

# Journal Club

Stephanie Ganal-Vonarburg

29<sup>th</sup> of September, 2016

# Paper #1

Article

Cell

## The Spectrum and Regulatory Landscape of Intestinal Innate Lymphoid Cells Are Shaped by the Microbiome

Meital Gury-BenAri,<sup>1,10</sup> Christoph A. Thaiss,<sup>1,10</sup> Nicolas Serafini,<sup>2,3</sup> Deborah R. Winter,<sup>1</sup> Amir Giladi,<sup>1</sup> David Lara-Astiaso,<sup>1</sup> Maayan Levy,<sup>1</sup> Tomer Meir Salame,<sup>4</sup> Assaf Weiner,<sup>1</sup> Eyal David,<sup>1</sup> Hagit Shapiro,<sup>1</sup> Mally Dori-Bachash,<sup>1</sup> Meirav Pevsner-Fischer,<sup>1</sup> Erika Lorenzo-Vivas,<sup>1</sup> Hadas Keren-Shaul,<sup>1</sup> Franziska Paul,<sup>1</sup> Alon Harmelin,<sup>5</sup> Gérard Eberl,<sup>6,7</sup> Shalev Itzkovitz,<sup>8</sup> Amos Tanay,<sup>9</sup> James P. Di Santo,<sup>2,3</sup> Eran Elinav,<sup>1,\*</sup> and Ido Amit<sup>1,11,\*</sup>

<sup>1</sup>Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>2</sup>Innate Immunity Unit, Institut Pasteur, 75015 Paris, France

<sup>3</sup>Institut National de la Santé et de la Recherche Médicale (INSERM), U1223 Paris, France

<sup>4</sup>Biological Services Unit, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>5</sup>Department of Veterinary Resources, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>6</sup>Department of Immunology, Institut Pasteur, 75015 Paris, France

<sup>7</sup>CNRS, URA 1961, 75015 Paris, France

<sup>8</sup>Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>9</sup>Department of Computer Science and Applied Mathematics and Department of Biological Regulation, Weizmann Institute of Science, Rehovot 76100, Israel

<sup>10</sup>Co-first author

<sup>11</sup>Lead Contact

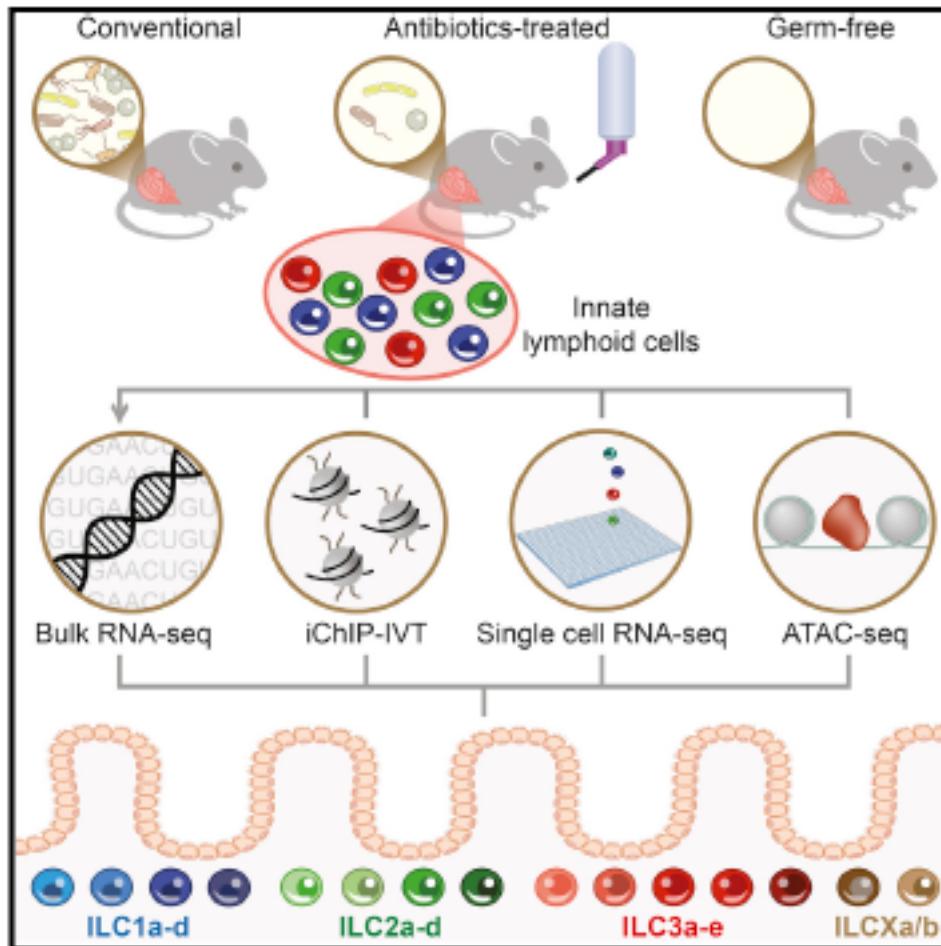
\*Correspondence: eran.elinav@weizmann.ac.il (E.E.), ido.amit@weizmann.ac.il (I.A.)

