The Pezcoller Foundation

Journal

Summary

News from the
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We have the great privilege to host in these pages the text of the last Korsmeyer Lecture by the prestigious winner of the 2014 Pezcoller Foundation-AACR International Award for Cancer Research dr. Elaine Fuchs, investigator Howard Hughes Medical Institute, Rebecca C. Lancefield Professor of the Laboratory of Mammalian Cell Biology and Development, The Rockefeller University, New York. Prof. Fuchs gave the lecture entitled "Stem Cells in Silence, Action and Cancer" at VIMM Venetian Institute of Molecular Medicine in Padua on May 7, two days before the Award Ceremony at the Buon Consiglio Castle in Trento and we express our gratitude for giving us the opportunity to publish it.

Please note that the annual Stanley J. Korsmeyer Lectureship has been started by the Pezcoller Foundation in 2006 in accordance with the AACR American Association for Cancer Research and the VIMM Venetian Institute of Molecular Medicine in Padua. The goal of this event is to honor the fundamental contribution of the late S. Korsmeyer who was the recipient of the Pezcoller Foundation-AACR International Award for Cancer Research in 2004. Although under heavy treatment for cancer, he presented his last European lecture at VIMM immediately before receiving the Pezcoller Award. Unluckily he passed away a few months later. Therefore we wish to remember Stanley Korsmeyer every year with a lecture given by the recipient of this Award.

The 2014 Pezcoller Symposium entitled "Cancers driven by Hormones" took place in Trento last June with a large participation of researchers under the leadership of Drs. David Livingston (Dana Farber Cancer Institute, Boston); Myles Brown (Dana Farber Cancer Institute, Boston); Arul Chinnaiyan (Michigan Center for Translational Pathology, Ann Arbor, MI); Antonella Farsetti (CNR, Rome Italy and Ist. Naz.Tumori, Regina Elena, Rome, Italy); Massimo Loda (Harvard Medical School, Boston); Roland Schuele (University of Freiburg Medical Center, Germany) and the support of Dr. Enrico Mihich (Dana Farber Cancer Institute, Boston). During the session we gave the "Pezcoller Begnudelli Awards" for the best posters to Giulia Piaggio, Institute Regina Elena, Roma, Italy; to Chiara Bellio, University of Padova Italy and to Wilbert Zwart The Netherlands Cancer Institute.

We are also glad to present the next 27th Pezcoller Symposium which will be held in Trento on June 18-20, 2015 and will be entitled "CHALLENGING ROADBLOCKS TO CANCER CURES."

Next September 2015 in Rovereto, we will give the Pezcoller Foundation-ECCO Recognition for Contribution to Oncology (€ 30.000,00) to a single individual for his/her professional life dedication to the improvement of cancer treatment, care and research. You will find the Call for Nomination in the next pages.

Gios Bernardi M.D.
Editor and Pezcoller Foundation President Emeritus

The winners of "2014 Pezcoller Beniudelli Awards" for the best posters.
Chiara Bellio, Department of Surgery, Oncology and Gastroenterology, University of Padova
Giulia Piaggio, Experimental Oncology Area, National Cancer Institute Regina Elena, Rome
Davide Bassi, President of the Pezcoller Foundation
Wilbert Zwart, The Netherlands Cancer Institute, Amsterdam

The S. Korsmeyer memorial lecture

by Elaine Fuchs

The following text has been fully reported by the recorded speech, with the consent of the author.

What a wonderful honor it is to thank the Pezcoller Foundation as well and the University of Padua and the Institute here for holding this lecture. It's particularly moving for me as well to deliver this lecture named after Stan Korsmeyer, one of the world's foremost cancer biologists, who delivered his last lecture here in Padua before his death due to cancer. My very first MD/PhD student, Anthony Letai, currently an Associate Professor at Harvard, received his post-doctoral training with Stan. One of my post-doctoral fellows, Sandra Zinkel, now on the faculty at Vanderbilt University, also transitioned to Stan's laboratory. I've always held a very high regard for Stan's research over the years, and I always encouraged my own students and fellow workers to consider Stan's laboratory for their advanced training. Thus, it is a moving experience for me to be able to deliver this lecture today in such a great institution, with such a rich history of science and medicine. This is my first opportunity to be in Padua, and although I have a number of faculty friends here, it is my first opportunity to interact with students and post-docs here at this wonderful University. Today, I will tell you a little bit about the work that my laboratory has been doing, largely since moving to Rockefeller University. I'm now reaching, my twelfth year since moving from the University of Chicago back in 2002.

