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## **Human auto-antibodies neutralizing type I interferons: strong, common, and universal determinants of life-threatening viral infections**

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### **General context and objectives of the project**

The immense inter-individual clinical variability during infection by any microbe, ranging from silent elimination to lethal disease, is an enigma posed at the turn of the 20<sup>th</sup> century (the “infection enigma”) <sup>1-7</sup>. A first step forward was made with the discovery of monogenic inborn errors of immunity (IEI) that underlie severe infectious diseases in otherwise healthy children, normally resistant to other infections <sup>3,6</sup>. These IEI generally impair the production or the response to a specific cytokine critical for the defence against a given microbe, eg type I interferons (IFNs) in viral infections. In a second step, the study of IEI has led to the discovery of their “autoimmune phenocopies”, ie the presence of auto-antibodies (auto-Abs) neutralizing a specific cytokine, particularly in elderly people <sup>8-12</sup>. IEI of type I IFNs underlie severe viral diseases, including herpes simplex encephalitis (HSE), critical influenza or COVID-19 pneumonia, and adverse reactions to live-attenuated viral vaccines<sup>8,13-35</sup>. Remarkably, auto-Abs neutralizing type I IFNs (AAN-I-IFN) underlie an unprecedented proportion of cases of a growing range of severe viral diseases <sup>9,12</sup>, with ~5% of cases of severe influenza pneumonia <sup>13</sup>, ~15% of cases of critical COVID-19 pneumonia <sup>13,33,36-39</sup>, ~20% of cases of hypoxemic Middle East respiratory syndrome (MERS) pneumonia <sup>40</sup>, ~30% of cases of adverse reactions to live-attenuated yellow fever vaccine <sup>37</sup>, and ~40% of cases of West Nile Virus (WNV) encephalitis<sup>41</sup>, particularly in middle-aged and elderly adults. AAN-I-IFN are common in the general population, with a prevalence around 0,3-1% under the age of 65 years, with a sharp increase from the age of 65 years onward, reaching ~4-7% over 80 years old <sup>30,42</sup>, and amounting to > 100 million carriers worldwide. The high proportions of cases (5-40%) explained by very high Odds Ratios (ORs) of severe infections associated with those auto-Abs (~100) are unprecedented among infectious diseases. It is therefore biologically and medically of major importance to determine the full range of consequences of these auto-Abs and to decipher their causes. Evidence that these auto-Abs can have a genetic basis came again from the study of IEI. Almost all patients with autoimmune polyendocrine syndrome type 1 (APS-1) due to rare biallelic loss of function (LOF) variants of *AIRE* gene have AAN-I-IFN<sup>43-47</sup>. We also showed that patients with rare inborn errors of the non-canonical NF-κB pathway also carry these auto-Abs <sup>48</sup>. The cause of these auto-Abs however remains unknown in the vast

majority of patients, including in all elderly individuals. **In this context, we hypothesized that i) these autoantibodies underlie other types of hitherto unexplained severe viral infections, especially encephalitis and pneumonia, in both children and adults; and ii) rare or common genetic defects can underlie the production of these auto-Abs, including over 65 years old.**

Therefore, the objectives of the project are to search for the consequences and causes of AAN-I-IFN, following a three-step strategy

- 1) To recruit cohorts of individuals carrying AAN-I-IFN or at high risk of carrying such auto-Abs, in particular patients with severe viral infections,
- 2) To test for AAN-I-IFN in these patients and to evaluate the risk of viral disease in carriers of these auto-Abs,
- 3) To search for rare and common genotypes underlying these auto-Abs by whole exome (WES) and whole genome sequencing (WGS), using a cutting-edge strategy developed in our laboratory to analyze such data.

## **Achievements and results**

### ***Collection of patients, test for AAN-I-IFN and WES/WGS analysis***

Through an important and large network of national and international collaborations, we have extended over the first year of the project our recruitment of adult and pediatric patients suffering from severe viral infection such as critical pneumonia due to respiratory viruses, encephalitis due to arboviruses (West Nile Virus, Powassan virus, Usutu virus, Ross River virus, Tick-borne encephalitis virus), and fulminant viral hepatitis. We have screened the plasma of those samples for the presence of AAN-I-IFN using a luciferase assay, as previously described. Whenever possible, the DNA of patients with AAN-I-IFN is further sent to whole genome sequencing. Thanks to this ongoing project, we have now WGS data for 370 patients with AAN-I-IFN.