# Highlights

- Comparison of transcriptomic and epigenetic (ChIP) phenotype of intestinal innate lymphoid cell subsets: ILC1, ILC2 and ILC3
- Single cell RNA-Seq following FACS-sorting and individual cell-indexing (*Paul et al., Cell, 2015*)
- There is functional compartmentalization within the three main ILC subsets:
  - ILC1a-d
  - ILC2a-d
  - ILC3a-e
  - ILCXa/b
- The commensal microbiota impacts on gene expression and epigenetic landscape of the individual ILC subsets (ABX, germ-free)
  - Acquisition of ILC3-like expression profile in ILC1 and ILC2 in absence of microbiota
  - Less plasticity of ILC3 → ILC1 in absence of microbiota

# Graphical abstract

## Graphical Abstract



# References

Review on ILC subsets:

**Innate lymphoid cells: A new paradigm in immunology.** Eberl, G., Colonna, M., Di Santo, J.P., and McKenzie, A.N. (2015). Science 348, aaa6566.

Literature on ILCs and microbiota:

**RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells.** Sanos, S.L., Bui, V.L., Mortha, A., Oberle, K., Heners, C., Johner, C., and Diefenbach, A. (2009). Nat. Immunol. 10, 83–91.

**Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense.** Satoh-Takayama, N., Vosshenrich, C.A., Lesjean-Pottier, S., Sawa, S., Lochner, M., Rattis, F., Mention, J.J., Thiam, K., Cerf-Bensussan, N., Mandelboim, O., et al. (2008). Immunity 29, 958–970.

**RORgt+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota.** Sawa, S., Lochner, M., Satoh-Takayama, N., Dulauroy, S., Be' rard, M., Kleinschek, M., Cua, D., Di Santo, J.P., and Eberl, G. (2011). Nat. Immunol. 12, 320–326.

# References

## Literature on ILC subset plasticity:

**A T-bet gradient controls the fate and function of CCR6-RORgt<sup>+</sup> innate lymphoid cells.** Klose, C.S., Kiss, E.A., Schwierzeck, V., Ebert, K., Hoyler, T., d'Hargues, Y., Goeppert, N., Croxford, A.L., Waisman, A., Tanriver, Y., and Diefenbach, A. (2013). *Nature* 494, 261–265.

**Regulated expression of nuclear receptor RORgt confers distinct functional fates to NK cell receptor-expressing RORgt(+) innate lymphocytes.** Vonarbourg, C., Mortha, A., Bui, V.L., Hernandez, P.P., Kiss, E.A., Hoyler, T., Flach, M., Bengsch, B., Thimme, R., Ho“ Ischer, C., et al. (2010). *Immunity* 33, 736–751.