Let me begin by giving you a brief introduction to stem-cell research on adult tissues. In the late 1800's, researchers began to use the term 'stem cells,' but at this time, it referred to the early germ cells, from which all the tissues and organs of our body are derived. In the early 1900s, the notion that stem cells exist in adult tissues first emerged. This came from the work of Alexander Maximov, who was a Russian scientist. He was a cytologist. He fled the Russian Revolution in the early 1900s to join the ranks of the University of Chicago, where he was studying the hematopoietic lineages. And what he noticed just by simple observation of the cells is that the cells appeared to be arising from a common lineage origin and predicted then that all the different immune cells come from a common progenitor cell existing within the bone marrow.

It wasn't until another sixty years later that experimental proof of the existence of stem cells in adult tissues came on the scene. And this came from the work of Till and McCollough in Canada. Back then they took a laboratory mouse, irradiated its bone marrow and then supplemented it with individual cells that were derived from a healthy bone marrow. They discovered individual cells that could be introduced into the irradiated mouse and reconstitute the entire hematopoietic system. And so it was at that point that it was realized that in fact stem cells do exist in adult tissues. And in fact we now know that virtually every tissue of the adult has a source of stem cells that can replenish the tissue cells that die from daily "wear and tear" or that are lose during injury.

It wasn't until another fifteen years later that the first stem cells were cultured and passaged long term without losing their

stemness. And this came from the pioneering work of Howard Green, who was then at the Massachusetts Institute of Technology in Boston. I was a student at the time at Princeton University, and when I heard a lecture by Howard Green, I was absolutely captivated by the fact that it is possible to isolate human cells from the skin, and culture them under conditions where they can grow and divide. Shortly after I began as a faculty member at the University of Chicago, my own students were generating 3-dimensional tissue cultures, which essentially recapitulated the epidermis from scratch in a Petri dish.
Howard Green went on to apply his culture methods for the treatment of burn patients. He and his coworkers took a small piece of the patient's good skin, expanded the cells in culture and then grafted them onto the burned area. Many burn trauma units now have tissue culture labs associated with them. Moreover, some thirty years later, the skin of these patients never showed signs of cancer or other abnormalities. This suggests that if cultured correctly, human tissue cells can be passaged in vitro for extended periods of time, without losing their stemness and also without their acquiring mutations that would lead to deleterious effects if used for regenerative medicine.
Howard Green's technology also formed the foundations for the successful culturing of embryonic stem cells. By adapting the use of fibroblast fetal layer, which was the key to growing epidermal cells in the laboratory, researchers could soon culture embryonic stem cells, opening up the door of stem cell technology as we know it today.
Another variation on this theme comes from one of your Italian colleagues down in Rome. Like me, Michele De Luca was a former post-doctoral fellow of Howard Green's laboratory. He took stem cells from a healthy eye of patients whose cornea of the other eye had been damaged irreversibly from an industrial accident. Images showing the blind eye before and after stem cell therapy are truly remarkable, illustrating a correction not only in appearance but also in vision. Some ten years later, a hundred patients treated with this type of therapy were still able to see from what once a blinded eye.
These are very good long-standing examples of the use of stem cells in a clinical setting. With ever advancing technologies, there will surely be more such examples in the future. This future success of stem cells in regenerative medicine is predicated on advances in our basic understanding of the properties of stem cells and learning what controls their behavior. My own laboratory has spent most of our time trying to understand the basic biology of stem cells, how these stem cells self-renew, do so long term, how they are able to differentiate to make tissues and how they differentiate to make different types of tissues.
Collectively, we and others in the field who study adult stem cells have learned that tissue stem cells reside in niches. And this is true whether we look at the hair follicle, at the intestine or at the hematopoietic system. And they also typically reside in two distinct states, a more quiescent stem cell state and a primed or activated stem cell state. The decision of a stem cell as to whether it is going to be quiescent or whether it's going to be activated and make tissue depends on the nature of the niche signals. When the inhibitory cues override the activating cues, the stem cells rest and do not make tissue; when enough activating signals accumulate in the vicinity, this tips the balance, mobilizing quiescent stem cells to become activated and enter the tissue-generating mode. As they do so, they generate short-lived progenitors. We sometimes refer to these cells as transit-amplifying cells. These progenitors progress to differentiate and make the bulk of the tissue. Thus, much of the tissue-generating capacity does not come from the stem cells but rather the short-lived progenitors that divide only briefly and then differentiate.
How often stem cells are active and for how long depends upon the various needs of the tissue. For example, the epidermis which is constantly turning over, or the intestine which is constantly turning over, have stem cells that spend most of their time in an active state. For tissues that undergo bouts of stem cell activity, for example lactation as in the mammary gland or the hair follicle through its cyclical spurts of hair growth, stem cells spend much of their time in a resting stage.
My laboratory has been interested in the stem cells of the skin and particularly of the hair follicle. As long as you are going to be a basic scientist and study basic biology, why not study something that is beautiful and interesting. Clearly nature has had a lot more fun and fancy in creating body surfaces than she had in creating any of the ugly organs

