City of Hope

The Helix

TO INFORM, EMPOWER AND CONNECT

Newsletter from the Irell & Manella Graduate School of Biological Sciences

SUMMER 2009

Graduate Research Highlights • Publication Update

DNA Repair Volume 7 May 3, 2008 Pages 788-800

RAD59 is required for efficient repair of simultaneous double-strand breaks resulting in translocations in *Saccharomyces cerevisiae*

Nicholas R. Pannunzio[1,2], Glenn M. Manthey[1], Adam M. Bailis[1]

[1]Department of Molecular Biology, Beckman Research Institute of City of Hope
1500 E. Duarte Road, Duarte, CA 91010-0269

[2]City of Hope Graduate School of Biological Sciences
1500 E. Duarte Road, Duarte, CA 91010-3000

Abstract

Exposure to ionizing radiation results in a variety of genome rearrangements that have been linked to tumor formation. Many of these rearrangements are thought to arise from the repair of double-strand breaks (DSBs) by several mechanisms, including homologous recombination (HR) between repetitive sequences dispersed throughout the genome. Doses of radiation sufficient to create DSBs in or near multiple repetitive elements simultaneously could initiate single-strand annealing (SSA), a highly efficient, though mutagenic, mode of DSB repair. We have investigated the genetic control of the formation of translocations that occur spontaneously and those that form after the generation of DSBs adjacent to homologous sequences on two, non-homologous chromosomes in *Saccharomyces cerevisiae*. We found that mutations in a variety of DNA repair genes have distinct effects on break-stimulated translocation. Furthermore, the genetic requirements for repair using 300 bp and 60 bp recombination substrates were different, suggesting that the SSA apparatus may be altered in response to changing substrate lengths. Notably, *RAD59* was found to play a particularly significant role in recombination between the short substrates that was partially independent of that of *RAD52*. The high frequency of these events suggests that SSA may be an important mechanism of genome rearrangement following acute radiation exposure.

Krist Azizian

First author and graduate student, Nicholas Pannunzio, studies DNA recombination and repair with his mentor, Adam Bailis, Ph.D.

See Interview *on page 5*

In this issue

The Helix highlights an impressive, first-author publication by a graduate student.

The Career Corner

Are You Ready for Your Job Search?

by Jonie Watanabe Tsuji, Career Counselor

Have you thought about a job search? Do you know what it takes to get a job? Would you be surprised to learn that it is more than just putting together a résumé and giving a good interview? Whether you are planning a career in academia or industry, searching for a job is the same — know yourself, market yourself, and network your way to your dream job.

So what is involved in a job search? The most important part of the job search is assessing yourself. Your values comprise the foundation of your job search because they represent your core. Think about what is important to you in a job: Is money all that matters? Is it important to work at a prestigious company? Must it be a job that helps others? Should it allow you to work only 40 hours a week? Ultimately, if you choose a job that goes against your values, you can be fairly certain you will be unhappy.

Similar to values is personality. Do you know your personality style? Where do you get your energy from (within yourself or in the company of others)? Are you the type of person that needs proof something exists, or do you think "out of the box?" How do you make decisions? Finally, are you the type to keep your options open, or do you need to know where you are going to be a year from now? If

See Job Search *on page 3*

The Helix gets to know Dawn Eastmond, Ph.D., associate dean for student development

The Helix: What is your research background? What was your thesis research at the University of Pennsylvania?

Dawn Eastmond: My Ph.D. is in biochemistry and molecular biophysics, but my thesis project was in a genetics lab. When I first joined the lab, my project, in very broad terms, was to study the function of a family of RNA-binding proteins. But, as you know, RNA-binding proteins are involved in the regulation of many aspects of eukaryotic gene expression. And, targeted interference with RNA-protein interactions could offer novel approaches to the modulation of expression profiles, alteration of developmental pathways and reversal of certain disease processes. My thesis project investigated a decoy strategy for the study of the alpha-CP subgroup of KH-domain RNA-binding proteins. These poly(C)-binding proteins have been implicated in a wide spectrum of post-transcriptional controls. Three categories of RNA decoys to alpha-CPs were studied: poly(C) homopolymers, native mRNA-binding sites and a high-affinity structure selected from a combinatorial library. Several sequences demonstrated optimal decoy properties when assayed for protein-binding and decoy bioactivity in vitro and in vivo. A subset of these transcripts was shown to mediate targeted inhibition of alpha-CP-dependent translation when expressed in either the nucleus or cytoplasm of transfected cells. These studies established the feasibility of developing RNA decoys that can selectively target biologic functions of abundant and widely expressed RNA binding proteins.

