Hi Reddit,
We're Paul Oberstein, MD and Manji Gulam, MD, PhD, from the Medical Oncology department at Columbia University Medical Center. We are so happy to be here and answer your questions! We work as part of a multidisciplinary center, the Pancreas Center at Columbia University, where we specialize in seeing patients with pancreatic cancer and other gastrointestinal malignancies.

Dr. Oberstein: Assistant Professor of Medicine within the Division of Medical Oncology at Columbia University Medical Center. My research focuses on developing novel clinical trials for patients with pancreatic cancer. Research trials emphasize novel agents and translation of promising concepts from the laboratory to the clinic. In particular, I am focused on developing collaborations to expand options for treatment as well as supportive care for patients with advanced cancer. I am the Principal Investigator for over 10 active trials including both therapeutic and supportive care studies, and am conducting research studying the interplay between tumor associated stroma and epithelial cells utilizing mouse models of pancreatic cancer in the Herbert Irving Comprehensive Cancer Center.

Pancreatic cancer: why is it so hard to treat?

Dr. Gulam: Assistant Professor of Medicine within the Division of Medical Oncology at the Columbia University Medical Center. I conduct translational research with the overall goal to develop new treatments for cancer. My focus is on gastrointestinal malignancies, particularly pancreas adenocarcinoma, on which I am conducting preclinical combination immunotherapy studies on genetically engineered mice with pancreas cancer in the laboratory at the Herbert Irving Comprehensive Cancer Center. I am currently the principal investigator of multiple novel combination studies that include immunotherapy in pancreas, esophageal, gastric, and liver cancers, and currently developing other unique strategies to tackle these difficult to treat diseases. I am the recipient of the Young Investigator Award for his preclinical studies in Pancreas Cancer by the American Society of Clinical Oncology.

Immune Targeting in Gastrointestinal Malignancies: Finding the Right Combination for the Right Site

Dr Oberstein signing as: PO
Dr Gulam signing as: MG

Edit: Hi Reddit! We're here, let's get to it.

Edit 2: Thanks for all your great questions, Reddit. We're signing off for now, but we'll be checking in tonight and tom morning so keep the questions coming.
What do you think drives this difference? What are the major differences between the head and tail of a normal pancreas? Do you think this is likely to be a cell autonomous effect or perhaps a microenvironment effect? As a clinician, do you think the anatomical location is an important prognostic factor? Thanks!

SirT6

Hi,

A SEER database study asked this question and found that patients with head of pancreas cancer did worse compared to those with tail of pancreas tumors. The anatomy of the head of the pancreas makes the resection more difficult due to vessel involvement compared to tail of pancreas tumors. It is unclear at this point whether a distinct biology exists that underlies the anatomical location. Best, GM.

How do you think Obama's PMI and Biden's Cancer Moonshot will affect the field of precision medicine in cancer treatment in the future? What do you see are the avenues where these initiatives will bring the most benefit to patient care in the short term? Long term?

p1percub

Hi, Both initiatives represent new collaborations that should lead to accelerated discovery and progress in helping patients. However the immediate impact is difficult to gauge. I think they will have the greatest benefit in helping prioritize research projects to pool efforts in this new and diverse field. And in the short term getting many expert stakeholders together will help identify some low hanging fruit that can impact patients in the short term. However the long term benefits will depend largely on funding, once we identify great projects we need to see them through the long and expensive course of clinical testing. PO

Dr. Manj, you in particular seem to be interested in applying immunotherapy (and in particular immune checkpoint blockade) to the treatment of PDA.

Can you comment on the expression of PD-L1 in PDA tumor samples by IHC? Was there an enrollment criteria for PD-L1 positivity in your ongoing trial? As I am sure you are aware, nivolumab recently failed to meet its endpoints in first-line NSCLC while pembrolizumab succeeded. The major difference in trial design between these studies was that pembrolizumab required that patients be >50% PD-L1 positive to enroll. How are you thinking about this result (and others) as continue with your current trials and begin to plan for others?

Additionally, what is the T-cell phenotype in these patients? Do you see T-cells either intratumor or accumulating at the periphery? Do they have an exhausted phenotype? Thanks!

SirT6

Hello, As you point out, the role of PD-L1 expression as a prognostic and predictive marker is being defined in multiple cancer subtypes and may be different dependent on the cancer subtype. In pancreas cancer, there have been studies which are looking at this question and one retrospective study evaluated 51 patients for PD-L1 expression and CD8 T cell infiltration and found PD-L1 expression to have a poor outcome. Interestingly, tumors which expressed elevated PD-L1 expression also had decreased CD-8 T cell infiltration. The current ongoing clinical trial here at Columbia University is not biomarker driven but tumor specimen will be collected both before and after treatment to evaluate these key questions. Furthermore, studies on archival tissue here at Columbia are underway to ask these questions with complementary global gene expression analysis on both tumor epithelium and stroma compartments. These studies will hopefully help determine the underlying
pathways which may dissect the role of not only PD-L1, but other regulators of immune response.

Dr. Oberstein, much of your work seems focused on understanding interactions between the role of tumor stroma in oncogenesis.