that people typically use as model systems for study!

But there is another reason for studying the hair follicle, and specifically the hair follicle of laboratory mouse. The mouse spends a great deal of its time making its fur coat, and with each hair follicle harboring a niche of stem cells, this means that there are a lot of hair follicle stem cells in the mouse. In addition, these hair follicles and their stem cells go through synchronized, cyclical bouts of activity. So, if you want to understand how stem cells go from a non tissue- generating mode to a generating mode, then the hair follicle turns out to be a wonderful system to study. And in fact we now know that stem cells spend much of their time at rest. During this time, the niche is abutted next to a small cluster of specialized mesenchymal cells called the dermal papillae. While the stem cells begin in a niche of inhibitory cues, the dermal papillae send out activating cues, which accumulate until eventually, a new hair cycle begins. At this time, we start to see the new hair follicle emerging from the base of the stem cell niche. They rapidly produce transit-amplifying cells, which produce the new follicle. In the mature state, the short-lived cells maintain contact with the dermal papillae at the base and the hair begins to grow. Eventually, a destructive phase ensues and the hair follicle returns to the resting phase, as the dermal papillae return to the bottom of the stem cell niche.

The resting phase gets longer as we age and we now understand many of the principles that underlie the molecular mechanisms of how these stem cells behave as they transition from a resting stage to a tissue-generating mode. The hair follicle has proven to be a good model system for understanding these basic molecular principles. To be able to purify and characterize these stem cells in more detail, some years ago, we made a transgenic mouse that allowed us to fluorescently tag the stem cells. We took advantage of this long period of quiescent time and we simply made a mouse where we could regulate the expression of a fluorescently tagged histone under the control of a tetracycline promoter. This allowed us to label all the stem cells of the skin and hair in green fluorescence, and then simply shut the expression of the histone transgene off, by applying tetracycline. Four weeks later the only fluorescent cells remaining bright green were those label-retaining, long-lived cells that infrequently divided. We then purified these cells by FACS, Fluorescence-activated cell sorting, placed the cells in culture, and then simply grafted the cells from a colony (all derived from a single cell parent) onto the back of a laboratory mouse which was hairless. The hairless mouse developed a fluorescently green tuft of hair, epidermis and sebaceous glands. And so, what this tells us is that these label-retaining cells are indeed stem cells, and that when cultured and engrafted, they are able to make three different types of tissue. And another interesting facet that we've learnt about stem cells, and again this is generally applicable to stem cells, is that when you take stem cells out of the context of their niche, they can acquire a broader capacity than what they normally have. Normally, these stem cells will only make hair, but then out of context, when we engraft them, they can also make epidermis and sebaceous glands.

