

LUCIO LUZZATTO

DATI DIVERSI DAI DATI RELATIVI ALLO SVOLGIMENTO DI INCARICHI O LA TITOLARITÀ DI CARICHE IN ENTI DI DIRITTO PRIVATO REGOLATI O FINANZIATI DALLA PUBBLICA AMMINISTRAZIONE O LO SVOLGIMENTO DI ATTIVITÀ PROFESSIONALI

POSITION TITLE: Honorary Professor of Hematology, University of Firenze, Florence, ITALY

ISTRUZIONE E FORMAZIONE:

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Genova, Genoa, ITALY	MD	July 24, 1959	Medicine
University of Pavia, ITALY	Specialist	1962	Hematology
Ministry of Education, Rome, ITALY	Lib Doc (PhD)	1968	Biochemistry
Royal College of Pathologists, UK	FRCPath	1982	Hematology
Royal College of Physicians, UK	FRCP	1983	Medicine

A. Personal Statement

The leitmotiv of my research has been to understand in depth blood diseases for the ultimate purpose to improve their management. In the area of G6PD we did extensive studies in population and biochemical genetics, and in the early eighties we cloned the G6PD gene. We took part in solving the 3D structure of human G6PD, and thus eventually we were able to work out the pathophysiology of G6PD deficiency at the molecular level. We did the first field studies and the first studies on the mechanism whereby G6PD deficiency protects from malaria, finding that this is an X-linked balanced genetic polymorphism in human populations. Recently we reported on the largest clinical study of drug-induced acute hemolytic anemia in G6PD deficient children: for the first time this has persuaded WHO and other health authorities that point of care testing for G6PD is necessary. In the area of paroxysmal nocturnal hemoglobinuria (PNH) we proved that this is a clonal disorder. Subsequently we have introduced the concept of conditional clonal selection and over the years we have provided extensive supporting evidence for this model: we have found that the existence of CD1d-restricted GPI-specific T cells are the key not only to the pathogenesis of PNH, but also of aplastic anemia in a substantial proportion of cases. In the meantime, I was the senior author of the paper that led to licencing eculizumab, a complement-blocking agent that has become the first PNH-specific medicine. PNH may prove a model for other clonal disorders of hematopoiesis, and this has been the lead for our tenet in the early nineties, now widely accepted, that leukemia is a genetic disease of hematopoietic cells, We have designed methodology to measure the somatic mutation rate of an individual by a simple test on peripheral blood granulocytes, and this has helped to pinpoint the role of stochastic events in oncogenesis. In the area of sickle cell disease (SCD) we have worked on the cellular mechanism of malaria selection for AS heterozygotes, and on the clinical relationships between G6PD deficiency and SCD; and I was also involved in constructing the first mouse model of sickle cell anemia. As newly appointed visiting professor at the Muhimbili University Hospital (MUHAS) in Dar es Salaam, Tanzania, I intend to work further on this topic in collaboration with Dr Julie Makani and her team at the SCD Center. I also intend to carry out research on the wide applicability of hydroxycarbamide in the management of SCD in Africa.

COMPETENZE PROFESSIONALI

1963-64 Fellow in Haematology, Department of Medicine, College of Physicians & Surgeons, Columbia Presbyterian Hospital, New York, NY, USA.

1964-67 Lecturer in Haematology, in charge of Blood Transfusion Unit Department of Pathology, University of Ibadan, Ibadan, Nigeria.

1967-1974 Senior Lecturer, then Professor (from 1968) and Head (from 1970), Department of Haematology, University of Ibadan, Ibadan, Nigeria; Consultant Haematologist, UCH, Ibadan, Nigeria,

1974-1981 Director, International Institute of Genetics and Biophysics, CNR, Napoli, Italy,

1981-1994 Professor of Haematology (University of London), and Director of Haematology Department, Royal Postgraduate Medical School (now Imperial College), London; Consultant Haematologist, Hammersmith Hospital, London, UK.

