

Science AMA Series: I'm UCLA Prof. Tim O'Sullivan, I Investigate how the immune system reacts to Cancer, Viral Infection, and Obesity. Ask Me Almost Anything!

TimothyOSullivan¹ and r/Science AMAs¹

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April 17, 2023

Abstract

Hi Reddit, The mammalian immune system is fascinatingly complex. Our understanding of how the immune system recognizes and responds to foreign pathogens has increased tremendously in the last 100 years, however, we still have a great deal to discover. This point is highlighted by the recent discovery of a heterogenous family of tissue-resident lymphocytes (white blood cells) called innate lymphocytes (ILCs), which have been reported to regulate fundamental processes such as host metabolism, wound healing, and host defense. Given the importance of ILCs in these processes, my research focuses on the molecular and cellular signals that activate and sustain certain types of ILCs (Group 1 ILCs) in specific contexts. Understanding these mechanisms could have implications for the treatment of cancer, viral infection, and type II diabetes. While research from the past few decades has revealed that the immune system bridges virtually all physiological systems as a central regulator of host homeostasis, the general public (as well as scientists in other fields) only have vague ideas about immune function. Specialized jargon rampant in the field represents a barrier for the understanding of important advances in immunology, and for public consensus on its translation to the clinic (e.g. vaccination). Therefore, Immunologists need to make their work more accessible by presenting it in public forums and communicating their studies in a clear manner to try and eliminate these barriers. I think that Reddit AMAs present an excellent opportunity to highlight exciting findings in Immunology, and demystify academic science through informed discussion! I am happy to answer questions about the immune system, innate lymphocytes, and the implications for tissue-resident immunity in health and disease. I'm also happy to answer any questions about our most recent work [http://www.cell.com/cell/fulltext/S0092-8674\(17\)31183-2](http://www.cell.com/cell/fulltext/S0092-8674(17)31183-2). Edit 1: Hi all! I'll start answering questions at 3pm ET!! Edit 2: Thanks again everyone for your excellent questions! Hopefully I have satisfactorily answered them. I'm signing off for now, but if you have further questions you can contact me through www.osullivanlab.com

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TIMOTHYOSULLIVAN [R/SCIENCE](#)

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CORRESPONDENCE:

DATE RECEIVED:
November 10, 2017

DOI:
10.15200/winn.151023.31856

ARCHIVED:
November 09, 2017

CITATION:
TimothyOSullivan , r/Science ,
Science AMA Series: I'm UCLA
Prof. Tim O'Sullivan, I

Hi Tim, and thank you for doing this AMA.

T-lymphocytes have received the lion's share of attention in terms of cancer immunity. I am always curious to hear people's perspectives on why this is - do you think they truly do the most when it comes to mediating anti-tumor responses, or do we just happen to have better tools and systems for studying and modulating these responses? We know that B-lymphocytes and ILCs all play roles in autoimmunity (hyperactivity), so I would be surprised if there was not a bigger role for them in cancer immunity (loss of activity).

[SirT6](#)

No problem! I think the reason that T cells get the most "press" so to speak is that previously and currently more immunologists tend to study T cell responses. Because of this early bias, the tools and

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literature for interrogating T cell responses were much more developed than in other cell types. In terms of the T cell bias in cancer immunotherapy, this is because of the success of checkpoint blockade therapy activating "exhausted" T cells in the tumor microenvironment as well as deletion of regulatory T cells that inhibit antitumor responses (but I wouldn't be surprised if other innate immune cell types are also impacted by the this therapy, and I've seen data that suggest exactly this point). You only know the role of each cell if you investigate it, and most researchers seem to be satisfied with looking at the role of T cells rather than interrogating ALL lymphocytes at once.

Having said that, I think that it is undeniable that T cell responses are crucial for antitumor responses when mutated antigens are present on tumor cells. However, when tumor cells mutate and lose MHC1 expression (the ability to present mutated antigen), then T cell responses will not matter because they can't become activated. Luckily, natural killer (NK) cells recognize downregulated MHC1 molecules to kill cancer cells in a process called "missing self recognition", but tumors can also evade NK cell responses in processes which we are only beginning to investigate.

All in all, your question is a very interesting one for the field of immunology. Now that we have the ability to collect more immunophenotypic parameters through multicolor flow cytometry, Cytof, and single-cell RNA sequencing, why aren't immunologists interrogating these questions from a more non-biased perspective?

I have intermittent eczema flare ups. Sometimes my body is fine for years and then flare. It sucks. The flare I'm currently dealing with started 2.5 years ago after I moved back to the US from Korea. Why does my body hate me?

[MudButt2000](#)

Could this at all be related to your handle? ;)

In all seriousness though, atopic dermatitis is associated with hyperactivation of type 2 immunity through the production of IL-4, IL-13 and IgGE. I believe there are some good clinical trials for neutralizing antibodies against IL-13 and IL-4 that you may want to look into! This is called dupilumab clinically (not sure what it is referred to by marketing). Ask your doctor!