**IL-1 is a critical regulator of group 2 innate lymphoid cell function and plasticity.** Ohne, Y., Silver, J.S., Thompson-Snipes, L., Collet, M.A., Blanck, J.P., Cantarel, B.L., Copenhaver, A.M., Humbles, A.A., and Liu, Y.J. (2016). *Nat. Immunol.* 17, 646–655.

# Paper #2

nature  
microbiology

ARTICLES

PUBLISHED: 22 AUGUST 2016 | ARTICLE NUMBER: 16140 | DOI: 10.1038/NMICROBIOL.2016.140

## Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice

Alexandra E. Livanos<sup>1</sup>, Thomas U. Greiner<sup>2</sup>, Pajau Vangay<sup>3</sup>, Wimal Pathmasiri<sup>4</sup>, Delisha Stewart<sup>4</sup>, Susan McRitchie<sup>4</sup>, Huilin Li<sup>5</sup>, Jennifer Chung<sup>1</sup>, Jiho Sohn<sup>1</sup>, Sara Kim<sup>1</sup>, Zhan Gao<sup>1</sup>, Cecily Barber<sup>1</sup>, Joanne Kim<sup>1</sup>, Sandy Ng<sup>1</sup>, Arlin B. Rogers<sup>6</sup>, Susan Sumner<sup>4</sup>, Xue-Song Zhang<sup>1</sup>, Ken Cadwell<sup>7,8</sup>, Dan Knights<sup>9,10</sup>, Alexander Alekseyenko<sup>11</sup>, Fredrik Bäckhed<sup>2,12</sup> and Martin J. Blaser<sup>1,13\*</sup>

# Highlights

- Pulsed therapeutic antibiotic treatment (PAT) in early life increases T1D incidence in the NOD mouse model
  - PAT alters ileal gene expression and metabolome in NOD mice
  - PAT leads to transient reduction in phylogenetic diversity and community structure of the microbiota
  - Certain genera can be used to predict if PAT NOD mice develop diabetes
- 
- **HYPOTHESIS:**  
PAT in eraly life → low diversity(antigen stimulation → weak intestinal barrier  
→ More translocation of bacteria/metabolites → systemic inflammation → T1D

# References

Type I diabetes in Non-obese diabetic (NOD) mice and microbiota:

**The NOD mouse: a model for insulin-dependent diabetes mellitus.** Leiter, E. H. Curr. Protoc. Immunol. Ch. 15, Unit 15.9 (2001).

**NOD mouse colonies around the world—recent facts and figures.** Pozzilli, P., Signore, A., Williams, A. J. & Beales, P. E. Immunol. Today 14, 193–196 (1993).

**Innate immunity and intestinal microbiota in the development of type 1 diabetes.** Wen, L. et al. Nature 455, 1109–1113 (2008).

**The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes.** Kostic, A. D. et al. Cell Host Microbe 17, 260–273 (2015).

# References

Early life ABX treatment, microbiome and metabolism/T1D in mice:

**Antibiotics in early life alter the murine colonic microbiome and adiposity.** Nature 488, 621–626 (2012).

**Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences.** Cox, L. M. et al. Cell 158, 705–721 (2014).

**Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment.** Nobel, Y. R. et al. Nat. Commun. 6, 7486 (2015).

**Antibiotics in early life alter the gut microbiome and increase disease incidence in a spontaneous mouse model of autoimmune insulin- dependent diabetes.** Candon, S. et al. PLoS ONE 10, e0125448 (2015).

**Maternal antibiotic treatment protects offspring from diabetes development in nonobese diabetic mice by generation of tolerogenic APCs.** Hu, Y. et al. J. Immunol. 195, 4176–4184 (2015).

Brown, K. et al. **Prolonged antibiotic treatment induces a diabetogenic intestinal microbiome that accelerates diabetes in NOD mice.** ISME J. 10, 321–332 (2016).