We then purified these cells and transcriptionally profiled them. We compared the stem cell transcripts to their committed progenitors, the transit-amplifying cells. What we have learned is that within the niche, the stem cells express a whole series of transcription factors, not expressed by the short-lived progeny. There are also factors like LGR5 that is a marker also of the intestinal stem cell niche and what we've learned is that when you are looking at the quiescent stem cells, their Wnt and Shh signals are very down and their BMP6 signals and FGF18 signals are high. And these are the signals that have then to be reversed in order to send the stem cells into the active tissue-generating mode. All of the various differentiation lineages are suppressed by the stem cells when they are in their quiescent niche and responding to this inhibitory micro-environment of the resting state.

We next used conditional knockout technology to ablate each of these different transcription factors in the skin epithelium and what we've learned from our studies is that TCF 3 and 4, Lhx2, Sox9 are all required for maintaining the stem cells properties of these hair follicle stem cells. And we learned that if we knock out TCF 3 and 4, the stem cells undergo precocious activation to make a new hair follicle. We learned that if we knock out Beta-catenin, that is the partner of TCF 3 and 4 in response to Wnt signaling, the stem

cells sit there in their niche and maintain all of their stemness characteristics, but now basically they never enter into a new hair cycle. This suggests that the purpose of Wnt/Beta-catenin signaling at the base of the stem cell niche is to relieve the suppressive characteristics of TCF 3 and 4. We then used ChIP-seq analysis and RNA-seq analysis in vivo to analyze chromatin remodeling that takes place during stem cell activation. While TCF 3 and 4 suppress genes required for hair follicle differentiation, Lhx2 on the other hand, suppresses genes for sebaceous gland differentiation. Sox9 suppresses epidermal differentiation.

Additional ChiP-seq analyses revealed that Nfatc1, which is downstream of BMP signaling and calcium signaling, controls the quiescent state of these cells. And in its absence we see that the stem cells undergo constitutive activation. NfiB plays yet again another role in adult hair follicles. This transcription factor regulates the crosstalk between the hair follicle stem cell and the melanocyte stem cells, which are part of the same niche. It's important for melanocyte stem cells to be able to differentiate at the same time as hair follicle stem cells in order for the melanin pigment to be transferred to the differentiating hair cells to provide the hair with pigment. In the absence of NfiB, the crosstalk between these two different types of stem cells is uncoupled. These data give us new insight in understanding how the stem cells are controlled, and what role the transcription factors have in the process.

We are currently studying the collection of these transcription factors, to look at the genes that are co-regulated by these stem cell factors. We hope that this will give us new insight in understanding what controls self-renewal properties of these stem cells and what controls certain essential features of these stem cells, and about the very fundamental nature of stem cells.

Another aspect that we have been learning is that when these stem cells first begin to be activated, they undergo asymmetric cell divisions to generate committed progeny. This is a process that my laboratory has been studying for quite a while, primarily in the embryonic epidermis. And what we showed is that relative to the underlying basement membrane, the mitotic spindle of embryonic epidermal progenitors begin to show a perpendicular arrangement, so that the division leads one daughter cell associated with the basement membrane and the other daughter cell suprabasal to the basement membrane. This sets up a scene that favors different fates for the two daughters.

In the adult hair follicle, perpendicular spindle alignments can also be visualized in the stem cells that are adjacent to the dermal papilla at the start of a new hair cycle. These cells also show signs of nuclear Beta-catenin at this time, suggesting that they are activating the WNT pathway. Interestingly, during their quiescent period, when they are not proliferating, the stem cells are making increasing levels of WNTs, while the dermal papillae cells produce increasing levels of BMP inhibitors, i.e. the two different signaling factors that are necessary to flip the cells from their quiescent state to their active tissue-generating mode.

