Researchers in the Department of Cell and Developmental Biology (CDB) at the University of Michigan are currently working to unlock the secrets of a key developmental signaling pathway in order to treat a number of vexing diseases.

In 1980, Christiane Nüsslein-Volhard and Eric Wieschaus performed a genetic screen in fruitflies, looking for genes involved in embryonic development. The genes were named based on the appearance of the mutant fruit flies. In one of the mutants, instead of hairs pointing in the same direction, as you would expect in a normal fruitfly, the embryos contained many extra bristles pointing in multiple directions. The mutant gene was therefore named Hedgehog for its resemblance to the spiky-haired animal. The gene associated with the mutation was cloned in 1992 and Nüsslein-Volhard and Wieschaus shared the Nobel Prize in 1995 for their groundbreaking work.

While there is one Hedgehog gene in flies, there are three in humans: Sonic Hedgehog, Indian Hedgehog and Desert Hedgehog. Each gene encodes for three different secreted proteins. “It turned out these were all human disease molecules. They all have very similar functions in humans and are all associated with various diseases,” said Scott Barolo, an Associate Professor of Cell and Developmental Biology and Director of the CDB graduate program. He sees this discovery as a breakthrough that provides a fundamental understanding of how cells talk to each other.

Currently, there are a total of nine researchers in CDB, eight in the Medical School and three in the Dental School, investigating how Hedgehog signaling may contribute to a host of diseases. Many labs focus on a specific organ, but researchers closely collaborate with each other in interdisciplinary research, since treatment for one disease could have potential implications for the treatment of others. The hope of finding new therapies for these diseases is driving researchers to explore the impacts of Hedgehog signaling gone awry. The research is particularly significant because it offers the chance for therapies for diseases where there currently aren’t effective treatments, like pancreatic cancer and brain tumors.

“Hedgehog signaling impacts almost every tissue in our body, throughout embryonic development and into adulthood,” says Ben Allen, an Assistant Professor in the Department of Cell and Developmental Biology. He said the goal is to better understand how the pathway works normally so that scientists can determine how it’s disrupted in different diseases and design treatments to correct those abnormalities.

Barolo explains that Hedgehog is the signaling pathway that coordinates gene expression so that all the cells are doing the right thing at the right time. In humans, those secreted proteins act in almost all of the tissues to perform a huge range of different functions. Abnormalities in the pathway can lead to both developmental and adult diseases. If there are problems in the signaling pathway, the cells aren’t getting the right instruction and will adopt the wrong fate and misbehave in development. “A very common problem in cancer is that cells are either not getting a signal they’re supposed to get or getting a signal they’re not supported to get. They’re getting bad instructions. The result is they over-proliferate and form a tumor,” he said.

Andrzej Dlugosz, a professor in the Departments of Dermatology and CDB, says the University of Michigan “has one of the largest groups of Hedgehog pathway researchers of any institution” and is at the forefront of Hedgehog signaling research, making a concerted effort to recruit top experts. The University of Michigan will be hosting the 2014 Hedgehog Signaling in Development and Disease conference, expected to draw 300 experts from all over the world.

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Deb Gumucio, Interim Chair of CDB, along with Allen and Barolo, have received a grant to find the targets of the Hedgehog pathway and what downstream targets are activated. Allen explains that if you can determine the genes that are activated by the Hedgehog pathway in cancer, you can work to identify a drug to target that gene.

Allen is studying the role of Hedgehog signaling during spinal cord development. He explains that during normal embryonic development, Hedgehog signaling is vital for the formation of different populations of neurons. In the absence of Hedgehog signaling, the neurons fail to form; with too much Hedgehog, extra neurons form that are no longer properly distributed. Either scenario results in malformation of the spinal cord that causes numerous developmental disorders and birth defects. Allen says the goal is to ensure a proper balance of Hedgehog signaling that allows for normal formation and maintenance of tissues, but prevents cancer.

Barolo is studying hedgehog in its developmental context. His lab is focused on the gene expression part of the equation: how does the Hedgehog pathway control the expression of genes in the receiving cell? He’s looking at genes that are turned on or off in response to the Hedgehog signal. He explains that Hedgehog diseases are the result of mutations in components of the Hedgehog pathway. His research involves manipulating the pathway and breaking it to see what happens. “We can simulate a disease condition by inactivating or activating the pathway, altering it from the normal state” and looking at effects on disease expression as a result. Examining a gene regulated by the pathway and whether it goes up or down when you change the signal helps understand the primary causes of the disease, he said.

The area where the role of Hedgehog signaling in promoting cancer growth is best understood is in basal cell carcinoma. It’s the most common but least dangerous type of skin cancer since it very rarely spreads, but when it metastasizes, there are no effective treatments, said Dlugosz. His team has generated mouse models showing that uncontrolled Hedgehog signaling causes basal cell carcinoma, and that turning off this signal leads to tumor regression. Basal cell carcinoma is usually the result of a mutation in a gene called Patched, which is a repressor molecule in the Hedgehog pathway. It serves as the brakes that prevent another molecule in the pathway, Smoothened, from being turned on and activating the pathway. Under normal conditions, Patched blocks Smoothened so the pathway is kept off. But with a cancer-causing mutation, Patched can no longer inhibit Smoothened. This results in a continuously-activated Smoothened, which leads to uncontrolled growth and basal cell carcinoma development.

