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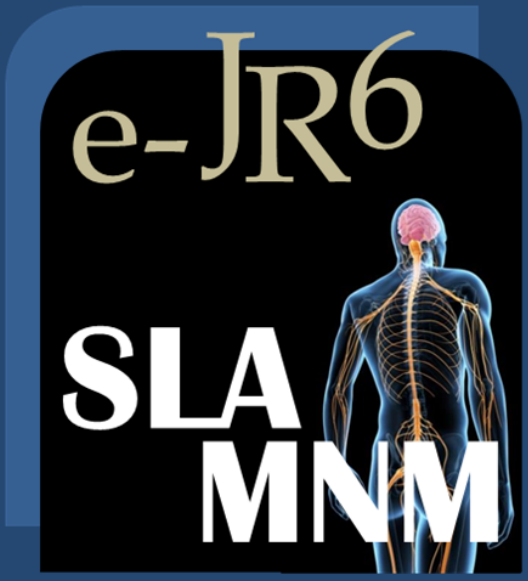
Filière de Santé Maladies Rares Sclérose Latérale Amyotrophique et Maladies du Neurone Moteur

filière de santé maladies rares

ARSLA
Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres Maladies du Motoneurone

6èmes Journées de la Recherche sur la SLA et les Maladies du Neurone Moteur

Programme et résumés des communications



21 et 22 Octobre 2020

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Devenues un rendez-vous incontournable des chercheurs français et francophones, les Journées Recherche, organisées tous les ans par la Filière de Santé FilSLAN en partenariat avec l'ARSLA autour la mi-octobre, arrivent en 2020 à leur 6° édition (JR6 FilSLAN/ARSLA). Elles unissent des objectifs de partage et d'actualisation des connaissances scientifiques dans le thème de la SLA. Traditionnellement organisées dans les locaux de l'ICM à Paris, elles ont cette année, crise COVID oblige, un contexte moins propice aux échanges puisqu'elles se déroulent en un format virtuel numérique, chacun derrière son ordinateur, mais la technologie moderne permet néanmoins des interactions à distance. Elles réunissent de l'ordre de 150 à 200 chercheurs institutionnels et cliniciens, plus de 50 équipes de recherche nationales sont représentées.
Elles démontrent la dynamique croissante de la recherche nationale sur le thème de la SLA. Les sessions scientifiques et posters, sont l'occasion stimulante pour de jeunes chercheurs de faire connaitre l'avancée de leurs travaux. Quatre communications sont récompensées par un prix ARSLA Jeunes Chercheurs après sélection par un jury émanant de son Conseil Scientifique.
Une caractéristique évolutive cette année : un grand nombre de communications sur le thème des traitements ou des pistes potentiellement prometteuses.

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HÄNDELSE
Organisation événementielle

Numéro d'agrément formateur : 11 75 17 79 875

SOMMAIRE

PROGRAMME

MERCREDI 21 OCTOBRE 2020

9h30 : Ouverture

Anne Sophie Lapointe (Cheffe de projet adjointe Mission Maladies Rares DGOS)
Valérie Goutines (Présidente ARSLA)
Claude Desnuelle (Animateur FILSLAN)

10h00 SESSION 1 : GENETIQUE ET MECANISMES MOLECULAIRES DES MALADIES DU NEURONE MOTEUR
MODERATION : *Severine Boillée (Paris), Frédérique René (Strasbourg)*

- **C1-Conférence : EVALUATION DE L'HYPOTHESE CORTICOFUGE DANS LA SLA**
  Caroline Rouaux
  Inserm U1118, Faculté de Médecine, Strasbourg – France

- **Présentations sélectionnées dans le thème de la session à partir de l'appel à communications**
  (10 minutes + 5 minutes de discussion)

PO1.1 – DE NOUVELLES MUTATIONS DANS LE GENE *ANXA11* ALTERENT LA STABILITE ET INDUISENT L'AGREGATION DE L'ANNEXINE A11 CHEZ DES PATIENTS ATTEINTS DE SCLEROSE LATERALE AMYOTROPHIQUE

Muratet F (1), Teyssou E (1)*, Amador MdM (1,2), Ferrien M (1), Lautrette G (3), Machat S (3), Boillée S (1), Larmonier T (4), Saker S (4), Leguern E (1,5), Cazeneuve C (5), Marie Y (1), Guegan J (1), Gyorgy B (1), Cintas P (6), Meininger V (7), Le Forestier N (2,8), Salachas F (1,2), Couratier P (3), Camu W (9), Seilhean D (1,10)*, Millecamps S (1)**

(1) Institut du Cerveau et de la Moelle épinière, ICM, Inserm U1127, CNRS UMR7225, Sorbonne Université, UPMC Univ Paris 6 UMRS1127, 75013 Paris, France ; (2) Département de Neurologie, Assistance Publique Hôpitaux de Paris (APHP), Centre de référence SLA Ile de France, Hôpital de la Pitié-Salpêtrière, 75013 Paris, France ; (3) Service de Neurologie, Centre de Référence SLA et autres maladies du neurone moteur, CHU de Limoges, 87000 Limoges, France ; (4) Banque d'ADN et de cellules du Généthon, 91000 Evry, France ; (5) Département de Génétique et Cytogénétique, Unité Fonctionnelle de neurogénétique moléculaire et cellulaire, APHP, Hôpital Pitié-Salpêtrière, 75013 Paris ; (6) Département de Neurologie, Centre de référence SLA, CHU de Toulouse, 31000 Toulouse ; (7) Hôpital des Peupliers, Ramsay Générale de Santé, 75013 Paris, France ; (8) Département de recherche en éthique, EA 1610, Etudes des sciences et techniques, Université Paris Sud/Paris Saclay, 91400 Orsay, France ; (9) Centre de référence SLA, Hôpital Gui de Chauliac, CHU et Université de Montpellier, 34000 Montpellier ; (10) Département de Neuropathologie, APHP, Hôpital Pitié-Salpêtrière, 75013 Paris, France.
*Equal contribution

PO1.2 - ETUDE DES EFFETS DE LA DELOCALISATION CYTOPLASMIQUE DE FUS DANS LES NEURONES ADULTES

Cassel R (1), Lorenc F (1), Dieterle S (1), De Tapia C (1), Goy M-A (1) et Dupuis L (1)

(1) INSERM U1118 « Mécanismes centraux et périphériques de la neurodégénérescence » Strasbourg, France

PO1.3 - DEVELOPMENT AND CHARACTERIZATION OF IN VITRO MODELS TO TEST THE EFFICIENCY OF GENE THERAPY APPROACHES IN *SOD1*-LINKED AMYOTROPHIC LATERAL SCLEROSIS

Delamare M (1), Elouej S (1), Bigot A (1), M. Cappella M (1), and Biferi MG (1)

(1) Center of Research in Myology - Sorbonne Université - INSERM U974 - Association Institut de Myologie (AIM). Faculté de Médecine, 105 Bd de l'Hôpital, 75013 Paris.

PO1.4 - PREMATURE TERMINATION CODONS IN *SOD1* CAUSING ALS ARE PREDICTED TO ESCAPE THE NONSENSE-MEDIATED MRNA DECAY

Guissart C (1,2), Mouzat K (1,2), Kantar K (1,2), Polge A (1), Raoul C (2) and Lumbroso S (1,2)

(1) Laboratoire de Biochimie et Biologie Moléculaire, CHU Nimes, Univ. Montpellier, Nimes, France, (2) The Neuroscience Institute of Montpellier, INM, INSERM, Univ. Montpellier, Montpellier, France.

PO1.5 - ZEBRAFISH MODEL AS A FUNCTIONAL TOOL TO ANALYSE PATHOGENICITY OF *SOD1* GENE VARIANTS

Chudinova A (1), Rossel M (2), Pittion S (3), Bernard E (4), Le-Masson G (5), Camu W (6), Raoul C (7), Lumbroso S (1), Mouzat K (1)

(1) Service de Biochimie et Biologie Moléculaire, CHU Nîmes, Nîmes, France, Motoneuron Disease: Pathophysiology and Therapy, INM, Univ. Montpellier, Montpellier ; (2) MMDN, Univ. Montpellier, EPHE, INSERM, U1198, PSL Research University, Montpellier, F-34095 France ; (3) Service de Neurologie, CHU de Nancy, Nancy, France ; (4) Centre SLA de Lyon, Hôpital neurologique P. Wertheimer, Hospices Civils de Lyon, Université de Lyon, Lyon, France, Institut NeuroMyoGène, CNRS UMR5310, INSERM U1217, Faculté de Médecine Rockefeller, Université Claude Bernard Lyon I, 8 Avenue Rockefeller, 69373, Lyon Cedex 08, France ; (5) Department of Neurology, Nerve-Muscle Unit and Centre de Référence Des Pathologies Neuromusculaires CHU Bordeaux (Groupe Hospitalier Pellegrin), University of Bordeaux, Place Amélie Raba-Léon, Bordeaux, France ; (6) ALS Center, Département de Neurologie, CHU Gui de Chauliac, Montpellier, France, Motoneuron Disease: Pathophysiology and Therapy, INM, Univ. Montpellier, Montpellier ; (7) Motoneuron Disease: Pathophysiology and Therapy, INM, Univ. Montpellier, Montpellier, France

PO1.6 - DYSFONCTIONNEMENTS DE LA MEMOIRE CHEZ LES SOURIS $FUS^{\Delta NLS/+}$ ET MODIFICATIONS EPIGENETIQUES ET TRANSCRIPTOMIQUES ASSOCIEES.

Tzeplaeff L (1,2), Seguin J (1), Cosquer B (1), Merienne K (1), LeGras S (3), Plassard D (3), Cassel JC (1), Dupuis L (2), Boutillier AL (1)

(1) LNCA, CNRS UMR 7364, Université de Strasbourg, Strasbourg, France (2) Inserm, UMR-S1118, Université de Strasbourg, Strasbourg, France ; (3) IGBMC, Plateforme GenomEast, Illkirch-Graffenstaden, France

12h00 SESSION POSTERS 1
Les présentateurs sont tenus d'être connectés à la réunion et prêts à être contactés

13h30 SESSION 2 : BIOMARQUEURS ET THERAPIES DANS LES MALADIES DU NEURONE MOTEUR
MODERATION : *Philippe Corcia (Tours), Stéphanie Duguez (Londonderry)*

- **C2-Conférence : REVISITING STUDY DESIGN IN ALS CLINICAL TRIALS**
  Leonard Van Den Berg
  UMC Utrecht Brain Centre, University Medical Centre Utrecht, The Netherlands

- **Présentations sélectionnées dans le thème de la session à partir de l'appel à communications**
  (10 minutes + 5 minutes de discussion)

PO2.1 - SPINAL CORD MRI FOR THE DESCRIPTION OF THE LONGITUDINAL EVOLUTION OF PRESYMPTOMATIC PATHOLOGY IN *C9ORF72* MUTATION CARRIERS: A THREE TIME-POINT STUDY.

Querin G (1,2,3), MD; PhD; Bede P(4), MD, PhD; Pellegrini-Issac M (5), PhD; Rinaldi D (6,7), PhD; Catala M (8), MD, PhD; Saracino D (6,7), MD; Salachas F (9), MD; Camuzat A (6), PhD; Marchand-Pauvert V (5), PhD; Cohen-Adad J (10), PhD; Colliot O (6,11,12), PhD; Le Ber I (6,7), MD, PhD; Pradat PF (5,9,13), MD, PhD; for the Predict to Prevent Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis (PREV-DEMALS) Study Group.

(1) APHP, Service de Neuromyologie, Hôpital Pitié-Salpêtrière, Paris, France ; (2) Institut de Myologie, Plateforme I-Motion Adultes, Paris, France ; (3) Sorbonne Université, Inserm UMRS 974, Centre of Research in Myology (CRM), Institut de Myologie, GH Pitié Salpêtrière, 75013 Paris, France ; (4) Computational Neuroimaging Group, Academic Unit of Neurology, Trinity College Dublin, Dublin, Ireland ; (5) Laboratoire d'Imagerie Biomédicale, CNRS, INSERM, Sorbonne Université, Paris, France ; (6) Institut du Cerveau et de la Moelle Épinière, Sorbonne Université, INSERM U1127, CNRS UMR 7225, Hôpital Pitié-Salpêtrière, Paris, France ; (7) Institute of Memory and Alzheimer's Disease, Center of Excellence of Neurodegenerative Disease, Sorbonne University, APHP, Département de Neurologie, Centre Référent SLA, Hôpital Pitié-Salpêtrière, Paris, France ; (8) APHP, Département de Neurologie, Hôpital Pitié-Salpêtrière, Sorbonne Université, CNRS UMR7622, INSERM ERL 1156, IBPS, Paris, France ; (9) APHP, Service de Neurologie, ALS Reference Center, Hôpital Pitié-Salpêtrière, Paris, France ; (10) NeuroPoly Lab, Institute of Biomedical Engineering, Polytechnique Montreal, Montreal, QC, Canada; Functional Neuroimaging Unit, CRIUGM, Université de Montreal, Montreal, QC, Canada ; (11) Aramis Project Team, Inria Research Center of Paris, Paris, France ; (12) Centre pour l'Acquisition et le Traitement des Images, Institut du Cerveau et de la Moelle Épinière, Paris, France ; (13) Northern Ireland Centre for Stratified Medicine, Biomedical Sciences Research Institute Ulster University, C-TRIC, Altnagelvin Hospital, Londonderry, United Kingdom.

PO2.2 - AB1-42 AND TAU AS POTENTIAL BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

Lanznaster D (1), Hergesheimer RC (1), Bakkouche SE (2), Beltran S (2), Vourc'h P (1,3), Andres CR (1,3), Dufour-Rainfray D (1,4), Corcia P (1,2), Blasco H (1,4)

(1) UMR 1253, iBrain, University of Tours, Inserm, Tours 37000, France ; (2) Centre Constitutif SLA, CHRU Bretonneau, Tours 37000,

France (3) CHU Tours, Service de Biochimie et Biologie Moléculaire, Tours 37000, France ; (4) CHU Tours, Service de MNIV, Tours 37000, France.

PO2.3 - MOLECULAR SCREENING OF FDA-APPROVED DRUGS IN HUMAN PLURIPOTENT STEM CELLS FOR THE TREATMENT OF RARE MONOGENIC DISEASES.

Gide J (1), Roussange F (2), Polvèche H (1), Auboeuf (3), Boland A (4), Deleuze JF (4), Cailleret M (2), Kabashi E (5), Peschanski M (1), Martinat C (2) and Baghdoyan S (2)

(1) CECS I-STEM, Corbeil-Essonnes ; (2) U861 INSERM, I-STEM, Corbeil-Essonnes, France ; (3) Laboratoire de Biologie et Modélisation de la Cellule, ENS de Lyon, France ; (4) CEA/Centre National de Génotypage, Evry, France ; (5) Institut Imagine, Paris, France

PO2.4 - THE UTILIZATION OF INTRABODIES FOR THE DEVELOPMENT OF THERAPEUTICS TARGETING PROTEIN AGGREGATION IN ALS

Hergesheimer R (1), Chami A (1), Haouari S (1), Martineau P (4), Vourc'h P (1,2), Andres C (1,2), Corcia P (1,3), Lanznaster D (1), Blasco H (1,2)

(1) UMR 1253, iBRAIN, Université de Tours, INSERM, Tours, France ; (2) CHU de Tours, Service de Biochimie et Biologie Moléculaire, Tours, France ; (3) CHU de Tours, Service de Neurologie, Tours, France ; (4) UMR 1194, IRCM, INSERM, Montpellier, France

PO2.5 - AAV-MEDIATED EXPRESSION OF ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF C9ORF72-FALS

Cappella M (1), Peche A (1), Giroux B (1), Cuandros Gamboa AL (1), Bigot A (1), Liu E (2), Bohl D (2), Biferi MG (1)

(1) Center of Research in Myology - Sorbonne Université - INSERM U974 - Association Institut de Myologie (AIM). Faculté de Médecine, 105 Bd de l'Hôpital, 75013 Paris ; (2) Institute for Brain and Spinal Cord - Sorbonne Université - INSERM U1127 – CNRS U7225. 47 Boulevard de l'Hôpital, 75013 Paris 02

PO2.6 - INHIBITION OF β-OXIDATION: A PROMISING THERAPEUTIC APPROACH FOR ALS.

Quessada C (1,2), Bouscary A (1,2), Ferri A (3), Valle C (3,4), Ngo ST (5,6,7), Loeffler JP (1,2), René F (1,2)

(1) Université de Strasbourg, UMR_S 1118, Fédération de Médecine Translationnelle, Strasbourg, France ; (2) INSERM, U1118, Mécanismes Centraux et Périphériques de la Neurodégénérescence, Strasbourg, France ; (3) Institute of Cell Biology and Neurobiology, CNR, Rome, Italy ; (4) IRCCS Fondazione Santa Lucia, Rome, Italy ; (5) Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD, Australia ; (6) Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia ; (7) Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia.

15h30 SESSION ARSLA

Organisation : *William Camu (Président du CS ARSLA)*

Modération *: Chantal Sellier (Strasbourg), Gwendal Le Masson (Bordeaux)*

- **Sélection de présentations sur projets de recherche financés par l'ARSLA.**
  (10 min + 5 minutes discussion)

POA1 – MODIFYING MACROPHAGES AT THE PERIPHERY HAS THE CAPACITY TO INCREASE ALS SURVIVAL

Chiot A (1), Zaïdi S (1), Iltis C (1), Ribon M (1), Berriat F (1), Schiaffino L (1 ,2), Jolly A (3), de la Grange P (3), Michel Mallat (1), Bohl D (1), Millecamps S (1), Seilhean D (1, 4), Lobsiger CS (1), Boillée S (1)

(1) Institut du Cerveau, ICM, Inserm U1127, CNRS UMR7225, Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France ; (2) Department of Neurological, Biomedical and Movement Science; University of Verone; Strada Le Grazie 8-37134 Verone, Italy ; (3) Genosplice, Paris, France. (4) Département de Neuropathologie, APHP, Hôpital Pitié-Salpêtrière, F-75013 Paris, France

POA2 – REDUCED AUTOPHAGY UPON C9ORF72 LOSS SYNERGIZES WITH DPR PROTEIN TOXICITY IN CELL MODELS OF ALS.

Boivin M (1), Pfister V (1), Gaucherot A (1), Ruffenach F (1), Negroni L (1), Sellier C (1), Charlet-Berguerand N (1)

(1) IGBMC, INSERM U1258, CNRS UMR7104, Université de Strasbourg, 67400 Illkirch, France

POA3 – SLA ET HOMEOSTASIE DES PROTEINES : FOCUS SUR LA SUMOYLATION

Dangoumau A (1), Maurel C (1), Chami A (1), Veyrat-Durebex C (1,2), Beltran S (1), Blasco H (1,2), Andres C (1,2), Corcia P (1,3), Vourc'h P (1,2)

(1) UMR 1253 iBrain, Université de Tours, Inserm, Tours (France) ; (2) Service de Biochimie et Biologie moléculaire, CHRU de Tours, Tours (France) ; (3) Service de Neurologie, Centre SLA, CHRU de Tours, Tours (France)

POA4 – LES STRATEGIES DE CHELATION CONSERVATRICE DU FER ET ANTI-FERROPTOTIQUES POURRAIENT-ELLES CONDUIRE A UNE NEUROPROTECTION DANS LA SCLEROSE LATERALE AMYOTROPHIQUE ?

Gouel F (1), Raoul C (2), Danel V (3), Timmerman K (1), Jonneaux A (1), Pleuvret M (3), Petrault M (1), Laloux C (1), Dutheil M (1), Bouchaoui H (1), Mahoney L (1), Kuchcinski G (4), Betrouni N (1), Viard R (4), Lopes R (4), Auger F (5), Huin V (6), Garçon G (7), Moreau C (3), Duce J (8), AS Rolland (1), Devedjian JC (1), Devos D (1,3)

(1) Département de Pharmacologie Médicale, Université de Lille, CHU-Lille, Inserm, Lille Neuroscience & Cognition, UMR-S1172 Centre COEN LICEND, I-SITE ULNE, Lille, France ; (3) Département de Neurologie, Centre ALS, Université de Lille, CHU-Lille, Inserm, Lille Neuroscience & Cognition, UMR-S1172 Centre COEN LICEND, I-SITE ULNE, Lille, France ; (4) Département de Neuroradiologie, Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 - UMS 2014 - PLBS, F-59000 Lille, France ; (5) Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 - UMS 2014 - PLBS - Plateforme d'imagerie du vivant et fonctions, F-59000 Lille, France ; (6) Univ. Lille, Inserm, CHU-Lille, Lille Neuroscience & Cognition, UMR-S1172, Team Alzheimer & Tauopathies, F-59000 Lille, France ; (7) Université de Lille, CHU Lille, Institut Pasteur de Lille, EA 4483 IMPECS-IMPact de l'Environnement Chimique sur la Santé humaine, France Université de Lille, CHU Lille, EA 2694- Santé publique : épidémiologie et qualité des soins, Lille, France ; (8) Alzheimer's Research UK Cambridge Drug Discovery Institute, University of Cambridge, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0AH, UK

POA5 – SPINAL MOTONEURON TMEM16F ACTS AT C-BOUTONS TO MODULATE MOTOR RESISTANCE AND CONTRIBUTES TO ALS PATHOGENESIS.

Soulard C (1), Salsac C (1), Mouzat K (1,2), Hilaire C (1), Roussel J (1), Mezghrani A (1), Lumbroso S (1,2), Raoul C (1), Scamps F (1)

(1) Inserm UMR1051, Institut des Neurosciences Montpellier, Université Montpellier, Montpellier, France ; (2) Laboratoire de Biochimie et Biologie Moléculaire, CHU Nîmes, Université Montpellier, Nîmes, France.

POA6 – LOW DOSE INTERLEUKIN-2 IN AMYOTROPHIC LATERAL SCLEROSIS IS WELL TOLERATED AND REGULATES MARKERS OF INFLAMMATION IN BLOOD.