### ***AAN-I-IFN are strong and common determinants of severe arboviral diseases***

Arboviral diseases are a growing global health concern, with transmission spreading worldwide. There is immense interindividual clinical variability following infection with any arbovirus. In large cohort of patients infected with tick-borne encephalitis virus (TBEV) or West Nile virus (WNV), we documented that patients with AAN-I-IFN have a very high risk of severe disease (relative risk >100), accounting for 10% of tick-borne encephalitis and 40% of WNV encephalitis. We further reported that AAN-I-IFN can also underlie severe forms of rarer arboviral infections. Specifically, we found AAN-I-IFN neutralizing high concentrations of IFN- $\alpha$ 2, IFN- $\beta$ , and/or IFN- $\omega$  in the single case of severe Powassan virus (POWV) encephalitis studied, two of three cases of severe Usutu virus (USUV) infection studied, and the most severe of 24 cases of Ross River virus (RRV) disease studied. These AAN-I-IFN were not found in any of the 137 individuals with silent or mild infections with these three viruses. Thus, auto-Abs neutralizing type I IFNs underlie an increasing list of severe arboviral diseases due to Flaviviridae (WNV, TBEV, POWV, USUV) or Togaviridae (RRV) viruses transmitted to humans by mosquitoes (WNV, USUV, RRV) or ticks (TBEV, POWV).

**Article 1:** Gervais A, Bastard P, Bizien L, Delifer C, Tiberghien P, Rodrigo C, Trespidi, F, Angelini M, Rossini G, Lazzarotto T, Conti F, Cassaniti I, Baldanti F, Rovida, F, Ferrari A,

Mileto D, Mancon A, Abel L, Puel A, **Cobat A**, Rice CM, Cadar D, Schmidt-Chanasit J, Scheid JF, Lemieux JE, Rosenberg ES, Agudelo M, Tangye SG, Borghesi A, Durand GA, Duburcq-Gury E, Valencia BM, Lloyd AR, Nagy A, MacDonald, MM, Simonin Y, Zhang SY, **Casanova JL**. Auto-Abs neutralizing type I IFNs in patients with severe Powassan, Usutu, or Ross River virus disease. *J Exp Med*. 2024 Dec 2;221(12):e20240942. doi: 10.1084/jem.20240942. Epub 2024 Nov 1. PMID: 39485284; PMCID: PMC11533500. <https://doi.org/10.1084/jem.20240942>

**Article 2:** Gervais A, Marchal A, Fortova A, Berankova M, Krbkova L, Pychova M, Salat J, Zhao S, Kerrouche N, Le Voyer T, Stiasny K, Raffl S, Schieber Pachart A, Fafi-Kremer S, Gravier S, Robbiani DF, Abel L, MacDonald MR, Rice CM, Weissmann G, Kamal Eldin T, Robatscher E, Erne EM, Pagani E, Borghesi A, Puel A, Bastard P, Velay A, Martinot M, Hansmann Y, Aberle JH, Ruzek D, **Cobat A\***, Zhang SY\*, **Casanova JL\***. Autoantibodies neutralizing type I IFNs underlie severe tick-borne encephalitis in ~10% of patients. *J Exp Med*. 2024 Oct 7;221(10):e20240637. doi: 10.1084/jem.20240637. Epub 2024 Sep 24. PMID: 39316018; PMCID: PMC11448868. <https://doi.org/10.1084/jem.20240637>

