Course Name: I Think Biology

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Department Name: Biology

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Week:4

Lecture:23

W4L23_Discussion on Cancer Biology

Good morning. This is part of the NPTEL course. Today we have Professor Ramray Bhat from IISc. He's a professor at IISc working on morphogenetics and also cancer biology.

Professor Ramray, welcome to the course. So I want to kind of start with you know your research. So could you tell us a little bit about what you work on? This is for the undergrad students. So maybe in a slightly simpler, broader terms, what you work on.

Sure, So my background is that of a developmental biologist. I was trained as a developmental biologist. So I bring the principles of development to try and understand how cancer starts in our bodies and how it spreads. What we try to do is we try to recreate the anatomy within our bodies in a laboratory setting where we can study it in real-time and in an imaging-tractable manner, which means we can study it under a microscope and we can actually see how cancer spreads by recreating the anatomy under a microscope. So this allows us to therefore understand and measure parameters like how fast does cancer spread. Why does it spread in a particular manner in an individual? Why does it spread faster in one individual as opposed to another? So these are the kind of questions that we ask in the context of cancers that commonly occur in women, breast and ovarian.

Ovarian, of course, exclusively in women and breast, which is predominantly occurs in women. So these are the two cancers that we look at. We ask why does it spread to certain organs in our body. Why does it not spread to other organs? That's fascinating. So you use certain model systems or do you use mice models or do you use cell lines or can you talk a little bit about that? Yes, We use plethora of model systems because the question that we ask determines which model would allow us better to answer that question or tackle that question. So we use cell lines.

We also use, which are human cell lines, we also we use mice in order to or we use what are called ex vivo models where we take out certain parts of the mice and put it under the microscope and then we build cancer within such portions where we can study it because looking deep within a mouse over long periods of time is not possible. We also work with patient samples. So we have collaborations with clinicians in hospitals who are able to

give us live tumor samples that we can then use to also try and ask more translational questions and also look at sort of more personalized investigations. Getting back to the question of why certain therapies work in some individuals, why does cancer spread faster in some individuals allows us to therefore look at inter-individual variations by looking at patient samples. So we work across all these different different aspects.

We also work with what is known as organoids or tumoroids which are again three-dimensionally reconstructed portions of these cells that we can use either from cell lines or from mice or from humans because okay when you are able to again replicate the three-dimensionality of these structures, again in an imaging tractable manner, it allows us to capture dynamics which one would not be able to capture otherwise. So these are the systems we use. So I had one question. I mean this is, I'm sure many people would have asked you this. What are some of the you know challenges in cancer research and certain things which we have made progress because it's such a tough disease and so many people have been working on it for so long.

Certain challenges and also certain things, breakthroughs which science has passed. There has been a lot of effort, a lot of resources that have gone into cancer research, cancer biology research from a very long time because it's a very difficult disease. I think one of the realizations that people have made, by saying people I mean the community that encompasses clinicians, clinician researchers as well as fundamental cancer biologists has been that each cancer is its own beast. What is discovered in one cancer does not necessarily translate immediately into the same kind of breakthrough in another cancer. okay. The molecular details, the cellular details as well as the systemic manifestations of each cancer is different, which is not surprising for clinicians because for clinicians even breast cancer in one individual can be markedly different from breast cancer in another individual.

So the pathology or the histology? It's very different. The histological signatures can be different. The molecular signatures can be different. That has been the bane of the research in the sense that there is so much variation that is thrown in this particular affliction that it becomes very difficult to make generalized statements and generalized principles are hard to find when it comes to cancers. In terms of breakthrough, what has really happened is this probably you know jumping on from that problem, that limitation of inter-individual variation, scientists have come to embrace what is then, therefore, can be called personalized precision medicine where one develops therapies that can be tailor-made for as per individual and that has led to discoveries that show that for some patients, for example in breast cancer, who have a type of breast cancer that is for instance driven by hormones, one can therefore use antagonists or inhibitors of those hormone functions to then target the cancer and break it down.

For others, there have been discoveries of certain special receptors that would be present in these types of breast cancer that can again where you can develop antibodies or other agents that can target those specific receptors and hence allow us to catch those cancer cells within a milieu of non-cancerous cells and therefore again take down those cells. But one therefore also needs to understand that there is a sizable population which for

example will not have hormone-driven or one of those receptor-positive cancers and in those cases we have to resort to harsh chemotherapeutic regimen and so on. So the other sort of problem that is harm-strung cancer research has been the fact that the agents or the chemotherapeutic drugs that are available, the number of those drugs and their efficacy has not really increased over time as much as we would have liked to and hence the breakthroughs that need to come now need to come increasingly towards developing new therapies that would be able to kill cancer cells in a more focused manner with as little side effects as possible. So there is a saturation point where the drugs are not newer drugs because they are only targeting either surface proteins or whatever. Yes, yes, yes.

