IMMUNOPATHOGENIC MECHANISMS, ANTIBODY BIOMARKERS AND NOVEL THERAPEUTIC TARGETS

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Dr Pittock is a salaried neurologist at Mayo Clinic and receives no commission based on Laboratory sales.
- Dr Pittock has received personal compensation for serving as a consultant for Roche, Sage Therapeutics, Arialys
- Dr Pittock has received personal compensation for serving on scientific advisory boards or data safety monitoring boards for Roche, UCB and Arialys
- Dr Pittock's institution has received compensation for serving as a consultant for Astellas and has received research support from Alexion/Astra Zeneca Rare Disease, Horizon/Amgen, Roche, Grifols, the National Institutes of Health and Adimmune
- Dr Pittock has the following patents issued or pending:
  - Patent# 9,891,219B2 (Application# 12-573942) - Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive – received Royalties
  - Patents for Kelch11, LUZP4, Septin, MAP1b Abs pending

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Dr. Pittock will discuss a variety of off-label products from multiple manufacturers

LEARNING OBJECTIVE

- **Explain** the distinct immunopathogenic mechanisms underlying T cell-mediated and antibody-mediated paraneoplastic neurological disorders.
- **Differentiate** between intracellular and cell-surface neural antibody targets and their implications for diagnosis, prognosis, and treatment.
- **Identify** current limitations in therapy, particularly for cytotoxic T cell-mediated disorders, and assess emerging strategies, including biologics, tolerogenic therapies, and CAR-T cell approaches.
- **Interpret** the clinical significance of antibody biomarkers in paraneoplastic neurologic syndromes and their associated cancer risk levels based on updated diagnostic criteria.
- **Evaluate** novel therapeutic targets under investigation and ongoing clinical trials that aim to address the current unmet needs in paraneoplastic neurology.

Key Message

- **Dual Immune Mechanisms:**
  Paraneoplastic neurological syndromes (PNDs) arise via *cytotoxic T-cell-mediated injury* (e.g., Hu, Yo) or *pathogenic autoantibodies targeting neural surface antigens* (e.g., NMDAR, AMPAR).

- **Antibody Biomarkers:**
  Antibodies targeting intracellular antigens (e.g., Hu, Yo, Ri) are *biomarkers*, not direct effectors of injury.
  In contrast, antibodies against cell surface antigens (e.g., NMDAR, LGI1) *mediate pathology* via receptor internalization, complement activation, or functional blockade.

- **Cancer Associations:**
  Antibodies are classified by cancer risk:
  - *High-risk (>70%):* Hu, Yo, Ri, Ma2, KLHL11
  - *Intermediate-risk (30–70%):* NMDAR, GABABR, CASPR2
  - *Low-risk (<30%):* LGI1, GAD65, MOG.

- **Diagnostic Implications:**
  Phenotype-specific antibody panels, supported by assays beyond line blots (e.g., cell-based, immunoprecipitation, ELISA, IFA), are critical for accurate diagnosis and reduce false positives.

Key Message

- **Therapeutic Gaps:**
  Despite biomarker advances, treatments for *T cell-mediated PNDs* (e.g., anti-Hu encephalomyelitis, anti-Yo cerebellar degeneration) have not advanced meaningfully in 50 years.
  Most therapies are ineffective once irreversible neuronal loss has occurred.

•**Emerging Targets & Trials:**

Phase II/III trials targeting antibody-mediated encephalitis include:

- •Anti-IL-6 (Satralizumab – LGI1, NMDAR)
- •FcRn inhibitors (Rozanolixizumab – LGI1)
- •Anti-CD19 (Inebilizumab – NMDAR)
- •CART CD19 (Stiff Person Syndrome)

•**Innovative Strategies Ahead:**

Future approaches include:

- •*CAR-T* cells targeting a widening repertoire of immune targets
- •*Tolerization*
- •*Proteasome inhibitors, BAFF/APRIL blockade, complement inhibitors* for antibody-mediated diseases.

•**Urgent Need for Collaborative Research:**

Given disease rarity and complexity, global, multi-institutional trials are vital to transform treatment of PNDs from empiricism to mechanism-based precision.

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