

# Natural Selections

A NEWSLETTER OF THE ROCKEFELLER UNIVERSITY COMMUNITY

## Natural Selections Interviews Rockefeller's Viviana Risca, Principal Investigator of the Laboratory of Genome Architecture and Dynamics

ALICE GADAU

At the age of fourteen, Viviana Risca spent her summer break unlike most teenagers. Every morning, she took the train from Long Island to work in Dr. Daniel Eichinger's parasitology laboratory at New York University. Despite the cabinet full of dead worms in formaldehyde she had to pass every morning, this first exposure to biological research was highly influential in propelling her into a lifetime of research. Since then she has been excited about using molecular techniques to understand the processes that occur in cells.

Viviana has now joined the Rockefeller community as one of the two new tenure-track assistant professors hired in 2018. After completing her Ph.D. in Biophysics at the University of California, Berkeley, she continued her scientific career as a postdoctoral scholar at Stanford University with Professor William J. Greenleaf. Viviana is interested in the biophysical rules that contribute to the dynamics and stability of the genome. In addition, she wants to understand how the three-dimensional genome architecture can regulate DNA-based processes.

**Alice Gadau: What is the central question you are trying to address in your lab, and how is this an expansion from your past work?**

**Viviana Risca:** The three-dimensional structure of the genome is controlled by its association with a variety of proteins, together making up a DNA-protein complex we call chromatin. Through the efforts of large-scale sequencing projects, we now know much of the linear sequence of bases that make up the human genome, but we are still far from fully understanding the mechanisms that control how and when the information encoded in DNA sequence is read out by transcription. A skin cell and a muscle cell contain the same genome, but



*Viviana Risca*

they express different sets of genes that give rise to their unique identities.

My lab seeks to understand how three-dimensional chromatin structure controls the ways in which various proteins, including those involved in transcription, access their binding sites on DNA in order to perform their biological functions. One of the driving hypotheses of our work is that chromatin structure acts as an integrator of many molecular inputs to modulate access to DNA. I am particularly interested in how chromatin modifications, inter-molecular interactions, and polymer effects give rise to specialized parts of the cell's nucleus that stably repress transcription and help maintain cell identity and normal cell function. Both chromatin structure and the processes that shape it are often perturbed in cancer, as well as during aging, and I hope that our work on these fundamental processes will provide useful leads toward better cancer

therapies and diagnostics.

As a postdoc at Stanford, I worked on exploring how the landscape of enzyme-accessible chromatin can give us insights into the regulatory networks that control gene expression in several cell types, including a cancer model, using a popular method called ATAC-seq. I also did a lot of technology development, which resulted in RICC-seq, a method for mapping chromatin fiber structure at high resolution, and ChAR-seq, a method for mapping contacts between RNA and DNA genome-wide. In my own lab, we will continue to use and develop these technologies, applying them toward the goal of understanding the basic biophysical and molecular mechanisms responsible for stable transcriptional repression and overall control of access to genomic DNA.

ALICE GADAU | NATURAL SELECTIONS

CONTINUED TO P. 2

**AG: How does three-dimensional genome architecture contribute to DNA regulatory processes?**

**VR:** Since the 1920s when Emil Heitz coined the terms euchromatin and heterochromatin, we have known that the cell nucleus is divided between regions of high and low chromatin density. Since then, we have learned that organization of chromatin is far from random—it is in fact organized at multiple length scales.

At short length scales, every 150–200 bp of eukaryotic genomes is wrapped around roughly 10 nm-wide histone complexes called nucleosomes. Regions of DNA that are depleted of nucleosomes tend to be hyper-accessible to exogenous enzymes we use to probe them, and we interpret these regions to be also accessible to endogenous proteins like transcription factors, chromatin remodelers and polymerases. Indeed, many of these proteins seem to localize to nucleosome-depleted DNA. We also know that some histone modifications, like lysine acetylation, is associated with low-density, euchromatic regions of the genome that tend to be more accessible to protein binding. The high-density, heterochromatic parts of the genome are less well understood, from a structural standpoint, and many labs, including my own, are currently trying to decipher the mechanisms that drive the exclusion of transcriptional machinery from these silent genomic regions. Candidate mechanisms that have been proposed include occlusion of binding sites by DNA buried in compacted chromatin, chemical exclusion by phase-separated liquid domains, and simple volume exclusion from high density regions.

