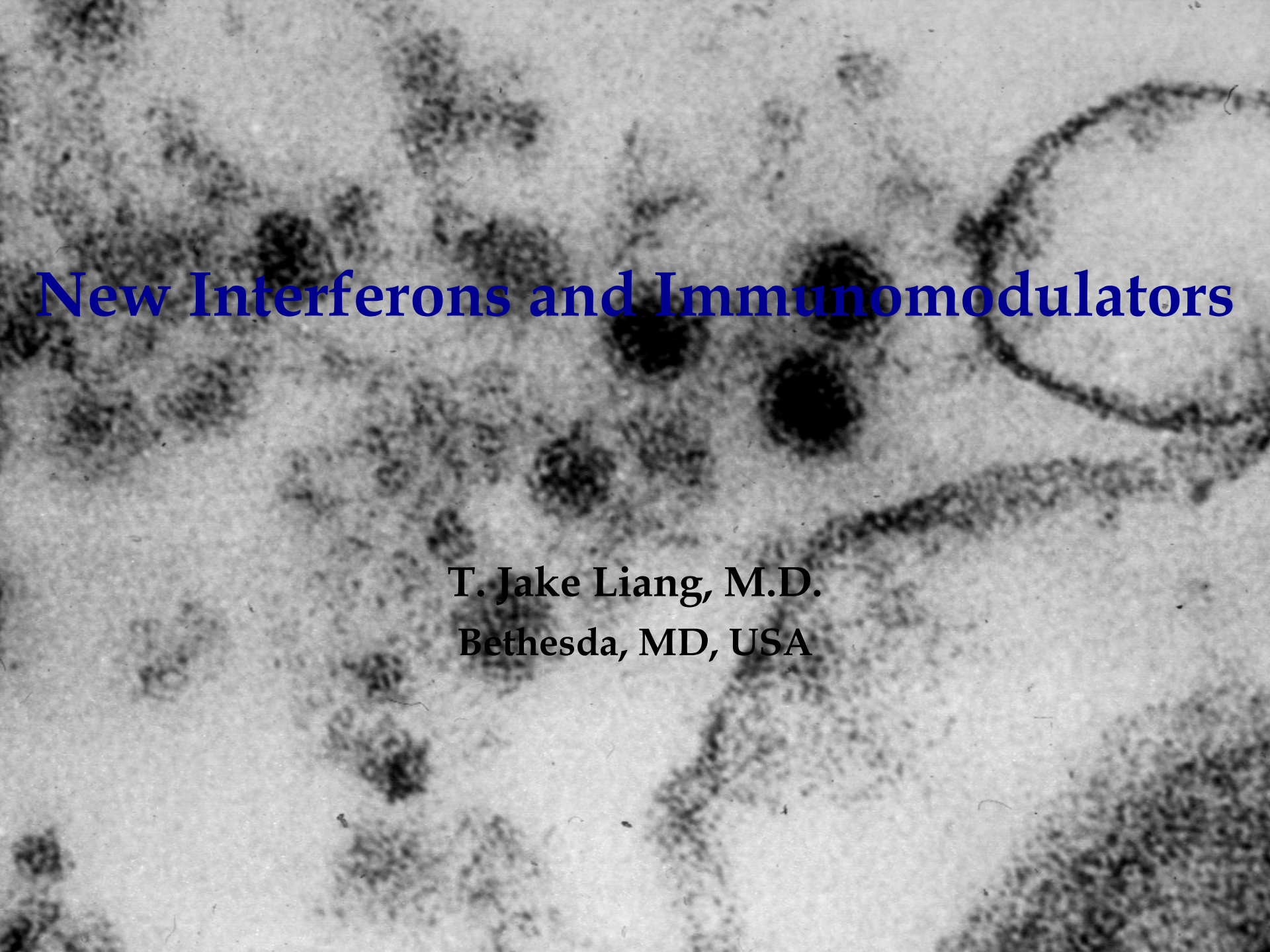
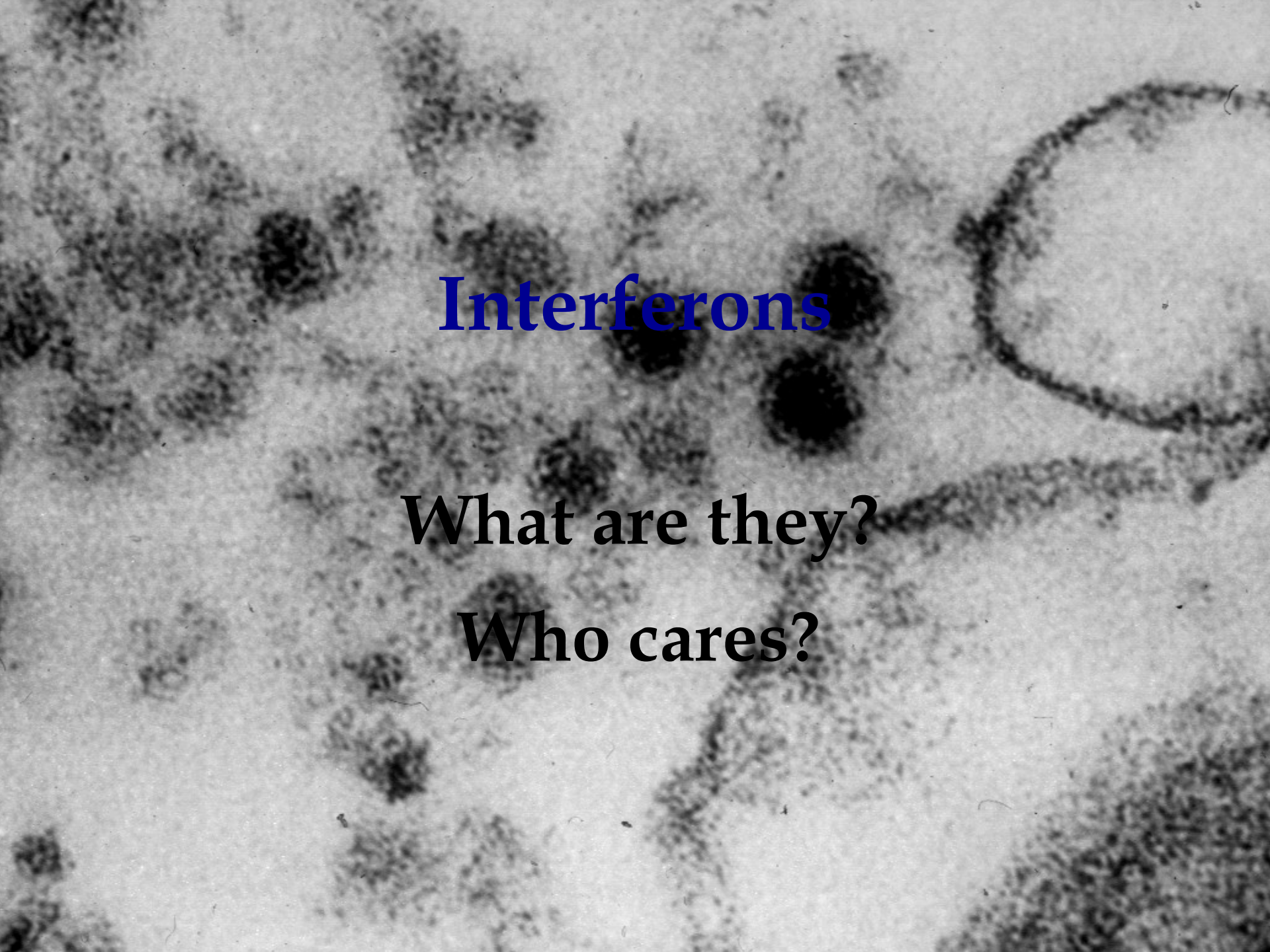