**Article 3:** Adrian Gervais, Francesca Trespidi, Alessandro Ferrari, Francesca Rovida, Astrid Marchal, Stefania Croce, Irene Cassaniti, Mattia Moratti, Jennifer Uhrlaub, David Florian, Karin Stiasny, Elisa Burdino, Micol Angelini, Lucy Bizien, Daniele Lillieri, Veronica Codullo, Tal Freund, Yael Paran, Avi Gadoth, Roni Biran, Alessandro Mancon, Camilla Lucca, Stefania Vogiatzis, Monia Pacenti, Melodie Aubart, Marco Zecca, Patrizia Comoli, Maria Avanzini, Jacques Fellay, Antonio Piralla, Francesca Conti, Dolci Alberto, Luisa Barzon, Valeria Ghisetti, Tiziana Lazzarotto, Danilo Cereda, Alessandro Aiuti, Emmanuelle Jouanguy, Paul Bastard, Margaret MacDonald, Charles Rice, Anne Puel, Laurent Abel, Giada Rossini, Davide Mileto, Yannick Simonin, Anna Nagy, David Hagin, Kristy Murray, Fausto Baldanti, Judith Aberle, **Aurélie Cobat**, Shen-Ying Zhang, **Jean-Laurent Casanova**, and Alessandro Borghesi. Autoantibodies neutralizing type I IFNs in 40% of patients with WNV encephalitis in seven new cohorts. *J Hum Immun* (*in press*)

### ***Identification of AAN-I-IFN in a fatal case of H5N1 avian influenza***

**Article 4:** Qian Zhang, Taylor S. Conrad, Marcela Moncada-Velez, Kaijun Jiang, Anastasija Cupic, Jonathan Eaton, Kimberly Hutchinson, Adrian Gervais, Ruyue Chen, Anne Puel, Paul Bastard, **Aurélie Cobat**, Theresa Sokol, Ryan Langlois, Lisa Miorin, Adolfo García Sastre, John A. Vanchiere, **Jean-Laurent Casanova**. Autoantibodies neutralizing type I IFNs in a fatal case of H5N1 avian influenza. *J Exp Med* (2026) 223 (3): e20251962. doi: 10.1084/jem.20251962

<https://doi.org/10.1084/jem.20251962>

Avian influenza A virus (IAV) H5N1 is an emerging threat of human pandemic. We described a 71-year-old man who died of H5N1 pneumonia and in whom we identified AAN-I-IFN. Causality between these AAN-I-IFN and lethal outcome of avian influenza in this patient is based on (1) our previous report that AA-I-IFN underlie about 5% of cases of critical pneumonia triggered by seasonal influenza viruses in three cohorts, (2) the rarity of this combination of AAN-I-FNs in individuals over 70 years old (<1%), and (3) the rarity of lethal avian influenza among infected individuals (<1%). AAN-I-IFNs underlie a growing number of severe viral diseases, particularly in the elderly. This case suggests they can also underlie life-threatening avian H5N1 influenza.

***AAN-I-IFN underlie over a third of patients with HSV-triggered fulminant viral hepatitis.***

**Article 5:** Adrian Gervais, Astrid Marchal, Soraya Boucherit, Anthony Abi Haidar, Lucy Bizien, Ahmet Yalcinkaya, Ella Sandström, Xiao-Fei Kong, Emmanuel Jacquemin, Olivier Bernard, Dominique Debray, Florence Lacaille, Philippe Ichai, Cigdem Arıkan, Etienne Javouhey, Bertrand Roquelaure, Frédéric Gottrand, Francesca Trespidi, Veronica Codullo, Lorenzo Cavagna, Nicolas Schleinitz, Mohamed Bousfiha, Naima Amenzoui, Ahmed Aziz Bousfiha, Trine Mogensen, Nanna Mørk, Sofie Jørgensen, Paul Bastard, Anne Puel, Alessandro Borghesi, Jody Rule, William Lee, Nils Landegren, **Aurelie Cobat\***, **Jean-Laurent Casanova\***, and Emmanuelle Jouanguy\*. Autoantibodies neutralizing type I IFNs in patients with fulminant herpes simplex virus hepatitis. *J Exp Med* (2026) 223 (3): e20251760. doi: 10.1084/jem.20251760

<https://doi.org/10.1084/jem.20251760>

Fulminant viral hepatitis (FVH) is a devastating condition caused by hepatotropic viruses such as hepatitis A virus (HAV), hepatitis B virus (HBV), and HSV-1/2. We studied an international cohort of 149 FVH patients and found that 37.5% of HSV-triggered FVH patients carried AAN-I-IFN on admission. Odds ratios for HSV-triggered FVH in individuals with AAN-I-IFN ranged from 35.3 to 1,895, according the IFN and concentration neutralized. These results contrasted with those obtained for 133 HAV- or HBV-triggered patients, none of whom had detectable AAN-I-IFN. This finding highlights auto-Abs against type I IFNs as a major determinant of HSV-FVH and paves the way for targeted preventive or therapeutic interventions.

