

BIOGRAPHICAL SKETCH

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NAME: Annamaria Vezzani

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

POSITION TITLE: Professor

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
General Certificate of Education, Italy	BA	1974	
University of Milan, Italy	Biol Sci Dr	1978	Biological Sciences
Mario Negri Institute, Milan, Italy	Biol Sci Dr	1979-1981	Neuropharmacology
University of Stockholm, Sweden	Post doc	1982	Neurochemistry
Maryland Psychiatric Res. Ctr. Univ. Maryland, MD, US	Post doc	1983-1984	Experimental Neurology

A. Personal Statement

The current research relates to the neurobiology of CNS diseases by covering neuroscience, neuropharmacology and neuroimmunology. More specifically, the laboratory studies with multidisciplinary approaches the molecular, structural, epigenetic and functional modifications in the brain potentially involved in the etiopathogenesis of seizures and the associated neurological co-morbidities. The research is focused on neuroactive inflammatory mediators, an hallmark of human epileptogenic brain tissue, and molecules apt to resolve neuroinflammation using adult and developmental models of epilepsy. We especially address acquired forms of epilepsy using *in vivo* and *in vitro* experimental models. Our research programme includes the preclinical discovery and clinical validation of novel predictive and prognostic biomarkers of epilepsy using noninvasive measures such as detection of blood molecules, MRI-based imaging and electrophysiological signatures. Using animal models we are developing novel target-specific disease-modifying drugs with the ultimate scope of translating the laboratory findings to the clinical applications.

1. **Vezzani A**, French J, Bartfai T, Baram TZ (2010) The role of inflammation in epilepsy. **Nature Rev Neurol.** 7:31-40 PMID:21135885
2. Nabbut R, **Vezzani A**, Dulac O, Chiron C (2011) Acute encephalopathy with inflammation-mediated status epilepticus. **Lancet Neurol.** 10:99-108 PMID:21163447
3. Baron R, Ferriero DM, Frisoni GB, Bettegowda C, Gokaslan ZL, Kessler JA, **Vezzani A**, Waxman SG, Jarius S, Wildemann B, Weller M. (2015) Neurology-the next 10 years. **Nat Rev Neurol**, 11:658-64. PMID:26503922.

B. Positions and Honors

1985-1988 Senior Researcher at the Neuropharmacology Department, Mario Negri Institute for Pharmacological Research, Milan, Italy

1989-1997 Chief of the Unit of "Excitatory amino acids and neurodegenerative disorders", Laboratory of Neuropharmacology, Mario Negri Institute for Pharmacological Research, Milan

1997-present Head of the Laboratory of Experimental Neurology, Mario Negri Institute for Pharmacological

Other Experience and Professional Memberships

2006-2009 Chair of the Commission on Neurobiology of International League Against Epilepsy (ILAE)

2006-2013 Associate Editor of *Epilepsia* for Basic Science

2013-2017 Member of the Commission of European Affairs of the ILAE

Past Member of the Benchmark Stewards AES and Translational Task Force of ILAE/AES

Current Member of the Research & Training Committee of American Epilepsy Society (AES)

Current Member of the Editorial Board *Epilepsy Res, Neuroscience, Epilepsy & Treatments; Neurobiol Dis*

Honors

1995 Recipient of the award for the best paper presentation at the 5th European Neuropeptide Club Meeting, Lund, Sweden, June 5, 1995

2002 Recipient of the John & Barbara Heffer Travel Fund Award, American Epilepsy Society, USA

2009 Recipient of the AES Recognition Award for Basic Science (translational research), 64th Annual AES meeting, Boston

2010 Recipient of the recognition "Alfabeto delle Prime Donne" by the Comune di Milano, Sindaco Letizia Moratti, March 8th 2010

