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Subject: Nomination of Prof Sarman Singh for Sun Pharma Award

Prof. Sarman Singh, hailing from a very small village of Aligarh, Uttar Pradesh was borne to parents with humble economic and educational background. Despite these difficulties, he competed, got selected and completed his MBBS course at the famous King George's Medical College, Lucknow. He completed his specialization from another prestigious PGIMER, Chandigarh where he specialized in Clinical Microbiology. He joined All India Institute of Medical Sciences, New Delhi in 1988. Where he transformed a challenge into opportunity. The Clinical Microbiology Division was most neglected area of Laboratory Medicine, but within in 15 years he transformed this into a world class diagnostic facility. Further, he achieved another landmark of getting selected as Director of the All India Institute of Medical Sciences, Bhopal in 2018.

Dr. Singh has proved himself as a sincere and hardworking medical scientist, highly respected teacher, authors of hundreds of papers and editor of several books and journal. He has good administrative and constitutional knowledge. He is a nationally and internationally acclaimed medical scientist for his outstanding research and academic achievements.

The main focus of Prof. Sarman Singh's research has been on developing more sensitive and cost-effective diagnostic methods for infectious diseases, particularly those that are difficult to diagnose and treat. Towards this goal, he has made several ground breaking discoveries in the field of pathophysiology of visceral Leishmaniasis or kala-azar. He was the first to develop and patenting a rapid and highly cost-effective diagnostic test for this disease. A novel recombinant antigen (Ld-KE16) was prepared from an Indian strain of L. donovani (Singh & Sivakumar 2003; Sivakumar et al, 2006) ((PCT/IN2003/000400) and the commercial rights of the test were transferred to the M/s Span Diagnostic Pvt Ltd through the Department of Biotechnology, Govt. of India. The company has made rapid diagnostic test (RDT) kits in various test formats, which were dedicated to the nation by the Honourable Minister of Science & technology, Government of India Shri Kapil Sibal on February 6, 2006. These RDTs have made the invasive and hazardous methods like bone marrow and splenic aspiration dispensable at a very affordable price (Singh 2006). It is a matter of pride that the diagnosis of kala-azar can now be made at a cost of less than Rs. 50 per patient in India using these trailblazing "Made in India" kits. These test kits are exceptionally accurate with 100% specificity and 98% sensitivity.

The disease kala-azar mainly affects the poor and down-trodden section of our society (Singh et al, 2000). Till rapid tests were made available, thousands of poor in the states of Bihar, W Bengal and Uttar Pradesh were dying due to this disease because of non-availability of sensitive, cost-effective and point-of-care diagnostic methods. It may be mentioned that with the availability of this

revolutionary test, the number of kala-azar deaths has come down significantly - thanks to the Government of India for their active surveillance, and free treatment combined with the *RDT kit developed by Dr. Singh that played a pivotal role in the national kala-azar elimination program.* This cutting edge technology is also saving of millions of dollars of the Indian Government every year on foreign exchange. *This is an important indigenous invention by a medical scientist, which has become an integral part of any national disease elimination programme*.

Beside the above, this work has been recognised by the prominent science agencies of India, notably the Department of Biotechnology (Product, process and Commercialisation award); Indian Council of Medical Research (Dr. BK Aikat Award); Medical Council of India (Dr. BC Roy Award); Government of Uttar Pradesh (Vigyan Ratna Award); Indian Medical Association (Med-Achiever Award); Delhi Medical Association (Chikitsa Ratna Award); Indian Society of Parasitology (Dr. BP Pandey Oration Award); Indian Association of Tropical Parasitology (Outstanding Researcher in Parasitology); Indus Foundation (Innovation Excellence Award); Society for Immunology and Immunopathology (Life Time achievement Award) and many more.

