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Meeting Overview: Interferon Lambda - Disease Impact and Therapeutic Potential

Thomas R. O'Brien
National Cancer Institute (NCI)

Howard A. Young
National Cancer Institute at Frederick, younghow@mail.nih.gov

Raymond P. Donnelly
Food and Drug Administration

Ludmila Prokunina-Olsson
National Cancer Institute (NCI)

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Meeting Overview: Interferon Lambda—Disease Impact and Therapeutic Potential

Thomas R. O'Brien,[1] Howard A. Young,[2] Raymond P. Donnelly,[3] and Ludmila Prokunina-Olsson[4]

A meeting entitled, ''Interferon Lambda: Disease Impact and Translational Potential,'' was held on the campus of the National Institutes of Health in Bethesda, Maryland, on October 25–26, 2018. To our knowledge, this was the first meeting that focused exclusively on interferon lambda (IFN-λ). The meeting's purpose was to enhance interdisciplinary communication and promote new collaborations. The gathering brought together an international group of scientists from a wide range of disciplines. Sessions included: IFN-λ Biology, Therapy and Genetic Variation; IFN-λ and Hepatitis C Virus Infection; IFN-λ in Other Infections; and IFN-λ—Hepatic Fibrosis and Cancer. The next meeting on IFN-λ is planned for 2020.

Keywords: cancer, genetics, hepatitis C virus, immunology, infectious diseases, interferon lambda

Background

On October 25–26, 2018 a meeting entitled, ''IFN-λ: Disease Impact and Translational Potential,'' was held on the campus of the National Institutes of Health in Bethesda, Maryland. To our knowledge, this was the first ever meeting to focus exclusively on IFN-λ. The meeting's purpose was to enhance interdisciplinary communication and promote new collaborations in research on IFN-λ, a rapidly developing field with tremendous translational potential for cancer, infectious diseases, and immunology.

Discovery of interferon lambda 1–3 and development of interferon lambda-based therapy

The interferon lambda (IFN-λ) family was discovered relatively recently (Kotenko and others 2003; Sheppard and others 2003; Prokunina-Olsson and others 2013), and knowledge of the functional range and mechanisms of these cytokines is still emerging. In 2003, 2 groups independently reported the discovery of IFN-λ1–3, as well as their cognate receptors (Kotenko and others 2003; Sheppard and others 2003). Those investigators demonstrated that IFN-λs (also known at type III IFNs) have striking similarities to type I IFNs (IFN-α/β) in that they induce expression of a host of antiviral and antiproliferative genes by signaling through the JAK/STAT pathway. The lambda receptor (IFN-λR1) was found to be more restricted in expression than receptors for type I IFNs, an observation that led to the development of pegylated-IFN-λ as a potentially better tolerated alternative to IFN-α drug products as a treatment for certain viral infections. Clinical trials for treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections were initiated. The clinical results from these trials demonstrated that pegylated-IFN-λ had a superior safety profile compared with pegylated-IFN-α, (Muir and others 2010, 2014; Chan and others 2016); however, it was deemed less effective than alternative treatments for these infections. Nonetheless, because of that developmental work, pegylated-IFN-λ is ready for deployment if new indications are identified.

Genetic studies and discovery of IFNL4

In 2009, genome-wide association studies (GWAS) demonstrated strong associations between single nucleotide polymorphisms (SNPs) in the IFN-λ chromosomal region and HCV clearance (Ge and others 2009; O'Brien 2009; Suppiah and others 2009; Tanaka and others 2009). Because of those findings, genotype for the rs12979860 SNP (commonly referred to as ''*IL28B*'') was developed as a clinical test to predict response to pegylated-IFN-α-based treatment of HCV. In 2013, the discovery of the fourth IFN-λ gene (*IFNL4*), the IFN-λ4 protein, and the *IFNL4*-ΔG/TT genetic

[1]Infections and Immunoepidemiology Branch, and [4]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
[2]Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute-Frederick, Frederick, Maryland.
[3]Division of Biotechnology Research and Review II, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland.

