NIH-FDA IIG

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NEWSLETTER

JANUARY 2022

PUBLICATIONS

Cholesterol 25-hydroxylase is a metabolic switch to constrain T cell-mediated inflammation in the skin.

Takahashi H, Nomura H, Iriki H, Kubo A, Isami K, Mikami Y, Mukai M, Sasaki T, Yamagami J, Kudoh J, Ito H, Kamata A, Kurebayashi Y, Yoshida H, Yoshimura A, Sun HW, Suematsu M, O'Shea JJ, Kanno Y, Amagai M.Sci Immunol. 2021 Oct 15;6(64):eabb6444. doi: 10.1126/sciimmunol.abb6444. Epub 2021 Oct 8.PMID: 34623903

CD4+ T cells limit pathogenic bystander T cell expansion by suppressing cholesterol biosynthesis via secreted 25-hydroxycholesterol.

Lessons in self-defence: inhibition of virus entry by intrinsic immunity.

Majdoul S, Compton AA.Nat Rev Immunol. 2021 Oct 13:1-14. doi: 10.1038/s41577-021-00626-8. Online ahead of print. PMID: 34646033

This review summarizes what is known and what remains to be understood about the intrinsic factors that form the first line of defense against virus infection.

Eosinophils are part of the granulocyte response in tuberculosis and promote host resistance in mice.

Bohrer AC, Castro E, Hu Z, Queiroz ATL, Tocheny CE, Assmann M, Sakai S, Nelson C, Baker PJ, Ma H, Wang L, Zilu W, du Bruyn E, Riou C, Kauffman KD; Tuberculosis Imaging Program, Moore IN, Del Nonno F, Petrone L, Goletti D, Martineau AR, Lowe DM, Cronan MR, Wilkinson RJ, Barry CE, Via LE, Barber DL, Klion AD, Andrade BB, Song Y, Wong KW, Mayer-Barber KD.J Exp Med. 2021 Oct 4;218(10):e20210469. doi: 10.1084/jem.20210469. Epub 2021 Aug 4.PMID: 34347010

Our findings uncover an unexpected recruitment of eosinophils to Mtb-infected lung tissue and a protective role for these cells in the control of Mtb infection in mice.

A genome-wide screen uncovers multiple roles for mitochondrial nucleoside diphosphate kinase D in inflammasome activation.

Ernst O, Sun J, Lin B, Banoth B, Dorrington MG, Liang J, Schwarz B, Stromberg KA, Katz S, Vayttaden SJ, Bradfield CJ, Slepushkina N, Rice CM, Buehler E, Khillan JS, McVicar DW, Bosio CM, Bryant CE, Sutterwala FS, Martin SE, Lal-Nag M, Fraser IDC.Sci Signal. 2021 Aug 3;14(694):eabe0387. doi: 10.1126/scisignal.abe0387.PMID: 34344832

Noncanonical inflammasome activation by cytosolic lipopolysaccharide (LPS) is a critical component of the host response to Gram-negative bacteria. Cytosolic LPS release is preceded by a PRR-induced priming signal required to induce transcription of inflammasome components and facilitate metabolic reprograming that fuels the inflammatory response. Using a prime-trigger IL-1 release assay with genome-wide gene perturbation, we find that mitochondrial nucleoside diphosphate kinases coordinate a metabolic "checkpoint" that allows macrophages to properly mount inflammatory responses to bacteria.

CD138 expression is a molecular signature but not a developmental requirement for RORt+ NKT17 cells.

Luo S, Kwon J, Crossman A, Park PW, Park JH.JCI Insight. 2021 Sep 22;6(18):e148038. doi: 10.1172/jci.insight.148038. PMID: 34549726

We have identify CD138 as a surface marker for invariant NKT17 cells. However, CD138 molecule is not required for thymic NKT17 cell development.

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Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment.