The issue of reservoirs of visceral leishmaniasis in India has remained dogmatic. The dictum has been that only post-kala-azar dermal leishmaniasis (PKDL) patients serve as reservoirs and there are no animal reservoirs in India, in contrast to the well-known animal reservoirs world-wide. In a spearheading study Dr. Singh working on the premise that in several areas where there are no PKDL cases (Dey et al, 2007), the outbreaks or sporadic cases of VL do occur (Singh et a, 2011). Furthermore, using novel PCR primers (PCT/IN2004/000395) his team also found that VL and PKDL strains are genetically different and both strains have differences in the anti-leishmanial drug susceptibility pattern (Mishra et al 2011). Therefore, in a radical approach, his team investigated thousands of animals in endemic areas as well as in non-endemic areas and found that goats are very potent animal reservoirs of VL in India (Singh et al 2013). These findings are bound to make important contribution in the kala-azar elimination programme.

The whole genome sequence (WGS) of several isolates of Leishmania donovani from VL patients has been sequenced, but it is a matter of pride that *Dr. Sarman Singh became the first in the world to carry out the WGS of the PKDL strain of Leishmania*. The sequence alignment data showed significant differences in the genome of PKDL strain as compared to VL strains (Gupta et al, 2015). The WGS also revealed a revolutionary finding that a major portion of *a saprophytic bacterial (Parvibaculum lavamentivorans DS-1)* genome *gets integrated into the genome of PKDL strain. On the basis of this discovery new biological phenomenon has been postulated, thereby this integration could be the triggering factor to manifest the two strains differently (the viscerotropic form becoming dermotropic). This landmark discovery also proved his hypothesis, that Leishmania donovani* undergoes in-vivo hybridization to manifest as PKDL. *These findings will go a long way in the eradication of old dogma about PKDL*.

India has distinction of having maximum cases of HIV, TB and Leishmaniasis. In an in-depth invited review in International Journal of Infectious Diseases Dr. Singh discusses the current scenario of HIV-leishmania co-infection and factors that contributed to help quell this duo, in contrast to the other co-endemic countries (Singh, 2014). However, the Leishmania and TB both are co-endemic in several parts of eastern India. It is also known that approximately 20% VL patients will have concomitant or subsequent Tuberculosis but there is no effective vaccine for these infections. Considering this as a major research challenge, for the first time *his team prepared a self-cleaving chimeric DNA vaccine which can be used against both TB and visceral leishmaniasis*

(Dey et al, 2008). This cutting edge innovation has been patented globally (PCT/IN2009/000093). The Department of Biotechnology who funded and licensed this this work, observed this invention as of high commercial value. The reputed journal Vaccine invited him to publish this innovative research to publish in their special issue (Dey & Singh, 2009) and again another reputed journal (Parasites and Vectors) invited him to write a systemic review on Leishmania vaccines (Srivastava et al 2015).

Miltefosine is a new drug approved for the treatment of VL in 2004 only but within few years of its introduction, the efficacy has gone down. To understand the mechanism of resistance, in an avant-garde study his team has discovered novel mutations in the genes of Leishmania; which impart resistance to miltefosine. These mutations can now be used as molecular markers to diagnose and predict miltefosine resistance in circulating strains at an initial stage_(Srivastava et al, 2016).

Tuberculosis is the main killer infectious diseases in India. On the top of that multi-drug resistant (MDR) and extensively drug resistant (XDR) forms have emerged forcing WHO to announce MDR-TB as health emergency. Dr. Singh for the first time reported high incidence of XDR-TB in Indian AIDS patients (Singh et al 2007). Though this publication created lot of discussion in Government, but finally it was accepted as realty and based on these findings Government of India implemented programmatic management of DR-TB (PMTD). Unfortunately, early and accurate diagnosis of TB has remained a major challenge for researchers and programme managers. In last 20 years several serological test kits were dumped in the Indian market for the diagnosis of PTB and EPTB. But these kits gave highly inaccurate results, leading to unnecessary treatment to hundreds of thousands of patients, and leaving several thousands TB patients untreated. Dr. Singh played crucial role in getting these (clinically non validated) serological kits banned for import, manufacture and use in India (The Independent, UK; Times of India; The Hindu; Deccan Herald; Spectrum; etc.) and live discussion on the all India Radio. The Editorial published in the IJMR (Singh & Katoch, 2011) catalysed this debate which to the contributed the decision taken by the Government of India in May 2012.

