

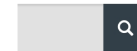
Treatment approaches in the human type I interferonopathies

Yanick Crow



THE UNIVERSITY
of EDINBURGH

Departments MyEd



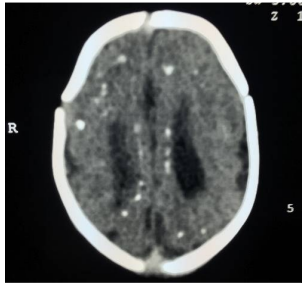
College of Medicine & Veterinary Medicine

MRC INSTITUTE OF GENETICS & MOLECULAR MEDICINE

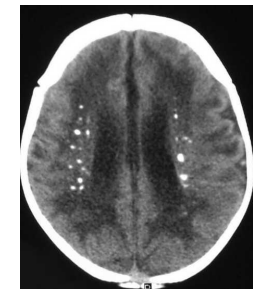
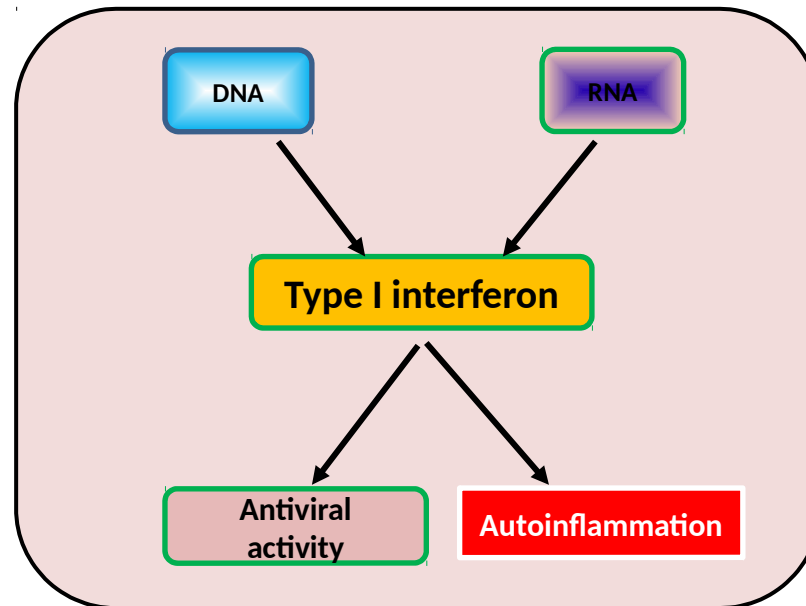
“We’re all mutants, basically. It’s hard to find a wild type.”

Sydney Brenner (2008)

Self versus non-self



Infection
(Zika)



Mendelian
(AGS)

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity*



Type I interferonopathies: a novel set of inborn errors of immunity

Yanick J. Crow

Genetic Medicine, University of Manchester, Manchester Academic Health Science Centre, Central Manchester Foundation Trust University Hospitals, Manchester, United Kingdom

**Insights into antiviral signalling,
self / non-self discrimination and the
basis of 'complex'
autoinflammatory / autoimmune
disease states**

The A946T variant of the RNA sensor IFIH1 mediates an interferon program that limits viral infection but increases the risk for autoimmunity

Jacquelyn A Gorman¹, Christian Hundhausen², John S Errett^{3,4}, Amy E Stone^{3,4} , Eric J Allenspach^{1,5} , Yan Ge⁶ , Tanvi Arkatkar¹, Courtnee Clough¹, Xuezhi Dai¹, Socheath Khim¹, Kathleen Pestal⁴, Denny Liggitt⁷, Karen Cerosaletti², Daniel B Stetson⁴, Richard G James^{1,5}, Mohamed Oukka^{1,4,5}, Patrick Concannon⁶, Michael Gale Jr^{3,4}, Jane H Buckner² & David J Rawlings^{1,4,5}

VOLUME 18 NUMBER 7 JULY 2017 NATURE IMMUNOLOGY

SCIENTIFIC REPORTS | 6:39378 | DOI: 10.1038/srep39378

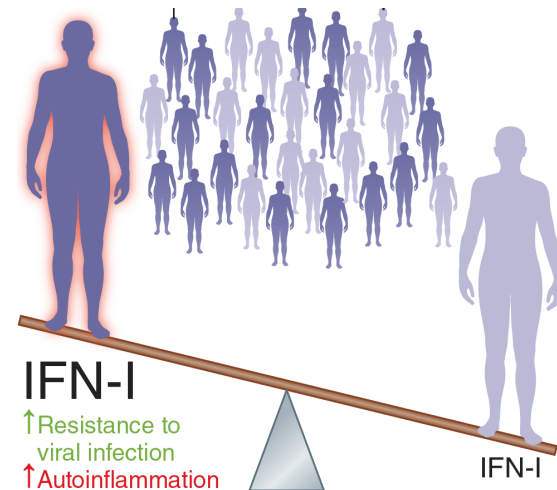
An IFIH1 gene polymorphism associated with risk for autoimmunity regulates canonical antiviral defence pathways in Cocksackievirus infected human pancreatic islets

Erna Domsgen^{1,*}, Katharina Lind^{1,*}, Lingjia Kong², Michael H. Hühn^{1,†}, Omid Rasool², Frank van Kuppeveld³, Olle Korsgren⁴, Riitta Lahesmaa² & Malin Flodström-Tullberg^{1,5}

RESEARCH ARTICLE

The common HAQ STING variant impairs cGAS-dependent antibacterial responses and is associated with susceptibility to Legionnaires' disease in humans

Juan S. Ruiz-Moreno¹, Lutz Hamann², Javeed A. Shah^{3,4}, Annelies Verbon⁵, Frank P. Mockenhaupt⁶, Monika Puzianowska-Kuznicka^{7,8}, Jan Naujoks¹, Leif E. Sander^{1,9}, Martin Witzenthat^{1,9,10}, John C. Cambier¹¹, Norbert Suttorp^{1,9,10}, Ralf R. Schumann², Lei Jin¹², Thomas R. Hawn³, Bastian Opitz^{1,9,*}, CAPNETZ Study Group[†]



 The Journal of Immunology

The Common R71H-G230A-R293Q Human *TMEM173* Is a Null Allele

Seema Patel, Steven M. Blauboer, Heidi R. Tucker, Samira Mansouri, Juan Sebastian Ruiz-Moreno, Lutz Hamann, Ralf R. Schumann, Bastian Opitz and Lei Jin

This information is current as of December 9, 2016.

BRIEF REPORT

Identification of a Pathogenic Variant in TREX1 in Early-Onset Cerebral Systemic Lupus Erythematosus by Whole-Exome Sequencing

Julia I. Ellyard,¹ Rebekka Jerjen,¹ Jaime L. Martin,¹ Adrian Y. S. Lee,¹ Matthew A. Field,¹ Simon H. Jiang,² Jean Cappello,¹ Svenja K. Naumann,¹ T. Daniel Andrews,¹ Hamish S. Scott,³ Marco G. Casarotto,¹ Christopher C. Goodnow,¹ Jeffrey Chaitow,⁴ Virginia Pascual,⁵ Paul Hertzog,⁶ Stephen I. Alexander,⁷ Matthew C. Cook,² and Carola G. Vinuesa¹

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 6, June 2015, pp 1592–1597

IFIH1 Mutation Causes Systemic Lupus Erythematosus With Selective IgA Deficiency

Lien Van Eyck,¹ Lien De Somer,² Diana Pombal,¹ Simon Bornschein,¹ Glynis Frans,³ Stéphanie Humblet-Baron,¹ Leen Moens,³ Francis de Zegher,⁴ Xavier Bossuyt,³ Carine Wouters,⁴ and Adrian Liston¹


Microglia-dependent synapse loss in type I interferon-mediated lupus

Allison R. Bialas¹, Jessy Presumey¹, Abhishek Das¹, Cees E. van der Poel¹, Peter H. Lapchak², Luka Mesin³, Gabriel Victora³, George C. Tsokos², Christian Mawrin^{4,5}, Ronald Herbst⁶ & Michael C. Carroll¹

Parkin and PINK1 mitigate STING-induced inflammation

Danielle A. Sliter¹, Jennifer Martinez², Ling Hao¹, Xi Chen³, Nuo Sun⁴, Tara D. Fischer¹, Jonathon L. Burman¹, Yan Li⁵, Zhe Zhang¹, Derek P. Narendra⁶, Huaibin Cai³, Max Borsche⁷, Christine Klein⁷ & Richard J. Youle^{1*}

IRF3 and type I interferons fuel a fatal response to myocardial infarction

Kevin R King¹⁻⁴, Aaron D Aguirre^{1,5}, Yu-Xiang Ye^{1,6}, Yuan Sun¹, Jason D Roh⁵, Richard P Ng Jr^{1,7}, Rainer H Kohler¹ , Sean P Arlauckas¹, Yoshiko Iwamoto¹, Andrej Savol^{8,9}, Ruslan I Sadreyev^{8,10}, Mark Kelly¹¹, Timothy P Fitzgibbons¹¹, Katherine A Fitzgerald¹², Timothy Mitchison¹³, Peter Libby⁴, Matthias Nahrendorf^{1,14} & Ralph Weissleder^{1,13}

Human type I interferonopathies

Monogenic disorders in which an upregulation of a type I interferon response may be directly relevant to disease pathogenesis

Human type I interferonopathies

An hypothesis

Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, and *ADAR*: a case-control study

www.thelancet.com/neurology Published online October 30, 2013

Gillian I Rice, Gabriella M A Forte, Marcin Szykiewicz, Diana S Chase, Alec Aeby, Mohamed S Abdel-Hamid, Sam Ackroyd, Rebecca Allcock, Kathryn M Bailey, Umberto Balottin, Christine Barnerias, Genevieve Bernard, Christine Bodemer, Maria P Botella, Cristina Cereda, Kate E Chandler, Lyvia Dabydeen, Russell C Dale, Corinne De Laet, Christian G E L De Goede, Mireia del Toro, Laila Effat, Noemi Nunez Enamorado, Elisa Fazzi, Blanca Gener, Madli Haldre, Jean-Pierre S-M Lin, John H Livingston, Charles Marques Lourenco, Wilson Marques Jr, Patrick Oades, Pärt Peterson, Magnhild Rasmussen, Agathe Roubertie, Johanna Loewenstein Schmidt, Stavit A Shalev, Rogelio Simon, Ronen Spiegel, Kathryn J Swoboda, Samia A Temtamy, Grace Vassallo, Catheline N Vilain, Julie Vogt, Vanessa Wermenbol, William P Whitehouse, Doriette Soler, Ivana Olivieri, Simona Orcesi, Mona S Aglan, Maha S Zaki, Ghada M H Abdel-Salam, Adeline Vanderver, Kai Kisand, Flore Rozenberg, Pierre Lebon, Yanick J Crow



