

I'm Zena Werb, I study cancer at the molecular level at UCSF. My lab is trying to uncover how cancer spreads through the body (metastasizes), which causes the majority of cancer deaths.

Dr_{ZenaWerb}¹andr/*ScienceAMAs*¹

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Abstract

Happy Breast Cancer Awareness Month. A cancer is described as metastatic when cells break off from a primary tumor and spread to other parts of the body. For example, if breast cancer cells travel to the lungs and form a tumor there, that is a metastasis, or a metastatic breast cancer tumor, not lung cancer. Even one cancerous cell can break off a tumor, travel through the bloodstream and lodge itself in new tissue. Metastatic cells can start growing into tumors of their own right away, but often lie dormant for days, weeks, or even decades, only to flare up long after the primary tumor has been removed. Metastases cause the vast majority of cancer deaths, particularly in the case of breast cancer, where the original tumor is rarely deadly on its own. But the process by which cancer cells escape a primary tumor, invade other parts of the body, and seed new cancerous growths is poorly understood. In breast cancer in particular, we suspect that metastases are influenced by the intrinsically stem-cell-like genetic programs needed for breast tissue to grow during puberty and pregnancy. Only a small fraction of cancer research funding goes towards understanding metastases, partly because these tiny rogue cells are hard to find and study. As a result, deadly metastatic cancers are still extremely difficult to treat. Most cancer drugs are developed to shrink primary tumors, and they often don't perform as well on metastatic tumors. My lab at UCSF is trying to uncover the biological mechanism underlying metastasis so we can finally understand how tumors shed cells, how the cells travel, how they survive, how they grow into new tumors, and how to stop them. In particular, we're interested in how the local biological environment influences metastases that land in different parts of the body. Here's a UCSF article a recent finding from my work: [Metastatic Breast Cancer Cells Turn On Stem Cell Genes](#) Here's my lab at UCSF I'll be back at 1 pm Et (10 am PT, 5 pm UTC) to answer your questions, ask me anything! EDIT: I am signed on. I am getting ready to answer questions. EDIT: Thanks for the questions. I am now signing off and getting back to research.

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Science AMA Series: I'm Zena Werb, I study cancer at the molecular level at UCSF. My lab is trying to uncover how cancer spreads through the body (metastasizes), which causes the majority of cancer deaths

DR_ZENA_WERB [R/SCIENCE](#)

ABSTRACT

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Here's a UCSF article a recent finding from my work: [Metastatic Breast Cancer Cells Turn On Stem Cell Genes](#) Here's [my lab at UCSF](#)

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CORRESPONDENCE:

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As someone who failed biology in the 10th grade, what are some ways I can possibly help the ongoing effort towards cancer research?

I read so much about the inefficiency of certain cancer foundations and to be honest a meaningful donation from my end would look pathetic to the bigger picture. I, like so many others I know, feel like I have much more to offer than my dollar. What are some real, effective ways for someone like me to contribute to the incredible research that's being done? Thank you for the time and for everything you're doing.

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[I Tiresias](#)

Exposure to science even as a young child is a critical part of your education and viewpoint. You can help by being an advocate for science in society and fighting against pseudoscience. You can support legislators and other leaders who understand the importance of science in society. As it is many researchers struggle to get funding from NIH.

Dr Werb, the ability of cancer cells to turn into endothelial cells (aka vascular mimicry) has been at least shown in glioblastoma and breast cancer (and maybe a few other tumor types). While still controversial its looking more and more like it might be a real phenomenon, but my impression is that most scientists, if they think it really happens, think it just provides a minor increase in angiogenesis. So my questions are:

- 1) Do you think vascular mimicry is a biologically significant effect in tumor biology?**
- 2) Do you think it would be proportional to an increase in cancer stem cells and their increased plasticity?**
- 3) Do you think that it might actually be involved in metastasis, as a tumor cell that could pass as an endothelial cell could have a much lower barrier to extravasation and intravasation?**

[mdbrooks](#)

I believe that the evidence for so-called vascular mimicry is real, but how significant or how regulated remains to be tested. Cancer cells are very plastic. As is the case for most things in cancer the variation is really large from tumor to tumor or even areas of a tumor. Whether this process contributes to metastasis is hard to predict.

