Cancer Never Stands Still: How Tumors Evolve, Spread & Outsmart Treatment Transcript

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Introduction to Cancer Evolution

Well, it's my absolute honor to have a Professor Swanton with me here today. You are a man that has been studying cancer for a long time. You are a clinician scientist, deputy clinical director at the Francis Crick Institute, UK, Cancer Research UK.

You're a chief clinician and your research really can advance our knowledge of that cell to cell genetic variability within tumors and molecular pathways that drive cancer to.

So I'm really, really excited about this discussion. So thank you so much for for joining me today, Professor Swanton. Great pleasure. Hi. Lovely to meet you.

So can you tell me a little bit in regards to that cancer evolution? What what it means kind of in everyday language for people to understand. Well, I think the best way of thinking about cancer evolution is a in terms of a disease that never stays the same.

I think you see this clinically in patients who you treat with targeted therapies. And over time, tumors acquire resistance to therapies or intrinsically resistant to therapies.

And I think what that tells you is that much like bacteria evolve routes towards genetic resistance, soda cancers do the same. And we started looking at this about 16, 17 years ago when we applied new clonal signaling technologies to large renal cancers and found that multiple, distinct biopsies in the same tumor would harbor different genetic events.

Some would be shared across all biopsies, the so-called trunk mutations, the early founder events. But then as tumors evolve, they acquire mutations in some parts of the tumor and some sub clones, but not others.

And it's that diversity that natural selection acts upon, and that diversity can play out in a number of ways genetically epigenetic and can occur even through treatment.

Tumor Heterogeneity and Trunk Mutations

Treatment itself can lead to DNA mutagenesis, but of course other other other mutagens like UV light, tobacco smoke can also lead to genetic diversity that ultimately creates this variability in sub clones in the same tumor that allow one or more to become resistant to a drug that perhaps the tumor and the patient has never been treated with before.

And for that sub clone to emerge and and results in treatment failure and drug resistance. And that's a challenge I think that a lot of kind of the normal Joes out there don't really understand.

We look upon, you know, a tumor as a homogenous type of, of substance where, you know, you put a needle and do biopsy in one location and then you think that that is kind of the, you know, the identity of the all the components within that tumor.

So how, how, how can you explain for people to really understand the complexity that that exists within the tumor and also the challenge sometimes with doing biopsies and gaining the appropriate information from that?

Yeah. So I think the first thing to say, yes, it is complicated, but the complexity can be distilled into simplicity. What is that simplicity? It's identifying the founder events in the tumor that are shared across every tumor region, in every

sub clone.

These are the trunk mutations. And and we know from, you know, the last sort of 1015 years of the optimal cellular target. So the trunk ones, the ones that are present in every tumor cell.

So take EGFR or Keras as an example. Keras mutant pancreas cancer EGFR moon lung cancer. Keras mutant G12, c mutant lung cancer. These diseases are optimally treated with Keras and EGFR inhibitors.

If those those mutations are present in the trunk of the tree, which they almost always are when they're present. In other words, if R mutations in lung cancer are very rarely sub clonal, they're almost always clonal, tranquil and tumor origins their founder genetic events that are present in every tumor cell and as a result they make very good targets, very good drug targets.

And they'll be found in every biopsy for the most part, with some exceptions. So the same pancreatic cancer and many other examples. So when you talked a little bit earlier, you talked about treatment failure because of the sub clonal diversities and such clonal them meaning that you have other drivers sort of say within that tumor.

And then you, you go with a chemo that attacks a certain component of that population, then the tumor, but then you have the diversities and making it hard.

Then for that chemo to impact that, so does does that then evolve that, that tumor in, in how it needs to be treated. Do we need to reassess and do another understanding of its kind of genetic diversity?

Yeah. So there's good examples of this in the literature now.

Drug Resistance and Clonal Selection

So for example, patients who are treated with EGFR inhibitors in the context of non-small cell lung cancer can develop mutations, get so-called gatekeeper mutations in in in a, a code on 793 and into methionine mutation.

And that causes resistance to the first second generation EGFR kinase inhibitors. And that that led to the ultimate approval of that helps combat those mutations and prolonged progression free survival times.