Bensimon G (1-3), Veyrune JL (4), Payan CAM (1,2), Suehs C (5), Juntas-Morales R (6), Pageot N (6), Masseguin C (7), Saker S (8), Mickunas M (9,10), Garlanda C (11,12), Locati M (12,13), Malaspina A (14), Andreasson U (15), Kirby J (16), Zetterberg H (15,17-19), Shaw PJ (16), Al-Chalabi A (20,21), Leigh PN (22), Tree T (9,10), De Vos J (4), Camu W (6)

(1) Department of Biostatistics, Clinical Epidemiology, Public Health and Innovation in Methodology (BESPIM), Nîmes University Hospital, Nîmes, France, (2) AP-HP.Sorbonne Université, Pitié-Salpêtrière Hospital, Department of Pharmacology, Paris, France, (3) Sorbonne Université Médecine, Department of Pharmacology, Paris, France, (4) Department for Cell and Tissue Engineering, Univ Montpellier, CHU Montpellier, Montpellier, France, (5) Departments of Medical Information and Respiratory Diseases, Univ Montpellier, CHU Montpellier, Montpellier, France , (6) Clinique du Motoneurone, CHU Gui de Chauliac, Univ Montpellier, Montpellier, France, (7) Delegation for Clinical Research and Innovation, Nîmes University Hospital, Nîmes, France, (8) DNA and Cell Bank, Genethon, Evry, France, (9) Department Immunobiology, Faculty of Life Sciences and Medicine, King's College London, London, UK, (10) NIHR Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK, (11) IRCCS Humanitas Clinical & Research Institute, Milan, Italy, (12) Humanitas University, Pieve Emanuele, Milan, Italy, (13) Department of Medical Biotechnologies and Translational Medicine, University Milan, Milan Italy, (14) Neuroscience and Trauma Centre, Institute of Cell and Molecular Medicine, Neuroimmunology Department, Barts and the London School of Medicine and Dentistry, London, UK, (15) Department of Psychiatry & Neurochemistry, University Gothenburg, Mölndal, Sweden, (16) Sheffield Institute for Translational Neuroscience, Department of Neuroscience, University of Sheffield, Sheffield, UK, (17) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, (18) Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK, (19) UK Dementia Research Institute at UCL, London, UK, (20) King's College London, Institute of Psychiatry Psychology and Neuroscience, Department of Basic and Clinical Neuroscience, London, UK, (21) Department of Neurology, King's College Hospital, London, UK, (22) The Trafford Centre for Biomedical Research, Brighton and Sussex Medical School, Falmer, Brighton, UK

17h00 Conclusions 1ère journée

JEUDI 22 OCTOBRE 2020

9h00 SESSION 3 : PHYSIOPATHOLOGIE DES MALADIES DU NEURONE MOTEUR
MODERATION : *Pierre François Pradat (Paris), Peter Bede (Dublin)*

- **C3-Conférence : LA RELAXATION DES EVENEMENTS SYNAPTIQUES INHIBITEURS PERMET DE COMPENSER LE MANQUE D'INHIBITION AU NIVEAU DES MOTONEURONES FŒTAUX DE LA SOURIS SOD1^{G93A}**

  Pascal Branchereau
  Martin E, Allain AE, Cazenave W, Supiot L, Hodeib F, Laupénie A, Dalvi U, Zhu H, Cattaert D
  Université de Bordeaux, CNRS, INCIA, UMR 5287, Bordeaux - France

- **Présentations sélectionnées dans le thème de la session à partir de l'appel à communications**
  (10 minutes + 5 minutes de discussion)

PO3.1 - L'EXPRESSION DE LA MUTATION SOD1^{G93A} DANS LES MOTONEURONES ET /OU LES MYOTUBES AFFECTE DIFFEREMMENT LA FONCTION NEUROMUSCULAIRE IN VITRO.

Benlefki S (1), Sanchez-Vicente A (1), Milla V (1), Lucas O (1), Soulard C (1), Younes R (1,2), Gergely C (3), Bowerman M (1), Raoul C (1), Scamps F (1), Hilaire C (1)

(1) INM, INSERM U1051, Université de Montpellier, Montpellier, France ; (2) Centre de recherche en Neurosciences, Faculté des Sciences Médicales, Université Libanaise, Beyrouth, Liban ; (3) Lab C. Coulomb, UMR5221 CNRS-UM, Université de Montpellier, Montpellier, France

PO3.2 - LE RECEPTEUR P2X4 DE L'ATP ACTEUR CLE DE LA PATHOGENESE DE LA SLA ET BIOMARQUEUR POTENTIEL

Bertin E (1), Martinez A (1), Fayoux A (2), Fernagut PO (1), Le Masson G (3) Bertrand S.S (2), Boué-Grabot E (1)

(1) Université de Bordeaux, IMN, CNRS UMR 5293, Bordeaux ; (2) Université de Bordeaux, INCIA, CNRS UMR 5287, Bordeaux; (3) Neurocentre Magendie, INSERM U1215, and Centre de référence SLA, CHU de Bordeaux, Bordeaux

PO3.3 - USING HUMAN PLURIPOTENT STEM CELLS DERIVED MOTOR NEURONS TO ADDRESS THE PATHOGENESIS OF SMA

Januel C (1), Tarhaoui J (1), Come J (2), Lesueur L (2), Morizur L (2), Peschanski M (2) and Martinat C (1)

(1) INSERM/UEVE UMR 861, I-STEM (Institute for Stem Cell Therapy and Exploration of Monogenic Diseases), AFM, Evry, France ; (2) CECS, I-STEM, AFM, Evry, France

PO3.4 – MODULATION OF CHOLESTEROL METABOLISM AS A NEW THERAPEUTICAL APPROACH FOR AMYOTROPHIC LATERAL SCLEROSIS

Wurtz G (1), Audouard E (1), Gillet-Legrand B (1), Cartier-Lacave N (1), Piguet F (1)

(1) INSERM U1127, Neurogencell, Paris Brain Institute, Paris

PO3.5 - NUTRITIONAL AND METABOLIC STATUS AT DIAGNOSIS AND SURVIVAL OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND FRONTOTEMPORAL DEMENTIA (FTD) COMPARED TO PATIENTS WITH ALS ALONE.

Jésus P (1,2,3), Fayemendy (1,2,3), Sourisseau H (1), Lautrette G (4), Preux PM (2,3,5), Couratier P (2,3,4), Desport JC (1,2,3)

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PO3.6 - NEURAL CORRELATES OF MOTOR IMAGERY OF GAIT IN AMYOTROPHIC LATERAL SCLEROSIS

Abidi M (1), De Marco G* (1)(2), Grami F (1), Termoz N (1,2) , Couillandre A (1)(2), Querin G (3,4), Bede P (3,4,5), Pradat PF (3,4,6)*

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* contributed equally as first authors.

11h00 C4-CONFÉRENCE : MITOCHONDRIAL DYSFUNCTION IN CHCHD10 RELATED NEURODEGENERATIVE DISEASES

Véronique Paquis Flucklinger

IRCAN Inserm U1081, CNRS UMR7284, UCA, Faculté de médecine, Nice, France - Centre de Référence des Maladies Mitochondriales de l'enfant et de l'adulte, CALISSSON, Service de génétique médicale, Hôpital Archet 2, Nice, France

12h00 SESSION POSTERS 2

Les présentateurs sont tenus d'être connectés à la réunion et prêts à être contactés

13h30 : Annonce des prix ARSLA

Christine Tabuenca (Directrice ARSLA), William Camu (Président du CS ARSLA)

Jury du Comité Scientifique ARSLA : Philippe Couratier (Limoges), Hélène Blasco (Tours), Pascal Branchereau (Bordeaux), William Camu (Président du CS ARSLA)

13h45 TABLE RONDE : CONTINUUM SLA/DFT : CONTROVERSES

MODERATION : *Luc Dupuis (Strasbourg), Philippe Couratier (Limoges)*

Situation du thème : (3 X 20 min, questions intégrées dans le débat)

- ✓ **TR1 - DFT ET DFT/SLA: UNE MEME SYMPTOMATOLOGIE COMPORTEMENTALE ?**

  Pasquier F (1,2), Lebert F (1,2), Danel V (3), Deramecourt V (1,2), Lebouvier T (2)

  (1) Inserm 1172, Labex DistAlz, LiCEND, Unité d'Expertise Cognitive et Motrice, Univ Lille ; (2) Centre de Référence Démence Rares ou Précoces, CHU de Lille ; (3) Centre de Référence SLA/MNM, CHU de Lille

- ✓ **TR2 - TRANSLATION AXONALE ET NEURODEGENERATION SLA/DFT**

  Piol D (1,2), Robberechts T (1,2), Da Cruz S (1,2,3)

  (1) VIB-KU Leuven Center for Brain and Disease Research, Leuven- Belgium ; (2) Department of Neurosciences, KU Leuven, Leuven, Belgium ; (3) Ludwig Institute for Cancer Research, University of California ; San Diego - USA

- ✓ **TR3 - LONGITUDINAL STUDY OF EXTRA-MOTOR MANIFESTATIONS IN AMYOTROPHIC LATERAL SCLEROSIS: CLINICAL AND IMAGING DATA**

  Benbrika S (1), Doidy F (1), Carluer L (1), Mondou A (1), Pélerin A (1), Eustache F (1), Viader F (1), Desgranges B (1)**

  (1) Normandie Univ, UNICAEN, PSL Université Paris, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, Caen, France

  *These authors contributed equally to this work.

Débat avec les participants

16h15 Fin des Journées / Conclusion Générale *(Claude Desnuelle, Animateur FILSLAN)*

Code présentation : C = conférence, PO = présentation orale, TR = table ronde, P = poster

Programme Sessions Posters

P01 : DECIPHERING THE ROLE OF THE ALS-LINKED GENE *TBK1* IN MOTOR NEURONS AND MICROGLIA

Lenoël I (1), Robaldo D (1), Badsi M (1), Philibert C (1), Lameth J (2), Mallat M (2), Brenner D (3), Weishaupt J (3), Bohl D (1), Millecamps S (1), Boillée S (1), Lobsiger CS (1)

(1) Institut du Cerveau - Paris Brain Institute - ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, équipe du Dr. Boillée ; (2) Institut du Cerveau - Paris Brain Institute - ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, équipe des Drs. Huillard et Sanson ; (3) Ulm University, Neurology Department, Germany.

P02 : *FUS* IS REQUIRED FOR MUSCLE ULTRASTRUCTURE AND MITOCHONDRIAL FUNCTION: INVOLVEMENT IN AMYOTROPHIC LATERAL SCLEROSIS

Picchiarelli G (1), Dieterlé S (1), Tueux J (1), Lagier-Tourenne C (3), Demestre M (4), Tzeplaeff L (5), Storkebaum E (2), Boutillier AL (5) Sellier C (1), Dupuis L (1)

(1) INSERM U1118, Mécanismes centraux et périphériques de la neurodégénérescence, Faculté de médecine, Strasbourg, France ; (2) Molecular neurogenetics laboratory, Max-Plank Institute, Muenster, Germany ; (3) Massachussetts General Hospital, Boston USA ; (4) Institute of Molecular and Cellular Anatomy, Ulm, Germany ; (5) Laboratoire de Neurosciences Cognitives et Adaptatives, Strasbourg, France.

P03 : PAS-INDUCED RECOVERY OF INTRACORTICAL INHIBITION IN PATIENTS WITH ALS

Lackmy-Vallée A (1), Peyre I (1,2), Querin G (3,4), Pradat PF (1,5) & Marchand-Pauvert V (1)

(1) Sorbonne Université, Inserm U1146, CNRS UMR 7371, Laboratoire d'Imagerie Biomédicale (LIB), Paris, France ; (2) Sorbonne Université, CNRS, Institut de Recherche et de Coordination en Acoustique Musique (IRCAM), UMR Sciences et Technologies de la Musique et du Son (STMS), Paris, France ; (3) Institut de Myologie, Plateforme I-Motion Adultes, Hôpital de la Pitié Salpêtrière, Paris, France ; (4) Service de Neuromyologie, APHP GH Pitié Salpêtrière, Paris, France ; (5) Département de Neurologie-Pôle des Maladies du Système Nerveux, APHP GH Pitié Salpêtrière, Paris, France.

P04 : ANNULATION

P05 : POTENTIAL MECHANISM OF GLIAL MEDIATED SPREADING OF *SOD1* IN AMYOTROPHIC LATERAL SCLEROSIS

Gosset P, Scamps F, Raoul C, Mezghrani A

The Institute for Neurosciences of Montpellier, Inserm UMR 1051, Univ Montpellier, Saint Eloi Hospital, Montpellier, France

P06 : DETERMINATION DE LA CONTRIBUTION DE L'HYPEREXCITABILITE CORTICALE AU DECLENCHEMENT ET A LA PROGRESSION DE LA SLA

Gilet J (1), Stuart-Lopez G (1), Goutagny R (2) et Rouaux C (1)

(1) Inserm U1118, Faculté de Médecine, Université de Strasbourg, France ; (2) LNCA, CNRS UMR7364, Université de Strasbourg, France

P07 : RECHERCHE DES BASES MOLECULAIRES ET CELLULAIRES DE L'HYPEREXCITABILITE CORTICALE DANS UN MODELE MURIN DE SLA

Brunet A (1), Chavant V (2), Goumon Y (2) et Rouaux C (1)

(1) Inserm U1118, Faculté de médecine, Université de Strasbourg, Strasbourg (France) ; (2) CNRS UPR3212, Institut des Neurosciences Cellulaires et Intégratives, Université de Strasbourg, Strasbourg (France)

P08 : INVESTIGATION INTO THE BIOMAGNIFICATION OF CYANOTOXINS IN THE ENVIRONMENT IN AUSTRALIA AND ITS POTENTIAL CORRELATION WITH NEUROINFLAMMATION AND NEURODEGENERATION MECHANISMS IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

Kazemi Shariat Panahi H. (1), Tan V.X. (1), Guillemin G.J. (1)

(1) MND Research Centre, Department of Biological Sciences, Faculty of Medicine and Health Sciences, Macquarie University, New South Wales, Australia

P09 : PRIMARY CULTURE OF SPINAL MOTOR NEURONS FROM *SOD1*(G93A) TG RAT ARE CHARACTERIZED BY DEFECT IN NEURONAL MATURATION AND HIGHER SENSITIVITY TO GLUTAMATERTIC STRESS.

Henriques A (1), Farrugia C (1), Rouvière L (1), Poindron P (1), Callizot N (1)

(1) Department of pharmacology, Neuro-Sys, Gardanne, France

P10 : TOWARDS ELUCIDATING THE ROLE OF OLIGODENDROCYTES IN FUS-ALS

Jamet M (1), Gonzalez de Aguilar JL(1), Dupuis L. (1)

(1) INSERM U1118: Mécanismes centraux et périphériques de la neurodégénérescence, Faculté de médecine, Strasbourg, France

P11 : TROPHICITE ET TOXICITE DES MACROPHAGES ET DES CELLULES MICROGLIALES HUMAINES ENVERS LES MOTONEURONES DANS LA SLA

Liu E (1), Lefebvre C (1), Ribon M (1), Salachas F (1,2), Lacomblez L (2), Peyrin JM (3), Courte J (3), Lobsiger C (1), Millecamps S (1), Boillée S (1), Bohl D (1)

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P12 : INFLAMMATORY S100A9/MRP14 PROTEIN DEFICIENCY EXACERBATES DISEASE IN *SOD1*G93A MICE.

Ribon M (1), Leone C. (1), Chiot A. (1), Berriat F. (1), Rampanana M. (1), Cottin J. (1), Bohl D. (1), Millecamps S. (1), Lobsiger C.S. (1), Heneka M. (2), Boillée S. (1)

(1) Institut du Cerveau, ICM, Inserm U1127, CNRS UMR7225, Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France ; (2) Department of Neurodegenerative Disease and Gerontopsychiatry/Neurology, University of Bonn Medical Center, 53127 Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), 53127 Bonn, Germany

P13 : GENERATION PAR KNOCK-IN ET CARACTERISATION D'UN MODELE DE SLA-DFT BASE SUR L'EXPRESSION CONDITIONNELLE DU MUTANT CHMP2B$^{INTRON\ 5}$

Liu H, Dirrig-Grosch S, Loeffler JP and René F

Mécanismes Centraux et Périphériques de la Neurodégénérescence, INSERM U1118, Université de Strasbourg, France

P14 : NEW DIRECTIONS FOR EARLY DIAGNOSIS OF MND: A LARGE-SCALE LONGITUDINAL ANALYSIS OF MULTIPLE BIOMARKERS TO FIND DIAGNOSTIC AND PROGNOSTIC "FINGERPRINTS"

Vanessa X. Tan (1), Gilles J. Guillemin (1)

(1) MND Research Centre, Department of Biological Sciences, Faculty of Medicine and Health Sciences, Macquarie University, New South Wales, Australia

P15 : VALEUR PREDICTIVE DES SOUS-POPULATIONS DES CELLULES MONONUCLEES SANGUINES DANS LA SLA

Brodovitch A (1, 2), Rousseau M (2), Heim X (2), Parlanti A (1), Delmont E (1), Grapperon AM (1), Attarian S (1), Verschueren A (1) and Boucraut J (2)**

(1) CRMN-SLA. Hôpital de la Timone, AP-HM ; Marseille ; (2) Laboratoire d'immunologie. Hôpital de la Conception, AP-HM, Marseille.
* Co-auteur

P16 : IMPAIRED CORTICAL CROSS-FREQUENCY COUPLING IS AN EARLY BIOMARKER OF CORTICAL HYPEREXCITABILITY IN MOUSE MODELS OF ALS

Scekic-Zahirovic J (1), Fischer M (1), Sinniger J (1), Stuart-Lopez G (1), Gilet J (1), Pradat PF (2), Marchand-Pauvert V (2), Goutagny R (3)*, Rouaux C (1)**

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* Equal contribution

P17 : ETUDE LONGITUDINALE DE L'INDEX DU NOMBRE D'UNITES MOTRICES (MUNIX) DANS LA SCLEROSE LATERALE AMYOTROPHIQUE

Harlay V (1), Grapperon AM (1), Boucekine M (2), Kribich H (1), Attarian S (1), Verschueren A (1)

(1) Centre de référence pour les maladies neuromusculaires et la SLA, CHU la Timone, Marseille (France) ; (2) Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie EA 3279, Aix-Marseille Université, Marseille (France)

P18 : MANIFOLD LEARNING IN AMYOTROPHIC LATERAL SCLEROSIS: DEVELOPMENT AND VALIDATION OF A PROGNOSTIC MODEL FOR FUNCTIONAL LOSS

Grollemund V (1,2), Pradat PF (3,4), Pradat-Peyre JF (1,5), Delbot F (1,5)

(1) LIP6, Sorbonne Université, Paris ; (2) FRS Consulting, Paris ; (3) LIB, INSERM, Paris ; (4) Neurologie, APHP, Paris ; (5) Modal'X, Université de Nanterre, Nanterre

P19 : FACTEURS PRONOSTIQUES APRES POSE DE GASTROSTOMIE CHEZ LES PATIENTS ATTEINTS DE SLA UTILISATEURS HABITUELS DE VNI : INFLUENCE DU STATUT RESPIRATOIRE

Hesters A (1), Amador MdM (1), Debs R (1), Le Forestier N (1), Lenglet T (1), Pradat PF (1), Salachas F (1), Gonzales-Bermejo J (2), Faure M (3), Galarza Jimenez MA (3), Morelot C (3), Bruneteau G (1)

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P20 : EPIDEMIOLOGY, GENETICS, CLINICAL FEATURES AND SURVIVAL OF AMYOTROPHIC LATERAL SCLEROSIS IN LATIN AMERICAN AND THE CARIBBEAN: A SYSTEMATIC REVIEW.

Erazo D (1), Luna J (1, 2), Preux P.M (1,2,3), Boumediene F (1), Couratier P (1,2)

(1) INSERM, Univ. Limoges, CHU Limoges, IRD, U1094 Neuroépidémiologie Tropicale, Institut d'Epidémiologie et de Neurologie Tropicale, GEIST, Limoges, France ; (2) Centre de Référence SLA et autres maladies du neurone moteur. CHU Limoges, France ; (3) CHU Limoges, Centre d'Epidémiologie de Biostatistique et de Méthodologie de la Recherche, Limoges, France.

P21 : TECH-ICOPA : TECHNOLOGIE INTERFACE CERVEAU-ORDINATEUR POUR L'AUTONOMIE.

Guy V (1), Guebba S (2), Bruno M (1) , Papadopoulo T (2), Sakarovitch C (3), Desnuelle C (1), Clerc M (2), Soriani MH (1)

(1) CHU Nice - Hôpital Pasteur 2 - URRIS - CRMR SLA-MNM ; (2) INRIA Sophia Antipolis - Equipe ATHENA ; (3) CHU Nice - Hôpital Cimiez - DRCI

P22 : FOLLOW-UP AND SURVIVAL AFTER GASTROSTOMY INDICATION IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Fayemendy (1,2,3), Vergonjeanne M (1) Sourisseau H (1), Calmel N (1) Lautrette G (4), Preux PM (2,3,5), Couratier P (2,3,4), Desport JC (1,2,3), Jésus P (1,2,3)

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P23 : COMPARISON OF THE FAT-FREE MASS OBTAINED BY IMPEDANCEMETRY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: DIRECT MEASUREMENT WITH DEVICE FORMULA VERSUS REFERENCE FORMULA.

Desbordes F (1), Fayemendy P (1,2,3), Sourisseau H (1), Calmel N (1), Preux PM (2,3,4), Couratier P (2,3,5), Jésus P (1,2,3), Desport JC (1,2,3)

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P24 : STUDY OF THE FAT-FREE MASS OBTAINED BY TWO DIFFERENT BODY COMPOSITION METHODS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: IMPEDANCEMETRY VERSUS MEASUREMENT OF THE FOUR SKIN FOLDS.