***Incontinentia pigmenti underlies autoantibodies to type I IFNs***

Human inborn errors of thymic T cell tolerance underlie the production AAN-I-IFN, which predispose to severe viral diseases. We analyzed 131 female patients with X-linked dominant incontinentia pigmenti (IP), heterozygous for loss-of-function (LOF) NEMO variants, from 99 kindreds in 10 countries. Forty-seven of these patients (36%) carried those AAN-I-IFN, a proportion 23 times higher than that for age-matched female controls. This proportion remains stable from the age of 6 years onward. On imaging, female patients with IP have a small, abnormally structured thymus. These results suggest that IP accelerates thymic involution, thereby underlying the production of AAN-I-IFN in at least a third of female patients with IP, predisposing them to life-threatening viral diseases.

**Article 6:** Rosain J, Le Voyer T, Liu X, Gervais A, Polivka L, Cederholm A, Berteloot L, Parent AV, Pescatore A, Spinosa E, Minic S, Kiszewski AE, Tsumura M, Thibault C, Esnaola Azcoiti M, Martinovic J, Philippot Q, Khan T, Marchal A, Charmeteau-De Muylder B, Bizien L, Deswarte C, Hadjem L, Fauvarque MO, Dorgham K, Eriksson D, Falcone EL, Puel M, Ünal S, Geraldo A, Le Floch C, Li H, Rheault S, Muti C, Bobrie-Moyrand C, Welfringer-Morin A, Fuleihan RL, Lévy R, Roelens M, Gao L, Materna M, Pellegrini S, Piemonti L, Catherinot E, Goffard JC, Fekkar A, Sacko-Sow A, Soudée C, Boucherit S, Neehus AL, Has C, Hübner S, Blanchard-Rohner G, Amador-Borrero B, Utsumi T, Taniguchi M, Tani H, Izawa K, Yasumi T, Kanai S, Migaud M, Aubart M, Lambert N, Gorochov G, Picard C, Soudais C, L'Honneur AS, Rozenberg F, Milner JD, Zhang SY, Vabres P, Trpinac D, Marr N, Boddaert N, Desguerre I, Pasparakis M, Miller CN, Poziomczyk CS, Abel L, Okada S, Jouanguy E, Cheynier R, Zhang Q, **Cobat A**, Béziat V, Boisson B, Steffann J, Fusco F, Ursini MV, Hadj-Rabia S, Bodemer C, Bustamante J, Luche H, Puel A, Courtois G, Bastard P, Landegren N, Anderson MS, **Casanova JL**. Incontinentia pigmenti underlies thymic dysplasia, autoantibodies to type I IFNs, and viral diseases. *J Exp Med*. 2024 Nov 4;221(11):e20231152. doi: 10.1084/jem.20231152. Epub 2024 Oct 1. PMID: 39352576; PMCID: PMC11448874.

<https://doi.org/10.1084/jem.20231152>

## Conclusions and perspectives

During the first year of this project, we have expanded our recruitment of patients and demonstrated that AAN-I-IFN underlie an increasing number of severe viral infections, accounting for 10 to 40% of critical cases and conferring extremely high risks. We also made important progress in uncovering genetic mechanisms underlying these autoantibodies, identifying incontinentia pigmenti as a cause of accelerated thymic involution and production of AAN-I-IFN. During the next two years, we will pursue our efforts of recruitment and AAN-I-IFN testing across additional viral infections to further delineate the full phenotypic spectrum of AAN-I-IFN-associated disease. We will also search for new genetic determinants, both rare and common, of AAN-I-IFN through WGS.

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