Most recently, we have been exploring the downstream signals. Once stem cells have been stimulated by WNTs and BMP-inhibitors at the base of the stem cell niche, what happens next? The emerging so-called transit-amplifying cells produce another signal, Sonic Hedgehog, and Shh then feeds back to the quiescent stem cells and appears to instruct them to self-renew, make the outer root sheath of the follicle, and restock the niche. In addition, Shh stimulates dermal papillae cells to produce higher levels of this BMP inhibitor and to start producing FG7 and 10 and together these stimuli result in the expansion of the transit-amplifying pool of cells that fuel hair growth. As the follicle matures and grows downward, the Shh signal moves too far away from the stem cell niche and the stem cell niche returns to the quiescent state.

Typically, we and others in the field have viewed the transit-amplifying population of cells as an obligatory intermediary in the stem cell lineage. The surprise was that it also serves as an important signaling centre, and dictates on the one hand the signal for stem cells to self-renew and on the other hand to fuel tissue production. When you consider the role of stem cells, all stem cells must be able to repair wounds. By having heterologous as well as cell lineage cues to stimulate stem cells, the right amount of transit-amplifying cells can be generated to repair the wound, and then stem cell activity can also be carefully controlled so that tissue growth can be stopped once the wound is closed. There

have to be mechanisms that control both the positive and the negative aspects of stem cells and we've now uncovered some of the signals that do it for the hair follicle.
As we were studying the basic mechanisms of how stem cells go from a non tissue-generating mode to a tissue-generating mode, we began to realize that if we over-activate the stem cells genetically we get mice that are tumor-prone. And if we under-activate the mechanism genetically we get mice that are tumor resistant. This implies that malignant progression involves the hijacking of the basic mechanisms that stem cells use to go from a non tissue-generating to a tissue-generating mode. Every single tissue of our body has to maintain this function in order to be able to repair tissues and replenish the cells that are dying. But when it is hijacked, to over-activate that signal, now we end up with tumor-prone situations.
These observations led us to wonder about the relationship between a cancer stem cell and a normal stem cell. Focusing on squamous-cell carcinomas, we began by fractionating the tumor and tested each population of cells that we isolated to find out which one of them or ones of them are important for tissue generation in this case in malignant tissue generation. We did so for four different genetic backgrounds and at near single cell level, a cell from a complex squamous-cell carcinoma introduced into a host recipient mouse gave rise to a squamous-cell carcinoma that resembled the parent. Such functional studies indicate that the population is highly enriched for so-called cancer stem cells or a tumor-initiating cells.
Transcriptionally, the cancer stem cells shared some commonalities with normal stem cells of the epidermis and hair follicles. What we know as a general feature of stem cells is that they have high levels of integrins. That's true of the cancer stem cells. But they have atypically high levels of Focal Adhesion Kinase and SRC activity downstream from activated integrins. Like normal stem cells, cancer stem cells reside at the epithelial-mesenchymal interface. But now the surrounding stroma is completely different. There are many inflammatory cells that are around, that are in the stroma. The dermal cells are also very different than the dermal cells that were present in the normal stem cell niche. Blood vessels around the tumor are also in a different state. So the entire microenvironment or niche of these stem cells is completely altered over normal stem cells. Not surprisingly, one of the stromal signals is TgfBeta, which generally plays an inhibitory role on epithelial cells. What we showed is that if in fact these cancer stem cells residing at the tumor-stroma interface can respond to TgfBeta, the number of cancer stem cells is low, and the stem cells exist in both primed/quiescent and activated states. However, if we conditionally remove the ability of the stem cells to respond to TgfBeta, by conditionally targeting the TgfBeta2 receptor, now what we find is that the number of stem cells goes up by a factor of 10. Moreover in human squamous-cell carcinomas, a cohort of them show epigenetic silencing of TgfBeta receptor 2, some of them show single mutations in the TgfBeta receptor 1. Thus, our basic science data are not only applicable to human stem cells, but also human cancers. Like normal stem cells, cancer stem cells also have high levels of self-renewing factors, such as Hmga-2 and Bmi1. However, beyond the above similarities, there is very little resemblance to normal epidermal stem cells, or hair follicle stem cells. The cancer stem cells express very high levels of cyclins and Tgf-alfa, an autocrine growth factor. They also show high levels of Epithelial mesenchymal-transition factors, such as the ones that Bob Weinberg has worked on. They show low levels of cadherin and alpha-catenin, which my laboratory conditionally ablated many years ago and showed an association with tumorigenesis. They express high levels of Kras and high levels of VEGF-A.
We are left with hundreds of differences between normal stem cells and the cancer stem cells. Which of these changes are significant for explaining the malignant state? The human cancer genome sequencing project faces similar daunting numbers of genes found mutated in more than one squamous-cell carcinoma from the head and neck. The reasons for studying this particular squamous-cell carcinoma, as opposed, for instance, to the skin squamous-cell carcinoma, is that head and neck cancers are the sixth most common cancer worldwide, there are 600,000 cases per year with 50% mortality rate. This is a very serious cancer, and yet relative to the number of people working on other cancers, this type of cancer is poorly studied.
In comparing our the human head and neck cancer mutations with our cancer stem cell