Rebière F (1), Fayemendy P (1,2,3), Sourisseau H (1), Calmel N (1), Preux PM (2,3,4), Couratier P (2,3,5), Jésus P (1,2,3), Desport JC (1,2,3)

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P25 : STUDY OF THE RELEVANT THRESHOLD OF RESTING ENERGY EXPENDITURE VARIATION TO SCREEN AT DIAGNOSIS PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS WITH THE HIGHER EVOLVING RISK.

Jésus P (1,2,3), Fayemendy (1,2,3), Sourisseau H (1), Lautrette G (4), Preux PM (2,3,5), Couratier P (2,3,4), Desport JC (1,2,3)

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P26 : SURVIVAL ACCORDING TO RESTING ENERGY EXPENDITURE (REE) VARIATION USING TWO REE FORMULAS AND WITHOUT INDIRECT CALORIMETRY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS).

Jésus P (1,2,3), Fayemendy (1,2,3), Sourisseau H (1), Lautrette G (4), Preux PM (2,3,5), Couratier P (2,3,4), Desport JC (1,2,3)

(1) Nutrition Unit, University Hospital of Limoges, Limoges, France ; (2) INSERM, U1094, Tropical Neuroepidemiology, School of Medicine of Limoges, Limoges, France ; (3) U1094, Tropical Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, University of Limoges ; (4) ALS Centre, University Hospital of Limoges, Limoges, France ; (5) Centre of Epidemiology, Biostatistic and Methodology of Research (CEBIMER), University Hospital of Limoges, Limoges, France

P27 : IMPACT OF CARE OF A HEALTH NUTRITIONAL NETWORK AT HOME ON EVOLUTION OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

Nasser Y (1), Fayemendy (1,2,3,4), Sourisseau H (1), Camel N (1), Lautrette G (5), Preux PM (2,3,6), Couratier P (2,3,5), Desport JC (1,2,3,4), Jésus P (1,2,3,4)

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P28 : AMBROXOL HYDROCHLORIDE SLOWS DOWN PHYSIOPATHOLOGY OF THE *CHMP2B*^{INTRON5} ALS-FTD MOUSE MODEL

Bouscary A (1,2), Quessada C (1,2), Dirrig-Grosch S (1,2), Turner B (3), Ngo S (4,5,6), Spedding M (7), Henriques A (8), Loeffler J.P (1,2), René F (1,2)

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P29 : THERAPEUTIC STRATEGIES FOR ALS/FTD USING CELLULAR AND MURINE MODELS

Ropert B (1), Vicens R (1), Bayot A (3), Augé G (1), Mauri-Crouzet A (1), Lespinasse F (1), Genin E (1), Delahodde A (2), Paquis-Flucklinger V (1)

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P30 : EVALUATION OF A 5-HT2B AGONIST IN A MURINE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

Arnoux A (1,2,3), Ayme-Dietrich E (2), Dieterlé S (1), Goy M-A (1), Schann S (3), Monassier L (2), Dupuis L (1)**

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* equally contributed

P31 : STUDY OF POTENTIAL OFF-TARGET CANDIDATE SITES FOR ANTISENSE SEQUENCES INDUCING EXON SKIPPING IN *SOD1*-LINKED AMYOTROPHIC LATERAL SCLEROSIS

Elouej S (1), Delamare M (1), Cappella M (1), Cohen-Tannoudji M (1), Astord S (1), Marais T (1), Giroux B (1), Pezet S (1), Biferi MG (1).

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P32 : IS THERE A ROLE FOR VITAMIN D IN AMYOTROPHIC LATERAL SCLEROSIS? A SYSTEMATIC REVIEW AND META-ANALYSIS.

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RÉSUMÉS DES PRÉSENTATIONS

Session 1 : Génétique et mécanismes moléculaires des maladies du neurone moteur

- **Conférence invitée**

C1-EVALUATION DE L'HYPOTHESE CORTICOFUGE DANS LA SLA

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De récentes études génétiques, fonctionnelles et histopathologiques menées sur les patients atteints de SLA familiale ou sporadique suggèrent un rôle du cortex cérébral dans l'initiation de la SLA, et une propagation de la maladie le long des projections corticofuges et notamment du tractus corticospinal. Par le biais de différents modèles murins, nous avons entrepris de tester l'hypothèse corticofuge de la SLA en tâchant de déterminer 1) la nature des atteintes corticales et leur cinétique, 2) la contribution des populations de neurones corticofuges au déclenchement et à la progression des atteintes motrices, et 3) la nature d'un potentiel message toxique véhiculé du cortex cérébral vers ses cibles.

L'absence de neurones corticofuges chez les souris *Sod1*^{G86R} permet de retarder de manière significative le déclenchement des symptômes moteurs et d'augmenter l'espérance de vie des animaux **[1]**, suggérant une toxicité des neurones corticofuges dans un contexte mimant la SLA. Ces résultats constituent une première démonstration expérimentale de l'hypothèse corticofuge.

Deux mécanismes de propagation ont été proposés : un mécanisme de type prion, avec propagation d'agrégats toxiques de protéines mal repliées le long des faisceaux neuronaux, et un mécanisme excitotoxique émanant d'une hyperexcitabilité corticale initiale. Nous avons testé ces deux possibilités. Nos résultats récents, publiés et non publiés, invalident la possibilité d'une propagation de type prion, et indiquent par ailleurs l'existence d'une hyperexcitabilité corticale extrêmement précoce chez les souris *Sod1*^{G86R} et *Fus*$^{\Delta NLS/+}$ **[2,3]**, en faveur d'une propagation d'activités neuronales aberrantes le long des projections corticofuges.

Nos travaux actuels visent à déterminer l'origine de l'hyperexcitabilité corticale dans les modèles murins de SLA, et à tester l'impact de cette hyperexcitabilité corticale sur le déclenchement et la progression de symptômes moteurs chez le rongeur. A terme, ces travaux permettront de déterminer si l'hyperexcitabilité corticale pourrait constituer une nouvelle cible thérapeutique dans le traitement de la SLA.

Références :

[1] Burg, T. *et al.* Absence of subcerebral projection neurons delays disease onset and extends survival in a mouse model of ALS. *bioRxiv* (2019). doi:10.1038/nn.4257

[2] Scekic-Zahirovic, J. *et al.* Genetic ablation of SOD1^{G37R} selectively from corticofugal projection neurons protects corticospinal neurons from degeneration without affecting ALS onset and progression. *bioRxiv* (2020). doi:10.1016/S0304-3940(02)00944-8

[3] Marques, C. *et al.* Early alterations of RNA metabolism and splicing from adult corticospinal neurons in an ALS mouse model. *bioRxiv* (2019). doi:10.1101/gr.1239303

Mots clés : Hypothèse corticofuge; Hyperexcitabilité corticale; Cible thérapeutique

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- **Présentations sélectionnées à partir de l'appel à communication**

PO1.1 – DE NOUVELLES MUTATIONS DANS LE GENE *ANXA11* ALTERENT LA STABILITE ET INDUISENT L'AGREGATION DE L'ANNEXINE A11 CHEZ DES PATIENTS ATTEINTS DE SCLEROSE LATERALE AMYOTROPHIQUE

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Des mutations dans *ANXA11* ont été récemment identifiées chez des patients présentant une Sclérose Latérale Amyotrophique (SLA) à début tardif sans trouble cognitif [1]. Ce gène code l'Annexine A11, une protéine de liaison aux phospholipides dépendante du calcium, impliquée dans la croissance cellulaire, le transport vésiculaire, l'exocytose, la survie et l'apoptose du fait de son interaction avec plusieurs partenaires protéiques tels que la calcycline (S100A6) et PDCD6/ALG2/PEFB1. L'analyse de l'exome de 150 formes familiales (FALS) et 100 cas sporadiques (SALS) a permis d'identifier dans une cohorte de 380 patients et identifié 3 variants rares dont un (L254V) responsable d'une SLA à début précoce. Deux autres mutations sont localisées dans le domaine prion de la protéine : la mutation D40Y est probablement pathogène puisqu'elle ségrége dans la famille concernée et affecte le même acide aminé que la mutation D40G d'ores et déjà décrite. Le variant G38R a été identifié chez 2 patients présentant des troubles cognitifs et une atteinte motrice spastique prédominante. L'analyse neuropathologique de l'un d'entre eux a montré des inclusions caractéristiques de SLA marquées par TDP43 ou la Cystatin C, associées à des accumulations d'Annexine A11, alors que cette forme mutée est moins stable in vitro dans les lymphoblastes. Nos résultats génétiques et neuropathologiques confirment que les mutations dans *ANXA11* sont responsables de SLA.

Références :
[1] Smith, B.N., Topp, S.D., Fallini, C., et al. (2017). Mutations in the vesicular trafficking protein annexin A11 are associated with amyotrophic lateral sclerosis. Sci. Transl. Med. 9.
Mots clés : Génétique, neuropathologie, ANXA11
Remerciements/financements : AFM Téléthon, ARSLA, l'ARMC, S.L.A.F.R., La longue route des malades de la S.L.A., Un pied devant l'autre.
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PO1.2 - ETUDE DES EFFETS DE LA DELOCALISATION CYTOPLASMIQUE DE FUS DANS LES NEURONES ADULTES

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La sclérose latérale amyotrophique (SLA) et la démence fronto temporale (DFT) sont deux maladies neurodégénératives incurables qui, malgré des symptômes très différents, sont génétiquement et cliniquement liées formant un continuum pathophysiologique. Les mutations dans le gène FUS, codant pour une protéine multifonctionnelle impliquée dans de nombreux processus cellulaires, peuvent affecter la séquence de localisation nucléaire (SLN) et entrainent des formes très sévères de SLA. Chez les patients porteurs d'une mutation FUS, on observe une délocalisation et la formation d'agrégats cytoplasmiques de FUS. De tels agrégats sont retrouvés également chez une fraction de patients DFT, même en absence de mutation germinale de FUS. Ici, nous avons créé un nouveau modèle de souris qui permet la troncation de la protéine FUS dans les neurones adultes (Fus cKI) par croisement d'une nouvelle lignée murine permettant la troncation conditionnelle de FUS et d'une lignée exprimant une activité CRE recombinase inductible dans les neurones adultes.

Après induction de la recombinaison, nous avons montré que les souris Fus cKI expriment une forme tronquée de la protéine FUS dans le cortex frontal et la moelle épinière. De façon surprenante, la troncation de FUS dans les neurones adultes ne provoque pas de troubles moteurs. Cependant, les souris Fus cKI développent une altération importante de la sociabilité et de l'exécution de tâches tandis que leur mémoire semble préservée, tableau clinique rappelant celui des patients atteints de DFT. Ces résultats suggèrent que la délocalisation de FUS dans les neurones adultes favorise un tableau clinique de DFT, et suggère que l'âge d'apparition des lésions pourrait être une clé de la diversité phénotypique du continuum SLA-DFT.

Mots clés : FUS troncation, Sclérose Latérale Amyotrophique, Démence Fronto Temporale
Financement : EpiFUS, ANR-16-CE92-0031 ; ToFU, ANR-16-CE16-0015
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PO1.3 - DEVELOPMENT AND CHARACTERIZATION OF IN VITRO MODELS TO TEST THE EFFICIENCY OF GENE THERAPY APPROACHES IN *SOD1*-LINKED AMYOTROPHIC LATERAL SCLEROSIS

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Mutations in the superoxide dismutase (SOD1) gene are linked to 20% cases of inherited Amyotrophic lateral sclerosis (ALS). ALS is a deathly motor neuron (MN) disorder defined by degeneration of MNs and atrophy of skeletal muscle (SM). Suppression of toxic mutant SOD1 in these tissues is an encouraging therapeutic possibility for SOD1-linked ALS. We have already reported that a molecular approach, using antisense oligonucleotides and adeno-associated viral vector serotype rh10 (AAV10), is able to mediate exon skipping of the human SOD1 (hSOD1) pre-mRNA [1]. Combined intravenous and intracerebroventricular delivery of viral particles led to a significant reduction in the levels of mutant hSOD1 in the whole body of SOD1G93A mice, particularly in MNs and SK, resulting in prolonged survival and recovery of neuromuscular functions.
The objective of this study is to test the efficiency of our gene therapy strategy in the human pathological context. We have generated in vitro models from SOD1 patient's dermal fibroblasts (expressing different mutations: A4V, L144F and G93D). Primary fibroblasts were immortalized and trans-differentiated into myoblasts upon conditional MyoD over-expression, using established protocols [2].

We analyzed SOD1 mRNA and protein expression under physiological condition or after proteasome inhibition, in fibroblasts and differentiated myotubes. After treatment with the proteasome inhibitor MG132, we observed a significant increase of hSOD1 mRNA and protein, in patient cells relative to controls. Proliferation in both cell types and differentiation properties in myotubes, were impaired in SOD1-mutant cells, with more striking effects in the A4V cell line (responsible of an aggressive disease progression in patients). In order to test the gene therapy effects in these in vitro models, we developed a protocol to efficiently transduce skeletal muscle cells with an AAV10 carrying a green fluorescent protein as reported gene. We plan now to assess the effect of hSOD1 silencing in this in vitro model, after transduction with the previously generated AAV10 expressing the antisense sequences.
Our results will contribute to the development of in vitro cellular models for SOD1-ALS. These models will be useful to understand the tissue-specific contribution of hSOD1 mutation to the disease and to test SOD1-silencing approaches.

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[2] Chaouch, S.; Mouly, V.; Goyenvalle, A.; Vulin, A.; Mamchaoui, K.; Negroni, E.; Di Santo, J.; Butler-Browne, G.; Torrente, Y.; Garcia, L.; Furling, D. Immortalized Skin Fibroblasts Expressing Conditional MyoD as a Renewable and Reliable Source of Converted Human Muscle Cells to Assess Therapeutic Strategies for Muscular Dystrophies: Validation of an Exon-Skipping Approach to Restore Dystrophin in Duchenne Muscular Dystrophy Cells. Hum. Gene Ther. 2009, 20 (7), 784–790. https://doi.org/10.1089/hum.2008.163.

Keywords: ALS; gene therapy; in vitro model

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Conflict of interest: The authors have no conflicting interests to disclose.

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PO1.4 - PREMATURE TERMINATION CODONS IN *SOD1* CAUSING ALS ARE PREDICTED TO ESCAPE THE NONSENSE-MEDIATED MRNA DECAY

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Currently, a minority of premature termination codons (PTCs) causing amyotrophic lateral sclerosis have been identified in the *SOD1* gene.
We analyzed their localization in *SOD1* to evaluate whether or not those PTCs are seen by the Nonsense-mediated mRNA decay (NMD).
Regarding the NMD rules we estimated that the region of *SOD1* obeying the NMD is located between nucleotides 151-301, which correspond to amino acids 50-100.
We found a total of 16 disease-associated-PTCs mutations in *SOD1* in the literature, including 4 nonsense mutations, 11 frameshift mutations and 1 deep intronic splicing mutation confirmed by transcript analysis. Our study shows that all of them can escape the NMD, resulting in the production of truncated protein. This finding supports the hypothesis that haploinsufficiency is not an underlying mechanism of *SOD1* mutant-associated ALS and suggests that PTCs found in the regions that trigger NMD are not pathogenic.

Keywords: ALS, *SOD1*, NMD.
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PO1.5 - ZEBRAFISH MODEL AS A FUNCTIONAL TOOL TO ANALYSE PATHOGENICITY OF *SOD1* GENE VARIANTS

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Regarding inheritance of Amyotrophic Lateral Sclerosis (ALS), 90% of cases are sporadic and 10% are familial. There are around 30 causative of ALS, the major ones being *C9ORF72, SOD1, FUS and TARDBP*. Mutations within the *SOD1* gene account for up to 20% of familial ALS cases worldwide [1]. Molecular diagnosis of ALS is based on the analysis of patients' genetic sequences in search for a disease-causing variant. One of the main issues in molecular diagnosis is the interpretation of variant pathogenicity. Variant classification is based on international criteria for pathogenicity analysis such as frequency in the population, effect on the protein, *in silico* predictions etc. Among them, functional data is considered an essential element for variant classification [2]. The emergence of next-generation sequencing led to increased number of new variants, some of which remain Variants of Unknown Significance (VUS) for which there is a lack of experimental evidence. In the meantime, the need for accurate and rapid variant interpretation is increasing in view of the increasing number of novel ALS genes and the potential of the emerging antisense therapies for *SOD1* gene.

We developed Zebrafish as a model for the functional analysis of candidate VUS, identified by routine genetic testing at Nîmes University Hospital. Here we present the study of 4 *SOD1* variants: *Ile150Met; Lys137*; delGlu134; Asp126Asn.* Transient overexpression of those variants using mRNA microinjection in 1-cell stage Zebrafish embryos, led to locomotor abnormalities and increased branching of motoneuronal axons in 2-day old larvae. Similar abnormalities were observed using the pathogenic variant *SOD1 Ala5Val*. We suggest that our model proves a pathogenic effect of those variants.

Our approach could serve as tool for molecular diagnosis, providing new functional evidence for reclassification of VUS. It can be applied to other genes, therefore providing a solution to the challenge of variant interpretation.

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Keywords: ALS, gene variants, functional analysis

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PO1.6 - DYSFONCTIONNEMENTS DE LA MEMOIRE CHEZ LES SOURIS FUS$^{\Delta NLS/+}$ ET MODIFICATIONS EPIGENETIQUES ET TRANSCRIPTOMIQUES ASSOCIEES.

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Les troubles cognitifs dans la SLA et la DFT sont associés à un pronostic vital diminué mais leurs mécanismes sous-jacents restent peu connus. Dans certains cas de SLA/DFT on observe une délocalisation cytoplasmique de la protéine FUS. FUS étant une protéine de liaison a l'ADN/ARN, impliquée dans toutes les étapes liées à la transcription, sa délocalisation pourrait induire des dérèglements d'expression génique, qui pourraient sous-tendre les troubles cognitifs. Nous avons utilisé un modèle murin, les souris *Fus*$^{\Delta NLS/+}$, pour caractériser les conséquences épigénomiques/transcriptomiques de la mutation de *Fus* au cours d'un apprentissage. Nous montrons que les souris *Fus*$^{\Delta NLS/+}$ présentent des altérations de la mémoire spatiale, suggérant un dysfonctionnement de l'hippocampe. Nos études transcriptomiques (RNA-sequencing) montrent peu de dérégulations au repos. En cours de l'apprentissage spatial, les gènes liés à l'activité neuronale (*Fos*, *Egr1*, *Arc…*) sont induits dans l'hippocampe des deux groupes. Cependant, chez les souris *Fus*$^{\Delta NLS/+}$, on observe davantage de gènes liés à la plasticité synaptique, et moins de gènes liés à l'activation transcriptionnelle comparé aux WT. Pour comprendre les bases épigénétiques de ces altérations, nous avons réalisé des expériences de ChIP-sequencing dans des noyaux neuronaux triés par FACS. Nous montrons que les marques d'histones associées à l'activation transcriptionnelle (H3K27ac, H3K4me3 et H4K12ac) sont fortement augmentées chez les *Fus*$^{\Delta NLS/+}$ et que les gènes qui portent ces histones modifiées sont significativement plus exprimés au repos et en cours d'apprentissage. Ces modifications transcriptionnelles/épigénétiques pourraient être causées par des cassures de l'ADN et une mauvaise réponse du dommage à l'ADN, des événements dépendants de la fonction de FUS [3]. En conclusion, la mutation de *Fus* provoquerait des modifications importantes sur la chromatine des neurones hippocampiques, induisant des dérégulations transcriptionnelles associées à l'apprentissage. Ces données permettent de mieux comprendre comment la délocalisation de FUS causeraient les déficits cognitifs associés à la SLA-FUS/DTF-FUS.

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Mots clés : SLA-DFT, Mémoire, Epigénétique

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Session 2 : Biomarqueurs et thérapies dans les maladies du neurone moteur

- **Conférence invitée**

C2-REVISITING STUDY DESIGN IN ALS CLINICAL TRIALS

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- **Présentations sélectionnées à partir de l'appel à communication**

PO2.1 - SPINAL CORD MRI FOR THE DESCRIPTION OF THE LONGITUDINAL EVOLUTION OF PRESYMPTOMATIC PATHOLOGY IN *C9ORF72* MUTATION CARRIERS: A THREE TIME-POINT STUDY.

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Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal dementia (FTD) share genetic susceptibility and a large portion of familial cases are due to *c9orf72* gene mutations. Brain and spinal cord (SC) imaging studies in asymptomatic *c9orf72* carriers have demonstrated white (WM) and grey matter (GM) degeneration up to 20 years before the expected symptom onset[1,2].

The objective of this study was to longitudinally describe using quantitative MRI the evolution of SC degeneration over 36-months in a cohort of asymptomatic *c9orf72* mutation carriers.

Methods: 72 asymptomatic individuals were enrolled in a longitudinal study of first-degree relatives of *c9orf72*-ALS and FTD patients. 40 (C9+) carried the pathogenic repeat expansion. Each subject underwent a 3T cervical SC MRI. Quantitative measures of GM and WM atrophy and DTI parameters were evaluated at baseline, after 18 and 36 months. Data were analysed on the total population and in two subgroups composed by subjects younger and older than 40 years of age.

Results: No significant difference in GM cross-sectional area was observed at baseline between C9+ and C9- subjects nor any evolution was identified over time. At baseline, significant WM atrophy was detected at each cervical vertebral level in C9+ subjects older than 40 years of age (p-value < 0.05), which was confirmed and remained stable after 18- and 36-months. A significant reduction of fractional anisotropy (FA) in the pyramidal

tracts was observed in C9+ subjects older than 40 years. FA reduction was progressive over time with a significant difference between the baseline and the 36-months evaluation (p = 0.02).
Discussion: Cervical SC imaging of *c9orf72* hexanucleotide carriers detect a stable WM atrophy associated with progressive pyramidal tract FA reduction which seems to be continuous but not linear. Longer follow-up and combination with brain imaging will further shed light on the longitudinal degeneration profile of *c9orf72* mutation carriers.