Hi Dr. Werb, thanks for doing this AMA. I enjoyed reading your paper very much.

I have to be honest, though, I didn't really see strong evidence for a stem cell connection in your analysis.

When I ran your [differentially expressed genes through ontology analysis](#), I didn't see much support for the idea that these metastatic colonies were turning on stem cell genes. Instead, I saw enrichment for pathways such as 'negative regulation of anoikis', 'EMT' and 'mammary gland branching/morphogenesis' -- all of which provide relatively easy explanations for how the cell acquired its metastatic potential. While there was a hint of 'stem cell gene' enrichment (OCT4, SOX2 etc.), it wasn't the most striking observation, to me. I think I would have been more convinced if you had provided evidence that turning off a subset of these 'stem cell genes' off reduces metastatic potential in some way (without impacting on primary tumor growth). Have you considered doing these experiments?

As a follow up, have you considered when a cell that will go on to form a metastatic outgrowth acquires these genetic changes? In the primary tumor, while circulating, or at the metastatic site? Depending on the answer, it could be important to consider how tissue microenvironment is participating in this differential gene expression as well.

[SirT6](#)

The aim of our study was to determine what metastatic cells are like. Clearly they share expression of some genes that are in stem cells but we did not try to say that they are stem cells. So far we have not validated the function of any of those genes so I can't say how important they are. What is important is not to categorize the cell but understand the process of metastasis. Where we go from here is to try to determine which characteristics lead to growth of large metastases. The genetic changes are being studied elsewhere, but the interaction with the microenvironment is probably the key.

I know that not all breast cancers are the same, some being fueled by hormones while others are not, etc. In terms of metastases, is one type of tumor more likely to metastasize than others? Also why do some cancer cells go dormant and how are they exactly "woken up?"

[sanstress](#)

You have pointed out a couple of the most important questions that need to be answered in cancer research if we are going to be able to control and hopefully cure breast cancer. The areas of dormancy and which cancers of the same type, e.g., estrogen positive breast cancers, will metastasize and which ones will remain indolent are where many researchers will be concentrating in the next 5-10 years. I hope we find an answer. Then we will be able to treat the patients who are likely to metastasize and not overtreat those who will not.

Do normal body tissues also shed cells but those cells die whereas cancer cells survive because they have tweaked the molecular processes in the cell to make themselves "immortal"?

I've quoted "immortal" because I've seen cancer cells referred to this way in popular science/medicine articles. Is this technically accurate at the molecular biology level in the cell? Is there any knowledge about how cancer cells do this? I know a number of cancer/chemotherapy drugs are proteasome inhibitors which work by shutting down the UPS, allowing tagged proteins to build up to the point that the cell initiates apoptosis.

If cancer cells truly are immortal, have they managed to inhibit the apoptosis triggering mechanisms in the cell? Do we know how they've managed to do this?

[shiningPate](#)

For the longest time metastasis, the dissemination of cells from a primary tumor was thought to be a unique hallmark of cancer, at least for carcinomas (leukemias, lymphomas and melanoma are different since the normal cells can go walk about). But in the past couple of years there have been a couple of publications showing that "normal" epithelial cells can escape and get into the blood stream. Interestingly, it seems to happen in cases of chronic inflammation. Cancers also develop surrounded by many inflammatory cells. So the dissemination seen in cancer may be something that occurs under the scenario of inflammation. However, whether the "normal cells can survive in distant tissues is not known except for cells from the fetus that escape and land in the mother's tissues and survive for many years.

Immortality of cancer cells is defined by the fact that at least a subpopulation may be able to grow beyond about 40 doublings that seems to be the limit in humans. But that may be the property of normal stem cells too. And normal stem cells as well as some cancer cells have turned on survival genes. The mechanisms vary and are being worked out. It would be ideal to be able to shut down the survival mechanisms.

