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OUTREACH

Armenise Symposium: Presenters Explore Cancer Genomics, Therapeutics

More than 80 participants converged on Stresa, Italy, for the 12th Annual Symposium of the Giovanni Armenise–Harvard Foundation, held June 20 to 23 at the Grand Hotel Bristol. The theme for this year was “Cancer: From Genes and Proteins to Pathways and Therapeutics,” and the lush setting was more fitting than one might think.

To the uninitiated, gardens appear to be all about growth. But true gardeners know that the real secret is controlling growth. Without judicious trimming and pruning, invasive plants run wild, and the garden suffers and may ultimately die. And this is essentially what happens when cancer cells escape normal control and proliferate in humans and other creatures.

The program grouped 21 oral presentations into three sessions: basic findings about pathways and mechanisms involved in tumor development, insights from model systems, and news about drug development and cancer treatment. “This meeting is about how basic science moves us closer to the clinic,” said Ed Harlow, head of the Department of Biological Chemistry and Molecular Pharmacology at HMS, who presented an overview of the conference during the closing session. Twenty-three poster presentations covered similar ground.

Harlow said the conference talks were much like the excellent meals enjoyed by the participants: a series of courses, showcasing many flavors and combinations, which sparked lively conversations. Recurring themes included gene discovery, cell metabolism, systems-level analysis of complex phenomena, epigenetic control of gene activity, using genetic information to improve treatment, and evolving perspectives on the stem cell theory of cancer.

Harlow praised keynote speaker Hans Clevers for offering up “a whole meal” instead of a single course. Clevers, who was initially interested in immunology, made what Harlow called “an extraordinary series of discoveries about how cells grow and divide in intestinal crypts.” As a result, Harlow said, he has secured a place as “one of the world’s leaders in stem cell research.”

Tales from the Crypt

Clevers addressed “Identification of Stem Cells in Small Intestine and Colon by a Single Marker Gene LGR5.” In fiction, the word “crypt” conjures up images of stillness and death. But in the intestine, crypts are wellsprings of life—tiny factories generating cells at a rate that makes the intestinal epithelium the fastest self-renewing tissue in adult mammals. In the small intestine, crypts are nestled between fingerlike villi that cover the intestinal walls like shag carpet. In the colon, they are pockets in a smooth surface.

Scientists long suspected that the deep recesses of these crypts harbored pluripotent stem cells, even though these cells had not been precisely described. Nothing else could explain how such tight quarters could give rise to four distinct cell types that proliferate at different rates, migrate to different locations, and perform such varied tasks as secreting protective mucus, extracting nutrients from food, and ferrying messages between bowel and brain.

For nearly two decades, the thin line between normal development and cancer has been the focus of the Clevers lab at the Hubrecht Institute for Developmental Biology and Stem Cell Research in Utrecht, the Netherlands.



Liza Green, HMS Media Services

In his closing address at the Armenise Symposium, Ed Harlow compared the event to a sumptuous meal, blending flavors and combinations in a feast of science and discovery.

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In his keynote, Clevers explained how he and his colleagues initially “stumbled” into the study of crypt stem cells—an enterprise that paid off last October with a groundbreaking characterization of these elusive cells in *Nature*.

The lab’s work on the canonical Wnt pathway led to investigation of normal tissue renewal in the gut, where the pathway—and especially Tcf-4—is essential for normal crypt formation. When the researchers compared Wnt signaling in normal and knockout mice, they found that Wnt activity peaks at the bottom of the crypt and weakens in cells higher on the crypt walls.

In mouse models, Clevers said his team found nearly 250 Tcf-4 target genes in normal crypt cells and tumors. In the normal crypt, most of these genes are expressed in “transit amplifying cells,” which proliferate rapidly for a few days before traveling to their posts elsewhere in the intestinal lining.

Clevers hypothesized that one or more of these genes might be definitive markers for hard-to-define stem cells supposedly lurking in the crypts. One likely marker was a Wnt target gene, Lgr5, which the researchers already knew was expressed only in cycling crypt base columnar (CBC) cells. Previously suspected as stem cells, these scarce cells are interspersed with terminally differentiated Paneth cells in the crypt bottom.

“This meeting is about how basic science moves us closer to the clinic.”

Lgr5 is leucine-rich-repeat-containing G-protein-coupled receptor 5, which is also known as Gpr49. It is abundant in cycling columnar cells at the crypt base and was also detected in rare cells in several other tissues. Using an inducible Cre knock-in allele and the Rosa26-LacZ reporter strain, the researchers traced cell lineages in adult mice.

The Lgr5⁺ crypt base columnar cell (CBC) did exactly what a stem cell should: it generated all epithelial lineages over a 60-day period.

CBC cells cycle every 24 hours for the life of the mouse, Clevers said, and he showed dramatic pictures of what he called a “clonal conveyor belt” that ferries cells from the base of the crypt to the tips of the villi. Each stem cell produces 30 to 40 clonal cells a day that climb the crypt walls and differentiate into every cell type found in the epithelium.

Clevers and his colleagues also screened a variety of adult stem cells and tumor types for Lgr5 expression, and found it in some mammary, liver, retina, and brain cells. The presence of Lgr5-expressing cells in many tumors raised the possibility that these might be cancer stem cells that help tumors grow and expand. In that case, they might be natural targets for chemo- or radiation therapy. Yet he and his colleagues found that the percentage of Lgr5-expressing cells decreases steadily as tumors grow.

Going forward, Clevers is continuing to explore the cancer stem cell hypothesis—a major theme in this year’s Armenise–Harvard Symposium.

International Science

On hand for the proceedings were Count Giovanni Auletta Armenise and HMS dean Jeffrey Flier, participating in his first Armenise–Harvard symposium since being named dean in July 2007. Members of the foundation’s board of trustees, scientific advisory board, and Italian Scholarship Advisory Committee also participated.

U.S. scientific delegates came from HMS and three affiliated hospitals in Boston. Italian delegates traveled from 13 Italian universities and research institutes, some as close as Milan and others as far south as Naples and Palermo. Senior scientists from multinational pharmaceutical companies were also present. (Expanded coverage of the talks appears online at http://www.hms.harvard.edu/armenise/symposia/symp12_2008/index.html.)

Speakers and delegates included young scientists who have benefited from junior faculty grants and career development awards supported by the foundation. Since last year’s symposium, four HMS junior faculty have received new support: Chenghua Gu, Tom Bernhardt, Monica Colaiacovo, and Johan Paulsson. Past grant recipients Marcia Haigis and Adrian Salic presented posters at this year’s conference.

Two new career development awards, which help outstanding young Italian researchers establish independent laboratories following postdoctoral training abroad, have been made to Rosa Bernardi and Nico Mitro. Bernardi joined six other career development awardees for dinner with Count Auletta during the Stresa gathering.

In addition to promoting scientific research in Italy, the foundation has also supported extraordinary reporting opportunities for Italian journalists who cover the science beat. Alice Andreoli and Silvia Bencivelli, who report for broadcast and print outlets, are the latest recipients of the annual science writer fellowships. They participated in the symposium, joined previous fellows for a science writing workshop in Milan on June 23, and later traveled to Boston to research stories of their choosing at HMS.

—*Carol Cruzan Morton*

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