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Keywords: C9orf72, presymptomatic subjects, spinal cord degeneration
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PO2.2 - AB1-42 AND TAU AS POTENTIAL BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, but its definitive diagnosis delays around 12 months. Although the research is highly active in the biomarker field, the absence of specific biomarkers for diagnosis contributes to this long delay. Another strategy of biomarker identification based on less specific but sensitive molecules may be of interest in clinical practice. For example, markers related to other neurodegenerative diseases such as Alzheimer's disease (AD) could be fully explored. Here, we compared baseline levels of amyloidβ1-42 (Aβ1-42), total Tau, and phosphorylated-Tau (phospho-Tau) protein in the cerebrospinal fluid (CSF) of ALS patients to controls and correlated it with clinical parameters of ALS progression collected over 12 months. We observed increased levels of Aβ1-42 (controls: 992.9 ± 358.3 ng/L; ALS: 1277.0 ± 296.6 ng/L; $p < 0.0001$) and increased Aβ1-42/phospho-Tau ratio and Innotest Amyloid Tau Index (IATI) (both $p < 0.0001$). IATI and the phospho-Tau/total Tau ratio correlated positively with ALSFRS-R and weight at baseline. Multivariate analysis revealed that baseline ALSFRS-R was associated with Aβ1-42 and phospho-Tau/total Tau ratio ($p = 0.0109$ and $p = 0.0013$, respectively). Total Tau and phospho-Tau levels correlated negatively with ALSFRS-R variation at months 6 and 9, respectively ($p = 0.02$ and $p = 0.04$, respectively). Phospho-Tau/total Tau ratio correlated positively with ALSFRS-R variation at month 9 ($p = 0.04$). CSF levels of Aβ1-42 could be used as a complementary tool to ALS diagnosis, and total Tau and phospho-Tau levels may help establishing the prognosis of ALS. Further studies merit exploring the pathophysiological mechanisms associated with these markers. Despite their lack of specificity, phospho-Tau/total Tau and Aβ1-42 should be combined to other biological and clinical markers in order to improve ALS management.

Keywords: ALS; biomarker; CSF
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PO2.3 - MOLECULAR SCREENING OF FDA-APPROVED DRUGS IN HUMAN PLURIPOTENT STEM CELLS FOR THE TREATMENT OF RARE MONOGENIC DISEASES.

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Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, repurposing of 'old' drugs to treat both common and rare diseases is increasingly becoming an attractive proposition. In this study, we evaluated the potential of using human pluripotent stem cells to identify repurposable drug candidates. For this purpose, we treated derivatives from human embryonic stem cells with 50 marketed drugs and we annotated the induced molecular changes by RNA deep sequencing. Focusing on genes previously involved in monogenic diseases, we identified drugs capable to modulate the expression of p62/SQSTM1, a gene known to be involved in Amyotrophic lateral sclerosis (ALS). Most ALS cases are sporadic but 5-10% of cases are familial, and involve a mutation in the SOD1, TARDBP, C9orf72, OPN or p62/SQSTM1 gene. We treated motor neurons differentiated from human embryonic stem cells and we showed that one of the drugs identified was capable to upregulate p62/SQSTM1, to promote its aggregation in puncta, appearing during autophagosme formation. To further explore this therapeutic potential, we have generated p62+/- and p62-/- human pluripotent stem cells by using CRISPR-Cas9 technology.

Thanks to these cellular tools, we highlighted the impairment of autophagy in p62+/- and p62-/- motor neurons. Treatment of the cells with the drug was able to restore autophagy. We next tested the potential of the drug in a zebrafish model of ALS caused by p62 knockdown. In vivo treatment improved the swimming of fishes without the induction of toxicity. Altogether, these results identify a FDA-approved molecule capable to modulate the autophagy pathway in human motor neurons through the induction of p62/SQSTM1. These data raise the question of the therapeutic potential of this molecule both for ALS but also for other neuromuscular disease associated with abnormal protein aggregation.

Keywords: SQSTM1/p62; autophagy; human pluripotent stem cells
Founding: ANR / ALS
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PO2.4 - THE UTILIZATION OF INTRABODIES FOR THE DEVELOPMENT OF THERAPEUTICS TARGETING PROTEIN AGGREGATION IN ALS

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To date, no compelling drugs exist for patients suffering from ALS. This calls for active research in drug development and biomarker exploration. One of the most attractive, putative targets in ALS is the DNA/RNA-binding protein TDP-43. While mostly localized in the nucleus under physiological conditions, the wild-type (wt) form is found aggregated in the cytoplasm in ≥95% of ALS patients - considered to be the hallmark of ALS. The aim of our study was to find innovative biopharmaceuticals preventing TDP-43 aggregation. A library of small-chain variable fragments (scFv) was screened against recombinant GFP-wtTDP-43-6xHis by phage display. Clones exhibiting affinity for wtTDP-43 were selected and purified, as well as one control clone with affinity for GFP. *In silico* binding site prediction suggested multiple potential binding sites for each anti-TDP-43 clone, including the C-terminus, which is heavily involved in the aggregation process of TDP-43. Flow cytometry demonstrated the binding of purified anti-TDP-43 scFv to permeabilized HEK293T cells, whereas no binding was observed for anti-GFP scFv, suggesting that the anti-TDP-43 scFv bound endogenous TDP-43 (n=3). Immunofluorescence of HEK293T co-transfected with wtTDP-43 and anti-TDP-43 scFv displayed cytoplasmic co-localization, compared to cells transfected with scFv only (n=2), suggesting that scFv could interact with the potentially cytotoxic, mis-localized TDP-43. Furthermore, MTT reduction assays on scFv/TDP-43 co-transfected cells showed a tendency towards increased viability compared to cells transfected with wtTDP-43 only (n=3). Immunoblot of extracts of co-transfected HEK293T revealed a decrease in the total amount of TDP-43, compared with cells transfected with wtTDP-43 only (n=1), which could represent a mechanism to diminish TDP-43 aggregation. Overall, these data indicate that we have obtained scFvs counteracting pathological effects produced by wtTDP-43 overexpression. In addition to confirming these preliminary findings, current work involves confirming scFv binding site by cytometry of cells bearing TDP-43 mutants specific to the predicted binding sites.

Keywords: aggregation, TDP-43, therapeutics

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PO2.5 - AAV-MEDIATED EXPRESSION OF ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF C9ORF72-FALS

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Amyotrophic lateral sclerosis (ALS) is the most frequent and fatal adult motor neuron disorder without an effective available cure. The most common genetic form of ALS (~40%) is caused by hexanucleotide G4C2 repeat expansion (HRE) in intron 1 of the C9ORF72 (C9) gene. Three non-exclusive pathological mechanisms have been proposed to explain neurotoxicity: loss of protein function, toxicity of nuclear HRE RNA and accumulation of dipeptide repeats (DPR). Huge research efforts are ongoing to find a cure for this disease. We are developing a gene therapy strategy, based on the expression of antisense (AS) sequences through Adeno Associated viral vectors (AAV) [1]. We designed AS sequences to simultaneously target the three pathological mechanisms of C9-ALS. For their delivery, we fused the AS to the U7 small nuclear RNA, which protect them from degradation and bring them into cell nuclei. We produced lentiviral and AAV vectors carrying the U7 RNA and different AS sequences against the C9 pre-mRNA, containing the HRE. We assessed the lentiviral vector-U7-AS efficacy in patient-derived immortalized fibroblasts and we observed up to 66% or 55% of reduction in the number of sense or antisense foci, respectively. There were no significant changes in the protein levels, in cells transduced with the therapeutic vector, compared to controls. The evaluation of lentiviral vector-U7-AS on DPR is ongoing in fibroblasts. We plan now to evaluate the efficacy of AAV-U7-AS in spinal motor neurons derived from C9 induced pluripotent stem cells. In parallel, we are testing this approach in vivo, using the C9 BAC mouse model (Jax SN 029099). After a single intracerebroventricular injection of one AAV-U7-AS against C9, we observed a significant decrease of HRE-containing C9 mRNA (Variant3) in the spinal cord of C9 mice, compared to non-injected or injected with an AAV carrying an U7-AS control. Overall, this work will contribute to the development of therapeutic approaches for C9-ALS.

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Keywords: Gene therapy, AAV, C9orf72-ALS

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Conflict of Interest: The authors have no conflicting interests to disclose.

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PO2.6 - INHIBITION OF β-OXIDATION: A PROMISING THERAPEUTIC APPROACH FOR ALS.

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The impairment of energy metabolism associated with ALS defines it as a systemic disease rather than just a pure motor neuron disease. Several studies have shown that patients with ALS [1] as well as murine models of ALS are hypermetabolic [2]. This hypermetabolism appears before the first motor symptoms in the murine model *Sod1*^{G86R}. The increase in energy expenditure in *Sod1*^{G86R} mice occurs in parallel with an increase in lipid oxidation (β-oxidation) and a decrease in glycolysis [3]. In this study, we aimed to assess whether restoring the energy balance has a beneficial effect on the development of ALS in *Sod1*^{G86R} mice. We treated mice with an inhibitor of β-oxidation (20 mg / kg / day in the drinking water for two weeks). Our results show that the inhibitor of β-oxidation treatment prevents weight loss, maintains muscular strength over time and reduces muscle denervation. In addition, it also limits the deregulation of metabolic markers in *Sod1*^{G86R} mice. Taken together, our results show that regulating the energy balance has beneficial effects on the course of the disease in *Sod1*^{G86R} mice and that such a pharmacological approach could be translated to human patients.

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Keywords: ALS; therapeutic approach; energy balance

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Session ARSLA

- **Présentations invitées sur projets financés par l'ARSLA**

POA1 : **MODIFYING MACROPHAGES AT THE PERIPHERY HAS THE CAPACITY TO INCREASE ALS SURVIVAL**

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Microglia and peripheral macrophages, combined, have been implicated in ALS, but without discriminating their respective roles. Microglial cells and peripheral macrophages have distinct developmental origins and are in specific environments, therefore we hypothesized that their reaction to the disease could be different. Indeed, motor neurons have their cell bodies in the CNS surrounded by microglial cells while their axons extend at the periphery and are in contact with peripheral macrophages. We now show that macrophages along peripheral motor neuron axons of ALS mice and patients react to neurodegeneration. In ALS mice, peripheral myeloid cell infiltration into the spinal cord was limited and disease duration dependent. Targeted gene modulation of the *reactive oxygen species* pathway in peripheral myeloid cells of ALS mice, using cell replacement, reduced both peripheral macrophage and microglial activation, delayed symptoms and increased ALS mouse survival. Transcriptomics revealed that sciatic nerve macrophages and microglia reacted very different to neurodegeneration, with abrupt temporal changes in macrophages and progressive, unidirectional activation in microglia. Modifying peripheral macrophages suppressed proinflammatory microglial responses, with a strong shift towards neuronal support. Thus, modifying macrophages *at the periphery* has the capacity to influence disease progression and is of therapeutic value for ALS.

Keywords: Neuro-inflammation, microglial cells, nerve macrophages
Funding: ARSLA, Fondation Thierry Latran, ERA-NET NEURON, NRJ-Institut de France, ARMC, S.L.A.F.R., La longue route des malades de la SLA, un pied devant l'autre.
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POA2 : **REDUCED AUTOPHAGY UPON C9ORF72 LOSS SYNERGIZES WITH DPR PROTEIN TOXICITY IN CELL MODELS OF ALS**

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An expansion of GGGGCC (G4C2) repeats within the C9ORF72 gene is the most common genetic cause of amyotrophic lateral sclerosis (ALS). These repeats lead to a decreased expression of the C9ORF72 protein, which regulates autophagy. Furthermore, sense and antisense transcripts with respectively expanded G4C2 or C4G2 repeats are translated into toxic dipeptide repeat (DPR) proteins. However, how these repeats are translated, and how this translation and the reduced expression of C9ORF72 modulate repeat toxicity are unclear. Using repeats embedded with the natural sense and antisense C9ORF72 sequence, We found that expanded G4C2 sense and C4G2 antisense repeats are translated through initiation to either canonical AUG or near-cognate start codons, which are located before the repeats. Consequently, C9ORF72 sense and antisense expanded repeats are respectively translated mostly into polyGA and polyPG proteins, and to a lesser degree into polyGR. However, these DPR proteins expressed under their native start codons are present at low levels as their accumulation is prevented by autophagy. Importantly, reduced expression of C9ORF72 leads to suboptimal autophagy that impairs clearance of DPR proteins leading to their toxic accumulation, ultimately resulting in neuronal cell death. Furthermore, pharmacological compound activating autophagy prevent neuronal cell death caused by DPR proteins accumulation upon C9ORF72 reduced expression. These results suggest the existence of a double hit pathogenic mechanism in ALS/FTD where the reduced expression of C9ORF72 synergizes the accumulation and toxicity of DPR proteins. Of clinical importance, drugs activating autophagy can prevent this pathogenic double hit mechanism.

Keywords: C9ORF72, RAN translation, Autophagy.
Funding acknowledgments: ARSLA 2017 “Therapeutic approach for Amyotrophic Lateral Sclerosis due to G4C2 expansion in C9ORF72”
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POA3 : **SLA ET HOMEOSTASIE DES PROTEINES : FOCUS SUR LA SUMOYLATION**

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Une des caractéristiques de la Sclérose Latérale Amyotrophique est la présence d’agrégats cytoplasmiques. Un défaut de régulation de l’homéostasie protéique, à savoir de la capacité à maintenir une bonne conformation, concentration et localisation cellulaire des protéines, apparaît aujourd’hui comme un mécanisme majeur dans la physiopathologie de la maladie.
Nous nous sommes intéressés au rôle joué par le processus cellulaire de SUMOylation dans la régulation de l’homéostasie des protéines SOD1 et TDP-43, deux protéines présentes dans les agrégats dans les motoneurones en dégénérescence. La SUMOylation consiste en la modification post-traductionnelle des protéines par liaison à une protéine Small Ubiquitin MOdifier (SUMO).
Nous avons tout d’abord observé qu’une inhibition globale de la voie de la SUMOylation par l’acide anacardique dans des cellules sur-exprimant TDP-43 réduit significativement la formation des agrégats, augmente la neuritogenèse et améliore la viabilité cellulaire. Nous avons ensuite montré que la protéine SUMO-1 colocalise dans les agrégats avec les protéines SOD1 ou TDP-43. L’inhibition spécifique des lysines cibles de la SUMOylation dans SOD1 et TDP-43 par mutagenèse dirigée affecte leur agrégation cytoplasmique. En effet l’inhibition de la SUMOylation de SOD1, sur-exprimées dans des cellules motoneuronales, réduit le nombre de cellules avec agrégats. L’inhibition de la SUMOylation de TDP-43 entraîne quant à elle une modification de la localisation intracellulaire des agrégats, qui apparaissent alors principalement nucléaires, et non plus cytoplasmiques. Ces modifications sont associées à une amélioration du fonctionnement globale des cellules et à une modification de l’expression de nombreux gènes impliqués dans la régulation de l’homéostasie protéique et dans la synaptogenèse.
Une meilleure connaissance des mécanismes post-traductionnelles des protéines impliquées dans la pathogenèse de la SLA, en particulier la SUMOylation et l’ubiquitinylation, permettra de mieux comprendre la physiopathologie de la SLA et pourrait conduire à de nouvelles pistes thérapeutiques.

Mots clés : SOD1, TDP-43, agrégats
Remerciements : Financements de l’ARSLA, Région Centre Val de Loire, Université de Tours, Inserm
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POA4 : LES STRATEGIES DE CHELATION CONSERVATRICE DU FER ET ANTI-FERROPTOTIQUES POURRAIENT-ELLES CONDUIRE A UNE NEUROPROTECTION DANS LA SCLEROSE LATERALE AMYOTROPHIQUE ?

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Le fer est essentiel à la survie et au fonctionnement cellulaire particulièrement pour la consommation énergétique élevée des neurones. Une dérégulation de l'homéostasie du fer a été observée dans plusieurs études précliniques et cliniques de la SLA. Les séquences d'IRM sensibles au fer (T2* et images pondérées de la sensibilité) montrent une accumulation dynamique de fer dans la voie motrice cortico-spinale chez les patients sporadiques et familiaux. Une accumulation précoce de fer se produit dans les neurones avant la dégénérescence, puis dans la microglie. La toxicité du fer a été basée sur les effets protecteurs de sa chélation dans plusieurs modèles animaux avec notamment une réduction de l'agrégation TDP-43.

Il est intéressant de noter que l'on a récemment découvert que ces altérations peuvent sensibiliser à une mort cellulaire dépendant du fer, appelée ferroptose, dont les principales caractéristiques sont la peroxydation des lipides, la déplétion spécifique en glutathion peroxydases-4 (Gpx4) (cofacteur glutathion), la mitochondriopathie et les modifications morphologiques différentes des autres voies de mort cellulaire (apoptose, nécrose et autophagie). L'ablation conditionnelle de la Gpx4 dans les neurones de souris entraîne une dégénérescence massive des motoneurones.
Les chélateurs du fer ont montré une grande efficacité contre la ferroptose. Afin de permettre l'utilisation chez l'humain, une nouvelle modalité thérapeutique, la "chélation conservatrice du fer" a été mise au point avec un médicament prototype. La déféripronе chélate le fer des mitochondries et le redéploie de manière extracellulaire vers la transferrine, transporteur physiologique, afin d'éviter l'anémie. La faisabilité et la sécurité ont été démontrées chez 23 patients, avec une réduction de l'accumulation cérébro-spinale en fer (IRM), du stress oxydatif et des chaines légères de neurofilaments (sang et LCR) et de l'ALSFRS. L'efficacité est actuellement évaluée dans le cadre d'un essai clinique randomisé (FAIR-ALS-II).
Les nouvelles stratégies de neuroprotection anti-ferroptotiques seront discutées.

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Mots clés : neuroprotection, ferroptosis, iron chelator
Remerciements / financements : ARSLA, PHRC-national, Apopharma Inc.
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POA5 : SPINAL MOTONEURON TMEM16F ACTS AT C-BOUTONS TO MODULATE MOTOR RESISTANCE AND CONTRIBUTES TO ALS PATHOGENESIS

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Neuronal Ca^{2+} entry elicited by electrical activity contributes to information coding via activation of K^+ and Cl^- channels. While Ca^{2+}-dependent K^+ channels have been extensively studied, the molecular identity and role of Ca^{2+}-activated Cl^- channels (CaCC) remain unclear. Here, we demonstrate that TMEM16F governs a Ca^{2+}-activated Cl^- conductance in spinal motoneurons. We show that TMEM16F is expressed in synaptic clusters facing pre-synaptic cholinergic C-boutons in α-motoneurons of the spinal cord. Mice with targeted exon deletion in *Tmem16f* display decreased motor performance under high-task exercise attributable to an increase in the recruitment threshold of fast α-motoneurons. Remarkably, loss of TMEM16F function in *SOD1^{G93A}* mice, a mouse model of amyotrophic lateral sclerosis (ALS) significantly reduces expression of an activity-dependent early stress marker and muscle denervation, delays disease onset and preserves muscular strength in male ALS mice. Thus, as a novel component of C-boutons, TMEM16F controls motoneuron excitability and impacts motor resistance as well as motor deterioration in ALS.
This study strongly supports a role for excitatory networks in the development of motoneuron disease in an ALS context and to the potential of ionic channels as therapeutic candidates.

Keywords: electrical activity, muscarinic regulation, motor performance
Acknowledgments: This work was supported by the Association pour la Recherche sur la Sclérose Latérale Amyotrophique, ARSLA (to F.S), the Association Française contre les Myopathies (to F.S), ANR Mimetic n°ANR-15-CE18-0017-01 (to F.S), ANR-14-RARE-0006 (to C.R). C. Soulard was supported by MENRT PhD grant and by ARSLA (PhD fellowship 4th year).
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POA6 : LOW DOSE INTERLEUKIN-2 IN AMYOTROPHIC LATERAL SCLEROSIS IS WELL TOLERATED AND REGULATES MARKERS OF INFLAMMATION IN BLOOD.

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Low-dose interleukin-2 (ld-IL-2) increases regulatory T-cells (Tregs) number and function in several auto-inflammatory conditions. As neuro-inflammation is a pathological feature of amyotrophic lateral sclerosis (ALS), we aimed to evaluate the pharmacodynamics and safety of ld-IL-2 in ALS patients.
This was a parallel three-arm, randomised, double-blind, placebo-controlled study. Patients were randomised (1:1:1) to either 1 MIU IL-2, 2 MIU IL-2, or placebo, administered sub-cuteanously daily for 5 days every 4 weeks for 3 cycles, and followed-up thereafter for 3 months. Eligibility criteria included age <75 years, disease duration <5 years, riluzole treatment >3 months, and a slow vital capacity ≥70% of normal. The primary outcome was Treg change (as a percentage of CD4+ T-cells) on day 8. Secondary outcomes were Treg number or frequency at all time points, Treg suppressive function, and plasma chemokine concentrations (CCL2, CCL17

and CCL18). Disease progression was assessed through ALSFRS-R, Slow Vital Capacity, and plasma NFL levels. Safety was assessed through clinical examination, adverse events reports, and routine laboratory tests.
All 36 randomised patients were alive at the end of the 6 months follow-up, and all but one completed all trial assessments. No drug-related serious adverse event (SAE) was observed, and no change in disease progression was evidenced through ALSFRS, SVC, or plasma NFL levels. Non-serious AEs occurred more often in the 1 or 2 MIU IL-2 groups as compared to placebo: injection site reactions (2MIU: n=12 [100%]; 1MIU: n=11 [91.7%]; placebo: n=1 [8.3%]) and flu-like symptoms (2MIU: n=3 [25%] and none with 1MIU and placebo).
Primary outcome analysis showed an increase ($p<0.0001$) at D8 in Tregs frequency of $CD4^+$ cells in the 2 MIU and 1 MIU arms as compared to placebo with a large effect size (ES) for both treatment groups: 2MIU ES=3.7 (IC95%: 2.3-4.9) and 1MIU ES=3.5 (IC95%: 2.1-4.6). At D64 after cycle 3 response was higher than after cycle 1 (+7.6% at 2MIU and +4.4% at 1MIU - $p<0.0001$). Treg suppressive function was significantly increased with 2 MIU ($p=0·008$) and 1 MIU ($p=0·005$). Plasma CCL2 decreased in a dose-related fashion ($p=0.0004$), while CCL17 and CCL18 plasma levels dose-dependently increased ($p=0.0033$ & $p=0.0105$).
In the context of this double-blind placebo-controlled randomised clinical trial we found that ld-IL-2 has a good safety profile and increased Treg numbers, frequency and function over 3 monthly cycles in ALS subjects. Altogether, the observed changes in Tregs and ALS-associated inflammatory markers, including CCL2 and monocyte phenotype, are in keeping with a shift to a lesser cytopathic environment.