C. Contributions to Science

Since the early '90, I pioneered research in the field of neuropeptides as modulators of epileptic phenomena. I discovered in collaboration with Gunther Sperk (University of Innsbruck) important aspects of the plasticity of somatostatin-, neuropeptide Y- and galanin-containing neurons, and their receptors, in experimental models and in human epileptic brain. These studies emphasized neuropeptides ability to affect synaptic transmission in diseased conditions and in modulating hyperexcitability of neuronal networks. We provided the first evidence of the powerful anticonvulsive actions of neuropeptide Y and somatostatin *in vivo* using peptide agonists, transgenic rats and knock-out mice, or viral vectors mediating neuropeptide overexpression in specific brain regions. *These studies contributed to the concept that the molecular plasticity of endogenous neuropeptide systems plays a crucial role in the termination of epileptic activity.* I initiated preclinical investigations on gene therapy approaches to epilepsy using viral vectors to induce the overexpression of neuropeptide Y and galanin in epileptic rat brain, thus *establishing, the proof-of-principle that gene therapy approaches may be a feasible alternative to epilepsy surgery* in drug-resistant temporal lobe epilepsy.

1. **Vezzani A**, Civenni G, Rizzi M, Monno A, Messali S, Samanin R. (1994) Enhanced neuropeptide Y release in the hippocampus is associated with chronic seizure susceptibility in kainic acid treated rats. **Brain Res.** 660:138-43. PMID:7827990
2. **Vezzani A**, Schwarzer C, Lothman EW, Williamson J, Sperk G. (1996) Functional changes in somatostatin and neuropeptide Y containing neurons in the rat hippocampus in chronic models of limbic seizures. **Epilepsy Res.** 26:267-79. PMID:8985706
3. Richichi C, Lin EJ, Stefanin D, Colella D, Ravizza T, Grignaschi G, Veglianesi P, Sperk G, During MJ, **Vezzani A**. (2004) Anticonvulsant and antiepileptogenic effects mediated by adeno-associated virus vector neuropeptide Y expression in the rat hippocampus. **J Neurosci.** 24:3051-9. PMID:8985706
4. El Bahh B, Balosso S, Hamilton T, Herzog H, Beck-Sickinger AG, Sperk G, Gehlert DR, **Vezzani A**, Colmers WF. (2005) The anti-epileptic actions of neuropeptide Y in the hippocampus are mediated by Y2 and not Y5 receptors. **Eur J Neurosci.** 22:1417-30. PMID:16190896
5. Noè F, Pool AH, Nissinen J, Gobbi M, Bland R, Rizzi M, Balducci C, Ferraguti F, Sperk G, During MJ, Pitkänen A, **Vezzani A**. (2008) Neuropeptide Y gene therapy decreases chronic spontaneous seizures in a rat model of temporal lobe epilepsy. **Brain** 131:1506-15. PMID:18477594

Since 1999, I begun intensive studies on the role of pro-inflammatory cytokines in the development of seizures. The results showed that epileptogenic injuries and recurrent seizures provoke extensive neuroinflammation in brain, and the consequent activation of specific inflammatory processes, such as the IL-1 β -IL-1R1 and High Mobility Group Box 1(HMGB1)-TLR4 axis, contribute significantly to increasing neuronal excitability, decreasing seizure threshold and promoting seizure-induced neuronal damage. Additional studies found that seizure-induced inflammation is developmentally regulated and could play a role in the age-dependent onset of

seizure-related neuropathology, and that IL-1beta is an important contributor to the threshold for febrile seizures in experimental models. I showed, together with Eleonora Aronica (Academic Medical Center, Amsterdam), that the IL-1beta- and HMGB1-related signaling are overexpressed in glia and neurons in epileptogenic human tissue. This novel evidence highlights previously unknown mechanisms involved in seizures, which can be relevant both for pediatric and adult epilepsy, and may be targeted for developing new treatments.