New Interferons and Immunomodulators

T. Jake Liang, M.D.

Bethesda, MD, USA



Interferons

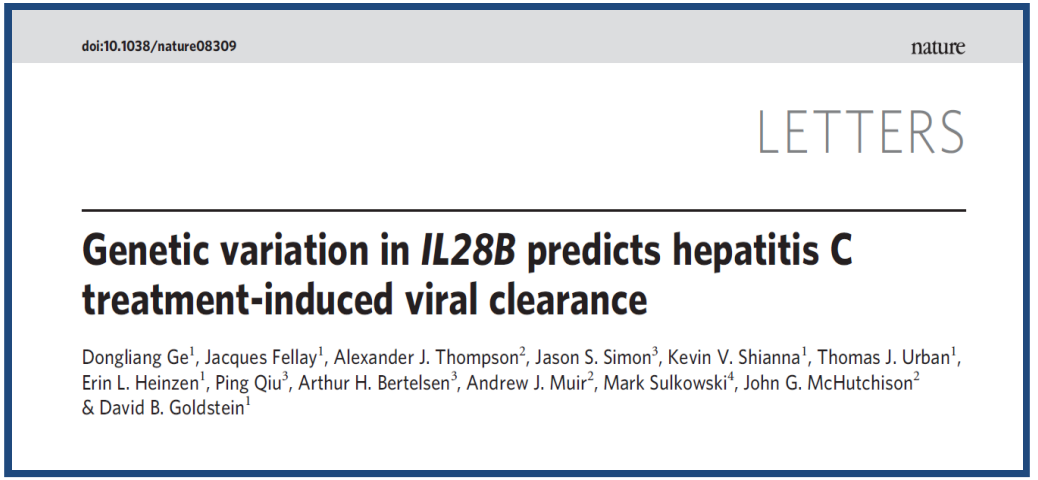
What are they?