Are they newer drugs in what sense? Like how do you envision a new drug to be more effective? Right, I think you know we've really hit saturation point when it comes to newer and newer drugs. I think what we probably need to move towards and I'm not an expert on cancer therapy but what I know from discussions with my clinician colleagues and so on is that newer combinations of drugs with newer combination modalities need to come in in order to be able to be given in a manner such that their side effects on other cells within the body is as minimal as possible. Also, these drugs need to reach the cancer cells in a way that allows them better access to these cancer cells. And that is one problem which is the problem of what we call the tumor microenvironment. The fact that the tumors are not just made of cancer cells, they are also made of a lot of acellular matter that surrounds these cells and that often is responsible for impeding access of these drugs or various localisation agents to the cancer cells.

When we are able to better understand the pathology of this microenvironment, we can then develop modalities that can crack through these environments and reach the cells, reach the right kind of cells, and then take them out. It's quite lengthy. I mean, it's very challenging and it's laborious and it needs collaboration between clinicians, researchers, doctors and different modalities. Yes, It does.

It does. In Fact we've increasingly moved to understand that the teams that are required to tackle cancer need to accommodate not just clinicians and fundamental cancer cell biologists and molecular biologists but has to bring in chemists, engineers, physicists. So as a researcher who is entrenched in interdisciplinary research, I speak with active matter physicists, I speak with mechanical engineers who bring in expertise in microfluidics, I speak with mathematicians who can model tumor populations and I speak with, of course, gynecological oncologists who are able to come together and bring all their expertise in terms of trying to understand and tackle cancer. Really, it's really nice to know about this. I think there's no other alternative. Yeah correct We need to do this now.

There's no other alternative. We need to break the silos and think together on problems that interest us. Yeah. Actually, I mean, all research is moving that way, right? It's all interdisciplinary and there is a merit to it.

I agree. I agree. I think the boundaries are breaking down and I think it's true for any discipline now that increasingly one needs to have a breadth of expertise looking on a single problem and the solution to that comes out earlier. Thinking about the Indian

scenario, so is there certain cancers which are more prevalent in the Indian population than others? And also adding on to that, has there been any like you know lifestyle changes in Indians which are kind of causing? I mean Is it too early to say that or can you even say that, okay, there are certain lifestyles which facilitate or which are leading to certain types of cancers? Right.

I don't think that India stands out. Again, I'm not a cancer epidemiologist, but from whatever data I have seen, I've not seen India or the Indian populations to be very drastically different in terms of the kind of cancers that afflict the Indian population as opposed to, say, the South Asian population, which I would consider to be a more accurate population to look at or you know how to put it the populations that encompass south of the Tropic of Cancer. In the sense that these populations, I think the association with cancer with, say, a lifestyle is something that would affect societies at similar socioeconomic conditions. So it would be true of sort of populations in South America and so on.

In India, of course, there are subtle variations. There's no question about that. There are subtle differences that we know that are there in terms of how, for instance, cancers are found or the incidence of cancer occurs in the Indian population as opposed to, say, the West. There are some kinds of breast cancers that occur to a greater degree in the Indian population. Again, but one needs to look at this more carefully, say, within the Indian population, because given that the Indian population consists of different ethnicities, whether there's a greater affliction, some are more prone and some are less prone.

But in terms of, you know, if you think about lifestyle changes, you know going back, say, 50 or 100 years back versus now, around the world, can there any kind of correlations be made? you know? Yes, yes. So cancer for the longest period of time has been thought, has been understood to be a disease that has very strong associations with lifestyle. And for example, the association of smoking with lung cancer and so on are well established now. And the cell biological understanding of how these lifestyle changes affect cancer and make things worse is pretty well known. The effect of diet, for instance, on colorectal cancer.

The lifestyle, you know, as populations move into higher economic brackets, lifestyle changes are inevitable as populations migrate from rural to urban settings. Lifestyle changes are inevitable as we embrace technology around us with all its good things as well as its ill things. We are, you know, we are dealing with plastics, we are dealing with microplastics, we are dealing with chemicals within things that we use, which are hormone mimetics, for example. correct yeah. All of these have, and of course with pollution at unprecedented levels, global warming, all of these play a role. In addition, of course, we are afflicted with an increasing number of non-communicable diseases, chronic diseases such as diabetes, hypertension, cardiovascular diseases.