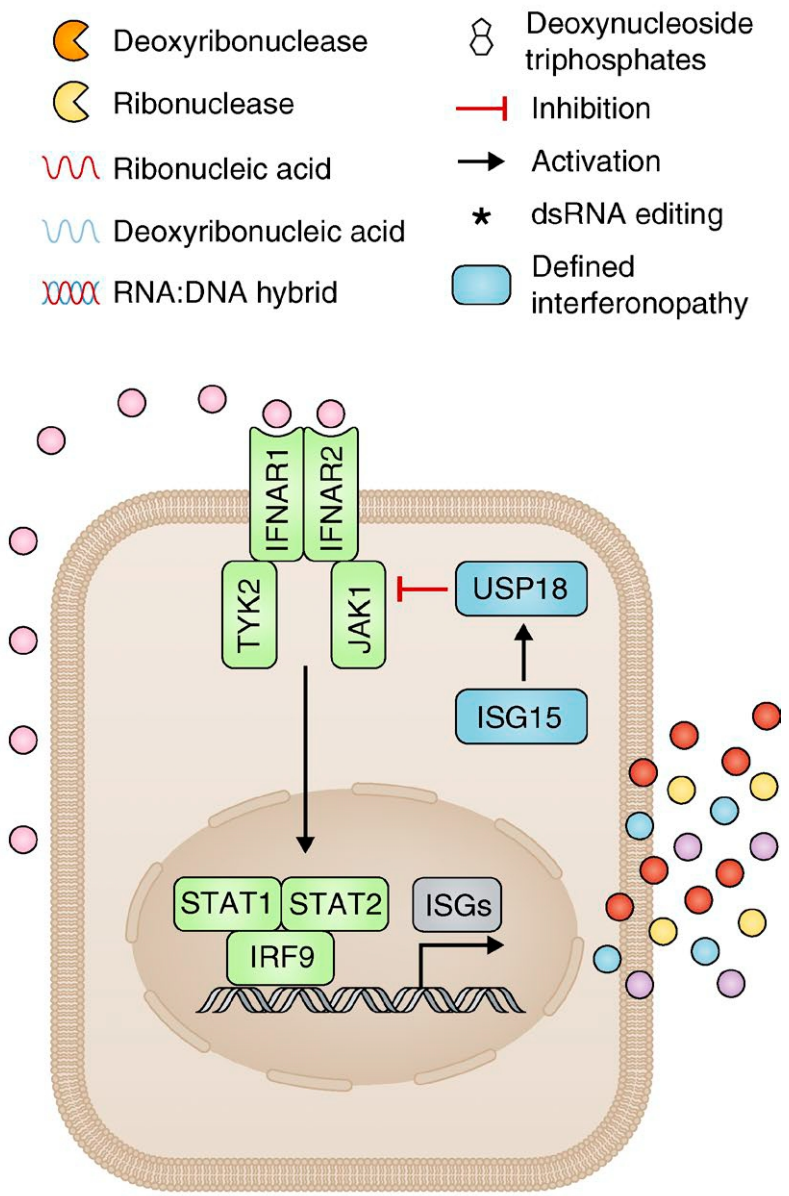
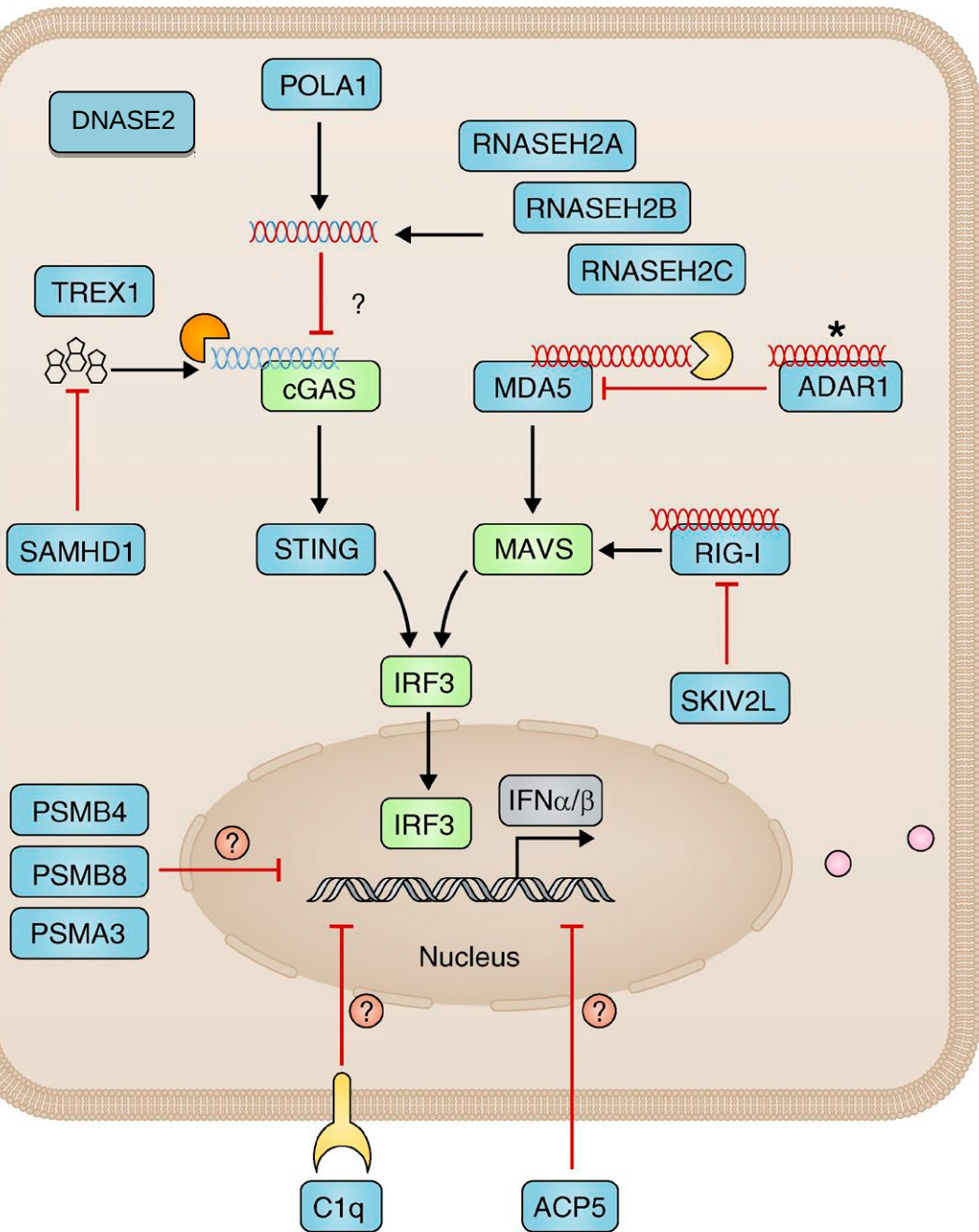
Published April 18, 2017

JEM

Technical Advances

Detection of interferon alpha protein reveals differential levels and cellular sources in disease

Mathieu P. Rodero,^{1*} Jérémie Decalf,^{3,5*} Vincent Bondet,^{3,5*} David Hunt,^{6,7*} Gillian I. Rice,⁸ Scott Werneke,^{3,5} Sarah L. McGlasson,^{6,7} Marie-Alexandra Alyanakian,¹⁰ Brigitte Bader-Meunier,^{11,15} Christine Barnerias,¹² Nathalia Bellon,¹³ Alexandre Belot,¹⁶ Christine Bodemer,^{2,13} Tracy A. Briggs,^{8,9} Isabelle Desguerre,¹² Marie-Louise Frémond,¹ Marie Hully,¹² Arn M.J.M. van den Maagdenberg,^{17,18} Isabelle Melki,^{1,11,19} Isabelle Meyts,^{20,21} Lucile Musset,²² Nadine Pelzer,¹⁷ Pierre Quartier,^{2,11} Gisela M. Terwindt,¹⁷ Joanna Wardlaw,⁷ Stewart Wiseman,⁷ Frédéric Rieux-Laucat,^{2,15} Yoann Rose,¹ Bénédicte Neven,^{2,11,15} Christina Hertel,²³ Adrian Hayday,^{24,25} Matthew L. Albert,^{3,4,5} Flore Rozenberg,²⁶ Yanick J. Crow,^{1,2,8,14**} and Darragh Duffy,^{3,4,5**}

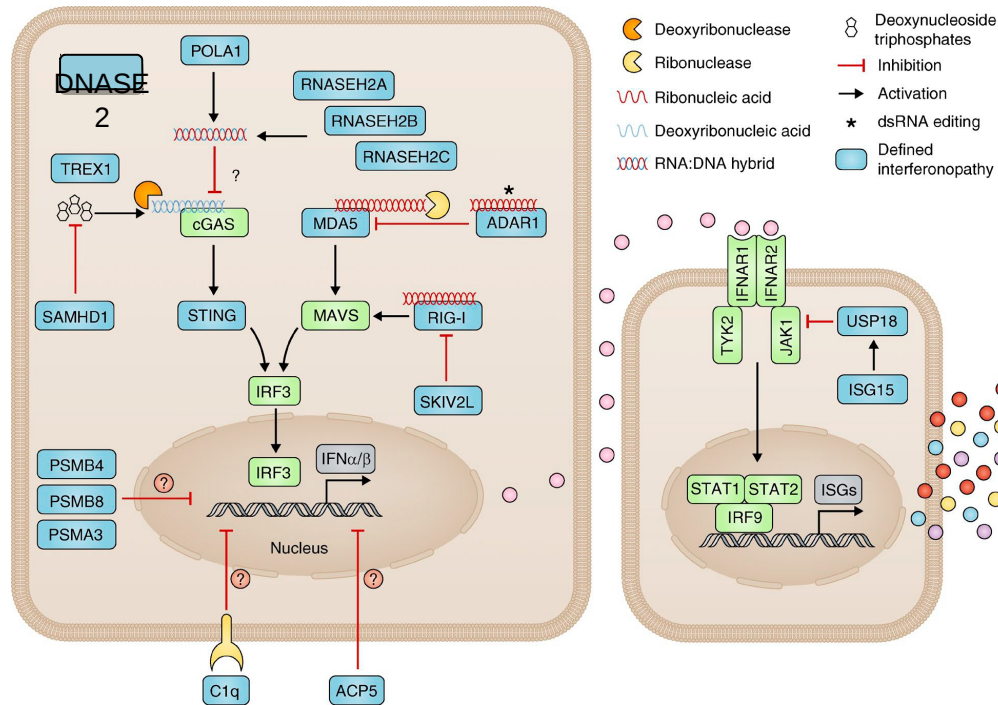


**DNA sensing via
STING (6)**

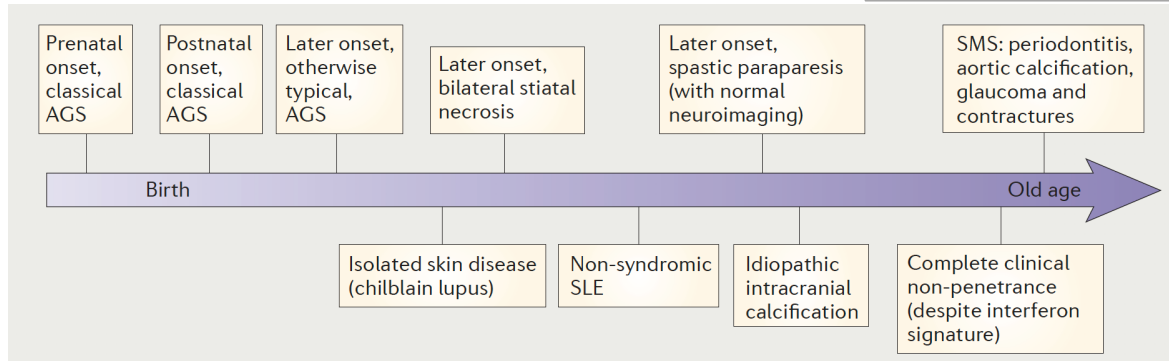
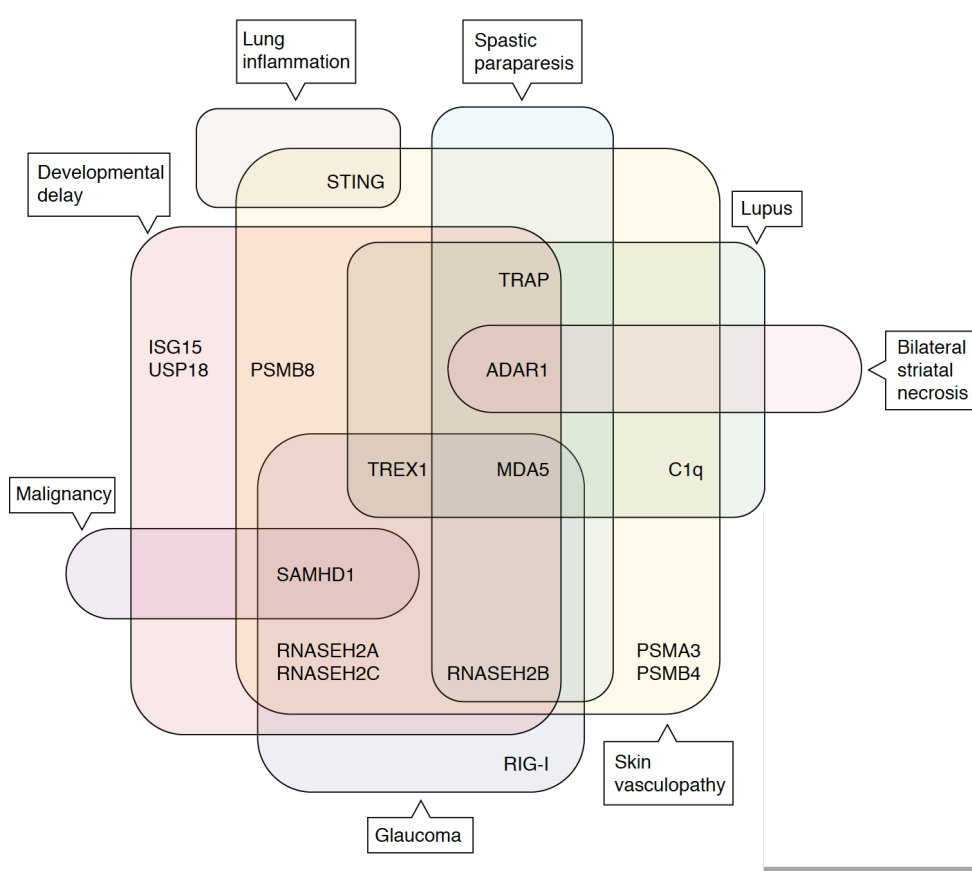
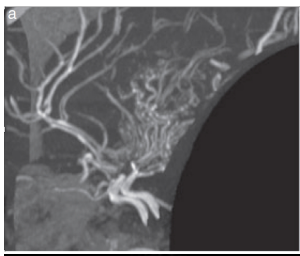
**TREX1
RNASEH2A
RNASEH2B
RNASEH2C
SAMHD1
DNASE2
STING**