Who cares?

The Interferon family

- Type 1: 3 subtypes, all cell types, IFNAR1 and 2
  - IFN-α, 14 species
  - IFN-β, 1 species
  - IFN-ω, 1 species
- Type II: IFN-γ, one species, activated T and NK cells, IFNGR1 and 2
- Type III: IFN-λ, 3 species (λ1, 2 and 3; IL29, IL28A, IL28B), possibly one more (λ4), all cell types; IFNLR1 and IL10RB (limited tissue distribution)

Interferon-λ: Antiviral Response & Hepatitis C



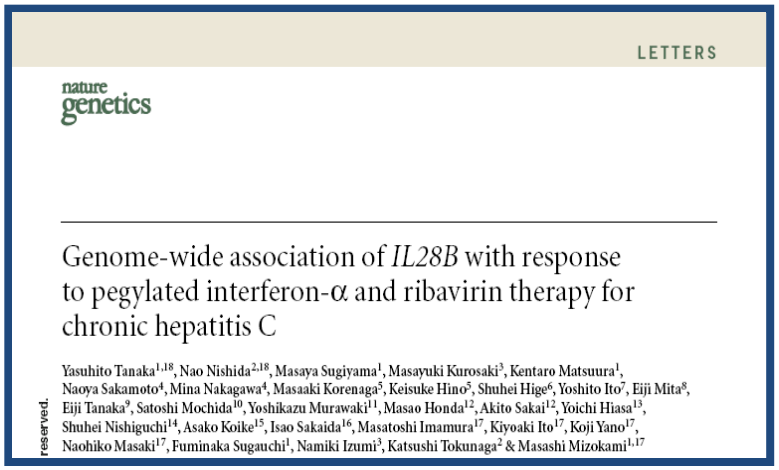
doi:10.1038/nature08309

nature

LETTERS

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

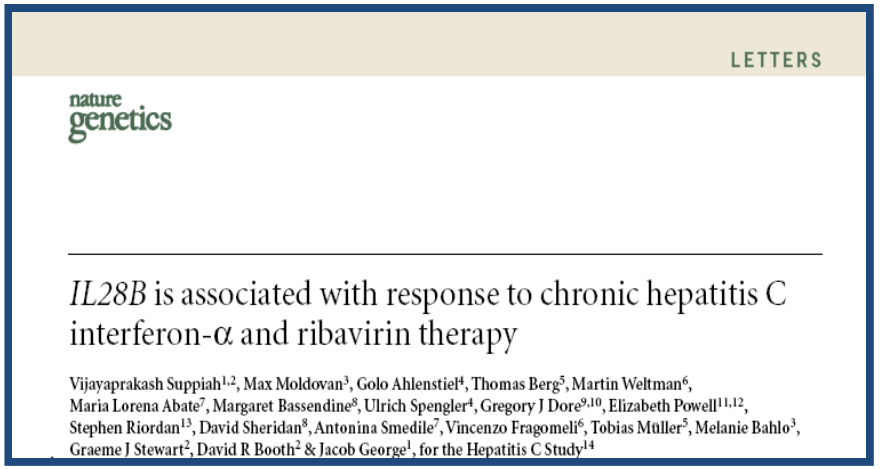
Dongliang Ge[1], Jacques Fellay[1], Alexander J. Thompson[2], Jason S. Simon[3], Kevin V. Shianna[1], Thomas J. Urban[1], Erin L. Heinzen[1], Ping Qiu[3], Arthur H. Bertelsen[3], Andrew J. Muir[2], Mark Sulkowski[4], John G. McHutchison[2] & David B. Goldstein[1]



nature genetics

Genome-wide association of *IL28B* with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