May your investigation have any outcome for the research of auto immune diseases?

[Phreakophil](#)

That would be very interesting! We would love to look at the role of ILC responses in type 1 inflammatory (IFN-gamma mediated) autoimmune diseases such a lupus. My thought is that because ILC1 responses matter as early sources of IFN-gamma in other models, such as diet-induced obesity and viral infection, then they should also play a role in these diseases as well. But we don't know yet!

We just got done with our Immunology unit in my physiology class and this was touched on by maybe 1 paragraph in my textbook and I was wondering if you had more insight on it.

The most popular theory regarding cancer, (as I understood it at least) is that cancerous cells are constantly present in our body but are neutralized by natural killer cells and macrophages before they have a chance to reproduce. From what I read though, it sounds like there was both evidence to support this theory as well as phenomena that this theory couldn't explain. With that in mind I was wondering what evidence there might be to support this theory as well as what situations or phenomena are unexplained by this theory.

[night117hawk](#)

A current hypothesis is that most cancers generally develop from random mutations made in the cells of your body over time (due to declining efficiency of DNA repair mechanisms). NK cells are great at recognizing tumor cells through either loss of MHC1 or by activating "stress signals" called NKG2D ligands. NKG2D ligands thought to be induced by DNA damage, but can also be induced on proliferating cells.

A lot of the evidence that immune system recognizes and eliminates cancer was demonstrated by my science grandpa Bob Schreiber at Wash U. This was shown by taking mice of various immune deficiency (either genetic or by antibody depletion) and inducing cancer by injection of subcutaneous carcinogen. Turns out, if you lack T cells, NK cells and interferons, the mice develop more cancer. Even more interesting is the fact that the tumors that developed in totally lymphocyte deficient mice are mostly REJECTED when transplanted into mice that have fully competent immune systems. This process is what we call "cancer immunoediting" in which immune cells recognize and eliminate highly immunogenic tumor clones, while tumors that mutate to evade the immune system eventually escape and show no immune activation, but rather immune suppression.

One interesting observation in AIDS patients or immunosuppressed patients is a much higher incidence of virally-induced tumors. There are also interesting observations in melanoma patients that do not respond to checkpoint blockade have mutations in IFN-gamma signaling genes or other immune signaling pathways (Jak-Stat), suggesting that melanoma could already have undergone immunoediting in these patients.

Have you done much research on the relationship between autophagy and intermittent fasting and have any comments on the potential immune system benefits it can potentially bring someone?

[finester39](#)

We haven't done any formal long-term fasting studies in mice, but I can tell you that 24 hours of fasting in mice induces autophagy in pretty much every immune cell that we looked at using an autophagy-specific reporter mouse (LC3-GFP). Our studies in addition to others have shown that autophagy is necessary for lymphocyte development, and for the optimal formation of lymphocyte memory. Modulating autophagy through stimulation of AMPK signaling, or inhibition of mTOR signaling can lead to larger numbers of memory lymphocytes, however these responses are harder to track in humans.

I'm also not sure you should fast when you get sick, but it's interesting that illness is often accompanied by loss of appetite. Not sure if there is any link, but it would be cool if this were a physiological mechanisms to boost lymphocyte memory formation.

Thanks for doing this AMA. I'm not familiar with ILCs; is there any evidence of them in the brain, or is the brain immunologically privileged in this regard? Also, are ILC products for local effect only or do they contribute to any systemic exposure to products (e.g., interleukins)?

[ALR3000](#)

There's actually recent evidence in mice that type 1 ILCs (either NK cells or ILC1) can contribute to autoimmune neuroinflammation. (https://www.nature.com/articles/ni.3816?WT.feed_name=subjects_immunology)

My guess is that proinflammatory cytokines are upstream of this response, but not sure what triggers those in this model. This paper is also a good example that ILC responses can act locally, but also prime their environment for circulating cell pathology.

What finding surprised you the most throughout your research?

[snaggletooth6456](#)

One of my most favorite findings was during my postdoc analyzing an experiment using parabiotic mice. Two cell types (NK cells and ILC1) that seemed at the time to only differ in one transcription factor, but share similar functions, had completely different phenotypes. ILC1 were always host-derived (non-circulating), and NK cells were always derived from both mice (circulating). This was a huge "Eureka" moment, helping to identify another lineage of innate-lymphocytes.

Hi and thanks for joining us today!

Any idea why the nasal flu vaccine wasn't effective?

[PHealthy](#)

Thanks for your comment!

I think the trouble with flu vaccines are that we can only try to predict which serotype will pop up in any given season. So while we can get it right, the heterogeneity of flu serotypes allows for more flu variants to infect people that have been vaccinated against a different serotype .

Disclaimer: Please get vaccinated though! Just because the flu vaccine doesn't always work does not prove that vaccines for polio and measles are not completely effective!