We also know that there is functional communication between genomic regions at much longer length scales spanning tens of thousands and sometimes hundreds of thousands of kilobases. Enhancer elements in the genome, which are acetylated, hyperaccessible, and bound by transcription factors when active, somehow must communicate with gene promoter regions because they regulate these promoters. This is thought to happen via DNA looping interactions in three dimensions, but the exact nature and dynamics of these contacts are an active area of research and not yet understood. Lastly, we also know that the cell nucleus is divided up into regions with different functional profiles, through associations with the nuclear lamina or self-association of po-

tentially phase-separated domains like the nucleolus. How this long-range organization relates to short-range chromatin folding is also an area that my lab plans to explore.

**AG: What is RICC-seq and how can it accurately examine short range DNA contacts?**

**VR:** RICC-seq stands for ionizing Radiation-Induced Correlated Cleavage. In the 1990s, it was shown that the pattern of DNA damage induced by X-rays or gamma-rays on a cell's genome is shaped by the way the DNA is folded into chromatin. RICC-seq takes advantage of this convenient property of chromatin. We irradiate cells with X-rays or gamma rays, carefully extract the short pieces of resulting single-stranded DNA, and then sequence those pieces. Their ends tell us about the pattern of DNA damage and consequently, about the way the DNA was folded in the original cell. This method works well for mapping high-resolution DNA-DNA contacts on the order of less than 10 nm and less than a thousand base pairs, making it complementary to other three-dimensional structure mapping methods like Hi-C, which work better for contacts spanning thousands of kilobases.

**AG: What makes RICC-seq novel from other sequencing techniques?**

**VR:** RICC-seq has two unique advantages. First, it can be performed on living cells that are not fixed or permeabilized. Therefore, we can probe chromatin structure in its native state. Second, it uses hydroxyl radicals generated by radiation as its probe. The radiation can penetrate all areas of the nucleus, no matter how dense, and the radicals are smaller than water and can easily diffuse. Therefore, we can get data from not only the low-density euchromatin in the nucleus, but also from highly compacted, dense heterochromatin.

**AG: What other tools are you incorporating in your lab to understand genome architecture?**

**VR:** RICC-seq is not a single-cell method and requires quite a bit of input material, so we will be combining it with lower-input methods like single cell or bulk ATAC-seq and RNA-seq, as well new cutting-edge technologies as they emerge. We will also be complementing this work with protein binding measurements like ChIP-seq or CUT&RUN, and microscopy that can tell us about the long-range organization of the nucleus. Lastly, we will also be collaborating

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with chromatin engineers to develop perturbations that will help us dissect causal and functional relationships between molecular factors and chromatin structure.

**AG: Are there other hobbies you have that incorporate science?**

**VR:** I've long loved incorporating skills that I pick up in the lab into my other hobbies. When I learned microscopy and optics, I also took up photography in my spare time, because the basic concepts are the same. I love art in general and see a lot of parallels between the lives of scientists and artists. We are both seeking fundamental truths, and both need to continually find ways to nurture our creativity. I also love to cook. I often use it to relax because it uses many of the same skills as biochemistry or molecular biology, but you can usually determine failure or success more rapidly than at the bench, and it is also easier to share your successes with your friends.

Lastly, I love science outreach and communications, but I would not call those hobbies. I think all of us as scientists have a responsibility to share our work with the public that, after all, supports our work through taxes and donations, to advocate for the societal benefits of basic research, and to equitably educate the next generation. ■



## With a Schmeear

AILEEN MARSHALL

New York City is known for many things—culture, nightlife, and food, to name a few. We already know about the widely recognized style of New York pizza and hot dogs. But did you know that the city is known for having the most authentic bagels? You can now get one anywhere, from a mass produced bagel in your local grocery store (generally not recommended) to many bakeries, delis, and restaurants around town, however they weren't always so widely available. Where did bagels come from?

Various ancient cultures had some form of a bagel-like bread. There are Egyptian hieroglyphics that depict everyday people with round shaped bread with a hole in the middle. The design makes for even cooking and allows for easy transport, since many can be carried on a stick or a string. The bagel as we know it probably evolved in Eastern Europe, particularly Poland, in the Middle Ages. The earliest mention of a bagel in writing was from 1610 in the “Community Regulations” of Krakow. There is a legend that they were invented in 1683 in honor of the Polish king Jan Sobieski for saving Austria from Turkish invaders, but the earlier mention casts doubt on the story.