Table 1. Meeting Program—"IFN-λ: Disease Impact and Translational Potential," National Institutes of Health, Bethesda, Maryland, October 25–26, 2018

Thursday, October 25, 2018

Session 1: IFN-λ Biology, Therapy and Genetic Variation
Moderators: Howard Young, Rune Hartmann
0910: *An Overview of the IFN-λ Proteins and Their Biological Functions*—Raymond Donnelly, Center for Drug Evaluation and Research, Food and Drug Administration, USA
0935: *Trials of IFN-λ1 in Chronic Hepatitis Virus Infections*—Jeffrey Glenn, Department of Gastroenterology, Stanford University School of Medicine, USA
1000: *Structure and Engineering of an IFN-λ Receptor Complex Provides a Blueprint for Developing the Next Generation IFN-λ Therapeutics*—Juan Mendoza, Department of Molecular and Cellular Physiology, Stanford University School of Medicine, USA
1045: *IFNL4 Discovery and Genetics*—Ludmila Prokunina-Olsson, Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA
1110: Selected Talk—*A Polymorphic Residue That Attenuates the Antiviral Potential of Interferon Lambda 4 in Hominid Lineages*—Connor Bamford, MRC-University of Glasgow Centre for Virus Research, UK

Session 2: IFN-λ and HCV Infection
Moderators: Barbara Rehermann, Jacob George
1135: *What Have We Learned from Studies of IFN-λ Variants and HCV?*—Thomas O'Brien, Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA
1200: *Broad Impact of Interferon Lambda 4 on Hepatitis C Virus Diversity*—Vincent Pedergnana, Human Genetics, Genome Institute of Singapore
1400: *How does IFN-λ impair HCV clearance?* Presentations/panel discussion:
Do Genetic Polymorphisms within the IFNL4 Gene Influence the Transcription of the IFNL3 Gene?—Rune Hartmann, Department of Molecular Biology and Genetics, Aarhus University, Denmark
Interferon Lambda 4 Accumulates in the Endoplasmatic Reticulum and Causes ER Stress—Markus Heim, Department of Biomedicine, University of Basel, Switzerland
Collaborative Roles of Type I and III Interferons in Viral Restriction—Ram Savan, Department of Immunology, University of Washington, USA

Session 3: IFN-λ—Hepatic Fibrosis and Cancer
Moderators: Thomas O'Brien, Ludmila Prokunina—Olsson
1540: *Association of IFN-λ Variants with Viral and Non-Viral Hepatic Fibrosis*—Jacob George, Storr Liver Centre, Westmead Institute for Medical Research/University of Sydney School of Medicine, Australia
1605: *IFNL3/IFNL4 Locus Genotype is Associated with HCV+ Liver Cancer and Enrichment of Mutations in the WNT Signaling Pathway*—Olusegun Onabajo, Division of Cancer Epidemiology and Genetics, NCI, USA
1630: *A Genetic Variant Near IFNL3 Associates with Mucinous Ovarian Carcinoma*—Linda Kelemen, Department of Public Health Sciences, The Medical University of South Carolina, USA
1655: *IFNL4 in Prostate Cancer: Association with Sexually Transmitted Infections, Survival and Interferon Signature in Tumors*—Tsion Minas, Center for Cancer Research, National Cancer Institute, USA

Friday, October 26, 2018

Session 4: IFN-λ in Other Infections
Moderators: Kim Green, Eric Meissner, Raymond Donnelly
0900: *Type III IFN Signaling in Placental Antiviral Defenses*—Carolyn Coyne, University of Pittsburgh School of Medicine, USA
0925: *IFN-λ and Viral Invasion Across Anatomic Barriers*—Helen Lazear, Department of Microbiology and Immunology, UNC School of Medicine, USA
0950: *IFN-λ and Bacterial Infections*—Jonathan Kagan, Harvard Medical School, USA
1035: *Regulation of Persistent Murine Norovirus Infection by the Microbiota and IFN-λ*—Megan Baldridge, Washington University School of Medicine, USA
1100: Selected Talk—*Type III Interferons Regulate Intestinal Inflammation*—Ivan Zanoni, Harvard Medical School, USA
1115: *IFN-λ in Gastrointestinal Infections and Homeostasis*—Sergei Kotenko, New Jersey Medical School, USA
1230: *IFN-λs Fine-Tune Front Line Antiviral Immunity Against Influenza Virus Infection for Optimal Protection and Minimal Host Damage*—Evangelos Andreakos, Center for Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Greece
1255: *IFN-λ Enhances Adaptive Antiviral Immunity by Boosting TSLP Release Upon Mucosal Immunization*—Peter Staeheli, Institute of Virology, Department for Medical Microbiology and Hygiene, University of Freiburg, Germany
1320: Selected Talk—*IFN-λ Directs Migratory Dendritic Cell Function to Orchestrate T Cell Immunity During Influenza Virus Infection*—Emily Hemann, University of Washington, USA
1345: Bonus Session—Roundtable Discussion on Extramural Funding
Moderators: Danielle Carrick (NCI) and Rudy Alarcon (NIAID)