Drugs that block the Hedgehog signaling pathway stop the uncontrolled growth and cause regression of human basal cell carcinoma. In January, 2012, the FDA approved Vismodegib, (trade name Erivedge) a Hedgehog inhibitor which binds and blocks the function of Smoothened. Dlugosz said it has proven incredibly effective in shrinking basal cell carcinomas. “This is a poster child for targeted therapy of hedgehog pathway driven cancers,” he said. He said the advantage is that it can be used in patients who are not good candidates for surgery, have aggressive tumors in difficult to treat areas like the eye, or where tumors have grown down to the bone and require amputation. But patients taking the drug experience several side effects, including hair loss and a loss of taste that is so severe many choose to stop taking the drug. That’s because hedgehog signaling is needed for normal functioning of taste buds and for hair growth, Dlugosz said. He has been awarded a research team grant to study the consequences of Hedgehog pathway inhibition on taste and smell, working with Allen, Charlotte Mistretta and Robert Bradley in the Dental School, and Jeffrey Martens in the School of Pharmacology. “We’re hoping that by better understanding the normal functions of the Hedgehog pathway in regulating taste and smell, we may be able to find a way to get around some of the side effects in basal cell carcinoma patients treated with Hedgehog inhibitors,” he said. Another possibility for some basal cell carcinoma patients is the use of a hedgehog inhibitor cream that would be applied to the skin but wouldn’t be absorbed by the body, minimizing side effects.

But mouse models indicate a complicating factor in the use of Vismodegib is that some regressed tumors leave behind a microscopic collection of non-growing tumor cells, so once the drug is stopped and Hedgehog signaling resumes, there is a re-growth of tumors at the same site. Dlugosz hopes to better understand whether it’s possible to predict if a tumor will grow back by performing biopsies before a visible tumor reappears. He says a possible solution could be to use the drug to shrink the tumor, and then excise any remaining tumor through a less invasive surgery. Though there have been setbacks, he sees great potential in this type of therapy. “Even though a majority of what I do is bench-based research, it’s fantastic to be able to see how patients do on these drugs and to watch these tumors shrink away.”

Gumucio has been exploring how Hedgehog signaling affects the health of the intestine, both in the embryo and in the adult. Gumucio, Scott Barolo, Marina Pasca di Magliano, Andrzej Dlugosz

Pictured on right, top to bottom: Ben Allen, Scott Barolo, Marina Pasca di Magliano, Andrzej Dlugosz

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Brandon Carpenter

Michelle Muza-Moons

Xing Fan

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Xing Fan, an Assistant Professor in Neurosurgery with a joint appointment in CDB, is focused on the way information develops in the gastrointestinal tract, especially in Inflammatory Bowel Disease. Currently, inflammatory bowel treatment blocks the immune system with steroids and other immuno-suppressants, since the condition often results from an overactive immune system. Initial studies in the laboratory indicate that if you decrease Hedgehog signaling in an animal, their GI tract is more prone to inflammation, "hinting that somehow Hedgehog signals are influencing the immune system." She believes that Hedgehog signals talk to certain types of immune cells and is in the process of trying to find out which ones. "I can't say that increasing the signal would necessarily provide us with benefit because it may have other effects we don't want, but getting a better understanding of what the signal does in the immune system might expose a good target in the future." Although there is limited data on how the Hedgehog communicates to the GI immune system, she believes this offers potential hope for GI-related diseases for which there is no silver bullet. "My dream is that we could figure out a way to make this a helpful therapy," she said.

Marina Pasca di Magliano, an author of one of the first papers still living within five years. Di Magliano is an Assistant Professor in 2003 showing that the Hedgehog signaling pathway is active in the gastrointestinal tract of human subjects. She has been jointly awarded a grant with Allen to determine the role of Hedgehog signaling in inflammatory bowel disease. She has been jointly awarded a grant with Allen to determine the role of Hedgehog signaling in inflammatory bowel disease. She has been jointly awarded a grant with Allen to determine the role of Hedgehog signaling in pancreatic cancer. She's looking into what happens in the cell in activated Hedgehog signaling to determine the impact on disease. Her lab has found that the gene KRAS is mutated in virtually every single human pancreatic cancer. Based on that, she put the mutated gene in the pancreas of a mouse. It caused the mouse to get tumors, while the tumors regressed when that mutated gene was turned off. Also, when KRAS is on, there is active Hedgehog signaling. "So we're trying to find out if Hedgehog signaling has a link to the KRAS mutation" associated with pancreatic cancer, she said. Pasca di Magliano added that no single drug will cure pancreatic cancer, but that different drugs or inhibitors could be combined to tackle the disease. She hopes within the next couple of years, to figure out how Hedgehog signaling works in this disease and said this offers a new avenue for treatment, in an area where "traditional therapy has failed quite miserably."