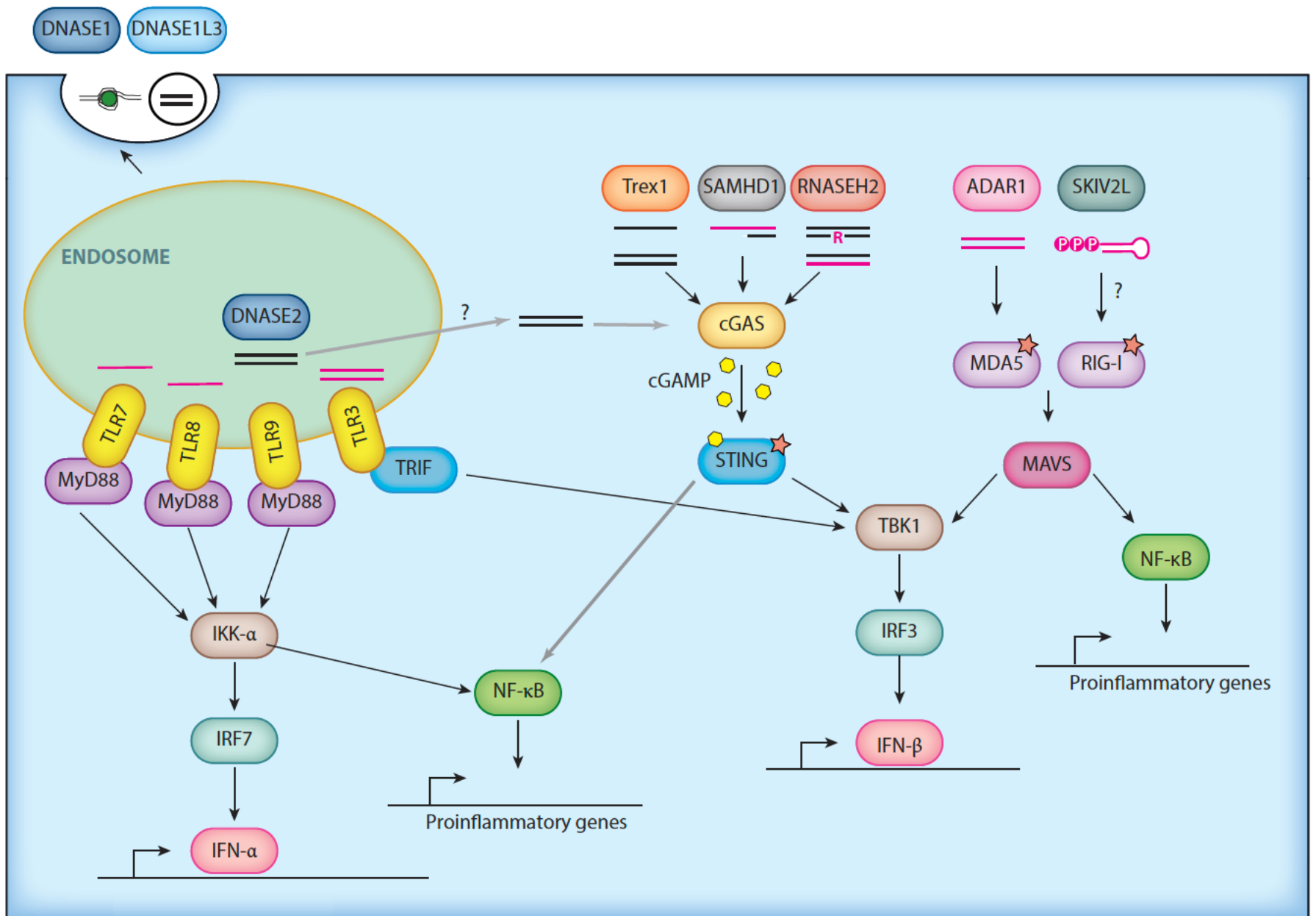
**RNA sensing via
MAVS (4)**

**ADAR1
SKIV2I
MDA5
RIGI**

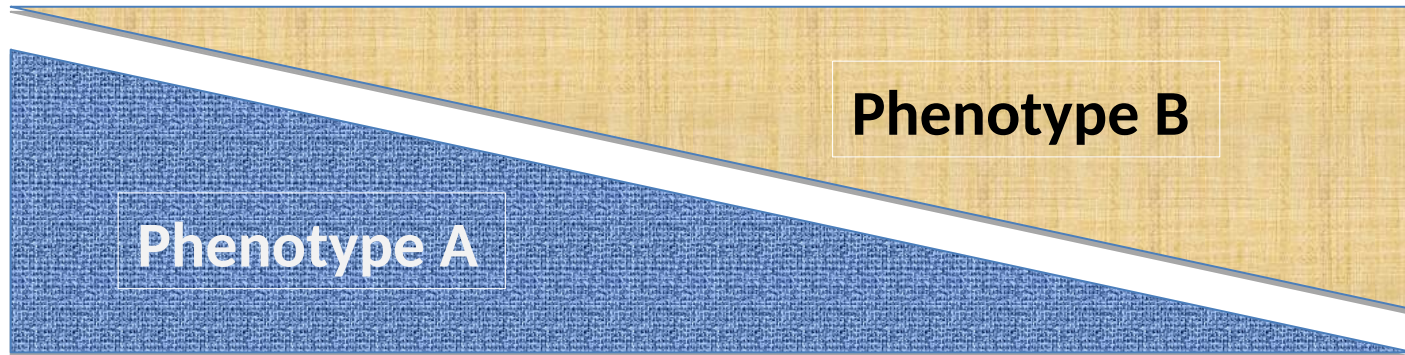


1. Self 'waste disposal'
2. Self 'marking'
3. Compartmentalisation
4. Changes in sensing thresholds





Non-interferon-mediated



Interferon-mediated

Nucleic acid driven inflammation

ORIGINAL ARTICLE

Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1 β Inhibition

Raphaela Goldbach-Mansky, M.D., Natalie J. Dailey, M.D., Scott W. Canna, M.D.,

Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors

Angeliki Giannelou,^{1,2} Hongying Wang,¹ Qing Zhou,¹ Yong Hwan Park,¹ Mones S Abu-Asab,³ Kris Ylaya,⁴ Deborah L Stone,¹ Anna Sediva,⁵ Rola Sleiman,⁶ Lucie Sramkova,⁷ Deepika Bhatla,⁸ Elisavet Serti,⁹ Wanxia Li Tsai,¹⁰ Dan Yang,¹¹ Kevin Bishop,¹² Blake Carrington,¹² Wuhong Pei,¹² Natalie Deutch,¹ Stephen Brooks,¹³ Jehad H Edwan,¹⁴ Sarita Joshi,¹⁵ Seraina Prader,¹⁶ Daniela Kaiser,¹⁷ William C Owen,¹⁸ Abdullah Al Sonbul,¹⁹ Yu Zhang,²⁰ Julie E Niemela,²¹ Shawn M Burgess,¹² Manfred Boehm,¹¹ Barbara Rehermann,⁹ JaeJin Chae,¹ Martha M Quezado,²² Amanda K Ombrello,¹ Rebecca H Buckley,²³ Alexi A Grom,²⁴ Elaine F Remmers,¹ Jana M Pachlopnik,¹⁶ Helen C Su,²⁰ Gustavo Gutierrez-Cruz,²⁵ Stephen M Hewitt,⁴ Raman Sood,¹² Kimberly Risma,²⁶ Katherine R Calvo,²¹ Sergio D Rosenzweig,²¹ Massimo Gadina,¹⁰ Markus Hafner,²⁴ Hong-Wei Sun,¹³ Daniel L Kastner,¹ Ivona Aksentijevich¹

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip J. Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubiniow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.

The Deubiquitinase OTULIN Is an Essential Negative Regulator of Inflammation and Autoimmunity

Rune Busk Damgaard,¹ Jennifer A. Walker,¹ Paola Marco-Casanova,¹ Neil V. Morgan,² Hannah L. Titheradge Paul R. Elliott,¹ Duncan McHale,⁵ Eamonn R. Maher,^{6,*} Andrew N.J. McKenzie,^{1,*} and David Komander^{1,7,*}

ORIGINAL ARTICLE

Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1 β Inhibition

Raphaela Goldbach-Mansky, M.D., Natalie J. Dailey, M.D., Scott W. Canna, M.D.,

Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors

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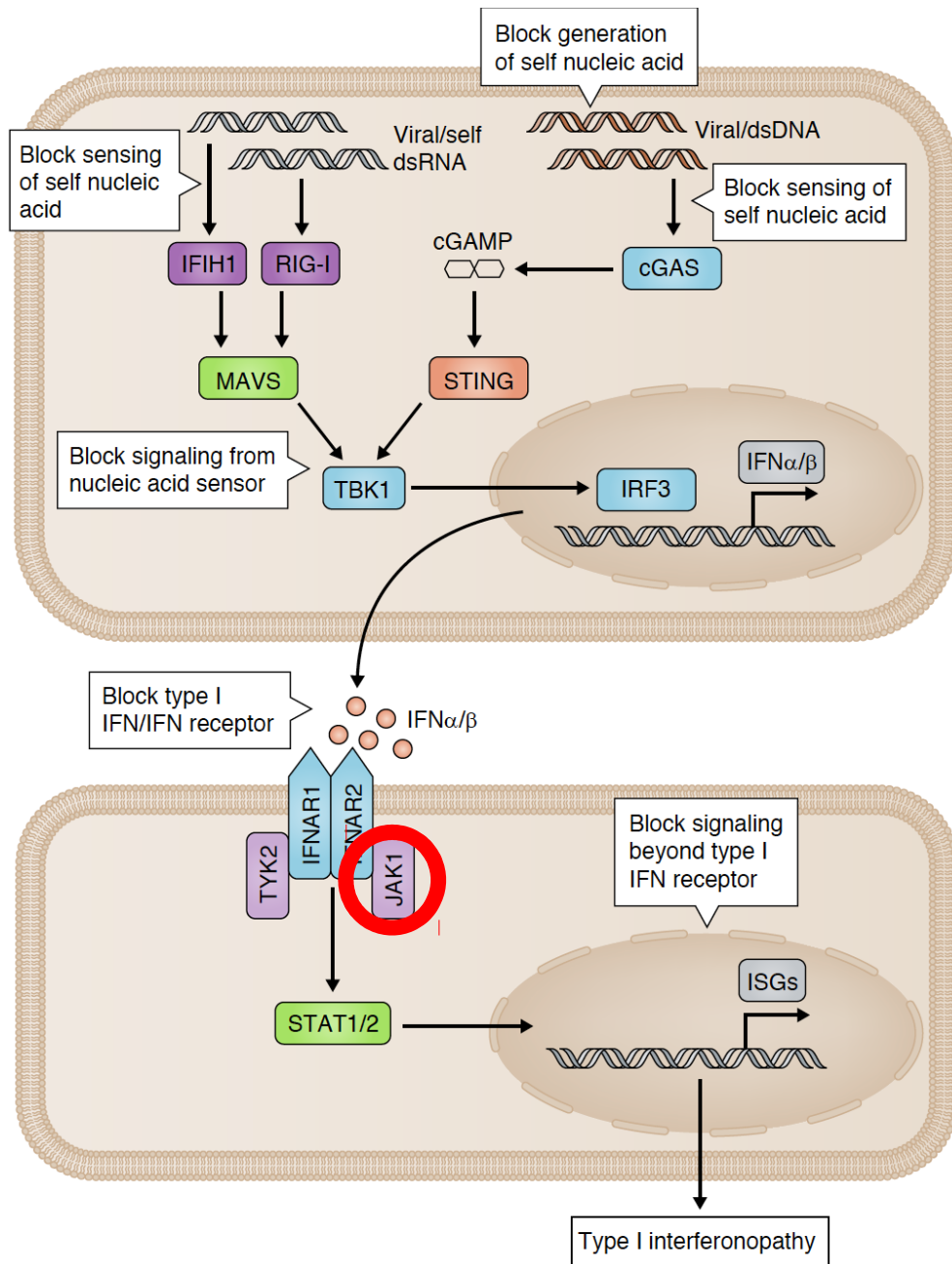
STING	Necker cohort (N = 16)	Literature (N = 17 published)	Not published
Biologics (number of the patients treated)	7/16 anti cytokines: 5 anti TNFa: 3 anti IL1: 2 anti IL6: 3	6/17 anti cytokines: 6 anti TNFa: 6 anti IL1: 1 anti IL6: 1	anti cytokines: 3 anti TNFa: 2 anti IL1: 1 anti IL6: 1

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., m Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., kov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., lip J. Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., shel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubiniow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.

