CURRICULUM VITAE

PERSONAL INFORMATION

Name	Vittorio Bellotti
Date of birth	05/02/1957
Nationality	Italian

EDUCATION

1992	PhD Biochemistry, University of Pavia, Italy.
1987	Specialization in Internal Medicine, University of Pavia, Italy with honours
1982	Medical Doctor (MD) – with honours, University of Pavia, Italy.

CURRENT POSITION

Feb 2022 –	Scientific Director of IRCCS Policlinico San Matteo, Pavia, Italy

PREVIOUS POSITIONS

2006 – Jan 2022	Full Professor of Biochemistry, Department of Molecular Medicine, University of Pavia, Italy (part time regime since 2011).
2011 – Jan 2022	Full Professor of Medical Biochemistry Metabolism & Experimental Therapeutics (part time regime) at University College London (UCL), London, UK; in 2020 he has been appointed Deputy Director of the Wolfson Drug Discovery Unit within the UCL Centre for Amyloidosis and Acute Phase Proteins and Deputy Director of the Department of Inflammation-Division of Medicine at UCL.
2000 – 2006	Associate Professor, Department of Biochemistry, University of Pavia, Italy.
1999 – 2004	Principal Investigator, Laboratory of Biotechnology, IRCCS Policlinico San Matteo, Pavia, Italy.
1992 – 2000	Assistant Professor, Department of Biochemistry, University of Pavia, Italy.

FELLOWSHIPS

2004 – 2005	Visiting Professor Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, University College London, London, UK.
1994 – 1995	Visiting Researcher, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.
1985 – 1987	Research Fellow, Cancer Research and Department of Pathology, Columbia University, New York, USA.
1983 – 1984	Research Fellow, Department of Haematology, University of Seattle, USA.

TEACHING ACTIVITIES

2018 – 2021	Mechanism of amyloidosis (within Molecular Basis of Disease Module), Applied Medical Sciences Degree, University College London, London, UK.
2016 – 2021	Biochemistry, School of Medicine, University of Pavia, Pavia, Italy.
2006 – 2012	Applied Biochemistry, School of Pharmacy, University of Pavia, Pavia, Italy.
2005 – 2021	Biochemistry, School of Pharmacy, University of Pavia, Pavia, Italy.
2000 – 2006	Applied Biochemistry, School of Pharmacy, University of Pavia, Pavia, Italy.

1995 – 2000 Applied Biochemistry, School of Pharmacy, University of Pavia, Pavia, Italy.

SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS

2011 – 2020 5 Postdocs; 2 PhD students; Erasmus students including 2 PhD students and 9 undergraduates at the Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, University College London, London, UK.

2000 – 2021 5 Postdocs;10 PhD students; 20 Master students at the Department of Molecular Medicine, Institute of Biochemistry, University of Pavia, Pavia, Italy.

CLINICAL-DIAGNOSTIC ACTIVITIES

2013 - 2021 Member of the clinical diagnostic board at UK National Amyloidosis Centre for the weekly review of proteomics data from patients' tissue biopsies for amyloid typing and diagnosis.

ORGANISATION OF SCIENTIFIC MEETINGS

2021 Promoter and organizer of the Italian Federation of Life Science (FISV) Symposium: Life science and Society, virtual meeting, 28 April 2021.

2021 Promoter and organizer of the LINXS Amyloid Workshop: Heart and Mind: linking *in vitro* science to the clinical context, virtual conference, 5 March 2021.

2019 Promoter and main organizer of the International Conference "Towards a cure for amyloid diseases: a successful example of precision and translational medicine", 13 -19 December 2019, Palazzo Vistarino, Pavia, Italy.

2014 – 2021 National Meeting for PhD students in Biochemical Sciences in Italy (Brallo di Pregola, Pavia, Italy)

2017 Promoter of the 1st European Amyloid proteomics workshop (1 December 2017, Royal Free Hospital, London, UK) to bring together leading experts in amyloid proteomics from the UK, France, Germany, Italy, Netherlands, Spain and Sweden and discuss how this new diagnostic tool is currently used in the European amyloidosis centres and work towards standardising and validating proteomics as a European diagnostic test for amyloidosis.