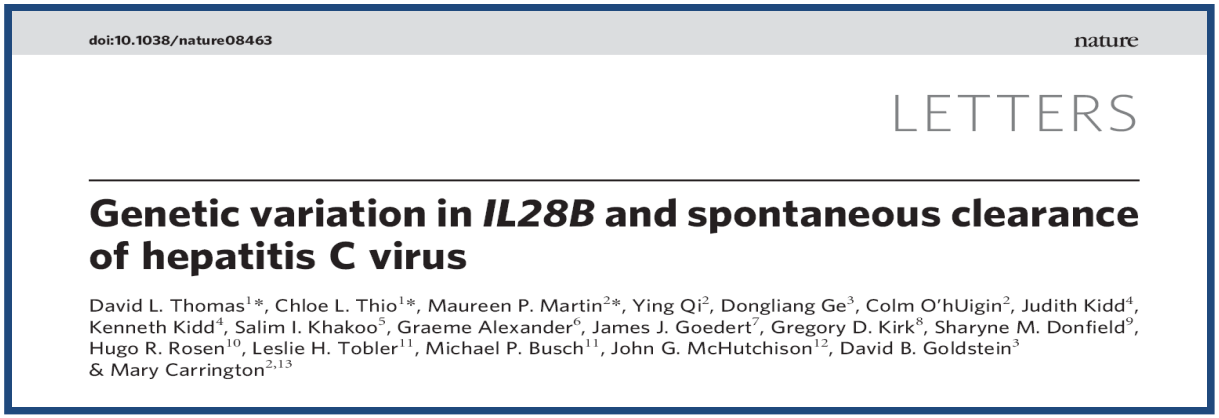
Yasuhito Tanaka[1,18], Nao Nishida[2,18], Masaya Sugiyama[1], Masayuki Kurosaki[3], Kentaro Matsuura[1], Naoya Sakamoto[4], Mina Nakagawa[4], Masaaki Korenaga[5], Keisuke Hino[5], Shuhei Hige[6], Yoshito Ito[7], Eiji Mita[8], Eiji Tanaka[9], Satoshi Mochida[10], Yoshikazu Murawaki[11], Masao Honda[12], Akito Sakai[12], Yoichi Hiasa[13], Shuhei Nishiguchi[14], Asako Koike[15], Isao Sakaida[16], Masatoshi Imamura[17], Kiyoaki Ito[17], Koji Yano[17], Naohiko Masaki[17], Fuminaka Sugauchi[1], Namiki Izumi[3], Katsushi Tokunaga[2] & Masashi Mizokami[1,17]



nature genetics

IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy

Vijayaprakash Suppiah[1,2], Max Moldovan[3], Golo Ahlenstiel[4], Thomas Berg[5], Martin Weltman[6], Maria Lorena Abate[7], Margaret Bassendine[8], Ulrich Spengler[4], Gregory J Dore[9,10], Elizabeth Powell[11,12], Stephen Riordan[13], David Sheridan[8], Antonina Smedile[7], Vincenzo Fragomeli[6], Tobias Müller[5], Melanie Bahlo[3], Graeme J Stewart[2], David R Booth[2] & Jacob George[1], for the Hepatitis C Study[14]