1994-2000 Chairman, Department of Human Genetics, Attending Physician in Genetics and Hematology, Memorial Hospital; Member of the Cell Biology and Genetics Programme, Sloan-Kettering Institute, Courtney Steel Chair, Memorial Sloan-Kettering Cancer Center; Professor of Medicine and Human Genetics, Cornell University Medical College, New York, NY, USA,

2000-2004 Scientific Director, National Institute for Cancer Research, Genova, Italy,

2002-2006 Professor of Haematology, DOBIG, University of Genova, Genova, Italy

2005-2015 Scientific Director, Istituto Toscano Tumori, Florence, Italy

2006- Professor of Haematology (honorary since 2008), University of Florence

ULTERIORI INFORMAZIONI

Professional Memberships (PARTIAL LIST)

- International Society of Haematology, since 1972
- University College Hospital Ibadan Medical Society, President-elect, 1968-70
- Nigerian Society for Haematology and Blood Transfusion; Foundation President, 1968; WHO Reference Center for G6PD in the African Region, 1968-1974
- Expert Panel on Abnormal Haemoglobins and Thalassemia of the International Committee on Standardization in Haematology, 1972-81
- Italian Association of Genetics: President 1979-81
- Executive Council, Italian Society of Haematology, 1977-80
- European Molecular Biology Organization (EMBO): Active Member since 1979
- American Society of Haematology, Honorary member since 1981
- Human Genome Organization (HUGO), Active member since 1993
- American Association of Physicians, since 1995
- Chairman, Ethics Committee, American Society for Gene Therapy (1997-2000)
- President, Federazione Italiana Scienze della Vita, 2008-2010
- President of the Scientific Advisory Board of the *Associazione Italiana Pazienti Emoglobina Parossistica Notturna*, 2008-

Honorary Degrees

Laurea ad honorem in Pharmacy, University of Urbino, Italy, 1990

DSc, University of Ibadan, Nigeria, 1998

Doctor *honoris causa* in Medicine, University of Patras, 2006.

Honours and Awards (Partial List)

Livierato Prize, University of Genova, 1957

Pasetto Prize, University of Genova, 1958

- Istituto Nazionale Assistenza Infortuni sul Lavoro Prize, 1960
- Ministero della Pubblica Istruzione Fellow, 1962
- Fulbright Senior Fellow, 1967
- Henry M. Stratton Lecture, XV International Congress of Haematology, 1974
- Pius XI Medal, 1976
- Sanremo International Prize for Human Genetics, 1982

- Ham-Wasserman Lecture, American Society of Haematology, San Francisco, CA, USA, 1988
- Oliver-Sharpay Lecture, Royal College of Physicians, 1988
- International Chiron Award for Biomedical Research, 1995
- Premio Napoli, 1995
- Nigerian Society of Haematology and Blood Transfusion: 25th Year Jubilee Lecture, 1997
- Premio Pier Camillo Beccaria, Associazione Angela Serra, Modena, Italy, 1999
- Premio Liguria, 2000
- James Blundell Award, British Society of Blood Transfusion, 2001
- Foreign Member, American Academy of Arts and Sciences, 2004.
- Montalenti Medal, University of Rome, 2007.
- Premio Giovanni Maria Pace, Trieste, 2007.
- Scientific Prize Accademia delle Scienze of Torino, 2011.
- Accademia dei Lincei Annual Prize in Biology, 2015.