HCV, hepatitis C virus; IFN-λ, interferon lambda.

Table 2. Poster Session-"IFN-λ: Disease Impact and Translational Potential," National Institutes of Health, Bethesda, Maryland, October 25, 2018

Poster no.	*Presenter*	*Title*	*Affiliation*
1	Casazza, Rebecca	IFN-λ signaling mediates fetal pathology during congenital Zika virus infection in mice	Department of Microbiology and Immunology, University of North Carolina at Chapel Hill
2	Chinnaswamy, Sreedhar	IFN-λ4: a risk factor in chronic HCV infections but a possible protective role in older women with allergic asthma	National Institute of Biomedical Genomics, West Bengal, India
3	Forero, Adriana	Distinct immune responses to type I and III IFNs are regulated by IFN regulatory factor 1	Department of Immunology, University of Washington
4	Gadalla, Shahinaz	Donor IFNL4 genotype and transplant-related mortality after hematopoietic cell transplantation in patients with acute leukemia	Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute
5	Harris, Loyall	Antiviral activity of IFN-λ against murine norovirus infection in a modified permissive human cell line	Caliciviruses Section, Laboratory of Infectious Disease, NIAID
6	Lubkowski, Jacek	Structural studies of the interface between the IFN-λ receptor 1 (IFNLR1) and human Janus kinase 1	Macromolecular Crystallography Laboratory, Center for Cancer Research, National Cancer Institute
7	Obajemu, Adeola	Mechanistic exploration of IFNL4 function using site-directed mutagenesis	Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute
8	Piontkivska, Helen	Role of IFN-regulated RNA editing in molecular evolution of the Zika virus	Kent State University
9	Schnepf, Daniel	Tyrosine kinase 2 is not required for IFN-λ mediated signaling and protection against lethal influenza, a virus infection in mice	Institute of Virology, Medical Center University of Freiburg, Freiburg, Germany
10	Stanifer, Megan	Differential induction of IFN-stimulated genes between type I and type III IFNs is independent of IFN receptor abundance	German Cancer Research Center (DKFZ)
11	Wang, Fang	Exploring the possible role of IFNL4 in liver cancer	Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute
12	Ye, Liang	IFN-λ enhances influenza immunity by stimulating TSLP release during intranasal immunization	Institute of Virology, Medical Center University of Freiburg, Freiburg, Germany
13	Gibson, Alexis	Genome-wide CRISPR/Cas9 knockout screen identifies importance of type III IFN response for cryptosporidium infection	Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania

polymorphism were reported (Prokunina-Olsson and others 2013). *IFNL4*-ΔG/TT is a common ''knockout'' variant that controls generation of IFN-λ4 protein. This polymorphism is one of the most highly selected variants in the human genome, with marked differences in allele frequency between racial groups (Prokunina-Olsson and others 2013; Key and others 2014). The rs12979860 SNP lies in intron 1 of *IFNL4* and is in strong linkage disequilibrium with *IFNL4*-ΔG/TT. *IFNL4*-ΔG/TT is the primary functional variant for spontaneous clearance of HCV and response to HCV treatment with IFN-α and ribavirin, (Prokunina-Olsson and others 2013; Aka and others 2014; O'Brien and others 2015) as the protein generating variant is deleterious for clearance of HCV. The mechanism underlying this paradoxical association is not completely clear; however, IFN-λ4 attenuates antiviral responses at least in part by enhancing negative regulation of IFN signaling (Obajemu and others 2017). New direct acting antiviral agents have revolutionized the treatment of chronic hepatitis C, and *IFNL4* genotype also predicts response to those regimens (Meissner and others 2014; O'Brien and others 2017a, 2017b).