doi:10.1038/nature08463

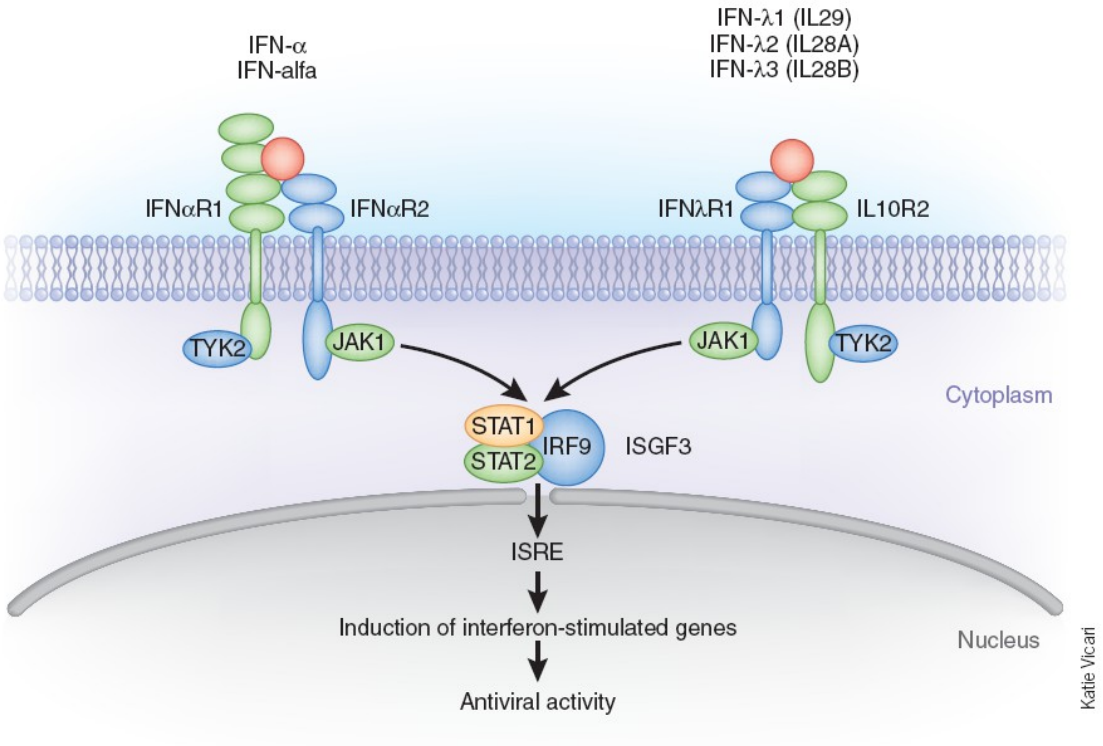
nature

LETTERS

Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus

David L. Thomas[1]*, Chloe L. Thio[1]*, Maureen P. Martin[2]*, Ying Qi[2], Dongliang Ge[3], Colm O'hUigin[2], Judith Kidd[4], Kenneth Kidd[4], Salim I. Khakoo[5], Graeme Alexander[6], James J. Goedert[7], Gregory D. Kirk[8], Sharyne M. Donfield[9], Hugo R. Rosen[10], Leslie H. Tobler[11], Michael P. Busch[11], John G. McHutchison[12], David B. Goldstein[3] & Mary Carrington[2,13]

IFN-α vs IFN-λ



- Different receptors
- IFN-λ receptor with limited tissue distribution (not in hematopoietic cells)
- Same signaling pathway
- Different kinetics and profiles of gene inductions

O'Brien TR, Nat Genet 2009

IFN-λ3/IL28B Polymorphisms and HBV Infection

- **IL28B SNPs (favorable in HCV) are associated with serologic response (HBeAg loss) to PEG-IFN in HBeAg-positive chronic hepatitis B**
- **IL28B SNPs are associated with post-IFN HBsAg loss in HBeAg-negative patients (genotype D)**
- **IL28B SNPs are associated with HBV chronicity?**

Sonneveld et al, Gastroenterol 2012; Lampertico et al, Hepatol 2013

Tseng et al, Antivir Ther; de Niet et al, Scan J Gastroenterol 2012; Zhang et al, J Viral Hepatitis 2013

Kim et al, PLoS One 2013;

Interferons in Hepatitis B and C Therapy

- **IFN-α: mainstay of therapy for HBV and HCV**
- **IFN-β: similar effect as IFN-α for HBV; used as induction therapy in HCV**
- **IFN-γ: never tested in HBV, though potent antiviral role in animal models; not effective in HCV**
- **IFN-λ (Peg-IFN-λ1)**
  - **HCV: similar efficacy as Peg-IFN-α but better side effect profile**
  - **HBV ?**

Munoz et al, J Hepatol 2002; Enomoto et al, J Interferon Cytokine Res 2007; Okushin et al, World J Gastroenterol 2008
Ishikawa et al, Hepatol Res 2012; Morikawa et al, Hepatol Res 2013
Guidotti et al, Annu Rev Pathol 2006; Soza et al, Hepatol 2005
Muir et al, Hepatol 2010; Muir et al, AASLD 2012

Peg-Interferon-λ in Hepatitis B Therapy

- Randomized-controlled study in HBeAg+ patients
- Comparing Peg-IFN-α with Peg-IFN-λ
- 48-wk treatment and 24 wk follow-up
- Endpoint: HBeAg loss and anti-HBe seroconversion
- Peg-IFN-λ less effective than Peg-IFN-α