C. Selected Peer-reviewed Publications (selected from over 350 peer-reviewed publications)

- Luzzatto L and Allan NC (1965) Different properties of glucose 6 phosphate dehydrogenase from human erythrocytes with normal and abnormal enzyme levels. *Biochemical and Biophysical Research Communications* 21:547-554.
- Luzzatto L, Usanga EA and Reddy S (1969) Glucose 6 phosphate dehydrogenase deficient red cells: resistance to infection by malarial parasites. *Science* 164:839-842.
- Luzzatto L, Nwachuku Jarrett E and Reddy S (1970) Increased sickling of parasitised erythrocytes as mechanism of resistance against malaria in the sickle cell trait. *Lancet* i:319-321.
- Oni SB, Osunkoya BO and Luzzatto L (1970) Paroxysmal nocturnal hemoglobinuria: evidence for monoclonal origin of abnormal red cells. *Blood* 36:145-152.
- Bienzle U, Ayeni O, Lucas O and Luzzatto L (1972) Glucose 6 phosphate dehydrogenase and malaria. Greater resistance of females heterozygous for enzyme deficiency and of males with non deficient variant. *Lancet* i:107-110.
- Babalola AOG, Beetlestone JG and Luzzatto L (1976) Genetic variants of human erythrocyte glucose 6 phosphate dehydrogenase. Kinetic and thermodynamic parameters of variants A, B and A in relation to quaternary structure. *Journal of Biological Chemistry* 251:2993-3002.
- Persico MG, Toniolo D, Nobile C, D'Urso M and Luzzatto L (1981) cDNA sequences of human glucose 6 phosphate dehydrogenase cloned in pBR322. *Nature* 294:778-780.
- Luzzatto L (1981). Sickle cell anaemia in Tropical Africa. *Clinics in Haematology* 10:757-784.
- Rotoli B, Robledo R, Scarpato N and Luzzatto L (1984) Two populations of erythroid cell progenitors in paroxysmal nocturnal hemoglobinuria. *Blood* 64:847-851.
- Martini G, Toniolo D, Vulliamy T, Luzzatto L, Dono R, Viglietto G, Paonessa G, D'Urso M and Persico MG (1986) Structural analysis of the X linked gene encoding human glucose 6 phosphate dehydrogenase. *EMBO Journal* 5:1849-1855.
- Vulliamy TJ, D'Urso M, Battistuzzi G, Estrada M, Foulkes NS, Martini G, Calabro V, Poggi V, Giordano R, Town M, Luzzatto L and Persico G (1988) Diverse point mutations in the human glucose 6 phosphate dehydrogenase gene cause enzyme deficiency and mild or severe hemolytic anemia. *Proceedings of the National Academy of Sciences USA* 85:5171-5175.
- Luzzatto L and Goodfellow P (1989). Sickle Cell Anaemia - A simple disease with no cure. *Nature* 337: 17-18.
- Greaves DR, Fraser P, Vidal MA, Hedges MJ, Roper D, Luzzatto L and Grosveld F (1990). A transgenic mouse model of sickle cell disorder. *Nature* 343:183-185.
- Hillmen P, Bessler M, Mason PJ, Watkins WM and Luzzatto L (1993) Specific defect in N acetylglucosamine incorporation in the biosynthesis of the glycosylphosphatidylinositol anchor in cloned cell lines from patients with paroxysmal nocturnal hemoglobinuria. *Proceedings of the National Academy of Sciences USA* 90:5272-5276.
- Luzzatto L and Pandolfi PP (1993). Leukaemia: a genetic disorder of haemopoietic cells. *British Medical Journal* 307: 579-580.
- O'Brien E, Kurdi Haidar B, Wanachiwanawin W, Carvajal JL, Vulliamy FJ, Cappadoro M, Mason PJ and Luzzatto L (1994) Cloning of the glucose 6 phosphate dehydrogenase gene from *Plasmodium falciparum*. *Molecular and Biochemical Parasitology* 64:313-326.
- Pandolfi PP, Sonati F, Rivi R, Mason PJ, Grosveld F and Luzzatto L (1995) Targeted disruption of the housekeeping gene encoding glucose 6 phosphate dehydrogenase (G6PD) *EMBO Journal* 14:5209-5215.
- Hillmen P, Lewis SM, Bessler M, Luzzatto L and Dacie JV (1995) Natural history of paroxysmal nocturnal hemoglobinuria. *New England Journal of Medicine* 333:1253-1258.

Naylor CE, Rowland P, Basak AK, Glover S, Mason PJ, Bautista JM, Vulliamy TJ, Luzzatto L and Adams MJ (1996) Glucose 6 phosphate dehydrogenase mutations causing enzyme deficiency in a model of the tertiary structure of the human enzyme. *Blood* 87:2974-2982.

Luzzatto L, Bessler M and Rotoli B (1997) Somatic mutations in paroxysmal nocturnal hemoglobinuria: a blessing in disguise? *Cell* 88:1-4.

Araten DJ, Nafa K, Pakdeesuwan K and Luzzatto L (1999) Clonal populations of hematopoietic cells with paroxysmal nocturnal hemoglobinuria genotype and phenotype are present in normal individuals. *Proceedings of the National Academy of Sciences USA* 96:5209-5214.

Karadimitris A, Araten DJ, Luzzatto L, Notaro R (2003) Severe telomere shortening affects both GPI- and GPI+ hematopoiesis in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 102: 514-516.

Araten DJ, Golde DW, Zhang RH, Thaler HT, Gargiulo L, Notaro R and Luzzatto L (2005). A Quantitative Measurement of the Human Somatic Mutation Rate. *Cancer Res* 65: 8111-8117.

Hillmen P, Young NS, Schubert J, Brodsky RA, Sociè G, Muus P, Roth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP and Luzzatto L (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *New England Journal of Medicine* 355:1233-1243.