Other diseases and conditions have been linked to *IFN-λ* genotypes. Hepatic fibrosis is a key factor in the pathway to liver cancer. Genotype for *IFNL4*-ΔG/TT or *IFNL4* rs12979860 predicts the rate of development of hepatic fibrosis and cirrhosis not only in HCV-infected patients but also in the settings of HBV infection or nonalcoholic fatty liver disease (Eslam and others 2015; Petta and others 2017). A GWAS for mucinous ovarian carcinoma, a rare cancer subtype that can be difficult to distinguish from metastatic carcinomas to the ovary, reported an association for a marker strongly linked with *IFNL4* genotype (Kelemen and others 2015). For both fibrosis and mucinous ovarian carcinoma, the IFN-λ4 protein generating *IFNL4* allele had a relatively strong protective association. The *IFNL4*-ΔG allele was also associated with the risk of aggressive prostate cancer in individuals at risk of sexually transmitted infections, presumably due to impaired clearance of some viral infections due to the presence of IFN-λ4 (Minas and others 2018). Furthermore, the *IFNL4*-ΔG allele associates with an IFN-related DNA damage resistance signature in prostate tumors, which may affect response to cancer immunotherapies; overall survival of prostate cancer patients was also reduced in carriers of this allele (Tang and others 2018).

IFN-λs protect against a range of infections

Recent studies demonstrated that IFN-λ plays an important role in a broad range of infections. Using murine models, investigators demonstrated that IFN-λ can act at tissue barriers to provide frontline immunological protection against neuroinvasive (West Nile virus), gastrointestinal (norovirus), and respiratory (influenza) viral infections, as well as at the placental barrier (Zika virus) (Baldridge and others 2015; Lazear and others 2015a, 2015b; Nice and others 2015; Bayer and others 2016; Galani and others 2017). Other studies have provided evidence that IFN-λ plays a role in bacterial and fungal infections (Espinosa and others 2017; Odendall and others 2017; Schnepf and Staeheli 2017). However, as mice produce only IFN-λ2 and IFN-λ3, the possible role of IFN-λ4 in these infections could not be addressed in those studies. However, strong evolutionary selection against the *IFNL4*-ΔG allele (Key and others 2014) suggests IFN-λ4 could impact infectious diseases besides HCV.

The Meeting

This meeting brought together an international group of scientists from a wide range of disciplines, including immunology, virology, human genetics, epidemiology, and hepatology. The agenda included 20 invited talks and 3 oral presentations that were selected from submitted abstracts (Table 1). Sessions included: IFN-λ Biology, Therapy and Genetic Variation; IFN-λ and HCV Infection; IFN-λ in Other Infections; and IFN-λ—Hepatic Fibrosis and Cancer. In addition, there was a lively poster session (Table 2) and a roundtable discussion regarding potential NIH funding opportunities for research projects.

This special issue of the *Journal of Interferon and Cytokine Research* includes articles by many of the scientists who gave presentations during the meeting. It provides an update to an earlier issue of *JICR* that focused on the biology and physiology of IFN-λ, (Donnelly and Kotenko 2010) and reflects the considerable recent progress regarding our knowledge of the IFN-λ genes, their corresponding proteins, and biological functions.

Future Meetings

As the meeting organizers, we were gratified by the excellent presentations, collegial discussions, and overall enthusiastic response to this meeting. Many attendees suggested that this should be the first in an ongoing series of meetings on IFN-λ. We plan to hold the next meeting in 2020.

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Author Disclosure Statement

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Address correspondence to:
Dr. Thomas R. O'Brien
Infections and Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
9609 Medical Center Drive
6E108, MSC 9767
Bethesda, MD 20892

E-mail: obrient@mail.nih.gov

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