

## **Averil I. Ma, M.D.**

Rainin Distinguished Professor of Medicine  
Director, Colitis and Crohn's Disease Center  
Chief, Division of Gastroenterology  
BMS and PIBS Graduate Programs  
Department of Medicine

### *Academic Office and Laboratory:*

Room S-1057, Box 0451  
University of California, San Francisco,  
San Francisco, CA 94143-0451  
Phone: 415-502-9404  
Email: [averil.ma@ucsf.edu](mailto:averil.ma@ucsf.edu)  
Website: <http://bms.ucsf.edu/faculty/ma.html>



### **Research Description**

Our laboratory has studied factors that regulate immune homeostasis for 14 years. We discovered the critical role of A20 in maintaining immune homeostasis by generating and characterizing A20 deficient mice (Lee et al, Science). We found that homeostatic Myd88 dependent signals drive a major portion of A20 restricted pro-inflammatory signals (Turer et al, J Exp Med). We utilized genetic epistasis and signaling approaches to unveil A20's functions in restricting TNF, TLR and NOD2 triggered NFkB signals (Lee et al, Science; Boone et al, Nature Immunology; Hitotsumatsu et al, Immunity). We found that A20 is a de-ubiquitinating enzyme (Boone et al, Nature Immunology) and collaborated with the Dixit lab to discover A20's E3 ligase activity (Wertz et al, Nature). Recently, we have turned to understanding the mechanisms by which A20 restricts specific ubiquitin dependent signaling cascades. We've hypothesized that A20 works in a larger protein complex. One major component of A20 mediated regulation of signaling is ABIN-1, a protein that binds to A20. We have discovered that ABIN-1, like A20, restricts TNF induced cell death and preserves embryonic survival (Oshima et al, Nature). Moreover, TNF deficiency rescues ABIN-1 deficiency. We are now poised to understand the physiological, cellular and biochemical mechanisms by which ABIN-1 regulates immune homeostasis. In collaborative studies, we have linked both A20 and ABIN-1 to human autoimmune diseases, demonstrating links between A20 SNPs and human SLE (Musone et al, Nature Genetics). We have recently shown that A20 deficiency in B cells causes SLE-like disease (Tavares et al, Immunity), while A20 deficiency in DCs leads to colitis and spondyloarthritis, a stereotypical syndrome of human IBD (Hammer et al, Nature Immunology). Understanding how A20, ABIN-1 and related proteins prevent inflammation and autoimmunity is now a major focus of our laboratory.

### **Education**

- 1976-80 Harvard College A.B. Magna Cum Laude, Biochemistry
- 1980-84 Columbia Medical School M.D. Alpha Omega Alpha, Medicine

### **Training**

- 1984-87 Residency, Internal Medicine, Massachusetts General Hospital, Boston, MA
- 1987-89 Clinical and Research Fellow, Gastroenterology, Columbia Presbyterian Medical Center, New York, NY

## Certification

- 1987 ABIM Certification in Internal Medicine
- 1993 ABIM Certification in Gastroenterology
- 2003 ABIM Re-certification in Gastroenterology

## Memberships and Affiliations

- 1989- American Gastroenterology Association
- 1995- Gastroenterology Research Group
- 2001 AGA/GRG Young Investigator Award
- 2001- American Society of Clinical Investigation (ASCI)
- 2009- American Association of Academic Physicians (AAAP)

## Service to Professional Organizations:

- 2000-present AGA abstract reviewer for DDW presentations
- 2004-present AGA Committee on Gastroenterology Research
- 2008-present AGA Nominating Committee, IMIBD section
- 2000-present Editorial Board, Current Opinion in Immunology
- 2002-2007 Editorial Board, Gastroenterology
- 2000-2002 Crohn's and Colitis Foundation of America Training Grants study section
- 2003-2005 Crohn's and Colitis Foundation of America Senior Grants study section
- 2009-2011 Crohn's and Colitis Foundation of America Training Grants study section
- 2012- Crohn's and Colitis Foundation of America Senior Grants study section
- 2000-2007 ad hoc NIH study section reviewer, GMA-2, GMPB, III, SE, CMI-A
- 2007-present Charter member, NIH CMI-A study section
- 2010-present Chair, CMI-A study section
- 2010-present Chair, Scientific Advisory Board, Kenneth Rainin Foundation