The Deubiquitinase OTULIN Is an Essential Negative Regulator of Inflammation and Autoimmunity

Rune Busk Damgaard,¹ Jennifer A. Walker,¹ Paola Marco-Casanova,¹ Neil V. Morgan,² Hannah L. Titheradge,^{3,4} Paul R. Elliott,¹ Duncan McHale,⁵ Eamonn R. Maher,^{6,*} Andrew N.J. McKenzie,^{1,*} and David Komander^{1,7,*}



J Allergy Clin Immunol. 2016 Aug 20. pii: S0091-6749(16)30797-7. doi: 10.1016/j.jaci.2016.07.015. [Epub ahead of print]

Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children.

Frémond ML¹, Rodero MP², Jeremiah N³, Belot A⁴, Jeziorski E⁵, Duffy D⁶, Bessis D⁷, Cros G⁸, Rice GI⁹, Charbit B¹⁰, Hulin A¹¹, Khoudour N¹¹, Caballero CM¹², Bodemer C¹³, Fabre M¹⁴, Berteloot L¹⁵, Le Bourgeois M¹⁶, Reix P¹⁷, Walzer T¹⁸, Moshous D¹⁹, Blanche S²⁰, Fischer A²¹, Bader-Meunier B²², Rieux-Laucat F³, Crow YJ²³, Neven B²⁴.

J Clin Invest. 2018 Apr 12. pii: 98814. doi: 10.1172/JCI98814. [Epub ahead of print]

JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies.

Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, Jesus AA, Chapelle DC, Kim H, Dill S, Colbert R, Failla L, Kost B, O'Brien M, Reynolds JC, Folio LR, Calvo KR, Paul SM, Weir N, Brofferio A, Soldatos A, Biancotto A, Cowen EW, Digiovanna JG, Gadina M, Lipton AJ, Hadigan C, Holland SM, Fontana J, Alawad AS, Brown RJ, Rother KI, Heller T, Brooks KM, Kumar P, Brooks SR, Waldman M, Singh HK, Nickeleit V, Silk M, Prakash A, Janes JM, Ozen S, Wakim PG, Brogan PA, Macias WL, Goldbach-Mansky R.



TREX1

Bénédicte Neven

D0



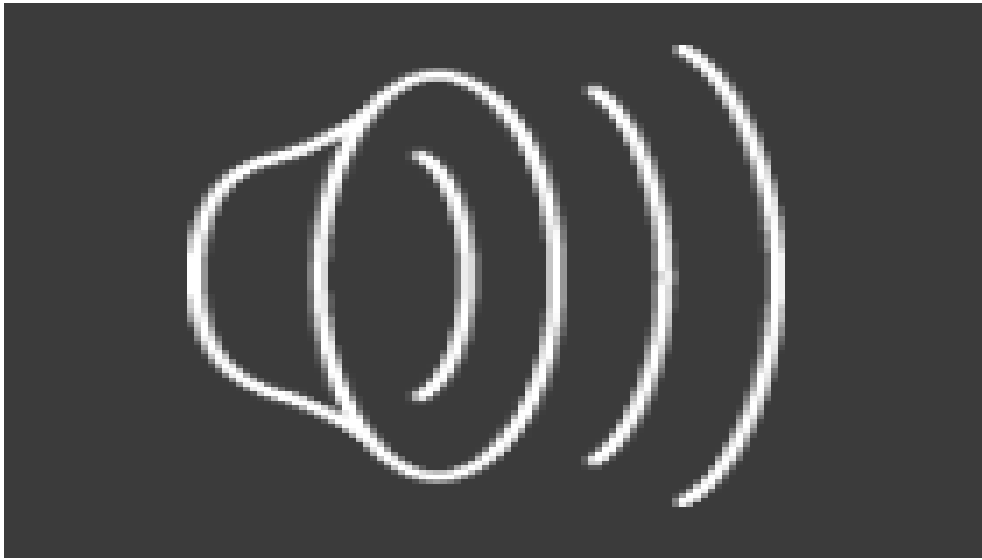


D0

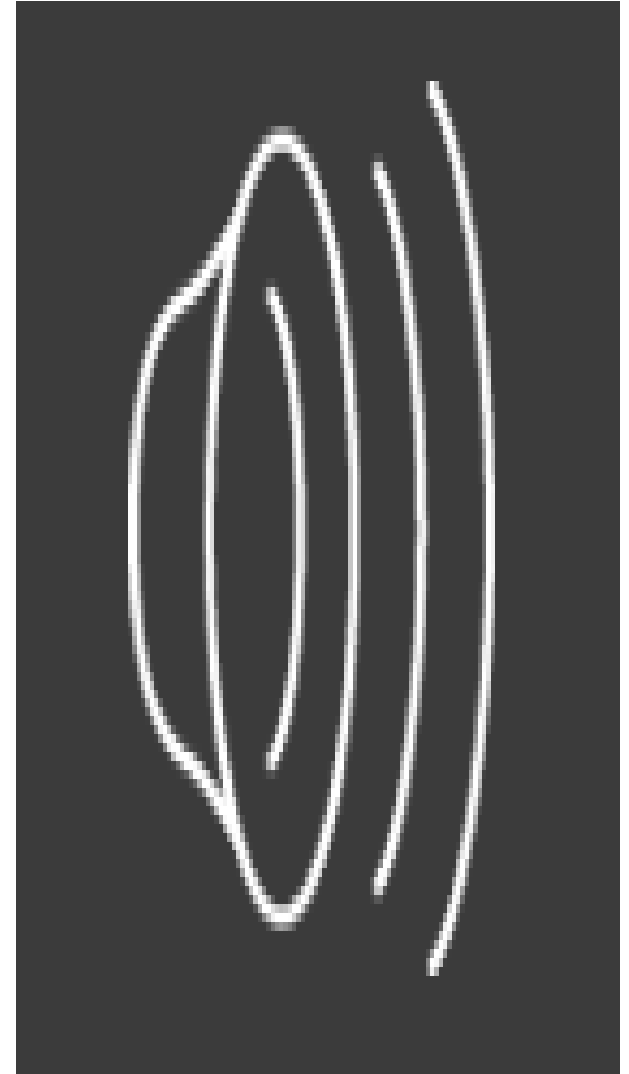


M2.5

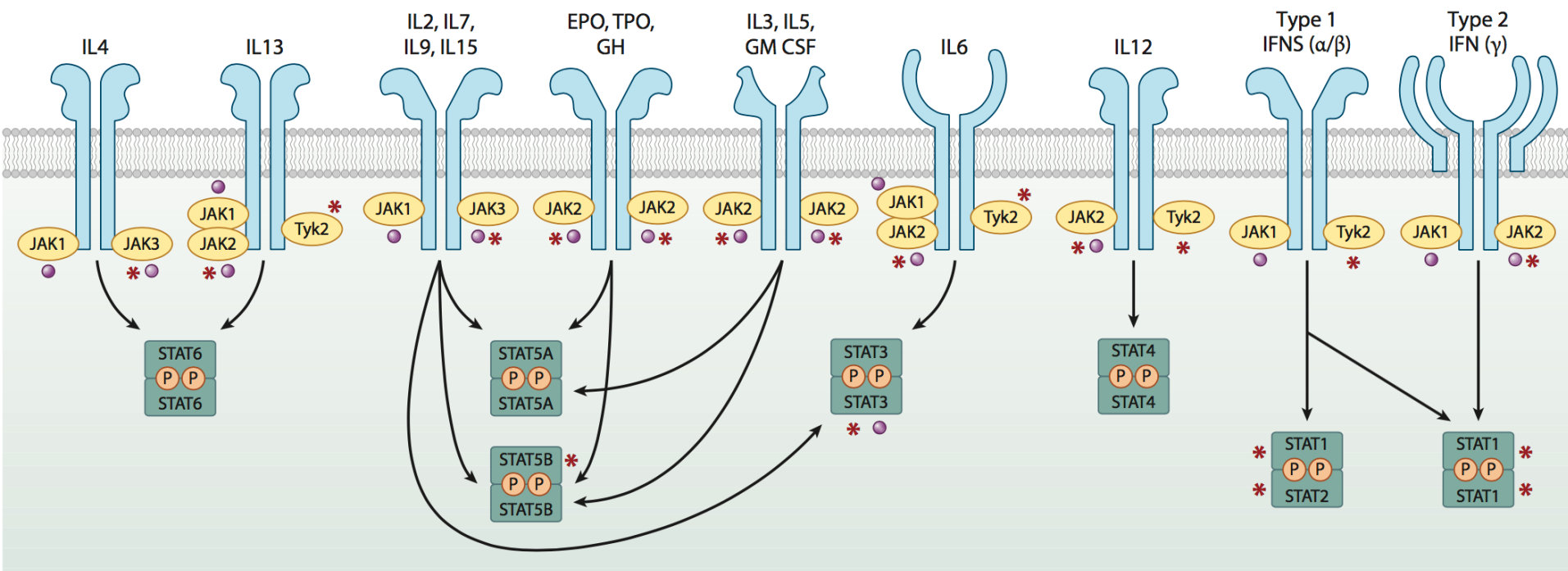




February 2016 (5 months of treatment)



August 2016 (11 months of treatment)

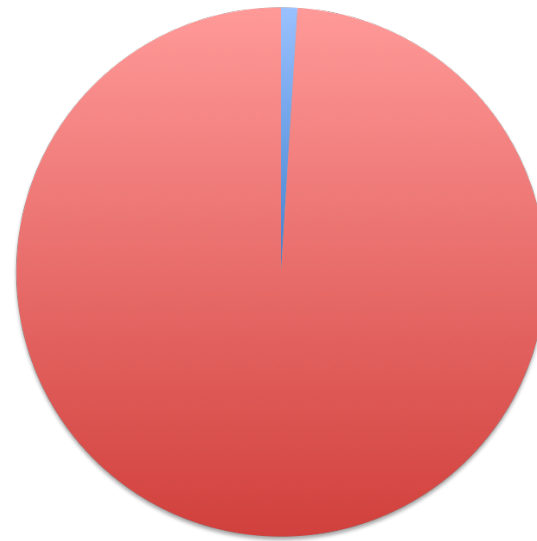


Annu. Rev. Med. 2015. 66:311–28

John J. O’Shea, Daniella M. Schwartz,
Alejandro V. Villarino, Massimo Gadina,
Iain B. McInnes, and Arian Laurence