Denise Bovee

Dawn Eastmond, associate dean for student development, ensures that graduate students remain well-adjusted as they develop their professional goals here at City of Hope.

TH: What were your responsibilities when you were at Wharton? How was that experience?

DE: While I was in graduate school, I looked for opportunities that combined my interest in biomedical research with my interest in the business world and mentoring young people. In this search, I found the Leadership, Education and Development (LEAD) Program. The LEAD Program is a national partnership between business and academia that identifies, selects and enables outstanding high-school juniors, particularly from historically underserved communities, to consider business as a career choice. At the Wharton School, we have developed an intense program where students learn business principles in a wide range of specialties, including accounting, marketing, corporate ethics, global analysis and information management, from leading executives and world-renowned professors. My role was managing the day-to-day operations of the program, including developing curricula, hiring of research associates and teaching assistants, and recruiting, selecting and mentoring participants.

TH: How did you discover City of Hope?

DE: When I told my colleagues at the university that I would be moving to the Los Angeles area, they were concerned about me finding a place that would be a good fit. We started talking about different institutions and laboratories I should consider. One of the professors mentioned City of Hope as a reputable institution that emphasizes humane patient care and interdisciplinary research.

TH: What are your responsibilities in the Department of Professional Education?

DE: As the new associate dean for student development, I will be working very closely with graduate school associate deans Steven Novak, Ph.D., and Michael Barish, Ph.D., as well as Queenie Du, graduate school administrator, in the recruitment, retention, training and advising of students in the Graduate School of Biological Sciences. I will work closely with the student body to ensure they develop individual educational plans and understand institutional requirements and resources. Furthermore, I will be responsible for the administration of the Eugene and Ruth Roberts Summer Student Academy, which is a huge honor. The program has a rich history of attracting and mentoring students from around the country. I hope to continue that tradition while introducing new initiatives and programs to the participants.

TH: Having been through graduate school, what advice do you have for graduate students?

DE: When I was in graduate school, I was very sensitive about the changing of the leaves because it meant another year in my thesis lab. One of the post-docs in the laboratory said to me, "Do not be so hard on yourself. It does not matter how long it takes you to get the Ph.D. because you will have it much longer than that." So that is my advice to you. It took me six years to get my Ph.D., and I have had it for four years now, and the time is just flying by.

Faculty Spotlight

City of Hope Faculty Profile • Janice Huss, Ph.D.

The Helix knows how tough it can be for first-year graduate students to choose a thesis lab. To help make the transition easier, we highlight faculty members and their research in an effort to help students make informed decisions about their mentor choices. In this issue, Janice Huss, Ph.D., assistant professor of gene regulation and drug discovery, answers a few questions so that we might get to know her better.

Position: I am an assistant professor in the Division of Gene Regulation and Drug Discovery.

Lab location: We are on the first floor of the Familian Sciences Building.

Team: My lab has one post-doctoral fellow, one research associate and typically one summer research intern. We are growing, so I am very interested in recruiting graduate students.

Current research: We are interested in how orphan nuclear receptor transcription factors regulate energy metabolism by characterizing their regulatory pathway components and target genes.

What question is your lab currently investigating?

We are investigating how an orphan receptor family, the estrogen-related receptors, link mitochondrial energy metabolism and muscle growth. They may coordinate the expression of genes encoding contractile proteins and mitochondrial enzymes during myocyte growth and differentiation. This has implications for type 2 diabetes, heart failure and muscle atrophy and growth in aging.

Denise Bovee

Janice Huss, assistant professor in the Division of Gene Regulation and Drug Discovery, studies orphan nuclear receptors and how they regulate energy metabolism.

What is one aspect of City of Hope research you would like to highlight for graduate students?