1. **Vezzani A**, Conti M, De Luigi A, Ravizza T, Moneta D, Marchesi F, De Simoni MG. (1999) Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. **J Neurosci.** 19:5054-65. PMID:10366638
2. Dube' C, **Vezzani A**, Behrens M, Bartfai T, Baram TZ. (2005) Interleukin-1beta contributes to the generation of experimental febrile seizures. **Ann Neurol**, 57:152-5. PMID:15622539
3. Balosso S, Maroso M, Sanchez-Alavez M, Ravizza T, Frasca A, Bartfai T, **Vezzani A**. (2008) A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. **Brain**, 131: 3256-65. PMID:18952671
4. Ravizza T, Gagliardi B, Noé F, Boer K, Aronica E, **Vezzani A**. (2008) Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. **Neurobiol Dis.** 29:142-60. PMID:17931873
5. Maroso, M, Balosso, S, Ravizza T, Liu, J, Aronca, E, Iyer, AM, Rossetti, C, Molteni, M, Casalgrandi, M, Manfredi, AA, Bianchi, ME, **Vezzani A** (2010) Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. **Nature Med**, 16:413-9. PMID:20348922

The new knowledge about the involvement of neuroinflammation in seizure mechanisms and possibly epileptogenesis was reinforced by our pharmacological and functional evidence that interference with these mechanisms mediates therapeutic effects in animal models.

1. **Vezzani A**, Moneta D, Conti M, Richichi C, Ravizza T, De Luigi A, De Simoni MG, Sperk G, Andell-Jonsson S, Lundkvist J, Iverfeldt K and Bartfai T. (2000) Powerful anticonvulsant action of IL-1 receptor antagonist upon intracerebral injection and astrocytic overexpression in mice. **Proc. Natl. Acad. Sci. USA**, 97: 11534-9. PMID:11016948
2. Ravizza T, Lucas SM, Balosso S, Bernardino L, Ku G, Noé F, Malva J, Randle JC, Allan S, **Vezzani A**. (2006) Inactivation of caspase-1 in rodent brain: a novel anticonvulsive strategy. **Epilepsia**. 47:1160-8. PMID:16886979
3. Maroso M, Balosso S, Ravizza T, Iori V, Wright CI, French J, **Vezzani A**. (2011) Interleukin-1 β biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice. **Neurotherapeutics**, 8:304-15. PMID:21431948
4. Iori V, Iyer AM, Ravizza T, Beltrame L, Paracchini L, Marchini S, Cerovic M, Hill C, Ferrari M, Zucchetti M, Molteni M, Rossetti C, Brambilla R, Steve White H, D'Incalci M, Aronica E, **Vezzani A** (2017). Blockade of the IL-1R1/TLR4 pathway mediates disease-modification therapeutic effects in a model of acquired epilepsy. **Neurobiol Dis.** 99:12-23 PMID: 27939857
5. Pauletti A, Terrone G, Shekh-Ahmad T, Salamone A, Ravizza T, Rizzi M, Pastore A, Pascente R, Liang LP, Villa BR, Balosso S, Abramov AY, van Vliet EA, Del Giudice E, Aronica E, Antoine DJ, Patel M, Walker MC, **Vezzani A** (2017). Targeting oxidative stress improves disease outcomes in a rat model of acquired epilepsy. **Brain**. 140(7):1885-1899 PMID: 28575153
6. Terrone G, Pauletti A, Salamone A, Rizzi M, Villa BR, Porcu L, Sheehan MJ, Guilmette E, Butler CR, Piro JR, Samad TA, **Vezzani A**. (2018) Inhibition of monoacylglycerol lipase terminates diazepam-resistant status epilepticus in mice and its effects are potentiated by a ketogenic diet. **Epilepsia**. 59:79-91

I also contributed to unveil the role of the blood brain barrier (BBB) in the mechanisms of pharmacoresistance in epilepsy, and to characterize the changes in BBB permeability properties as a contributing factor to seizures and epileptogenesis.