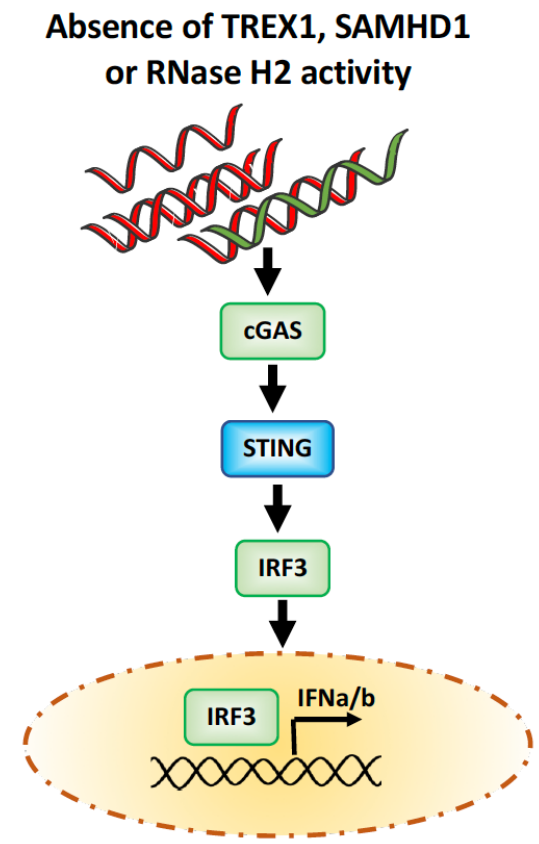
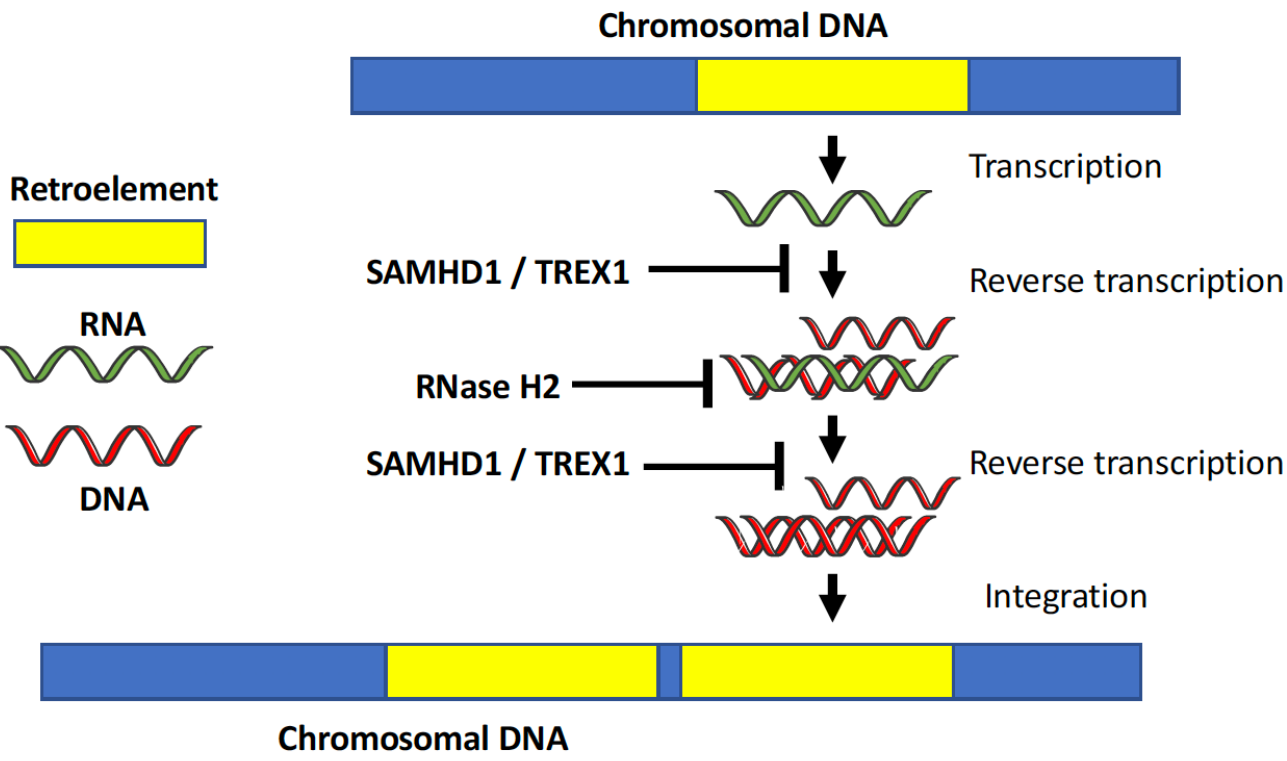
The conceptual distinction between self and non-self breaks down when considering endogenous retroelements

HUMAN GENOME



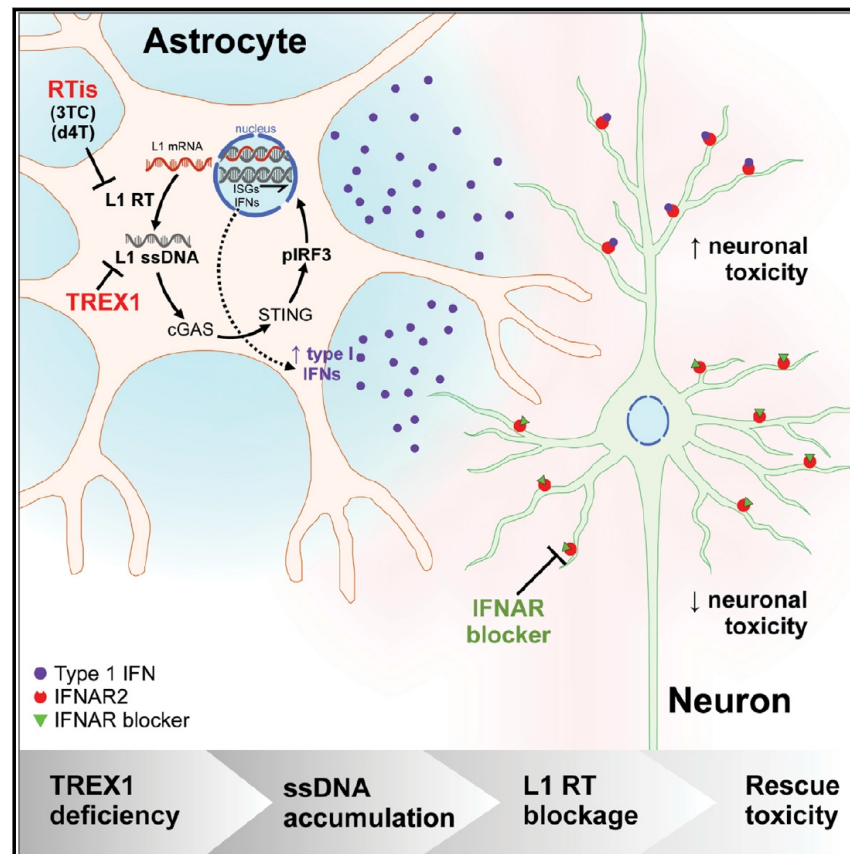
■ Genes

■ Non-coding



Modeling of TREX1-Dependent Autoimmune Disease using Human Stem Cells Highlights L1 Accumulation as a Source of Neuroinflammation

Charles A. Thomas,^{1,2,3,8} Leon Tejwani,^{1,2,3,4,8} Cleber A. Trujillo,^{1,2,3} Priscilla D. Negraes,^{1,2,3} Roberto H. Herai,^{1,2,3,5} Pinar Mesci,^{1,2,3} Angela Macia,^{1,2,3} Yanick J. Crow,^{6,7} and Alysson R. Muotri^{1,2,3,9,*}



Example: "Heart attack" AND "Los Angeles"

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Trial record **1 of 1** for: NCT02363452

[Previous Study](#) | [Return to List](#) | [Next Study](#)

Reverse Transcriptase Inhibitors in AGS (RTIs in AGS)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified October 2015 by Assistance Publique - Hôpitaux de Paris

Sponsor:

Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):

Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:

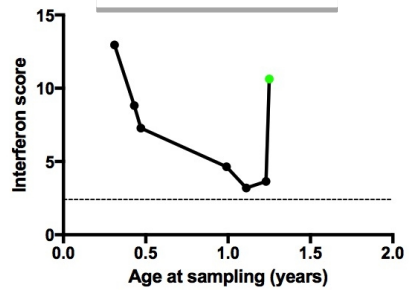
NCT02363452

First received: January 15, 2015

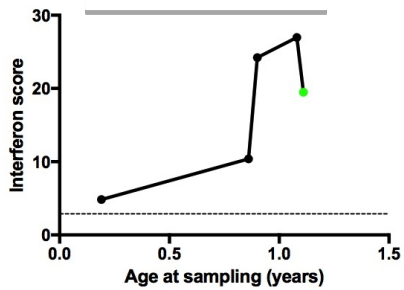
Last updated: October 5, 2015

Last verified: October 2015

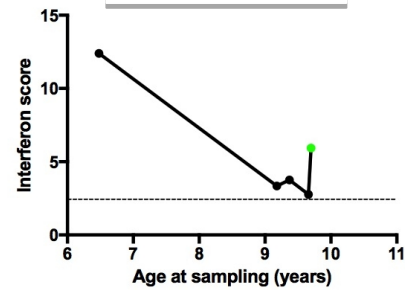
[History of Changes](#)



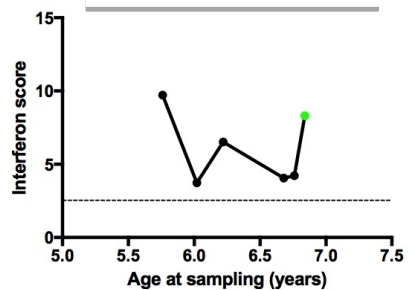
Treatment started



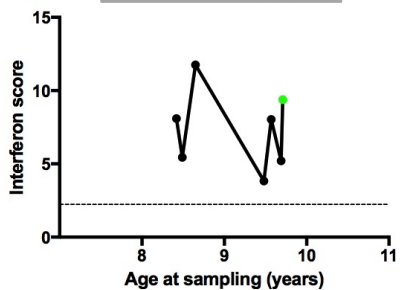
Treatment started



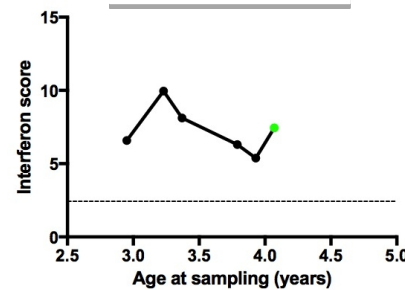
Treatment started



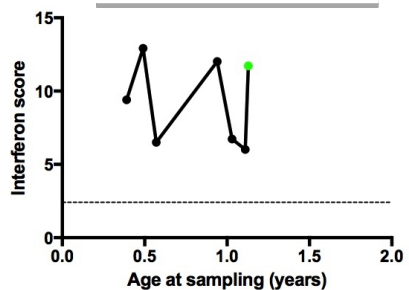
Treatment started



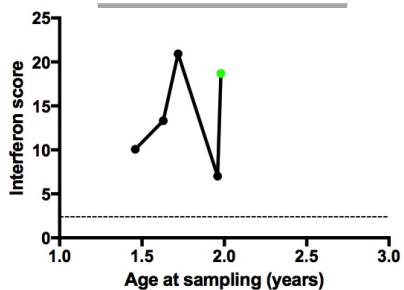
Treatment started



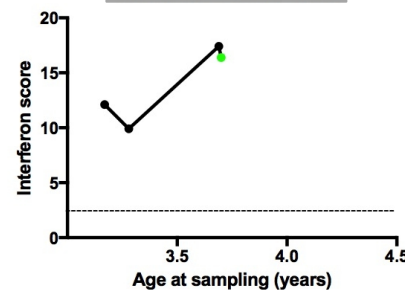
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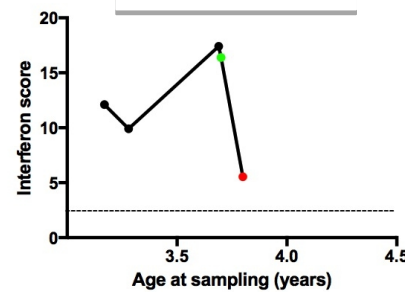
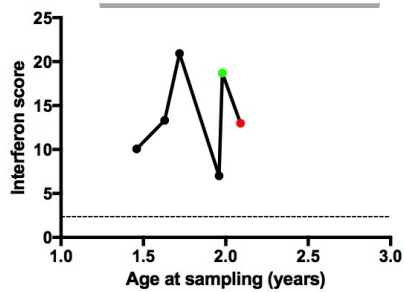
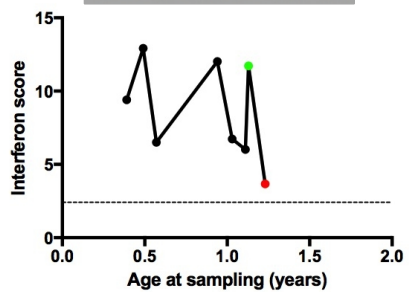
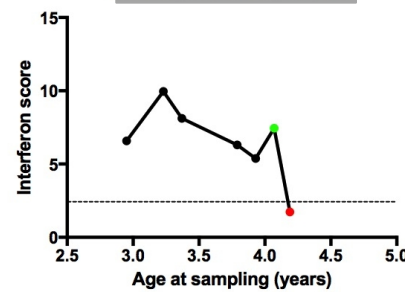
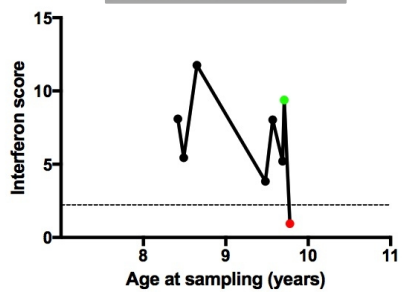
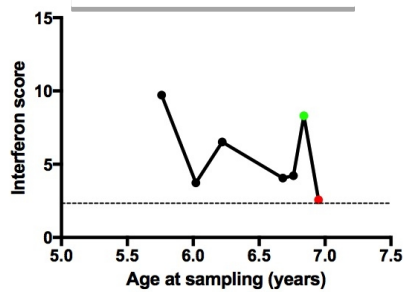
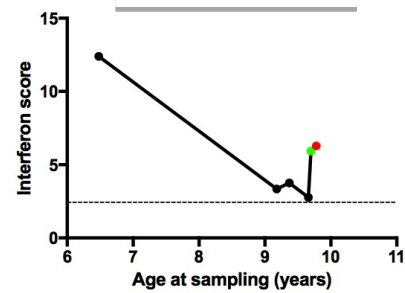
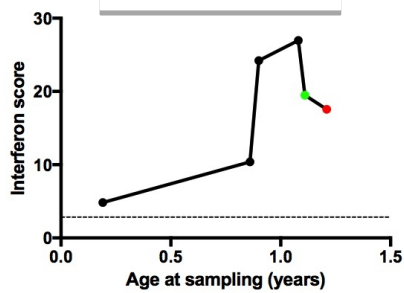
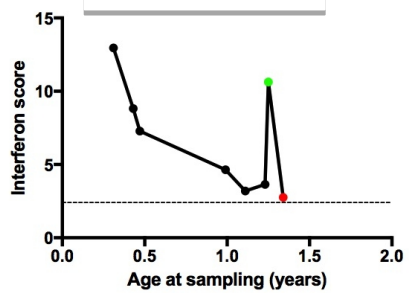
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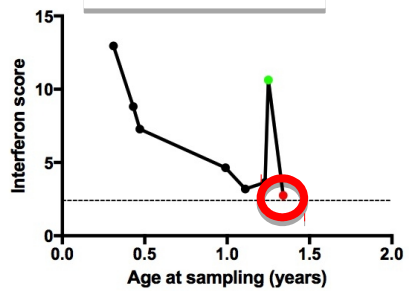