I have a question about UCSF and alternative medicine research. You seem like a scientist grounded in reality. How do you feel about research conducted there on homeopathy, acupuncture, or other pseudoscientific methods? What is the deal with a prestigious institution endorsing such questionable research? Thank you!

Edit: here's a link <http://www.osher.ucsf.edu/research/current-research/>

[yazd](#)

I don't believe in pseudoscience and wish that such papers did not persist and continue to influence the gullible.

That said, there may be valid alternatives to "Western" medicine. It is also nonscientific to dismiss things without a scientific reason. The Nobel prize in medicine this year that went to the isolation of a drug for malaria was based on traditional Chinese herbal medicine.

Hi Professor,

What is your stand on mTORC1 over-stimulation as a risk factor of carcinogenesis, particularly in regards to overconsumption of calories and obesity? To my understanding, research shows that mTORC1 inhibits autophagy, an important process which protects against cancer by isolating damaged organelles, allowing cell differentiation, and increasing protein catabolism. Since mTORC1 is a nutrient-sensitive kinase that relies primarily on cellular energy input, this relationship seems to suggest that continuous overfeeding can increase the risk of carcinogenesis in humans. Would you say this is true?

[dustofoblivion123](#)

I am not an expert in mTORC1 so I can't really answer this.

Hello Dr. Werb,

I did some lab work for a research lab at Sloan-Kettering back in high school. One of the things we were testing was the role of macrophages in aiding the spread of cancer. I haven't really thought much about it since, but would be curious to know if this research bore any fruit, so here goes:

Do macrophages play a role in the metastasis of certain types of cancer, particularly of the endocrine system?

[cispinescum](#)

The evidence for tumor associated macrophages playing a role in cancer is very strong both in patients and in model systems. At least in model systems macrophages can foster metastasis. Indeed there are therapies being tested in the clinic that target these macrophages to see if that can reduce cancer growth. Which cancers might be the best targets for anti-macrophage types of therapy is still not known.

I had a few questions:

1) In addition to your multiplex PCR approach, would it be possible to use single cell RNA-seq to perhaps take a larger and more unbiased look at the transcriptome of these cells? What might you expect/hope to find?

2) Have you looked at clonality of these cells? Do they always arise from a single clone? Or do you think multiple clones can arise from one primary? Could a brainbow model perhaps help answer this question?

3) Do you think the initial birth of a metastatic clone is a cell autonomous effect or a niche effect within the tumor microenvironment? Do you think there are experiments that could answer this question? Do you think this could be a targetable step in tumor growth/development?

Thanks for taking the time to do an AMA!

[bli](#)

1. You must be looking over my shoulder. We are doing single cell RNAseq as we speak. What we hope to find are metastasis associated genes that we can then use to find rare metastatic cells in tissues of patients.

2. Good question. We don't have the answer yet, but by looking in tumors from different individuals we are seeing properties that are common to metastases and to specific tissues in which they lodge.
3. Since in even very metastatic tumors metastatic take is a rare event, we still cannot be sure if that is a specific property of the tumor cell that takes or a stochastic event in concert with the microenvironment. I would put my money on the latter.

Hi Doctor! My mom had breast cancer five years ago and it was treated, but the cancer showed up earlier this year in her liver; and it recently spread to her pancreas. I realize funding is an issue, but what do you think is the primary hurdle to discoveries in metastases research? If funding were not an issue, how much do you think discoveries and treatments would speed up?

[vacatola](#)

I am sorry about your mother's cancer recurrence.

It is interesting that the barrier to metastasis research may not have been funding but people willing to study metastasis in detail. In fact less than 10% of the NIH funding for cancer over the past 10-15 years has been on metastasis. This has always puzzled me. Drug companies find metastasis too expensive to use for drug testing. The experiments are long and may not give simple answers. And while many tumors will already have spread (even if there are no detectable mets) at the time of diagnosis, the therapies now used may not target these hidden cells. There now seems to be increased interest. If the research looks for the science behind metastasis and for therapies that target it I think there will be important discoveries. Of course money will help, but great ideas are more important.