2017 Promoter and main organizer of the International Conference "Scientific fraud, growth and prevention", 17-18 November 2017, University of Pavia, Pavia, Italy.

2004 Promoter and main organizer of the International Conference "Dialysis-related amyloidosis: from molecular mechanisms to therapies", 9-13 December 2004, University of Pavia, Pavia, Italy.

ORGANISATION OF SOCIO-CULTURAL EVENTS

2018 Promoter of the event "I pozzi del silenzio: riflessioni sul lato oscuro della ricerca" to discuss the role of scientific research and its ethical limits through the theatrical representation of the Unit 731 story performed by PhD students of Biochemistry at the University of Pavia.

2018 Member of the Scientific board coordinating an European network of scientists (http://www.linxs.se/integrative-structural-biology) and organising regular workshops on the advance of basic research strategic to better understand the molecular bases of pathophysiology of systemic amyloidosis and offer new tools for diagnosis and therapy.

2013 Founder of the "Circolo Culturale Universitario Giorgio Errera" (www.circoloerreraunipv.it) to give the opportunity of an open dialogue on scientific, socio-cultural and political hot topics and their effects to the University life at Pavia.

INSTITUTIONAL RESPONSIBILITIES

2019 – 2020 Member of the Board of Full Professors for Scientific Sector of Biochemistry, Italy.
2014 – 2021 Member of the Committee for PhD in Biomedical Sciences; University of Pavia, Pavia, Italy.
2013 – 2021 Undergraduate Student Personal Tutor, School of Medicine, University College London, London, UK.

REVIEWING ACTIVITIES

2019 – 2021 Editorial Board member of Scientific Reports.
2014 – present Editorial Board member of Frontiers in Molecular Biosciences.
2008 – 2013 Editorial Board member of the Journal of Biological Chemistry.
2000 – present Editorial Board member of Amyloid: The Journal of Protein Folding Disorders.

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

2014 – present Member of the Association of Physicians of Great Britain and Ireland.
2000 – present Member of the Italian Society of Biochemistry.

INVITED PRESENTATIONS TO PEER-REVIEWED, INTERNATIONALLY ESTABLISHED CONFERENCES AND/OR INTERNATIONAL ADVANCED SCHOOLS.

In the last decade Bellotti has been invited on a regular basis to the International Symposium on Amyloidosis (Rome, Italy 2010; Groningen, the Netherlands 2012; Indianapolis, USA 2014; Uppsala, Sweden 2016; Kumamoto, Japan 2018 and Tarragona, Spain 2020).
He maintained international recognition in the field of research as exemplified by a number of invited talks including the following:

2014 Histology Masterclass sponsored by Pfizer, Vienna, Austria, October 16-18, 2014.
2014 The American Society of Nephrology and Postgraduate Education sponsored symposium: Kidney Week Basic & Clinical Science Symposia, Amyloidosis and the kidney: novel Discoveries and Therapies, Philadelphia USA, November 11-16, 2014.
2015 Pfizer sponsored symposium: Advances and Research in TTR Amyloidosis, early diagnosis, improving outcomes IV, Prague, Czech Republic, March 6-7 2015.
2017 Joint Symposium IPR (Institute for Protein Research, Osaka University)/RSC (Research School of Chemistry, Australian National University), Osaka, Japan, December 3-5, 2017.
2018 Amyloidosis Research consortium (ARC) Research Strategy Roundtable meeting, Miami, USA, January 26-27, 2018.
2018 International Symposium on Molecular Mechanism of Progression and Therapeutics of Amyloidosis Shinshu University, Matsumoto, Japan, August 24, 2018.
2019 LINXS Amyloid Workshop: Mind the gaps in amyloid fibre structure analyses, Lund, Sweden, November 21-22, 2019.
2021 Pfizer Medical Advisory Board on Hereditary ATTR amyloidosis, virtual meeting, 14-15 January 2021.
2021 LINXS Amyloid Workshop: Heart and Mind: linking *in vitro* science to the clinical context, virtual conference, 5 March 2021.
2021 Italian Federation of Life Science (FISV) Symposium: Life science and Society, virtual meeting, 28 April 2021.