Dr. Singh worked untiringly to find out novel molecular tools and biomarkers for the diagnosis and differentiation of drug susceptible and drug resistant Mycobacterium tuberculosis. His laboratory has recently made a revolutionary discovery in this field. After screening hundreds of proteins of MTB, his team identified 5 novel proteins/antigens which are over-expressed only during the invivo drug resistance development. The genes were cloned and proteins expressed, purified and used on various categories of patients showing the sensitivity and specificity of these proteins between 98.2% -100% and 89.1 - 98.2%, respectively (Singh et al, 2015, Singh et al, 2016*). Using these novel proteins, development of a point-of-care (POC) rapid test is underway. This innovation will be a game changer in the area of TB diagnostics not only for India but globally. The Foundation for Newer Innovative Diagnostics (FIND) has shown interest in this innovation and very soon this innovation will move towards application in public health.

He has also used his epidemiological skills acquired during his training at University of Michigan (USA) and has done various field studies. He has formed a network of scientists working on Tuberculosis in India. In a spearheading study his team screened 628 isolates of MTB collected from various parts of the country, genotyped these and did drug susceptibility testing to uncover how the socio-geographical factors influence the prevalence of various genotypes of MTB. *This was unique and first study of its kind*. The Beijing genotype of MTB which is most prevalent in NER-India is having highest vulnerability for drug resistance while EAI genotype (found mainly in

South India) having least preponderance for drug resistance (Singh et al, 2015). In this study he for the first time successfully documented the impact of population migration on the prevalence of various mycobacterial genotypes in different. This study was judged as the best study of 2015-16 carried out at the AIIMS and Dr. Singh was awarded First Prize in Research Excellence by the hon'ble Minister of Health and Family welfare, Government of India, Sri JP Nadda. The study has got wide coverage in the print media and Department of Biotechnology (NER-BPMC) has announced a special call for proposals to deal with this menace.

Dr. Singh has also done pioneering work in the field of non-tuberculous mycobacteria (NTM) often neglected by clinicians and medical microbiologists as contaminants. In AIDS era these NTM have gained much importance but the conventional methods of identification are neither reproducible nor very specific. His team has developed novel sets of multiplex-PCR primers for the diagnosis and differentiation of Mycobacterium tuberculosis, M. avium, M. kansasii and other NTM, directly from the clinical samples in a single tube (PCT/IN2004/000396). These PCR primers and the process have been found highly sensitive and specific and are being routinely used at AIIMS and many other laboratory settings throughout the country (Singh et al, 2006, Gopinath et al, 2009, Kumar et al 2014a). The PLoS Neglected Tropical Disease published Dr. Singh's "Personal Opinion: on this subject, which is highly cited. This has made a paradigm shift in the understanding of NTM disease in India. Using the same gene targets, a new technology known as loop mediated isothermal amplification (LAMP) assay has also been developed by him with a commercial partner (Kumar et al, 2014b). The technology is being evaluated across the country and soon may be taken up by the Government of India.

Currently molecular tools have become essential to understand the pathophysiology and drug targets. Dr. Singh has moved with the time. His laboratory is equipped with all modern tools including 6 laser flow cytometer and New Generation Sequencer (NGS), beside all routine diagnostic tools and services. His laboratory caters diagnostic (routine and specialised) tests with precision and accuracy. For his quality services his laboratory is recognised as training centre for whole Asia region for new TB diagnostics by the Stop-TB division of WHO (Geneva) and also by the central TB division of Government of India.