Bagels came to this country with Eastern European immigrants in the late nineteenth century. By 1900, there were seventy bagel bakeries on the Lower East Side. In 1907 the International Beigel Bakers Union was founded, which had the effect of limiting production mostly to this city. As these immigrants assimilated and moved across the country, so too did the popularity of and demand for bagels. Murray Lender, a Polish immigrant, opened a wholesale bagel bakery in New Haven, Connecticut in 1927, one of the few outside New York at the time. A turning point came in 1956, when the Lenders bought a freezer. They soon realized they could ship frozen bagels to distant retailers without them going stale. Today bagels are common in supermarkets, but Lenders' bagels are the only mass produced bagels that retain authenticity.

By tradition, bagels are made by letting the shaped wheat-based dough sit for twelve hours at a cool temperature, around 40° to 50° F. Then they are boiled for about a minute before they are baked. It is the boiling that gives them the sheen on the crust. True bagels have a dense chewy texture with a crust that has a slight snap when bitten.



*Assorted bagels*



*Bagels with lox*

They should have absolutely no resemblance to white Wonder Bread. Some say that New York City water gives bagels a better taste. According to the Smithsonian, the ratio of calcium to magnesium in our water binds with the gluten in the dough to give the bagels the accurate degree of chewiness.

Bagels come in different flavors including onion, sesame seed, poppy seed, cinnamon raisin, pumpernickel, rye, whole wheat, and egg. An “everything bagel” has some combination of these ingredients, having evolved from bakeries trying to use up all the dough they had left over. Bagels can be eaten as is or toasted, and usually topped with either butter, cream cheese (a schmeear), jelly, lox, tomatoes, onions, capers, or some combination of these. Around Saint Patrick's Day, you may see some bagels dyed green. Different cities have their own style of bagels. In Chicago bagels are not boiled but baked with steam, giving them a very soft

texture. Montreal's bagels have dough containing malt and sugar but no salt. Honey is added to the boiling water for a sweeter taste. In London, bagels are smaller with a courser texture and more air bubbles. Since there is no legal regulation, many companies produce what they call “bagels” that are very far from the real thing.

Here in New York City, there are several famous bagel places as well as many smaller neighborhood establishments. The most familiar are Zabar's, Russ and Daughters, the Second Avenue Deli, and Ess-a-Bagel. Another well-known store, H&H Bagels, is characteristically New York in that it was founded by a Puerto Rican family. The closest source to our university is Bagelworks, on First Avenue at 66th Street. So enjoy a typical city Sunday morning tradition and pick up the *New York Times* and a couple of bagels with a cream cheese and spend the rest of the morning relaxing with them. ■

Photo Courtesy of unemployedeater.com

Photo Courtesy of Stu Spivack





Photo Courtesy of Michael Joseph

Inner Sleeve of Beggars Banquet.

## Culture Corner

### Celebrating the 50th Anniversary of *Beggars Banquet* by The Rolling Stones

BERNIE LANGS

In December of 1968 The Rolling Stones released *Beggars Banquet* just months before they would be introduced as “the greatest rock and roll band in the world.” The record, which features tunes by the songwriting team of Mick Jagger and Keith Richards at the very peak of their creativity, has a consistent, unified sound. Richards’ guitar work on *Beggars* ranges from nuanced and subtle to in-your-face, airplane engine electric power chords, ringing out and enveloping Jagger’s vocals in a cocoon of creative textures. Charlie Watts on drums and Bill Wyman on bass anchor all of the music with exactitude and precision. The band’s fifth member, Brian Jones, was fading away at the time of recording into an introverted state of confusion and a paranoid drugged out haze. Jones only contributed here and there, his last gasp of what he did best as a musician, putting the cherry atop the sweet sundae of the Stones’ tracks. It would be his final album as a Stone, as he was asked to leave after the record was completed so the group could bring in virtuoso guitarist Mick Taylor. Just a month after exiting the band, Jones died, drowning in his swimming pool.