The majority of new students approach the City of Hope Graduate School of Biological Sciences with an interest in basic and translational cancer research. I would encourage students also to consider labs within the Department of Diabetes and Metabolic Diseases Research when choosing rotations. They may discover an area of research that they previously never considered, or a way to integrate their passion for tumor biology with the dynamic field of metabolic regulation. For example, there has recently been a renewed interest in the area of targeting tumor bioenergetics as a way to regulate cancer cell growth and metastasis.

What is your philosophy toward graduate and post-doctoral trainees?

Scientific inquiry is an inherently self-starting endeavor, and graduate school is immersion training for developing the skills needed to conduct independent research. I want to train independent, critical thinkers in the lab. Constructive debate among lab members over data interpretation, the next experiment to perform and the best technique to use reflects a healthy lab dynamic and tells me I am doing my job.

Job Search

Continued from page 1

your personality conflicts with your work environment (for example, you are an extravert working in an isolated cubicle), you may find that you are often frustrated at work.

In addition to values and personality, skills are another aspect of finding a job match. What skills do you have? Aside from gene cloning and PCR, what transferable skills do you have? For example, you may have negotiated a reduced price on lab equipment or were able to come in under budget on a project within the lab. Or you may have taken on a leadership role, whether in the lab or for the Graduate Student Organization or the Postdoctoral Association. These all represent valid, transferable skills that you should consider.

Once you have done your self-evaluation, you can begin to market yourself. Translate your values and skills into a résumé (curriculum vitae, for academia). Come up with a 30-second personal advertisement that you can use to respond to a potential employer when they ask, "So, tell me about yourself." Do your homework on the companies (or universities) you are targeting: Get information, and do some research. Finally, make sure you have some form of support system, whether that is family, friends or your friendly neighborhood career counselor.

The job search does not have to be scary. Just take it one step at a time. If you need help any step of the way, send me an e-mail at jtsuji@coh.org and make an appointment. We can help you get from "How do I get a job?" to "You're hired, now let's talk salary!"

City of Hope™

1500 E. Duarte Road
Duarte, CA 91010
www.cityofhope.org

Little Flem Goes a Long Way

by Nicholas Pannunzio

Antibiotics have yet to celebrate the centennial of their discovery, but a world without them would be difficult to imagine. Developed countries would still be seeing a huge tuberculosis mortality rate due to a pandemic level of Mycobacterium tuberculosis infections. Outbreaks from Yersinia pestis, the causative agent of plague, would not be a medical rarity, but a common occurrence. Even simple cuts and scrapes would be cause for alarm, as they can lead to life-threatening infections of the opportunistic Staphlyococcus aureus. Even more difficult to fathom is that, in the hands of almost anyone else, the discovery of the prototypical antibiotic may never have happened. The story of Alexander Fleming's accidental discovery of penicillin is a famous cautionary tale to all scientists that serendipity will always favor the prepared mind. Astoundingly, while the medical significance of this discovery is obvious today, Fleming's find was not immediately noticed, and it was not until around 10 years later that antibiotics began to see widespread use.

According to Alan Lightman's book, *The Discoveries*, Fleming, or "Little Flem," as some called him due to his short stature, possessed a quiet personality. One colleague at St. Mary's Hospital Medical School in London wrote that he "never liked talking, but when he did make up his mind to express a judgment in words, you could be perfectly certain that it would be in the highest degree intelligent." In addition to this, his bench displayed a sort of organized chaos, with culture plates lying around for weeks at a time. He would even poke fun at his lab mates "for being too neat and tidy, for carefully putting away their test tubes at the end of the day." It was on one of his old plates of Staphylococcus, which had been left out in the open, that he noticed a fluffy white mold. Instead of trashing the "contaminated" plate, he took a closer look and saw that "the patch of staphylococci closest to the mold had been miraculously dissolved." This mold was found to be a colony of Penicillium, so Fleming named the bacteria-killing substance it produced "penicillin." In May of 1929, Fleming published his paper, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of B. Influenzae," where he used filtrates of the Penicillium growth broth to demonstrate the ability of this unknown compound to kill some strains of bacteria, but not others.