Lam KC, Araya RE, Huang A, Chen Q, Di Modica M, Rodrigues RR, Lopès A, Johnson SB, Schwarz B, Bohrnsen E, Cogdill AP, Bosio CM, Wargo JA, Lee MP, Goldszmid RS.Cell. 2021 Oct 14;184(21):5338-5356.e21. doi: 10.1016/j.cell.2021.09.019. Epub 2021 Oct 7. PMID: 34624222

In this cover-featured article, we use murine models and patient samples to demonstrate that gut microbiota triggers the STING-type I IFN pathway to program the anticancer activity of innate immune cells in the tumor microenvironment. We show that this pathway can be induced by high-fiber diet, fecal microbiota transplant from ICB-responder patients, or bacteria-derived cyclic dinucleotides, offering new approaches to harness innate immunity to improve cancer therapies.

Can gut microbes predict efficacy and toxicity of combined immune checkpoint blockade?

Lam KC, Goldszmid RS. Cancer Cell. 2021 Oct 11;39(10):1314-1316. doi: 10.1016/j.ccell.2021.09.013.PMID: 34637746

This is a Spotlight article on a recent Nature Medicine report by Andrews et al, 2021 describing a role for gut microbiota in response and toxicity to combined immune checkpoint blockade (ICB) targeting CTLA-4 and PD-1. This Spotlight highlights the key findings of the article, provides contrast with previous studies using ICB monotherapies, and makes suggestions to advance mechanistic insight into the microbiota-mediated control of combined ICB.

Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells.

Chauss D, Freiwald T, McGregor R, Yan B, Wang L, Nova-Lamperti E, Kumar D, Zhang Z, Teague H, West EE, Vannella KM, Ramos-Benitez MJ, Bibby J, Kelly A, Malik A, Freeman AF, Schwartz DM, Portilla D, Chertow DS, John S, Lavender P, Kemper C, Lombardi G, Mehta NN, Cooper N, Lionakis MS, Laurence A, Kazemian M, Afzali B. Nat Immunol. 2021 Nov 11. doi: 10.1038/s41590-021-01080-3. Online ahead of print.PMID: 34764490

We identified complement receptor engagement as a regulator of a T cell-intrinsic autocrine/paracrine Vitamin D activation system involved in Th1 shut-down. Signaling through this system caused genome-wide remodelling of histone acetylation and recruited a transcription factor network comprising of VDR, JUN, STAT3 and BACH2, which together shaped the transcriptional response to Vitamin D. Th cells in COVID-19 were Th1 skewed and showed de-repression of genes downregulated by VitD, either because of lack of VitD substrate and/or abnormal regulation.

Renal diseases and the role of complement: Linking complement to immune effector pathways and therapeutics

Freiwald T, Afzali B. Renal diseases and the role of complement: Linking complement to immune effector pathways and therapeutics. Adv Immunol. 2021;152:1-81. doi:10.1016/bs.ai.2021.09.001

Deposition of complement components is recognized as a hallmark of a variety of kidney diseases, where it is indeed associated with damage to the self. The provenance and the pathophysiological role(s) played by complement in each kidney disease is not fully understood. In this review we present and summarize the evidence for the roles of complement in a number of kidney diseases and discuss the available clinical evidence for complement inhibition.

The state of complement in COVID-19

Afzali B, Noris M, Lambrecht BN, Kemper C. The state of complement in COVID-19. Nat Rev Immunol. December 2021. doi:10.1038/s41577-021-00665-1

Hyperactivation of the complement and coagulation systems is recognized as part of the clinical syndrome of COVID-19. Here we review systemic complement activation and local complement activation in response to the causative virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and their currently known relationships to hyperinflammation and thrombosis. We also provide an update on early clinical findings and clinical trial evidence that suggest potential therapeutic benefit of complement inhibition in severe COVID-19.