*Beggars Banquet* was the first Stones album produced in the studio by

the late Jimmy Miller. Miller would go on to work with The Stones on their finest albums, including *Sticky Fingers* and *Exile on Main Street*. Glyn Johns served as the studio engineer on *Banquet* and Nicky Hopkins provided piano for the band, shining on these tracks with his individual style. The late Hopkins may have been the greatest keyboardist who served as a hired hand for any major popular music band.

I was eleven years old when *Beggars Banquet* was released in America. My siblings and friends all knew that this record was something special, appearing a year after The Beatles released their genius LP, *Sgt. Pepper’s Lonely Hearts Club Band*. Nothing on *Beggars* was similar to *Pepper’s*. The compositions penned by Jagger and Richards remained rooted in the chord structures of traditional blues and also continued the Stones’ extrapolations on Chuck Berry’s “1-4-5” structure of early rock and roll composition, a pattern also derived from the blues. Lennon and McCartney’s songs on *Pepper’s* dazzle in experimental melodic complexity amid George Martin’s nuanced production. Martin and The Beatles would selectively celebrate their tracks with orchestral strings and woodwinds when

the moment called for it. In contrast, the Stones stayed minimalistic on their records and could easily move from studio to stage with their tunes centered around two guitars, bass, drums, and piano, with small horns thrown in at times for variety.

*Beggars* kicks off with the infamous “Sympathy for the Devil” which was viewed in 1968 as reflective of the Stones’ image of danger and dark mystery. Even in my youth, however, I was intrigued by the serious nature of the lyrics and how deeply poetic they were in contrast to a lot of throw-away songs at the time. As Jagger steps into the guise of Lucifer, he’s more Oscar Wilde’s horrific gentleman Dorian Gray than a horror flick notion of the Devil. The character takes the listener on a tour of mankind’s violent history and sings with intensity as he describes his role both as observer and bloody instigator. The song’s exotic descriptions include gems such as “I lay traps for troubadours who get killed before they reach Bombay” and “I watched in glee as you kings and queens fought for ten decades for the gods they made,” which may be the only reference in pop and

CONTINUED TO P. 5



rock music to The Hundred Years' War. Lucifer is a "beggar" who demands sympathy for what he's watched us do and what he has had to endure. Yet he also threatens that "if you meet me have some courtesy, have some sympathy, have some taste; use all your well-learned politeness, or I'll lay your soul to waste."

Jean-Luc Godard, the French New Wave director, filmed the Stones recording "Sympathy" and put some of the footage in his movie "Sympathy for the Devil." I find that movie ridiculous and unwatchable and wish someone would extract the footage of the band, add moments that didn't make the final cut, and release it on its own (note that director Peter Jackson is currently taking the best parts of footage of The Beatles' mess of a 1970 documentary "Let It Be" and adding many new scenes of them playing that were left on the cutting room floor). Godard captures how the band began with Mick Jagger strumming "Sympathy" on a guitar and how after some standard arrangements, the piece shifts to the heavy percussive Latin background sound, which is heard on the album. The congas and drums conjure the devil like Shakespeare's witches brewing evil tidings from a boiling kettle. The song builds to a frenzy and fades away with the singer's echoing falsetto cries as Lucifer spirals downwards to hell—the band plays furiously amid Richard's sharp lead guitar work knifing through the mix. Lyrically, the words have more in common with England's grand poetic tradition than the good vibrations and flower power anthems spilling out on the radio at the time. If Bob Dylan can win the Nobel Prize in literature for his groundbreaking lyrics, Jagger and Richards surely qualify as Britain's Poet Laureates.

*Beggars* has fabulous moments of acoustic guitar-centered songs. After "Sympathy" fades out, the next tune is "No Expectations," a Jagger and Richards song that mirrors the classic "Love in Vain" by American bluesman Robert Johnson. The Stones would record "Love in Vain" for their next album, *Let it Bleed* and while Johnson's tune is about unrequited love and features images of trains leaving the station with

one's lost lover, the narrator of "No Expectations" is broken-hearted and requests in the opening lines, "Take me the station and put me on a train, I've got no expectation to pass through here again" and ends with a similar plea to be sent off far away in an airplane. The song's narrator describes the fleeting nature of the love he's lost, "like the water, splashing on a stone" and notes, "Our love is like our music—it is here and then it's gone." Brian Jones plays a wicked slide acoustic guitar, which resolves on an "open" E chord that Keith Richards must have been awed by, even through his anger with Jones' continual dragged out confusion.