But of course, evolution is a fickle beast. And, you know, there are resistance events to this third generation of EGFR tyrosine kinase inhibitors, including things like Mets amplification or additional mutations in EGFR, such as C7 nine seven s, for which people are developing new drugs for and obviously met inhibitors that are required at resistance in sub clones to Austin Knibb are also being developed, and there have been some very promising data at last week in this regard after Austin Merton had failure.

So yes, it's very well established that subclinical evolution drives drug resistance in those acquired sub clones. If analyzed correctly, if they have actionable alterations, can sometimes result in further benefits if the appropriate drug is used.

And so I mean how I usually explain that. Then please correct me if this is an inappropriate way to explain it. I kind of tell patients that it is almost like you look at a big city, let's say.

New York and within New York. Yes, there are certain components that are there similarities. You know, there are all human beings. And but then you have Little Italy, you have Chinatown, you have.

And so you have then these different aspects that are very unique for these neighborhoods. And they need to be addressed differently. Yeah. That's true.

I think that's not a bad analogy, actually. I take it one step further than that, actually. And it's an area that we're increasingly interested in is, is crosstalk.

It's communities. It's communities of cells that collaborate to boost the tumor genetic potential or the metastatic potential of cells. And we are we, for example, have some evidence last year showing a disease of aging, clonal hematopoiesis of indeterminate potential.

This phenomenon where in your bone marrow or bone marrow, stem cells that release myeloid white blood cells, that that allow us to fight infection and what have you, as we age, these stem cells in our bone marrow acquire mutations that make them fitter.

And those fit, those fitter clones get into the blood and they become hyper inflammatory as a result of those mutations that I mentioned, two and three, for example.

And it turns out these these myeloid codes with those so-called chip mutations, clonal hematopoiesis of indeterminate potential, they penetrate tissues and we think cause chronic inflammation in the tissues that somehow potentiate and cross talks of the tumor to to drive think we hypothesize.

Tumor Crosstalk and Immune Evasion

And we've got some evidence of this in our clinical studies. Poor relapse free survival in early stage lung cancer. So we think it makes the metastatic process as well.

So so it's almost like they then share intelligence. Yeah different intelligence agencies and they share intelligence to optimize their their goal which is to drive their own survival.

I think one has to be a little bit careful to infer intelligence and an anthropomorphic view of cancer. This is simply a result of genetic diversity and selection playing out over time.

There's no intelligence or thought behind this, so we've got to be careful not to mislead patients using phrases like cancer's a clever enemy. It's not clever.

It's simply a reflection of just the overwhelming genetic diversity that's presence in a, in a, in a solid tumor. And so when you say crosstalk, what how does that crosstalk take place?

And if there's so one obvious example is where tumor cells reduce the expression of their or rather, put the brakes on T cell immunity through upregulation of checkpoint molecules.

So they sort of suppress being recognized by the immune cells. And they can do this by up regulating receptors like Pd-l1, or by losing the flags on the cells that allow antigen to be presented, so-called HLA loss.

So there are multiple ways in which tumor cells adapt over time to reduce recognition by the immune system or to dampen down immune mediated attack, and that sort of crosstalk between a predatory T cell and and its prey, the tumor cell.

So essentially you're saying it's more of a kind of a natural selection process that the epigenetic changes in one sub clone is, is kind of what's making it survive.

And then because it's surviving, then it is then replicating. Exactly. Right. Exactly right. Yeah. Okay. And so you started you initiated or part of, you know, trace or X, you know, that's what you're running right now.

Are these the kind of questions that are being answered then with that program? Yeah, very much so. We're studying how tumors are initiated, how they start and how they progress over space and time, how they metastasize, how they acquire immune evasion, how they acquire resistance to drug therapy, ultimately, how they acquire new genome instability mechanisms that allow them to become more diverse, genetically diverse over space and time, and how all of those biological processes impact clinical outcome.

And and so with that understanding this, you know, what are strategies that you feel should be developed in order

to be able to effectively kind of outsmart these kind of genetic selection process that takes place for the cancer's own survival?

