A YEAR, SO UNEXPECTEDLY DIFFERENT

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Being at the Wissenschaftskolleg these ten past months was a transforming experience. I interacted with so many interesting and wonderful people and had the time and opportunities needed to think about my research in new ways. Making Wiko work meant overcoming my usual inertia and extracting myself from the habit of sculpted routines. In so doing, I learned more about what I like and where I want to go. I felt freedom at Wiko and in Berlin. I want to return to both.

Modus operandi

During my Wiko year I found what 24 hours in a day really meant. I can work for about 8 to 10 hours, but being freed of many usual responsibilities, left me with about 10 hours of free time daily. Much of this was spent reading or listening to music, but there were still usually a few hours a day to occupy. These extracurricular activities included going to concerts, art museums, and exhibits, and walking between 10 and 50 kilometers a week. I plan to create a website to give the poems and feet a place to live and move.

I was selective about travel and gave invited talks in Toulouse, Paris, Dublin, Oxford, Roscoff, Berlin, Munich, and Kiel. Outside of a few personal trips to Montpellier, I really decided to experience Berlin, in particular wandering the streets of Mitte and Friedrichshain-Kreuzberg. My favorite hangout was *Esra* on Oranienburger Straße. I was also selective about communication with the outside world, which presented unexpected challenges. The biggest was interfacing with my laboratory at the University of Montpellier. Keeping projects going meant skypes and occasional visits either to Montpellier or my students and postdocs visiting me in Berlin. I did try a "skype as necessary" policy for the first few months of my stay, and this resulted in several crises, which were generally unpleasant. After weeks of mounting stress, I adopted a one-skype-per-week policy with students and postdocs. Even if we occasionally had little to say, this worked wonders.

Accomplished

During my year at Wiko I commenced, developed, and completed a range of projects, some linked to the theme of evolution and cancer, others not. I spent significant time writing grants, and two major ones were funded. I also wrote three new full presentations: the Wiko Colloquium, which presents evolution, and more specifically social evolution, for interdisciplinary audiences; a Seminar on how evolution can explain tumor progression within an individual, levels of cancer protection in different species, and preventive approaches to managing the disease; a Visuals presentation on the Chinchorro

culture, which were peoples living in the Atacama desert between about 7000 B.C. and 1500 B.C. and who employed "artificial mummification" as a mortuary ritual[1].

My main ongoing research project is a laboratory investigation of host-parasite coevolution, involving the bacterium *Pseudomonas aeruginosa* and an assemblage of different viruses ("bacteriophages") that infect and kill this bacterium. Scientists have long debated the dynamic form of coevolution, that is, perpetual reciprocal adaptations between hosts and their parasites. The two main types of coevolution are "arms race" dynamics, in which interaction traits escalate through time, and "fluctuating selection" dynamics, where traits cycle through time. We used experimental evolution between *P. aeruginosa* and a panel of its lytic phages and found the full known range of coevolutionary dynamics. In a manuscript that I wrote while at Wiko[2], we argue that coevolutionary pattern is determined by where phages typically attack on the bacterial cell: whether they adsorb directly to receptors on the bacterial outer membrane or rather use retractable Type IV pili (appendages that certain bacteria use to crawl over surfaces). We currently do not know exactly why using different receptors should percolate up to drive patterns in coevolutionary dynamics. Our findings are relevant to the employment of phages in preventing or combating bacterial infections, and more specifically those acquired in hospitals. Such "nosocomial" infections are responsible for about 10 % of deaths in hospitals and *P. aeruginosa* is a major nosocomial pathogen. Our findings suggest that coevolution is a phage-specific process that introduces complexity that should be considered in the use of phage as disinfectants in hospital environments to kill recalcitrant bacteria and as therapeutics for certain types of bacterially derived diseases, where phage replace or are used in conjunction with antibiotics so as to control infections while managing the emergence of antibiotic resistance[3].

I started several projects while at Wiko, the main one of which will be a contribution to the forthcoming special issue of the *Philosophical Transactions of the Royal Society* that

1 Marquet, P., Santoro, C. M., Latorre, C., Standen, V. G., Abades, S. R., Rivadeneira, M. E., and Hochberg, M. E. (2012). "Emergence of social complexity among coastal hunter-gatherers in the Atacama Desert of northern Chile." *PNAS* 109:14754–14760.

2 Betts, A., Kaltz, O., and Hochberg, M. E. (2014). "Contrasted coevolutionary dynamics between a bacterial pathogen and its bacteriophages." *PNAS* 111: 11109–11114.

3 Torres-Barcelo, C., Arias-Sánchez, F., Vasse, M., Ramsayer, J., Kaltz, O., and Hochberg, M. E. (2014). "A window of opportunity to control the bacterial pathogen *Pseudomonas aeruginosa* combining antibiotics and phages." *PLoS ONE 9(9)*.

I am co-editing with Carlo Maley. Specifically, I have become interested in conflicting claims regarding the extent to which we should expect to observe cancers in different species in natural environments. Data from zoos suggest typical levels of about 5 %, but some species (for example, cheetahs) experience about 25 % mortality due to cancer. The problem with this kind of data as a reflection of cancer rates in natural habitats is that zoo environments promote species longevity, and because cancer is considered to be largely a disease associated with aging, we would expect to see higher cancer incidences than in the wild. My prediction is that for most animal species, the incidence of cancer-related deaths should generally be very low in the wild, but there are a number of factors to take into consideration in assessing this. One way to gain a better idea of the forces that may be involved in the evolution of protection against cancer (for example, reinforcement of tumor suppressor genes) is to develop and analyze mathematical models. The central argument of the article that I am currently writing with Hanna Kokko is that the achievement of multicellularity and its subsequent refinement and maintenance through *millions of generations* of natural selection, has essentially conquered cancer, that is, the unregulated growth, multiplication, and spread of an individual organism's cells into local and/or distant tissues and organs. Before developing this argument, by "conquered" I mean that multicellular organisms have evolved an array of "tools" to prevent the emergence or spread of cancers that would otherwise constitute significant threats to survival and reproduction *at points in an organism's lifetime where natural selection is a significant force*.

