## Background

Nipocalimab binds to FcRn with high affinity which prevents IgG recycling, leading to reduced serum levels of total IgGs, including pathogenic IgG autoantibodies. Rapid, sustained lowering of IgG was observed in the phase 2 VIVACITY study in generalized myasthenia gravis (gMG) and in phase 1 healthy volunteers. In gMG patients, nipocalimab induced rapid and sustained lowering of anti-AChR autoantibodies and MG-ADL scores, but no serious adverse events including clinically significant infections.

## Design/Methods

Nipocalimab was evaluated extensively in vitro and in nonhuman primate-based chronic toxicology studies to evaluate selectivity, tolerability, safety and immunopharmacology. Safety, tolerability and immune-focused assessments in clinical phase 1 and Phase 2 MG studies were also completed (NCT02828046, NCT03772587).

## Results

Nipocalimab binds specifically in vitro to FcRn without activation of effector function or inhibition of antigen presentation. In nonhuman primates administered up to 300 mg/kg nipocalimab QW for up to 6 months, sustained lowering of IgG was observed without adverse effects. Immunotoxicology identified no effect on immune cell phenotypes; CD8 T cell, NK or innate cell functions; T-dependent neoantigen IgM responses. Neoantigen IgG production was observed, but with lowered peak IgG titers consistent with the anticipated increase in IgG clearance with nipocalimab. In clinical studies, nipocalimab demonstrated a reproducible selective decrease in total serum IgG, including all subclasses of IgG, with no effect on IgM, IgA, IgE, CH50, C3, C4, inflammatory cytokines or acute phase proteins including, C-reactive protein (CRP).

## Conclusions

These data suggest that nipocalimab can selectively lower IgG and IgG autoantibodies while preserving cellular immunity, complete IgM response and IgG production after neoantigen challenge. Overall, nipocalimab's selective effect on IgG recycling provides a mechanistic rationale for potentially decreased infection risk despite substantial IgG lowering.

**Disclosure:** Dr. Ling has received personal compensation for serving as an employee of Janssen Pharmaceuticals (Johnson&Johnson). Dr. Ling has stock in Janssen Pharmaceuticals (Johnson&Johnson). Dr. Ling has received intellectual property interests from a discovery or technology relating to health care. Dr. Ling has received intellectual property interests from a discovery or technology relating to health care. Mr. Tyler has received personal compensation for serving as an employee of AVROBIO, INC. Mr. Beneduce has received personal compensation for serving as an employee of Janssen Pharmaceuticals of Johnson and Johnson. Mr. Beneduce has received stock or an ownership interest from Janssen Pharmaceuticals of Johnson and Johnson. Mr. Beneduce has received intellectual property interests from a discovery or technology relating to health care. Ms. Yu has received personal compensation for serving as an employee of Janssen Pharmaceuticals. Ms. Yu has received personal compensation for serving as an employee of Momenta Pharmaceuticals. Ms. Yu has stock in Johnson and Johnson. Dr. Brown has received personal compensation for serving as an employee of Janssen Pharmaceuticals. Dr. Brown has received personal compensation for serving as an employee of Momenta Pharmaceuticals. Dr. Brown has received stock or an ownership interest from Janssen Pharmaceuticals. Dr. Brown has received stock or an ownership interest from Momenta Pharmaceuticals. Dr. Brown has received intellectual property interests from a discovery or technology relating to health care. Dr. Kumar has received personal compensation for serving as an employee of GlaxoSmithKline. Dr. Kumar has received personal compensation for serving as an employee of Checkmate Pharmaceuticals. Dr. Kumar has received stock or an ownership interest from GSK. Dr. Kumar has received stock or an ownership interest from Checkmate Pharmaceuticals. Dr. Xu has nothing to disclose. Dr. Duffner has received personal compensation for activities with Momenta Pharmaceuticals. Dr. Avery has received personal compensation for serving as an employee of Lyndra Therapeutics. Dr. Avery has received personal compensation for serving as an employee of Xilio Therapeutics. Dr. Avery has received personal compensation for serving as an employee of Kisbee Therapeutics. Dr. Avery has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Momenta Pharmaceutical. Dr. Avery has received stock or an ownership interest from Life Biosciences.

### Validation of MATCH Score: A Predictive Tool for Identification of Patients With Kelch-Like Protein-11 Autoantibodies

M Bakri Hammami, Mohamed Rezk, Divyanshu Dubey

## Objective

To validate performance of the MATCH score using an independent paraneoplastic neurological syndrome (PNS) cohort.