Further studies are needed to investigate whether these changes are reflected in the CNS and favourably impact on ALS disease progression.

Keywords: Amyotrophic lateral sclerosis, low-dose Interleukin-2, neuro-inflammation
Funding: This study was funded by a government call-for-tender for academic/investigator-driven research (French Ministry of Health, PHRC-I, 2014, n° 14-056), the French ALS patient Association ARSLA and EU H2020 Grant No. 633413. The Sponsor (CHU-Nimes, France) of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of Interest: Drs. Camu, Mickunas, Payan, Juntas Morales, Pageot, Masseguin, Suehs, De Vos, Saker, Andreasson and Veyrune have nothing to disclose; Drs. Bensimon, Tree, Leigh, Locati, Garlanda, report no conflict of interest; Dr. Bensimon reports grants from French Health Ministry (PHRC-I), grants from ARSLA, grants from EU-H2020, during the conduct of the study; In addition, Dr. Bensimon has a patent (number: B75649EPD40021) pending, and a patent (WO 2012123381 A1) with royalties paid to APHP, INSERM, Sorbonne Universite. Drs. Bensimon, Tree, Leigh, Locati, Garlanda, Shaw, Kirby, Malaspina have a patent # B75649EPD40021 pending; Dr. Malaspina reports grants from H2020 PHC-13-2014, grants from MND Association UK, grants and other from Barts and the London Charity, UCB Pharma SPRL, during the conduct of the study; other from F. Hoffmann-La Roche Ltd outside the submitted work; Dr. Zetterberg reports personal fees from Samumed, Roche Diagnostics, Denali, CogRx, Wave, outside the submitted work; Dr. Kirby reports grants from The Nimes University Hospital Center (CHU Nimes), grants from EU Horizon 2020, during the conduct of the study;Dr. Shaw reports grants from EU HORIZON 2020 PHC 13 2014 -2018 E 6,459,121 outside the submitted work; Dr. Al-Chalabi reports involvement in OrionPharma investigation and consultancies from Mitsubishi Tanabe Pharma, Cytokinetics Inc, Chronos Therapeutics, GSK, Lilly, and Biogen Idec, outside the submitted work.
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Session 3 : Physiopathologie des maladies du neurone moteur

- **Conférence invitée**

C3-LA RELAXATION DES EVENEMENTS SYNAPTIQUES INHIBITEURS PERMET DE COMPENSER LE MANQUE D'INHIBITION AU NIVEAU DES MOTONEURONES FŒTAUX DE LA SOURIS $SOD1^{G93A}$

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La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative dévastatrice ciblant les neurones moteurs (MNs) et diagnostiquée tardivement lors de la vie adulte. Dans le but d'identifier des changements précoces impliqués dans les phénomènes de neuro-dégénérescence de la SLA, nous avons analysé les afférences GABAergiques/glycinergiques au niveau des MNs fœtaux de la souris SOD1G93A (SOD) en parallèle à l'homéostasie chlorure. Nos résultats montrent que les IPSCs sont moins fréquents chez les animaux SOD en accord avec une réduction des terminaisons synaptiques VIAAT. Les MNs SOD présentent un EGABAAR (ECl) 10 mV plus dépolarisé que les MNs WT, ceci en association avec une réduction de KCC2. D'une manière intéressante les IPSCs GABAergiques/glycinergiques et les courants évoqués GABAAR montrent une cinétique plus lente dans leur phase de relaxation, ce phénomène étant corrélé à une concentration intracellulaire en chlorure [Cl-]i plus importante. Des simulations numériques révèlent que la relaxation plus lente des évènements synaptiques agit comme un mécanisme compensateur permettant de renforcer l'inhibition GABA/glycine lorsque le EGABAAR est plus dépolarisé. Nous ne savons pas comment de tels mécanismes évoluent au cours des processus pathophysiologiques de la maladie mais nos données indiquent que, tout au moins pour sa forme familiale SOD1, la SLA peut être considérée comme une maladie neuro-développementale.

Mots clés : souris fœtale SOD1G93A, homéostasie chlorure, activité synaptique inhibitrice
Remerciements : Marie-Paule Algeo, Marie-Alix Derieppe et Nathalie Argenta sont remerciées pour leur excellente gestion de l'animalerie souris.
Financements : Université de Bordeaux, CNRS et ARSLA
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- **Présentations sélectionnées à partir de l'appel à communication**

PO3.1- L'EXPRESSION DE LA MUTATION SOD1^{G93A} DANS LES MOTONEURONES ET /OU LES MYOTUBES AFFECTE DIFFEREMMENT LA FONCTION NEUROMUSCULAIRE IN VITRO.

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La sclérose latérale amyotrophique (SLA) est une maladie neurodégénérative mortelle caractérisée par la dégénérescence précoce de la jonction neuromusculaire (JNM) et la perte des motoneurones conduisant à une paralysie musculaire progressive. Il est maintenant bien démontré que la dégénérescence des motoneurones n'est pas due exclusivement à un processus cellulaire autonome, mais implique aussi d'autres types de cellules. Le muscle squelettique, principale cible des motoneurones, est un acteur majeur de la survie des motoneurones et de la synaptogenèse pendant le développement.
Nous avons mis au point un modèle murin de JNM in vitro, permettant d'étudier la contribution différentielle des motoneurones et des cellules musculaires exprimant la mutation SOD1G93A, sur le dysfonctionnement neuromusculaire.
Nous montrons que :
(i) Ce système de co-culture primaire permet la formation de JNM fonctionnelles et favorise l'expression de l'isoforme de la chaîne lourde de la myosine (MHC : myosin heavy chain) rapide et fatigable (type II-b), la plus vulnérable à la pathologie;
(ii) L'expression de la mutation SOD1G93A dans les myotubes n'empêche pas la formation d'une JNM fonctionnelle mais conduit à la diminution de la fréquence de contraction et à une baisse du niveau de transcription de l'isoforme lente de la MHC (type I), la plus résistante à la SLA;

(iii) Par contre, l'expression de la mutation SOD1G93A dans les motoneurones modifie fortement la formation d'une JNM fonctionnelle, que les myotubes expriment ou non la mutation.
Nos résultats suggèrent que les motoneurones sont un facteur majeur dans le processus de démantèlement de la JNM dans un modèle expérimental de SLA (1).

Référence :
(1) Benlefki S, Sanchez-Vicente A, Milla V et al., Expression of ALS-linked SOD1 mutation in motoneurons or myotubes induces differential effects on neuromuscular function in vitro, Neuroscience 2020;435:33–43
Mots clés : Jonction Neuromusculaire, Activité Electrique, Contraction Musculaire
Remerciements : ce travail a été soutenu par l'Inserm, l'association pour la recherche sur la SLA (ARSLA, subvention n° R14071FF), l'ANR Mimetic (subvention n° 15-CE18-0017), l'association française contre les myopathies (AFM, subvention n° 19496) et le LabEx NUMEV (ANR-10-LABX-20).
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PO3.2 - LE RECEPTEUR P2X4 DE L'ATP ACTEUR CLE DE LA PATHOGENESE DE LA SLA ET BIOMARQUEUR POTENTIEL

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Les récepteurs-canaux P2X de l'ATP exprimés dans les neurones et les cellules gliales du SNC sont impliqués dans de nombreuses maladies neurologiques et neurodégénératives dont la SLA, maladie des motoneurones fatale et incurable. Des travaux réalisés chez la souris SOD1-G93A, modèle murin modélisant la SLA, suggèrent l'implication des P2X4 motoneuronaux dans la pathogénèse de la SLA. Afin de déterminer le rôle de P2X4 dans cette maladie, nous avons créé de nouvelles lignées de souris transgéniques SOD1 chez lesquelles l'expression de P2X4 a été soit supprimée (SOD1/P2X4KO) soit augmentée en surface en supprimant la séquence responsable de l'internalisation du récepteur (SOD1/P2X4KI). La modification de l'expression de P2X4 chez ces animaux améliore les performances motrices et prolonge la durée de vie indiquant que P2X4 joue un rôle complexe dans la progression de la SLA. Nous montrons également que si P2X4 est exprimé dans les motoneurones spinaux durant la phase asymptomatique chez les souris SOD1, son expression augmente fortement dans la microglie activée durant la phase symptomatique. La modification de l'expression de P2X4 chez les souris SOD1 a d'ailleurs un impact sur l'expression des marqueurs astrocytaires et microgliaux suggérant un rôle dans la réactivité gliale spinale. P2X4 est également exprimé dans les macrophages. Nous avons observé une forte augmentation de l'expression de P2X4 à la surface des macrophages périphériques des souris SOD1 et ce bien avant l'apparition des premiers symptômes de la maladie. Enfin, nos résultats indiquent que l'augmentation de P2X4 en surface résulte de l'altération progressive de son mécanisme d'internalisation provoquée par les protéines SOD1 mal conformées. Nous mettons actuellement au point la détection de P2X4 à partir d'échantillons sanguins humains afin de déterminer si la présence aberrante de P2X4 à la surface des monocytes des patients peut servir de bio-marqueur pour le diagnostic précoce de la SLA.

Mots clés : P2X, SOD1G93A, modèle transgénique
Financements : Ce projet est financé par l'ARSLA , la FRC et le LabEx BRAIN ANR-10-LABX-43.
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PO3.3 - USING HUMAN PLURIPOTENT STEM CELLS DERIVED MOTOR NEURONS TO ADDRESS THE PATHOGENESIS OF SMA

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Spinal muscular atrophy is the most common genetic cause of infant mortality characterized by the specific degeneration of lower motoneurons (MNs) in the spinal cord, leading to progressive paralysis and muscle atrophy. SMA etiology relates to an insufficient amount of SMN (survival motor neuron) protein, which results from mutations in the SMN1 gene. Despite the ubiquitous expression of SMN protein, it is still unclear why MNs are one of the most affected cell types. Understanding this specific cellular tropism is critical but requires access to the relevant cell type. In this present study, we demonstrated that the reduced expression of SMN lead to a decreased survival of hiPSC-derived MNs rather than a defect in their generation. We identified that this phenotype can be rescued by kenpaullone, an inhibitor of several CKDs as well as JNK, likely through a JNK dependent mechanism. By a transcriptomic approach, we identified SMA-specific changes in early MNs that include genes involved in synaptic plasticity. Interestingly, these genetic defects were rescued by kenpaullone treatment. These findings suggest that alteration in synaptic organization might be a new therapeutic target for SMA. Furthermore, several studies suggest that pathological changes of the neuromuscular junction (NMJ) precede the motor neuronal loss. Therefore, it is critical to evaluate the NMJ formed by SMA patients' MNs, and to identify drugs that can restore the normal condition. We thus developed an in vitro co-culture strategy to study the interaction between MNs and its skeletal muscle target. Altogether, our results demonstrate the potential offered by hiPSC to shed light on the cellular and molecular bases of selective MN vulnerability in SMA.

Keywords: Spinal muscular atrophy (SMA), Human induced pluripotent stem cells (hiPSCs), Co-culture system.
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PO3.4 – MODULATION OF CHOLESTEROL METABOLISM AS A NEW THERAPEUTICAL APPROACH FOR AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease and is characterized by the progressive loss of upper and lower motor neurons, leading to paralysis and death. Accumulation of cholesterol in the central nervous system (CNS) has been reported to actively contribute to the disease progression in Alzheimer's disease, Huntington's disease, Spinocerebellar ataxia and more recently ALS. Cholesterol is essential for myelin compartment, but also for its functional and structural role in plasmatic membrane. However, in the CNS, cholesterol is synthetized in situ and is not able to freely cross the blood brain barrier (BBB). Cholesterol-24-hydroxylase (CYP46A1) allows the conversion of cholesterol to 24-hydroxycholesterol, able to cross the BBB, thus regulating cholesterol homeostasis. Furthermore, this enzyme is a key neuronal stress response such as oxidative stress or protein aggregation. Therefore, we hypothesized that CYP46A1 could be relevant for a therapy in ALS to target both familial and sporadic forms of ALS independently from their genetic origin. In the severe $SOD1^{G93A}$ model, we overexpressed CYP46A1 using a new AAV serotype (AAVi) able to cross the BBB after intravenous injection. As a first step, we confirmed that the AAVi viral vector has a specific tropism for the CNS and especially motoneurons. Secondary, we demonstrated a significant and prolonged motor rescue of animals treated pre or post-symptomatically, but also a preventive effect on myelin loss, compared to untreated animals. Evaluation of this therapeutic strategy is ongoing in another model of ALS.

Keywords: gene therapy; metabolism; CYP46A1
Acknowledgements: we would like to thank the ARSLA organization
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PO3.5 - NUTRITIONAL AND METABOLIC STATUS AT DIAGNOSIS AND SURVIVAL OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND FRONTOTEMPORAL DEMENTIA (FTD) COMPARED TO PATIENTS WITH ALS ALONE.

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Rationale: About 5%–10% of ALS patients suffer from frank ALS/FTD. No studies have investigated nutritional and metabolic status in ALS/FTD and its impact on survival. The aims of this study were i) to study nutritional and metabolic status of ALS/FTD compared to ALS patients, ii) to study survival according to the disease and metabolic status.
Methods: Three months after diagnosis, nutritional assessments and body composition were performed. Resting energy expenditure measured (mREE) by indirect calorimetry and calculated (cREE) were used for the calculation of REE variation. Functional (ALSFRS-R) and respiratory (Forced Vital Capacity [FVC]) assessments were collected. Survival by Log-rank test and multivariate analysis with Cox model were also used.
Results: 446 patients were included, 421 ALS patients and 25 (5.6%) ALS/FTD patients. Median age at diagnosis and sex were not significantly different. ALSFRS-R was not significantly different but FVC was lower in ALS/FTD patients (79.5% vs. 93.0%, p=0.042). ALS/FTD patients had a higher weight loss (-10.3% vs -5.0%, p=0.004). Body composition was not significantly different. However, ALS/FTD had less often a REE variation over 10% (32.0% vs. 53.9%, p=0.03). ALS/FTD patients had more often gastrostomy placement (68.0% vs. 40.1%, p=0.006). In univariate analysis, ALS/FTD patients had an increased risk of death compared to ALS patients (HR = 1.97, p=0.001) but not in multivariate analysis. In multivariate analysis, regardless of type of ALS (ALS and ALS/DFT) a higher fat mass (+1%) was associated with a reduced risk of death (HR = 0.98, p=0.03) and a greater weight loss (-1%) with an increased risk of death (HR = 1.03, p<0.0001).
Conclusion: ALS/FTD patients would seem to have a lower survival compared to patients with ALS alone. Regardless of the form of ALS, as described previously in literature, nutritional status and body composition were associated with the risk of death.

Keywords: amyotrophic lateral sclerosis, frontotemporal dementia, survival
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PO3.6 - NEURAL CORRELATES OF MOTOR IMAGERY OF GAIT IN AMYOTROPHIC LATERAL SCLEROSIS

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Background and Objectives
Gait impairment is understudied and poorly characterised in Amyotrophic Lateral Sclerosis (ALS), despite increasing evidence of considerable extrapyramidal and cerebellar dysfunction. Gait impairment adds to the considerable motor disability of ALS patients and requires target multidisciplinary interventions. The objective of this study is to assess gait imagery specific-networks and functional adaptation in ALS.
Methods
Seventeen ALS patients with lower motor neuron predominant (LMNp) disability, fourteen patients with upper motor neurons predominant (UMNp) disease and fourteen healthy controls performed a dual motor imagery task on fMRI; normal and precision. The Movement Imagery Questionnaire – Revised Second Version (MIQ-rs) was used to appraise movement imagery in each participant. Study-group specific activation patterns were evaluated during motor imagery of gait. Additional voxel based functional connectivity analyses were carried out using the supplementary motor area, cerebellum and striatum as seed regions.
Results
Our data revealed a significant increase in imagery time in UMNp patients compared to controls and LMNp during imagined gait. UMNp patients exhibited decreased SMA, DLPFC and superior parietal lobule activation

and increased orbitofrontal, parietal and cerebellar signal during imagined locomotion. Increased functional connectivity of the striato and parieto-cerebellar circuits was also demonstrated. Additional activation was detected in the insula and cingulate cortex.
Conclusions
Our results suggest functional reorganisation in ALS. Enhanced striato- and parieto-cerebellar networks in UMNp ALS patients are likely to represent a compensatory response to impaired postural control. Activation of insular and cingulate regions suggest that fear of falling is a an implication of gait disturbance in ALS

Keywords: Amyotrophic Lateral Sclerosis, motor imagery of gait, functional connectivity
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Conférence « hors thème »

C4-MITOCHONDRIAL DYSFUNCTION IN CHCHD10-RELATED NEURODEGENERATIVE DISEASES

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Recently, we provided the genetic evidence showing that mitochondrial dysfunction can trigger motor neuron disease (MND). We reported patients, carrying the p.Ser59Leu heterozygous mutation in the CHCHD10 gene, from a large family with a mitochondrial myopathy associated with MND. Rapidly, our group and others reported CHCHD10 mutations in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD)-ALS and other neurodegenerative diseases. We generated knock-in (KI) mice, carrying the p.Ser59Leu mutation, which mimics the mitochondrial myopathy with mtDNA instability presented by the patients from our original family. Before 14 months of age, all KI mice develop a fatal mitochondrial cardiomyopathy associated with enhanced mitophagy. Mutant animals also display pathognomonic signs of ALS including degeneration of neuromuscular junctions (NMJs) and motor neurons, significant motor neuron loss in lumbar spinal cord and TDP-43 proteinopathy. Furthermore, our data show that pathological effects of the p.Ser59Leu mutation target the muscle prior to NMJ and motor neurons, and are in favor with a key role for muscle in MND associated with CHCHD10 mutations. We also showed that motor neurons differentiated from human iPSCs carrying the p.Ser59Leu mutation were much more sensitive to caspase-dependent cell death than control cells.

The models that we generated allowed us to dissect the molecular mechanisms responsible for the observed phenotypes, that are different in heart and brain tissues, and that will be discussed.

Mots clés : MND, CHCHD10, mitochondria
Financements : ANR, AFM, Fondation Maladies Rares
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Table ronde

CONTINUUM SLA/DFT : CONTROVERSES

TR1-DFT ET DFT/SLA: UNE MEME SYMPTOMATOLOGIE COMPORTEMENTALE ?

Pasquier F (1,2), Lebert F (1,2), Danel V (3), Deramecourt V (1,2), Lebouvier T (2)

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TR2-TRANSLATION AXONALE ET NEURODEGENERESCENCE SLA/DFT

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Motor neurons are highly polarized cells projecting axons that extend up to one meter. The axonal volume can exceed more than one thousand times that of soma. These exceptional features require unique solutions for protein homeostasis. Recently we uncovered a role of ALS/FTD-causative protein FUS in axonal translation and

demonstrated that ALS/FTD-causing FUS mutations suppress local protein synthesis in adult mouse axons prior to disease symptoms **[1]**. Consistent with our findings, mutant FUS-dependent impaired axonal translation was also reported by others in a neuronal cell line **[2]** and in *Xenopus* neurons **[3]**.
Together, evidence points to disrupted axonal protein synthesis as a key contributor to axon degeneration and neuromuscular junction (NMJ) loss, one of the earliest events in ALS. However, the underlying mechanisms are still unknown. We propose that local mRNA translation and the specific local compartmentalization of the translation machinery are crucial for the regulation of the mature motor axon and the functioning of NMJs, and that its disruption underlies neurodegeneration.
We are combining sophisticated mouse models and human iPSC-derived motor neurons using compartmented microfluidic chambers. To map the composition of the translation machinery and translating mRNAs in healthy and ALS motor axons we are in the midst of performing an unbiased *in vivo* analysis of the local translatome (mRNAs that are actively translated) in healthy and diseased motor axons by exploiting unique reporter transgenic mouse lines coupled with high-throughput RNA sequencing. The mechanisms driving axonal maintenance and loss are then validating by fluorescence *in situ* hybridization, new labelling approaches to visualize nascent proteins using superresolution microscopy and new iPSC-derived functional NMJs that we developed.
Together, our work has the potential to further our understanding of how mature axons and their synapses with muscles are lost in ALS and may identify targets for effective therapeutic intervention.