The association of these diseases with cancer is something that is increasingly being looked at and epidemiological studies are implicating that, you know, comorbidities make cancer incidence and cancer progression far worse. We also are now confronted with an

increasingly aged population. And again, the link between aging and cancer is something that is well-established. So there's a little doubt in my mind that the lifestyle changes that have occurred for the worse within our populations, within South Asian populations are playing a deep role in the way we are finding more and more cancers in our households. Of course, a big role also has come, has been the advancement in social medicine and in our abilities to also surveil our populations better in order to catch cancer earlier, which would have gone unnoticed, especially in semi-urban and rural populations.

We have improved our surveillance and social medicine infrastructure. Yeah And that is also leading to an increase in our finding of incidence of cancer. Correct correct. But the fact that things have gotten worse, there's no doubt about that. I mean, I wonder whether we, I mean, having known this, because probably the West has already kind of gone through this and, you know, we are in some ways, we are I mean, yes, a lot of rural population is moving to the urban areas and we are seeing the implications of it. And I wonder whether we can kind of say that, Ok, like it's advisable not to do these kinds of things or it's advisable to do certain things much more than others.

So I don't know whether that's I am sure it's not easy to say those kinds of things. But has there any attempts being kind of. Yes, so in the sense that, you know, at least I think the kind of what so if we think of some cancers as having very, very clear links with lifestyle changes or habits, such as say, with lung cancer and smoking yeah and with oral cancer and tobacco chewing, yeah I think, you know, some of these cancers are preventable yeah that's true, in the sense that we can we can at least decrease the preponderance, not that, you know, somebody who doesn't chew tobacco doesn't get oral cancer. That happens. But the associations are pretty strong.

So some of these cancers, one can decrease the burden by having better, you know, better tools to be able to communicate these messages. And it is being done. You know, our governments have since quite some time been aware of these things, both, of course, governments in the West as well as governments out here in South Asia. However, yes, the communication probably can be enhanced and I'm sure can be improved. And then the burden of cancer burden, at least for some cancers, we would be able to be in a better position to handle that.

OK, I want to move away from actually talking about cancer. now but I want to kind of tell the students about you have a unique background where you have done an MBBS and you have done a PhD. So I want to kind of ask you, what are the advantages of having these two very unique degrees and how do you leverage that in your own work? Sure. I would say there are advantages and disadvantages, which I have at least understood, you know, since having spent some time first, of course, in the clinic and then in research. The advantages are that the depth in human biology that one acquires as part of one's medical education, especially in India, where it's, you know, medical education is taken very seriously because we are trying to build a caterer of very good clinicians.

So the depth of human biology that one acquires is immense and incredible and helps somebody like myself who has done the MBBS understand diseases at a systemic level

and treat the disease keeping the patient in mind. It helps at that level. The disadvantage, there are disadvantages as well. In our focus, very strong focus on human biology and the human condition, we also get a very anthropocentric view of what one can call pathology, which need not be so, which need not be human pathology. Correct. And so a sense of comparative pathology or comparative biology is something that one loses on. Yeah

One also, and this may be more of a view with medical education in India. One does not get as thorough a grounding in molecular biology as one would have in a non-medical undergraduate degree in biology. And so I have personally, of course, felt this deficiency and sought to mitigate that in various ways. But so that therefore there are advantages and disadvantages. However, I would definitely wish that there are more sort of clinician researchers or researchers who have taken this particular route through their undergraduate education to have entered biology.

That's great to know. I had one more question. This is again with respect to the undergrads. I mean, what would your advice be for the new undergrads who are listening to you and you know who are curious about biology and want to kind of pursue? And also, actually, this course will be taken by non-biologists as well, who are curious to learn more about biology. Right. My only message or take-home message yes for anybody who is interested in biology at the undergraduate level, my suggestion would be that biology increasingly is getting less narrative and increasingly more analytic in terms of, again, an interdisciplinary focus needs to be brought in into the study of biology at the very early level. So I think it's inevitable that one needs tools and concepts from the physical sciences, from physics, chemistry, mathematics, engineering to understand and tackle biology, also to understand biology at a very deep level.

And so it is important therefore that when one takes on biology at one's undergraduate level, she should not shun the physical sciences, but rather embrace it and therefore develop a more holistic view of sciences rather than even break it down into natural and physical sciences. There's much to be learned from all disciplines and getting a holistic sort of understanding of things. Yeah, that was great. I can also add one more thing. yeah even at an undergraduate level, one must therefore also be aware and appreciate and be empathetic to the biology that surrounds us.

I think it's important that we study biology at an undergraduate level, not just to understand the world around us, but also to make the world a better place. So I think some sense of social responsibilities are also important to inculcate right at very early on. Yeah, I totally agree with you. And yeah, I mean, even in our own university, we keep reiterating all the actual facts that things that you mentioned.

With that, I would like to thank you. Thank you so much for talking to us and thanks again. My pleasure and privilege.