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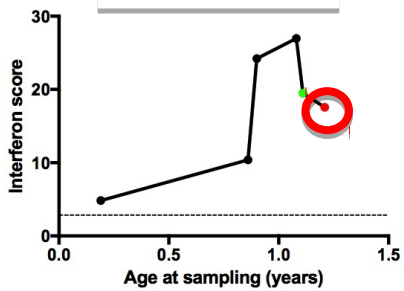


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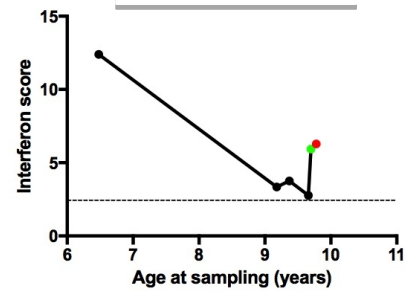




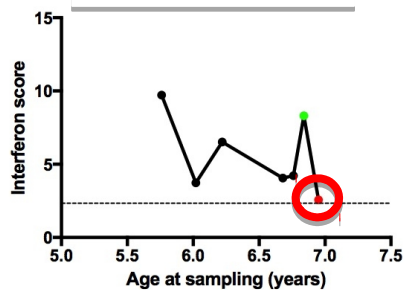
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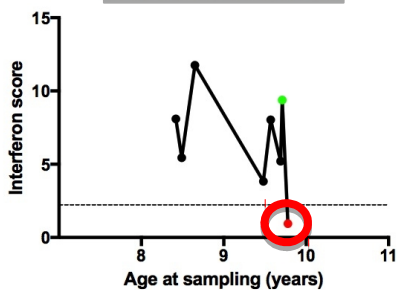
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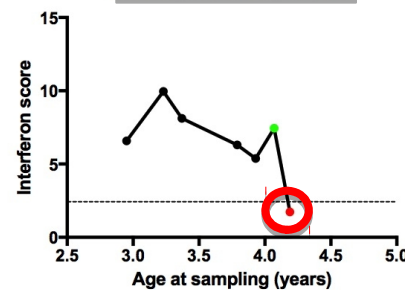
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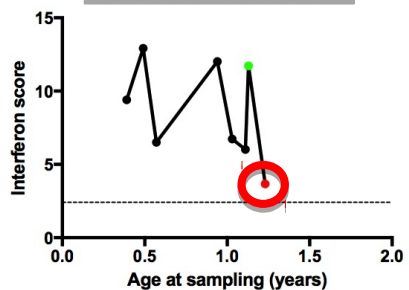
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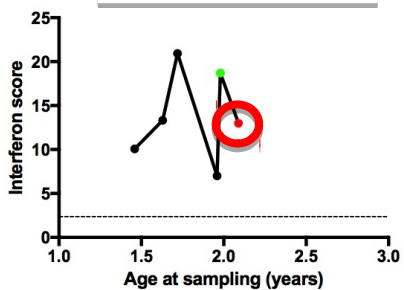
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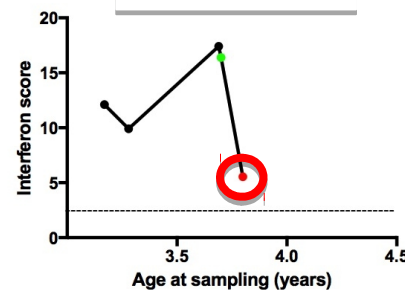
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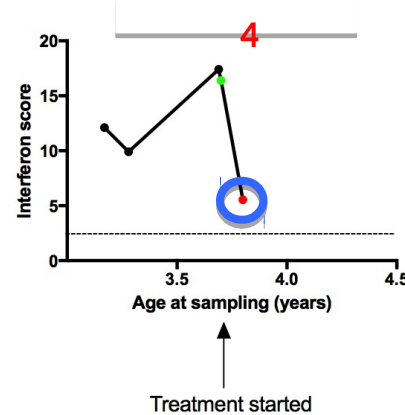
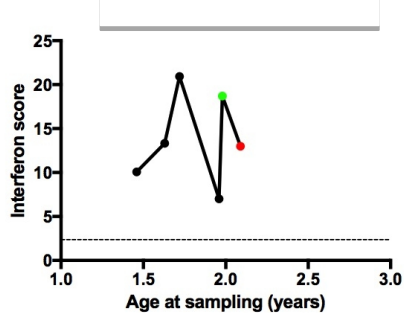
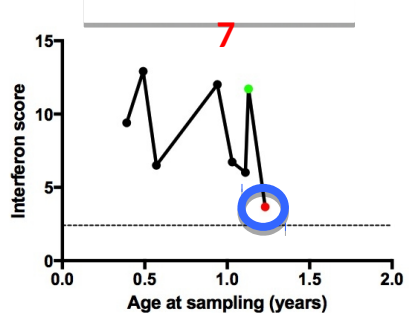
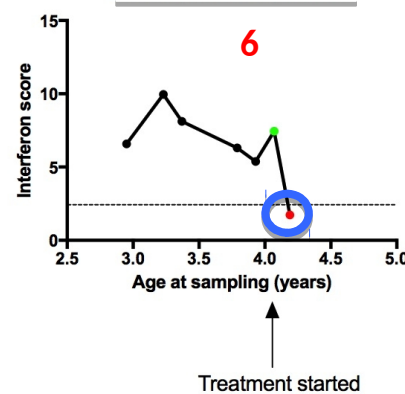
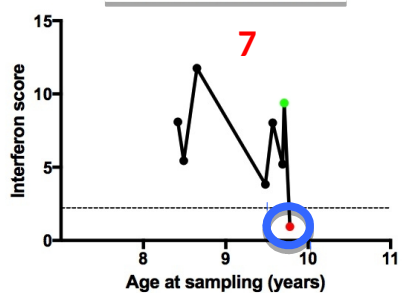
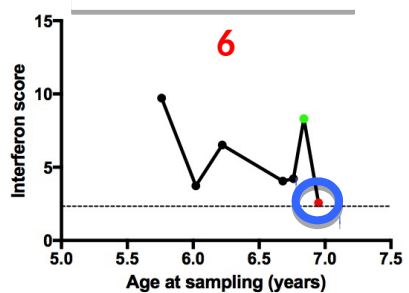
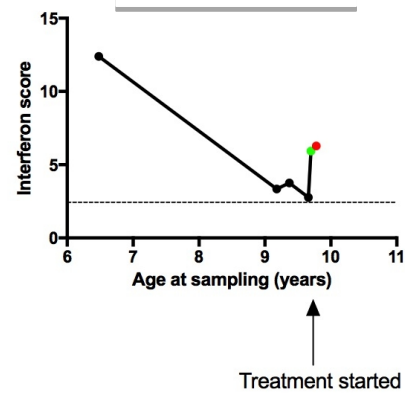
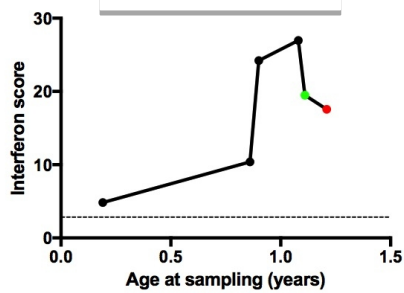
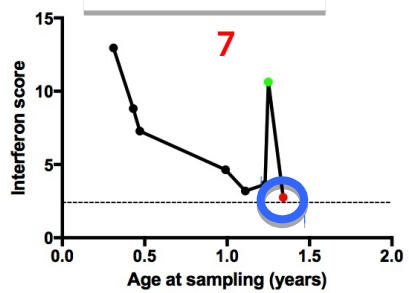
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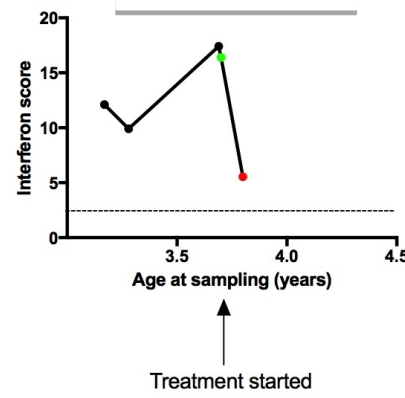
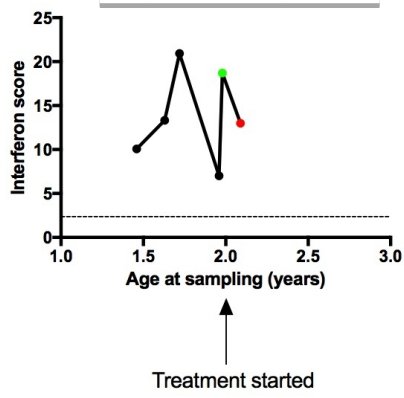
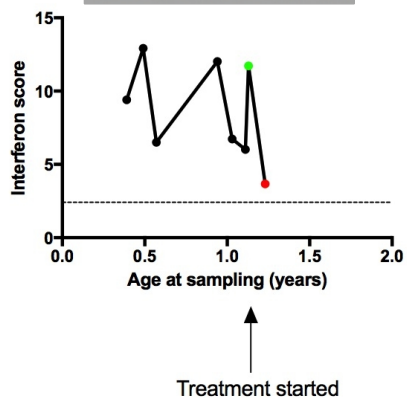
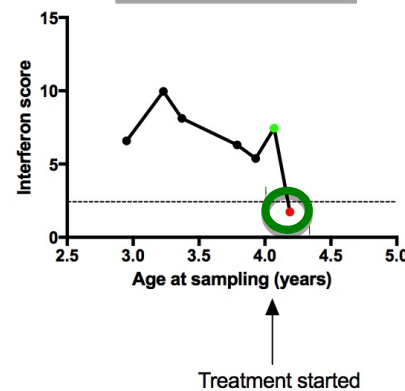
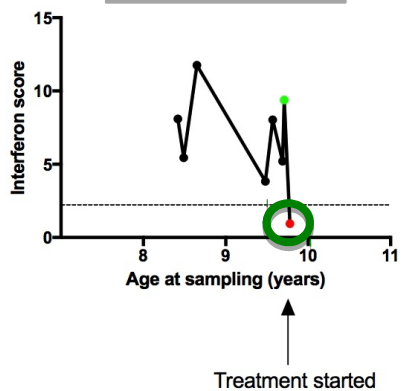
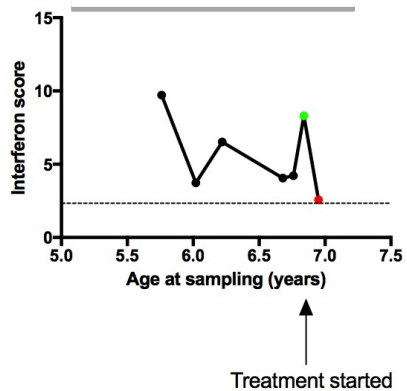
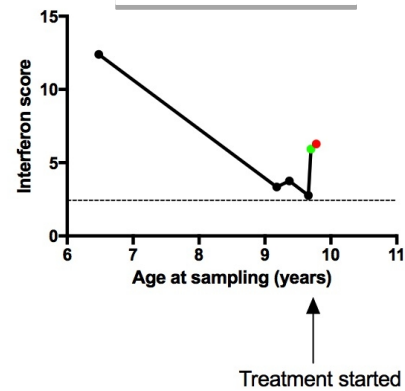
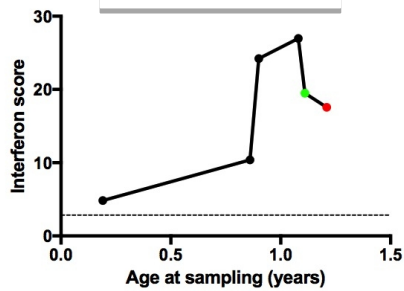
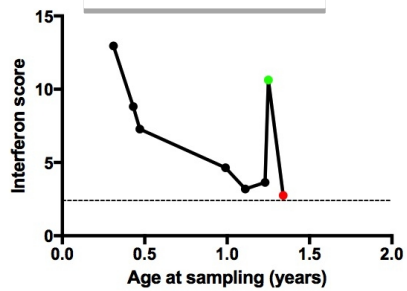