TRACE and Cancer Progression Research

Well, I think the the obvious point is that I made earlier that we need to be targeting the trunk, all alterations, the founder, mutations, founder events that are present in every tumor cell and really finding more and more efficient ways of doing that.

And we shouldn't take our minds and attention off that challenge. We've done. Community's done an excellent job so far, but I think we've got further to go.

I think the second point is the early detection is extremely important. So in my disease, in lung cancer, we know that only detection of disease improves outcomes.

And we've got low dose CT screening programs that can detect cancers lung cancers before, cancers metastasize. Once they metastasize, they're largely incurable.

But in the early stages of disease, the majority of patients will be cured by surgery and adjuvant therapy. Early detection is crucial. So I would say if you're a smoker, have been heavy smoker, engage and participate in low dose CT screening programs, that's absolutely crucial.

And of course prevention and do not, you know, and give up smoking if you possibly can. And certainly do not start if you haven't smoked. And then last but not least, I think well, two points actually.

Other approaches are sort of early detection of relapse after surgical resection. In the adjuvant setting. We're developing minimal residual disease tools to track tumor evolution and escalate therapy in the absence of macroscopic disease on a CT scan in patients who have microscopic disease in the blood, we want to try to eliminate that while we can maximize the chances of cure.

And before the disease comes back using tumor informed circulating tumor DNA detection approaches, which we've developed through tracer X and had had had a lot of success with.

And last but not least, we're very interested in really going right back to the beginning, this big bang of how the tumor starts in the first place. And understanding that what's becoming increasingly apparent is that it's not all about the mutation.

Targeting Founder Mutations and Early Detection

You know, mutations are important and necessary, but not sufficient to drive cancer. What else is required? Well, we know increasingly that inflammation is required to drive that cancer initiation process, and that initiation event is promoted by white blood cells like the macrophages that absorb pollutants from our environments, either from tobacco exposure or from just air pollution from our urban lives.

And that chronic inflammation, we think, collaborates with the EGFR mutant clones to trigger tumor initiation, and trying to stop that with anti-inflammatories or appropriate small molecules or antibody approaches to to block key inflammatory processes that collaborate with the EGFR activating mutation or the Keras mutation, I think are going to be crucial.

So the age old adage prevention is better than cure. I think it's going to be super important to consider. Yeah, I would say the best cancers, the one you never get.

And obviously early detection and understanding the process is going to empower you to be able to be in that position. So yeah, I want to get into the circulating tumor DNA a little bit.

But inflammation. So it's centrally if we can control inflammation and also identify what is driving the inflammation in individual here. Use the example of macrophages absorbing the chemicals from from smoking.

So is there a way is it essentially then lifestyle exposure chemical have metal exposures. These type of things that you feel is what initiating that inflammatory process.

You know within the body that can then turn on a lot of these inflammatory drivers. Yeah. Yeah I think that's exactly right. And I think environmental exposures can do this.

But also aging the aging process itself can do this. So an obvious example is the clonal Mattapoisett example I gave you earlier. We know clonal hematopoiesis is associated now with lung cancer risk, actually developing lung cancer initiating lung cancer and lung cancer progression after surgical resection.

So and we think the background inflammation that chip causes is central to those two processes. And we're trying to work out what those are. Now we've got some clues from our air pollution work that we started about five years ago just before Covid.

Air pollution has long been known to be a risk factor for lung cancer, but people didn't know why. We found that air pollutants cause interleukin one beta release, and the interleukin one beta collaborates with mutations in those epithelial cells to trigger, we think, early tumor initiation.

Now, there is good evidence for this actually from a trial with an anti one beta drug called Cantos, I should say a conflict of interest. I've recently been appointed a non-executive director of Novartis.

The drug is from Novartis, so please bear that in mind. Notwithstanding that we did this work before I was appointed and what we found is from our in vitro work and our animal work that I one beta was important in in tumor radiation, and that was very familiar in the context of the Cantos trial that used an anti one beta drug in the context of cardiovascular risk prevention, which met its primary endpoint.

But in that trial, they also showed that anti one beta led to a dose dependent reduction in new lung cancer primaries during the course of the five years of the study, to the extent where there was a 67% reduction in new lung cancers at the highest dose.