Prof. Singh is an acknowledged and respected name in the field of Toxoplasmosis in India for both medical and veterinary fraternity. His Toxoplasma reference laboratory is the only centre in entire India which is maintaining and distributing the *Toxoplasma gondii* strains to other researchers for the last 26 years continuously. Because of his spearheading teachings through webinars, print media and on other platforms including the FOGSI, ISP, IATP, IAMM, etc he has been able to convince the thousands of Gynaecologists, Obstetricians, Paediatricians and Medical /veterinary microbiologists of India, that bad obstetric history (BOH) is a misnomer and that Toxoplasma causes multiple abortions is only a myth (Singh & Pandit 2004; Singh et al, 2014). He is now the last word for Gynaecologists and Obstetricians of India regarding the diagnosis and management of congenital/antenatal toxoplasmosis. He has saved several unwarranted terminations of precious pregnancies suspected to have intrauterine toxoplasmosis on the basis of inaccurate test methods. His work has been cited in several reputed reference and text books-notably, the Infectious Diseases of fetus and neonates (Remington & Klein), Practical Obstetric Problem (Ian Donald); Toxoplasmosis: A comprehensive Clinical Guide (David et al), International Encylopedia of Public Health (Academic Press); Practical Guide to high-risk Pregnancy and delivery (Arias); Internal Medicine: an Illustrated Radiological Guide (Tubaikh) to name a few. It is worth mentioning that for his work on Toxoplasmosis he has been honoured by the Indian Academy of Tropical Parasitology as well as by the Indian Society of Parasitology. Beside TORCH infections his original work on mother-to-child transmission of Hepatitis E virus has been cited in almost all text books of paediatrics and Obstetrics, for examples – Principles and Practice of Infectious Diseases (Bennett et al); Infectious Diseases of fetus and neonates (Remington & Klein); Practical Obstetric Problem (Ian Donald); Viral Infections of Humans (Kaslow et al) and Avery's Neonatology.

He was the first to document first case of HIV-Leishmania co-infection in India (Singh et al 2000a) and also high incidence rates of hepatitis B and Hepatitis C virus infections in Kala-azar patients of Bihar who were receiving multiple injections of sodium antimony gluconate (Singh et al, 2000b). He for the first time documented that circumcised patients had lower incidence of Hepatitis C and HIV virus infections in India. These findings were noticed by WHO and its Safe Injection Global Network (SIGN) division organised a special meeting with Government of India (in 2001) and highlighted the need for safe injection practices in India. Dr. Singh was special invitee in this meeting to present his findings. This advisory issued by the WHO to India based on his findings changed the scenario of injection practices in India.

As a physician scientist also he has contributed immensely in the Clinical Practice. For the first time from India, he reported mucosal involvement by Leishmania donovani in an AIDS patient and Prof. Singh coined a new clinical condition- post-kala-azar mucosal leishmaniasis (PKML) and published in the Lancet (Singh, 2004). This clinical term is now being used by other authors also (Singh 2014). He has treated rare clinical conditions like genitourinary enterobiasis (Singh et al, 1989), Scalp Phthiriasis (Singh et al, 1990), Hookworm granuloma of Gastric Os (Singh 1999), Toxoplasmosis in an immunocompetent surgeon, and many more. He has successfully carried out clinical trials of herbal immunomodulators in AIDS patients. He was running a pre- and post-test counselling clinic for HIV/AIDS and TORCH infections for the last 20 years at AIIMS, New Delhi and was supervises more than 5 lakh investigations each year.

Indeed Dr. Singh has several firsts to his credit, whether it pertains to new discoveries, novel innovations, finding new pathogens, clinical conditions or disease manifestations. His keen interest in new discoveries and scientific dissemination started from his early residency days at PGIMER, Chandigarh. Dr. Singh was the *first to report fungal contamination (Trichosporon beigelli) of UGI endoscopes instead of routine decontamination procedures (Singh et al 1989). This work has been cited in several l text books of Gastroenterology.* He also reported new species of Trichuris (vulpis) in Onges tribes of Nicobar (Singh et al 1993) and new genotypes of Mycobacterium tuberculosis in India.

In addition to research, teaching and patient care he is helping various Government organizations like UPSC, DBT, ICMR, ICAR in the academic and administrative processes, and on being on their task forces. Dr. Singh has been member of Peer Team of NAC and Inspector of the MCI. Dr. Singh has also been on the research advisory committees/examiner of more than 25 central and state universities. He is also member of scientific advisory committees of JIMPER, Pondicherry; RMRC, Jodhpur and National JALMA Institute for Tuberculosis. He is grant reviewer for DST, DBT, DHR, ICMR, CSIR, BIRAC/IKP, BCIL of India, etc. He is also international grant reviewer for Medical Research Council, Government of South Africa; Ministry of Science and Technology, Life Sciences Division. Government of Israel and Ministry of Health (General Director for Scientific Research and Health Innovation), Italy. He is also abstract reviewer for World AIDS conference (IAS,

Geneva) consecutively for 9th year and also for CROI (USA) and ICASA (South Africa) for last 3 years.