The best acoustic performance on *Beggars* is, "Prodigal Son," written by Robert Wilkins, a reverend who recorded in the 1920s and 1930s. I'm not certain how old I was when I realized that the story of the song is Biblical, the famous tale of the arrogant youth who leaves home to find the world a harsh, punishing place and later crawling back to his father for forgiveness. Jagger singing affects a Southern, African-American spiritualist tone and Richards' acoustic chords and lead flourishes are passionate and heartfelt. After Jagger's last line, "My son was lost but now he is found" you can hear Richards give a guttural cry of "Hey!" as he brings it on home. One may venture that Mick and Keith would be absolutely content each day to sit on a porch in Mississippi in the summer sun, playing guitars and singing songs while swigging moonshine from a jug.

The rock songs on *Beggars* are fantastic, especially "Parachute Woman" and "Stray Cat Blues." "Stray Cat Blues" in particular is an example of the Stones' swaggering sexuality. When I was teaching myself guitar as a teenager, I would tune up to *Beggars* to play along with the album, and the rhythmic intensity of "Parachute Woman" was difficult to master. When I finally got it down, it was almost as if the guitar took over in the song for itself, and the intensity of the trancing repeating riffs brought me to a plane of surprising joy and newfound release. I could never truly master Keith's leading stabs in "Stray Cat Blues" but Jimmy Page would give them homage on Led Zepelin's final album, *In Through the Out*

*Door*.

The greatest masterpiece song on *Beggars* is "Street Fighting Man." It is a slice of English history in living color, summing up the frustration of being a young man with energy and new ideas in 1960s London. It speaks of revolution, revelation, rebellion, and resignation all in one set of lyrics. Even if youth should run rampant through the city streets and "kill the King" they will ultimately be reduced to nothing more than bit players in a culturally limited rock and roll band. The sound of "Street Fighting Man" is the most complex in terms of instrumentation on *Beggars*. Charlie Watts and Keith Richards recorded their initial drums and acoustic guitars on a cassette recorder and Jimmy Miller manipulated that sound to abstract perfection. Additional guitars, percussion, and piano were added later and Brian Jones contributed well-placed drones on a sitar. Jagger's vocals are menacing, multi-tracked, and startlingly direct. I've listened to the song for fifty years and it is fresh on each hearing.

*Beggars* closes out with a beautiful song "Salt of the Earth," an ode to the working class men and women of Great Britain. At the same time, in the song's middle break Jagger admits that while on stage performing, the crowd is nothing but a "swirling mass of grays and blacks and whites" that don't seem real to him and are actually "strange" in his eyes. The song hits a galloping peak and they give pianist Nicky Hopkins the honor of having it fade out to his manic right hand banging out a set of rapid chords.

The album's release was delayed in 1968 because the record companies in America and Britain balked at the LP's cover art of a dirty public bathroom with graffiti about the Stones and the songs on *Beggars*. It was eventually released with a white cover and a mock invitation to the banquet. The inner sleeve, however, boasts a black and white photo with shades of muted colors of the Stones celebrating like peasants who have invaded the King's table in the Dark Ages. It may be the greatest match of image and personality in a band in the history of rock music, a fitting idea for an incredible piece of music. ■

# Pets of Tri-I

POOJA VISWANATHAN

In this issue, *Natural Selections* interviews Muffin and Velvet, the cats who live with Sarah Mereby (Fuchs Lab, The Rockefeller University) and Eddie Spencer. I wasn't able to meet these lovely creatures but Sarah graciously transmitted my questions to them and their answers to me. Please write me at [pviswanath@mail.rockefeller.edu](mailto:pviswanath@mail.rockefeller.edu) if you have pets!

**Pooja Viswanathan: How old are you? In human years?**

**Velvet:** We are 21 years old and 1.5 years old in human years.

**PV: Is there a story behind your names?**

**V:** I was named by the people that work at the shelter that I am from. It is very fitting since my coat is very soft and sleek.

**Muffin:** I was named by my hoomans. They told me I am super cute and small like a muffin. I'm not so small anymore though.