Inflammation, Aging, and Cancer Initiation

I mean, really a phenomenal result, and one we're very interested in teasing apart and potentially trying to mimic in further further studies with potentially new drugs to limit inflammation as we age to prevent cardiovascular disease and lung cancer.

And these are the reasons I believe they looked at repurposed drugs like aspirin, Celebrex to help to and they've seen impact utilizing those repurposed drugs.

Yeah, yeah. In this case, you know, the problem with the term anti-inflammatory is anti-inflammatory. And inflammation covers a multitude of biological processes.

There are a myriad of different inflammatory mechanisms. And there's not going to just be one that is that is collaborating with those mutated epithelial cells to induce cancer.

They're going to be several and they're going to be different across tissues. I would believe this is one particular target, however, that's common to more than one age related pathology.

I one beta triggers both cardiovascular disease we think and lung cancer. And so there's a tantalizing potential that you could reduce the risks of two separate age related pathologies by blocking one inflammatory pathway, which is tremendously exciting.

Yeah. If you look at cardiovascular and cancer, you get number one. And number two in cost of death right there. The impact is going to be huge. Exactly.

And that's what we're going to spend the next ten years working on. That's phenomenal. And so you're talking about what do you say is 67%. Did I hear you right. Yeah.

67% reduction in the trial. And now the bear in mind, this wasn't a pre-specified endpoint. It was an analysis that occurred after the study. It was mandated by the FDA because the FDA were concerned there might be more cancers.

And in this study, they showed that 67% reduction in the number of new lung cancer primaries at the highest dose of anti one beta. And it was dose dependent.

And I would assume that I know you're focusing on on online, but I am that this translates over to other types of cancers as well. That's a that's a big question.

Lung cancer is obviously the most one of the most prevalent cancers. So they had the greatest power to address that in lung cancer. But there were also hints in other cancers too.

Yeah. Okay. And you're also talking one of the challenges with and monitoring as as the limitations. It's only so many times you can do a scan, so much die you can put into a body.

And so there's that limitation then to look and see what what's truly going on. And here you brought in then being able to monitor it then utilizing then then blood testing.

You mentioning circulating tumor DNA can can you talk a little bit about how we can understand utilizing that technology, what's going on with with the cancer.

So yeah, good question. One of the big problems with cycling is as you know, it's like looking for a needle in a haystack. The amount of time in blood after a surgical procedure is very, very low indeed and sometimes undetectable in patients who've had successful surgery.

But we learned from my hematology colleagues that minimal residual disease or molecular residuals, residual disease is extremely important determinant of outcome.

And we spent ten years studying this now in lung cancer and tracer X through various industry partnerships. And we've got very good evidence now that if you have CT DNA in your blood, that is DNA derived from the tumor.

And we know that because we're looking for the same mutations in the in the blood that are present in the tumor that's been resected, if you have a detectable from the tumor in the blood six weeks after surgery, the chance of your tumor coming back without any further treatment are very high indeed, well above 90%.

And that's that looks like it's the same. Actually, it's a possibly bit of an exaggeration, but well above 85%. It's very high. And, that we're learning that's very similar across other tumor types as well.

Circulating Tumor DNA and MRD Monitoring

And in other words, the positive predictive value for relapse in untreated patients in the adjuvant setting, if you've gotten DNA in your blood six weeks after surgical resection, is is very high indeed.

So that gives you an opportunity to then offer therapy or escalate adjuvant therapies, to try to clear the ctDNA and to try to reduce it to undetectable levels.

And I think it stands to reason from first principles that eradication of disease is going to be a lot easier, or at least more feasible, I should say, when the burden of disease that is the burden of genetic diversity, which correlates

with the burden of disease, is at its lowest point, and that's going to be immediately post-surgery.

And so there is this tantalizing opportunity now where we could start to think about bringing late phase trials into the very early phase setting and using MRD as a response biomarker, much like we use CT imaging in the late phase setting to be able to monitor response and benefit from treatment, and hopefully find the right drug for the right patient at the right time to eradicate their disease, if that makes sense.