signature, we are still left with nearly 400 genes that are differentially expressed or mutated in the cancer stem cells relative to the normal progeny, and which have been associated with genetic mutations in humans. In comparing mRNA expression profiles versus Exome or GWAS sequencing, the first includes both genetic and epigenetic changes, while the second only identifies genetic alterations. We know that epigenetic changes play a very important role in cancer, and hence clearly genetic and mRNA analyses are important in considering cancer-related changes that might be significant. The challenge for all is to identify which of this myriad of changes are disease-relevant and which of these are mere bystanders. While conditional targeting on a one-by-one gene basis works very nicely for a few genes, conventional mouse genetics becomes impractical when it comes to exploiting the reams of data now available from genome-wide analyses. We have to change the way in which we approach functional analysis in order to be able to keep up with the genome era.

Two people in my laboratory teamed together to develop a remarkable new strategy that has revolutionized how we do functional studies in mice. The first one is Geulah Livshits who is now in Scot Lowe's laboratory doing her post-doctoral fellowship. She was a graduate student in my lab. And she and Slobodan Beronja, who is now on the faculty at the Fred Hutchison Cancer Center were able to overcome this hurdle. In working with lentiviral RNA technology to knock down genes, we began to realize that lentivirus only enters the first epidermal layer that it sees. Shortly after gastrulation, at nine and a half days of gestation, the surface epithelium exists as one single layer of cells. That layer contains the unspecified progenitors that will give rise to the mammary gland, to the hair follicle, to the epidermis, to the corneal epithelium of the eye, and to the oral epithelium of the head and neck. Thus by administering short-term anesthesia to the mother, we can inject the embryonic sacks where the embryos reside, with high titer lentivirus. The virus enters and stably integrates its DNA into the single-layered surface ectoderm. By letting the embryos develop, we learned that the surface epithelium is very well transduced with the lentiviral delivered DNA, which is then propagated to all the skin epithelial cells as the mice develop. So we can take now advantage of using the general generic promoters of the lentivirus and essentially knock down genes in a matter of one day or two in a way that it took us a matter of years to do. In fact we can knock down many genes in this way. We began to also dissect entire molecular pathways.

We essentially are simply treating the embryo surface as a Petri dish of cells, but these are progenitor cells, unspecified progenitors. And these are now in their native context. We are not taking the cells out of their context and put them into culture, which invariably induces a stress response to the cells. We are not submerging them in serum-containing medium, as growth factors which are generally artificial. We are exposing them to their normal heterologous signals, their normal sub-lineage signals, and their normal systemic signals. And now under the behavior of this context, clonal expansion of these cells is remarkably uniform. And so this now allows us to return to the initial question that we were addressing and that is how do we identify which are the driver genes and which are the bystanders in those big cancer genome sequencing efforts that we are getting.

In the experiment published earlier this year, we prepared a library that contains lentiviruses which harbor shRNAs for ~350 genes that are either mutated in head and neck cancer in humans or altered in our cancer stem cell signature. We then transduced embryos from tumor-prone mice. Relative to adult mice derived from transducing their WT littermate embryos with this library, and relative to the tumor-prone mice that did not receive the library, the tumor-prone mice that received the library began to develop skin, mammary and head and neck squamous cell carcinomas. After excising the tumors, we then determined which shRNAs were being selected for in the tumors.

