Technology Phase IIb Grant Butler (PI) 2019 - 2022
Novel Plasmodial Surface Anion Channel Inhibitors as Antimalarial Drugs
Role: Key Collaborator

Completed Research Support

Medicines for Malaria Venture Desai (PI) 11/01/2005 - 2008
PSAC antagonists as Lead Compounds for Antimalarial Development
A drug discovery project that used high-throughput screening, medicinal chemistry, and *in vitro* and *in vivo* studies to identify PSAC antagonists suitable for advancement into drug development.
Role: PI

R01 AI079347-01A1 Marr (PI) 2009-2016
High-Throughput Cell Mechanical Property Testing for Label-Free Assaying
A project to develop methods for modeling, detecting, and sorting of malaria-infected red blood cells via high-throughput mechanical property testing.
Role: Key Collaborator

PHS SBIR-Advanced Technology Grant Butler (PI) 2013 - 2017
Novel Plasmodial Surface Anion Channel Inhibitors as Antimalarial Drugs
Role: Key Collaborator

DoD Congressionally Directed Medical Research Program Butler (PI) 2016-2019
Novel Thiazepinone Plasmodial Surface Anion Channel Inhibitors as Antimalarial Drugs
Role: Key Collaborator