Mitochondrial C5aR1 activity in macrophages controls IL-1 production underlying sterile inflammation

Niyonzima N, Rahman J, Kunz N, et al. Mitochondrial C5aR1 activity in macrophages controls IL-1 production underlying sterile inflammation. Sci Immunol. 2021;6(66):eabf2489. doi:10.1126/sciimmunol.abf2489

We show that the complement protein C5a signals on mitochondrial membranes through C5aR1 in human macrophages to control IL-1 production in response to cholesterol crystal (CC) uptake. C5a/C5aR1 signaling altered mitochondrial activity and increased reactive oxygen species production, promoting IL-1 gene expression and processing. In a mouse model of atherosclerosis, in which CC accumulates in arterial walls, deletion of C5aR1 in myeloid cells reduced the severity of cardiovascular disease. These results identify a function for intracellular complement proteins in myeloid cell mitochondrial metabolism and responses to sterile inflammation.

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2022 IIG Workshop

Planning is underway for the annual NIH-FDA IIG Workshop

With the new year comes a new workshop. The survey data and feedback from last year are in, and with that the IIG Steering Committee is actively working on plans for 2022 to make it the best IIG workshop yet! Even though pandemic constraints are impacting options for planning the location and dates, we're working on creative solutions for an in-person event. More information will be available soon, so stay tuned!

Wishing the IIG community a happy and productive New Year!

Credit: Carol M. Highsmith

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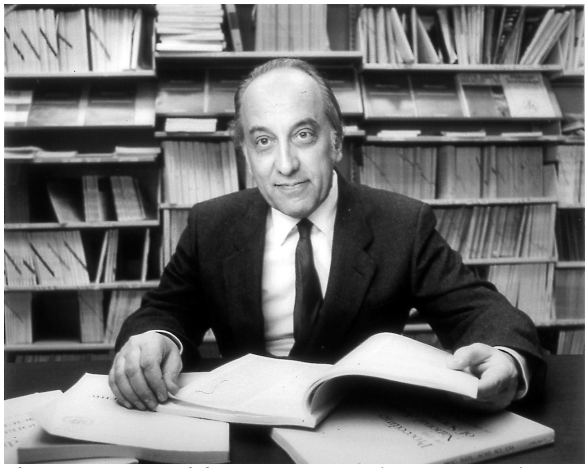
Celebrating the memory of Dr. Waldmann

The NIH-FDA IIG community would like to celebrate the remarkable 65-year long scientific career of Dr. Waldmann at the NIH. The years of research conducted in his lab have contributed to major immunological advances that were critical for developing several immunotherapeutic approaches.

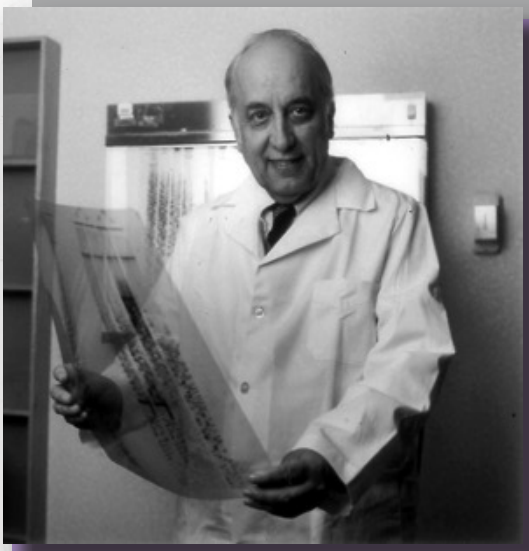


Thomas A. Waldmann, M.D. (1930-2021)

Dr. Waldmann came to the NIH in 1956 and was a part of the Metabolism Branch under Nat Berlin. He later became the Branch Chief of the Metabolism Branch, now the Lymphoid Malignancies Branch, in 1971.

During the early phases of his career, his research focused on RBCs and erythropoiesis. He then started investigating the metabolism of secreted proteins, including albumin and immunoglobulins, where he made his first major contribution determining the serum half-life of human IgG in vivo. His work in immunoglobulin metabolism led him to Ig production.