SCIENTIFIC ACTIVITY

After a research fellowship at the Department of Haematology at the University of Seattle (USA) to study pathophysiology of iron metabolism, Bellotti spent 18 months in the laboratory of Professor Elliott Osserman at the Cancer Research Centre of Columbia University in New York (USA) from 1985 to 1987, as a part of his training in internal medicine abroad. Here he developed a strong interest in the molecular mechanisms of diseases caused by protein aggregation and deposition.

From 1987 to 1995 in Italy first at the University Hospital of Pavia and then in the Department of Biochemistry of the Pavia University, he continued the collaboration with clinicians, biochemists and biophysicists aiming to elucidate the molecular basis of the process of protein aggregation in amyloidosis and light chain deposition disease. This period was particularly formative and he became expert in clinical pathology of protein aggregation diseases and protein biochemistry.

In September 1994 he joined, for a sabbatical year, the team of Professor Mark Pepys at the Hammersmith Hospital in London (UK). Here he demonstrated that the amyloidogenic variants of lysozyme were less stable than the wild type thus providing the basis for a currently accepted model for fibrillogenesis by globular proteins. These results were published in Nature at the beginning of 1997.

In 1999 he was appointed Principal Investigator in the laboratory of Biotechnology at the University Hospital of Pavia where he organized a proteomics and protein biochemistry platform for the investigation of proteins causing degenerative diseases. During the period 1999-2004, Vittorio Bellotti established a network of collaborations with other groups with complementary scientific and technological expertise. Under his direction, his team achieved significant results in the characterization of the amyloidogenesis of apolipoprotein AI and β2-microglobulin *in vitro*. His pioneering work on the role of β2-microglobulin misfolding in Dialysis Related Amyloidosis (DRA) includes the identification of the truncated form lacking the first six N-terminal residues, ubiquitous in osteoarticular amyloid deposits and now considered a crucial pathogenic factor for the disease. His reputation in the field was confirmed by the invited review on the molecular mechanism of amyloidosis published in the New England Journal of Medicine in 2003 and the publication of a monographic issue of Biochimica Biophysica Acta in December 2005 in which he was an invited editor with Professors Yuji Goto (University of Osaka, Japan) and Professor Gennaro Esposito (University of Udine, Italy).

In September 2004 he joined, for a second sabbatical year, the laboratory of Professor Mark Pepys at the Royal Free Hospital in London where he was involved in a project aimed at the identification of new ligands of potential pharmaceutical interest for different proteins including transthyretin, serum amyloid P component, and C reactive protein.

In September 2005 he returned to Pavia where he continued his research as director of the Protein Biochemistry and Pathology of Protein Misfolding Diseases at the University of Pavia. He continued his multi-disciplinary approach to study the molecular basis of protein aggregation and the identification of potential inhibitors. In particular, he continued his work on β2-microglobulinn showing that collagen and heparin have a prominent role in its conversion into amyloid fibrillar deposits; the anti-amyloid properties of a small library of analogues of tetracycline were also investigated and doxycycline was the most effective inhibitor of β2-microglobulin fibrillogenesis *in vitro*. The therapeutic effect of doxycycline was then confirmed in an off label clinical study enrolling patients affected by dialysis related amyloidosis thus providing a good example of basic research translated into clinical practice. Based on this study, the European Medicines Agency has approved doxycycline as an orphan drug for β2-microglobulin type amyloidosis. The extensive biochemical work carried out in vitro has been complemented by the creation of appropriate animal models in his laboratories such as the transgenic *C. elegans* strains expressing β2-microglobulin isoforms to monitor the process of amyloidogenesis *in vivo*.

In 2010 he started a fruitful collaboration with Professor Lode Wyns, Director of the Vlaams Instituut voor Biotechnologie in Bruxelles, for production of nanobodies against β2-microglobulin. After one year of intense collaboration involving exchange of PhD students between the two laboratories, some nanobodies able to stabilise β2-microglobulin and prevent amyloid fibril formation have been identified. These molecules may provide novel tools for investigation of amyloid formation and constitute a prototype for biotechnological drugs against amyloidosis.