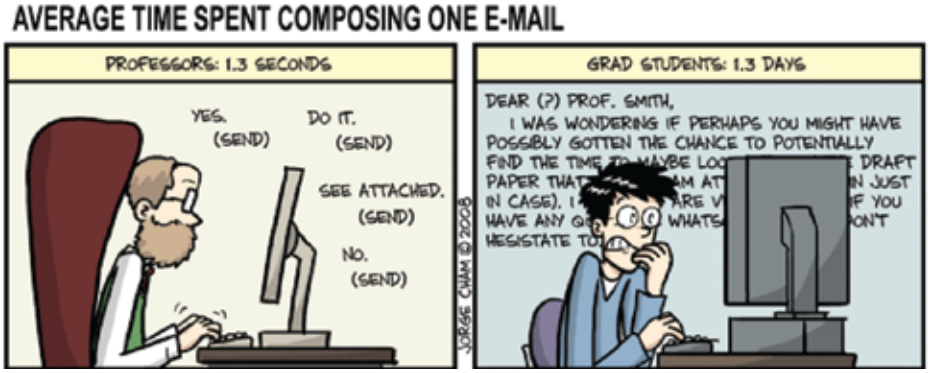
Far from being heralded as a medical breakthrough, Fleming's discovery went largely unnoticed by the scientific community. His paper was published during a time when most leaders in the field believed that using vaccines to stimulate a patient's immune system was the best way to cure disease, not by using chemicals. In fact, it was thought that most of these chemicals would be too toxic to the body to be useful to fight disease. Within his paper Fleming states, "It is suggested that it [penicillin] may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes." His former mentor, Almroth Wright, asked him to delete this statement as it suggested that the body's immune system was incapable of fighting disease on its own. Although shy, Fleming stood his ground and kept this phrase in the paper, recognizing the importance of his discovery.

The next hurdle to overcome was how to concentrate and purify the active agent in penicillin and make it useful as a medicine. This task was beyond Fleming's capabilities and would require skilled chemists that also recognized the validity of his discovery. It was not until 1938 that Howard Florey and Ernst Boris Chain, who would share the Nobel Prize with Fleming in 1945, generated copious amounts of pure penicillin that could be mass produced for the general public. The success of penicillin spurred on researchers to search for drugs to treat other

See Flem *on page 5*

The Funny Pages

Doing a Ph.D. is like becoming all of the Seven Dwarfs. In the beginning you're Dopey and Bashful. In the middle, you are usually Sneezy, Sleepy and Grumpy. But at the end, they call you Doc, and then you're Happy.



Interview *Continued from page 1*

The Helix: Nick, tell us about your paper.

Nicholas Pannunzio: Our paper focuses on the phenomenon of translocation formation. People have shown that exposure to ionizing radiation (IR) leads to double strand breaks in the chromosome. One of the most long-lived effects of this damage is translocation, so we are interested in studying the molecular mechanisms that go into forming these translocations. To study this we have built a substrate in S. cerevisiae, where you have two pieces of a gene, HIS3, on two non-homologous chromosomes, chromosomes 15 and 3. Basically, we induced a break either with IR or engineered cut sites near these substrates and looked at how they come together to form a translocation, ending up with a product that is part chromosome 15 and part chromosome 3. Once we had this system set up, we looked at several proteins that we know are involved in translocation formation. Specifically, we looked at the genes involved in single strand annealing (SSA), which is unique in that it does not require all the components that other types of homologous recombination pathways use. SSA is a simple mechanism where ssDNA comes together to anneal, so you do not necessarily have the unwinding that is required for the strand invasion process, because the substrate is already there.

TH: Has this phenomenon (SSA) been studied in other model systems?

NP: Maria Jasin's lab used mouse embryonic stem cells and observed stimulation in SSA products. If you look at lymphoma patients and sequence the junctions at which these translocations occur in their tumor cells, it varies in the amount of homology you see, indicating that SSA may play a role with non-homologous end-joining in translocation formation.

TH: What have you learned from authoring a paper?

NP: What I learned was that you have to have a story to tell. I realized that you should have a way of drawing people into your story and convincing them as you go along. So, I would write something, give it to Adam [Bailis, Ph.D., associate professor of molecular biology], and it would come back blood red with markups. The paper went through several rounds of this. Eventually, you develop a flow where you actually have a story.

TH: What were the benefits of writing a paper on your own?

