THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Below is an interview with Gabriele Romano, a Translational Molecular Pathology department postdoctoral fellow in the lab of Dr. Lawrence Kwong at The University of Texas MD Anderson Cancer Center.

Brief description (5-10 sentences) about the main focus and highlights of your research.

My research activity is focused on the study of molecular mechanisms involved in cancer drug resistance and the identification of effective counter-therapies. I currently work on melanoma cancer mouse models and human samples to identify and validate promising therapeutic targets in combination with MAPK pathway inhibitors. In particular, I am combining my experience on experimental models with computational biology approaches, in order to create a unique platform for the development of molecularly-driven cancer therapy. This approach recently produced the first study on clinical resistance to MEK+CDK4 inhibition, which characterized the molecular effectors underlying such resistance and validated a rationally-identified counter-therapy.

The Origin Story

1) What are the discoveries that have lead up to your current work?
   Melanoma treatment has been revolutionized in the last 20 years by the advent of targeted therapy and immunotherapy. A lot of drug combinations have been approved or are in clinical trials right now for the treatment of melanoma patients, and one of these combinations (MEK+CDK4 inhibitors) has shown promising results for a group of patients (e.g. NRAS mutation) that generally do not have many viable therapeutic approaches, in particular if immunotherapy fails or it is not a possible strategy. Nevertheless, the clinical trials on MEK+CDK4 inhibitors have shown cases of initial response to therapy followed by relapse and drug resistance. My mentor (Dr. Kwong) and I were interested in understanding the biology underlying such resistance, hypothesizing that tumor heterogeneity might be the key to this phenomenon.

2) How did you come up with this hypothesis & what got you interested?
   The study focused on a single patient who had a great response in the first months of therapy but eventually relapsed and failed all the successive therapeutic approaches. The great collaborative environment within our department (Translational Molecular Pathology) but also with other departments (i.e. Melanoma Medical Oncology, Genomic Medicine) and also with Rice University allowed us to longitudinally study the patient's samples, following the evolution of the tumor throughout the various treatments. After sequencing the tumor samples we realized that there was a clone of resistant cells that expanded upon treatment and was likely responsible for the relapse and eventual lack of response.

3) What spurred this study or this question?
   Our interest in understanding if resistant subclones can be identified early and targeted with personalized therapeutic approaches.

So what?

1) Why is your research important? What are the possible real world applications?
   With our study we laid a blueprint for the identification of resistant subclones and for the development of possible counter-therapies. The ideal cancer treatment, from my point of view, is the one that looks at the

biological mechanisms that rule that specific individual cancer, and based on such mechanisms strategizes a precise course of therapy.

2) What kind of response have you gotten from your research / findings?
Great feedback in conferences and discussions with colleagues. I was also recently awarded the Outstanding Research Publication Award for Translational Research at MD Anderson that was an incredible honor for me. We hope to have positively contributed to the discussion about tumor heterogeneity, adding an important piece of information in the path that leads towards a more rationale-guided and personalized cancer treatment.

3) What question(s) or challenge(s) were you setting out to address when you started this work?
The most important question was: "was the resistance-conferring clone pre-existent or acquired during treatment"?

4) Why were those important?
Because if the clone was already there we could design a path of diagnosis and treatment completely different from the case in which it was acquired during the therapy. We still do not know the proportion of "pre-existent" resistant populations vs "acquired" resistant populations in cancer, but with our paper we demonstrated that, for example, with the analysis of multiple samples of the same tumor there is the possibility to detect potential source of resistance and exploit their vulnerabilities.

5) Big picture: What's your assessment of the current state of your research?
We have recently published the paper explaining our findings, and we hope that our work can have a positive impact on diagnosis and treatment of melanoma patients. The incredible environment of MD Anderson often allows quick translation of research, through the amazing collaboration between researchers and clinicians.

6) Why is your area of scientific discovery relevant for ordinary citizens of this country?
Unfortunately, melanoma cases have been on the rise in the last 20 years. About 100,000 new melanomas are expected to be diagnosed in US in 2019 and about 7,000 people are expected to die of melanoma. With the advances of medical research survival rates have improved incredibly, however, there is a lot of work to do in terms of prevention and treatment.

7) What happens next in the process of discovery?
We are now trying to understand if we can apply our findings in other subsets of patients and, if not, why, and how are these patients different. Mouse models will be precious allies in this phase.

Light up the interview

1) What has been / was your most important scientific finding? Your most surprising finding?
My most important scientific finding was for sure the identification of the resistance-conferring mutation (PIK3CAE545K). The most surprising one, for sure, realizing that the mutation was already present in the tumor at a 0.15% frequency before the start of treatments!

2) Are your methods generally accepted? Are they unusual or novel?
We use commonly accepted molecular oncology methods, but in the last work we also used a new technique set-up by a collaborator at Rice University. This technique allowed us to increase the resolution in detecting our mutation in patient samples. Also, we often use personalized algorithms when we perform computational studies.

3) Is there controversy in this area? If so, how do other studies differ from this paradigm shift?

More than controversy there is discussion. A lot has been said about resolution of Next Generation Sequencing, for example, but we believe that resolution is as important as multi-region analysis: we demonstrated that multiple samples of the same patient can contain precious information and potentially lead to identify many more patients with actionable mutations.

4) Do you have pet peeves about the way this area is covered?
I don't: I believe that there is a fruitful and fascinating debate about tumor heterogeneity and how to address it in the scientific community right now. Different scientists may have different angles, but as long as this conversation keeps the patient's needs as a main goal, we all can benefit from it.

5) What's next?
My research is going on with the study of mechanisms of drug resistance, in various subtypes of melanoma. I am focusing both on the acquired and intrinsic mechanism of drug resistance, studying new targets and new drug combinations that might be useful for specific groups of patients.

Personal details

1) Briefly, what most excites you about your work?
The single most exciting thing is knowing that I am making a difference. The idea that even only one person is going to benefit from what I do every day is not simply exciting, but the whole point about this work in my opinion.

2) What hobbies do you have outside of research?

I love traveling, scuba diving and playing soccer.

Quirky details

1) What do you think is most interesting or cool about your work? (e.g. whether that's how you made the discovery, a surprising setback or a quirky characteristic).
Working with mice is for sure the part I think is the coolest. After months of in vitro work, computational studies, hypothesis verified and hypotheses dismissed, you finally get to try your idea in mice. If it works, you know that your research has the potential to be actually useful to human beings. This last work was incredibly exciting: we identified a drug combination based on a confluence of in vitro and computational data. Nobody had ever tested that specific combination of drugs, but we predicted it would work and it did: most of resistant tumors in mice disappeared. That was amazing!

2) Do you have any entertaining story that would like to share? (e.g. ever had an outcome that was not expected, views on public policy, path taken to now, inspiration, etc.)
This was my first project as a postdoc and it was an amazing journey. I have a great mentor, Larry Kwong, who guided me and taught me an amazing amount of things: I actually grew as a scientist and as a person during this work. When I arrived here at MD Anderson, I had not seen or performed a Whole Exome Sequencing or a Reverse Phase Protein Array before, neither had I known how to interpret the resulting data. I studied a lot, read a lot, made a few mistakes and something awesome came out: I am very proud of what we were able to produce, but I truly hope this is only the beginning.