## Selected Publications

- Lodolce JP, Boone DL, Dassopoulos T, Chai S, Swain RE, Trettin S, and Ma A. 1998. Interleukin-15Ra maintains lymphoid homeostasis by supporting lymphocyte homing and proliferation. **Immunity** 9;669-676.
- Lee EG, Boone DL, Chai S, Libby S, Chien M, Lodolce JP, and Ma A. 2000. Failure to regulate TNF induced NF-kB and cell death responses in A20 deficient mice. **Science** 289;2350-54.
- Wertz IE, O'Rourke KM, Zhou H, Eby M, Aravind L, Seshagiri S, Wu P, Wiesmann C, Baker R, Boone DL, Ma A, Koonin EV, Dixit VM. 2004. De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. **Nature** 430;694-699.
- Boone DL, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, Hurley P, Chien M, Chai S, Hitotsumatsu O, McNally E, Pickart C, and Ma A. 2004. The ubiquitin modifying enzyme A20 is essential for terminating TLR signaling. **Nature Immunology** 5;1052-60.
- Ma A and Turer EE. 2006. E2 enzymes expand the Ubi-verse of immune receptor signaling. **Nature Immunology** 7;903-904.
- Hitotsumatsu O, Ahmad RC, Tavares R, Wang M, Philpott D, Turer EE, Lee BL, Shifrin N, Advincula R, Malynn BA, Werts C, and Ma A. 2008. The ubiquitin editing enzyme A20 restricts NOD2 triggered signals. **Immunity** 28;381-390.
- Musone SL, Taylor KE, Lu TT, Nititham J, Ferreira RC, Ortmann W, Shifrin N, Petri MA, Kamboh MI, Manzi S, Seldin MF, Gregersen PK, Behrens TW, Ma A, Kwok PY and Criswell LA. 2008. Multiple polymorphisms in the TNFAIP3 [A20] region are

independently associated with systemic lupus erythematosus. **Nature Genetics** 40;1062-1064.

- Ma A. 2008. Unresolved ER stress inflames the intestine. **Cell** 134;724-726.
- Mortier E, Woo T, Advincula R, Gozalo S, and Ma A. 2008. IL-15Ra chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans-presentation. **J Exp Med** 205;1213-1225.
- Oshima S\*, Turer EE\*, Callahan JA, Advincula R, Chai S, Barrera J, Shifrin N, Lee B, Woo T, Yen B, Malynn BA, and Ma A. 2009. ABIN-1 is a ubiquitin sensor that restricts TNF induced cell death and sustains embryonic development. **Nature** 457;906-910.
- Malynn BA and Ma A. 2009. A20 takes on tumors: tumor suppression by a ubiquitin editing enzyme. **J Exp Med** 206;977-980.
- Mortier E, Advincula R, Kim L, Chmura S, Barrera J, Reizis B, Malynn BA, and Ma A. 2009. Macrophage and dendritic cell derived IL-15Ra support distinct CD8+ T cell subsets. **Immunity** 31;811-822.
- Ashida H, Kim M, Schmidt-Supprian M, Ma A, Ogawa M, and Sasakawa C. 2010. A bacterial E3 ubiquitin ligase IpaH9.8 effector targets NEMO/IKK $\gamma$  to dampen the host NF- $\kappa$ B-mediated inflammatory response. **Nature Cell Biology** 12;66-73.
- Shembade N, Ma A, and Harhaj E. 2010. Inhibition of NF $\kappa$ B signaling by A20 through disruption of ubiquitin enzyme complexes. **Science** 327;1135-39.
- Tavares RM, Turer EE, Liu C-L, Advincula R, Scapini P, Rhee L, Barrera J, Lowell CA, Utz PJ, Malynn BA, and Ma A. 2010. The ubiquitin modifying enzyme A20 restricts B cell survival and prevents autoimmunity. **Immunity** 33;181-191.
- Hammer GE, Turer EE, Taylor KE, Fang CJ, Advincula R, Oshima S, Barrera J, Huang EJ, Hou B, Malynn BA, Reizis B, Franco A, Criswell LA, Nakamura MC, and Ma A. 2011. Dendritic cell expression of A20 preserves immune homeostasis and prevents colitis and spondyloarthritis. **Nature Immunology** (in press).