As the director of the All India Institute of Medical Sciences, Bhopal, he has completely transformed this Institute within 3 years. He has brought transparency and systematics in the institutional functioning, and this has resulted in faith and respect in the patients and employees of the organization. On the font of service delivery, beside the routine mandated services such as IPD and OPD, teaching of UG and PG courses several innovative services with futuristic vision have been started. These include Green Campus; Poison Information Centre; Postgraduate Course in Chemical Biological Radiological Nuclear Emergencies (CBRNE) with IGNOU and INMAS, New Delhi; and Centre for the Translational Medicine. This center has dedicated faculty and state of the art infrastructure and equipment like Whole Genome Sequencer, automated Nucleic Acid extractor, Flow cytometer, Atomic absorption system, and the In-vivo image analyzer to conduct the drug and vaccine trial in animals. The faculty of this center is mandated to develop new diagnostic and human devices, drugs, vaccines, and systems based on artificial intelligence. The facility will be unique gift to whole central India. With his untiring efforts, Cancer Treatment Center and Radiotherapy services are unique of the kinds in Government sector in this region.

During the period of COVID pandemic, his leadership has been valuable. AIIMS, Bhopal initiated the first clinical trial in the April 2020 for the management of COVID-19 and AIIMS, Bhopal has been made Center of Excellence (CoE) for clinical care and helping the state Government in various ways, including certifying and mentoring all medical colleges of the state for COVID testing, advising the state through various task forces and advisory committees. Probably this is the only central Government 500+ bedded dedicated COVID-19 hospital where despite of high burden of Covid-19 cases in both the waves, no healthcare worker required ICU and no fatality of any healthcare worker till date

AIIMS Bhopal under the leadership of Prof Sarman Singh has started playing a pivotal role for achieving excellence in medical care and academics in the state of Madhya Pradesh. His team is mentoring all medical colleges of the states be it diagnostics, treatment guidelines or mitigation of the epidemic. He has untiringly worked through media and other systems to educate the public of the state through electronic (RSTV, NDTV, ABV News, AajTak, Bansal News, TV9, Sadhna TV channel, India New, Door Darshan, All India Radio, all types of social media, the PIB, PTI, Outlook and almost all print media. He motivated his team to undertake autopsy studies on dead bodies of the COVID-19 patients, and this initiative is significant in our country. The findings of unique and humane research will be far-reaching and provide new insights in the pathology of the COVID-19 and alleviate fears in the family members of deceased patients, who often leave the dead relatives unattended. For his societal concerns and social education the Public Relation Society of India (PRSI) awarded with most prestigious "Pride of India" Award in 2021.

AIIMS Bhopal under his research leadership has outshined with more than 45 research grants from various national and international agencies including the ICMR, DST, DBT, BIRAC, DHR, WHO, UNICEF, MP Govt. AIIMS, Bhopal has made its mark among new AIIMSs, in the field of Research during the Directorship of Prof. Singh. A total of 233 Publications were made in the last two years.

Prof. Singh himself has supervised more than 17 PhD and 5 MD students, all are pursuing their career successfully – in the USA, South Korea, UK, Germany and in India. Dr. Singh is voracious writer, dedicated researcher, loved teacher by his students, an able administrator and a visionary. This is evident from his high citation index of >11500, i10 index of 204 and h-index of 50.

It is noteworthy that on the basis of his outstanding research and publication, Royal College of Pathologist (London) has awarded him FRCP. Furthermore, in 2020 his name also found place in the world's top 2% of the scientists (https://tech-talk.org/2020/11/22/indian-researchers-who-were-top-2-in-2019-stanford-study/) a rare distinction to only a handful scientists.

I am pleased to nominate him for the Sun Pharma Science Foundation Award 2021.

(V.M. Katoch)

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