In 2011 he joined UCL to lead a project aimed to study the pathogenesis of systemic amyloidosis at the Centre for Amyloidosis and Acute Phase Proteins (University College London, London, UK). Working in close

connection with the clinicians, he achieved a significant advance in the field with the discovery and characterization of the first amyloidogenic variant of β2-microglobulin, D76N, in which he highlighted the link between biomechanical forces and amyloid conversion of globular proteins, further confirmed with synuclein, a newly identified amyloidogenic D25V apolipoprotein C3 protein variant and, transthyretin (TTR).

In 2014, following another clinical case in which a large kindred were affected by a highly aggressive TTR variant, S52P, he demonstrated that a selective proteolytic cleavage of the peptide bond 48-49 in the mature protein and subsequent release of the 49-127 fragment in the presence of fluid agitation were required to prime fibrillogenesis of S52P TTR *in vitro*. Later he confirmed the general importance of biomechanical forces in amyloid formation with the discovery that a mechano-enzymatic mechanism underlies transthyretin amyloidosis in general and that this mechanism may apply to several types of amyloidoses. More recently using a combination of bioinformatics and recent experimental work, he has identified that plasmin, a key enzyme of the fibrinolytic pathway, may prime the selective cleavage and fibrillogenesis of TTR *in vitro* producing fibrils with morphology and composition which are indistinguishable from natural amyloid fibrils.

The identification of the mechano-enzymatic mechanism and putative culprit proteases has enabled the development of another branch of his research leading to novel and patentable compounds to take forward into the clinic.

GRANT SUPPORT (2015-2020)

2018-2021 University College London-Technology Funds "ATTR stabiliser", £ 1,500,000.
2018-2021 UK Medical Research Council (MR/R016984/1) "Mechano-enzymatic cleavage of transthyretin in systemic amyloidosis: elucidation of mechanism and characterization of putative proteases" £ 409,573.
2016-2020 Italian Ministry of Health (RF 2013-02355259) "Cardiac amyloidosis: molecular mechanism and innovative therapies for a challenging aging related cardiomyopathy" € 80,715.
2016-2019 European Union H2020 (Empir Neuromet 15HLT04): "Innovative measurements for improved diagnosis and management of neurodegenerative diseases" £ 149,375.
2015-2018 Telethon Foundation (GGP14127) "Familial ß2-microglobulin amyloidosis: from the elucidation of the pathogenic mechanism to the discovery of novel effective drugs" € 136,400.

TEN REPRESENTATIVE PUBLICATIONS AS SENIOR AUTHOR (selected from **183** full articles in peer reviewed journals).

1. Raimondi, S., Mangione, P.P., Verona, G., Canetti, D., Nocerino, P., Marchese, L., Piccarducci, R., Mondani, V., Faravelli, G., Taylor, G.W., Gillmore, J.D., Corazza, A., Pepys, M.B., Giorgetti, S. **Bellotti, V**. Comparative study of the stabilities of synthetic and natural *ex vivo* transthyretin amyloid fibrils. *J Biol Chem* 295:11379-11387, 2020.
2. Corazza, A., Verona, G., Waudby, C.A., Mangione, P.P., Bingham, R., Uings, I., Canetti, D., Nocerino, P., Taylor, G.W., Pepys, M.B., Christodoulou, J., **Bellotti, V**. Binding of Monovalent and Bivalent Ligands by Transthyretin Causes Different Short- and Long-Distance Conformational Changes. *J Med Chem* 62:8274-8283, 2019.
3. Mangione, P.P., Verona, G., Corazza, A., Marcoux, J., Canetti, D., Giorgetti, S., Raimondi, S., Stoppini, M., Esposito, M., Relini, A., Canale, C., Valli, M., Marchese, L., Faravelli, G., Obici, L., Hawkins, P.N., Taylor, G.W., Gillmore, J.D., Pepys, M.B., **Bellotti, V**. Plasminogen activation triggers transthyretin amyloidogenesis *J Biol Chem* 293:14192-14199, 2018.
4. Verona, G., Mangione, P.P., Raimondi, S., Giorgetti, S., Faravelli, G., Porcari, R., Corazza, A., Gillmore, J.D., Hawkins, P.N., Pepys, M.B., Taylor, G.W., **Bellotti, V**. Inhibition of the mechano-enzymatic amyloidogenesis of transthyretin: role of ligand affinity, binding cooperativity and occupancy of the inner channel. *Sci Reports* 7:182, 2017.
5. Valleix, S., Verona, G., Jourde-Chiche, N., Nédelec, B., Mangione, P.P., Bridoux, F., Mangé, A., Dogan, A., Goujon, J.M., Lhomme, M., Dauteuille, C., Chabert, M., Porcari, R., Waudby, C.A., Relini, A., Talmud, P.J., Kovrov, O., Olivecrona, G., Stoppini, M., Christodoulou, J., Hawkins, P.N., Grateau, G., Delpech, M.,