Absolutely. And, you know, like you mentioned, I mean, the less diversity. So the less tumor burden you have, the more impactful, I would believe, you know, something like chemo or whatever therapy that is appropriate for that individual would have because there is less escape mechanism, sort of say that that's available.

Yeah. Yeah, yeah, I think that's right. I'm my assumption and I think this is yet. Well actually it is already proven that you can cure patients in the adjuvant setting and you can rarely cure patients in the metastatic setting.

So we know that adjuvant chemotherapy, which rarely ever cures patients in the static setting, is associated with somewhere between a four and 12% overall survival benefit in the annual setting.

So that tells you that you can cure relapsing early relapsing metastatic disease before it's detectable on a CT scan that you can't do once you've got macroscopic evidence of disease on a CT scan.

And I think that's a crucial and very important observation and really has motivated us to develop these technologies because of that opportunity. Now, in line with that, we we found consistent with this in our last paper in this area late last year, late 2025, in cell, James Black and colleagues, we showed that if patients after surgery who get adjuvant chemotherapy have a low level of circling tumor DNA below a threshold of 80 parts per million, but half of those patients find we can eradicate down to undetectable levels CTD and a with adjuvant therapy.

And those patients, if we eradicate the soap carrying human DNA to undetectable levels, those patients have not yet relapsed. Now, in contrast, if you have a burden of ctDNA above 80 parts per million, we haven't yet found an example of a patient whose ctDNA is eradicated by chemotherapy.

And I think that tells you that potentially the ones we're curing are the patients who have very low levels of circulating tumor DNA from therapy, and the numbers are small.

And we've got to we've got a bottom that out in our subsequent tracer studies. But that's what it's looking like. And so a lot of times when a person is dealing with metastatic where you have kind of the initial tumor and to now the locations, surgeons are very hesitant.

And then doing surgery at that time. Yeah. So is there with with what you're saying. Then if we are able to do surgery in some fashion to reduce the tumor burden and then bring in the adjuvant type of chemotherapy, obviously if the CT DNA is low enough, would that be a strategy to be considered?

It's a it's an excellent question. And I think there are a few things I'd like to say about that question.

Metastatic Disease and Aggressive Local Treatment

Traditionally in my medical oncology training, the the mantra is that operating on metastatic disease is relatively futile. And where where it's been tested, it hasn't proven of immense value.

But I think the reality is the answer is much more nuanced than that, particularly in the modern era of early detection. Only detection of recurrence, lower volume disease, metastatic recurrence, newer therapies, newer targeted therapies, but also new radiation approaches with stereotactic therapies which have very limited toxicity to normal tissue and are very, very accurate in being able to abate deep seated metastases.

And I think those opportunities together have changed the landscape of how we manage metastatic disease. So that's the clinical perspective. The scientific one is as interesting.

I think we've recently published data from our tracer program that was integrated with our autopsy program called piece. And in that study, we showed very clearly in lung cancer that the majority of metastases seed other metastases.

In other words the metastases begin to behave like new primaries, new primary tumors seeding metastases. And so again, it is logical to consider that if a patient has limited number of metastatic sites, it would make sense to treat them as aggressively as possible to stop them seeding other metastatic size.

And there there are, you know, increasing number of studies that are looking at this, actually with some very tantalizing data that suggests that is the case, that operating or ablated or treating aggressively metastatic disease improves outcome.

It's early days, but it's certainly anecdotally something we see quite a lot, particularly in, in in oncogene driven lung cancers that have been successfully treated with drugs like automotive, for example, we see these patients acquire resistant disease.

Maybe only one site two is after siting treatment. And what we often do is oblate that site with with stereotactic radiotherapy or surgery and put them back on drug treatment.

And they're fine for another year or so until maybe they develop another metastasis which we ablaze. And the cycle continues. And we have many patients who've been on treatment with surgical procedures or radiation approaches for for, which seems to be holding the disease at bay.

And of course, that's not a randomized study, and it's very anecdotal, but my bet is had we left those metastases, they would have seeded other metastases.