Unexpectedly, Myh9, encoding myosin IIa, was at the top of our list in this tumor-suppressor screen. While known tumor suppressors, such as Brca1 and p53, score in this screen, Myh9 had not been a focus in cancer. Yet three different shRNAs targeting Myh9 were found in the tumors, and on their own, each conferred dose dependent oncogenic effects. We made a conditional knockout of Myh9 and showed that on a TGFbetaII receptor-null background, even one single allele loss of Mhy9 confers

tumorgenecity to these animals relative to the controls and the loss of both confers very strong tumorgenecity. Daniel Schramek in my lab has focused on mechanisms, and certainly one is the actomyosin cystoskeleton, which is perturbed by the Mhy9 knockout.
But in addition, Daniel discovered that surprisingly, Myosin-IIa functions in the accumulation of nuclear P53 in response to DNA damage. We traced this defect to a nuclear export problem, and when the export blocker is employed, it can rescue the functionality of p53 on a Myosin IIa null background.
In searching the various different databases from the Human cancer genome sequencing project, we find a small cohort of squamous-cell carcinomas that show strong reduction in Myh9 messenger RNA. Patients whose tumors harbor the least amount of Myosin IIa are associated with the poorest prognosis.
Myh9 is a big gene, and finding genetic alterations in any big gene doesn't necessarily mean that they are functionally important. However, by assigning a functional impact score of where we find the mutations of Myh9 in human cancer patients, and where they reside relative to functional domains of Myosin-IIa, what we find is that a number of these Myh9 mutations cluster in the ATPase domain, or in functional regions of the Myosin-IIa tail. By bioinformatics alone, Myh9 is 16th on the list of the >300 genes mutated in human SCCs.
In addition, weak or no immunostaining for Myosin-IIa are seen in 25-30% human cancers. 5% of patients harbor Myh9 mutations. In cervical squamous-cell carcinomas, 15% of them show mutations in Myh9. 15% of these human cancers show a loss of Myh9 heterozygosity, which could be relevant, given that loss of a single allele of Myh9 has a measurable effect in mice SCCs. Lung and cervical cancers show hemizygosity in 26% of cases. 46% of invasive breast carcinomas show hemizygosity. We don't know if that is relevant yet.
In the past year, we've also carried out a genome wide screen for genes which when dampened in expression confer a growth advantage to the skin epithelium. This work was that of Slobodan Beronja who was then in my group. For this screen, we used 78,000 lentiviruses encompassing the entire mouse genome. At the top of this list was beta-catenin, a well established oncogene in SCC and many other tumors. Three of the top ten were RAS downstream regulators. The list is rich with interesting genes, a number of which have already been implicated as oncongenes in cancers, in squamous-cell carcinomas or in other types of epithelial cancers. And there are many more that we still have to sift through.
So, for young students, and post-docs sitting in the audience I would just say: sometimes when you are focused on your science, it's very hard to see the forest through the trees. You see a lot of trees, but basically sometimes it helps to stand back, take a breath and look at your data again. And also, you should sit around the coffee table once in a while or have a beer with your colleagues. Take a break from your bench work to think about your science. I have many students and postdocs in my group who are from many different countries in Europe. Right now I am missing representation from Italy. If you don't come to my lab, I encourage you to go abroad for a part of your training. The experience will broaden your horizons and impact your science and your development as an independent investigator. I would like to thank again my hosts, both the Pezcoller Foundation and the Institute here for asking me to give this lecture. Thank you.

2015 Pezcoller Symposium

'CHALLENGING ROADBLOCKS TO CANCER CURES'

June 18-20, 2015
Trento, Italy

Its program has been formulated by

Dr. David Livingston
(Dana Farber Cancer Institute, Boston, MA)

Dr. Angelika Amon
(Massachusetts Technology Institute, Cambridge, MA)

Dr. Anne-Lise Børrensen-Dale
(Norwegian Radium Hospital, Oslo, N)

Dr. Massimo Loda
(Dana Farber Cancer Institute, Boston, MA)

Dr. Stefano Piccolo
(University of Padua School of Medicine, I)

Dr. William Sellers
(Novartis Institutes of Bio Medical Research, Cambridge, MA)

With the support of Dr. Henry Mihich
(Dana Farber Cancer Institute, Boston)

Focus of the Symposium: Cancer therapy is a topic of vigorous and increasingly promising research. However, only in rare instances is it curative, especially in advanced cancer. This symposium will focus on why greater success has not occurred and how a group of exceedingly perceptive leaders in the field are attempting to confront this problem. As a major part of the meeting, successful endeavors in major research areas will be discussed in detail.