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Keywords: Axonal mRNA translation ; Axonal degeneration and Neuromuscular junction (NMJ) loss ; FUS-mediated disease
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TR3-LONGITUDINAL STUDY OF EXTRA-MOTOR MANIFESTATIONS IN AMYOTROPHIC LATERAL SCLEROSIS: CLINICAL AND IMAGING DATA

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Objectives: Extra-motor manifestations occur in 50% of patients with amyotrophic lateral sclerosis (ALS). These mainly concern cognition and behaviour. Depression and anxiety are less frequent. Little is known about how these manifestations change as the disease progresses. Similarly, although cortical thinning has been well documented at disease onset, there are scant data about cortical thinning over time and how this correlates with extra-motor manifestations. The present study therefore assessed cognitive, emotional and psychological state and cortical thinning in a group of patients with ALS at baseline and after a follow-up period. **Methods:** We assessed executive functions, facial emotion recognition, depressive and anxious symptoms, and cortical thinning in 43 patients with ALS at baseline, comparing them with 28 healthy controls, and 21 of them 9 months later. We looked for links among the extra-motor manifestations and correlations with cortical thickness. **Results:** At baseline, patients had poor executive function and recognition of complex emotions

from the eyes, and more anxious and depressive symptoms than controls. At follow-up, only inhibition abilities had worsened. Cortical thinning was observed in bilateral precentral regions and other parts of the cerebral cortex at baseline. Over time, it worsened in motor and extra-motor areas. Executive functions correlated with thinning in the middle and inferior frontal gyrus and orbitofrontal cortex. **Conclusions**: During follow-up, there was little deterioration in extra-motor manifestations and psychological state, despite continuing cortical thinning. Patients with affective ToM changes seemed less depressed than the others. Impaired mental flexibility was subtended by prefrontal regions with cortical thinning.

Keywords: Amyotrophic lateral sclerosis, cognition, emotion
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Acknowledgments: The authors are grateful to the patients, relatives and healthy controls for their participation. The authors would also like to thank the clinicians of Caen University Hospital's Neurology Department who made it possible to collect the clinical and cognitive data, and the Cyceron MRI staff members who carried out the imaging. Finally, we thank Charlotte Postel for her help with using FreeSurfer.
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SESSION POSTERS

P01 : DECIPHERING THE ROLE OF THE ALS-LINKED GENE *TBK1* IN MOTOR NEURONS AND MICROGLIA

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Mutations in the ubiquitously expressed *TANK-Binding Kinase 1* gene (*TBK1*) have recently been implicated in ALS and act by a dominant loss-of-function mechanism. Such a mechanism might be easier to study than unknown gain-of-toxic-functions or mixtures with loss-of-functions, linked to most other ALS-genes. TBK1 is involved in autophagy and innate immunity, suggesting that mutations in *TBK1* could lead to ALS by both cell-autonomous (autophagy deregulation in motor neurons) and cell-non-autonomous mechanisms (altered

response in microglia). To decipher the role of TBK1 in these two cell types, we have generated mice with *Tbk1* deletion specifically in motor neurons or microglial cells. Mice with *Tbk1* deletion in motor neurons do not develop any motor phenotype until 2 years, but exhibit increased age-related alterations of the neuromuscular junctions. During my master's internship, we found that *Tbk1* deletion in motor neurons is not sufficient to induce their loss at 22 months, which does not exclude presence of dysfunctions in the motor neurons. To test this, we investigated if deletion of *Tbk1* in motor neurons could change their selective vulnerability to ALS by assessing the distribution of the different motor neuron subpopulations. Then, we tested if motor neurons with *Tbk1* deletion reveal signs of autophagy deregulation by looking at the formation of pathological inclusions of p62, a target of TBK1. To study the effects of *Tbk1* deletion on microglial responses, we optimized cultures of primary microglial cells from mice with *Tbk1* deletion. During my upcoming PhD, this will allow us to assess how *Tbk1* deletion affects microglial responses to pro- and anti-inflammatory stimuli, and whether it contributes to motor neuron degeneration in a non-cell autonomous manner. This project could help better understand the ALS disease mechanism and the contribution of pathological motor neuron-microglia interactions.

Mots clés : TBK1, Mouse model, Microglial cells.
Financements : ARSLA, ARMC, S.L.A.F.R., La longue route des malades de la SLA, Un pied devant l'autre.
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P02 : *FUS* IS REQUIRED FOR MUSCLE ULTRASTRUCTURE AND MITOCHONDRIAL FUNCTION: INVOLVEMENT IN AMYOTROPHIC LATERAL SCLEROSIS

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Mutations in the RNA-binding protein FUS cause juvenile forms of amyotrophic lateral sclerosis (ALS), with early onset and rapid disease progression. Most FUS mutations are located in or nearby the C-terminal nuclear localization sequence of FUS, leading to cytoplasmic accumulation of the protein. Our laboratory previously developed a conditional *Fus* Knock-In model of ALS [1, 2]. These mice display a constitutive deletion of NLS that can be rescued to the wild type situation upon CRE-mediated recombination. We recently demonstrated a critical role for FUS in stimulating the neuromuscular junction related gene expression program in subsynaptic nuclei of skeletal muscles, raising the question of potential other functions for FUS in skeletal muscle [3]. Transcriptome analysis of muscles of knock-in *Fus* mice and of *Fus* knock-out animals revealed striking common downregulation of genes related to mitochondrial function. Consistent with this, mitochondrial degeneration and disorganization of myofibrillar ultrastructure was focally affected and muscle and mitochondrial gene expression was deregulated in adult heterozygous *Fus* knock-in mice. *Fus* knockdown in C2C12 cells recapitulated altered gene expression levels and mitochondrial abnormalities observed *in vivo* in *Fus* mutant mice, suggesting a loss of function mechanism. Indeed, FUS ChIP sequencing in C2C12 cells revealed that the FUS protein bound to the TSS of a number of genes related to mitochondrial function. Importantly, analysis of motifs in FUS-bound chromatin regions suggested that these genes could be related by a set of ETS transcription factors.

Our current work focuses on the identification of mechanistic links between ETS transcription factors, mitochondrial function and FUS, and addressing the relevance of this pathway in patients.

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Keywords: FUS, Mitochondria, Muscle
Acknowledgements: ANR, ARSLA, Fondation Thierry Latran, Frick foundation for ALS research, AFM telethon, ALS association and Strasbourg university (MENESR).

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P03 : PAS-INDUCED RECOVERY OF INTRACORTICAL INHIBITION IN PATIENTS WITH ALS

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Backgrounds: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motoneurons. While the aetiology of ALS rem.ains unknown, current evidence from transcranial magnetic stimulation (TMS) studies suggest that cortical hyperexcitability is an early mechanism involved in selective motor neuron death [1]. In this view, electrophysiogical methods that are able to modulate the cortical excitability may help to improve the balance between excitation and inhibition in the motor cortex in attempt to slow down the disease progression. Paired associative stimulation (PAS) combines TMS applied over the motor cortex and electrical stimulation of peripheral nerve afferents. This method induces changes in synaptic transmission in cortical and spinal neuron networks that outlast the period of application [2]. To date, only one study has revealed modification in motor evoked potentials (MEPs) after PAS in ALS [3].
Objective: This study aims to explore the effects of PAS on intracortical inhibition (ICI) which is impaired in sporadic and familial ALS [1].
Methods: Thirteen newly-diagnosed ALS patients followed in Department of Neurology at the Pitié Salpêtrière hospital were included. Short and long ICI were explored using electromyogram recordings and paired-pulse TMS methods. Both inhibitions were estimated in patients before and 60 minutes after one session of repeated PAS (N=2000, TMS over arm motor area + electrical stimulations of radial nerve afferents).
Results: These preliminary results suggest that PAS enhance GABAA inhibition evoked in the motor cortex in patients. They support that PAS paradigm may help ICI to recover and to counteract cortical hyperexcitablity in ALS.
Conclusion: This study provides evidence that PAS paradigm may induce plastic changes in sensorimotor networks in ALS patients. Further investigations are needed to shed light on potential of PAS paradigms to induce long term neuroplasticity to develop new therapeutic approaches in ALS.

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Keywords: Electrophysiology, humans, amyotrophic lateral sclerosis (ALS)
Conflict of interest: The authors have no conflicts of interest to declare and have no competing financial interests.
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P04 : ANNULATION

P05 : POTENTIAL MECHANISM OF GLIAL MEDIATED SPREADING OF *SOD1* IN AMYOTROPHIC LATERAL SCLEROSIS

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OBJECTIVES: Amyotrophic lateral sclerosis (ALS) is characterized by the selective loss of upper and lower motoneurons leading in a few years to paralysis and death. The most frequent forms are sporadic. Among the familial forms of the disease, the first gene identified codes for an ubiquitous protein, superoxide dismutase type 1 (SOD1). Transgenic mice expressing mutated human forms of SOD1 faithfully summarize the main features of the disease. Insufficient degradation of these aberrant proteins induces a gain in intracellular toxic

function in motoneurons. However, numerous studies have shown that the loss of motor functions is due to a combination of deleterious non-cell autonomous mechanisms encountered in many cell types including glial cells. Indeed, it appears that cellular interactions and in particular the spread of toxic molecules such as mutant SOD1 could play a role in the disease. Here, we propose to assess the role in SOD1-related ALS of an unconventional secretion pathway for misfolded proteins.
METHODS: We study the ubiquitin specific protease (USP)19- dependent "unconventional" secretion of $SOD1^{G93A}$ mutant using primary co-culture system of motoneurons and oligodendrocytes and analyze the cellular and tissue expression of USP19 during the different stages of the disease by immunofluorescence in a mouse transgenic model for $SOD1^{G93A}$.

RESULTS: Our preliminary data show *in vitro* that the USP19 deubiquitinase promotes the secretion of mutant $SOD1^{G93A}$ as well as of the wild-type form. At a more integrated level, immunofluorescence analyses reveal that USP19 is particularly expressed in glial cells of the spinal cord, in particular in oligodendrocytes.
CONCLUSION: These results allow us to define the bases for a targeted intervention in these ALS transgenic mice and they will provide new knowledge on the mechanisms of SOD1 propagation necessary for the development of new therapies.

Keywords: Amyotrophic lateral sclerosis, SOD1, USP19
Acknowledgments: ARSLA fundings, ANR "SPREADALS" fundings.
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P06 : DETERMINATION DE LA CONTRIBUTION DE L'HYPEREXCITABILITE CORTICALE AU DECLENCHEMENT ET A LA PROGRESSION DE LA SLA

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Un ensemble d'études des patients SLA met en avant une possible origine corticale de la SLA et une propagation corticofuge de la maladie. Deux mécanismes de propagation corticofuge ont été proposés : la propagation de type prion d'aggrégats de protéines mal-repliées, ou la propagation d'activités neuronales aberrantes conduisant à une excitotoxicité glutamatergique [1]. Dans le modèle murin $Sod1^{G86R}$, l'absence de neurones à projection subcérébrale (NPSC, une des deux principales populations de neurones corticofuges) s'avère bénéfique, et suggère un rôle délétère du cortex cérébral sur ses cibles, en accord avec l'hypothèse corticofuge [2]. Ces mêmes animaux présentent une hyperexcitabilité corticale très précoce (Scekic-Zahirovic *et al.,* en préparation), permettant d'envisager une propagation corticofuge de nature électrophysiologique. En revanche, l'ablation génétique du transgène $SOD1^{G37R}$ dans les NPSC n'améliore pas le phénotype de ce modèle transgénique, écartant le mécanisme de type prion [3].
S'appuyant sur ces travaux, mon projet vise à tester l'hypothèse d'une propagation corticofuge de nature électrophysiologique. Plus précisément, nous allons tester l'effet du « silencing » des NPSC sur le déclenchement des symptômes et la survie des souris $Sod1^{G86R}$. Pour cela, nous générons des souris $Sod1^{G86R}$;$CrymCreER^{T2}$, exprimant de manière ubiquitaire le transgène $Sod1^{G86R}$, ainsi qu'une forme inductible de la CRE recombinase dans les NPSC. Le cortex moteur sera injecté avec un AAV CRE-dépendant exprimant le récepteur DREADD hMD4(Gi) permettant le silencing des neurones qui l'expriment en réponse à la fixation de son ligand synthétique, la Clozapine-N-Oxide (CNO), administrée dans l'eau de boisson.

L'utilisation d'approches électrophysiologiques, comportementales, histologiques, et moléculaires permettront d'évaluer l'effet du silencing des NPSC chez les souris $Sod1^{G86R}$, et de mieux comprendre la nature du message corticofuge toxique mis en évidence chez ces animaux. A terme, ce projet de recherche contribuera à déterminer si l'hyperexcitabilité corticale pourrait constituer une nouvelle cible thérapeutique dans le traitement de la SLA.

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Mots clés : Hypothèse Corticofuge, Hyperexcitabilité Corticale, Silencing neuronal
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P07 : RECHERCHE DES BASES MOLECULAIRES ET CELLULAIRES DE L'HYPEREXCITABILITE CORTICALE DANS UN MODELE MURIN DE SLA

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Les patients atteints de SLA présentent une hyperexcitabilité corticale précoce, voire pré-symptomatique dans le cas des porteurs de mutations sur le gène *SOD1*, et négativement corrélée à la survie [1]. Au laboratoire, Jelena Scekic-Zahirovic a mis en évidence une hyperexcitabilité corticale précoce et persistante dans le modèle murin Sod1^{G86R}, ainsi que dans le modèle Fus$^{\Delta NLS}$ (Scekic-Zahirovic et al., résultats non publiés).
Mon travail de thèse vise à identifier les bases moléculaires et cellulaires qui sous-tendent cette altération du fonctionnement des réseaux corticaux. En absence d'altération majeure des populations d'interneurones corticaux inhibiteurs, nous nous sommes penchés sur les différents neurotransmetteurs connus pour moduler l'excitabilité du cortex moteur [2]. Une analyse en spectrométrie de masse de tissus de souris sauvages et Sod1^{G86R} à 45 jours, 60 jours (pré-symptomatiques) et 90 jours (premiers symptômes moteurs) a mis en évidence une baisse d'un tiers des niveaux de noradrénaline significative à tous les âges étudiés, non seulement dans le cortex moteur mais également dans l'hippocampe et la moelle épinière. Par des approches de biologie moléculaire, d'histologie et de pharmacologie, nous étudions à présent le système noradrénergique chez les souris Sod1^{G86R}, et sa contribution à l'hyperexcitabilité corticale observée chez ces animaux. A terme nous espérons tester l'effet d'un rééquilibrage de l'excitabilité corticale sur le déclenchement et la survie de souris modélisant la SLA, en vue de potentiels développements thérapeutiques.

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Mots clés : Hyperexcitabilité Corticale ; Noradrénaline
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P08 : INVESTIGATION INTO THE BIOMAGNIFICATION OF CYANOTOXINS IN THE ENVIRONMENT IN AUSTRALIA AND ITS POTENTIAL CORRELATION WITH NEUROINFLAMMATION AND NEURODEGENERATION MECHANISMS IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

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Many cyanotoxins are acute toxins and do not have the capacity to bio-concentrate and accumulate in the environment. However, toxic non-protein amino acids such as β-methylamino-L-alanine (BMAA) produced by most cyanobacterial strains can bioconcentrate in the environment.
BMAA and its isomers aminoethyl glycine (AEG) and 2,4-diaminobutyric acid (2,4DAB) are a neurotoxin present in cyanobacteria and have been linked to the increased incidence of sporadic Amyotrophic Lateral Sclerosis

(ALS)[1, 2]. Although 10% of ALS cases are familial, the remaining 90% are considered sporadic that could be caused by a complex interplay of genetic susceptibility and environmental risk factors.
In spite of the increasing frequency and toxicity of cyanobacterial blooms in recreational and drinking water catchments in Australia [3], the levels of BMAA and other "small" cyanotoxins are not quantitated in water or food. Water treatment methods in Australia are not standardized, nor records of levels of cyanotoxins centralized, thus, the scale of the problem is not fully understood.
The aims of this project are to 1) develop new methods for the detection of BMAA and its natural isomers from sediment, freshwater/saltwater, and several aquatic species; 2) to geolocalise cyanobacterial blooms in Australia in real time using the MERIS satellite; 3) to show that these levels of biotoxins could be associated with neuroinflammatory and neurodegenerative mechanisms present in patients with sporadic ALS using UHPLC-MS/MS and immunohistochemical detection in plasma, serum, archival brain and spinal cord tissue.
The overall study will highlight the increasing impact of the biomagnification of cyanotoxins in the Australian environment and its possible link with sporadic ALS.

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Keywords: Cyanotoxins, neurotoxicity, environment
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P09 : PRIMARY CULTURE OF SPINAL MOTOR NEURONS FROM *SOD1*(G93A) TG RAT ARE CHARACTERIZED BY DEFECT IN NEURONAL MATURATION AND HIGHER SENSITIVITY TO GLUTAMATERTIC STRESS.

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Amyotrophic lateral sclerosis (ALS) is a rare motor neuron disease, characterized by degeneration and loss of upper and lower motor neurons. The loss of spinal motor neurons in ALS is caused by complex and multifactorial pathological events. Glutamate excitotoxicity is known to participate in neuronal death in ALS. Some familial cases are linked to gain-of-function mutations of superoxide dismutase type-1 (SOD1), an antioxidant enzyme. In addition, mutations on genes involved in RNA metabolism (e.g. tarbp/TDP-43, fus) are found in inherited and sporadic forms of ALS. TDP43 proteins are abnormally translocated from the nucleus to the cytoplasm. Aggregates of TDP43 are found in the motor neurons of the majority of ALS patients.
Here, using primary culture of motor neurons from SOD1(G93A) Tg rats, we investigated their maturation and their sensitivity to a glutamatergic stress.
Neuronal maturation was assessed by immunostaining with a pan-neuronal marker (MAP2), a marker of mature neurons (NFh, neurofilament, heavy chain) and a late marker of maturation of motor neurons (ChAT). Neuronal survival, integrity of the neurite network and abnormal translocation of TDP43 were studied by immunostaining.
SOD1(G93A) Tg MNs cultures showed lower maturation, expressing less NFh and ChAT markers. In basal condition, we observed abnormal translocation of TDP43 in motor neurons from SOD1(G93A) Tg culture when compared to WT. In addition, a higher sensitivity to glutamate was observed. It was associated with an exacerbated cytoplasmic distribution of TDP43.
Altogether, our results indicate a delay in neuronal maturation and a higher sensitive to glutamatergic stress, which could originate from a basal TDP43 pathology, linked to the toxic gain of function of the G93A mutation in SOD1.

Keywords: in vitro, TDP43, SOD1 G93A

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P10 : TOWARDS ELUCIDATING THE ROLE OF OLIGODENDROCYTES IN FUS-ALS

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In the CNS, oligodendrocytes support motor neurons through two essential mechanisms. They provide motor neurons axons with a compact multilayered myelin sheath, therefore ensuring proper electrical activity, and they provide neurons with metabolic support through monocarboxylate transporters (MCT1). Several dysfunctions of those cells have been observed in the pathogenesis of Amyotrophic Lateral Sclerosis, raising the question of their implication in the development of the disease. First, inclusions of ALS-linked proteins TDP-43 and FUS have been observed in oligodendrocytes from ALS patients. Furthermore, previous research demonstrated abnormalities in proliferation and differentiation of oligodendrocytes progenitors as well as myelin defects and compromised expression of the monocarboxylate transporter MCT1 in SOD1 based models. Importantly, removal of mutant SOD1 expression delays disease onset and increases survival of mutant SOD1 mice, while expression of mutant SOD1 in oligodendrocytes is sufficient to trigger motor neuron death in cultured cells and in zebrafish. It remains currently unknown whether oligodendrocyte dysfunction contributes to *FUS*-ALS. Preliminary evidence showed a late defect in myelin related gene expression in *Fus* knock-in mice. The aim of my doctoral work is to determine the role of oligodendrocytes in *FUS*-ALS. To this aim, we will explore oligodendrocytic defects in mouse models of ALS, and use mouse genetics to modulate expression of mutant FUS in oligodendrocytes. We will further explore how unconventional secretion mediated by USP19 might participate in the disease process.

Keywords: ALS, FUS, Oligodendrocytes, USP19
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P11 : TROPHICITE ET TOXICITE DES MACROPHAGES ET DES CELLULES MICROGLIALES HUMAINES ENVERS LES MOTONEURONES DANS LA SLA

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Dans la Sclérose Latérale Amyotrophique (SLA), de nombreuses évidences indiquent aujourd'hui que la neuro-inflammation joue un rôle important dans la progression de la pathologie. La particularité du motoneurone spinal est qu'il est situé à la fois dans le système nerveux central avec son corps cellulaire au contact des cellules microgliales et en périphérie avec son axone au contact des macrophages. Notre hypothèse est que ces deux types de macrophages pourraient contribuer de façon distincte à la dégénérescence motoneuronale, et constituer deux cibles thérapeutiques différentes. Afin d'étudier ces cellules chez l'homme et dans différentes formes de SLA, nous utilisons des cellules souches pluripotentes induites (iPSc) de patients, et nous différencions maintenant en routine ces iPSc en motoneurones (MNs) ainsi qu'en macrophages et en cellules microgliales. De plus, pour mimer leur environnement, nous utilisons des puces microfluidiques permettant de séparer les corps cellulaires des MNs de leurs axones dans deux compartiments distincts.

D'une part, nous étudions les défauts intrinsèques des macrophages et des cellules microgliales dérivées des iPSc SLA, tels que la sécrétion basale de cytokines ainsi que les réponses à des stimuli inflammatoires, les capacités d'endocytose et les altérations de leurs voies de dégradation. Nos résultats tendent à montrer que les 2 types de macrophages présentent des altérations intrinsèques propre à chaque type de macrophages et distinctes en fonction des formes de SLA. D'autre part, des co-cultures de cellules porteuses ou non des mutations SLA, sont réalisées pour étudier la toxicité des macrophages et microglie, envers les MNs. Les premiers résultats montrent des modifications sécrétoires de cytokines liées aux différentes mutations SLA étudiées. La souffrance axonale et la mort des MNs sont actuellement analysées, et une analyse transcriptomique est en cours afin d'identifier des gènes dérégulés ainsi que des voies inflammatoires perturbées qui pourraient offrir de nouvelles cibles thérapeutiques.

Mots clés : neuro-inflammation, iPSc, puces microfluidiques
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P12 : INFLAMMATORY S100A9/MRP14 PROTEIN DEFICIENCY EXACERBATES DISEASE IN *SOD1*G93A MICE.