Kontush, A., Gillmore, J.D., Kalopissis, A.D., **Bellotti, V**. D25V apolipoprotein C-III variant causes dominant hereditary systemic amyloidosis and confers cardiovascular protective lipoprotein profile. *Nature Commun* 7:10353, 2016.

6. Marcoux, J., Mangione, P.P., Porcari, R., Degiacomi, M.T., Verona, G., Taylor, G.W., Giorgetti, S., Raimondi, S., Sanglier-Cianferani, S., Benesch, J.L., Cecconi, C., Naqvi, M.M., Gillmore, J.D., Hawkins, P.N., Stoppini, M., Robinson, C.V., Pepys, M.B., **Bellotti, V**. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. *EMBO Mol Med* 7:1337-1349, 2015.

7. Porcari, R., Proukakis, C., Waudby, C.A., Bolognesi, B., Mangione, P.P., Paton, J.F., Mullin S., Cabrita, L.D., Penco, A., Relini, A., Verona, G., Vendruscolo, M., Stoppini, M., Tartaglia, G.G., Camilloni, C., Christodoulou, J., Schapira, A.H., **Bellotti, V**. The H50Q mutation induces a 10-fold decrease in the solubility of α-synuclein. *J Biol Chem* 290:2395-2404, 2015.

8. Mangione, P.P., Porcari, R., Gillmore, J.D., Pucci, P., Monti, M., Porcari, M., Giorgetti, S., Marchese, L., Raimondi, S., Serpell, L.C., Chen, W., Relini, A., Marcoux, J., Clatworthy, I.R., Taylor, G.W., Tennent, G.A., Robinson, C.V., Hawkins, P.N., Stoppini, M., Wood, S.P., Pepys, M.B., **Bellotti, V**. Proteolytic cleavage of Ser52Pro variant transthyretin triggers its amyloid fibrillogenesis. *Proc Natl Acad Sci USA* **111**:1539-1544, 2014.

9. Mangione, P.P., Esposito, G., Relini, A., Raimondi, S., Porcari, R., Giorgetti, S., Corazza, A., Fogolari, F., Penco, A., Goto, Y., Lee, Y.H., Yagi, H., Cecconi, C., Naqvi, M.M., Gillmore, J.D., Hawkins, P.N., Chiti, F., Rolandi, R., Taylor, G.W., Pepys, M.B., Stoppini, M., **Bellotti, V**. Structure, folding dynamics and amyloidogenesis of Asp76Asn β2-microglobulin: roles of shear flow, hydrophobic surfaces and α crystallin. *J Biol Chem* 288:30917-30930, 2013.

10. Valleix, S., Gillmore, J.D., Bridoux, F., Mangione, P.P., Dogan, A., Nedelec, B., Boimard, M., Touchard, G., Goujon, J.M., Lacombe, C., Lozeron, P., Adams, D., Lacroix, C., Maisonobe, T., Planté-Bordeneuve, V., Vrana, J.A., Theis, J.D., Giorgetti, S., Porcari, R., Ricagno, S., Bolognesi, M., Stoppini, M., Delpech, M., Pepys, M.B., Hawkins, P.N., **Bellotti, V**. Hereditary systemic amyloidosis due to Asp76Asn variant β2-microglobulin. *New Engl J Med* 366:2276-2283, 2012.

PUBLICATION SUMMARY AND BIBLIOMETIC INDEXES. Full articles on peer reviewed journals: **183**. H-Index: **46** (Scopus). Total citations: **8915** (Scopus).