## Background

Kelch-like protein 11 (KLHL11)-IgG is a high-risk paraneoplastic antibody associated with rhombencephalitis. MATCH score is a composite clinical model recently developed to predict KLHL11-IgG positivity

## Design/Methods

Retrospective review of cases with definite or probable PNS who underwent neural specific autoantibody evaluation at Mayo Clinic Neuroimmunology laboratory between January 2001 and December 2021 was performed. MATCH score was calculated for all patients to assess the score's discriminative ability

## Results

186 patients who met the definite or probable PNS criteria were identified. The MATCH score was = 4 in 31/36 patients who were KLHL11-IgG positive and in 17/150 patients who were KLHL11-IgG negative but positive for other high-risk autoantibodies including CRMP5, ANNA1, PCA1 and amphiphysin, among others, or seronegative to all antibodies. MATCH Score's sensitivity, specificity, positive and negative predictive value were 86%, 89%, 65% and 96%, respectively. The score showed an excellent discriminative ability with an AUC of 0.924 [95% CI 0.885-0.962].

## Conclusions

MATCH score is a sensitive and specific tool to identify patients likely to be KLHL11-IgG positive. Utilization of MATCH score can improve pretest probability. However, some KLHL11-IgG cases with motor neuronopathy or limbic encephalitis presentation or those without a detectable testicular cancer at the time of initial assessment may potentially be missed.

**Disclosure:** Dr. Hammami has received intellectual property interests from a discovery or technology relating to health care. Dr. Rezk has nothing to disclose. The institution of Dr. Dubey has received personal compensation in the range of $500-$4,999 for serving as a Consultant for UCB. The institution of Dr. Dubey has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Astellas. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for AGRIMS. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for Advances in Neurology. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for Moffit Cancer Center. Dr. Dubey has received research support from Department of Defense. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care.

### Caveolae-Associated Protein (cavin)-4 Autoantibodies in Immune Mediated Rippling Muscle Disease

M Bakri Hammami, Grayson Beecher, Andrew Knight, Teerin Liewluck, James Triplett, Abhigyan Datta, Surendra Dasari, Youwen Zhang, Matthew Roforth, Calvin Jerde, Stephen Murphy, William Litchy, Anthony Amato, Vanda Lennon, Andrew McKeon, John Mills, Sean Pittock, Margherita Milone, Divyanshu Dubey

## Objective

To describe a novel autoantibody biomarker of Immune mediated rippling muscle disease (iRMD).

## Background

iRMD is a rare immunotherapy-responsive myopathy characterized by wave-like muscle contractions (rippling) and percussion/stretch-induced muscle mounding. However, serological biomarker of this disease is lacking.

## Design/Methods

A Retrospective review was done to identify iRMD patients with stored sera in Mayo Neuroimmunology laboratory. Archived sera from IRMD patients were evaluated for a common biomarker of IRMD using phage immunoprecipitation sequencing (PhIP-Seq).

## Results

Archival sera from 10 patients with clinical diagnosis of iRMD were retrieved. Whole human proteome PhIP-Seq identified peptides corresponding to different regions of the cavin-4 in sera of iRMD patients. Eight of the ten iRMD cases were positive for cavin-4 IgG by immunofluorescent cell-based-assay (CBA) using cavin-4-transfected COS7 cells. The cavin-4-reactive IgG in all 8 positive sera was of IgG1 subclass. None of the disease control sera (98 immune-mediated myopathy/neuromuscular junction disorders, 20 autoimmune CNS diseases and 123 healthy subjects) contained cavin-4-reactive IgG. Furthermore, none of the iRMD patients' sera were positive for caveolin-3 IgG. The majority of seropositive cases were males (6/8, 75%) with median age of 51 years (range 18-76). Three seropositive patients had co-existing myasthenia gravis (38%). Creatine Kinase was elevated in 6/7 tested patients (median 771 U/L, range: 132-2625 U/L). Muscle biopsy was performed in 7 of the 8 cavin-4 IgG seropositive patients; 6/6 specimens analyzed immunohistochemically revealed a mosaic pattern of sarcolemmal cavin-4 immunoreactivity. Three of 6 seropositive patients who received immunotherapy had complete resolution of symptoms; one had mild improvement and two had no change.

## Conclusions

Cavin-4 IgG is a novel and specific serological autoantibody biomarker identified in iRMD. Depletion of cavin-4 expression in iRMD patient muscle biopsies suggests the potential role of this autoantigen in disease pathogenesis.

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# Anti-Neuronal Nuclear Antibody 3 Autoimmunity Targets Dachshund Homolog 1

Anastasia Zekeridou, Binxia Yang, Vanda Lennon, Guo Yong, Liang Wu, Claudia Lucchinetti, Andrew McKeon, Sean Pittock, Eoin Flanagan

## Objective

To identify the autoantigen defined by Anti-Neuronal Nuclear Antibody-type 3 (ANNA3)-IgG and describe the clinical phenotype of seropositive patients.

## Background

ANNA3 was described in 11 patients with multifocal neurological presentations and cancer; its detection is based on the characteristic immunofluorescence staining on mouse tissue sections; ignorance of the antigen's molecular identity has precluded its ready detection in clinical practice.

# Caveolae-Associated Protein (cavin)-4 Autoantibodies in Immune Mediated Rippling Muscle Disease

M Bakri Hammami, Grayson Beecher, Andrew Knight, et al.

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