I remember one study (though I am having difficulty finding the link to it now) where researchers used CAR-T cells to destroy the tumor desmoplasia surrounding PDA. The hope was that this would allow better access of drugs to the tumor, and facilitate reduction in tumor burden. Surprisingly, however, in this study, destroying the tumor desmoplasia actually resulted in a metastatic phenotype. It appeared that the desmoplasia was also acting to physically constrain the growing tumor.

I was wondering if you could comment on how this affects your thinking about therapeutic strategies that seek to modulate interactions between tumor and tumor stroma in PDA. Thanks!

SirT6

Thanks for the question. I was part of a group that worked on these studies and published a paper showing exactly this, when we depleting tumor stroma with Hedgehog inhibition the tumors were more aggressive and lethal. This work was done in a mouse model of pancreatic cancer so the exact role in humans is still unknown. However it definitely has led us to modify out thinking about these approached. In general we know that tumor stroma is heterogeneous and modifying some parts may still be very effective in increasing the immunogenicity of tumors or perhaps to control growth directly. But we proceed with caution. PO

Hello and thanks for the AMA!

Regarding pancreatic cancer specifically, and searching for novel approaches at treatment: how feasible is immunotherapy in your research? Additionally, do you feel that immunotherapy is receiving enough support from funding/other oncologists/other researchers? Why/why not?

Thanks again!

DragonFive

Thanks for the question- Currently, immunotherapy as monotherapy has not been promising in pancreatic adenocarcinoma. However, patients who have mutations in DNA repair mechanism (microsatelite -high) like in colon cancer appear to be responding to immunotherapy as a single agent. Unfortunately, less than 5% of pancreas adenocarcinoma tumors have this mutation. Pancreas cancer has an immunosuppressive environment for which pathways are currently being studied. Combination therapies which negate these immunosupresive pathways in combination with immunotherapy is predicted to be the way forward. Pancreas cancer funding continues to lag behind despite it being one of the most aggressive solid tumors. As it is not one of the more common tumors, such as lung, colon, and breast, it does not get the attention it deserves, despite leading to high mortality.

Drs Oberstein and Gulam, thanks for doing this AMA.

I have collaborated on developing statistical methods that aim to allow personalized medicine (e.g. https://www.ncbi.nlm.nih.gov/pubmed/26988928), but am curious about your perspective as clinical doctors and researchers.

What would you say are the main hurdles to implementing techniques for personalized medicine in practice? Can you think of things that methodologists, statisticians, and data scientists could do to...
overcome some of these hurdles? In other words, what work is needed from us to make personalized medicine work in practice?

Thank you again!

daob_stats

Hi, Thanks for your work on this. Our current regulatory pathways emphasize pretty fixed statistical methods and studies which usually require hundreds of subjects in a carefully controlled setting. The proliferation of individualized data and the shift to smaller studies requires new methodologies. On the other hand, we are always overall optimistic about our novel treatment paradigms and need statistical rigor to validate new therapies. There are currently new methods to conduct phase 1 studies and we would benefit from increased efforts to develop methodologies for N of 1 and small, targeted studies.

Thank you for doing this AMA! What has been your greatest discovery so far?

lightly-sauteed-peas

Hi, My greatest discovery has been in the interaction between the tumor environment and the tumor cells themselves. We have found that some tumor surrounding cells seem to prevent tumors from acting worse and if we target these cells the tumors may become more aggressive. Overall, this is a reminder of the complexity of tumor interactions and also points to the promise of emerging therapies. PO

Thank you all for spending your time fielding questions.

A rather arbitrary question, but here goes; what do you not like about personalized medicine in cancer treatment?

James364

This is a hard question, one of the biggest challenges we have as clinicians is our reliance on personal anecdotes. If we see something work really well for one person or in one setting, there is a temptation to try it elsewhere. In most treatment strategies we have large clinical trials to guide us and we practice “evidence based medicine”. In personalized medicine, we just don’t have the evidence base yet to completely guide therapy and we must rely on extrapolation and modeling- I worry that we may sometimes get it wrong. PO

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James364

Hello, Personalized medicine has revolutionized a subset of cancers for which actionable driver mutations have been identified, such as metastatic melanoma (BRAF), non-small cell lung cancer (EGFR, BRAF, ROS, and ALK rearrangement). In pancreas cancer, mutations in KRAS, PS3, SMAD, are common but unfortunately there are no available targeted therapies for these mutated proteins. Mutations in BRCA are found in familial pancreas cancer and PARP inhibitors are being currently studied.
Hello,

Thanks for doing this AMA!

I have a family friend who was diagnosed with glioblastoma multiforme last year. In the course of his treatment, he was given a new therapy technique that involves the use of a skull-cap with electrodes that emit a static electric field, combined with a new drug, to try and halt tumor growth. This technique was written about in this paper:

http://jamanetwork.com/journals/jama/fullarticle/2475463?resultClick=3

So far, it looks like the therapy has stopped (for the most part) the growth of the tumor. I'm wondering what your thoughts are on new treatments like these- are there any other promising treatments for cancer on the horizon? How seriously should we take these kinds of treatment?

Thanks for your time!