NP: It gives you pause because you are looking at data all the time, so it gives you a chance to think about the context of what you are doing and what the data actually mean. Also, you really have to read a lot of papers in order to write your own. You basically pore over PubMed, and it gives you citations that you always reference as key papers to enhance your thinking process. So, one of the biggest things that I got out of this is really knowing the literature.

TH: Having gone through the process, does it strengthen your belief in the peer-review system?

NP: It does. I am not really sure what the alternative is, but our paper is stronger now, having gone through the peer-review process. Not to say that the system is not wrought with problems and that there is always politics involved. In the end, giving it to someone else and asking, "What do you think of this?" helps you out a lot. It gives you another person's perspective to contemplate alongside your own thinking.

Flem: Little Goes a Long Way

Continued from page 4

microbial infections. In 1943, Selman Waxman discovered streptomycin, the first antibiotic used to successfully treat tuberculosis, ushering in an era when it appeared that no bacteria was safe from treatment and that science would eventually find a cure for all microbial infections.

Unfortunately, the success of antibiotics is quickly being overshadowed by the emerging number of antibiotic-resistant bacterial strains, leading to the consequent dwindling of the arsenal of effective drugs used to combat these bugs. However, their discovery is one of the triumphs of science and demonstrates the impact that basic research can have on humanity. Also, it provides proof that even if your research leads to one of the most significant medical breakthroughs in human history, whether through years of hard labor or a stroke of good fortune, its merit may not be immediately recognized. Remember that you need the courage of your convictions to be able to convince others of the value of your find.

Mission Statement

The Helix newsletter seeks to inform, empower and connect our student body in order to focus and promote our graduate school's growth and accomplishments.

Through *The Helix*, we intend to inform City of Hope and its faculty that our graduate program remains accomplished in research, ultimately reflecting the caliber of our students and our program.

The Helix also seeks to empower. To inspire, motivate and give confidence to our graduate students as they explore and accomplish their goals.

Furthermore, by connecting our students, we can nurture an academic environment, establish collaborations and initiate scientific progress.

Off the Bench

What are graduate students doing away from the lab?

Each term, the Graduate Student Organization elects one gregarious student to uphold the position of social chair, a responsibility not to be taken lightly. All you need to do is go on one outing to realize that this job entails more than just organizing social events. Take a closer look. The social chair is charged with the demanding task of mixing the glue that keeps our student body connected and, quite frankly, sane. If you have not already, be sure to go to a graduate school social event in the near future. You will be pleasantly surprised. Below are some highlights from fun past events.

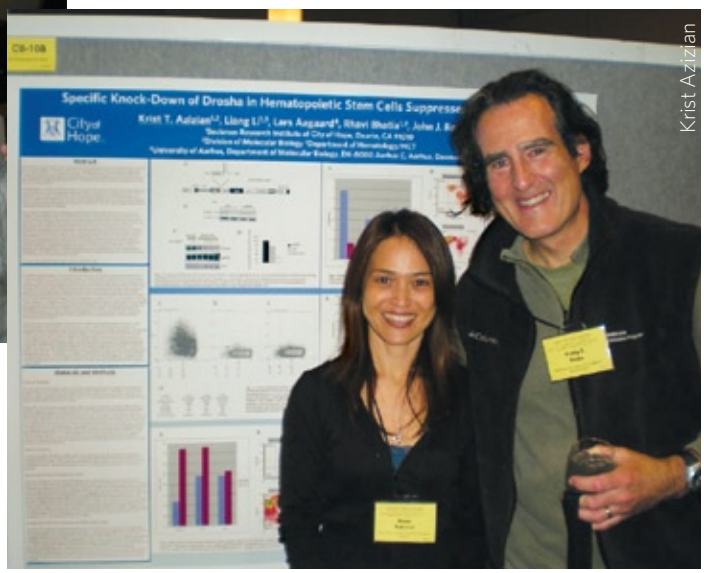
The City of Hope Graduate School of Biological Sciences class of 2008. From left are Seung-Gi Jin, Damon Meyer, Chen Wu, Valerie Chavez and Daniel Kim.

Amanda Gunn

Graduate students show off their Halloween spirit at a fun Beckman Pub in October. From left are Lauren Liddell, Patrick Perrigue, Cassondra McHugh, Swati Kadam, the Ninja of Doom, Nicole Bennardo, Stephanie Nay and El Blue Fuego.