Hello Professor O'Sullivan, I recently happened across a few articles talking about the use of T-Cells with chimeric antigen-receptors (carT-Cells) in cancer therapy. To me as someone without much expertise in the field they seemed like a very promising approach ,provided it is possible to find tumormarkers with sufficient specificity for the cancer in question that can be detected by the cells. Since you are an expert, i wanted to ask your opinion on this therapeutic approach, especially on whether or not you think this technology has potential to become a major asset in cancer therapy.

[Colim](#)

I'm certainly no expert on CAR T cells, but I'll give you my two cents ;)

I think this therapy is amazing for blood cancers that have defined antigens that are not shared by other host cells (e.g. CD19, CD20 aka B cell lymphomas). In solid tumors, you would have to know the patients specific mutated antigen (sequencing), and then develop a specific CAR T cell clone for that patient (which is expensive and takes a while). Not only that, but you'd have to hope that the mutated antigen is present on the bulk of the cancer cells (which is rarely the case due to tumor heterogeneity). You also might have the disadvantage of any T cell therapy, which is tumor-intrinsic loss of MHC1 expression (but previous sequencing would be able to tell you this). The other disadvantage is if your CAR T cell antigen actually happens to be an unknown self-antigen (and now you get autoimmunity).

Personally I think antigenic-specific approaches to treating cancer are working under specific circumstances and are amazing! However, I personally think that using NK cells for cancer immunotherapy would have a broader impact given that they have less of a chance to cause autoimmunity and actually have better cytokine and killing capacity than antigen-specific T cells on a per-cell basis.

Hey, thanks for taking the time to do this AMA event!

Couple of questions. Feel free to pick and choose! I'm wordy in the mornings. 1. What do you think the public most misunderstands about the immune system and the complexities of the immune response? 2. Where do we find ILCs? And are they a "big" part (number-wise) of the total number of cells in the immune system? 3. I think it's relatively "easy" for people to comprehend that immune system cells like ILCs play roles in wound healing and host defense. After all, it's the immune system! But I think it's surprising to many that ILCs play roles in metabolism and, more generally, that the immune system plays a big role in homeostasis. Are there a couple of examples of the roles the immune system plays in these "non-immune" functions? And ILCs?

[kiri-kin-tha](#)

I think publicly people do not understand how vaccination works, the composition of their immune system, and the fact that it's ok to be a little dirty! There's really no need for antibacterial agents in your home, you have an immune system and commensal bacteria that do the heavy lifting. Unless of course you just eat undercooked meat all the time :/

ILCs can be found in pretty much every organ analyzed in mice. This is mostly because NK cells circulate through the blood and survey peripheral organs for viral infection and transformed tumor cells. Other ILCs seem to be more enriched at barrier surfaces (i.e. ILC3s are only found in the gut during homeostasis). ILCs are not a relatively large population of cells (by number) compared to T cells. However, they produce more cytokines on a per-cell basis, and are quicker to respond than adaptive cells that require antigen for their activation. Thus, ILCs may be more important in early tissue responses to setup T cell responses, and in periods of low-grade tissue pathology.

You'd be surprised how "easy" it is for anyone to understand anything. Certain topics are harder or easier to understand based on your academic background, interest, and desire for information.

There are a ton of examples of how ILCs regulate the non-immune functions of mammalian biology. I'll kindly guide you to this review for the sake of time ;)

<http://jem.rupress.org/content/early/2016/10/05/jem.20160525>

Do you think that studies done on rats are good indicators for how the treatment will work on humans? Or, in other terms, how similar are human and rat immune systems?

[sargassss](#)

There's a great deal of genetic conservation between mouse, rat, and human immune systems. Thus studying the immune system in mice has led us to learn about fundamental immunology concepts, such as why vaccines work in humans.

Of course there's a lot of differences between mouse and human immune systems (markers, heterogeneity, and we know less about the human immune system). A lot more to be done in human immunology for sure!

Hi Prof - thanks for the AMA. What's known about the immune system interactions in Eczema? Personally I get a few days warning of a cold when my Eczema gets much worse, I've heard it said that others have the opposite behaviour. What's going on with this interaction - and is there anything useful that we can do given a few days notice of an infection like that? What are your thoughts about whether Eczema is driven by immune system changes or the immune system changes are a consequence of skin barrier changes.

[trebligdivad](#)

Have to state that I am not a medical doctor and don't know the intricacies of symptoms associated with Eczema. From an immunology perspective, atopic dermatitis is associated with hyperactivation of type 2 immunity through the production of IL-4, IL-13 and IgGE. ILC2s could have some role to play in this as major producers of IL-5 in other model systems (which is upstream of IL-4 production). ILC2s have been suggested to be impacted by type 1 responses to increase the amount of IFN-gamma production, although I'm not sure how this would make dermatitis worse...

[deleted]

[\[deleted\]](#)

I'm terribly sorry that this happened to your husband! I should mention that that I do not have an MD degree and do not practice medicine, so I'm sorry that I can't be of any help to you. My expertise is in basic immunology in research settings. I hope all is well and this doesn't turn up again though!!