Dingli D, Luzzatto L, Pacheco JM (2008). Neutral evolution in paroxysmal nocturnal hemoglobinuria. *Proc Natl Acad Sci U S A*. 105:18496-500.

Maeda T, Ito K, Merghoub T, Poliseno L, Hobbs RM, Wang G, Dong L, Maeda M, Dore LC, Zelent A, Luzzatto L, Teruya-Feldstein J, Weiss MJ, Pandolfi PP (2009). LRF is an essential downstream target of GATA1 in erythroid development and regulates BIM-dependent apoptosis. *Developmental Cell* 17: 527-40.

Luzzatto L (2010). The rise and fall of the antimalarial Lapdap: a lesson in pharmacogenetics. *Lancet* 376: 739-41.

Peruzzi B, Araten DJ, Notaro R, Luzzatto L (2010). The use of PIG-A as a sentinel gene for the study of the somatic mutation rate and of mutagenic agents in vivo. *Mutation Research* 705: 3-10.

Pamba A, Richardson ND, Carter N, Duparc S, Premji Z, Tiono AB and Luzzatto L (2012) Clinical spectrum and severity of hemolytic anemia in glucose 6 phosphate dehydrogenase deficient children. *Blood* 120:4123-4133.

Luzzatto L. (2012). Sick cell anaemia and malaria. *Mediterr J Hematol Infect Dis*. 4:e2012065.

Rondelli T, Berardi M, Peruzzi B, Boni L, Caporale R, Dolara P, Notaro R, Luzzatto L (2013). The frequency of granulocytes with spontaneous somatic mutations: a wide distribution in a normal human population. *PLoS One*. 8:e54046.

Gargiulo L, Papaioannou M, Sica M, Talini G, Chaidos A, Richichi B, Nikolaev AV, Nativi C, Layton M, de la Fuente J, Roberts I, Luzzatto L, Notaro R and Karadimitris A (2013) Glycosylphosphatidylinositol specific, CD1d restricted T cells in paroxysmal nocturnal hemoglobinuria. *Blood* 121:2753-2761.

Makarona K, Caputo VS, Costa JR, Liu B, O'Connor D, Iskander D, Roper D, Robertson L, Bhatnagar N, Terpos E, Georgiou E, Papaioannou M, Layton DM, Luzzatto L, Roberts I, Karadimitris A (2014). Transcriptional and epigenetic basis for restoration of G6PD enzymatic activity in human G6PD-deficient cells. *Blood* 124:134-41.

Luzzatto L, Seneca E (2014). G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. *Br J Haematol*. 164:469-80.

Luzzatto L, Hollak CE, Cox TM, Schieppati A, Licht C, Kääriäinen H, Merlini G, Schaefer F, Simoens S, Pani L, Garattini S, Remuzzi G (2015). Rare diseases and effective treatments: are we delivering? *Lancet* 385:750-2.

Luzzatto L, Pandolfi PP (2015), Causality and Chance in the Development of Cancer. *N Engl J Med*. 373:84-8.

Lucio Luzzatto has published a book for the lay public: *Capire il Cancro* (Understanding Cancer), Rizzoli, 2006; reprinted in paperback in 2009.

D. Research Support

I had my first RO1 NIH grant award when I was in Ibadan, Nigeria in 1972. In Naples, Italy, I had a block grant from the Italian CNR. When I was in London, UK, I had an MRC Programme Grant that ran for 15 years, and support from the MRC and the Wellcome Trust for additional projects and Research Training Fellows. When I was at Sloan-Kettering I had an NIH RO1 grant for PNH: I was PI of a Program-Project grant for gene therapy, and PI for a T32 training grant, in addition to other non-NIH support. Back in Italy I had a block grant from the Ministry of Health, and competitive grants from the *Associazione Italiana Ricerca sul Cancro*. On the other side of the divide, a partial list is as follows. I have served on MRC Project Grants Committees, on CNR Project Grants Committees, on the Telethon Scientific Advisory Board, on NIH Study sections. For the past 4 years I have been chair of the SAB of the Italian Cystic Fibrosis Foundation. Currently I am a member of the *Life Sciences 7 Panel* of the European Research Council (ERC); and chair of the SAB of the Josep Carreras Research Institute in Barcelona, Spain.

Firenze, 01 Ottobre 2015

Firma