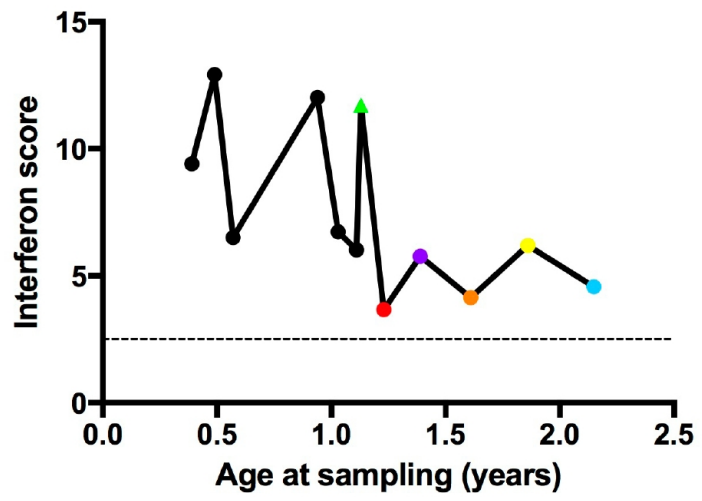
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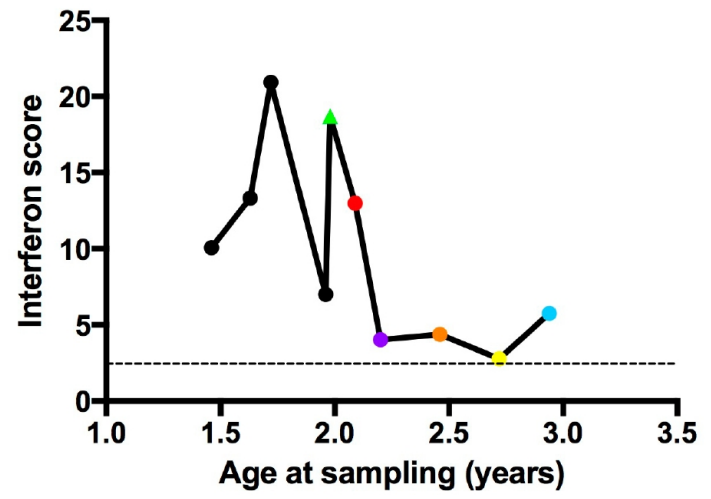
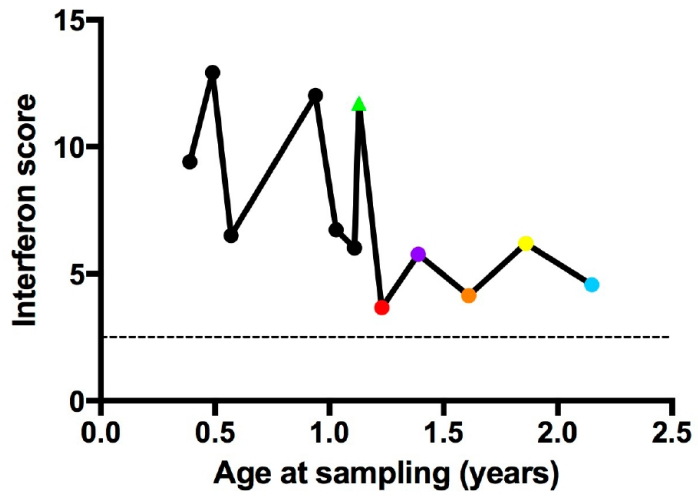
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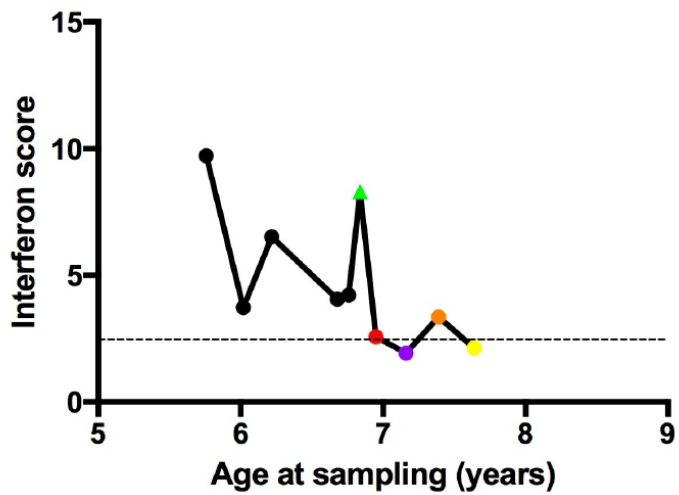
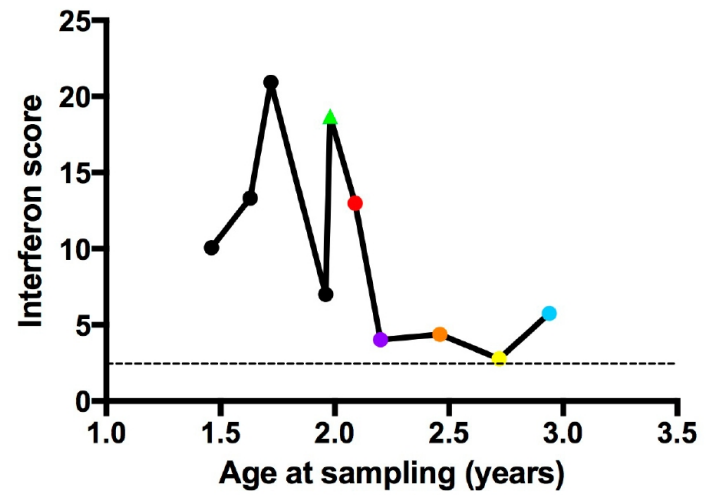
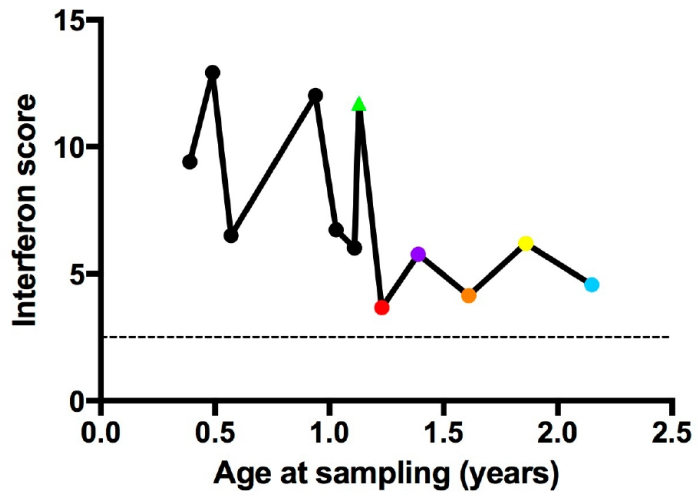


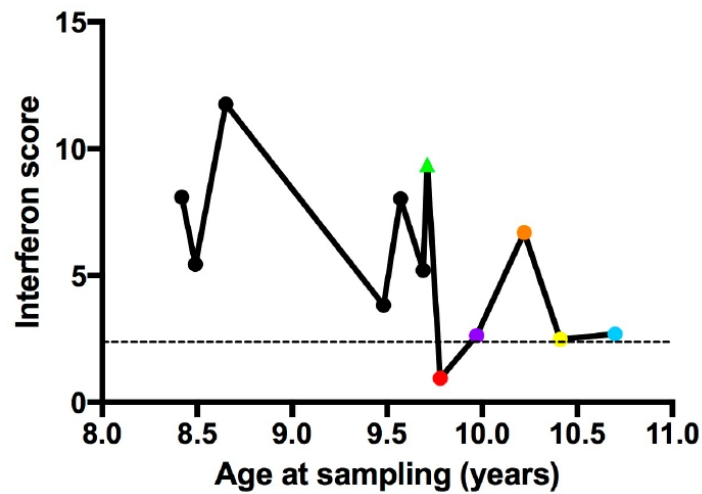
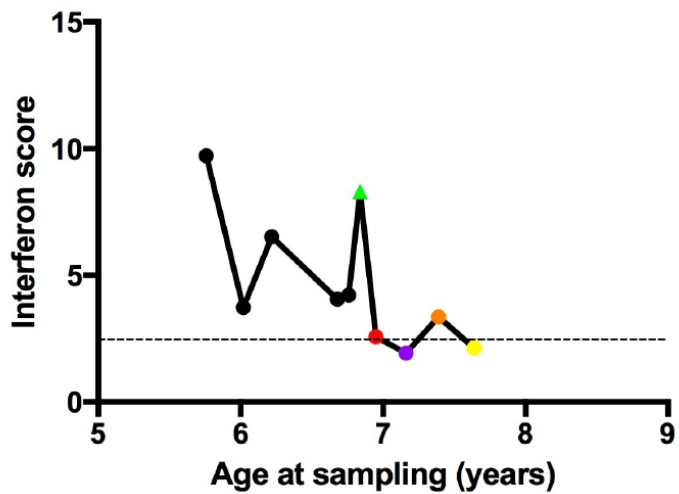
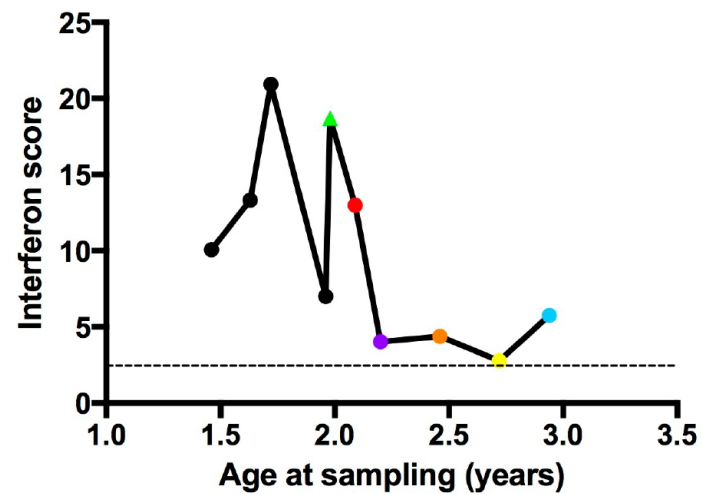
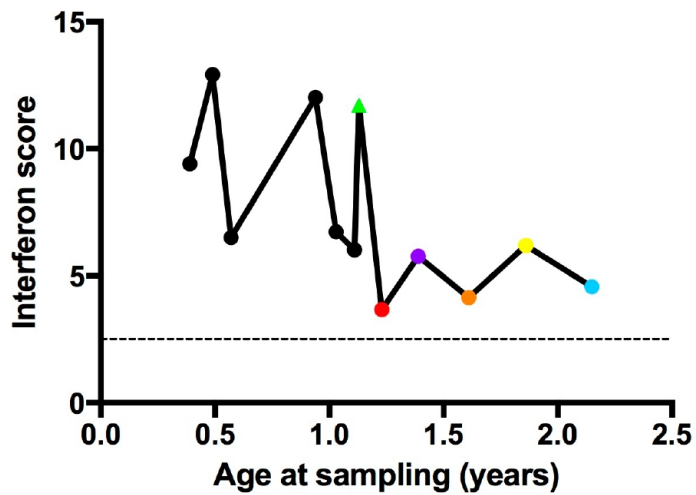