**PV: What is your first memory?**

**M:** My first memory was waking up to find I had been put in a mailbox in the middle of winter. I was so scared! Thankfully I was rescued by the local shelter, which led to me meeting my hoomans. Meeting my hoomans is my favorite memory.

**V:** My first memory was meeting Muffin at the shelter. The shelter told me that I was the only survivor of all my siblings. Muffin has been my friend and a part of my family ever since.

**PV: Which humans do you live with? When did you meet them?**

**V:** We live with Sarah Mereby and Eddie Spencer. We met them at the shelter in January 2018.

**PV: How do they belong in the Tri-I community?**

**M:** Sarah is a Research Specialist at The Rockefeller University.

**PV: Where do you live?**

**V:** We live in Montclair, NJ. We just moved from Lyndhurst, NJ. We love our new house. We got to learn how to go up and down stairs and there are so many new places for us to hide. Also there are plenty of birds and squirrels to watch from the window.

**PV: If you could live anywhere else in the world, where would you live?**

**V:** I would live wherever my hoomans and Muffin would live.

**M:** I would live in a restaurant since I love to eat and would help eat any leftovers.

**PV: What are your favorite foods?**



*Muffin (left) and Velvet (right)*

**M:** I love to eat canned cat food. I do not have a favorite flavor. I eat so quickly that I can't even remember what flavor I had or whether I had a full bowl to begin with. I also love to try to eat Velvet's portion. Never know if Velvet had a better flavor or was given more food than me.

**V:** I love Friskies Shreds. My favorite flavor is salmon. I am very picky and have taught my hoomans to only give my shreds and not pate. Ew. I also like treats: Ahi Tuna flavor! I also like to drink water out of hooman's glass. It always tastes best when it's nice and cold. Sharing with hooman is the best. Although I don't know why they get mad at me when I take a small lick of their water.

**PV: What is your favorite weekend activity?**

**V:** We like to hang out with our hoomans on the weekends. That's the best. We normally like to watch TV with hoomans and sit in our cat tree while looking out the window. We also like to play with hooman. We love our feather toys.

**M:** I like to snuggle with Eddie.

**V:** I like to follow hoomans everywhere around the house to make sure to help them if they need my assistance.

**PV: Besides your human roomie, who is your favorite human in the Tri-I community?**

**V:** I have met Stephanie who works at Memorial Sloan Kettering. I love making new friends.

**M:** I can't remember. I am a bit afraid of meeting new people.

**PV: Do you have a funny story to share with us?**

**V:** One time hoomans brought home a cat stuffed animal that is about the same size as us. We were so convinced it was real. It was very scary. We both approached it very



*Muffin (top) and Velvet (bottom). Photos by Sarah Mereby and Eddie Spencer.*

slowly and pawed at it. We were worried we were being replaced by a new cat. Thankfully it's just a decoration. It wishes it could be like us.

**PV: Is there some way we can see more pictures of you on the interwebs?**

**V:** You can follow us on the Instagram account @catasticday or use the hashtag #muffinandvelvet.

**PV: If you could have any human ability, what would it be?**

**M:** Being able to open cans of cat food. That's the dream.

**V:** Being able to play the piano. I love when hoomans play piano. It's very relaxing. I've attempted to play the piano myself by jumping on the piano keys but it doesn't sound as good as when hooman plays. ■

Photos Courtesy of Sarah Mereby



## ***Life on a Roll***

### ***Aurora over Snaefellsnes***

MEGAN ELIZABETH KELLEY  
(TWITTER @MEGANEKELLEY)

On the Northern coast of the Snaefellsnes peninsula in Iceland, there is a horse farm nestled between the water and the mountains where I stayed for a few nights. As is typical for winter in Iceland, the wind howled, rain alternated with snow, and clouds often obscured the stars, but for a few hours one night the skies opened up and unveiled the Aurora Borealis. At times, swirling light shimmered overhead like idle tracings, while at other times there

seemed to be a green spotlight blazing across the sky. The wind and rain continued to blow in from the side—I realized that I was still in my pajamas and they were stacking up poorly against the elements, but the awe-inspiring sight of the aurora kept me outside for hours. I was grateful when the clouds eventually rolled in over the mountains, as I needed sleep and could not have otherwise torn myself away from such a sight. ■