Chan et al, AASLD 2012; BMS website

New Interferons for Hepatitis Therapy

- **Albuferon: albumin-conjugated IFN-α2b; halted development**
- **Locteron: controlled release interferon-α2b, microsphere-based, every 2 weeks, comparable effect as Peg-IFN in hepatitis C**

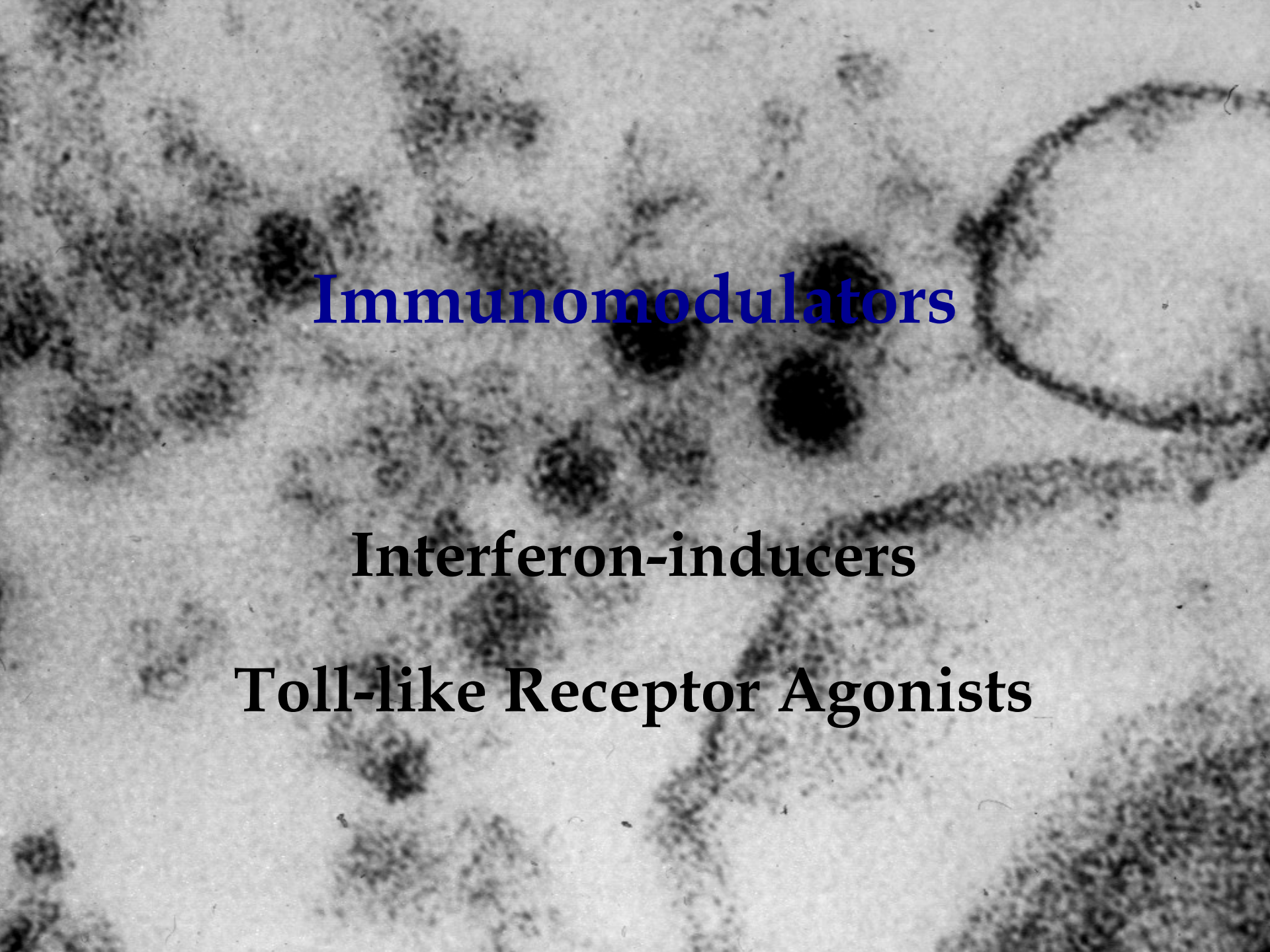
- **Omega Duros Interferon: extended release depot for 3-12 months**

- **Interferon-α XL: controlled release, Medusa hydrogel, weekly dosing**
- **Oral interferon (Beloferon): single amino acid substitution of IFN-α, oral administration**