Graduate students prepare for a cool, refreshing splash during a trip to the amusement park Raging Waters.

First-year graduate students (clockwise from left) Greg Cherryholmes, Supriya Deshpande, Swati Kadam, Marisa Bowers, Lauren Liddell and Renzo Corzano get acquainted during Bowling Night, part of their two-week orientation before classes begin.



Krist Azizian

Kumi Sakurai (left) flashes a sparkling smile along with 2006 Nobel Laureate Craig Mello, Ph.D., at a Keystone Symposium meeting last March in Whistler, British Columbia. Mello received the honor for his co-discovery of RNA interference, a subject for which Sakurai will soon receive her doctorate.

First-year graduate student Swati Kadam (center) adds to her royal riches during Casino Night, a Beckman Pub theme jointly sponsored by the associations for graduate students and post-doctoral fellows. Graduate students Heather Johnston (left) and Nicole Bennardo (right) test their luck for a royal flush and a chance to wear the crown.

Su Yang

Graduate students Rafael Flores (left) and Jason Hei Chan mix it up with the minstrels at a recent graduate school trip to the local renaissance fair.

Living Lean and Green: Tips on how to build healthy habits for ourselves and the environment

by Amanda Gunn

As I glance out my window, I can barely see a vague outline of the mountains I am so fortunate to have in my backyard. Let us be honest here: That haze hampering my view is not fog.

What can we do as graduate students at City of Hope to maintain our way of living with minimal impact on the environment? The answer is not necessarily just the rideshare program offered to us. While this is a fabulous opportunity to reduce emissions, and I fully recommend it, simply putting our names on a list is not enough.

Being scientists, many students have heard of the "Hundredth Monkey Syndrome." The name stems from an experiment where one monkey on an island was taught to wash her food prior to eating it. This trait spread through her family and slowly caught on around the island. Interestingly, when one hundred monkeys caught on, the monkeys on a neighboring island began washing potatoes as well.

If we want to bring about social change, we need to live mindfully — to think before we act. We must be aware of the consequences of our actions for ourselves and for the environment. By taking on this responsibility individually, we each might continue to influence others until one day we have "one hundred monkeys."

Here are some easy examples of how we each can "live green" every day without substantially altering our lives:

- Carpool, Rideshare, Public Transportation — Skip traffic, reduce emissions, enhance social awareness. What is there not to love about this? Riding a bike or walking to work is even better for our health.
- Recycle — Do not wait for somebody else to do it. Do not throw food items into the recycle bins. By collecting cans and bottles from lab lunchrooms and turning them in to a recycling center, we can even make a little money. There is a recycling center just one block from City of Hope.
- Shop Local and Shop Organic — Our economy is struggling, and every penny we spend counts more than ever. We can support local farmers by purchasing food items produced within 100 miles of our homes. We also can shop organic to help avoid pesticides. And while we're at it, we can shop using reusable shopping bags.
- Skip the Meat — Fact: Methane produced by cows contributes significantly to global warming. On top of that, the hormones found in meat products have been implicated in breast, prostate and ovarian cancers. While not everyone is comfortable becoming vegan, we can still have an impact by reducing our animal product consumption to twice a week.

So now that we are carpooling to work with our animal-friendly locavore lunch packed in a reusable container, consider how much healthier this lifestyle is for the planet — and ourselves. Many people do not see the point in living green because they do not believe they will see the environmental impact in their lifetimes. And we will not if nobody tries. On the other hand, making green choices in our diet and exercise can have us looking and feeling our best in no time.

As students at City of Hope, if we all band together to change both for ourselves and for the environment, can we be that "hundredth monkey"?

A very warm welcome to our first year graduate students!

Marisa Bowers
Deepti Chadalavada
Greg Cherryholmes
Jessica Christenson
Renzo Corzano
Supriya Deshpande
Wen Jin
Heather Johnston
Swati Kadam
Ching-Ying Kuo
Samuel LaBarge
Lauren Liddell
Cassondra McHugh
Patrick Perrigue
Nicholas Snead
Margaret Wear

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Marisa Bowers
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Check out our calendar for upcoming events! (*Use your g-mail account*)
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