And over time we would have lost tumor control that we didn't lose. In the context of of this approach of aggressive metastatic management. So so centrally, if you can control the the situation because you have or we're talking about the the evolution of the cancer in regards to selectivity, the their their kind of genetic makeup that makes them resistance to treatment.

And the further you allow that to take place and more seeding in different areas, you're creating more diversity that's harder to treat. So if you can kind of hit it harder sooner, it is less likely to be like this wildfire that just goes out of control.

That's right. I think that's basically it in a nutshell. Yeah. Okay. And and you're also so one of the issues is also early detection. And you touched on that.

So with the circulating tumor DNA I mean you need to have a biopsy to be able to match that as that's that's correct. Right. Yeah. That's correct. Yeah.

And so how so you can't really use that technology in or you can't, you know, that's exactly spot on. You can't use a tumor informed approach to detect a tumor that you haven't yet detected.

Because you need to know what the tumor mutations are to create a barcode. If you like to detect the tumor in the blood, you need other approaches that are tumor agnostic to, to detect cancers in asymptomatic individuals.

Grail Screening and Detecting Aggressive Cancers

And there are various companies that are developing those tumor agnostic approaches, including Grail, that that rely on methylation marks from normal tissue and tumor to detect emergent tumors in a patient's body.

And with Grail, the challenges are if it's a tumor that is a slow growing kind of one of these little puttering, maybe prostate or breast, you know, it is not as easily detectable.

Yeah. But those exactly the tumor types which overdiagnosis is a problem you'll recall is the tumor. These are the tumors where DCIs and and low grade low Gleason score prostate cancers never result in mortality.

That that that the whole arguments are screening is troublesome for because you're over diagnosing tumors that will never cause trouble in the patient.

I think one of the things I'm more enthusiastic about the Grail assay is that it detects aggressive tumors that really, really need to be managed urgently through surgical resection and chemotherapy or adjuvant adjuvant approaches.

And from your understanding, I mean, because it's always obviously Grail then as a, as an expense for the individual, for the patient. But it is a phenomenal way of, of screening these aggressive tumors that you you really need to kind of step in quickly to, to address.

So should it be a yearly should it be a biannual? I mean, what would be kind of an appropriate Tatton for an individual that is concerned? So first of all, I probably should declare my conflicts of interest here if they're not on the preamble.

But I sit on the Grail. SAB I was chief investigator for the NHS gallery randomized 142,000 patients study investigating the grill assay. So I've worked on this essay for a time, and I think that's important.

And we use Grail at our center. Yeah. Because I think it's a nominal test. So I would have conflict of interest as well. So the question is for people that are concerned and and since we're dealing with one of the leading causes of death, cancer, and we are screening some of the most aggressive type of cancer utilizing technology like Grail.

What would be an appropriate pattern frequency of testing for an individual? Yes. And this is a very good question. And I think I talk as a scientist, not as a Grail SAB member here.

But I think one of the things I've been shocked by looking at the data and thinking about the disease and thinking about the whole screening paradigm, is that the most aggressive cancers have relatively short dwell time.

So that is, they take a relatively short period from inception to metastatic disease. And that means that the window of opportunity for detection is relatively short, too.

That is, detection and cure is shorter than I'd imagined. And I don't know what the right answer is to your question, but I think there is a good case for asking would we be better doing the Grail test every six months or every year?

And I don't know the answer to that, but I think it's it's a it's an important question. And I think it's important because the time it takes for aggressive tumors to migrate from stage 1 to 2 to 3 to 4 is shorter than I thought it would be when we first set this trial up five years ago.

Yeah, and that's a scary part. And it seems to be I had cancer patients. They come with a colorectal, and all of a sudden it's in the liver. And all of a sudden it's I mean, it just kind of moves quickly or pancreatic you can have within three months.

You know the individual may be, you know, failing treatment. So exactly. Yeah it's scary. Well, Professor Swanton, this this is phenomenal. You're doing incredible work and this is so groundbreaking what you're doing.

And I really appreciate you taking the time to explain this for our audience. So thank you so much. Thank you so much. Love to meet you. Thank you I do appreciate it. Pleasure. Thank you. Thank you. Bye