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Amyotrophic lateral sclerosis (ALS) is characterized by motor-neuron degeneration associated with neuro-inflammation. Our team showed that microglial cells and macrophages play an important role in disease progression. MRP8 and MRP14 (S100A8 and S100A9, respectively) belong to the calcium binding protein S100 family involved in reactive oxygen species (ROS) production and regulation of TNF release through Toll-like receptor 4 binding. MRP8 and MRP14 are expressed and secreted by inflammatory myeloid cells including microglial cells and macrophages. The aim of this study was to evaluate the role of MRP14 in ALS mouse model. MRP14 knock-out in ALS mice was expected to be beneficial since in Alzheimer's disease mouse models deleting S100A9 was associated with increased phagocytosis of amyloid plaques. In this study, we show that microglial reactivity is not altered in $SOD1^{G93A}$::MRP14-/- mice compared to $SOD1^{G93A}$::MRP14+/+ mice with typical increased activation over the disease course. However, deleting MRP14 in $SOD1^{G93A}$ mice led to a faster disease progression after reaching the symptomatic stage. This was associated with a decreased motor-neuron number in $SOD1^{G93A}$::MRP14-/- mice compared to $SOD1^{G93A}$::MRP14+/+ mice at the symptomatic stage. This study provides evidence that MRP14 is not required for overall microglial activation in ALS mice. However, modulation of MRP14 expression affects motor-neuron survival and disease course in ALS mice.

Keywords : Neuro-inflammation, MRP14, microglial cells.
Financements : ERA-NET NEURON, ARSLA, Fondation Thierry Latran, NRJ-Institut de France, ARMC, S.L.A.F.R., La longue route des malades de la SLA, un pied devant l'autre.
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P13 : GENERATION PAR KNOCK-IN ET CARACTERISATION D'UN MODELE DE SLA-DFT BASE SUR L'EXPRESSION CONDITIONNELLE DU MUTANT CHMP2B$^{INTRON\ 5}$

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La sclérose latérale amyotrophique (SLA) et la démence fronto-temporale (DFT) sont deux maladies neurodégénératives fatales qui constituent les deux extrêmes d'un même continuum génétique, clinique et histopathologique. Bien que dans chacune de ces pathologies des populations neuronales distinctes dégénèrent sélectivement en début de maladie, il apparait maintenant qu'elles présentent des mécanismes et des causes génétiques communes. En effet 15 à 20% des patients atteints de SLA développent une DFT et réciproquement. Parmi les gènes associés à ces deux maladies, des mutations du gène *CHMP2B* (Charged Multivesicular Body Protéine 2B) ont été observées chez des patients atteints de SLA, de FDT et de SLA-DFT. Trois modèles de souris transgéniques basés sur la surexpression du mutant CHMP2B$^{intron\ 5}$ sous contrôle de promoteurs hétérologues ont été générés [1-3]. Ces souris développent toutes, plus ou moins précocément, des phénotypes qui rappellent en partie la SLA et/ou la DFT en fonction du promoteur utilisé.
Afin de nous rapprocher de la situation observée chez l'homme nous avons généré par recombinaison homologue une souris exprimant de façon conditionnelle le mutant CHMP2B^{intron5} au niveau d'un ou de 2 allèles du gène *Chmp2B*. Les cellules exprimant le mutant co-expriment la YFP permettant leur visualisation directe. De plus, la séquence insérée est floxée pour permettre ultérieurement la restauration de l'allèle normal après recombinaison médiée par la CRE recombinase.
Dans ce modèle les souris hétérozygote i5/+ ainsi que les souris homozygotes i5/i5 sont viables, fertiles et ne présentent pas d'anomalies morphologiques évidentes. L'expression de la YFP confirme l'expression neuronale du mutant. Contrairement aux souris surexprimant la mutation CHMP2Bintron5, cette lignée ne développe pas d'altération motrice majeure. Cependant l'analyse comportementale a permis de mettre en évidence chez

souris i5/i5 des changements comportementaux rappelant ceux observés chez les patient atteint de DFT. Une cartographie de l'expression du mutant et des analyses biochimiques et histologiques sont actuellement en cours pour préciser les populations neuronales mécanismes mis en œuvre dans les changement comportementaux observés.

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Mots clés : continuum SLA-DFT, CHMP2B, modèle murin
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P14 : NEW DIRECTIONS FOR EARLY DIAGNOSIS OF MND: A LARGE-SCALE LONGITUDINAL ANALYSIS OF MULTIPLE BIOMARKERS TO FIND DIAGNOSTIC AND PROGNOSTIC "FINGERPRINTS"

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A lack of suitable biomarkers for amyotrophic lateral sclerosis (ALS) hampers monitoring of disease progression, furthermore, limits assessment of therapy efficiency during clinical trials.
Over the last 4 years, our team has quantified multiple inflammatory, immunological and metabolic markers (>90 different molecules) in longitudinal serum and urine samples from ALS patients. We specially looked at the Kynurenine Pathway (KP) profile. The KP is activated by inflammation and is known to be dysregulated in ALS [1] and appeared to be the best predictor for multiple sclerosis subtyping [2].
Even if this large project is still in progress, we have already identified some biomarkers (such as neurofilaments, neopterin, ferritin, Kynurenic acid…) able to significantly differentiate between controls versus ALS patients and also predict disease progression.
Using plasma samples from 134 ALS patients and 118 healthy individuals from the Macquarie University MND Biobank for a proteomic study, we recently found that the most significant metabolism markers were associated with muscle activity: Creatine was 49% elevated in ALS patients, while creatinine and methylhistidine decreased by 20% and 24%, respectively. Additionally, the ratio of creatine versus creatinine increased 370% in male, and 200% in female, ALS patients.
All together these findings suggest that combining multiple blood biomarkers could significantly help to predict and follow disease progression. The next step for us is to perform the biostatistical analysis with all the different molecules identified as ALS biomarkers, and using larger datasets to produce a clinically relevant and specific biomarker sets for ALS subtyping, progression and likely response to treatment.

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Keywords: Biomarker, Longitudinal, Kynurenine
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P15 : VALEUR PREDICTIVE DES SOUS-POPULATIONS DES CELLULES MONONUCLEES SANGUINES DANS LA SLA

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La neuroinflammation et sa potentielle valeur prédictive dans la Sclérose Latérale Amyotrophique (SLA) peut être appréciée par l'évaluation en cytométrie en flux multicouleur des populations de cellules immunes sanguines. Nous avons réalisé une analyse préliminaire sur une cohorte de 20 patients SLA comparée à deux cohortes de patients atteints de PIDC (n=22) et de sujets sains (n=10).
La répartition de sous populations des lymphocytes T (LyT) CD3+/CD8+ et CD3+/CD4+ peut être quantifiée en fonction de l'expression de CD45RA et CCR7. On différencie ainsi les LyT naïfs (TN : CD45RA+/CCR7+), les LyT effecteurs mémoires (TEM: CD45RA-/CCR7-) ; les LyT central mémoires (TCM : CD45RA-/CCR7+) et les LyT effecteurs mémoires ré-exprimant CD45RA (TEMRA : CCR7-/CD45RA+). L'expression de CCR6 et CXCR3 permet d'analyser l'orientation des LyT CD4 vers le phénotype Th1-like (CXCR3+/CCR6+), Th2-like (CXCR3-/CCR6-) or Th17-like (CXCR3-/CCR6+). Les sous-populations de monocytes sont définies sur la base de l'expression des marqueurs de surface CD14 et CD16. Enfin, CD16 et CD56 permettent de définir les différentes populations de cellules Natural Killers (NK). Nous avons enfin étudié l'expression membranaire de GPR56, un régulateur de la chimiotaxie exprimé sur les NK et TEMRA. La valeur prédictive des différentes populations a été évaluée en fonction du score clinique ALSFRS et de la pente ALSFRS ((48 – score ALSFRS) / Durée (mois)).
Les résultats les plus significatifs sur ces cohortes de taille modérée concernent les lymphocytes EM qui sont augmentés chez les patients SLA par rapport aux sujets sains ($p = 0{,}0025$ pour les LyT CD4 et $p = 0{,}029$ pour les LyT CD8). La proportion de lyT TEM CD8+ est de plus corrélée avec le score ALSFRS ($r_p = 0.71$, $p = 0.0013$) et la pente ALSFRS ($r_p = -0.59$, $p = 0.013$).
En conclusion, l'analyse des sous-populations de cellules immunitaires sanguines pourrait être associée à l'analyse de biomarqueurs solubles, comme les neurofilament-Light ou les cytokines, pour évaluer la sévérité et l'évolutivité de la SLA.

Mots clés : Cytométrie en flux, cellules mononuclées sanguines ; SLA
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P16 : IMPAIRED CORTICAL CROSS-FREQUENCY COUPLING IS AN EARLY BIOMARKER OF CORTICAL HYPEREXCITABILITY IN MOUSE MODELS OF ALS

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Cortical hyperexcitability (CtHEx) is an early feature of sporadic and familial ALS, along with other neurodegenerative diseases that affect the brain. Importantly, CtHEx is not found in ALS mimicking disorders (Kennedy's disease and SMA) [1] and thus could represent a useful biomarker for ALS differential diagnosis. However, CtHEx has only been demonstrated using the threshold tracking method of the paired-pulse transcranial magnetic stimulation (ttTMS) [1], a method that proves difficult to use with disease progression. Consequently, there is a crucial need for new approaches to monitor CtHEx. Electroencephalograpy (EEG) can be used to investigate brain oscillatory activity, and in particular cross-frequency coupling (CFC), which is highly dependent on proper Excitation/Inhibition balance [2] and early altered in numerous neuropsychiatric disorders [3].
We therefore started assessing whether CFC characterization might prove useful to investigate early network alterations in ALS. To this aim, we first ran longitudinal 24 hours-long ElectroCorticoGraphic recordings coupled with ElectroMyoGraphic and Video recordings on the *Sod1^{G86R}* mouse model of the disease. Our results show that theta-gamma CFC is significantly decreased during Rapid Eye Movement (REM) sleep in the *Sod1^{G86R}* mice. This phenotype is present as early as 45 days of age, long before disease onset, and remains until disease end stage. Importantly, CFC uncoupling is also detected in presymptomatic *FUS$^{\Delta NLS}$* but not in *CHMP2B^{intron5}* mice, two other ALS models. To test

whether the cortical Excitation/Inhibition imbalance that we unraveled corresponds to hyper- or hypoexcitability, we tested the susceptibility of the *Sod1^{G86R}* mice to a convulsant drug, pentylentetrazol (PTZ). *Sod1^{G86R}* present significantly increased susceptibility to PTZ than controls, indicating that altered CFC coupling likely results from CtHEx. Finally, patients are being enrolled and recorded by EEG to evaluate the biomarker potential of CFC. Preliminary CFC analysis of one ALS patient reveals strong theta-gamma uncoupling compared to control.

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Keywords: Cortical HyperExcitability (CtHEx), ElectroCorticoGraphy (ECoG), Cross-Frequency Coupling (CFC).
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P17 : ETUDE LONGITUDINALE DE L'INDEX DU NOMBRE D'UNITES MOTRICES (MUNIX) DANS LA SCLEROSE LATERALE AMYOTROPHIQUE

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L'objectif de notre étude prospective était d'évaluer l'intérêt de la méthode MUNIX [1] pour le suivi des patients et de confirmer sa valeur en tant que biomarqueur pronostique dans la SLA [2]. Nous avons recueilli des données cliniques chez des patients atteints de SLA, notamment l'ALSFRS-R, la capacité vitale (CV), la date de décès, et des données électrophysiologiques chez les patients et des sujets sains : potentiel global d'action musculaire (CMAP), index du nombre d'unités motrices (MUNIX), index de la taille des unités motrices (MUSIX), dans quatre muscles : tibial antérieur (TA), court abducteur du pouce (APB), abducteur du cinquième doigt (ADM) et deltoïde (DEL), et calculé la somme des MUNIX et des MUSIX des 3 muscles APB+ADM+TA (score MUNIX 3) et des 4 muscles APB+ADM+TA+DEL (score MUNIX 4).
Les données des patients ont été recueillies tous les 3 mois sur 1 an.
82 patients ont été inclus au 1er bilan, 62 patients ont été revus à 3 mois, 48 à 6 mois et 33 à un an. Les scores MUNIX 3 et 4 étaient corrélés à l'ALSFRS-R au cours du suivi des patients, et diminuaient de façon progressive pendant le suivi plus rapidement que l'ALSFRS-R, ce qui en fait des marqueurs de suivi intéressants. Le MUNIX du deltoïde et le MUNIX score 4 étaient corrélés positivement de façon significative avec la CV et pourraient donc être des marqueurs de l'insuffisance respiratoire neuromusculaire dans la SLA et donc des éléments pronostiques intéressants. Nous rapportons aussi une corrélation positive entre le score MUSIX 4 réalisé au 1er bilan et la survie, ce qui pourrait refléter une ré-innervation compensatrice efficace de meilleur pronostic. Ainsi, les scores MUNIX et MUSIX peuvent être considérés comme des paramètres intéressants pour le suivi des patients et comme biomarqueurs pronostiques.

Références :
[1] Stein F, Kobor I, Bogdahn U, et al. Toward the validation of a new method (MUNIX) for motor unit number assessment. J Electromyogr Kinesiol 2016;27:73-7.
[2] Neuwirth C, Barkhaus PE, Burkhardt C, et al. Tracking motor neuron loss in a set of six muscles in amyotrophic lateral sclerosis using the Motor Unit Number Index (MUNIX): a 15-month longitudinal multicentre trial. J Neurol Neurosurg Psychiatry, 2015;86 :1172-9.
Mots clés : SLA, MUNIX, biomarqueur
Remerciements : Ce travail a été fait dans le cadre de l'étude PULSE. Pas de conflit d'intérêt à déclarer.
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P18 : MANIFOLD LEARNING IN AMYOTROPHIC LATERAL SCLEROSIS: DEVELOPMENT AND VALIDATION OF A PROGNOSTIC MODEL FOR FUNCTIONAL LOSS

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Amyotrophic Lateral Sclerosis (ALS) is an inexorably progressive neurodegenerative condition with no effective disease modifying therapies. In this highly heterogeneous condition, the development and validation of reliable prognostic models is a recognised research priority. We present a prognostic model for functional loss in ALS where result uncertainty is taken into account. Patient data were reduced and projected onto a 2D space using Uniform Manifold Approximation and Projection (UMAP), a novel non-linear dimension reduction technique. Information from 3,242 patients was included as development data originating from past clinical trials, and real-world population data as validation data. Predictors included age, gender, region of onset, symptom duration, weight at baseline, functional impairment, and estimated rate of functional loss. UMAP projection of patients shows an informative 2D data distribution. As limited data availability precluded complex model designs, the projection was divided into three zones with relevant functional loss estimates using confidence bounds. The marginal, intermediate, and significant 1-year functional loss zones were defined with, respectively, 83% (+/- 3%) of the population with an ALSFRS score higher than 20, 89% (+/- 4%) of the population with an ALSFRS score between 10 and 30 and 88% (+/- 7%) of the population with an ALSFRS below 20. Predicted 1-year functional loss was estimated using zone membership. This approach requires a limited set of features, is easily updated, improves with additional patient data, and accounts for results uncertainty.

Mots clés : Machine learning, PRO-ACT, patient stratification
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P19 : FACTEURS PRONOSTIQUES APRES POSE DE GASTROSTOMIE CHEZ LES PATIENTS ATTEINTS DE SLA UTILISATEURS HABITUELS DE VNI : INFLUENCE DU STATUT RESPIRATOIRE

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Les facteurs pronostiques de survie après gastrostomie chez les patients atteints de SLA, comme l'âge aux premiers symptômes et le statut nutritionnel [1], sont connus mais n'ont pas été étudiés chez les patients utilisateurs habituels de VNI. Le but de notre étude était donc de déterminer ces facteurs spécifiquement dans cette sous-population grandissante de patients SLA. Nous avons rétrospectivement analysé les données de 92 patients SLA utilisateurs habituels d'une VNI hospitalisés entre 2014 et 2017 pour la pose d'une gastrostomie. La survie a été évaluée par la méthode de Kaplan-Meier et les facteurs prédictifs de survie recherchés par une analyse multivariée selon le modèle de Cox. Nos résultats ont montré que la survie médiane globale après gastrostomie était de 231 jours et le taux de mortalité à 30 jours à 5,9%. Le risque de décès chez les patients traités par VNI était affecté par l'âge aux premiers symptômes (HR 1.047, p=0.006), l'indice de masse corporelle < 20 kg/m² au moment de la pose de gastrostomie (HR 2.012, p=0.016) et la présence d'un encombrement bronchique (HR 2.614, p=0.001). Chez les patients dépendants à la VNI (durée d'utilisation quotidienne $\geq$ 16h/jour), le délai moyen de survenue du décès était significativement plus court par rapport aux patients non dépendants à la VNI (133 vs. 250 jours, p = 0,04) et le taux de mortalité à 30 jours était plus élevé (21.4 vs 2.8 %, p = 0,03). Cette étude a permis de montrer que la présence d'un encombrement bronchique et la dépendance préopératoire à la VNI sont associés à une mortalité plus élevée. Ces critères devraient donc être évalués et pris en compte dans le processus de décision de mise en place d'une sonde de gastrostomie chez les patients atteints de SLA et ventilés.

Référence :
[1] ProGas Study Group, Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study, Lancet Neurology 2015;14(702–9)
Mots clés : gastrostomie, VNI, encombrement
Conflits d'intérêt : Pas de conflits d'intérêts.
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P20 : EPIDEMIOLOGY, GENETICS, CLINICAL FEATURES AND SURVIVAL OF AMYOTROPHIC LATERAL SCLEROSIS IN LATIN AMERICAN AND THE CARIBBEAN: A SYSTEMATIC REVIEW.

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Introduction: Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease. The evidence suggests heterogeneity between geographic areas and populations in terms of epidemiology, genetics and phenotypes (1–3). However, there is limited information of ALS in Latin America. We conducted a systematic review that aimed to describe epidemiology, frequency of genetic mutations, clinical characteristics, and survival of ALS in this region.

Methods: We reviewed Medline, Scopus, Scielo and LILACS databases up to April 2020, using the following search terms "Amyotrophic lateral sclerosis", or "Motor neuron disease" in combination with the list of Latin American countries from the United Nations. Observational studies were included with no time and language limitations. A methodological analysis was performed using the basic principles of descriptive epidemiology.

Results: A review of 1036 records identified 36 studies, covering 13 Latin American countries. According to the original reports, ALS occurrence varied widely from country to country with a standardized incidence (1990 US population) ranging from 0.3 per 100,000 person-years follow up (PYFU) in Ecuador to 3.6 per 100,000 PYFU in Uruguay. A low proportion of the C9orf72 expansion was reported in Cuba and Brazil. We identified specific clinical characteristics: i) age at onset was between 50 and 60 years; ii) bulbar onset was broadly variable ranging from 10% to 40%; iii) survival time was higher than 40 months in half of the studies. Data from multiethnic populations reported a higher risk of developing ALS in Caucasians compared to Admixed and Black populations.

Conclusion: This review provides an overall perspective of ALS variability across Latin America and highlights specific differences when comparing to European and North America countries. Nevertheless, we cannot draw firm conclusions because of different methodological concerns and bias within the studies. Finally, there is a need of original studies with standard methodology in Latin America.

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[1] Marin B, Boumédiene F, Logroscino G, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: A meta-analysis. International Journal of Epidemiology. 2017;46(1):57–74.

[2] Luna J, Logroscino G, Couratier P, et al. Current issues in ALS epidemiology: Variation of ALS occurrence between populations and physical activity as a risk factor. Rev Neurol (Paris). 2017;173(5):244–53.

[3] Zou Z-Y, Zhou Z-R, Che C-H, et al. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2017;88(7):540–9.

Keywords: Epidemiology, clinical characteristics, Latin America.

Declaration of interest: The authors report no conflict of interest.

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Une Interface Cerveau Ordinateur (ICO) enregistre l'activité électrique cérébrale, traite les signaux, les traduit en commandes. Le P300 Speller est une ICO adaptée à la Sclérose Latérale Amyotrophique [1] permettant une communication alternative améliorée par attention visuelle sur clavier virtuel, avec bonnet d'électroencéphalographie, électrodes, amplificateur et câbles. Cette technologie peut permettre de pallier les situations de handicaps moteurs.

La faisabilité d'utilisation du P300 Speller dans la SLA a été démontrée par notre première étude : 20 patients, 2 sessions de 3 épreuves à 3 mois d'intervalle avec une population d'âge moyen de 62 ans. 65 % des patients ont sélectionné correctement plus de 95% des symboles. Des échelles visuelles analogiques ont évalué positivement: confort, facilité d'utilisation, utilité du système avec une moyenne ≥ 8,7/10. Grâce à l'intégration de l'arrêt optimal des flashs et de la prédiction de mots, le taux de transfert d'informations s'est avéré supérieur à celui rapporté pour le dispositif de poursuite oculaire. Le P300 Speller permet donc une communication alternative efficiente [2]. La satisfaction des patients est excellente. Dans cette étude, l'âge, le niveau d'éducation, la maitrise de l'utilisation d'un ordinateur, les capacités cognitives des patients n'ont eu aucune influence sur les résultats [3]. Cependant l'ergonomie du système n'est pas adaptée à une utilisation écologique.

Une nouvelle étude clinique est en cours avec double objectif :

- Développer un prototype de casque ergonomique, confortable, sans fil, avec amplificateur miniaturisé, fabriqué à partir d'une modélisation du scalp (scanner 3D), intégrant des électrodes sèches commercialisées, permettant une utilisation prolongée pour des personnes en situation de handicap.
- Diminuer le nombre d'électrodes, améliorer le traitement des signaux pour augmenter l'efficience et la rapidité du système.