During the late 1970'S Dr. Waldmann's laboratory discovered the first human T suppressor cells. In an effort to develop an antibody to CD4+ T cell activation markers, Takashi Uchiyama and Sam Broder in Dr. Waldmann's laboratory developed monoclonal anti-Tac, for T cell activation marker antibody, which turned out to be the first antibody to the human IL-2 receptor chain. The ligand was identified as CD25, the IL-2Ra, the receptor for IL-2. This discovery of IL-2Ra occurred in Dr. Waldmann's laboratory together with Warren Leonard and Warner Greene. The expression of IL-2Ra turned out to be at such high levels on adult T-cell leukemia (ATL) cells that anti-Tac could kill these tumor cells. This led to the development of anti-Tac antibody into a humanized therapeutic antibody, Daclizumab, which was used to cure a subset of ATL patients. This treatment for ATL was also later licensed to treat multiple sclerosis.



"[Tom] was a wonderful mentor, both as a role model and as a coach..."

Dr. Waldmann's laboratory was always in motion, and in 1994 they discovered a cytokine with the activity like that of IL-2 but distinct. The discovered molecule IL-15 was also discovered by scientists at Immunex, now known as Amgen, around the same time. Dr. Waldmann also orchestrated the development of cGMP-grade IL-15 in his quest to translate the use of IL-15 as a treatment for cancer.

"Dr. Waldmann had the clear vision to recognize and capture opportunities where one discovery led to another. Dr. Waldmann was an encyclopedia of knowledge and constantly came up with valuable insights and diverse expertise to solve any problem. His work has left a massive imprint on immunology and the many immunologists he has mentored. He is a wonderful colleague and member of the scientific community whose presence will be sorely missed but realized in all his scientific underpinnings"– Jay Berzofsky, Immunity, Dec 2021.

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Celebrating the memory of Dr. Waldmann

The following excerpt and pictures were shared by Jay A. Berzofsky, Vaccine Branch, CCR, NCI, who had the privilege of having Dr. Waldmann as his mentor and colleague since 1976.

In Jay Berzofsky's words, "Tom was my mentor for nearly 28 years, from the time he hired me as a tenure-track equivalent investigator in 1976 until I moved to become Chief of the Vaccine Branch in 2004. He was a wonderful mentor, both as a role model and as a coach. It was appreciated that Tom promoted the independence of the Principal Investigators (PIs) in his Branch. He instilled in us the importance of translating basic science discoveries to the clinic to benefit patients. One principle I learned from Tom as a role model was to be always prepared. Tom would never travel to a University to talk without first reading the recent publications of all the faculty members with whom he was scheduled to meet. Similarly, when there was a budget meeting with Al Rabson, he would come with a long memo in which he detailed all the questions and issues to be discussed. As a coach, Tom rehearsed talks with members of his lab or PIs and taught us how to make clear, simple, easily read slides and present logically, with only the number of concepts presented that an audience could absorb in the time allotted for the talk. All of us in the Branch improved our science and our presentations from Tom's mentoring. Tom was also an enthusiastic photographer, former president of the NIH Camera Club. No matter how busy, he was always happy to share his knowledge of photography with fellow photo enthusiasts. He was also a great friend, collaborator, and father- figure to his entire scientific family. Beyond Tom's many major landmark contributions already cited, his most incredible legacy may be the vast number of outstanding scientists in their own right who owe their success at least in part to Tom's mentoring. We will all miss him tremendously"

Please see the following articles for additional tributes to Dr. Waldmann

NIH Intramural Research Program Blog: https://irp.nih.gov/blog/post/2021/10/nih-mourns-the-passing-of-thomas-a-waldmann

National Cancer Institute Center for Cancer Research in Memoriam: https://ccr.cancer.gov/news/article/in-memoriam-thomas-a-waldmann-md-1930-2021

Obituary, Immunity 2021, https://doi.org/10.1016/j.immuni.2021.11.012

To view Waldmann's 2015 interview as part of the AAI Oral History Project, visit www.aai.org/About/History/AAI-Awardees/ThomasAWaldmann.

Leonard, W.J. Thomas Alexander Waldmann (1930–2021). Nat Immunol 22, 1467–1468 (2021). https://doi.org/10.1038/s41590-021-01076-z

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Immmunology Interest Group

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January 2022

January 19, 2022

Marion Pepper

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February 2022

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Philippa Marrack

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