Dzyublyk et al, J Viral Hepat 2011; Jansen et al EASL 2011
Buckwold et al, Antiviral Res 2007; www.Intarcia.com
Trepo et al, AASLD 2011; www.Flamel.com
www.Armarbio.com

New Interferons for Viral Hepatitis Therapy

- Improved pharmacokinetics
- Stronger antiviral activities
- Fewer side effects
- Better compliance
- Reduced cost?
- Interferon-intolerant patients and limited access to DAAs in HCV patients

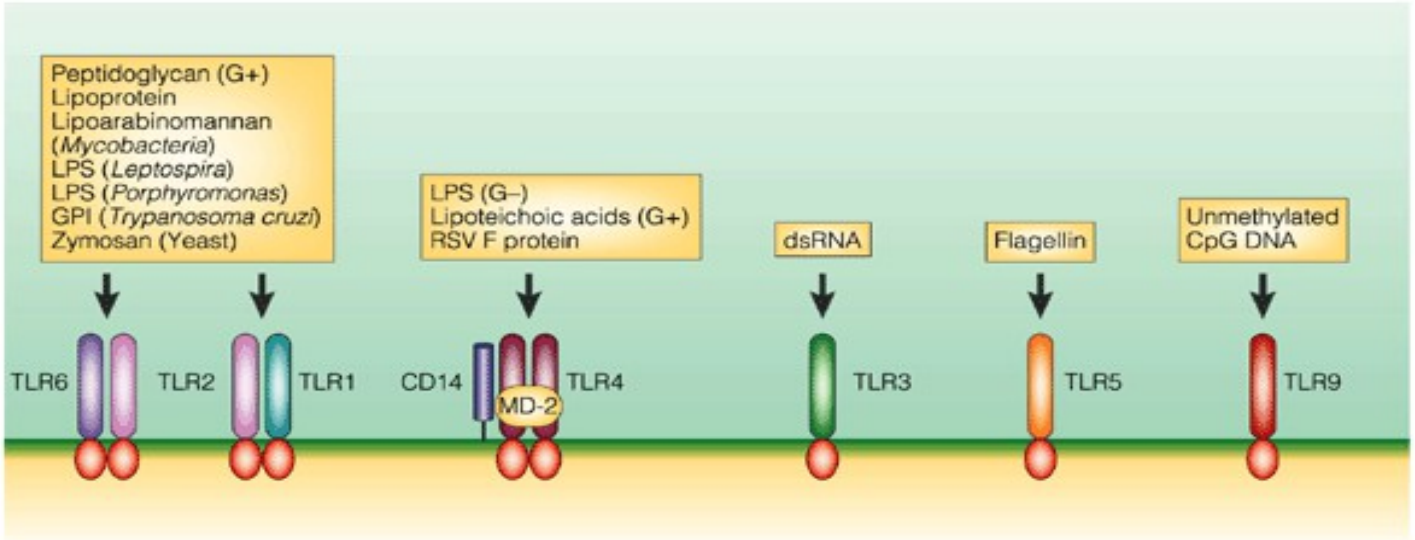


Immunomodulators

Interferon-inducers

Toll-like Receptor Agonists

Toll-like Receptors



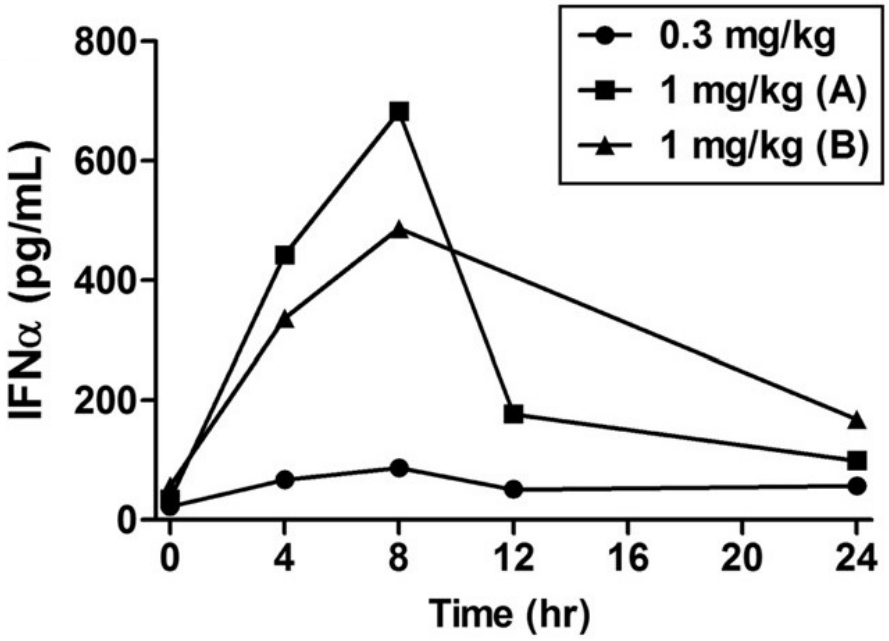
- **Play a key role in innate and adaptive immunity**
- **Recognize structurally conserved molecules from microbes as pattern recognition receptors (PRR)**
- **Induction of type I interferons and other cytokines**
- **More than 13 different TLRs**
- **TLR3: viral dsRNA; TLR7/8: viral ssRNA; TLR9: CpG DNA sequences**