Austion66

This technology is very exciting and the study you quoted showed positive results in the treatment of glioblastoma. It is clearly an out of the box kind of therapy but the mechanism of action depends on targeting cell division and is similar to the goal of many chemotherapy agents. We should take these treatments very seriously because they have completed rigorous testing in clinical trials. However, I don't think this particular technology is as relevant in pancreatic cancer because of the location of the tumor. In general, if a therapy is tested appropriately and there are signs it may help our patients, we will take it very seriously. PO

Hi Dr. Manji, you say that you are conducting translational research with a goal towards developing new treatments for cancer. Do you think that immunotherapy will ultimately be the best course for these types of cancers, or do you think it will end up being split with small molecules? What are your thoughts on combination therapies and are they being tried in the clinic? What about ADCs?

girl123

Thanks for the question. We have to look at the underlying tumor biology to drive cancer therapy and not the anatomical disease, itself. Targeted therapy does have a role in cancers such as non-small cell lung cancer, renal cancer, metastatic melanoma, etc. In metastatic melanoma, targeted therapy does not normally result in a durable response and resistant quickly follows. Immunotherapy appears to lead to more durable responses. Combination targeted and immunotherapy may be beneficial as targeted therapy may result in neoplastic cell death leading to increased exposure of tumor antigens which could enhance immunotherapy efficacy. GM

Hello Drs. and thank you for this AMA!

What drove you to start investigating pancreatic cancer? Was it the significant difficulties associated with its treatment or some other reason?

rseasmith

As a physician researcher I am primarily interested in building collaborations between scientific discovery and treatments for patients. I got interested in pancreatic cancer research because there seemed to be so many opportunities to conduct this kind of translational research and to help make a difference for patients. There are many challenges in this work, the biggest being that we don't have
treatments that work well enough but this is also a huge motivation for all of us to continue working to bring new therapies to the clinic. PO

Dr. Oberstein: Thank you for your hard work in this incredible field. I know big discoveries are waiting to be made, and I was wondering what you see on the horizon beyond therapies with monoclonal antibodies, or to be more exact, in the realm of genetic manipulation of somatic cells or nanotechnology? Is there anything to this? Thank you in advance.

**propinquitycogent**

It may be difficult to accurately predict where the big discoveries lie but we certainly think they are out there. In addition to targeted therapies, we expect that manipulation of the immune environment will lead to improved therapies for pancreatic cancer. Immunotherapy has had a profound impact on treatment in other cancer types and we expect that we will find ways to use it in pancreatic cancer but we are not there yet. As we learn more about the tumor and patient specific immune setting of pancreatic tumors we are optimistic that we will identify new therapeutic combinations. I think we are not yet able to genetically manipulate somatic cells in the clinical but we hope this technology will also continue to grow. Nanotechnology remains another option and is the subject of ongoing clinical trials. In general though, we expect to see incremental steps where we improve outcomes for a subset of patients and then develop more individualized therapy until we hopefully have something for everyone.

PO

It is my understanding that one of the reasons pancreatic cancer is particularly difficult to treat is because of the time between onset of cancer growth and ultimately detection. Some cancers we are good at catching very early, but pancreatic cancer is, or appears to be, asymptomatic until pretty late.

Is this something that you see as being a solvable problem? How are we looking to improve the detection time of patients with pancreatic cancer and do you think this will significantly improve the outcomes of these patients?

**g1r123**

We think you are correct and that early detection is one of the biggest challenges in pancreatic cancer. We know that patients who undergo surgery for what appears to be a limited tumor (no sign of spread) will have a 90% chance of tumor recurring if they have no further therapy- clearly the disease is out there early on. Unlike some tumors we do not yet have effective methods to catch this early and because of the location of the pancreas this is challenging. But I do think it's solvable. The more we learn about tumors and tumor proteins the more we are able to identify unique markers of disease. Once these are well defined and differentiated from "normal" we may be able to use blood, stool or even biomarker based imaging tests to detect these cells early on and remove the tumors before they spread or possibly when they are pre-cancerous (like colon polyps). PO

Hey there! Do nanoparticles have a current place in pancreatic cancer treatment? Are they still stuck in the lab or have they transitioned to clinical/pre-clinical trials of some sort? Do you have reservations about their potential when compared to other novel approaches?

Some background: I shared lab space with a group that was trying to develop nanoparticles for use in pancreatic cancer treatment. From what I understand, their plan was to deliver the particles to the pancreas, excite the particles (which would be doped with some absorbing chemical e.g. indocyanine green), and then allow slow diffusion of the drugs into the organ. If I recall correctly, their assertion was that the heated particles could "bore" into the pancreas, allowing for more targeted treatment, though I
may be mistaken.

Thank you doing this AMA!

RoRoRoBoat

Nanoparticles can describe different things. There are currently FDA approved drugs that have a role in pancreatic cancer that utilize nano-particle based deliver systems (nab-paclitaxel and liposomal irinotecan) but what you are describing is more direct methods of nanoparticle therapy that are still in the experimental phase. As a clinical approach, we view this like any other targeted technology- it needs to make sense and go through appropriate testing but should be used if effective. PO