Le design de cette étude clinique de prototypage est identique à celui de la première étude. Les premiers résultats seront présentés.

Références :

[1] Soriani MH et al. Interface cerveau-ordinateur (BCI) : un moyen de communication alternative dans la SLA. 2016. Revue Neurologique, 172:S1

[2] Clerc M, Guy V et al. Les interfaces cerveau-ordinateur 2, Technologie et applications. 2016. Iste éditions

[3] Guy V, Soriani MH et al. Brain computer interface with the P300 speller: Usability for disabled people with amyotrophic lateral sclerosis. 2018 Jan. Ann Phys Rehabil Med. 61(1): 5-11

Mots clés : Interface Cerveau Ordinateur (ICO) ; Communication Alternative Améliorée (CAA) ; Sclérose Latérale Amyotrophique (SLA)

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P22 : FOLLOW-UP AND SURVIVAL AFTER GASTROSTOMY INDICATION IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Rationale: Benefit of gastrostomy on survival in ALS is unclear and its placement is probably too late. The aims of our work were in patients with indication of gastrostomy and who accepted or refused gastrostomy to study from the indication of gastrostomy to the last assessment or death i) the evolution of nutritional and neurological status and ii) the survival.
Methods: Patients included had assessment of their neurological (onset form, ALSFRS-R), nutritional status, body composition and respiratory status (forced vital capacity, non-invasive ventilation [NIV]). Statistical analysis was done by using Mann-Whitney test, Chi² tests, Kaplan-Meier with Log-rank and Cox model.
Results: One hundred and fifty-five patients with indication of gastrostomy were included, 68.4% had accepted gastrostomy placement. Nutritional status and body composition at indication and at last assessment were not significantly different in patients with or without gastrostomy. At last assessment, in patient with gastrostomy ALSFRS-R was lower (14.0 vs. 20.5 points, p=0.01). Since gastrostomy indication median survival was higher in patient who accepted gastrostomy (10.3 vs 7.9 months, p=0.01). Gastrostomy was negatively associated with the risk of death in univariate analysis (HR: 0.64, p=0.01), but not in multivariate analysis. In multivariate analysis, weight loss and ALSFRS-R slope during follow-up were positively associated with the risk of death (aHR: 1.62; p=0.0002 and aHR: 2.37; p<0.0001, respectively). An increased delay between gastrostomy indication and VNI placement was negatively associated with the risk of death (aHR: 0.95; p=0.0003).
Conclusion: In patients with indication of gastrostomy and who accepted gastrostomy, survival seems higher. However, independently of gastrostomy placement, factors positively associated with the risk of death were a more important alteration of nutrition status and of functional status between indication of gastrostomy and last assessment. It also seems important to consider placement of NIV after indication of the gastrostomy and not the reverse.

Keywords: Gastrostomy, survival, evolution
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P23 : COMPARISON OF THE FAT-FREE MASS OBTAINED BY IMPEDANCEMETRY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: DIRECT MEASUREMENT WITH DEVICE FORMULA VERSUS REFERENCE FORMULA.

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Rationale: Body composition can be assessed in ALS by biolelectric impedancemetry analysis (BIA) using a validated reference formula [1]. This formula is more complex to use than the direct measurement obtained by a BIA device. The aim of the study was to compare the agreement for the Fat-Free Mass (FFM) obtained by BIA with reference formula or with the formula of the device.
Methods: Patients had measurements of FFM by direct measurement with Bodystat Quadscan 4000® (FFMdev) and by the reference formula (FFMref) also requiring the measurement of the tricipital skin fold. A simple regression test was applied between the two values of FFM and the agreement was determined using the method of Bland and Altman. The repeatability coefficient was studied for the impedance at 50 kHz, from 6 consecutive measurements in 15 patients.
Results: Study population included 343 ALS patients. The mean age was of 66.5 years ± 11.0 years, the M/F sex ratio was of 1. FFMref was of 43.9 ± 9.8 kg and FFMdev was of 41.7 ± 11.0 kg. The repeatability coefficient of the impedance at 50 kHz was of 0.53 ± 1.28%.
The correlation between the two types of measures was very good (R at 0.90, p <0.0001). On the other hand, the limits of agreement on the Bland and Altman graph were + 7.6 and -11.9 kg, with an average risk of error

of 12.3% which is not acceptable in clinical practice. FFMdev underestimated the FFM on average with 2.2 ± 5.0 kg (5.0%) compared to the FFMref.
Conclusion: Measuring the FFM directly on the BIA device is associated with a too important risk of error to be able to be used in clinical practice. For the measurement of FFM during ALS, it is therefore necessary to use the formula validated for this pathology.

Reference:
[1] Desport JC, Preux PM, Bouteloup-Demange C et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. Am J Clin Nutr 2003;77:1179–85.
Keyword: body composition, biolelectric impedancemetry analysis, reference formula
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P24 : STUDY OF THE FAT-FREE MASS OBTAINED BY TWO DIFFERENT BODY COMPOSITION METHODS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: IMPEDANCEMETRY VERSUS MEASUREMENT OF THE FOUR SKIN FOLDS.

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Rationale: The total body bioelectric impedance analysis (BIA) with a validated equation [1] allows to assess the body composition during ALS, but requires the appropriate equipment. Measuring body composition using the four skin folds is simple to perform but not validated in ALS. The aim of our work was to study the agreement of measurements of Fat-Free Mass (FFM) by BIA compared to the skin folds method.
Methods: ALS patients had a BIA at 50 kHz and the measurement of the four skin folds (tricipital, bicipital, subscapular and super-iliac) performed 3 times on each side and then averaged. The Fat Mass (FM) obtained from the formula of Siri and Durnin & Womersley, allowed us to obtain the FFMsf (weight minus FM). The FFMimp in BIA was calculated using the validated equation also requiring the measurement of the tricipital skin fold. The correlation between the two methods was evaluated by linear regression and the agreement by the Bland-Altman method.
Results: 1045 measurements were studied. The mean age of the patients was 65.0 ± 11.6 years and the sex ration M / F ratio was of 1.1. FFMimp was of 46.1 ± 9.1 kg and FFMsf of 44.5 ± 9.3 kg. There was a good correlation between the two methods ($R = 0.91$, $p < 0.0001$). On the other hand, the agreement limits on the Bland and Altman graph were +5.7 and -8.9 kg, with an average risk of error of 16.4% which is not acceptable in clinical practice. FFMsf underestimated the FFM on average with 1.6 ± 3.7 kg (3.6%) compared to FFMimp obtained by BIA.
Conclusion: The measurement of body composition in ALS by skin folds method underestimates FFM compared to BIA with reference formula. Skin folds method although simple and inexpensive, cannot be used to determine FFM in ALS patients.

Reference:
[1] Desport JC, Preux PM, Bouteloup-Demange C et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. Am J Clin Nutr 2003;77:1179–85.
Keywords: body composition, biolelectric impedancemetry analysis, skin folds method
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P25 : STUDY OF THE RELEVANT THRESHOLD OF RESTING ENERGY EXPENDITURE VARIATION TO SCREEN AT DIAGNOSIS PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS WITH THE HIGHER EVOLVING RISK.

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Rationale: Increase of metabolic rate in ALS is defined by more than +10% of resting energy expenditure (REE) variation between measured REE (mREE) and calculated REE (cREE). However, REE variation during ALS is a prognostic factor for the survival in patients with a REE variation over +20%. This study aimed to study the relevant threshold of REE variation according to several cREE formulas to screen patients with the higher evolving risk.
Methods: mREE was measured by indirect calorimetry (IC) and cREE was calculated using 12 formulas. Functional (ALSFRS-R slope) and respiratory (Forced vital capacity slope) evolution between diagnosis and last assessment and survival by Log-rank test according to two thresholds of REE variation 10% and 20% were studied.
Results: 315 patients with a median age at IC of 66.6 years with a sex ratio of 1.0 were included. Depending on the predictive equation, REE variation over 10% and 20% was found in 35.2% to 76.3% and in 14.6% to 53.3% of patients, respectively. Patients with REE variation over 10% with Harris Benedict (HB) 1919 had a worst respiratory evolution (-3.2 %/month, p = 0.03). Patients with REE variation over 20% with HB 1919 and HB 1984 had a lower survival (HR = 1.42 (1.10 − 1.99), p = 0.01; HR =1.38 (1.06 − 1.92), p = 0.02, respectively). Moreover, with this same threshold with Mifflin formula patients had a worst functional (-1.4 point/month, p = 0.02) and respiratory (-3.5 %/month, p = 0.03) evolution and a lower survival (HR = 1.42 (1.14 − 1.83), p = 0.003).
Conclusion: In clinical practice REE formulas, such as HB 1919, HB 1984 or Mifflin, can be used as a reference value compared to IC with a threshold of REE variation of 20% to screen at diagnosis ALS patients with a higher evolving risk.

Keywords: resting energy expenditure, survival, evolution.
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P26 : SURVIVAL ACCORDING TO RESTING ENERGY EXPENDITURE (REE) VARIATION USING TWO REE FORMULAS AND WITHOUT INDIRECT CALORIMETRY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS).

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Rationale: The increase of resting energy expenditure (REE) variation over 20% in ALS is a prognostic factor for the survival. Measurement of REE by indirect calorimetry (IC) compared to REE predicted with formula (Harris and Benedict [HB] 1919) is necessary to obtain the REE variation. However, IC is not available in many centres Jésus et al. formula is a validate formula to predict REE in ALS and can be used in the absence of an IC. The aim of this work was to study the survival of ALS patients according to REE variation with IC or Jésus formula.
Methods: Nutritional assessments and body composition were performed at diagnosis. REE was measured by IC (mREE) and by Jésus formula (Jésus REE). cREE was calculated using HB 1919 and Mifflin. Survival was studied by Log-rank test (Hazard Ratio [HR], confidence interval [CI] 95%) according REE variation under or over 20%.
Results: 395 ALS patients with a median age at IC of 66.8 years with a sex ratio of 1.1 were included. With REE measured by IC, REE variation over 20% was found in 21.0% and 43.0% with HB 1919 and Mifflin formulas as cREE respectively. With Jésus REE, REE variation over 20% was found in 5.1% and 25.6% with HB 1919 and

Mifflin formulas as cREE, respectively. REE variation over 20% was more frequently found using IC than with Jésus formula (p<0.0001). Survival according to the IC and Jésus formula with HB 1919 and Mifflin formula as cREE is presented in table 1.
Conclusion: In the absence of IC to assess the metabolic rate of ALS patients, Jésus formula seems interesting associated with HB 1919 or Mifflin formulas for the calculation of REE variation at diagnosis of the disease.

Table 1: Survival according to the IC and Jésus formula.

	REE variation >20% vs. <20% HR (95%CI)	p
mREE/HB1919 REE	1.42 (1.07 – 1.90)	**0.007**
mREE/Mifflin REE	1.61 (1.28 – 2.01)	**<0.0001**
Jésus REE/HB1919 REE	1.62 (1.01 – 2.92)	**0.045**
Jésus REE/Mifflin REE	2.06 (1.54 – 2.76)	**<0.0001**

Keywords: resting energy expenditure, REE variation, survival
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P27 : IMPACT OF CARE OF A HEALTH NUTRITIONAL NETWORK AT HOME ON EVOLUTION OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

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Rational: In ALS, the nutritional status is a predictive factor for survival. In the Limousin region, a healthcare network specialized in nutrition (LINUT) assesses ALS patients at home in order to optimize their nutritional care. The aims of our study were i) to compare the patients' nutritional, neurological and respiratory evolution, and ii) to evaluate survival with or without LINUT support.
Methods: ALS patients treated in Limoges's ALS centre between January1, 2007 and December 31, 2019 had nutritional, neurological and respiratory evaluations. Inclusion in LINUT was recorded, otherwise patients were assigned to the control group. Statistical analysis used Mann-Whitney test, Chi2 test and Cox model. Propensity score (PS) was calculated to adjust results (p_{ps}).
Results: 306 patients were included (112 LINUT and 194 controls). Median time to the network's first visit was 4.3 months after diagnosis with a median number of visits of 2.5 per patient. After adjustment on PS, patients' characteristics at diagnosis were identical between the two groups. There was no difference in nutritional evolution during follow-up between the two groups. However, the evolution of ALSFRS-R score and forced vital capacity was greater in LINUT group (-15 points vs -12 points, p_{ps} = 0.04 and -31.4 % vs -12.7 %, p_{ps}= 0.003, respectively). Inclusion in LINUT had no impact on survival. Predictive factors positively associated with risk of death were weight loss at diagnosis (HR=1.05, p=0.001) and during follow-up (HR=1.05, p=0.006), time to gastrostomy (HR= 1.09, p<0.0001), and ALSFRS-R score variation during follow-up (HR=1.06, p<0.0001).
Conclusion: In our study, the nutritional status was a predictive factor for survival in ALS. However, LINUT interventions at home had no impact on either nutritional status or survival, but patients included in network improved faster. However, their quality of life was not evaluated and this might be an idea for future research.

Keywords: Nutritional network, nutritional care, evolution
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P28 : AMBROXOL HYDROCHLORIDE SLOWS DOWN PHYSIOPATHOLOGY OF THE *CHMP2B*^{INTRON5} ALS-FTD MOUSE MODEL

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Several experimental data suggest a link between sphingolipid metabolism and the pathophysiology of amyotrophic lateral sclerosis (ALS) [1]. Glucosylceramide (GlcCer) is a sphingolipid precursor of gangliosides. GlcCer is degraded by GBA1 and GBA2 enzymes, which are two beta-glucocerebrosidases (GBA). Recently, we have shown that GBA2 inhibition is beneficial in the *Sod1*^{G86R} ALS mouse model. A treatment with ambroxol hydrochloride, known to inhibit the enzymatic activity of GBA2, preserves the neuromuscular junctions of denervation and the motor neurons of neurodegeneration. It also improves motor functions and increases the lifespan of these mice [2]. Fronto-temporal dementia (FTD) and ALS share a common clinical, genetic and histopathological continuum. The encouraging results in *Sod1*^{G86R} mice led us to test the effects of ambroxol on motor and behavioral alterations in the *CHMP2B*^{intron5} ALS-FTD mouse model. Our data show that ambroxol preserves the motor axis (motor neuron - neuromuscular junction - muscle) of a second model of the disease. At the cellular level, ambroxol promotes the clearance of protein aggregates and reduces neuroinflammation. In addition, it slows the progression of behavioral alterations associated with FTD.

Thus, our results associated with those of the literature show the therapeutic potential of AMB for the treatment of ALS and allow us to envisage a repositioning of the molecule in this field.

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Keywords: ALS-FTD ; GBA ; therapeutic approach

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P29 : THERAPEUTIC STRATEGIES FOR ALS/FTD USING CELLULAR AND MURINE MODELS

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The identification of a point mutation (p.S59L) in the *CHCHD10* gene was the first genetic evidence demonstrating that mitochondrial dysfunction can trigger a motor neuron disease. We identified this mutation in a large family touched by a mitochondrial myopathy associated with signs of Amyotrophic Lateral Sclerosis (ALS) or Fronto Temporal Dementia (FTD) [1]. Since, we have shown that this mutation leads to the disorganisation of the MICOS complex (MItochondrial contact site and Cristae Organizing System) that normally maintains mitochondrial cristae structure. We have generated a mouse model and human motor neurons derived from iPSCs, both carrying the mutation p.S59L and a yeast mutant reproducing the MICOS loss. We now have relevant cellular and murine models as these models exhibit the phenotypes found in the patients [2]. The aim of our project is to identify and test drugs that could recover the deleterious phenotypes

due to the p.S59L mutation and the loss of MICOS. We identified, from two repurposed libraries, two compounds able to efficiently rescue the growth defect presented by our yeast mutant strain. One of these molecules also rescues the fragmentation of the mitochondrial network and the loss of mitochondrial cristae found in patient fibroblasts [3]. We are currently testing its effects on the iPSC-derived motor neurons before starting a trial on our murine model. We also aim to decipher its mechanisms of action.

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Key words: Mitochondrie – Sclérose Latérale Amyotrophique – Traitement
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P30 : EVALUATION OF A 5-HT2B AGONIST IN A MURINE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: Degeneration of brainstem serotonin neurons has recently been demonstrated in ALS patients and mouse models and was found responsible for the development of spasticity [1,2]. Consistent with involvement of central serotonin pathways, the 5-HT_{2B} receptor (5-HT_{2B}R) was upregulated in microglia of ALS mice. Its deletion worsened disease outcome in the *Sod1*(G86R) mouse model and led to microglial degeneration [3]. In ALS patients, a polymorphism in *HTR2B* gene leading to higher receptor expression in CNS, was associated with increased survival in patients as well as prevention of microglial degeneration [3]. These studies suggest that the clinical phenotype of ALS patients is partially caused by the degeneration of serotonergic neurons and that microglial 5-HT_{2B} receptor is critical for survival of this cell type in ALS spinal cord. The aim of our study was to determine the effect of a 5-HT_{2B} agonist : BW723C86 (BW), in the *Sod1*(G86R) mouse model of ALS.
Material and methods: Seventy-five-days-old *Sod1*(G86R) mice were treated with either 1 or 3mg/kg/d of BW, or vehicle. Muscular strength and body weight were monitored twice a week. Mice were sacrificed at end-stage. RT-qPCR were performed on cervical and thoracic spinal cord and were used to monitor a wide range of processes such as inflammation, homeostasis and disease-associated-microglia modulation. Immunostaining was performed on lumbar spinal cord.
Results: We did not observe differences in survival or muscle strength upon BW treatment. Genes related to homeostatic or disease associated microglia were similarly regulated in the spinal cord of all groups. BW was present in expected amounts in both brain and plasma of treated mice.
Discussion/Conclusion: BW, as a 5-HT_{2B}R agonist, neither showed efficacy in *Sod1*(G86R) mice, nor demonstrated ability to engage its microglial target. Further research is warranted using other 5-HT_{2B} agonists, other modes of administration and/or other ALS models with slower and earlier microglial involvement.

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Keywords: serotonin, microglia, Sod1
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P31 : STUDY OF POTENTIAL OFF-TARGET CANDIDATE SITES FOR ANTISENSE SEQUENCES INDUCING EXON SKIPPING IN *SOD1*-LINKED AMYOTROPHIC LATERAL SCLEROSIS

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Among the genetically defined Amyotrophic lateral sclerosis (ALS) cases, about 20% are caused by mutations in the superoxide dismutase 1 (SOD1) gene. Given to the toxic gain-of-function role of SOD1, the most promising therapeutic approach is the suppression of SOD1 mRNA and protein in the affected tissues. We have previously reported the high therapeutic potential of an exon-skipping strategy using the administration of an antisense oligonucleotide sequence (ASO) against mutant human SOD1 (hSOD1) inserted in an AAV10-U7 vector (AAV10-U7-hSOD1) [1]. This approach led to reduction of mutant human SOD1 levels in the SOD1G93A-ALS mouse model improving disease phenotype. However, the use of ASOs brings the risk of unselective targeting inducing toxicity via ASOs hybridization to complementary regions of unintended RNAs and consequent off-target effects (OTE). Therefore, the objective of this study is to estimate the OTE of SOD1-ASO in human and mouse RNA sequences by *in silico* and RNA sequencing analysis.

First, we estimated the general number of complementary binding sites of SOD1-ASO in human or mouse transcripts by *in silico* predictions using the Basic Local Alignment Search Tool, a sensitive search engine for nucleotide sequence databases. Our analysis showed that the number of OTE increases dramatically together with the number of tolerated mismatches.

In order to test the expression pattern of some possible off-target candidates, we performed qRT-PCR analysis in HEK293T cells and in spinal cords from SOD1G93A mice treated or not with the AAV10-U7-hSOD1. Our results showed no significant effect on selected mRNAs after ASO expression in both conditions. Nevertheless, extensive analysis using comprehensive studies are necessary to explore the effect of all potential off-targets sites. We thus plan to perform an in-depth RNA sequencing analysis using newly generated in vitro models of the disease. Our results will contribute to the development of a safe AAV-mediated SOD1 silencing approach for clinical translation.

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Keywords: ALS, antisense oligonucleotides, gene therapy, exon skipping, off-target effects.

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P32 : IS THERE A ROLE FOR VITAMIN D IN AMYOTROPHIC LATERAL SCLEROSIS? A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Several research studies about vitamin D in ALS patients have been discussing its role as a biomarker or a therapeutic option. In order to clarify scientific evidence, we performed a systematic review and meta-analyses regarding the potential role of vitamin D in ALS patients.
Methods: Systematic review of clinical trials, cohorts and case control studies retrieved from PubMed, EMBASE and Cochrane databases reporting vitamin D level as a putative biomarker for ALS diagnosis for prognosis, or presenting the effect of vitamin D supplementation in ALS patients were analyzed. Whenever possible, data were pooled by using a random effect model, with assessment of heterogeneity.
Results: From 2996 articles retrieved we finally included 13 studies, 12 observational (50% prospective) and one clinical trial. We found that ALS patients present slightly lower levels of vitamin D than control subjects (mean difference -6 ng/ml, 95% CI [-10.8; -1.3]), but important confounding factors were not considered. We found no relation between vitamin D levels and ALSFRS-R, with highly heterogeneous results. Discordant results were reported in three studies regarding survival. Finally, five studies reported the effects of vitamin D supplementation with discordant results. Two of them showed a small improvement, while two others showed a deleterious effect on ALSFRS-R. One very small clinical trial with important methodological limitations showed some improvement in ALSFRS-R with high doses of vitamin D compared to normal doses.
Conclusions: Our review did not find evidence to support a role of vitamin D on ALS diagnosis, prognosis or treatment. Most of studies had important limitations, mostly regarding the risk of bias for not considering confounding factors. Vitamin D supplementation should be offered to ALS patients to avoid other healthy issues related with vitamin D deficiency, but there is not enough evidence to support vitamin D as a therapy for ALS.

Keywords: ALS, vitamin D, meta-analysis
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