Evolved protection is never perfect, meaning that lethal cancers are expected to occur sporadically at evolutionarily responsive points in an organism's life. Rather, cancer should more commonly occur at ages where selection is relatively relaxed, defenses reduced or absent, and the cancer obtainable given the rate limiting processes affecting cells of mutation, multiplication, and metastasis. What this essentially means is that we expect in humans, for example, that cancers should be rare from birth until reproductive maturity, then increase gradually, and finally grow steadily as we age and senesce. Because of resource transfers from adults to children, we should expect that natural selection acts on certain traits during and even after our normal reproductive lives, resulting in protracted senescence and thus the onset of most lethal cancers years or even decades after reproduction typically ceases in our 40s. This expectation is indeed borne out by data, but to understand it more generally, we need develop a more global theory for this phenomenon that can also be applied to other animal species. What we know from empirical study is that in the few long-lived and/or large-bodied species studied so far (naked mole rats and

elephants), special adaptations for resisting cancers are present, which is consistent with, but not proof of, the action of Darwinian selection. That is, the attainment through evolution of large body sizes or long lifespans in natural contexts requires that cancer protection coevolve. This is consistent with a theory I previously developed[4] on how parasites and pathogens constitute strong forces limiting the evolution of lifespan and body size. Longer lifespans and (correlated) larger body plans can only evolve if explicit resistance adaptations also evolve. Such coevolutionary phenomena are expected to emerge over thousands of generations or more, and as such are a form of macroevolution.

We intend to complement our theory with a data survey across different species and in different habitats. Our expectation is that species with the highest cancer rates live either in protected situations or in carcinogenic environments. The former includes natural parks, zoos, or access to health care (for example, humans and domesticated animals). Species in these environments live longer and, therefore, are more likely to develop a life-threatening cancer. Evolution cannot provide a natural means for fighting such cancers, in part because, as mentioned above, these cancers emerge at ages that are largely shielded from natural selection, but also since it would probably require thousands of generations, if ever, for novel cancer suppression genes to emerge and spread through a population.

On the opposite end of the spectrum are stressful and carcinogenic environments, such as polluted areas, but also lifestyle behaviors that increase the probability of mutagenesis and hence of cancers being obtained through a multistage process. These situations are increasingly studied in humans, resulting in the well-known associations between smoking, alcohol consumption, obesity, and certain cancers. Thus, our overall expectation going from favorable to natural to stressful environments is a U-shaped curve for cancer incidence. The fewest cancers should be observed in species living in habitats untouched by humans.

Mille mercis

Interacting with the Wiko staff was fantastic. Even in the few challenges and occasional misunderstandings that naturally occur during an event as complex as a sabbatical, we were always able to work things out to positivity. I would like to thank the staff – they *all*

4 Hochberg, M. E., Michalakis, Y., and deMeeus, T. (1992). "Parasitism as a constraint on the rate of life history evolution." *Journal of Evolutionary Biology* 5:491–504.

made a difference for me, but a few made such a big difference: Vera-at-the-front-desk's advice and always-there-to-help, Vera-workshop-organizer's dedication and friendliness, Katarzyna's professionalism and understanding, Katharina's help with organizing my stay, Lena's wonderful smile. Thanks too to Jens Rolff for welcoming me to his group at the Freie Universität and giving me the possibility for future visits.

I would like to express my sincere thanks to Luca Giuliani, Thorsten Wilhelmy, and Reinhart Meyer-Kalkus for directing this wonderful institute. I am particularly indebted to Paul Schmid-Hempel, who extended the invitation to spend a year at Wiko and to organize the Cancer Focus Group. I thank Carlo Maley, Athena Aktipis, Ula Hibner, Hanna Kokko, and Paul Ewald for accepting to be Cancer Focus Group Fellows. The Focus Group was a success in numerous ways: new projects, scientists joining who otherwise would not have had the opportunity at Wiko to interact on the subject of evolution and cancer (Adam Wilkins, Amy Boddy, Jerry Wilkinson, Gunther Jansen, Robin Bush, and Steve Frank), an exciting and productive Workshop, and most of all, free discussion of ideas that may lead to future projects. Special thanks to Athena and Carlo for their leadership in structuring Focus Group meetings.

Joining other Fellows for daily meals led to exciting and enriching interactions. I will retain many wonderful memories from Wiko – economics discussions with Bruce; Wendy-study-buddy in the dining room; kitchen splitting with Tong and Natasha; wonderful Berlin visits with Oli, Rob, Andrei, Marie, Clara, Eric, Dabbah, Franck and family, Julia, Samim, Peter, and Christine; going to meals between Jaffé and the dining room with Kathleen and Pippa; Conversations with Olivia; music, movies, and miscellany with Kasia, Andy, Lars, and Nina; cognac with Yuri and Lisa; hair ruffling with Mahua; banter in the coffee line with Jahnavi; philosophy with Paul; North Americanisms and more with Jerry, Cindy, Felix, Jamie; poems with David; face-to-face breakfast converse with Hanna; rap concert and grossly oversized meals with my son Julien and his friend Morgan; wine-seriousness and old, forgotten, rotten cheese with Gunther; and champagne and darts with some of the above …

Last but not least, an overflow of thanks to my wife Joelle, who made the sacrifices so that I could live this 10-month experience that is The Wiko.