Goals of the Symposium: This meeting will attempt to illuminate major forces-both known and hypothesized- that block the discovery and development of curative cancer treatment. It will also articulate scientific advances and new areas of research aimed at overcoming these roadblocks. In addition, with significant audience participation, the leading edges of current therapeutics research work will be actively discussed and assessed.

For scientific matters contact dr. David Livingston, David_Livingston@dfci.harvard.edu, for posters and local organizational matters contact the Pezcoller Foundation Pezcoller@pezcoller.it

2015 Pezcoller Foundation-ECCO Recognition for Contribution to Oncology

Award Commitee

The Award Committee is composed of 3 representatives from the Pezcoller Foundation and 3 representatives from the European CanCer Organisation (ECCO).

Those representatives are appointed by their respective Board of Directors and are not eligible for receiving the award.
The ECCO CEO and ESO Director are ex-officio members of the Award Committee.

The Award Committee will convene in April 2015 under the Chairmanship of the ECCO President, Martine Piccart, Institut Bordet, Belgium.

Call for Nominations

ECCO – the European CanCer Organisation and the Pezcoller Foundation are pleased to announce the Call for Nominations for the 2015 Pezcoller Foundation-ECCO Recognition for Contribution to Oncology.

For 2015, in collaboration with ECCO – The European CanCer Organisation, the Pezcoller Foundation-ECCO Recognition for Contribution to Oncology will be awarded to a single individual for his/her professional life dedication to the improvement of cancer treatment, care and research. The award is open to all professions and specialties within the oncology field.

Nominations will be accepted for candidates irrespective of race, gender or nationality. Institutions, groups or associations are not eligible. Self-nominations will not be considered.
Candidates must be nominated on the official form by one who is, or has been, affiliated with a university or medical institution.

A curriculum vitae and description of the candidate's professional contribution to the field of oncology should be included with the application form.

Nominators are requested to keep their nomination confidential and to refrain from informing the nominee. The awardee will be selected by an International Committee appointed by the ECCO President with the agreement of the Council of the Pezcoller Foundation. The decision concerning the 2015 winner will be taken in April 2015.

The award consists of a prize of 30.000 EUR and a commemorative plaque. The Award Ceremonies will be held in Rovereto (Italy), on 11 September 2015 and in Vienna, during the 18th ECCO - 40th ESMO - European Cancer Congress as a Plenary Lecture to be delivered during the Presidential Session of Sunday 27 September 2015.

About the Pezcoller Foundation

The Pezcoller Foundation was established in 1980 through a most generous donation from Professor Alessio Pezcoller, a dedicated Italian surgeon, who devoted his life to his profession. Professor Pezcoller not only made important contributions to medicine but through his generosity and foresight, provided his lifetime's savings for others to do likewise.

Formerly, until 1997, the Pezcoller Foundation presented an award in collaboration with the European School of Oncology (ESO). The Pezcoller Foundation-ECCO Recognition for Contribution to Oncology builds on this tradition.

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Fondazione Pezcoller

More Information:
For more information about the nomination process and to submit a completed form and support documentation please contact
Davi Kaur:
Tel: + 32 2 775 29 31, Fax: +32 2 775 02 00,
Email: davi.kaur@ecco-org.eu

Nomination forms can be downloaded at:
www.ecco-org.eu
*(select "**About ECCO**" > "**Awards**")*
and must be completed and received by
15 March 2015.

Save the date!

27th Pezcoller Symposium

June 18-20, 2015
Trento, Italy

Challenging Roadblocks to Cancer Cures

The Pezcoller Foundation

Journal

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