1. Rizzi M, Caccia S, Guiso G, Richichi C, Gorter JA, Aronica E, Aliprandi M, Bagnati R, Fanelli R, D'Incalci M, Samanin R, **Vezzani A**. (2002) Limbic seizures induce P-glycoprotein in rodent brain: functional implications for pharmacoresistance. **J Neurosci.** 22:5833-9. PMID:12122045

2. Marchi N, Guiso G, Caccia S, Rizzi M, Gagliardi B, Noé F, Ravizza T, Bassanini S, Chimenti S, Battaglia G, **Vezzani A**. (2006) Determinants of drug brain uptake in a rat model of seizure-associated malformations of cortical development. **Neurobiol Dis**. 24:429-42. PMID:17027274
3. Marcon J, Gagliardi B, Balosso S, Maroso M, Noé F, Morin M, Lerner-Natoli M, **Vezzani A**, Ravizza T. (2009) Age-dependent vascular changes induced by status epilepticus in rat forebrain: implications for epileptogenesis. **Neurobiol Dis**. 34:121-32. PMID:19320047
4. Librizzi L, Noè F, **Vezzani A**, de Curtis M, Ravizza T. (2012) Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. **Ann Neurol**. 72:82-90. PMID:22829270
5. Weissberg I, Wood L, Kamintsky L, Vazquez O, Milikovsky DZ, Alexander A, Oppenheim H, Ardizzone C, Becker A, Frigerio F, **Vezzani A**, Buckwalter MS, Huguenard JR, Friedman A, Kaufer D. (2015) Albumin induces excitatory synaptogenesis through astrocytic TGF- β /ALK5 signaling in a model of acquired epilepsy following blood-brain barrier dysfunction. **Neurobiol Dis**. 78:115-25 PMID:25836421

We discovered a potential novel molecular and mechanistic biomarker of epilepsy, namely the inflammatory mediator High Mobility group Box 1 (HMGB1), that is involved in seizure generation and predicts the therapeutic response to drugs and the development of epilepsy, or seizure relapse, both in *in vivo* rodent models of acquired epilepsy, and in pharmaco-resistant patients.

1. Walker LE, Frigerio F, Ravizza T, Ricci E, Tse K, Jenkins RE, Sills GJ, Jorgensen A, Porcu L, Thippeswamy T, Alapirtti T, Peltola J, Brodie MJ, Park BK, Marson AG, Antoine DJ, **Vezzani A**, Pirmohamed M. Molecular isoforms of high-mobility group box 1 are mechanistic biomarkers for epilepsy. *J Clin Invest*. 2017 Jun 1;127(6):2118-2132. PMID: 2850464; * shared last co-authorship

We described noninvasive imaging (magnetic resonance spectroscopy) and behavioral cognitive deficit features which are predictive of epilepsy development after experience of an epileptogenic risk factor in animal models.

1. Filibian M, Frasca A, Maggioni D, Micotti E, **Vezzani A**, Ravizza T. (2012) In vivo imaging of glia activation using 1H-magnetic resonance spectroscopy to detect putative biomarkers of tissue epileptogenicity. *Epilepsia*. 53:1907-16. PMID: 23030308
2. Pascente R, Frigerio F, Rizzi M, Porcu L, Boido M, Davids J, Zaben M, Tolomeo D, Filibian M, Gray WP, **Vezzani A**, Ravizza T. Cognitive deficits and brain myo-Inositol are early biomarkers of epileptogenesis in a rat model of epilepsy. *Neurobiol Dis*. 2016; 93:146-55. PMID: 27173096

Complete List of Published Work since 1982 until 2017 in:

<https://moh-it.pure.elsevier.com/en/persons/annamaria-vezzani/publications/>

Total number of citations 14913, h-index= 66

Patent Citations

Treating seizures using ICE inhibitors Conf No. 3896 (serial No 11/130,659), Docket No VPI/04-120 US, Filed May 16 2005