What if the notion of the break away cell is all wrong? Meaning that isn't the mechanism of metastases. Also, what effect if any does diet and exercise have on the system as a whole? Example a stress free vegetarian that runs a 5k 5 days a week and goes to the gym and lifts weights 3 days a week. How would their "cancer" profile differ from an average individual?

[BassPlayaYo](#)

Cells need to go walkabout from the primary tumor for metastasis. There may be possibilities other than the breakaway mechanism.

I don't know how being healthy effects metastasis, but certainly it would help in coping with the nasty effects of therapy.

I am interested in going into the molecular cellular field as well, as someone who's already in the field, what do you find to be the most rewarding aspects of this career?

[lp5390](#)

I am delighted that you are interested in this aspect of science. What I find rewarding is doing what I love every day, thinking about great questions in biology and medicine and then trying to solve them. I am also thrilled by the potential for helping people and curing disease.

I have a family stomach cancer in which the gene is broken which can result in cancer or no cancer. There is a 50% chance. I won't have to act on it for at least 7 to 10 years. What sort of technology's do you think will be available by then and do you think there will be an alternate to just removing the stomach?

[DarcyTheFrog](#)

Since I am not a clinician I can't predict what will be available to patients. However, the question of which cell might become cancer and which will remain mutated but not progress is one of the most important problems in cancer biology. After all if you have a germline mutation you have billions of cells with the mutant in them but only 1 or 10 or so ever get to the stage of cancer. I don't know if we ever will be able to predict such a rare event.

Thank you for doing the AMA and for your valuable research!

My daughter's name is Zina :)

My question is: what do you think is more cost- and time-effective: research on curing cancer or preventing cancer? I've always agreed that an ounce of prevention is worth a pound of cure. Do you agree?

[vbullinger](#)

I agree that prevention is more effective than a cure. But some cancers may not be preventable since some mutations occur during normal processes such as cell replication because the enzymes involved are not perfect.

Hi! I work at UCSC on MedBook, an online genomics-based cancer research tool. We currently have a couple users at UCSF (Adam Foye, Jack Youngren, Eric Small).

If you could pick one tool to be developed to explore clinical/genomic data from patients, what would it be?

[mokolodi1](#)

What I would really like to see are data sets with parallel genomic information, RNA expression, proteomic and epigenetics, for patients that have metastasized and those who have not. But these data may be some years off still. What tool you would use is beyond my expertise.

Dr. Werb,

Thank you for doing this AMA. I haven't read your paper yet, but reading through the link you provided I wanted to ask you- do you think that the activation of these stem cell genes is inherently the property of the disseminated cancer cells? Or do you think that the reason these genes are activated is because of the foreign environment (as in an environment different from their origin) that these cells are in?

Thank you in advance for your answer!

[rambobilai](#)

I have heard of this. However the causal evidence in support or denial is still lacking.

Hi Professor Werb,

After having read "Hallmarks of Cancer" and parts of "Biology of Cancer", i got a few burning questions.

1) In the book "Biology of Cancer", it says that all cancer cell stems from only one mutant cell. But if one cell has the opportunity to mutate and becomes a cancer cell, why can't the others? Can't there be two or several different cell lines in one single cancer mass?

2) I understand that cancer cells can live without attaching to ECM, and this is one of the traits that enables them to metastasize. But why does metastasis happen in a specific region? (for

example, along the lymph system, or concentrated in liver...) Is it that some regions are more suited for the growth of cancer cells? And what would happen if metastatic cancer cells never attach to the ECM again? Will they be able to proliferate without attaching to ECM, considering their un-suppressed proliferation and genetic instability?

Thank you for doing this AMA, I have been very interested in Cancer research after being a research assistant in Duke's Oncology lab for a month last year. Now i am a freshman at UC Berkeley. Could you please give some suggestions on where to find research opportunities in the Bay Area? Participating in research is Awesome!