For glioblastoma, 97% of patients die within the second year. For medulloblastoma, more than 40% of patients die within five years. Fan sees targeting developmental signaling pathways as creating the opportunity for development of far more effective therapies. He explains that these types of cancers are composed of two compartments, cancer stem cell-like cells and non-cancer stem-cell-like cells. Scientists have believed that cancer stem-like cells are the origin of the cancer and are required for ongoing tumor growth, but the current therapy only targets non cancer stem-like cell populations. Fan says that another signaling pathway "plays such an important role in disease," she said. She hopes to continue researching Hedgehog, and is eager to study its role in another disease in the future. Barolo says the process leading to treatments is starting to accelerate because there's an understanding of how Hedgehog signaling events are related. With that comes the promise of better therapies in the future. "Our understanding of how Hedgehog works is getting more sophisticated, so the therapeutic approaches will get more sophisticated and targeted as well," she said.

The University of Michigan will be hosting the 2014 Meeting on Hedgehog Signaling in Development and Disease August 4th - 8th, 2014. Ben Allen is currently organizing this meeting along with an advisory committee of Scott Barolo, Marina Pasca Di Magliano, Andrej Drkulos, Deb Gumucio & Sunny Wong. For more information visit hedgehog2014.com or email hedgehog2014@umich.edu.
**NEW DEPARTMENT PROGRAMS & INITIATIVES**

**Pluripotent Stem Cell Initiative**

Professor Sue O’Shea is leading the way in establishing the Pluripotent Stem Cell Core as the premier teaching and training program for human iPSC and hES work in the University.

Since the Stem Cell Core was established, it has trained over 70 individuals across the University to derive and grow human embryonic stem cells and induced pluripotent stem cells.

Work in the core has resulted in the establishment of more than 50 new iPS lines, and with Gary Smith, 20 new human ES lines, many of which have specific disease mutations, allowing for the first time, the study of these difficult human diseases in a dish.

From the initial investment from the Endowment for Basic Sciences, this initiative has shown a great return on investment of over 9 times and yielded 36 grants that resulted from data generated in this core. To build on these successes the core will continue:

- Training scientists to culture and characterize hESC and hiPSC.
- Providing reagents and equipment for pluripotent stem cell culture.
- Providing hands on assistance with hiPSC derivation: from fibroblast expansion to hiPSC line derivation.
- Providing assistance with the directed differentiation of pluripotent stem cells to desired adult cell types.
- Developing new coursework to introduce students to the fundamentals of stem cell biology.

By providing training and support, researchers throughout the University will have the skillsets and tools needed to bolster their own exploration of this critical field.

**U-M researchers were the first to develop iPSC models of epilepsy (2012) and of bipolar disorder (2013).**

They were also the first to find pancreatic and head-and-neck stem cells and stem cells in solid tumors, finding them in breast cancer in 2003.

**New course aims to demystify fluorescence microscopy**

The department is launching a new course, Quantitative Fluorescence Microscopy (CDB560), directed by Ajit Joglekar & Shiv Sivaramakrishnan, in Winter 2014. The course will combine lectures, hands-on tutorials, and paper discussions to teach graduate students, new or senior, the theory and practice of Quantitative Fluorescence Microscopy and digital image processing in Cell Biology.

Fluorescence microscopy allows researchers to look inside live cells and observe specific proteins and organelles in order to understand the molecular origins and mechanisms of disease. Quantitative fluorescence microscopy can extend these experimental conclusions from observations to detailed biophysical mechanisms. In the first half, students will learn the best practices in designing quantitative fluorescence experiments, the basics of electronic imaging and image processing, as well as cutting-edge fluorescence-based methods used in Cell Biology. The second half will use primary literature describing fundamental discoveries in cell biology that were enabled by fluorescence techniques as case studies for further analyzing the design of experiments and image analysis techniques. Hands-on tutorials involving freely available software, Image J, will be used throughout the course to demonstrate and practice basic image analysis.

This introductory course will be limited to 15 students. Interested students should contact either Ajit (ajitj@umich.edu) or Shiv (sivaraj@umich.edu).

**Faculty chalk talks**

Faculty are helping each other compete successfully for dwindling NIH dollars by participating in chalk talk sessions in which PIs can present their grant outlines to faculty colleagues and receive constructive feedback.

**M1 Curriculum Update**

The medical school is revamping the M1 curriculum; included among expected changes are consolidation of histology to one semester and movement of embryology to the Fall term. New teaching concepts, including case based learning, are also being rolled out.

**Alumnae Showcases**

We are participating in showcases for alumnae all over the country, in an effort to keep them abreast of our accomplishments and enlist their help and support in our future success. Want to join us or know someone who does, Send us an email at: cdb-alumni-update@umich.edu

**Webpage Redesign**

We have redesigned our web page to be easier to navigate and better communicate our research goals. This is an ongoing effort as we try to better hone the information and tools students, faculty, staff, alumni & donors are seeking.

Have a suggestion? Send it to cdb-web@umich.edu