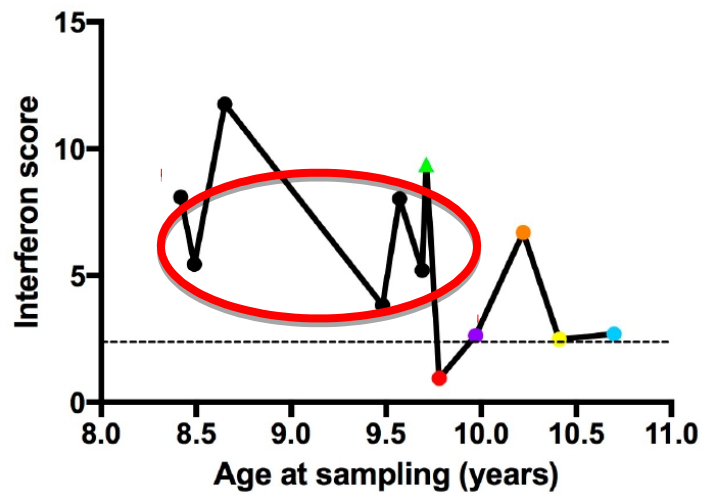
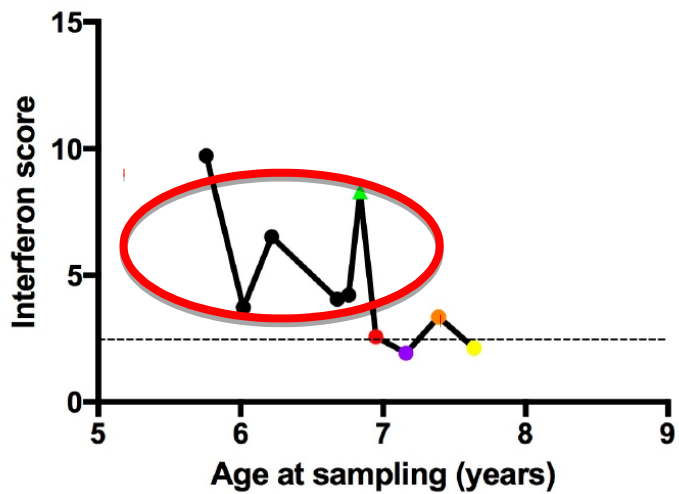
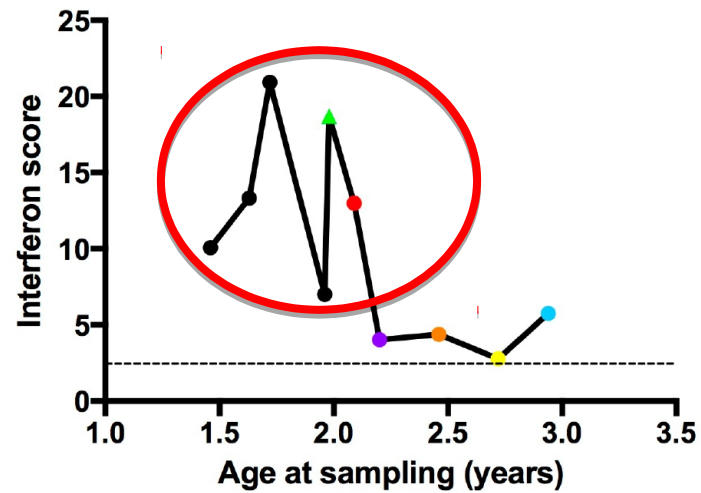
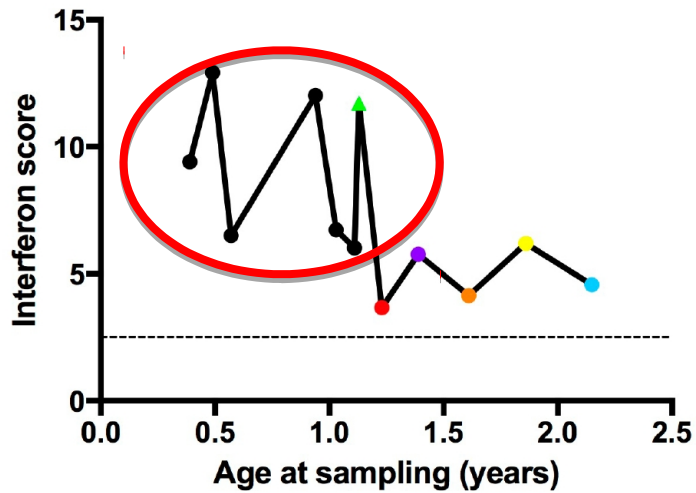


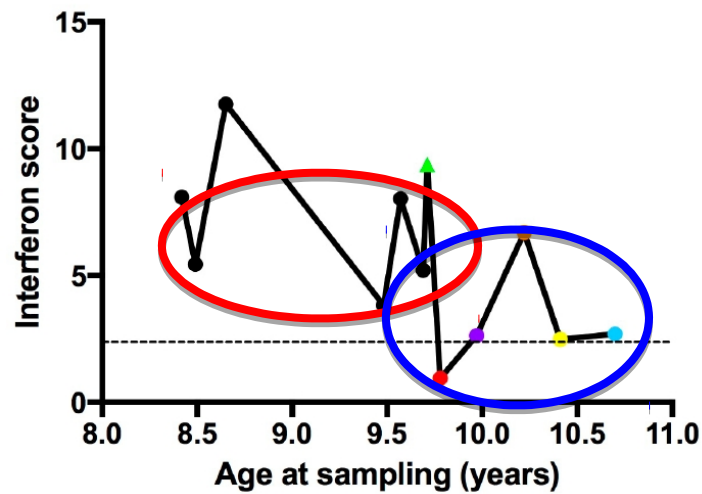
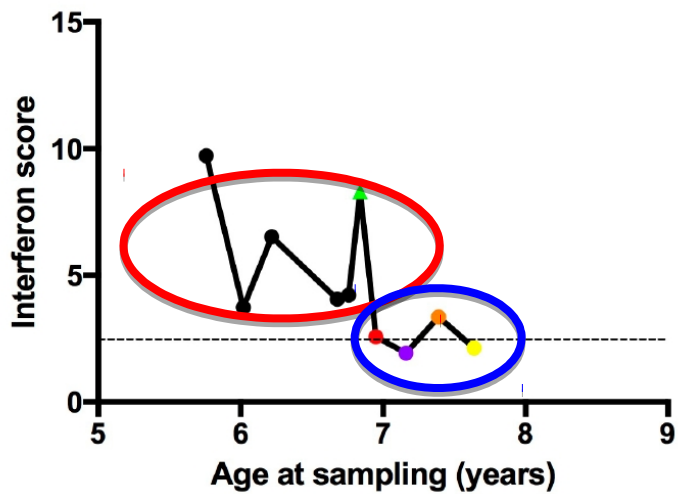
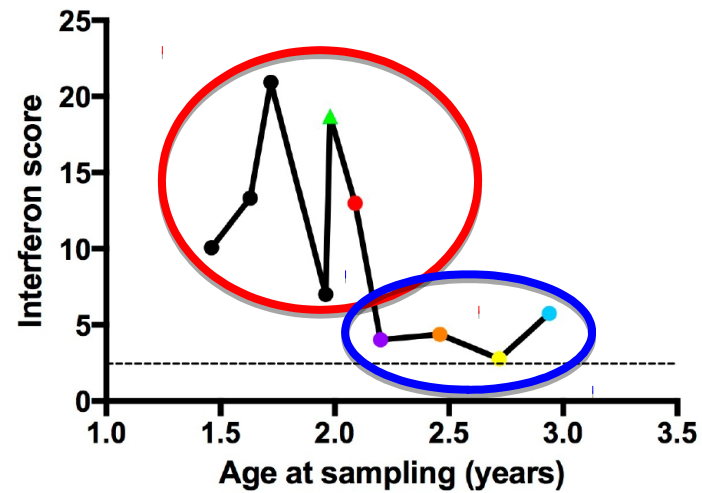
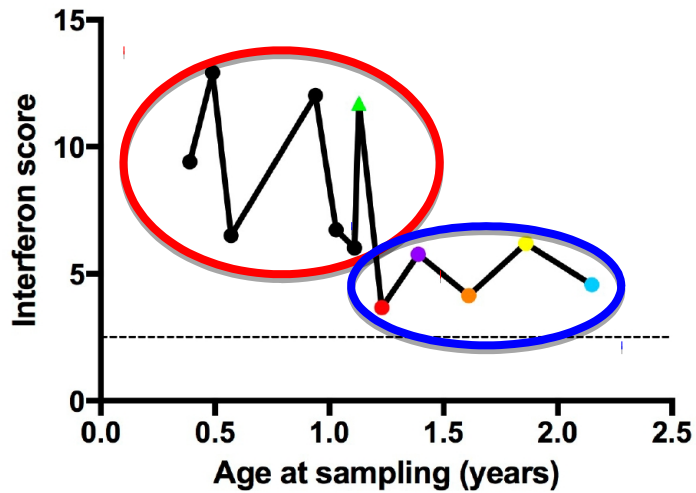
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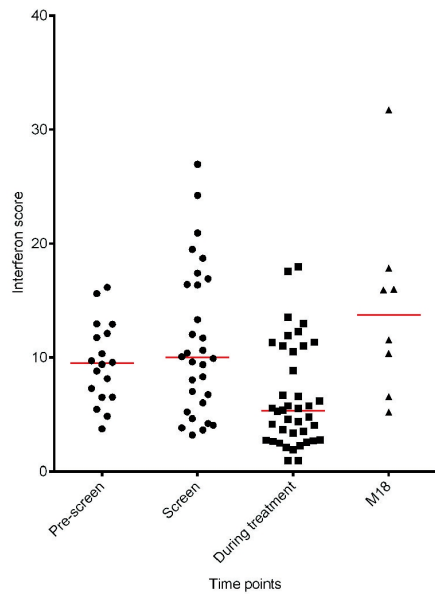
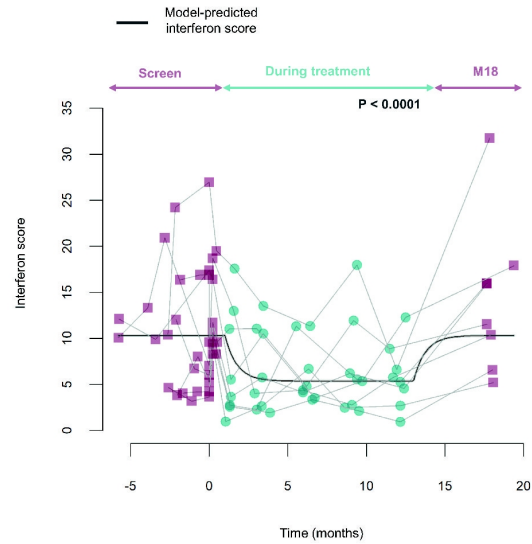
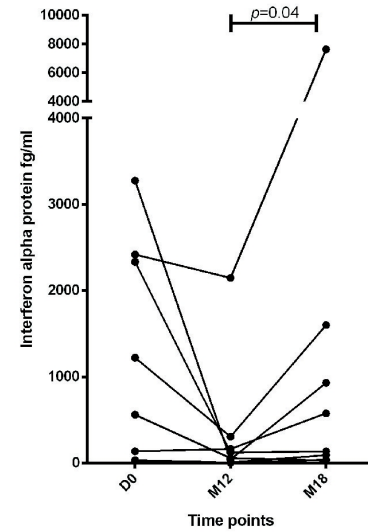
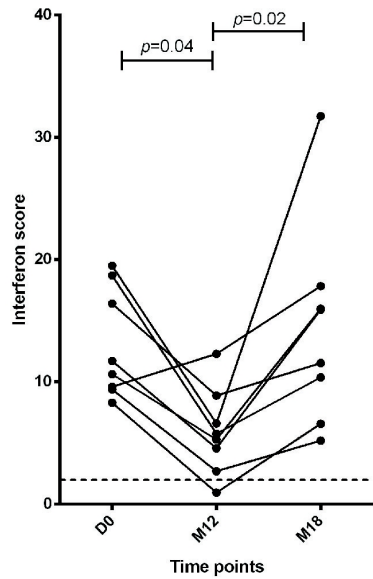
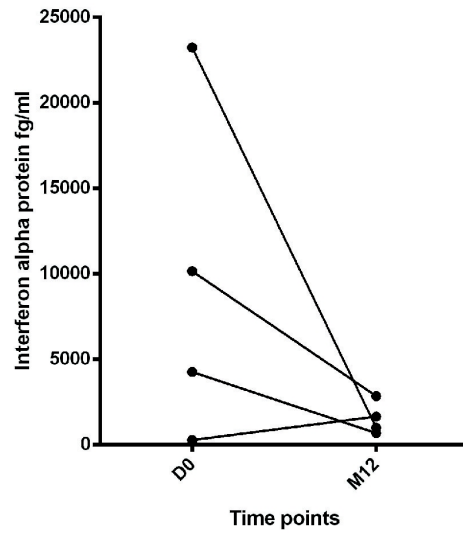
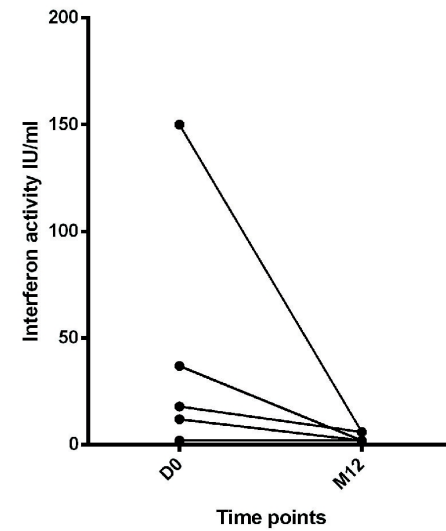










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