[vanguard-qi](#)

1. You have just discovered the fundamental issue in cancer. We may have millions of mutations but only one in three of us will get cancer. Is it that we have such great surveillance mechanisms that most of the potential cancer cells get destroyed? Or do the cells that become cancer make all the right additional mutations to take hold? Or is it that even with all the mutations it is the cell's neighborhood or microenvironment that is critical to whether a cell behaves pretty much like a normal cell or is able to escape. Or all or any of the above? We still are looking for the answer.
2. Adhesion to the extracellular matrix (ECM) is something that most normal cells must do or they die. Some cancer cells have turned on survival mechanisms so they don't die and are able to survive the metastatic processes. It is still a rare event. Some cancer cells may make just enough ECM to help them survive. Many cancer cells use fibrin as the matrix component to keep them alive. Except for rare epithelial cancers, most cells do not proliferate very well in suspension. Of course some of these have been exploited as cell lines that can be grown in bottles in culture for research.

As for research opportunities for a senior thesis type study, many scientists at UCB, UCSF and Stanford are happy to take on undergraduates as long as you can commit a reasonable amount of time over 1-2 years so you can actually work on a project. Emailing the professors is worth while. Look at what research is being done on the Cancer Center websites under each faculty member.

I've read that anti-CD47 antibodies can dramatically inhibit metastasis by causing cancer cells that enter the blood stream to be mopped up by the immune system. Any thoughts?

[ConfirmedCynic](#)

Cancer immunotherapy is a hot topic these days and is leading to some dramatic effects and even cures. I don't know whether anti-CD47 is one of the magic bullets. Timr will tell.

The *Metabolic Theory of Cancer* is a phrase that I've encountered recently on my twitter feed. As I understand it, it claims that cancer is not primarily a disease of genetics, but rather a metabolic disease brought on by (modern) poor diet and nutrition, and can therefore be tied up with the so called diseases of civilization.

I would like to know your take on this concept, and how it may, or may not, affect cancer treatment or prevention.

[packet_wrangler](#)

Most diseases turn out to have altered metabolism. Who's on first? Does the genetic change lead to the metabolic dysfunction or the changes in metabolism (because of our life styles) allow the mutations that we all harbor to become manifest?

Thanks very much for doing this. A few questions for you. First though, I'm not a scientist so please forgive me for the broad nature of my questions.

q: Is there a reason you picked breast cancer versus another cancer?

q: Is it worth studying multiple cancers if you are trying to understand how Cancer (big C) spreads versus one type of cancer?

I've read several stories in the last few years where scientists have tried to focus on cancer and viruses in general as opposed to specific cancers. Perhaps they are looking for a notable cancer signature or genetic marker or a protein they all share, etc or they are [studying naked mole rats](#) because they don't get cancer, since their immune system seems to laser on on rapidly dividing and/or clumping cells. In other words they are looking to reverse engineer an existing successful process.

There is also the [DRACO project](#) that came out of MIT that tries to find meta-characteristics of viruses. Admittedly, that project doesn't seem to have made much progress since that story broke four or five years ago. Nevertheless, it seemed to me that targeting the characteristics of viruses and cancers in general may be the most effective and salable approach.

As an engineer, chemotherapy and how it was developed always seemed to be what we called "brute force." Aka hurl a bunch of chemicals at something and see what dies. It is slow and hard to scale. When I started to read about newer ideas around treating cancers they made sense to me, as they seemed more like reusable code versus one off installations in computer software.

[buddha33](#)

I picked breast cancer because it affect such a large number of women. I have also done some research in prostate cancer, glioblastoma and colon cancer. I want to do research that helps people.

Some studies of cancer depend on whether you have a good model system in mice so you can do experiments. But ultimately I hope that my findings might happy to other cancers. But to get ahead scientifically you must focus your investigations.

Dr. Werb, I know that no one knows this answer, but I am curious if someone closer to the problem might be able to share ome insight.

We can stop worrying about cancer in?

a) 5 years b) 10 years c) 50 years d) Forget about it

[gregdbowen](#)

So long as we live long, cancer, which is a disease of longevity in humans, may be inevitable. But if we succeed with therapies to make cancer a disease that we live with but don't die of we can come to a point where we swear about cancer but don't worry about it. Realistically that is unlikely before 50 years.