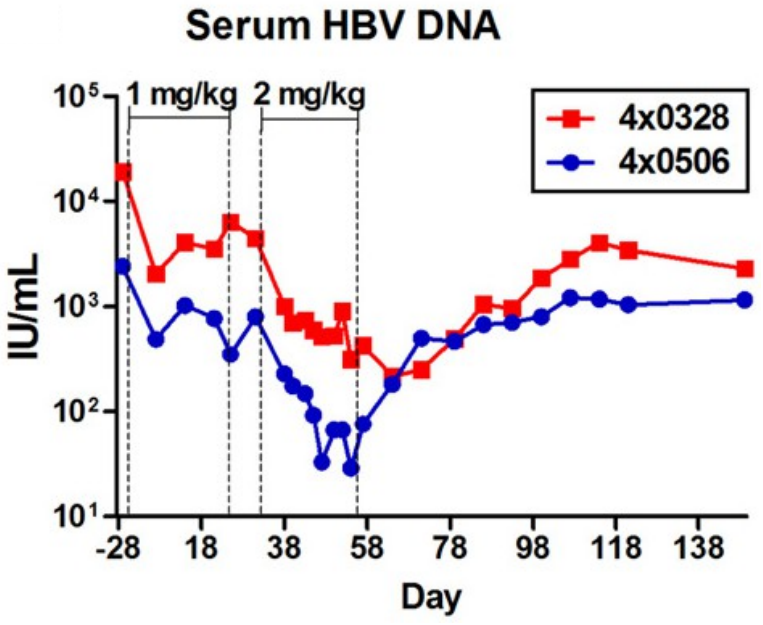
TLR Agonists in Clinical Development for Viral Hepatitis

- **TLR3 agonist**
  - Poly ICLC (Hiltonol), anti-cancer drug, preclinical development as antiviral, good safety profile (Oncovir)
- **TLR7 agonist**: preferred for antiviral therapy
  - Imidazoquinoline: Imiquimo (Aldara), Resiquimod, PF-4878691 (3M/Coley/Pfizer)
  - Nucleoside analog: ANA245 (Isatoribine), 975, 773 (Anadys/Roche); SM-276001 (Sumitomo), GS-9620 (Gilead)
  - Weak antiviral effects (HCV) in clinical trials and substantial side effects
- **TLR8 agonist**: proinflammatory, cancer therapy
  - VTX-2337 and 1463 (VentiRx)
- **TLR9 agonist**: weaker interferon inducer
  - CPG10101 (Coley/Pfizer), IMO-2125 (Idera)
  - Weak antiviral (HCV) effects in clinical trials; vaccine adjuvant

Effect of GS-9620 in HBV-Infected Chimpanzees

- Potent interferon-inducer and high selectivity, high hepatic extraction and less systemic exposure
- Three HBV-infected chimpanzees
- GS-9620 at 1-2 mg/kg, oral administration, 3 times weekly for 4 weeks
- Follow viral titers, and levels of IFN-α and interferon-stimulated genes in both serum and liver





Lanford et al, Gastroenterol 2013

TLR Agonists for Viral Hepatitis Therapy

- Oral formulation
- Less systemic exposure
- Side effects the major concern
- Better compliance
- Combination therapy with NA in HBV patients
- Interferon-intolerant patients and limited access to DAAs in HCV patients

New Interferons and Immunomodulators: Take Home Messages

- Probably no advantage in HCV therapy
- Potentially of value in HBV therapy
- Newer forms of IFNs need to be tested against standard Peg-IFN for various parameters
- TLR agonists in development and have promise
- Need to be used in combination with other anti-HBV drugs
- Potentially curative in HBV